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Organic Compounds of Sulphur, Selenium, and Tellurium

VOLUME 3

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ISBN 0 85186 279 9
ISSN 0305-9812

A Specialist Periodical Report

Organic Compounds of Sulphur, Selenium, and Tellurium

Volume 3

A Review of the Literature Published between April 1972 and March 1974

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The Chemical Society
Burlington House, London W1V 0BN

ISBN: 0 85186 279 9
ISSN: 0305-9812
Library of Congress Catalog Card No. 77–23818

Filmset in Northern Ireland at The Universities Press, Belfast
Printed by photolithography and bound in Great Britain at
The Pitman Press, Bath.

Preface

The general aims and structure of this third Volume of 'Organic Compounds of Sulphur, Selenium, and Tellurium' remain those set out in the Preface to Volume 1.

In accordance with intention expressed in the Preface to Volume 1 to give more detailed treatment to unusually important or topical subjects, a new chapter is introduced in this volume entitled 'β-Lactam Antibiotics, Other Sulphur-containing Natural Products, and Related Compounds'.

'Theoretical Aspects of Organosulphur and Organoselenium Compounds' is a review for the period April 1970 to March 1974, with emphasis in this volume on conjugated systems. A review of the chemistry of Thiepins, Dithiins, and Thiazepines has been omitted. A review of these subjects, covering the four-year period April 1972 to March 1976, will appear in Volume 4. Reviewing of all other material covered in this Volume is for the two-year period April 1972 to March 1974.

D. H. R.

Abbreviations

The following abbreviations have been used:

c.d.	circular dichroism
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
cod	cyclo-octadiene
DABCO	diazabicyclo-octane
DCCI	dicyclohexylcarbodi-imide
DME	dimethoxyethane
DMF	*NN*-dimethylformamide
DMSO	dimethyl sulphoxide
e.s.c.a	electron spectroscopy for chemical analysis
e.s.r.	electron spin resonance
g.l.c.	gas–liquid chromatography
HMPA	hexamethylphosphoric triamide
LAH	lithium aluminium hydride
NBS	*N*-bromosuccinimide
n.m.r.	nuclear magnetic resonance
PPP	Pariser–Parr–Pople
py	pyridine
SCF	self-consistent field
THF	tetrahydrofuran
t.l.c.	thin-layer chromatography
Ts	toluene-*p*-sulphonyl

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1

Aliphatic Organo-sulphur Compounds, Compounds with Exocyclic Sulphur Functional Groups, and their Selenium and Tellurium Analogues

BY G. C. BARRETT

The layout adopted in Volumes 1 and 2 of this Series is retained, though spectroscopic and other physical properties are given an integrated account (Section 2) this year. This allows easier comparison to be made for the different sulphur-containing functional groups; it is also a device, one of several employed on this occasion, to save space, so that an ever-increasing volume of important work can be contained within a smaller number of pages.

1 Text-books and Reviews

Text-books and monographs include the reappearance of Suter's book,[1] and a competitor with the same title,[2] and others on sulphur,[3] and on selenium[4] and tellurium[5] compounds. General reviews of developments in organo-sulphur chemistry,[6] organo-selenium compounds,[7] and organo-tellurium compounds[8] are available, and more specialized reviews include: protection

[1] 'The Organic Chemistry of Sulphur', by C. M. Suter, Gordon and Breach, New York, 1971.
[2] 'The Organic Chemistry of Sulphur', ed. S. Oae, Plenum Press, London, in the press (cited in *Tetrahedron Letters*, 1973, 4751 and *J.C.S. Perkin I*, 1973, 59).
[3] 'Chemistry and Biochemistry of the Sulphydryl Group in Amino-acids, Peptides and Proteins', by M. Friedman, Pergamon, Oxford, 1973; 'Sulphur Research Trends', ACS Advances in Chemistry Series No. 110, 1971; 'The Determination of Sulphur-containing Groups', by M. R. F. Ashworth, Vol. 1, Academic Press, London, 1972; 'The Analytical Chemistry of Sulphur and its Compounds', ed. J. H. Karchmer, Wiley–Interscience, New York, 1972.
[4] 'Organic Selenium Compounds', ed. D. L. Klayman and W. H. Gunther, Wiley–Interscience, New York, 1973.
[5] 'Tellurium', ed. W. C. Cooper, Van Nostrand, New York, 1971.
[6] D. R. Hogg, in MTP International Review of Science, Organic Chemistry Series One, Vol. 2, p. 259, 1973; L. Field, *Synthesis*, 1972, 101.
[7] A. Fredga, *Kem. Tidskr.*, 1972, **84**, 26, 31.
[8] N. Petragnani, *Ann. New York Acad. Sci.*, 1972, **192**, 10.

of the —SH group,[9] sulphur-centred radicals,[10] sulphuranes[11] and hypervalent Se and Te compounds,[12] selenides of thiophen, furan, and selenophen,[13] (alkylthio)acrylates,[14] sulphoxides (synthesis and reactions[15c] and behaviour in strong acid[15g,16a]), dimethyl sulphoxide with DCCI[17,18] or with P_2O_5,[18] or Ac_2O[18] as an oxidant, sulphoximines in synthesis,[16b] quadricovalent S as a chiral centre,[15b] electronic effects of the sulphonyl group,[15d] synthesis of aliphatic thiocyanates,[19] sulphinic acids[15a] and sulphite esters,[15h] sulphenes,[15e] sulphonyl isocyanates,[15f] thiolsulphinates,[15i] and Bunte salts.[20]

2 Spectroscopic and Other Physical Properties

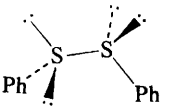
Mention is made of those papers in which data are interpreted in terms of the electronic structure of the functional groups, their chemical properties, or their conformational behaviour; data compilations are excluded.

Photoelectron Spectra.—Information on electronic structure may be obtained through this technique concerning interactions between a sulphur functional group and its neighbouring atoms, where *d*-orbital involvement has been inferred previously, often only tentatively, from chemical properties. C—S hyperconjugation (σ–π mixing) is no more effective in allyl methyl sulphide than analogous C—H hyperconjugation in propene, in contrast with the equivalent silane.[21] Comparisons of photoelectron spectra of H_2S, RSH, and R_2S show increasing delocalization of the sulphur lone pair with increasing substitution,[22,23] but only a small effect of *d*-orbital bonding on the π-orbitals of the benzene ring in thiophenol[24] and no p_π–d_π back-bonding in aryl methyl sulphides.[25]

[9] R. G. Hiskey, V. R. Rao, and W. G. Rhodes, in 'Protecting Groups in Organic Chemistry', ed. J. F. W. McOmie, Plenum Press, London, 1973, p. 235.
[10] J. L. Kice, in 'Free Radicals', Vol. 2, Wiley, New York, 1973, p. 711; L. A. Singer, *Selective Organic Transformations*, 1972, **2**, 239.
[11] B. M. Trost, *Fortschr. Chem. Forschung*, 1973, **41**, 1.
[12] J. I. Musher, *Ann. New York Acad. Sci.*, 1972, **192**, 52.
[13] V. P. Litvinov, A. N. Sukiasyan, and Ya. L. Goldfarb, *Khim. geterotsikl. Soedinenii*, 1972, 723.
[14] K. D. Gundermann, *Intra-Sci. Chem. Reports*, 1972, **6**, 91.
[15] *Internat. J. Sulfur Chem.* (*B*), 1971, **6**; (*a*) C. J. M. Stirling, p. 277; (*b*) O. N. Soerensen, p. 321; *ibid.*, 1972, **7**; (*c*) G. Tsuchihashi, p. 185; (*d*) F. G. Bordwell, p. 187; (*e*) T. Nagai, p. 207; (*f*) J. W. McFarland, p. 319; *Internat. J. Sulfur Chem.* (*C*), 1972, **7**; (*g*) G. Modena, p. 95; *Internat. J. Sulfur Chem.*, 1973, **8**; (*h*) J. G. Tillett, p. 289; (*i*) N. Isenberg, p. 307.
[16] (*a*) G. Scorrano, *Accounts Chem. Res.*, 1973, **6**, 132; (*b*) C. R. Johnson, *ibid.*, p. 310.
[17] J. G. Moffatt, in 'Oxidation', ed. R. L. Augustine, Dekker, New York, 1971, p. 1.
[18] G. H. Jones and J. G. Moffatt, *Methods Carbohydrate Chem.*, 1972, **6**, 315.
[19] D. Knoke, K. Kottke, and R. Pohloudek-Fabini, *Pharmazie*, 1973, **28**, 574, 617.
[20] S. Oae, G. Tsukamoto, and T. Kurusu, *Kagaku* (*Kyoto*), 1971, **26**, 1066.
[21] W. Schafer and A. Schweig, *J.C.S. Chem. Comm.*, 1972, 824; *Tetrahedron Letters*, 1972, 5205.
[22] H. Bock and G. Wagner, *Angew. Chem. Internat. Edn.*, 1972, **11**, 150; *Chem. Ber.*, 1974, **107**, 68.
[23] P. Mollere, H. Bock, G. Becker, and G. Fritz, *J. Organometallic Chem.*, 1973, **61**, 127.
[24] D. C. Frost, F. G. Herring, A. Katrib, C. A. McDowell, and R. A. N. McLean, *J. Phys. Chem.*, 1972, **76**, 1030.
[25] H. Bock, G. Wagner, and J. Kroner, *Chem. Ber.*, 1972, **105**, 3850.

Sulphimides carry a larger positive charge on sulphur than in the corresponding sulphoxides.[26] Differences in functional-group polarization are found in the series dimethyl sulphone, sulphoximide, and sulphur di-imide, and in comparisons of $MeSO_2F$ with F_2SO_2, or of $MeSO_2Cl$ with Cl_2SO_2.[27] Through-conjugation and spiro-conjugation between the sulphonyl group and π-orbitals of vinyl groups are shown by comparing dimethyl sulphone with methyl vinyl sulphone and divinyl sulphone.[28] However, the inductive effect of the sulphonyl group has a greater polarizing effect on neighbouring functional groups.

Dipole Moments.—Conformations of arene thiolsulphonates $ArSSO_2Ar$ and the corresponding thiolsulphinates[29b] are similar[29a,29b] to that of a disulphide (1) or a sulphinate in its preferred synclinal conformation; the stereo-

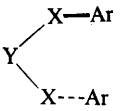


(1)

Thiolsulphinate: one oxygen in place of lone pair on one sulphur atom
Thiolsulphonate: two oxygen atoms in place of two lone pairs on one sulphur atom

chemical control exerted through *gauche* interaction of the two C—S bonds is now well-established.[29]

α-Disulphones, RSO_2SO_2R,[29b] are also represented by (1; oxygen atoms in place of lone pairs), while *gem*-disulphones,[29d] diacyl sulphides,[29c] sulphonic anhydrides,[29c] and thioanhydrides are represented by (2), as



(2)

determined by *gauche* interactions of the polar bonds —C—SO_2— and O—C—S—C.[29c] Selenides and diselenides are similar to their S analogues.[29e] Whereas thioacetals $CH_2(SAr)_2$ adopt a *trans-gauche* conformation,[30] trithio-orthoformates $CH(SAr)_3$ exist in various proportions of two *gauche* conformations.[30] Sulphoxides and sulphones

[26] C. E. Mixan and J. B. Lambert, *J. Org. Chem.*, 1973, **38**, 1350.
[27] B. Solouki, H. Bock, and R. Appel, *Angew. Chem. Internat. Edn.*, 1972, **11**, 927.
[28] C. Muller and A. Schweig, *Tetrahedron*, 1973, **29**, 3973.
[29] (*a*) O. Exner, D. N. Harpp, and J. G. Gleason, *Canad. J. Chem.*, 1972, **50**, 548; (*b*) P. Dembech, P. Vivarelli, V. Jehlicka, and O. Exner; *J.C.S. Perkin II*, 1973, 488; (*c*) O. Exner, P. Dembech, G. Seconi, and P. Vivarelli, *ibid.*, p. 1870; (*d*) O. Exner, V. Jehlicka, and J. Firl, *Coll. Czech. Chem. Comm.*, 1972, **37**, 466; (*e*) K. Sindelar and O. Exner, *ibid.*, p. 2734.
[30] A. N. Vereshchagin, L. A. Monetina, I. I. Lapkin, N. S. Zelenina, and B. A. Arbuzov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 1765.

have been studied,[31] and much effort is being concentrated upon studies of diaryl disulphides[32a,c] and di-2-pyridyl and di-4-pyridyl disulphides.[32b,33]

Nuclear Magnetic Resonance Spectra.—Natural-abundance ^{33}S n.m.r. of representative sulphur compounds appears to offer little scope for structural identification purposes; the broad absorption peaks render chemical-shift measurement very inaccurate.[34] Some ^{1}H–^{77}Se and ^{1}H–^{125}Te double-resonance studies reveal a similar structure-dependence of ^{77}Se and ^{125}Te chemical shifts, comparable with that of ^{31}P.[35]

^{13}C Chemical shifts of ring-substituted phenyl vinyl ethers[36] compared with their thio-analogues show the greater efficiency of S in transmitting electronic effects through greater bond polarization. ^{19}F N.m.r. studies of the series *m*- and *p*-F-C_6H_4-SX, -SOX, -SF_3, -SO_2X, and -SF_5 indicate the balance between π-acceptance by sulphur *d*-orbitals and p–π donation to the aromatic ring.[37]

The first report of Eu(dpm)$_3$ shift-reagent studies with thiols[38] indicates that the thiol proton resonance suffers a much smaller induced shift compared with alcohols, but the shift, at a maximum in CS_2 as solvent, is structure-dependent. Sulphides also interact less strongly than corresponding ethers with Eu(fod)$_3$.[39] Eu([$^2H_{27}$]fod)$_3$ greatly simplifies the ^{1}H n.m.r. spectra of thiolsulphinates.[40] Chiral Eu shift reagents permit the estimation of the enantiomeric purity of partially resolved methyl *p*-tolyl sulphoxide,[41] while the chiral-solvent technique is used[42] for the same purpose with [$^{12}CH_2$]benzyl [$^{13}CH_2$]benzyl sulphoxide and similarly labelled DMSO. A downfield shift of the aromatic proton resonances in chloromethyl *p*-nitrophenyl sulphide in the presence of Et_4NCl is accompanied by an upfield shift for the CH_2 resonances, attributed to close contact with Cl^-.[43]

Conformational information derived from n.m.r. and i.r. studies of 2,4-dinitrophenyl 2-chloroalkyl sulphides ArSCHR^{1}CHClR^2 reveals a weak repulsive interaction between Cl and SAr,[43a] while an intramolecular attractive

[31] Y. Y. Borovikov, Y. P. Egorov, A. M. Penchuk, and T. A. Khimchenko, *Zhur. org. Khim.*, 1973, **43**, 2476.
[32] (*a*) G. C. Pappalardo and G. Ronsisvalle, *Tetrahedron*, 1972, **28**, 4147; *J. Mol. Structure*, 1973, **16**, 167; (*b*) *J.C.S. Perkin II*, 1973, 701; (*c*) G. C. Pappalardo and S. Pistara, *Tetrahedron*, 1972, **28**, 1611.
[33] C. L. Cheng and G. L. D. Ritchie, *Austral. J. Chem.*, 1973, **26**, 1785.
[34] H. L. Retcofsky and R. A. Friedel, *J. Amer. Chem. Soc.*, 1972, **94**, 6579.
[35] (*a*) H. McFarlane, E. Christina, and W. McFarlane, *J.C.S. Dalton*, 1973, 2416; (*b*) W. McFarlane and R. J. Wood, *ibid.*, 1972, 1397.
[36] O. Kajimoto, M. Kobayashi, and T. Fueno, *Bull. Chem. Soc. Japan*, 1973, **46**, 1422.
[37] W. A. Sheppard and R. W. Taft, *J. Amer. Chem. Soc.*, 1972, **94**, 1919.
[38] H. Yanagawa, T. Kato, and Y. Kitahara, *Tetrahedron Letters*, 1973, 2137.
[39] T. C. Morrill, R. J. Optiz, and R. Mozzer, *Tetrahedron Letters*, 1973, 3715.
[40] L. E. Legler, S. L. Jindal, and R. W. Murray, *Tetrahedron Letters*, 1972, 3907.
[41] H. Nozaki, K. Yoshino, K. Oshima, and Y. Yamamoto, *Bull. Chem. Soc. Japan*, 1972, **45**, 3495.
[42] W. H. Pirkle and M. S. Pavlin, *J.C.S. Chem. Comm.*, 1974, 274.
[43] J. Hayami, N. Tanaka, N. Hihara, and A. Kaji, *Tetrahedron Letters*, 1973, 385.
[43a] G. M. Underwood, C. T. Watts, and C. A. Kingsbury, *J. Org. Chem.*, 1973, **38**, 1553; G. M. Underwood, A. K. Chan, T. Green, C. T. Watts, and C. A. Kingsbury, *ibid.*, p. 2735; G. M. Underwood and C. A. Kingsbury, *J.C.S. Perkin II*, 1973, 947.

interaction is demonstrated[44] between a sulphone or sulphoxide group and an alkoxide function, using 5-substituted 1,3-dioxans, and its strength is of about the same order as an intramolecular hydrogen bond for the sulphone. Solution conformations are deduced for ring-substituted diphenyl sulphides and disulphides.[45]

Protonation equilibria for aliphatic sulphoxides in H_2SO_4, as determined by n.m.r., compare well with data obtained earlier by u.v. and c.d. methods.[46a,e] pK_{BH^+} Values obtained similarly for sulphinates[46b] and sulphides[46c] have been reported; values for sulphides are some 4 units more positive than for corresponding ethers, and a basicity order $R_2S > RSSR \sim RSH$ emerges,[46c] in interesting contrast with the oxygen series (MeOH is more basic than MeOMe). ^{13}C N.m.r. of DMSO and diethyl sulphoxide reveal *O*-protonation in strong acid since both CH_3 and CH_2 resonances are shifted to higher field.[46d]

N.m.r. data for sulphones[47a] and sulphoximines[47b] have been interpreted.

Ultraviolet and Circular Dichroism Spectra.—U.v. spectra of benzene-, toluene-, and mesitylene-thiols and derived alkyl sulphides show bands in the 205—230, 235—270, and 275—300 nm wavelength regions, which are structure- and solvent-sensitive;[48] a predominantly conjugative interaction between S and aryl chromophores is revealed, with solvent shifts attributed to hydrogen-bonding to S. Detailed calculations have permitted assignments of transitions responsible for the absorption features near 200, 220, and 240 nm for simple alkyl sulphides.[49,50] Substituted aryl allyl sulphides and selenides show variations in λ_{max} related to Hammett σ constants,[51] with electron-donating ability order allyl Se ≥ allyl O > allyl S. Near-u.v. absorption of sulphoxides has been discussed,[52] and the thiolsulphinate absorption maximum at 254 nm (in hexane) has been exploited in estimation of the cysteine thiolsulphinate produced enzymically from *S*-allyl-L-cysteine sulphoxide present in onion.[53]

The c.d. of alkyl 2-phenylbutyl sulphides is interpreted in terms of

[44] E. Eliel and S. A. Evans, *J. Amer. Chem. Soc.*, 1972, **94**, 8587.
[45] G. C. Pappalardo, *Spectrochim. Acta*, 1973, **A29**, 2055.
[46] (*a*) P. Bonvicini, A. Levi, V. Lucchini, and G. Scorrano, *J.C.S. Perkin II*, 1972, 2267; (*b*) R. Curci, A. Levi, V. Lucchini, and G. Scorrano, *ibid.*, 1973, 531; (*c*) P. Bonvicini, A. Levi, V. Lucchini, G. Modena, and G. Scorrano, *J. Amer. Chem. Soc.*, 1973, **95**, 5960; (*d*) G. Gatti, A. Levi, V. Lucchini, G. Modena, and G. Scorrano, *J.C.S. Chem. Comm.*, 1973, 251; (*e*) P. Bonvicini, A. Levi, and G. Scorrano, *Gazzetta*, 1972, **102**, 621.
[47] G. Montaudo, P. Finocchiaro, E. Trivellone, F. Bottino, and P. Maravigna, *J. Mol. Structure*, 1973, **16**, 299; S. Oae, K. Harada, K. Tsujihara, and N. Furukawa, *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 49.
[48] I. W. Jones and J. C. Tebby, *J.C.S. Perkin II*, 1973, 1125.
[49] J. S. Rosenfield and A. Moscowitz, *J. Amer. Chem. Soc.*, 1972, **94**, 4797.
[50] G. L. Bendazzoli, G. Gottarelli, and P. Palmieri, *J. Amer. Chem. Soc.*, 1974, **96**, 11.
[51] G. A. Chmutova and V. I. Neonilina, *Zhur. fiz. Khim.*, 1972, **46**, 201.
[52] A. Mangini, M. Pallotti, M. Tiecco, A. Dondini, and P. Vivarelli, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 69.
[53] G. G. Freeman and F. McBreen, *Biochem. Soc. Trans.*, 1973, **1**, 1150.

interaction between phenyl and sulphur chromophores.[54] The optical activity of cysteine and its derivatives has unusual features due to the sulphur chromophores, and a c.d. study of common sulphur-containing amino-acids has been made.[55] In particular, the high optical rotation of the disulphide L-cystine has been taken as evidence for a chiral disulphide grouping but it is in fact due to accumulated optical rotatory power from three staggered rotamers in solution.[56] An inherently dissymmetric disulphide chromophore explanation is adopted for interpretation of the near-u.v. c.d. of disulphide-bridged peptides, and the temperature-dependence of the c.d. of cystine derivatives is accounted for by changes of the dihedral angle;[57] the spacing of the c.d. bands of chiral disulphides is largest when the dihedral angle is 0°.[58] Calculations[59] for orbital models of the chiral disulphide moiety provide estimates for rotation barriers in fair agreement with microwave data, and their u.v.-spectroscopic properties strongly reflect *d*-orbital participation in the excited states associated with the lowest-lying transitions.[59c] The right-handed screw-sense of the disulphide chromophore with dihedral angle 120° is associated with a negative c.d. band near 240 nm.[59d]

Infrared Spectra.—A large batch of papers has appeared in the period under review concerning self-association of alkanethiols[60a,f] and of thiophenols,[60a,g] as demonstrated by i.r. (and n.m.r.).[60d-f] Inert solvents, or weak oxygen[60c] or nitrogen[60b] bases, were used, and temperature and concentration effects[60b] studied; apart from evidence for 1:1 dimer formation in inert solvents, SH···O association[60c] and SH···π-bonding in thiophenols,[60a,g] in $PhCMe_2SH$,[60d] and between thiols and furan[60c] were demonstrated. The proton-donor ability of the thiol proton and the proton-acceptance ability of bivalent sulphur have been reviewed in comparison with oxygen,[61] also the proton-acceptor properties of alkyl isothiocyanates, which form hydrogen bonds through N.[62] Pronounced hydrogen-bonding is found[63] in NH_2-C(:NH)SO_2H.

I.r. and Raman spectra of dialkyl disulphides[64] and benzyl sulphides[65]

[54] P. Biscarini, G. Gottarelli, B. Samori, and G. D. Nivellini, *Tetrahedron*, 1972, **28**, 4139.
[55] G. Jung, M. Ottnad, and M. Rimpler, *European J. Biochem.*, 1973, **35**, 436.
[56] J. P. Casey and R. B. Martin, *J. Amer. Chem. Soc.*, 1972, **94**, 6141.
[57] T. Takagi, R. Okano, and T. Miyazawa, *Biochim. Biophys. Acta*, 1973, **310**, 11.
[58] L. A. Neubert and M. Carmack, *J. Amer. Chem. Soc.*, 1974, **96**, 943.
[59] (*a*) D. B. Boyd, *J. Amer. Chem. Soc.*, 1972, **94**, 8799; (*b*) *Theor. Chim. Acta*, 1973, **30**, 137; (*c*) J. Webb, R. W. Strickland, and F. S. Richardson, *J. Amer. Chem. Soc.*, 1973, **95**, 4775; (*d*) R. W. Woody, *Tetrahedron*, 1973, **29**, 1273.
[60] (*a*) R. Bicca de Alencastro and C. Sandorfy, *Canad. J. Chem.*, 1972, **50**, 3594; (*b*) *ibid.*, 1973, **51**, 985; (*c*) R. Bicca de Alencastro, *ibid.*, 1974, **52**, 738; (*d*) O. P. Yablonskii, L. F. Lapuka, N. M. Rodionova, and V. E. Mazaev, *Zhur. priklad. Spectroskopii*, 1973, **19**, 565; (*e*) *ibid.*, p. 750; (*f*) S. J. Hu and S. I. Miller, *Org. Magn. Resonance*, 1973, **5**, 197; (*g*) G. Geiseler, H. Seidel, and J. Fruwert, *Spectrochim. Acta*, 1973, **A29**, 1385.
[61] I. Zuika and J. Bankovskis, *Uspekhi Khim.*, 1973, **42**, 39.
[62] S. Stankovsky, S. Kovac, M. Dandarova, and M. Livar, *Tetrahedron*, 1973, **29**, 1825.
[63] D. de Filippo, G. Ponticelli, E. F. Trogu, and A. Lai, *J.C.S. Perkin II*, 1972, 1500.
[64] H. Sugeta, A. Go, and T. Miyazawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 3407.
[65] K. Doerffel and B. Adler, *J. prakt. Chem.*, 1972, **314**, 401.

provide conformational information, and aliphatic sulphides[66] and disulphones $RSO_2(CH_2)_nSO_2R$[67] ($n = 1$—6) have been studied with the same objective. I.r. data feature prominently in studies of electronic interactions in vinyl sulphides,[68a] *meta*-substituted benzenethiols[68b] and related sulphides,[68b] and *meta*- and *para*-substituted methyl phenyl sulphoxides and sulphones.[68c] Sulphur *d*-orbital acceptance is identified for phenyl sulphides, sulphoxides, and sulphones where the phenyl group carries a strongly electron-donating substituent,[68b,c] while substituted analogues less capable of relaying charge to the sulphur grouping show $MeSO_2$ to be a resonance acceptor while MeSO, SMe, SH, and SBu^t are resonance donors.

Mass Spectra.—While most papers eligible for citation in this section could be described as routine and useful, unusual features are to be found in the mass spectra of many organosulphur compounds. Vinyl sulphides share the unusual mechanistic aspects by which the mass spectra of their oxygen analogues are interpreted,[69a,b] though the base peak at *m/e* 60 is $MeCH{=}S^+$ when H is transferred from position 2 in pentyl vinyl sulphide, and $CH_2{=}CHSH^+$ when H is transferred from positions 3 or 4,[69b] though this was earlier assigned to the former.[69a] S-Migration occurs in the molecular ion of ethyl thiobenzoate,[69c] and S to O migration in styryl sulphoxides and sulphones on electron impact.[70] An example of the *ortho*-effect, loss of Cl· from the molecular ions of chloro diphenyl ethers, sulphides, and sulphoxides, is not observed in corresponding sulphones, which take a more favourable rearrangement path.[71]

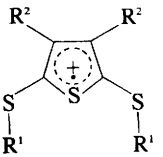
Mass spectra of sulphinate esters and isomeric sulphones are clearly differentiated.[72] A preliminary communication of the results of ion cyclotron resonance studies of 2-methoxyethanethiol and related compounds describes gas-phase reactions involving $CH_2{=}O^+$—Me.[73]

Similarities are noted between the mass spectra of aliphatic and aromatic selenides with analogous sulphides and phosphines.[74a] Selenoxides show the expected fragments derived from the selenate rearrangement product.[74c] Extensions of these studies cover selenium dihalides (no molecular ion is seen[74b]), seleninic acids and esters,[74d] and selenones.[74e] Mass spectra of diaryl tellurides are very much like those of S and Se analogues.[75]

[66] M. Ohsaku, Y. Shiro, and H. Murata, *Bull. Chem. Soc. Japan*, 1972, **45**, 3480.
[67] K. Dathe, K. Doerffel, and E. Muller, *Z. Chem.*, 1972, **12**, 425.
[68] (*a*) A. R. Katritzky, R. F. Pinzelli, and R. D. Topsom, *Tetrahedron*, 1972, **28**, 3441; (*b*) N. C. Cutress, T. B. Grindley, A. R. Katritzky, and R. D. Topsom, *J.C.S. Perkin II*, 1974, 263; (*c*) N. C. Cutress, T. B. Grindley, A. R. Katritzky, M. Shome, and R. D. Topsom, *ibid.*, p. 268.
[69] (*a*) M. Katoh, D. A. Jaeger, and C. Djerassi, *J. Amer. Chem. Soc.*, 1972, **94**, 3107; (*b*) K. B. Tomer and C. Djerassi, *ibid.*, 1973, **95**, 5335; (*c*) *Org. Mass Spectrometry*, 1973, **7**, 771.
[70] T. H. Kinstle and W. R. Oliver, *Org. Mass Spectrometry*, 1972, **6**, 699.
[71] I. Granoth, *J.C.S. Perkin II*, 1972, 1503.
[72] W. H. Baarschers and B. W. Krupay, *Canad. J. Chem.*, 1973, **51**, 177.
[73] J. K. Kim, J. K. Pau, and M. C. Caserio, *J.C.S. Chem. Comm.*, 1974, 121.
[74] (*a*) E. Rebane, *Acta Chem. Scand.*, 1973, **27**, 2861; (*b*) *ibid*, p. 2870; (*c*) *Chemica Scripta*, 1973, **4**, 219; (*d*) *ibid.*, 1974, **5**, 5; (*e*) *ibid.*, p. 65.
[75] K. J. Irgolic and W. S. Haller, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 267.

Electron Spin Resonance Spectra.—The complexity of reaction mixtures from ceric ion oxidation of thiols is clearly demonstrated by e.s.r.; in representative cases[76] at least seven different species can be recognized. Ti^{III}–H_2O_2 oxidation of β-hydroxy-sulphides produces both C- and S-centred radicals,[77] while studies of *syn*- and *anti*-α-sulphonyliminoxyl radicals[78] and alkylsulphinyl and alkylsulphonyl radicals[79] deal with cleaner samples.

Continuing interest in rotation barriers about single bonds in acyclic radicals, as determined by the interpretation of e.s.r. data, is illustrated in a study of $R^1\dot{C}HSR^2$ radicals[80] and alkane-, arene-, and alkoxy-sulphonyl radicals (obtained[81] by high-intensity u.v. irradiation of sulphinic acids in the presence of di-t-butyl peroxide at low temperatures). Further evidence for hindered rotation about the C—S bond in these species is obtained,[80,81] and an unusual order of proton hyperfine splittings $|a|(\beta\text{-H}) > |a|(\alpha\text{-H}) \sim |a|(\gamma\text{-H})$ is reported[81] for propanesulphonyl radicals. The potential of the e.s.r. method in conformational analysis is shown in studies of radical cations (3) from 2,5-bis(alkylthio)thiophens, where the S-*cis*-*cis* conformer (3) is identified as more stable than other rotamers;[82] this is assumed to be the case too for the neutral molecule.



(3)

Other Physical Studies.—Bond lengths in 4-dimethylaminophenyl phenyl sulphide between S and C are shorter than in other diaryl sulphides,[83] and a conclusion is drawn that sulphur 3*d* orbitals are not involved in conjugation with neighbouring π-systems. The bond energy of the C—Se bond in dibenzyl diselenide is 57 kcal mol^{-1} from heat of combustion and heat of sublimation measurements.[84]

Thermodynamic acid dissociation constants for a series of thiophenols correlate well with the Hammett σ-constants of ring substituents,[85] and pK_a values for aryl β-disulphones and β-keto-sulphones in DMF vary with substitution patterns in the aryl moiety, indicating conjugation through the

[76] J. C. Kertesz, W. Wolf, and H. Hayase, *J. Magn. Resonance*, 1973, **10**, 22.
[77] B. C. Gilbert, J. P. Larkin, and R. O. C. Norman, *J.C.S. Perkin II*, 1973, 272.
[78] J. J. Zeilstra and J. B. F. N. Engberts, *Tetrahedron*, 1973, **29**, 4299.
[79] T. Kawamura, P. J. Krusic, and J. C. Kochi, *Tetrahedron Letters*, 1972, 4075.
[80] E. A. C. Lucken and B. Poncioni, *Helv. Chim. Acta*, 1972, **55**, 2673.
[81] A. G. Davies, B. P. Roberts, and B. R. Sanderson, *J.C.S. Perkin II*, 1973, 626.
[82] C. M. Camaggi, L. Lunazzi, and G. Placucci, *J.C.S. Perkin II*, 1973, 1491.
[83] G. Bandoli, D. A. Clemente, E. Tondello, and A. Dondini, *J.C.S. Perkin II*, 1974, 157.
[84] M. R. Arshadi and M. Shabrang, *J.C.S. Perkin II*, 1973, 1732.
[85] P. De Maria, A. Fini, and F. M. Hall, *J.C.S. Perkin II*, 1973, 1969.

sulphone grouping.[86] The origin of the enhancement of the acidity of a CH group adjacent to sulphur has a satisfactory theoretical basis.[87] A β-amino-group enhances the acidity of an alkanethiol.[88]

Electron-diffraction studies for dimethyl sulphone[89] and polarographic data for alkenes and alkynes bearing sulphonium, sulphinyl, and sulphonyl groups[90] are reported. Data of practical importance in analysis have been obtained for the relationship of structure of bivalent sulphur compounds to the temperature-dependence of the electron-capture mechanism.[91]

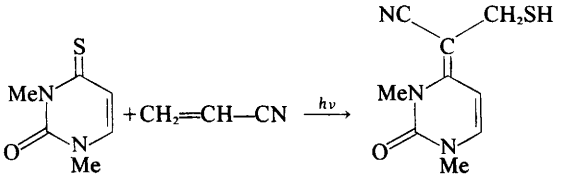
3 Thiols

Preparations.—α-Mercapto-α-amino-acids $R^1NHCR^2(SH)CO_2H$ are obtained from corresponding chloro-compounds[92] or from 4-chloro-oxazol-5(4*H*)-ones.[93] Conventional methods are also used for synthesis of thio-resorcinols (from benzene-1,3-disulphonic acids *via* sulphonyl chlorides, reduced with red P–I_2–AcOH,[94] or from resorcinols *via* Newman–Kwart rearrangement of *O*-dimethylaminothiocarbonyl-resorcinols followed by alkaline hydrolysis[95]). Dithiols are unexpectedly obtained[96] from ethyl α-acetonylacetate by treatment with H_2S in acid solution at −40 °C. Mercapto-ethylation of aliphatic amines is best achieved by a modification of the well-established method using episulphides, in aqueous solution in the presence of a silver salt.[97] Methyl sulphides ArSMe may be demethylated by chlorination to $ArSCCl_3$ followed by acid methanolysis,[98] while aryl diphenylmethyl sulphides are susceptible to electrolytic reduction to the thiophenol.[99]

A variation of the use of thiourea for converting alkyl halides into thiols uses *N*-acetylthiourea;[100] although reaction with an alkyl halide in refluxing EtOH is slow, a separate hydrolysis step is not required and the method may prove useful for the synthesis of water- or alkali-sensitive thiols. Other methods based upon thiocarbonyl derivatives are exemplified by the addition of allylic Grignard reagents to thioketones, giving βγ-unsaturated

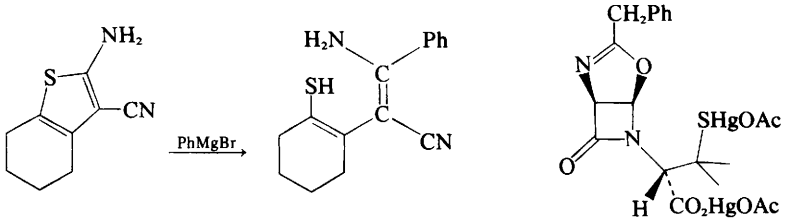
[86] V. M. Neplynev, V. P. Kukhar, R. G. Dubenko, and P. S. Pelkis, *Zhur. org. Khim.*, 1972, **8**, 2174.
[87] S. Wolfe, L. M. Tel, and I. G. Csizmadia, *Theor. Chim. Acta*, 1973, **31**, 355.
[88] Y. L. Kostyukovskii, Y. A. Bruk, L. V. Pavlova, N. M. Slavachevskaya, A. V. Kokushkina, B. S. Mirkin, and I. A. Belenkaya, *Zhur. obshchei Khim.*, 1972, **42**, 662.
[89] M. Hargittai and I. Hargittai, *J. Mol. Structure*, 1974, **20**, 283.
[90] R. W. Howsam and C. J. M. Stirling, *J.C.S. Perkin II*, 1972, 847.
[91] M. Satouchi and T. Kojima, *Analyt. Letters*, 1972, **5**, 931.
[92] S. M. Patel, J. O. Currie, and R. K. Olsen, *J. Org. Chem.*, 1973, **38**, 126.
[93] P. M. Pojer and I. D. Rae, *Austral. J. Chem.*, 1972, **25**, 1737.
[94] F. Voegtle, R. G. Lichtenhaler, and M. Zuber, *Chem. Ber.*, 1973, **106**, 719.
[95] H. J. Kurth, U. Kraatz, and F. Korte, *Chem. Ber.*, 1973, **106**, 2419.
[96] F. Duus, *Acta Chem. Scand.*, 1973, **27**, 466.
[97] R. Luhowy and F. Meneghini, *J. Org. Chem.*, 1973, **38**, 2405.
[98] J. M. Lavanish, *Tetrahedron Letters*, 1973, 3847.
[99] G. Farnia, A. Ceccon, and P. Cesselli, *J.C.S. Perkin II*, 1972, 1016.
[100] D. L. Klayman, R. J. Shine, and J. D. Bower, *J. Org. Chem.*, 1972, **37**, 1532.

thiols[101] (see also ref. 188*b*), and synthesis of adamantane-2-thiol from the thione by treatment with Bu^{n}Li followed by aqueous acid.[102] Only about 5% 2-adamantyl butyl sulphide is formed in this reaction, while use of PhLi gives *ca.* 25% thiol and 75% sulphide.[102] Useful syntheses based upon the thiobenzophenone dianion $Ph_2\bar{C}—\bar{S}$ include the synthesis of $Ph_2C(SH)$-CO_2H by its reaction with CO_2.[103] An unusual photochemical addition of acrylonitrile to the 4-thiouracil derivative (4) gives the thiol (5) and its geometrical isomer.[104]



(4) (5)

Ring-opening of sulphur heterocycles to give thiols is illustrated in recent papers by thiazole cleavage (Na–NH_3 gives substituted propenethiolates),[105] thiophen cleavage (6) → (7),[106] and a novel penicillin cleavage reaction, potassium benzylpenicillinate with mercury(II) acetate in AcOH giving (8).[107]



(6) (7) (8)

Thiols as Nucleophiles.—Aryl-oxirans yield mixtures of 1- and 2-aryl-2-phenylthioethanols with PhSNa, proportions being determined by substituents on the oxiran.[108] Glutathione is not more nucleophilic than simple thiols towards benzene oxide,[109] thus disposing of a theory that this tripeptide has a special detoxification function for arene oxide intermediates

[101] M. Dagonneau and J. Vialle, *Tetrahedron*, 1974, **30**, 415.
[102] V. Rautenstrauch, *Helv. Chim. Acta*, 1974, **57**, 496.
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[105] S. Hoff and A. P. Blok, *Rec. Trav. chim.*, 1974, **93**, 18.
[106] R. Heckendorn and A. R. Gagneux, *Tetrahedron Letters*, 1973, 2279.
[107] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Chem. Comm.*, 1973, 477; *J.C.S. Perkin I*, 1974, 181.
[108] A. Behzadi and L. N. Owen, *J.C.S. Perkin I*, 1973, 2733.
[109] D. M. E. Reuben and T. C. Bruice, *J.C.S. Chem. Comm.*, 1974, 113.

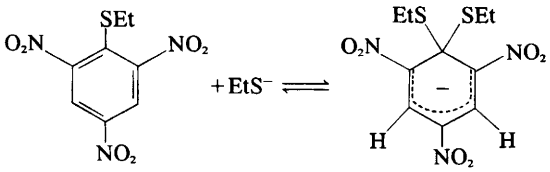
involved in drug metabolism and tyrosine biosynthesis. The four isomers of dibenzylmercaptocyclohexanediol obtained by reaction of the *cis-trans*-mixture of cyclohexa-1,4-diene dioxide with $PhCH_2SNa$ have been isolated and characterized.[110]

One or both vinylic fluorines in $CF_3CR{=}CF_2$ can be substituted by reaction with a sodium thiolate.[111] Corresponding reactions with arylhalogeno-alkynes proceed *via* an α-addition–elimination mechanism,[112] but with 2-chloro- or -bromo-1,1-diphenylpropenes an allenic elimination–addition mechanism is ruled out (though this path is followed by the corresponding reaction with phenoxides).[113] Selective homotropic intermolecular hydrogen-bonding in alkyl halides in $Cl(CH_2)_{m\ or\ n}CONHCONHR$ mixtures accounts for the exclusive formation of symmetrical bis-sulphides with ethane-1,2-dithiol.[114] Reductive dehalogenation of aryl halides by thiophenol,[115] and substitutions of pentachloro- and polychlorofluoro-pyridines[116] and 4-substituted-2-nitrochlorobenzenes[117] with benzenethiols have been reported. A four-centre concerted mechanism is proposed[118] for the reaction of PhHgSPh with picryl chloride. Demethylation of bromo-anisoles with NaSEt gives bromophenols.[117a]

The greater reactivity of sulphur nucleophiles, compared with their oxygen analogues, towards methyl benzenesulphonate,[119] and the 10^4-fold rate enhancement in the reaction of long-chain alkanethiols with *p*-nitrophenyl acetate in the presence of stearyl trimethylammonium bromide, above the critical micellar concentration,[120] are the subjects of recent papers dealing with nucleophilic attack by thiols on esters. Steric effects have been assessed for their influence on the nucleophilicity of alkyl-substituted benzenethiolate anions towards *N*-ethylmaleimide[121] and towards disulphides.[122] Reactions of cysteine and cysteamine with H_2O_2 show kinetics characteristic of nucleophilic attack of the thiolate at oxygen;[123] the rate decreases as the pH is raised, and this suggests that hydrogen-bonding between the peroxide and $—NH_3^+$ facilitates the reaction.

[110] G. E. McCasland, A. K. M. Anisuzzaman, S. R. Naik, and L. J. Durham, *J. Org. Chem.*, 1972, **37**, 1201.
[111] S. R. Sterlin, V. M. Izmailov, V. L. Isaev, A. A. Shal, R. N. Sterlin, B. L. Dyatkin, and I. L. Knunyants, *Zhur. Vsesoyuz. Khim. obshch. im. D.I. Mendeleeva*, 1973, **18**, 710.
[112] P. Beltrame, P. L. Beltrame, M. G. Cattania, and M. Simonetta, *J.C.S. Perkin II*, 1973, 63.
[113] M. Ballabio, P. L. Beltrame, and P. Beltrame, *J.C.S. Perkin II*, 1972, 1229.
[114] T. Mukaiyama, T. Endo, Y. Kojima, and T. Sato, *J. Amer. Chem. Soc.*, 1972, **94**, 7575; T. Endo, T. Sato, S. Sato, and T. Mukaiyama, *Chem. Letters*, 1973, 1201.
[115] M. W. Barker, S. C. Lauderdale, and J. R. West, *J. Org. Chem.*, 1972, **37**, 3555.
[116] J. Bratt and H. Suschitzky, *J.C.S. Perkin I*, 1973, 1689.
[117] P. Carniti, P. Beltrame, and S. Cabiddu, *J.C.S Perkin II*. 1973, 1430.
[117a] G. I. Feutrill and R. N. Mirrington, *Austral. J. Chem.*, 1972, **25**, 1719.
[118] C. Dell'Erba, G. Guanti, M. Novi, and G. Leandri, *J.C.S. Perkin II*, 1973, 1879.
[119] A. Kyllonen and J. Koskikallio, *Suomen Kem.*, 1972, **45**, *B*, 212.
[120] W. Tagaki, T. Amada, Y. Yamashita, and Y. Yano, *J.C.S. Chem. Comm.*, 1972, 1131.
[121] D. Semenow-Garwood, *J. Org. Chem.*, 1972, **37**, 3797.
[122] D. Semenow-Garwood, and D. C. Garwood, *J. Org. Chem.*, 1972, **37**, 3804.
[123] J. P. Barton, J. E. Packer, and R. J. Sims, *J.C.S. Perkin II*, 1973, 1547.

Addition Reactions of Thiols.—Ethylthiopicrate adds EtS^- to give the first *gem*-di(alkylthio) analogue (9) of a Meisenheimer adduct.[124] Thiophenoxide–1,3,5-trinitrobenzene adducts (heats of formation have been measured[125])

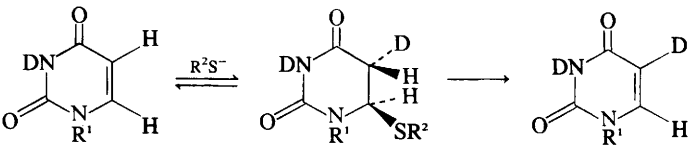


(9)

are in equilibrium with their component species, and carbon basicity values derived from equilibrium constants are in good agreement with the nucleophilic reactivities of substituted thiophenoxides derived from their reaction with 1-chloro-2,4-dinitrobenzene.[126]

Base-catalysed addition to aryl vinyl sulphones sets up the order $PhO^- < HO^- < EtO^- \ll PhS^-$ (relative nucleophilicities 1:20:378:37 800).[127] Various forms of acid catalysis can be used; with $TiCl_4$, EtSH adds to vinyl ketones to give β-ethylthio-ketones,[128] and acid-catalysed addition of thiols to the αβ-unsaturated carbonyl grouping in dehydrocyclodipeptides gives α-adducts under kinetic control, which slowly isomerize to β-adducts.[129] Germacrone and acoragermacrone (sesquiterpene vinyl ketones), in adding PhSH from AcOH solution, undergo cyclization to guiaine derivatives.[130] Thiolate anions add in *trans* fashion to cyclohexenes,[131] 4-t-butyl-1-cyanocyclohexene giving an adduct with axial PhS.[131b]

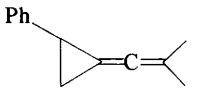
Cysteine-catalysed H–D exchange at the 5-position of uridylic acid is rationalized by an addition–elimination sequence (10) → (11).[132]



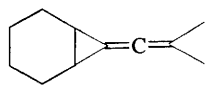
(10) (11)

[124] G. Biggi and F. Pietra, *J.C.S. Perkin I*, 1973, 1980; *J.C.S. Chem. Comm.*, 1973, 229.
[125] J. W. Larsen, K. Amin, S. Ewing, and L. L. Magid, *J. Org. Chem.*, 1972, **37**, 3857.
[126] M. R. Crampton and M. J. Willison, *J.C.S. Perkin II*, 1974, 238.
[127] P. De Maria and A. Fini, *J.C.S. Perkin II*, 1973, 1773.
[128] T. Mukaiyama, T. Izawa, K. Saigo, and H. Takei, *Chem. Letters*, 1973, 355.
[129] P. J. Machin and P. G. Sammes, *J.C.S. Perkin I*, 1974, 698.
[130] (*a*) M. Iguchi, M. Niwa, and S. Yamamura, *Tetrahedron Letters*, 1973, 1687; (*b*) *ibid.*, p. 4367.
[131] (*a*) A. van Bruijnsvoort, E. R. de Waard, J. L. van Bruijnsvoort-Meray, and H. O. Huisman, *Rec. Trav. chim.*, 1973, **92**, 937; (*b*) R. A. Abramovitch, M. R. Rogic, S. S. Singer, and N. Venkateswaran, *J. Org. Chem.*, 1972, **37**, 3577.
[132] Y. Wataya, H. Hayatsu, and Y. Kawazoe, *J. Amer. Chem. Soc.*, 1972, **94**, 8927.

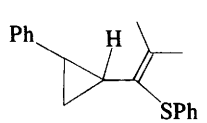
Addition of thiols to diketen gives γ-alkylthio-β-butyrolactones,[133] which suffer rearrangement, or loss of CO_2 to give the allyl sulphide. Radical addition of thiophenol to the allenes (12) and (12a) gives vinyl and allyl sulphides (13) and (14), respectively.[134] The radical pathway is normally



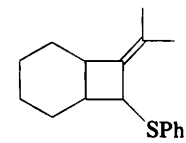
(12)



(12a)



(13)



(14)

followed in additions of thiols to multiple bonds, in the absence of ionic intermediates and ion-forming catalysts, and there are many projects under way in this field. A useful survey[135] establishes the order of reactivity towards alkanethiols for acyclic conjugated dienes > vinyl derivatives > intracyclic olefins. Factors determining *exo*/*endo* ratios in free-radical addition of thiols to norbornenes have been delineated;[136a] norborn-2-en-5-one gives 2- and 3-*exo*- and 7-*anti*-sulphides in this reaction, the latter compound being formed through rearrangement of the intermediate resulting from radical attack at position 2, or through formation of the non-classical homo-enolized radical from this intermediate.[136b] Related studies concern 5-substituted 1,2,3,4,7,7-hexachloronorbornadiene[136c] and adduct formation at the cyclobutene double bond in tricyclo[4,2,2,$0^{2,5}$]deca-3,7-diene-9,10-dicarboxylic anhydride;[136d] *exo*-addition of thiophenols is observed with *exo*- or *endo*-2-cyanobicyclo[2,2,1]hept-5-ene.[137]

Free-radical conditions are appropriate for addition of thiols to alkynes,[138] but base catalysis is involved in most of the studies on this topic; $R^1COC{\equiv}CH + R^2SH$ gives $R^1COCH_2CH(SR^2)_2$ in the presence of Triton B,[139] and arenethiols give 2- and 3-(arylthio)prop-2-en-1-ols with prop-2-yn-1-ol.[140] Structure-dependence of the stereochemistry of the addition of thiols to alkynes has been studied;[141] although electron-withdrawing substituents facilitate addition, the addition is less *trans*-selective when the activating group is a carbonyl-containing function.[141]

[133] G. A. Hull, F. A. Daniher, and T. F. Conway, *J. Org. Chem.*, 1972, **37**, 1837.
[134] R. Gompper and D. Lach, *Tetrahedron Letters*, 1973, 2687.
[135] D. W. Grattan, J. M. Locke, and S. R. Wallis, *J.C.S. Perkin I*, 1973, 2264.
[136] (*a*) D. I. Davies and M. J. Parrott, *Tetrahedron Letters*, 1972, 2719; *J.C.S. Perkin I*, 1973, 2205; (*b*) D. I. Davies, D. J. A. Pearce, and E. C. Dart, *ibid*, p. 433; (*c*) D. R. Adams and D. I. Davies, *ibid.*, 1974, 246; (*d*) G. I. Fray, G. R. Green, D. I. Davies, L. T. Parfitt, and M. J. Parrott, *ibid.*, p. 729.
[137] R. A. Babakhanov, I. G. Mursakulov, F. S. Sultanov, S. A. Movla-Zade, and A. K. Ibad-Zade, *Azerb. Neft. Khoz.*, 1973, **53**, 36.
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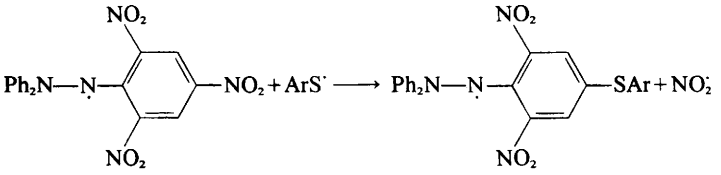
[139] E. N. Prilezhaeva and I. L. Mikhelashvili, *Zhur. org. Khim.*, 1973, **9**, 1129.
[140] A. Behzadi and L. N. Owen, *J.C.S. Perkin I*, 1974, 25.
[141] W. E. Truce and G. J. W. Tichenor, *J. Org. Chem.*, 1972, **37**, 2391.

Generation and Reactions of Thiyl Radicals.—Pulse radiolysis studies of thiols[142] in aqueous solutions at different pH's provide information on the competition between H^+ and RSH for the hydrated electron e^-_{aq}, which reacts with RSH to give $R^{\cdot}+SH^-$; the hydroxyl radical produced concurrently by H_2O cleavage produces thiyl radicals.

Quantitative study of H abstraction by thiyl radicals is feasible using RS^3H as solvent.[143] An unusual displacement reaction has been demonstrated for 2,2-diphenyl-1-picrylhydrazyl (15), which, on reaction with 2,4,6-tri-t-butylbenzenethiol, produces the arylthiyl radical by H abstraction, which then displaces NO_2 from a second hydrazyl.[144]



(15)

The dithiothreitol radical can exist in an ionized form (16) or as neutral species (17).[145]

(16) (17)

Reactions of Thiols with Organophosphorus Compounds.—Autoxidation of thiols can be prevented by addition of tri-n-butylphosphine; when the thiol solution is to be used, the phosphine is removed by extraction with a dilute solution of sulphur in $CHCl_3$.[146]

Protection of —SH Groups.—Although silylation of functional groups has become a valuable means of transient protection, and can be applied to thiols (RSH → $RSSiMe_3$ using hexamethyldisilazane and imidazole),[147] S-protection problems are mostly those of cysteine, and must be solved so that peptide-coupling and selective de-protection techniques can be applied. The *S*-acetamidomethyl group[148] has been put to use in protection of the

[142] (*a*) J. W. Purdie, H. A. Gillis, and N. V. Klassen, *Canad. J. Chem.*, 1973, **51**, 3132; (*b*) T. L. Tung and R. R. Kuntz, *Radiation Res.*, 1973, **55**, 256; (*c*) M. Z. Hoffmann and E. Hayon, *J. Phys. Chem.*, 1973, **77**, 990.

[143] W. A. Pryor, G. Gojon, and J. P. Stanley, *J. Amer. Chem. Soc.*, 1973, **95**, 945.

[144] J. Flood, K. E. Russell, and J. A. Stone, *J.C.S. Chem. Comm.*, 1972, 482.

[145] P. C. Chan and B. H. J. Bielski, *J. Amer. Chem. Soc.*, 1973, **95**, 5504.

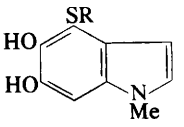
[146] A. Kirkpatrick and J. A. MacLaren, *Analyt. Biochem.*, 1973, **56**, 137.

[147] R. S. Glass, *J. Organometallic Chem.*, 1973, **61**, 83.

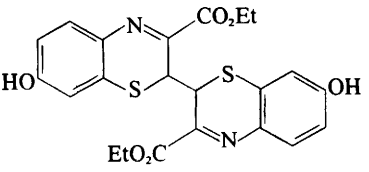
[148] D. F. Veber, J. D. Milkowski, S. L. Varga, R. G. Denkewalter, and R. Hirschmann, *J. Amer. Chem. Soc.*, 1972, **94**, 5456.

cysteine SH group for an oxytocin synthesis.[149] A new group, 9-anthrylmethyl, is introduced by treating the sodium salt with 9-chloromethylanthracene and removed with MeSNa–DMF for 2h at 0 °C.[150] Further details are given for 4-picolyl[151] and 2,2,2-trichloroethoxycarbonyl[152] protection methods, which share the same de-protection method, electrolytic reduction. The *S*-methoxymethylcarbamyl function, produced by the reaction of a thiol with $MeOCH_2NCO$, is cleaved at pH 9.6, and is advocated for cysteine protection.[153] Cleavage of the *S*-(*p*-nitrobenzyl) group, not previously described in peptide chemistry, is brought about in two steps by hydrogenation to the amine followed by treatment with $HgSO_4$–H_2SO_4.[154]

Thiols in Biochemistry.—Space available restricts the present coverage to a few key references. *N*-Acetyl-cysteine and -penicillamine react with adrenochrome to give the indolyl sulphides (18),[155] (but see also ref. 650) while *p*-benzoquinone gives two diastereoisomers of (19) with L-cysteine ethyl ester.[156] Other observations with possible significance



(18)



(19)

in biochemistry include the catalysis by cysteine or glutathione of charge transfer between aldehydes and amines,[157] the enhancement by thiophenol of the catalytic activity of quinuclidine for the racemization of 1-nitro-1-phenylethane by the hydrogen-abstraction mechanism,[158] and the oxidation at carbon suffered by thioglycolic acid, $HSCH_2CO_2H$, when it is a ligand attached to $(en)_2Cr^{III}$, with Np^{VI} or Ce^{IV}, rather than at sulphur (*cf.* aldehyde dehydrogenase action).[159]

Cysteine and cystine residues in proteins are converted into *S*-cyanocysteine residues with 2-nitro 5-thiocyanatobenzoic acid, providing a point in the peptide chain at which selective cleavage can be performed.[160]

[149] P. Marbach and J. Rudinger, *Helv. Chim. Acta*, 1974, **57**, 403.
[150] N. Kornblum and A. Scott, *J. Amer. Chem. Soc.*, 1974, **96**, 590.
[151] A. Gosden, D. Stevenson, and G. T. Young, *J.C.S. Chem. Comm.*, 1972, 1123.
[152] M. F. Semmelhack and G. E. Heinsohn, *J. Amer. Chem. Soc.*, 1972, **94**, 5139.
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[155] W. S. Powell and R. A. Heacock, *Bio-org. Chem.*, 1973, **2**, 191; *Canad. J. Chem.*, 1974, **52**, 1019.
[156] G. Prota and E. Ponsiglione, *Tetrahedron Letters*, 1972, 1327.
[157] A. Szent-Gyorgi and J. McLaughlin, *Proc. Nat. Acad. Sci. U.S.A.*, 1972, **69**, 3510.
[158] D. F. DeTar and D. M. Coates, *J. Amer. Chem. Soc.*, 1974, **96**, 942.
[159] C. J. Weschler, J. C. Sullivan, and E. Deutsch, *J. Amer. Chem. Soc.*, 1973, **95**, 2720.
[160] G. R. Jacobson, M. H. Schaffer, G. R. Stark, and T. C. Vanaman, *J. Biol. Chem.*, 1973, **248**, 6583.

Estimation of —SH groups in biological samples through the use of Ellman's reagent, 5,5'-dithio-bis-(2-nitrobenzoic acid),[161,162] is based upon spectrophotometric determination at 412 nm of the 3-carboxylato-4-nitrothiophenolate anion; discrepancies between published absorptivity figures are resolved in favour of 14.14±0.17 per millimole.[163] Other estimation methods include the similar use of 6,6'-dithiodinicotinic acid,[161] or *via* *p*-chloro[^{203}Hg]mercuribenzoate adduct formation.[161] A new method uses 4,4'-bisdimethylaminodiphenylcarbinol, which gives a resonance-stabilized carbonium-immonium ion in acid solution, λ_{max} 612 nm in 4M-guanidine hydrochloride, reaction with —SH groups resulting in an equivalent loss of absorbance.[164] Fluorescent tagging groups for —SH groups in proteins include iodoacetamidoethyl derivatives of 5-naphthylamine-1-sulphonic acid and its 1,8-isomer[165] and *N*-(3-pyrenyl)maleimide.[166]

Thiolacids and Thiolesters.—Novel preparative methods for thiolesters use alkyl trimethylsilyl sulphides[167] or aluminium analogues Me_2AlSR[168] with carboxylic esters. Authentic selenobenzoic acid PhCOSeH is an unstable liquid,[169] readily forming the selenoanhydride PhCOSeCOPh with loss of H_2Se. Triethylenediamine is effective in converting a thiolacid–acid chloride mixture into the unsymmetrical anhydride, while NEt_3 gives the symmetrical thioanhydride.[170] Keten reacts with di-n-butyl phenylthioboronite to give the vinyloxyborane $CH_2{=}C(SPh)\text{-}O\text{-}BBu^n_2$, the forerunner of a series of considerable potential in synthesis; hydrolysis gives phenyl thioacetate.[171]

Hydrolysis kinetics for thiolesters deal with triphenylmethyl thiolbenzoates[172] ($A_{AL}1$ mechanism), hydrolysis[173b] and Ag^+-assisted n-butylaminolysis[173a] of ethyl thiolbenzoate, and thiolesters with an activating group attached to the carbonyl group.[174]

Trifluorothioacetic acid undergoes free-radical and nucleophilic addition to olefins and ketones respectively, paralleling in many ways the well-known reactions of thioacetic acid.[175] Novel uses of thiolesters in synthesis

[161] Y. Ando and M. Steiner, *Biochim. Biophys. Acta*, 1973, **311**, 26.
[162] A. Dietz and H. M. Rubinstein, *Clinical Biochem.*, 1972, **5**, 136.
[163] H. B. Collier, *Analyt. Biochem.*, 1973, **56**, 310.
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[165] E. N. Hudson and G. Weber, *Biochemistry*, 1973, **12**, 4154,
[166] J. K. Wellman, R. P. Szaro, A. R. Frackelton, R. M. Dowben, J. R. Bunting, and R. E. Cathou, *J. Biol. Chem.*, 1973, **248**, 3173.
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[168] E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, 1973, **95**, 5829.
[169] K. A. Jensen, L. Boeje, and L. Henricksen, *Acta Chem. Scand.*, 1972, **26**, 1465.
[170] S. Motoki and H. Satsumabayashi, *Bull. Chem. Soc. Japan*, 1972, **45**, 2930.
[171] T. Mukaiyama, K. Inomata, and M. Muraki, *J. Amer. Chem. Soc.*, 1973, **95**, 967.
[172] A. N. Assad and R. Tewfik, *Egypt. J. Chem.*, 1972, **15**, 85.
[173] (*a*) B. Boopsingh and D. P. N. Satchell, *J.C.S. Perkin II*, 1972, 1288; (*b*) *ibid.*, p. 1702.
[174] R. Hershfield and G. L. Schmir, *J. Amer. Chem. Soc.*, 1973, **95**, 3994.
[175] P. Weeks and G. L. Gard, *J. Fluorine Chem.*, 1972, **1**, 295.

include the use of ethyl thiochloroformate EtSCOCl as alkylating agent for thioamides [$RCSNH_2$ gives $RC(=NH_2^+)SEt\ Cl^- + COS$],[176] and the use of *S*-(2-pyridyl)thioates with Grignard reagents for the synthesis of ketones.[177] Methyl thiobenzoate gives dibenzoylmethane on treatment with lithium 2,2,6,6-tetramethylpiperidide in THF at room temperature *via* a dipole-stabilized carbanion, $PhCOSCH_2^- \leftrightarrow PhC(O^-)=S^+-CH_2^-$, and this supports the suggestion[178] that the thiolester grouping may be a useful dipole-stabilizing appendage to a carbanion centre.

Photolytic and thermal cleavage of thiolesters gives quite different product mixtures. While *S*-pentyl thiobenzoate gives mainly PhCHO and dipentyl disulphide on u.v. irradiation, but no thiobenzoic acid, the corresponding benzoate gives 40% benzoic acid.[179] The characteristic initial cleavage step involves the *S*-acyl bond of a thiolester, the products being readily accounted for on the basis of thiyl and acyl radical formation.[180] Inconclusive results are obtained through CNDO/2–SCF MO calculations aimed at evaluating the importance of *d*-orbitals in the structure of the —S—CO— grouping.[181] Gas-phase pyrolysis of aliphatic thiolesters follows first-order kinetics in giving thiolacid and olefin.[182] *S*-Methoxymethyl thioacetate, however, gives $MeCO_2Me + CH_2=S + MeCOSMe$ by a four-centre mechanism.[183]

4 Sulphides

Preparations.—2,6-Dialkylphenols give mixtures of 4,4′-mono-, -di-, -tri-, and -tetra-sulphides with S in refluxing EtOH,[184] and 1,2-dimethoxybenzene gives di(3,4-dimethoxyphenyl) selenide with selenious acid (SeO_2 in aqueous solution).[185] A new selenide synthesis[186] employs an aldehyde or ketone MeCOR, selenium, and two equivalents of a Grignard reagent (ArMgBr gives ArCMeRSeAr). Adding Li, Te, and an alkyl halide in sequence to an aryl iodide ArI gives the telluride ArTeAlkyl.[187]

The formation of sulphides from thiones by reaction with Grignard

[176] S. L. Razniak, E. M. Flagg, and F. Siebenthall, *J. Org. Chem.*, 1973, **38**, 2242.
[177] T. Mukaiyama, M. Araki, and H. Takei, *J. Amer. Chem. Soc.*, 1973, **95**, 4763.
[178] P. Beak and R. Farney, *J. Amer. Chem. Soc.*, 1973, **95**, 4771.
[179] Y. Ogata, K. Takagi and Y. Takayanagi, *J.C.S. Perkin I*, 1973, 1244.
[180] J. R. Grunwell, N. A. Marron, and S. I. Hanhan, *J. Org. Chem.*, 1973, **38**, 1559; J. E. Gano and H. G. Corkins, *J.C.S. Chem. Comm.*, 1973, 294.
[181] J. R. Grunwell and S. I. Hanhan, *Tetrahedron*, 1973, **29**, 1473; J. R. Grunwell and H. S. Baker, *J.C.S. Perkin II*, 1973, 1542.
[182] P. C. Oele, A. Tinkelenberg, and R. Louw, *Tetrahedron Letters*, 1972, 2375; D. B. Bigley and R. E. Gabbott, *J.C.S. Perkin II*, 1973, 1293.
[183] P. C. Oele and R. Louw, *J.C.S. Chem. Comm.*, 1972, 848.
[184] T. Fujisawa, K. Hata, and T. Kojima, *Synthesis*, 1973, 38.
[185] T. Weiss, W. Nitsche, F. Bohnke, and G. Klar, *Annalen*, 1973, 1418.
[186] I. I. Lapkin, N. V. Bogoslovskii, and N. I. Zenkova, *Zhur. obshchei Khim.*, 1972, **42**, 1972.
[187] J. L. Piette, R. Lysy, and M. Renson, *Bull. Soc. chim. France*, 1972, 3559.

reagents has been explored for aliphatic and aromatic substrates.[188] Thiobenzophenone gives diphenylmethyl sulphides,[188a] while aliphatic thiones (*e.g.* thiocamphor) can give mixtures of thiol, sulphide, and vinyl sulphide,[188b,d] the latter indicating homolysis of the initial adduct.

Alkylation of thiols is represented by their reaction with *O*-alkyl *NN'*-dicyclohexylureas at 100—110 °C,[189] and β-keto-sulphide synthesis using $CF_3S^-Ag^+$ and α-bromoketones;[190] an alternative route to β-keto-sulphides employs an aldehyde and $LiCH(SPh)_2$, and treatment of the adduct with MeLi.[191] Sulphur ylides are now shown[192] to be capable of acting as C—S transfer agents, in addition to their well-known ability to alkylate through carbon. Among five products from cyclopropenium cations and $Me_2S^+CH_2^-$ are a 3-methylthio-cyclobutene and a 3-methylthiomethyl-cyclopropene.[192] The use of Bunte salts in sulphide synthesis is illustrated by the synthesis of 1- or 2-naphthyl sulphides from the naphthols with sodium benzylthiosulphate.[193]

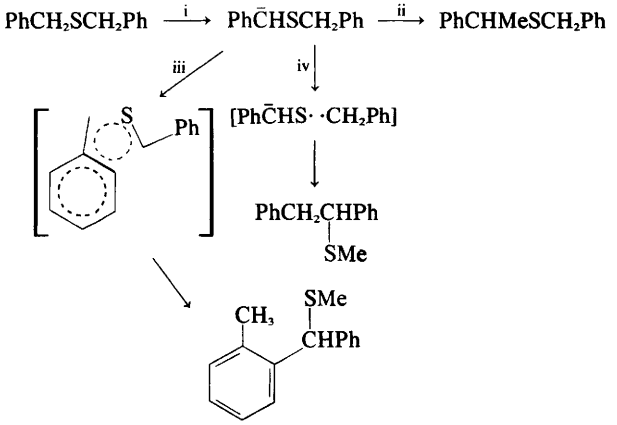
Unusual methods are often the rule with Se or particularly Te analogues of bivalent sulphur compounds. Di-pentafluoroethyl telluride $Te(C_2F_5)_2$ and the corresponding ditelluride are obtained by treating $Te_4(AsF_6)_2$ with tetrafluoroethylene in the presence of SO_2 or SO_2F_2;[194] diaryl ditellurides give corresponding tellurides by refluxing in dioxan with Cu powder.[195]

Saturated Aliphatic Sulphides; Aryl Sulphides.—Reactivity of aryl alkyl sulphides towards Br_2 in AcOH decreases in the order Pr^i, Et, Me,[196] though the opposite order applies to the oxygen analogues.

Rearrangement of $R^1CH(SR^2)CHO$ to the β-keto-sulphide $R^1COCH_2SR^2$ takes place in dioxan with H_2SO_4,[197] while secondary amines give the enamines $R^1C(SR^2)=CHNR^3_2$. Benzylthiotrimethylsilane rearranges rapidly with excess t-butyl-lithium to give $PhCH(SH)SiMe_3$, the first example of a Wittig-type rearrangement involving migration from S to a carbanion centre (a reaction that is well known in the oxygen series).[198] The change is reversible in the presence of a radical catalyst. The formation of a rearranged hydrolysis product, $R^1SCH_2CMe(OH)COR^2$, from $ClCH_2CMe(SR^1)COR^2$ is readily understood on the basis of episulphonium intermediates,[199] and a similar assumption accounts for the solvolytic behaviour

[188] (*a*) M. Dagonneau and J. Vialle, *Bull. Soc. chim. France*, 1972, 2067; (*b*) M. Dagonneau and J. Vialle, *Tetrahedron Letters*, 1973, 3017; (*c*) D. Pacquier and J. Vialle, *Compt. rend.*, 1972, **275**, *C*, 589; (*d*) M. Dagonneau, D. Paquer, and J. Vialle, *Bull. Soc. chim. France*, 1973, 1699.
[189] E. Vowinkel and C. Wolff, *Chem. Ber.*, 1974, **107**, 496.
[190] L. M. Yagupolskii and O. D. Smirnova, *Zhur org. Khim.*, 1972, **8**, 1990.
[191] I. Kuwajima and Y. Kurata, *Chem. Letters*, 1972, 291.
[192] B. M. Trost, R. C. Atkins, and L. Hoffmann, *J. Amer. Chem. Soc.*, 1973, **95**, 1285.
[193] S. P. Phadnis, *Indian J. Chem.*, 1972, **10**, 699.
[194] H. L. Paige and J. Passmore, *Inorg. Nuclear Chem. Letters*, 1973, **9**, 277.
[195] I. D. Sadekov, A. Y. Bushkov, and V. I. Minkin, *Zhur. obshchei Khim.*, 1973, **43**, 815.
[196] S. Ahmed and J. L. Wardell, *Tetrahedron Letters*, 1972, 2363.
[197] P. Duhamel, L. Duhamel, and J. Chauvin, *Compt. rend.*, 1972, **274**, *C*, 1233.
[198] A. Wright, D. Ling, P. Boudjouk, and R. West, *J. Amer. Chem. Soc.*, 1972, **94**, 4784.
[199] D. Greiciute, J. Kulis, and L. Rasteikiene, *Zhur. org. Khim.*, 1973, **9**, 1837.

of halogenoalkyl sulphides $ArS(CH_2)_nX$;[200] cyclic sulphonium salt formation is easier for the 2-halogenoethyl compounds than for 4-halogenobutyl analogues, and a phenyl group attached to the X-bearing carbon accelerates ring formation. Sulphur participation is also implicated in the cyclization of $PhSCMe_2CH_2COMe$ to 3-methyl-2-isopropylbenzothiophen,[201] and in explaining the stereochemical course of the replacement of the amino-group of *S*-(2-pyridyl)cysteine derivatives by Br followed by thiazolidine ring formation[202] (replacement of NH_2 by Br involves retention of configuration). Factors determining the competition between Stevens and Sommelet rearrangements have been delineated for dibenzyl sulphide (Scheme 1);[203] the radical pathway is favoured at higher temperatures but solvent is also important. Important uses of sulphenyl-stabilized carbanions are surveyed in a later section of this Chapter.



Reagents: i, Bu^nLi; ii, MeI, −78 °C, TMEDA–THF; iii, MeI, warming towards room temp (Sommelet); iv, MeI, higher temperatures (Stevens)

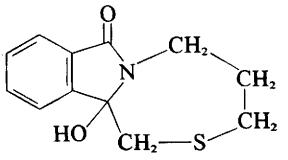
Scheme 1

Azodicarboxylate esters give α-substitution products with aliphatic sulphides [*e.g.* $R^1SCH_2R^2$ gives $R^1SCHR^2N(CO_2Et)NHCO_2Et$];[204] u.v.-irradiation improves yields. Chloromethyl *p*-tolyl sulphide gives αβ-epoxysulphides (*cis–trans* mixtures) with aldehydes, catalysed by DABCO,[205] thus completing the series αβ-epoxy-sulphide, sulphoxide, sulphone.

Photolysis of dimethyl sulphide vapour gives ethane and dimethyl

[200] R. Bird and C. J. M. Stirling, *J.C.S. Perkin II*, 1973, 1221.
[201] D. D. MacNicol and J. J. McKendrick, *Tetrahedron Letters*, 1973, 2593.
[202] K. Undheim and G. A. Ulsaker, *Acta Chem. Scand.*, 1973, **27**, 1390.
[203] J. F. Biellmann and J. L. Schmitt, *Tetrahedron Letters*, 1973, 4615.
[204] G. E. Wilson and J. H. E. Martin, *J. Org. Chem.*, 1972, **37**, 2510.
[205] D. F. Tavares and R. E. Estep, *Tetrahedron Letters*, 1973, 1229.

disulphide as a result of C—S fission,[206a] and $MeSH + Me_2S_2$ through triplet mercury-photosensitized decomposition, the latter being shown to be a remarkably pressure-sensitive process;[206c] methyl ethyl sulphide is photolysed into ethane and the two symmetrical disulphides, and several minor products.[206b] Singlet C reacts with sulphides in a frozen matrix to give CS and biradicals.[207] Photodecarboxylation of *N*-phthaloylamino-acids generally proceeds smoothly but is accompanied by side-product formation in the case of methionine, (20)[208] being formed in 38% yield, a surprisingly high



(20)

figure which prompts a broader study of this synthesis of azathiacycloheptanols. Pyrolysis or photolysis of diastereoisomeric 1,2-bis(phenylthio)alkanes RCH(SPh)CH(SPh)R gives alkenes through a stepwise homolysis path, loss of the first PhS group leaving a radical which expels the second PhS group to form the alkene faster than it can rotate, possibly implicating a bridged radical intermediate.[209] Cation radicals Ph—$\dot{\ddot{S}}^{+}$—R are formed by anodic oxidation of phenyl sulphides.[210]

Unsaturated Sulphides.—Many of the known methods for synthesis of unsaturated sulphides are put to use in recent work, though there are some novel observations. Dichloromaleimides give 2,3-dialkylthiomaleimides with thiolates,[211] monothiobenzil PhCOCSPh undergoes a thermal ene reaction with 2-methylpent-2-(and -1-)ene to give desyl alkenyl sulphides,[212] and aldehydes or ketones give vinyl sulphides with 1-trimethylsilyl-1-phenylthiomethyl-lithium.[213] It is rare to find cases of introduction of unsaturation into saturated sulphides, but two papers are notable; that describing lead tetra-acetate oxidation of the cysteinylvaline oxazolone (21) to give the corresponding trityl vinyl sulphide,[214] and another on the conversion of α-phenylthiocyclohexanone into the cyclohexenone oxime (22), the tentative

[206] (*a*) P. M. Rao and A. R. Knight, *Canad. J. Chem.*, 1972, **50**, 844; (*b*) D. R. Tycholiz and A. R. Knight, *ibid.*, p. 1734; (*c*) *J. Amer. Chem. Soc.*, 1973, **95**, 1726.

[207] P. S. Skell, K. J. Klabunde, J. H. Plonka, J. S. Roberts, and D. L. Williams-Smith, *J. Amer. Chem. Soc.*, 1973, **95**, 1547.

[208] Y. Sato, H. Nakai, H. Ogiwara, T. Mizoguchi, Y. Migita, and Y. Kanaoka, *Tetrahedron Letters*, 1973, 4565.

[209] P. B. Shevlin and J. L. Greene, *J. Amer. Chem. Soc.*, 1972, **94**, 8447.

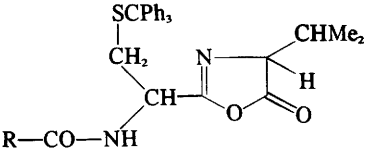
[210] S. Torii and K. Uneyama, *Tetrahedron Letters*, 1972, 4513.

[211] D. M. Lynch and A. J. Crovetti, *J. Heterocyclic Chem.*, 1972, **9**, 1027.

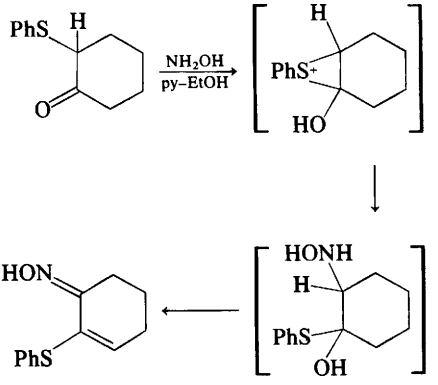
[212] M. J. Loadman, B. Saville, M. Steer, and B. K. Tidd, *J.C.S. Chem. Comm.*, 1972, 1167.

[213] F. A. Carey and A. S. Court, *J. Org. Chem.*, 1972, **37**, 939.

[214] R. B. Morin and E. M. Gordon, *Tetrahedron Letters*, 1973, 2163.



(21)



(22)

mechanism showing that the reaction is not all that it appears[215] seems open to verification through labelling studies. Pyrolysis of thioacetals is a well-established route to vinyl sulphides [*e.g.* $R^1SCHMeCH(SR^2)_2$ with $(EtO)_2$-POH at 170—190 °C gives $R^1SCH{=}CMeSR^2$,[216a] but some rearrangement accompanies the use of Bu^tOK[216b,c]] and the intermediate alkylthio-carbonium ion can give alternative products,[217] a possibility whose value in synthesis may have been overlooked. Thioacetal mono-*S*-oxides give vinyl sulphides under milder conditions, and the route has been used in a synthesis of dehydro-L-methionine, a methionine antagonist, $MeSCH{=}CHCH(NH_3^+)$-CO_2^-.[218]

Syntheses of vinyl sulphides based on alkynes include disulphide bond insertion ($R_2S_2 + CH{\equiv}CH \rightarrow RSCH{=}CHSR$[219]) or thiol addition (*e.g.* prop-2-ynethiol + cyanoalkyne gives $CH{\equiv}CCH_2SCR{=}CHCN$[220]).

[215] L. Baczynskyj, S. Mizsak, and J. Szmuszkovicz, *J. Org. Chem.*, 1972, **37**, 4104.

[216] (*a*) A. S. Atavin, B. A. Trofimov, A. I. Mikhaleva, and I. P. Vasilev, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 2014; (*b*) B. A. Trofimov, A. S. Atavin, A. I. Mikhaleva, and V. A. Pestunovich, *Zhur. org. Khim.*, 1972, **8**, 1989; (*c*) A. S. Atavin, A. I. Mikhaleva, V. A. Pestunovich, A. G. Cheborareva, V. I. Kaigorodova, and B. A. Trofimov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 2334.

[217] E. R. de Waard, H. R. Reus, and H. O. Huisman, *Tetrahedron Letters*, 1973, 4315.

[218] K. Balenovic and A. Deljac, *Rec. Trav. chim.*, 1973, **92**, 117.

[219] B. A. Trofimov, N. K. Gusarova, A. S. Atavin, S. V. Amosova, A. V. Gusarov, N. I. Kazantseva, and G. A. Kalabin, *Zhur. org. Khim.*, 1973, **9**, 8.

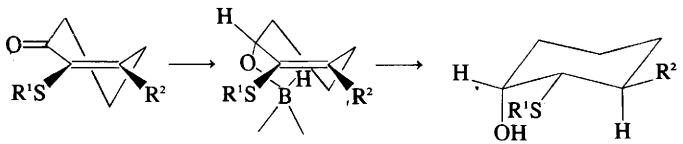
[220] R. A. van der Welle and L. Brandsma, *Rec. Trav. chim.*, 1973, **92**, 667.

Dimethylprop-2-ynylsulphonium bromide isomerizes to the allene, which is susceptible to nucleophilic addition, giving a product mixture including the demethylation product MeSCH=CMeX (X = nucleophile).[221] (+)-1-Adamantyl allyl ethyl sulphonium fluoroborate undergoes [2,3]-sigmatropic rearrangement to give a mixture of adamantyl ethyl and allyl sulphides and (−)-(*R*)-1-adamantyl pent-4-en-2-yl sulphide,[222] *i.e.* with inversion at carbon; chirality is 'transferred' from S to C with at least 94% optical induction.

Cleavage of 1,1-dichloro-2-phenylthiocyclopropanes with Bu^{t}OK gives phenylthio-enynes, *e.g.* $PhSC{\equiv}CCMe{=}CH_2$ from the 3,3-dimethyl homologue, *via* $PhSCHCCl{=}CMe_2$ and $PhSCH{=}CClCMe{=}CH_2$.[223] The corresponding sulphonyl compounds do not suffer cleavage, giving cyclopropyl ketals with alkoxides.

cis-Addition of Grignard reagents to alkynyl methyl sulphides in the presence of copper(I) halides gives the corresponding vinyl sulphides.[224] A substantial study of the addition reactions of (alkylthio)vinylacetylenes[225] and their Se and Te analogues is being made; addition to the triple bond by AcOH,[225b] MeSCl,[225c] and halogens[225f] occurs, while Li complexes react with O_2 and H_2O to give $R^1CH_2CH(OH)C{\equiv}CSR^2$,[225a] and secondary amines add to Se and Te analogues to give allenes $R_2NCH_2CH{=}C{=}CHSeMe$ and the Te analogue;[225e] EtMgBr adds to the selenide to give $PrCH{=}C{=}CHSeMe$ while the Te analogue gives EtTeMe.[225d] Di(alk-1-ynyl) sulphides give dithiins and their Se and Te analogues with Na_2S, Na_2Se, or Na_2Te, respectively.[226]

Both carbonyl and alkene functions in α-benzylthio-enones (23) are reduced stereospecifically with $NaBH_4$ in EtOH at room temperature *via*

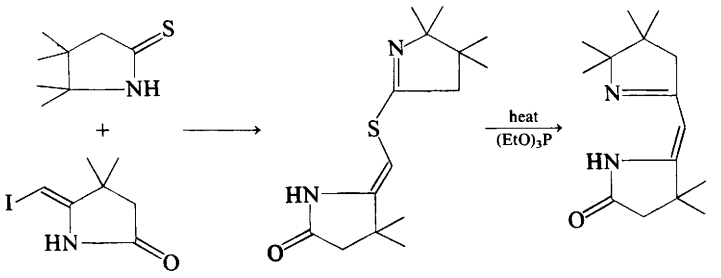


(23)

1,2-addition to C=O followed by intramolecular hydrogen transfer, possibly facilitated by activation of the intermediate alkoxyborohydride by the

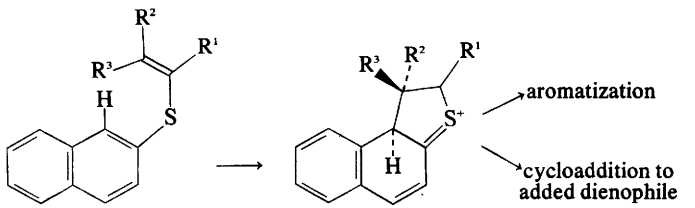
[221] J. W. Batty, P. D. Howes, and C. J. M. Stirling, *J.C.S. Perkin I*, 1973, 59.
[222] B. M. Trost and R. F. Hammen, *J. Amer. Chem. Soc.*, 1973, **95**, 962.
[223] W. E. Parham, S. Kajigaeshi, and S. H. Groen, *Bull. Chem. Soc. Japan*, 1972, **45**, 509; W. E. Parham, W. D. McKown, V. Nelson, S. Kajigaeshi, and N. Ishikawa, *J. Org. Chem.*, 1973, **38**, 1361.
[224] P. Vermeer, C. de Graaf, and J. Meijer, *Rec. Trav. chim.*, 1974, **93**, 24.
[225] (*a*) S. I. Radchenko, L. N. Cherkasov, and A. N. Krivosheya. *Zhur, org. Khim.*, 1972, **8**, 28; (*b*) S. I. Radchenko, *ibid.*, p. 1329; S. I. Radchenko and I. B. Lopatina, *ibid.*, p. 1153; (*c*) S. I. Radchenko and A. A. Petrov, *ibid.*, p. 1572; (*d*) S. I. Radchenko and L. N. Cherkasov, *ibid.*, p. 1988; (*e*) M. L. Petrov, S. I. Radchenko, B. S. Kupin, and A. A. Petrov, *ibid.*, 1973, **9**, 663; (*f*) S. I. Radchenko and V. A. Naumov, *ibid.*, p. 1798.
[226] J. Meijer, P. Vermeer, H. D. Verkruijsse, and L. Brandsma, *Rec. Trav. chim.*, 1973, **92**, 1326.

sulphide, acting as a Lewis base.[227] The sulphide-contraction procedure encapsulated in the Vitamin B_{12} synthesis of a few years ago has some drawbacks at the vinyl sulphide synthesis stage, but an alternative synthesis using iodinated enamides (24) and thiolactam has been developed,[228] and the



(24) (25) (26)

contraction step further exemplified in the reaction (25) → (26). 2-Naphthyl vinyl sulphides (27) undergo regiospecific photocyclization to thiocarbonyl ylides under non-oxidative conditions.[229]



(27)

A new type of thio-Claisen rearrangement is observed for 1-alkynyl 2-alkynyl sulphides $R^1C{\equiv}CSCH_2C{\equiv}CR^2 \rightarrow CH_2{=}C{=}CR^2{-}CR^1{=}C{=}S$, the product being trapped as the thioamide by adding a secondary amine.[230] Allyl (2,2-dicyanovinyl) sulphides undergo thio-Claisen rearrangement only reluctantly.[231] A selenoallylic rearrangement [a 1,3-shift; $Bu^nCH(SePh)CMe{=}CH_2$ gives $Bu^nCH{=}CMeCH_2SePh$] has been demonstrated[232] in a broad project generally demonstrating the greater reactivity of organoselenium compounds compared with their sulphur analogues.

[227] J. W. de Leeuw, E. R. de Waard, P. F. Foeken, and H. O. Huisman, *Tetrahedron Letters*, 1973, 2191.
[228] E. Gotschi, W. Hunkeler, H. J. Wild, P. Schneider, W. Fuhrer, J. Gleason, and A. Eschenmoser, *Angew. Chem. Internat. Edn.*, 1973, **12**, 910.
[229] A. G. Schultz and M. B. DeTar, *J. Amer. Chem. Soc.*, 1974, **96**, 296.
[230] J. Meijer, P. Vermeer, H. J. T. Bos, and L. Brandsma, *Rec. Trav. chim.*, 1974, **93**, 26.
[231] K. Hartke and G. Golz, *Chem. Ber.*, 1974, **107**, 566.
[232] K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, 1972, **37**, 3973.

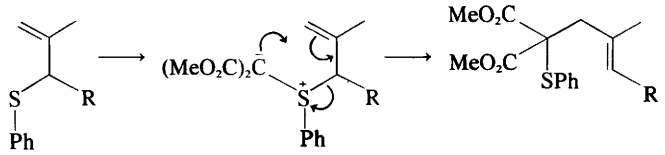
Cycloaddition reactions are reported for vinyl[233] and allyl[234] sulphides with dimethyl azodicarboxylate[233] and with diazomethane.[234] In the latter case, the direction of addition is influenced by the activation by sulphur of the double bond, and since in allyl benzyl ether the oxygen plays no role in directing the incoming 1,3-dipole, the study is claimed to provide chemical evidence for p_π–d_π interaction in allyl and vinyl sulphides.[234] Benzyne adds to an alk-1-ynyl sulphide anion through sulphur, giving $PhSCHR^1$-$CHR^2C{\equiv}CH$ through subsequent proton transfer and [2,3]sigmatropic rearrangement.[235]

γ-Radiolysis[236a] and u.v.-photolysis[236b] studies of *S*-(*cis*-prop-1-enyl)-L-cysteine reveal products of both *cis*- and *trans*-prop-1-enylthiyl radicals, volatile products from γ-radiolysis being the various possible sulphides, while u.v.-irradiation gives only *ca.* 2% yield of sulphides, the main products being alanine and prop-1-enethiol, with substantial amounts of 2,4-, 3,4-, and 2,5-dimethylthiophens and 3-methylthiophen.

Reactions of Sulphides with Carbenes and Nitrenes; α-Thiocarbenes.—Bis(methoxycarbonyl)carbene, produced photochemically from dimethyl diazomalonate, gives stable sulphonium bis(methoxycarbonyl)methylides with alkyl and aryl sulphides, while dialkyl disulphides give alkylthiomalonates.[237a] Corresponding reactions with alkylthiotrimethylsilanes give Si—S insertion products *via* the analogous sulphonium methylide,[237f] while allyl sulphides give C=C addition products as well as insertion into the allyl sulphide C—S bond.[237c] Vinyl sulphides add carbene at S as well as at C=C.[237d] Nitrenes similarly add to S and substitute at the α-CH_3 group in $Me_2C{=}CMeSEt$.[237d] Sulphonium cyclopentadienylides are formed from dimethyl sulphide and diazo cyclopentadiene on irradiation,[237e] while corresponding products from di-isopropyl and di-t-butyl sulphides are unstable, giving cyclopentadienyl sulphides through Hofmann and Stevens rearrangements. *ortho*-Substitution of the phenyl ring is observed, as well as carbene insertion products, when phenyl- and diphenyl-diazomethane are photolysed in the presence of an aliphatic sulphide (*e.g.* $Ph_2CN_2 + Me_2S \rightarrow$ *o*-methylthiomethylbenzylbenzene + Ph_2CHCH_2SMe).[237b] Allylic sulphonium ylides formed in this way from allyl sulphides rearrange, the overall process

[233] J. Firl and S. Sommer, *Tetrahedron Letters*, 1972, 4713.
[234] I. Ojima and K. Kondo, *Bull. Chem. Soc. Japan*, 1973, **46**, 2571.
[235] L. Brandsma, S. Hoff, and H. D. Verkruijsse, *Rec. Trav. chim.*, 1973, **92**, 272.
[236] (*a*) H. Nishimura and J. Mizutani, *J.C.S. Chem. Comm.*, 1972, 738; *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 213; (*b*) H. Nishimura, T. Hanzawa, and J. Mizutani, *Tetrahedron Letters*, 1973, 343; *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 2393.
[237] (*a*) W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyama, S. Nakaido, and T. Migita, *J. Org. Chem.*, 1972, **37**, 1721; (*b*) W. Ando, M. Yamada, E. Matsuzaki, and T. Migita, *ibid.*, p. 3791; (*c*) W. Ando, S. Kondo, K. Nakayama, K. Ichibori, H. Kohoda, H. Yamato, I. Imai, S. Nakaido, and T. Migita, *J. Amer. Chem. Soc.*, 1972, **94**, 3870; (*d*) W. Ando, H. Fujii, T. Takeuchi, H. Higuchi, Y. Saiki, and T. Migita, *Tetrahedron Letters*, 1973, 2117; (*e*) W. Ando, Y. Saiki, and T. Migita, *Tetrahedron*, 1973, **29**, 3511; (*f*) W. Ando, K. Konishi, T. Hagiwara, and T. Migita, *J. Amer. Chem. Soc.*, 1974, **96**, 1601.

providing a useful stereoselective *trans*-substituted olefin synthesis (28) → (29).[238]



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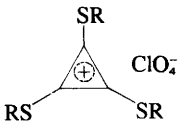
Further work on the reactions of alkylthiocarbenes, generated photochemically or thermally from tosylhydrazones or α-diazo-ketones, describes isomerization $RS(CH_2)_3\ddot{C}Ph \rightarrow RS(CH_2)_2CH{=}CHPh$,[239a] episulphonium[239c] and thietan ylide[239b] formation, and vinyl sulphide formation from α- and γ-alkylthiocarbenes.[239b,c] The mode of generation of the carbene is important in determining products, $RSCH_2CH_2COCN_2H$ on thermolysis in the presence of Cu^+ giving cyclic products, but giving keten $RSCH_2CH_2CH{=}C{=}O$ by u.v. irradiation in the absence of Cu^+.[239a] α-Alkyl-[240] or α-aryl-thiocarbenes[241] are readily generated from corresponding α-halogenomethyl sulphides with base, and their use in cyclopropane synthesis has been described.[240,241a,b] [*e.g.*[240] $MeSCHCl_2 + Bu^tOK$ + alkene gives a 1-chloro-1-methylthiocyclopropane together with the carbene dimer $MeSC(Cl){=}C(Cl)SMe$]. In the addition of ArSCH: to an enamine, the *cis*-isomer predominates.[241b] Saturated sulphides add PhSCH: at sulphur, and in the case of $PhCH_2SPh$, the adduct rearranges to *o*-bis-(phenylthio)methyl-toluene, a thioacetal which is readily hydrolysed to the aldehyde.[241c] Allyl phenyl sulphide gives an adduct which rearranges similarly to $CH_2{=}CHCMe_2CH(SPh)_2$, and the method is advocated[241c] for the introduction of a formyl group in a masked form, $-CH(SPh)_2$.

Thiocyclopropenium Cations.—The reaction of tetrachlorocyclopropene with a thiol in the presence of $HClO_4$ gives a mixture of the corresponding trithiocyclopropenium perchlorate (30) and tetrathiopropenium perchlorate



(30)

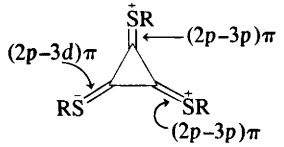
[238] P. A. Grieco, D. Boxler, and K. Hiroi, *J. Org. Chem.*, 1973, **38**, 2572.

[239] K. Kondo and I. Ojima, (*a*) *J.C.S. Chem. Comm.*, 1972, 860; (*b*) *Chem. Letters.*, 1972, 119; (*c*) *Bull. Chem. Soc. Japan*, 1973, **46**, 1539.

[240] R. A. Moss and F. G. Pilkiewicz, *Synthesis*, 1973, 209.

[241] (*a*) M. Saquet, *Compt. rend.*, 1972, **275**, *C*, 283; (*b*) R. H. Rybrandt and F. E. Dutton, *Tetrahedron Letters*, 1972, 1933; (*c*) S. Julia, C. Huynh, and D. Michelot, *ibid.*, p. 3587.

$(RS)_2C^+—CH=C(SR)_2\,ClO_4^-$.[242] While the latter product is a useful source of tetrathio-allenes,[242a] the synthetic uses of the cyclopropenium salt, and its electronic structure,[242b] are particularly intriguing. Although a substantial contribution of the hetero-[3]radialene structure (31) to the ground-state



(31)

structure of the cation might be expected,[242b] owing to the additional $(2p–3d)\pi$ conjugation possibilities, in fact this hypothesis is discounted by the close similarity between the chemical shift ($\delta = 2.93$) for the methylthio-compound and that ($\delta = 3.09$) for $(MeS)_3C^+$. The salts react with nucleophiles to give RS-substitution products with amines,[242c,d] 1,2-di-(alkylthio)cyclopropanones with dilute aqueous NaOH, together with tetrathio-allenes,[242d] and compounds RSCH=C(SR)C(SR)=X [X is $=N^+Et_2$ or $=C(CN)_2$] with diethylamine and malononitrile, respectively.[242d]

Sulphides in Synthesis.—This section is concerned with reactions of sulphides which may be exploited in carbon–carbon bond formation, or controlled introduction of functional groups, or for functional-group protection.

A series of papers has appeared concerned with a general indole synthesis from anilines, and specific *ortho*-alkylation of aromatic and heteroaromatic amines.[243] The general scheme involves *N*-chlorination (Bu^{t}OCl) followed by reaction with a dialkyl sulphide, spontaneous Sommelet–Hauser rearrangement of the resulting *N*-aryl sulphimide placing an alkylthiomethyl group *ortho* to the amine group; desulphurization gives the *o*-methylaniline.[243a] β-Carbonylsulphides react further to cyclize to 3-methylthioindoles[243f,g] or -oxindoles.[243d,f]

Methods for the introduction of an α-alkylthio-group into an aliphatic ketone have been established, involving either treatment of the silyl enol ether derived from the ketone with MeLi and a sulphenyl chloride, or α-carbanion formation from the ketone with the Li salt of a secondary amine, followed by treatment with a disulphide or a sulphenyl halide.[244]

[242] (*a*) R. Gompper and U. Jersak, *Tetrahedron Letters*, 1973, 3409; (*b*) Z. Yoshida, S. Miki, and S. Yoneda, *ibid.*, p. 4731; (*c*) Z. Yoshida, H. Konishi, Y. Tawara, and H. Ogoshi, *J. Amer. Chem. Soc.*, 1973, **95**, 3043; (*d*) Z. Yoshida, S. Yoneda, T. Miyamoto, and S. Miki, *Tetrahedron Letters*, 1974, 813.

[243] (*a*) P. G. Gassman and G. Gruetzmacher, *J. Amer. Chem. Soc.*, 1973, **95**, 588; (*b*) P. G. Gassman and T. J. van Bergen, *ibid.*, p. 590; (*c*) P. G. Gassman and T. J. van Bergen, *ibid.*, p. 591; (*d*) P. G. Gassman and T. J. van Bergen, *ibid.*, p. 2718; (*e*) P. G. Gassman and C. T. Huang, *ibid.*, p. 4453; (*f*) P. G. Gassman, T. J. van Bergen, and G. Gruetzmacher, *ibid.*, p. 6508; (*g*) P. G. Gassman, D. P. Gilbert, and T. J. van Bergen, *J.C.S. Chem. Comm.*, 1974, 201.

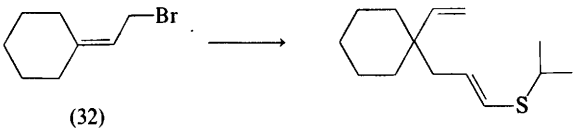
[244] D. Seebach and M. Teschner, *Tetrahedron Letters*, 1973, 5113.

α-Thiolated ketones are useful in syntheses of αβ-unsaturated ketones. Michael addition of α-carbonyl carbanions to α-methylthio-acrylates followed by conversion of the adduct into the dithioacetal ($LiNPr^i_2$–$TolSO_2SMe$) and hydrolysis provides a route to a novel 1,4-dicarbonyl series $XCO(CH_2)_2COCO_2Me$.[245] β-Alkylthio-αβ-unsaturated esters, prepared from the β-keto-esters, and corresponding ketones, give the corresponding β-alkyl analogues by displacement of the alkylthio-group using lithium dialkylcuprates.[246a] αβ-Unsaturated sulphides add organocopper reagents at the β-carbon, reductive desulphurization completing a useful alkane synthesis.[246b]

Novel syntheses of alkenes and alkynes from α-chloro- and αα-dichlorosulphides, respectively, are superficially similar to the Ramberg–Bäcklund rearrangement of α-halogenosulphones in their outcome, $ArCH_2SCHClAr$ giving[247a] predominantly *trans*-ArCH=CHAr *via* the episulphide in the presence of base, and $ArCH_2SCCl_2Ar$ giving[247b] the diaryl alkyne with Ph_3P–Bu^tOK in THF. Ketones are formed from β-keto-sulphides with $(Me_2N)_3P$,[248] and from vinyl sulphides by addition of $TiCl_4$ in an anhydrous solvent, followed by addition of H_2O.[249] Clean conversion of the vinyl sulphide moiety into a ketone is the last step in a number of synthetic applications of sulphur functional groups in aliphatic and alicyclic synthesis. 2-Pyridyl benzyl sulphide $PhCH_2SC_5H_4N$ gives the α-cuprated sulphide by successive treatment with PhLi and CuI, from which *trans*-PhCH=CHPh is obtained on hydrolysis, illustrating a general synthesis of symmetrical alkenes.[250] 2-Alkylthio-thiazolines have been used further (see Volume 2, p. 18) in aliphatic synthesis;[251] 2-thiazolinyl methyl sulphide gives successively $LiCH_2S$- and RCH_2S- thiazolines (with an alkyl halide RX), cleavage with MeI giving RCH_2I, overall an homologation procedure $RX \rightarrow RCH_2I$,[251a] while the *S*-allyl analogue on similar treatment gives $RCH{=}CHCH_2I$, which on hydrolysis gives the αβ-unsaturated aldehyde RCH=CHCHO.[251a] A 1,5-diyne synthesis starting from the *S*-propargyl-thiazoline proceeds *via* lithiation, reaction with a propargyl halide, and final Zn–AcOH cleavage.[251b] Related procedures based upon α-sulphenyl carbanions use $MeSC{\equiv}CCH(OEt)_2 + LiNEt_2 \rightarrow MeSC{\equiv}C\bar{C}(OEt)_2 \leftrightarrow MeS\bar{C}{=}C{=}C(OEt)_2$ as a synthon for the acylacetate unit, an alkyl halide giving $MeSCR{=}C{=}C(OEt)_2$, which on hydrolysis in the presence of Hg^{2+} gives $RCOCH_2CO_2Et$;[252] ketones give 3-methylthio-$\Delta^{2,3}$-butyrolactones.[252] *trans*-γ,δ-Unsaturated aldehydes $RCH{=}CHCH_2CH_2$-CHO are obtained by alkylation of 1-vinylthio-allyl-lithium anions followed

[245] R. J. Cregge, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 2603.
[246] (*a*) G. H. Posner and D. J. Brunelle, *J.C.S. Chem. Comm.*, 1973, 907; (*b*) *J. Org. Chem.*, 1973, **38**, 2747.
[247] R. H. Mitchell, (*a*) *Tetrahedron Letters*, 1973, 4395; (*b*) *J.C.S. Chem. Comm.*, 1973, 955.
[248] D. N. Harpp and S. M. Vines, *J. Org. Chem.*, 1974, **39**, 647.
[249] T. Mukaiyama, K. Kamio, S. Kobayashi, and H. Takei, *Bull. Chem. Soc. Japan*, 1972, **45**, 3723.
[250] T. Mukaiyama, K. Narasaka, and M. Furusato, *Bull. Chem. Soc. Japan*, 1972, **45**, 652.
[251] K. Hirai and Y. Kishida (*a*) *Tetrahedron Letters*, 1972, 2743; (*b*) *ibid.*, p. 2117.
[252] R. M. Carlson and J. L. Isidor, *Tetrahedron Letters*, 1973, 4819.

by their thio-Claisen rearrangement and hydrolysis,[253b] and a similar anion $CH_2{=}C(OEt)CHLiSCH{=}CH_2$ has been used as the equivalent of the (unknown) enolate anion $LiCH_2COCH_2CH_2CHO$ in a synthesis of *cis*-jasmone.[253c] 1-(Alkylthio)vinyl-lithium reagents give ketones by reaction with halides, acyloins by reaction with aldehydes, and $\alpha\beta$-unsaturated ketones by reaction with epoxides.[253a] Alkylthioallyl-lithium reagents are unsatisfactory for selective coupling with allylic halides, but the corresponding copper reagents (obtained by treating the organolithium with CuI in ether) are effective in the process, exclusive γ-alkylation being observed with $[CuCH_2CH{=}CHSPr^i]_n$ by S_N2'-type displacement, *e.g.* (32) → (33).[253d]



(32) (33)

Elegant syntheses of artemisia ketone (34),[254] (±)-C_{17}-*Cecropia* juvenile hormone from (35),[255] and in the triterpene series (36)[256] illustrate further the scope of these methods (Scheme 2).

1-Lithiocyclopropyl phenylsulphide is employed[257] for spiroannelation of cyclohexanones, addition being followed by generation of the tertiary carbonium ion by treatment with $SnCl_4$ in CH_2Cl_2; 4-t-butylcyclohexanone gives 7% (37) and 93% (38).[257c]

Phenylthiomethyl-lithium gives adducts with cyclic ketones which may be converted into esters with acylating agents, thence into alkenes by reductive elimination;[258] this process is therefore an alternative to the Wittig reaction for the transformation $R_2C{=}O$ to $R_2C{=}CH_2$. Esters undergo two-fold addition of phenylthiomethyl-lithium, $R^1CO_2R^2 \rightarrow R^1C(OH)(CH_2SPh)_2 \rightarrow R^1C(Me){=}CH_2$.[258] The reagent provides an alternative route to oxirans from ketones if the one-step route using sulphur ylides happens to fail.[259] Alkylthiomethyl isocyanides $RSCH_2NC$ give more powerfully nucleophilic anions than their sulphonyl analogues (see refs. 503, 504) and

[253] (*a*) K. Oshima, K. Shimoji, H. Takahashi, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, 1973, **95**, 2694; (*b*) K. Oshima, H. Takahashi, H. Yamamoto, and H. Nozaki, *ibid.*, p. 2693; (*c*) K. Oshima, H. Yamamoto, and H. Nozaki, *ibid.*, p. 4446; (*d*) K. Oshima, H. Yamamoto, and H. Nozaki, *ibid.*, p. 7926.

[254] D. Michelot, G. Linstrumelle, and S. Julia, *J.C.S. Chem. Comm.*, 1974, 10.

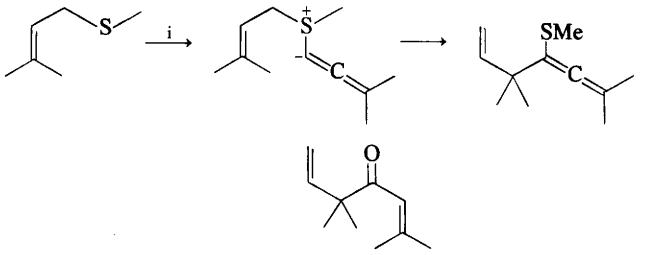
[255] K. Mori, M. Ohki, and M. Matsui, *Tetrahedron*, 1974, **30**, 715.

[256] E. E. van Tamelen, M. P. Seiler, and W. Wierenga, *J. Amer. Chem. Soc.*, 1972, **94**, 8229.

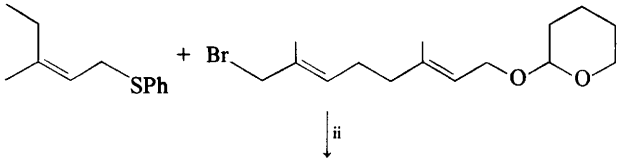
[257] (*a*) B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, 1973, **95**, 2038; (*b*) B. M. Trost, D. Keeley, and M. J. Bogdanowicz, *ibid.*, p. 3068; (*c*) B. M. Trost and D. E. Keeley, *ibid.*, 1974, **96**, 1252.

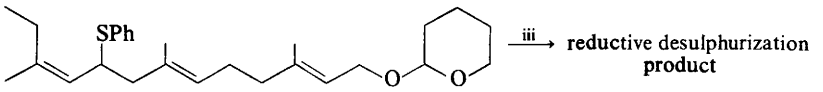
[258] R. L. Sowerby and R. M. Coates, *J. Amer. Chem. Soc.*, 1972, **94**, 4758.

[259] J. R. Shanklin, C. R. Johnson, J. Ollinger, and R. M. Coates, *J. Amer. Chem. Soc.*, 1973, **95**, 3429.



(34)





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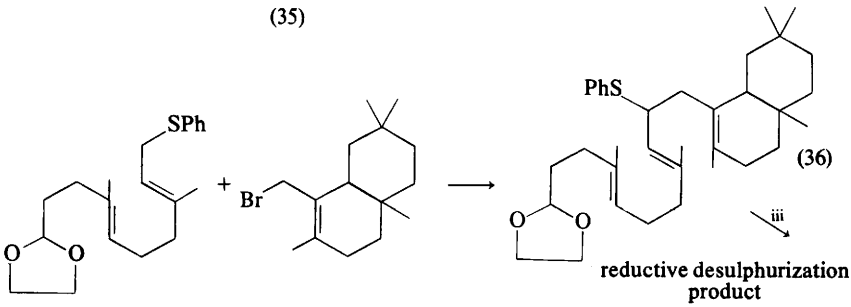
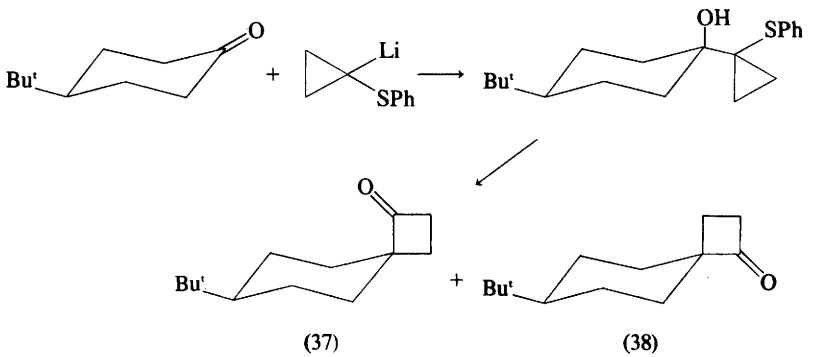


Reagents: i, $LiC{\equiv}CCMe_2Cl$; ii, Bu^nLi–DABCO; iii, desulphurization with $Li–EtNH_2$

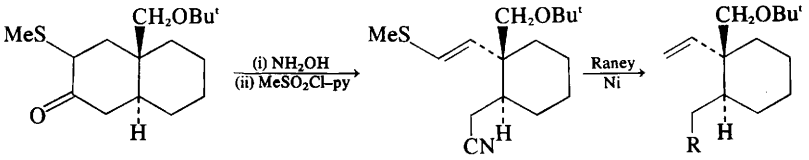
Scheme 2



(37) (38)

have similar potential in synthesis.[259a] Lithiation followed by acetylation gives RSCHAcNC, which gives a 4-alkylthio-5-methyl-oxazole on cyclization.[259a]

Among numerous methods by which an α-methylene group can be introduced into a lactone is found the use of methylthiomethyl iodide, *S*-methylation of the α-methylthiomethyl lactone being followed by elimination of Me_2S.[260] A ring-cleavage proceedure in the decalone series (39) → (40) depends upon the introduction of a methylthio-substituent;[261] a



(39) (40)

vinylcyclohexane results from Raney-nickel desulphurization. A furan synthesis using n-butylthiomethylene derivatives of ketones R^1CO-$CR^2{=}CHSBu^n$ (R^1 and R^2 appear at 3- and 4-positions in the furan formed on treatment with dimethylsulphonium methylide) has been used[262] in syntheses of perillene ($R^1 = H$, $R^2 = Me_2C{=}CHCH_2CH_2$) and dendrolasin ($R^1 = H$, $R^2 = Me_2C{=}CHCH_2CH_2CMe{=}CHCH_2CH_2$).

As a new method of protection of phosphate groups during nucleotide synthesis, the *O*-2-(arylthio)ethyl group, $ArSCH_2CH_2O$—, is removed[263] by oxidation to the sulphone with *N*-chlorosuccinimide followed by dilute NaOH; this procedure requires a shorter exposure to reagents, and milder alkaline treatment, than the alternative[264] $NaIO_4$–2M-NaOH procedure.

Sulphides as Reagents.—Sulphide-mediated oxidation of primary and secondary alcohols to aldehydes and ketones, using a dialkyl sulphide, *N*-chlorosuccinimide or Cl_2, and Et_3N, has been fully established with representative compounds[265] and used for synthesizing two key intermediates in prostaglandin syntheses.[265c] The intermediate sulphoxonium ion, *e.g.* Me_2S^+—$OCHR^1R^2$ Cl^-, formed from the alcohol by reaction with the initially formed sulphimine, gives the aldehyde or ketone, Me_2S, and H^+NEt_3, or else the alkyl halide R^1R^2CHCl in the absence of a base. The procedure is analogous to the oxidant action of DMSO in the presence of a proton source, and

[259a] A. M. van Leusen and H. E. van Gennep, *Tetrahedron Letters*, 1973, 627; U. Schollkopf and E. Blume, *ibid.*, p. 629.
[260] R. C. Ronald, *Tetrahedron Letters*, 1973, 3831.
[261] P. A. Grieco and K. Hiroi, *Tetrahedron Letters*, 1973, 1831.
[262] M. E. Garst and T. A. Spencer, *J. Amer. Chem. Soc.*, 1973, **95**, 250.
[263] K. L. Agarwal, M. Fridkin, E. Jay, and H. G. Khorana, *J. Amer. Chem. Soc.*, 1973, **95**, 2020.
[264] S. A. Narang, O. S. Bhanot, J. Goodchild, R. H. Wightman, and S. K. Dheer, *J. Amer. Chem. Soc.*, 1972, **94**, 6183.
[265] (*a*) E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Letters*, 1972, 4339; (*b*) E. J. Corey and C. U. Kim, *J. Amer. Chem. Soc.*, 1972, **94**, 7586; (*c*) *J. Org. Chem.*, 1973, **38**, 1233.

DMSO–Cl_2 is indeed an efficient alternative to the known DMSO oxidant systems.[266]

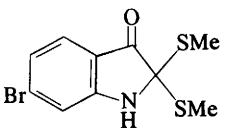
A modification to the alkene ozonolysis reaction employs dimethyl sulphide to reduce the ozonide to a keto-aldehyde.[267] Decomposition of benzoyl peroxide is accelerated by aliphatic sulphides or disulphides, owing to nucleophilic attack by sulphur at oxygen.[268] An extension of work described in 1969 by the same authors showing the ability of sulphides and thiols to quench photo-excited benzophenone has been described.[269]

4-Benzylthiopyridine is an efficient benzylating agent for aromatic compounds, in the presence of CuCl and $ZnCl_2$.[270]

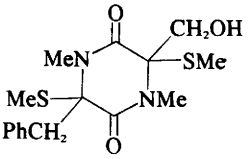
Heteroaryl Sulphides.—Syntheses based on simple inorganic sulphur reagents are commonly used, and are illustrated for imidazopyridyl sulphides,[271] di(2-pyrrolyl) sulphides and sulphides derived from related five-membered heterocycles,[272] and di(3-pyrrolyl) sulphides.[273] In the latter case, the sulphur reagent with which a 2,2′,3′-trisubstituted pyrrole is converted into the sulphide is SO_2 or SCl_2.[273]

Extensive studies are being conducted on a series of methylthio-purines, concerned with synthesis and effects of the methylthio-substituent upon structure and reactivity of other functions.[274,275] 6-Alkylseleno-9-(β-D-ribofuranosyl)purines are reductively deselenized to nebularine in near-quantitative yield with Raney nickel.[276]

Sulphides Related to Natural Products.—Among naturally-occurring sulphides providing synthetic challenges are 6-bromo-2-methylthioindoleninone and its 2,2-bis(dimethylthio) analogue (41),[277] from gastropod molluscs, a new fungal metabolite (42),[278] and all-*trans*-Me(C≡C)$_2$CH=C(SMe)-(CH=CH)$_2$CH=CH$_2$ from *Buphthalmum salicifolium*.[279]



(41)

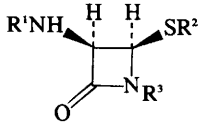


(42)

[266] E. J. Corey and C. U. Kim, *Tetrahedron Letters*, 1973, 919.
[267] G. Just and G. Reader, *Tetrahedron Letters*, 1973, 1521.
[268] W. A. Pryor and H. T. Bickley, *J. Org. Chem.*, 1972, **37**, 2885.
[269] J. B. Guttenplan and S. G. Cohen, *J. Org. Chem.*, 1973, **38**, 2001.
[270] K. Maekawa, K. Narasaka, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 1973, **46**, 3478.
[271] E. E. Glover, K. D. Vaughan, and D. C. Bishop, *J.C.S. Perkin I*, 1973, 2595.
[272] M. J. Broadhurst, R. Grigg, and A. W. Johnson, *J.C.S. Perkin I*, 1972, 1124.
[273] A. Treibs, L. Schulze, F. H. Kreuzer, and H. G. Kolm, *Annalen*, 1973, 207.
[274] F. Bergmann, M. Rahat, and D. Lichtenberg, *J.C.S. Perkin I*, 1973, 1225; M. Kleiner, *ibid.*, p. 2019; F. Bergmann, M. Rahat, and I. Tamir, *ibid.*, 1974, 470.
[275] R. J. Badger, D. J. Brown, and J. H. Lister, *J.C.S. Perkin I*, 1973, 1906.
[276] G. H. Milne and L. B. Townsend, *J.C.S. Perkin I*, 1973, 313.
[277] J. T. Baker and C. C. Duke, *Tetrahedron Letters*, 1973, 2481.
[278] G. M. Strunz, C. J. Heissner, M. Kakushima, and M. A. Stillwell, *Canad. J. Chem.*, 1974, **52**, 325; R. L. De Vault and W. Rosenbrook, *J. Antibiotics*, 1973, **26**, 532.
[279] F. Bohlmann and P. D. Hopf, *Chem. Ber.*, 1973, **106**, 3621.

Analogues of monosaccharides include 4-thio-D-glucose[280a] and 4-deoxy-1-thio-D-glucose derivatives,[280b] and 5-deoxy-5-seleno-D-xylose[281a] and -ribose derivatives[281b] have been synthesized and are representative of a large number of similar analogues synthesized in recent years. Studies in the synthesis of modified lincomycins deal with the formation of the β-bromo-anomer on treatment of the α-2-alkoxyethylthio-hexopyranose from celesticetin with Br_2, while the β-bromo-anomer gives the β-methylthio-analogue *via* the isothiouronium salt;[282] the β-methylthio-anomer shows no tendency to isomerize to the α-orientation.[282]

Methylthiolation of penicillin Schiff bases and cephalosporin analogues gives 6α-methylthiopenicillins or 7α-methylthiocephalosporins, by successive treatment with NaH and $MeSSO_2Me$ or MeSCl.[283] Sulphides derived from penicillins, and synthetic analogues, include 4-alkylthioazetidin-2-ones (43) produced by thiazolidine cleavage,[284,285] or by addition of thioimidates to



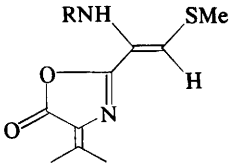
(43)

$R^1 = PhOCH_2O$— or phthaloyl;
$R^2 = CH(CO_2Me)_2$, NHR', CMe_2CHO, $CH_2C{\equiv}CH$, CPh_3, or CH_2CO_2H;
R^3 = H, $C(CO_2R''){=}CMe_2$, $CH(CO_2R'')CMe{=}CH_2$, or $COCMe_2OH$

acyl chlorides[286,287] or to ketens[288] (when different substituents appear at positions 1, 3, and 4 on the 4-alkylthioazetidin-2-one). Methyl 6,6-dibromopenicillanate gives the 3,3-dibromo-4-methylthioazetidinone carrying $C(CO_2Me){=}CMe_2$ as N-substituent, which may be replaced by H with OsO_4,[285] while the azetidinone ring of 6-bromopenicillanates does not survive MeI treatment; $MeSCH{=}CBrCONHC(CO_2Me){=}CMe_2$ is formed.[285] The rearrangement product from penicillin G and methyl chloroformate has the stereochemistry shown in (44) at the exocyclic double bond,[289] the opposite of that previously assigned.

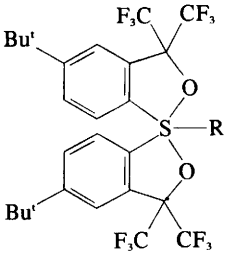
Sulphuranes.—Higher valency states are more commonly encountered in Se and particularly Te chemistry than in that of S, but recent developments indicate that sulphuranes offer more than academic interest. Conversion of

[280] (*a*) L. Vegh and E. Hardegger, *Helv. Chim. Acta*, 1973, **56**, 1792, 2020; (*b*) *ibid.*, p. 2079.
[281] T. Van Es and J. J. Rabelo (*a*) *Carbohydrate Res.*, 1973, **29**, 252; (*b*) *ibid.*, 1973, **30**, 381.
[282] B. Bannister, *J.C.S. Perkin I*, 1973, 1676.
[283] W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young, and J. E. Dolfini, *J. Org. Chem.*, 1973, **38**, 943.
[284] M. Numata, Y. Imashiro, I. Minamida, and M. Yamaoka, *Tetrahedron Letters*, 1972, 5097; J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 57, 58; R. J. Stoodley and N. S. Watson, *J.C.S. Perkin I*, 1973, 2105; 1974, 252; J. C. Sheehan, D. Ben-Ishai, and J. U. Piper, *J. Amer. Chem. Soc.*, 1973, **95**, 3064.
[285] J. P. Clayton, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1974, 22.
[286] R. Lattrell, *Angew. Chem. Internat. Edn.*, 1973, **12**, 925.
[287] A. K. Bose and J. L. Fahey, *J. Org. Chem.*, 1974, **39**, 115.
[288] M. D. Bachi and M. Rothfield, *J.C.S. Perkin I*, 1972, 2326.
[289] C. J. Veal and D. W. Young, *J.C.S. Chem. Comm.*, 1974, 266.



(44)

a sulphide into the alkoxysulphonium chloride $PhC(CF_3)_2O\overset{+}{S}R_2\ Cl^-$ with the corresponding hypochlorite, followed by reaction with the corresponding alkoxide, gives the sulphurane $[PhC(CF_3)_2O]_2SR_2$;[290a] alternatively, the sulphide can be treated with a metal alkoxide and Cl_2 at −78 °C.[290a] These sulphuranes, which have an approximate trigonal-bipyramidal structure about S with alkoxy-groups occupying apical positions,[290] are efficient dehydrating agents for alcohols, for example giving the hitherto inaccessible unrearranged olefin from tricyclopropylcarbinol in 32% yield.[290b,f] An additional synthetic application is rapid cleavage of secondary amides below room temperature.[290g] A new generation of sulphurane oxides, *e.g.* (45b),[290d] prepared from (45a) by RuO_4 oxidation,[290e] may eventually be shown to possess additional potential in organic synthesis.



(45) (a) R = lone pair;
(b) R = O

Alkyl and aryl difluorosulphuranes are readily obtained by treatment of corresponding sulphides with trifluoromethyl hypofluorite.[291,292] Tetrafluoro-analogues R_2SF_4 are obtained in some cases,[291,292] and perfluoroalkyl derivatives RSF_4Cl are described.[292]

Tetraphenylsulphurane is the principal intermediate in the reaction of phenyl-lithium with $Ph_3S^+\ BF_4^-$, leading to biphenyl and diphenyl sulphide.[293]

[290] (*a*) R. J. Arhart and J. C. Martin, *J. Amer. Chem. Soc.*, 1972, **94**, 4997; (*b*) R. J. Arhart and J. C. Martin, *ibid.*, p. 5003; (*c*) I. C. Paul, J. C. Martin, and E. F. Perozzi, *ibid.*, p. 5010; (*d*) E. F. Perozzi, J. C. Martin, and I. C. Paul, *ibid.*, 1974, **96**, 578; (*e*) E. F. Perozzi and J. C. Martin, *ibid.*, 1972, **94**, 5519, (*f*) L. J. Kaplan and J. C. Martin, *ibid.*, 1973, **95**, 793; (g) J. A. Franz and J. C. Martin, *ibid.*, p. 2017.

[291] D. B. Denney, D. Z. Denney, and Y. F. Hsu, *J. Amer. Chem. Soc.*, 1973, **95**, 4064.

[292] G. Haran and D. W. A. Sharp, *J. Fluorine Chem.*, 1973, **3**, 423.

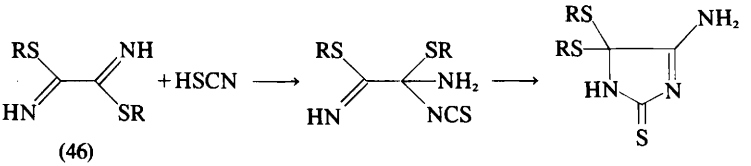
[293] D. Harrington, J. Weston, J. Jacobus, and K. Mislow, *J.C.S. Chem. Comm.*, 1972, 1079.

Di-(2-hydroxy-2-propylphenyl) selenide gives the selenurane analogue (45a; CH_3 in place of CF_3, H in place of Bu^t) of the sulphurane (45a) through a simple procedure (Br_2 followed by Et_3N).[294] Easy access to higher valency states for selenium derivatives may account for some differences in properties of bivalent sulphur compounds compared with their selenium analogues; for example, phenyl vinyl selenide $PhSeCH{=}CH_2$ does not polymerize with benzoyl peroxide, as does the vinyl sulphide, but gives the dibenzoate $PhSeCH(OCOPh)CH_2(OCOPh)$ *via* the selenurane $PhSe(OCOPh)_2CH{=}CH_2$.[295]

Among the many recent reports concerning telluranes, little is to be found of significant organic chemical interest, though a synthesis of biaryls from bis(aryl)tellurium dihalides or diaryl tellurides by treatment with degassed Raney nickel is notable.[296] Some leading references are 296, 297, and also others discussed in the 'Sulphenyl Halides' section.

5 Thioacetals and Related Compounds

Preparations.—Representative standard procedures are illustrated in the thiolysis of *gem*-dihalides $Cl_2CHCO_2H \rightarrow (EtS)_2CHCO_2H$,[298] 1,1-dibromocyclopropanes to 1-bromo-1-methylthiocyclopropanes to 1,2-di(methylthio)cyclopropanes *via* the methoxy analogue,[299] and in thiolysis of α-chloro-sulphides;[300] thiolysis of α-dimethylamino-acetals or (MeO—CH—NMe_2) $MeSO_4^-$, gives $(RS)_2CHNMe_2$.[301] More unusual observations concern the isomerization of dithiodiglycolic acid to $HO_2CCH_2SCH(SH)CO_2H$,[302] and isomerization accompanying the reaction of *SS'*-dimethyldithiooxaldimidate (46) with HSCN.[303] Treatment of a 2-alkylthio-4-bromo-

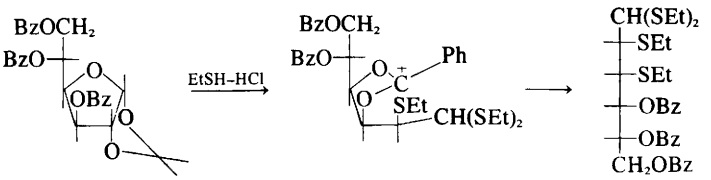


(46)

thiophen with EtLi and an alkyl bromide provides a novel type of thioacetal, $R^1SC(SR^2){=}CHC{\equiv}CMe$.[304]

[294] H. J. Reich, *J. Amer. Chem. Soc.*, 1973, **95**, 964.
[295] Y. Okamoto, R. Homsany, and T. Yano, *Tetrahedron Letters*, 1972, 2529.
[296] J. Bergman, *Tetrahedron*, 1972, **28**, 3323.
[297] B. C. Pant, *J. Organometallic Chem.*, 1974, **65**, 51.
[298] R. J. Cregge, J. L. Herrmann, J. E. Richman, R. F. Romanet, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 2595.
[299] D. Seebach, M. Braun, and N. du Preez, *Tetrahedron Letters*, 1973, 3509.
[300] H. Boehme, H. Bezzenberger, and O. Mueller, *Arch. Pharm.*, 1973, **306**, 268.
[301] H. Bredereck, G. Simchen, and H. Hoffmann, *Chem. Ber.*, 1973, **106**, 3725.
[302] J. Tohier, *Bull. Soc. chim. France*, 1972, 2533.
[303] V. P. Shah, R. Ketcham, K. J. Palmer, and R. Y. Wong, *J. Org. Chem.*, 1972, **37**, 2155.
[304] S. Gronowitz and T. Frejd. *Acta Chem. Scand.*, 1973, **27**, 2242.

Preparations of thioacetals from their parent aldehydes or ketones are commonplace procedures based upon acid-catalysed reaction with thiols, and there are numerous applications in synthesis for the derivatives. Alkanethiolysis of 3,5,6-tri-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose proceeds beyond the thioacetal-forming step, however, the locations of benzoyl groups in the product (47) verifying the nature of the intermediate



(47)

in this reaction.[305a] The notion that ethanethiolysis of protected monosaccharide diethyldithioacetals could be a progressive replacement of oxygen functions by EtS groups receives further support in the outcome of the reaction with 3-*O*-benzoyl-1,2,5,6-di-isopropylidene-α-D-glucofuranose, where EtS groups are introduced in order at carbons 1, 2, 3, and 6.[305b]

α-Keto-keten dithioacetals are obtainable in one step from aliphatic ketones by treatment with NaH, CS_2, and MeI.[306–309] These derivatives may be converted into α-isopropylidene or α-t-butyl ketones by reaction with lithium dimethylcuprate.[307]

Reactions.—Nucleophilic addition to conjugated keten dithioacetals, analogous to Michael addition to αβ-unsaturated ketones, can be accompanied by alkylation at the sulphur-bearing carbon atom leading to doubly alkylated αβ-unsaturated ketones.[310] Aldose keten diphenyldithioacetals $(PhS)_2C{=}CHCH(OR^1)R^2$ are decomposed by aqueous acids, but otherwise (R^1 = Me) the double bond is exceptionally inert to addition processes.[311] Important uses of saturated dithioacetals in synthesis are based upon derived carbanions, which can take part in Michael addition reactions with αβ-unsaturated ketones, the resulting dithioacetal being converted into the 1,4-dicarbonyl compound by treatment with *N*-bromosuccinimide in MeCN.[298] Several papers have appeared describing novel alternative methods for the conversion of thioacetals into aldehydes or ketones, using

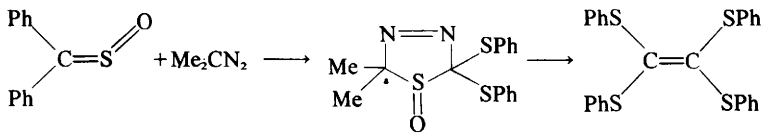
[305] G. S. Bethell and R. J. Ferrier, (*a*) *J.C.S. Perkin I*, 1972, 1033, 2873; (*b*) *ibid.*, 1973, 1400.
[306] I. Shahak and Y. Sasson, *Tetrahedron Letters*, 1973, 4207.
[307] E. J. Corey and R. H. K. Chen, *Tetrahedron Letters*, 1973, 3817.
[308] L. Dalgaard, L. Jensen, and S. O. Lawesson, *Tetrahedron*, 1974, **30**, 93.
[309] L. Dalgaard, H. Kolind-Andersen, and S. O. Lawesson, *Tetrahedron*, 1973, **29**, 2077.
[310] D. Seebach, M. Kolb, and B. T. Grobel, *Angew. Chem. Internat. Edn.*, 1973, **12**, 69.
[311] B. Berrang, D. Horton, and J. D. Wander, *J. Org. Chem.*, 1973, **38**, 187.

AgO–MeOH–H_2O,[312a] Tl^{III} trifluoroacetate,[312b] ceric ammonium nitrate,[312c] I_2–DMSO,[312d] MeI–acetone–H_2O,[312e] FSO_3Me–liquid SO_2–H_2O,[312e] and on the use of trialkylboranes for conversion of α-lithiothioacetals into aldehydes and ketones.[312f]

Keten *S,N*-acetals, *e.g.* $CH_2{=}C(SR^1)NR^2_2$,[313] and *N*-acyl analogues[314] have been described, and their use in synthesis of 2-dialkylaminopyran-4-ones by reaction with diketen.[313]

Thio-orthoesters $(RS)_3CH$ are formed from trimethyl orthoformate by treatment with a thiol in the presence of a Lewis acid;[315] while alkylthio-compounds of this series are thermally unstable, the lithium derivative $(RS)_3CLi$ may be alkylated [MeLi gives $(RS)_3CMe$] and gives the tetrathioethylene $(RS)_2C{=}C(SR)_2$ on treatment with cyclohexene oxide;[315] iodine oxidation gives the hexathio-ethane $(RS)_3C{-}C(SR)_3$,[316] which on pyrolysis above 100 °C (R = Ph) gives Ph_2S_2, $(PhS)_2CHPh$, $(PhS)_3CH$, $(PhS)_2C{=}C(SPh)_2$, and $C(SPh)_4$, the same product mixture being obtained on pyrolysis of $C(SPh)_4$ at 165—230 °C.[316] The formation of $(PhS)_3C^{\cdot}$ radicals, by C—C homolysis of $(PhS)_3C{-}C(SPh)_3$ or by C—S homolysis of $C(SPh)_4$, is a satisfactory explanation for these results.[316]

Tetra(phenylthio)ethylene is formed to the extent of 30% during retro-cycloaddition of the sulphine–dimethyldiazomethane cycloadduct (48) by dimerization of the corresponding carbene.[317]



(48)

Tetra(ethylthio)ethylene in acetone gives Et_2S_2 and EtSCOCOSEt as main products of Rose-Bengal-sensitized photo-oxidation,[318] while tris-(ethylthio)ethylene gives mainly EtSCOCHO and Et_2S_2 in acetone but $(EtS)_2CHCOSEt$ and EtSOSEt in MeOH, the latter product by photo-oxygenation of the disulphide.[318] *cis*-Bis(ethylthio)ethylene in acetone gives mainly $(EtS)_2CHCHO$ on photo-oxygenation.[318]

[312] (*a*) D. Gravel, C. Vaziri, and S. Rahal, *J.C.S. Chem. Comm.*, 1972, 1323; (*b*) T. L. Ho and C. M. Wong, *Canad. J. Chem.*, 1972, **50**, 3740; (*c*) T. L. Ho, H. C. Ho, and C. M. Wong, *J.C.S. Chem. Comm.*, 1972, 791; (*d*) J. B. Chattopadhyaya and A. V. Rama Rao, *Tetrahedron Letters*, 1973, 3735; (*e*) M. Fetizon and M. Jurion, *J.C.S. Chem. Comm.*, 1972, 382; (*f*) S. Yamamoto, M. Shiono, and T. Mukaiyama, *Chem. Letters*, 1973, 961.

[313] R. Gompper and J. Stetter, *Tetrahedron Letters*, 1973, 233.

[314] W. Walter and J. Krohn, *Annalen*, 1973, 443.

[315] D. Seebach, K. H. Geiss, A. K. Beck, B. Graf, and H. Daum, *Chem. Ber.*, 1972, **105**, 3280.

[316] D. Seebach and A. K. Beck, *Chem. Ber.*, 1972, **105**, 3892.

[317] L. Thijs, A. Wagenaar, E. M. M. van Rens, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3589.

[318] W. Ando, J. Suzuki, T. Arai, and T. Migita, *Tetrahedron*, 1973, **29**, 1507; *J.C.S. Chem. Comm.*, 1972, 477.

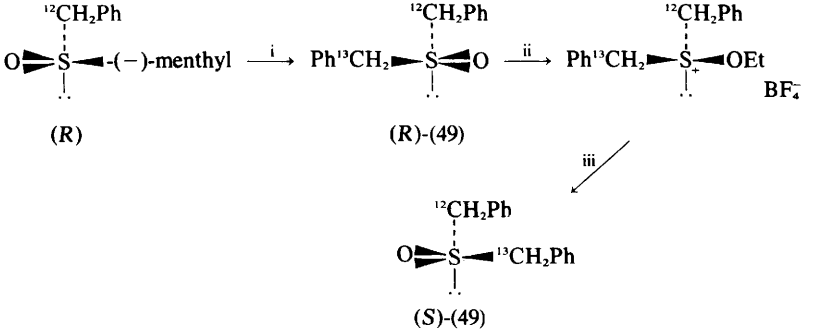
6 Sulphoxides

Preparations.—The latest crop of papers describing methods for oxidation of sulphides to sulphoxides, without over-oxidation to the sulphone, deal with standard methods, *e.g.* H_2O_2–Ac_2O–room temperature for conversion of ethynyl sulphides into the corresponding (thermally unstable) sulphoxides,[319] $NaIO_4$,[378,400] ethereal chloroamine,[320] and a fascinating example of the coming generation of insoluble reagents, *viz.* *N*-chloro-Nylon 66 for quantitative oxidation of sulphides in hydroxylic solvents.[321] The O_2–V_2O_5 system has been intensively studied as an example where optimization of the procedure must take account of product inhibition.[322] Sulphides without α-hydrogen atoms give sulphoxides with ceric ammonium nitrate in MeCN–H_2O,[323] while $HAuCl_4$ is shown[324] to be a stereospecific oxidant, $Au^{III} \rightarrow Au^{I}$, towards L-methionine, *via* a methionine–$AuCl_3$ complex which reacts stereospecifically with a second methionine substrate molecule.

Allenic sulphoxides $ArSOCH{=}C{=}CR^1R^2$ are available through the reaction of sulphenyl halides with propargyl alcohols $HC{\equiv}CCR^1R^2OH$.[325] Friedel–Crafts reactions with toluene-*p*-sulphinyl chloride in the presence of $AlCl_3$, $SnCl_4$, or $SbCl_5$ give aryl *p*-tolyl sulphoxides,[326] and an analogous product is obtained unexpectedly, using toluene-*p*-sulphonyl chloride with isoquinoline as substrate in the presence of excess NaH.[327]

Optically active sulphoxides are available through reactions of organometallic reagents with epimers of 1,2,3-oxathiazolidine 2-oxide derived from *l*-ephedrine[328] (details in Volume 2, p. 36), or from chiral sulphinates[329,330] by reaction with Grignard reagents. The synthesis of a chiral sulphoxide (49), in which optical rotatory power derives from isotopic dissymmetry of the benzyl CH_2 groups, is displayed in Scheme 3.[329] The procedure for the conversion of the (*R*)-sulphoxide into its (*S*)-enantiomer shown in Scheme 3 involves inversion at sulphur in the ethoxysulphonium intermediate;[331] the procedure can be brought about with retention of configuration at sulphur using pyridine in CH_2Cl_2,[331] unless the alkoxysulphonium salt carries a substituent at S containing an α-hydrogen, in which case an α-pyridinio-sulphide is formed, a process analogous to the Pummerer rearrangement of sulphoxides. Optically active γ-disulphoxides have

[319] V. I. Laba, A. V. Sviridova, and E. N. Prilezhaeva, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.* 1972, 212.
[320] G. D. Rees and J. K. Sugden, *Amer. Lab.*, 1973, **5**, 48 (*Chem. Abs.*, 1973, **79**, 52 396j).
[321] Y. Sato, N. Kunieda, and M. Kinoshita, *Chem. Letters*, 1972, 1023.
[322] A. V. Mashkina, P. S. Makoveev, and N. I. Polovinkina, *Kinetika i Kataliz*, 1972, **13**, 124.
[323] T. L. Ho and C. M. Wong, *Synthesis*, 1972, 561.
[324] E. Bordignon, L. Cattalini, G. Natile, and A. Scatturin, *J.C.S. Chem. Comm.*, 1973, 878.
[325] L. Horner and V. Binder, *Annalen*, 1972, **757**, 33.
[326] T. Fujisawa, M. Kakutani, and N. Kobayashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 3615.
[327] M. Natsume, S. Kumadaki, Y. Kanda, and K. Kiuchi, *Tetrahedron Letters*, 1973, 2335.
[328] F. Wudl and T. B. K. Lee, *J. Amer. Chem. Soc.*, 1973, **95**, 6349.
[329] K. K. Andersen, S. Colonna, and C. J. M. Stirling, *J.C.S. Chem. Comm.*, 1973, 645.
[330] R. E. Estep and D. F. Tavares, *Internat. J. Sulfur Chem.*, 1973, 279.
[331] R. Annunziata, M. Cinquini, and S. Colonna, *J.C.S. Perkin I*, 1973, 1231.



Reagents: i, $Ph^{13}CH_2MgCl$; ii, $Et_3O^+ BF_4^-$; iii, aq. NaOH

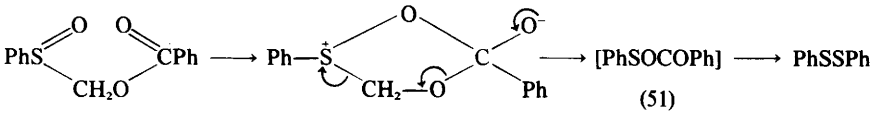
Scheme 3

been prepared from di-(−)-menthyl ethane-1,2-disulphinate in the same way.[332] An alternative route has been established based upon the configurational stability of α-sulphinyl carbanions, optically active $RSOCH_2^-$, prepared from the optically active sulphoxide by Li–Et_2NH, being treated with copper(II) chloride to give $RSOCH_2CH_2SOR$ with enantiomeric purity >97%.[333] Similar studies in stereochemical aspects of sulphoxide formation from sulphinyl carbanions and sulphinates have been reported.[334] Reaction between sulphoxides and alkyl-lithiums give α-lithiated sulphoxides but also C—S cleavage, $R^1SOR^2 + R^3Li$ giving $R^1SOR^3 + R^2Li$, the more electronegative group being displaced with inversion of configuration at sulphur;[335] this reaction may be exploited to synthesize optically active dialkyl sulphoxides with inversion from optically active aryl alkyl sulphoxides,[335] but C—S cleavage can be avoided in large degree by using MeLi or Pr^i_2NLi for efficient α-lithiation.

Properties and Reactions of Sulphoxides.—Simple reactions resulting in the reduction of sulphoxides to sulphides, reported recently, concern $SnCl_2$–HCl,[336] $NaHSO_3$ (SO_2 is ineffective),[337] RCS_2H,[338] and MeCOCl.[339] During the reaction of butyl methyl sulphoxide with L-cysteine, (+)-2-mercaptopropionic acid, or other optically active thiols, the (−)-(*R*)-sulphoxide accumulates, indicating that the (*S*)-enantiomer is reduced faster by the thiol.[340]

[332] H. Nieuwenhuyse and R. Louw, *J.C.S. Perkin I*, 1973, 839.
[333] C. A. Maryanoff, B. E. Maryanoff, R. Tang, and K. Mislow, *J. Amer. Chem. Soc.*, 1973, **95**, 5839.
[334] N. Kunieda, J. Nokami, and M. Kinoshita, *Chem. Letters*, 1973, 871.
[335] J. P. Lockard, W. C. Schroek, and C. R. Johnson, *Synthesis*, 1973, 485; T. Durst, M. J. LeBelle, R. van den Elzen, and K. C. Tin, *Canad. J. Chem.*, 1974, **52**, 761.
[336] T. L. Ho and C. M. Wong, *Synthesis*, 1973, 206.
[337] C. R. Johnson, C. C. Bacon, and J. J. Rigau, *J. Org. Chem.*, 1972, **37**, 919.
[338] S. Oae, T. Yagihara, and T. Okabe, *Tetrahedron*, 1972, **28**, 3203.
[339] T. Numata and S. Oae, *Chem. and Ind.*, 1973, 277.
[340] N. Bregant, K. Balenovic, and V. Polak, *Bull. Sci. Cons. Acad. Sci. Arts. R.S.F. Yugoslav., Sect. A*, 1972, **17**, 289.

Cleavage of $Ph_2CHSOCH_2Ph$ with SO_2Cl_2 in CH_2Cl_2 in the presence of CaO or pyridine gives Ph_2CHCl and α-toluenesulphinic acid, possibly *via* phenylsulphine, PhCH=S=O.[341] The reaction of DMSO with acetylene illustrates another cleavage process, in this case giving more than ten products, including $MeSSCH{=}CH_2$ and $(CH_2{=}CH)_2S$.[342] A new sulphoxide fragmentation is shown by benzoyloxymethyl sulphoxide (50), the course of the fragmentation into formaldehyde and an unstable anhydride (51) being supported by ^{18}O studies.[343]



(50) (51)

Regioselectivity in acetic-anhydride-induced Pummerer reactions of steroidal sulphoxides is determined by steric factors; with axial 6β-alkylsulphinyl-5α-cholestanes,[344] only 6-alkylthiocholest-5-enes are formed, representing acetoxylation of the more highly substituted α-carbon atom, $RSOCH_2X \rightarrow R\overset{+}{S}(OAc)CH_2X \rightarrow R\overset{+}{S}{=}CHX \rightarrow RSCH(OAc)X$.

Intramolecular effects observed for *o*-methylsulphinylphenol[345] in terms of hydrogen bonding by ^1H n.m.r. indicate a rather weaker hydrogen bond than that in *o*-hydroxyacetophenone; maximum conjugative interaction between the phenyl and sulphinyl groups is achieved in only one specific conformation.[345] *o*-Methylsulphinylbenzoic acid shows in its reactions (halide ion racemization and reduction of the sulphoxide) the influence of a neighbouring carboxylate grouping, as suggested earlier (Volume 2, p. 40).[346] The influence takes the form of attack of carboxylate on protonated sulphinyl sulphur rather than nucleophilic attack by sulphinyl oxygen on carboxyl, to give an acyloxy-sulphonium ion.[346]

Resolution of *dl*-methyl *p*-tolyl sulphoxide to the extent of $2.25 \pm 0.25\%$ enrichment of the (*R*)-(+)-enantiomer is achieved by irradiation in the presence of the chiral sensitizer (*R*)-(+)-*N*-acetyl-1-(1-naphthyl)ethylamine during 50 h.[347] The process is one of equilibration rather than selective destruction of the (*S*)-enantiomer. Racemization parameters for sulphoxides in comparison with sulphimides[348] and sulphonium ions[349] and comparisons with analogous species from elements near S in the Periodic Table

[341] C. Y. Meyers and G. J. McCollum, *Tetrahedron Letters*, 1973, 289.
[342] B. A. Trofimov and S. V. Amosova, *Zhur. org. Khim.*, 1972, **8**, 2614.
[343] T. J. Maricich, R. A. Jourdenais, and C. K. Harrington, *J. Amer. Chem. Soc.*, 1973, **95**, 2378.
[344] D. N. Jones, E. Helmy, and R. D. Whitehouse, *J.C.S. Perkin I*, 1972, 1329.
[345] U. Folli, D. Larossi, and F. Taddei, *J.C.S. Perkin II*, 1973, 848.
[346] D. Landini and F. Rolla, *J.C.S. Perkin II*, 1972, 1317.
[347] G. Balavoine, S. Juge, and H. B. Kagan, *Tetrahedron Letters*, 1973, 4159.
[348] D. Darwish and C. E. Scott, *Canad. J. Chem.*, 1973, **51**, 3647; B. C. Menon and D. Darwish, *Tetrahedron Letters*, 1973, 4119.
[349] R. D. Baechler, J. D. Andose, J. Stackhouse, and K. Mislow, *J. Amer. Chem. Soc.*, 1972, **94**, 8060.

have been discussed.[349] Spontaneous interconversion of epimeric disulphoxides formed on oxidation of the dithioacetal $(PhCH_2S)_2CPh_2$, an example of kinetic and equilibrium control,[350] is made possible by the lower bond energies of the C—S bonds in the disulphoxide, permitting a room-temperature homolytic dissociation–recombination mechanism to operate.[350]

A mechanistic study of O-exchange based upon ^{18}O-labelled optically active phenyl or methyl *p*-tolyl,[351a] or methyl butyl[351b] sulphoxide shows that a change of mechanism from S_N2-type to *A*-1-type occurs at H_2SO_4 concentrations above 95%, when cation-radical intermediates —$\overset{+}{S}$·— or dications —$\overset{+}{S}$— are involved.[351a,b] Methylation of optically active sulphoxides using $\overset{+}{M}eI$–HgI_2 gives optically active oxosulphonium salts.[351c]

Photolysis of sulphoxides gives alkyl and sulphinyl radicals,[352] H-abstraction from solvent, and bimolecular disproportionation (giving R_2S and R_2SO_2) accounting for the eventual products. Irradiation of 2-nitrophenyl phenyl sulphoxide gives 2-nitrosophenyl sulphone as sole product.[352b] Thermal decomposition of sulphoxides under drastic conditions gives mainly SO_2 and hydrocarbons (CH_4 and C_2H_4 from DMSO at 297—350 °C[353]), but thermolysis of t-alkyl sulphoxides to sulphenic acids can be achieved under controlled conditions,[510] as revealed by i.r., n.m.r., and trapping studies. Dialkyl sulphoxides exert their anti-oxidant action towards the autoxidation of hydrocarbons by thermolysis into sulphenic acids, which are powerful radical scavengers.[511]

α-Sulphinyl Carbanions.—Further applications of α-sulphinyl carbanions in synthesis (in addition to several papers describing well-known alkylation reactions not cited here) include addition to imines [(R)-(+)-$TolSOCH_2Li + PhCH{=}NPh \rightarrow PhCH(CH_2SOTol)NHPh$, which with Ni gives (R)-(−)-PhCH(Me)NHPh][354a] and a symmetric synthesis of alcohols by reactions of chiral α-sulphinyl carbanions with aldehydes, ketones, or oxirans.[354b] Sodium methylsulphinyl methylide reacts with cyclopentanones in an unexpectedly complicated way[355] through initial base-catalysed condensation to give α-cyclopentylidenecyclopentanone, addition of the carbanion giving (52), from which (53) is formed by ring-opening and thiolate-elimination stages.

Important uses in synthesis have been demonstrated for carbanions

[350] C. Y. Meyers, L. L. Ho, A. Ohno, and M. Kagami, *Tetrahedron Letters*, 1974, 729.

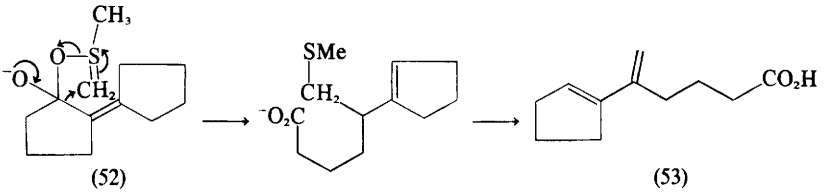
[351] (*a*) N. Kunieda and S. Oae, *Bull. Chem. Soc. Japan*, 1973, **46**, 1745; (*b*) S. Oae, M. Moriyama, T. Numata, and N. Kunieda, *ibid.*, 1974, **47**, 179; (*c*) K. Kamiyama, H. Minato, and M. Kobayashi, *ibid.*, 1973, **46**, 3895.

[352] (*a*) J. R. Shelton and K. E. Davis, *Internat. J. Sulfur Chem.*, 1973, **8**, 217; K. Gollnick and H. U. Stracke, *Pure Appl. Chem.*, 1973, **33**, 217; (*b*) R. Tanikaga and A. Kaji, *Bull. Chem. Soc. Japan*, 1973, **46**, 3814.

[353] F. C. Thyrion and G. Debecker, *Internat. J. Chem. Kinetics*, 1973, **5**, 583.

[354] (*a*) G. Tsuchihashi, S. Iriuchijima, and K. Maniwa, *Tetrahedron Letters*, 1973, 3389; (*b*) G. Tsuchihashi, S. Iriuchijima, and M. Ishibashi, *ibid.*, 1972, 4605.

[355] W. T. Comer and D. L. Temple, *J. Org. Chem.*, 1973, **38**, 2121.



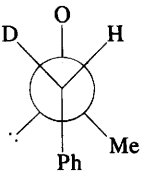
(52) (53)

derived from α-alkylthioalkyl sulphoxides,[218] readily obtained[356] from dithioacetals $CH_2(SR)_2$ with H_2O_2 in AcOH. Products from the addition of methyl methylthiomethyl sulphoxide carbanion $MeSO\bar{C}HSMe$ to ketones are readily hydrolysed into α-alkoxy-aldehydes or α-hydroxyaldehydes, or converted into hydroxyethyl ketones or α-hydroxy-acetals;[357,360a] corresponding use of 1,3-dithian and related dithioacetals (*e.g.* ref. 298) is now likely to be eclipsed by the sulphoxide procedure because the adducts are more readily hydrolysed or otherwise modified. Addition to immonium salts $R^1CH{=}\overset{+}{N}R^2_2\ Cl^-$ gives β-methylthio-enamines through elimination of MeSOH;[358] phenylacetic acid derivatives $ArCH_2CO_2R$ are obtained by condensation of methyl methylthiomethyl sulphoxide with an aldehyde, to give $ArCH{=}C(SMe)SOMe$, followed by acid treatment in the presence of an alcohol ROH.[359] Alkylation of ethyl ethylthiomethyl sulphoxide followed by treatment in ether with a trace of 70% $HClO_4$ or $HgCl_2$ gives the corresponding aldehyde RCHO, with diethyl disulphide.[360b] The alkylated reagent can be used in Michael addition reactions,[360b] hydrolysis of the adducts providing a simple synthesis of 1,4-dicarbonyl compounds; the process is illustrated in a new synthesis of *cis*-jasmone.[360d] β-Hydroxy-sulphoxides $R^1SOCH(SR^2)CH(OH)R^2$ obtained from these reagents with an aldehyde R^2CHO give keten dithioacetal mono-*S*-oxides $R^1SOC(SR^1){=}CHR^2$ by acetylation followed by KOH treatment,[360a] and these are Michael acceptors, adding carbanions,[360e,f] *e.g.* $R^2\bar{C}HCO_2R^1$,[360f] to give regio-stable carbanions $R^1O_2CCHR^2\bar{C}(SMe)SOMe$ when $R^2 = Bu^t$, but generally the product of further alkylation is the α-alkylated ester.

Stereochemical studies concerning α-sulphinyl carbanions have clarified the conflict of interpretation of recent years of kinetic preference in exchange of diastereotopic protons α to the sulphinyl group. Studies of cyclic sulphoxides[361–363] have shown that small changes in dihedral angle

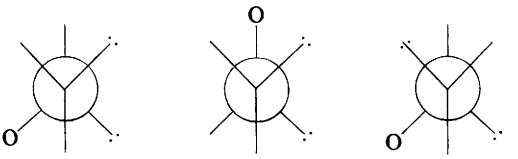
[356] K. Ogura and G. Tsuchihashi, *Bull. Chem. Soc. Japan*, 1972, **45**, 2203.
[357] K. Ogura and G. Tsuchihashi, *Tetrahedron Letters*, 1972, 2681.
[358] L. Duhamel, P. Duhamel, and N. Mancelle, *Bull. Soc. chim. France*, 1974, 331.
[359] K. Ogura and G. Tsuchihashi, *Tetrahedron Letters*, 1972, 1383.
[360] (*a*) J. L. Herrmann, J. E. Richman, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 4707; (*b*) J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, *ibid.*, p. 3267; (*c*) *ibid.*, p. 3271; (*d*) *ibid.*, p. 3275; (*e*) J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo, and R. H. Schlessinger, *ibid.*, p. 4711; (*f*) J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, and R. H. Schlessinger, *ibid.*, p. 4715.
[361] S. Bory and A. Marquet, *Tetrahedron Letters*, 1973, 4155.
[362] R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *J. Amer. Chem. Soc.*, 1972, **94**, 8795.
[363] J. F. King and J. R. Du Manoir, *Canad. J. Chem.*, 1973, **51**, 4082.

between the sulphinyl S—O bond and the neighbouring C—H bonds have a considerable effect on the relative rates of H—D exchange of the α-protons.[362] α-Lithiation of cyclic sulphoxides is faster than that of benzyl methyl sulphoxide,[363] although rates are subject to striking solvent effects;[362] the *cis*-proton is replaced, a result not in agreement with predictions based upon MO calculations. Treatment of (*S*,*S*)-α-deuterio benzyl methyl sulphoxide (54) with MeLi at −60 °C during 1 min, then addition of



(54)

MeI and determination of deuterium content, gives a measure of the kinetic isotope effect and selectivity factor for the reaction, when data are compared with those for the (*R*,*S*)-diastereoisomer;[364] the figures (2.5±0.4 and 1.7±0.3, respectively) are very different from those determined similarly by Nishio[365] (7.0 and 0.66, respectively),[364] though different conditions were used. Greater selectivity is observed for benzyl t-butyl sulphoxide, when deprotonation with MeLi and reprotonation follow the same stereochemical course, probably retention in both steps.[364] There is now general agreement that the most stable configuration for the α-sulphinyl carbanion is that in which the carbanion lone pair is *trans* to the oxygen of the sulphinyl group, as in (55), which is more stable than (56), rotamer (57) being least stable; several papers point out that



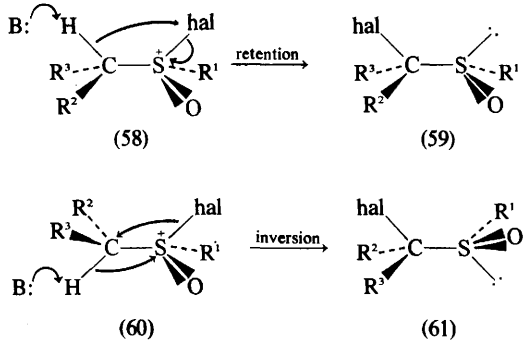
(55) (56) (57)

experimental data do not support the predictions of MO calculations concerning the relative stability of α-sulphinyl carbanions.[362,363,365] Previous discrepancies now being explained on the basis of incorrect configurational assignments to 1-phenylethyl *para*-substituted phenyl sulphoxides, now re-assigned on the basis of o.r.d. and c.d. data,[366] there is agreement that protonation of asymmetric α-sulphinyl carbanions proceeds with

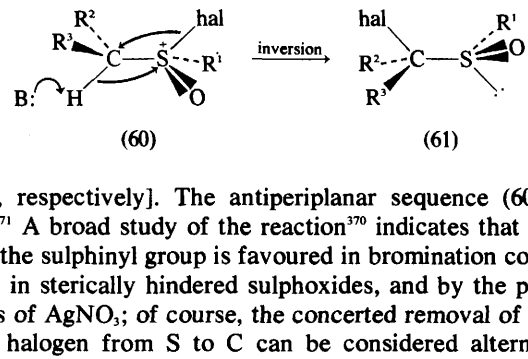
[364] R. Viau and T. Durst, *J. Amer. Chem. Soc.*, 1973, **95**, 1346.
[365] K. Nishihata and M. Nishio, *Tetrahedron Letters*, 1972, 4839; *J.C.S. Perkin II*, 1972, 1730.
[366] K. Nishihata and M. Nishio, *J.C.S. Perkin II*, 1973, 758.

retention.[365] The ratio of exchange and epimerization rates for (*R*,*S*)-methyl 1-phenylethyl sulphoxide in 0.74M-NaOD–D_2O at 56 °C is 1.30, consistent with either two rapidly inverting pyramidal carbanions or a single planar carbanion, as opposed to slowly inverting or non-inverting carbanions.[367]

α-Halogenated Sulphoxides.—Sulphoxides give α-halogenated derivatives by treatment with dichloroiodobenzene or with Br_2–pyridine;[368] when the α-carbon is a chiral or a prochiral centre, only one of the two possible diastereoisomeric α-halogeno-sulphoxides is obtained, though when bromination is performed in the presence of $AgNO_3$, inversion of configuration at S is observed.[369] This appears to be the first example of inversion at a chiral centre without substitution of the substituents conferring chirality, through attachment of a group to the chiral centre and subsequent loss of that group.[369] Two stereochemically different mechanisms can be envisaged for electrophilic α-halogenation,[370] involving either retention of configuration at both S and C, or inversion of configuration at both centres [(58) to (59); or



(58) (59)



(60) (61)

(60) to (61), respectively]. The antiperiplanar sequence (60) to (61) is favoured.[370,371] A broad study of the reaction[370] indicates that predominant inversion at the sulphinyl group is favoured in bromination compared with chlorination, in sterically hindered sulphoxides, and by the presence of a molar excess of $AgNO_3$; of course, the concerted removal of H by B: and the shift of halogen from S to C can be considered alternatively as a two-step process, displacement of halogen followed by intermolecular attack at C,[371] and no doubt more will be reported in due course on this interesting example of the individualistic behaviour of sulphinyl sulphur.

Some C—S bond cleavage is observed in the reaction of dibenzyl

[367] M. B. D'Amore and J. I. Brauman, *J.C.S. Chem. Comm.*, 1973, 398.
[368] M. Cinquini and S. Colonna, *J.C.S. Perkin I*, 1972, 1883.
[369] M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J.C.S. Perkin I*, 1972, 1886.
[370] P. Calzavara, M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Amer. Chem. Soc.*, 1973, **95**, 7431.
[371] J. Klein and H. Stollar, *J. Amer. Chem. Soc.*, 1973, **95**, 7437.

sulphoxide or benzyl phenyl sulphoxide with SO_2Cl_2,[372] or NBS, or NCS.[611] A route to α-chlorobenzyl sulphoxides[372] is therefore necessarily more circuitous, involving oxidation of αα-dichlorobenzyl sulphide to the sulphoxide with peracid, followed by $(Me_2N)_3P$ reduction. Hydroxyalkyl sulphoxides $PhSO(CH_2)_nCH_2OH$ give chloro-analogues when $n = 4$, but corresponding chloro-sulphones $PhSO_2(CH_2)_nCH_2Cl$, *via* cyclic alkoxy-oxosulphonium salts, when $n = 1$—3.[373]

A new synthesis of α-chloro-sulphoxides by the reaction of sulphinyl chlorides with diazoalkanes[374] can be modified usefully[375] to give iodoalkyl sulphoxides when performed in the presence of an alkali-metal iodide ($RSOCl+CH_2N_2+MI \rightarrow RSOCH_2I$).

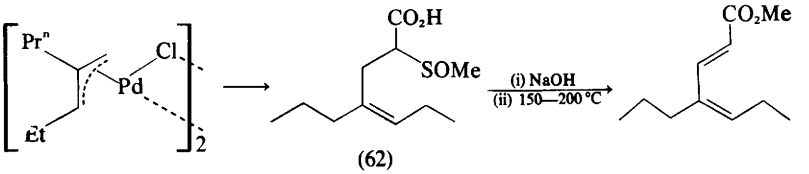
α-Halogeno-sulphoxides, like the corresponding sulphones, show low reactivity towards electrophiles, and substitution is often based upon an elimination–addition procedure.[368] Nucleophilic substitution of the halogen with Pr^nO^- or EtS^- follows S_N2 kinetics but at low rates, governed by steric effects;[376] optically active substitution products are obtained in such reactions with optically active bromomethyl *p*-tolyl sulphoxide,[377] but secondary amines give racemic toluene-*p*-sulphenamides. α-Phosphoryl sulphoxides have been prepared by treatment of a chloromethyl sulphide with $(RO)_3P$ followed by oxidation with $NaIO_4$.[378] Debromination of αα′-dibromobenzyl sulphoxide with HMPT involves inversion of configuration at each carbon centre.[379] Stepwise conversion of the substrate into carbanion and intramolecular bromine displacement with cyclization is involved;[379] if this is so, then the preferred conformation predicted on the basis of MO calculations (carbanion lone pair on an sp^3-hybridized carbon directed along the bisectrix of the S—O—S— lone pair angle) receives experimental support,[379] in contradiction to more recent conclusions.[362,363,365]

β-Keto-sulphoxides and Related Compounds.—Synthesis of β-keto-sulphoxides may be achieved using an arylsulphinyl chloride for α-substitution of a methyl ketone,[380] or through reaction between an α-lithiated chloromethyl sulphoxide PhSOCHLiCl and an aldehyde followed by further α-lithiation of the adduct PhSOCHClCH(OLi)R to bring about rearrangement into $PhSOCH_2COR$.[381]

The characteristic reactions of β-keto-sulphoxides are similar to those of other active-methylene compounds; *C*- and *O*-alkylation of metal salts are

[372] B. B. Jarvis and M. M. Evans, *J. Org. Chem.*, 1974, **39**, 643.
[373] T. Durst, K. C. Tin, and M. J. V. Marcil, *Canad. J. Chem.*, 1973, **51**, 1704.
[374] C. G. Venier, H. H. Hsieh, and H. J. Barager, *J. Org. Chem.*, 1973, **38**, 17.
[375] C. G. Venier and H. J. Barager, *J.C.S. Chem. Comm.*, 1973, 319.
[376] M. Cinquini, D. Landini, and A. Maia, *J.C.S. Chem. Comm.*, 1972, 734.
[377] T. Numata and S. Oae, *Bull. Chem. Soc. Japan*, 1972, **45**, 2794.
[378] M. Mikolajczyk and A. Zatorski, *Synthesis*, 1973, 669.
[379] B. B. Jarvis, S. D. Dutkey, and H. L. Ammon, *J. Amer. Chem. Soc.*, 1972, **94**, 2136.
[380] N. K. Chapovskaya, L. K. Khyazeva, and N. S. Zefirov, *Zhur. org. Khim.*, 1973, **9**, 1014.
[381] I. Kuwajima and Y. Fukuda, *Tetrahedron Letters*, 1973, 327.

often in competition, but thallium enolates offer no particular advantages in attempts to promote the tendency towards *C*-alkylation.[382] Dianions PhSO-$\bar{C}$HCO$\bar{C}$HR, prepared by successive treatment with NaH and Bu^{n}Li, are alkylated specifically at the γ-carbon,[383] and may be used in aldol reactions, in Michael addition reactions, and in a synthesis of 1,4-dicarbonyl compounds by reaction with oxirans.[383b] Racemic and *meso*-MeSOCH$_2$CO-(CH$_2$)$_n$COCH$_2$SOMe have been used (n=8) in a synthesis of octadeca-1,17-diene-5,14-dione, symmetrical di-alkylation with allyl bromide being followed by removal of the methylsulphinyl groups.[384] π-Allyl-palladium complexes may be alkylated by MeSOCH$_2$CO$_2$Me and other active-methylene compounds in the presence of bis(diphenyl)phosphinoethane, pyrolysis of the adducts (62; *cis–trans* mixture) giving conjugated dienes.[385]



(62)

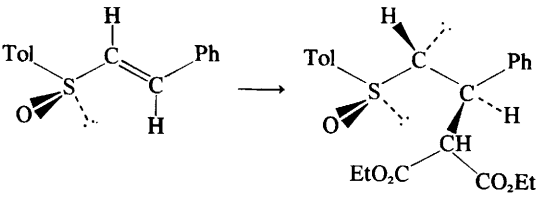
Cyclization of arylethyl methylsulphinylmethyl ketones in the presence of TFA gives a 1-methylthiotetralin-2-one through Pummerer rearrangement of the initially formed trifluoroacetoxysulphonium salt;[386] a second example of the use of β-keto-sulphoxides in synthesis of cyclic compounds concerns condensation with 2,4,5-triamino-pyrimidines to give 6-substituted pteridines.[387]

β-Hydroxyalkyl sulphoxides[388] can exist in diastereoisomeric forms, and *X*-ray analysis has been employed to define the absolute configuration of (*R*,*S*)-*threo*-2-hydroxy-2-phenyl-2-(2,4-dimethoxyphenyl)ethyl methyl sulphoxide.[388b]

Unsaturated Sulphoxides.—Addition of an alkynyl-lithium to an organoborane R$_3$B gives (R$^1_3$B$\bar{C}$≡CR^2)Li$^+$, which with methanesulphinyl chloride gives an unstable vinyl sulphoxide R$^1_2$BCR^1=CR^{2}SOMe, which gives the alkyne R^{1}C≡CR^2, the net result being the anti-Markownikov reductive alkynylation of an alkene, since R$_3$B is prepared by hydroboration of an alkene.[389]

[382] J. Hooz and J. Smith, *J. Org. Chem.*, 1972, **37**, 4200.
[383] (*a*) I. Kuwajima and H. Iwasawa, *Tetrahedron Letters*, 1974, 107; (*b*) P. A. Grieco and C. S. Pogonowski, *J. Org. Chem.*, 1974, **39**, 732.
[384] Y. Yamamoto and H. Nozaki, *Bull. Chem. Soc. Japan*, 1972, **45**, 1167.
[385] B. M. Trost and T. J. Fullerton, *J. Amer. Chem. Soc.*, 1973, **95**, 292.
[386] Y. Oikawa and O. Yonemitsu, *Tetrahedron Letters*, 1972, 3393.
[387] A. Rosowsky and K. K. N. Chen, *J. Org. Chem.*, 1973, **38**, 2073.
[388] (*a*) H. Fillion and A. Boucherle, *Bull. Soc. chim. France*, 1972, 2699; (*b*) H. Fillion and D. Tranqui, *Bull. Soc. chim. France*, 1974, 484.
[389] M. Naruse, K. Utimoto, and H. Nozaki, *Tetrahedron Letters*, 1973, 1847.

Substantial applications in synthesis have been established for (*R*)-(+)-*trans*-styryl *p*-tolyl sulphoxide (63), which gives (64) on Michael reaction with diethyl malonate on the basis that the most stable conformation of the α-sulphinyl carbanion has the lone pair on carbon *trans* to sulphinyl oxygen in a polar solvent. The addition of a proton to (64) gives as the major (51%)



(63) (64)

product the (*R*,*R*)-diastereoisomer,[390a] formed under kinetic control. Addition of methoxide using NaOMe–MeOH under reflux during 37 h (thermodynamic control) gives the corresponding diastereoisomer (64; OMe in place of malonate residue) as *minor* product (28%).[390b] A further example of asymmetric induction by a chiral sulphinyl group is provided by the addition of hypobromous acid or BrOMe to (63), resulting in diastereoisomer [64; Br in place of α-H, H in place of lone pair on C; OH in place of β-H, H in place of $CH(CO_2Et)_2$] as major product (9:1 in comparison with reversed configurations at α- and β-carbons).[390c] Reductive debromination of the HOBr adduct ($NaBH_4$–$CoCl_2,6H_2O$–MeOH) gives (*S*)-2-hydroxy-2-phenylethyl *p*-tolyl-(R)-sulphoxide.[390c]

Phenyl allyl sulphoxide gives a sulphoxide-stabilized anion $PhSO\bar{C}H$-$CH{=}CH_2$ with $LiPr^i_2N$, which can be alkylated with an alkyl iodide;[391] the reagent is effectively a synthon for the vinyl anion $\bar{C}H{=}CHCH_2OH$, treatment of the alkylated reagent with $(MeO)_3P$ in MeOH giving trisubstituted allyl alcohols stereoselectively (*e.g.*[391b] $PhSOCHRCMe{=}CH_2$ gives $RCH{=}CMeCH_2OH$ as a *cis–trans*-mixture, in which the *trans*-isomer predominates).

Irradiation of methyl styryl sulphoxide or the corresponding sulphide in alcohols or AcOH gives addition products $PhCH(OR)CH_2SOMe$.[392]

A detailed study of the mechanism of the allyl sulphoxide–sulphenate rearrangement and its uses in synthesis has been reported. Rates of steroidal allyl sulphoxide rearrangements are influenced by chirality at sulphur,[393] and configurational aspects established for compounds of this

[390] (*a*) G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, *Tetrahedron Letters*, 1973, 323; (*b*) G. Tsuchihashi, S. Mitamura, and K. Ogura, *ibid.*, 1973, 2469; (*c*) *ibid.*, 1974, 455.

[391] D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, (*a*) *Tetrahedron Letters*, 1973, 1385; (*b*) *ibid.*, p. 1389.

[392] N. Miyamoto, K. Urimoto, and H. Nozaki, *Tetrahedron Letters*, 1972, 2895; N. Miyamoto and H. Nozaki, *Tetrahedron*, 1973, **29**, 3819.

[393] D. N. Jones, J. Blenkinsopp, A. C. F. Edmonds, E. Helmy, and R. J. K. Taylor, *J.C.S. Perkin I*, 1973, 2602.

series of known absolute configuration reveal these rearrangements to be suprafacial with respect to the allyl system.[393] Uses in synthesis include a stereospecific trisubstituted alkene synthesis, shown for racemic (*E*)-nuciferol [$ArSOCHRCMe{=}CH_2 \rightarrow ArSOCH_2CMe{=}CHR$ (R = H, Ar = *p*-tolyl-$CHMeCH_2CH_2$)],[394] and in the synthesis of hasubanan alkaloid analogues, starting with a Diels–Alder addition with 1-phenylsulphinylbutadiene to form a 3-phenylsulphinylcyclohexene, which is then subjected to rearrangement and hydrolysis to give the allyl alcohol.[395] γ-Chloroallyl sulphoxides also rearrange rapidly,[396] the resulting α-chloroalkyl alkane- or benzene-sulphenate losing the corresponding sulphenyl chloride to give a vinyl ketone. Rearrangement of allyl sulphoxides in the presence of trimethyl phosphite gives cleavage products from the sulphenate, consistent with the operation of a general Michaelis-Arbuzov reaction.[397] The unsaturated 4-hydroxyalkenyl sulphoxide $PhCH(OH)CH{=}CHCH_2SOBu^t$ (*cis*-isomer) undergoes cleavage of the t-butyl group during cyclization with *N*-chlorosuccinimide to a sulphinate, and this gives SO_2 and *trans*-1-phenylbuta-1,3-diene through a $_\pi4_s + _\pi2_s$ cycloreversion.[398] A two-step process is not precluded by the results. This diene synthesis has a simpler use in synthesis related to it;[399] β-hydroxy-sulphides $R^1SOCHR^2CR^3R^4OH$ give alkenes $R^2CH{=}CR^3R^4$ on treatment with *N*-bromo- or -chloro-succinimide or SO_2Cl_2, and since β-hydroxy-sulphoxides are obtained from aldehydes or ketones, the overall process is analogous to the Wittig alkene synthesis.

Sulphoxides and Selenoxides in Alkene Synthesis.—Controlled introduction of unsaturation into aliphatic systems under mild conditions by way of sulphoxides is illustrated[400] for carbonyl compounds; an aliphatic ester added to one equivalent of lithium *N*-cyclohexyl-*N*-isopropylamide in THF, to which is added dimethyl disulphide, gives better than 80% yields of α-methylthio-ester. Oxidation ($NaIO_4$) to the sulphoxide, followed by heating at 120 °C or in refluxing toluene, gives the αβ-unsaturated ester. Alkylation of ketone and carboxylate enolates with $PhCH_2SCH_2Br$, followed by oxidation and pyrolysis, offers a route to α-methylene derivatives.[401]

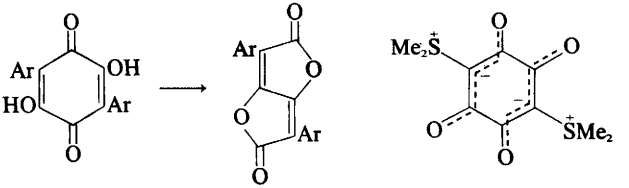
The fact that selenoxides are converted into alkenes under much milder conditions than the corresponding sulphoxides has stimulated several workers to study methods for the introduction of a suitable selenium grouping into various aliphatic substrates. Reduction of diphenyl diselenide

[394] P. A. Grieco, *J.C.S. Chem. Comm.*, 1972, 702; P. A. Grieco and R. S. Finkelhor, *J. Org. Chem.*, 1973, **38**, 2245.
[395] D. A. Evans, C. A. Bryan, and C. L. Sims, *J. Amer. Chem. Soc.*, 1972, **94**, 2891.
[396] P. T. Lansbury and J. E. Rhodes, *J.C.S. Chem. Comm.*, 1974, 21.
[397] D. A. Evans and G. C. Andrews, *J. Amer. Chem. Soc.*, 1972, **94**, 3673.
[398] F. Jung, M. Molin, R. van den Elzen, and T. Durst, *J. Amer. Chem. Soc.*, 1974, **96**, 935.
[399] F. Jung, N. K. Sharma, and T. Durst, *J. Amer. Chem. Soc.*, 1973, **95**, 3420.
[400] B. M. Trost and T. N. Salzmann, *J. Amer. Chem. Soc.*, 1973, **95**, 6840.
[401] H. J. Reich and J. M. Renga, *J.C.S. Chem. Comm.*, 1974, 135.

with $NaBH_4$ in EtOH gives PhSeH, which on reaction with oxirans[402b] gives β-hydroxyalkyl phenyl selenides, oxidation by H_2O_2 and standing at room temperature during 10 h giving the allylic alcohol. α-Methylene-γ-butyro- and -δ-valero-lactones may be prepared efficiently from α-methyl analogues *via* α-phenylseleno-derivatives.[404] Benzeneselenenyl bromide PhSeBr has been used[402c,d,403a,405] for α-phenylselenenylation of ketones and for electrophilic addition to alkenes.[402d] The alkene adducts solvolyse readily in AcOH or alcohols, oxidation giving allylic acetates or ethers in high yield.[402d] Benzeneselenenyl trifluoroacetate adds to alkenes and alkynes[403b] (*e.g.* PhC≡CH gives $CF_3CO_2CPh{=}CHSePh \rightarrow PhCOCH_2SePh$) while PhSeBr adds to an alkene in the presence of silver trifluoroacetate at low temperatures to give the corresponding trifluoroacetoxy-adduct, which on treatment with $NaHCO_3$ gives β-hydroxy-selenides, which give allylic alcohols[402b,405b] on oxidation followed by elimination of PhSeOH.

The *syn*-nature of the selenoxide elimination has been proved,[402a] and the propensity of selenoxides to form hydrates, thus slowing down the elimination, has been confirmed through $H_2{}^{18}O$ incorporation during spontaneous elimination of PhSeOH from an allylic selenoxide.[402a]

Applications of Dimethyl Sulphoxide and other Sulphoxides as Oxidants.—Dimethyl sulphoxide, in combination with Ac_2O, P_2O_5, DCCI, and other reagents (Volume 1, p. 82; Volume 2, p. 53), offers useful selectivity in the oxidation of primary or secondary alcohol functions in sensitive molecules, and a recent example is the oxidation of the 3-hydroxy-group in a 1,2,5,6-*O*-protected D-mannitol, without epimerization, by DMSO–Ac_2O.[406] 2,5-Dihydroxybenzo-1,4-quinones give ring-contracted di-lactones if the 3- and 6-positions are also substituted (65)→(66), but sulphonium ylide (67) is formed from the unsubstituted dihydroxyquinone, with DMSO–Ac_2O.[407] αβ-Elimination accompanies oxidation of partially



(65) (66) (67)

[402] (*a*) K. B. Sharpless, M. W. Young, and R. F. Lauer, *Tetrahedron Letters*, 1973, 1979; (*b*) K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, 1973, **95**, 2697; (*c*) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *ibid.*, p. 6137; (*d*) K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, 1974, **39**, 429.

[403] (*a*) H. J. Reich, I. L. Reich, and J. M. Renga, *J. Amer. Chem. Soc.*, 1973, **95**, 5813; (*b*) H. J. Reich, *J. Org. Chem.*, 1974, **39**, 428.

[404] P. A. Grieco and M. Miyashita, *J. Org. Chem.*, 1974, **39**, 120.

[405] D. L. J. Clive (*a*) *J.C.S. Chem. Comm.*, 1973, 695; (*b*) *ibid.*, 1974, 100; D. L. J. Clive and C. V. Denyer, *ibid.*, 1973, 253.

[406] T. B. Grindley, J. W. Bird, W. A. Szarek, and J. K. N. Jones, *Carbohydrate Res.*, 1972, **24**, 212.

[407] R. J. Wikholm and H. W. Moore, *J. Amer. Chem. Soc.*, 1972, **94**, 6152.

acetylated sugars with DMSO–SO_3–Et_3N if an acetoxy-group is suitably located with respect to the OH group undergoing oxidation.[408] A useful procedure for the conversion of styrenes into benzoylalkenes in one step employs DMSO–*N*-bromosuccinimide, addition to the double bond giving the β-bromo-α-alkyloxysulphonium cation, thence to the product PhCO-$CR{=}CR_2$.[409] Oxidation of alcohols to aldehydes and ketones with DMSO–Cl_2, *via* $Me_2\overset{+}{S}(=O)Cl\ Cl^-$, is feasible, without side-reactions, below room temperature.[266] However, the corresponding Br compound gives $MeSOCH_2OR$ with alcohols ROH,[415] through Pummerer-type rearrangement of the intermediate alkoxysulphoxonium ion. Further details have been published[410] concerning cyclic carbonate formation during DMSO–$NaHCO_3$ treatment of a γ-hydroxyalkyl toluene-*p*-sulphonate (Volume 2, p. 55).

Simple alkyl bromides are inert to DMSO even at high temperatures,[411] but are converted into the corresponding aldehydes in the presence of $AgBF_4$. In conjunction with this report, due note should be taken of a violent explosion occurring after 120 h when DMSO was heated with MeBr at 66 °C (although a previous ten operations of this leisurely preparation of trimethyloxysulphonium bromide were uneventful).[412] Dimethyl bromomethylfumarate on treatment with DMSO–$NaHCO_3$ gives the vinyl sulphide $CH_2{=}C(CO_2Me)CH(CO_2Me)CH(CO_2Me)C(CO_2Me){=}CHSMe$ rather than the expected butenolide.[413]

DMSO can be boiled under reflux for long periods largely unchanged (3.7% of volatile decomposition products after 72 h) but under air or O_2 in a sealed tube, kept just below the boiling point (189 °C) for 68 h, it is completely transformed into paraformaldehyde, dimethyl sulphide, and bis(methylthio)methane, water, and dimethyl disulphide.[414] Peroxides catalyse the decomposition, as does $MeSO_3H$.[414] The formaldehyde formed in this way can be used for *in situ* methylene acetal formation with oxidation products of alcohols and diols.[415] Reduction of DMSO with Br_2+HBr gives Me_2S, $MeSO_3H$, and paraformaldehyde, while diphenyl sulphoxide is unchanged.[416]

Methylthiomethylation of vanillin in DMSO (Volume 2, p. 51) gives more products than previously observed.[417]

Diphenyl selenoxide or Ph_2SeCl_2 in the presence of amines bring about

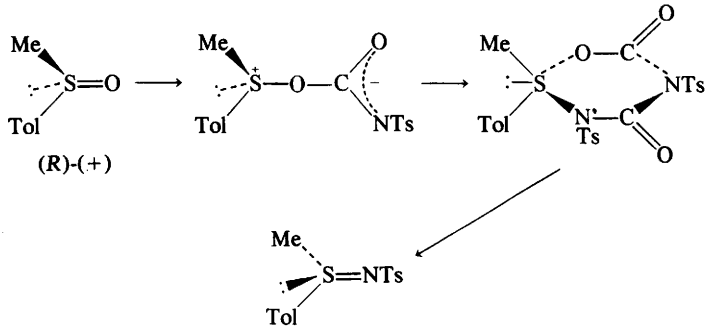
[408] D. M. Mackie and A. S. Perlin, *Carbohydrate Res.*, 1972, **24**, 67.
[409] G. A. Morrison and M. I. Qureshi, *Tetrahedron*, 1972, **28**, 4239.
[410] N. Bosworth, P. D. Magnus, and R. Moore, *J.C.S. Perkin I*, 1973, 2694.
[411] B. Ganem and R. K. Boeckman, *Tetrahedron Letters*, 1974, 917.
[412] M. G. Scaros and J. A. Serauskas, *Chem. in Britain*, 1973, **9**, 523.
[413] C. F. Garbers, A. J. H. Labuschagne, C. J. Meyer, and D. F. Schneider, *J.C.S. Perkin I*, 1973, 2016.
[414] D. L. Head and C. G. McCarty, *Tetrahedron Letters*, 1973, 1405.
[415] S. Hanessian, G. Yang-Chung, P. Lavallee, and A. G. Pernet, *J. Amer. Chem. Soc.*, 1972, **94**, 8929.
[416] T. Aida, N. Furukawa, and S. Oae, *Tetrahedron Letters*, 1973, 3853.
[417] J. Doucet and A. Robert, *Compt. rend.*, 1972, **275**, *C*, 451.

amination and oxidation of catechols to quinones;[418a] the selenoxide oxidizes acyl hydrazides to symmetrical diacylhydrazines.[418c] Aliphatic selenoxides react with 2,4-dinitrophenylhydrazine to replace the hydrazine substituent;[418b] the mechanism by which 2-phthalimidoethyl 2,4-dinitrophenyl selenide is formed in this way using 2-phthalimidoethyl methyl selenoxide will be worthy of study to provide further understanding of reactions at selenium.

7 Sulphimides and Sulphoximides

Nitrogen analogues of sulphoxides and sulphones are receiving increasing attention and merit a separate section this year. Stereochemical studies represent a major feature in recent papers.

Sulphimides.—(*S*)-(−)-2-Carboxyphenyl methyl *N*-toluene-*p*-sulphonyl sulphimide (68; 2-carboxyphenyl in place of Tol) may be prepared by the reaction of the corresponding sulphide with Chloramine-T, followed by conventional resolution, or from the optically active sulphoxide by reaction with *NN'*-bis(toluene-*p*-sulphonyl)sulphur di-imide.[419] Acid-catalysed hydrolysis gives the sulphoxide with retention of configuration, and anchimeric assistance by carboxylate is demonstrated, as for reactions of the sulphoxide itself.[419,346] (*R*)-(+)-Methyl-*p*-tolyl sulphoxide reacts with toluene-*p*-sulphonyl isocyanate to give the corresponding *N*-toluene-*p*-sulphonyl sulphimide (68) with net inversion,[420] though product and recovered sulphoxide are partly racemized. The same sulphoxide reacts with toluene-



(*S*)-(−)-(68)

p-sulphinylnitrene with retention of configuration,[421] the route to the enantiomer of (68) being considered to involve a four-membered cyclic

[418] (*a*) I. Perina, N. Bregant, and K. Balenovic, *Bull. Sci. Cons. Acad. Sci. Arts R.S.F. Yugoslav., Sect. A*, 1973, **18**, 3; (*b*) K. Balenovic, M. Molnar, Z. Ciblic, and N. Kovacevic, *ibid.*, p. 130; (*c*) K. Balenovic, R. Lazic, V. Polak, and P. Stern, *ibid.*, 1972, **17**,147.

[419] O. Bohman and S. Allenmark, *Tetrahedron Letters*, 1973, 405; *Chemica Scripta*, 1973, **4**, 202.

[420] D. C. Garwood, M. R. Jones, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95**, 1925.

[421] T. J. Maricich and V. L. Hoffmann, *Tetrahedron Letters*, 1972, 5309.

sulphurane to account for the observed stereochemistry. Partial racemization in these reactions is not unexpected in the light of the facile thermal racemization demonstrated[422] for aryl methyl sulphimides.

Reactions at sulphimide nitrogen include cleavage of the *N*-toluene-*p*-sulphonyl group from racemic (68) with conc. H_2SO_4 to give the 'free' sulphimide ArS(=NH)Me,[423] which can be converted into the *N*-chloro-derivative with *N*-chlorosuccinimide.[424] Reactions at sulphur include conversion into *N*-toluene-*p*-sulphonylsulphur di-imines by reaction of analogues of (68) with Chloramine T,[425] the corresponding sulphoximide also being formed; and the reaction with Grignard reagents to give sulphonium salts.[426]

Rearrangement of *N*-aryl dimethylsulphimides into *o*-methylthiomethylanilines in the presence of NEt_3[427] has been studied over a number of years, and recently developed into a specific *ortho*-alkylation procedure and into a versatile indole synthesis.[243]

Sulphoximides.—Sulphoxides are among the best reagents for intercepting nitrenes, and sulphoximides are thus formed. In the simplest procedure,[428] hydrazoic acid gives methyl phenyl sulphoximide PhS(O)(NH)Me with methyl phenyl sulphoxide; in more complex cases, $Pb(OAc)_4$-oxidized *N*-amino-lactams[429] or toluene-*p*-sulphonyl azide in the presence of a copper salt[430] react readily with sulphoxides. Arenesulphinamidates ArS(NTs)OR react with Grignard reagents to give sulphoximides, with inversion of configuration;[431] this is one of a number of steps in a study of reactions at chiral sulphur which has been developed to the point of establishing the first monoligostatic stereochemical cycle.

An L-glutamine antimetabolite produced by an unclassified *Streptomycete* has been identified as a tripeptide containing an L-methionine *N*-phosphonosulphoximide residue.[432]

N-Substitution reactions include methylation with $HCHO–HCO_2H$[428,431] and *N*-dimethylation with $Me_3O^+ BF_4^-$, also *N*-toluene-*p*-sulphonylation (accompanied by *S*-dealkylation).[431] Conversion into sulphoxides is brought about with nitrous acid, in high yield and with 99% retention,[431] or with S or

[422] N. Furukawa, K. Harada, and S. Oae, *Tetrahedron Letters*, 1972, 1377.
[423] N. Furukawa, T. Omata, T. Yoshimura, T. Aida, and S. Oae, *Tetrahedron Letters*, 1972, 1619.
[424] N. Furukawa, T. Yoshimura, and S. Oae, *Tetrahedron Letters*, 1973, 2113.
[425] N. Furukawa, T. Omata, and S. Oae, *J.C.S. Chem. Comm.*, 1973, 590.
[426] S. Oae, T. Yoshimura, and N. Furukawa, *Bull. Chem. Soc. Japan*, 1972, **45**, 2019.
[427] P. Claus and W. Rieder, *Monatsh.*, 1972, **103**, 1163.
[428] C. R. Johnson, J. R. Shanklin, and R. A. Kirchhoff, *J. Amer. Chem. Soc.*, 1973, **95**, 6462.
[429] D. J. Anderson, D. C. Horwell, E. Stanton, T. L. Gilchrist, and C. W. Rees, *J.C.S. Perkin I*, 1972, 1317.
[430] C. R. Johnson, R. A. Kirchhoff, R. J. Reischer, and G. F. Katekar, *J. Amer. Chem. Soc.*, 1973, **95**, 4287.
[431] T. R. Williams, A. Nudelman, R. E. Booms, and D. J. Cram, *J. Amer. Chem. Soc.*, 1972, **94**, 4684.
[432] D. L. Pruess, J. P. Scannell, H. A. Ax, M. Kellett, F. Weiss, T. C. Demny, and A. Stempel, *J. Antibiotics*, 1973, **26**, 261.

PhSSPh with retention,[433] or photochemically.[429] Methyl phenyl *N*-methylsulphoximide gives adducts with ketones after conversion into its carbanion, from which either tertiary alcohols are obtained by Al–Hg reduction under neutral conditions, or alkenes by reduction in aqueous acid, thus providing an alternative to the Wittig methylenation reaction.[428] Oxosulphonium ylides formed by *N*-dimethylation followed by carbanion formation with NaH are useful as alkylidene-transfer reagents.[434] Uses of sulphoximides in heterocyclic synthesis[435,436] have been reported; methyl phenyl sulphoximide reacts through N with ethoxymethylene malonate esters.[436]

8 Sulphones

Preparations.—Oxidation of sulphoxides to sulphones by O_2 in the presence of soluble iridium or rhodium catalysts,[437] and by hydroperoxides in the presence of base,[438] has been demonstrated. The use of Br_2–OAc^- is advocated as a useful alternative to the commonly used H_2O_2 procedure for the oxidation of sulphoxides to sulphones, involving a bromosulphonium salt intermediate.[439] Two new syntheses of [^{16}O, ^{18}O]sulphones starting from a chiral [^{16}O]sulphoxide have been established,[440] one using (dichloro-iodo)-benzene in $H_2{}^{18}O$ in the presence of $AgNO_3$, the other involving conversion into the ethoxysulphonium salt with Et_3O^+ BF_4^- followed by hydrolysis with $Na^{18}OD$–$D_2{}^{18}O$ in dioxan. Since the latter route involves a hydrolysis step known to proceed with inversion of configuration, and leads to the enantiomer of the sulphone formed by the $PhICl_2$ route, the use of (dichloro-iodo)benzene as oxidant for sulphoxides is thereby shown to proceed with inversion.[440]

Oxidation of sulphides with H_2O_2 to sulphones is catalysed by $ZrCl_4$ or $Zr(NO_3)_4$,[441] while trichloroisocyanuric acid converts methionine residues in peptides into the sulphone (though with some destruction of other readily oxidized amino-acid residues).[442]

Sulphone syntheses based upon sulphinic acids include addition to activated alkenes,[443a] condensation of salts RSO_2^- Na^+ with Mannich bases[443b] or with an aldehyde and a urea or a thiourea in a Mannich-type reaction,[444] and reaction with a diazoalkane;[445] benzhydryl *p*-tolyl sulphone is formed

[433] S. Oae, Y. Tsuchida, and N. Furukawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 648.
[434] C. R. Johnson and E. R. Janiga, *J. Amer. Chem. Soc.*, 1973, **95**, 7692.
[435] T. R. Williams and D. J. Cram, *J. Org. Chem.*, 1973, **38**, 20.
[436] A. C. Barnes, P. D. Kennewell, and J. B. Taylor, *J.C.S. Chem. Comm.*, 1973, 776.
[437] H. B. Henbest and J. Trocha-Grimshaw, *J.C.S. Perkin I*, 1974, 607.
[438] Y. Ogata and S. Suyama, *J.C.S. Perkin II*, 1973, 755.
[439] B. G. Cox and A. Gibson, *J.C.S. Perkin II*, 1973, 1355.
[440] R. Annunziata, M. Cinquini, and S. Colonna, *J.C.S. Perkin I*, 1972, 2057.
[441] N. W. Connon, *Org. Chem. Bull.*, 1972, **44**, 1.
[442] M. Z. Atassi, *Tetrahedron Letters*, 1973, 4893.
[443] P. Messinger, *Arch. Pharm.*, 1973, **306**, (*a*) p. 458; (*b*) p. 603.
[444] H. Meijer, R. M. Tel, J. Strating, and J. B. F. N. Engberts, *Rec. Trav. chim.*, 1973, **92**, 72.
[445] M. Kobayashi, H. Minato, and H. Fukuda, *Bull. Chem. Soc. Japan*, 1973, **46**, 1266.

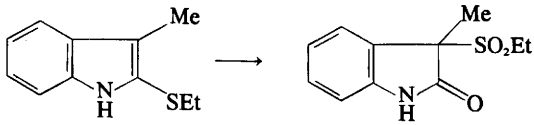
from toluene-*p*-sulphinic acid and diphenyldiazomethane in a non-polar solvent, but the same reactants give benzhydryl toluene-*p*-sulphinate in a polar medium.[445] α-Halogeno-ketones MeOCHXCOR (X=Cl or Br) react with sulphinate salts to give sulphones by nucleophilic substitution of the halogen; the thiolsulphonate $R'SO_2SR'$ also formed in this reaction derives from the sulphinate ester R'SOOCH(OMe)COR formed by *O*-alkylation of the sulphinate anion.[446]

Reduction of Sulphones.—Reduction of sulphones to sulphides is not an easy practical proposition, but di-isobutylaluminium hydride is shown to be effective.[447]

Cleavage and Rearrangement of Sulphones.—Sulphonyl radicals formed by cleavage of sulphones and sulphonamides in toluene solution over Na have been studied.[448] Methyl heptafluoro-n-propyl sulphone rather remarkably undergoes hydrolysis in dilute aqueous NaOH at 100 °C to give $MeSO_3H$ and $CF_3CF_2CHF_2$.[449]

Aryl ethers $ArOCH_2C{\equiv}CCH_2SO_2Ph$ have been studied from the points of view of thermal isomerization and *ortho*-Claisen rearrangement.[450] Smiles rearrangement of diaryl sulphones continues to provide projects for study, and trifluoromethyl-substituted phenyl mesityl sulphones provide a representative example, metallation with BuLi in the *ortho*-position of the trifluoromethylphenyl group initiating rearrangement to the sulphonic acid.[451] The intervention of benzyne in the rearrangement of t-butyl phenyl sulphone with Bu^nLi, giving *o*-(*o*-t-butylphenyl)benzenesulphinic acid, has been discussed.[452]

A novel oxidative rearrangement involving the sulphonyl group has been reported for the 2-indolyl sulphide (69), which gives the sulphoxide with 1 mole of H_2O_2, but the rearranged sulphone (70) together with the expected



(69) (70)

2-indolyl sulphone with 3 moles of H_2O_2 in AcOH.[453] There is precedent for comparable 1,2-migration of a methoxycarbonyl group in oxidative reactions of indoles.[454]

[446] K. Schank and A. Weber, *Chem. Ber.*, 1972, **105**, 2188.
[447] J. N. Gardner, S. Kaiser, A. Krubiner, and H. Lucas, *Canad. J. Chem.*, 1973, **51**, 1419.
[448] H. Stetter and K. A. Lehmann, *Annalen*, 1973, 499.
[449] R. N. Haszeldine, R. B. Rigby, and A. E. Tipping, *J.C.S. Perkin I*, 1973, 676.
[450] K. C. Majumdar and B. S. Thyagarajan, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 93.
[451] V. N. Drozd and T. R. Saks, *Zhur. org. Khim.*, 1973, **9**, 2544.
[452] F. M. Stoyanovich, R. G. Karpenko, G. I. Gorushkina, and Ya. L. Goldfarb, *Tetrahedron*, 1972, **28**, 5017.
[453] T. Hino, H. Yamaguchi, and M. Nakagawa, *J.C.S. Chem. Comm.*, 1972, 473.
[454] R. M. Acheson, *Accounts Chem. Res.*, 1971, **4**, 177.

Ring Substitution of Aryl Sulphones.—The influence of the sulphonyl group on reactions of substituted phenyl sulphones has been studied in relation to nucleophilic substitution of *p*-halogenophenyl aryl[455] or trifluoromethyl aryl sulphones,[456] by phenoxide anions and other species.

α-Halogeno-sulphones.—The reaction of dialkyl sulphones with CCl_4 in the presence of KOH results in a haloform reaction with methyl sulphones, and higher homologues unexpectedly give αβ-unsaturated sulphonic acids, *via* *gem*-α-dichloroalkyl sulphones.[457] An α-chloro-episulphone intermediate is formed first, dehydrochlorination followed by ring-opening giving the product. *gem*-α-Dichlorination is preferred to αα′-dichlorination.[458] The suspected intermediate in the rearrangement of benzhydryl benzyl sulphone with CCl_4–KOH, the α-chlorobenzhydryl derivative, has been synthesized unambiguously from the sulphide, treatment with *N*-chlorosuccinimide giving an unstable α-chlorobenzhydryl sulphide [gives $Ph_2C(SCH_2Ph)_2$ above 0 °C], which gives the α-chloro-sulphone by *m*-chloroperbenzoic acid oxidation.[459] α-Lithiated sulphones give α-chloro-analogues with hexachloroethane.[472]

Further details on reactions of 5-bromo-5-methanesulphonylbicyclo-[2,2,1]hept-2-enes (Volume 2, p. 63), undergoing homolytic C—Br bond cleavage in aqueous NaOH, or in the presence of free-radical initiators, or photochemically, have been published,[460] and further work on the stereochemistry of the Ramberg–Backlund reaction, racemic $PhCHBrSO_2CHBrPh$ with Ph_3P giving *trans*-stilbene while the *meso*-diastereoisomer gives *cis*-stilbene, inversion at both centres taking place.[461] γ-Methanesulphonyl-γ-benzoylbutyronitrile gives an unstable α-halogenosulphone, which undergoes loss of the benzoyl group.[462]

Kinetics of reduction of α-halogenobenzyl phenyl sulphones by Ph_3P have been determined,[463] revealing slower reaction of iodides compared with bromides. Another surprising property, reaction with EtMgBr of a chloromethyl aryl sulphone to give $ArSO_2CHClMgBr$, which resists α-elimination and is thermally stable, taking part in a number of simple Grignard reactions, has been reported.[464]

Other α-Functional Sulphones.—Nucleophilic displacement of halogen from α-halogenosulphones has long been known to be a sluggish reaction, but

[455] W. T. Reichle, *J. Org. Chem.*, 1972, **37**, 4254.
[456] K. V. Solodova, A. E. Kuznetsov, and S. M. Shein, *Zhur. org. Khim.*, 1972, **8**, 574.
[457] C. Y. Meyers and L. L. Ho, *Tetrahedron Letters*, 1972, 4319.
[458] C. Y. Meyers, L. L. Ho, G. J. McCollum, and J. Branca, *Tetrahedron Letters*, 1973, 1843.
[459] C. Y. Meyers, L. L. Ho, A. Ohno, and M. Kagami, *Tetrahedron Letters*, 1973, 4751.
[460] M. Oku and J. C. Philips, *J. Amer. Chem. Soc.*, 1973, **95**, 6495.
[461] F. G. Bordwell and B. B. Jarvis, *J. Amer. Chem. Soc.*, 1973, **95**, 3585.
[462] D. Diller and F. Bergmann, *J. Org. Chem.*, 1972, **37**, 2147.
[463] B. B. Jarvis and J. C. Saukaitis, *Tetrahedron Letters*, 1973, 709; *J. Amer. Chem. Soc.*, 1973, **95**, 7708.
[464] H. Stetter and K. Steinbeck, *Annalen*, 1972, **766**, 89.

only mild conditions are needed for displacement of trifluoromethanesulphonate from $ArSO_2CH_2OSO_2CF_3$.[465] A substantial study of α-nitrosulphones has begun,[466,467] synthesized from α-iodo-nitro-alkanes by reaction with sulphinate salts,[466] or by free-radical combination of toluene-*p*-sulphonyl iodide and a metal nitronate.[467b] Derived anion radicals have been studied,[467a] and the reaction with $NaNO_2$, giving aldoximes $RSO_2CH{=}NOH$ and furoxans.[467c]

Thermal decomposition of diazomethyl aryl sulphones gives numerous products, some derived from the sulphonylcarbene [*e.g.* 1,2,3-tris-(arylsulphonyl)cyclopropanes] and others from the arylsulphonyl radical (disulphides, thiolsulphonates, and arylsulphonylmethanesulphonates).[468] Conversion of *N*-nitrosocarbamates $ArSO_2CHRN(NO)CO_2Et$ into α-diazoalkyl sulphones is rendered more difficult if R is a space-demanding grouping.[469]

β-Keto-sulphones.—An efficient route to β-keto-sulphones involves the reaction of a sulphonyl chloride with a trimethylsilyl enol ether in the presence of CuCl.[470] The preparation and reactions of $SO_2(CH_2CHO)_2$ have been explored.[471]

α-Sulphonyl Carbanions.—Sulphones give α-lithio-, αα- and αα′-dilithio-, and trilithio-derivatives with Bu^nLi in benzene.[472] More commonly, αα′-dilithiated derivatives are formed in this way,[473—476] from which αβ-unsaturated sulphones may be formed by condensation with ketones.[475,476] Stereochemical inferences resulting from the observation that nucleophilic addition to an αβ-unsaturated sulphone gives both possible stereoisomers are that the addition is non-concerted and therefore proceeds with carbanion inversion, and that the reverse process proceeds *via* carbanion inversion rather than *syn*- and *anti*-elimination, a distinction not hitherto made.[474]

Bis(sulphonyl)methanes.—The enhanced acidity of bis(sulphonyl)methanes $(R^1SO_2)_2CHR^2$ has been related to that of cyano-analogues.[477] Both methylene protons in these compounds ($R^2{=}H$) can be substituted by

[465] K. Hovius and J. B. F. N. Engberts, *Tetrahedron Letters*, 1972, 2477.
[466] N. Kornblum, M. M. Kestner, S. D. Boyd, and L. C. Cattran, *J. Amer. Chem. Soc.*, 1973, **95**, 3356.
[467] J. J. Zeilstra and J. B. F. N. Engberts, (*a*) *Rec. Trav. chim.*, 1973, **92**, 954; (*b*) *ibid.*, 1974, **93**, 11; (*c*) *Synthesis*, 1974, 49.
[468] R. A. Abramovitch, V. Alexanian, and E. M. Smith, *J.C.S. Chem. Comm.*, 1972, 893.
[469] A. M. van Leusen, J. Strating, and D. van Leusen, *Tetrahedron Letters*, 1973, 5207.
[470] Y. Kuroki, S. Murai, N. Sonoda, and S. Tsutsumi, *Organometallic Chem. Synth.*, 1972, **1**, 565.
[471] J. E. McCormick and R. S. McElhinney, *J.C.S. Perkin I*, 1972, 1335.
[472] J. Kattenberg, E. R. de Waard, and H. O. Huisman, *Tetrahedron*, 1973, **29**, 4149.
[473] J. B. Evans and G. Marr, *J.C.S. Perkin I*, 1972, 2502.
[474] N. Bosworth and P. D. Magnus, *J.C.S. Perkin I*, 1973, 2319.
[475] V. Pascali, N. Tangari, and A. Umani-Ronchi, *J.C.S. Perkin I*, 1973, 1166.
[476] V. Pascali and A. Umani-Ronchi, *J.C.S. Chem. Comm.*, 1973, 351.
[477] F. Hibbert, *J.C.S. Perkin II*, 1973, 1289.

reaction with alkyl halides R^1SCH_2Cl,[478a] and bis-adducts $(PhSO_2)_2CHCH_2$-$CH(SO_2Ph)_2$ are formed by aldol condensation with HCHO;[479] the same product is formed with $MeOCH_2Cl$ [though an alkylated bis(sulphonyl)-methane gives the methoxymethyl derivative[478b]] and with *N*-chloromethyl-phthalimide.[479] Additional derivatives of $(PhSO_2)_2CH_2$ include enamines, Mannich bases, alkanols, and alkenes.[479]

The reaction of bis(mesitylsulphonyl)methane with 3 equivalents of an arenesulphonyl azide gives the corresponding bis(sulphonyl)diazomethane, together with thiolsulphonate and hydrazone.[480] The diazomethane gives the corresponding bis(sulphonyl)carbene $(ArSO_2)_2C$: readily,[481] judging by the formation of C—H insertion products together with mesitoic acid and dimesityl disulphide; these last two products are accounted for by rearrangement of the carbene into $ArSO_2C(Ar)=SO_2$, which loses SO_2 to give the α-keto-sulphoxide *via* $ArSO_2\ddot{C}Ar$.

Electroreduction of tris(sulphonyl)methanes $(ArSO_2)_3CH$ gives bis-(sulphonyl)methanes.[482]

Unsaturated Sulphones.—Elimination by phenoxide is best represented by an *E*2cb mechanism for the conversion of 2-phenylsulphonylethyl chloride, bromide, toluene-*p*-sulphonate, and dimethylsulphonium iodide into the vinyl sulphone.[483] A rather different elimination route is represented by treatment of β-hydroxy-sulphoxides with *N*-bromosuccinimide, giving vinyl sulphones *via* β-hydroxy-bromosulphoxonium salts.[484] (±)-2,3-Bis-(phenylsulphonyl)butane suffers $PhSO_2H$ elimination with (*R*)-α-phenyl-ethylamine, giving $MeCH=CMeSO_2Ph$, incomplete reaction leaving unchanged starting material enriched in the (−)-isomer.[485] The *meso*-diastereo-isomer can be distinguished from the (±)-isomer through its inability to provide optically active material through the same procedure. Alternative routes to vinyl sulphones involve condensation reactions: piperidine-catalysed Knoevenagel condensation of benzaldehyde with bis-(ethylsulphonyl)methane gives stereospecifically rearranged (*E*)-αβ-bis-(ethylsulphonyl)styrene rather than the expected ββ-isomer;[486] a modified Horner–Wittig reaction is represented by condensation of aldehydes or ketones with $(EtO)_2POCH_2SO_2R$;[487] condensation of alkyl sulphones R^1CH_2-SO_2R^2 with CS_2 and an alkyl iodide R^3I gives $R^1C(SO_2R^2)=C(SR^3)_2$;[488]

[478] (*a*) H. Boehme and H. Russmann, *Arch. Pharm.*, 1973, **306**, 58; (*b*) H. Boehme, H. Russman, and M. Junga, *ibid.*, 1972, **305**, 931.
[479] L. A. Carpino, *J. Org. Chem.*, 1973, **38**, 2600.
[480] G. Heyes and G. Holt, *J.C.S. Perkin I*, 1973, 189.
[481] W. T. Flowers, G. Heyes, and G. Holt, *J.C.S. Perkin I*, 1973, 2438.
[482] G. Jeminet, J. G. Gourcy, and J. Simonet, *Tetrahedron Letters*, 1972, 2975.
[483] S. Oae, Y. Kadoma, and Y. Yano, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 29.
[484] H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Letters*, 1973, 2463.
[485] J. L. Greene and P. B. Shevlin, *J.C.S. Chem. Comm.*, 1972, 874; corrigendum, *ibid.*, p. 1200.
[486] A. R. Friedman and D. R. Graber, *J. Org. Chem.*, 1972, **37**, 1902.
[487] G. H. Posner and D. J. Brunelle, *J. Org. Chem.*, 1972, **37**, 3547.
[488] D. Ladurec, P. Rioult, and J. Vialle, *Bull. Soc. chim. France*, 1973, 637.

phenyldiazomethane gives an episulphide with $TolSO_2CSSPh$, the adduct giving $TolSO_2C(SPh)=CHPh$ on treatment with $(MeO)_3P$.[489]

Addition of sulphonyl iodides to allenes gives $CH_2=C(SO_2R)CH_2I$ and $CH_2=CICH_2SO_2R$ with propa-1,2-diene, but only analogues of the former adduct using phenylallene and 3-methylbuta-1,2-diene.[490] Morpholinoethylenes give β-morpholinovinyl sulphones by reaction with α-halogenomethanesulphonyl chlorides in the presence of NEt_3.[491]

The sequence $ArSO_2CH_2OR \rightarrow$ α-acyl-α-alkoxymethyl sulphone $\rightarrow ArSO_2C(OR^1)=C(OR^2)R^3$ gives a mixture of (*E*)- and (*Z*)-isomers.[492]

Di-allenic sulphones are formed by double [2,3]sigmatropic rearrangement of propargylic sulphoxylates, obtained from propargyl alcohols, *e.g.* $CH\equiv CCMe_2OH$, with SCl_2 at −70 °C.[493] A first cycle gives $Me_2C=C=CHSOOCMe_2C\equiv CH$, the second being brought about in solution in refluxing $CHCl_3$.

αβ-Unsaturated sulphones react as activated alkenes in cycloaddition reactions, giving 1- or 2-pyrrolines with diazomethane, depending on reaction conditions.[494] Methyl vinyl sulphone–cyclopentadiene adducts[460,495] are shown to be epimer mixtures.[495] H_2O_2 converts vinyl sulphones into butadienes and peroxides.[496]

Sulphones in Synthesis.—Most applications of sulphones in synthesis are based upon the α-sulphonyl carbanion. A step in a proof by synthesis of a revised structure assignment to dehydroisolongistrobine involves condensation of a β-keto-sulphone with *o*-nitrobenzyl bromide in the presence of Bu^{t}OK, reduction by Al amalgam in water cleaving the sulphonyl function.[497] The same reductive desulphonylation method is used in a conversion of ketones into alkenes through condensation with an α-sulphonyl dicarbanion giving the vinyl sulphone,[476,498] and in a 1,5-diene synthesis involving α-allylation of an allyl sulphone.[499] Using an aliphatic ketone as a function at which a *gem*-dialkyl grouping can be constructed involves its conversion into a vinyl sulphone followed by addition of an organocuprate(I) reagent; specific β-addition takes place, Na amalgam giving the *gem*-dimethyl compound when a dimethylcuprate is used.[500]

α-Benzoyl-α-sulphonyl carbanions give cyclopropanes with α-bromoketones, in some cases, but generally give 1,4-dicarbonyl compounds,

[489] S. Holm and A. Senning, *Tetrahedron Letters*, 1973, 2389.
[490] W. E. Truce, D. L. Heuring, and G. C. Wolf, *J. Org. Chem.*, 1974, **39**, 238.
[491] P. D. Buttero and S. Maiorana, *J.C.S. Perkin I*, 1973, 2540.
[492] K. Schank, H. Hasenfratz, and A. Weber, *Chem. Ber.*, 1973, **106**, 1107.
[493] S. Braverman and D. Segev, *J. Amer. Chem. Soc.*, 1974, **96**, 1245.
[494] R. Helder, T. Doornbos, J. Strating, and B. Zwanenburg, *Tetrahedron*, 1973, **29**, 1375.
[495] J. C. Philips and M. Oku, *J. Org. Chem.*, 1972, **37**, 4479.
[496] E. N. Prilezhaeva and L. I. Shmonina, *Zhur. org. Khim.*, 1972, **8**, 548.
[497] M. A. Wuonola and R. B. Woodward, *J. Amer. Chem. Soc.*, 1973, **95**, 284.
[498] M. Julia and J. M. Paris, *Tetrahedron Letters*, 1972, 4731.
[499] M. Julia and D. Arnould, *Bull. Soc. chim. France*, 1973, 743.
[500] G. H. Posner and D. J. Brunelle, *Tetrahedron Letters*, 1973, 935.

reductive removal of the sulphonyl group being achieved with Zn.[501] Oxocyclohexanecarboxylic acids are formed through addition of α-alkynyl-α-sulphonyl carbanions to acrylic esters.[502]

Toluene-*p*-sulphonylmethyl isocyanide $TolSO_2CH_2N{=}C$, on treatment with a base, gives a reactive species with both a nucleophilic centre (α-sulphonyl carbanion) and an electrophilic centre (isocyanide carbon). The compound therefore has some potential in heterocyclic synthesis,[503] condensation with ketones giving 4-toluene-*p*-sulphonyl-oxazolines which can be converted into cyanides[503e] or into α-hydroxy-aldehydes.[503f] With suitable reagents, the isocyanide can give oxazoles,[503b] imidazoles,[503c] and thiazoles.[503d] The primary condensation product with a ketone R^1COR^2 is $R^1R^2C{=}C(SO_2Tol)NHCHO$ in aqueous work-up conditions, acid hydrolysis to the next higher homologous carboxylic acid $R^1R^2CHCO_2H$ adding a new synthesis procedure to those already available in this area.[504]

Thermal pericyclic rearrangement of an aryl allyl sulphone $ArSO_2CR^1R^2{-}CR^3{=}CR^4R^5$ at *ca.* 290 °C places the aryl substituent at the γ-position of the allylic system, SO_2 being eliminated to give $ArCR^4R^5CR^3{=}CR^1R^2$.[505] Isomerization to the vinyl sulphone can occur with t-butyl allyl sulphones on treatment with K_2CO_3 in acetone.

9 Sulphenic Acids

Preparations.—Sulphenic acids have become less elusive in recent years with growing appreciation of the factors controlling their stability. t-Butylsulphenic acid Bu^tSOH is moderately stable[510] in solution in solvents favouring hydrogen-bonding, and in general, steric factors are also important in conferring a degree of stability on these compounds.[510] Pyrolysis of sulphoxides remains the method by which an equilibrium concentration of sulphenic acids can be maintained,[506–510] though this reaction is generally performed in the presence of reagents which trap the sulphenic acid as it is

[501] B. Koutek. L. Pavlickova, and M. Soucek, *Coll. Czech. Chem. Comm.*, 1973, **38**, 3872.
[502] M. Yahimoto, N. Ishida, and Y. Kishida, *Chem. and Pharm. Bull (Japan)*, 1972, **20**, 2137.
[503] (*a*) A. M. van Leusen, G. J. M. Boerma, R. B. Halmholdt, H. Siderius, and J. Strating, *Tetrahedron Letters*, 1972, 2367; (*b*) A. M. van Leusen, B. E. Hoogenboom, and H. Siderius, *ibid.*, p. 2369; (*c*) A. M. van Leusen, and O. H. Oldenziel, *ibid.*, p. 2373; (*d*) O. H. Oldenziel and A. M. van Leusen, *ibid.*, p. 2777; (*e*) O. H. Oldenziel and A. M. van Leusen, *ibid.*, 1973, 1357; (*f*) O. H. Oldenziel and A. M. van Leusen, *ibid.*, 1974, 163, 167.
[504] U. Schollkopf and R. Schroder, *Angew. Chem. Internat. Edn.*, 1972, **11**, 311.
[505] J. B. Hendrickson and R. Bergeron, *Tetrahedron Letters*, 1973, 3609.
[506] T. S. Chou, J. R. Burgtorf, A. L. Ellis, S. R. Lammert, and S. P. Kukolja, *J. Amer. Chem. Soc.*, 1974, **96**, 1609.
[507] (*a*) I. Ager, D. H. R. Barton, G. Lucente, and P. G. Sammes, *J.C.S. Chem. Comm.*, 1972, 601; (*b*) R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes, and M. V. Taylor, *J.C.S. Perkin I*, 1973, 1182; (*c*) I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *ibid.*, p. 1187 (*d*) D. H. R. Barton, I. H. Coates, P. G. Sammes, and C. M. Cooper, *J.C.S. Chem. Comm.*, 1973, 303.
[508] (*a*) R. B. Morin, E. M. Gordon, T. McGrath, and R. Shuman, *Tetrahedron Letters*, 1973., 2159; (*b*) R. B. Morin, E. M. Gordon, and J. R. Lake, *ibid.*, p. 5213.
[509] J. A. Howard and E. Furimsky, *Canad. J. Chem.*, 1974, **52**, 555.
[510] J. R. Shelton and K. E. Davis, *Internat. J. Sulfur Chem.*, 1973, **8**, 197, 205.

formed. Most of the studies in this area have been performed with penicillin sulphoxides, and more than ten years have elapsed before it has proved possible to isolate a stable penicillin-derived sulphenic acid in crystalline form.[506] A penicillin sulphoxide ester, refluxed in EtOAc during 10 min and the solution then evaporated, gives a mixture of unchanged sulphoxide (less soluble) and sulphenic acid, characterized by i.r. bands at 1179, 1154, and 770 cm^{-1}.[506]

Reactions of Sulphenic Acids.—In continuation of previous work, penicillin sulphenic acids have been trapped with vinyl ethers and keten acetals,[507a] with thiols,[507b] alkenes, and alkynes.[507c,d] A variety of products from thermolysis of *N*-benzyloxycarbonyl-L-(*S*-t-butyl)cysteinyl-L-valine methyl ester *S*-oxide must derive from an intermediate sulphenic acid,[508b] and isothiazolones and thiazinones formed from penicillin sulphoxides are also satisfactorily accounted for on the same basis.[508a]

The t-butylsulphinyl radical has been identified in the photolysis product of di-t-butyl peroxide and t-butylsulphenic acid,[509] in toluene or isopentane at −40 to −60 °C, and the powerful anti-oxidant action of dialkyl sulphoxides on the autoxidation of hydrocarbons has been ascribed to radical-scavenging properties of the sulphenic acid produced from the sulphoxide on thermolysis.[511]

Sulphenates.—The trimethylsilyl ester of a penicillin sulphenic acid is a useful protected derivative, permitting some base-catalysed transformations to be performed elsewhere in the molecule;[512] the ester reacts with $(MeO)_3P$ to give a mixture of 4-methylthio-azetidinone and the penicillin, an important observation in relation to the synthesis of modified penicillins. Methoxymethyl phenyl sulphoxide undergoes facile Meisenheimer rearrangement into $PhSOCH_2OMe$;[513] although the sulphoxide–sulphenate conversion is normally an equilibrium lying in favour of the sulphoxide, in this case[513] the sulphenate decomposes slowly into PhSSOPh and $(MeOCH_2)_2O$, a novel sulphenate reaction, possibly involving free-radical intermediates. Benzhydryl sulphenates Ph_2CHOSR rearrange more rapidly into sulphoxides in polar solvents,[514] the trichloromethanesulphenates ($R=CCl_3$) decomposing into $PhCH_2Cl$ on long standing.

Kinetic studies of the n-butylaminolysis of *p*-nitrophenyl triphenylmethanesulphenate reveal second-order characteristics, while reaction with benzamidine is first-order, as it is with carboxylic esters.[515] S—O *versus* C—O fission has been contemplated for solvolysis of benzyl trichloromethanesulphenates, which provide the first example of C—O fission, to give $Cl_2C{=}S{=}O$.[516] Ethyl benzenesulphenate reacts with phosphites to give

[511] P. Koelewijn and H. Berger, *Rec. Trav. chim.*, 1972, **91**, 1275.
[512] T. S. Chou, *Tetrahedron Letters*, 1974, 725.
[513] T. J. Maricich and C. K. Harrington, *J. Amer. Chem. Soc.*, 1972, **94**, 5115.
[514] F. A. Abdulvaleeva, A. A. Khodak, and N. S. Zefirov, *Zhur. org. Khim.*, 1972, **8**, 433.
[515] E. Ciuffarin, L. Senatore, and L. Sagramora, *J.C.S. Perkin II*, 1973, 534.
[516] S. Braverman and D. Reisman, *Tetrahedron Letters*, 1973, 3563.

ethoxy-thiophenoxy-phosphoranes, adding to the very few compounds of this class so far known;[517] further reaction causes substitution of thiophenoxy- by ethoxy-groups.

Sulphenyl Halides.—Sulphenyl chlorides are readily available by chlorinolysis of disulphides, and this remains the most commonly used method of synthesis. Chlorinolysis of penicillin esters gives the sulphenyl chloride,[518] and a route to an azetidinone sulphenyl chloride has been devised in which the relatively unstable sulphenic acid produced by penicillin sulphoxide pyrolysis is treated with $SOCl_2$ in CCl_4 to give [43; R^2=Cl, R^3=CH(CO_2Me)CMe=CH_2].[519] Sulphenyl iodides may be important intermediates in reactions at disulphide bridges in peptides and proteins, and a report of the preparation of a stable sulphenyl iodide is notable.[520] The observation that methanesulphenyl chloride dimerizes (in SO_2 in the presence of a Lewis acid) to give $MeS\overset{+}{S}MeCl\,Cl^- \leftrightarrow MeS\overset{+}{=}SMeCl\,Cl^-$ [521] may be useful in explaining the course of certain electrophilic reactions of sulphenyl chlorides, and should stimulate a search for new reactions of aliphatic compounds of this series.

Preparations of fluorochloroalkanesulphenyl chlorides and pseudohalides[522] and pentafluorobenzenesulphenyl chloride[523] have been reported with substitution reactions (*e.g.*[523] C_6F_5SCl+AgNCO gives C_6F_5SNCO), and synthetic uses of trichloromethanesulphenyl chloride have been succinctly summarized[524] ($Cl_3CSCl+H_2O_2 \rightarrow Cl_3CSO_2Cl$ which, with H_2S, gives Cl_3C-SO_2H).

Chlorocarbonylsulphenyl chloride ClCOSCl and related compounds have uses in synthesis, of thiazol-2-ones,[525] and of alkyl chlorides[526] from the corresponding thiols. The latter procedure involves a disulphide RSSCOCl, treatment with Ph_3P giving the alkyl chloride, though some elimination accompanies the substitution reaction, and is the major reaction for cyclohexanethiol.[526] Whereas aminolysis of ClCOSCl occurs at carbonyl carbon, that of FCOSCl involves displacement of Cl from S.[527]

αα-Dichloroalkanesulphenyl chlorides formed from (phenylthio)acetamides $R_2NCOCH_2SCH_2Ph$ with SO_2Cl_2 by cleavage of the benzyl–sulphur bond[528] give products of sulphenyl chloride displacement with

[517] L. L. Chang and D. B. Denney, *J.C.S. Chem. Comm.*, 1974, 84.
[518] S. Kukolja, *J. Amer. Chem. Soc.*, 1972, **94**, 7590.
[519] S. Kukolja and S. R. Lammert, *J. Amer. Chem. Soc.*, 1972, **94**, 7169.
[520] L. Field and J. E. White, *Proc. Nat. Acad. Sci. U.S.A.*, 1973, **70**, 328.
[521] G. Capozzi, V. Lucchini, and G. Modena, *Chimica e Industria*, 1972, **54**, 41.
[522] A. Haas and W. Hinsch, *Chem.-Ztg.*, 1972, **96**, 75.
[523] R. J. Neil and M. E. Peach, *J. Fluorine Chem.*, 1972, **1**, 257.
[524] U. Schollkopf and P. Hilbert, *Annalen*, 1973, 1061.
[525] K. Grone and H. Heitzer, *Annalen*, 1973, 1018.
[526] D. L. J. Clive and C. V. Denyer, *J.C.S. Chem. Comm.*, 1972, 773.
[527] A. Haas, J. Helmbrecht, W. Klug, B. Koch, H. Reinke, and J. Sommerhof, *J. Fluorine Chem.*, 1973, **3**, 383.
[528] W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, 1972, **37**, (*a*) p. 1526; (*b*) p. 3818.

nucleophiles, but give $R_2NCOCOSCl$ on acid hydrolysis and R_2NCO-CN in liquid NH_3.[528a] Carbamoyl chlorosulphines ArNHCOCCl=S=O are formed with aqueous $NaHCO_3$.[528b] One of the simplest functional-group conversions, conversion of an aliphatic acid $RCH_2CH_2CO_2H$ into its acid chloride with thionyl chloride, can in fact be made to give the sulphenyl chloride $RCH_2CCl(SCl)COCl$ and even the β-chloro-analogue RCHCl-CCl(SCl)COCl,[529a] the latter compound also being available from the same treatment of the αβ-unsaturated acid.[529] The minor product RCH=CCl-COCl appears to have been formed by SCl_2 elimination[529b] but other possibilities appear to be more reasonable explanations.

Substitution reactions of simple sulphenyl chlorides with features of additional interest include 1,3-dithiolan formation by reaction of 1,2-disulphenyl chlorides at a methylene group α to —CHO;[530] formation of α-chloro-β-keto-sulphides from sulphenyl chlorides and adducts of phosphines with 1,2-dicarbonyl compounds;[531] free-radical substitution of saturated alkanes by C_6Cl_5SCl;[532] and synthesis of αα-dinitroalkyl sulphides by treatment of *gem*-dinitroalkanes with sulphenyl chlorides in the presence of base.[533]

Addition of sulphenyl halides to multiple bonds continues to be one of the more intensively studied addition processes, and many examples have been published in the period under review. Normal *trans*-addition of arenesulphenyl chlorides to alkenes is not shown for *cis*-anethole,[534] the first case of non-stereospecific addition, considered to involve an open carbonium ion rather than the usual episulphonium ion.[534] A broad study has been made[535] of the effects of temperature and solvent on the addition of arenesulphenyl chlorides to *cis*- and *trans*-1-phenylpropene. Further studies have been made of the dehydrochlorination which follows the addition of MeSCl to an alkene when MeSCl is present in excess;[536] *trans*-stilbene gives *erythro*-MeSCH(Ph)CH(Ph)Cl, dehydrochlorination giving a 4:1 *cis–trans* mixture. Orientation of addition to unsymmetrical alkenes is generally determined by the electronic character of alkene substituents for electrophilic addition, though the initially formed adduct may isomerize [MeCH=CHCO-X+RSCl → RSCHMeCHClCOX → MeCHClCH(SR)COX].[537] Under free-radical conditions, CF_3SCl adds to methyl acrylate to give both α- and

[529] (*a*) A. J. Krubsack and T. Higa, *Tetrahedron Letters*, 1973, 125; (*b*) *ibid.*, p. 4515.
[530] C. M. Leir, *J. Org. Chem.*, 1972, **37**, 887.
[531] D. N. Harpp and P. Mathiaparanam, *J. Org. Chem.*, 1972, **37**, 1367.
[532] D. D. Tanner, N. Wada, and B. G. Brownlee, *Canad. J. Chem.*, 1973, **51**, 1870.
[533] V. I. Erashko, A. V. Sultanov, S. A. Shevelev, and A. A. Fainzilberg, *Izvest. Akad. Nauk S.S.S.R, Ser. khim.*, 1972, 1226; 1973, 350.
[534] G. H. Schmid and V. J. Nowlan, *J. Org. Chem.*, 1972, **37**, 3086.
[535] (*a*) G. H. Schmid and V. M. Csizmadia, *Canad. J. Chem.*, 1972, **50**, 2465; (*b*) G. H. Schmid, V. M. Csizmadia, V. J. Nowlan, and D. G. Garratt, *ibid.*, p. 2457.
[536] M. Oki, A. Nakamura, and K. Kobayashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 3610.
[537] H. Chartier, *Bull. Soc. chim. France*, 1972, 2887; V. Zabelaite, L. Rasteikiene, M. G. Linkova, and I. L. Knunyants, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 1589; L. Rasteikiene, T. Pranskiene, M. G. Linkova, and I. L. Knunyants, *ibid.*, p. 2322; L. Rasteikiene, T. Pranskiene, V. Zabelaite, Z. Stumbrevichute, M. G. Linkova, and I. L. Knunyants, *ibid.*, p. 2247.

β-(trifluoromethylthio)acrylic acid esters after dehydrochlorination, while addition of CF_3SH to methyl propiolate gives the β-isomer.[538] Addition of PhSCl to a vinyl sulphide gives $PhSCR^1{=}C(SR^2)R^3$ while an oxygen analogue gives the Markownikov adduct.[539] β-Keto-sulphides are formed by the addition of a sulphenyl chloride to a trimethylsilyl enol ether.[540]

Detailed studies have been made of the addition of sulphenyl halides to triple bonds, addition to ethyl but-3-ynoate giving $CH(hal){=}C(SR)CH_2CO_2$-Et by an Ad_E2 process, while ICl adds by a combination of Ad_E3 and Ad_E4 mechanisms;[541] addition to sulphonyl cyanides, giving $R^1SO_2CCl{=}NSR^2$, follows the expected course.[542] Kinetic studies of the additions of 2,4-dinitrobenzenesulphenyl chloride to 1-phenylpropyne[543] and to phenylallene[544] [the latter giving $PhCH{=}CH(SAr)CH_2Cl$] have been reported.[544]

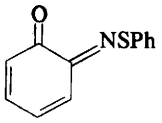
Corresponding studies of the addition of phenylselenenyl halides to alkenes reveal no differences with S analogues.[545] However, higher valency analogues, *e.g.* $PhSeBr_3$ and Ph_2SeBr_2,[546] and alkoxy-analogues $PhSe(OMe)_2Br$[546] are available for study, and will be likely to provide new reactions for which comparisons with organo-sulphur chemistry will be inappropriate. Representative of a broad study of organo-tellurium compounds, $TeCl_4$ gives a low yield of Ph_2TeBr_2 by reaction with $PhN_2^+ BF_4^-$ in the presence of Zn, followed by addition of Br_2.[547]

Sulphenamides.—Though most often prepared in the most straightforward way, by aminolysis of a sulphenyl chloride, new routes are proposed from time to time. Aryl methyl sulphoxides give aryl sulphenamides $ArSNR_2$ with aminoboranes $PhB(NR_2)_2$, $B(NR^1R^2)_3$, or Ph_2BNR_2.[548] A diaryl sulphide gives a sulphenamide in some cases on reaction with an *N*-chloro-imide,[549] and diaryl disulphides give sulphenimines $ArSN{=}CMe_2$ with NH_3, $AgNO_3$, and acetone in MeOH[550] (the reaction fails with aliphatic disulphides and diaryl ketones). Aromatic *N*-formyl sulphenamides may be prepared in a few cases by *N*-formylation, but more generally from a sulphenyl chloride and

[538] J. F. Harris, *J. Org. Chem.*, 1972, **37**, 1340.
[539] M. Oki and K. Kobayashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 687.
[540] S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *J.C.S. Chem. Comm.*, 1972, 946.
[541] J. Tendil, M. Verney, and R. Vessiere, *Tetrahedron*, 1974, **30**, 579.
[542] H. Kristinsson, *Tetrahedron Letters*, 1973, 4489.
[543] T. Okuyama, K. Izawa, and T. Fueno, *J. Org. Chem.*, 1974, **39**, 351.
[544] K. Izawa, T. Okuyama, and T. Fueno, *J. Amer. Chem. Soc.*, 1973, **95**, 4090.
[545] E. G. Kataev, T. G. Mannafov, E. G. Berdnikov, and O. A. Komarovskaya, *Zhur. org. Khim.*, 1973, **9**, 1983.
[546] V. Horn and R. Paetzold, *Z. anorg. Chem.*, 1973, **398**, 173, 179, 186.
[547] A. N. Nesmeyanov, L. G. Makarova, and V. N. Vinogradova, *Izvest Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 983.
[548] R. H. Cragg, J. P. N. Husband, G. C. H. Jones, and A. F. Weston, *J. Organometallic Chem.*, 1972, **44**, C37.
[549] M. Furukawa, Y. Fujino, Y. Kojima, M. Ono, and S. Hayashi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2024.
[550] (*a*) F. A. Davis, W. A. R. Slegeir, and J. M. Kaminski, *J.C.S. Chem. Comm.*, 1972, 634; (*b*) F. A. Davis, W. A. R. Slegeir, S. Evans, A. Schwartz, D. L. Goff, and R. Palmer, *J. Org. Chem.*, 1973, **38**, 2809.

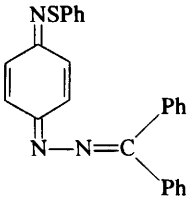
formamide.[551] Primary thioamides are sulphenylated by sulphenyl chlorides at both S and N,[552] but secondary thioamides only at S.[552]

Disulphenamides, *e.g.* $(CF_3S)_2NH$,[553] and trisulphenamides[554] are prepared easily by further sulphenylation of sulphenamides with sulphenyl chlorides, though a greater degree of N-substitution may be accompanied by decreased stability, leading to the disulphide and N_2, *via* $(PhS)_2N\cdot$ in the case of $(PhS)_3N$.[554a] Tribenzenesulphenamide reacts with phenol to give (71), thus



(71)

providing the basis of a useful *ortho*-amination procedure.[554a] Ring-expansion reactions with $(PhS)_3N$ have been illustrated (tetraphenyl-furan or -pyrrole gives tetraphenyl-pyrimidine; tetracyclone gives tetraphenyl-2-pyridone),[554b] and phenylsulphenylation (acetone *p*-nitrophenylhydrazone gives phenyl *p*-nitrophenyl sulphide) and phenylsulphenamidation [benzophenone hydrazone gives $Ph_2C{=}NSPh$ and (72)] are illustrated broadly.[554]



(72)

Sulphenamides give mono- and di-sulphenylated products with active-methylene compounds, and react with enamines to give β-keto-sulphides.[555] Sulphenimines $ArSN{=}CMe_2$ also give β-keto-sulphides by treatment with an acid chloride in the presence of a base, this interesting rearrangement involving primary cleavage into the sulphenyl chloride, followed by aryl sulphenylation of the *N*-benzoylimine to give $ArSCH{=}CMeNHCOPh$, which on hydrolysis gives $ArSCH_2COCH_3$.[556] Formation of amides by the reaction of sulphenamides with thiolesters, anhydrides, or acyl chlorides is catalysed by Ph_3P or $(EtO)_3P$, and a recent study[557] describes further development of this amide synthesis discovered some years ago.

[551] C. Christopherson and P. Carlsen, *Tetrahedron Letters*, 1973, 211.
[552] W. Walter and H. W. Meyer, *Annalen*, 1973, 462; W. Walter and C. O. Meese, *ibid.*, p. 832.
[553] A. Haas and R. Lorenz, *Chem. Ber.*, 1972, **105**, 3161.
[554] D. H. R. Barton, I. A. Blair, P. D. Magnus, and R. K. Norris, *J.C.S. Perkin I*, 1973, (*a*) p. 1031; (*b*) p. 1037.
[555] T. Kumamoto, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 1972, **45**, 866.
[556] F. A. Davis and E. B. Skibo, *J. Org. Chem.*, 1974, **39**, 807.
[557] E. A. Parfenov, V. A. Fomin, and A. M. Yurkevich, *Zhur. obshchei Khim.*, 1973, **43**, 1202.

Thermal rearrangement of arenesulphenanilides ArSNHAr' into 2- and 4-amino-diphenyl sulphides is accounted for in terms of homolysis of the S—N bond, since disproportionation products, aryl disulphides, and azobenzenes, are also formed;[558,559] 2-nitrobenzenesulphenanilides give 2-aminobenzenesulphonanilides and other products, transfer of O from N to S being intramolecular.[558] Bis-(2-nitrophenyl) disulphide gives 2-aminobenzenesulphonamides in amine solvents, and the sulphenanilide–sulphonamide pathway is thought to include the disulphide. Acid-catalysed arenesulphenanilide–aminophenyl sulphide rearrangements are considered to be intramolecular in character (in spite of the title of the paper: 'Evidence for an Intermolecular . . .').[559b]

The torsional barrier of the S—N bond in sulphenamides is ascribed in part to (p_π–d_π) bonding,[550a,560a] the extent of this contribution being very low, however, in benzenesulphenylaziridines.[560a] Trichloromethanesulphenylaziridines and CF_3 analogues show much smaller barriers to rotation and the idea is advanced[560b] that σ–π conjugation in the inversion transition state is responsible. The substantial barrier in more general cases together with the axial pseudoasymmetry of the sulphenamide grouping allow distinction to be made between *meso*- and (±)-diastereoisomers of secondary amines of the type $(PhCHMe)_2NH$ after conversion into the sulphenamide, on the basis of ^1H n.m.r. non-equivalence.[561] This topic has been studied in depth by Raban and co-workers in recent years, and a full account of torsional diastereoisomerism of *N*-arenesulphonyl-*N*-alkylsulphenamides carrying a chiral centre in the alkyl moiety has been published.[562] N.m.r. studies of chlorosulphenamides Et_2NSCl and Pr^i_2NSCl in [$^2H_8$]toluene show that the geminal methyl protons and CH_2 protons become diastereotopic on the n.m.r. time-scale in the range 0—30 °C, accounted for on the basis of restricted rotation about the S—N bond rather than halogen exchange,[563] even though halogen exchange can be established between Et_2NSCl and Et_2NSBr in solution.[563]

10 Thiocyanates and Isothiocyanates

Preparations of Thiocyanates.—Syntheses from metal thiocyanates have been described involving aryl thallium(III) acetate perchlorates and copper(II) thiocyanate,[564] and the Se analogue using KSeCN with alkyl

[558] F. A. Davis and R. P. Johnston, *J. Org. Chem.*, 1972, **37**, 854, 859.
[559] (*a*) F. A. Davis, E. R. Fretz, and C. J. Horner, *J. Org. Chem.*, 1973, **38**, 690; (*b*) F. A. Davis, C. J. Horner, E. R. Fretz, and J. F. Stackhouse, *ibid.*, p. 695.
[560] (*a*) D. Kost, W. A. Stacer, and M. Raban, *J. Amer. Chem. Soc.*, 1972, **94**, 3233; (*b*) M. Raban and D. Kost, *ibid.*, p. 3234.
[561] D. Kost and M. Raban, *J. Amer. Chem. Soc.*, 1972, **94**, 2533.
[562] M. Raban, E. H. Carlson, S. K. Lauderback, J. M. Moldowan, and F. B. Jones, *J. Amer. Chem. Soc.*, 1972, **94**, 2738.
[563] W. R. Jackson, T. G. Kee, R. Spratt, and W. B. Jennings, *Tetrahedron Letters*, 1973, 3581.
[564] S. Uemura, S. Uchida, M. Okano, and K. Ichikawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 3254.

halides.[565] Bis-(2-bromoethyl) selenide reacts abnormally with KSeCN in giving ethylene, $BrCH_2CH_2SeCN$, Se, and KBr,[565] though similar results have been recorded by earlier workers for an analogous reaction with mustard gas. A direct preparation of thiocyanates uses a sulphenyl chloride and Me_3SiCN,[566] and a new synthesis of vinyl thiocyanates from *N*-nitrosoacetylaminomethylcarbinols[567] has been described.

Uridine or 2′-deoxyuridine give the 5-thiocyanato-derivatives by substitution with thiocyanogen chloride,[568] opening a route to biologically active 5-mercaptopyrimidines through dithiothreitol reduction of the thiocyanate.

A novel ring-cleavage reaction involving mesoionic 1,3,4-thiadiazoles leads to *S*-cyanothioimidates $R^1N{=}CR^2SCN$.[569]

Electrophilic and free-radical reactions of alkenes leading to thiocyanates have been reported for thiocyanogen[570—572] and thiocyanogen chloride,[573,574] and a novel equivalent procedure[575] in which alkoxythiocyanates $R^1OCR^2R^3CH_2SCN$ are formed from an alkene and an alcohol in the presence of $(AcO)_3Tl$, to which KSCN is added 30 minutes after thallation. Thiocyanation of allylbenzenes $ArCH_2CH{=}CH_2$ gives the rearrangement product $NCSCH_2CHArCH_2SCN$ predominantly,[571] and thiocyanation of alkenes in AcOH gives mixtures of thiocyanato-, isothiocyanato-, and acetoxy-substituted alkanes,[572,574] and chloro-substituted analogues also when thiocyanogen chloride is involved.[574]

Properties of Thiocyanates.—Continuing studies of thiocyanate isomerization through gas-phase pyrolysis[576] maintain the view that a highly concerted six-centre transition state with very little charge separation is involved. Rearrangement of benzhydryl thiocyanate in solution through ion-pair return has been studied, leading to an estimate for the volume of activation.[577]

Photolysis of methyl thiocyanate or methyl isothiocyanate at wavelengths in the vacuum-u.v. causes the production of fluorescence due to thiocyanate excited radicals.[578]

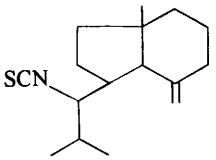
Preparations of Isothiocyanates.—Preparations from isocyanides have been studied by several groups, showing that aryl isocyanides with elemental

[565] B. Lindgren, *Acta Chem. Scand.*, 1973, **27**, 726.
[566] W. Lidy and W. Sundermeyer, *Tetrahedron Letters*, 1973, 1449.
[567] M. S. Newman and W. C. Liang, *J. Org. Chem.*, 1973, **38**, 2438.
[568] T. Nagamachi, P. F. Torrence, J. A. Waters, and B. Witkop, *J.C.S. Chem. Comm.*, 1972, 1025.
[569] R. M. Moriarty and A. Chin, *J.C.S. Chem. Comm.*, 1972, 1300.
[570] R. P. Welcher and P. F. Cutrufello, *J. Org. Chem.*, 1972, **37**, 4478.
[571] V. R. Kartazhov, E. V. Skorobogatova, and I. V. Bodrikov, *Zhur. org. Khim.*, 1973, **9**, 214, 535.
[572] L. S. Silbert, J. R. Russell, and J. S. Showell, *J. Amer. Oil Chemists' Soc.*, 1973, **50**, 415.
[573] A. L. Love and R. K. Olsen, *J. Org. Chem.*, 1972, **37**, 3431.
[574] (*a*) R. G. Guy and I. Pearson, *J.C.S. Perkin II*, 1973, 1359; (*b*) R. G. Guy and I. Pearson, *J.C.S. Perkin I*, 1973, 281.
[575] H. Mitani, T. Ando, and Y. Yukawa, *Chem. Letters*, 1972, 455.
[576] N. Barroeta, V. de Santis, and R. Mazzali, *J.C.S. Perkin II*, 1972, 769.
[577] K. R. Brower, *J. Amer. Chem. Soc.*, 1972, **94**, 5747.
[578] P. D'Amario, G. Di Stefano, M. Lenzi, and A. Mele, *J.C.S. Faraday I*, 1972, **68**, 940.

sulphur[579] or with another isothiocyanate[579] are converted into aryl isothiocyanates; aliphatic isocyanides give isoselenocyanates similarly by reaction with Se in the presence of NEt_3.[580] Conversion of an aliphatic cyanide $MeSCH{=}CHCH_2CN$ into the isothiocyanate present in radish root involves reduction to the unsaturated primary amine followed by treatment with Cl_2CS,[581] a reagent which reacts with imines lacking α-hydrogen atoms to give α-chloro-isothiocyanates, and with imines more generally (*e.g.* $R^1R^2CHCPh{=}NH$) to give αβ-unsaturated isothiocyanates (*e.g.* $R^1R^2C{=}CPhNCS$).[582] α-Halogenoacyl chlorides give α-halogenoacyl isothiocyanates on treatment with Me_3SiNCS.[583] A novel cleavage method for secondary amides, which is being studied further for its relevance in peptide chemistry, involves successive treatment with NaH, giving R^1CONR^2, and CS_2, giving $R^1COS^- + R^2NCS$.[584]

2-Isothiocyanatoacrylic esters $R^1R^2C{=}C(CO_2Et)NCS$ are formed from α-isothiocyanato-acetates and -ketones *via* oxazolidine-2-thione anions in the presence of a base,[585] and 2-siloxyalkyl or 2-siloxyphenyl isothiocyanates are formed thermally from *N*-silylated oxazolidine-2-thiones.[586]

A new naturally occurring isothiocyanate (73) has been isolated from the sponge *Axinella cannabina*.[587]



(73)

Reactions of Isothiocyanates.—Pyrolysis of but-3-enyl and 1-methylprop-2-enyl isothiocyanates gives buta-1,3-diene and HNCS in the primary reaction;[588] eventual products include the thiocyanate formed by re-addition of HNCS and pyrolysis products of the hydrocarbon.

Benzoyl isothiocyanate reacts with Grignard reagents R^1R^2CHMgX at isothiocyanate carbon, giving *N*-benzoylthioamides, from which keten *S,N*-acylals $R^1R^2C{=}C(SCOR^3)NHCOPh$ are formed by further acylation.[589]

[579] J. H. Boyer and V. T. Ramakrishnan, *J. Org. Chem.*, 1972, **37**, 1360.
[580] N. Sonoda, G. Yamamoto, and S. Tsutsumi, *Bull. Chem. Soc. Japan*, 1972, **45**, 2937.
[581] L. Brandsma, P. Vermeer, J. G. A. Kooijman, H. Boelens, and J. T. M. Maessen, *Rec. Trav. chim.*, 1972, **91**, 729.
[582] W. I. Gorbatenko, W. A. Bondar, and L. I. Samaraj, *Angew. Chem. Internat. Edn.*, 1973, **12**, 842.
[583] A. V. Fokin, A. F. Kolomiets, Y. N. Studnev, A. I. Rapkin, and V. I. Yakutin, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 1210.
[584] I. Shahak and Y. Sasson, *J. Amer. Chem. Soc.*, 1973, **95**, 3440.
[585] D. Hoppe, *Angew. Chem.*, 1973, **85**, 659, 660, 909; *Angew. Chem. Internat. Edn.*, 1973, **12**, 923.
[586] H. R. Kricheldorf, *Annalen*, 1973, 772.
[587] F. Cafieri, E. Fattorusso, S. Magno, C. Santacroce, and D. Sica, *Tetrahedron*, 1973, **29**, 4259.
[588] N. Barroeta and R. Mazzali, *J.C.S. Perkin II*, 1973, 839.
[589] W. Walter and J. Krohn, *Annalen*, 1973, 476.

Further examples of multifunctional isothiocyanates include aryl formamidinoyl-isothiocyanates $R^1_2NC(=NR^2)NCS$, which may be isomerized into 3*H*-quinazoline-4-thiones and which undergo well-known amine addition and cycloaddition reactions associated with simpler isothiocyanates;[590] and sulphonyl isothiocyanates, for which 1,3-dipolar cycloaddition to alkyl azides has been demonstrated,[591] thermolysis of the resulting thiatriazolines giving sulphonyl carbodi-imides $ArSO_2N{=}C{=}NR$.

Conversion of trityl isoselenocyanate into the isocyanide can be brought about by treatment with various tervalent phosphorus compounds.[592]

11 Sulphinic Acids

Preparations.—SO_2 Insertion into metal–carbon σ-bonds has been studied in previous years mainly from the point of view of C—S *versus* C—O bond formation, as far as structure interests are concerned, but the stereochemistry of the insertion reaction has been given more attention in the period under review. Insertion into a C—Fe bond is highly stereospecific, retention of configuration at a chiral Fe centre being established.[593,594] Tetraarylstannanes give $Ar_2Sn(O_2SAr)_2$ in liquid SO_2,[595] while benzyltrimethylstannanes[596] and other aliphatic analogues[595] vary in the number of C—Sn bonds which are inserted.

Trichloromethanesulphinic acid is available[524] by H_2S reduction of Cl_3C-SO_2Cl, prepared from Cl_3CSCl by H_2O_2 oxidation. Hydrazine reduces perfluoroalkanesulphonyl fluorides to the sulphinic acids above 30 °C.[597]

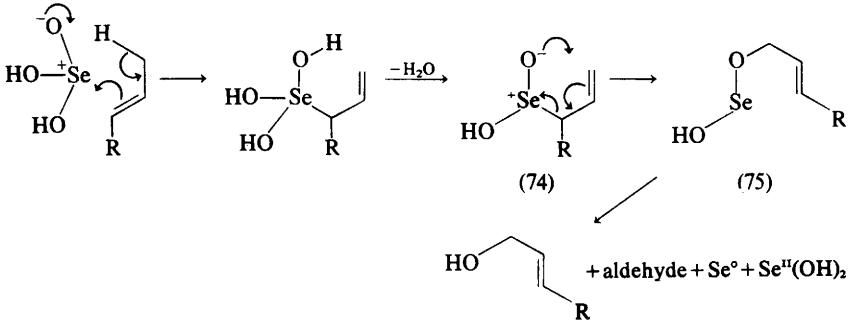
Sulphone cleavage reactions leading to sulphinic acids, in addition to the Smiles rearrangement of diaryl sulphones,[451,452] are represented in the recent literature by alkaline hydrolysis of thioxanthen-9-one 10,10-dioxides, giving benzophenone-2′-hydroxy-2-sulphinic acids,[598] and a novel sulphinate elimination shown by bis(mesitylsulphonyl)diazomethane.[480]

Standard methods of synthesis are illustrated for 3-aminopropanesulphinic acid, starting from homocystamine.[599]

Allylic oxidation of alkenes by SeO_2 can be considered to involve the hydrated form of the reagent, $SeO(OH)_2$, or acetoxy-analogues, depending on the reaction media used, prior addition to the alkene *via* an ene reaction being followed by a [2,3]sigmatropic shift[600] of the allylseleninic acid

[590] W. Abraham and G. Barnikow, *Tetrahedron*, 1973, **29**, 691.
[591] E. van Loock, J. M. Vandensavel, G. L'Abbe, and G. Smets, *J. Org. Chem.*, 1973, **38**, 2916.
[592] L. J. Strangeland, T. Austad, and J. Songstad, *Acta Chem. Scand.*, 1973, **27**, 3919.
[593] T. G. Attig and A. Wojcicki, *J. Amer. Chem. Soc.*, 1974, **96**, 262.
[594] T. C. Flood and D. L. Miles, *J. Amer. Chem. Soc.*, 1973, **95**, 6460.
[595] U. Kunzo, E. Lindner, and J. Koola, *J. Organometallic Chem.*, 1972, **40**, 327.
[596] C. J. Moore and W. Kitching, *J. Organometallic Chem.*, 1973, **59**, 225.
[597] C. Harzdorf, J. N. Meussdoerffer, H. Niederprum, and M. Wechsberg, *Annalen*, 1973, 33.
[598] O. F. Bennett, M. J. Bouchard, R. Malloy, P. Dervin, and G. Saluti, *J. Org. Chem.*, 1972, **37**, 1356.
[599] C. De Marco and A. Rinaldi, *Analyt. Biochem.*, 1973, **51**, 265.
[600] K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, 1972, **94**, 7154.

(74)→(75).[601] Evidence in support of the ene reaction is supplied by trapping intermediates as seleninolactones.[601]



Reactions of Sulphinic Acids.—Disproportionation reactions of unsymmetrical disulphides $AcNHCH_2CH_2SS(CH_2)_4SO_2Na$ into the two possible symmetrical disulphides in water at 60 °C take place to the extent of about 50%, while the sulphone and sulphonate analogues (SO_2CH_2Ph or SO_3Na in place of SO_2Na) are stable to the conditions;[602] anchimeric assistance by the sulphinate anion thus demonstrated is more than 300 times as effective in terms of rate enhancement as that of a carboxylate grouping.[602] A novel redox reaction is illustrated by treatment of *o*-nitrobenzenesulphinic acid with NaI–EtOH to give orthanilic acid (*o*-aminobenzenesulphonic acid) and *o*-nitro-iodobenzene.[603]

Pyrolysis of sodium toluene-*p*-sulphinate has been studied as part of a programme aimed at interpreting side-reactions in toluene-*p*-sulphonylhydrazone pyrolyses. Below 300 °C, only toluene and toluene-*p*-thiol are formed, but additional products formed at 320—340 °C are 4,4′-bitolyl and ditolyl sulphide and disulphide.[604] Surprisingly, toluene-*p*-sulphenic acid is claimed to have been identified in pyrolysates by mass spectrometry and g.l.c., though this 'disappeared' within 30 minutes.[604] In view of the care which has to be taken to prevent decomposition of sulphenic acids so that they may be studied (see Section 9), some doubt must be cast upon this claim. The ^{18}O content of recovered sulphinic acid and disproportionation products (thiolsulphonate and sulphonic acid), formed from arenesulphinic acids heated in $H_2{}^{18}O$–H_2O during several hours, was approximately the same;[605] a sulphinylsulphone intermediate is suggested for the disproportionation reaction.[605] The rate of O exchange of toluene-*p*-sulphinic acid is considerably faster than that of methyl phenyl sulphoxide.[605]

[601] D. Arigoni, A. Vasella, K. B. Sharpless, and H. P. Jensen, *J. Amer. Chem. Soc.*, 1973, **95**, 7917.
[602] Y. H. Khim and L. Field, *J. Org. Chem.*, 1972, **37**, 2714.
[603] A. Wagenaar and J. B. F. N. Engberts, *Tetrahedron Letters*, 1973, 4601.
[604] P. Y. Johnson, E. Koza, and R. E. Kohrman, *J. Org. Chem.*, 1973, **38**, 2967.
[605] M. Kobayashi, H. Minato, and Y. Ogi, *Bull. Chem. Soc. Japan*, 1972, **45**, 1224.

Sulphinate Esters.—A new preparation from disulphides involves chlorination in alcohol solvents at −20 °C,[606] and a further new route is announced,[607] in which *N*-alkyl-*N'*-toluene-*p*-sulphonylhydrazines $TolSO_2NHNHCH_2CH_2R$ give toluene-*p*-sulphinates $TolSOOCH_2CH_2R$ and the alkene $RCH{=}CH_2$ on oxidation with SeO_2, CrO_3, or HgO, probably *via* radical intermediates. Pyrolysis of n-butyl sulphoxylate Bu^nOSOBu^n is suggested to involve conversion into the sulphinate as first step, *en route* to SO_2, S, Bu^nOH, and but-1-ene.[608] Standard routes are illustrated in preparations of phenylmethanesulphinates and amides.[609]

The β-cyclodextrin inclusion technique is suitable for the resolution of simple alkyl alkanesulphinates.[610]

Cleavage of benzylic sulphoxides and t-butyl analogues with *N*-bromo- or -chloro-succinimides gives the benzyl or t-butyl halide and an ethyl alkane- or arene-sulphinate, the ethanol in the $CHCl_3$ used as solvent providing the nucleophile for attack at sulphur on the intermediate bromosulphoxonium cation.[611] Use of an optically active sulphoxide leads to the conclusion that the reaction is largely of S_N1 character.

Rearrangement of 2-furfuryl benzenesulphinates gives the sulphone 2-furyl-CH_2SO_2Ph but also 3-(2-methylfuryl) phenyl sulphone by way of ionic intermediates.[612] Photolysis of alkyl toluene-*p*-sulphinates gives products of alkoxyl and arenesulphinyl radicals, including return to the starting material since optically active sulphinates undergo partial racemization under irradiation.[613] A study has been made of equilibria established between aryl methanesulphinates and oxygen nucleophiles.[614]

Sulphinyl Halides.—While the general route to sulphinyl halides starts with the sulphenyl halide, alternatives have been devised based on cleavage of α-trichlorosulphoxides with Cl_2 in aqueous media[615b] (the sulphoxides being formed by perchlorination of dialkyl sulphides[615a]), and based upon sulphenic acids.[616] The nucleophilic character of the sulphur atom in a sulphenic acid is shown by conversion of the —SOH group into a sulphinyl chloride,[616] *via* an *S*-chloro-intermediate $—\overset{+}{S}(Cl)—OH$, which gives up a proton to Cl^-. This reaction has been demonstrated using the sulphenic acid

[606] I. B. Douglass, *J. Org. Chem.*, 1974, **39**, 563.
[607] O. Attanasi, L. Caglioti, and F. Gasparrini, *J.C.S. Chem. Comm.*, 1974, 138.
[608] F. Mathey and J. P. Lampin, *Tetrahedron Letters*, 1972, 3121.
[609] E. Wenschuh and H. Lankau, *Z. Chem.*, 1973, **13**, 427.
[610] M. Mikolajczyk and J. Drabowicz, *Tetrahedron Letters*, 1972, 2379.
[611] F. Jung and T. Durst, *J.C.S. Chem. Comm.*, 1974, 4.
[612] S. Braverman and T. Globerman, *Tetrahedron Letters*, 1973, 3023.
[613] M. Kobayashi, H. Minato, Y. Miyaji, T. Yoshioka, K. Tanaka, and K. Honda, *Bull. Chem. Soc. Japan*, 1972, **45**, 2817.
[614] L. Senatore, E. Ciuffarin, A. Fava, and G. Levita, *J. Amer. Chem. Soc.*, 1973, **95**, 2918.
[615] (*a*) J. S. Grossert and R. F. Langler, *J.C.S. Chem. Comm.*, 1973, 49; (*b*) J. S. Grossert, W. R. Hardstaff, and R. F. Langler, *ibid.*, p. 50.
[616] S. Kukolja and S. R. Lammert, *Angew. Chem. Internat. Edn.*, 1973, **12**, 67.

(43; R^2=OH) derived from a penicillin sulphoxide, thus leading to a mixture of diastereoisomeric sulphinyl chlorides which proved to be inseparable.[616]

Controlled hydrolysis of CF_3SF_3 gives CF_3SOF.[617]

Sulphinamides.—*N*-(Alkyl- and aryl-thio)phthalimides are converted into corresponding sulphinamides with one equivalent of *m*-chloroperbenzoic acid,[618] and are shown to be useful intermediates in the preparation of other sulphinamides, and of sulphinates. Sulphinyl hydrazodicarboxylates RSON(NHCO$_2$Et)CO$_2$Et are found among the reaction products of penicillin sulphoxides with diethyl azodicarboxylate.[619] Sulphoximides have been used as starting materials for sulphinamides, *N*-methylation (HCHO–HCO$_2$H) of methyl tolyl sulphoximide proceeding smoothly, this derivative giving a labile toluene-*p*-sulphinamide TolSONMe(Tos) with toluene-*p*-sulphonyl chloride and pyridine, *N*-tosylation being accompanied by *S*-demethylation.[431]

N-Alkoxy-benzenesulphinamides $ArSONR^1OR^2$ undergo a novel *N*- to *S*-alkoxy-group migration when $R^1 = H$, to give a sulphonimidate ester.[620] This is the first reported migration of a substituent from N to adjacent S. The eventual products (R^1=H, R^2=Me) are $ArSO_2NHMe$, $ArSO_2NH_2$, and the methyl ether ROMe when the reaction is conducted in an alcohol ROH. The reaction takes a different course in the *N*-alkyl series, indicating easier S—N bond cleavage. *N*-Alkylation of sulphonamides is effected by successive treatment with sodium in liquid NH_3, and then an alkyl halide.[621]

Racemization of sulphinamides in solution in an inert solvent involves a radical-chain mechanism.[622] Rotation barriers concerning the S—N bond in halogenosulphinamides and rapid halogen exchange in the case of the Cl and Br compounds have been estimated by variable-temperature n.m.r. methods.[623]

12 Sulphonic Acids

Preparation.—While most papers relevant to this section deal with aromatic sulphonation, there are interesting developments too in reagents for introduction of the sulphonic acid grouping, and in the chemistry of aliphatic sulphonic acids.

SO_3 Insertion studies of polarized bonds include indium trialkyls[624] and

[617] J. M. Shreeve, *Accounts Chem. Res.*, 1973, **6**, 387.
[618] D. N. Harpp and T. G. Back, *Tetrahedron Letters*, 1972, 5313.
[619] S. Terao, T. Matsuo, S. Tsushima, N. Matsumoto, T. Miyawaki, and M. Miyamoto, *J.C.S. Chem. Comm.*, 1972, 1304.
[620] T. J. Maricich, R. A. Jourdenais, and T. A. Albright, *J. Amer. Chem. Soc.*, 1973, **95**, 5831.
[621] E. Wenschuh and W. D. Riedmann, *Z. Chem.*, 1972, **12**, 29.
[622] R. E. Booms and D. J. Cram, *J. Amer. Chem. Soc.*, 1972, **94**, 5438.
[623] W. R. Jackson, T. G. Kee, and W. B. Jennings, *J.C.S. Chem. Comm.*, 1972, 1154; addendum, *ibid.*, 1973, 596.
[624] H. Olapinski and J. Weidlein, *J. Organometallic Chem.*, 1972, **35**, C53.

trimethylsilylalkynes,[625] the product obtained in the latter case ($RC{\equiv}CSO_3SiMe_3$) being obtained from the same starting material by treatment with $ClSO_2OSiMe_3$.[625]

Alkane sulphonation by $SO_2 + O_2$[626] and α-sulphonation of *N*-alkyl-β-alanines[627] illustrate conventional studies in sulphonic acid synthesis; sulphonation at C-1 in cyclopentanesulphonic acid proceeds *via* a relatively stable mixed anhydride when SO_3 is used as sulphonation reagent.[628]

Aromatic sulphonation studies have been particularly extensive in recent years, and novel substitution procedures involve *N*-alkylsulphamic acids at 150—195 °C for the sulphonation of benzene derivatives in excellent yields;[629] generally, sulphuric acid, $H_2S_2O_7$, or SO_3 are used in current studies of sulphonation of alkylbenzenes,[630—632] anisole,[633] *o*-toluidine,[634] *N*-di- and tri-methyl anisidinium cations,[635] bromobenzene,[636] biphenyl,[637] 2-methylnaphthalene,[638] series of benzenesulphonic acids,[631,639,640] and phenylalkanesulphonic acids.[641] Sodium sulphite gives three different anionic σ-complexes with 1,3,5-trinitrobenzene, the 1:1-complex, and *cis*- and *trans*-1:2-complexes.[642] Selenonation of polyalkylbenzenes with acetylselenic acid (H_2SeO_4–Ac_2O) gives isomer mixtures similar to those obtained on sulphonation.[643] *C*-2- or *C*-3-sulphonation of indoles is achieved using pyridinium-1-sulphonate in refluxing benzene.[644]

Bisulphite addition to cytosine[645] and cytidine 5′-phosphate[646,647] accounts for the accelerated deamination rates of these 4-amino-pyrimidines, optimum pH being 5 at high bisulphite concentration for maximum rates.[645] 5-Carboxypyrimidine decarboxylation is catalysed by bisulphite through

[625] P. Bourgeois, G. Merault, N. Duffaut, and R. Calas, *J. Organometallic Chem.*, 1973, **59**, 145.
[626] B. Bjellqvist, *Acta Chem. Scand.*, 1973, **27**, 3180.
[627] S. Levi, D. Gertner, and A. Zilkha, *Israel J. Chem.*, 1973, **11**, 587.
[628] E. Tempesti, L. Giuffrè, G. Sioli, M. Fornaroli, and G. Airoldi, *J.C.S. Perkin I*, 1974, 771.
[629] F. L. Scott, J. A. Barry, and W. J. Spillane, *J.C.S. Perkin I*, 1972, 2663.
[630] H. Cerfontain, A. Koeberg-Telder, and E. van Kuipers, *J.C.S. Perkin II*, 1972, 2091.
[631] H. Cerfontain, Z. R. H. Nienhuis, and W. A. Zwart-Voorspuy, *J.C.S. Perkin II*, 1972, 2087.
[632] M. I. Vinnik and L. D. Abramovich, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 833.
[633] U. Svanholm and V. D. Parker, *J.C.S. Perkin II*, 1972, 962.
[634] A. Courtin and K. Brenneisen, *Chimia (Switz.)*, 1972, **26**, 307.
[635] J. R. Blackborow, *J.C.S. Perkin II*, 1972, 2387.
[636] E. P. Kukushkin, T. I. Potapova, A. A. Spryskov, and N. I. Lytkina, *Izvest. V.U.Z., Khim. i khim. Tekhnol.*, 1972, **15**, 378.
[637] A. P. Zaraiski and O. I. Kachurin, *Zhur. org. Khim.*, 1973, **9**, 991.
[638] P. H. Gore and A. S. Siddiquei, *J.C.S. Perkin I*, 1972, 2344.
[639] A. Koeberg-Telder and H. Cerfontain, *J.C.S. Perkin II*, 1973, 633.
[640] A. Koeberg-Telder, C. Ris, and H. Cerfontain, *J.C.S. Perkin II*, 1974, 98.
[641] Z. R. H. Nienhuis, W. J. Spillane, and H. Cerfontain, *Canad. J. Chem.*, 1972, **50**, 1591; A. Koeberg-Telder, Z. R. H. Nienhuis, and H. Cerfontain, *ibid.*, 1973, **51**, 462; H. Cerfontain and Z. R. H. Schaasberg-Nienhuis, *J.C.S. Perkin II*, 1973, 1413.
[642] C. F. Bernasconi and R. G. Bergstrom, *J. Amer. Chem. Soc.*, 1973, **95**, 3603.
[643] C. Ris and H. Cerfontain, *J.C.S. Perkin II*, 1973, 2129.
[644] G. F. Smith and D. A. Taylor, *Tetrahedron*, 1973, **29**, 669.
[645] R. Shapiro, V. di Fate, and M. Welcher, *J. Amer. Chem. Soc.*, 1974, **96**, 906.
[646] M. Sono, Y. Wataya, and H. Hayatsu, *J. Amer. Chem. Soc.*, 1973, **95**, 4745.
[647] E. I. Budovskii, E. D. Sverdlov, and G. S. Monastyrskaya, *F.E.B.S. Letters*, 1972, **25**, 201.

5,6-addition to give the 6-sulphonic acid,[648] the mechanism common to all these pyrimidine reactions. Cytidine 5′-phosphate with $NaHSO_3$ and $MeONH_2$ gives a diastereoisomeric mixture of the 6-sulphonic acids, with the nitrogen function at C-4 retained in the form =NOMe.[647] A bisulphite adduct of isoalloxazine A has been isolated, carrying the sulphonate group at a ring-junction carbon (C-4a) when the fused benzene ring carries sulphonate groups, otherwise at N (N-5).[649] Aminochromes (indoline-5,6-diones) with a 3-OH group, such as adrenochrome, add bisulphite at a ring-junction carbon[650] (Volume 2, p. 81), while thiols add at an adjacent carbon to give (18);[155] sulphonation at C-2 in the pyran ring of catechin under simulated conditions for extraction of polyflavanoids from bark (aq. $NaHSO_3$–Na_2SO_3) is taken to be the general site of sulphonation in this series.[651]

Further sulphonation of tetrachlorobenzene-1,4-disulphonic acid to give the hexasulphonic acid is reported through a nucleophilic substitution pathway (Na_2SO_3–$CuSO_4$–H_2O at 100 °C for 4 h).[652] Photodesulphonation of anthraquinone-1-sulphonate involves firstly one-electron reduction and desulphonation of the anion radical,[653] while replacement of SO_3H occurs on photochlorination or photo-amination.[654] Photolysis or thermolysis of $(m\text{-}NO_2C_6H_4SO_2)_2O$ in $PhNO_2$ gives products of aromatic substitution by the arenesulphonyloxyl free radical.[655]

Methanesulphonic acid reacts as a strong acid towards polyalkylbenzenes, and as a reagent, since isomerization products and aryl methyl sulphones are produced.[656]

Sulphonates.—Novel syntheses are reported for methyl arenesulphonates (activated benzene + MeO_3SF at 100 °C)[657] and more generally,[658] employing $R^1COP(O)(OR^2)_2$ for esterification of sulphonic acids. A photo-Fries rearrangement (76) → (77) is notable.[659]

Developments of standard uses of sulphonate esters in synthesis include the use of magnesium halides $MgBr_2$[660] and MgI_2[661] for conversion into alkyl

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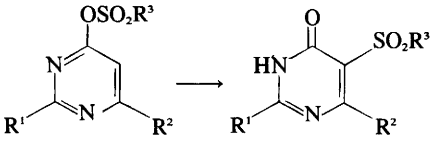

(76) (77)

halides, and the use of methanesulphonates for alkylation of malonates, by which homologation by two carbon atoms may be achieved ($MeSO_3R \rightarrow RCH_2CO_2H$).[662] Toluene-*p*-sulphonyl protection of alcohols and amines would be exploited more often, perhaps, with more convenient deprotection methods than those currently available, and solutions of alkali metals in HMPA are advocated for cleavage of sulphonates and sulphonamides under mild conditions.[663] S—O Cleavage may be observed during electrolytic reduction of toluene-*p*-sulphonates,[664] and in cases where attack at the esterifying carbon is prevented by steric or other reasons. Formaldehyde, produced with *trans*-1,5-diphenylpenta-1,4-diene (20% yield), is considered to arise in this way from $PhCH{=}CHCH_2OTs$.[664]

Nonafluorobutanesulphonates ('nonaflates') are solvolysed 1.5—2 times faster than triflates,[665a] and their vinylic esters, prepared by addition of the sulphonic acid to alkynes[665b] or through treatment of a ketone with the acid anhydride,[665c] have been employed in solvolysis studies aimed at further understanding of vinyl cations as solvolysis intermediates. Studies of vinyl triflates have continued with the same objective;[666] the picture is not so simple as it first appeared, in that vinyl solvolyses now appear to be anomalous compared with solvolyses of saturated analogues, and interpreted better as an S_N1 process with partial inversion of configuration, possibly explained by the solvation characteristics of the ion-pairs concerned.[666] Earlier concepts, *e.g.* solvolysis of triarylvinyl arenesulphonates interpreted as an S_N1 process through a 'selective' vinyl cation,[667] may need to be reassessed, though the whole issue is clearly contentious. Continuing studies of *trans*-2-halogeno-,[667a] *trans*-2-methylthio-,[668a] -arylsulphonyl-,[670] and -(*N*-aryl)methylamino-[668b,669] vinyl arenesulphonates provide a new benzil synthesis through a novel internal redox

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[670] G. Melloni and G. Modena, *J.C.S. Perkin I*, 1972, 1355.

reaction of the 2-aminovinyl compounds, also their use in indole synthesis by $AlCl_3$-catalysed cyclization, and the further development of earlier interests in solvolysis and benzothiophen synthesis with rearrangement.[670]

Hydrolysis of *p*-nitrophenyl toluene-*p*-sulphonate in Et_3N–Et_3NH^+ buffers is not subject to Et_3N catalysis, as found earlier for α-disulphones, but less sterically hindered tertiary amines are effective to some extent in accelerating the hydrolysis.[671]

A protonation study of the mixed anhydride $MeCOOSO_2CF_3$ indicates two basic sites, carbonyl oxygen or sulphonyl oxygen, depending on the acidity of the solvent.[672]

Sulphonyl Peroxides.—Aroyl arenesulphonyl peroxides, *e.g.*[673] $PhCOOOSO_2Tol$, transfer oxygen to nucleophiles, ($Ph_3P \rightarrow Ph_3PO$; $Ph_2S \rightarrow Ph_2SO$) with formation of the mixed anhydride,[673a] and react with Grignard reagents to give sulphonates and benzoic acid.[673a] ^{18}O-Labelling shows that SO_2 oxygen atoms are not transferred, but carbonyl oxygen is transferred to the extent of 42% to Ph_2S, explained by the demonstration[673b] that 'carboxy-inversion' of the peroxide to give phenyl toluene-*p*-sulphonyl carbonate can occur. Aryl benzoates and toluene-*p*-sulphonates are formed by reaction with aromatic solvents, generally in higher yield under O_2 than under N_2.[673c]

Sulphonyl Halides and Sulphenes.—Preparations of more than routine interest include the conversion of thioglycolic acid into dichloromethanesulphonyl chloride by Cl_2–conc. HCl[674] and the conversion of sulphonyl chlorides into fluorides by ion-exchange chromatography.[675]

The high reactivity of alkanesulphonyl chlorides in the presence of a tertiary amine is accounted for on the basis of elimination to the sulphene ($RCH_2SO_2Cl \rightarrow RCH{=}SO_2$) and may be exploited[676] in H—D exchange ($CH_3SO_2Cl \rightarrow CD_3SO_3H$ as major product with DABCO–D_2O). Calculations[677] to show that sulphenes and *N*-sulphonylamines resemble isocyanates rather than ketens in terms of orbital energies help to account for their tendency to undergo non-concerted addition, and their lesser relative electrophilic nature. Sulphene itself (better regarded[678] as complexed to the amine by which it is generated, $CH_2{=}SO_2 + NEt_3 \rightarrow \bar{C}H_2SO_2\overset{+}{N}Et_3$) rapidly dimerizes in the absence of nucleophiles to give $MeSO_2\bar{C}HSO_2\overset{+}{N}Et_3$, oligomerization and hydrolysis providing $MeSO_2CH_2SO_3H$ and $MeSO_2CH(SO_2CH_2SO_2Me)SO_3H$ and possibly $(MeSO_2)_2CHSO_3H$ and

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homologues.[678,679] $MeSO_2CH{=}SO_2$ gives corresponding phenyl sulphonates with PhOH.[679] Prop-2-yne-1-sulphonyl chloride may generate the allenic sulphene $CH_2{=}C{=}C{=}SO_2$ with Et_3N.[680] *N*-Methanesulphonylphthalimide gives sulphene and phthalimide at 600 °C.[695] A novel observation concerns retro-Diels–Alder conversion of sulphene cyclo-adducts on heating, the generated sulphene being trapped by a primary amine.[681] Novel evidence for the intermediacy of sulphenes in alkanesulphonyl chloride reactions is deduced from the stereoselectivity accompanying the reaction of camphor-10-sulphonyl chloride with menthylamine.[682] The small amount of sulphonamide produced directly from the sulphonyl chloride is formed without kinetic resolution.[682]

Perfluoroalkanesulphonyl fluorides give sulphonates and Me_3SiF with trimethylsilyl ethers, and sulphonamides with bis(trimethylsilyl)amines.[683]

Kinetic studies of nucleophilic substitution of arenesulphonyl chlorides involve primary amines,[684] pyridines,[684] and secondary amines.[685] Aminolysis is accelerated by added salts.[685] Thiophen-2-sulphonyl chloride reacts slower than benzenesulphonyl chloride with anilines in MeOH, indicating a less positive sulphonyl sulphur.[686] Electrochemical reduction of arenesulphonyl chlorides in MeCN–MeCl gives a mixture of methyl arenesulphonate and methyl aryl sulphide.[687] α-Toluenesulphonyl iodide $PhCH_2SO_2I$ undergoes SO_2 extrusion under u.v.-irradiation to give benzyl iodide, considered to involve homolysis of the S—I bond.[688] Toluene-*p*-sulphonyl iodide undergoes photochemical addition to styrenes,[689] sulphonyl radicals also being involved in the thermolysis of arenesulphonyl iodides in halogenobenzenes C_6H_5X (X=Cl, Br, or I), resulting in halogen substitution,[690] and in the Cu-catalysed addition of arenesulphonyl chlorides to alkenes.[691] The sulphonyl radical addition to alkenes is energetically rather unfavourable, and its reversibility is shown by the fact that 2-butenes undergo *cis–trans* isomerization in these reaction mixtures.[691]

Sulphonamides.—Cleavage of sulphonamides by alkali metals in HMPA,[663] bis-(2-methoxyethoxy)aluminium hydride,[692] and 40% H_2SO_4 in AcOH,[693] has been described.

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While most reactions performed with sulphonamides involve substituents at N, carbenoids obtained by metallation of chloromethanesulphonamides $LiCH(Cl)SO_2NR_2$ are shown[694] to undergo nucleophilic addition to aldehydes, cyclopropane ring formation with alkenes, and condensation with imines.[694] *N*-Methanesulphonylphthalimide is an excellent sulphene precursor at 600 °C,[695] trapped with $EtNH_2$; the *N*-benzenesulphonyl analogue gives only phthalimide and benzaldehyde with $EtNH_2$.[695] *N*-Alkylation of primary and secondary perfluoroalkanesulphonamides with 1,2-alkylene carbonates[696] gives *N*-hydroxyethyl derivatives; 4-(tetrachloropyridine)sulphonamides carrying an *N*-(2-hydroxyethyl) group undergo double Smiles-type rearrangement $C_5HCl_4NSO_2NHCH_2CH_2OH \rightarrow C_5HCl_4NOCH_2CH_2NH \rightarrow C_5HCl_4NNHCH_2CH_2OH$)[697] and the same mechanism has been proposed[698] for conversion of 2-chloroethyl analogues $ArSO_2NHCH_2CH_2Cl$ into 2-hydroxyethyl arylamines.

NN-Dichloromethanesulphonamide reacts with THF to give $MeSO_2NH_2$ and *N*-(2-tetrahydrofuryl)methanesulphonamide;[699] reactions of *N*-bromo-*N*-sodiobenzenesulphonamide (bromamine B) with *p*-nitrophenolate,[700] and kinetics of the reactions of *N*-chloro- and *N*-methyl-sulphonamide anions with methyl methanesulphonate[701] are further examples of studies involving *N*-halogenosulphonamides. *N*-Benzylsulphonamides give *N*-trichloromethanesulphenyl derivatives rather than 1,2-benzisothiazolines as claimed earlier, on reaction with Cl_3CSCl.[702] The acidity of the sulphonamide protons in aminobenzenesulphonamides enables selective acylation to be effected by treatment of the *N*-sodio-derivative with reactive carboxylate esters.[703] Sulphonamidyls $RSO_2\dot{N}R$, formed from biphenyl-2-sulphonamides by persulphate oxidation, cyclize readily to sultams.[704]

Uses in synthesis have been developed for sulphonamides and related compounds; *N*-methylpyrrolidine gives *N*-methyl-*N*-toluene-*p*-sulphonylpyrrolidinium perchlorate with toluene-*p*-sulphonyl chloride and $AgClO_4$, the salt being a selective tosylating agent for NH_2 in the presence of OH.[705] 2,4,6-Tri-isopropylbenzenesulphonyl hydrazide undergoes thermal decomposition more readily than benzene or toluene analogues into di-imide and the sulphinic acid, and it is therefore a more effective reagent for di-imide hydrogenation of alkenes.[706] *N*-Arenesulphonylimidazoles are useful in

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polynucleotide synthesis, bringing about coupling of protected deoxyribonucleotides at 3′-hydroxyl and 5′-phosphate groupings, for which carbonyl di-imidazole is ineffective.[707] *N*-Aryl-*N*-acyl trifluoromethanesulphonamides are acylating agents towards alcohols, and trifluoromethanesulphonylating reagents towards amines;[708a] the latter property permits their use in a synthesis of secondary amines, from primary amines or from alkyl halides *via* $R^1NHSO_2CF_3$, which is further alkylated with an alkyl halide R^3X to give R^1NHR^3 after sulphonamide cleavage.[708b,c] Trifluoromethanesulphonamides are more satisfactory in this Gabriel-type synthesis than the phenacylsulphonyl analogues advocated earlier.

Sulphonyl Cyanides and Isocyanates.—The potential in synthesis of sulphonyl-activated cyanide is shown by its ability to add to dienes under very mild conditions, giving pyridines and pyridones after *in situ* dehydrogenation and hydrolysis.[709] Addition of Cl_2, SCl_2, and S_2Cl_2 to sulphonyl cyanides gives novel adducts, $(RSO_2CCl{=}N)_2S$ with SCl_2 for example.[710] Sulphonyl isocyanates give stable 1,4-dipoles [$RSO_2N{=}C(O^-)CR_2\overset{+}{C}RNR_2$ and other canonical forms] with ββ-dialkyl-enamines.[711]

Sulphonyl Azides.—As sources of sulphonylnitrenes, these derivatives continue to receive substantial attention. Methanesulphonyl azide photolysed in hydrocarbon solvents and in alcohols gives C—H and O—H nitrene-insertion products,[712] and *N*-arylmethanesulphonamides with benzene derivatives, *via* benzaziridines.[713] Arylsulphonyl azides react thermally with pyridine and related six-membered nitrogen heterocycles to give sulphonylamino-substitution products in many cases, but mostly *N*-sulphonylimino-ylides are formed.[714] Continuing studies of reactions of toluene-*p*-sulphonyl azide with indoles (Volume 2, p. 93) deal with 1- and 3-substituted indoles,[715] and cyclohept- and cyclo-oct-indoles.[716]

Trifluoromethanesulphonyl azide ('triflyl azide') reacts with alkylamines to give alkyl azides.[717] A novel preparation of imidate esters is illustrated for cyclohexanone methyl enol ether, which with an arenesulphonyl azide gives $RC(OMe){=}NSO_2Ar$ (R = cyclopentyl) *via* a Δ^2-triazoline.[718]

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13 Disulphides, Polysulphides, and their Oxy-sulphur Analogues

Preparations of Disulphides, Hydropolysulphides, and Polysulphides.—Procedures for the conversion of thiols into disulphides are supplemented by new modifications; autoxidation of thiols catalysed by CuCl and pyridine gives a mixture of disulphide and thiolsulphinate;[719] cobalt maleonitriledithiolate in tertiary amine buffers catalyses the autoxidation only to the disulphide stage.[720] Dithiobis(thioformates)[721] and cyanogen bromide[722,723] are effective, the latter reagent giving mixed disulphides, often in major amount, from mixtures of thiols.[723] Photolysis of liquid EtSH gives H_2 + EtSSEt, while a mixture of EtSH and MeSSMe is converted into MeSH + EtSSEt + MeSSEt, the latter being found in diminishing amounts as the irradiation is prolonged.[724]

Thiols react with sulphenylthiocarbonates (from RSH + ClSCOOMe) to give disulphides,[725] the method being suitable for preparation of unsymmetrical disulphides and illustrated with cystine peptides. Treatment of a thiol with ethylenethiourea, H_2O_2, and HCl gives the mixed disulphide,[726] and penicillin disulphides (43; R^2 = 2-benzothiazolylthio) are obtained by treating a penicillin sulphoxide with the heteroaromatic thiol.[727]

Fusion of 1-naphthylamine with sulphur gives bis-(1-amino-2-naphthalene) trisulphide rather than the 4,4-disulphide as earlier claimed.[728] Allyl[729] and phenyl[753] sulphides react with S_8 to give corresponding disulphides,[729] but saturated sulphides do not react;[729] the process is believed to start through nucleophilic attack of the sulphide on S_8 to give $R\overset{+}{S}(S_8^-)R$.

Photolysis of S_2Cl_2 in alkane solvents gives alkyl chlorides, di- and poly-sulphides, HCl, and sulphur.[730] Di-2-indolyl disulphides are formed by treating 3-substituted indoles with S_2Cl_2, minor products being mono- and tri-sulphides.[731] Diethyl acetylenedicarboxylate adds to S_2Cl_2 to give the bis-(2-chlorovinyl) disulphide.[732]

Reactions involving sulphenylating agents concern sulphenyl chlorides: Cl_3CSCl treated with HBr and then KF gives CF_3SSCF_3,[733] and a sulphenyl

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[729] R. D. Baechler, J. P. Hummel, and K. Mislow, *J. Amer. Chem. Soc.*, 1973, **95**, 4442.
[730] D. D. Tanner and B. G. Brownlee, *Canad. J. Chem.*, 1973, **51**, 3366.
[731] T. Hino, T. Suzuki, S. Takeda, N. Kano, Y. Ishii, A. Sasaki, and M. Nakagawa, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2739.
[732] W. Ried and W. Ochs, *Chem. Ber.*, 1972, **105**, 1093.
[733] R. E. A. Dear and E. E. Gilbert, *Synthesis*, 1972, 310.

chloride in liquid H_2S gives the trisulphide.[734] Thiolsulphonates react with thiolate anions, *e.g.* $RC{\equiv}CSLi$, to give mixed disulphides $R^1C{\equiv}CSSR^2$,[735] and a thiocyanate reacts with a thiol to give the disulphide and CN^-, consistent with a role for CN^- or thiolate anion in the equilibration of disulphide mixtures.[736]

$NaBH_2S_3$ has sulphuration properties towards oxirans[737a,b] to give bis-(2-hydroxyethyl) disulphides, and towards aldehydes ($PhCHO \rightarrow PhCH_2SS\text{-}CH_2Ph$);[737b] cyclic disulphides are formed with $\alpha\beta$-unsaturated ketones.[737b]

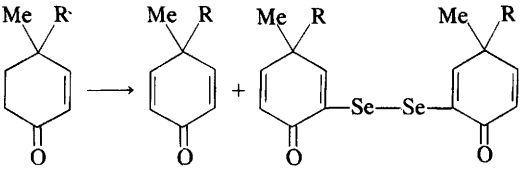
Conversion of thiocamphor into the divinyl disulphide derived from its thio-enol tautomer is brought about with *N*-bromosuccinimide or Chloramine T.[738] Thiones generally give thio-ozonides with amines or thiols, but thioadamantanone gives 2,2′-bis-(2-phenylthioadamantyl) disulphide on treatment with thiophenol.[739]

Red crystals formed from the reaction of 2-nitrothiophen with aliphatic secondary amines in the cold are tentatively assigned the structure $\{R_2NCH{=}CHCH{=}C(NO_2)\}_2S_2$;[740] a very similar cleavage reaction with amines involving a stable five-membered heteroaromatic system, 2-bromo-5-nitrothiazole, was reported some time ago.[741]

In addition to specific disulphides and related compounds discussed later in this Section, the preparation of *meso*- and *d,l*-bis(α-phenylethyl) disulphide[742] and the synthesis and n.m.r. spectrum of aryl hydropolysulphides ArS_xH ($x = 2$—7)[743] are of particular interest.

Selenium-containing by-products, usually selenate esters, often occur in SeO_2 oxidation mixtures, and in addition to the expected product (the cyclohexadienone) from (78) a 14% yield of the diselenide (79) is obtained;[744] this, on treatment with H^+, gives the selenide dienone–phenol rearrangement product (80). Further details are available concerning the selenotrisulphide formed from glutathione with sodium selenite,[745] with the suggestion that a tetrathioselenium species $Se(SR)_4$ is formed with a large excess of selenite. Ditellurides are formed in a conventional way from an aromatic Grignard reagent and Te, followed by oxidation;[746] aliphatic Grignard reagents do not react with Te.

[734] T. P. Vasileva, M. G. Linkova, O. V. Kildisheva, and I. L. Knunyants, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 2379.
[735] J. Meijer, H. E. Wijers, and L. Brandsma, *Rec. Trav. chim.*, 1972, **91**, 1423.
[736] M. M. Kayser and M. S. Gibson, *Canad. J. Chem.*, 1973, **51**, 3499.
[737] (*a*) J. M. Lalancette and A. Freche, *Canad. J. Chem.*, 1971, **49**, 4047; (*b*) J. M. Lalancette and M. Laliberte, *Tetrahedron Letters*, 1973, 1401.
[738] M. M. Campbell and D. M. Evgenios, *J.C.S. Perkin I*, 1973, 2866.
[739] M. M. Campbell and D. M. Evgenios, *J.C.S. Perkin I*, 1973, 2862.
[740] G. Guanti, C. Dell'Erba, and G. Leandri, *J.C.S. Chem. Comm.*, 1972, 1060.
[741] A. O. Illvespaa, *Helv. Chim. Acta*, 1968, **51**, 1723.
[742] E. Larsson, *Z. analyt. Chem.*, 1973, **266**, 205.
[743] H. J. Langer and J. B. Hyne, *Canad. J. Chem.*, 1973, **51**, 3403.
[744] J. N. Marx and L. R. Norman, *Tetrahedron Letters*, 1973, 2867.
[745] M. Sandholm and P. Sipponen, *Arch. Biochem. Biophys.*, 1973, **155**, 120.
[746] W. S. Haller and K. J. Irgolic, *J. Organometallic Chem.*, 1972, **38**, 97.



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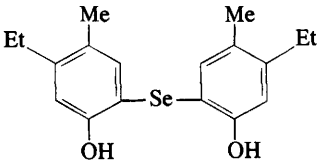

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Reactions of Disulphides.—Most of the reactions of disulphides are based upon S—S cleavage, and subsequent interaction of cleavage products with reagents, though photolysis of di-t-butyl disulphide is shown by photo-CIDNP studies[747] to give $Bu^tSS\cdot + Bu^t\cdot$ *via* the triplet excited state of the disulphide.

Reduction of disulphides to component thiols remains an important topic for study, and Ph_3P[748] or Bu^n_3P[146] are suitable in aqueous media for reduction of disulphides and for preventing autoxidation of thiols on storage. Quantitative reduction of disulphides by an insolubilized thiol[749] is an ingenious procedure likely to be much used in biochemistry.

Cleavage rates[750] of disulphides using CN^- [750,751] or OH^- [750] are poorly correlated with Hammett σ-values in the diaryl series. Cleavage by *trans*-$IrCl(CO)(PPh_3)_2$ has been reported,[752] also oxidative cleavage[753] of di-(2,4-dinitrophenyl) disulphide under mild conditions, giving 2.5% of the sulphoxide and 87% 2,4-dinitrobenzenesulphonic acid.

Reactions by which disulphides are converted into sulphides have been considerably augmented in number recently. Di-(2,4-dinitrophenyl) disulphide gives the corresponding sulphide by refluxing in alcohol solvents,[753]

[747] S. M. Rosenfeld, R. G. Lawler, and H. R. Ward, *J. Amer. Chem. Soc.*, 1972, **94**, 9255.
[748] L. E. Overman, J. Smoot, and J. D. Overman, *Synthesis*, 1974, 59.
[749] M. Gorecki and A. Patchornik, *Biochim. Biophys. Acta*, 1973, **303**, 63.
[750] D. A. R. Happer, J. W. Mitchell, and G. J. Wright, *Austral. J. Chem.*, 1973, **26**, 121.
[751] K. Tanaka, *Bull. Inst., Chem. Res., Kyoto Univ.*, 1972, **50**, 433.
[752] C. T. Lam and C. V. Senoff, *Canad. J. Chem.*, 1973, **51**, 3790.
[753] B. I. Stepanov, V. Y. Rodionov, and T. A. Chibisova, *Zhur. org. Khim.*, 1974, **10**, 79.

and this, with other properties, is considered to confirm the isomerization possibility disulphide → thiosulphoxide [RSSR → RS(S)R]. However, conversion of bis(aminomethyl)disulphide into the monosulphide by hydrogenation is thought to implicate aminomethanethiol as an intermediate.[754] Cleavage by reagents which react as sources of electrophilic halogen is illustrated by $ArSSAr' + Ar''SO_2NCl_2 \rightarrow ArSCl + Ar'S(Cl)=NSO_2Ar''$ (where Ar' is less electronegative than Ar),[755] and by $C_2F_5SeSeC_2F_5 + ClF \rightarrow C_2F_5SeF_3$.[756]

Uses of disulphides as sulphenylating agents are illustrated by reactions with 2,6-di-t-butylphenol in the presence of NaOEt, giving 4-arylthio-substitution products,[757] and with active-methylene compounds,[758] for which *gem*-disulphenylation could be achieved only in one case, an α-halogenonitrile, by reaction at elevated temperatures.[758] Disulphides react with 2-vinylbiladiene-a,c under irradiation, to give sulphides;[759] this may be relevant to the mechanism of photocatabolism of bilirubin. Disproportionation of disulphide mixtures $R^1SSR^1 + R^2SSR^2$ into the mixed disulphide gives equilibrium mixtures of composition close to the statistical value in all cases, except those where R^1 or R^2 is a tertiary alkyl group, where the operation of a steric effect (a 'cogwheel' effect) is apparent.[760]

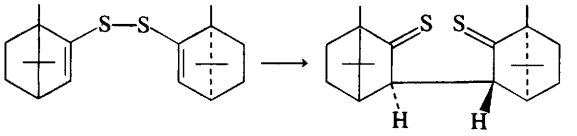
Bunte salts (thiosulphates $RSSO_3^- Na^+$) are more akin to sulphenyl derivatives than to disulphides, though S—S cleavage is usefully considered against a background of disulphide cleavage procedures. δε-Unsaturated Bunte salts give tetrahydrothiophens as major products on I_2–H_2O oxidation rather than the expected disulphides, probably *via* the sulphenyl iodide.[761] Sodium desyl thiosulphate $PhCOCHPhSSO_3^- Na^+$ readily gives monothiobenzil in aqueous alkali.[762]

Insertion reactions of disulphides by nitrenes lead to sulphenamides,[763] and 1,2-di(alkylthio)alkenes, *e.g.* $Bu^iSCH=CHSBu^i$[764] formed by the reaction of acetylene with the disulphide under pressure in the presence of KOH, consist of *cis–trans* mixtures in which the *cis*-isomer greatly predominates; (p_π–d_π) interaction is proposed as an explanation of the high thermodynamic stability of the *cis*-isomer.

The divinyl disulphide (81), formed from thiocamphor with *N*-bromosuccinimide or Chloramine T, undergoes a stereospecific Cope-type rearrangement on heating,[738] while a related disulphide undergoes a quite

[754] K. R. Henery-Logan and S. Abdou-Sabet, *J. Org. Chem.*, 1973, **38**, 916.
[755] E. S. Levchenko and L. V. Budnik, *Zhur. org. Khim.*, 1973, **9**, 212.
[756] C. D. Desjardins, C. Lau, and J. Passmore, *Inorg. Nuclear Chem. Letters*, 1973, **9**, 1037.
[757] T. Fujisawa and T. Kojima, *J. Org. Chem.*, 1973, **38**, 687.
[758] T. Fujisawa, K. Hata, and T. Kojima, *Chem. Letters*, 1973, 287.
[759] P. Manitto and D. Monti, *J.C.S. Chem. Comm.*, 1972, 1301.
[760] B. Nelander and S. Sunner, *J. Amer. Chem. Soc.*, 1972, **94**, 3576.
[761] R. D. Rieke, S. E. Bales, and L. C. Roberts, *J.C.S. Chem. Comm.*, 1972, 974.
[762] B. Saville and M. Steer, *J.C.S. Chem. Comm.*, 1972, 616.
[763] W. Ando, H. Fujii, and T. Migita, *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 143.
[764] B. A. Trofimov, N. K. Gusarova, and S. V. Amosova, *Zhur. org. Khim.*, 1972, **8**, 272.

different photo-rearrangement (82) → (83).[765] A [2,3]sigmatropic rearrangement of diallyl selenides [(—CR=CHCH$_2$Se)$_2$ to (—CH=CHCHRSe)$_2$] proceeds in two stages, one cycle giving a selenoselenoxide which can be



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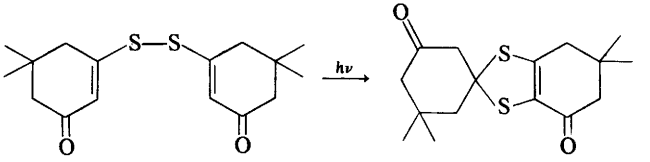


(82) (83)

intercepted by Ph_3P, providing the selenide.[232] The diallyl diselenide rearrangements follow the same course established earlier (Volume 2, p. 96) for corresponding disulphides, though, as usual, the Se compound is more reactive than its S analogue.[232]

Pulse radiolysis studies of disulphides in aqueous solutions continue,[766] the major processes $e^-_{aq} + RSSR \rightarrow (RSSR)^- \rightleftharpoons RS\cdot + RS^-$ and $H\cdot + RSSR \rightarrow R\dot{S}SHR$ being followed by absorption spectrophotometry.

An interesting observation by which a comparison of a sulphide with the corresponding disulphide can be made concerns solvolysis rates of chloromethyl methyl disulphide and the corresponding sulphide.[767] $MeSSCH_2^+$ is shown to be of lower stability than $MeSCH_2^+$ and this is probably because charge delocalization in the disulphide is precluded by the preferred conformation (dihedral angle near 90°) of the C—S—S—C grouping.[767]

Thiolsulphinates.—Dye-sensitized photo-oxidation of dialkyl disulphides[318,768] gives thiolsulphinates, as minor products.[318] Disulphide oxidation, rather than oxidation of the thiol to the sulphenic acid, is probably the origin of the thiolsulphinate formed from PhSH and O_2 in the presence of CuCl and pyridine.[719] Ring-opening of ethylene episulphoxide in MeOH gives $MeOCH_2CH_2SOSCH_2CH_2OMe$,[769] while a mixture of disulphide and thiolsulphonate is formed in AcOH owing to disproportionation of the initially formed thiolsulphinate.[769] Thiolsulphinate

[765] L. Dalgaard and S. O. Lawesson, *Tetrahedron Letters*, 1973, 4319.
[766] M. Z. Hoffman and E. Hayon, *J. Amer. Chem. Soc.*, 1972, **94**, 7950.
[767] E. Block, *J. Org. Chem.*, 1974, **39**, 734.
[768] R. W. Murray and S. L. Jindal, *J. Org. Chem.*, 1972, **37**, 3516.
[769] K. Kondo, A. Negishi, and I. Ojima, *J. Amer. Chem. Soc.*, 1972, **94**, 5786.

disproportionation in AcOH–1% H_2O is first-order and shows a three-halves-order dependence on thiolsulphinate concentration in 60% dioxan under acid or nucleophile catalysis.[770b] Sulphenic acid intermediates in thiolsulphinate cleavage[770–772] arise through protonation, giving $RS\overset{+}{S}(OH)R$, followed by nucleophilic attack, Nu^- giving RSNu + RSOH, recombination and hydrolysis to RSSR + RSO_2H, the latter reacting with RSNu to give the thiolsulphinate.[770b] Racemization of thiolsulphinates (Volume 2, p. 97) is accounted for on the basis of cleavage into sulphenic acid followed by recombination.[770a] A novel rearrangement[771b] EtSOSMe + EtSOH + $H^+ \rightarrow EtSO\overset{+}{S}(SEt)Me \rightarrow EtSOCH_2SSEt$ permits the synthesis of α-hetero-atom-substituted disulphides. Hydrolysis of sulphenates into sulphenic acids is followed by thiolsulphinate formation, from which disproportionation products are obtained;[772] disulphide hydrolysis can be depicted similarly, through initial nucleophilic substitution at S followed by cleavage into the sulphenate anion and thiolate ion.[772] Indeed, 2-nitro-4-trifluoromethylbenzenesulphenate is responsible for the blue colour of hydrolysis solutions of the corresponding disulphide,[772] a reaction which can be followed by an ingenious use of ^{19}F n.m.r.[772]

Secondary amines react with benzyl phenylmethanethiolsulphinate to give dibenzyl di- and tri-sulphides, benzaldehyde, and thiobenzamides,[773a] while enamines are arylsulphenylated by aryl benzenethiolsulphinates.[773b]

Thiolsulphonates.—Novel preparative procedures have been described, based upon alkylthiolation of sulphinate salts with *N*-alkylthiosuccinimides ($RSO_2^- \rightarrow RSO_2SR$),[774] alkylation of thiolsulphonate salts ($RSO_2S^- \rightarrow RSO_2SR$),[775] and pyrolysis of arenesulphonylhydrazides ($ArSO_2NHNH_2 \rightarrow ArSO_2SAr$, with the sulphonamide and disulphide as minor products).[776]

Deoxygenation of thiolsulphonates and sulphoxides occurs over Fe at 200 °C at low pressures,[777a] while diaryl sulphides are formed by pyrolysis of aryl arenethiolsulphonates over Cu.[777b] A simple scheme to describe thiolsulphonate–amine equilibria is inadequate, and account must be taken of cleavage to the sulphenamide being followed by hydrolysis and accumulation of decomposition products of the sulphenic acid.[778]

Synthesis of *S*-aroyl thiolsulphonates $RCOSSO_2R$ provides compounds

[770] J. L. Kice and J. P. Cleveland, *J. Amer. Chem. Soc.*, 1973, **95**, (*a*) p. 104; (*b*) p. 109.
[771] (*a*) E. Block and S. W. Weidman, *J. Amer. Chem. Soc.*, 1973, **95**, 5046; (*b*) E. Block and J. O'Connor, *ibid.*, p. 5048.
[772] D. R. Hogg and J. Stewart, *J.C.S. Perkin II*, 1974, 43, 436.
[773] M. Furukawa, S. Tsuiji, Y. Kojima, and S. Hayashi, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, (*a*) p. 2391; (*b*) p. 1965.
[774] Y. Abe and J. Tsurugi, *Chem. Letters*, 1972, 441.
[775] B. G. Boldyrev, E. N. Obukhova, and E. N. Rochnyak, *Zhur. priklad. Khim.*, 1972, **45**, 888.
[776] H. Meier and I. Menzel, *Synthesis*, 1972, 267.
[777] T. Fujisawa, K. Sugimoto, and M. Ohta, *Chem. Letters*, 1973, (*a*) p. 1241; (*b*) p. 237.
[778] E. Ciuffarin, L. Senatore, and G. Giovannini, *J.C.S. Perkin II*, 1972, 2314.

which may be regarded as mixed anhydrides, and which may prove to be aroylating agents with enhanced reactivity.[779]

α-Disulphones.—An earlier conclusion (Volume 2, p. 99) that hydrolysis of aryl α-disulphones $ArSO_2SO_2Ar$ is subject to general base catalysis is now modified to part nucleophilic and part general base catalysis.[671] Studies of nucleophilic attack at S in these compounds have involved twenty different nucleophiles;[780] and reaffirm the earlier view that the nucleophiles show the same relative reactivity towards sulphur in these compounds as they do towards carbonyl carbon in ketones and related compounds.[780] Alkaline hydrolysis of aryl α-disulphones shows a large positive ρ-value.[781]

Photolysis of aryl α-disulphones in aromatic solvents gives products derived from arenesulphonyl radicals (*i.e.* $ArSO_3H$, $ArSO_2OSO_2Ar$, $ArSO_2S$-Ar, $ArSO_2Ar$, SO_2, and biaryls).[782]

[779] S. Kato and M. Mizuta, *Bull. Chem. Soc. Japan*, 1973, **46**, 860.
[780] J. L. Kice and E. Legan, *J. Amer. Chem. Soc.*, 1973, **95**, 3912.
[781] J. L. Kice, *J. Org. Chem.*, 1972, **37**, 1865.
[782] M. Kobayashi, K. Tanaka, and H. Minato, *Bull. Chem. Soc. Japan*, 1972, **45**, 2906.

2
Small Ring Compounds of Sulphur and Selenium

BY D. C. DITTMER

1 Reviews

A review of saturated, heterocyclic, three-membered rings has been published,[1] and the literature for 1972 concerned with heterocyclic chemistry has been surveyed.[2a] The chemistry of three-membered, sulphur-containing rings has been reviewed.[2b] The n.m.r. spectra of small-ring sulphur heterocyclic compounds and other heterocycles have been discussed.[3] Selenium-containing cyclic compounds, including three- and four-membered rings, have been reviewed.[4]

2 Thiirans

Physical Properties and Theoretical Treatments.—Photoelectron spectroscopy of thiiran indicates that the sulphur lone pair ($3p\pi$) orbital has a higher binding energy (by 0.4 eV) than the corresponding orbital in dimethyl sulphide. This slight stabilization may reflect *d*-orbital participation in the bonding in thiiran. CNDO/2–LCAO–SCF calculations gave ionization potentials in agreement with those found experimentally.[5] A redetermination of the structure of thiiran by microwave spectroscopy established a carbon–carbon bond length of 1.484 Å,[6] slightly less than that determined previously (1.492 Å).[7] The microwave spectrum of cyclohexene sulphide

[1] D. R. Boyd and B. J. Walker, in 'Aliphatic, Alicyclic, and Saturated Heterocyclic Chemistry', ed. W. Parker (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 1, Part II, p. 293.

[2] (*a*) I. D. Blackburne, M. J. Cook, and C. D. Johnson, *Annual Reports*, 1973, **69B**, 425; (*b*) N. S. Isaacs, *Internat. J. Sulfur Chem.*, 1973, **8**, 63.

[3] T. J. Batterham, 'NMR Spectra of Simple Heterocycles', John Wiley and Sons, New York, 1973.

[4] L. Mortillaro and M. Russo, 'Organic Selenium Compounds: Their Chemistry and Biology', ed. D. L. Klayman, and W. H. Günther, John Wiley and Sons, New York, 1973, p. 380; R. B. Silverman, *ibid.*, p. 532.

[5] D. C. Frost, F. G. Herring, A. Katrib, and C. A. McDowell, *Chem. Phys. Letters*, 1973, **20**, 401.

[6] K. Okiye, C. Hirose, D. G. Lister, and J. Sheridan, *Chem. Phys. Letters*, 1974, **24**, 111.

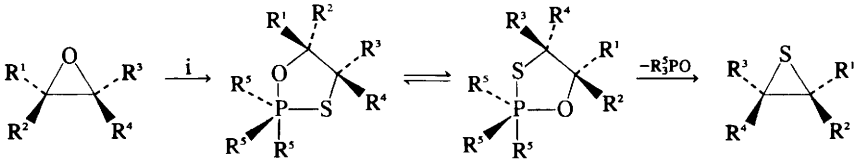
[7] G. L. Cunningham, jun., A. W. Boyd, R. J. Myers, W. D. Gwinn, and W. I. le Van, *J. Chem. Phys.*, 1951, **19**, 676.

indicates that it exists in a twisted half-chair conformation similar to that of cyclohexene oxide.[8] The c.d. of (*R*)-(+)-propylene sulphide has been recorded and interpreted by means of MO theory.[9] The vacuum-u.v. spectrum of thiiran has been interpreted.[10] *X*-Ray analysis of the structures of single crystals of 2α,3α-epithio-5α-androstan-17β-yl *p*-bromobenzoate[11] and (2*S*, 3*S*)-1-cyano-2-hydroxy-3,4-epithiobutane-α-naphthylurethane[12] (from the enzymic hydrolysis of certain thioglucosides) has been accomplished.

A number of MO calculations on thiirans, including consideration of ground and excited states and one-electron properties such as the dipole moment, have been reported.[13] Calculations indicate that while addition of a sulphur atom in the ^1D state to ethylene to form ground-state thiiran is favourable, addition of a sulphur atom in the ^3P state is unfavourable and would require an appreciable activation energy, which is contrary to experiment.[14] The properties of saturated, heterocyclic compounds containing a *d*-orbital acceptor atom have been related to ring size in the three- to seven-membered range.[15] The ring-opening, *via* carbon–carbon bond cleavage, of thiiran should involve either a through-conjugated structure and/or an ylide structure according to calculations involving an *spd* atomic-orbital basis set. Biradical intermediates for the same mode of ring opening were favoured for oxiran and aziridine.[16]

Formation.—A convenient and rapid synthesis of thiirans (yields 35—90%) consists of treatment of epoxides with triphenyl- or tri-n-butyl-phosphine sulphide in the presence of acid. *cis*-Stilbene oxide gave exclusively *cis*-stilbene sulphide. (*S*)-(−)-Methylphenyl-n-propylphosphine sulphide gave, with a twofold excess of cyclohexene oxide, the (*S*)-(−)-oxide, indicating that this reaction proceeds with retention of configuration at phosphorus.[17a] A mechanism involving two inversions was suggested for the conversion of 2α,3α-epoxycholestane into the 2β,3β-epithio-isomer, as shown in Scheme 1. Epithiochlorohydrin is obtained by treatment of epichlorohydrin with di-(*O*-ethyl)dithiophosphoric acid and triethylamine.[17b]

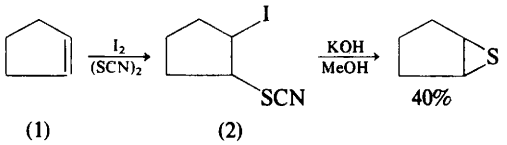
[8] R. Kewley, *Canad. J. Chem.*, 1973, **51**, 529.
[9] G. L. Bendazzoli, G. Gottarelli, P. Palmieri, and G. Torre, *Mol. Phys.*, 1973, **25**, 473.
[10] N. Basco and R. D. Morse, *Chem. Phys. Letters*, 1973, **20**, 404.
[11] K. Utsumi-Oda and H. Koyama, *J.C.S. Perkin II*, 1973, 1866.
[12] R. B. Bates, R. A. Grady, and T. C. Sneath, *J. Org. Chem.*, 1972, **37**, 2145.
[13] O. P. Strausz, H. E. Gunning, A. S. Denes, and I. G. Csizmadia, *J. Amer. Chem. Soc.*, 1972, **94**, 8317; I. Absar, L. J. Schaad, and J. R. Van Wazer, *Theor. Chim. Acta*, 1973, **29**, 173; A. S. Denes and I. G. Csizmadia, *Internat. J. Sulfur Chem.*, 1973, **8**, 47; A. B. Sannigrahi and S. N. Mohammad, *Indian J. Chem.*, 1973, **11**, 902; G. L. Bendazzoli, G. Gottarelli, and P. Palmieri, *J. Amer. Chem. Soc.*, 1974, **96**, 11.
[14] O. P. Strausz, R. K. Gosavi, A. S. Denes, and I. G. Csizmadia, *Theor. Chim. Acta*, 1972, **26**, 367.
[15] P. E. Peterson, *J. Org. Chem.*, 1972, **37**, 4180.
[16] K. Yamaguchi and T. Fueno, *Chem. Phys. Letters*, 1973, **22**, 471.
[17] (*a*) T. H. Chan and J. R. Finkenbine, *J. Amer. Chem. Soc.*, 1972, **94**, 2880; *Internat. J. Sulfur Chem.*, 1973, **8**, 45; (*b*) O. N. Nuretdinova and B. A. Arbuzov, *Mater. Nauch Konf., Inst. Org. Fiz. Khim. Akad. Nauk. S.S.S.R.*, 1969, 17 (*Chem. Abs.*, 1973, **78**, 29 513).



Reagents: i, R_3^5PS–CF_3CO_2H

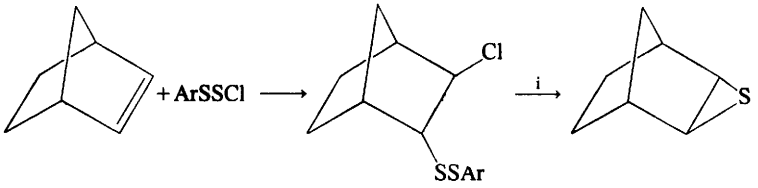
Scheme 1

Moderate yields (26—57%) of thiirans are obtained directly from olefins, *e.g.* (1), on treatment with iodine–thiocyanogen, followed by hydrolysis of the thiocyanate (2) so formed and the displacement of iodide ion. The



(1) (2)

method was not applicable to non-cyclic olefins.[18] Thiirans also may be obtained by the reaction of olefins with arenethiosulphenyl chlorides followed by treatment with sodamide or sodium sulphide (Scheme 2);[19] or



Reagents: i, $NaNH_2$

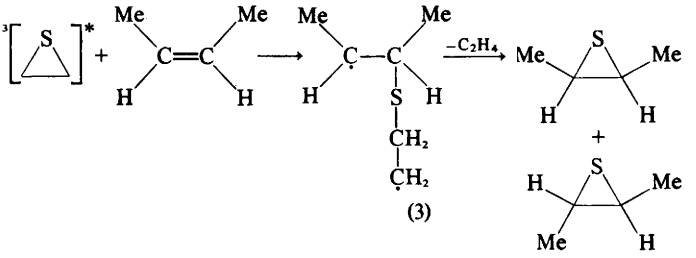
Scheme 2

by treatment of olefins with thioacetyl chloride, hydrolysis of the resulting β-chlorothioacetate, and cyclization of the β-chloro-thiol.[20] A sodium fluoride–silicon carbide catalyst was used to produce thiiran from ethylene, hydrogen sulphide, and air at 410 °C.[21]

Further investigations into the reaction of sulphur atoms with olefins to yield thiirans have established absolute rate constants and a negative temperature dependence on the rate constants for the reaction of sulphur in its ^3P state, obtained by flash photolysis of carbon oxysulphide, with

[18] J. C. Hinshaw, *Tetrahedron Letters*, 1972, 3567.
[19] T. Fujisawa and T. Kobori, *Chem. Letters*, 1972, 935, 1065.
[20] N. M. Karimova, M. G. Linkova, O. V. Kildisheva, and I. L. Knunyants, U.S.S.R. P. 376 378, Apr. 5, 1973 (*Chem. Abs.*, 1973, **79**, 78 594).
[21] H. Nakajima and M. Chono, U.S. P. 3 746 723, July 17, 1973 (*Chem. Abs.*, 1973, **79**, 78 593).

cis-but-2-ene and tetramethylethylene.[22] Sulphur atoms in their ^3P and ^1D states, obtained by electrical discharge through carbon oxysulphide or carbon disulphide, react with ethylene to yield thiiran, ethanethiol, and small quantities of polymer,[23] results analogous to those obtained in the photochemical generation of sulphur atoms.[24] During the direct or benzophenone-sensitized photolysis of thiiran, the sulphur atom is transferred to added olefins to yield substituted thiirans. The addition of sulphur is not stereospecific, and it is suggested that some species, *e.g.* (3), other than

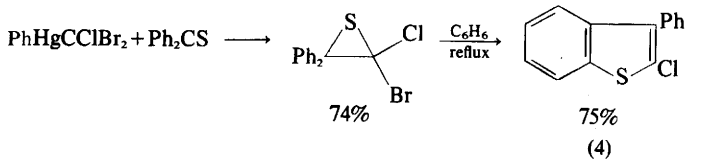


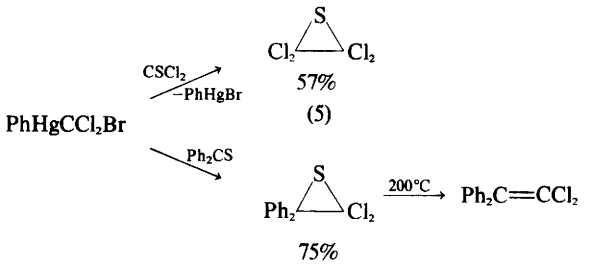
sulphur in its ^3P state may be responsible for the loss of stereochemistry. In the presence of propylene, some 3-thiahex-1-ene was produced. A mechanism was suggested.[25]

Thiirans are said to be obtained in high yields by thermolysis (215—250 °C) of mercaptoalkyl acetates over alumina.[26] Cyclization of chloro-mercaptocarboxylic acid derivatives gave derivatives of thioglycidic acid.[27] 3-Aryl-2,2-dicyano-oxirans failed to give thiirans with thiourea; instead, 2-amino-4-oxo-5-aryl-2-thiazolines were obtained.[28a] The thiourea method, however, is in general use.[28b]

Thiocarbonyl compounds are precursors of thiirans in a variety of reactions in which, formally, a methylene group or substituted methylene group is added across the carbon–sulphur double bond. Halogen-substituted thiirans are obtained by treatment of thiophosgene or thiobenzophenone with phenyl(trihalogeno)mercury compounds. The thiirans may lose sulphur or rearrange to thiophens, *e.g.* (4), depending on the nature of the halogen substituents. The first synthesis of tetrachlorothiiran (5) was claimed; it was

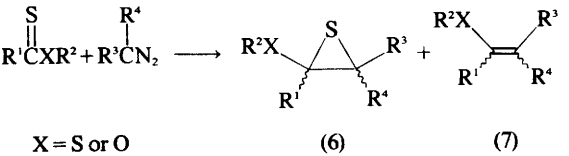
[22] D. D. Davis, R. B. Klemm, W. Braun, and M. Pilling, *Internat. J. Chem. Kinetics*, 1972, **4**, 383; D. D. Davis and R. B. Klemm, *ibid.*, 1973, **5**, 841.
[23] J. D. van Drumpt, *Rec. Trav. chim.*, 1972, **91**, 906.
[24] H. E. Gunning and O. P. Strausz, *Adv. Photochem.*, 1966, **4**, 150.
[25] R. Kumar and K. S. Sidhu, *Indian J. Chem.*, 1973, **11**, 899.
[26] Y. Labat, Ger. Offen, 2 222 239, November 16, 1972 (*Chem. Abs.*, 1973, **78**, 43 244).
[27] N. M. Karimova, M. G. Linkova, O. V. Kildisheva, and I. L. Knunyants, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 1788 (*Chem. Abs.*, 1974, **80**, 70 619); *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 1973, **22**, 223.
[28] (*a*) M. Ferrey, A. Robert, and A. Foucaud, *Compt. rend.*, 1973, **277**, *C*, 1153; (*b*) G. T. Izotov and M. F. Sorokin, *Trudy Moskov. Khim-Teknol. Inst.*, 1972, No. 77, 66 (*Chem. Abs.*, 1972, **78**, 147 694).





difficult to desulphurize the thiiran by triphenylphosphine, only traces of tetrachloroethylene being obtained.[29]

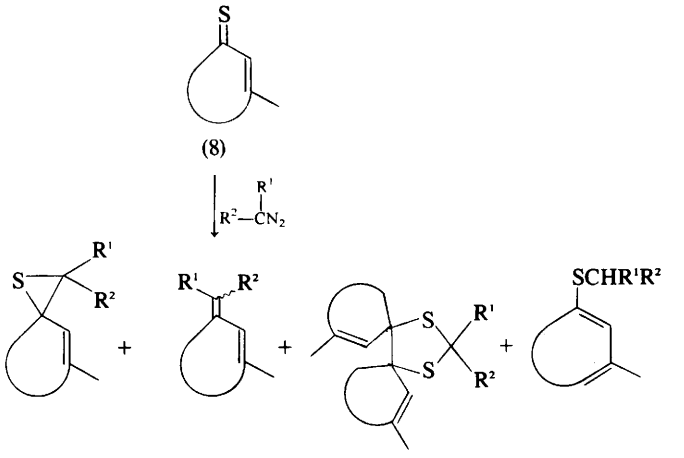
The reactions of thioketones,[30–32] thiono-esters,[30] and dithio-esters[30,33] with diazoalkanes yield thiirans (6) and often the olefinic product (7) formed by



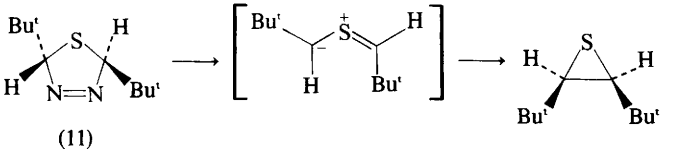
desulphurization of the thiiran. If the thiocarbonyl group is capable of enolization, olefin is more likely to be formed. With thiofenchone and 2-diazopropane, only olefin could be isolated.[30] Treatment of cyclic, $\alpha\beta$-unsaturated thioketones (8) with diazoalkanes yields not only thiirans and olefins but also dithiolans (9) and products from *S*-alkylation (10). The relative amount of thiirans and dithiolans depends on the nature of the diazoalkane, the temperature, and the order of addition of the reagents.[34]

Thermolysis of several thiadiazolines, *e.g.* (11), gave thiirans *via* extrusion of nitrogen accompanying conrotatory ring closure. Thiadiazoline (12) did not yield episulphide.[35] Thiirans and olefins are obtained by treatment of

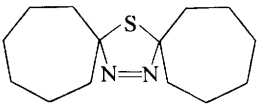
[29] D. Seyferth, W. Tronich, R. S. Marmor, and W. S. Smith, *J. Org. Chem.*, 1972, **37**, 1537.
[30] J. M. Beiner, D. Lecadet, D. Paquer, A. Thullier, and J. Vialle, *Bull. Soc. chim. France*, 1973, 1979; J. M. Beiner, D. Lecadet, D. Paquer, and A. Thullier, *ibid.*, p. 1983; J. M. Beiner, D. Paquer, A. Thullier, and J. Vialle, Fifth Symposium on Organic Sulfur Chemistry, Lund, Sweden, June 5–9, 1972, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 239.
[31] D. Paquer and R. Pou, *Bull. Soc. chim. France*, 1972, 3887.
[32] A. Sammour, M. I. Selim, A. F. M. Fahmy, and K. Elewa, *Indian J. Chem.*, 1973, **11**, 437.
[33] S. Holm and A. Senning, *Tetrahedron Letters*, 1973, 2389.
[34] P. Metzner, *Bull. Soc. chim. France*, 1973, 2297.
[35] J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, 1972, **37**, 4045.



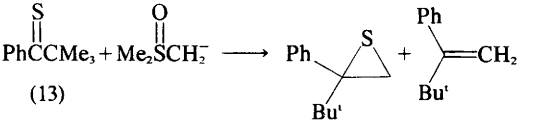
(8) (9) (10)



(11)



(12)

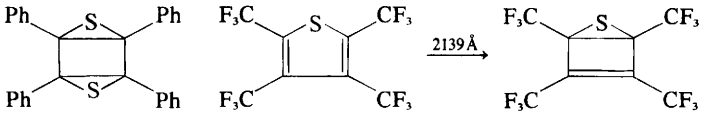


(13) 40%

non-enolizable thioketones, *e.g.* (13), with dimethylsulphoxonium methylide. Dithiobenzoates yield only olefins, presumably *via* a thiiran intermediate.[36]

Although the highly strained bis-thiiran (14) was not obtained on irradiation of 2,5-diphenyl-1,4-dithiin,[37] photolysis of tetra(trifluoromethyl)thiophen (15) gave the thiiran (16).[38] A previous structure for the product was

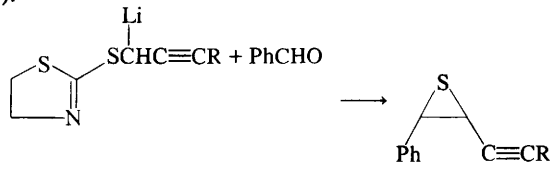
[36] D. Lecadet, D. Paquer, and A. Thullier, *Compt. rend.*, 1973, **276**, *C*, 875.
[37] K. Kobayashi and T. Ohi, *Chem. Letters*, 1973, 643.
[38] H. A. Wiebe, S. Braslavsky, and J. Heicklen, *Canad. J. Chem.*, 1972, **50**, 2721.



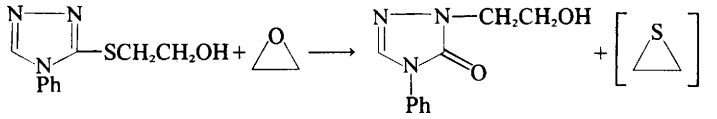
(14) (15) (16)

corrected.[39] A small amount of what was alleged to be 2,3-bis(trifluoromethyl)thiiren was formed also.

Low yields of a mixture of *cis*- and *trans*-acetylenic thiirans (18) were obtained by treatment of lithium salts of 2-propargylthiothiazolines (17) with benzaldehyde. A mechanism was proposed.[40] Thiiran was proposed as a product, although not identified, in the reaction of oxiran with 3-β-hydroxyethylthio-1,2,4-triazoles (19) to yield *N*-β-hydroxyethyltriazolinones (20).[41]

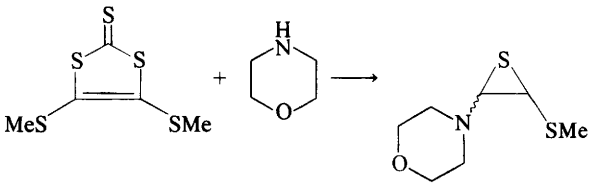


(17) (18)



(19) (20)

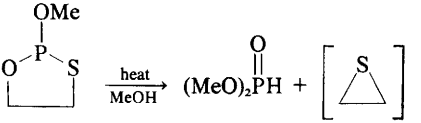
Treatment of 4,5-bis(methylthio)-1,3-dithiole-2-thione (21) with morpholine gave a complex mixture of products among which was a mixture of *cis*- and *trans*-thiirans (22), obtained in moderate yield. A thiiren intermediate was suggested.[42] Photolysis of ethylene trithiocarbonate produces



(21) (22)

[39] E. C. Wu and J. Heicklen, *J. Amer. Chem. Soc.*, 1971, **93**, 3432.
[40] K. Hirai, H. Matsuda, and Y. Kishida, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2067.
[41] L. A. Vlasova and I. Y. Postovskii, *Chem. Heterocyclic Compounds*, 1973, **7**, 658.
[42] S. Wawzonek and S. M. Heilmann, *J. Org. Chem.*, 1974, **39**, 511.

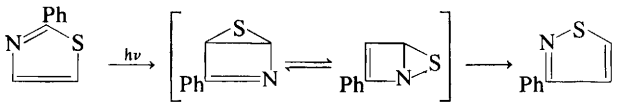
thiiran,[43] and thermolysis of oxathiophospholan (23) is alleged to yield thiiran, although only the phosphorus-containing product (24) was characterized.[44]



(23) (24)

A number of substituted thiirans have been obtained by displacement of chlorine from chloromethylthiiran.[45] Aryloxymethylthiirans have been used for the synthesis of antidepressant thiomorpholine derivatives,[46] and thiolcarbamates derived from 2-mercaptomethylthiiran are claimed to be herbicides.[47] A dimethylthiiran substituted with a long carbon chain containing a dienoate group is said to be insecticidal.[48]

Intermediates in Reactions.—A family of excited-state structures for thiophens in which a two-atom fragment is wrenched 90° out of the plane formed by the remaining three atoms is suggested as being preferable to a previously proposed family of structures involving thiirans to account for the photochemically induced valence-bond isomerizations observed.[49] Thiiran intermediates (26) and (27) have been suggested to account for photochemical isomerizations of phenylthiazoles (25);[50] and thiiran intermediates may be involved in the extrusion of sulphur from thiepins, *e.g.*



(25) (26) (27)

[43] H. Chandra and K. S. Sidhu, *Indian J. Chem.*, 1972, **10**, 1089.

[44] D. Bernard, P. Savignac, and R. Burgada, *Bull. Soc. chim. France*, 1972, 1657.

[45] (*a*) A. M. Kuliev, K. Byashimov, K. Z. Guseinov, and F. N. Mamedov, *J. Org. Chem.* (*U.S.S.R.*), 1972, **8**, 2303; (*b*) A. M. Kuliev, K. Byashimov, and F. N. Mamedov, *Izvest. Akad. Nauk Turkm. S.S.R; Ser. Fiz-Tekh. Khim. Geol. Nauk.*, 1972, 119 (*Chem. Abs.*, 1972, **77**, 34 211); *Doklady Akad. Nauk Azerb. S.S.R.*, 1973, **29**, 33 (*Chem. Abs.*, 1973, **79**, 91 854); (*c*) S. I. Sadykh-Zade, V. A. Dzhafarov, and S. K. Kyazimov, *Uch. Zap., Azerb. Univ. Ser. Khim. Nauk*, 1971, No. 3, p. 42 (*Chem. Abs.*, 1973, **78**, 15 929); (*d*) B. A. Arbuzov, O. N. Nuretdinova, and F. F. Guseva, *Mater. Nauch. Konf., Inst. Org. Fiz. Khim. Akad. Nauk S.S.S.R.*, 1969, 14 (*Chem. Abs.*, 1973, **78**, 29 517).

[46] R. Hull, B. J. McLoughlin, and M. G. David, B.P., 1 327 331, Aug. 23, 1973 (*Chem. Abs.*, 1973, **79**, 146 532).

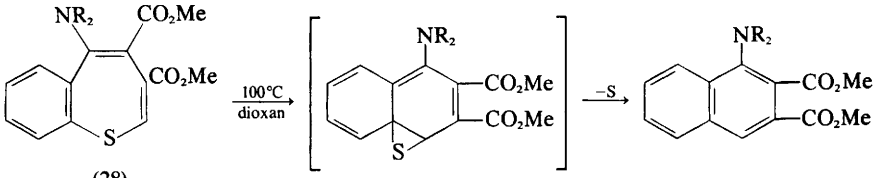
[47] W. C. Doyle, jun., U.S.P. 3 634 457, Jan. 11, 1972; 3 728 371, Apr. 17, 1973 (*Chem. Abs.*, 1972, **77**, 34 286; 1973, **79**, 5246).

[48] J. B. Siddall and C. A. Henrick, U.S.P., 3 723 462, Mar. 27, 1973; 3 775 432, Nov. 27, 1973 (*Chem. Abs.*, 1973, **78**, 159 402; 1974, **80**, 59 849).

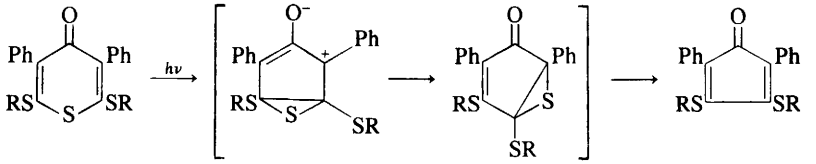
[49] R. M. Kellogg, *Tetrahedron Letters*, 1972, 1429.

[50] C. Vernin, C. Riou, H. J. M. Dou, L. Bouscasse, J. Metzger, and G. Loridan, *Bull. Soc. chim. France*, 1973, 1743.

(28).[51] The photochemical conversion of thiopyrones such as (29) into cyclopentadienones (32) also may proceed *via* thiirans (30) and (31).[52]

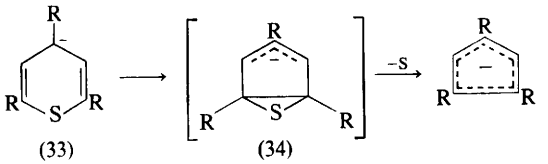


(28)

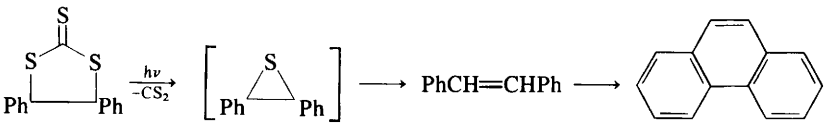


(29) (30) (31) (32)

Thiapyran (or thiabenzene) anions (33) expel sulphur, possibly *via* a thiiran intermediate (34).[53] Diphenylthiiran (35) has been considered as an intermediate in the photochemical decomposition of stilbene trithiocarbonate to phenanthrene. Atomic sulphur in a triplet state may be involved in



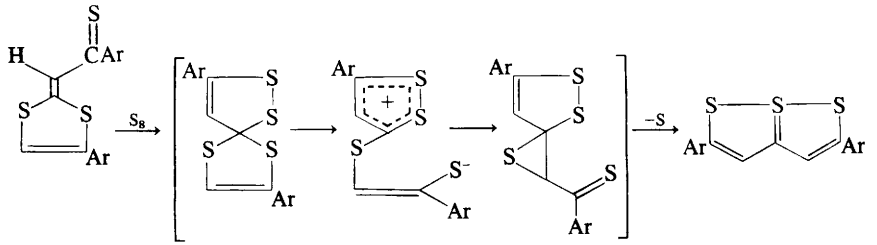
(33) (34)



(35)

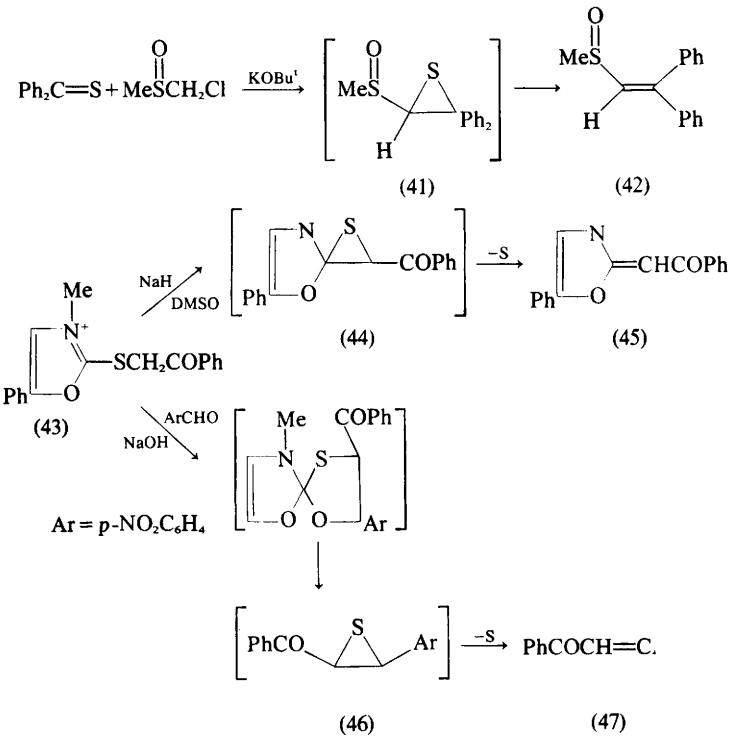
the dehydrogenation step which leads to the formation of phenanthrene.[54] Other reactions in which thiirans are suggested as intermediates are the sulphur-catalysed rearrangement of 2-thioacylmethylene-1,3-dithioles (36) to 1,6,6a-trithiapentalenes (40) *via* (37) → (38) → (39),[55] the reaction of

[51] D. N. Reinhoudt and C. G. Kouwenhoven, *J.C.S. Chem. Comm.*, 1972, 1232, 1233.
[52] N. Ishibe, M. Odani, and R. Tanuma, *J.C.S. Perkin I*, 1972, 1203.
[53] R. R. Schmidt and U. Burkert, *Tetrahedron Letters*, 1973, 4355.
[54] J. A. Moore and T. Isaacs, *Tetrahedron Letters*, 1973, 5033; *cf.* ref. 43.
[55] S. Davidson and D. Leaver, *J.C.S. Chem. Comm.*, 1972, 540.



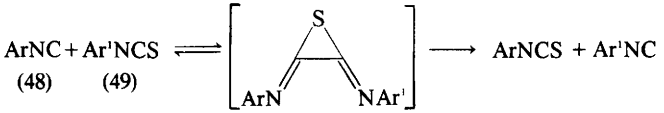
(36) (37) (38) (39) (40)

thiobenzophenone with chloromethyl methyl sulphoxide *via* (41) to yield olefin (42),[56] the desulphurization of oxazolium salt (43) to methylene derivative (45) *via* (44),[57] reaction of (43) with *p*-nitrobenzaldehyde to yield (47) *via* (46),[57] the photochemical decomposition of 4-oxo-3,4-dihydro-3,1,2-benzothiadiazine,[58a] and the interconversion of aryl isocyanides (48) and aryl isothiocyanates (49) *via* (50).[58b] Thiirans now are not believed to be



(41) (42) (43) (44) (45) (46) (47)

[56] G. Tsuchihashi and K. Ogura, *Bull. Chem. Soc. Japan*, 1972, **45**, 2023.
[57] Y. Ueno and M. Okawara, *Bull. Chem. Soc. Japan*, 1972, **45**, 1797.
[58] (*a*) A. T. Fanning, jun., G. R. Bickford, and T. D. Roberts, *J. Amer. Chem. Soc.*, 1972, **94**, 8505; (*b*) J. H. Boyer and V. T. Ramakrishnan, *J. Org. Chem.*, 1972, **37**, 1360.



(50)

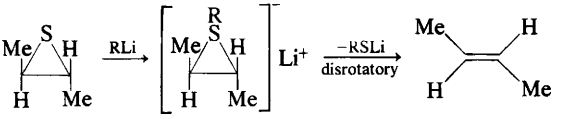
intermediates in the reactions of carboxylic acids with thionyl chloride to give benzo[*b*]thiophens.[59]

Thiiran ions are reported to be formed during the mass spectrometric investigation of 1,3-dithiolan or oxathiolan derivatives.[60] Bridged thiiran radicals may be involved in the addition of thiols to norbornenes[61] and in the thermolysis of 1,2-bis(phenylthio)ethanes.[62]

Chemical Properties.—Thiirans are desulphurized to olefins by molybdenum complex (51),[63a] hydridopentacarbonylmanganese,[63b] di-iron enneacarbonyl,[64] tri-iron dodecacarbonyl,[64] tungsten hexachloride,[65] and molybdenum pentachloride.[65] The desulphurization is stereospecific in several cases.[63b,64] The reaction of *cis*- and *trans*-2,3-dimethylthiirans with n-butyl-lithium,

$$HMo(C_5H_5)(CO)_2[P(OPh)_3]$$

(51)

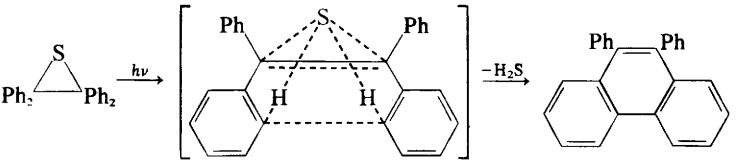


(52)

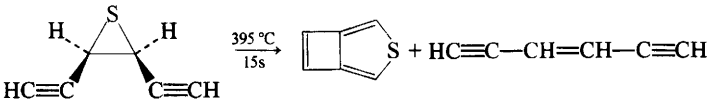
which yields the corresponding but-2-enes with retention of stereochemistry, is believed to proceed *via* intermediates (52).[64]

Photolysis (Pyrex filter) of tetraphenylthiiran (53) in cyclopentene gave 9,10-diphenylphenanthracene (54) quantitatively, cyclopentene episulphide (25%), bis-cyclopent-3-en-1-yl (40%), hydrogen sulphide (5%), hydrogen, traces of cyclopentanethiol, and a yellow solid, probably sulphur.[66] Thermal desulphurization (gas phase) of the *cis*-acetylenic thiiran (55) yields unstable thienocyclobutadiene (56) and *cis*- and *trans*-bis-acetylenic olefins (57). The *trans*-isomer of (55) gave only olefin, and both isomers in solution gave

[59] A. J. Krubsack and T. Higa, *Tetrahedron Letters*, 1973, 125.
[60] G. Conde-Caprace and J. E. Collins, *Org. Mass Spectrometry*, 1972, **6**, 415; R. H. Cragg, J. P. N. Husband, and A. F. Weston, *J.C.S. Dalton*, 1973, 568.
[61] D. I. Davies, D. J. A. Pearce, and E. C. Dart, *J.C.S. Perkin I*, 1973, 433.
[62] P. B. Shevlin and J. C. Greene, jun., *J. Amer. Chem. Soc.*, 1972, **94**, 8447.
[63] (*a*) W. Beck, W. Danzer, and G. Thiel, *Angew. Chem.*, 1973, **85**, 625; (*b*) W. Beck, W. Danzer, and R. Höfer, *ibid.*, p. 87.
[64] B. M. Trost and S. D. Ziman, *J. Org. Chem.*, 1973, **38**, 932.
[65] L. A. Korotneva, G. P. Belonovskaya, and B. A. Dolgoplosk, *Doklady Akad. Nauk S.S.S.R.*, 1972, **207**, 899 (*Chem. Abs.*, 1972, **78**, 111 027).
[66] R. C. Petterson, A. L. Hebert, G. W. Griffin, I. Sarkar, O. P. Strausz, and J. Font, *J. Heterocyclic Chem.*, 1973, **10**, 879.



(53)



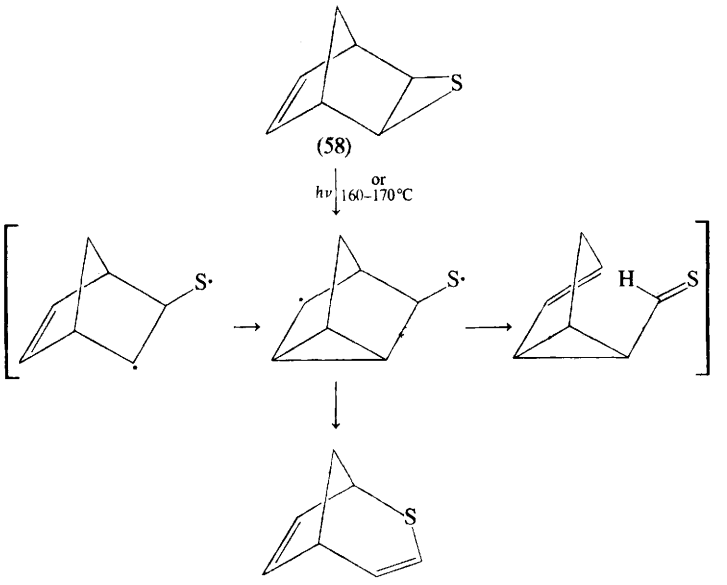
(55) (56) (57)

solely olefin with greater than 90% retention of configuration. The kinetics were complex, indicating a more complicated mechanism than the simple cheletropic extrusion of a sulphur atom.[67] Both methyl[68] and phenyl[69] radicals desulphurize thiirans to alkenes in the gas phase. The stereochemistry present in the thiiran is lost in the alkene.

The photochemistry of thiirans and thiirens has been reviewed.[70] *exo*-2,3-Epithionorborn-5-ene (58) decomposes photochemically or thermally to 2-thiabicyclo[3,2,1]octa-3,6-diene (59) and other products by a stepwise process.[71]

Treatment of thiirans with $NaBH_2S_3$ yields polysulphides which can be reduced in moderately good yields to dithiols by lithium aluminium hydride.[72] However, *trans*-2,3-diphenylthiiran gave only *trans*-stilbene and thiiran itself gave a polymer. Silver nitrate facilitates the reaction of thiirans with primary aliphatic amines, the reaction proceeding at 25 °C and the product being easily separated as a silver complex. Yields of aminoethanethiols are 40—90%.[73] Attack by nucleophiles such as the anion of ethyl cyanoacetate,[74] Grignard reagents,[75,76] potassium thiocyanate,[76,77] and amines[76] on carbon of a thiiran ring gives useful ring-opened products which in some cases can undergo cyclization to five- and six-membered rings.[74,75]

[67] K. Peter, C. Vollhardt, and R. G. Bergman, *J. Amer. Chem. Soc.*, 1973, **95**, 7538.
[68] E. Jakubowski, M. G. Ahmed, E. M. Lown, H. S. Sandhu, R. K. Gosavi, and O. P. Strausz, *J. Amer. Chem. Soc.*, 1972, **94**, 4094.
[69] J. K. Weseman, R. Williamson, J. L. Greene, jun., and P. B. Shevlin, *J.C.S. Chem. Comm.*, 1973, 901.
[70] N. R. Bertoniere and G. W. Griffin, 'Organic Photochemistry', ed. O. L. Chapman, Marcel Dekker, New York, 1973, p. 181.
[71] T. Fujisawa and T. Korbori, *J.C.S. Chem. Comm.*, 1972, 1298.
[72] J. M. Lalancette and M. Laliberté, *Tetrahedron Letters*, 1973, 1401.
[73] R. Luhowy and F. Meneghini, *J. Org. Chem.*, 1973, **38**, 2405.
[74] M. Furukawa, K. Nagato, Y. Kojima, and S. Hayashi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2262.
[75] V. I. Dronov and V. P. Krivonogov, *Khim. geterotsikl. Soedinenii*, 1972, 1186 (*Chem. Abs.*, 1972, **77**, 164 400); *Chem. Heterocyclic Compounds*, 1973, **6**, 1106, 1506; V. I. Dronov, V. P. Krivonogov, and V. S. Nikitina, *ibid.*, p. 312.
[76] H. Takeda, *Yakugaku Zasshi*, 1972, **92**, 1117 (*Chem. Abs.*, 1972, **77**, 164 335).
[77] K. Jankowski and R. Harvey, *Synthesis*, 1972, 627; *Canad. J. Chem.*, 1972, **50**, 3930.

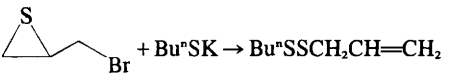


(58)

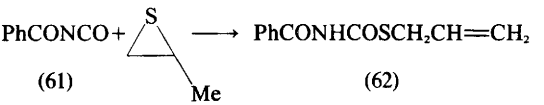
(59)

Thiocyanate ion can cause isomerization of thiirans.[77] The reactivity of 2-methylthiiran to hydrochloric acid has been compared with the reactivities of 2-methyloxiran, 2-methylaziridine, and methylcyclopropane.[78] Treatment of 2-chloromethyl- and 2-alkoxymethyl-thiirans with aqueous chlorine yields the corresponding 1,3-dichloropropane- or 1-alkoxy-3-chloro-2-sulphonyl chlorides. Hydrochloric acid alone yields the 2-thiol.[79]

Nucleophilic attack on the sulphur atom of 2-bromomethylthiiran by potassium thiobutoxide yields the disulphide (60).[80] Attack by the sulphur atom of 2-methylthiiran on benzoyl isocyanate (61) yields a mixture believed to contain (62).[81]



(60)



(61) (62)

[78] H. Kakiuchi and T. Iijima, *Bull. Chem. Soc. Japan*, 1973, **46**, 1568.

[79] T. Kuwamura, E. Kameyama, and M. Nakajima, *Bull. Chem. Soc. Japan*, 1972, **45**, 1244; E. Kameyama, M. Nakajima, and T. Kuwamura, *ibid.*, p. 3222.

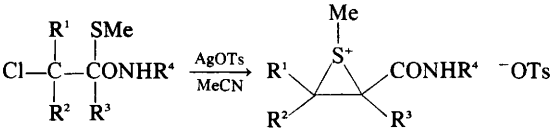
[80] O. N. Nuretdinova and B. A. Arbuzov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 550 (*Chem. Abs.*, 1972, **77**, 101 303).

[81] B. A. Arbuzov, N. N. Zobova, F. B. Balabanova, and E. N. Ofitserov, *Proc. Acad. Sci. U.S.S.R., Chem. Sect.*, 1973, **209**, 230.

The polymerization of thiirans generally[82a] and of stereoregular and optically active polymers of thiirans has been reviewed.[82b] The development of optical activity in the polymerization of racemic 2-methylthiiran by n-butyl-lithium–lithium(−)-menthoxide depends on the selective polymerization of (*S*)-2-methylthiiran by the catalyst system, the selective desulphurization of (*R*)-2-methylthiiran, and the selective decomposition of (*S*)-polymer chains.[83] Crystalline polymers of racemic isopropylthiiran were obtained with initiators, *e.g.* diethylzinc or cadmium tartrate.[84] A number of polymers and copolymers involving thiirans have been reported.[85]

3 Thiiranium Cations

Formation.—Stable thiiranium ions (63) were alleged to be formed by treatment of amides of α-methylthio-β-chloroisobutyric acids and of



(63)

$R^1 = R^2 = R^4 = H, R^3 = Me$

$R^1 = R^2 = Me, R^3 = H, R^4 = Ph$

α-methylthio-β-chloroisovaleric acids with silver toluene-*p*-sulphonate.[86] Analyses for the correct elemental composition were given. The compounds were water-soluble and said to have high electrical conductivity in 50% dioxan.

Intermediates in Reactions.—Tricyclic zwitterionic thiiranium ions are suggested as intermediates in the photochemical rearrangement of thiazoles, *e.g.* (64) → (65), (66) → (67), (68). The incorporation of deuterium from added D_2O was observed, supporting the intermediacy of (66).[87] The

[82] (*a*) F. Lautenschlaeger, *J. Macromol. Sci.*, 1972, **A6**, 1089; (*b*) P. Sigwalt, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972; *Internat. J. Sulfur Chem.* (*C*), 1972, **7**, 83.

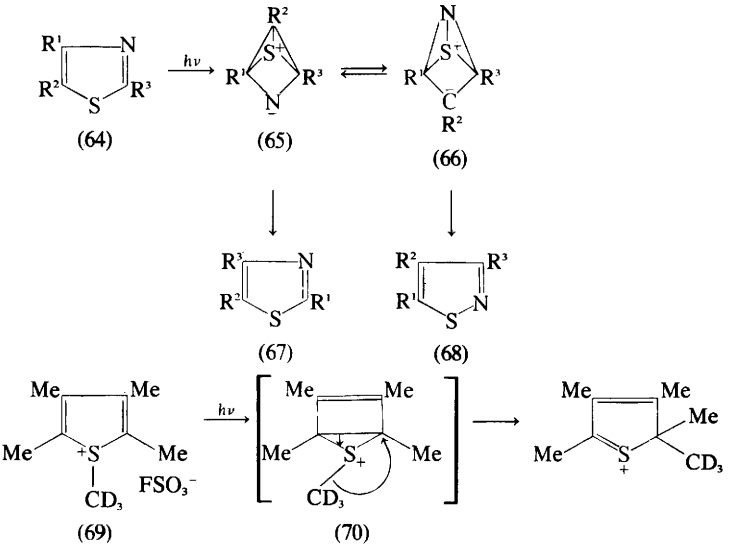
[83] A. D. Aliev, I. P. Solomatina, and B. A. Krentsel, *Macromolecules*, 1973, **6**, 797.

[84] P. Dumas, N. Spassky, and P. Sigwalt, *Compt. rend.*, 1973, **277**, *C*, 939.

[85] A. A. Oswald, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972; *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 245; L. L. Stotskaya, G. A. Oreshkina, and B. A. Krentsel, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972; *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 246; J. L. Villa, U.S.P. 3 767 672, October 23, 1973 (*Chem. Abs.*, 1974, **80**, 84 213); S. Hashimoto and T. Yamashita, *Kobunshi Kagaku English Edn.*, 1973, **2**, 280; W. Cooper, P. T. Hale, and J. S. Walker, *Polymer*, 1974, **15**, 175; S. Borleau, *Inform. Chim.*, 1973, No. 117, p. 107; F. Lautenschlaeger and P. Zeeman, *J. Polymer Sci., Part A-1, Polymer Chem.*, 1972, **10**, 3519.

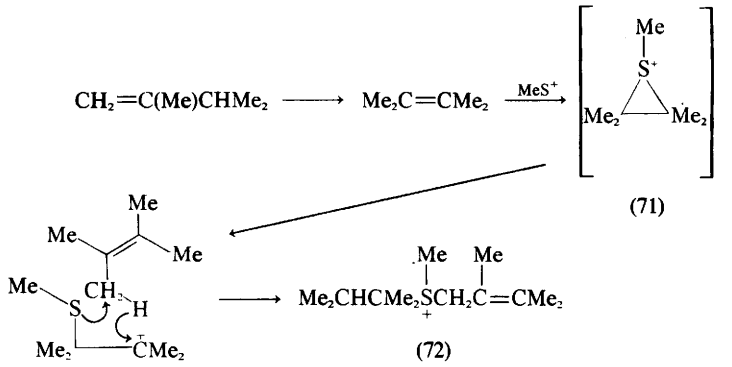
[86] O. V. Kildisheva, M. G. Linkova, L. P. Rasteikene, V. A. Zabelaite, N. K. Potsyute, and I. L. Knunyants, *Proc. Acad. Sci. U.S.S.R., Chem. Sect.*, 1972, **203**, 331.

[87] M. Maeda and M. Kojima, *Tetrahedron Letters*, 1973, 3523.



photochemically induced migration of an alkyl group from sulphur to carbon in thiophenium ions (69) may proceed *via* a thiiranium ion (70), although no evidence *pro* or *contra* was given; other possibilities were discussed.[88]

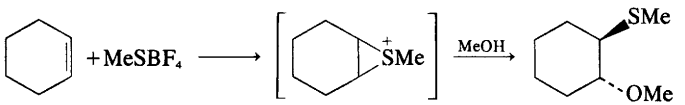
Treatment of 2,3-dimethylbut-1-ene or 2,3-dimethylbut-2-ene with methanesulphenyl bromide and silver 2,4,6-trinitrobenzenesulphonate gave the acyclic sulphonium salt (72), possibly *via* thiiranium salt (71). It was believed that the but-1-ene isomerized to the but-2-ene under the reaction conditions. Ethylene, *cis*- and *trans*-but-2-ene, 3,3-dimethylbut-1-ene, and



[88] H. Hogeveen, R. M. Kellogg, and K. A. Kuindersma, *Tetrahedron Letters*, 1973, 3929.

cyclohexene gave only oils or semi-solids, which were not characterized.[89] The possibility of a quadricovalent thiiran intermediate in the reaction of methanesulphenyl and toluene-*p*-sulphenyl chlorides with cyclohexene has received some support.[89b]

Addition of positive sulphur species, RS^+, usually derived from sulphenyl halides, to olefins is commonly assumed to proceed by way of thiiranium ions,[90] the reactions often showing the stereochemistry expected for *trans*-addition. For instance, the reaction of cyclohexene with methanesulphenyl tetrafluoroborate is believed to form an intermediate thiiranium ion (73), which then reacts with nucleophiles to give *trans*-methylthio-derivatives, *e.g.* (74).[91] Addition of thiocyanogen chloride to olefins may



(73) (74)

proceed *via* a thiiranium ion although such an intermediate is not supported by the lack of stereospecificity observed.[92]

Thiiranium ions are popular intermediates in reactions involving a good leaving group β to a sulphide functional group. Rearrangements and a *trans*-stereochemistry with respect to the entering nucleophile (as well as the leaving group) and the sulphur-containing group often are observed when the above situation occurs.[93] Solvolysis of ω-halogeno-alkyl sulphides reveals that three-membered cyclic sulphonium ions are formed more rapidly than five-membered ions.[94] The enthalpy of activation for formation of the three-membered ring is less than for the five-membered ring. The formation of the three-membered ring has a more negative entropy of

[89] (*a*) E. Carbin, G. K. Helmkamp, W. M. Barnes, and M. Sundaralingam, *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 129; (*b*) E. Carbin, Ph.D. Thesis, Univ. California at Riverside, 1972 [*Diss. Abs. Internat.* (*B*), 1972, **33**, 2524].

[90] R. D. Rieke, S. E. Bales, and L. C. Roberts, *J.C.S. Chem. Comm.*, 1972, 974; H. Chartier, *Bull. Soc. chim. France*, 1972, 2887; S. Kukolja and S. R. Lammert, *J. Amer. Chem. Soc.*, 1972, **94**, 7169; L. P. Rasteikene, T. A. Pranskene, M. G. Linkova, and I. L. Knunyants, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 1972, **21**, 2254; M. T. Mustafaeva, V. A. Smit, and V. F. Kucherov, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 1973, **22**, 1304; K. Izawa, T. Okuyama, and T. Fueno, *J. Amer. Chem. Soc.*, 1973, **95**, 4090.

[91] M. Z. Krimer, V. A. Smit, and A. A. Shamshurin, *Proc. Acad. Sci. U.S.S.R., Chem. Sect.*, 1973, **208**, 90.

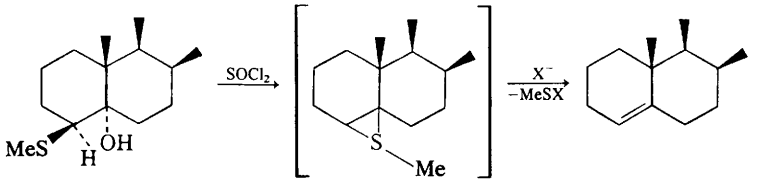
[92] R. G. Guy and I. Pearson, *J.C.S. Perkin II*, 1973, 281, 1359.

[93] G. A. Hull, F. A. Daniker, and T. F. Conway, *J. Org. Chem.*, 1972, **37**, 1837; G. S. Bethell and R. J. Ferrier, *J.C.S. Perkin II*, 1972, 2873; 1973, 1400; M. S. Khan and L. N. Owen, *J.C.S. Perkin I*, 1972, 2060, 2067; N. Wigger and C. Ganter, *Helv. Chim. Acta*, 1972, **55**, 2769; P. H. McCabe and C. M. Livingston, *Tetrahedron Letters*, 1973, 3029; A. Behzadi and L. N. Owen, *J.C.S. Perkin I*, 1973, 2733; R. Mantione and H. Normant, *Bull. Soc. chim. France*, 1973, 2261; D. I. Greichute, Y. Y. Kulis, and L. P. Rasteikene, *J. Org. Chem.* (*U.S.S.R.*), 1974, **9**, 1860; C. Leroy, M. Martin, and L. Bassery, *Bull. Soc. chim. France*, 1974, 590.

[94] R. Bird and C. J. M. Stirling, *J.C.S. Perkin II*, 1973, 1221; R. Bird, A. C. Knipe, and C. J. M. Stirling, *ibid.*, p. 1215.

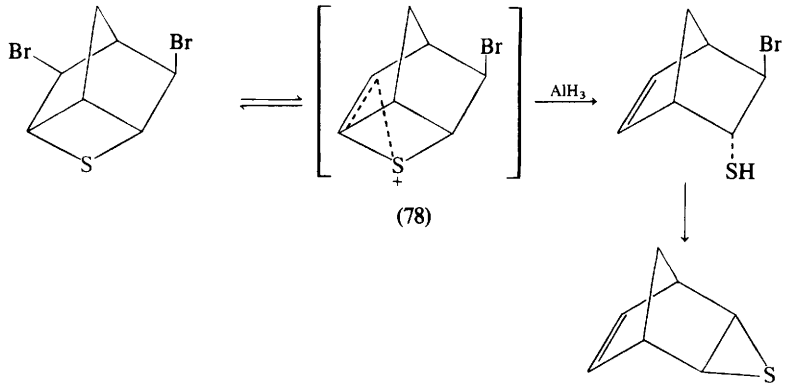
activation, which is contrary to the view that the formation of three-membered rings is favoured by a less negative entropy change because of less restriction of rotamer populations in the starting material and is disfavoured by an enthalpy change associated with ring strain. In the case of ω-halogeno-alkylamines, the three-membered intermediate is formed more slowly than the five-membered intermediate.

In the majority of cases involving thiiranium ion intermediates, nucleophiles attack carbon. In some cases, however, a displacement reaction appears to occur on sulphur. Treatment of steroidal hydroxy-sulphide (75) with thionyl chloride in pyridine gave mainly the 4-ene (77); a thiiranium ion



(75) (76) (77)

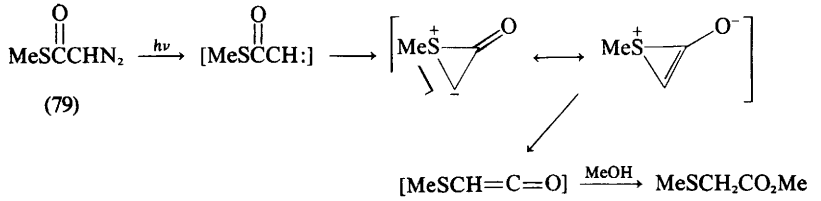
(76) was suggested, which underwent nucleophilic attack on sulphur. The 4α,3β-isomer gave the same result.[95] Tetracyclic thiiranium ion (also a thietanium ion) (78) undergoes attack on sulphur by hydride ion.[96]



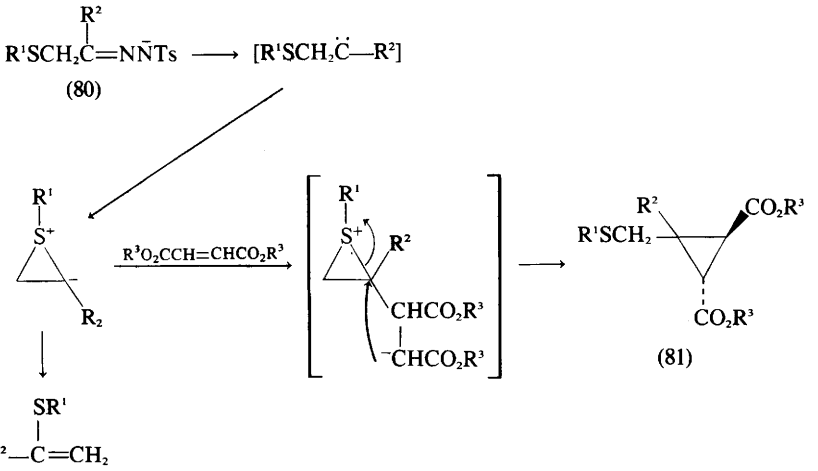
(78)

Thiiranium ylides have been posulated as intermediates in the photolysis of *S*-methyl diazothioacetate (79)[97] and in the thermolysis or photolysis of salts of α-arylthio- and α-alkylthio-toluene-*p*-sulphonylhydrazones (80).[98] In the latter case the ylides were trapped with diethyl maleate and dimethyl

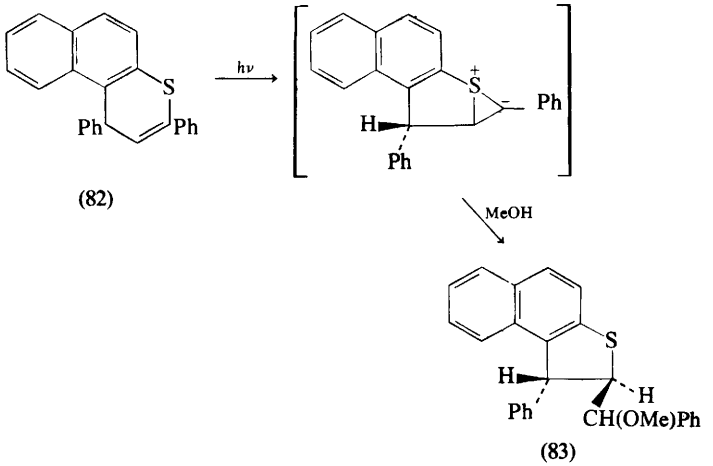
[95] D. N. Jones, J. Blenkinsopp, A. C. F. Edmonds, E. Helmy, and R. J. K. Taylor, *J.C.S. Perkin I*, 1973, 2602.
[96] S. D. Ziman and B. M. Trost, *J. Org. Chem.*, 1973, **38**, 649.
[97] S. S. Hixon and S. H. Hixon, *J. Org. Chem.*, 1972, **37**, 1279.
[98] I. Ojima and K. Kondo, *Bull. Chem. Soc. Japan*, 1973, **46**, 1539.


MeSCCHN2
hν
[MeSCCH:]
MeS
O
O⁻
[MeSCH=C=O]
MeOH
MeSCH2CO2Me

(79)


R²
R¹SCH2C=NNTs
[R¹SCH2C—R²]
R¹
S+
R2
R³O2CCH=CHCO2R³
R²
CHCO2R³
CHCO2R³
R²
CO2R³
R¹SCH2
CO2R³
SR¹
R²—C=CH2

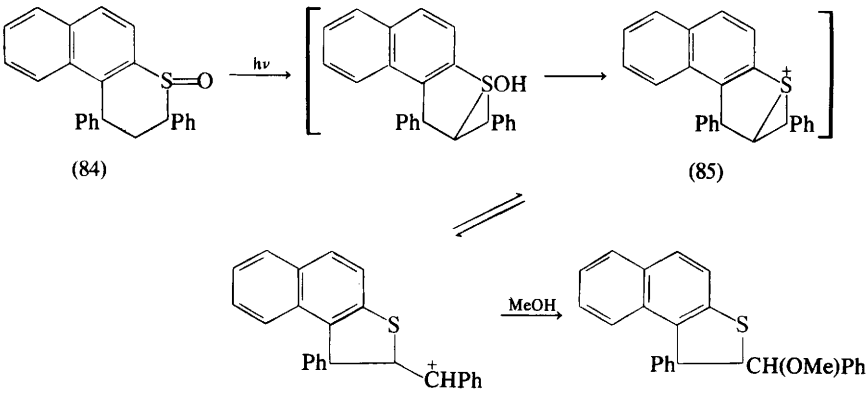
(80) (81)


S
Ph
Ph
hν
S+
Ph
H
Ph
MeOH
S
H
Ph
H
CH(OMe)Ph

(82) (83)

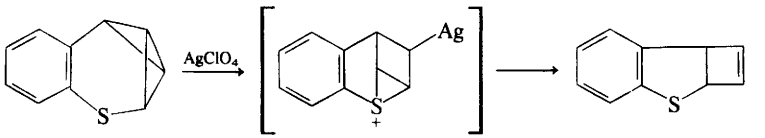
fumarate to give cyclopropanes (81). Products from carbene insertion also were obtained. A thiiranium ylide was suggested as an intermediate in the photochemical rearrangement of vinyl sulphide (82) to the five-membered ring system (83).[99a]

The mechanism of the photodehydration of sulphoxide (84) may involve thiiranium ion (85).[99b] Thiiranium ions also are suggested as possible



(84) (85)

intermediates in the reduction of an α-thiomethylhemiaminal,[100] the reduction of α-thioalkyl or α-thioaryl esters by mercaptide ions,[101] the silver-ion-catalysed rearrangement of (86) to (87),[102] and the reaction of α-(phenylthio)-cyclohexanone with hydroxylamine.[103]



(86) (87)

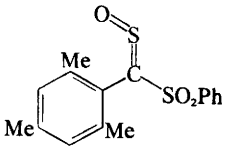
Thiiranium intermediates were ruled unlikely in the addition of 1-methyl-1-thionia-2-thiacyclohexane 2,4,6-trinitrobenzenesulphonate to olefins and dienes[104] and in the 'ene' reaction of monothiobenzil with 2-methylpent-2-ene.[105]

4 Thiiran 1-Oxides

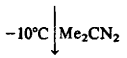
Formation.—Methods for the synthesis of thiiran 1-oxides and their chemical reactions have been reviewed.[106] An equimolar mixture (72% yield)

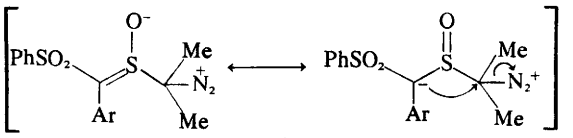
[99] (*a*) A. G. Schultz and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 4791; (*b*) *ibid.*, p. 4787.
[100] R. T. La Londe, C. F. Wong, and K. C. Das, *J. Amer. Chem. Soc.*, 1973, **95**, 6342.
[101] Y. Aufauvre, M. Verny, and R. Vessiere, *Bull. Soc. chim. France*, 1973, 1373.
[102] I. Murata, T. Tatsuoka, and Y. Sugihara, *Tetrahedron Letters*, 1974, 199.
[103] L. Baczynskyj, S. Mizsak, and J. Smuszkovicz, *J. Org. Chem.*, 1972, **37**, 4104.
[104] N. E. Hester and G. K. Helmkamp, *J. Org. Chem.*, 1973, **38**, 461.
[105] M. J. Loadman, B. Saville, M. Steer, and B. K. Tidd, *J.C.S. Chem. Comm.*, 1972, 1167.
[106] A. Negishi, *Yuki Gosei Kagaku Kyokai Shi*, 1973, **31**, 331 (*Chem. Abs.*, 1974, **80**, 59 804).

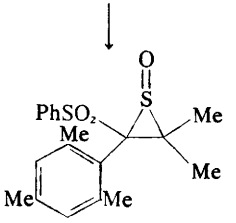
of diastereomeric thiiran 1-oxides (89) is obtained by treatment of isomeric mesitylphenylsulphonyl sulphines (88) with 2-diazapropane. Other sulphines (thiocarbonyl *S*-oxides) gave Δ^3-1,3,4-thiazoline 1-oxides. Thiiran



(88)

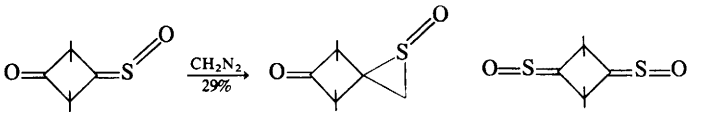






(89)

oxide formation was believed favoured when sulphines with bulky substituents were substrates.[107] Thiobenzophenone *S*-oxide and thiofluorenone *S*-oxide gave thiiran 1-oxides with aryldiazomethanes; the thiiran oxides decomposed readily to olefins, even during chromatography.[108] The spirothiiran 1-oxide (91) was obtained from cyclic sulphine (90) and



(90) (91) (92)

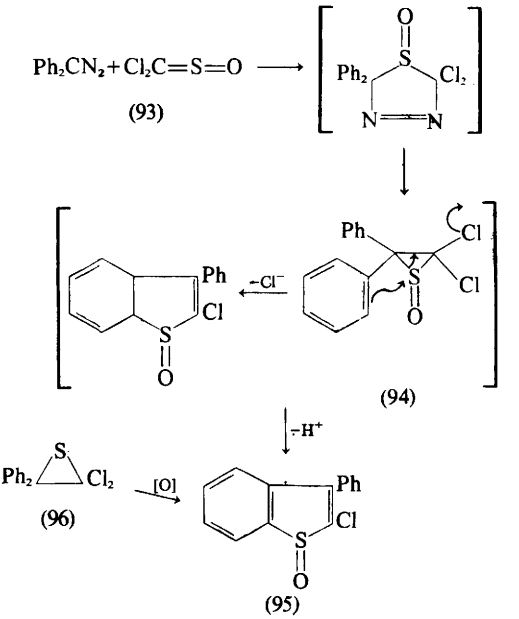
diazomethane.[109] Bis-sulphine (92) was believed to yield a mixture of bis-spiro-thiiran *S*-oxides.

[107] L. Thijs, A. Wagenaar, E. M. van Rens, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3589; B. Zwanenburg, A. Wagenaar, and L. Thijs, V Symposium on Organic Sulfur Chemistry, Lund, Sweden, June 1972, *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 223.

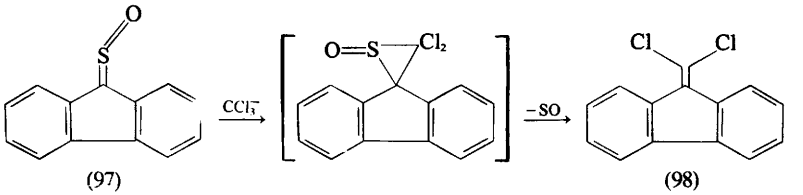
[108] B. F. Bonini and G. Maccagnani, *Tetrahedron Letters*, 1973, 3585.

[109] B. Zwanenburg, A. Wagenaar, L. Thijs, and J. Strating, *J.C.S. Perkin I*, 1973, 73.

Intermediates in Reactions.—Treatment of dichlorosulphine (93) with diphenyldiazomethanes (and other diaryldiazomethanes) yields 2-chlorobenzo[*b*]thiophen 1-oxide (95), also obtained along with the 1,1-dioxide on oxidation of 2,2-dichloro-3,3-diphenylthiiran (96). A mechanism involving a



thiiran 1-oxide (94) was proposed.[110] Thiiran 1-oxides are suggested intermediates in the reaction of diazomethane with diaryl sulphines to yield olefins[111] and in the formation of 9-dichloromethylenefluorene (98) from 9-thiofluorenone *S*-oxide (97) and the trichloromethyl anion.[112] Thiiran 1-oxide was not considered an important intermediate, if it is formed at all, in the thermolysis of dimethyl sulphoxide.[113]

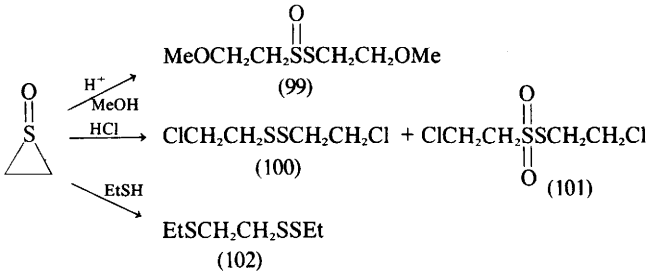


(97) (98)

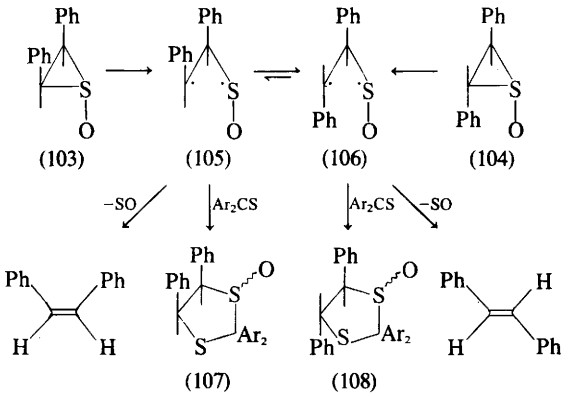
[110] L. Thijs, J. Strating, and B. Zwanenburg, *Rec. Trav. chim.*, 1972, **91**, 1345.
[111] C. G. Venier and C. G. Gibbs, *Tetrahedron Letters*, 1972, 2293.
[112] C. G. Venier, C. G. Gibbs, and P. T. Crane, *J. Org. Chem.*, 1974, **39**, 501.
[113] F. C. Thyrion and G. Debecker, *Internat. J. Chem. Kinetics*, 1973, **5**, 583.

Chemical and Physical Properties.—The vertical ionization energies (9.66, 9.78 eV) of thiiran 1-oxide and a number of other sulphoxides (*e.g.* DMSO, 9.01, 10.17 eV) have been determined.[114]

The acid-catalysed reaction of thiiran 1-oxides with methanol yields thiolsulphinates, *e.g.* (99); with acetic acid or dry hydrogen chloride, a mixture of disulphide (100) and thiolsulphonate (101) is obtained, and with ethanethiol, a mercaptoethyl disulphide (102). The ring opening is generally



stereospecific, inversion occurring at the ring carbon attacked by the nucleophile. Alcohols attack preferentially the most highly substituted carbon atom, while the better nucleophile ethanethiol attacks the less hindered carbon. The nature of nucleophilic attack on unsymmetrically substituted thiiran 1-oxides was considered as a function of the nucleophilicity, the nature of the substituents, the polarity of the medium, and the bulk of the nucleophile.[115] The stereochemistry of the thermal dethionylation of isomeric 2,3-diphenylthiiran 1-oxides (103) and (104) indicated the possible existence of biradical intermediates (105) and (106), which were trapped by di-*p*-anisyl thioketone to yield adducts (107) and (108).[116] Sulphur



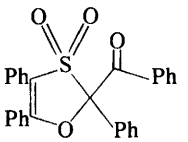
[114] H. Bock and B. Solonki, *Angew. Chem.*, 1972, **84**, 436.
[115] K. Kondo, A. Negishi, and I. Ojima, *J. Amer. Chem. Soc.*, 1972, **94**, 5786.
[116] K. Kondo, M. Matsumoto, and A. Negishi, *Tetrahedron Letters*, 1972, 2131.

monoxide, extruded from thiiran 1-oxide, apparently in a triplet state, is trapped by dienes to yield 2,5-dimethyl-3-thiolen S-oxides.[117]

5 Thiiran 1,1-Dioxides

Physical Properties and Theoretical Considerations.—The microwave rotational spectra of ^{32}S and ^{34}S isotopic species of thiiran 1,1-dioxide have given a number of structural parameters, *e.g.* r_{C-C} 1.586 Å, r_{C-S} 1.76 Å, ∠OSO 124°.[118] The Raman spectrum has been compared with the spectra of thiiran and thiiran 1-oxide, the C—H stretching vibrations being similar for all three compounds. Variations in the scissoring vibrations are observed, the sulphone absorbing at 1375, 1388 cm^{-1}, the sulphoxide at 1400, 1418 cm^{-1}, and the sulphide at 1426, 1450 cm^{-1}.[119] Analysis of the ^1H n.m.r. spectrum as an AA'BB'X (X=^{13}C) system has been accomplished. The chemical shift of the ring protons is fairly sensitive to variation of solvent, changing from δ 3.04 (CCl_4) to δ 2.00 (C_6D_6).[120]

Consideration of theoretical aspects of bonding in thiirans, thiiran 1-oxides, and thiiran 1,1-dioxides has led to an explanation for the long carbon–carbon bond in the dioxide. The molecule is considered as a complex of ethylene with sulphur dioxide, analogous to the complexes of transition metals with olefins. The sulphone group populates the π^* level of ethylene and withdraws electrons from the π level, weakening the carbon–carbon bond and lengthening it. Electron-withdrawing substituents (π-acceptors) on the thiiran dioxide are predicted to weaken the carbon–carbon bond; electron-supplying substituents (π-donors) will have the opposite effect. Carbon–carbon bond cleavage should be disrotatory in thiiran dioxide, but conrotatory in thiiran itself.[121] The stability of a compound purported to be 2,3-dibenzoyl-2,3-diphenylthiiran 1,1-dioxide[122] was questioned on these theoretical grounds, and, in fact, the structure has been shown to be that of an oxathiole 1,1-dioxide (109), and the purported

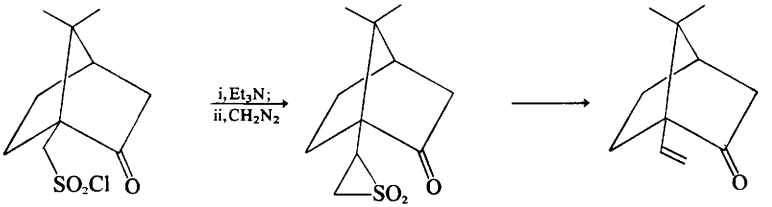


(109)

[117] P. Chao and D. M. Lemal, *J. Amer. Chem. Soc.*, 1973, **95**, 920; D. M. Lemal and P. Chao, *ibid.*, p. 922.
[118] H. Kim, *J. Chem. Phys.*, 1972, **57**, 1075.
[119] G. M. Kuzyants and V. T. Aleksamyan, *J. Struct. Chem.*, 1973, **13**, 576.
[120] M. Ueyama, K. Tori, and M. Fukuyama, *Org. Magn. Resonance*, 1972, **4**, 441.
[121] R. Hoffmann, H. Fujimoto, J. R. Swenson, and C. Wan, *J. Amer. Chem. Soc.*, 1973, **95**, 7644; R. Hoffman, XXIII Internat. Congress Pure and Applied Chemistry, Boston, Mass., July 1971, Butterworths, London, 1971, vol. 2, p. 233.
[122] D. C. Dittmer and G. C. Levy, *J. Org. Chem.*, 1965, **30**, 636; D. C. Dittmer, G. C. Levy, and G. E. Kuhlmann, *J. Amer. Chem. Soc.*, 1969, **91**, 2097.

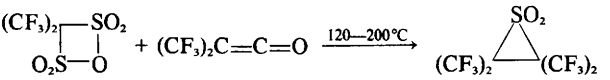
thiiran precursor is apparently the corresponding oxathiole, although some reactions of the latter, such as desulphurization to dibenzoylstilbene, may be explained by invoking the thiiran as an intermediate.[123]

Formation.—Treatment of the sulphene derived from (1*S*)-camphor-10-sulphonyl chloride (110) with diazomethane gave unstable, epimeric thiiran 1,1-dioxides (111) which decomposed above their melting points, 81—86 and



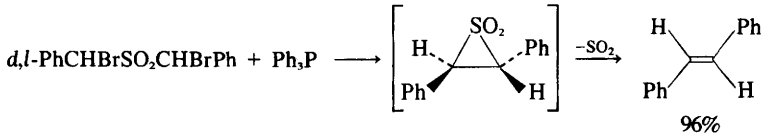
(110) (111) (112)

100—106 °C, respectively, to (1*S*)-7,7-dimethyl-1-vinyl-2-norbornanone (112).[124] The reaction of anhydride (113) with bis(trifluoromethyl)keten gave a trimer and a 15% yield of thiiran 1,1-dioxide (114).[125]



(113) (114)

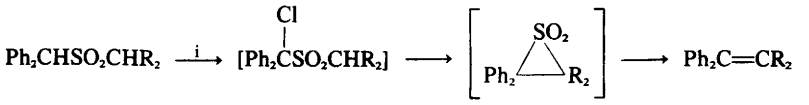
Intermediates in Reactions.—The utility of the Ramberg–Bäcklund rearrangement and the involvement of thiiran 1,1-dioxides in synthesis has been reviewed.[126] Treatment of *d,l*- and *meso*-bis-α-bromobenzyl sulphone with triphenylphosphine gave *trans*- and *cis*-stilbene, respectively, *via* α-sulphonyl carbanions which undergo cyclization at the remaining chiral centre to yield *trans*- and *cis*-2,3-diphenylthiiran 1,1-dioxides as intermediates (Scheme 3). Inversion occurred at each chiral centre.[127] Thiiran



Scheme 3

[123] U. Jacobsson, T. Kempe, and T. Norin, *J. Org. Chem.*, 1974, **39**, 2722, T. Norin, personal communication; T. Kempe, Dissertation, Royal institute of Technology, Stockholm, Sweden.
[124] T. Kempe and T. Norin, *Acta Chem. Scand.*, 1973, **27**, 1452.
[125] G. A. Sokolskii, V. M. Pavlov, V. M. Golovkin, V. F. Gorelov, and I. L. Knunyants, *Khim. geterotsikl. Soedinenii*, 1974, 42 (*Chem. Abs.*, 1974, **80**, 95 899).
[126] L. A. Paquette, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June 1972, *Internat. J. Sulfur Chem.* (*C*), 1972, **7**, 73.
[127] F. G. Bordwell and B. B. Jarvis, *J. Amer. Chem. Soc.*, 1973, **95**, 3585.

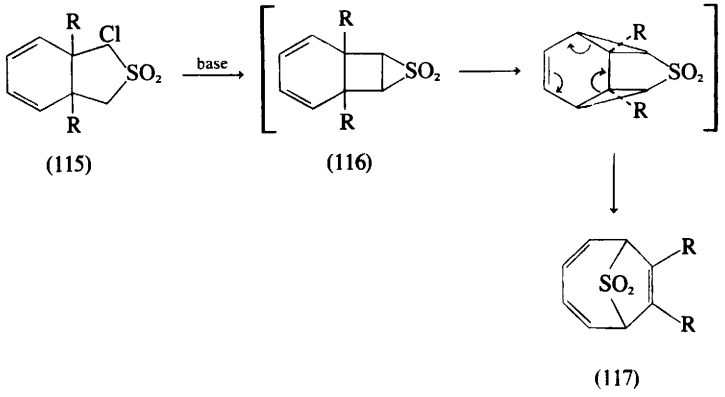
1,1-dioxide intermediates are suggested for the reaction of sulphones with carbon tetrachloride–potassium hydroxide,[128] *e.g.* as shown in Scheme 4.



Reagents: i, CCl_4–KOH

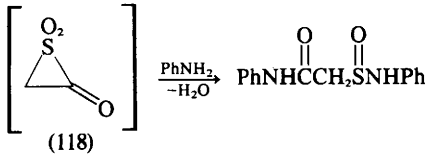
Scheme 4

Carbon–carbon bond cleavage of the strained thiiran 1,1-dioxide intermediate (116) followed by rearrangement to (117) is suggested to explain the course of the base-induced elimination of hydrogen chloride from (115).[129]



(115) (116) (117)

2-Oxothiiran 1,1-dioxide (118) is said to be obtained at low temperatures from keten and sulphur dioxide and was trapped by various reagents. It also formed a polymer.[130] Attempts to observe unstable thiiran 1,1-dioxide intermediates in the decomposition of certain 2,5-dihydrothiophen *S*-dioxides were unsuccessful.[131]



(118)

[128] C. Y. Meyers, W. S. Matthews, G. J. McCollum, and J. C. Branca, *Tetrahedron Letters*, 1974, 1105; C. Y. Meyers and L. L. Ho, *ibid.*, 1972, 4319.

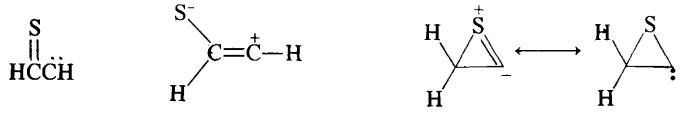
[129] L. A. Paquette, R. H. Meisinger, and R. E. Wingard, jun., *J. Amer. Chem. Soc.*, 1973, **95**, 2230.

[130] J. M. Bohen and M. M. Joullié, *J. Org. Chem.*, 1973, **38**, 2652. J. M. Bohen, Ph.D. Thesis, Univ. of Pennsylvania, 1973 [*Diss. Abs. Internat.* (*B*), 1973, **34**, 1420].

[131] W. L. Prins and R. M. Kellogg, *Tetrahedron Letters*, 1973, 2833.

6 Thiiren Derivatives

Theoretical Considerations.—Calculations (CNDO/2, *ab initio*) on thiiren indicate that 3*d*-orbital participation is likely to be unimportant in the structure and bonding. Calculations on thiiren 1-oxide indicate an inversion barrier of *ca.* 20 kcal mol^{-1}. The inversion barrier for *S*-protonated thiiren is calculated as 85 kcal mol^{-1}. Thiiren is compared with azirine and oxiren.[132] Other calculations (MINDO/3 and NDDO) on thiiren indicate that it should be relatively stable (heat of formation 205.4 kJ mol^{-1}) and that thiirens may be reasonable intermediates in reactions. Heats of formation of oxiren, 1*H*-azirine, cyclopropene, and the cyclopropenyl anion were calculated also. Thiiren is predicted to be more stable than the acyclic, isomeric carbene (119), the zwitterion (120), and the cyclic zwitterion-carbene



(119) (120) (121)

(121).[133] Hückel MO calculations have been done on thiiren and a large number of other sulphur-containing heterocyclic compounds.[134] Mobius and Hückel 'aromaticity' in thiiren 1,1-dioxide have been discussed. Because of the presence of the former, resulting from the sulphur d_{xy} orbital, thiiren 1,1-dioxides are not comparable to cyclopropenones. Calculations and hydrogen-bonding measurements on thiiren 1,1-dioxides indicate less negative charge on oxygen than in dimethyl sulphone. The smaller polarity of the S—O bond in thiiren 1,1-dioxide also is accompanied by a decrease in bond order, opposite to the effect in a series of dialkyl sulphones.[135]

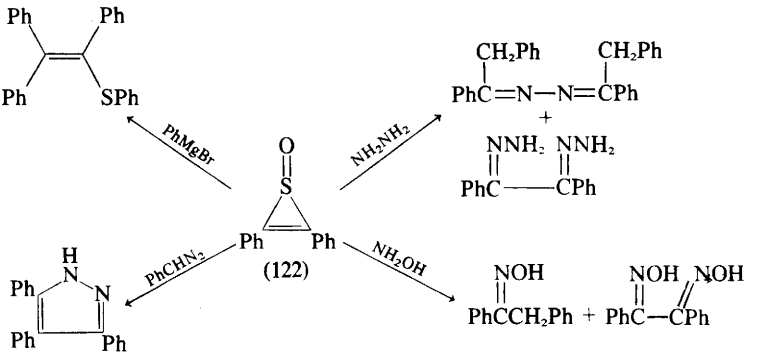
Intermediates in Reactions.—Attempts to prepare metal complexes of thiirens resulted in the formation of complexes of thioketocarbenes instead.[136,137] Treatment of 1,2,3-thiadiazoles and -selenadiazoles with di-iron enneacarbonyl gives thioketo- and selenoketo-carbene complexes. The formation of two carbene complexes from unsymmetrically substituted thia- or selena-diazoles suggests the intermediacy of a thiiren or seleniren complex.[137]

[132] D. T. Clark, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972, *Internat. J. Sulfur Chem.* (*C*), 1972, **7**, 11.
[133] M. J. S. Dewar and C. A. Ramsden, *J.C.S. Chem. Comm.*, 1973, 688.
[134] R. A. Hess, jun., and L. J. Schaad, *J. Amer. Chem. Soc.*, 1973, **95**, 3907.
[135] F. De Jong, A. J. Noorduin, T. Bouwman, and M. J. Janssen, *Tetrahedron Letters*, 1974, 1209.
[136] G. N. Schrauzer and H. Kisch, *J. Amer. Chem. Soc.*, 1973, **95**, 2501.
[137] P. G. Mente and C. W. Rees, *J.C.S. Chem. Comm.*, 1972, 418; T. L. Gilchrist, P. G. Mente, and C. W. Rees, *J.C.S. Perkin I*, 1972, 2165; T. L. Gilchrist, G. Gymer, and C. W. Rees, XXIII Internat. Congress Pure and Applied Chemistry, Boston, Mass., July, 1971, Butterworths, London, 1971, vol. 2, p. 275.

Thiirenium ions were invoked as intermediates to explain the enhanced rate of solvolysis of *trans*-1,2-dimethyl-2-methylthiovinyl 2,4,6-trinitrobenzenesulphonate,[138] in substitution reactions of β-phenylthiovinyl sulphonates,[139] and in additions of benzenesulphenyl chloride to diacetylenes.[139] Rationalizations of the mass spectra of various sulphur-containing five- and six-membered cyclic compounds have involved thiirenium ions.[140]

Support was obtained for the intermediacy of thiiren 1,1-dioxides in the reaction of αα-dihalogeno-sulphones with base to yield αβ-unsaturated sulphonic acids.[141]

Chemical Properties.—Some reactions of 2,3-diphenylthiiren 1-oxide (122), whose synthesis had been reported previously,[142] have been described.[143] It



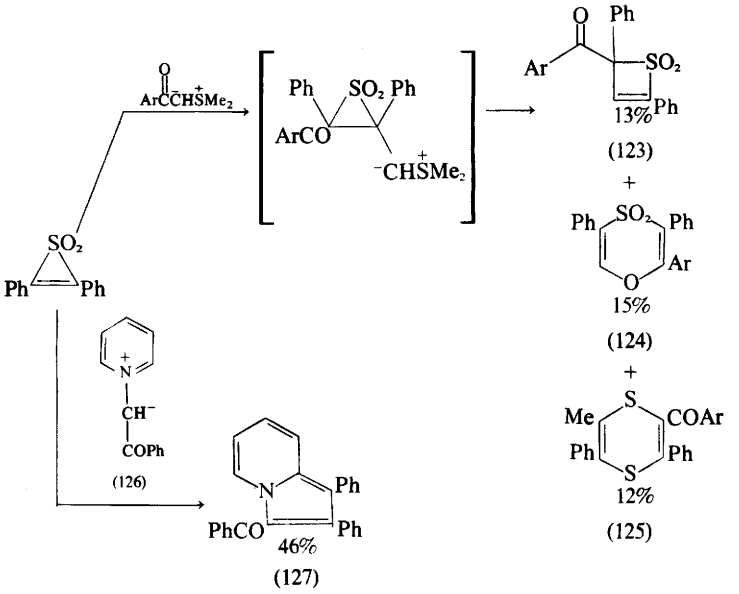
decomposes thermally to benzil and photochemically to diphenylacetylene. It could not be reduced catalytically. Reaction with hydrazine, 2,4-dinitrophenylhydrazine, hydroxylamine, phenylmagnesium bromide, and phenyldiazomethane gave products derived by rupture of the ring. The ^{19}F n.m.r. shielding parameters of a series of *m*- and *p*-fluorinated phenyl derivatives indicated that the substituent parameter σ_I decreases in the order thiiran 1,1-dioxide > thiiran 1-oxide > cyclopropenone and that σ_R decreases in the order cyclopropenone > thiiran 1,1-dioxide > thiiran 1-oxide.

The decomposition of thiiren 1,1-dioxides into sulphur dioxide and acetylenes is catalysed by transition-metal complexes of Pd^0, Pt^0, and Ir^I.

[138] A. Burighen, G. Modena, and U. Tonellato, *J.C.S. Perkin II*, 1972, 2026.
[139] G. Modena, G. Scorrano, and U. Tonellato, *J.C.S. Perkin II*, 1973, 493.
[140] (*a*) E. Barni, *J. Heterocyclic Chem.*, 1972, **9**, 501; (*b*) W. Schroth, H. Bahn, and R. Zschernitz, *Z. Chem.*, 1973, **13**, 424; (*c*) E. Fanghänel, R. Ebisch, and B. Adler, *Z. Chem.*, 1973, **13**, 431; (*d*) B. Adler and E. Fanghänel, *J. prakt. Chem.*, 1973, **315**, 1139; (*e*) R. Tabacchi, *Helv. Chim. Acta*, 1974, **57**, 324; (*f*) G. Julien, E. Vincent, J. Porte, and J. Roggers, *Org. Mass Spectrometry*, 1973, **7**, 463.
[141] C. Y. Meyers, L. L. Ho, G. J. McCollum, and J. Brance, *Tetrahedron Letters*, 1973, 1843.
[142] L. A. Carpino and H.-W. Chan, *J. Amer. Chem. Soc.*, 1971, **93**, 785.
[143] H.-W. Chan, Ph.D. Thesis, Univ. Massachusetts, 1972 [*Diss. Abs. Internat.* (*B*), 1972, **33**, 2525].

The metal is believed to act as an electron donor, causing a decrease in the bond order of the carbon–carbon double bond, which in turn causes the reactivity of the complexed thiiren 1,1-dioxide to approach that of a thiiran 1,1-dioxide, which is thermally less stable than its unsaturated counterpart.[144]

Treatment of 2,3-diphenylthiiren 1,1-dioxide with acyl-substituted sulphonium ylides gives a thiet dioxide (123), an oxathiin dioxide (124), and a dithiin (125). An intermediate acyl thiiran 1,1-dioxide was suggested. The pyridinium ylide (126) gave 3-benzoyl-1,2-diphenylindolizine (127).[145]



7 Three-membered Rings containing Sulphur and One or Two other Heteroatoms

Formation and Properties.—Stable thiadiaziridine 1,1-dioxides (129) have been obtained by treatment of *NN'*-dialkylsulphamides (128) with t-butyl hypochlorite and base.[146–148] The t-butyl derivative is rather labile but the

[144] D. N. Reinhoudt, C. G. Kouwenhoven, and J. P. Visser, *J. Organometallic Chem.*, 1973, **57**, 403.

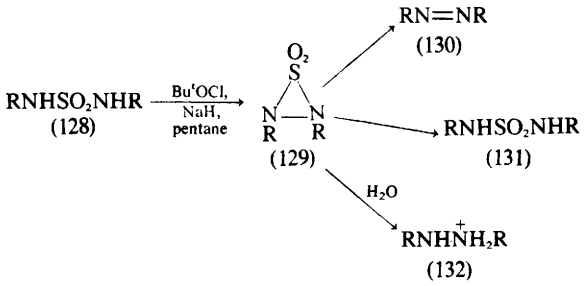
[145] Y. Hayasi, H. Nakamura, and H. Nozaki, *Bull. Chem. Soc. Japan*, 1973, **46**, 667.

[146] J. W. Timberlake and M. L. Hodges, *J. Amer. Chem. Soc.*, 1973, **95**, 634; J. W. Timberlake and M. L. Hodges, Abstracts of Papers, 165th National Meeting, Amer. Chem. Soc., Dallas, Texas, April, 1973, ORGN 50.

[147] H.-H. Chang and B. Weinstein, *J.C.S. Chem. Comm.*, 1973, 397; H. Chang and B. Weinstein, Abstracts of Papers, 166th National Meeting, Amer. Chem. Soc., Chicago, Illinois, August 1973, ORGN 48.

[148] H. Quast and F. Kees, *Tetrahedron Letters*, 1973, 1655.

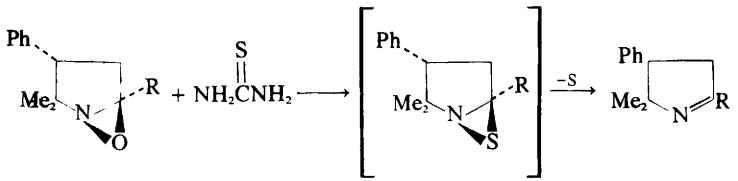
t-octyl and 1-adamantyl derivatives are quite stable. The structure of the t-octyl derivative has been determined by *X*-ray analysis: bond lengths are S—N, 1.62 Å; N—N, 1.67 Å.[149] Treatment of the 1,1,3,3-tetramethylbutyl (t-octyl) derivative with lithium aluminium hydride, chlorine, t-butyl hypochlorite, sodium methoxide, hydrogen chloride, phenyl-lithium, or heat



gives principally the azo-compound (130). Treatment with Grignard reagents, thiophenol, or hydrogen gives the sulphamide (131). Water yields the hydrazine salt (132) with the t-butyl derivative. No reaction occurred with hydrogen peroxide or potassium permanganate.[150] The t-butyl derivative gave an adduct with 1,3-diphenylisobenzofuran.[147] The adamantyl derivative decomposed to the extent of 43% after 15 min in boiling mesitylene whereas the t-butyl derivative decomposed completely in that time to sulphur dioxide and *trans*-2,2'-azoisobutane.[148]

The heteroborane 1-thia-*closo*-decaborane is a bicapped, Archimedean antiprism containing three-membered boron–sulphur rings.[151]

Intermediates in Reactions.—Attempts to prepare thiaziridines or selenaziridines by treatment of oxaziridines (133) with thiourea, potassium thiocyanate, potassium ethylxanthate, potassium selenoxanthate, and triphenylphosphine sulphide gave imines (135) instead, although



(133) (134) (135)

thiaziridines (134) were believed to be intermediates.[152] Neither were thiaziridines obtained by the decomposition of 1,4,2-oxathiazolidines.

[149] L. M. Trefonas and L. D. Cheung, *J. Amer. Chem. Soc.*, 1973, **95**, 636.
[150] J. W. Timberlake, M. L. Hodges, and A. W. Garner, *Tetrahedron Letters*, 1973, 3843.
[151] W. R. Pretzer and R. W. Rudolph, *J. Amer. Chem. Soc.*, 1973, **95**, 931.
[152] D. S. Black and K. G. Watson, *Austral. J. Chem.*, 1973, **26**, 2159, 2177, 2473, 2491.

Thiaziridines were suggested as intermediates in the thermal decomposition of iminothiocarbonyl compounds[153] and in the reaction of thiobenzophenone with aminosulphuric acid.[154] Thiaziridinium ions were considered as possible intermediates in the reaction of quaternary salts of disubstituted thioamides with sodium azide[155] and in the photochemical rearrangement of methylisothiazoles.[156] Thiazirines and thiazirinium cations have been proposed as intermediates in the light-catalysed decomposition of 4-phenyl-1,3,2-oxathiazolylio-5-oxide,[157] in the mass spectrometric fragmentation of 1,2,3- and 1,3,4-thiadiazoles and 1,3-thiazoles,[158] in the thermolysis of a sulphoximide,[159] and in the mass spectrometric fragmentation of *C*-sulphonylthioformamides.[160] A thiadiaziridine 1-oxide may be an intermediate in the thermal or photochemical reaction of aryl azides with *N*-sulphinylamines,[161] and a thiadiaziridine resonance structure was invoked to account for the increased electron density at C-4 in 1,2,3-thiadiazole 2-oxides.[162] Three-membered rings containing one sulphur and one oxygen atom (thioxirans) have been put forth as intermediates in the oxidation of *C*-sulphonylthioformamides,[160,163] in the mass spectrometric fragmentation of sulphines,[164] in the bis-(*S*-*p*-tolyl) ester of diphenic acid,[165] and in the decomposition of the dimethyl sulphoxide radical.[166] The retention of configuration at the sulphur atom during halogenation of optically active sulphoxides in the absence of metal ions has been interpreted on the basis of a cyclic three-membered intermediate containing sulphur and halogen.[167] An intermediate containing three sulphur atoms in a ring was suggested in the reaction of tetrahydrothiophen with di-isopropoxy disulphide.[168]

8 Thietans

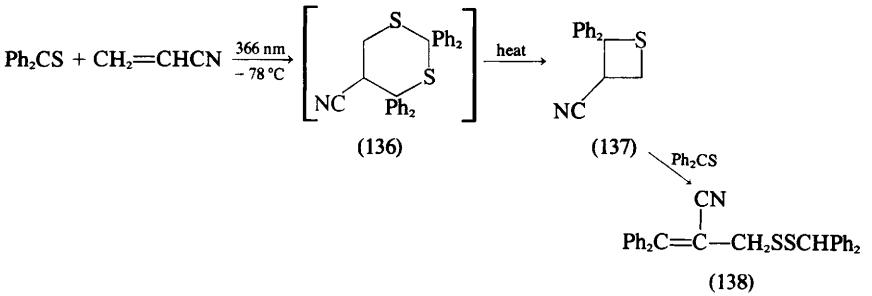
Physical Properties.—The structure of 2-isopropylidene-1,1,7,7,9,9-hexamethyl-3,5,10,11-tetrathiodispiro[3,1,3,2]undecane-8-thione, which contains

[153] S. Tamagaki, K. Sakaki, and S. Oae, *Bull. Chem. Soc. Japan*, 1973, **46**, 2608.
[154] M. M. Campbell and D. M. Evgenios, *J.C.S. Perkin I*, 1973, 2862.
[155] S. I. Mathew and F. Stansfield, *J.C.S. Perkin I*, 1974, 540.
[156] A. Lablache-Combier and A. Pollet, *Tetrahedron*, 1972, **28**, 3141.
[157] A. Holm, N. Harrit, K. Bechgaard, O. Buchardt, and S. E. Harnung, *J.C.S. Chem. Comm.*, 1972, 1125; V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 194.
[158] K. T. Potts and R. Armbruster, *J. Heterocyclic Chem.*, 1972, **9**, 651; K. T. Potts, R. Armbruster, E. Houghton, and J. Kane, *Org. Mass Spectrometry*, 1973, **7**, 203; A. Shoeb, S. P. Popli, and R. Gopalchari, *ibid.*, p. 555.
[159] D. J. Anderson, D. C. Horwell, E. Stanton, T. L. Gilchrist, and C. W. Rees, *J.C.S. Perkin I*, 1972, 1317.
[160] N. H. Nilsson, C. Jacobson, O. N. Sørensen, N. K. Haunsøe, and A. Senning, *Chem. Ber.*, 1972, **105**, 2854.
[161] L. Benati, G. de Luca, G. Maccagnani, and A. Tundo, *J.C.S. Chem. Comm.*, 1972, 702.
[162] P. Braun, K.-P. Zeller, H. Meier, and E. Müller, *Tetrahedron*, 1972, **28**, 5655.
[163] N. H. Nilsson and A. Senning, *Angew. Chem.*, 1972, **84**, 293.
[164] A. Tangerman, L. Thijs, A. P. Anker, and B. Zwanenburg, *J.C.S. Perkin II*, 1973, 458; A. Tangerman and B. Zwanenburg, *ibid.*, p. 461.
[165] J. Martens, K. Praefcke, and H. Schwarz, *Tetrahedron Letters*, 1973, 3707.
[166] K. Gollnick and H.-U. Stracke, *Pure Appl. Chem.*, 1973, **33**, 217.
[167] M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J.C.S. Perkin I*, 1972, 1886.
[168] H. Matsuyama, H. Minato, and M. Kobayashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 1512.

a thietan ring with an α-isopropylidene group, has been determined by *X*-ray analysis.[169] The structure of thietan has been studied by electron diffraction,[170] and its ring-puckering vibrations have been investigated by i.r. and low-frequency Raman spectroscopy.[171] The ^{1}H n.m.r. spectrum of thietan oriented in a nematic solvent indicates that the ring is not rigidly planar because of the puckering vibrations.[172a] I.r. studies on 3-chlorothietan indicate that there is one conformer, either planar or puckered.[172b] The ion–cyclotron resonance spectrum of 2,4-dimethylthietan has been recorded.[173]

Formation.—Treatment of epichlorohydrin with potassium thioacetate yields 3-acetoxythietan;[17b] 2-chloromethylthiiran with potassium thioacetate or potassium di-(*O*-ethyl)dithiophosphate gives the corresponding 3-substituted thietan.[45d] 3,3-Bis(hydroxymethyl)thietan is obtained by treatment of pentaerythritol with diethyl carbonate followed by treatment of the cyclic carbonate with potassium thiocyanate.[174]

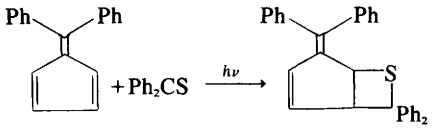
The photocycloaddition of thiocarbonyl compounds to olefins often gives thietans. The thietan (137) formed from thiobenzophenone and acrylonitrile at 366 nm is derived from the thermal decomposition of the 1,3-dithian (136) believed to be produced *via* the second excited singlet state (π, π^*) of the thioketone. Irradiation at 577 nm gives only a very small amount of thietan. The thietan reacts further with thiobenzophenone to give disulphide (138).[175]



(136) (137) (138)

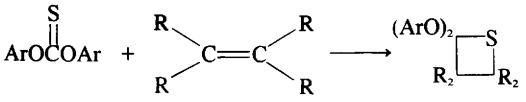
[169] C. D. Shirrell and D. E. Williams, *Acta Cryst.*, 1973, **B29**, 2128.
[170] K. Karakida, K. Kuchitsu, and R. K. Bohn, *Chem. Letters*, 1974, 159.
[171] H. Wieser and J. A. Duckett, *J. Mol. Spectroscopy*, 1974, **50**, 443; J. R. Durig, A. C. Shing, L. A. Carreira, and Y. S. Li, *J. Chem. Phys.*, 1972, **57**, 4398.
[172] (*a*) C. L. Khetrapal, A. C. Kunwar, and A. Saupe, *Mol. Phys.*, 1973, **25**, 1405; P. F. Swinton, *J. Magn. Resonance*, 1974, **13**, 304; A. d'Annibale, L. Lunazzi, G. Fronza, R. Mondelli, and S. Bradamante, *J.C.S. Perkin II*, 1973, 1908; (*b*) B. A. Arbuzov, A. R. Remizov, and O. N. Nuretdinova, *Zhur. priklad. Spektroskopii*, 1973, **19**, 733 (*Chem. Abs.*, 1974, **80**, 47 354).
[173] K. B. Tomer and C. Djerassi, *J. Amer. Chem. Soc.*, 1973, **95**, 5335.
[174] P. E. Throckmorton, U.S.P. 3 644 404, Feb. 22, 1972 (*Chem. Abs.*, 1972, **76**, 140 766).
[175] P. de Mayo and A. A. Nicholson, *Israel J. Chem.*, 1972, **10**, 341; P. de Mayo and H. Shizuka, *Mol. Photochem.*, 1973, **5**, 339; *J. Amer. Chem. Soc.*, 1973, **95**, 3942; D. R. Kemp, A. H. Lawrence, C. L. Liao, R. O. Lautfy, P. de Mayo, A. A. Nicholson, and S. Paszyc, XXIII Internat. Congress Pure and Applied Chemistry, Boston, Mass., July 1971, Butterworths, London, 1971, vol. 1, p. 367.

A patent claims good yields of thietans from thiobenzophenone and acrylonitrile, *trans*-dichloroethylene, methyl acrylate, vinyl acetate, and styrene.[176] Irradiation of 6,6-diphenylfulvene and thiobenzophenone gave thietan (139); no thietan was obtained with cyclo-octatetraene (only a



(139)

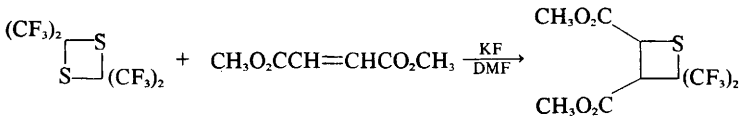
1,4-adduct was obtained) or norbornene and only a low yield (7%) was obtained with acenaphthylene.[177] Further details of the reaction of adamantanethione with olefins have been reported.[178] The photoaddition of *O*-alkyl thiobenzoates to olefins yields 2-phenyl-2-alkoxythietans,[179] and high yields of thietans (141) are obtained by irradiation of mixtures of thionocarbonates (140) and olefins.[180] 2,2-Dichlorothietans are obtained from



(140) (141)

olefins and thiophosgene,[181] but cyclohexa-1,3-diene gave only the product of a 4+2 cycloaddition.[182]

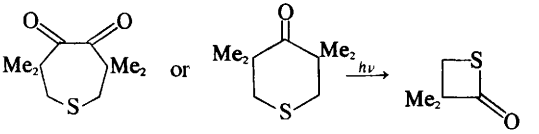
Thietans substituted with two trifluoromethyl groups (143) are obtained by treatment of hexafluorothioacetone dimer (142) and olefins (*e.g.* cyclohexene, dimethyl maleate) with potassium fluoride–DMF.[183]



(142) (143)

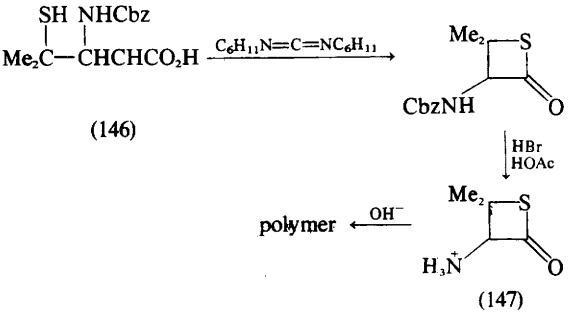
2-Thietanones (β-thiolactones) have been obtained by hydrolysis of 2,2-dichlorothietans,[181] by photolysis of diketone (144) or thiacyclohexanone

[176] A. Ohno, Y. Ohnishi, and G. Tsuchihashi, U.S.P. 3 779 880, Dec. 18, 1973 (*Chem. Abs.*, 1974, **80**, 120 736).
[177] T. S. Cantrell, *J. Org. Chem.*, 1974, **39**, 853.
[178] C.-C. Liao, Ph.D. Thesis, University of Western Ontario, 1972 [*Diss. Abs. Internat.* (*B*), 1973, **34**, 139].
[179] A. Ohno, T. Koizumi, and Y. Akasaki, *Bull. Chem. Soc. Japan*, 1974, **47**, 319.
[180] H. Gotthardt and M. Listl, *Tetrahedron Letters*, 1973, 2849.
[181] H. Gotthardt, *Tetrahedron Letters*, 1973, 1221.
[182] H. J. Reich and J. E. Trend, *J. Org. Chem.*, 1973, **38**, 2637.
[183] T. Kitazume and N. Ishikawa, *Chem. Letters*, 1973, 267.



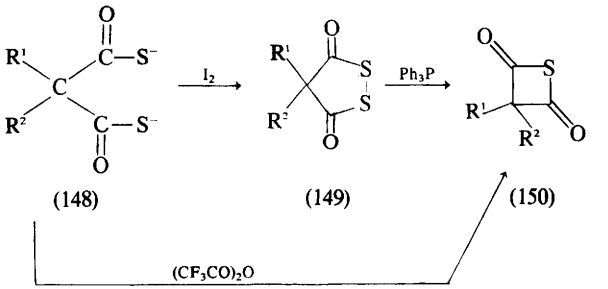
(144) (145)

(145),[184] and from *N*-benzoxycarbonylpenicillamine (146).[185] In the latter case, the benzoxycarbonyl group can be removed; the amino-derivative (147) is stable only as a salt. Thietan-2,4-diones (150) are obtained in good



(146) (147)

yield by treatment of bis-pyridinium salts of bis-thiomalonic acids (148) with trifluoroacetic anhydride, or by treatment of 1,2-dithiolan-3,4-diones (149) with triphenylphosphine.[186] 2-Thietanols are claimed to be obtained from $\alpha\beta$-unsaturated aldehydes and hydrogen sulphide and are said to be useful as flavouring substances and aromas.[187]



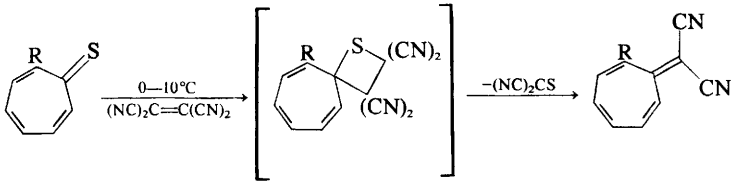
(148) (149) (150)

[184] J. Kooi, H. Wynberg, and R. M. Kellogg, *Tetrahedron*, 1973, **29**, 2135.

[185] W. S. Hanley, P. L. Kelly, W. J. Sanders, J. E. White, and L. Field, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 213; L. Field, W. S. Hanley, P. L. Kelly, W. J. Sanders, J. E. White, I. A. Jaffe, and P. Merryman, *J. Medicin. Chem.*, 1973, **16**, 1152.

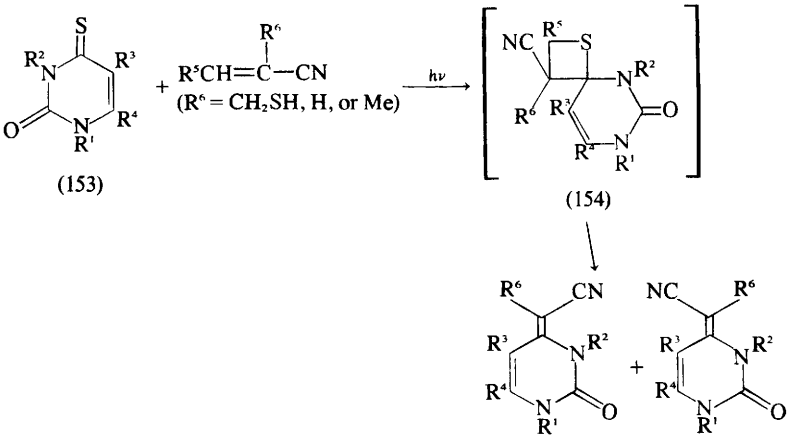
[186] J. H. Schauble and J. D. Williams, *J. Org. Chem.*, 1972, **37**, 2514.

[187] P. Dubs, H. Kuentzel, and M. Pesaro, Ger. Offen. 2 314 103, Oct. 18, 1973 (*Chem. Abs.*, 1974, **80**, 14 833).

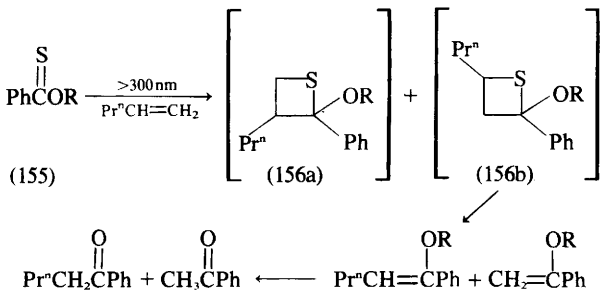


(151) (152)

Intermediates in Reactions.—The reaction of tetracyanoethylene with tropothiones (151) is believed to proceed *via* thietan (152).[188] The light-catalysed cycloadditions of 4-thiouracil derivatives (153) to $\alpha\beta$-unsaturated nitriles[189] and of *O*-alkyl thiobenzoates (155) to olefins[190] are believed to involve thietan intermediates (154) and (156a, b), respectively. A quasi-thietan transition state (158) has been invoked for the conversion of (157)

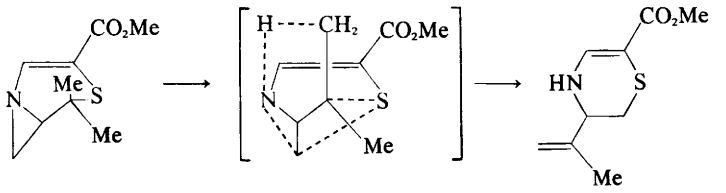


(153) (154)



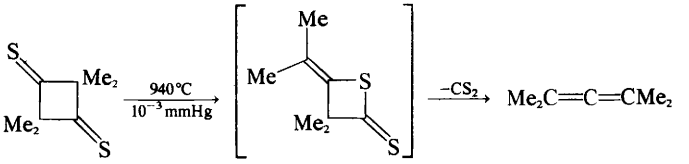
(155) (156a) (156b)

[188] T. Machiguchi, K. Okuma, M. Hoshino, and Y. Kitahara, *Tetrahedron Letters*, 1973, 2011.
[189] J. L. Fourrey, P. Jouin, and J. Moron, *Tetrahedron Letters*, 1973, 3229.
[190] A. Ohno, T. Koizumi, and Y. Akazaki, *Tetrahedron Letters*, 1972, 4993.



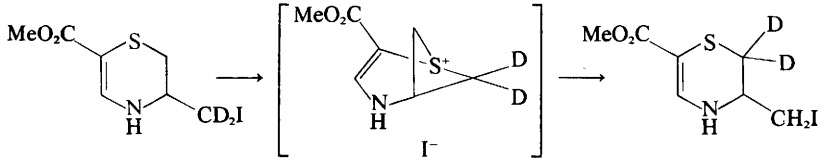
(157) (158) (159)

into (159).[191] Flash thermolysis of tetramethylcyclobutane-1,3-dithione (160) yields tetramethylallene and carbon disulphide, probably *via* the 2-thioketothietan (161).[192]



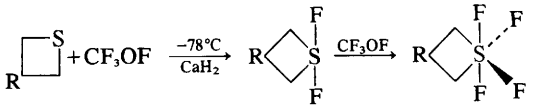
(160) (161)

Tricyclic thietanium ions were considered as intermediates in the photorearrangements of methylisothiazoles[156] and in the rearrangements of dihydro-1,4-thiazine (162).[193] No evidence was obtained for a thietan ylide in the decomposition of sodium salts of toluene-*p*-sulphonylhydrazones of cyclic sulphides.[194]



(162)

Chemical Properties.—The difluorosulphuranes (163a, b)[195a] and the tetrafluoropersulphuranes (164a, b)[195b] were obtained by treatment of the

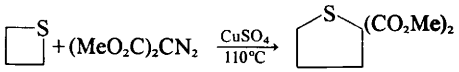


(163a) R = H (164a) R = H
(163b) R = Me (164b) R = Me

[191] J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 1973, 2460.
[192] G. Seybold, *Tetrahedron Letters*, 1974, 555.
[193] A. R. Dunn and R. J. Stoodley, *J.C.S. Perkin I*, 1972, 2509.
[194] P. Y. Johnson, E. Koza, and R. E. Kohrman, *J. Org. Chem.*, 1973, **38**, 2967.
[195] (*a*) D. B. Denney, D. Z. Denney, and Y. F. Hsu, *J. Amer. Chem. Soc.*, 1973, **95**, 4064; (*b*) *ibid.*, p. 8191.

corresponding thietans with trifluoromethyl hypofluorite, a general synthesis for acyclic, alicyclic, and aryl fluorosulphuranes. The compounds are unstable at room temperature. The ^{19}F n.m.r. spectra of (163b) indicate ionization at −40 to −20 °C, but no evidence of pseudorotation. The ^{19}F n.m.r. spectra of (164a) and (164b) support the assignment of structures which involve two axial and two equatorial fluorines.

Treatment of 3-chlorothietan with potassium thiophenoxide[196] or potassium thiobutoxide[80] gave phenyl or n-butyl allyl disulphide. The thietan ring in a tricyclic system is opened in various reactions.[96] While most cyclic sulphides give ylides on treatment with dimethyl diazomalonate, thietan gave 26% of ring-expanded product (165). In the absence of copper sulphate a polymer was obtained.[197]



(165)

3-Chloropropyl thioesters are formed by the reaction of thietan with acid chlorides. Hydrogen chloride alone gave a small amount of 3-chloropropanethiol at room temperature but polymeric material at 30—100 °C.[198] Charge-transfer complexes of thietan with electron-acceptors such as maleic anhydride, tetranitromethane, or tetracyanoethylene are believed to be intermediates in polymerization.[199] The cationic polymerization of 3,3-dimethylthietan has been described.[200] Treatment of 2-thietanones with MeCOSCl gave 1,2-dithiolan-3-ones.[201]

The light-catalysed decomposition of thietan yields ethylene and thioformaldehyde as the primary products. Propylene, formerly considered as a primary product, is believed to arise from a secondary photoreaction of thioformaldehyde and thietan.[202] A similar light-catalysed cleavage occurs with 2-phenyl-2-alkoxythietans.[179] The kinetics of thermolysis at 860—1170 K of thietan to thioformaldehyde and ethylene have been investigated;[203] thermolysis at 490 °C also is believed to yield thioformaldehyde.[204] Thietan-2,4-diones decompose thermally to ketens.[186]

[196] B. Arbuzov and O. N. Nuretdinova, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1971, 2594 (*Chem. Abs.*, 1972, **76**, 126 681).

[197] W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyama, S. Nakaido, and T. Migita, *J. Org. Chem.*, 1972, **37**, 1721.

[198] B. V. Kurgane and S. A. Giller, *Chem. Heterocyclic Compounds*, 1973, **7**, 557.

[199] G. A. Oreshkina, L. L. Stotskaya, and B. A. Krentsel, *Proc. Acad. Sci. U.S.S.R., Chem. Sect.*, 1972, **207**, 933; L. L. Stotskaya, G. A. Oreshkina, and B. A. Krentsel, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972; *Internat. J. Sulfur Chem* (*A*), 1972, **2**, 246.

[200] E. J. Goethals and W. Drijivers, *Makromol. Chem.*, 1973, **165**, 329.

[201] T. P. Vasileva, M. G. Linkova, O. V. Kildisheva, and I. L. Knunyants, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 489 (*Chem. Abs.*, 1972, **77**, 34 395).

[202] D. R. Dice and R. P. Steer, *J. Phys. Chem.*, 1973, **77**, 434.

[203] P. Jeffers, C. Dasch, and S. H. Bauer, *Internat. J. Chem. Kinetics*, 1973, **5**, 545.

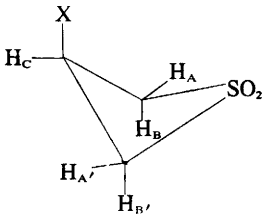
[204] J. P. Buchanan, Ph.D. Thesis, Univ. Maryland, 1972 [*Diss. Abs. Internat.* (*B*), 1972), **33**, 106].

9 Thietan 1-Oxides

Heats and enthalpies of oxidation of *cis*- and *trans*-3-t-butylthietan 1-oxides to the 1,1-dioxides by perlauric acid at 298 K have been determined.[205] The structures of *cis*-2,4-diphenylthietan 1-oxide[206] and the seven-co-ordinate complex of 3,3-dimethylthietan 1-oxide with the shift reagent $Eu(dpm)_3$[207] have been established by *X*-ray analysis. The mass spectrum of thietan 1-oxide shows fragmentation to $C_3H_5^+$ and $C_3H_5S^+$.[208]

10 Thietan 1,1-Dioxides

Physical Properties.—Structure determinations by *X*-ray analysis of 2,2-dimethylthietan 1,1-dioxide[209] and of 3-chlorothietan and 3-hydroxythietan 1,1-dioxides[210] have been accomplished. The vibrational frequencies of the sulphone group in thietan 1,1-dioxide and a number of other sulphones have been compared with hydrogen-bonding ability, calculated π charge densities and S—O bond orders.[211] The signs of the proton coupling constants (^4J) in 3-substituted thietan 1,1-dioxides (166) have been determined and found to

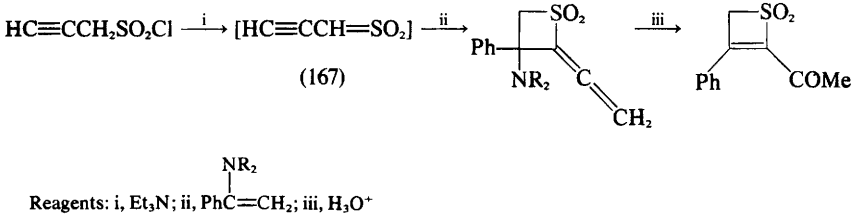


(166) X = Cl, OH, or OAc

be similar to those in cyclobutanes. $J_{AA'}$ and $J_{BB'}$ were positive and $J_{AB'}$ and $J_{A'B}$ were negative. The ring was believed to be puckered; no significant averaging of axial and equatorial protons was observed from 150 to −130 °C.[212]

Formation and Chemical Properties.—The structure of one of the adducts obtained from azibenzil and sulphur dioxide has been determined to be an oxathiin[213] instead of the thietan-3-one 1,1-dioxide proposed earlier.[214] Derivatives of 3-aminothietan 1,1-dioxide have been obtained by addition of

[205] S. A. Khan, T. McAllister, and H. Mackle, *J.C.S. Chem. Comm.*, 1973, 121.
[206] G. L. Hardgrove, jun., J. S. Bratholdt, and M. M. Lein, *J. Org. Chem.*, 1974, **39**, 246.
[207] J. J. Uebel and R. M. Wing, *J. Amer. Chem. Soc.*, 1972, **94**, 8910.
[208] S. Tamagaki and S. Oae, *Bull. Chem. Soc. Japan*, 1972, **45**, 1767.
[209] M. L. Ziegler, J. Weiss, H. Schildknecht, N. Grund, and H. E. Sasse, *Annalen.*, 1973, 1702.
[210] G. D. Andreetti, G. Bocelli, and P. Sgarabotto, *Cryst. Struct. Comm.*, 1973, **2**, 323, 499.
[211] F. De Jong and M. J. Janssen, *Rec. Trav. chim.*, 1973, **92**, 1073.
[212] C. Cistaro, G. Fronza, R. Mondelli, S. Bradamante, and G. Pagani, *Tetrahedron Letters*, 1973, 189.
[213] N. Yatsuoka, N. Kasai, M. Tanaka, T. Nogai, and N. Tokura, *Acta. Cryst.*, 1972, **B28**, 3393.
[214] T. Nogai, M. Tanaka, and N. Tokura, *Tetrahedron Letters*, 1968, 6293.

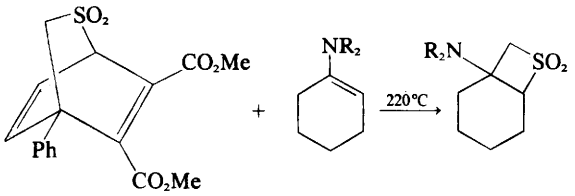


(167)

Reagents: i, Et_3N; ii, $PhC(NR_2)=CH_2$; iii, H_3O^+

Scheme 5

chlorosulphene[215] and the acetylenic sulphene (167)[216] to enamines (Scheme 5). Extrusion of sulphene from (168) in a retro-Diels–Alder reaction has been demonstrated by trapping it with the morpholine enamine of cyclohexanone.[217]



(168)

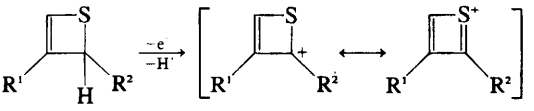
Some of these 3-aminothietan 1,1-dioxide derivatives have been claimed to be useful as anti-inflammatory agents[218] and as sedatives.[219] Cycloadditions of sulphenes with αβ-unsaturated sulphides also yield thietan sulphones.[220] Aryl propargyl sulphones eliminate sulphur dioxide under electron impact. *ortho*-Substituents reduce the amount of sulphur dioxide, and a substituted thietan 1,1-dioxide intermediate was suggested.[221]

The carbanion obtained by treatment of 3,3-dimethylthietan 1,1-dioxide with n-butyl-lithium reacts with a variety of electrophilic reagents. Bromination is effected by the bromo-derivative of Meldrum's acid but halogenations by bromine, *N*-bromosuccinimide, and *N*-chlorobenzotriazole were unsuccessful.[222] The anion also is reported to react with acid chlorides and aromatic aldehydes to give the expected adducts.[223]

[215] C. T. Goralski and T. E. Evans, *J. Org. Chem.*, 1972, **37**, 2080.
[216] S. Bradamante, P. Del Buttero, and S. Maiorana, *J.C.S. Perkin I*, 1973, 612; P. Del Buttero and S. Maiorana, *ibid.*, p. 2540.
[217] J. F. King and E. G. Lewars, *J.C.S. Chem. Comm.*, 1972, 700; *Canad. J. Chem.*, 1973, **51**, 3044.
[218] M. H. Rosen and H. M. Blatter, U.S.P. 3 729 487, April 24, 1973 (*Chem. Abs.*, 1973, **79**, 18 556).
[219] M. Wolf, U.S.P. 3 632 579, Jan. 4, 1972 (*Chem. Abs.*, 1972, **76**, 99 497).
[220] N. P. Petukhova, W. I. Kurilkin, and E. N. Prilezhaeva, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972, *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 243.
[221] D. K. Bates and B. S. Thyagarajan, *Internat. J. Sulfur Chem.*, 1973, **8**, 57.
[222] J. P. Marino, *J.C.S. Chem. Comm.*, 1973, 861.
[223] J. P. Marino and D. P. Hesson, Abstracts of Papers, 163rd National Meeting, Amer. Chem. Soc., Boston, Mass., April, 1972, ORGN 89.

11 Thiets

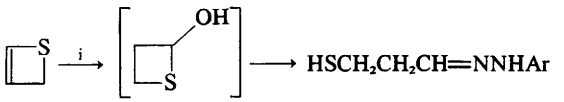
The syntheses of five thiets (169) *via* the cycloadducts of sulphenes to enamines have been reported.[224] They are thermally unstable and undergo



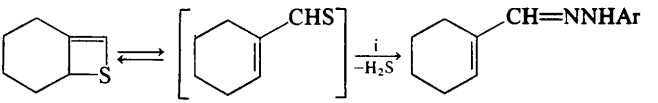
(169) a: $R^1 = R^2 = H$
b: $R^1R^2 = (CH_2)_4$
c: $R^1R^2 = (CH_2)_5$
d: $R^1 = Et$, $R^2 = Me$
e: $R^1 = Pr^n$, $R^2 = Et$

(170)

ring-opening with acidic 2,4-dinitrophenylhydrazine (Scheme 6). The mass spectra of the thiets show abundant ions for the parent molecule minus a hydrogen atom, suggesting the possibility of formation of thiet cations (170).



(169a)



(169b)

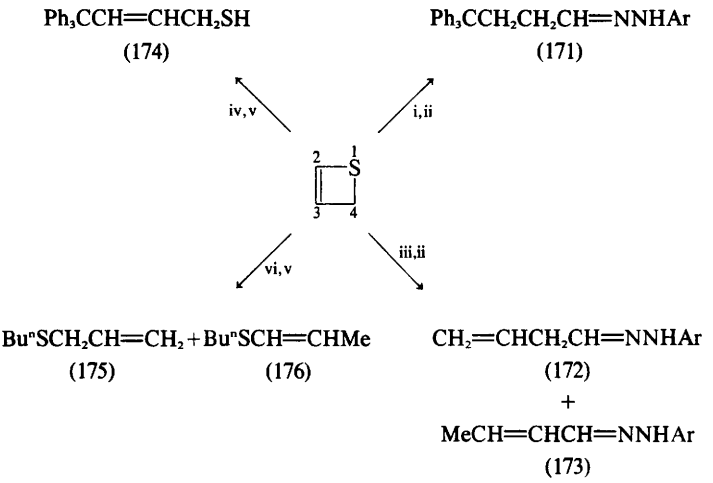
Reagents: i, $ArNHNH_2$–H^+, H_2O

Scheme 6

Evidence (n.m.r.) was presented indicating proton exchange of thiet itself in sodium methoxide–[^{2}H]methanol was faster than the rate of exchange of diallyl sulphide under the same conditions. However, the thiet could not be recovered from the reaction. Treatment of thiets with stronger bases, such as alkyl-lithium reagents, resulted in formation of deep red-purple solutions from which only ring-opened products could be obtained.[225] Although the anion of thiet is formally a 6π-electron system, simple Hückel MO calculations indicate a stability less than that of the anion of cyclopentadiene; proper allowance for electron repulsions would doubtless further reduce the calculated stabilization. The mode of ring opening of thiet by

[224] D. C. Dittmer, P. L. Chang, F. A. Davis, M. Iwanami, I. K. Stamos, and K. Takahashi, *J. Org. Chem.*, 1972, **37**, 1111.
[225] D. C. Dittmer, P. L. Chang, F. A. Davis, I. K. Stamos, and K. Takahashi, *J. Org. Chem.*, 1972, **37**, 1116.

organolithium and potassium reagents depends on the reagent (Scheme 7). Triphenylmethylpotassium attacks C-4 to yield a thioaldehyde (96% yield), isolated as a 2,4-dinitrophenylhydrazone (171). The potassium salt of dimethyl sulphoxide also attacks C-4 to yield a thioaldehyde, from which the methyl sulphenate anion has been eliminated, the product mixture (52%

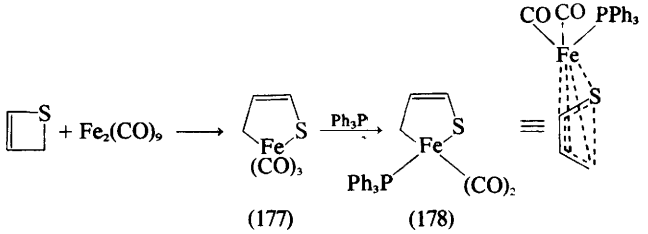


Reagents: i, Ph_3CK; ii, $ArNHNH_2$; iii, $MeS(O)CH_2K$; iv, Ph_3CLi; v, H^+; vi, Bu^nLi

Scheme 7

yield) also being identified as its 2,4-dinitrophenylhydrazones (172) and (173). Triphenylmethyl-lithium apparently attacks C-2, the $\alpha\beta$-unsaturated thiol (174) being obtained. n-Butyl-lithium attacks sulphur to yield sulphides (175) and (176) in 45% yield.

Treatment of thiets with di-iron enneacarbonyl yields complexes, *e.g.* (177), of thioacrolein.[226] *X*-Ray analysis of thioacrolein triphenylphosphine dicarbonyliron (178) established the structure.[227]



[226] K. Takahashi, M. Iwanami, A. Tsai, P. L. Chang, R. L. Harlow, L. E. Harris, J. E. McCaskie, C. E. Pfluger, and D. C. Dittmer, *J. Amer. Chem. Soc.*, 1973, **95**, 6113.
[227] R. L. Harlow and C. E. Pfluger, *Acta. Cryst.*, 1973, **B29**, 2633.

Certain spirobenzothiets are said to be useful in the synthesis of 1,3-diazacycloalkene salts and benzothiazepins, the former being hypertensive agents and the latter coronary blood-vessel dilators.[228] Fragmentation of the photochemical adducts of carbonyl compounds with 2,5-dimethylthiophen may proceed *via* thiets.[229] Thiet cations have been proposed as intermediates in the mass spectrometric fragmentation of isothiazoles,[230] thiazoles,[140e] 1,3-dithiole-2-thiones,[140d] 1,3-dithiolen-2-ones,[140d] *S*-ethyl thiobenzoate,[231] and thianaphthene sulphones.[232]

12 Thiet 1,1-Dioxides and Thiet 1-Oxides

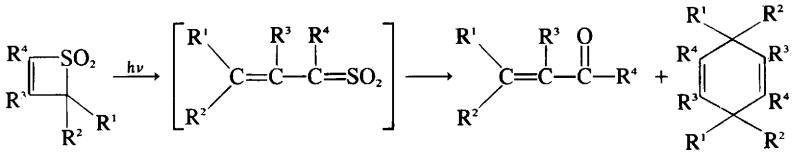
The magnitudes and signs of all C–H and H–H coupling constants for thiet 1,1-dioxide have been determined,[233] and its microwave spectrum has been recorded.[234]

The synthesis and properties of optically active thiet 1,1-dioxides have been reviewed.[235] The generation of sulphenes from *p*-nitrophenyl sulphonates is claimed to have advantages in the preparation of 3-amino-4-arylthiet 1,1-dioxides from acetylenic amines, principally in the avoidance of the presence of triethylamine hydrochloride, which is believed to cause isomerization of the thiet derivative.[236] Several other thiet dioxides have been obtained by reaction of a sulphene with an acetylenic amine.[218,237,238] They are claimed to be anti-inflammatory agents.[218,238] The formation of a thiet 1,1-dioxide from acetylenic sulphine (167) and an enamine has been noted previously.[216] A number of substituted thiet dioxides have been prepared by addition of sulphene to enamines followed by a Cope elimination of the amine. These compounds were tested for analgesic activity but none was found.[239] Thiet 1,1-dioxide (123) is obtained from 2,3-diphenylthiiren 1,1-dioxide and aroyl-substituted sulphonium ylides.[145] An improvement in the synthesis of 2*H*-benzo[*b*]thiet 1,1-dioxide has been reported.[240] A cation of pyridothiet 1-oxide was suggested as a

[228] H. Hagen, A. Amann, and H. Giertz, Ger. Offen. 2 219 841, Oct. 25, 1973; 2 215 606, October 11, 1973 (*Chem. Abs.*, 1974, **80**, 14 955, 14 970).
[229] C. Rivas and R. A. Bolivar, *J. Heterocyclic Chem.*, 1973, **10**, 967.
[230] J. Julien, E. Vincent, J. Poite, and J. Roggero, *Org. Mass Spectrometry*, 1973, **7**, 463.
[231] K. B. Tomer and C. Djerassi, *Org. Mass Spectrometry*, 1973, **7**, 771.
[232] V. S. Falko, V. I. Khvostenko, V. E. Udre, and M. G. Voronkov, *Chem. Heterocyclic Compounds*, 1973, **7**, 300.
[233] G. Fronza, A. Gamba, R. Mondelli, and G. Pagani, *J. Magn. Resonance*, 1973, **12**, 231.
[234] W. Ralowski, S. Ljunggren, and J. Mjöberg, *Acta Chem. Scand.*, 1973, **27**, 3128.
[235] L. A. Paquette, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972, *Internat. J. Sulfur Chem.* (*C*), 1972, **7**, 73.
[236] L. W. Christensen, *Synthesis*, 1973, 534.
[237] M. E. Kuehne and H. Linde, *J. Org. Chem.*, 1972, **37**, 1846.
[238] M. H. Rosen and H. M. Blatter, U.S.P. 3 644 632, Feb. 22, 1972 (*Chem. Abs.*, 1972, **76**, 140 484); U.S.P. 3 639 614, February 1, 1972 (*Chem. Abs.*, 1972, **76**, 113 051).
[239] J. E. Coates, Ph.D. Thesis, Univ. British Columbia, 1972 [*Diss. Abs. Internat.* (*B*), 1972, **33**, 2537].
[240] B. Lamm and J. Simonet, *Acta Chem. Scand.*, 1974, **B28**, 147.

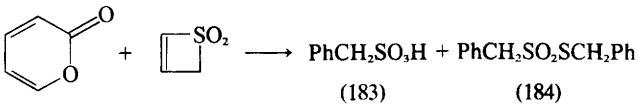
fragment in the mass spectrum of a thieno-pyridine sulphone.[241] Thiet 1-oxides have not yet been obtained as stable substances.

Photolysis of thiet 1,1-dioxides (179), either at 235 nm or at 350 nm with a sensitizer, yields unsaturated ketones (181) by loss of sulphur monoxide from a vinyl sulphine intermediate (180). A small amount of cyclohexadiene



(179) (180) (181) (182)

(182) was formed also.[242] Thermolysis of 2,4-diarylthiet 1,1-dioxides also yields $\alpha\beta$-unsaturated ketones. The reaction of water with 2,4-diphenylthiet 1,1-dioxide gave 1,3-diphenylpropene-3-sulphonic acid. Hydrogen cyanide and nitroethane add to the double bond of these thiet dioxides to give thietan dioxides.[239] Treatment of thiet 1,1-dioxide with α-pyrone did not yield a cycloadduct; instead, benzylsulphonic acid (183) and benzyl α-toluenethiosulphonate (184) were obtained, probably by decomposition of



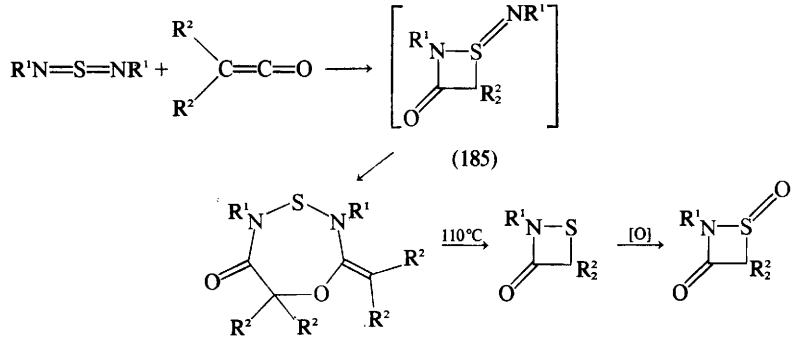
(183) (184)

an intermediate adduct. Neither 6-methyl-2-pyrone nor 3-phenylthiet 1,1-dioxide underwent this reaction.[243] Thiet 1,1-dioxide tetracarbonyliron has been prepared and yields $Fe_3S_2(CO)_9$ in refluxing hexane.[244] A platinum complex also has been reported.[144] 2*H*-Benzo[*b*]thiet 1,1-dioxide and other cyclic sulphones are cleaved at the aryl–sulphonyl bond to yield sulphinate ions in a two-electron process at an electrode.[240]

13 Four-membered Rings containing Nitrogen and One Sulphur Atom

Thiazetidines and Thiazetes.—The reaction of sulphur di-imides with ketens leads ultimately to 1,2-thiazetidine derivatives (187) by way of intermediates (185) and (186). Oxidation of (187) with *m*-chloroperbenzoic acid leads to the *S*-oxide (188).[245] The 1,2-thiazetidine intermediate proposed to account

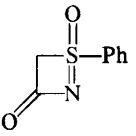
[241] L. H. Klemm and R. E. Merrill, *J. Heterocyclic Chem.*, 1972, **9**, 293.
[242] R. F. J. Langendries and F. C. De Schryver, *Tetrahedron Letters*, 1972, 4781; O. L. Chapman, XXIII Internat. Congress Pure and Applied Chemistry, Boston, Mass., July 1971, Butterworths, London, 1971, vol. 1, p. 330.
[243] J. E. McCaskie, T. R. Nelsen, and D. C. Dittmer, *J. Org. Chem.*, 1973, **38**, 3048.
[244] J. E. McCaskie, P. L. Chang, T. R. Nelsen, and D. C. Dittmer, *J. Org. Chem.*, 1973, **38**, 3963.
[245] T. Minami, K. Yamataka, Y. Ohshiro, T. Agawa, N. Yasuoka, and N. Kasai, *J. Org. Chem.*, 1972, **37**, 3810.



(185)

(186) (187) (188)

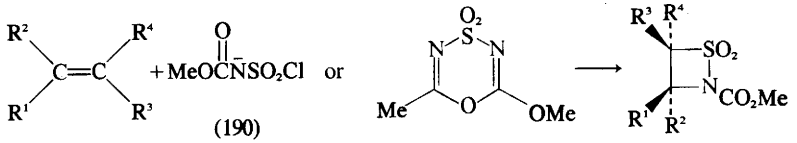
for the products from α-thioalkyloximes under conditions for the Beckmann rearrangement has been shown to be unnecessary.[246] The cycloaddition of *N*-sulphinylaniline to keten at −78 °C gave unstable *N*-phenyl-1,2-thiazetidin-3-one 1-oxide.[130] Further details of the synthesis of (189) have



(189)

been reported.[247] A similar compound has been suggested as an intermediate in the bromination of methyl 2-methylsulphonimidoyl-5-methylphenyl ketone.[247]

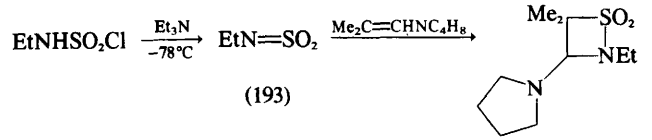
1,2-Thiazetidine 1,1-dioxides (192) are obtained by treatment of olefins with salts of methoxycarbonylsulphamoyl chloride (190)[248] or with oxathiadiazines (191).[249] Electron-rich olefins yield thiazetidine dioxides



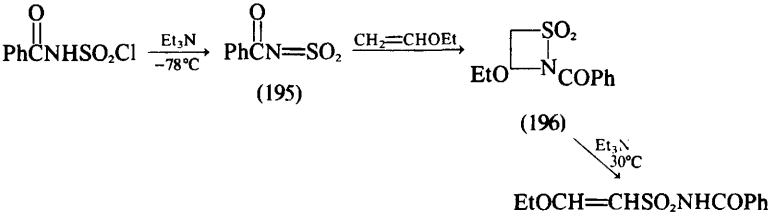
(190) (191) (192)

(194) and (196) with *N*-sulphonylethylamine (193) and *N*-sulphonylbenzamide (195), respectively.[250] Treatment of benzylideneanilines with

[246] R. K. Hill and D. A. Cullison, *J. Amer. Chem. Soc.*, 1973, **95**, 2923.
[247] T. R. Williams and D. J. Cram, *J. Org. Chem.*, 1973, **38**, 20; T. R. Williams, Ph.D. Thesis, Univ. California at Los Angeles, 1971 [*Diss. Abs. Internat* (*B*), 1972, **32**, 5120].
[248] E. M. Burgess and W. M. Williams, *J. Amer. Chem. Soc.*, 1972, **94**, 4386.
[249] E. M. Burgess and W. M. Williams, *J. Org. Chem.*, 1973, **38**, 1249.
[250] G. M. Atkins, jun., and E. M. Burgess, *J. Amer. Chem. Soc.*, 1972, **94**, 6135.

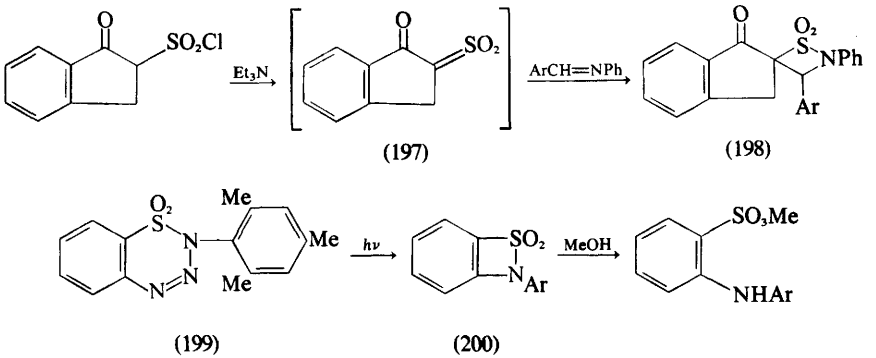


(193) (194)



(195) (196)

α-keto-sulphene (197) gave (198).[251] The stable benzo-1,2-thiazete 1,1-dioxide (200) was obtained by photolysis of (199). It is solvolysed readily.[252]

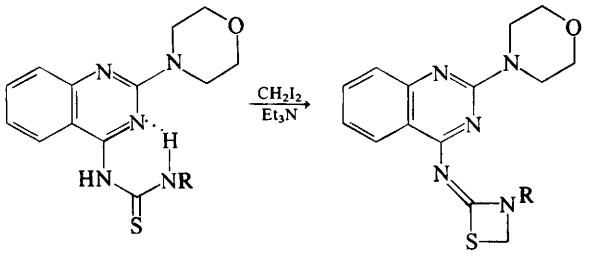


(197) (198)

(199) (200)

Good yields of 1,3-thiazetidines (202) are obtained by treatment of the unsymmetrically substituted thioureas (201) (in which hydrogen-bonding appears necessary for success) with di-iodomethane.[253a] The formation and properties of some other 1,3-thiazetidines have been surveyed.[253b] Photolysis of a mixture of a thioketone and a nitrile yields *N*-thioacylketimines, possibly *via* a thiazete.[254] Another thiazete was discarded as a possible intermediate in the acyl migration from sulphur to nitrogen observed in *S*-benzoylisothiouronium salts.[255]

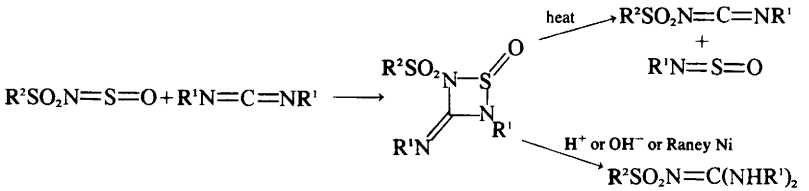
[251] O. Tsuge and M. Noguchi, *Chem. Letters*, 1974, 113.
[252] G. Ege and E. Beisiegel, *Annalen.*, 1972, **763**, 46.
[253] (*a*) W. Ried, W. Merkel, and O. Mösinger, *Annalen*, 1973, 1362; (*b*) H. Ulrich, XXIII Internat. Congress Pure and Applied Chemistry, Boston, Mass., July 1971, Butterworths, London, 1971, vol. 2, p. 265.
[254] D. S. L. Blackwell, P. de Mayo, and R. Suau, *Tetrahedron Letters*, 1974, 91.
[255] R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1972, **94**, 2823.



(201) (202)

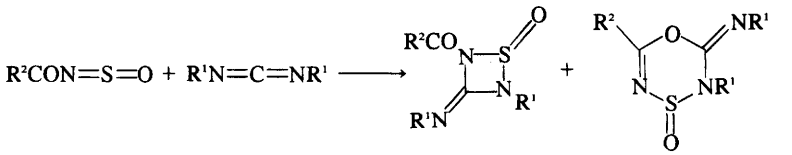
Oxathiazetidines.—*N*-Sulphinylanilines react with pyridine-2-aldehydes to give adducts formulated as *cis*- and *trans*-1,2,3-oxathiazetidine 2-oxides. Thermolysis of the adducts yields sulphur dioxide and a Schiff base.[256] A similar *S*-oxide is suggested as an intermediate in the reaction of sulphinylamines with pyrylium salts to yield pyridinium salts and sulphur dioxide.[257]

Rings containing Two Nitrogen Atoms.—3-Imino-1,2,4-thiadiazetidine 1-oxides (203) are thermally unstable substances obtained from *N*-sulphinylsulphonamides and carbodi-imides. *N*-Sulphinylacylamides yield a mixture



(203)

of 3-imino-4-acyl-1,2,4-thiadiazetidine 1-oxides (204) and 5-imino-1,2,4,6-thioxadiazines (205).[258] The mass spectrum of 1-methyl-3,5-diphenyl-1,2,4,6-thiatriazine shows a fragment ion, *m/e* 149, which may have structure



(204) (205)

[256] T. M. Pozdnyakova, N. M. Sergeyev, N. I. Gorodetskaya, and N. S. Zefirov, *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 109; N. S. Zefirov and T. M. Pozdnyakova, *Moscow Univ. Chem. Bulletin*, 1973, 97.

[257] N. S. Zefirov, G. N. Dorofeenko, and T. M. Pozdnyakova, *J. Org. Chem.* (*U.S.S.R.*), 1973, **9**, 391.

[258] T. Minami, M. Fukuda, M. Abe, and T. Agawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 2156.

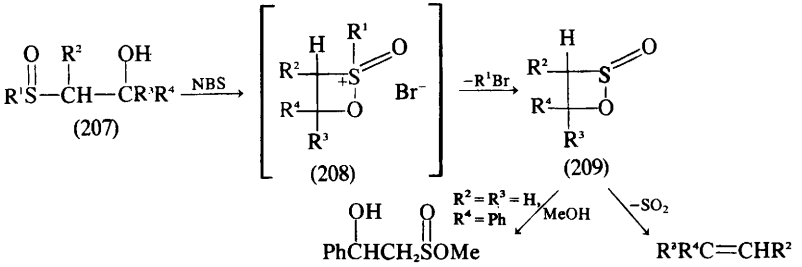
(206).[259] A thiadiazete intermediate has been considered in the decomposition of a benzothiadiazine derivative.[58a]

(206)

14 Four-membered Rings containing Oxygen and One Sulphur Atom

Sultones and Sultines (1,2-Oxathietan 2,2-Dioxides and 1,2-Oxathietan 1-Oxides).—The synthesis and properties of fluorinated β-sultones have been reviewed,[260] and the fluorine n.m.r. spectra of several trifluorosultones have been analysed.[261] Several preparations of sultones involving the addition of sulphur trioxide to olefins[262] and to pentamethyleneketen[263] have been reported. Fluorinated sultones also have been prepared by treatment of fluoroethylenes with a cylic, four-membered sulphate (210).[264] Fluorosulphonates are obtained from the reaction of several of the fluorinated sultones with methanol[264] or by isomerization.[262b] Fluorosulphonic acid is obtained from the β-sultone of tetrafluoroethane on treatment with pyrosulphuric acid.[265]

β-Sultines (209) have been obtained by treatment of β-hydroxy-sulphoxides (207) with *N*-bromosuccinimide, *N*-chlorosuccinimide, or sulphuryl

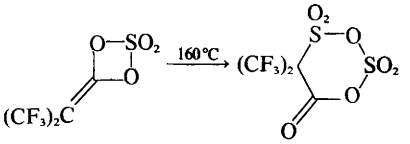


chloride at room temperature. These sultines decompose readily to olefins by a stereospecific *cis*-elimination and react with methanol to give sulphinate esters.[266] Sultine intermediates have been considered for the addition of

[259] M. Haake, H. Fode, and K. Ahrens, *Z. Naturforsch.*, 1973, **28b**, 539.
[260] I. L. Knunyants and G. A. Sokolski, *Angew. Chem.*, 1972, **84**, 623.
[261] K. W. Jolley, L. H. Sutcliffe, and K. L. Williamson, *Spectrochim. Acta*, 1974, **30A**, 511.
[262] (*a*) M. Nagayama, O. Okumura, S. Noda, and A. Mori, *J.C.S. Chem. Comm.*, 1973, 841; (*b*) M. A. Belaventsev, L. L. Mikheev, V. M. Pavlov, G. A. Sokolskii, and I. L. Knunyants, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 1972, **21**, 2441; (*c*) F. Pueschel and D. Prescher, East Ger. P. 83 996, Aug. 20, 1971 (*Chem. Abs.*, 1972, **78**, 72 111).
[263] E. Tempesti, L. Giuffre, M. Fornaroli, and G. Airoldi, *Chem. and Ind.*, 1973, 183.
[264] G. A. Sokolskii, V. M. Pavlov, S. A. Agafonov, and I. L. Knunyants, *Khim. geterotsikl. Soedinenii*, 1973, 178 (*Chem. Abs.*, 1973, **78**, 136 135).
[265] M. A. Belaventsev, V. M. Pavlov, G. A. Sokolskii, and I. L. Knunyants, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 1973, **22**, 1519.
[266] F. Jung, N. K. Sharma, and T. Durst, *J. Amer. Chem. Soc.*, 1973, **95**, 3420.

sulphur dioxide to olefins and ketens[263,267a] and in the reaction of *N*-sulphinylaniline with nitrosobenzene.[267b] The sultine-like intermediate (208) was used to rationalize the reaction of β-hydroxy-sulphoxides with *N*-bromosuccinimide.[266,268] In one case, β-sultines were the product;[266] and in another an αβ-unsaturated sulphone was obtained.[268]

Oxathietans, Oxathiets, and Dioxathietans.—Oxathietan intermediates have been considered in the reaction of thiocarbonyl ylides with diphenylketen[269] and in the vapour-phase thermolysis of *S*-methoxymethyl thioacetates.[270] The behaviour of solutions of monothiobenzil may indicate isomerization to an oxathiet.[271] The photo-oxidation of tetramethyl-3-thiocyclobutane-1,3-dione by oxygen may proceed *via* a 1,2-dioxa-3-thietan.[272] The 1,3-dioxa-2-thietan 2,2-dioxide (210) was obtained by treatment of 3,3,3-trifluoro-2-trifluoromethylpropanoic acid with sulphur trioxide.[273] It is cleaved by various nucleophiles to bis-trifluoromethylketen, which dimerizes,[274] and its reactions with fluoroethylenes have been determined.[264] Thermolysis of (210) yields anhydride (211).[275]



(210) (211)

15 1,2-Dithietans and 1,3-Dithietans

1,2-Dithietan derivatives have been considered as possible intermediates in the dimerization of 3,5-diaryl-1,2-dithiolyl radicals formed in the cathodic reduction of 3,5-diaryl-1,2-dithiolium ions[276] and in the oxidative desulphurization of *sym*-trithians and thioketals by iodine in DMSO.[277]

The results of efforts to elucidate the structure of a compound derived from thioacetic acid, for which dithietan or thiiran structures once were considered and which is now established as a thioadamantane, have been

[267] (*a*) G. C. Bernardi, G. Moggi, and D. Sianesi, *Ann. Chim.* (*Rome*), 1972, **62**, 95; (*b*) T. M. Pozdnyakova and N. S. Zefirov, *J. Org. Chem.* (*U.S.S.R.*), 1972, **8**, 1120.

[268] H. Taguchi, Y. Yamamoto, and H. Nozaki, *Tetrahedron Letters*, 1973, 2463.

[269] R. M. Kellogg, *J. Org. Chem.*, 1972, **38**, 844.

[270] P. C. Oele and R. Louw, *J.C.S. Chem. Comm.*, 1972, 848.

[271] (*a*) B. Saville and M. Steer, *J.C.S. Chem. Comm.*, 1972, 616; B. Saville, personal communication; (*b*) W. Küsters and P. de Mayo, *J. Amer. Chem. Soc.*, 1973, **95**, 2383.

[272] J. J. Worman, M. Shen, and P. C. Nichols, *Canad. J. Chem.*, 1972, **50**, 3923.

[273] V. M. Pavlov, M. A. Belaventsev, V. F. Gorelov, G. A. Sokolskii, and I. L. Knunyants, *Khim. geterotsikl. Soedinenii*, 1973, 13 (*Chem. Abs.*, 1973, **78**, 97 524).

[274] V. M. Pavlov, A. A. Alekseev, G. A. Sokolskii, and I. L. Knunyants, *Khim. geterotsikl. Soedinenii*, 1972, 306 (*Chem. Abs.*, 1972, **77**, 61 855).

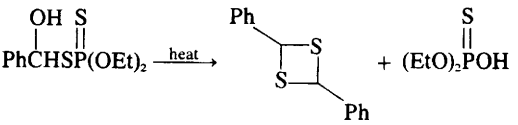
[275] V. M. Pavlov, V. N. Derkochev, G. A. Sokolskii, and I. L. Knunyants, *Khim. geterotsikl. Soedinenii*, 1973, 1321 (*Chem. Abs.*, 1974, **80**, 27 221).

[276] K. Bechgaard, V. D. Parker, and C. T. Pedersen, *J. Amer. Chem. Soc.*, 1973, **95**, 4373.

[277] J. B. Chattopadhyaya and A. V. Rao, *Tetrahedron Letters*, 1973, 3735.

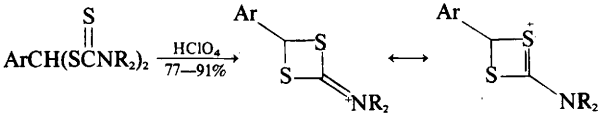
reviewed.[278] A theoretical treatment of the 1,3-dithiacyclobutyl biradical indicates that it would be planar if the *d*-orbitals on sulphur were used; but that if they are omitted, a bent biradical with a substantial barrier to inversion is predicted.[279]

1,3-Dithietans commonly are formed by dimerization of thiocarbonyl compounds. Intersystem crossing from the second excited singlet state ($\pi \rightarrow \pi^*$) to the first triplet state is significant in the photochemical formation of the 1,3-dithietan derived from adamantanethione. Its formation on irradiation of the thione at 250 nm is quenched by 1,1'-azoisobutane, indicating an intermediate triplet state.[280] Other dithietans have been obtained by irradiation of the trimer of cyclohexanethione or thioacetone,[281] irradiation of dibenzyl thioketone,[272] treatment of carbohydrates with phosphorus pentasulphide in boiling aqueous pyridine,[282] treatment of perfluoropropene with sulphur and potassium fluoride at 120 °C in an autoclave,[283a] and by treatment of perfluoroisobutene with sodium hydrosulphide.[283b] The adduct (212) of benzaldehyde and *OO*-diethyl



(212) (213)

dithiophosphoric acid decomposes thermally to thiobenzaldehyde, isolated as its dimer (213).[284] 2-Dialkylamino-4-aryl-1,3-dithietan-2-ylium salts (215) are obtained by treatment of benzylidenebis-(*NN*-dialkyldithiocarbamates) (214) with strong acids or dimethyl sulphate.[285] I.r. data indicate that more



(214) (215)

double-bond character exists in the C=N bond in (215) than in the analogous five-membered cyclic salt. Substituted dithietans have been

[278] A. Fregda, V Symposium Organic Sulfur Chemistry, Lund, Sweden, June, 1972, *Internat. J. Sulfur Chem.* (*C*), 1972, **7**, 1.

[279] J. K. George and C. Trindle, *Internat. J. Sulfur Chem.*, 1973, **8**, 83.

[280] A. H. Lawrence and P. de Mayo, *J. Amer. Chem. Soc.*, 1973, **95**, 4084.

[281] T. Nishio, M. Yoshioka, H. Aoyama, and N. Sugiyama, *Bull. Chem. Soc. Japan*, 1973, **46**, 2253.

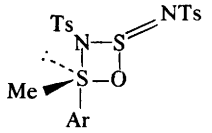
[282] J. N. Dominguez and L. N. Owen, *Carbohydrate Res.*, 1972, **22**, 225.

[283] (*a*) B. L. Dyatkin, S. R. Sterlin, L. G. Zhuravkova, B. I. Martynov, E. I. Mysov, and I. L. Knunyants, *Tetrahedron*, 1973, **29**, 2759; (*b*) S. R. Sterlin, L. G. Zhuravkova, B. L. Dyatkin, and I. L. Knunyants, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1971, 2517 (*Chem. Abs.*, 1972, **76**, 126 829).

[284] S. Oae, A. Nakanishi, and N. Tsujimoto, *Chem. and Ind.*, 1972, 575.

[285] Y. Ueno and M. Okawara, *Chem. Letters*, 1973, 863.

prepared as acaricides[286a] and as fungicides.[286b] A 1,3-cyclodisiladithietan was obtained by refluxing SiS_2 with 2,6-dimethylphenol.[287] Trigonal-bipyramidal intermediates, *e.g.* (216), are believed to be involved in the



(216)

conversion of sulphoxides into sulphimides in benzene or methylene chloride solution, in which retention of configuration is observed.[288] 3,3-Bis(trifluoromethyl)-1,2,4-oxadithietan 2,2,4,4-tetroxide has been obtained from (211).[275]

The dimer of hexafluorothioacetone (217) reacts, as shown in Scheme 8, with mercuric fluoride–potassium fluoride to give the mercuric mercaptide of perfluoropropane-2-thiol;[283] in DMF, potassium fluoride promotes the reaction of (217) with alcohols, thiols, thiophenols, and olefins to give products derived from the thioacetone monomer.[289a] Reaction with styrene gave the bis-Diels–Alder adducts (218) and (219); thietan (220) is obtained with cyclohexene.[289b] Amino-alcohols, *o*-aminophenol, *o*-aminothiophenol, and *o*-phenylenediamine yield 2,2-bis(trifluoromethyl)-1,3-heterocyclic derivatives, *e.g.* (221).[289c] 1,3-Dithietans did not react with $Fe_2(CO)_9$ and were discarded as possible intermediates in the *ortho*-metallation reactions of thiobenzophenones.[290] The hydrolysis reactions of a 1,3-cyclodisiladithietan and its reaction with *o*-hydroxymercuribenzoic acid have been investigated.[291]

Treatment of 2,6-dimethyl-4-pyrone with disulphene in acetic anhydride gave a 2-exomethylene 1,3-dithietan disulphone (222) in 2% yield. Treatment with n-butylamine gave the dihydropyridine derivative (223).[292] A number of exomethylene 1,3-dithietans have been prepared as fungicides, nematocides, herbicides, molluscicides, and bactericides.[293] A simple method for the synthesis of 2-diacylmethylene 1,3-dithietans consists of treating the tetrabutylammonium salt of the anion of the diacylmethane with

[286] (*a*) R. W. Addor and S. Kantor, Ger. Offen. 2 305 517, Aug. 16, 1973 (*Chem. Abs.*, 1973, **79**, 115 553); (*b*) N. V. Philips, Gloeilampenfabriken, Neth. Appl. 7 101 259, Aug. 1, 1972 (*Chem. Abs.*, 1972, **77**, 152 151).

[287] W. Wojnowski and M. Wojnowska, *Z. anorg. Chem.*, 1973, **397**, 69.

[288] F. G. Yamagishi, D. R. Rayner, E. T. Zwicker, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95**, 1916; D. C. Garwood, M. R. Jones, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95**, 1925.

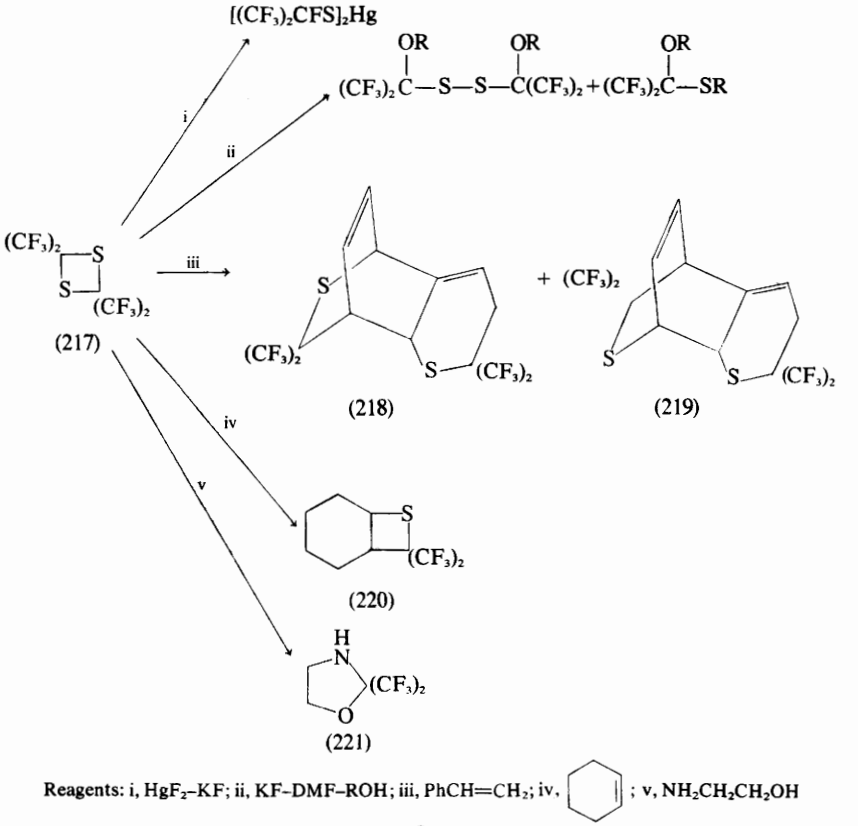
[289] (*a*) T. Kitazume and N. Ishikawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 3285; (*b*) *Chem. Letters*, 1973, 267; (*c*) *Bull. Chem. Soc. Japan*, 1974, **47**, 785.

[290] H. Alper and A. K. Chan, *J. Amer. Chem. Soc.*, 1973, **95**, 4905; *Inorg. Chem.*, 1974, **13**, 232.

[291] W. Wojnowski and M. Wojnowska, *Z. anorg. Chem.*, 1973, **398**, 167.

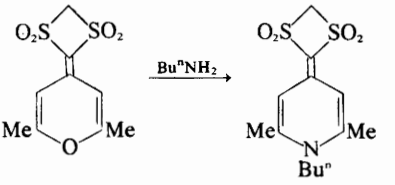
[292] G. Seitz and H. Moennighoff, *Arch. Pharm.*, 1973, **306**, 389 (*Chem. Abs.*, 1973, **79**, 66 227).

[293] K. Taninaka, H. Kurono, S. Mine, A. Hirano, and H. Tanaka, Ger. Offen. 2 316 921, Oct. 25, 1973 (*Chem. Abs.*, 1974, **80**, 14 935); S. A. Greenfield, U.S.P. 3 772 331, November 13, 1973 (*Chem. Abs.*, 1974, **80**, 47 969).



Reagents: i, HgF_2–KF; ii, KF–DMF–ROH; iii, $PhCH{=}CH_2$; iv, ; v, $NH_2CH_2CH_2OH$

Scheme 8

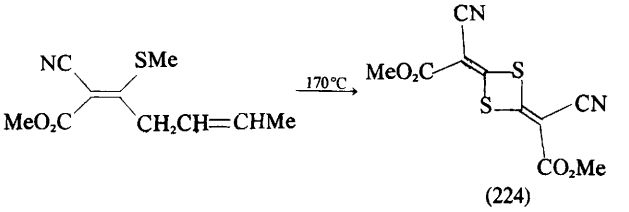


(222) (223)

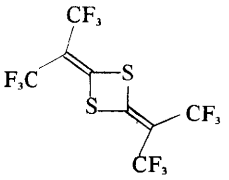
carbon disulphide.[294] Thermal decomposition of methyl crotyl keten mercaptals gave desaurins,[294] *e.g.* (224). Desaurin (225) is obtained from perfluoroisobutene and various salts of sulphur-containing acids.[283b,295] Esters of the dimercaptide salt of 2-cyano-3,3-dimercaptopropenoic acid are

[294] L. Dalgaard, L. Jensen, and S.-O. Lawesson, *Tetrahedron*, 1974, **30**, 93; L. Dalgaard, H. Kolind-Andersen, and S.-O. Lawesson, *ibid.*, 1973, **29**, 2077.

[295] D. C. England, M. C. Raasch, and W. A. Sheppard, U.S.P. 3 694 460, Sept. 26, 1972 (*Chem. Abs.*, 1973, **78**, 16 161).



(224)

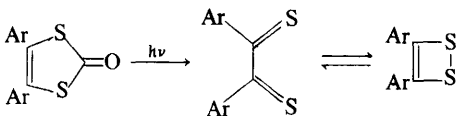


(225)

said to yield desaurins on treatment with chloroformate esters.[296] Investigation of 2,4-(3'-bornanonylidene)-1,3-dithietan has revealed that the substance was a mixture of two isomers.[297] Desaurin (224) undergoes ring opening with primary amines.[298]

16 1,2-Dithiets

The photochemical decomposition of vinylene dithiocarbonate (226) gave dithiobenzil (227), which was in equilibrium with the corresponding dithiet (228). The activation energy for ring opening of the dithiet was *ca.* 15 kcal

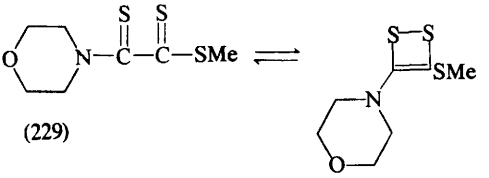


Ar = *p*-$Me_2NC_6H_4$ (226) (227) (228)

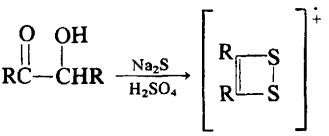
mol^{-1} less than that for the ring opening of cyclobutenes, a consequence of the weaker S—S bond. The activation energy for ring closure is relatively low (17.5 kcal mol^{-1}), which is said to suggest considerable delocalization of π-electrons in the dithiet.[271b] Photolysis of the diphenyldithiolone (226; Ar = Ph) did not give dithiobenzil-dithiet as above but instead gave tetraphenyl-1,4-dithiin. However, the mass spectrum of the diphenyl derivative was interpreted on the basis of dithiet formation.[299] The n.m.r.

[296] K. Peseke, East Ger. P. 99 365, August 5, 1973 (*Chem. Abs.*, 1974, **80**, 120 900).
[297] J. Sotiropoulos and A. Lamazouere, *Compt. rend.*, 1973, **276**, *C*, 1115.
[298] K. Peseke, East Ger. P. 99 364, August 5, 1973 (*Chem. Abs.*, 1974, **80**, 120 901).
[299] W. Schroth, H. Bahn, and R. Zschernitz, *Z. Chem.*, 1973, **13**, 424.

spectrum of dithione (229) shows the presence of two different thiomethyl groups, which was said to indicate an equilibrium between dithione and dithiet (230).[300] 1,2-Dithiet radical cations (231) are obtained by treatment of

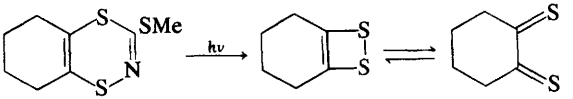


(229) (230)



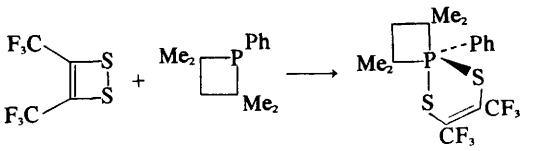
(231)

α-hydroxy-ketones or α-diketones with sodium sulphide (or sodium thiosulphate or sodium dithionite) and sulphuric acid. Bis(trifluoromethyl)-1,2-dithiet yields a cation radical directly when dissolved in sulphuric acid.[301] Photolysis of 3-methylmercapto-4,5-tetramethylene-1,4,2-dithiazine (232) is believed to proceed *via* dithiet (233) or α-dithiodiketone (234), which was



(232) (233) (234)

trapped as a molybdenum complex. The mass spectrometric fragmentation pattern of the dithiazine appears to involve a dithiet cation radical.[140c]



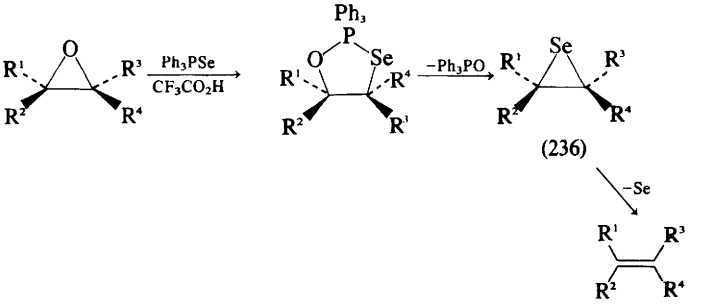
(235)

[300] S. Wawzonek and S. M. Heilmann, *J. Org. Chem.*, 1974, **39**, 511.
[301] G. A. Russell, R. Tanikaga, and E. R. Talaty, *J. Amer. Chem. Soc.*, 1972, **94**, 6125.

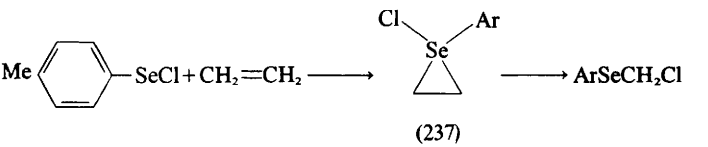
Dithiet cation radicals also may be involved in the mass spectrometric fragmentation of 1,3-dithiole-2-thiones and the corresponding 2-ones.[140d] Treatment of 1,2-bis(trifluoromethyl)dithiet with cyclopentadienylindium(I) gave 1,2-dithiolen complexes[302] and with cyclic phosphines and phosphites, phosphoranes (235).[303]

17 Selenium Derivatives

A review on selenium compounds has appeared.[4] A seleniran (236) was suggested as an intermediate in the stereospecific conversion of sulphoxides



into olefins with triphenylphosphine selenide[304] and in the cyclization of *para*-substituted phenyl allyl selenides in boiling quinoline.[305] Unsuccessful attempts to prepare selenaziridines have been reported.[152] Addition of toluene-*p*-selenyl chloride to [1-^{13}C]ethylene yields a seleniran (237) [1-



chloro-1-(4′-tolyl)selenacyclopropane], identified by ^{1}H n.m.r., ^{13}C n.m.r., and the ^{13}C–^{77}Se spin–spin coupling constants. The structure is believed to be that of a trigonal bipyramid.[306] It isomerizes slowly. The possibility of

[302] A. F. Berniaz and D. G. Tuck, *J. Organometallic Chem.*, 1973, **51**, 113.
[303] N. J. De'Ath and D. B. Denney, *J.C.S. Chem. Comm.*, 1972, 395.
[304] D. L. J. Clive and C. V. Denyer, *J.C.S. Chem. Comm.*, 1973, 253.
[305] E. G. Kataev, G. A. Chmutova, A. A. Musiva, and A. P. Anastaseva, *J. Org. Chem.* (*U.S.S.R.*), 1972, **8**, 1560.
[306] D. G. Garratt and G. H. Schmid, *Canad. J. Chem.*, 1974, **52**, 1027.

seleniren intermediates in the reaction of di-iron enneacarbonyl with selenadiazoles has been considered.[137]

A substituted selenetan was obtained by treatment of pentaerythritol with diethyl carbonate and KSeCN.[174] A compound obtained in low yield by treatment of perfluoropropene with selenium and antimony pentafluoride was assigned tentatively a 1,3-diselenetan structure.[307]

[307] Y. L. Kopaevich, G. G. Belenkii, E. I. Mysov, L. S. German, and I. L. Knunyants, *Zhur. Vsesoyuz. Khim. obshch. im D. I. Mendeleeva*, 1972, **17**, 226 (*Chem. Abs.*, 1972, **77**, 101 427).

3

Saturated Cyclic Compounds of Sulphur and Selenium

BY T. DURST

1 Introduction

A number of the more general reviews on sulphur chemistry include material pertinent to this Report. Among these are the application of ESCA to organosulphur compounds,[1] the synthesis and properties of optically active sulphur compounds, including cyclic sulphoxides and sulphites,[2] and synthetic aspects of the Ramberg–Backlund reaction.[3] Seven-membered-ring compounds containing sulphur[4] and organosulphur compounds with adamantane structures[5] have been reviewed in detail. The synthesis of sulphur-containing cyclophanes and their utility in the general synthesis of cyclophanes has also been discussed.[6]

Comparatively little new work has been reported with respect to saturated cyclic selenium compounds. A general treatise on organoselenium chemistry including various aspects of cyclic selenium compounds has appeared.[7] The proceedings of a symposium on organoselenium chemistry have been published.[8]

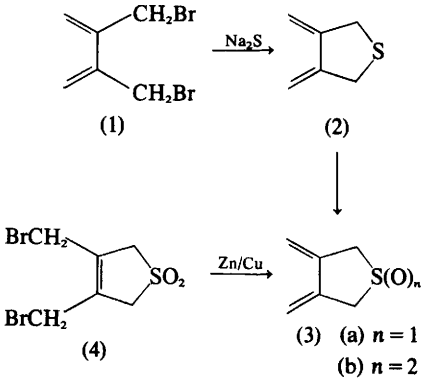
2 Thiolans, Thians, Thiepans, Thiocans, and their Oxides and Dioxides

Synthesis.—In general, the previously known methods of constructing sulphur-containing rings, such as intramolecular displacements by thiolate anions, intramolecular addition of thiol radicals to carbon–carbon multiple

[1] B. Lindberg, *Internat. J. Sulfur Chem.* (*C*), 1972, **7**, 33.
[2] A. Nudelman. *Internat. J. Sulfur Chem.* (*B*), 1972, **7**, 241.
[3] L. Paquette, *Internat. J. Sulfur Chem.* (*C*), 1972, **7**, 73.
[4] L. Field and D. L. Tuleen, 'Heterocyclic Compounds', ed. A. Rosowsky, Wiley–Interscience, New York, 1973, Vol. 26, pp. 573—666.
[5] A. Fredga, *Internat. J. Sulfur Chem.* (*C*), 1972, **7**, 1.
[6] F. Vögtle and P. Neumann, *Synthesis*, 1973, 85.
[7] 'Organic Selenium Compounds. Their Chemistry and Biology', ed. D. L. Klayman, Wiley, New York, 1973.
[8] *Ann. New York Acad. Sci.*, 1972, vol. 192.

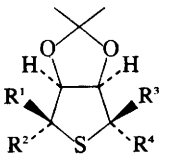
bonds, and participation of a suitably placed sulphur atom in the electrophilic addition to double bonds, were used.

For example, the 3,4-dimethylenethiolan (2) was prepared in 60% yield by the reaction of (1) with Na_2S.[9] Oxidation of (2) gave the corresponding sulphoxide and sulphone; all three compounds were fairly susceptible to polymerization. The sulphone could also be prepared in low yield by Zn–Cu couple reduction of 3,4-(dibromomethyl)sulpholene (4) in HMPA.[9] As expected, the sulphone (3b) readily underwent Diels–Alder reactions



with dimethyl acetylenedicarboxylate or sulphur dioxide, thereby furnishing bicyclic derivatives.

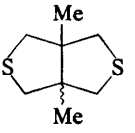
All three possible 2,5-dimethyl-*cis*-3,4-isopropylidenedioxythiolans (5)



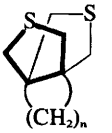
(5) (a) $R^1 = R^3 = H$, $R^2 = R^4 = Me$
(b) $R^1 = R^3 = Me$, $R^2 = R^4 = H$
(c) $R^1 = R^4 = Me$, $R^2 = R^3 = H$

have been synthesized in an unambiguous manner from hexane-2,3,4,5-tetraols of known configuration.[10] A 92% yield of a 1:1 mixture of both isomers of 1,5-dimethyl-3,7-dithiabicyclo[3,3,0]octane (6) was obtained when the tetramesylate of 2,3-dimethyl-2,3-dihydroxymethyl-butane-1,4-diol was heated with Na_2S in anhydrous DMSO.[11a] The configurations of the isomers were deduced from their n.m.r. spectra. A similar route was used to prepare the dithiapropellanes (7) and the corresponding oxathiapropellanes.[11b]

[9] S. Saheh, and Y. Ganoni, *Tetrahedron Letters*, 1973, 2365.
[10] R. Lett, S. Bory, B. Moreau, and A. Marquet, *Bull. Soc. chim. France*, 1972, 2299.
[11] (*a*) K. Weinges, M. Weber, and K. Klessing, *Chem. Ber.*, 1973, **106**, 2305; (*b*) K. Weinges, K. Klessing, and R. Kolb, *ibid.*, p. 2298.

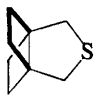


(6)



(7) $n = 1$—5

The thiolan ring of the thiapropellane (8), a potential precursor of 2,2,2-propellane, was also formed by the action of sodium sulphide on the appropriate dimesylate.[12] Unfortunately the Stevens rearrangement of the sulphonium salt (9) did not lead to a ring contraction but rather to the fragmentation (9) → (10). A variety of related five-membered-ring sul-



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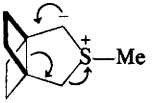
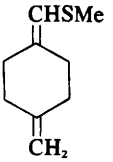


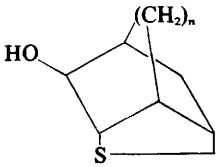
(9)



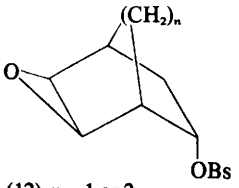
(10)

phonium salts underwent similar base-catalysed fragmentations.[12] The synthesis of 4,9-dithiatricyclo[4,4,0,$0^{2,7}$]decane has been reported.[13]

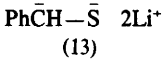
The tricyclic sulphides (11) were formed by intramolecular opening of an epoxide by a thiolate ion that was generated *in situ*.[14] The precursors (12) were readily obtained by reduction and brosylation of the Diels–Alder product of cyclopenta-1,3-diene (cyclohexa-1,3-diene) and ethyl acrylate. Various reactions of (11), including conversion into the parent heterocycle, were described. The dilithio-salt (13), obtained from toluene-α-thiol and two



(11) $n = 1$ or 2



(12) $n = 1$ or 2,
Bs = bromobenzenesulphonate

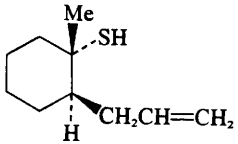


(13)

equivalents of butyl-lithium in THF, when quenched with 1,3-dibromopropane and epichlorohydrin, afforded 2-phenylthiolan and 4-hydroxy-2-phenylthiolan, respectively.[15] 2-Phenylthians should also be accessible from (13).

[12] I. Lantos and D. Ginsberg, *Tetrahedron*, 1972, **28**, 2507.
[13] N. S. Zefirov, S. V. Rogozina, and R. A. Kyandzhetsian, *Zhur. org. Khim.*, 1972, **8**, 1448 (*Chem. Abs.*, 1972, **77**, 139 852).
[14] C. R. Johnson and W. D. Kingsburg, *J. Org. Chem.*, 1973, **38**, 1803.
[15] D. Seebach and K.-H. Geiss, *Angew. Chem.*, 1974, **86**, 202.

The ring opening of episulphides with allylmagnesium bromide provides a potentially valuable route to either thiolans or thians.[16] Thus the unsaturated sulphide (14), prepared from 1-methylcyclohexene episulphide and allylmagnesium bromide, was cyclized in the presence of H_2SO_4 to the thiolan (15) (97%), while the thian (16) was produced in 92% yield on photolysis.



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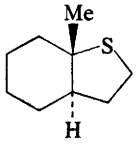

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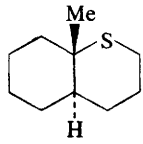


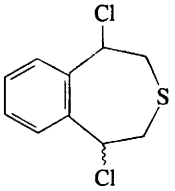
(16)

Unsaturated sulphides suitable for cyclization to thiolans have also been obtained by the addition of allylmagnesium bromide to thioketones such as thiobenzophenone, thiopinacolone, and thiocamphor.[17] As a synthetic method this is of limited use because of the general inaccessibility of thiocarbonyl compounds. The formation of unsaturated thiols by the reaction of allylmagnesium bromide with thioketones is unusual; in general, such reactions lead to the formation of sulphides.[18] Photochemical cyclization of 4-mercaptomethylcyclohexene did not lead to 2-thiabicyclo[2,2,2]-octane[19] but rather to 7-thiabicyclo[3,2,1]octane.[20] The former product was prepared *via* a Diels–Alder reaction between thiophosgene and cyclohexa-1,3-diene followed by $LiAlH_4$ reduction of the chlorine atoms α to the sulphur and finally di-imide reduction of the double bond. Photolysis of 3-(β-mercaptoethyl)cyclohexene gives a mixture of perhydrothianaphthene and 2-thiabicyclo[3,3,1]nonane.[20] Unsaturated allylic or benzylic sulphides $R^1CH{=}CH(CH_2)_nSR^2$ ($R^1 = H$ or Me; $R^2 =$ allyl or benzyl; $n = 3$) undergo photochemical carbon–sulphur bond cleavage followed by intramolecular addition of the thiol radical to the double bond.[21] Mixtures of five- and six-membered-ring sulphides were obtained.

Oxidation of pent-4-enyl thiosulphate with iodine in refluxing ethanol–water gave mainly 2-ethoxymethylthiolan together with a smaller amount of 2-hydroxymethylthiolan and two very minor unidentified products.[22] The expected disulphide gave the same product mixture upon treatment with iodine; however, it was not considered to be an intermediate in the thiol reaction. Both the thiol and the disulphide were thought to give initially a sulphenyl iodide followed by intramolecular attack on the double bond, resulting in an episulphonium salt which was converted into products

[16] V. I. Dronov and V. P. Krivonogov, *Khim. geterotsikl. Soedinenii*, 1972, 622, 1186 (*Chem. Abs.*, 1972, **77**, 139 738e, 164 400w).
[17] M. Dagoneau and J. Vialle, *Tetrahedron*, 1974, **30**, 415.
[18] (*a*) P. Beak and J. W. Worley, *J. Amer. Chem. Soc.*, 1970, **92**, 4142; *ibid.*, 1972, **94**, 597; (*b*) M. Dagoneau, D. Paquer, and J. Vialle, *Bull. Soc. chim. France*, 1973, 1699.
[19] J.-M. Surzur, R. Nouguier, M.-P. Crozet, and C. Dupuy, *Tetrahedron Letters*, 1971, 2035.
[20] H. J. Reich and J. E. Trend, *J. Org. Chem.*, 1973, **38**, 2637.
[21] J.-M. Surzur, G. Bastien, M.-P. Crozet, and C. Dupuy, *Compt. rend.*, 1973, **276**, *C*, 289.
[22] R. D. Riecke, S. E. Bales, and L. C. Roberts, *J.C.S. Chem. Comm.*, 1972, 974.

by attack of the solvents. Addition of sulphur dichloride to *o*-divinylbenzene did not lead to the expected thiepin derivative (17) from which it was hoped to prepare benzo[*d*]thiepin.[23] The reaction resulted in the formation of the benzothiopyran (18), which isomerized on standing, or, more efficiently, on chromatography over silica gel to the dihydrothiophen (19).



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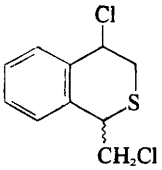
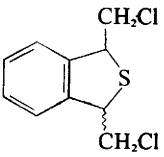
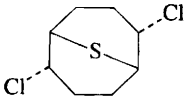


(18)



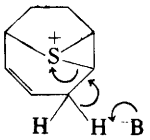
(19)

Transannular additions of sulphur dichloride to cyclic dienes continue to be used as a route to bi- and poly-cyclic sulphur-containing rings. The initial product (20) from the addition of SCl_2 to cyclo-octa-1,5-diene has been converted into 2,6-diketo-9-thiabicyclo[3,3,1]nona-3,7-diene.[24] When (20) was heated with collidine the conjugated diene (21) was obtained.[25] This product was suggested to arise *via* sulphur participation in the elimination process [see (22)] since neither the sulphoxide nor the sulphone underwent



(20)

(21)



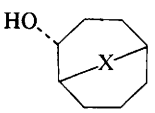
(22)

the same reaction. Five-membered-ring sulphonium salts were formed in 70—80% yield upon bromination of $RS(CH_2)_3CH{=}CH_2$.[26]

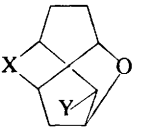
The synthesis of 2-oxa-7-thiatwistane and 2-oxa-7-thiaisotwistanes[27a] and the corresponding sulphoxides[27b] and sulphones,[27b] also starting from (20), has been described. The route outlined below is patterned after the synthesis of the corresponding dithia-analogues described earlier.[27c] Thus the reaction of (24a) with mercuric nitrate led to (25a), which upon reduction with $NaBH_4$ gave the parent compound (23a). Compound (25a) was transformed into the bromide (26a), which upon solvolysis in acetic acid containing AgOAc furnished a mixture of acetates having the twistane (28a) and the isotwistane (27a) skeleton. The reactions described above were also carried out in the sulphoxide and sulphone series[27c] and the products

[23] T. J. Barton and R. C. Kippenhan jun., *J. Org. Chem.*, 1972, **37**, 4194.
[24] D. D. MacNicol, P. H. McCabe, and R. A. Raphael, *Synthetic Comm.*, 1972, **2**, 185.
[25] P. H. McCabe and C. M. Livingston, *Tetrahedron Letters*, 1973, 3029.
[26] M. C. Leroy, M. Martin, and L. Bassery, *Compt. rend.*, 1973, **276**, *C*, 1311.
[27] (*a*) N. Wigger and C. Ganter, *Helv. Chim. Acta*, 1972, **55**, 2769; N. Wigger, N. Stücheli, H. Szczepanski, and C. Ganter, *ibid.*, p. 2791; (*c*) C. Ganter and N. Wigger, *ibid.*, p. 481.

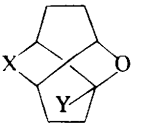
interrelated. A number of the oxidations from the sulphide to the sulphoxide stage in these compounds, *e.g.* (27a) and (29a), occurred with high specificity owing to the ability of the group Y to bond with the oxidizing agent and thus deliver it to the reaction zone from a specific direction. Detailed n.m.r. data, including solvent effects, were reported.



(24) (a) X = S
(b) X = SO
(c) X = SO_2



(23) Y = H
(25) Y = $HgNO_3$
(26) Y = Br
(27) Y = OAc
(29) Y = OH



(28) Y = OAc

Dieckmann-type cyclizations have been used to prepare *cis*-2-thiahydrindan-3-one[28] and *trans*-2-thia-4-decalone.[28a] The stereochemistry of the latter product was assigned with the help of [Eu(dpm)$_3$]-induced shifts observed for the parent and partly deuteriated samples;[28b] for these compounds the Eu(dpm)$_3$ shift reagent complexed preferentially to the carbonyl rather than the thio-group. Octahydrothiopyrano[3,2-*b*]thiopyran[29a] and 2,3,4,10-tetrahydrothiopyrano[3,2-*b*]-1-benzothiopyran[29b] have been prepared. 2-Thiaadamantane-4,8-dione has been converted into a number of 4-substituted 2-thia-adamantanes.[30] All four stereoisomers of 4-benzoylamino-3-hydroxy-2-(5-methoxycarbonylbutyl)thiolan have been isolated and characterized.[31]

No reports of the synthesis of fully saturated thiepan or thiocan derivatives seem to have appeared. Photolysis of diallyldimethylsilane in pentane at −78 °C in the presence of H_2S gave a 25% yield of 5,5-dimethyl-5-sila-1-thiacyclo-octane.[32]

The structures of several natural products containing a thiolan ring have been determined. Among these are breynolide (30), which is a degradation product of a bio-active sulphur-containing glycoside,[33] and several related alkaloids, *e.g.* thiobinupharidine (31), isolated from *Nuphar* plant material.[34]

[28] (*a*) A. Van Bruijnsvoort, E. R. de Waard, J. L. Van Bruijnsvoort-Meray, and H. O. Huisman, *Rec. Trav. chim.*, 1973, **92**, 937; (*b*) A. Van Bruijnsvoort, C. Kruk, E. R. de Waard, and H. O. Huisman, *Tetrahedron Letters*, 1972, 1737.

[29] (*a*) T. E. Young and L. J. Heitz, *J. Org. Chem.*, 1973, **38**, 1563; (*b*) T. E. Young, L. J. Heitz, and D. J. Steklenski, *ibid.*, p. 1567.

[30] J. Janku and S. Landa, *Coll. Czech. Chem. Comm.*, 1972, **37**, 2269.

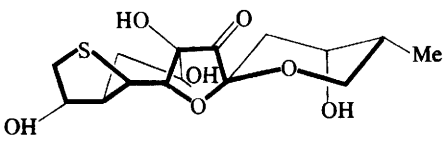
[31] S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, T. N. Polyanskaya, I. M. Kustanovich, and V. M. Berezovskii, *Khim. geterotsikl. Soedinenii*, 1972, 897 (*Chem. Abs.*, 1972, **77**, 151 777z).

[32] K. E. Konig and W. P. Weber, *Tetrahedron Letters*, 1973, 3151.

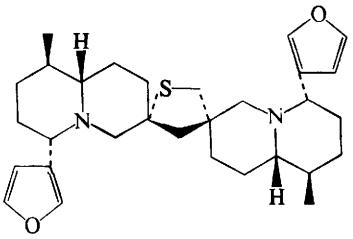
[33] K. Sasaki and Y. Hirata, *Tetrahedron Letters*, 1973, 2439.

[34] (*a*) C. F. Wong and R. T. LaLonde, *J. Org. Chem.*, 1973, **38**, 3225; (*b*) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Amer. Chem. Soc.*, 1973, **95**, 6342; (*c*) R. T. LaLonde and C. F. Wong, *Phytochemistry*, 1972, **11**, 3305; (*d*) J. T. Wrobel, A. Iwanow, J. Szychowski, J. Poplowski, C. K. Yu, T. I. Martin, and D. B. MacLean, *Canad. J. Chem.*, 1972, **50**, 1968; (*e*) J. T. Wrobel, M. Gielynska, A. Iwanow, and W. Starzec, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1973, **21**, 551.

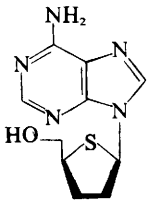
Thiocordycepin (32), a sulphur analogue of the nucleoside antibiotic cordycepin, has been synthesized.[35]



(30)

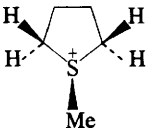


(31)

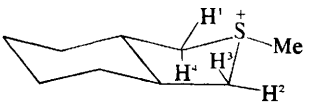


(32)

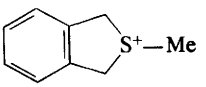
Reactions and Properties.—Thiolan and thian derivatives continue to be used in the study of stereoselective reactions involving the diastereotopic methylene protons α to sulphoxides and sulphonium salts. A re-investigation of the base-catalysed exchange of 1-methylthiolanium iodide (33) showed that the α-hydrogens *cis* to the *S*-methyl group exchanged between 12 [36] and 28 [37] times faster than those *trans*. The stereochemistry of the more rapidly exchanging proton was determined by nuclear Overhauser experiments.[37] Comparison of the geminal coupling constant of (33), $J = 13$ Hz, with those of model compounds such as (34), $J = 12$ and 13 Hz, and (35), $J = 16$ Hz, indicated that the preferred conformation of (33) is the half-chair.[37] Hydrogen–deuterium exchange in (34) also occurred stereoselectively, again the fastest exchanging proton being *cis* to the S-methyl group.[38] The relative rates for H-1:H-2:H-3:H-4 were approximately



(33)



(34)

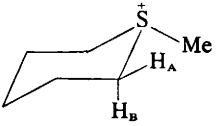


(35)

[35] G. S. Ritchie and W. A. Szarek, *J.C.S. Chem. Comm.*, 1973, 686.
[36] (*a*) O. Hofer and E. L. Eliel, *J. Amer. Chem. Soc.*, 1973, **95**, 8045; E. L. Eliel, *Angew. Chem. Internat. Edn.*, 1972, **11**, 747.
[37] A. Garbesi, G. Barbarella, and A. Fava, *J.C.S. Chem. Comm.*, 1973, 155.
[38] G. Barbarella, A. Garbesi, A. Boicelli, and A. Fava, *J. Amer. Chem. Soc.*, 1973, **95**, 8051.

1:200:3:3. The determination of the exchange rate for the slowest exchanging proton was complicated by the stereomutation at sulphur, which occurred at approximately the same rate as the exchange. This stereomutation, which interconverts H-1 and H-2, and also H-3 and H-4, occurs *via* pyramidal inversion at sulphur.

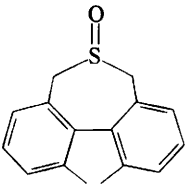
Essentially no selectivity was observed between H_A and H_B in 1-methylthianium iodide (36).[36a] The lack of selectivity is apparently not due to ring



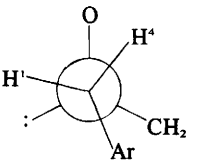
(36)

flipping since the hydrogens of the α-methylene group in both of the diastereomeric 1,2-dimethylthianium iodides also showed no selectivity. The results for the six-membered-ring series are not in accord with theoretical predictions.[39] Various explanations for the discrepancy, such as a possible non-Brønsted relationship between the kinetic and thermodynamic acidities,[36a] exchange of the more rapidly exchanging hydrogen with inversion[36a] (see, however, refs. 38 and 41), and the influence of solvent,[36a] were suggested. Pertinent to the above problem is the *X*-ray structure determination of (36), which showed a chair conformation somewhat more folded than that of cyclohexane; the methyl group is equatorial.[40]

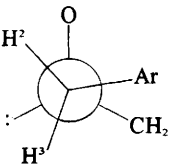
A detailed analysis of the relative rates of exchange of the four α-hydrogens in the conformationally fixed biaryl sulphoxide (37) [see also part structures (37a) and (37b)] has appeared.[41] The relative rates of



(37)



(37a)



(37b)

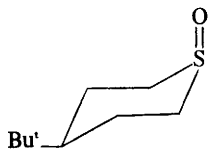
exchange of the various hydrogen atoms showed a large solvent dependence: *viz.*, for H-1:H-2:H-3:H-4 in Bu^{t}OD–Bu^{t}OK they were 1:1100:300:1300; in CD_3OD–CD_3OK, 1:200:7600:30. This is in agreement with earlier results obtained for the rates of exchange of the diastereotopic hydrogens of benzyl methyl sulphoxide, which also showed large solvent

[39] S. Wolfe, *Accounts Chem. Res.*, 1972, **5**, 102.
[40] R. Gerdil, *Helv. Chim. Acta*, 1974, **57**, 489.
[41] R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *J. Amer. Chem. Soc.*, 1972, **94**, 8795.

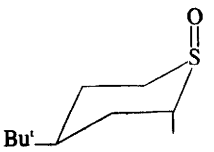
effects.[42] The exchange results indicated a large angular dependence on carbanion stability, especially in the region where the carbanion and sulphur lone pairs are nearly eclipsed (H-1 *vs.* H-2 *vs.* H-3). A rationalization, assuming adherence to the Brønsted equation, of the validity of the relative rates of exchange of diastereotopic protons as a measure of the relative stability of the carbanions was presented.[41]

A study of the H–D exchange in 1,3-dihydrobenzo[c]thiophen 2-oxide has been carried out both kinetically ($NaOD–D_2O$) and by studying quenching of the α-lithio salt.[43] Under the former conditions the hydrogens *trans* to the oxygen are exchanged 67 times faster than the *cis*, while the latter conditions gave mainly the *cis*-monodeuteriated product. Exchange results in $CD_3OD–CD_3OK$ have also been reported for 2-thiabicyclo[2,2,1]heptane 2-oxides.[41] In this system, exchange *cis* to the S=O bond was preferred and therefore opposite to the expectation based on the results for dihydrothiophen *S*-oxide.[43] Several comparisons of the experimental results with those predicted on the basis of *ab inito* calculations by Wolfe, Csizmadia, and co-workers[39,44] have been made.[41,43,45] There is general agreement that the situation is quite complex. A review on α-sulphinyl carbanions has appeared.[45]

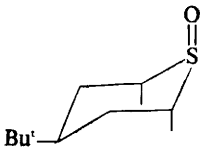
α-Methylation of *cis*- and *trans*-4-t-butylthian *S*-oxides (38) and (39) *via* the lithio-salts occurred in a highly stereoselective manner,[49a] with the methyl group showing a strong tendency to enter *trans* to the S=O bond, *e.g.* (38) → (40) and (39) → (41). This tendency, especially when S=O is axial, must be fairly strong since it held even in the case of the introduction of the second methyl group, despite formidable adverse steric effects, *e.g.* (40) led mainly to (42). Similarly, (41) gave (43). The relative stabilities of the intermediate carbanions were again highly dependent on their relationship to the sulphoxide geometry.



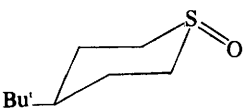
(38)



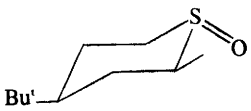
(40)



(42)



(39)

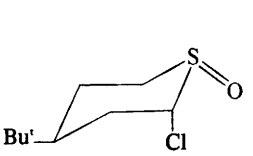


(41)

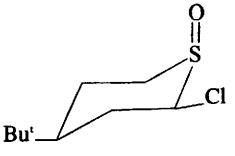
(43)

[42] T. Durst, R. R. Fraser, M. R. McClory, R. B. Swingle, R. Viau, and Y. Y. Wigfield, *Canad. J. Chem.*, 1970, **48**, 2148.
[43] J. F. King and J. R. du Manoir, *Canad. J. Chem.*, 1973, **51**, 4082.
[44] S. Wolfe, A. Rauk, and I. G. Csizmadia, *Canad. J. Chem.*, 1969, **47**, 113.
[45] T. Durst and R. Viau, *Intra-Sci. Chem. Reports*, 1973, **7**, 63.

Detailed studies of the α-chlorination of substituted thian *S*-oxides have been published.[46] This reaction also showed remarkable stereoselectivity, and the determination of the stereochemistry of the products has given valuable mechanistic information. Monochlorination of either *cis*- or *trans*-4-t-butylthian *S*-oxide gave the same products; the major one, (44), formed in 95% yield, had the oxygen atom equatorial and the chlorine axial.[46a,c] The minor chlorination product (45) also had the chlorine atom and sulphur lone-pair '*trans*'.[46a]

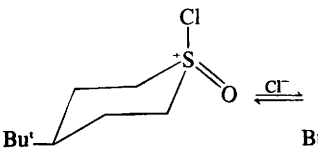


(44)

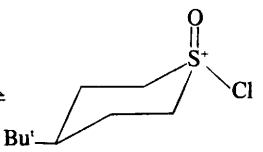


(45)

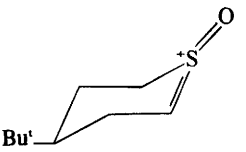
Further chlorination of (44) resulted in exclusive formation of the diaxial dichloride (oxygen equatorial), with no evidence of *gem*-halogenation. Thus halogenation of sulphoxides was rationalized as proceeding *via* tetrahedral chloroxosulphonium ions, which can readily equilibrate (46) ⇌ (47). Concerted *trans*-elimination from (46) followed by preferential axial attack by Cl^- on the intermediate oxosulphenium ion (48)—the sulphur lone-pair and



(46)



(47)



(48)

Cl atom become *trans*—led to (44). Product analysis of a variety of other thian *S*-oxides fully supported the above mechanism. α-Bromination of six-membered-ring sulphoxides proceeded similarly.[47] Highly stereoselective α-chlorinations have also been reported for five-membered-ring sulphoxides;[46a,48] the major products resulted from '*trans*'-addition to the intermediate oxosulphenium ion. A survey and discussion of the methods available for the assignment of configurations of cyclic sulphoxides has been made.[49] Benzene-, trifluoroacetic acid-, and [Eu(dpm)$_3$]-induced shifts were shown to be most reliable. A comparison of the size of J_{gem} of the

[46] (*a*) S. Bory, R. Lett, B. Moreau, and A. Marquet, *Compt. rend.*, 1973, **276**, *C*, 1323; (*b*) S. Iriuchijima, M. Ishihashi, and G. Tsuchihashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 921; (*c*) J. Klein and H. Stollar, *J. Amer. Chem. Soc.*, 1973, **95**, 7437.

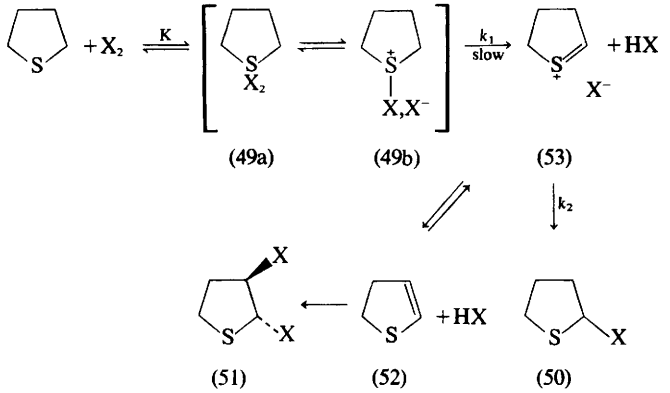
[47] S. Iriuchijma and G. Tsuchihashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 929.

[48] E. Casadevall and M. M. Bouisset, *Tetrahedron Letters*, 1973, 2975.

[49] (*a*) R. Lett, S. Bory, B. Moreau, and A. Marquet, *Bull. Soc. chim. France*, 1973, 2851; *Tetrahedron Letters*, 1972, 4921; (*b*) R. R. Fraser, T. Durst, M. R. McClory, R. Viau, and Y. Y. Wigfield, *Internat. J. Sulfur Chem.* (*A*), 1971, **1**, 133.

α-methylene group is also generally a good criterion for determining the S=O geometry if both isomers are available; J_{gem} is less negative when the sulphur lone pair is axial.

Irradiation of thiolan in the presence of sulphur dioxide yielded small amounts of di-2-thiolanyl sulphone.[50] Bromination of thiolan with Br_2 in methylene chloride at 10 °C gave a 1:1 mixture of recovered thiolan and *trans*-2,3-dibromothiolan, isolated as the methanolysis product *trans*-2-methoxy-3-bromothiolan.[51] Chlorination under similar conditions produced a mixture of starting material, 2-chlorothiolan, and *trans*-2,3-dichlorothiolan.[51] Unstable 1:1 molecular complexes between the halogens and thiolan were shown to be intermediates. The bromine complex (49a; X = Br), efficiently brominated cyclohexane.[51a] The *trans*-2,3-dihalides (51) were obtained by halogenation of the intermediate 4,5-dihydrothiophen (52) with (49). In the chlorination reaction, the ratio of the mono- to the di-chlorination product, (50)/(51), was very susceptible to changes in solvent: it was 18.3 in CCl_4, 14.5 in benzene, 2.5 in CH_2Cl_2, and 0.5 in MeCN. The ratio (50):(51) was also susceptible to added reagents (in CH_2Cl_2): >80:1 when HCl or lutidinium chloride were added and <0.3:1 upon addition of BF_3, TFA, or toluene-*p*-sulphonic acid.[51b] The experimental results can be accommodated by Scheme 1. The solvent effects were rationalized in terms of the hard and soft acid and base theory.[51b] As the solvent poiarity increases, Cl^- becomes a softer base and thus less likely to attack the hard carbonium ion (53). The addition of HCl shifts the equilibrium (52) ⇌ (53)



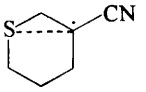
Scheme 1

by protonation of the former; the lutidinium chloride may do likewise; both reagents increase the Cl^- concentration, thus favouring the formation of (50). The other acids were suggested to reduce the availability of chloride ion, thereby decreasing k_2.[50b] The detailed mechanism for the formation of

[50] H. Takeuchi, T. Nagai, and N. Tokura, *Bull. Chem. Soc. Japan*, 1973, **46**, 695.
[51] (*a*) G. E. Wilson jun., and R. Albert, *J. Org. Chem.*, 1973, **38**, 2156; (*b*) *ibid.*, p. 2160.

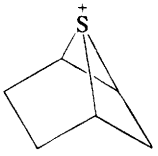
the sulphocarbonium ion (53) from (49) was discussed.[51b] Competitive kinetic H/D isotope effects of 5.1 and 3.6 for the chlorination and bromination, respectively, pointed to a fairly symmetrical *E*2 transition state for the elimination of HCl, with the dehydrobromination tending somewhat toward the *E*1 transition state.

Interest continues in the possible transannular stabilization of intermediates by a suitably placed sulphur atom in five- to seven-membered rings. Smaller entropies and less positive enthalpies of activation in the decomposition of both azobis(1-cyano-3-thiacyclohexane) and the 4-thia-analogue compared to the cyclohexane derivatives have been interpreted in terms of a 1.7 to 1.8 kcal mol^{-1} stabilization of the radicals, *e.g.* (54) by

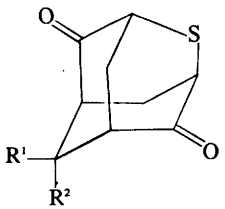


(54)

sulphur participation.[52] Analysis of the complex series of products formed on photolysis of 3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-dione suggested the formation of a charge-transfer complex between the excited state of the ketone and the sulphur as one of the several photochemical pathways.[53] Decomposition of the sodium salts of a number of toluene-*p*-sulphonyl hydrazones attached to sulphur-containing rings gave products which did not indicate interaction between the carbene and the sulphur atom (ylide formation).[54] All the monomeric products obtained were best explained as the result of simple insertion of the carbene into an α-C—H bond. Acetylation (refluxing acetic acid–acetic anhydride) of an 80:20 mixture of 8-thiabicyclo[3,3,1]octan-3-ol gave a single acetate; the sulphonium ion (55) is a likely intermediate.[54] Prolonged heating of 9-thiabicyclo[3,3,1]nonane-2,6-dione with acetic anhydride and sulphuric acid at temperatures above 145 °C resulted in the formation of two products, (56a) and (56b), having adamantane skeletons.[55] These substances probably arose *via* acetylation at



(55)



(56) (a) $R^1R^2 = CH_2$

(b) $R^1 = Me$, $R^2 = OAc$

[52] A. Ohno and Y. Ohnishi, *Tetrahedron Letters*, 1972, 339.

[53] (*a*) P. Y. Johnson, *Tetrahedron Letters*, 1972, 1991; (*b*) J. Kooi, H. Wynberg, and R. M. Kellogg, *Tetrahedron*, 1973, **29**, 2135.

[54] P. Y. Johnson, E. Koza, and R. E. Kohrman, *J. Org. Chem.*, 1973, **38**, 2967.

[55] P. H. McCabe and W. Routledge, *Tetrahedron Letters*, 1973, 3919.

C-3 in the starting material followed by an intramolecular aldol condensation. The exomethylene compound (56a) can be obtained from (56b) by acetate pyrolysis. Addition of HBr or HCl to 13-thiabicyclo[8,2,1]tridecane 13-oxide was reported to give an oxosulphonium salt by participation of the sulphur lone-pair[56] rather than the expected oxysulphonium salt. Oximes of cyclic β-keto-sulphides undergo carbonium ion fragmentations under certain Beckmann rearrangement conditions.[57] For example, 3-thiacyclohexanone oxime and $SOCl_2$ produced $NC(CH_2)_3SCH_2Cl$ in 72% yield. With toluene-*p*-sulphonyl chloride–pyridine a small amount of the normal Beckmann product was obtained.

The ratio of $(M-OH)^+$ to M^+ in the mass spectra of cyclic sulphoxides varies with the distance between the SO group and the nearest β or γ hydrogen. It is larger for thian *S*-oxide (1.21) than for thiolan *S*-oxide (0.24).[58] The ratio was only 0.02 for *exo*-2-thiabicyclo[2,2,1]heptane 2-oxide; the *endo*-isomer was not examined. A detailed interpretation and comparison of the mass spectral fragmentation patterns of tetrahydrothiopyran-3-one, 6-methyl-tetrahydrothiopyran-3-one, and the corresponding pyran and *N*-methylpiperidones has been reported.[59] The fragmentation patterns of the sulphur and oxygen analogues are quite similar but differ substantially from those of the heterocycles, which do not have the 3-keto-group. The molecular ion was suggested to arise from scission of the 2,3-bond, with the charge residing either on the heteroatom or on the carbonyl group. The latter species fragmented further by loss of $H_2C{=}S$ while the ion carrying the charge at sulphur lost either CO or HĊO.

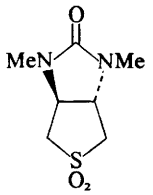
Electronegative substituents (Cl, Br, or OAc) in the 3-position of thians showed a greater preference for the equatorial position than in the corresponding cyclohexanes but the 4-substituted derivatives behaved oppositely.[60a] Oxidation of the sulphide to the sulphone enhanced the above tendencies. Thus the preferred conformation of 4-chlorothian 1,1-dioxide has the chlorine axially oriented ($K=3$). Transannular dipole–dipole interactions were suggested to cause these effects. These observations are similar to the findings that the methylsulphonyl group in 5-methylsulphonyl-1,3-dioxans also showed a strong axial preference.[60b]

A variety of transformations of sulpholane derivatives have been reported. Conditions which gave reproducibly a 50—60% yield of 3,4-epoxysulpholane have been described.[61] The epoxide was readily transformed into the *trans*-3,4-diol (conditions specified), which was then cleaved to $SO_2(CH_2CHO)_2$. This dialdehyde was cyclized to a number of

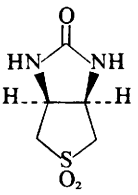
[56] N. N. Novitskaya, R. V. Kunakova, and G. A. Tolstikov, *Khim. geterotsikl. Soedinenii*, 1973, 861 (*Chem. Abs.*, 1973, **79**, 91 970m).
[57] R. K. Hill and D. A. Cullison, *J. Amer. Chem. Soc.*, 1973, **95**, 2923.
[58] S. Tagamaki and S. Oae, *Bull. Chem. Soc. Japan*, 1972, **45**, 1767.
[59] J. H. Block, D. H. Smith, and C. Djerassi, *J. Org. Chem.*, 1974, **39**, 279.
[60] (*a*) H. Remane, R. Borsdorf, and A. Zschunke, *Z. Chem.*, 1971, **11**, 427; (*b*) E. L. Eliel and S. A. Evans jun., *J. Amer. Chem. Soc.*, 1972, **94**, 8587.
[61] J. E. McCormick and R. S. McElhinney, *J.C.S. Perkin I*, 1972, 1335.

1,4-dithian and 1,4-oxathian derivatives.[61] 3,4-Epoxysulpholane reacted with sulphur tetrafluoride to give the 3,4-difluoro-derivative,[62] which on exposure to Na_2CO_3 formed 4-fluoro-4,5-dihydrothiolan 1,1-dioxide. Aniline and 3,4-dibromosulpholane yielded 4-anilino-4,5-dihydrothiolan 1,1-dioxide,[63] whereas under controlled conditions, methylamine and the *trans*-3,4-dibromide gave the *trans*-3,4-dimethylamino substitution product.[64] This compound was cyclized with $COCl_2$ to (57), which has the biotin ring system, the ring fusion, however, being *trans*. The *X*-ray structure determination of (57) showed that both rings were highly twisted and did not have the envelope structure associated with biotin derivatives. The conformation of biotin-related sulphoxides has been investigated by n.m.r.[46a]

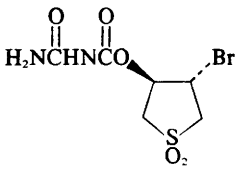
The *cis*-fused ring system (58) was prepared from *trans*-3-bromo-4-hydroxysulpholane *via* a series of interesting rearrangements.[65] The reaction of the bromohydrin with $COCl_2$ followed by urea gave (59), which in the presence of $NaHCO_3$ eliminated HBr, cyclized *via* attack by nitrogen on the $\alpha\beta$-unsaturated sulphone, re-formed the unsaturated system, and lost CO_2, (59) → (60) → (61). Finally, (61) was converted into (58) by using Na_2CO_3.



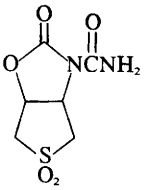
(57)



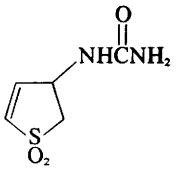
(58)



(59)



(60)



(61)

Transformations analogous to (59) → (61) followed by further isomerizations of the double bond were observed when the reaction product of the bromohydrin and isocyanates, *e.g.* phenyl isocyanate, was treated with triethylamine or stronger bases.[65]

[62] V. I. Golikov, A. M. Aleksandrov, L. A. Alekseeva, T. E. Bezmenova, and L. M. Yagupolskii, *Zhur. org. Khim.*, 1973, **9**, 2428 (*Chem. Abs.*, 1974, **80**, 47 745p).

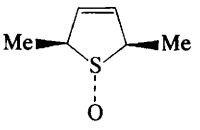
[63] T. E. Bezmenova and P. G. Dul'nev, *Khim. geterotsikl. Soedinenii*, 1972, 1193 (*Chem. Abs.*, 1973, **78**, 4049f).

[64] F. Ellis, P. G. Sammes, M. B. Hursthouse, and S. Neidle, *J.C.S Perkin I*, 1972, 1560.

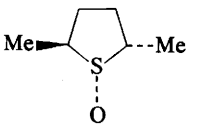
[65] F. Ellis and P. G. Sammes, *J.C.S. Perkin I*, 1972, 2866.

The elimination of SO_2 from 4,5-dihydrothiophen 1,1-dioxides continues to be used as a mild synthesis of 1,3-dienes. Included in these reports is a new synthesis of dihydrothiophen 1,1-dioxides based on the reaction of α-mercaptocarbonyl compounds with vinylphosphonium salts,[66] the synthesis of 3,4-dimethylene-*N*-arylpyrrolidones,[67] and the generation of tetramethylene-ethane as a transient intermediate.[68] Extrusion of SO_2 from *cis*-[1,3-$^2H_2$]-1,3-dihydrobenzo[*c*]thiophen 2,2-dioxide at 430—440 °C gave *trans*-[1,2-$^2H_2$]benzocyclobutene, as expected on the basis of a disrotatory formation of *o*-quinodimethane and SO_2 followed by conrotatory cyclization of the diene.[69] At higher temperatures the stereochemical integrity was lost because of the isomerization of the product. The parent peak in the mass spectrum of 1,3-dihydrobenzo[*c*]thiophen 2,2-dioxides resulted from loss of SO_2.[70] The addition of SO_2 to appropriate diallenes gave 2,5-dialkylidenethiolan 1,1-dioxides;[71] such compounds have in a few instances been isolated in relatively poor yield by base-catalysed condensation of 3-sulpholene with aliphatic aldehydes.[72] The base-catalysed condensation between 3-ketothiolan and methyl cyanoacetate has been reported[73] and the products thus obtained were converted into fused dihydrothiophens. The Ramberg–Backlund rearrangement of a thiadecalin sulphone ($KOH–CCl_4–Bu^tOH$) has been observed.[74] The highly strained thiolan 1,1-dioxide obtained by oxidation of (8) with ozone was found to lose SO_2 at 25 °C with a half-life of about 2.5 h to give 1,4-dimethylenecyclohexane.[12]

Sulphur monoxide, generated by thermolysis of thiiran oxide in toluene, has been shown to add to 1,3-dienes with surprising stereoselectivity despite the fact that the addition involved attack of triplet SO on the diene, usually present in the *s-trans*-conformation.[75] For example, *trans,trans*- and *cis,trans*-hexa-2,4-diene gave the sulphoxides (62) and (63) in ratios of 13:87



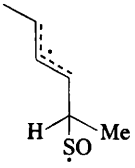
(62)



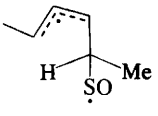
(63)

[66] J. M. McIntosh and H. B. Goodbrand, *Tetrahedron Letters*, 1973, 3157; J. M. McIntosh, H. B. Goodbrand, and G. M. Masse, *J. Org. Chem.*, 1974, **39**, 202.
[67] R. M. Ottenbrite and P. V. Alston, *J. Heterocyclic Chem.*, 1973, **10**, 785.
[68] T. Beetz and R. M. Kellogg, *J. Amer. Chem. Soc.*, 1973, **95**, 7925.
[69] J. R. du Manoir, J. F. King, and R. R. Fraser, *J.C.S. Chem. Comm.*, 1972, 541.
[70] I. U. Numanov, I. M. Nasyrov, A. A. Bakaev, M. P. Ibragimov, and G. Karimov, *Doklady Akad. Nauk. Tadzh. S.S.R.*, 1973, **16**, No. 11, p. 34 (*Chem. Abs.*, 1974, **80**, 69 924y).
[71] K. Kleveland and L. Skattebøl, *J.C.S. Chem. Comm.*, 1973, 432.
[72] M. M. Gerasimov and K. G. Murtazina, *Khim. Seraorg. Soedinenii, Soderzh. Neftyakh. Nefte prod.*, 1972, **9**, 230 (*Chem. Abs.*, 1973, **79**, 126 187).
[73] K. Gewald and J. Schael, *J. prakt. Chem.*, 1973, 39.
[74] J. Kattenberg, E. R. de Waard, and H. O. Huisman, *Tetrahedron Letters*, 1973, 1481.
[75] (*a*) P. Chao and D. M. Lemal, *J. Amer. Chem. Soc.*, 1973, **95**, 920; (*b*) D. M. Lemal and P. Chao, *ibid.*, p. 922.

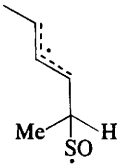
and 95:5, respectively. The high stereoselectivity required the unusual premise that carbon–carbon bond rotation within an allylic radical, (64) → (65), be faster than rotation about a single bond, (64) → (66).[75b] A



(64)



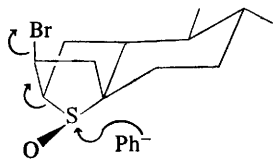
(65)



(66)

bonding interaction between the *p*-orbital of C-3 and the SO group could possibly significantly impede rotation about C-2—C-3 and lower the barrier to rotation about C-3—C-4. The retrograde diene–SO reaction has been observed both thermally[75,76] and photochemically;[76] it is only slightly stereoselective. Thiolen isomerizations, *e.g.* (63) ⇌ (62), competed with the thermal SO extrusion.[75b]

Kishi and co-workers have continued their studies of steroidal sulphoxides.[77] A number of 3-substituted 5α-cholestane-2α-5-*anti*-episulphoxides were prepared in high epimeric purity upon oxidation of the precursor sulphides with oxidizing agents such as *m*-chloroperbenzoic acid, H_2O_2, and $NaIO_4$.[77b] t-Butyl hypochlorite in methanol at −78 °C gave almost exclusively the *syn*-sulphoxide.[77b] The structures were assigned on the basis of aromatic-solvent-induced shifts,[77a] [Eu(dpm)$_3$]-induced shifts,[77b] dipole moments,[77a] and chromatographic behaviour.[77b] The isomerization of the sulphoxide group was also studied, the *anti*-isomer being thermodynamically more stable. The bromosulphoxide of part structure (67) reacted with



(67)

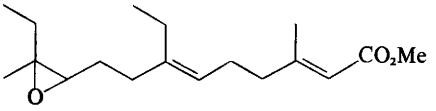
excess phenyl-lithium in ether to give cholesta-2,4-diene in 89% yield. The suggested mechanism is highly unusual! It involves attack at sulphur to give a sulphurane intermediate followed by cleavage of the C—S bond and elimination of Br^- to furnish 5α-(*R*)-phenylsulphinylcholest-2-ene (all these steps may be concerted[77]), and finally formation of the diene by a *cis*-elimination of phenylsulphenic acid.

An imaginative stereospecific synthesis of *Cecropia* juvenile hormone

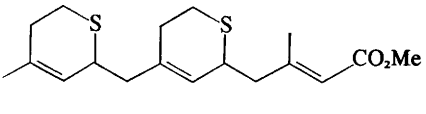
[76] W. L. Prins and R. M. Kellogg, *Tetrahedron Letters*, 1973, 2833.

[77] (*a*) T. Komeno, M. Kishi, H. Watanabe, and K. Tori, *Tetrahedron*, 1972, **28**, 2767; (*b*) M. Kishi and T. Komeno, *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 1.

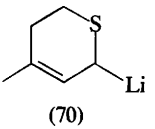
(C_{18}J.-H) (68) using 4-thiacyclohexanone[70a,b] or the corresponding sulphoxide[70c] as starting material has been completed by three groups. All groups used the concept that the carbon skeleton of C_{18}J.-H should be formed in a stereospecific manner by the desulphurization of (69), which was assembled *via* the three subunits A, B, and C, with each research group using minor variations of the following theme. The dimeric unit AB was obtained in good yield from the reaction of the lithio-salt of 4-thia-1-methylcyclohex-1-ene (70) with the epoxide (71) followed by dehydration, both of



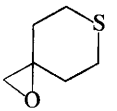
(68)



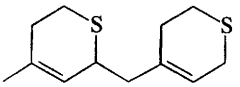
(69)



(70)



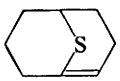
(71)



AB

the components having been prepared from 4-thiacyclohexanone. Alkylation of the monolithio-salt of the dimer AB with the appropriate allylic halide gave (69).

The highly strained 9-thiabicyclo[3,3,1]non-1-ene (72) has been synthesized in 65% yield by a t-butoxide-mediated elimination of methanesulphonic acid from the methanesulphonate of 9-thiabicyclo[3,3,1]nonan-1-ol.[78]

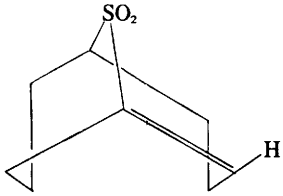


(72)

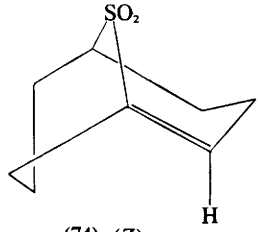
A comparison of the spectroscopic properties of (72) with those of non-strained vinyl sulphides gives some interesting results. The chemical shift of the vinyl hydrogen of (72), $\delta = 6.25$, is deshielded by almost 1 p.p.m. compared to the corresponding hydrogen atom in six-membered-ring vinyl sulphides. It was suggested[78] that in (72) steric constraints disallowed the dative resonance between sulphur and the π-system ($R^1S^+{=}CH{-}\bar{C}HR^2$) but did not interfere with acceptive resonance ($R^1\bar{S}{=}CH{-}\overset{+}{C}HR^2$), thus strongly deshielding the vinyl hydrogen. The u.v. spectrum of (72), $\lambda_{max} = 210$ nm ($\varepsilon = 4560$) and 196 nm ($\varepsilon = 4700$), is quite different from that of 2-methylthiacyclohex-2-ene, $\lambda_{max} = 248$ nm ($\varepsilon = 2700$) and 228 nm ($\varepsilon = 6000$), indicating a complete disruption of the normal conjugation due to twisting.

[78] C. B. Quinn and J. R. Wiseman, *J. Amer. Chem. Soc.*, 1973, **95**, 6120.

The spectrum of (72) appears to be a combination of bands due to the isolated chromophores of a dialkyl sulphide and a double bond. The existence of 9-thiabicyclo[3,3,1]non-1-enes having both the *E* (73) and *Z* (74)



(73) (*E*)



(74) (*Z*)

stereochemistry about the double bond has been demonstrated.[79] Thus the reaction of potassium t-butoxide with *endo*-2-chloro-9-thiabicyclo[3,3,1]-nonane 9,9-dioxide gave the *endo*-2-t-butyl ether *via* the *E*-isomer (73), while a similar reaction with 1-bromo-8-methyl-9-thiabicyclo[3,3,1]nonane 9,9-dioxide afforded the same 2-*endo*-ether *via* (74). The olefins (73) and (74) were also trapped with 1,3-diphenylisobenzofuran, and the structure of one of the two adducts obtained from (73) was determined by single-crystal *X*-ray diffraction.[79] The adducts formed from (73) and (74) and 1,3-diphenyl-isobenzofuran were shown to have the same stereochemistry. Olefin (73) was suggested to be more strained than (74) since its double bond is *trans* with respect to the six-membered ring and *cis* with regard to the eight-membered ring; this situation is reversed in (74).

2-Methoxy-5-thiacyclohexene has been suggested as a potentially useful alcohol-protecting group applicable in nucleotide synthesis.[80] Acetals are formed from the above enol ether and alcohols in the usual manner and are hydrolysed back to the alcohols with $t_{1/2} = 2$ min. in 0.01M-HCl, 4:1 aqueous dioxan at 20 °C. The protecting group can be made more stable to acid by oxidation of the sulphide to sulphone; the retardation of the hydrolysis rate was approximately 2×10^3.

Photoelectron spectra have been reported for a number of sulphur heterocycles, including thiolan,[81a] thian,[81b] 1,3- and 1,4-dithian,[81b] 1,4-oxathian,[81b] and 7-thiabicyclo[2,2,1]heptane.[81a] The effects have been compared with those of the corresponding oxygen heterocycles. Lone-pair interactions in six-membered-ring heterocycles having the heteroatoms *para* seem to occur primarily *via* through-bond mechanisms.[81b] When the heteroatoms are *meta* the interaction is mainly through-space.[81b] The e.s.r. spectrum of free radicals α to sulphur in thians and thiolans has been measured and interpreted.[82] Electron-diffraction data have been obtained and used to

[79] C. B. Quinn, J. R. Wiseman, and J. C. Calabrese, *J. Amer. Chem. Soc.*, 1973 **95**, 6121.

[80] J. H. van Boom, P. van Deursen, J. Meeuwse, and C. B. Reese, *J.C.S. Chem. Comm.*, 1972, 766.

[81] (*a*) J. C. Bunzli, D. C. Frost, and L. Weiler, *J. Amer. Chem. Soc.*, 1973, **95**, 7880; (*b*) D. A. Sweigart and D. W. Turner, *ibid.*, 1972, **94**, 5599.

[82] (*a*) E. A. C. Lucken and B. Poncioni, *Helv. Chim. Acta*, 1972, **55**, 2673; (*b*) E. A. C. Lucken and B. Poncioni, *Tetrahedron*, 1972, **28**, 867.

determine the conformation of sulpholane.[83] (*S*)-(+)-6-Methyltetrahydrothiopyran-3-one, its oxide, and its dioxide have been synthesized, and their o.r.d. curves have been determined and compared with those of the corresponding oxygen and nitrogen analogues.[84] A review of medicinal aspects of thiolan and thian derivatives has appeared.[85]

The structures of the adducts between the halogens and thian and selenan in ethylene dichloride solution have been investigated by n.m.r. and conductivity measurements.[86] Thian dibromide[51] and thian di-iodide exist as molecular complexes, with the former showing considerable ionic character. The shape of the six-membered ring in these compounds is similar to that of thian itself and of *S*-methylthianium tetrafluoroborate, the geometry around sulphur being trigonal. Selenan di-iodide was also assigned a molecular complex structure, similar to that of thian di-iodide. In contrast, a trigonal-bipyramidal structure was found for selenan dibromide. Solutions of the di-iodide were very weakly conducting but those of the dibromide essentially non-conducting.

The crystal structure of 4-thiatelluran dibromide showed a trigonal-bipyramidal geometry about tellurium.[87] Lambert and co-workers[88] have determined the conformational preference of Se substituents in selanans using the J_{gem} of the α-protons as a probe. The axial preference for H in protonated selanan, O in the oxide, and CH_3 in the methylated derivative is somewhat larger than in the corresponding sulphur analogues: for example, 84:16 in favour of the axial oxygen in the selenan oxide, compared to 62:38 for thian oxide. Presumably the increase in C—X bond length in going from the S to the Se heterocycles brings the *syn*-1,3- and -1,5-interactions into a still more attractive region of the potential well. The barrier to ring inversion in selenan oxide is 8.2 kcal mol^{-1} at −30 °C.[88]

3 Compounds with Two Sulphur or Selenium Atoms in the Ring and their Oxy-sulphur Analogues

Cyclic Disulphides.—Most of the syntheses of these types of compounds involved oxidation of the open-chain dithiols. Asparagusic acid, or 1,2-dithiolan-4-carboxylic acid, a new plant-growth inhibitor, has been isolated from extracts of etiolated asparagus[89] and its structure confirmed by synthesis.[90] Brugeriol and isobrugeriol, *trans*- and *cis*-4-hydroxy-1,2-dithiolan

[83] V. A. Naumov, V. N. Semashko, and S. A. Shaiduline, *Zhur. strukt. Khim.*, 1973, **14**, 595 (*Chem. Abs.*, 1973, **79**, 125 415b).
[84] M. J. Cook and C. Djerassi, *J. Amer. Chem. Soc.*, 1973, **95**, 3678.
[85] G. D. Rees and J. K. Sugden, *Pharm. Acta. Helv.*, 1972, **47**, 481.
[86] J. B. Lambert, D. H. Johnson, R. G. Keske, and C. E. Mixan, *J. Amer. Chem. Soc.*, 1972, **94**, 8172.
[87] C. Knobler and J. D. McCullough, *Inorg. Chem.*, 1972, **11**, 3026.
[88] J. B. Lambert, C. E. Mixan, and D. H. Johnson, *Tetrahedron Letters*, 1972, 4335.
[89] H. Yanagawa, T. Kato, Y. Kitahara, N. Takahashi, and Y. Kato, *Tetrahedron Letters*, 1972, 2549.
[90] H. Yanagawa, T. Kato, H. Sagani, and Y. Kitahara, *Synthesis*, 1973, 607.

1-oxide, respectively, have been prepared by cyclization of 2-hydroxypropane-1,3-dithiol with $Et_3\overset{+}{N}—SO_2\bar{N}CO_2Me$ followed by oxidation with 30% H_2O_2;[91] the *trans*-isomer was more mobile on silica gel. A number of 4,4-dialkyl-1,2-dithiolan-3,5-diones were synthesized by iodine oxidation of bisthiomalonic acids.[92] The reaction of these cyclic disulphides with triphenylphosphine in benzene at 60 °C gave 3,3-dialkylthietan-2,4-diones in 80—90% yield. The thietans were also obtained by heating the bisthiomalonic acids at *ca.* 80 °C. In contrast, monothio-acids were formed at room temperature *via* loss of COS.[92] Treatment of thio-β-lactones with acetylsulphenyl chloride and zinc dichloride at 80 °C resulted in the formation of acetyl chloride and 1,2-dithiolan-3-ones in yields of *ca.* 80%.[93]

The *cis*- and *trans*-isomers of 4,5-dihydroxy-1,2-dithian have been obtained in about 50% yield from the reaction of Na_2S_2 and *dl*- and *meso*-1,4-dichlorobutane-2,3-diols, respectively.[94] The corresponding thiolsulphinates and thiosulphonates were prepared by oxidation with sodium periodate and H_2O_2 in acetic acid. The thiolsulphinates underwent desulphurization and ring contraction to thiolan *S*-oxides in relatively poor yield upon treatment with tris(dimethylamino)phosphine in benzene solution; with tri-n-butylphosphine, the thiolsulphinates underwent deoxygenation to the 1,2-dithians. The 1,2-glycol function was cleaved with periodate to 3,4-dithia-adipaldehyde.

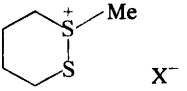
Oxidation of *cis*- and *trans*-1,2-dithian-4,5-diacetates with a variety of common oxidizing agents (30% H_2O_2, $KMnO_4$, CrO_3, KIO_4 in aqueous acetone) gave the 1-monoxide in yields up to 85%, but attempts at further oxidation with these reagents failed to give the 1,1-dioxide.[95a] It was eventually found that KIO_4 in aqueous isopropyl alcohol, preferably in the presence of I_2, effected the desired oxidation. This procedure was also used to prepare 2,3-benzodithian 2,2-dioxide[95b] but failed when applied to 1,2-dithian-4-carboxylic acid.[95a] The sulphinic acid salt $Ac(CH_2)_2SS(CH_2)_4$-SO_2Na disproportionates much more readily to the two possible symmetrical disulphides than the corresponding sulphonate salt.[95a] The acceleration in the rate of cleavage of the S—S bond is due to the sulphinate anion acting as an internal nucleophile. The isolation of 1,2-dithian 1,1-dioxide, the product of such an interaction, when the reaction was carried out in the presence of the thiol trap *N*-ethylmaleimide confirmed the mechanism. A number of similar disproportions with other disulphides were also investigated,[95b] as were possible neighbouring-group effects due to a carboxylate group δ to the disulphide linkage.[95c] The product of the reaction

[91] A. Kato and T. Okutami, *Tetrahedron Letters*, 1972, 2959.
[92] J. H. Schauble and J. D. Williams, *J. Org. Chem.*, 1972, **37**, 2514.
[93] T. P. Vasil'eva, M. G. Lin'kova, O. V. Kil'disheva, and I. L. Knunyants, *Izvest. Akad. Nauk. S.S.S.R., Ser. khim.*, 1972, 489 (*Chem. Abs.*, 1972, **77**, 34 395m).
[94] J. E. McCormick and R. S. McElhinney, *J.C.S. Perkin I*, 1972, 2795.
[95] (*a*) L. Field and Y. H. Khim, *J. Org. Chem.*, 1972, **37**, 2710; (*b*) P. K. Srivastava and L. Field, *ibid.*, p. 4196; (*c*) Y. H. Khim and L. Field, *ibid.*, p. 2714.

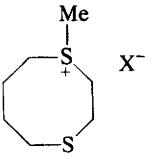
of 1,2-dithian 1,1-dioxide with Na_2S is the trisulphide $[NaO_2S(CH_2)_4]_2S_3$, which was found to have some anti-radiation activity.[96]

The oxidation of 1,2-dithian and the 3-methyl and 3,6-dimethyl analogues with H_2O_2 in acetic acid has been studied.[97] The rate of oxidation, especially from the monoxide to the dioxide stage, decreased with increasing substitution α to the disulphide group. In the mono-oxidation of 3-methyl-1,2-dithian, a mixture of products was obtained, as judged by the observation of two methyl signals in the n.m.r. spectrum. Since the components could not be separated it was impossible to ascertain whether the mixture was due to positional isomers or geometric isomers or both. Further oxidation of the monoxide gave a mixture of dioxides in a 5:1 ratio, thus indicating that the monoxide mixture was at least partly composed of positional isomers.

Details concerning the reaction of the *S*-methylated-1,2-dithian (75) with olefins, which resulted in cleavage of the S—S bond and expansion to an eight-membered ring, *e.g.* (76), are now available.[98] A variety of



(75) X = 2,4,6-trinitrobenzenesulphonate



(76)

unsubstituted and mono- and 1,2-di-substituted olefins were successfully employed. No adducts were isolated from (75) and *cis*-stilbene, 2-methylpropene, or methylenecyclohexane because of adverse steric or electronic interactions. A concerted mechanism was suggested for the reaction mainly because all stepwise processes were considered to have serious flaws. A ten-membered ring was obtained from (75) and 2,3-dimethylbuta-1,3-diene; other conjugated dienes did not react.

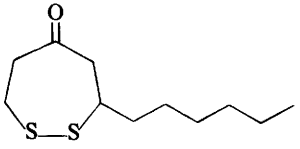
The relative rates of *S*-methylation of disulphides with methyl fluorosulphonate have been related to the CSSC dihedral angle.[99] Lipoic acid, a 1,2-dithiolan, is about 11 times more reactive than 1,2-dithian and 33 times more reactive than acyclic disulphides, as represented by diethyl disulphide. The effect has been attributed to a destabilization of the nucleophile with a decreasing CSSC dihedral angle for the following reason: each sulphur atom in the disulphides is largely unhybridized and hence the highest occupied orbital is mainly non-bonding and, on combination of the adjacent lone pairs, this leads to an orbital splitting which should increase with decreasing

[96] L. Field and Y. H. Khim, *J. Medicin. Chem.*, 1972, **15**, 312.
[97] N. Isenberg and H. F. Herbrandson, *Internat. J. Sulfur Chem.* (A), 1971, **1**, 179.
[98] N. E. Hester and G. K. Helmkamp, *J. Org. Chem.*, 1973, **38**, 461.
[99] R. F. Hudson and F. Filippini, *J.C.S. Chem. Comm.*, 1972, 726.

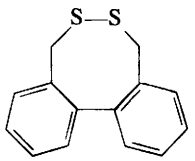
dihedral angle. The orbital splitting has been verified by studying photoionization spectra.[100]

The seven-membered-ring disulphide (77) has been isolated from a species of Hawaiian alga[101] and the structure confirmed by the following synthesis: the reaction of 2-nonenal with vinyl-lithium followed by oxidation with DDQ gave the undeca-1,4-dien-3-one, which readily added thiolacetic acid to each double bond. The dithiol ester thus produced was hydrolysed to the dithiol with methanol–HCl. Cyclization to (77) was effected with iodine in pyridine. A dimeric fourteen-membered-ring tetrasulphide was obtained as by-product.

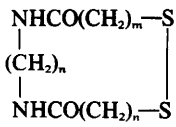
In the crystal state, the dibenz-fused 1,2-dithiocin (78) exists in the pseudo-chair conformation[102] in which the CSSC dihedral angle is 54.3°, and thus fairly far from the ideal angle of *ca.* 90°. This conformation is apparently favoured over the pseudo-tub form, in which the CSSC angle is close to ideal, because in the latter form all phenyl–phenyl resonance is inhibited. The medium-ring disulphides (79) are formed very readily when



(77)



(78)

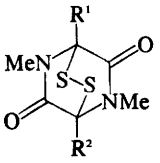


(79) $m = 1$ or 2
$n = 2$ or 3

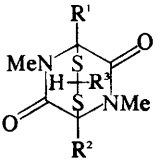
ethylenediamine and trimethylenediamine are mixed with esters of dithiodiacetic and dithiodipropionic acids in the absence of solvent.[103] The same products could also be obtained by oxidation of the appropriate dithiols with iodine solution. No cyclic products were obtained when either the acid or amine carried alkyl substituents.

A general synthesis of 3,6-epidithiopiperazine-2,5-diones (80), which represent a common structural feature of the natural products of the gliotoxin–sporidesmin class, has been developed.[104] Both the *cis*- and *trans*-isomers of 1,4-dimethylpiperazine-2,5-dione-3,6-dithiol (81) were converted into the thioacetal (82) upon treatment with BF_3,Et_2O. The reaction of (82) with one equivalent of butyl-lithium in THF at −78 °C gave the lithio-salt (83) to the complete exclusion of (84). Alkylation of (83) followed by a second treatment with butyl-lithium gave (85), which could again be quenched with electrophilic reagents. The thio-acetal bridge was converted into the required disulphide bridge by oxidation to a

[100] H. Bock and G. Wagner, *Angew. Chem.*, 1972, **84**, 119.
[101] A. E. Asato and R. E. Moore, *Tetrahedron Letters*, 1973, 4941.
[102] G. H. Wahl jun., J. Bordner, D. N. Harpp, and J. G. Gleason, *J.C.S. Chem. Comm.*, 1972, 985.
[103] T. C. Owen, J. M. Fayadh, and J. S. Chen, *J. Org. Chem.*, 1973, **38**, 937.
[104] Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, 1973, **95**, 6940.



(80)



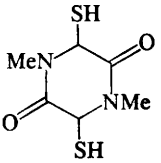
R^3 = *p*-methoxyphenyl

(82) $R^1 = R^2 = H$

(83) $R^1 = Li, R^2 = H$

(84) $R^1 = H, R^2 = Li$

(85) R^1 = alkyl, $R^2 = Li$



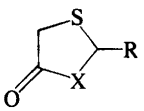
(81)

monosulphoxide and subsequent treatment with $HClO_4$. The overall procedure thus allowed for the preparation of unsymmetrically substituted 3,6-epidithiopiperazine-2,5-diones, as illustrated by the successful synthesis of dehydrogliotoxin[105a] and sporidesmin A.[105b] Sporidesmin G, which has a 3,6-tetrathio bridge, has been isolated[106a] and its structure determined by *X*-ray analysis.[106b]

1,3-Dithiolans and 1,3-Dithians.—*Synthesis.* The synthesis of 1,3-dithiolans and 1,3-dithians, which were intended for use as reagents, will be referred to in the section on Reactions, especially if the method used differs substantially from the well-known procedures.

Only a few syntheses of this class of heterocycle have been reported when the compounds were not intended for immediate further synthetic utilization. A simple preparation of 1,3-dithiolan-2-one involved the reaction of ethanedithiol with phosgene in the presence of pyridine at 0 °C.[107] The same authors also reported the synthesis of mercaptothioacetic acid and its reaction with aldehydes to form, *via* loss of H_2O or H_2S from the intermediate (86), 2-substituted 1,3-dithiolan-4-ones (87a) and 2-substituted 1,3-oxathiolan-5-ones (87b). The yields were in the range 25—40% for (87a)

(86)



(87) (a) X = S

(b) X = O

and 5—15% for (87b).[107] Thermolysis of *cis*- and *trans*-stilbene episulphoxides in the presence of di-*p*-anisyl thioketone resulted in the formation of a diastereomeric mixture of 1,3-dithiolan 1-oxides.[108] The products were

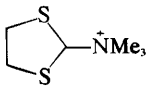
[105] (*a*) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *ibid.*, p. 6942; (*b*) Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *ibid.*, p. 6943.

[106] (*a*) E. Francis, R. Rahman, S. Safe, and A. Taylor, *J.C.S. Perkin I*, 1972, 470; (*b*) M. Przybylska, E. M. Gopalakrishna, A. Taylor, and S. Safe, *J.C.S. Chem. Comm.*, 1973, 554.

[107] S. Satsumabayashi, H. Takahashi, T. Tanaka, and S. Motoki, *J. Org. Chem.*, 1973, **38**, 3953.

[108] K. Kondo, M. Masumoto, and A. Negishi, *Tetrahedron Letters*, 1972, 2131.

apparently formed by the trapping of the biradical obtained from C—S bond rupture of the episulphoxide by the thioketone. Only two of the four possible diastereomers, both having retained the preferred *trans* arrangement of the phenyl groups, were obtained from *trans*-stilbene episulphoxide, while all four possible products were obtained from the *cis*-episulphoxide. The results show that the biradical obtained from the *cis*-isomer has a sufficiently long lifetime to allow for carbon–carbon bond rotation. 1,3-Dithiolans resulted from the addition of diazo-compounds to $ArSO_2C(S)SPh$.[109] The reaction of amines with the dithiolanylammonium salt (88) in DMF resulted in displacement of trimethylamine and the



(88)

formation of new 2-substituted 1,3-dithiolans.[110a] The salt (88) thus behaves as an electrophilic 1,3-dithiolan-transfer reagent. With amines such as benzylamine, aniline, and *N*-methylaniline, attack occurred *via* the nitrogen, thus leading to 2-amine-substituted-1,3-dithiolans, while indole and *NN*-dimethylaniline reacted *via* carbon attack, at the 3-position in the former and *para* in the latter reagent. 2-Dimethylamino-1,3-dithenium salts and their corresponding five-membered-ring analogues were reduced to 2-dimethylamino-1,3-dithians and 2-dimethylamino-1,3-dithiolans, respectively, upon reaction with sodium dihydrobis(methoxyethoxy)aluminate in THF at −5 °C;[110b] the same reduction, albeit in lower yield, took place with $NaBH_4$ or $LiAlH_4$. Spiro-compounds having two 1,3-dithan rings were obtained from the reaction of propane-1,3-dithiol with cyclohexane-1,4-dione and $C(CH_2SH)_4$ with cyclohexanone in the presence of an acid catalyst.[111] The dione and tetrathiol produced sulphur-containing spiro-polymers.

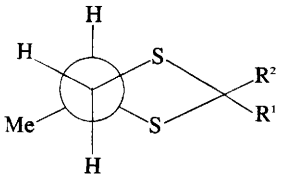
The preferred conformations and diastereomer equilibria of a number of 2-alkyl-4-methyl- and 2-alkyl-2,4-dimethyl-1,3-dithiolans have been determined by n.m.r. studies and chemical equilibration.[112] In the dialkyl series the *cis*-isomers were slightly more stable than the *trans*, but in general, the energy differences between the diastereomers were quite small. Representative values for the equilibrium constant for *trans* ⇄ *cis* are shown in Figure 1. In the trialkyl series the *trans*-isomers were found to be more stable. The geminal coupling constants for the methylene group at C-5 ranged from −11.2 to −11.5 Hz, which is considerably more negative than for

[109] S. Holm and A. Senning, *Tetrahedron Letters*, 1973, 2389.

[110] (*a*) K. Hiratani, T. Nakai, and M. Okawaro, *Bull. Chem. Soc. Japan*, 1973, **46**, 3510; (*b*) *ibid.*, p. 3872.

[111] W. J. Bailey and R. L. Hinrichs, *Polymer Preprints Amer. Chem. Soc., Div. Polymer Chem.*, 1970, **11**, 598 (*Chem. Abs.*, 1972, **77**, 20 050j).

[112] R. Keskinen, A. Nikkila, and K. Pihlaja, *J.C.S. Perkin II*, 1973, 1376.



(89) *cis*-series: R^1 = alkyl, R^2 = H
trans-series: R^1 = H, R^2 = alkyl

Alkyl group R^1 *or* R^2	*K* (*trans*⇌*cis*) *at* 378 K
Me	0.95
Et	1.05
Pr^i	1.15
Bu^t	1.19

Figure 1

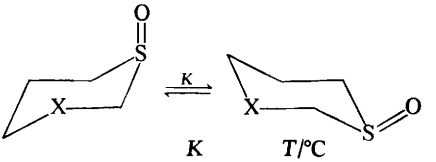
1,3-dioxolan (−7.1 to −7.3 Hz) and 1,3-oxathians (−9.0 to −9.2 when α to oxygen and −9.7 to −10.2 when α to sulphur). The decrease in J_{gem} is partly due to an electronegativity effect, but highly indicative that the hydrogens on C-5 should be staggered with respect to the sulphur lone pairs. Based on these results and on vicinal coupling constants, the most probable conformation was suggested to be (89). It was pointed out, however, that energy differences between (89) and other conformations would be small, and thus the 1,3-dithiolan ring is relatively flexible, like 1,3-dioxolan.

The barrier to rotation of the t-butyl group in a series of 2-t-butyl-1,3-dioxo-oxathia- or -dithia-rings not only varied with the size of the other substituent at position 2 but also depended on the preferred geometry of the heterocycle.[113] For example, the barrier is higher (9.6 kcal mol^{-1} at −83 °C) for 2-methyl-2-t-butyl-1,3-dithian than for the corresponding dioxan (8.7 kcal mol^{-1} at −110 °C), the difference being attributed to the larger van der Waals radius of sulphur compared to oxygen and a larger CSC bond angle compared to COC, which leads to greater interactions between the t-butyl group and the heteroatoms in the 1,3-dithian. The anomalous behaviour observed in the corresponding five-membered rings, the barrier for t-butyl–C-2 rotation in the dithiolan being greater than that in the dithian while that in the dioxolan was less than that in the dioxan, could not be satisfactorily explained. The conformation having the ethyl group in the axial position is slightly favoured for 2-ethyl-2-methyl-1,3-dithian, but in the 2-isopropyl-2-methyl analogue the larger isopropyl group again prefers the equatorial position.[114]

The S=O bond in 1,3-dithian 1-oxide (92) showed a considerable equatorial preference,[115] in contrast to a marked axial preference in 1,3-oxathian 3-oxide (91)[115a] and a relatively slight axial preference in thian

[113] P. E. Stevenson, G. W. Anderson, and C. H. Bushweller, *J. Amer. Chem. Soc.*, 1972, **94**, 4743.
[114] K. Pihlaja, D. M. Jordan, A. Nikkila, and H. Nikander, *Adv. Mol. Relaxation Processes*, 1973, **5**, 227.
[115] (*a*) L. Van Acker and M. Anteunis, *Tetrahedron Letters*, 1974, 225; (*b*) M. J. Cook and A. P. Tonge, *ibid.*, 1973, 849.

1-oxide (90).[116] Low-temperature studies gave the equilibrium constants shown. The introduction of a 5,5-dimethyl group into all three sulphoxides



	K	T/°C
(90) X = CH_2	0.47	−90
(91) X = O	0.19	−98
(92) X = S	5.67	−102

shifted the equilibrium strongly in favour of the isomer having S=O equatorial.[115a] In the case of 5,5-dimethyl-1,3-oxathian, the ratio of equatorial to axial S=O was 90:10, indicating that a 1,3 S=O–methyl interaction is unfavourable by 1.3 kcal mol^{-1} in the 1,3-oxathian ring system.[115a] A 90:10 mixture of *trans*- and *cis*-2-t-butyl-1,3-dithian 1-oxide was obtained by oxidation of the corresponding dithian with periodate.[115b] Each pure isomer was equilibrated *via* the carbanions at C-2, using NaOD–DMSO at 85 °C, to a 68:32 mixture in which the *trans*-isomer was favoured. The chemical equilibration results were thus in agreement with the n.m.r. studies. The preferred conformations of the various compounds in these studies were determined by measurements of solvent-induced n.m.r. shifts[115a] and of dipole moments.[115b] Two discussions dealing with conformational aspects of 1,3-dithians have appeared.[117] Dipole-moment measurements have been made for 1,3-dithiolans,[118] and the e.s.r. spectrum[119] and the ^1H n.m.r. spectrum[120] in the nematic solvent *N*-(*p*-methoxybenzylidene)-*p*-n-butylamine have been recorded for 1,3-dithiolan-2-thione. Hydrogen-bonding between 1,3-dithiolan-2-thione and various phenols has been investigated by i.r. spectroscopy.[121] The *X*-ray crystal structure determination for the same compound indicated a puckered structure with nearly C_2 symmetry and a torsional angle of 44° about the C—C bond.[122] Long-range couplings of *ca.* 0.5—0.7 Hz have been observed in several 2-substituted 1,3-dithiolan tetroxides.[123]

Reactions. The major effort in this area has been the continued demonstration of the versatility of these compounds, especially the 1,3-dithians, as

[116] (*a*) J. B. Lambert and R. G. Keske, *J. Org. Chem.*, 1966, **31**, 3499; J. B. Lambert, D. S. Bailey, and C. E. Mixan, *ibid.*, 1972, **37**, 377.

[117] (*a*) A. V. Bogatskii, *Voprosy Stereokhim.*, 1971, **1**, 3; (*b*) A. V. Bogatskii, L. N. Vostrova, V. N. Somchinskaya, T. I. Davidenko, O. S. Stepanova, and A. I. Gren, *ibid.*, 1972, **1**, 62 (*Chem. Abs.*, 1972, **77**, 139 347).

[118] B. A. Arbuzov, E. N. Klimovitskii, L. K. Yuldasheva, and G. N. Sergeeva, *Izvest. Akad. Nauk. S.S.S.R., Ser. khim.*, 1973, 2422 (*Chem. Abs.*, 1973, **80**, 47 884k).

[119] D. A. Sweigart and D. W. Turner, *J. Amer. Chem. Soc.*, 1972, **94**, 5599.

[120] M. A. Raza and L. W. Reeves, *J. Chem. Phys.*, 1972, **57**, 821.

[121] S. Mukherjee, S. K. De, and S. R. Pilit, *Indian J. Chem.*, 1973, **11**, 1011.

[122] B. Klewe and H. M. Seip, *Acta Chem. Scand.*, 1972, **26**, 1860.

[123] L. A. Sternson, A. W. Sternson, and R. S. Egan, *Tetrahedron Letters*, 1973, 1315.

reagents in synthetic work. Paralleling this has been the improvement of old, and the development of new, mild, high-yield methods for the removal of the sulphur ring and the regeneration of the carbonyl group.

1,3-Dithiolans or 1,3-dithians were converted into their parent aldehydes or ketones in 75—90% yield by heating the thioacetal or thioketal with excess methyl iodide in moist acetone[124a] or aqueous alcohol (55—83%)[124b] and by treatment with methyl fluorosulphonate in benzene[124c] or liquid sulphur dioxide[124a] followed by 2M-NaOH and H_2O, respectively. Since only a small amount of water is required in the last procedure, the method was found useful for the preparation of ^{18}O-labelled compounds. The hydrolysis of the thiolan ring in substances containing a basic nitrogen function by the sulphonium salt route was successful only when the basic nitrogen was first converted into a quaternary ammonium salt.[124d] Dethioacetalizations have also been carried out in 70—85% yield by the reaction of 1,3-dithiolan or 1,3-dithian derivatives with four equivalents of ceric ammonium nitrate in 3:1 aqueous acetonitrile for 3 minutes at room temperature,[125] in 45—97% yield by reaction with Chloramine T in aqueous methanol,[126] in 70—98% yield when homogenized with one equivalent of ice-cold concentrated H_2SO_4 for 10 minutes followed by addition of this mixture to water with vigorous stirring,[127] and by refluxing with a ten-fold excess of silver oxide in aqueous ethanol (73—85%).[128] Iodine in DMSO at about 100 °C converted 1,3,5-trithians and 1,3-dithiolans into their parent carbonyl compounds in 75—95% yield.[129] In the reaction involving 2,4,6-triphenyl-*s*-trithian, dimethyl sulphide and elemental sulphur were obtained in 76 and 88% yield, respectively, in addition to benzaldehyde. This appears to be a very intriguing reaction from both a synthetic and mechanistic point of view. Although the report is not specific on the point, iodine is apparently needed only in catalytic amount, since DMSO is acting as the oxidant. Presumably, the first step in the reaction is the formation of a trithian–iodine complex[88] or iodosulphonium salt followed by attack by the oxygen of DMSO at the ring carbon, causing cleavage of the carbon–sulphur bond. The remaining part of the mechanism is obscure. The four-membered-ring disulphide (93), whose decomposition to all the reaction products is outlined by the arrows, was put forth as a plausible intermediate.[129]

The reaction of 2-lithio-2-trimethylsilyl-1,3-dithian (94) with aldehydes and ketones is apparently the method of choice for the synthesis of ketone

[124] (*a*) M. Fetizon and M. Jurion, *J.C.S. Chem. Comm.*, 1972, 382; (*b*) H.-L. Chang, *Tetrahedron Letters*, 1972, 1989; (*c*) T.-L. Ho and C. M. Wong, *Synthesis*; 1972, 561; (*d*) T. Oishi, H. Takechi, K. Kememoto, and Y. Ban, *Tetrahedron Letters*, 1974, 11.

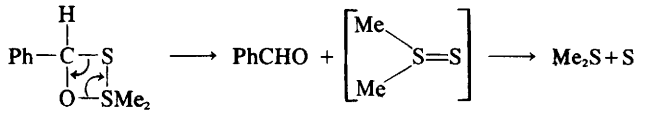
[125] (*a*) T.-L. Ho, C. H. Ho, and C. M. Wong, *J.C.S. Chem. Comm.*, 1972, 791; (*b*) H. C. Ho, T.-L. Ho, and C. M. Wong, *Canad. J. Chem.*, 1972, **50**, 2718.

[126] W. Huurdeman, H. Wynberg, and D. W. Emerson, *Synthetic Comm.*, 1972, **2**, 7.

[127] T.-L. Ho, H. C. Ho, and C. M. Wong, *Canad. J. Chem.*, 1973, **51**, 153.

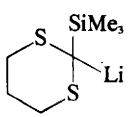
[128] (*a*) D. Gravel, C. Vaziri, and S. Rahal, *J.C.S. Chem. Comm.*, 1972, 1323; (*b*) J. B. Chattopadhyaya and A. V. R. Rao, *Indian J. Chem.*, 1973, **11**, 1331.

[129] J. B. Chattopadhyaya and A. V. R. Rao, *Tetrahedron Letters*, 1973, 3735.

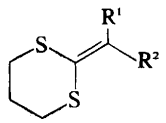


(93)

thioacetals (95).[130] The reaction can be done at temperatures varying from 0 °C[130a] to −80 °C[130e] and the reported yields were generally good[130a,d] to

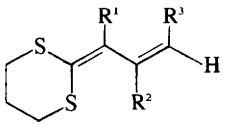


(94)

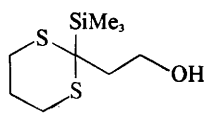


(95)

excellent[130e] for both aldehydes and ketones, whether enolizable, non-enolizable, or even relatively hindered. αβ-Unsaturated aldehydes and ketones such as crotonaldehyde, mesitylene oxide, and cyclohexen-2-one underwent 1,2-addition and furnished 1,3-dienes, *e.g.* (96). The ketone thioacetals are valuable intermediates and were subjected to further reactions in the following manner: (*a*) reduction to 2-substituted 1,3-dithians upon treatment with trimethylsilane in the presence of acid,[130a,d] (*b*) hydrolysis to carboxylic acids,[130d] and (*c*) reaction with alkyl-lithiums, which resulted in addition to the carbon–carbon double bond and the formation of more complex 2-alkyl-2-lithio-1,3-dithians.[130d] Addition of butyl-lithium to (96a) furnished a lithio-derivative which alkylated exclusively α to sulphur upon quenching with methyl iodide.[131] Keten thioacetals bearing three heteroatoms on the double bond, *e.g.* [95; $R^1 = H$, $R^2 = N(alkyl)_2$], were obtained from (94) and *NN*-dialkylformamides;[130d,e] ethyl benzoate and (94) gave 2-benzoyl-1,3-dithian.[130e] Epoxides and (94) furnished the γ-trimethylsilyl alcohols (97),



(96) (a) $R^1 = H, R^2 = R^3 = Me$
(b) $R^1 = R^2 = H, R^3 = Ph$



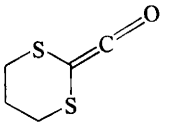
(97)

which could conceivably fragment to cyclopropanes.[130d] This did not occur! Heating (97) or its alkoxide resulted in either no reaction or in transfer of the trimethylsilyl group from carbon to oxygen.

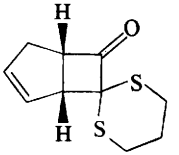
[130] (*a*) F. A. Carey and A. S. Court, *J. Org. Chem.*, 1972, **37**, 1926; (*b*) D. Seebach, T. B. Grobel, A. K. Beck, M. Braun, and K. H. Geiss, *Angew. Chem. Internat. Edn.*, 1972, **11**, 443; (*c*) P. F. Jones and M. F. Lappert, *J.C.S. Chem. Comm.*, 1972, 526; (*d*) P. F. Jones, M. F. Lappert, and A. C. Szary, *J.C.S. Perkin I*, 1973, 2272; (*e*) D. Seebach, M. Kolb, and B. T. Grobel, *Chem. Ber.*, 1973, **106**, 2277.

[131] D. Seebach, M. Kolb, and B. T. Groebel, *Angew. Chem.*, 1973, **85**, 42.

The vinyl thioacetals (96) underwent cycloaddition reactions with tetracyanoethylene and maleic anhydride.[132] The reaction was being investigated for use as a possible synthesis of cyclohexen-2-ones but was not found to be general enough to be of value since only the two very reactive dienophiles mentioned above gave cycloaddition reactions with (96). The acid chloride of 1,3-dithian-2-carboxylic acid is dehydrohalogenated by triethylamine to (98), which was trapped efficiently with cyclopentadiene to form the cyclobutanone (99).[133] This compound underwent ring fragmenta-

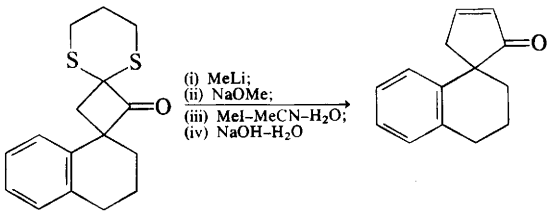


(98)



(99)

tion in the presence of hydroxide or methoxide ion to the *cis*- and *trans*-3,4-disubstituted cyclopentene derivatives, respectively. The overall effect, after the removal of the dithian ring, was the stereospecific addition of two one-carbon units to each carbon of a double bond. A similar base-catalysed ring opening of an α-dithianylcyclobutanone was used in the synthesis of deoxypodocarpate,[134] and in the conversion of the cyclobutanone (100) into the cyclopentenone (101). In the last two examples the



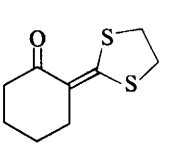
(100) (101)

removal of the dithian ring was accomplished very effectively with methyl iodide in aqueous acetonitrile.[134]

Cyclohexanone reacted with carbon disulphide in the presence of lithium 2,6-di-t-butyl-4-methylphenolate to form a dithio-acid salt which was trapped with ethylene dibromide, thus forming the keten thioacetal (102).[135] Keten thioacetals were also formed in excellent yield when bis(dimethylalumino)ethane-1,2-dithiolate reacted with esters which possessed an α-hydrogen, in methylene chloride–toluene solution at −78 °C.[136] Lactones

[132] F. A. Carey and A. S. Court, *J. Org. Chem.*, 1972, **37**, 4474.
[133] E. Cossement, R. Biname, and L. Ghosez, *Tetrahedron Letters*, 1974, 997.
[134] B. M. Trost and M. Preckel, *J. Amer. Chem. Soc.*, 1973, **95**, 7862.
[135] E. J. Corey and R. H. K. Chen, *Tetrahedron Letters*, 1973, 3817.
[136] E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, 1973, **95**, 5829.

and the above aluminium reagent formed dithio-orthoesters of the type (103). The ease of formation of (102) and (103) from esters and lactones,



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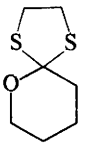
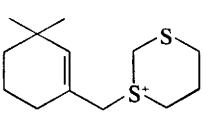
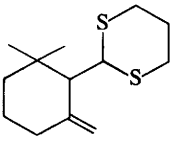


(103)

respectively, coupled with the many mild hydrolysis methods,[124–129] suggested that these compounds could serve as base-stable ester- and lactone-protecting groups.[136] Another potential synthetic utility of compounds such as (102) has been indicated.[136] The open-chain analogue of (102), obtained by trapping the dithio-acid salt with methyl iodide,[135] reacted cleanly with 2 and 3 equivalents of dimethylcopper lithium, affording 2,2-dimethylalkylidene- and 2-t-butyl-cyclohexanone in high yield.[135] A new synthesis of βγ-unsaturated aldehydes starting from allylic halides and 1,3-dithians has been described[136] and applied to the synthesis of γ-cyclocitral.[137] Thus, 1-bromomethyl-3,3-dimethylcyclohex-1-ene reacted with 1,3-dithian to form the sulphonium salt (104), whose ylide, generated from (104) and butyl-lithium at −80 °C, rearranged to (105). Subsequent hydrolysis yielded γ-cyclocitral.



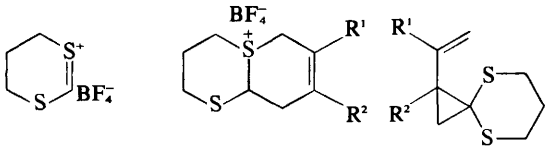
(104)



(105)

The Diels–Alder-type cycloaddition between 1,3-dithienium fluoroborate (106), obtained from 1,3-dithian and trityl fluoroborate, and 1,3-dienes formed the basis of a new and efficient synthesis of Δ^3-cyclopentenones.[138] Simple 1,3-dienes such as butadiene, isoprene, or 2,3-dimethylbutadiene reacted rapidly with (106) to give (107); (107b) was obtained stereospecifically from (106) and isoprene in 95% yield. Treatment of the sulphonium salts (107) with butyl-lithium at −78 °C gave an ylide which rearranged on warming to the cyclopropyl-dithian (108). The latter, when heated further to 200 °C, underwent the well-known vinylcyclopropane to cyclopentene transformation. Hydrolysis of the dithian thus obtained furnished cyclopentenones. The overall yield of 3-methylcyclopent-3-enone from (106) and isoprene was greater than 83%.

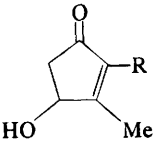
[137] E. Hunt and B. Lythgoe, *J.C.S. Chem. Comm.*, 1972, 757.
[138] E. J. Corey and S. W. Walinsky, *J. Amer. Chem. Soc.*, 1972, **94**, 8932.



(106) (107) (108)

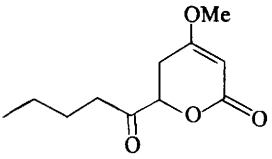
(a) $R^1 = R^2 = H$
(b) $R^1 = H, R^2 = Me$

The prostaglandin ring system, 4-hydroxycyclopent-2-en-1-one, was assembled by the reaction of 2-lithio-2-alkyl-1,3-dithians with chloroacetaldehyde diethylacetal, hydrolysis of the acetal group, addition of 2-lithio-2-methyl-1,3-dithian to the resultant aldehyde, removal of both dithian rings with $HgCl_2$–HgO–MeOH, and finally, base-catalysed cyclization of the 1,4-diketone thus produced.[139] In the above sequence, when the 2-alkyl group was n-butyl and n-pentyl, the final products were dihydroallethrolone (109) and dihydrocinerone (110), respectively.



(109) $R = C_3H_7$
(110) $R = C_4H_9$

2-Lithio-2-(2,2-dimethoxyethyl)-1,3-dithian, when it reacted with ketones and epoxides, led to intermediates which were converted in somewhat low yield into 3-furanones and dihydro-γ-pyrones, respectively.[140] 2-Methyl-2-lithio-dithian reacted efficiently with spiro-epoxide groups at positions 3 and 17 in steroids.[141] The products obtained in this manner were further elaborated; for example, 3α-ethyl-3β-hydroxy-5α-cholestane,[141a] 3-acetonyl-Δ^2-androstane,[141a] and both isomers of 17-acetonyltestosterone[141b] were prepared. The carbon skeleton, including the δ-lactone ring, of pestalotin (111), a synergist of gibberelin, was constructed in one step by the reaction

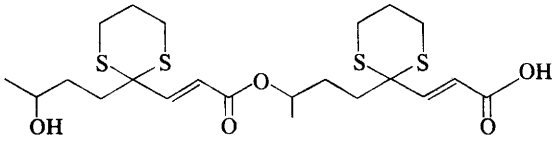


(111)

[139] W. D. Woessner and R. A. Ellison, *Tetrahedron Letters*, 1972, 3735.
[140] F. Sher, J. L. Isidor, H. R. Taneja, and R. M. Carlson, *Tetrahedron Letters*, 1973, 577.
[141] J. B. Jones and R. Graysham, *Canad. J. Chem.*, 1972, **50**, 1407, 1414.

of the dianion of methyl acetoacetate with 2-butyl-2-formyl-1,3-dithian.[142]

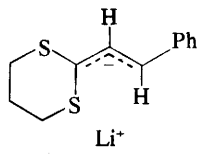
Various substituted and unsubstituted 2-lithio-1,3-dithians have served as key reagents in other syntheses of natural products. Among the examples are: intramolecular ring opening of an epoxide by a 1,3-dithian carbanion to give, eventually, a cyclohexanone derivative used in the preparation of monoterpenoid structures;[143] the formation of the 1,4-diketone which leads to *cis*-jasmone upon exposure to base;[126,144] the construction of the chain and the protection of the keto-groups in the unsaturated acid-ester (112), which,



(112)

upon cyclization and removal of the dithian rings, gave pyrenophorin, a sixteen-membered bis-lactone;[145] the preparation of branched-chain sugars;[146] and an approach to the synthesis of illudins M and S.[147] Dithian carbanions continue to be used in cyclophane synthesis.[148]

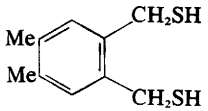
Aldehydes were converted into the corresponding esters by initial dithian formation, metallation, reaction with dimethyl disulphide, and finally hydrolysis of the 2-thiomethyl-1,3-dithians so obtained with $HgCl_2$–HgO in aqueous alcohols.[149] The yields of methyl or ethyl esters were high but attempts to prepare t-butyl esters by this route failed and produced only acids in moderate yield. Thiomethylation or deuteriation of the allylic lithio-salt (113) occurred exclusively α to sulphur. Dithianyl carbanions



(113)

[142] D. Seebach and H. Meyer, *Angew. Chem. Internat. Edn.*, 1974, **13**, 77.
[143] S. Torii, Y. Matuyama, M. Isihara, and K. Uneyama, *Chem. Letters*, 1973, 947.
[144] R. A. Ellison and W. D. Woessner, *J.C.S. Chem. Comm.*, 1972, 529.
[145] E. W. Colvin, T. A. Purcell, and R. A, Raphael, *J.C.S. Chem. Comm.*, 1972, 1031.
[146] (*a*) H. Paulsen, V. Sinnwell, and P. Stadler, *Angew. Chem. Internat. Edn.*, 1972, **11**, 149; (*b*) H. Paulsen, V. Sinnwell, and P. Stadler, *Chem. Ber.*, 1972, **105**, 1978; (*c*) A. M. Sepulchre, A. Gateau-Olesker, G. Lukacs, G. Vass, S. D. Gero, and W. Voelter, *Tetrahedron Letters*, 1972, 3945, 3948; (*d*) G. Lukacs, A. M. Sepulchre, A. Gateau-Olesker, G. Vass, S. D. Gero, R. D. Guthrie, W. Voelter, and E. Breitmeier, *ibid.*, p. 5163; (*e*) A. M. Sepulchre, G. Lukacs, G. Vass, and S. D. Gero, *Bull. Soc. chim. France*, 1972, 4000.
[147] T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, T. Hisamitsu, T. Kamada, and F. Sakan, *Bull. Soc. Chem. Japan*, 1972, **45**, 1136.
[148] (*a*) H. Gswend, *J. Amer. Chem. Soc.*, 1972, **94**, 8430; (*b*) M. Nakazaki, K. Yamamoto, and M. Ito, *J.C.S. Chem. Comm.*, 1972, 443.
[149] R. A. Ellison, W. D. Woessner, and C. W. Williams, *J. Org. Chem.*, 1972, **37**, 2757.

added to the carbon–nitrogen double bond of some immonium salts[150] and at the 4-position of pyridine[151] to give 1,4-dihydropyridines, which were trapped with acetic anhydride as *N*-acetyl-1,4-dihydropyridines (70—80%) or oxidized with *p*-quinone to 4-substituted pyridines (40—70%). 3-Acetyl-2-methylcyclohex-2-en-1-one was obtained from 2-lithio-2-methyl-1,3-dithian and 3-isobutoxy-2-methylcyclohex-2-en-1-one followed by hydrolysis.[152] The anion derived from 2-ethoxycarbonyl-1,3-dithian underwent conjugate addition with $\alpha\beta$-unsaturated esters and amides;[153] hydrolysis of the products led to 1,4-dicarbonyl compounds. The possible use of the dithiol (114), which reacted with aldehydes to give 1,3-dithiepins, as an

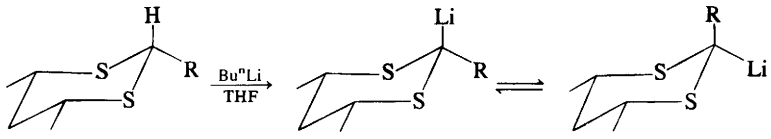


(114)

alternative to propane-1,3-dithiol, which gives dithians, has been suggested.[154] The advantages, such as reduced odour and generally crystalline derivatives, are probably not sufficient to warrant a change. Ethane-1,2-dithiol continues to be used as a ketone-protecting group.[155]

Further investigations to determine the magnitude and origin of the equatorial stereoselectivity observed for reactions involving the 2-lithio-derivatives of conformationally locked 1,3-dithians have been made.[156] The dithians (115) having a variety of 2-substituents in the equatorial position isomerized *via* the 2-lithio-derivatives (116) and (117), with greater than 99.7% selectivity, to (118), in which these substituents occupy the sterically less favourable axial position. The ester (115b) was converted into (118b) *via* either the lithium or sodium salt. The quenching of the salts was assumed to occur stereospecifically with retention of configuration. Based on the isomerization of (115d) to (118d) with greater than 99.7% selectivity, the equatorial preference of 2-lithium in 1,3-dithians (117) *vs.* (116) was computed to be greater than 6 kcal mol^{-1} [3.4 kcal mol^{-1} to account for the observed selectivity, to which is added 2.7 kcal mol^{-1} because the t-butyl group is axial in (117d) and equatorial in (116d)]. The equatorial to axial interconversions were independent of solvent changes ranging from n-hexane to hexamethylphosphoramide, which indicated that (116) and (117)

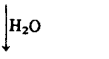
[150] P. Duhamel, L. Duhamel, and N. Nancelle, *Tetrahedron Letters*, 1972, 2991.
[151] T. Taguchi, M. Nishi, K. Watanabe, and T. Mukaiyama, *Chem. Letters.*, 1973, 1307.
[152] M. Bonnet and F. Winternitz, *Compt. rend.*, 1972, **274**, *C*, 1469.
[153] J. L. Hermann, J. E. Richmann, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 2599.
[154] S. Rozen, I. Shahak, and E. D. Bergmann, *Tetrahedron Letters*, 1972, 1837.
[155] (*a*) A. R. Pinder, S. J. Price, and R. M. Price, *J. Org. Chem.*, 1972, **37**, 2202; (*b*) K. Kojima and K. Sakai, *Tetrahedron Letters*, 1972, 3337; (*c*) M. E. Scalan and S. MacKenzie, *J. Org. Chem.*, 1972, **37**, 1579.
[156] (*a*) E. L. Eliel, A. A. Hartmann, and A. G. Abatjoglou, *J. Amer. Chem. Soc.*, 1974, **96**, 1807; (*b*) E. L. Eliel, A. G. Abatjoglou, and A. A. Hartmann, *ibid.*, 1972, **94**, 4786.

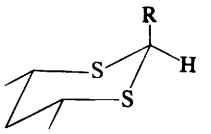


(115) (a) R = Me
(b) R = CO_2Me
(c) R = CH_2OLi
(d) R = Bu^t

(116)

(117)





(118)

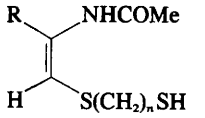
existed as carbanions or carbanion–lithium ion pairs rather than covalent lithium species. The overwhelming preference for lithium to be equatorial is mainly thermodynamic and not kinetic in origin, and may be explained by the '*gauche* effect'[39] or possibly by the presence of a structure wherein the lithium is held equatorially by the co-operative effect of the carbanion and one of the electron pairs on sulphur; see, however, ref. 46. The kinetic selectivity for removal by butyl-lithium of the equatorial *vs.* axial hydrogens in (115; R = H) was found to be 8.6:1, and thus much less than the thermodynamic preference. The kinetic isotope effect, k_H/k_D, in this reaction was 2.5.[156]

Several studies dealing with mono- and di-alkylation of 1,3-dithiolan, 1,3-dithian, and 1,4-dithian have been reported.[157] Since these sulphonium salts were generally converted into ylides, a more detailed discussion can be found in the chapter on ylide chemistry.

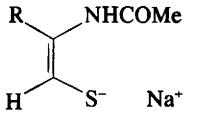
1,4-Dithians, 1,4-Dithiepans, and 1,5-Dithiocans.—A new synthesis of 2-acetamido-2-alkyl-1,4-dithians and 1,4-dithiepans (121) is based on the trifluoroacetic-acid-catalysed cyclization of the unsaturated thiols (119).[158] The required compounds were produced by ring cleavage (using sodium in liquid ammonia) of 2,3-dihydro-4*H*-1,4-thiazin-3-ones to the vinyl thiolate (120) followed by alkylation with 2-bromoethanethiol or 3-bromopropanethiol. Appropriate alkylations of (120) followed by cyclizations were also used in the synthesis of 1,4-oxathians, 1,4-oxathiepans, and morpholine derivatives. Addition of H_2S to 3-thiaglutaraldehyde 3,3-dioxide, obtained

[157] (*a*) C. P. Lillya, E. F. Miller, P. Miller, and R. A. Sahatjian, *Internat. J. Sulfur Chem.* (*A*), 1972, **1**, 79; (*b*) M. Hetschko and J. Gosselck, *Chem. Ber.*, 1974, **107**, 123; (*c*) H. Boehme and W. Krack, *Annalen*, 1972, **758**, 143; (*d*) I. Stahl and J. Gosselck, *Tetrahedron*, 1973, **29**, 2323; (*e*) *Tetrahedron Letters*, 1972, 989; M. Hetschko and J. Gosselck, *ibid.*, 1972, 1691.

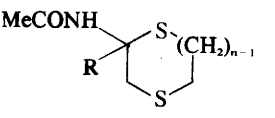
[158] S. Hoff, A. P. Block, and E. Zwanenburg, *Rec. Trav. chim.*, 1973, **92**, 890.



(119)



(120)

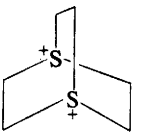


(121)

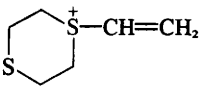
R = alkyl, $n = 2$ or 3

by periodate cleavage of *cis*-3,4-dihydroxythiolan 1,1-dioxide, gave 2,6-dihydroxy-1,4-dithian 4,4-dioxide.[94] Sulphur dichloride reacted with 1,1-disubstituted olefins to give, *via* divinyl sulphides, highly substituted 1,4-dithians.[159]

The reaction of the sulphonium dication (122) with NaOD–D_2O led to 1,4-dithian having only the hydrogen atoms α to one of the sulphur atoms exchanged for deuterium.[160] Thus ring opening to (123) occurred prior to

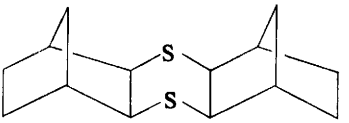


(122)



(123)

exchange in (122), but (123) or its D_2O addition product exchanged its hydrogen α to positively charged sulphur faster than it decomposed to 1,4-dithian. A similar initial fragmentation of (122) took place in the presence pf pyridine but further reaction of (123) with pyridine occurred mainly at C-2, and resulted in the formation of open-chain products. An *X*-ray structure determination of (122) showed D_{3h} symmetry in which the S—S bond distance (3.13 Å) is significantly less than the van der Waals S–S separation. Thermolysis in diphenyl ether, or photolysis at high concentration in acetonitrile, of *exo*-2,3-epithionorborn-5-ene yielded some 1,4-dithian (124) *via* dimerization of the biradical generated by carbon–sulphur bond cleavage.[161]

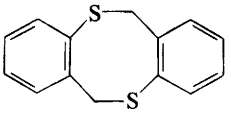


(124)

1,5-Dithiacyclo-octane-3,7-dione, when oxidized with one equivalent of H_2O_2 in acetic acid, gave a monoxide which added water reversibly, the

[159] M. Muestaedt, P. Schneider, and D. Martinez, *J. prakt. Chem.*, 1973, 315.
[160] E. Deutsch, *J. Org. Chem.*, 1972, **37**, 3481.
[161] T. Fujisawa and T. Kobori, *J.C.S. Chem. Comm.*, 1972, 1298.

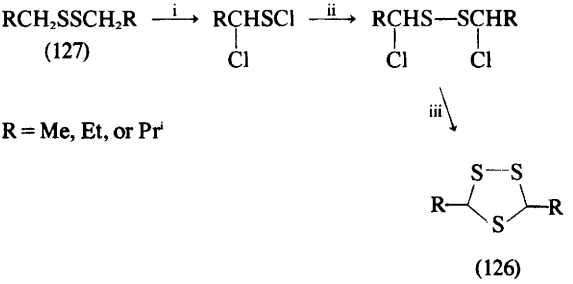
equilibrium favouring the bicyclic structure 3,7-dithia-9-oxabicyclo[3,3,1]-nonane 3-oxide.[162] The 3,7-dioxide corresponding to the latter compound and a simple tetroxide were also prepared. The crystal structure of the monoxide has been determined.[163] Several heterocycles have been prepared starting from 1,5-dithiacyclo-octan-3-one and involving the reaction of the carbonyl group,[164] and benzyl *o*-chloromethylphenyl sulphide was converted in 38% yield into the bibenz-fused 1,5-dithiocin (125) upon heating under reduced pressure.[165]



(125)

4 Compounds containing Three or More Sulphur Atoms

1,2,4-Trithiolans, 1,3,5-Trithians, and 1,2,4,5-Tetrathians.—A new route to 3,5-dialkyl-1,2,4-trithiolans (126) starting from dialkyl disulphides of the type (127) has been developed[166] and is shown in Scheme 2. The method



(127)

R = Me, Et, or Pr^i

(126)

Reagents: i, $2Cl^-$, −10 to +20 °C; ii, KI; iii, Na_2S

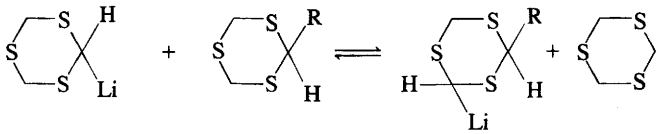
Scheme 2

gave trithiolans in up to 57% yield based on disulphide. In each case the reaction yielded (126) as a diastereomeric mixture, which was readily separated by vapour-phase or column chromatography. The assignment of configuration was made on the basis of nuclear Overhauser effects. The n.m.r. spectra of (126) were independent of temperature down to −117 °C, indicating that the barrier to pseudorotation of the ring is less than 6 kcal

[162] R. Gustafsson, *Internat. J. Sulfur Chem.* (A), 1971, **1**, 233.
[163] S. Abrahamsson and G. Rehnberg, *Acta Chem. Scand.*, 1972, **26**, 3309.
[164] V. P. Arya, *Indian J. Chem.*, 1972, **10**, 812.
[165] A. K. Youssef and M. A. Ogliaruso, *Org. Prep. Proceed. Internat.*, 1973, **5**, 133 (*Chem. Abs.*, 1973, **79**, 105 228q).
[166] S. B. Tjan, J. Haakman, C. J. Teunis, and H. G. Peer, *Tetrahedron*, 1972, **28**, 3489.

mol^{-1}. Two full papers discussing mechanistic and synthetic aspects of the formation of 3,3,5,5-tetraphenyl-1,2,4-trithiolan from thiobenzophenone and Chloramine T have appeared.[167] This route to 1,2,4-trithiolans is apparently extremely limited and cannot be applied to thiobenzophenones having electron-donating groups. Among aliphatic thiones, thioadamantanone underwent the trithiolan formation, whereas thiocamphor did not. The formation of a dispiro-1,2,4-trithiolan has been observed in the reaction of 4,4-dibromo-2,2,5,5-tetramethyltetrahydrofuran-3-one with potassium alkylxanthates.[168]

An evaluation of the synthetic potential of 2-lithio-1,3,5-trithian (128), including a comparison with 2-lithio-1,3-dithian, has been made.[169] The major advantage of (128) over 2-lithio-1,3-dithian is apparently the cost factor, 1,3,5-trithian being considerably less expensive than 1,3-dithian. An important disadvantage of 1,3,5-trithian is its low solubility in THF compared to its anion, which often leads to complications owing to the transfer of the lithium from unreacted starting material to product, as expressed by the equilibrium between (128)+(129) and (130)+(131). This



(128) (129) (130) (131)

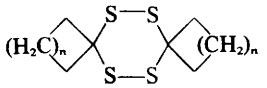
complication did not occur when (128) reacted with primary alkyl iodides or bromides, but mixtures were obtained from reactions of (128) with the less reactive secondary halides. Metallation of monoalkylated trithians occurred at one of the two unsubstituted sites and led eventually to the product having both substituents in the equatorial position. Thus the high equatorial preference for lithium in 2-lithio-1,3-dithian[156] is also present in 1,3,5-trithians. Mercury(II)-assisted solvolysis of (129) gave clean carbonyl formation at the substituted carbon if the R group was electron-donating. α-Deuteriated aromatic aldehydes have been prepared from 2,4,6-triaryl-1,3,5-trithian.[170] Surprisingly, the rate of base-catalysed H–D exchange at the 2-position in 1,3,5-trithian was considerably accelerated by oxidizing the sulphur at position 5 to a sulphinyl or sulphonyl group.[171]

Chlorination of 1,3,5-trithian in acetic acid–water mixtures proceeded *via* a series of intermediates, among them bischloromethyl sulphide, to

[167] (*a*) M. M. Campbell and D. M. Evignos, *J.C.S. Perkin I*, 1973, 2862; (*b*) *ibid.*, 1973, 2866.
[168] K. Praefke, G. Hohne, P. Weyersthal, and B. Klabuhn, *Tetrahedron Letters*, 1973, 977.
[169] D. Seebach, E. J. Corey, and A. K. Beck, *Chem. Ber.*, 1974, **107**, 367.
[170] J. B. Chattopadhyaya, A. V. R. Rao, and K. Venkataraman, *Indian J. Chem.*, 1973, **11**, 987.
[171] M. Fukunaga and M. Oki, *Chem. Letters*, 1972, 1081.

chloromethylsulphonyl chloride.[172] Photolysis of 2,4,6-triphenyl-1,3,5-trithian led to a mixture of stilbenes and phenanthrene,[173] while hexamethyl-1,3,5-trithian gave, among other products, tetramethyl-1,3-dithietan. The photolysis of other related trithians was also studied.[173]

Hexatrifluoromethyl-1,3,5-trithian hexoxide, produced in 75% yield by heating the anhydride of hexafluoropropane-2,2-disulphonic acid,[174a] underwent ring opening with amines to form sulphonamides of the type $(CF_3)_2CHSO_2NR_2$.[174b] Weak anomeric effects were suggested as the cause of the axial preference of substituents such as benzoyloxy and phenyl in 1,3,5-trithians.[175] The photoelectron spectra of 1,3,5-trithian, the 1-oxide, 1,3,5-trioxide, 1,1-dioxide, and hexoxide have been recorded.[176] Tetrafluoroethylene, when heated in the presence of sulphur at 440 °C, gave a mixture of fluorinated sulphur compounds from which 4,4,5,5-tetrafluoro-1,2,3-trithiolan and 5,5,6,6-tetrafluoro-1,2,3,4-tetrathian were isolated in 10 and 60% yield, respectively.[177] Variable-temperature n.m.r. studies on the tetrathians (132) and (133) indicated the presence of both the chair and the



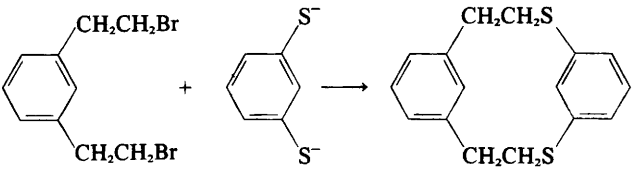
(132) $n = 3$
(133) $n = 4$

twist conformations.[178] In (132) the chair form is more stable than the twist (2.2:1) whereas in (133), as in duplodithioacetone, the twist conformation is favoured by a similar ratio. The barrier to tetrathian twist pseudorotation in (133) is similar to that for the interconversion from twist to chair conformation and equal to approximately 16 kcal mol^{-1}. These data suggested that the chair form is an intermediate in the twist pseudorotation.[178]

Large Ring Disulphides, including Sulphur-containing Cyclophanes.—Much of the work in this area has been summarized in a general review on cyclophanes,[6] and in four full papers which discuss in detail a considerable

[172] J. S. Grossert and R. F. Langler, *J.C.S. Chem. Comm.*, 1973, 49.
[173] T. Nishio, M. Yoshioka, H. Aoyama, and N. Sugiyama, *Bull. Chem. Soc. Japan*, 1973, **46**, 2253.
[174] (*a*) G. A. Sokol'skii, V. M. Pavlov, G. M. Golovkin, V. F. Gorelov, and I. L. Knunyants, *Khim. geterotsikl. Soedinenii*, 1974, 42 (*Chem. Abs.*, 1974, **80**, 95 899p); (*b*) G. A. Sokol'skii, V. M. Pavlov, U. V. Ezhov, and I. L. Knunyants, *Khim. geterotsikl. Soedinenii*, 1974, 48 (*Chem. Abs.*, 1974, **80**, 95 901h).
[175] M. Oki, T. Sugawara, and H. Iwamura, *Chem. Letters*, 1973, 997.
[176] H. Iwamura, M. Fukumaga, and K. Kushida, *J.C.S. Chem. Comm.*, 1972, 450.
[177] C. G. Krespan, W. R. Brasen, and N. H. Cripps, *Adv. Chem. Ser.*, 1972, **110**, 179.
[178] C. H. Bushweller, G. U. Rao, and F. H. Bisset, *Internat. J. Sulfur Chem.* (*A*), 1971, **1**, 216.

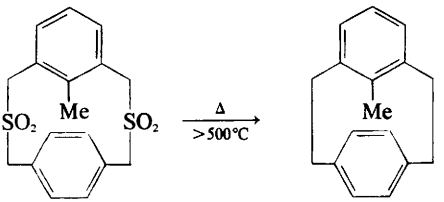
portion of the recent work of the Boekelheide group.[179–182] Sulphur-containing cyclophanes have been of considerable interest in their own right but even more so as intermediates in the preparation of highly strained non-sulphur-containing cyclophanes. The synthesis of the sulphur cyclophanes is usually based on the reaction of the appropriate dihalides with the potassium salt of a dithiol under high-dilution conditions.[183a] The yields are often remarkably high, *e.g.* (134)+(135)→(136) in 85% yield. Even rela-



(134) (135) (136)

tively poor yields are still very useful because of the accessibility of the starting materials.

Three methods have been employed for the removal of the sulphur and the conversion of, for example, [3,3]metacyclophanes into a [2,2]metacyclophane.* Pyrolysis of the bis-sulphones has been found to occur at temperatures above 500 °C under reduced pressure to afford in good to excellent yields various [2,2]cyclophanes,[181,182,184–186] *e.g.* (137) to (138) in 90%

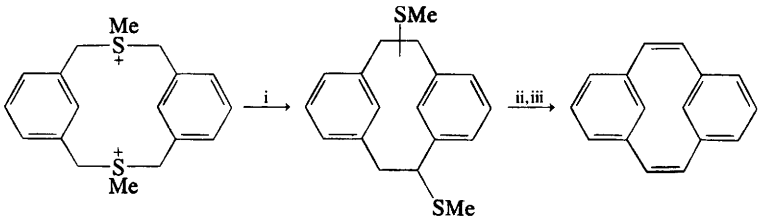


(137) (138)

* A number of examples of each type of reaction have been reported using essentially the same procedures but employing different substrates. Because of space limitations they cannot all be discussed in detail, but references are made wherever appropriate. In addition, other aspects pertaining to the sulphur-containing cyclophanes, such as the degree of distortion of the aromatic rings, rates of ring inversion, and detailed stereochemistry, were considered to be outside the scope of this Report.

[179] R. H. Mitchell and V. Boekelheide, *J. Amer. Chem. Soc.*, 1974, **96**, 1547.
[180] V. Boekelheide, P. H. Anderson, and T. H. Hylton, *J. Amer. Chem. Soc.*, 1974, **96**, 1558.
[181] S. A. Sherrod, R. L. daCosta, R. A. Barnes, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1974, **96**, 1565.
[182] V. Boekelheide, K. Galuszko, and K. S. Setzo, *J. Amer. Chem. Soc.*, 1974, **96**, 1578.
[183] (*a*) F. Vögtle, *Chem. and Ind.*, 1972, 346; (*b*) F. Vögtle and R. G. Lichtenthaler, *Tetrahedron Letters*, 1972, 1905; (*c*) *Angew. Chem. Internat. Edn.*, 1972, **11**, 535; (*d*) *Synthesis*, 1972, 480.
[184] V. Boekelheide and R. A. Hollins, *J. Amer. Chem. Soc.*, 1973, **95**, 3201.
[185] (*a*) V. Boekelheide and C. H. Tsai, *J. Org. Chem.*, 1973, **38**, 3931; (*b*) V. Boekelheide and P. H. Anderson, *ibid.*, p. 3928.
[186] H. A. Staab and M. Haenel, *Chem. Ber.*, 1973, **106**, 2190.

yield.[185b] The loss of SO_2 from (137) presumably occurs *via* biradical intermediates and is typical of the behaviour of dibenzylic sulphones. As might be expected, the two sulphur dioxide molecules are lost consecutively; it was found, however, that the second SO_2 was lost more readily than the first probably because of the extra strain energy in the [3,2]cyclophane monosulphones compared to the starting [3,3]cyclophane bis-sulphones.[181] The removal of sulphur to form a saturated bridge has also been accomplished by photolysis of the bis-sulphides in the presence of trialkyl phosphites.[187,188] Yields reported for the conversion of several [3,3] into [2,2] systems ranged from 50 to 85%. [2,2]Cyclophanes having ethylene bridges have been successfully obtained by a double Stevens rearrangement of [3,3]cyclophane bis-sulphonium salts, *e.g.* (139), to [2,2]cyclophanes having two thiomethyl groups attached to the bridging carbons. Methylation of the latter followed by reaction with KOBu^t eliminated the sulphonium salts and gave the ethylene bridges (see Scheme 3). This route has been used to



(139) (140) (141)

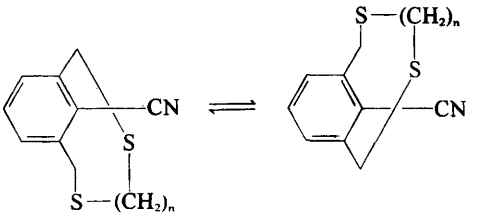
Reagents: i, NaH–THF; ii, $(MeO)_2\overset{+}{C}H$; iii, KOBu^t

Scheme 3

prepare, among others, *anti*-[2,2]metacyclophane-1,9-diene,[179] [2,2]meta-paracyclophane-1,9-dienes bearing a variety of substituents at the 8-position,[180] [2,2,2](1,3,4)cyclophane-1,9,17-triene,[184] [2,2](2,7)naphthalenophane-1,11-diene,[189] and a bridged [18]annulene.[190]

The variation in the barrier to ring inversion depicted by (142) $\rightleftharpoons$ (143) has been determined by the coalescence temperature of the signal due to the benzylic hydrogens for X = CN, Br, or Cl and $n = 3$—10.[191a] No inversion occurred on the n.m.r. time-scale for $n \leqslant 7$. When $n = 8$, the $\Delta G^{\ddagger}$ (T_c) are: for CN, 23.6 kcal mol^{-1} (200 °C); for Br, 22.5 kcal mol^{-1} (178 °C); for Cl, 15.4 kcal mol^{-1} (40 °C). The $\Delta G^{\ddagger}$ values for CN when $n = 9$ and 10 are 14.5 and 9.7 kcal mol^{-1}, respectively. A similar study has been reported for 2,6-bridged pyridine *N*-oxide.[191b]

[187] V. Boekelheide, I. D. Reingold, and M. Tuttle, *J.C.S. Chem. Comm.*, 1973, 406.
[188] J. Bruhin and W. Jenny, *Tetrahedron Letters*, 1973, 1215.
[189] (*a*) J. R. Davy and J. A. Reiss, *J.C.S. Chem. Comm.*, 1973, 806; (*b*) J. R. Davy and J. A. Reiss, *Tetrahedron Letters*, 1972, 3639.
[190] J. R. Lawson, R. duVernet, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1973, **95**, 956.
[191] (*a*) F. Vögtle, P. Neumann, and M. Zuber, *Chem. Ber.*, 1972, **105**, 2955; (*b*) F. Vögtle and H. Risler, *Angew. Chem. Internat. Edn.*, 1972, **11**, 727.



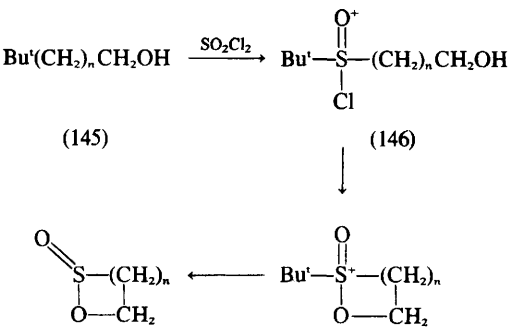
(142) (143)

The synthesis of sulphur-containing macrocycles related to the crown ethers has been reported.[192,193] In several examples the successful inclusion of sodium ion into the cavity, as measured by the solubility of sodium permanganate in benzene containing the macrocycle, was observed.[193]

5 Compounds containing Sulphur or Selenium and Oxygen

Sultines, Sultones, and Related Systems.—A general synthesis of sultines (144) (cyclic sulphinate esters), based on the reaction of t-butyl hydroxyalkyl sulphoxides (145) with SO_2Cl_2 or *N*-chlorosuccinimide, has been developed.[194] The method was shown to be suitable for the preparation of sultines varying in ring size from 5 to 8 and having a variety of alkyl or aryl substitution patterns.

The transformation from (145) to (144) occurred *via* initial formation of the chloro-oxosulphonium salt (146), then cyclization to the alkoxyoxosulphonium salt (147), followed by cleavage of the carbon–sulphur bond to give



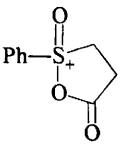
(145) (146)

(144) (147)

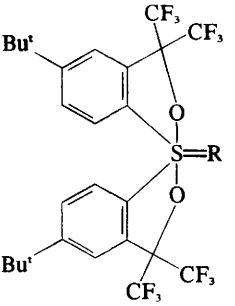
$n = 2—5$

[192] D. Pellissard and R. Louis, *Tetrahedron Letters*, 1972, 4589.
[193] F. Vögtle and E. Weber, *Angew. Chem.*, 1974, **86**, 126.
[194] (*a*) N. K. Sharma, F. Jung, and T. Durst, *Tetrahedron Letters*, 1973, 2863; (*b*) F. Jung and T. Durst, *J.C.S. Chem. Comm.*, 1973, 4; (*c*) F. Jung, N. K. Sharma, and T. Durst, *J. Amer. Chem. Soc.*, 1973, **95**, 3420.

(144) and the Bu^t carbocation.[194b] Details of the chlorination of ω-phenylsulphinyl alcohols to ω-phenylsulphonyl chlorides, which was shown to involve intermediates similar to (147), have appeared.[195] The conversion of 3-phenylsulphinylpropionic acid and 3-phenylsulphinylpropionamide into 3-phenylsulphonylpropionyl chloride and 3-phenylsulphonylpropionitrile also proceeded *via* cyclic oxosulphonium salts, for example (148).[195] The cyclic sulphurane (149),[196] in contrast to open-chain sulphuranes and other known cyclic sulphuranes,[197] is very stable to hydrolysis, as evidenced by its recovery after refluxing in basic or acidic tetrahydrofuran for 2 hours. Oxidation of (149) with RuO_4 afforded the sulphurane oxide (150) in nearly quantitative yield.[196]

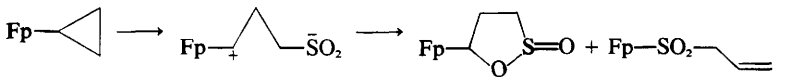


(148)



(149) R = lone pair
(150) R = O

The σ-bonded cyclopropyl–iron complex (151) reacted with SO_2 to give mainly the sultine (152) and a small amount of the metal allyl sulphone (153).[198] Electrophilic attack on the C-1—C-2 bond of the cyclopropane by SO_2 should give the intermediate (154), which can either cyclize to (151) or,



(151) (154) (152) (153)

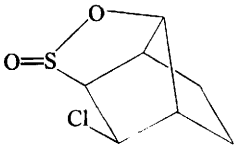
Fp = (h^5-C_5H_5)Fe(CO)$_2$

via a 1,2-hydride shift followed by attack of the sulphinate anion at the metal, lead to (153).

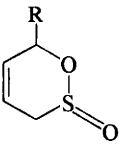
A γ-sultine (155) was obtained from thionyl chloride and *exo*-tricyclo-[3,2,1,$0^{2,4}$]oct-6-en-*anti*-8-ol.[199] The electrophilic *exo-cis*-addition to the double bond in a [2,2,1] system is somewhat unusual, but the structure of (155)

[195] T. Durst, K.-C. Tin, and J. M. V. Marcil, *Canad. J. Chem.*, 1973, **51**, 1704.
[196] E. F. Perrozi and J. C. Martin, *J. Amer. Chem. Soc.*, 1972, **94**, 5519.
[197] I. Kaporitz and A. Kalman, *J.C.S. Chem. Comm.*, 1971, 649.
[198] A. Cutler, R. W. Fish, W. P. Giering, and M. Rosenblum, *J. Amer. Chem. Soc.*, 1972, **94**, 4354.
[199] K. Hendrick and B. L. Johnson, *Austral. J. Chem.*, 1972, **25**, 2263.

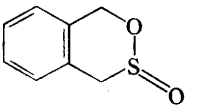
seems secure, and its assignment was based on n.m.r. coupling constants. Surprisingly, bicyclo[2,2,1]hept-2-en-*syn*-7-ol and $SOCl_2$ did not lead to a sultine but only to the replacement of the OH group by chlorine. γ-Sultines bearing a phenyl group α to oxygen were photolysed to phenylcyclopropanes and SO_2.[194a] δ-Sultines having a 4,5-double bond, *e.g.* (156) and (157), readily lost SO_2 thermally to give *trans*-1-phenylbuta-1,3-diene and *o*-xylylene, respectively.[200] The latter compound was trapped with reactive dienophiles such as maleic anhydride. In the absence of added trapping agents, *o*-xylylene captured the evolved SO_2 and gave 1,3-dihydrobenzo[*c*]thiophen 2,2-dioxide. The ease of the loss of SO_2 together with its apparent stereospecificity indicated that the extrusion of SO_2 from (156) and (157) was a concerted retro-Diels–Alder reaction.



(155)

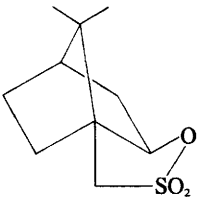


(156) (a) R = H
(b) R = Ph

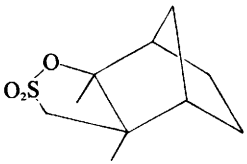


(157)

During a study of the mechanism of the thermal rearrangement of 10-isobornyl sultone (158) to *exo*-camphene sultone (159),[201] the *endo*-camphene sultone (160) was isolated after partial isomerization; however, (160) is probably not a direct intermediate but a dead-end product which underwent re-ionization under the reaction conditions and eventual conversion into the thermodynamically more stable (159). Two possible mechanisms for the rearrangement (158) to (159) were considered. The first



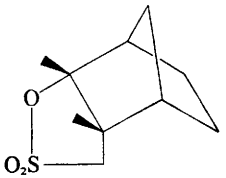
(158)



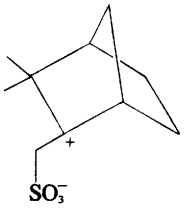
(159)

involved ionization, a Wagner–Meerwein (W–M) shift to the intermediate (161), from which (159) or (160) can be obtained *via* an *endo*- or *exo*-2,3-methyl shift, respectively, followed by cyclization. Model-compound studies[201a] of deuterium labelling[201b] and rearrangement studies using optically active compounds[201b] indicated that the above pathway was a

[200] F. Jung, M. Molin, R. Van Den Elzen, and T. Durst, *J. Amer. Chem. Soc.*, 1974, **96**, 935.
[201] (*a*) D. R. Dimmel and W. Y. Fu, *J. Org. Chem.*, 1973, **38**, 3778; (*b*) *ibid.*, p. 3782.

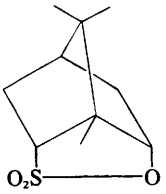


(160)

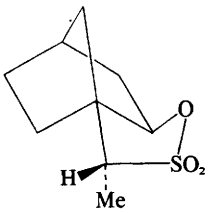


(161)

minor one and that a more circuitous route from (161) to (159) involving, sequentially, an *exo*-2,3-methyl-shift, a W–M rearrangement, a 2,6-hydride shift, a second W–M rearrangement, and finally ring closure, was more important. The sultone (161) could follow a similar pathway after initial ring opening. Sulphonation of α-pinene and 8-methylcamphene with sulphur dioxide–dioxan complex at −78 °C in methylene chloride gave poor to fair yields of the sultones (162) and (163), respectively.[202a] Under these reaction



(162)



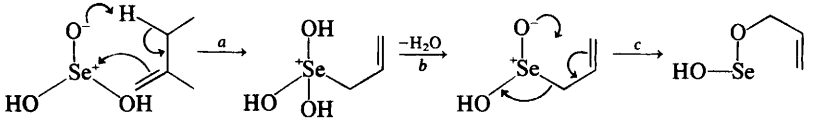
(163)

conditions methyl migrations, which occurred to a considerable extent when acetic acid was used as solvent, were absent. The reaction of the sultones (162) and (163) with aluminium hydride caused desulphurization to the corresponding alcohols, whereas reduction by lithium aluminium hydride gave only a small amount of desulphurization, the major products being mercapto-alcohols and sulfinate esters.[202b]

The isolation of the selenolactone (164) upon reaction of (*l*)-isopulegol (165) with SeO_2 in Bu^{t}OH has helped clarify the mechanism of the allylic oxidation of olefins by SeO_2.[203a] In the proposed mechanism it is suggested that allylselenic acids,[203b] formed by an initial ene addition of a $\rangle Se^+—O^-$ moiety (Step *a* in Scheme 4), are key intermediates. Dehydration of the selenic acids (Step *b*) followed by a 2,3-sigmatropic shift (Step *c*) would yield selenic esters and, upon hydrolysis, allylic alcohols. The intermediacy of allylselenic acids in the oxidation is strongly supported by their being trapped to form a lactone when there is a suitably placed hydroxy-group.

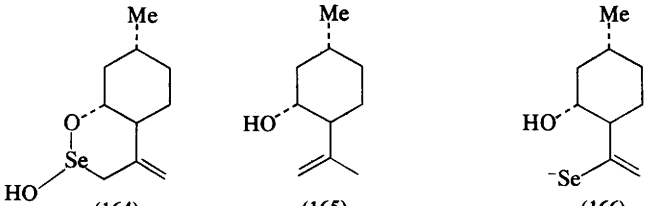
[202] (*a*) J. Wolinsky, R. L. Mahrenke, and E. J. Eustace, *J. Org. Chem.*, 1973, **38**, 1428; (*b*) J. Wolinsky, and R. Law, *Synthetic Comm.*, 1972, **2**, 327.

[203] D. Arigoni, A. Vasella, K. B. Sharpless, and H. P. Jenson, *J. Amer. Chem. Soc.*, 1973, **95**, 7917; K. B. Sharpless and R. F. Lauer, *ibid.*, 1972, **94**, 7154.



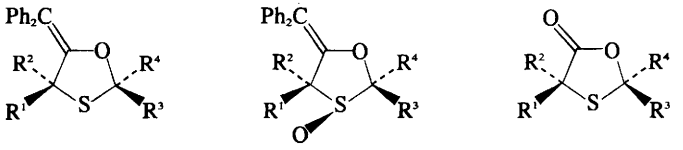
Scheme 4

The structure of the lactone was based on analytical and spectroscopic data and on its reduction to the hydroxy-selenide (166), which was trapped with benzyl chloride.[203a]



(164) (165) (166)

1,3-Oxathiolans, 1,3-Oxathians, 1,4-Oxathians, and Related Compounds.—5-Diphenylmethylene-1,3-oxathiolans (167a and b) were formed in excellent yield by the 1,3-cycloaddition of thiocarbonyl ylides to diphenylketen.[204] Since the generation of the ylides and the cycloaddition step both occurred stereospecifically, the formation of specific isomers due to substitution at positions 2 and 5 was possible. The *trans* stereochemistry, and thereby the stereochemistry of the addition reaction, was proved for (167a) by the observation of a N.O.E. enhancement of both methine hydrogens upon saturation of one of the Bu^t resonances. The oxathiolans were oxidized with *m*-chloroperbenzoic acid to sulphoxides (168) and sulphones; ozonolysis removed the 5-diphenylmethylene group and gave (169). From a synthetic



(167) (168) (a) (169) (a)

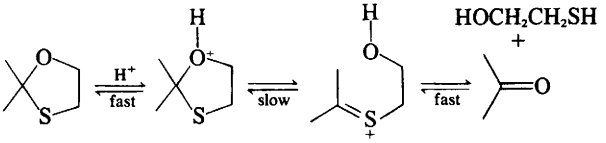
(a) $R^1 = R^4 = Bu^t$, $R^2 = R^3 = H$
(b) $R^1 = R^4 = Et$, $R^2 = R^3 = H$
(c) $R^1 = R^2 = R^3 = R^4 = Me$

point of view the reaction is of rather limited value owing to its lack of generality; for example, neither the *cis*-isomer of (167a) nor (167c) could be prepared.

[204] R. M. Kellogg, *J. Org. Chem.*, 1973, **38**, 844.

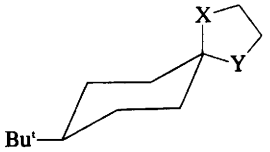
Aliphatic aldehydes and mercaptoacetic acid underwent oxathiacetal formation in benzene solution even in the absence of catalysts to give 2-alkyl-5-oxo-1,3-oxathiolans (20—55%).[205] The formation of the corresponding 5-aryl derivatives was slower and required heating of the two components in benzene with toluene-*p*-sulphonic acid as catalyst. These compounds were also obtained as the minor products from the condensation of mercaptothioacetic acid with aldehydes.[107] (Dimethylamino)methyloxosulphonium acylmethylides underwent a novel $CuSO_4$-induced conversion into 5-substituted 1,3-oxathiole 3-oxides.[206] (See also Chapter 6.) These substances were found to be extremely acid-sensitive, which prevented their successful oxidation to the sulphone state or their alkylation to oxysulphonium salts.

The latest studies on the acid-catalysed hydrolysis of 2,2-dialkyl-1,3-oxathiolans agree that hydrolysis in moderately strong acid media occurs by an *A*-1 mechanism as shown in Scheme 5, in which the ring ruptures at the

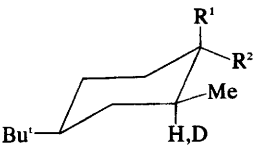


Scheme 5

acetal carbon–oxygen bond.[207] Evidence supporting this mechanism was obtained from the size and variations in the α-deuterium kinetic isotope effects observed in the hydrolysis of the spiro-oxathioacetals (170) and (171).[207a] The comparatively large sizes of the isotope effects, 1.32 and 1.11,



(170) (a) X = O, Y = S
(b) X = S, Y = O



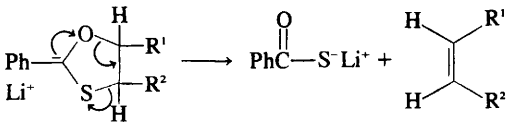
(171) (a) R^1 = OTs, R^2 = H
(b) R^1 = H, R^2 = OTs

respectively, were considered to be in agreement with a transition state which was close to a carbonium ion in character. These isotope effects are similar in size with those observed for the hydrolysis of 1,3-dioxolans, for which an *A*-1 mechanism is accepted. The larger isotope effect for (170a) *vs.* (170b) indicated initial carbon–oxygen bond cleavage, based on the earlier observation that the $k_H/k_D = 2.08$ for the toluene-*p*-sulphonate (171a) in which the C—H bond in question and the toluene-*p*-sulphonyl group have a

[205] S. Satsumabayashi, *Bull. Chem. Soc. Japan*, 1972, **45**, 913.
[206] C. R. Johnson and P. E. Rogers, *J. Org. Chem.*, 1973, **38**, 1793.
[207] (*a*) K. Pihlaja, *J. Amer. Chem. Soc.*, 1972, **94**, 3330; (*b*) F. Guinot and G. Lamaty, *Tetrahedron Letters*, 1972, 2569.

trans-diaxial arrangement was considerably larger than in (171b), in which there is a *gauche* arrangement between these two groups.[208] Activation parameters and solvent deuterium isotope effects have been measured for the hydrolysis of 2-methyl- and 2,2-dimethyl-1,3-oxathiolan[207a] and found to support the above mechanism. The n.m.r. spectrum of 2,2-dimethyl-1,3-oxathiolan taken in FSO_3H–SbF_5 at −60 °C showed a triplet at 10.9 p.p.m. due to the $\overset{+}{O}H_2$ of the dication formed by C—O bond cleavage;[209] for comparison, the $\overset{+}{S}H_2$ due to the dication obtained in a similar manner from 2,2-dimethyl-1,3-oxathiolan occurred at 7.3 p.p.m. ($T = -30$ °C).[209]

Carbanions derived from 2-phenyl-1,3-oxathiolans by reaction with lithium diethylamide undergo stereospecific fragmentation of the five-membered ring to olefins and lithium thiobenzoate, *e.g.* (172) → (173).[210a] The



(172) (173)

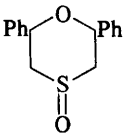
anion (172) was generated with the milder base $LiNEt_2$ compared to butyl-lithium, which was necessary to obtain the anions derived from the 2-phenyl-1,3-dioxolans,[210b] and thus this decomposition could be applied to the synthesis of a greater variety of olefins: *cis*-stilbene, *trans*-cyclo-octene, *cis,trans*-cyclo-octa-1,5-diene, and tetramethylethylene were successfully obtained by this route.[210a] Attack by ethylmagnesium bromide occurred at C-2 in 4,4-diphenyl-2-aryl-1,3-oxathiolan-5-ones and resulted in the formation of carboxylic acids.[211]

Investigations of conformational aspects of 1,3-oxathians and comparisons of the results with these for 1,3-dioxan and 1,3-dithian continue to be made.[212] Coupling constants of a number of 1,3-oxathians were interpreted as indicating a chair conformation in which the oxygen side is less flattened than in 1,3-dithian.[212a] 1,3-Oxathians having *syn*-1,3-methyl groups were found to exist in twist or mixtures of twist and chair conformations.[213] Equilibrium constants in CCl_4 at 25—65 °C between a number of epimeric di- and tri-alkyl-1,3-oxathians have been determined and the data were used to compile values of conformational energies for axial methyl, ethyl, and isopropyl groups in position 2 and for an axial methyl group in positions 4, 5, and 6 in 1,3-oxathians.[212b] The conformational

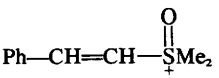
[208] M. Tichy, J. Hapala, and J. Sicher, *Tetrahedron Letters*, 1969, 3739.
[209] F. Guinot, G. Lamaty, and H. Munsch, *Bull. Soc. chim. France*, 1971, 541,
[210] (*a*) M. Jones, P. Temple, E. J. Thomas, and G. H. Whitlam, *J.C.S. Perkin I*, 1974, 433; (*b*) J. N. Hines, M. J. Peagram, E. J. Thomas, and G. H. Whitlam, *ibid.*, 1973, 2332.
[211] E. G. Frandsen and C. T. Pedersen, *Acta Chem. Scand.*, 1972, **26**, 1301.
[212] (*a*) P. Pasanen, *Suomen Kem.*, 1972, **45**, *B*, 363; (*b*) P. Pasanen and K. Pihlaja, *Tetrahedron*, 1972, **28**, 2617.
[213] J. Jalonen, P. Pasanen, and K. Pihlaja, *Org. Mass. Spectrometry*, 1973, **7**, 949.

energy of a 2-axial methyl group was found to be 3.25 kcal mol^{-1}, which is, as expected, between the values 4.07 kcal mol^{-1} obtained earlier for 1,3-dioxan and 1,3-dithian. Values were 3.25 and 3.55 kcal mol^{-1} for 2-axial ethyl and 2-axial methyl and 1.76, 0.74, and 2.93 kcal mol^{-1} for an axial methyl group at positions 4, 5, and 6. Differences in ionization potentials and in the appearance potentials of the molecular ion minus 15 peak (loss of C-2-methyl) for a number of epimeric 2,4-dimethyl-, 2,4,6-trimethyl-, and 2,2,4,6-tetramethyl-1,3-oxathians have been shown to reflect differences in ground-state energies.[213] The conformational energies of axial methyl groups in various positions determined by this method agreed closely with earlier values obtained in solution and suggested that conformational energies of various groups in the oxathians were similar in the gas phase and in non-polar solvents.

An unusual 1,4-oxathian synthesis, the formation of (174) in 12% yield, was observed in the phase-transfer-catalysed generation of dimethyloxosulphonium methylide and its reaction with benzaldehyde.[214] A possible pathway to (174) involves protonation and dehydration of the initial ylide–benzaldehyde adduct to give (175). Ylide formation at a methyl



(174)



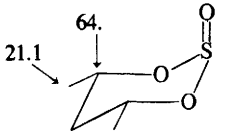
(175)

group, attack at a second molecule of aldehyde, and an intramolecular addition by the oxyanion generates the ring from which (174) can be formed by a protonation and demethylation sequence. 2-Acetamido-2-alkyl-1,4-oxathians and 1,4-oxathiepans were obtained by cyclization of the unsaturated alcohols (119; OH in place of SH),[158] and 2,6-dialkoxy-1,4-oxathians were formed on hydrolysis of $[ROCH(Cl)CH_2]_2S$, which in turn resulted from the reaction of enol ethers with sulphur dichloride.[215] Diethyl azodicarboxylate inserted preferentially into the C—H bond α to sulphur in 1,4-oxathian,[216] while chlorination gave 3-chloro-1,4-oxathian.[217] The average angle of ring puckering in 1,4-oxathian is 58.3°, as determined by electron-diffraction measurements.[218]

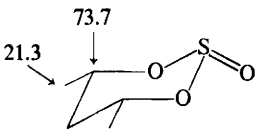
Cyclic Sulphites and Related Compounds.—Conformational aspects of these ring systems have continued to hold the major attention in this area.

[214] A. Merz, and G. Maerkl, *Angew. Chem.*, 1973, **85**, 867.
[215] M. Muehlstaedt, D. Martinitz, and P. Schneider, *J. prakt. Chem.*, 1973, **315**, 940.
[216] E. G. Wilson jun., and J. H. E. Martin, *J. Org. Chem.*, 1972, **37**, 2510.
[217] V. S. Blagoveshchenskii, I. V. Kazimirchik, I. V. Alekseeva, and N. S. Zefirov, *Zhur. org. Khim.*, 1972, **8**, 1325 (*Chem. Abs.*, 1972, **77**, 101 488).
[218] G. Schultz, I. Hargittai, and L. Hermann, *J. Mol. Structure*, 1972, **14**, 353.

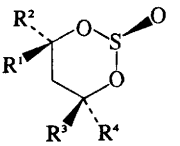
Carbon-13 n.m.r. has been brought into play[219] in order to help further elucidate the complex conformational behaviour of the six-membered-ring sulphites since ^{13}C chemical-shift differences are generally more sensitive to steric factors than proton shifts.[219a] Using the compounds (176) and (177) as models, an axial S=O group was found to shield the carbons at the 4- and 6-position in the ring by about 9 p.p.m. relative to the S=O group being equatorial. Equatorial methyl groups at C-4 and C-6 seemed to be unaffected by the stereochemistry of the S=O bond. Based on the data obtained above, (178) and (179) were judged to be mainly in the conformations having



(176)



(177)



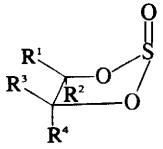
(178) $R^1 = R^2 = R^4 = H$, $R^3 = Me$
(179) $R^1 = R^2 = R^4 = Me$, $R^3 = H$

the S=O bond axial, in contrast to earlier interpretations based on ^1H n.m.r. and dipole-moment measurements, which had indicated these compounds to be a mixture of twist forms and a chair form having S=O equatorial. *trans*-4-t-Butyl-1,3,2-dioxathiolan 2-oxide was shown to exist primarily in the conformation having the S=O and the Bu^t groups axial.[219a]

Undecoupled ^{13}C n.m.r. spectra of trimethylene sulphite and several alkyl-substituted sulphites have also been obtained, and various ^{13}C–H coupling constants were determined.[219b] Detailed studies of ^1H n.m.r. spectra, including an analysis of the vicinal coupling constants, of *cis*-5-substituted-1,3,2-dioxathian 2-oxides indicated that these compounds existed in chair conformations with the S=O group axial.[220a] Similar studies showed that *trans*-4-methyl-1,3,2-dioxathian 2-oxide also adopted the chair conformation, S=O being axial,[220b] but surprisingly the 4-phenyl isomer was suggested to exist either in a chair–non-chair equilibrium or in a non-chair conformation.[220b] Gas-phase electron-diffraction studies[221] agreed with ^{13}C n.m.r. results regarding the preferred conformation of (179). The barrier to chair–chair interconversion of 1,3,2-dioxathians was found to 11.2 kcal mol^{-1} at −42 °C.[222] This compares with 9.9 and 13.2 kcal mol^{-1} previously found for 1,3-dioxan and 1,2,3-trithian. Both *cis*- and *trans*-4,6-dimethyl-1,3,2-dioxathian appeared to exist in a chair conformation. Comparison of the chemical shifts for the 4- and 6-axial hydrogens in *cis*-4,6-dimethyl-1,3,2-dioxathian and the 2-axial oxide (176) allowed the estimation that an axial S=O in a sulphite deshields the *syn*-axial hydrogens by approximately

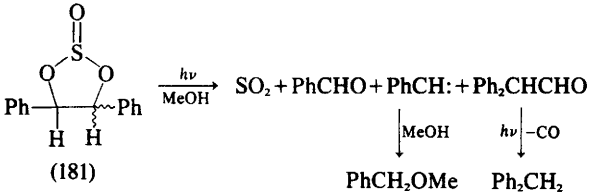
[219] (*a*) G. W. Buchanan, J. B. Stothers, and G. Wood, *Canad. J. Chem.*, 1973, **51**, 3746; (*b*) P. Albriktsen, *Acta Chem. Scand.*, 1973, **27**, 3889.
[220] (*a*) P. Albriktsen, *Acta Chem. Scand.*, 1972, **26**, 1783; (*b*) *ibid.*, p. 3678.
[221] F. J. Mustoe and J. L. Hencher, *Canad. J. Chem.*, 1972, **50**, 3892.
[222] G. Wood, R. M. Srivastava, and B. Adlam, *Canad. J. Chem.*, 1973, **51**, 1200.

0.7 p.p.m.[222] The conformational behaviour of ethylene sulphites has been investigated by n.m.r.[223] and i.r. spectroscopy.[223,224] Based on i.r. stretching frequencies of the S=O bond in different solvents, similarities in the various coupling constants observed for different sulphites, and benzene-induced solvent shifts, it appeared that all sulphites studied existed in basically the same conformation (180) in solution.



(180)

Details of the photolytic decomposition of several arylpinacol sulphites have been published.[225] Photolysis of either *meso*- or *dl*-hydrobenzoin sulphite (181) in methanol gave a mixture consisting of benzyl methyl ether,



(181)

diphenylmethane, benzaldehyde, and sulphur dioxide. The benzyl methyl ether was formed from the reaction of a photolytically generated carbene with the solvent methanol. Diphenylmethane was suggested to arise from a competing process *via* photodecarbonylation of diphenylacetaldehyde, which in turn is probably the result of a photochemically induced loss of SO_2 from (181) coupled with a 1,2-phenyl migration. Phenylcarbene generated from (181) was shown to be chemically indistinguishable from the species obtained by photolysis of phenyldiazomethane and *trans*-2,3-diphenyloxiran since the carbene from all three sources gave the same mixture of insertion products into the C—H bonds of pentane and the same *syn*:*anti* ratio of *cis*-2,3-dimethyl-1-phenylcyclopropane upon reaction with *cis*-but-2-ene.[225]

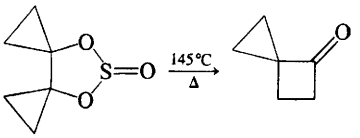
Thermolysis of the 2,3-dispirocyclopropyl sulphite (182) afforded, presumably *via* dicyclopropylidene oxide, the cyclobutanone (183).[226] Benzpinacol sulphite gave tetraphenylethylene oxide in virtually quantitative

[223] (*a*) C. H. Green and D. G. Hellier, *J.C.S. Perkin II*, 1973, 243; (*b*) *ibid.*, p. 1966; (*c*) A. B. Remizov, R. I. Kozlova, N.N. Vakhrusheva, and T. G. Mannafov, *Zhur. priklad. Spektroskopii*, 1973, **19**, 109 (*Chem. Abs.*, 1973, **79**, 77 919).

[224] B. A. Arbuzov, I. V. Anominova, A. N. Vereschchagin, and L. K. Yuldasheva, *Izvest. Akad. Nauk. S.S.S.R., Ser. khim.*, 1973, 3334 (*Chem. Abs.*, 1974, **80**, 59 283z).

[225] G. W. Griffin and A. Manmade, *J. Org. Chem.*, 1972, **37**, 2589.

[226] J. M. Denis and J. M. Conia, *Tetrahedron Letters*, 1972, 4593.



(182) (183)

yield upon heating to 145 °C,[225] but the hydrobenzoin sulphites (181) were stable up to 170 °C.[225] The hydrolysis of cyclic sulphite esters has been reviewed.[227]

Ethylene sulphate underwent ring opening with nucleophiles such as amines, mercaptides, acetylides, and alkyl-lithiums to give β-substituted ethyl sulphates.[228]

[227] J. G. Tillet, *Internat. J. Sulfur Chem.* (*C*), 1971, **6**, 23.
[228] D. A. Tomalia and J. C. Falk, *J. Heterocyclic Chem.*, 1972, **9**, 891.

4

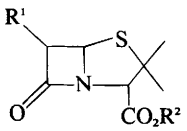
β-Lactam Antibiotics, other Sulphur-containing Natural Products, and Related Compounds

BY J. G. GLEASON

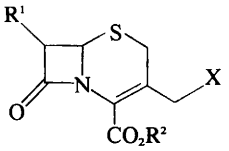
1 Introduction

The purpose of this chapter is to provide a comprehensive review of the developments in the chemistry of β-lactam antibiotics and other sulphur-containing natural products during the period March 1972—March 1974. Earlier works will be cited where necessary to provide a more complete overview.

Research in the β-lactam antibiotic area has continued at a high level of activity, with the ultimate aim of obtaining new antibiotics with increased potency, spectra of activity, and resistance to enzymatic degradation. The major thrust of current research has been in modifications of the nuclei and side chains of both penicillin (1) and cephalosporins (2; X = H or OAc), as

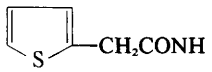


(1)



(2)

R¹

(a) aminoadipyl
(b) $PhOCH_2CONH$
(c) $PhCH_2CONH$
(d) ArCH=N
(e) 
(f) Phthalimido
(g) Ph_3CNH

R²

(z) H
(y) Me
(x) CH_2Ph
(w) Bu^t
(v) CH_2CCl_3
(u) $CHPh_2$

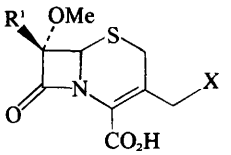
well as the total synthesis of new β-lactam systems related to these known antibiotics. In addition, work continues in the isolation of novel β-lactam antibiotics from fermentation processes, while speculation and study

continue on the biosynthesis and modes of biological action of these antibiotics.

A major monograph covering many of the aspects of the biology and chemistry of cephalosporins and penicillins up to 1972 has appeared.[1] The chemical interconversion of the β-lactam antibiotics has been the subject of one review[2] while a second covers the general synthetic methods for β-lactams, including cephalosporins and penicillins.[3] Earlier reviews on the mechanism by which β-lactams effect their antibacterial activity[4] and the structure–activity relationships of penicillins[5] and cephalosporins[6] should be noted.

2 Fermentation and Biosynthetic Aspects

Cephamycins (3; a),* a novel class of cephalosporins, produced by certain *Streptomyces*[7] fungi and actinomycetes,[8] have been shown[7,9] to possess a



(3) X = OCOC(OMe)=CHC$_6$H$_4$OSO$_2$H (Cephamycin A)
X = OCOC(OMe)=CHC$_6$H$_4$OH (Cephamycin B)
X = OCONH$_2$ (Cephamycin C)
X = OAc

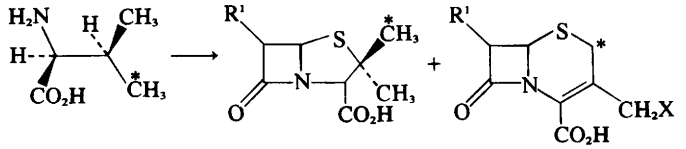
7α-methoxy-group heretofore unknown in the general group of cephalosporins and penicillins. No corresponding penicillins from natural sources have been detected.

The biosynthesis of the β-lactam antibiotics continues to be a subject of considerable interest and speculation. The ring systems of both penicillin and cephalosporins have been shown to be formed from L-valine and

* The general code, as defined for formulae (1) and (2), will be used throughout this Report. For publications in which several substituents R^1 and R^2 have been employed, or where a general class of compounds is implied, R^1 and R^2 will not be specified.

[1] E. H. Flynn, 'Cephalosporins and Penicillins; Chemistry and Biology,' Academic Press, New York, 1972.
[2] R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Accounts Chem. Res.*, 1973, **6**, 32.
[3] A. K. Mukerjee and R. C. Srivastava, *Synthesis*, 1973, 327.
[4] J. L. Strominger, P. M. Blumberg, H. Suginaka, J. Umbreit, and G. G. Wickus, *Proc. Roy. Soc.*, 1971, **B179**, 369.
[5] J. H. Nayler, *Proc. Roy. Soc.*, 1971, **B179**, 357.
[6] M. L. Sassiver and A. Lewis, *Adv. Appl. Microbiol.*, 1970, **13**, 163.
[7] R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whiney, *J. Amer. Chem. Soc.*, 1971, **93**, 2308.
[8] T. W. Miller, R. T. Goegelman, R. G. Weston, I. Putter, and F. J. Wolf, *Antimicrobial Agents & Chemotherapy*, 1972, **2**, 132.
[9] G. Albersschonberg, B. H. Arison, and J. L. Smith, *Tetrahedron Letters*, 1972, 2911.

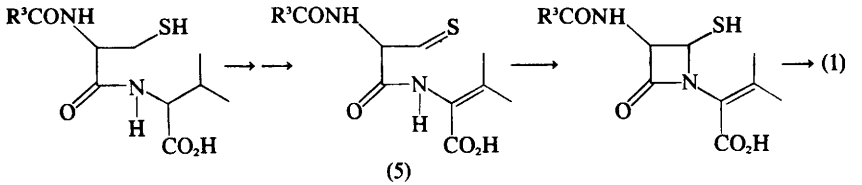
L-cysteine, possibly *via* the tripeptide *S*-(L-2-aminoadipoyl)cysteinyl-valine.[10] That the isopropyl group of valine is incorporated in a stereospecific manner into both penicillin N (1; a) and cephalosporin C (2; a, X = OAc) by a *Cephalosporium acremonium* mutant has been demonstrated by fermentation in the presence of the chiral (2*S*, 3*R*)-[4-^{13}C]valine (4).[11] Complementary results were obtained with the (2*S*, 3*S*)-diastereomer.[12]



(4) [^{14}C]-(1) [^{14}C]-(2)

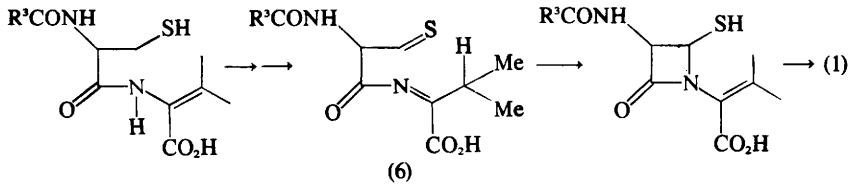
Deacetylcephalosporin C (2; a, z, X = OH) has been proposed as the penultimate product in the biosynthesis of (2; a, z, X = OAc).[13]

The intervening steps between the tripeptide or amino-acid constituents and β-lactam products remain a mystery. Closely related proposals involving a dehydrovaline tripeptide by Arnstein[14] (Scheme 1) and Baldwin[15] (Scheme 2) have been advanced. Thioaldehyde (5), a postulated intermediate in Scheme 1 and one which by simple tautomerism could afford the



(5)

Scheme 1

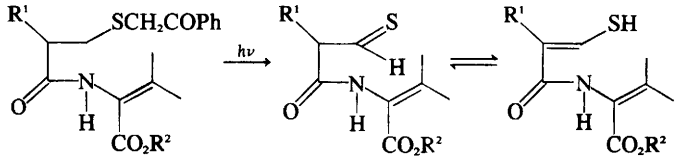


(6)

Scheme 2

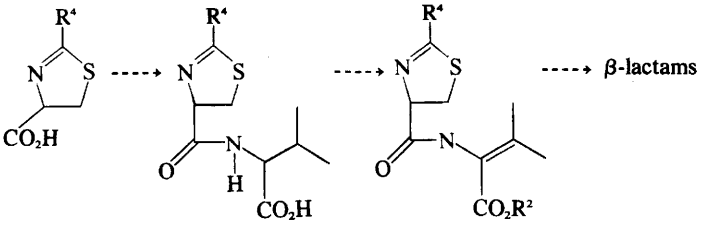
intermediate (6) in Scheme 2, has been synthesized by a Norrish type II

[10] P. A. Lemke and D. R. Brannon in ref. 1, p. 370.
[11] N. Neuss, C. H. Nash, J. E. Baldwin, P. A. Lemke, and J. B. Grutzner, *J. Amer. Chem. Soc.*, 1973, **95**, 3797.
[12] H. Kluender, C. H. Bradley, C. J. Sih, P. Fawcett, and E. P. Abraham, *J. Amer. Chem. Soc.*, 1973, **95**, 6149.
[13] Y. Fujisawa, H. Shirafuji, M. Kida, and K. Nara, *Nature New Biol.*, 1973, **246**, 154.
[14] H. R. V. Arnstein, *Ann. Reports*, 1958, **54**, 339.
[15] J. E. Baldwin, S. B. Haber, and J. Kitchin, *J.C.S. Chem. Comm.*, 1973, 790.



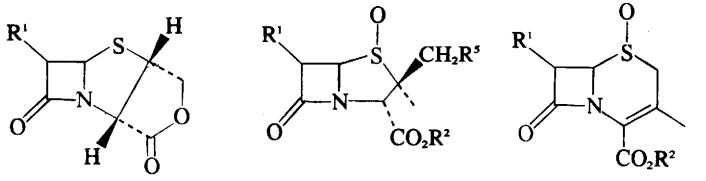
(7) (5)

cleavage of (7; c, y).[16] *In vitro* transformation of (5; c, y) into a β-lactam, however, could not be achieved. A somewhat different proposal by Cooper[17] involved biological oxidation of a cysteinyl-valine derivative (8) followed by β-lactam closure of the resulting (9). In support of this proposal, it was

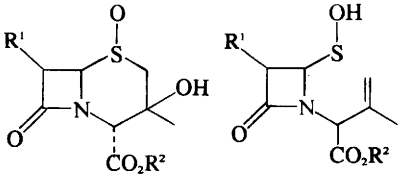


(8) (9)

demonstrated that peracid oxidation of (9; v, $R^4 = PhOCH_2$) gave a mixture of penicillins (10; b), (11; b, v), and (12; b, v) and cephalosporin sulphoxides (13; b, v) and (14; b, v). These products possibly result from acid-catalysed ring opening of (9; v, $R^4 = PhOCH_2$) to the sulphenic acid (15; b, v), the cyclization of which is well known.[2]



(10) (11) $R^5 = H$ (12) $R^5 = OH$ (13)



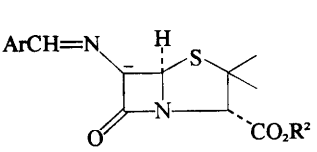
(14) (15)

[16] J. Cheney, C. J. Moore, J. A. Raleigh, I. A. Scott, and D. W. Young, *J.C.S. Chem. Comm.*, 1974, 47.

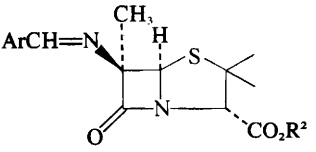
[17] R. D. G. Cooper, *J. Amer. Chem. Soc.*, 1972, **94**, 1018.

3 Modification of the β-Lactam Ring System

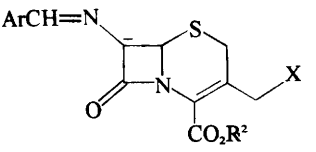
Modification at C-6(7).—The discovery of 7-methoxycephalosporins as potent antibacterials,[7,8] coupled with an early prediction[18] that alkylation at C-6 should enhance the biological activity of penicillin, generated considerable interest in the functionalization α to the β-lactam carbonyl group. Use of an aryl Schiff base to increase the acidity of the C-6 proton permitted the generation of anion (16) by sodium hydride[19] or other strong bases.[20,21] Alkylation of (16) by methyl iodide occurred preferentially from the less hindered α face, affording (17) as the major isomer. Similarly, stereoselective methylation of the cephalosporin anions (18; X = H)[19,20] and (18; X = OAc)[20,21] yielded α-methylated products (19; X = H or OAc).



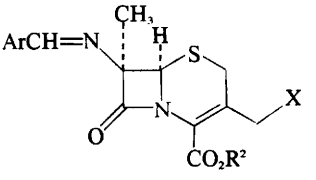
(16)



(17)



(18)

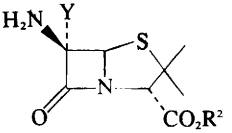


(19)

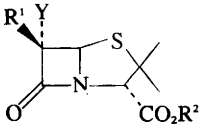
Alkylation,[21] acylation,[21] hydroxyalkylation,[22] and carbonylation[23] of these anions by reactive halides or aldehydes have been reported. Oxidation of (16; x), however, resulted in dimerization and nitrone formation.[24]

Although direct methoxylation of these anions has not been achieved, indirect routes have been developed. Thiomethylation of anion (16) with methoxycarbonylmethyl disulphide[25] or methyl methanethiosulphonate[26] afforded, after hydrolysis of the benzylidene group, the 6β-amino-6α-thiomethylpenicillin (20; d). Mercuric-chloride-catalysed methanolysis of (22; d, x) afforded the 6α-methoxypenicillin (23; d, x) with retention of

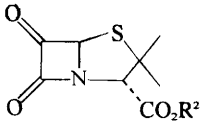
[18] J. L. Strominger and D. J. Tipper, *Amer. J. Med.*, 1965, **39**, 708.
[19] E. H. Bohme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, 1971, **93**, 4324.
[20] R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Letters*, 1972, 375.
[21] E. H. W. Bohme, H. E. Applegate, J. B. Ewing, P. T. Funke, M. S. Puar, and J. E. Dolfini, *J. Org. Chem.*, 1973, **38**, 230.
[22] D. B. R. Johnston, S. M. Schmitt, R. A. Firestone, and B. G. Christensen, *Tetrahedron Letters*, 1972, 4917.
[23] W. A. Spitzer, T. Goodson, R. J. Smithey, and I. G. Wright, *J.C.S. Chem. Comm.*, 1972, 1138.
[24] R. A. Firestone, N. Schelechow, and B. G. Christensen, *J.C.S. Chem. Comm.*, 1972, 1106.
[25] W. A. Spitzer and T. Goodson, *Tetrahedron Letters*, 1973, 273.
[26] T. Jen, J. Frazee, and J. R. E. Hoover, *J. Org. Chem.*, 1973, **38**, 2857.



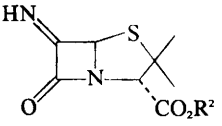
(20) Y = SMe
(21) Y = OMe



(22) Y = SMe
(23) Y = OMe
(26) Y = Br



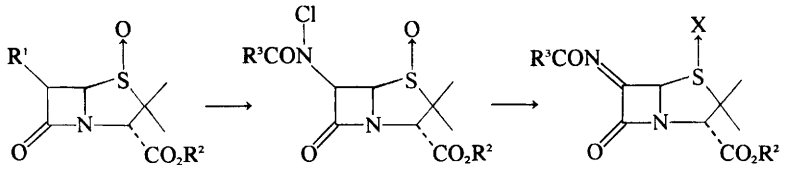
(24)



(25)

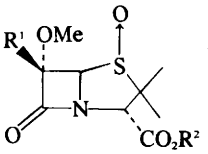
configuration at C-6, while hydrolysis gave the unusual 6-oxopenicillin (24).[26] Thus, like the alkylation of anions (16) and (18), approach of methanol to the imine (25) occurs from the sterically less hindered α face. Alternatively, low-temperature chlorination and subsequent methanolysis permitted a similar stereospecific transformation of (22; c, v) into (23; c, v).[25] In this case, an acylimine intermediate has been postulated. Silver-oxide-catalysed methanolysis of 6-bromopenicillin (26; d, x), obtained by NBS bromination of anion (16), also permits the stereospecific introduction of a methoxy-group.[27] Analogous syntheses of 7α-methoxycephalosporins (3; X = H or OAc) have been reported.[25–28]

Hypochlorite oxidation of suitable penicillin derivatives has allowed a more direct route to 6α-methoxypenicillins.[29–31] Thus *N*-chlorination–dehydrochlorination of the penicillin sulphoxide (27; b, y) in a borate buffer generated the acylimine (29; y, R^3 = $PhOCH_2$) *via* the *N*-chloro-amide (28; y, R^3 = $PhOCH_2$); stereospecific addition of methanol occurred from

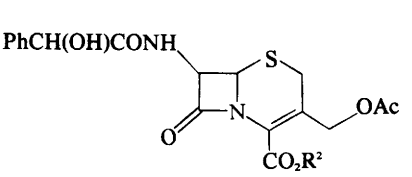


(27) (28) (29) X = O
(33) X = :

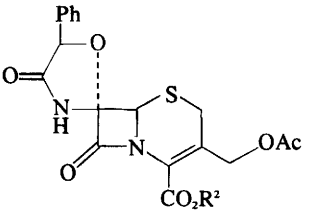
[27] L. D. Cama and B. G. Christensen, *Tetrahedron Letters*, 1973, 3505.
[28] W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young, and J. E. Dolfini, *J. Org. Chem.*, 1973, **38**, 943.
[29] J. E. Baldwin, F. J. Urban, R. D. G. Cooper, and F. L. Jose, *J. Amer. Chem. Soc.*, 1973, **95**, 2401.
[30] G. A. Koppel and R. E. Koehler, *J. Amer. Chem. Soc.*, 1973, **95**, 2403.
[31] R. A. Firestone and B. G. Christensen, *J. Org. Chem.*, 1973, **38**, 1436.



(30)



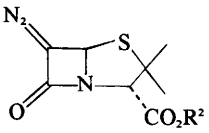
(31)



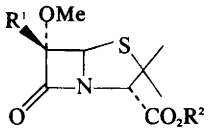
(32)

the less substituted α face to give the α-methoxylated penicillin sulphoxide (30; b, y). Because of the sensitivity of the thiazolidine sulphur to hypochlorite, Baldwin *et al.* found it necessary to work with the penicillin sulphoxides and sulphones, a limitation which has been circumvented by the generation at low temperatures of the amide anion of the penicillin prior to hypochlorite oxidation.[30,31] The use of lithium methoxide for the generation of the amide anion, which as well as acting as catalyst for dehydrochlorination provided a source of methanol, permitted a simple one-step synthesis of *C*-6-methoxylated penicillins.[30] Cephalosporins undergo similar transformations,[30,32] for example, conversion of (31; u) into (32; u);[32] neither double-bond isomerization nor *C*-2-chlorination was observed. Hydration of (33; x, $R^5 = PhCH_2$) has also been reported; attack again occurs stereospecifically, affording (22; c, x, Y = OH).[31]

In a third approach to this problem of C-6(7) functionalization, use was made of a 6-diazopenicillin (34).[33] Its reaction with bromine azide at low temperature followed by methanolysis afforded (35), which could be reduced to the 6α-methoxypenicillin. Alternatively, methanolysis in the presence of *N*-bromoacetamide afforded (36), which was converted into



(34)

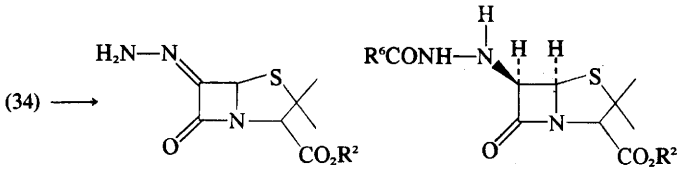


(35) $R^1 = N_3$
(36) $R^1 = Br$

[32] G. A. Koppel and R. E. Koehler, *Tetrahedron Letters*, 1973, 1943.
[33] L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, 1972, **94**, 1408.

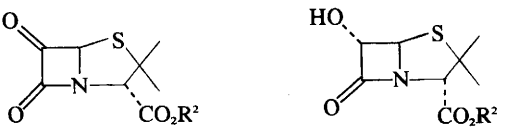
(21) by reaction with lithium azide and subsequent reduction. These displacement reactions are remarkable in view of the reported failure of penicillin and cephalosporin to undergo S_N2-type displacement at C-6(7).[34] Similar transformations were reported in the cephalosporin series,[33] and it was this route which permitted the first partial synthesis of the cephamycins.[35]

Diazopenicillin (34) has been utilized as a starting point for the synthesis of a number of other 6-substituted penicillins. Triphenylphosphine reduction of (34) afforded a phosphine oxide complex of (37), which was converted into (38; z, $R^6 = PhOCH_2$) by acylation followed by borohydride



(37) (38)

reduction and deprotection; the latter is an effective antibiotic against a penicillin-resistant strain of *Staphylococcus aureus*.[36] Hydrolysis of (34) afforded the α-hydroxypenicillin (39; x),[37] from which the 6-ketopenicillin (24; x) was obtained by mild oxidation.[38] Borohydride reduction of this ketone afforded exclusively the β-hydroxypenicillinate (40; x), the phenoxyacetyl ester (41; z) of which exhibited weak antibacterial activity.[38,39] Acetyl esterases which convert (42) back into (40) have been reported.[40] Ketones (24) react with certain phosphorus ylides, which, after reduction and deblocking, afford analogues of penicillin, *e.g.* (43), in which the 6-amino-group has been replaced by a methylene group.[39] These compounds also exhibit weak antibacterial activity.



(24) (39)

[34] I. McMillan and R. J. Stoodley, *Tetrahedron Letters*, 1966, 1205; *J. Chem. Soc. (C)*, 1968, 2533; R. B. Morin, B. G. Jackson, E. H. Flynn, R. W. Roeske, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1396.

[35] R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Letters*, 1972, 2907.

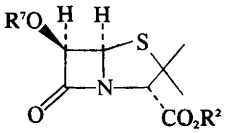
[36] D. M. Brunwin and G. Lowe, *J.C.S. Chem. Comm.*, 1972, 192.

[37] D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, 1967, **50**, 1327.

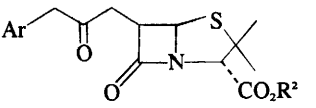
[38] Y. S. Lo and J. C. Sheehan, *J. Amer. Chem. Soc.*, 1972, **94**, 8253.

[39] J. C. Sheehan and Y. S. Lo, *J. Org. Chem.*, 1973, **38**, 3227.

[40] K. R. Henery-Logan, *J. Antibiotics*, 1973, **26**, 697.

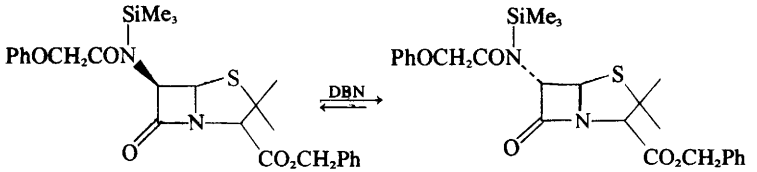


(40) $R^7 = H$
(41) $R^7 = PhOCH_2CO$
(42) $R^7 = MeCO$

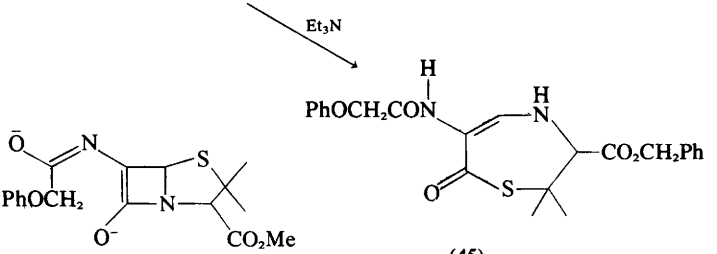


(43)

Epimerization.—The base-catalysed C-6 epimerization of penicillins continues to attract interest.[41—45] With weak bases, direct epimerization fails for penicillins containing a secondary amide chain, presumably because of the greater acidity of the amide proton compared with H-6.[41,42] This problem has been circumvented by protecting the amide proton as its silyl derivative (44).[41] Epimerization was accomplished with diazabicyclo[4, 3, 0]non-5-ene (DBN); with triethylamine, thiazepine (45) formation is a major side-reaction. The epipenicillins may also be obtained by epimerization of the penicillin sulphoxides followed by reduction with phosphorus tribromide.[42] Direct C-6 epimerization of penicillins *via* a vicinal dianion has been reported by Koppel.[43] Thus, the dianion (46), generated by 2.5 equivalents



(44) epi-(44)

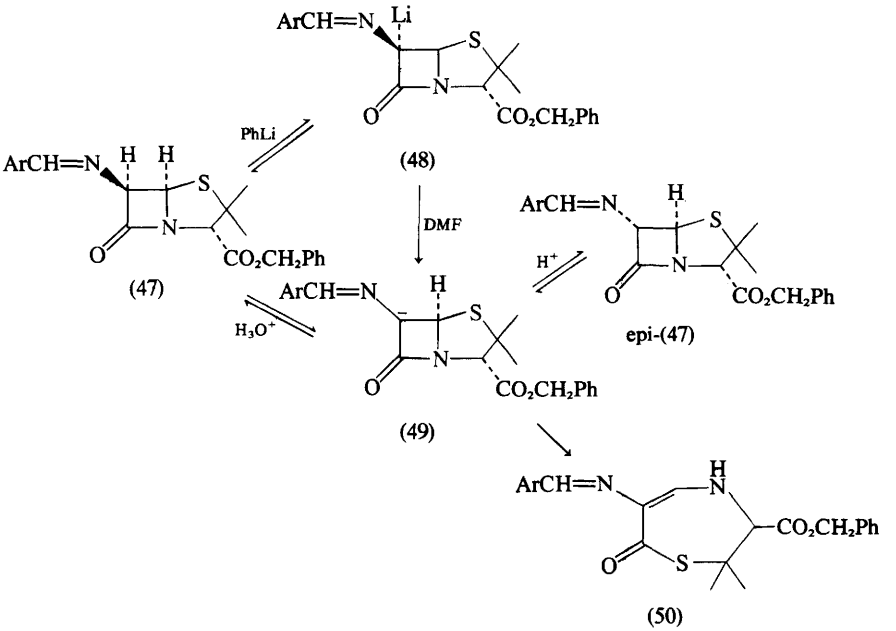


(45) (46)

of lithium di-isopropylamide at −80 °C and subsequently protonated with methanol–formic acid, afforded the expected 4:1 epipenicillin–penicillin equilibrium mixture.

[41] A. Vlietinck, E. Roets, P. Claes, G. Janssen, and H. Vanderhaeghe, *J.C.S. Perkin I*, 1973, 937; A. Vlietinck, E. Roets, P. Claes, and H. Vanderhaeghe, *Tetrahedron Letters*, 1972, 285.
[42] P. Claes, A. Vlietinck, E. Roets, H. Vanderhaeghe, and S. Toppet, *J.C.S. Perkin I*, 1973, 932.
[43] G. A. Koppel, *Tetrahedron Letters*, 1973, 4233.
[44] J. R. Jackson and R. J. Stoodley, *J.C.S. Perkin I*, 1972, 895.
[45] R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, 1974, **39**, 437.

Since it is the β-epimers and not the α- or epi-penicillins and -cephalosporins which are biologically active, and since most total syntheses thus far reported yield the undesirable α-isomers (see below), the kinetically controlled epimerization of 7α-amino- to 7β-amino-penicillins reported by Firestone and co-workers[45] is of particular significance. Thus, an anion [*i.e.* (49) was generated at the C-6 position by treatment of the penicillin Schiff base (47) with phenyl-lithium. The initially formed complex (48) maintains configuration since (47) is regenerated on acidification. In DMF, the free anion (49) is believed to be formed, which on protonation under non-reversible conditions (THF–H_2O–excess HOAc) afforded the kinetically determined mixture of (47) and (epi-47) in a ratio of 2 : 1. Thiazepine (50) was

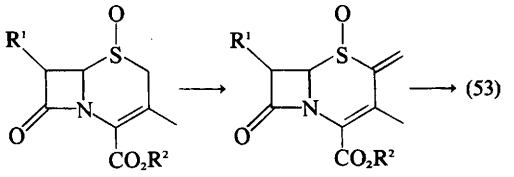


observed as a minor by-product. In a similar way, 7-epicephalosporins were largely epimerized to the natural β configuration.

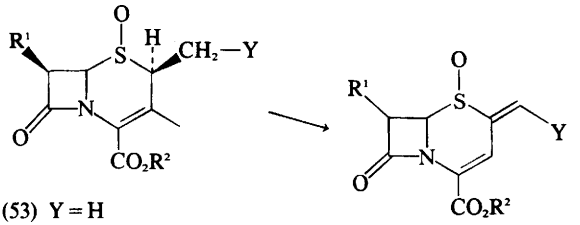
Modifications in the Thiazine Ring.—The allylic position at C-2 in the 3-cephem sulphoxides (51) is quite reactive, and under Mannich conditions (formaldehyde, secondary amine salts) gave the *exo*-methylene-3-cephem (52; b, w);[46,47] presumably, loss of the amino-function occurred under the reaction conditions. Both hydrogenation and addition of thiols

[46] I. G. Wright, C. W. Ashbrook, T. Goodson, G. V. Kaiser, and E. M. Van Heyningen, *J. Medicin. Chem.*, 1971, **14**, 420.

[47] G. V. Kaiser, C. W. Ashbrook, T. Goodson, I. G. Wright, and E. M. Van Heyningen, *J. Medicin Chem.*, 1971, **14**, 426.



(51) (52)

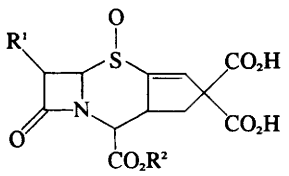


(53) Y = H
(54) Y = S-alkyl or S-aryl
(55) Y = $CH(CO_2CH_2CCl_3)_2$

(56) Y = S-alkyl or S-aryl

occurred primarily from the least hindered side, affording (53; b, w) and (54; b, w), respectively. The latter compound underwent facile dehydration to the thiomethylene derivative (56; b, w) in acetic acid–sodium acetate solution.[47] Addition of di-trichloroethyl malonate to (52; b, v) afforded (55; b, v), which on allylic bromination at C-3, cyclization, and bromination–dehydrobromination gave the 4–6–5-fused β-lactam (57; b, z).[48] (Dimethylamino)-phenyloxosulphonium methylide with the diene sulphoxide (52; b, v) afforded the C-2-spirocyclopropyl-cephalosporin (57; b).[49] Sulphoxide reduction of these compounds was accomplished in the usual manner. Chlorination at C-2 of cephalosporins and their sulphoxides has been reported.[50] In the former instance, however, the 2-chloro-3-cephem (59; b) was too unstable to isolate, but it was trapped by reaction with alcohols to give (60; b) or with acetate ion to give the 2-acetoxy-3-cephem (61; b). This compound was also obtained by Pummerer rearrangement of (51; b, x).

Modification at C-3 of the thiazine ring is an area which has been extensively exploited, and an excellent review of the pre-1972 literature has



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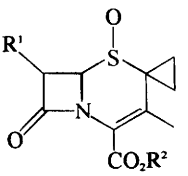

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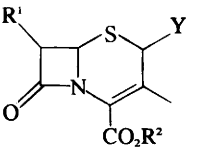
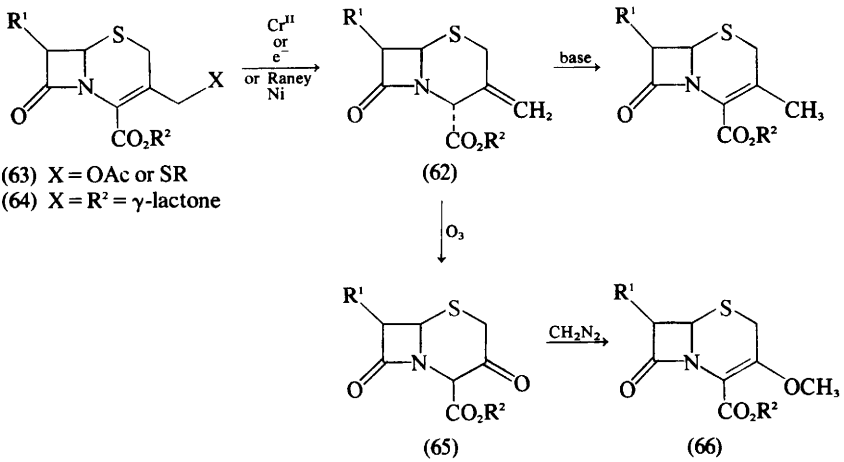


(59) Y = Cl
(60) Y = O-alkyl
(61) Y = OAc

[48] D. O. Spry, *J.C.S. Chem. Comm.*, 1973, 671,
[49] D. O. Spry, *Tetrahedron Letters*, 1973, 2413.
[50] D. O. Spry, *Tetrahedron Letters*, 1972, 3717.

been included in a monograph.[1] Recent interest has centred on the 3-*exo*-methylene-cephalosporins (62), which were first prepared by reduction of 3-acetoxymethylcephalosporins (63) by chromium(II) salts.[51] Subsequently, electrochemical reduction of 3-substituted cephalosporins[52,53] and the cephalosporin lactone (64)[53] or the desulphurization by Raney nickel of cephalosporins in which the acetoxy-group has been replaced by a sulphur nucleophile[54] have been reported to yield (62). The stereochemistry at C-4 of (62; b, y) has been shown to be α by chemical[55] and spectroscopic[56] methods. Base rapidly isomerizes the double bond to the Δ^3 position,[51—55] while ozonolysis of (62) is reported to give the 3-ketone (65), alkylation of which afforded the enol ether (66).[57] A 3-methylene-4-methoxy-cephalosporin



(63) X = OAc or SR
(64) X = R² = γ-lactone

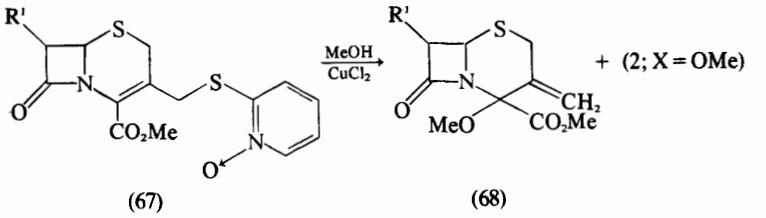
(62)

(65) (66)

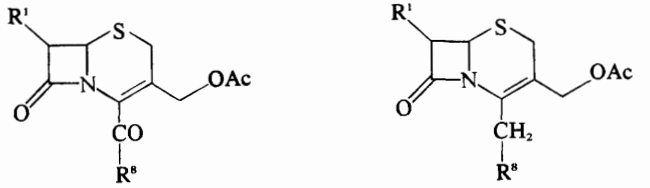
(68; e) was also obtained as a by-product in the $CuCl_2$-catalysed displacement of the 2-pyridylthio-*N*-oxide group of (67; e) with methanol.[58]

Modifications of cephalosporins at C-4 have been generally disappointing from a biological standpoint (see, however, the recent work of Sheehan and co-workers, to be discussed later). Acid chloride (69; e) was reduced to the alcohol (70; e) by $LiAl(Bu^tO)_3H$ without disruption of the β-lactam ring,[59] while the homologous acid (71; e) and methyl ketone (72; e) were prepared from the diazo-ketone (73; e). All of these compounds exhibited poor antibacterial activity.

[51] M. Ochiai, O. Aki, A. Morimoto, T. Okada, and H. Shimadzu, *J.C.S. Chem. Comm.*, 1972, 800.
[52] M. Ochiai, O. Aki, A. Morimoto, T. Okada, and K. Shinozaki, *Tetrahedron Letters*, 1972, 2341.
[53] M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki, and Y. Asahi, *J.C.S. Perkin I*, 1974, 258.
[54] R. R. Chauvette and P. A. Pennington, *J. Org. Chem.*, 1973, **38**, 2994.
[55] D. O. Spry, *Tetrahedron Letters*, 1973, 165; M. Ochiai, O. Aki, S. Morimoto, and T. Okada, *ibid.*, 1972, 3241.
[56] M. Ochiai, E. Mizuta, O. Aki, A. Morimoto, and T. Okada, *Tetrahedron Letters*, 1972, 3245.
[57] Belg. P. 801 596; 801 597; 801 598.
[58] M. Ochiai, O. Aki, A. Morimoto, T. Okada, and T. Kaneko, *Tetrahedron Letters*, 1972, 2345.
[59] T. Jen, B. Dienel, J. Frazee, and J. Weisbach, *J. Medicin. Chem.*, 1972, **15**, 1172.



(67) (68)



(69) $R^8 = Cl$
(72) $R^8 = CH_3$
(73) $R^8 = CH_2N_2$

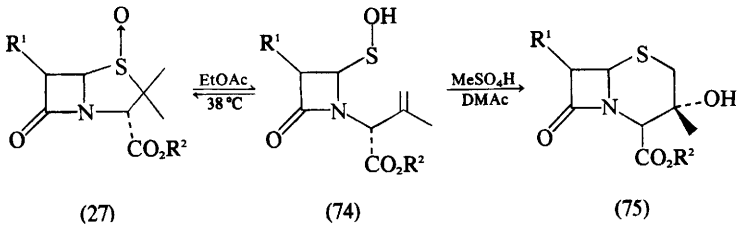
(70) $R^8 = OH$
(71) $R^8 = CO_2H$

4 Partial Synthesis of Cephalosporins and Penicillins

The search for novel β-lactam antibiotics has been severely restricted by the relative inaccessibility of these ring systems by stereospecific total syntheses. Because of the availability of both the penicillin and, more recently, cephalosporin nuclei from fermentation processes, partial synthesis of new ring systems from these starting materials has been extensively investigated. The penicillin–cephalosporin interconversions continue to be studied while new degradative procedures have permitted the synthesis of useful snythons by complete removal of the thiazoline ring of penicillin.

The first general method of transforming a penicillin into a cephalosporin, the acid-catalysed rearrangement of penicillin sulphoxides, continues to receive attention. That this rearrangement proceeds *via* a sulphenic acid derivative has been further confirmed by isolation of the crystalline sulphenic acid (74; f, y) from the thermal rearrangement of the penicillin sulphoxide (27; f, y).[60] This intermediate slowly reverts to the penicillin at 38 °C, and, on treatment with methanesulphonic acid in dimethylacetamide, cyclizes to cephalosporin (75; f, y). Trapping of (74) by oxidation to the sulphinyl chloride (76; f, y) has been reported; cyclization to a cephalosporin sulphoxide was accomplished under base catalysis.[61] Treatment of penicillin sulphoxides with azo-compounds also effects rearrangement to

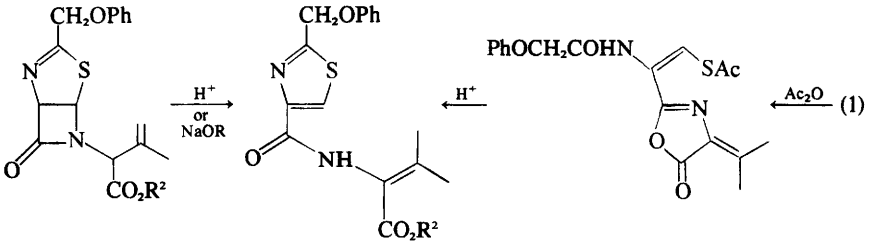
[60] T. S. Chou, J. R. Burgtorf, A. L. Ellis, S. R. Lammert, and S. Kukolja, *J. Amer. Chem. Soc.*, 1974, **96**, 1609.
[61] S. Kukolja and S. R. Lammert, *Angew. Chem.*, 1973, **85**, 40.



(27) (74) (75)

(76) (77)

the cephalosporin nucleus;[62] sulphinyl hydrazodicarboxylates (77; R⁹ = Me or Et) are formed as by-products. The conversion of hetacillin sulphoxide into cephalexin has been described,[63] as have multiple rearrangements of penicillin sulphoxides to the 2-*C*-bis- and tris-α-acetoxypenicillin derivatives.[64] In the presence of trimethyl phosphite, the penicillin sulphoxide rearrangement takes a different course and a thiazoline-β-lactam (78; z) is formed in low yield.[65] This product is transformed into the substituted thiazole (79; z) on treatment with either acids or bases. This thiazole is also obtained by acid hydrolysis of (80), a minor product of the rearrangement,



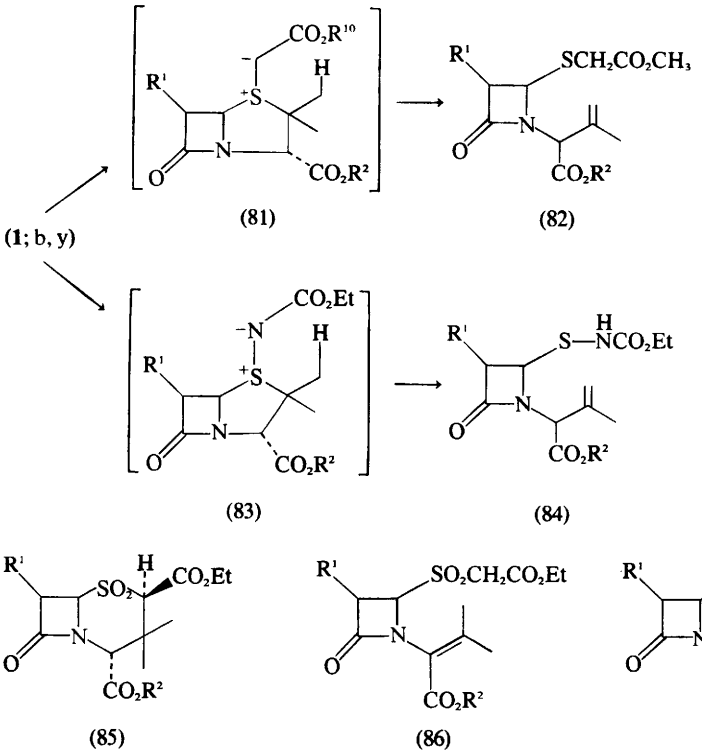
(78) (79) (80)

catalysed by acetic anhydride, of penicillin (1; b, z).[66] The substituted thiazole (79; z) exhibited antifungal and antibacterial properties. Closely

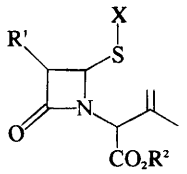
[62] S. Terao, T. Matsuo, S. Tsushima, N. Matsumoto, T. Miyawaki, and M. Miyamoto, *J.C.S. Chem. Comm.*, 1972, 1304.
[63] W. J. Gottstein, P. F. Misco, and L. C. Cheney, *J. Org. Chem.*, 1972, **37**, 2765.
[64] D. O. Spry, *J.C.S. Chem. Comm.*, 1973, 259.
[65] R. D. G. Cooper, U.S.P. 3 594 389.
[66] S. P. Kukolja and R. B. Morin, U.S.P. 3 758 488.

related to penicillin sulphoxide ring-opening reactions are the rearrangements of penicillin sulphonium ylides and sulphilimines to 2-azetidinones.[67] The formation of (81; b, y) was implicated in the reaction of penicillin (1; b, y) with a diazomalonate ester in which 2-azetidinone (82; b, y) was the major product. Similarly, the intermediacy of (83; b, y) was suggested by analogy in the formation of (84; b, y) from penicillin in its reaction with ethyl azidoformate. Both (82; c, y) and (84; b, y) have been transformed into cephalosporins, the former giving the cepham (85; c, y) *via* cyclization of the sulphone (86; c, y)[68] while the latter, on acid treatment, yielded the desacetoxycephalosporin (2; b, y, X = H).[67] The similar conversion of cephalosporin (2; c, y, X = H) into the penicillin (87; c, y) by ethyl diazoacetate has been described.[69]

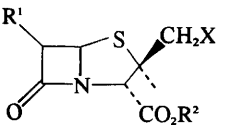
Derivatives of sulphenic acids have been utilized in cephalosporin–penicillin interconversions. The sulphenyl chloride (88; f, y), obtained by chlorinolysis of penicillin, cyclized to the penicillin (89; f, y) and



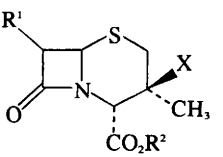
[67] M. Numata, Y. Imashiro, I. Minamida, and M. Yamaoka, *Tetrahedron Letters*, 1972, 5097.
[68] M. Yoshimoto, S. Ishihara, E. Nakayama, E, Shoji, and H. Kuwano, *Tetrahedron Letters*, 1972, 4387.
[69] M. Yoshimoto, S. Ishihara, E. Nakayama, and N. Soma, *Tetrahedron Letters*, 1972, 2923.



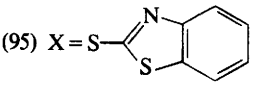
(88) X = Cl
(94) X = Br



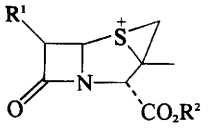
(89) X = Cl
(90) X = OAc



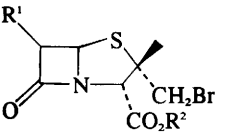
(91) X = Cl
(92) X = OH



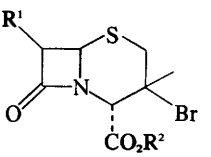
(95) X = S



(93)



(96)



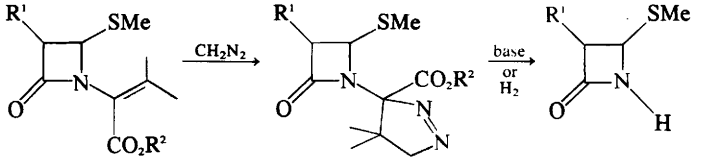
(97)

the cephalosporin (90; f, y).[70] Ring contraction of (90; f, y) to the penicillin (91; f, y) was effected by silver nitrate. Conversion of a cephalosporin into a penicillin was also observed on treatment of (92; f, y) with thionyl chloride–triethylamine; (2; f, y, X = H) and (90; f, y) were the isolated products. The thiiranium ion (93) was proposed as a common intermediate in these transformations. In contrast to the cyclizations of (88), the sulphenyl bromide (94), formed by bromination of the disulphide (95), afforded the β-bromomethyl-penicillin (96) and 3α-bromocephalosporin (97).[71] The difference in the stereochemistry of the products of cyclization of the sulphenyl chloride and bromide has not been explained.

The sulphenic acids produced on thermal rearrangement of penicillin sulphoxides have been trapped by a variety of reagents, including thiols[71,72] and acetylene and olefin derivatives[73] such as norbornadiene, keten dimer, vinyl ethers,[74] keten acetals, and acetylenedicarboxylates.[75] Removal of the nitrogen substituent of the resulting 2-azetidinones, *e.g.* (98; c, v), was achieved by addition of diazomethane to the olefin followed by base treatment or reduction of the intermediate pyrazoline (99).[73,74]

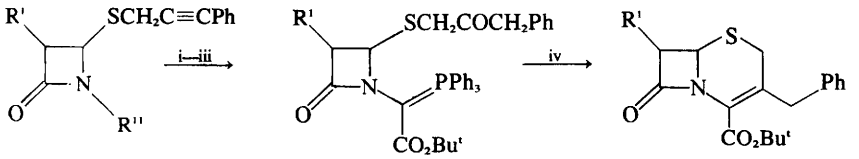
Because of the potential importance of monocyclic β-lactams, *e.g.* (100),

[70] S. Kukolja and S. R. Lammert, *J. Amer. Chem. Soc.*, 1972, **94**, 7169.
[71] T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakayuchi, and T. Oku, *Tetrahedron Letters*, 1973, 3001.
[72] R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes, and M. V. Taylor, *J.C.S. Perkin I*, 1973, 1182.
[73] I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *J.C.S. Perkin I*, 1973, 1187.
[74] I. Ager, D. H. R. Barton, G. Lucente, and P. G. Sammes, *J.C.S. Chem. Comm.*, 1972, 601.
[75] D. H. R. Barton, I. H. Coates, P. G. Sammes, and C. M. Cooper, *J.C.S. Chem. Comm.*, 1973, 303.



(98) (99) (100)

in the synthesis of new ring systems, several penicillin degradation routes have been explored. Base-catalysed ring opening of penicillin afforded an intermediate thiol which could be intercepted by propargyl halides to give the 2-azetidinone (101; g, x).[76] Removal of the N-substituent in this case was effected by permanganate oxidation.[76,77] Addition of a glyoxylate ester to the unsubstituted 2-azetidinone (102; g) so obtained, transformation into the stable phosphorus ylide, and hydration of the triple bond[78] gave an intermediate (103; g, w), which underwent cyclization to the cephalosporin (104; g, w).[76]



(101) $R^{11} = C(:CMe_2)CO_2R^2$
(102) $R^{11} = H$

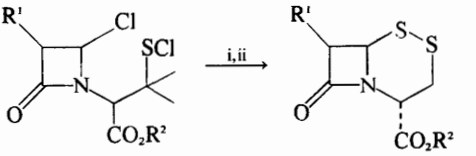
(103) (104)

Reagents: i, Bu^tO_2CCHO; ii, $SOCl_2$, Ph_3P; iii, piperidine; iv, Δ

Scheme 3

In addition to the S—C-2 bond cleavages described thus far, both S—C-5 and C-3—N bond cleavage have been explored in penicillin degradation. Chlorinolysis of penicillin effects S—C-5 cleavage, affording the 4-chloro-2-azetidinone (105; t, y), from which the cephalosporin disulphide (106; f, z) was prepared (Scheme 4).[79] The structure and stereochemistry of (106) were determined by *X*-ray techniques.[80] Chlorinolysis of an *N*-trityl-anhydropenicillintoluene-*p*-sulphonate (107; g) gave, after hydrolysis, a sulphur-free 2-azetidinone (108; z, $R^1 = NH_2$),[81] which cyclized to the oxazoline (109) on reaction with chloroformate esters. Allylic bromination of (108; f, y) afforded a monobromide (110),[82] from which the azacephem (111; f, y) was obtained by

[76] J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 58.
[77] E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1972, 229.
[78] J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 57.
[79] S. Kukolja, *J. Amer. Chem. Soc.*, 1972, **94**, 7590.
[80] S. Kukolja, P. V. DeMarco, N. D. Jones, M. O. Chaney, and J. W. Pashcal, *J. Amer. Chem. Soc.*, 1972, **94**, 7592.
[81] S. Wolfe, W. S. Lee, G. Kannengiesser, and J. B. Ducep, *Canad. J. Chem.*, 1972, **50**, 2894.
[82] S. Wolfe, W. S. Lee, J. B. Ducep, and G. Kannengiesser, *Canad. J. Chem.*, 1972, **50**, 2898.

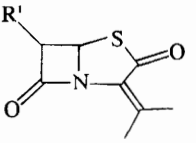


(105) (106)

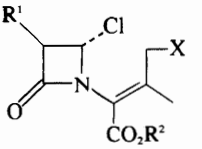
Reagents: i, BuSH; ii, H^+

Scheme 4

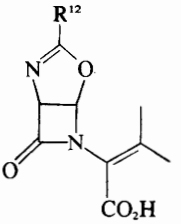
sequential treatment with azide ion and reduction.[83] S—C-2 cleavage of penicillin may also be effected by mercury(II) acetate.[84,85] Thus, potassium benzylpenicillinate (1; c, $R^2 = K^+$) was converted into the oxazoline-2-azetidinone (112; R^2 = HgOAc), which on decarboxylation afforded (113); the



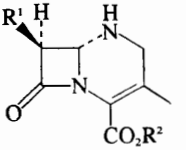
(107)



(108) X = H
(110) X = Br



(109)

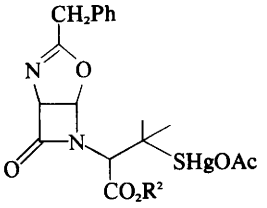


(111)

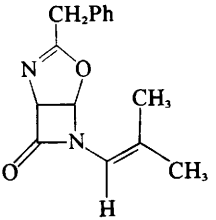
oxazoline opened readily with acetic acid to give the 4-acetoxy-2-azetidinone (114).[84] Although removal of the N-substituent has not been described, oxidative removal of the acrylic acid group from (115; v) was reported to give (116) in fair yields.[77]

The N—C-3 bond of penicillin may be selectively cleaved to afford azetidinones useful in the synthesis of novel β-lactams. Utilizing a modification[87,88] of the original procedure of Sheehan,[86] the isocyanate

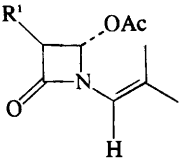
[83] S. Wolfe, J. B. Ducep, G. Kannengiesser, and W. S. Lee, *Canad. J. Chem.*, 1972, **50**, 2902.
[84] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1973, 32.
[85] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Chem. Comm.*, 1973, 477.
[86] J. C. Sheehan and K. G. Brandt, *J. Amer. Chem. Soc.*, 1965, **87**, 5468.
[87] K. Heusler, *Helv. Chim. Acta*, 1972, **55**, 388.
[88] B. Fechtig, H. Bickel, and K. Heusler, *Helv. Chim. Acta*, 1972, **55**, 417.



(112)



(113)



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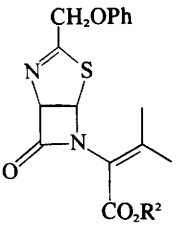

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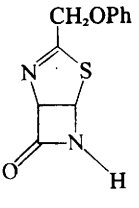
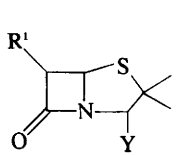
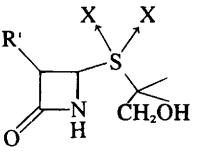


(116)

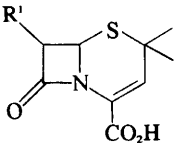
(117; b) obtained on Curtius rearrangement of penicillin was trapped as the trichloroethylcarbamate (118; b, v); Zn–acetic acid hydrolysis of (118) afforded the carbinolamide (119; b). Borohydride reduction cleaved the N—C-3 bond to give the carbinol (120; b), from which the cephem (121; b) was obtained[89] by known methods. Oxidative fragmentation of (119; R^1 = BOCNH) gave a vinyl thioether (122; R^1 = BOCNH), which on



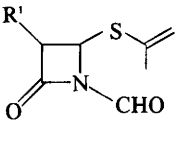
(117) Y = NCO
(118) Y = $NHCO_2R^2$
(119) Y = OH



(120) X = :
(127) X = O



(121)



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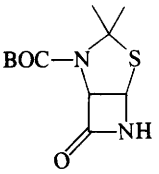

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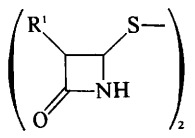
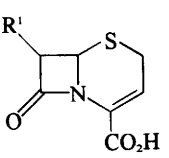


(124)



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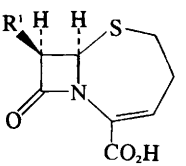
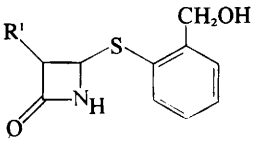


(126)

[89] R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 408.

subsequent transformation afforded the thiazolidine (123; c),[87] an intermediate in the total synthesis of cephalosporins.[1] Iodine oxidation and acylation of the thiazolidine (122; c) gave the 2-azetidinone disulphide (124; c),[90] from which the desacetoxymethylcephem (125; c)[90] and homocephem (126; c)[91] were prepared by previously described methods. The sulphone (127; b), obtained by an analogous Curtius rearrangement of the acyl azide of penicillin sulphone,[92,93] has been reported to undergo a novel displacement reaction with thiols. The reaction of (127; b) with 2-hydroxymethylthiophenol gave a 1:1 mixture of *cis*- and *trans*-substituted phenyl thioethers (128; b),[93a] from which the benzocepham carbinol (129; b) could be obtained by oxidative cyclization. A similar cyclization of a penicillin derivative has also been reported.[93b] Complete removal of the thiazolidine ring by borohydride reduction[92] and selective S—C-2 bond cleavage of 2-azetidinones[94] has been described. The use of di-isopropylhydrazine for carboxy-group protection[95] and *o*-nitrobenzoates as protecting groups for penicillin carbinols[96] has been described.



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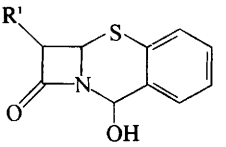


(129)

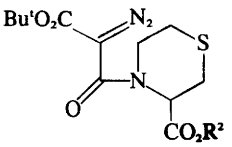
5 Total Synthesis of Penicillins and Cephalosporins

Approaches to the total synthesis of penicillins, cephalosporins, and their analogues continue to be reported, but success in this area has been limited. The efforts of a number of groups have been concentrated on formation of the β-lactam ring either by C-5—C-6(C-6—C-7) bond formation, both photolytically and chemically, or by the addition of a keten or keten precursor to a cyclic imine.

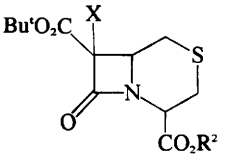
The formation of a fused β-lactam by intramolecular insertion of a suitable carbene was first reported by Corey *et al.* in 1965.[97] By generating such a carbene by photolysis of α-diazo-amides, Lowe and his co-workers have developed a fairly general synthesis of nuclear analogues of the penicillins and cephalosporins.[98,99] Thus, photolysis of the diazomalonate

[90] R. Scartazzini and H. Bickel, *Helv. Chim. Acta*, 1972, **55**, 423.
[91] R. Scartazzini, J. Gosteli, H. Bickel, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 2567.
[92] J. C. Sheehan and C. A. Panetta, *J. Org. Chem.*, 1973, **38**, 940.
[93] (*a*) J. C. Sheehan, H. C. Dalzell, J. M. Greenwood, and D. R. Ponzi, *J. Org. Chem.*, 1974, **39**, 278; (*b*) J. C. Sheehan and J. U. Piper, *ibid.*, 1973, **38**, 3492.
[94] J. C. Sheehan, D. Benishai, and J. U. Piper, *J. Amer. Chem. Soc.*, 1973, **95**, 3064.
[95] D. H. R. Barton, M. Girijavallabhan, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 929.
[96] Dr. H. R. Barton, I. H. Coates, and P. G. Sammes, *J.C.S. Perkin I*, 1973, 599.
[97] E. J. Corey and A. M. Felix, *J. Amer. Chem. Soc.*, 1965, **87**, 2518.
[98] D. M. Burnwin and G. Lowe, *J.C.S. Perkin I*, 1973, 1321; *J.C.S. Chem. Comm.*, 1972, 589.
[99] G. Lowe and M. V. J. Ramsay, *J.C.S. Perkin I*, 1973, 479.

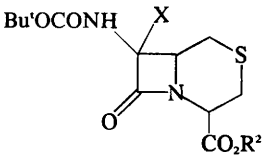
(130; w) gave a mixture of *cis*- and *trans*-β-lactam (131; w).[98] Although Curtius rearrangement of both *cis*- and *trans*-(131; w) gave the undesired *trans*-product (132; w), the corresponding 7α-methyl derivative (133; w) afforded the desired *cis*-β-lactam (134; w). Chlorination–dehydrochlorination introduced the Δ^3 double-bond, affording (135) after deprotection. This 'isocephalosporin' did not possess antibacterial activity.



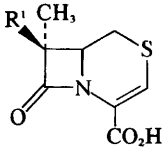
(130)



(131) X = H
(133) X = α-Me

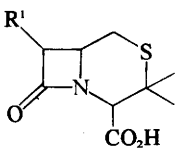


(132) X = β-H
(134) X = α-Me

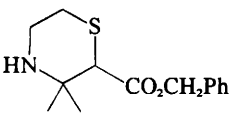


(135)

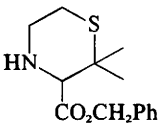
An attempted synthesis of (136) failed when the addition of mercaptoethylamine to benzyl 3,3-dimethyl-2-bromoacrylate gave (137) and not the desired (138).[99] The tetrahydrothiazine (137) was transformed into the cephalosporin analogue (139; c) by the route previously described. The photolysis of diazomalonate has also been used in the synthesis of the oxa-penam



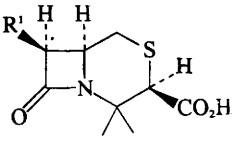
(136)



(137)



(138)

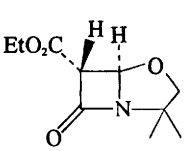


(139)

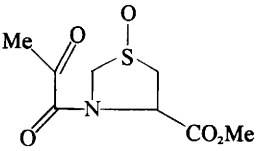
(140); in this case, however, the lability of the ring system precluded further manipulation.[100] The generation of the fused β-lactam (142) by photolysis of the pyruvamide (141) has been reported.[101]

The C-6—C-7 bond in cephalosporins has also been formed by non-photochemical processes. It has been shown that intramolecular attack

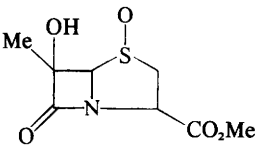
[100] B. T. Golding and D. R. Hall, *J.C.S. Chem. Comm.*, 1973, 293.
[101] K. R. Henery-Logan and C. G. Chen, *Tetrahedron Letters*, 1973, 1103.



(140)

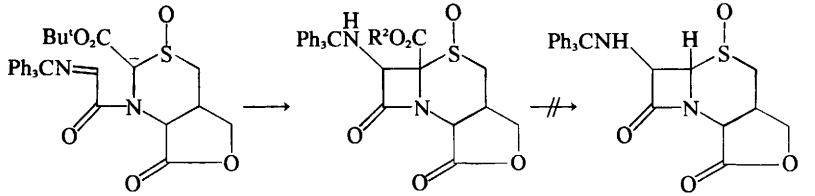


(141)



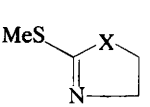
(142)

by a carbanion [*e.g.* (143)] on an *N*-tritylimine α to an amide function results in β-lactam formation.[102] Thus sulphoxide (143) underwent cyclization to β-lactam (144; w) in the presence of potassium t-amylate. Decarboxylation of the corresponding acid (144; z) to (145), however, could not be realized.

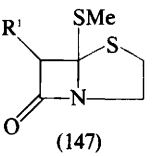


(143) (144) (145)

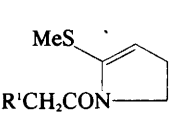
The addition of ketens or keten precursors to cyclic imines to form β-lactams has been known for some time and has been reviewed in two monographs.[103] Using this method, Bose and co-workers were able to synthesize epi-penicillins in very few steps.[103] The addition is successful with thioimidates[104–106] and dithioimidates[107] such as (146), from which (147) can be obtained. However, when imine–enamine tautomerism is possible [*e.g.* (148)], the reaction fails and the acylenamine (149) is formed in



(146) X = S
(148) X = CH_2



(147)

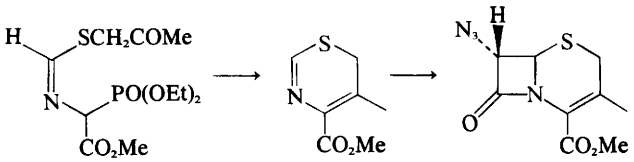


(149)

[102] R. Heymes, G. Amiard, and G. Nomine, *Bull. Soc. chim. France*, 1973, 2343.
[103] M. S. Manhas and A. K. Bose, 'Synthesis of Penicillin, Cephalosporin C and Analogs,' Marcel Dekker, New York, 1969; M. S. Manhas and A. K. Bose, 'β-Lactams, Natural and Synthetic, Part 1,' Wiley–Interscience, New York, 1971.
[104] A. K. Bose and J. L. Fahey, *J. Org. Chem.*, 1974, **39**, 115.
[105] A. K. Bose, J. C. Kapur, B. Dayal, and M. S. Manhas, *J. Org. Chem.*, 1974, **39**, 312; A. K. Bose, H. P. S. Chawla, B. Dayal, and M. S. Manhas, *Tetrahedron Letters*, 1973, 2503; A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *ibid.*, 1972, 2823.
[106] M. D. Bachi and M. Rothfield, *J.C.S. Perkin I*, 1972, 2326; M. D. Bachi and O. Goldberg, *ibid.*, p. 2332; M. D. Bachi and O. Goldberg, *J.C.S. Chem. Comm.*, 1972, 319; R. Lattrell, *Angew. Chem.*, 1973, **85**, 983; M. D. Bachi and K. J. Ross Petersen, *J.C.S. Chem. Comm.*, 1974, 12.
[107] A. K. Bose, J. L. Fahey, and M. S. Manhas, *J. Heterocyclic Chem.*, 1973, **10**, 791.

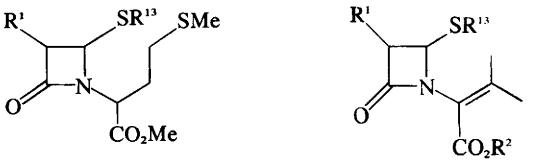
preference to the β-lactam.[104] The use of an *exo*-methylene substituent to block tautomerism has been reported.

The total synthesis of cephalosporins, utilizing a keten addition, has been described.[108] Cyclization of the phosphonate (150) gave the 6*H*-thiazine (151), which on reaction with azidoacetyl chloride–triethylamine afforded the



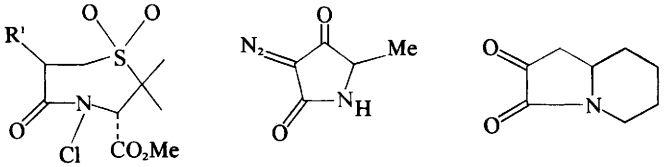
(150) (151) (152)

β-lactam (152). Reduction of the azide to epi-desacetoxycephalosporin and epimerization at C-7 *via* the *p*-nitrobenzaldehyde imine completed the total synthesis of the desacetoxycephalosporin (2; z, $R^1 = NH_2$, X = H). The use of the mixed anhydride of trifluoroacetic and azidoacetic acids in place of the more explosive azidoacetyl chloride in similar β-lactam syntheses has been reported to give comparable yields.[109] Addition of phthalimido- or azido-acetyl chloride to suitable thioimidates gave monocyclic β-lactams (153) and (154), which may serve as intermediates in the synthesis of β-lactam antibiotics.[106]



(153) $R^{13} = CH_2Ph$ or Ph_3C (154)

Other approaches to fused β-lactams have been described. An attempted transannular cyclization of the 1,4-thiazepine sulphone (155; f) to the penicillin ring system failed; the products obtained were those resulting from ring cleavage and elimination.[110] A photolytic Wolff rearrangement of



(155) (156) (157)

[108] R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Letters*, 1973, 4645, 4649, 4653.
[109] A. K. Bose, J. C. Kapur, S. D. Sharma, and M. S. Manhas, *Tetrahedron Letters*, 1973, 2319.
[110] M. H. Benn and R. E. Mitchell, *Canad. J. Chem.*, 1972, **50**, 2195.

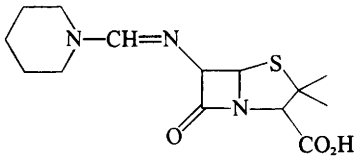
(156)[111] and oxidative ring contraction of the α-keto-amide (157)[112] have been reported to give 3-carboxy-β-lactam derivatives, and these approaches may prove useful in the synthesis of novel antibiotics.

6 Structure–Activity Considerations

Since most of the research in the penicillin–cephalosporin areas has been carried out with the ultimate aim of discovering new, more potent antibiotics, the understanding of the mode of action of these important drugs is of considerable importance. It is generally believed that the β-lactam antibiotics inhibit bacterial cell-wall biosynthesis by irreversibly inhibiting the transpeptidase enzyme responsible for cross-linking of the peptide chains of the peptidoglycan of the cell wall.[113] It has further been proposed that penicillin and cephalosporins exert their action by mimicking the *d*-alanyl-alanine terminus of the peptidoglycan, the normal substrate for the transpeptidase enzyme.[114]

Evidence has been presented which suggests that more than one target site may be involved in *E. coli* bacteria,[115] and that for *B. subtilis* the binding of penicillin to a particulate transpeptidase enzyme preparation may occur through formation of a thiolester.[116] The intimate details of this inhibition are still unclear, although acylation by the β-lactam appears to play an important role. Extended Hückel and CNDO/2 calculations have been used in obtaining a correlation between biological activity and certain aspects of the electronic structure of the β-lactam ring.[117] Electron populations, not atomic charges and bond strengths of the C—N bond, correlate with observed antibacterial activity. Comparisons of hydrolysis rates with enzyme inhibition rates have been attempted, with limited success, for 7-substituted cephalosporins.[118] The problem of the mode of action of the β-lactam antibiotics has become more confused with the discovery that the semisynthetic penicillin (158)[119] blocks cell-wall biosynthesis but does not inhibit murein transpeptidase, D-alanine carboxypeptidase, or murein endopeptidase, as do other penicillins.[120] Thus this penicillin possesses a new, unique, and as yet unknown, mode of action.

[111] G. Lowe and D. D. Ridley, *J.C.S. Chem. Comm.*, 1973, 328; G. Lowe and D. D. Ridley, *J.C.S. Perkin I*, 1973, 2024; G. Lowe and H. Wing Yeung, *ibid.*, p. 2907.
[112] D. R. Bender, L. F. Bjeldanes, D. R. Knapp, D. R. McKean, and H. Rapoport, *J. Org. Chem.*, 1973, **38**, 3439.
[113] J. L. Strominger, P. M. Blumberg, H. Suginaka, J. Umbreit, and G. G. Wickus, *Proc. Roy. Soc.*, 1971, **B179**, 369; V. Lorian, *Arch. Internat. Med.*, 1971, **128**, 623; J. L. Strominger, *Harvey Lectures*, 1970, **64**, 179.
[114] D. J. Tipper and J. L. Strominger, *Proc. Nat. Acad. Sci. U.S.A.*, 1965, **54**, 1133.
[115] R. Hartmann, J. U. Höltje, and U. Schwarz, *Nature*, 1972, **235**, 426.
[116] P. J. Lawrence and J. L. Strominger, *J. Biol. Chem.*, 1970, **245**, 3653.
[117] R. B. Hermann, *J. Antibiotics*, 1973, **26**, 223; D. B. Boyd, *J. Medicin. Chem.*, 1973, **16**, 1195; *J. Amer. Chem. Soc.*, 1972, **94**, 6513.
[118] P. P. K. Ho, R. D. Towner, J. M. Indelicato, W. J. Wilham, W. A. Spitzer, and G. A. Koppel, *J. Antibiotics*, 1973, **26**, 313.
[119] F. Lund and L. Tybring, *Nature New Biol.*, 1972, **236**, 135.
[120] J. T. Park and L. Burman, *Biochem. Biophys. Res. Comm.*, 1973, **51**, 863.



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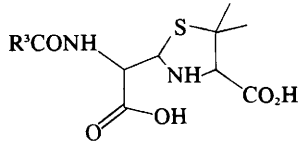
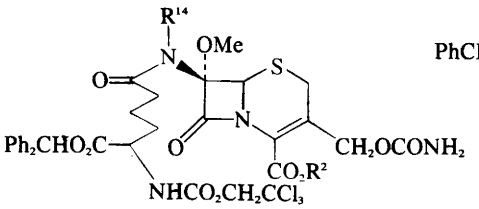


(159)

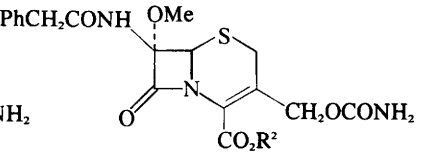
In the absence of greater understanding of the mode of action of the β-lactam antibiotics, the generation of structure–activity data has remained one of trial and error. Cycloaddition of acetylenes to the azide of 7-acylamido-3-azidomethylcephalosporanic acids afforded a series of 3-(1,2,3-triazol-1-ylmethyl)cephalosporanic acids[121] while the syntheses of 7-mandeloylaminocephalosporins,[122] 6-thioacylamino-,[123] α-sulpho-,[124] 6-amidino-,[125] cyanoamidino-,[126] and levomycetin adipinyl-pencillins[127] have been described in publications.

Imidazole-catalysed hydrolysis of benzylpenicillin to a penicilloic acid (159) has been described.[128] The analogous alcoholysis or amidation, also catalysed by imidazole *in vitro*, has been implicated in penicillin allergy.[128a]

The ability of some micro-organisms to synthesize semi-synthetic penicillins from 6-aminopenicillin is well recognized, but no micro-organisms have been observed to perform similar syntheses on cephalosporins. However, enzymatic coupling of 7-aminocephalosporins with amino-acid esters has been described.[129] The enzyme utilized was derived from *Pseudomonadacea*



(160) $R^{14} = H$
(161) $R^{14} = PhCH_2CO$

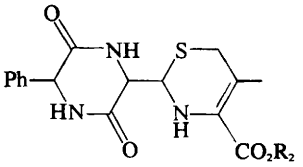


(162)

[121] D. Willner, A. M. Jelenevsky, and L. C. Cheney, *J. Medicin. Chem.*, 1972, **15**, 948.
[122] J. R. E. Hoover, G. L. Dunn, D. R. Jakas, L. L. Lam, J. J. Taggart, J. R. Guarini, and L. Phillips, *J. Medicin. Chem.*, 1974, **17**, 34.
[123] A. Winther and A. Senning, *Acta Chem. Scand.*, 1973, **27**, 1456.
[124] S. Morimoto, H. Nomura, T. Fugono, I. Minami, and T. Ishiguro, *J. Antibiotics*, 1973, **26**, 146; S. Morimoto, H. Nomura, T. Ishiguro, T. Fugono, and K. Maeda, *J. Medicin. Chem.*, 1972, **15**, 1105.
[125] I. Buskooszczapowicz and J. Cieslak, *Acta. Polon. Pharm.*, 1973, **30**, 43.
[126] H. J. Petersen, *J. Medicin. Chem.*, 1974, **17**, 101.
[127] L. B. Sokolov, K. M. Nichugovskaya, M. S. Polyak, and M. P. Karpenko, *Antibiotiki*, 1972, **17**, 1075.
[128] H. Bundgaard, *J. Pharm. Pharmacol.*, 1972, **24**, 985.
[128] [a] B. B. Levine and Z. Ovary, *J. Exp. Med.*, 1961, **144**, 875; A. L. deWeck, *Internat. Arch. Allergy Appl. Immunol.*, 1963, **22**, 245.
[129] T. Takahashi, Y. Yamazaki, K. Kato, and M. Isono, *J. Amer. Chem. Soc.*, 1972, **94**, 1435.

and the overall yields were good. Enzymatic oxidation of the free amino-group on the side-chain of cephalosporin C (2; z, X = OAc) has also been described.[130] The replacement of the aminoadipyl side-chain of the cephamycins has been accomplished by a novel exchange reaction.[131] Acylation of the trichloroethyl carbamate derivative (160; u) gave the imide (161; u), which on zinc–acetic acid cleavage afforded the acylated cephamycin (162; u); benzhydryl 2-piperidone-6-carboxylate was the by-product. The utility of acetyl mixed anhydride as carboxy-group protection during 7-acylamido cleavage of cephalosporins has been described.[132] The synthesis of cephaprin (2; z, R^1 = 4-pyridyl-SCH_2CONH) has been reported,[133] as has a new procedure for the synthesis of 7-phthalimido-8-t-butoxy-5,8-seco-desacetylcephalosporanic acid lactone, a key intermediate in the synthesis of cephalosporins.[134]

Intramolecular ring opening of β-lactams has been described. Piperazine-2,5-dione (163; v) was obtained by cyclization of a 7α-aminophenylacetamido-Δ^3-cephalosporin; the analogous penicillin ring-opening does not occur because of steric hindrance.[135] Intramolecular rearrangement of 6-phenylureido-penicillin (1; z, R^1 = PhNHCONH) occurred readily, affording the hydantoin (164).[136]



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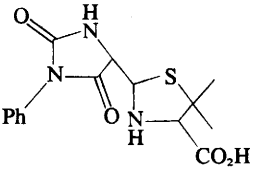
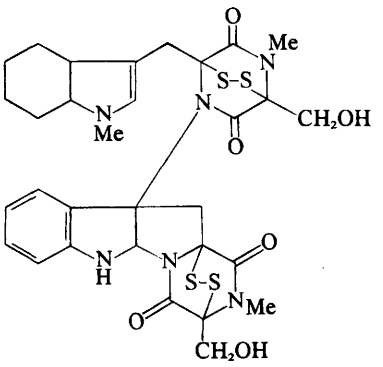


(164)

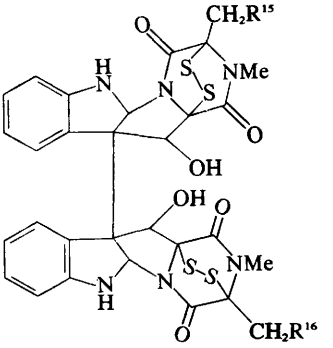
7 Epidithiodioxopiperazines

The epidithiodioxopiperazine structure is a common functionality in a growing series of natural products of the gliotoxin–sporidesmin class, several members of which possess antibacterial, antiviral, and cytotoxic activity. Several new epidithiodioxopiperazines have been reported: chetomin (165),[137] verticillins A (166) and B (167),[138] dihydroxychaetocin (168),[139]

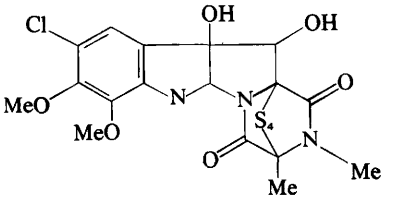
[130] P. Mazzeo and A. Romeo, *J.C.S. Perkin I*, 1972, 2532.
[131] A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, *J. Amer. Chem. Soc.*, 1972, **94**, 1410.
[132] R. R. Chauvette, H. B. Hayes, G. L. Huff, and P. A. Pennington, *J. Antibiot. Tokyo*, 1972, **25**, 248.
[133] L. B. Crast, R. G. Graham, and L. C. Cheney, *J. Medicin. Chem.*, 1973, **16**, 1413.
[134] N. N. Girotra and N. L. Wendler, *Tetrahedron Letters*, 1972, 5301.
[135] J. M. Indelicato, T. T. Norvilas, and W. J. Wheeler, *J.C.S. Chem. Comm.*, 1972, 1162.
[136] H. Bundgaard, *Acta Pharm. Suecica*, 1973, **10**, 309.
[137] S. Safe and A. Taylor, *J.C.S. Perkin I*, 1972, 472.
[138] H. Minato, M. Matsumoto, and T. Katayama, *J.C.S. Perkin I*, 1973, 1819.
[139] D. Hauser, H. R. Loosli, and P. Niklaus, *Helv. Chim. Acta*, 1972, **55**, 2182.



(165)



(166) $R^{15} = R^{16} = H$
(167) $R^{15} = H, R^{16} = OH$
(168) $R^{15} = R^{16} = OH$

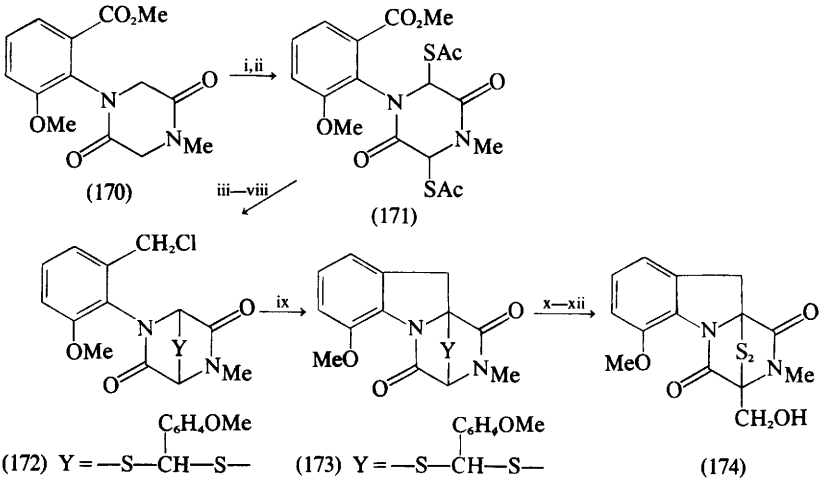


(169)

the tetrasulphide sporidesmin G (169),[140] and four compounds of undetermined structure, *viz.* Melinacidins II–IV[141] and verticillin C.[138]

Considerable effort has been expended on the total synthesis of this novel class of compounds. Functionalization of diketopiperazines has been accomplished in general by oxidative methods; lead tetra-acetate,[142] peroxides,[143] and NBS[144,145] have been employed for this purpose. Thus, oxidative acetoxylation of (170) followed by its reaction with thiolacetic acid and hydrolysis of the bis-thiolester yielded the bis-thiol (171) (Scheme 5).[144,146] Lithiation of the anisaldehyde adduct (172) derived from (171) effected cyclization to the dehydrogliotoxin nucleus. Methoxymethylation of (173) followed by oxidative degradation of the dithioketal to the disulphide and subsequent cleavage by boron trichloride of the methyl ether completed

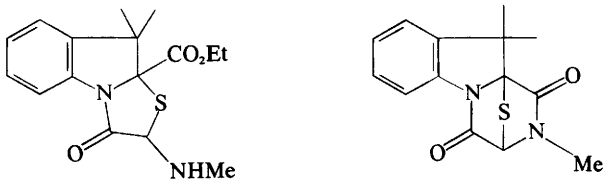
[140] E. Francis, R. Rahman, S. Safe, and A. Taylor, *J.C.S. Perkin I*, 1972, 470.
[141] A. D. Argoudelis, *J. Antibiot. Tokyo*, 1972, **25**, 171.
[142] E. Ohler, F. Tataruch, and U. Schmidt, *Chem. Ber.*, 1973, **106**, 396.
[143] E. Ohler, F. Tataruch, and U. Schmidt, *Chem. Ber.*, 1973, **106**, 165.
[144] Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, 1973, **95**, 6492.
[145] Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *J. Amer. Chem. Soc.*, 1973, **95**, 6493.
[146] Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, 1973, **95**, 6490.



Reagents: i, NBS–benzoyl peroxide; ii, CH_3COSK; iii, HCl; iv, *p*-$MeOC_6H_4CHO$–BF_3; v, NaOH; vi, *NN'*-carbonyldi-imidazole; vii, $LiBH_4$, 0 °C; viii, $(C_8H_{18})_3P$–CCl_4; ix, BuLi, AcOH; x, BuLi–$MeOCH_2Cl$; xi, *m*-$ClC_6H_4CO_3H$; xii, BCl_3.

Scheme 5

the first total synthesis of dehydrogliotoxin (174). The total synthesis of sporidesmin A by an analogous route has been described.[145] An alternative synthesis of dehydrogliotoxin failed when the desired cyclization of (175) to (176) could not be realized.[147]

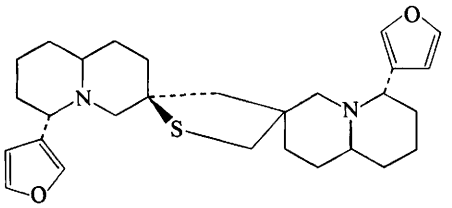


(175) (176)

8 Other Sulphur-containing Natural Products

In addition to β-lactam antibiotics and epidithiodioxopiperazines, investigations of several other sulphur-containing natural products have been reported. The three-dimensional structure of thiobinupharidine (177) has been proposed on the basis of chemical and spectroscopic evidence.[148] A new alkaloid, isolated from *Nuphar luteum*, was shown to be the closely related neothiobinupharidine sulphoxide (178).[149] Four new plant-growth

[147] H. C. Ottenheym, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, 1973, **95**, 1989.
[148] R. T. Lalonde, C. F. Wong, and K. C. Das, *J. Amer. Chem. Soc.*, 1973, **95**, 6342.
[149] J. T. Wrobel, A. Iwanow, J. Szychowski, J. Poplawski, C. K. Yu, T. I. Martin, and D. B. Maclean, *Canad. J. Chem.*, 1972, **50**, 1968.



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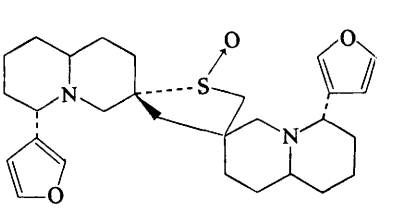

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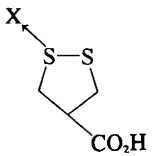
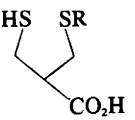
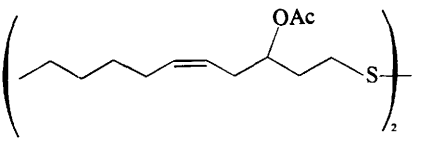


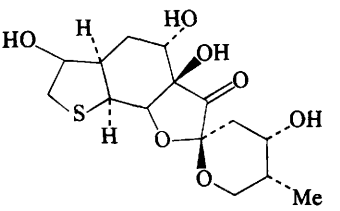
(179) X = :
(180) X = O



(181) R = H
(182) R = COMe



(183)



(184)

inhibitors isolated from etiolated *Asparagus officinalis* have been identified as asparagusic acid (179), the *S*-oxide (180), dihydroasparagusic acid (181), and the *S*-acetyl derivative (182).[150,151] Disulphide (183), isolated from a Hawaiian *Dictyopteris* species, was suggested as a precursor of undeca-1,3,5-trienes found in natural essential oils.[152] The structure of a degradation product, breynolide (184), of the natural product breynin A was elucidated by *X*-ray techniques.[153]

[150] H. Yanagawa, T. Kato, Y. Kitahara, N. Takahashi, and Y. Kato, *Tetrahedron Letters*, 1972, 2549.
[151] H. Yanagawa, T. Kato, and Y. Kitahara, *Tetrahedron Letters*, 1973, 1073.
[152] R. E. Moore, J. Mistysyn, and J. A. Pettus jun., *J.C.S. Chem. Comm.*, 1972, 326.
[153] K. Sasaki and Y. Hirata, *Tetrahedron Letters*, 1973, 2439.

5
Thiocarbonyl and Selenocarbonyl Compounds

BY F. DUUS

1 Introduction

More than one thousand papers dealing with the chemistry of thiocarbonyl compounds have appeared during the two-year period under consideration. In order to comply with the requirements of a secure coverage of this comprehensive material within the permitted limits of space, this chapter has been worked out in a more compressed form than in the preceding volumes. Thus selenocarbonyl compounds are here treated together with their sulphur analogues instead of being reviewed in a separate section. In the opinion of the Reporter, this Report should preferentially deal with generation, reactivity, and physical properties of the thiocarbonyl function as such rather than of the compounds containing this function. Papers reporting on known thiocarbonyl compounds, in which the thiocarbonyl function plays no part in reactions or has no special interest for structural and physical reasons, are, therefore, generally not included in the collection of references. Apart from a small change in the organization of the material, this chapter otherwise follows the lay-out of the corresponding chapters in the foregoing volumes, which also may be consulted as the natural background for the present review.

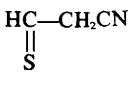
Reviews.—Two papers, surveying the progress in the chemistry of simple aliphatic[1] and aromatic[2] thioketones during the period 1964—1972, have appeared recently. Two other comprehensive reviews deal with the chemistry of thiocarbonyl halides[3] and the synthesis of *N*-substituted thioureas.[4] Synthesis, co-ordination chemistry, and analytical application of monothio-β-diketones,[5] synthesis and properties of transition-metal

[1] D. Paquer, *Internat. J. Sulfur Chem.* (*B*), 1972, **7**, 269.
[2] D. Paquer, *Internat. J. Sulfur Chem.*, 1973, **8**, 173.
[3] K. T. Potts and C. Sapino, 'The Chemistry of Acyl Halides', ed. S. Patai, Interscience, London, 1972, p. 349.
[4] V. Mozolis and S. Jokubaityte, *Uspekhi Khim.*, 1973, **42**, 1310.
[5] E. Uhlemann, H. Müller, and P. Thomas, *Z. Chem.*, 1971, **11**, 401.

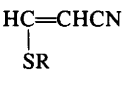
dithio-β-diketonates,[6] the chemistry of 2-indolinethiones,[7,8] α-ureidoalkylation of thioureas,[9] the chemistry of *N*-hydroxy-derivatives of thiourea,[10] the chemistry of dithiocarboxylic acids,[11] and sulphenes as chemical intermediates[12] are the subjects of more specialized recent papers. A broader spectrum of thiocarbonyl compounds are treated in reviews on thione—enethiol tautomerism[13,14] and alkylation reactions of organic sulphur compounds.[15] An interesting paper by Mayer and Wittig[16] reports on the coherence between taste and chemical constitution of thiocarbonyl compounds.

2 Thioaldehydes

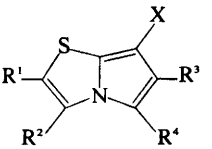
Synthesis.—The condensation of acetonitrile with ethyl thionoformate by means of butyl-lithium has been reported to yield thioformylacetonitrile (1) after subsequent treatment of the intermediate lithium salt (2) with hydrochloric acid.[17] The thioaldehyde could not be isolated, but it was reasonably stable in solution in the tautomeric enethiol form (3), and was characterized as its stable *S*-methyl derivative (4).[17] Several new, stable thioaldehydes, (5) and (6), have been synthesized by solvolysis of the Vilsmeier salts (7) and (8) with aqueous sodium hydrogen sulphide.[18] Some deuteriated analogues of (6) were similarly prepared from the corresponding salts (9).[18] The thioaldehydes (10) were isolated as amorphous solids from the cycloaddition reaction of 1,2-dithiole-3-thione with propiolic acid or its



(1)

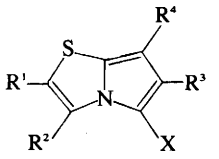


(2) R = Li
(3) R = H
(4) R = Me

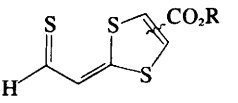


(5) X = CHS
(7) X = $CH\overset{+}{N}Me_2\ \bar{P}O_2Cl_2$

[6] S. W. Schneller, *Internat. J. Sulfur Chem.* (*B*), 1972, **7**, 295.
[7] T. Hino, *Internat. J. Sulfur Chem.* (*B*), 1972, **7**, 217.
[8] T. Hino and M. Nakagawa, *Yuki Gosei Kagaku Kyokai Shi*, 1972, **30**, 603.
[9] H. Petersen, *Synthesis*, 1973, 2433.
[10] G. Voss and E. Fischer, *Wiss. Z. Univ. Rostock, Math.-Naturwiss. Reihe*, 1972, **21**, 123 (*Chem. Abs.*, 1973, **79**, 31 387).
[11] S. Oae, T. Yagihara, and A. Nakanishi, *Kagaku* (*Kyoto*), 1972, **27**, 589, 673.
[12] T. Nagai and N. Tokura, *Internat. J. Sulfur Chem.* (*B*), 1972, **7**, 207.
[13] R. Mayer, 'Sulphur in Organic and Inorganic Chemistry', ed. A. Senning, Marcel Dekker, New York, 1972, Vol. 3, p. 325.
[14] A. I. Kol'tsov and G. M. Kheifets, *Uspekhi Khim.*, 1971, **40**, 1646.
[15] T. Oishi and M. Mori, *Internat. J. Sulfur Chem.* (*B*), 1972, **7**, 225.
[16] R. Mayer and F. Wittig, *Z. Chem.*, 1972, **12**, 91.
[17] K. Hartke and O. Günther, *Annalen*, 1973, 1637.
[18] R. K. Mackie, S. McKenzie, D. H. Reid, and R. G. Webster, *J.C.S. Perkin I*, 1973, 657.

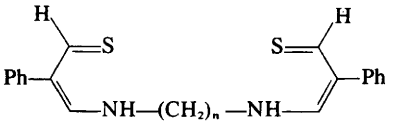


(6) X = CHS
(8) X = $CH\overset{+}{N}Me_2\ \bar{P}O_2Cl_2$
(9) X = $CD\overset{+}{N}Me_2\ \bar{P}O_2Cl_2$

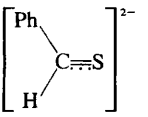


(10) R = H or Me

methyl ester.[19] A convenient synthetic route to tetra-aza macrocyclic compounds involved the apparently stable thioaldehydes (11) as precursors.[20] The lithium salt of toluene-α-thiol reacted with butyl-lithium at −5 °C in THF–pentane surroundings, affording an orange suspension of the thiobenzaldehyde dianion (12).[21] The dianion was reactive towards a variety of electrophiles (E), yielding adducts (13) or (14) depending on the molar ratios between the reactants.[21]



(11) $n = 2$ or 3



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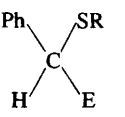


(13) R = H
(14) R = E

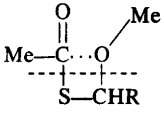
Transient Species.—The formation of seven different products by the photolysis reaction of *S*-(*cis*-prop-1-enyl)-L-cysteine was explained by assuming different reaction courses of a common precursor, the initially formed radical (15).[22] The transient existence of (15) was supported by e.s.r.

$$Me—\dot{C}H—CH=S \leftrightarrow Me—CH=CH—\dot{S}$$

(15)

evidence.[22] Attempts to recrystallize monosubstituted *sym*-trithians resulted in the formation of a mixture of un-, mono-, di-, and tri-substituted *sym*-trithians.[23] The authors explained this observation by the occurrence of an initial dissociation of the starting trithian into monomeric thials that subsequently trimerized rapidly in different combinations.[23] Vapour-phase thermolysis of *S*-methoxymethyl thioacetates gave, apparently *via* the four-centred transition state (16), methyl acetate and a thial RCHS.[24] The latter was identified by mass spectrometric analysis of the outlet from the

[19] H. Davy and J. Vialle, *Compt. rend.*, 1972, **275**, *C*, 625.
[20] S. C. Tang, G. N. Weinstein, and R. H. Holm, *J. Amer. Chem. Soc.*, 1973, **95**, 613.
[21] D. Seebach and K.-H. Geiss, *Angew. Chem.*, 1974, **86**, 202.
[22] H. Nishimura, T. Hanzawa, and J. Mizutani, *Tetrahedron Letters*, 1973, 343.
[23] D. Seebach, E. J. Corey, and A. K. Beck, *Chem.Ber.*, 1974, **107**, 367.
[24] P. C. Oele and R. Louw, *J.C.S. Chem. Comm.*, 1972, 848.



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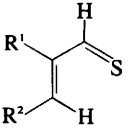

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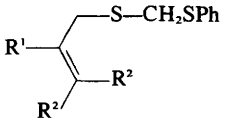
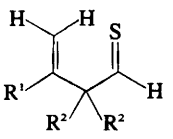


(18)

katharometer system. The spontaneous, thermal decomposition of some 3,4-disubstituted thiets was found to be initiated by ring-opening to the $\alpha\beta$-unsaturated thioaldehydes (17), which, however, polymerized rapidly.[25] The reaction of dithioacetals (18) with lithium di-isopropylamide was interpreted in terms of intermediate $\beta\gamma$-unsaturated thials (19).[26] Thioformaldehyde appeared as a primary product in the photodecomposition of thietan vapour.[27] By means of ion–cyclotron resonance spectroscopy it was shown[28] that the fragment corresponding to the base peak at m/e 60 in the mass spectrum of pentyl thiovinyl ether has the thioacetaldehyde structure (20), when hydrogen transfer occurs from position 2 of the pentyl chain. Hydrogen transfer from positions 3 and 4 leads to $C_2H_4S^+$ ions possessing the vinylthiol structure (21).[28]



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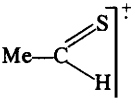

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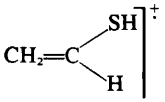


(21)

Reactions.—The conversion of thials of the structure (10) into 1,6,6a-S^{IV}-trithiapentalenes by means of phosphorus pentasulphide is well known. However, Davy and Vialle have now reported[19] that thioacetamide may also effect this conversion. Reaction of the thials (11) with ethylenediamine or trimethylenediamine yielded tetra-aza macrocyclic compounds.[20]

3 Thioketones and Selenoketones

Synthesis.—A traditional route to particularly non-enethiolizable thiotekones is based on the reaction of the corresponding ketones with phosphorus pentasulphide in boiling aromatic hydrocarbons. Assuming a very polar intermediate in this reaction, Scheeren and his co-workers[29] suggested the advantageous application of more polar solvents such as acetonitrile, THF, and diglyme. Their experiments actually revealed a much

[25] D. C. Dittmer, P. L.-F. Chang, F. A. Davis, M. Iwanami, I. K. Stamos, and K. Takahashi, *J. Org. Chem.*, 1972, **37**, 1111.

[26] S. Julia, V. Ratovelomanana, and C. Huynh, *Compt. rend.*, 1974, **278**, *C*, 371.

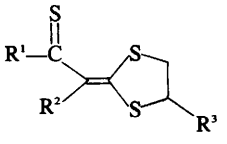
[27] D. R. Dice and R. P. Steer, *J. Phys. Chem.*, 1973, **77**, 434.

[28] K. B. Tomer and C. Djerassi, *J. Amer. Chem. Soc.*, 1973, **95**, 5335.

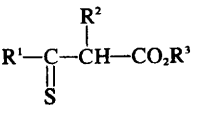
[29] J. W. Scheeren, P. H. J. Ooms, and R. J. F. Nivard, *Synthesis*, 1973, 149.

faster conversion rate, and also that the thioketones thus prepared were obtained in excellent yields.[29] Several other papers[30–33] report on the successful application of this reaction under the traditional conditions. The thioketones (22) and (23) could be isolated as products in the reaction of the corresponding ketones with phosphorus pentasulphide under exceptionally mild conditions,[34] but they rearranged easily with elimination of ethylene and 1,3-butadiene, respectively, to 1,2-dithiole-3-thiones, the products obtained under the normal conditions.[34] The action of phosphorus pentasulphide on β-diketones in the presence of iodine or perchloric acid generally led to 1,2-dithiolylium salts,[35–37] which were also obtained using hydrogen disulphide as the thionation agent.[35–37] Oae and his co-workers introduced recently *OO*-diethyl dithiophosphonic acid as a thionation agent, but their experiments showed that the reaction course was very dependent on the starting ketone.[38] Thus aromatic ketones yielded the corresponding thioketones, whereas cyclohexanone and benzaldehyde under similar conditions gave 1,3-dithietans.[38]

Aliphatic thioketones are normally most conveniently synthesized by the action of hydrogen sulphide on the parent ketone in acidic surroundings. However, a well-defined reaction course may depend strictly on the reaction conditions, as also demonstrated recently in an investigation[39] of the acid-catalysed reaction of β-ketoesters with hydrogen sulphide. The α-substituted β-thioxo-esters (24) were particularly difficult to obtain owing to the great tendency of these compounds to add a further hydrogen sulphide molecule to form *gem*-dithiols.[39] In acidic reaction medium the α-unsubstituted β-thioxo-esters (24; $R^2 = H$) rapidly tautomerize into the more stable enethiol form (25; $R^2 = H$) containing an intramolecular hydrogen bond, but this possibility of stabilization is reduced for the



(22) $R^3 = H$
(23) $R^3 = CHCH_2$



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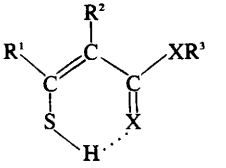


(25) X = O
(26) X = S; R^1 = *p*-$MeOC_6H_4$; $R^2 = H$; R^3 = Me or Et

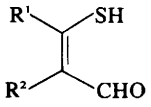
[30] J. Daunis, M. Guerret-Rigail, and R. Jacquier, *Bull. Soc. chim. France*, 1972, 3198.
[31] F. Eiden and D. Döcher, *Arch. Pharm.*, 1972, **305**, 691.
[32] S. Carboni, A. Da Settimo, D. Bertini, P. L. Ferrarini, O. Livi, and I. Tonetti, *J. Heterocyclic Chem.*, 1972, **9**, 801.
[33] F. Clesse, J.-P. Pradere, and H. Quiniou, *Bull. Soc. chim. France*, 1973, 586.
[34] J. Maignan and J. Vialle, *Bull. Soc. chim. France*, 1973, 2388.
[35] D. Barillier, C. Gy, P. Rioult, and J. Vialle, *Bull. Soc. chim. France*, 1973, 277.
[36] D. Barillier, P. Rioult, and J. Vialle, *Bull. Soc. chim. France*, 1973, 3031.
[37] J. P. Guemas and H. Quiniou, *Bull. Soc. chim. France*, 1973, 592.
[38] S. Oae, A. Nakanishi, and N. Tsujimoto, *Chem. and Ind.*, 1972, 575.
[39] F. Duus, *Tetrahedron*, 1972, **28**, 5923.

α-substituted compounds owing to the crowding in (25; $R^2 = H$). The 3-mercapto-3-(*p*-methoxyphenyl)propenoic dithioesters (26) have been synthesized by treatment of the analogous 3-hydroxy-compounds with hydrogen sulphide and dry hydrogen chloride.[40] The compounds (26) were isolated as rather unstable, red crystals, but were not characterized otherwise. The hydrogen sulphide method has been used for the synthesis of new thioacyl cycloalkanes,[41] 2-cycloalkenethiones,[42] and monothio-β-diketones.[43,44] The action of hydrogen sulphide on β-diketones in the presence of iodine afforded, however, 1,2-dithiolylium salts.[45] The reaction of benzophenone anil with hydrogen sulphide gave thiobenzophenone.[46]

A method of choice for the generation of a thiocarbonyl group is to treat the corresponding vinylic chloride with a suitable thionating agent such as sodium sulphide or sodium hydrogen sulphide. Several papers, reporting on the application of this method, have appeared.[47-51] Thus Weissenfels and Pulst were able to synthesize a great number of novel β-thioxo-aldehydes by treatment of the appropriate β-chlorovinyl aldehydes with sodium sulphide in aqueous media.[49-51] The products, which predominantly exist in the enethiol form (27), were not in all cases stable enough to be isolated. β-Mercaptocinnamic aldehyde (27; $R^2 = H$), for example, was characterized both as its nickel(II) complex and as its dimer.[50] Some enamino-thioketones (28) were synthesized by the reaction of the corresponding β-chlorovinyl methineimmonium salts (29) with sodium sulphide.[52] Yoshida and his co-workers obtained the diaminocyclopropenethiones (30) as white, crystalline solids in high yields by treatment of the cyclopropenium salts (31) and (32) with sodium sulphide in methanol.[53,54] 3-Bromo-4-chloro-6,7-dimethoxycinnoline reacted with thiourea to form the thione (33), whereas its reaction with phenylthiourea afforded a thiazolocinnoline derivative.[55]

With the intention of preparing nitriles from primary thioamides, Fujita and his co-workers allowed several of the latter type of compounds to react with *NN'*-dialkyl phenylpropiolamidines, and they obtained, besides the

[40] J. Maignan and J. Vialle, *Bull. Soc. chim. France*, 1973, 1973.
[41] D. Paquer and J. Vialle, *Compt. rend.*, 1972, **274**, *C*, 1846.
[42] P. Metzner and J. Vialle, *Bull. Soc. chim. France*, 1972, 3138.
[43] R. Belcher, W. I. Stephen, I. J. Thomson, and P. C. Uden, *J. Inorg. Nuclear Chem.*, 1972, **34**, 1017.
[44] R. C. Burton and T. R. Sweet, *Analyt. Chim. Acta*, 1973, **64**, 273,
[45] A. R. Hendrickson and R. L. Martin, *J. Org. Chem.* 1973, **38**, 2548.
[46] M. M. Campbell and D. M. Evgenios, *J.C.S. Perkin I*, 1973, 2862.
[47] R. Pinel and Y. Mollier, *Bull. Soc. chim. France*, 1973, 608.
[48] C. Temple, B. H. Smith, and J. A. Montgomery, *J. Org. Chem.*, 1972, **37**, 3601.
[49] M. Weissenfels and M. Pulst, *Tetrahedron*, 1972, **28**, 5197.
[50] M. Pulst, M. Weissenfels, and L. Beyer, *Z. Chem.*, 1973, **13**, 287.
[51] M. Weissenfels and M. Pulst, *J. prakt. Chem.*, 1973, **315**, 873.
[52] J. Liebscher and H. Hartmann, *Z. Chem.*, 1972, **12**, 417.
[53] Z. Yoshida, H. Konishi, Y. Tawara, and H. Ogoshi, *J. Amer. Chem. Soc.*, 1973, **95**, 3043.
[54] Z. Yoshida, H. Konishi, Y. Tawara, K. Nishikawa, and H. Ogoshi, *Tetrahedron Letters*, 1973, 2619.
[55] A. N. Kaushal and K. S. Narang, *Indian J. Chem.*, 1972, **10**, 675.



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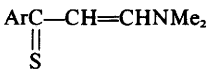

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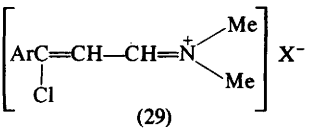

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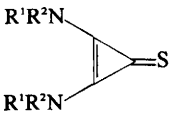

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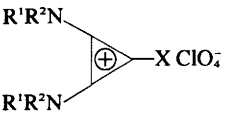
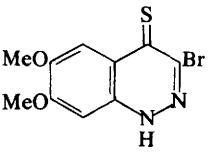


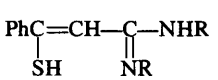
(31) X = Cl
(32) X = NMePh



(33)

desired nitriles, the β-mercaptocinnamamidines (34).[56] The latter compounds were also by-products in a similar reaction between *NN'*-dialkyl phenylpropiolamidines and *N*-substituted dithiocarbamates, affording isothiocyanates as the main products.[57]

A recent, important paper[58] by Raasch describes bis(trifluoromethyl)thioketen as an effective thioacylating agent. Thus the thioketen was added to bicyclobutane, yielding as a primary product the enethiol (35), which, however, within 16 minutes rearranged completely into the thione (36). Vinylogues of thioamides were obtained[58] by addition of the thioketen to indole [affording, as an example, (37)], 1,3,3-trimethyl-2-methyleneindoline, and 6-(dimethylamino)fulvene, respectively. The base-promoted condensation reactions of thiono- or dithio-esters with acetonitrile,[17] the diethyl ester of cyanomethanephosphonic acid,[59] and CH acidic thioamides[60] resulted in formation of the expected products (38), (39), and (40), respectively. Several of these products were, however, isolated as their *S*-methyl derivatives because of their instability. Two papers report on



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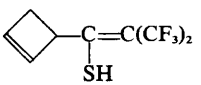

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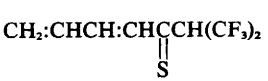

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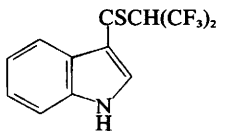

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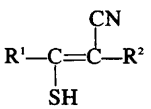
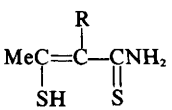


(38) $R^2 = H$
(39) $R^2 = PO(OEt)_2$

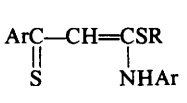


(40) R = CN or CO_2R^1

[56] H. Fujita, R. Endo, and K. Murayama, *Bull. Chem. Soc. Japan*, 1972, **45**, 1582.
[57] H. Fujita, R. Endo, and K. Murayama, *Chem. Letters*, 1973, 883.
[58] M. S. Raasch, *J. Org. Chem.*, 1972, **37**, 1347.
[59] K. Hartke and O. Günther, *Arch. Pharm.*, 1974, **307**, 144.
[60] F. Meissner and K. Hartke, *Arch. Pharm.*, 1972, **305**, 902.

the preparation of ethyl thioaceto-thionoacetate by base-promoted self-condensation of ethyl thionoacetate.[39,61]

Several sulphur-containing heterocyclic compounds have been found convertible into thioketones by appropriate ring-opening reactions. Thus *N*-(5-aryl-3*H*-1,2-dithiole-3-ylidene)arylamines reacted with Grignard reagents with cleavage of the S—S bond to give the thiones (41).[62] The thiones (42) were the products in the reaction of 2-phenyl-4*H*-3,1-benzothiazine-4-thione with aromatic hydrocarbons under Friedel–Crafts conditions.[63] Sykes and Ullah treated[64] some isothiazolium salts (43) with benzylamine or aniline and obtained as products the enamino-thioketones (44). The salts (43) were, however, quite unreactive towards a variety of compounds containing the thiolo-group, with the exception of thiophenol, which reacted to form (45).[64] The facts that no benzenethiolate residue was incorporated into the product and that diphenyl disulphide was formed as a by-product suggested to the authors that the latter reaction is a reduction rather than being due to an initial nucleophilic attack of thiophenol.[64] The action of methylamine on the isothiazolium salts (46) yielded the thiones (47) in only few cases, and then only as by-products—the main product was usually a 6a-thia-1,6-diazapentalene.[65] The enethiols (48) were the products in a



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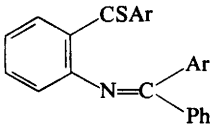

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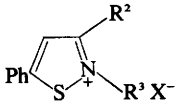

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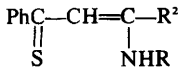
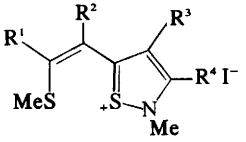


(44) R = Ph, $PhCH_2$

(45) $R = R^3$ [in (43)]



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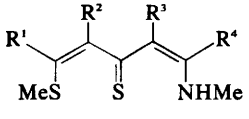

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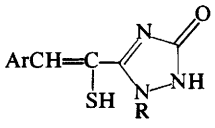


(48)

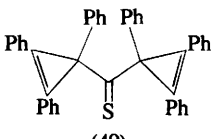
[61] A. R. Hendrickson and R. L. Martin, *Austral. J. Chem.*, 1972, **25**, 257.
[62] F. Boberg and W. von Gentzkow, *Annalen*, 1973, 247.
[63] A. Sammour, M. I. Selim, A. F. M. Fahmy, and K. Elewa, *Indian J. Chem.*, 1973, **11**, 437.
[64] P. Sykes and H. Ullah, *J.C.S. Perkin I*, 1972, 2305.
[65] A. S. Ingram, D. H. Reid, and J. D. Symon, *J.C.S. Perkin I*, 1974, 242.

recyclization reaction of 5-arylidene-1,3-thiazolidin-2-ones with hydrazines.[66]

Several papers report on the synthesis of interesting thioketones by less common routes. Trost and his co-workers isolated bis-(1,2,3-triphenylcyclopropenyl) thioketone (49) from the reaction mixture resulting from the addition of thiophenylcyclopropenium bromide to a solution of dimethylsulphonium methylide in THF.[67] The thione (50) was obtained as a by-product in the reaction of phenylacetonitrile with diethyl sulphite (affording 4,5-diphenylisothiazol-3-ol as the main product).[68]

Bis-(2-aryl-1-oxoinden-3-yl) sulphides are reported to be cleaved at the sulphur bridge by sodium methoxide, yielding the monothio-derivative of the corresponding 2-arylindane-1,3-diones.[69] 1-Phenylvinyl allyl sulphide, when generated photochemically from the sodium salt of α-allylthioacetophenone tosylhydrazone, underwent a spontaneous thio-Claisen rearrangement in the dark and at room temperature to give the violet thioketone (51).[70] The photolysis of 1-alkyl-2-phenylethyl thionobenzoates gave styrenes and thioketones (52).[71,72]

Monothiobenzil (53) has recently been synthesized by treatment of sodium *S*-desyl thiosulphate (54) with aqueous sodium hydroxide.[73] The



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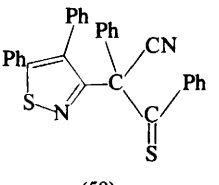

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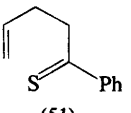

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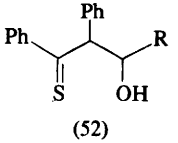

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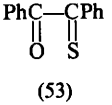

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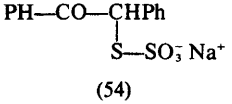


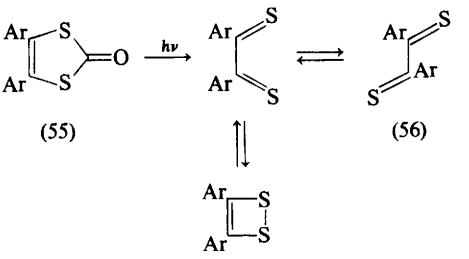
(54)

investigators further reported[73] that monothiobenzil, being apparently monomeric in the deep blue methylene chloride solution, polymerized to a green glassy substance on removal of the solvent. However, on renewed

[66] V. N. Artemov, S. N. Baranov, N. A. Kovach, and O. P. Shvaika, *Doklady Akad. Nauk S.S.S.R.*, 1973, **211**, 1369.
[67] B. M. Trost, R. C. Atkins, and L. Hoffman, *J. Amer. Chem. Soc.*, 1973, **95**, 1285.
[68] M. D. Scott, *J.C.S. Perkin I*, 1972, 1432.
[69] V. A. Usov, N. A. Korchevin, Y. S. Tsetlin, and M. G. Voronkov, *Zhur. org. Khim.*, 1973, **9**, 2149.
[70] I. Ojima and K. Kondo, *Bull. Chem. Soc. Japan*, 1973, **46**, 1539.
[71] D. H. R. Barton, M. Bolton, P. D. Magnus, P. J. West, G. Porter, and J. Wirz, *J.C.S. Chem. Comm.*, 1972, 632.
[72] D. H. R. Barton, M. Bolton, P. D. Magnus, and P. J. West, *J.C.S. Perkin I*, 1973, 1580.
[73] B. Saville and M. Steer, *J.C.S. Chem. Comm.*, 1972, 616.

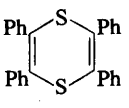
dissolution, the green polymer again dissociated to the monomeric species, as evidenced by both u.v. monitoring and the reappearance of the blue colour.[73]

The first stable α-dithione, 4,4'-bis(dimethylamino)dithiobenzil, has been synthesized by photolysis of the vinylene dithiocarbonate (55; Ar = *p*-$Me_2NC_6H_4$).[74] The dark red, crystalline product was found to have the structure (56) in the solid state, whereas it exists in solution as an equilibrium mixture of the valence tautomers (56) and (57). The equilibrium concentration of the dithiet form (57) was found to depend on the solvent, the temperature, and on the presence or absence of light. A kinetic study showed[74] that the tautomerization process cleanly follows reversible first-order kinetics, *i.e.* a reversible formation of any dimer can be excluded. The enthalpy and entropy changes for the process (57) → (56) were determined

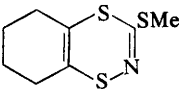


(55) (56) (57)

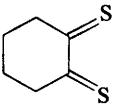
as $\Delta H^\circ = -4.9$ kcal mol^{-1} and $\Delta S^\circ = -12.5$ e.u.[74] In contrast to these findings, the photolysis of 4,5-diphenyl-1,3-dithiol-2-one (54; Ar = Ph) gave a high yield of tetraphenyl-1,4-dithiin (58), and no dithiobenzil.[75] On the other hand, the primary product from the photolysis of 3-methylmercapto-5,6-tetramethylene-1,4,2-dithiazine (59) was also formulated as an α-dithione (60).[76] The latter photolysis was carried out in the presence of molybdenum hexacarbonyl, and (61) was the product actually isolated.[76]



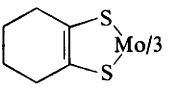
(58)



(59)



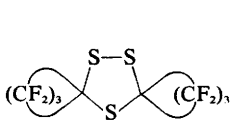
(60)



(61)

[74] W. Küsters and P. de Mayo, *J. Amer. Chem. Soc.*, 1973, **95**, 2383.
[75] W. Schroth, H. Bahn, and R. Zschernitz, *Z. Chem.*, 1973, **13**, 424.
[76] E. Fanghänel, R. Ebisch, and B. Adler, *Z. Chem.*, 1973, **13**, 431.

Transient Species.—Monomeric, simple thioketones were considered to be the reactive intermediates in the photolysis reactions of some *sym*-trithians,[77] and in some reactions of the hexafluorothioacetone dimer with nucleophiles.[78] Hexafluorothioacetone and perfluorocyclobutanethione were regarded as likely intermediates in the reactions of hexafluoropropylene and perfluorocyclobutene, respectively, with elemental sulphur in the presence of fluoride ions, yielding as main products 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietan and the trithiolan (62), respectively.[79] The sulphur-containing heterocyclic compounds obtained by the action of hydrogen sulphide on 1,4-diketones,[80] 1,5-diketones,[81] and 1,2,3-triketones[82] were considered to be formed by a spontaneous ring-closure reaction of primarily generated thioketones. The thermally induced ring-closure of 1-cyanoalken-2-yl propargyl sulphides to 5-cyano-2*H*-thiopyrans and 4-cyano-2-methylthiophens was rationalized[83] by a mechanism involving as a key intermediate the thione (63), generated by a [3,3]sigmatropic rearrangement of the sulphide. The thioketone (64) was proposed[84] as intermediate in the photorearrangement of the disulphide (65) to the spirocompound (66).



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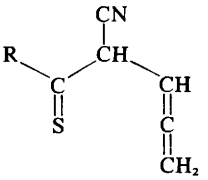
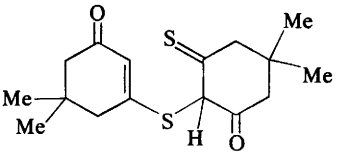


(63)



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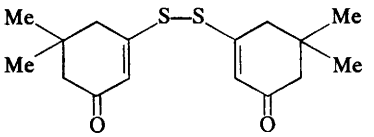
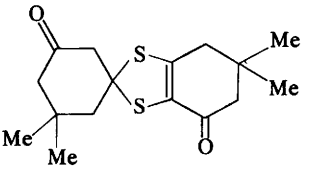


(65)



(66)

[77] T. Nishio, M. Yoshioka, H. Aoyama, and N. Sugiyama, *Bull. Chem. Soc. Japan*, 1973, **46**, 2253.

[78] T. Kitazume and N. Ishikawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 3285.

[79] B. L. Dyatkin, S. R. Sterlin, L. G. Zhuravkova, B. I. Martynov, E. I. Mysov, and I. L. Knunyants, *Tetrahedron*, 1973, **29**, 2759.

[80] F. Duus, *Acta Chem. Scand.*, 1973, **27**, 466.

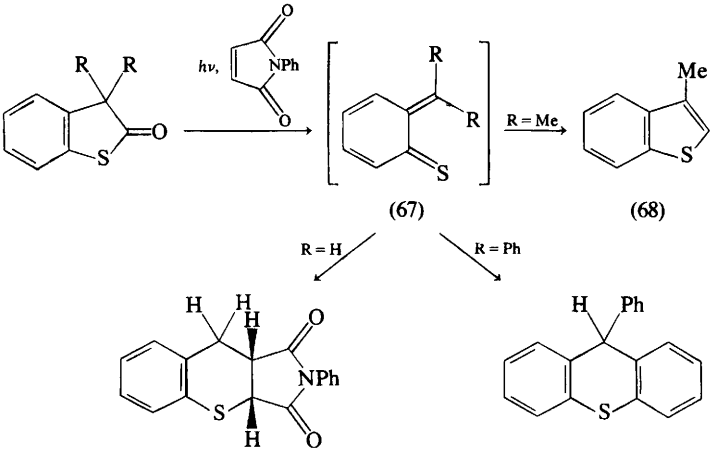
[81] V. G. Kharchenko, N. M. Kupranets, S. K. Klimenko, and M. N. Berezhnaya, *Zhur. org. Khim.*, 1972, **8**, 390.
V. G. Kharchenko, S. K. Klimenko, T. V. Stolbova, and N. S. Smirnova, *Zhur. org. Khim.*, 1973, **9**, 2434.

[82] A. Chinone, K. Inouye, and M. Ohta, *Bull. Chem. Soc. Japan*, 1972, **45**, 213.

[83] R. A. van der Welle and L. Brandsma, *Rec. Trav. chim.*, 1973, **92**, 667.

[84] L. Dalgaard and S.-O. Lawesson, *Tetrahedron Letters*, 1973, 4319.

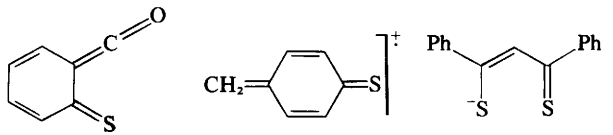
A recent study of the photoreaction of the thiolactones (67) in the presence of *N*-phenylmaleimide afforded good chemical evidence for the intermediacy of the *ortho*-quinoid thioketone (68).[85] Thus the intermediate (68) reacted with the trapping agent only when the former was unsubstituted; in the other cases, intramolecular pericyclic reactions occurred prior to intermolecular trapping (Scheme 1).[85] Another *ortho*-quinoid thioketone



Scheme 1

(69) was suggested as the reactive intermediate in the thermolysis of thianaphthenequinone.[86] The peak at *m/e* 122 in the mass spectrum of 5-methyl-2-oxobenzotrithiole was assigned to the radical cation (70).[87]

Dithio-β-diketones were known hitherto only as their transition-metal complexes. However, the anion (71) of dithiodibenzoylmethane has now been reported to be generated by cathodic reduction of the corresponding 3,5-diphenyl-1,2-dithiolylium ion.[88] The anion (71) appeared to be fairly stable in its deep red acetonitrile solution. The reduction process was formulated[88] as two successive one-electron reductions followed by a very fast S—S bond cleavage. This interpretation was found to agree with the

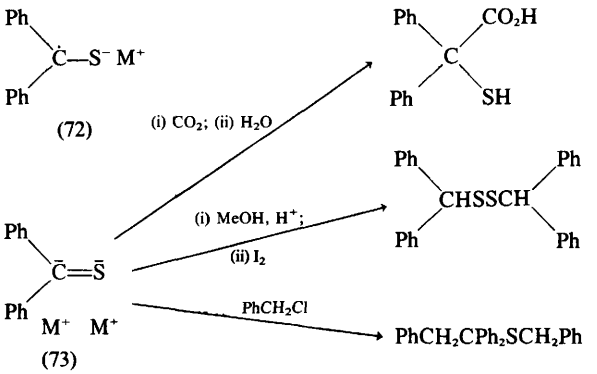


(69) (70) (71)

[85] G. Jacqmin, J. Nasielsky, G. Billy, and M. Remy, *Tetrahedron Letters*, 1973, 3655.
[86] O. Tsuge, M. Tashiro, S. Kanemasa, and K. Takasaki, *Chem. Letters*, 1972, 827.
[87] K. Steinle and M. Schmidt, *Z. Naturforsch.*, 1973, **28b**, 686.
[88] K. Bechgaard, V. D. Parker, and C. Th. Pedersen, *J. Amer. Chem. Soc.*, 1973, **95**, 4373.

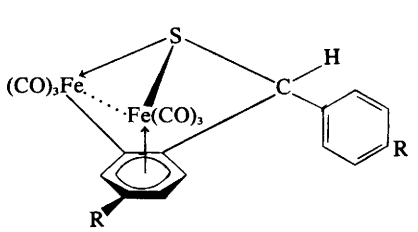
results of CNDO calculations.[89] The more long-lived product generated by flash photolysis of 3,5-diphenyl-1,2-dithiolylium salts appeared to be identical with (71).[90]

Metal Complexes.—Minoura and Tsuboi have studied the reactivity of thiobenzophenone towards alkali metals.[91] When dissolved in THF under an atmosphere of nitrogen, the thioketone reacted with one equivalent of alkali metal to form the rather unreactive radical anion (72). With more than two equivalents of alkali metal, however, the very reactive dianion complex (73) was formed according to the equilibrium (72) + Na ⇄ (73). The structure of (73) was established mainly on the basis of the reactions with electrophilic reagents. Thus the reactivity of (73) closely parallels that of the thiobenzaldehyde dianion (12).[21]



A full paper by Alper and Chan, describing in detail the formation of sulphur-donor ligand *ortho*-metallated complexes (74) by the reaction of substituted thiobenzophenones with di-iron enneacarbonyl, $Fe_2(CO)_9$, has appeared.[92] The complexes (74) appeared to be valuable starting materials in the synthesis of the little-known isobenzothiophen heterocycles.[92] Related *ortho*-metallated thiobenzophenone complexes of ruthenium were found to have a different structure (75).[93] Some non-aromatic thioketones also react with di-iron enneacarbonyl, but these reactions appear to be more complicated.[94] Thus adamantanethione yielded no less than four different complexes, of which (76) was the prevailing one (71%). Thiocamphenilone (77) formed a complex analogous with (76), but such a complex could not be obtained with thiofenchone (78), presumably for steric reasons.[94] Two

[89] C. Guimon, D. Gonbeau, G. Pfister-Guillouzo, K. Bechgaard, V. D. Parker, and C. Th. Pedersen, *Tetrahedron*, 1973, **29**, 3695.
[90] C. Th. Pedersen and C. Lohse, *Tetrahedron Letters*, 1972, 5213.
[91] Y. Minoura and S. Tsuboi, *J. Org. Chem.*, 1972, **37**, 2064.
[92] H. Alper and A. S. K. Chan, *J. Amer. Chem. Soc.*, 1973, **95**, 4905.
[93] H. Alper and A. S. K. Chan, *J. Organometallic Chem.*, 1973, **61**, C59.
[94] H. Alper and A. S. K. Chan, *Inorg. Chem.*, 1974, **13**, 232.



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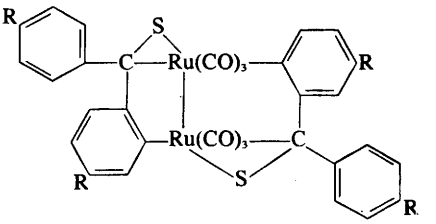
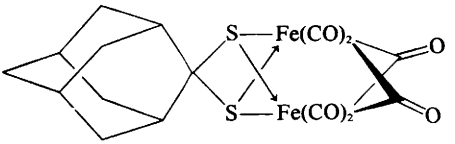


(75)



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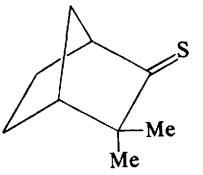

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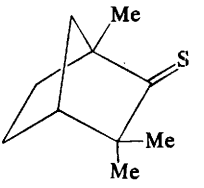
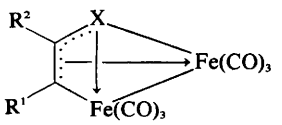


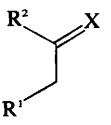
(78)

groups of workers have reported on the preparation of novel iron complexes (79) of thio- and seleno-ketocarbenes (80).[95,96] The complexes were formed by heating or by light irradiation of 1,2,3-thiadiazoles,[95,96] 1,2,3-selenadiazoles,[95,96] or 1,4-dimethylnickel(II) bis(*cis*-stilbenedithiolate)[96] in the presence of di-iron enneacarbonyl.

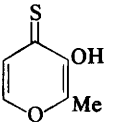
Metal chelates of thio-analogues of β-diketones are still the subject of current research, and a variety of papers, dealing with preparation, reactions, and physical properties of such compounds, have appeared during the period under review.[43,97-102] A recent paper, describing the preparation and properties of a series of metal chelates of 2-methyl-3-hydroxy-4-thiopyrone (81), should also be studied.[103]



(79) X = S or Se



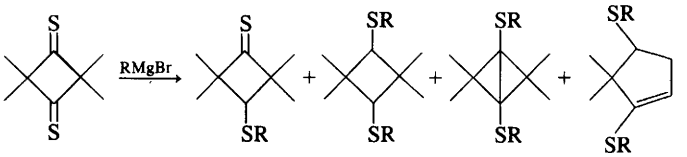
(80) X = S or Se



(81)

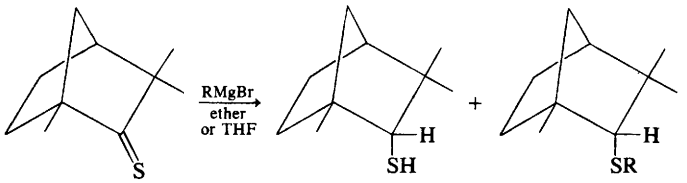
[95] P. G. Mente and C. W. Rees, *J.C.S. Chem. Comm.*, 1972, 418.
T. L. Gilchrist, P. G. Mente, and C. W. Rees, *J.C.S. Perkin I*, 1972, 2165.
[96] G. N. Schrauzer and H. Kisch, *J. Amer. Chem. Soc.*, 1973, **95**, 2501.
[97] E. Uhlemann and U. Eckelmann, *Z. Chem.*, 1972, **12**, 298.
[98] H. Schnorr, V. Pohl, E. Uhlemann, and P. Thomas, *Z. Chem.*, 1973, **13**, 143.
[99] E. Uhlemann and U. Eckelmann, *Z. Chem.*, 1974, **14**, 66.
[100] S. Kawanishi, A. Yokoyama, and H. Tanaka, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 262; S. Kawanishi, N. Hongo, A. Yokoyama, and H. Tanaka, *ibid.*, 1973, **21**, 2613; S. Kawanishi, A. Yokoyama, and H. Tanaka, *ibid.*, p. 2653.
[101] T. Honjyo and T. Kiba, *Bull. Chem. Soc. Japan*, 1972, **45**, 185.
[102] E. Uhlemann and B. Schuknecht, *Analyt. Chim. Acta*, 1974, **69**, 79.
[103] E. Uhlemann, H. Motzny, and G. Wilke, *Z. anorg. Chem.*, 1973, **401**, 255.

Reactions.—The discovery of the thiophilic nature of the addition reaction between organometallic compounds and aromatic thioketones (see Vol. 2) has initiated much recent research in this field. French chemists have studied especially the reaction of Grignard reagents with thioketones.[104–113] Thus thiobenzophenone was found to react with Grignard reagents according to the general thiophilic mechanism, yielding benzhydryl alkyl (or aryl) sulphides.[104] Thiopivalophenone also yielded the thiophilic addition product, but, in addition, other products were formed in minor amounts, the yields being dependent on the Grignard reagent used and the reaction conditions.[105] Possessing two thiocarbonyl groups, tetramethylcyclobutane-1,3-dithione (82) was found to react with alkyl magnesium bromides according to the thiophilic mechanism, yielding the products (83) and (84), but also in this case the reaction course was susceptible to changes in reaction conditions, and products such as (85) and (86) were produced preferentially in extended



(82) (83) (84) (85) (86)
(R = Me, Et, or Bu^t)

reactions with Grignard reagents containing a small alkyl group.[106] The most common by-product in the Grignard reactions of thioketones that cannot exist in the enethiol form is a reduction product,[105,107] which under appropriate reaction conditions may even be the main product, as in the reaction between thiofenchone and alkyl magnesium bromides (Scheme 2).[107] However, *C*-alkylated and *S,C*-dialkylated products have also been

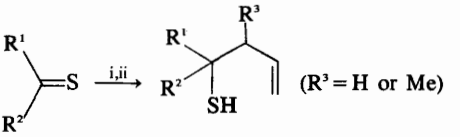


(R = Et, Pr^i, or Bu^t) (55—90%) (2—35%)

Scheme 2

[104] M. Dagonneau and J. Vialle, *Bull. Soc. chim. France*, 1972, 2067.
[105] M. Dagonneau, *Compt. rend.*, 1973, **276**, *C*, 1683.
[106] M. Dagonneau, P. Metner, and J. Vialle, *Tetrahedron Letters*, 1973, 3675.
[107] M. Dagonneau, D. Paquer, and J. Vialle, *Bull. Soc. chim. France*, 1973, 1699.
[108] D. Paquer and J. Vialle, *Compt. rend.*, 1972, **275**, *C*, 589.
[109] D. Paquer and R. Pou, *Bull. Soc. chim. France*, 1972, 3887.
[110] P. Metzner and J. Vialle, *Bull. Soc. chim. France*, 1973, 1703.
[111] M. Dagonneau and J. Vialle, *Tetrahedron*, 1974, **30**, 415.
[112] M. Dagonneau, J.-F. Hemidy, D. Cornet, and J. Vialle, *Tetrahedron Letters*, 1972, 3003.
[113] M. Dagonneau and J. Vialle, *Tetrahedron Letters*, 1973, 3017.

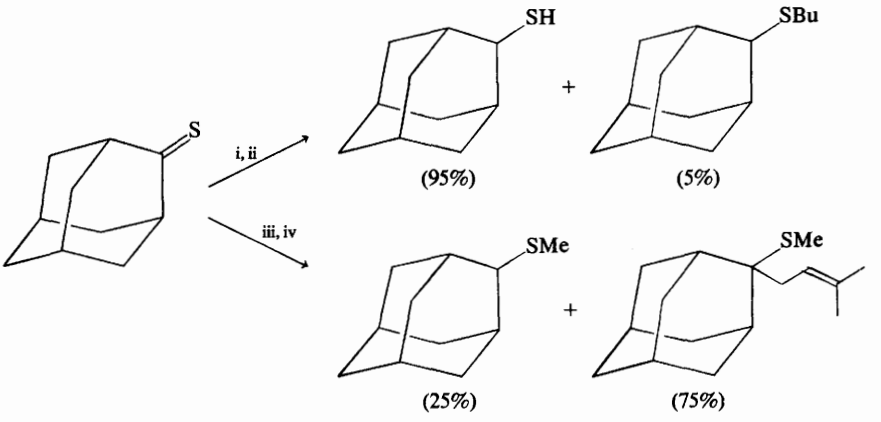
observed in some cases,[105,108] and enethiolizable thioketones often produce an alkyl vinyl sulphide as an additional product in their reactions with Grignard reagents.[107–109] Cyclic $\alpha\beta$-unsaturated thioketones show individual variation in their reactions with alkyl magnesium bromides, yielding a variety of products,[110] whereas, on the other hand, thiobenzophenone, thiopivalophenone, thiopinacolone, thiocamphor, and thiofenchone reacted with allylic Grignard reagents to form only a *C*-alkylation product (Scheme 3).[111]

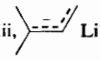


Reagents: i, $R^3CH{:}CHCH_2MgBr$; ii, H^+

Scheme 3

Considering these results, it can be clearly concluded that Grignard reagents do not react with thioketones exclusively according to a thiophilic mechanism. However, the same conclusion appears to be justifiable also with respect to other organometallic reagents. According to a very recent paper,[114] adamantanethione is indeed subject to a thiophilic attack by butyl-lithium to a certain extent, but a *C*-alkylation product is formed preferentially by its reaction with prenyl-lithium (Scheme 4).

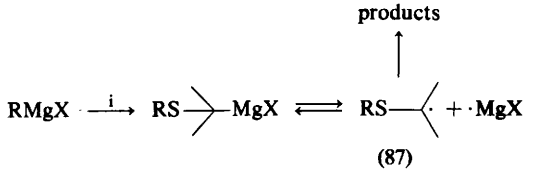


Reagents: i, BuLi; ii, H^+; iii,  Li^+; iv, MeI

Scheme 4

[114] V. Rautenstrauch, *Helv. Chim. Acta*, 1974, **57**, 496.

The possibility that the general thiophilic addition reaction involves free radicals had been suggested already by Beak and Worley (see Vol. 2), but Dagonneau and his co-workers, using e.s.r. monitoring techniques, have now presented definitive evidence for the intermediacy of free radicals of the type (87) in the thiophilic Grignard reactions of several thioketones.[105,106,112,113] The e.s.r. spectral observations led Dagonneau and Vialle[113] to explain the thiophilic addition by the mechanism shown in Scheme 5, and, furthermore, to suggest that the homolytic cleavage of the starting Grignard reagent may very well be the initiation of the process.

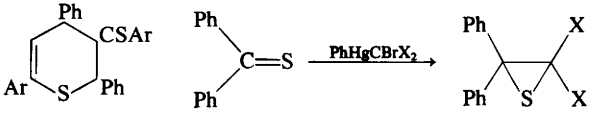


(87)

Reagents: i, $\rangle C{=}S$

Scheme 5

In an attempt to synthesize a thiochalcone by the reaction of 3-(*NN*-diethylamino)-1-(*p*-methoxyphenyl)propene-1-thione with phenyl magnesium bromide, in analogy with a well-known synthesis of chalcones, Quiniou and his co-workers obtained instead the thiopyran (88), a formal dimer of the thiochalcone expected.[115] The thiirans (89) were formed by the reaction of



(88) Ar = 4-$MeOC_6H_4$ (89) X = Cl or Br

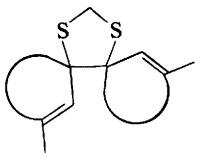
thiobenzophenone with phenyl(trihalogenomethyl)mercury compounds.[116]

A recent study of the reactivity of $\alpha\beta$-unsaturated cyclic thioketones towards some common reduction agents revealed that lithium aluminium hydride affords selectively the corresponding $\alpha\beta$-unsaturated cyclic thiols, whereas sodium borohydride, besides reducing the thione group, also effects a partial reduction of the double bond.[110] 1-Methyl-3-ethoxycarbonyl-4-thioxo-1,4-dihydrocinnoline was found to be effectively desulphurated by Raney nickel.[30]

Many papers have reported on the reaction of thioketones with diazoalkanes.[17,59,60,109,117–121] The normal products are thiirans or/and substituted vinyl alkyl sulphides, depending on the ability of the thione to exist in

[115] J.-P. Pradere, G. Bouet, and H. Quiniou, *Tetrahedron Letters*, 1972, 3471.
[116] D. Seyferth, W. Tronich, R. S. Marmor, and W. E. Smith, *J. Org. Chem.*, 1972, **37**, 1537.
[117] J. M. Beiner, D. Lecadet, D. Paquer, A. Thuillier, and J. Vialle, *Bull. Soc. chim. France*, 1973, 1979.
[118] J. M. Beiner, D. Lecadet, D. Paquer, and A. Thuillier, *Bull. Soc. chim. France*, 1973, 1983.
[119] D. I. Biskupskaya and A. V. Voropaeva, *Khim. geterotsikl. Soedinenii*, 1971, **7**, 1688.
[120] P. Metzner, *Bull. Soc. chim. France*, 1973, 2297.
[121] T. Machiguchi, Y. Yamamoto, M. Hoshino, and Y. Kitahara, *Tetrahedron Letters*, 1973, 2627.

the enethiol form.[17,59,109,117–119] αβ-Unsaturated cyclic thioketones reacted anomalously with diazoalkanes, yielding with diazomethane mainly dithiolans (90), whereas higher homologues of diazoalkanes afforded mainly dienes (91).[120] Tropothione (92) gave the compound (93) upon treatment with diazomethane.[121] Benzenediazonium-*o*-carboxylate reacted with thiobenzophenones as a 1,4-dipole, yielding the heterocyclic compounds (94).[122]



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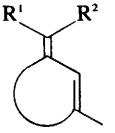

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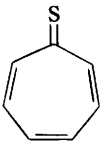

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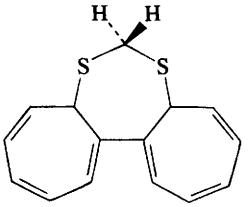
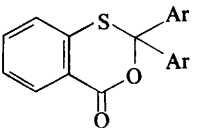


(93)

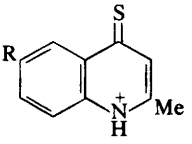


(94)

S-Alkylation of enethiolizable thioketones by means of a base and an alkyl halide has been performed in many cases (refs. 17, 39, 40, 60, 62, 109, and 123), and appears to be the way most often used to characterize unstable thioketones.[18,60] The 4-thionoquinaldines (95) gave, upon treatment with methyl iodide, a mixture of *S*- and *N*-methylated products,[119] and 1-methyl-3-ethoxycarbonyl-4-thioxo-1,4-dihydrocinnoline was smoothly *S*-methylated by methyl iodide, yielding (96).[30] β-Mercaptoaldehydes (27) have been converted into thiopyrans (97) by reaction with an appropriate β-chlorovinylaldehyde and successive base-promoted ring-closure of the sulphide first formed.[49] The diaminocyclopropenethiones (30) reacted with methyl iodide in the presence of potassium perchlorate, affording the salts (98) quantitatively.[53] The action of dimethylsulphoxonium methylide on simple aliphatic thioketones led to *S*-methylation of the potential enethiols, whereas otherwise thiirans were obtained.[124] The base-catalysed reaction of thiobenzophenone with chloromethyl sulphoxide gave as product the αβ-unsaturated sulphoxide (99), being probably formed by desulphurization

[122] H. Tokunaga, T. Kawashima, and N. Inamoto, *Bull. Chem. Soc. Japan*, 1972, **45**, 2220.
[123] P. Metzner and J. Vialle, *Bull. Soc. chim. France*, 1973, 1317.
[124] D. Lecadet, D. Paquer, and A. Thuillier, *Compt. rend.*, 1973, **276**, *C*, 875.

of initially generated 2,2-diphenyl-3-methylsulphinylthiiran.[125] The thionoquinaldines (95) were found to be *S*-cyanoethylated by reaction with acrylonitrile.[119] Keten reacts with β-thioketo-esters[109] and thioamide vinylogues (100),[126] yielding a *cis–trans* mixture of acetylated enethiols, and 1(2*H*)-thiopyran-2-ones, respectively.



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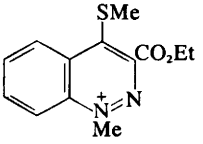

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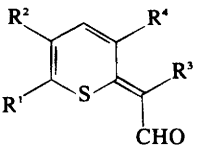

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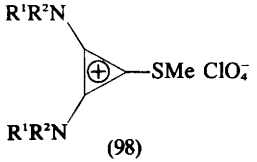

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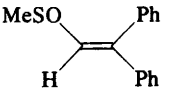

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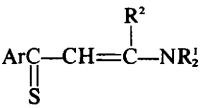


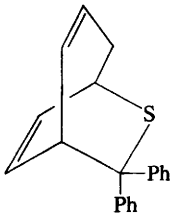
(100)

The applicability of thioketones in the synthesis of heterocyclic compounds has been further demonstrated. The Diels–Alder reaction of thiobenzophenone with 1,3,5-cycloheptatriene gave the (2 + 4) cycloadduct (101) in 40% yield.[127] Cycloheptatrienethione (92) yielded the (8 + 2) cycloadduct (102) quantitatively by reaction with maleic anhydride, and the bicyclic compound (103) in 65% yield by reaction with dimethyl acetylenedicarboxylate.[128] Compound (103) was considered to be a rearrangement product of the probably primarily formed (8 + 2) cycloadduct intermediate (104).[128] The *in situ* addition of nitrile oxides to aromatic thioketones resulted in formation of 1,4,2-oxathiazoles,[129] whereas 1,4,2-oxathiazolidines were the products in the reactions of some alicyclic thiones with nitrones.[130] The formation of thio-ozonides (1,2,4-trithiolans) by treatment of thioketones with amines or chloramine T was investigated recently.[46,131]

β-Aryl-α-mercapto-acrylic acids have been reported to undergo cyclocondensation reactions with aldehydes, benzaldimines, phenyl isothiocyanate, and ω-nitrostyrene, yielding five-membered heterocyclic compounds containing the —S—C(=CHAr)—CO— moiety.[132] A new route to substituted 1(2*H*)-thiopyran-2-ones has been suggested by the formation of (105)

[125] G. Tsuchihashi and K. Ogura, *Bull. Chem. Soc. Japan*, 1972, **45**, 2023.
[126] J.-C. Meslin and H. Quiniou, *Bull. Soc. chim. France*, 1972, 2517.
[127] Y. Ohnishi, Y. Akasaki, and A. Ohno, *Bull. Chem. Soc. Japan*, 1973, **46**, 3307.
[128] T. Machiguchi, M. Hoshino, S. Ebene, and Y. Kitahara, *J.C.S. Chem. Comm.*, 1973, 196.
[129] R. Huisgen and W. Mack, *Chem. Ber.*, 1972, **105**, 2815.
[130] D. St. C. Black and K. G. Watson, *Austral. J. Chem.*, 1973, **26**, 2491.
[131] M. M. Campbell and D. M. Evgenios, *J.C.S. Perkin I*, 1973, 2866.
[132] A. M. Harhash, M. H. Elnagdi, and S. O. Abdallah, *Indian J. Chem.*, 1973, **11**, 128.

in the reaction of α-phenyl-β-mercaptocinnamaldehyde (27; $R^1 = R^2 = Ph$) with malonodinitrile.[133] 1,6-Dioxa-6a-thiapentalenes have been elegantly synthesized by treatment of 4*H*-pyran-4-thiones with thallium(III) trifluoroacetate in acetonitrile and subsequent hydrolysis of the primarily formed thallium(III) salt (106).[134] Elemental sulphur appeared to be the most



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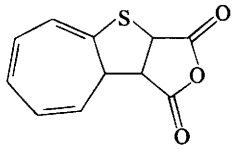

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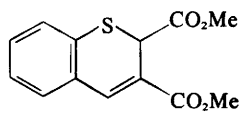

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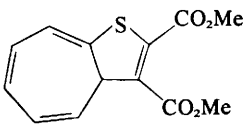
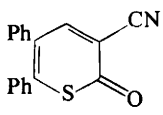


(104)



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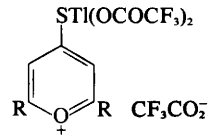


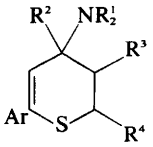
(106) R = H, Me, or CO_2Et

effective catalyst for the rearrangement of 2-thioacylmethylene-1,3-dithioles to 1,6,6a-trithiapentalenes.[135]

Thioamide vinylogues (100) have been reported to yield Diels–Alder adducts on treatment with substituted alkenes[136] and sulphenes.[137] In the former case, the heterocyclic compounds (107) and/or (108) were produced, depending on the substituents.[136] In the latter case, the unsubstituted sulphene afforded merely (109), whereas solely the de-aminated products (110) were formed in reactions with benzylsulphene.[137] 3-Alkylthio-1-aryl-3-arylamino-2-propene-1-thiones (41) have been converted into 3-arylamino-1,2-oxazoles, 3-arylaminopyrazoles, and the quinoline derivatives (111) by treatment with hydroxylamine, hydrazine, and sulphuric acid, respectively.[138] The formation of 2-imino-2*H*-thiopyrans by spontaneous ring-closure of β-mercaptovinyl-acrylonitriles (112) has been reported recently.[139]

Because it has special bonding characteristics, 2,3-diphenylcyclopropenethione has received considerable attention as a dipolarophile, this being

[133] M. Weissenfels and S. Illing, *Z. Chem.*, 1973, **13**, 130.
[134] D. H. Reid and R. G. Webster, *J.C.S. Chem. Comm.*, 1972, 1283.
[135] S. Davidson and D. Leaver, *J.C.S. Chem. Comm.*, 1972, 540.
[136] J.-P. Pradere and H. Quiniou, *Compt. rend.*, 1972, **275**, *C*, 677.
[137] M. Bard, J. C. Meslin, and H. Quiniou, *J.C.S. Chem. Comm.*, 1973, 672.
[138] F. Boberg and W. von Gentzkow, *Annalen*, 1973, 256.
[139] J. Liebscher and H. Hartmann, *Z. Chem.*, 1973, **13**, 342.



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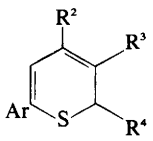

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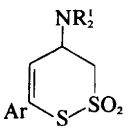

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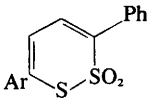

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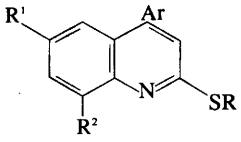

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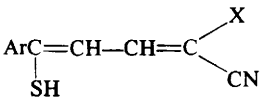


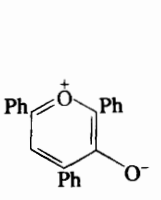
(112) X = CN, $CONH_2$, or CO_2Et

demonstrated lately by its reactions with the pyrylium betaine (113)[140] and the pyridinium-*N*-(acyl)imines (114),[141] yielding the thioketone (115) and the oxazinethiones (116), respectively. Diphenylcyclopropenethione reacted with α-morpholinostyrene in a manner analogous with that of the corresponding cyclopropenone to form the betaine (117).[142] However, in its reaction with tetracyanoethylene oxide, the cyclopropenethione behaved as a normal thioketone, yielding 1,2-diphenyl-3-(dicyanomethylene)-cyclopropene (tetracyanoethylene oxide reacted with thiobenzophenone to form 1,1-diphenyl-2,2-dicyanoethylene; see Vol. 1), whereas the corresponding cyclopropenone reacted with the ethylene oxide to open the ring and form the αβ-unsaturated δ-lactone (118).[143]

Japanese workers have reported on some interesting reactions of thiobenzophenones with salicyloyl chloride and *o*-mercaptobenzoyl chloride, respectively.[122] In the former case, the heterocyclic compounds (119) were formed, probably by a nucleophilic attack of the hydroxy-group of salicyloyl chloride on the thiocarbonyl C-atom of the thiobenzophenones, followed by a ring-closure and elimination of hydrogen chloride. Benzophenones reacted analogously with salicyloyl chloride, but were unreactive towards *o*-mercaptobenzoyl chloride.[122] However, the latter compound reacted readily with thiobenzophenone in a thiophilic manner, yielding the disulphide (120).[122] Thiocamphor, in contrast to camphor itself, reacted very rapidly, and without catalyst, with primary benzylic amines to give the corresponding camphorimines in nearly quantitative yields.[144]

The thermal addition of aromatic thioketones to tetramethylallene has been studied by Gotthardt,[145] who obtained as products the open-chain

[140] K. T. Potts, A. J. Elliott, and M. Sorm, *J. Org. Chem.*, 1972, **37**, 3838.
[141] J. W. Lown and K. Matsumoto, *Canad. J. Chem.*, 1972, **50**, 584.
[142] T. Eicher and S. Böhm, *Tetrahedron Letters*, 1972, 3695.
[143] J. W. Lown and K. Matsumoto, *Canad. J. Chem.*, 1972, **50**, 534.
[144] I. Shahak and Y. Sasson, *Synthesis*, 1973, 535.
[145] H. Gotthardt, *Chem. Ber.*, 1972, **105**, 2004.



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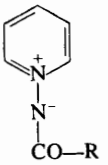

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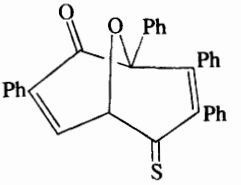

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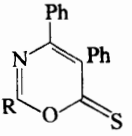

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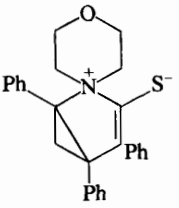

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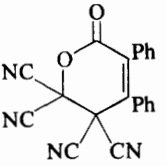

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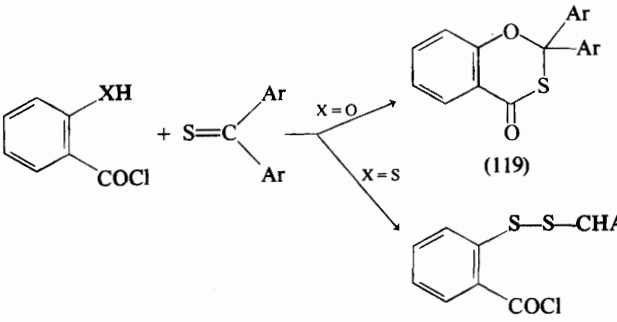


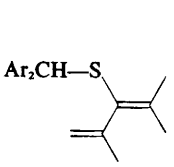
(119)

(120)

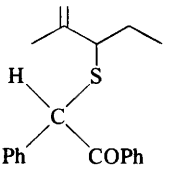
sulphides (121). The simultaneous reduction of the thiocarbonyl group and displacement of the double bond also characterized the thermally induced addition reactions of monothiobenzil (53) with 2-methylpent-1-ene and 2-methylpent-2-ene, respectively, affording allylic sulphides, in the latter case, as an example, the sulphide (122).[146] Tropothione (92) and its 2-methyl-substituted analogue reacted anomalously[128] with tetracyanoethylene, yielding 8,8-dicyanoheptafulvenes (123).[147]

In an attempt to find a new synthetic route to sulphines, Zwanenburg and Janssen[148] treated some aromatic and alicyclic thioketones with ozone at −78 °C, and found that only the sterically more hindered thioketones

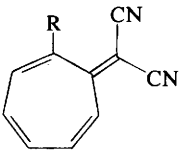
[146] M. J. Loadman, B. Saville, M. Steer, and B. K. Tidd, *J.C.S. Chem. Comm.*, 1972, 1167.
[147] T. Machiguchi, K. Okuma, M. Hoshino, and Y. Kitahara, *Tetrahedron Letters*, 1973, 2011.
[148] B. Zwanenburg and W. A. J. Janssen, *Synthesis*, 1973, 617.



(121)

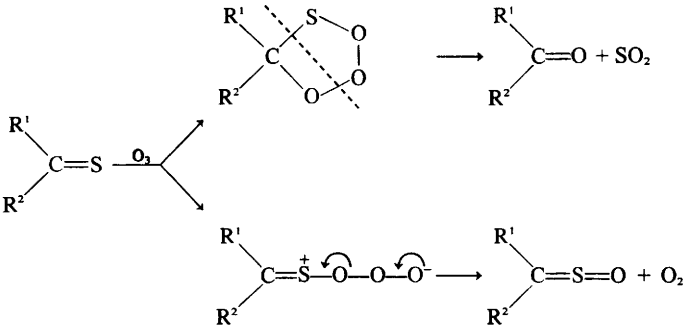


(122)



(123) R = H or Me

yielded sulphines. Sterically less hindered thiones were oxidized to the corresponding ketones. The authors explained the difference in thione reactivity by assuming, in the latter case, the formation of an intermediate cycloaddition product that spontaneously loses sulphur dioxide to yield a ketone (Scheme 6). In the case of the sterically more crowded thioketones, an open-chain species was assumed as the alternative intermediate leading to the sulphine formation, as the formation of a cycloadduct intermediate was considered unlikely for steric reasons (Scheme 6). [148] Among several

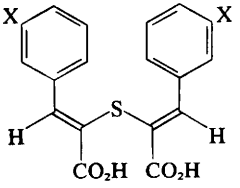


Scheme 6

oxidation agents tested, only benzonitrile oxide was found capable of converting the enamino-thioketones (100) into the corresponding enamino-ketones.[149] Iodine oxidation of the thioketones (41) afforded isothiazolium iodides,[138] whereas an isothiazolo[2,3-*a*]pyridinium salt was formed by hydrogen peroxide oxidation of 2-pyridylmethyl isopropyl thioketone in the presence of perchloric acid.[150] The sulphides (124) were unexpectedly formed by the reaction of β-(3-halogenophenyl)-α-mercaptoacrylic acids with an excess of iodine.[151]

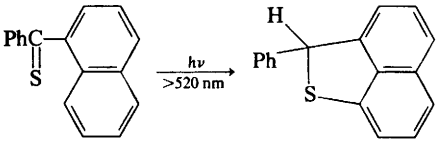
The flash thermolysis of tetramethylcyclobutane-1,3-dithione (82) has been reported to yield dimethylthioketen as the main product.[152] Traces of diphenylacetylene were isolated after the thermolysis of diphenylcyclopropenethione at 150 °C.[153]

[149] M. Bard, G. Duguay, and H. Quiniou, *Compt. rend.*, 1972, **274**, *C*, 1641.
[150] G. G. Abott and D. Leaver, *J.C.S. Chem. Comm.*, 1973, 150.
[151] T. R. Bosin and E. Campaigne, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 261.
[152] G. Seybold, *Tetrahedron Letters*, 1974, 555.
[153] G. Laban and R. Mayer, *Z. Chem.*, 1972, **12**, 20.



(124) X = F, Cl, or Br

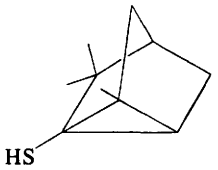
The photochemical reduction of thiobenzophenone by dihydro-aromatic compounds has been studied by Ohnishi and Ohno,[154] who, on the basis of product analyses and relative reactivities of the hydrogen donors, proposed a mechanism involving as the important intermediate the radical $Ph_2\dot{C}SH$, formed by hydrogen-gathering of thiobenzophenone in the (n, π^*) triplet state. Certain aromatic thioketones PhCSR, having an adjacent vacant *peri*-position to the thiobenzoyl group (R = 1-napththyl, 1-pyrenyl, 6-chrysenyl, or 3-perylenyl), rearranged on irradiation to thiophane derivatives, as exemplified by the case of 1-naphthyl phenyl thioketone (Scheme 7).[155] A similar rearrangement is unknown for the corresponding ketones, a



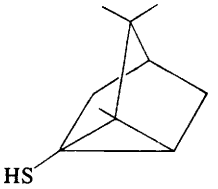
Scheme 7

fact that was attributed to the different nature of the lowest singlet state of the ketones.[155] The photolysis of thiofenchone and thiocamphor afforded the cyclopropanethiols (125) and (126), respectively, besides the corresponding thiols.[156] It was considered likely that (125) and (126) were formed from the corresponding excited thiones by β-hydrogen abstraction. The thiol (126) rearranged thermally at 135 °C to thiocamphor, whereas (125) by a similar treatment underwent a partial homothioketonization, yielding both thiofenchone and the thione (127) in about 3:2 ratio.[156] The first examples of photochemical dethiocarbonylation reactions have appeared. Diphenylcyclopropenethione yielded diphenylacetylene upon irradiation,[153] and hexaphenylbenzene was formed in 94% yield by the photolysis of the thione (49), presumably *via* the intermediate thioketone (128).[67] 2,6-Diphenyl-4*H*-pyran-4-thione, and its thiopyran analogue, were desulphurized on irradiation, yielding (129).[157] Tetramethyl-3-thiocyclobutane-1,3-dione and tetramethylcyclobutane-1,3-dithione were both converted into tetramethylcyclobutane-1,3-dione on photolysis in the presence of oxygen.[158] Photooxygenations of this type have been reported earlier in the case of

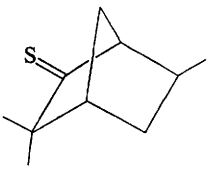
[154] Y. Ohnishi and A. Ohno, *Bull. Chem. Soc. Japan*, 1973, **46**, 3868.
[155] R. Lapouyade and P. de Mayo, *Canad. J. Chem.*, 1972, **50**, 4068.
[156] D. S. L. Blackwell and P. de Mayo, *J.C.S. Chem. Comm.*, 1973, 130.
[157] N. Ishibe, M. Sunami, and M. Odani, *Tetrahedron*, 1973, **29**, 2005.
[158] J. J. Worman, M. Shen, and P. C. Nichols, *Canad. J. Chem.*, 1972, **50**, 3923.



(125)



(126)



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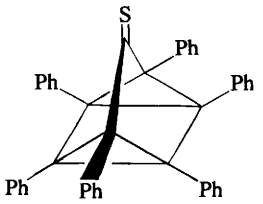
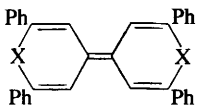


(128)

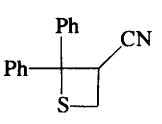


(129) X = O or S

conjugated thiones, and are believed to proceed by the attack of singlet oxygen on the thiocarbonyl group. Irradiation of dibenzyl thioketone under the same conditions afforded, however, only the usual thione dimerization.[158]

The photocycloaddition of thiobenzophenone to acrylonitrile at 366 nm is known to give the thietan (130). It has now been shown that the reactive state of the thione under these conditions is the second excited (π, π^*) singlet,[159] and that the 1,3-dithian (131) is an intermediate in this reaction.[160] In contrast to earlier findings, irradiation at longer wavelengths (>500 nm) has been found also to result in product formation.[160,161] The heterocyclic compounds (132) and (133) were the main products in the latter photolysis reaction, and their formation was interpreted in terms of an intermediate lowest triplet state of thiobenzophenone.[161] The irradiation of thiobenzophenone in tetramethylethylene solution at −78 °C afforded two 1:1 adducts, (134) and (135), respectively.[160] Various thietans were the products in the photocycloaddition reactions of some aromatic thioketones with tetramethylallene, 2,4-dimethylpenta-1,3-diene, dimethyl fumarate, and dimethyl maleate, respectively.[162] The nitrile function has also been found to be susceptible to addition by the excited thione group.[163] Thus several alicyclic and aromatic thioketones, on irradiation in acetonitrile solution, have been converted into *N*-thioacylketimines (136), probably *via* an intermediate 1,3-thiazetine (137).[163] Two recent papers by de Mayo and his

[159] P. de Mayo and H. Shizuka, *J. Amer. Chem. Soc.*, 1973, **95**, 3942.
[160] P. de Mayo and A. A. Nicholson, *Israel J. Chem.*, 1972, **10**, 341.
[161] P. de Mayo and H. Shizuka, *Mol. Photochem.*, 1973, **5**, 339.
[162] H. Gotthardt, *Chem. Ber.*, 1972, **105**, 2008.
[163] D. S. L. Blackwell, P. de Mayo, and R. Suau, *Tetrahedron Letters*, 1974, 91.



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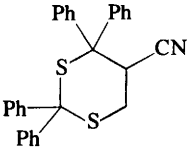

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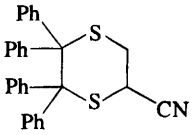

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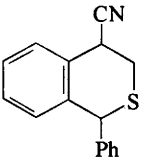
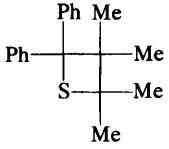
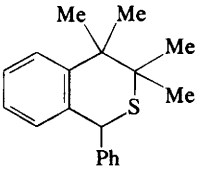


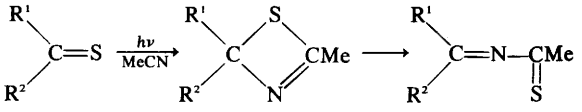
(133)



(134)



(135)



(137) (136)

co-workers deal especially with mechanistic aspects of the thioketone photochemistry.[164,165]

4 Thioketens and Selenoketens

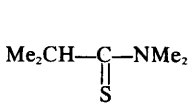
The majority of the papers that during the past two years have been dealing with thioketens report on these compounds as transient species or postulated intermediates. However, one of two exceptional papers describes the successful synthesis of the hitherto unknown dimethylthioketen (138).[152] This deep red compound, which actually had been postulated earlier to be an intermediate in the thermolysis of tetramethylcyclobutane-1,3-dithione (82), appeared as the main product by flash thermolysis of (82). In order to avert dimerization, (138) was trapped at −196 °C together with added trichlorofluoromethane, and was thus characterized spectroscopically as a solute, as well as by its reaction with dimethylamine to afford the thioamide (139). The thioketen (138) decomposed immediately at room temperature, whereas the half-life of its ~0.3 molar trichlorofluoromethane solution at −70 °C was found to be 60 minutes.[152]

Methylthioketen played a part in a likely mechanism accounting for the formation of *NN*-diethylthiopropionamide in the reaction of methyl propargyl disulphide with diethylamine.[166] Perfluoroisobutene reacted with elemental sulphur in the presence of fluoride ions to give mainly the desaurin (140),

[164] A. H. Lawerence, P. de Mayo, R. Bonneau, and J. Joussot-Dubien, *Mol. Photochem.*, 1973, **5**, 361.
[165] A. H. Lawrence and P. de Mayo, *J. Amer. Chem. Soc.*, 1973, **95**, 4084.
[166] J. Meijer, H. E. Wijers, and L. Brandsma, *Rec. Trav. chim.*, 1972, **91**, 1423.

the dimer of the probably primarily formed bis(trifluoromethyl)thioketen (141).[79] The formation of 1,4-dithiafulvenes by the photolysis of some 1,2,3-thiadiazoles has been rationalized in terms of intermediate thioketens.[167] On treatment with base, 4-substituted 1,2,3-selenadiazoles were converted into 2,ω-disubstituted 1,4-diselenafulvenes.[168] This stereoselective reaction, affording solely or mainly the isomer (142), was thought to involve the selenoketens (143) as intermediates. The reaction of the sulphides (144) with dialkylamines, leading to thioamides and/or 2-aminothiophens, was interpreted in terms of an initial, thermally induced thio-Claisen rearrangement of (144) to the thioketen (145), which reacted subsequently with the amine present.[169] The unknown thioacylthioketen (146) played a part in a plausible mechanism accounting for the formation of 2,3,5,6-tetraphenylthieno[3,2-*b*]thiophen in the Bamford–Stevens reaction of the hydrazone (147).[170]

(138) R = Me
(141) R = CF_3



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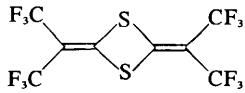
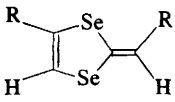
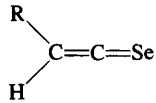


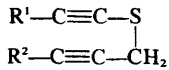
(140)



(142)



(143)



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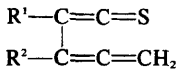

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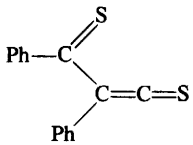

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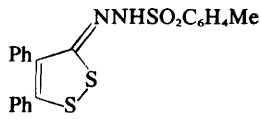
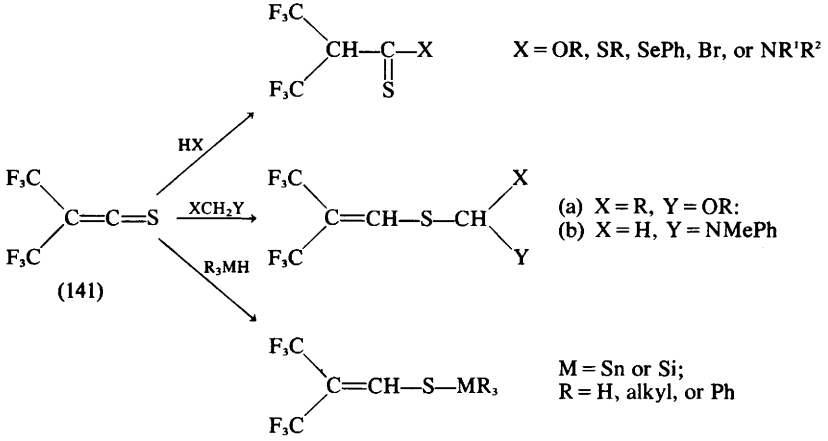


(147)

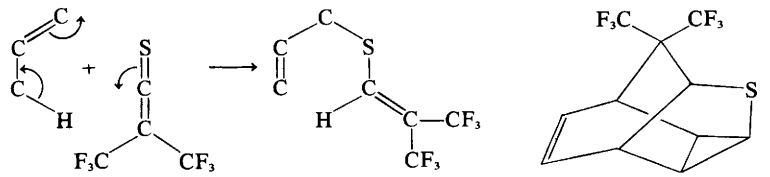
Raasch has extended his studies of the reactivity of bis(trifluoromethyl)thioketen (141).[58] Scheme 8 gives a survey of the reactions that have been carried out. Thus common nucleophilic agents such as alcohols, thiols, primary, and secondary amines, *etc.*, react with (141) with conservation of the C=S double bond, whereas the C=C double bond remains in the products of the reactions of (141) with certain ethers, dimethylaniline, and hydrides of tin and silicon. Compound (141) reacted with a variety of olefinic substances in accordance with the general ene-reaction formalism, yielding allyl vinyl sulphides (148). The formation

[167] K.-P. Zeller, H. Meier, and E. Müller, *Annalen*, 1972, **766**, 32.
[168] I. Lalezari, A. Shafiee, and M. Yalpani, *J. Org. Chem.*, 1973, **38**, 338.
[169] J. Meijer, P. Vermeer, H. J. T. Bos, and L. Brandsma, *Rec. Trav. chim.*, 1974, **93**, 26.
[170] H. Behringer and E. Meinetsberger, *Tetrahedron Letters*, 1973, 1915.



Scheme 8

of (149) by the reaction of (141) with cycloheptatriene was rationalized in terms of an ene reaction, followed by bond rearrangement and an intramolecular Diels–Alder reaction. The addition reactions of (141) with bicyclobutane, indole, 1,3,3-trimethyl-2-methyleneindoline, and 6-(dimethylamino)fulvene afforded thioketones [for example (35) and (37), as described in the previous section].



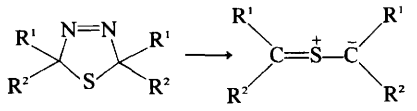
(148) (149)

5 Thiocarbonyl Ylides, Thiocarbonyl *S*-Imides, and their Selenium Analogues

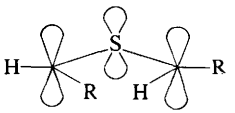
A recent, full paper[171] by Kellogg and his co-workers elaborates previous short communications (see Vol. 2) in describing the generation of the unstable thiocarbonyl ylides (150) from 1,3,4-thiadiazolines (151), and in reporting on the reactivity and properties of these ylides, with special regard to the stereochemical aspects. On the basis of steric considerations, the authors concluded that the ylides (150) are non-planar.[171] The *trans*-thiocarbonyl ylides (152) were found to add suprafacially in a 1,3 manner over

[171] J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, 1972, **37**, 4045.

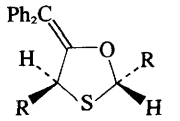
the carbonyl function of diphenylketen, affording *trans*-2,4-disubstituted 5-(diphenylmethylene)-1,3-oxathiolans (153).[172] The photolysis of naphthyl vinyl sulphides (154) under non-oxidative conditions has been reported to give naphtho[2,1-*b*]dihydrothiophens (155), probably as the result of a stereospecific hydrogen migration in the primarily generated intermediate thiocarbonyl ylide (156).[173] The intermediacy of (156) was corroborated by the fact that the multicyclic compounds (157) were produced when the photolysis of (154) was carried out in the presence of the dipolarophile



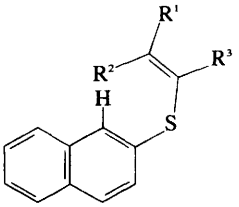
(151) (150)



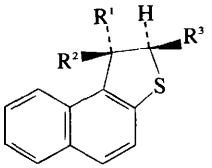
(152) R = Et or Bu^t



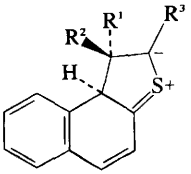
(153) R = Et or Bu^t



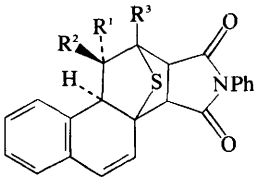
(154)



(155)



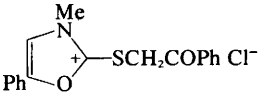
(156)



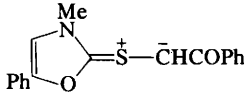
(157)

N-phenylmaleimide.[173] The formation of 2-phenacylidene-3-methyl-5-phenyl-1,3-oxazoline by the treatment of the salt (158) with sodium hydride in DMSO was considered to proceed through the thiocarbonyl ylide (159).[174] However, the thiocarbonyl ylide (160), which in a similar manner to that mentioned above was generated from its corresponding dithiolanium salt, instead underwent a spontaneous ring-closure, yielding the spiro-compound (161).[174] The thiocarbonyl ylide dipolar characteristics of phenyl-substituted thieno[3,4-*c*]pyrroles, phenyl-substituted thieno[3,4-*c*]thiophens, and the thieno[3,4-*f*]benzo[*c*]thiophen (162) have been substantiated by their reactions with dipolarophiles.[175] The first representative (164) of the hitherto

[172] R. M. Kellogg, *J. Org. Chem.*, 1973, **38**, 844.
[173] A. G. Schultz and M. B. DeTar, *J. Amer. Chem. Soc.*, 1974, **96**, 296.
[174] Y. Heno and M. Okawara, *Bull. Chem. Soc. Japan*, 1972, **45**, 1797.
[175] K. T. Potts and D. McKeogh, *J. Amer. Chem. Soc.*, 1973, **95**, 2749, 2750.



(158)



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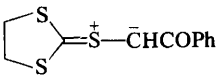
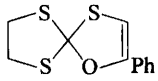
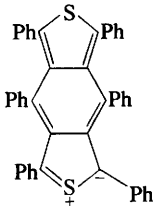


(160)



(161)



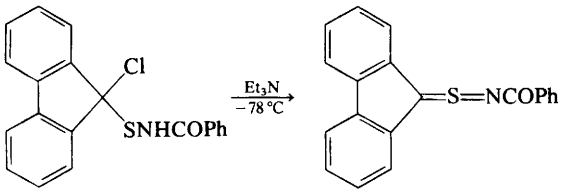
(162)

unknown thione *S*-imides has been synthesized by the reaction of benzamide-*N*-sulphonylchloride with diazofluorene and subsequent treatment of the product (163) of this reaction with triethylamine at −78 °C.[176] Compound (164) was isolable at −78 °C as deep red crystals. On warming the THF solution of (164), a cyclization reaction occurred spontaneously, yielding the oxathiazole (165). On treatment with triethylamine, the product of the reaction of benzamide-*N*-sulphonyl chloride with diphenyldiazomethane afforded the oxathiazole (166) directly.[176] The reactivity of (164) has been illustrated by its reactions with enamines and 1-(diethylamino)prop-1-yne.[176] In the former case isothiazolines were formed as the result of a 1,3-cycloaddition reaction, whereas the ynamine yielded the unstable heterocyclic compound (167). Some thiocarbonyl *S*-imides (168) have been synthesized by treatment of the corresponding 1,2-dithiole-3-thiones with appropriate chloramines.[177] The thermal rearrangement of (168) to the benzo-1,2-dithiole-3-imines (169) was studied at the same time, and a rearrangement mechanism involving an intermediate thiaziridine was deduced on the basis of kinetic measurements.[177] The selenocarbonyl imide (170), prepared by the same method as its sulphur analogue, was found to react with primary amines to yield mainly the products (171) and (172).[178] Compound (172) was formed in a moderate yield on treatment of (170) with hydrogen sulphide or thiols.[178]

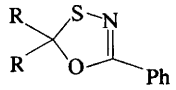
6 Sulphines

A new route to sulphines, in which the sulphine function is flanked by bulky groups, has been found in the oxidation of the corresponding thiocarbonyl

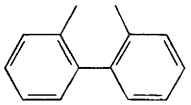
[176] E. M. Burgess and H. R. Penton, *J. Amer. Chem. Soc.*, 1973, **95**, 279.
[177] S. Tamagaki, K. Sakaki, and S. Oae, *Bull. Chem. Soc. Japan*, 1973, **46**, 2608.
[178] S. Tamagaki and K. Sakaki, *Tetrahedron Letters*, 1974, 1059.



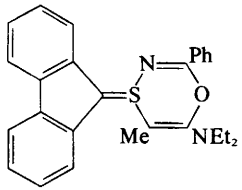
(163) (164)



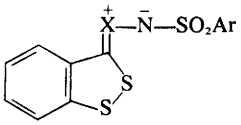
(165) RR =



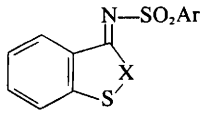
(166) R = Ph



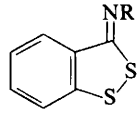
(167)



(168) X = S
(170) X = Se; Ar = Ph



(169) X = S
(172) X = Se; Ar = Ph

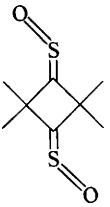


(171)

compounds with equimolar amounts of ozone (see Scheme 6, in Section 3).[148] The first representatives of sulphines derived from alicyclic thioketones have been synthesized recently by common peracid oxidation of adamantanethione, tetramethyl-3-thioxocyclobutanone, and tetramethylcyclobutane-1,3-dithione.[179] The latter compound gave a mixture of the isomers (173) and (174) by the oxidation. *N*-Monosubstituted carbonyl chlorosulphines (175) have been prepared by treatment of the sulphenyl chlorides (176) with aqueous sodium bicarbonate.[180] Related *NN*-disubstituted sulphines were not accessible by this method, but could be synthesized by peracid oxidation of the corresponding thioacyl chlorides.[180]

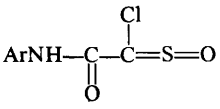
The participation of sulphine intermediates has been reported in the periodate-promoted oxidative rearrangement of *C*-sulphonylthioformamides to *S*-sulphonylthiourethanes,[181] and in the formation of α-toluenesulphinic acid or benzhydryl benzyl sulphone by the reaction of benzhydryl benzyl sulphoxides with sulphuryl chloride.[182]

[179] B. Zwanenburg, A. Wagenaar, L. Thijs, and J. Strating, *J.C.S. Perkin I*, 1973, 73.
[180] W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, 1972, **37**, 3818.
[181] N. H. Nilsson and A. Senning, *Angew. Chem.*, 1972, **84**, 293.
[182] C. Y. Meyers and G. J. McCollum, *Tetrahedron Letters*, 1973, 289.



(173)

(174)



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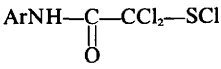
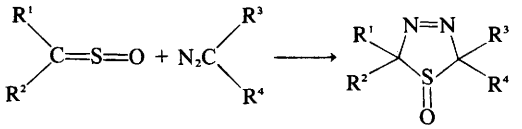


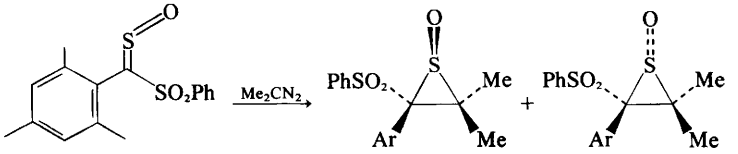
(176)

The reaction of sulphines with diazoalkanes or aryl-substituted diazomethanes has been studied by several groups of workers.[179,183–188] Although the reaction course was found to depend on the nature of the reactants, the rather comprehensive experimental material available seems to reflect clearly that the normal reaction of sulphines with diazoalkanes is a cycloaddition reaction leading to the formation of Δ^3-1,3,4-thiadiazoline 1-oxides (177).[183–186] The observation that different products were obtained by the action of 2-diazopropane on different geometrical isomers of the



(177)

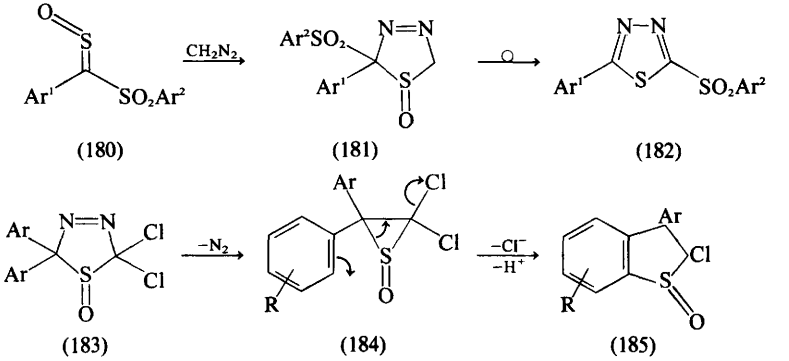
same sulphine led Zwanenburg and his co-workers to conclude[185] that the cycloaddition reaction is a stereospecific process, and that most probably the product formation takes place in a concerted manner. The same authors further noticed[185] that each of the geometrical isomers of the sulphine (178) reacts with 2-diazopropane, yielding the same 1:1 mixture of isomeric episulphoxides (179). On this basis it was pointed out[185] that episulphoxide



(178) (179) Ar = 2,4,6-$Me_3C_6H_2$

[183] B. F. Bonini, G. Maccagnani, A. Wagenaar, L. Thijs, and B. Zwanenburg, *J.C.S. Perkin I*, 1972, 2490.
[184] C. G. Venier and C. G. Gibbs, *Tetrahedron Letters*, 1972, 2293.
[185] L. Thijs, A. Wagenaar, E. M. M. van Rens, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3589.
[186] B. Zwanenburg and A. Wagenaar, *Tetrahedron Letters*, 1973, 5009.
[187] L. Thijs, J. Strating, and B. Zwanenburg, *Rec. Trav. chim.*, 1972, **91**, 1345.
[188] B. F. Bonini and G. Maccagnani, *Tetrahedron Letters*, 1973, 3585.

formation can hardly proceed *via* an intermediate Δ^3-1,3,4-thiadiazoline 1-oxide, as assumed previously. The idea[185] that the anomalous formation of episulphoxides is a consequence of steric requirements may find support in the observation of Bonini and Maccagnani[188] that aromatic sulphines, which on treatment with diazoalkanes yield Δ^3-1,3,4-thiadiazoline 1-oxides, react with aryldiazomethanes, affording mixtures of diastereoisomeric episulphoxides. Zwanenburg and Wagenaar have further observed[186] that the reaction of the sulphines (180) with diazomethane yields the rearrangement products (182). The intermediacy of (181) in this reaction was confirmed by its successful isolation in one case (Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-MeC_6H_4), and by the fact that the isolated compound (181) rearranged to (182) when chromatographed on silica. An elimination–addition mechanism was suggested for the rearrangement (181) → (182).[186] The reaction of dichlorosulphine with diaryldiazomethanes resulted also in the formation of a rearrangement product (185).[187] The intermediacy of a Δ^3-1,3,4-thiadiazoline



(180) (181) (182)

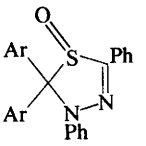
(183) (184) (185)

1-oxide (183) in the latter reaction was again proved by the successful isolation of (183) in one case (Ar = 4-MeC_6H_4). The likely rearrangement mechanism proposed[187] involved as a precursor to (185) the episulphoxide (184), being generated from (183) by nitrogen extrusion.

1:1 Adducts (186) were formed by the regiospecific, but non-stereospecific, reaction of diphenylnitrilimine with diaryl sulphines.[189] Sulphines of the type (187) reacted with aromatic sulphenyl chlorides in a thiophilic manner, yielding (188).[190] The sulphenic acid (189), a tautomer of (187), was considered as the reactive species in the latter reaction. The nucleophilic attack of azide ions on thiobenzoyl chloride *S*-oxide gave the yellow, very unstable sulphine (190), which decomposed rapidly to benzonitrile at room temperature with the evolution of gas, but which at −80 °C could be characterized by means of i.r. spectroscopy.[191] 9-Thiofluorenone

[189] B. F. Bonini, G. Maccagnani, L. Thijs, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3569.
[190] F. Klivenyi, G. Stajer, A. E. Szabo, and J. Pintye, *Acta Chim. Acad. Sci. Hung.*, 1973, **75**, 177.
[191] A. Holm and L. Carlsen, *Tetrahedron Letters*, 1973, 3203.

S-oxide reacted with dichlorocarbene under neutral conditions, yielding 9-(dichloromethylene)fluorene.[192] A convenient method for the preparation of 9- and 10-deuteriated camphors has been introduced in the reduction of the corresponding chlorosulphoxides, for example (191), by deuteriated amalgamated aluminium and/or Raney nickel.[193]



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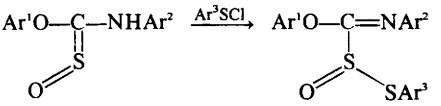
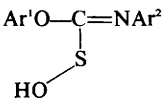


(187) (188)



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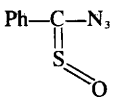

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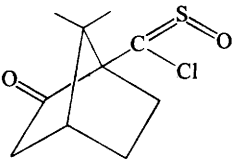


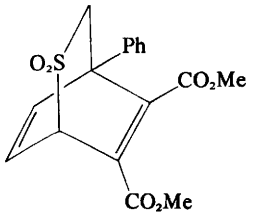
(191)

7 Sulphenes

Although the chemistry of sulphenes no longer constitutes an undiscovered field of organic chemistry, the compounds themselves have never been isolated, and our knowledge of these compounds to date is based exclusively on their reactions *in situ* and on the low-temperature i.r. data of the parent sulphene (see Vol. 2). However, on the basis of semi-empirical MO calculations, Snyder[194] recently suggested that sulphenes with electron-donating groups should be the more stable ones, and hence they are the ones with the best possibility of isolation.

The thermolysis of the bicyclic compound (192), purposedly designed to undergo a thermal reverse Diels–Alder reaction to form sulphene and an aromatic co-fragment, indeed afforded the co-fragment, 2,3-(dimethoxycarbonyl)biphenyl, almost quantitatively, whereas the fate of the generated sulphene could be established only when the thermolysis was carried out in the presence of a suitable trapping agent.[195] Sulphene has also been reported to be generated by the thermolysis of the phthalimide (193) at 600 °C.[196] Sulphenes of the type (194) were considered as likely intermediates in the

[192] C. G. Venier, C. G. Gibbs, and P. T. Crane, *J. Org. Chem.*, 1974, **39**, 501.
[193] G. C. Joshi and E. W. Warnhoff, *J. Org. Chem.*, 1972, **37**, 2383.
[194] J. P. Snyder, *J. Org. Chem.*, 1973, **38**, 3965.
[195] J. F. King and E. G. Lewars, *J.C.S. Chem. Comm.*, 1972, 700; *Canad. J. Chem.*, 1973, **51**, 3044.
[196] W. J. Mijs, J. B. Reesink, and U. E. Wiersum, *J.C.S. Chem. Comm.*, 1972, 412.



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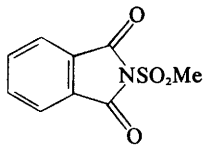

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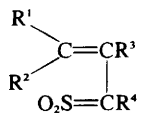
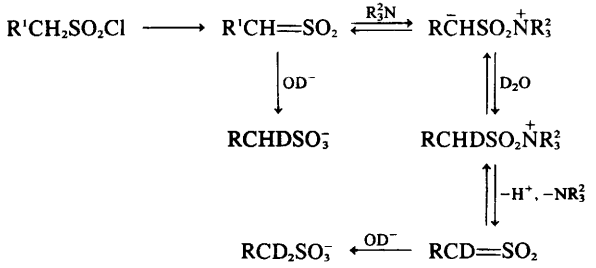


(194)

photolysis reactions of thiet 1,1-dioxides, which gave $\alpha\beta$-unsaturated ketones as products.[197]

King and his co-workers have observed[198] that alkanesulphonyl chlorides with more than one α-hydrogen atom react with deuterium oxide in the presence of sterically unhindered tertiary amines to form alkanesulphonates having more than one of the α-hydrogen atoms exchanged. This observation was rationalized in terms of a reaction sequence involving intermediate sulphenes and zwitterions (Scheme 9).[198] Kinetic studies in connection with

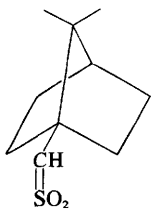


Scheme 9

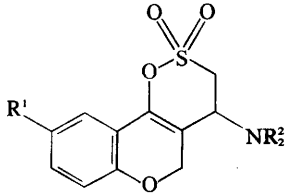
deuterium exchange revealed that the reaction of camphor-10-sulphonyl chloride with menthylamine proceeds principally *via* the sulphene (195).[199] 3-Dialkylaminomethylene-4-chromanones reacted with sulphene to give the cyclo-adduct (196).[200] The reactions of some representative sulphenes with triphenylphosphine have been found to occur with elimination of sulphur dioxide and formation of triphenylphosphonium salts.[201] Methylsulphonylmethanesulphonic acid and its phenyl and 4-nitrophenyl esters have been synthesized by the reaction of methylsulphonylsulphene (197) with water and the appropriate phenols, respectively.[202] Sulphene reacted with macrocyclic enamines in the normal way, yielding thietan SS-dioxides,[203]

[197] R. J. F. Langendries and F. C. De Schryver, *Tetrahedron Letters*, 1972, 4781.
[198] J. F. King, E. A. Luinstra, and D. R. K. Harding, *J.C.S. Chem. Comm.*, 1972, 1313.
[199] J. F. King, S.-K. Sim, and S.-K. Li, *Canad. J. Chem.*, 1973, **51**, 3914.
[200] P. Schenone, G. Bignardi, and S. Morasso, *J. Heterocyclic Chem.*, 1972, **9**, 1341.
[201] J. F. King, E. G. Lewars, and L. J. Danks, *Canad. J. Chem.*, 1972, **50**, 866.
[202] A. Senning, *Synthesis*, 1973, 211.
[203] S. Hünig, and H. Hoch, *Chem. Ber.*, 1972, **105**, 2197.

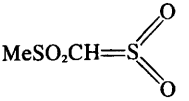
whereas benzoylsulphene, on treatment with enamines derived from cyclohexanone, gave mainly open-chain sulphones.[204] The cycloaddition reactions of sulphenes with ynamines,[205,206] ketenimines,[207] and thioamide vinylogues[137] have also been described recently.



(195)



(196)



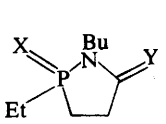
(197)

8 Thioamides and Selenoamides

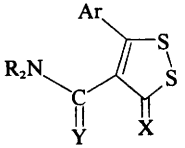
Synthesis.—The majority of the papers dealing with the synthesis of thioamides or their selenium analogues report on the application of standard methods. Thus a variety of open-chain aliphatic[29,208,209] and aromatic[210] as well as cyclic[32,211–221] amides have been converted into the corresponding thioamides by treatment with phosphorus pentasulphide in boiling polar[29,219] or, most commonly, non-polar solvents. The action of

[204] O. Tsuge, S. Iwanami, and S. Hagio, *Bull. Chem. Soc. Japan*, 1972, **45**, 237.
[205] M. E. Kuehne and H. Linde, *J. Org. Chem.*, 1972, **37**, 1846.
[206] L. W. Christensen, *Synthesis*, 1973, 534.
[207] O. Tsuge and S. Iwanami, *Org. Prep. Proced. Internat.*, 1971, **3**, 283.
[208] V. Skaric, B. Gaspert, and D. Skaric, *Croat. Chem. Acta*, 1973, **45**, 495.
[209] M. F. A. Abdel-Lateef and Z. Eckstein, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1971, **19**, 705.
[210] M. Jancevska and V. Prisaganec, *Croat. Chem. Acta*, 1972, **44**, 295; M. Jancevska and V. Prisaganec, *God. Zb. Prir.-Mat. Fak. Univ., Skopje, Mat. Fiz. Hem.*, 1972, **22**, 217 (*Chem. Abs.*, 1973, **78**, 124 372); M. Jancevska, V. Prisaganec, and K. Risteska, *ibid.*, p. 225 (*Chem. Abs.*, 1973, **78**, 147 514); V. Prisaganec and M. Jancevska, *ibid.*, p. 231 (*Chem. Abs.*, 1973, **78**, 147 509).
[211] V. A. Sedavkina and G. V. Bespalova, *Khim. geterotsikl. Soedinenii*, 1972, 333.
[212] D. De Filippo, A. Lai, E. F. Trugo, G. Verani, and C. Preti, *J. Inorg. Nuclear Chem.*, 1974, **36**, 73.
[213] K.-H. Weber and A. Bauer, *Annalen*, 1973, 1974.
[214] S. N. Baranov and B. E. Zhitar, *Khim. geterotsikl. Soedinenii*, 1971, 145.
[215] A. K. Bose, J. L. Fahey, and M. S. Manhas, *J. Heterocyclic Chem.*, 1973, **10**, 791.
[216] A. P. Grishchuk, T. V. Perova, and B. L. Parnovskii, *Khim. geterotsikl. Soedinenii*, 1971, 112.
[217] R. O. Kochkanyan, *Khim. geterotsikl. Soedinenii*, 1971, 140.
[218] N. M. Turkevich and D. P. Boikov, *Dopovidi Akad. Nauk Ukrain. R.S.R., Ser. B*, 1971, **33**, 1016 (*Chem. Abs.*, 1972, **76**, 153 713).
[219] O. P. Shvaika, V. N. Artemov, V. E. Kononenko, and S. N. Baranov, *Khim. geterotsikl. Soedinenii*, 1973, 930.
[220] J. Daunis, Y. Guindo, R. Jacquier, and P. Viallefont, *Bull. Soc. chim. France*, 1972, 1975.
[221] H. Maehr, M. Leach, and V. Toome, *J. Heterocyclic Chem.*, 1972, **9**, 1389; J. P. Marquet, J. D. Bourzat, J. Andre-Louisfert, and E. Bisaqui, *Tetrahedron*, 1973, **29**, 435; M. P. Thakur and S. K. P. Sinha, *J. Indian Chem. Soc.*, 1972, **49**, 1185; M. Robba, M. Maume, and J. C. Lancelot, *Tetrahedron Letters*, 1973, 3239; M. Robba, P. Touzot, and R.-M. Riquelme, *Compt. rend.*, 1973, **276**, C, 1591; M. Ikehara and M. Muraoka, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 550.

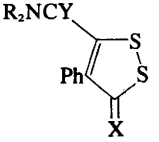
phosphorus pentasulphide on the azaphospholanone 2-oxide (198)[222] and the carbamoyl 1,2-dithiole-3-ones (201)[223] and (204)[224] yielded the corresponding thioamides (200), (203), and (206), respectively, as a result of a subsequent reaction of the primarily formed compounds (199), (202), and (205),



(198) X = Y = O
(199) X = S, Y = O
(200) X = Y = S

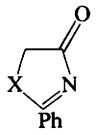


(201) X = Y = O
(202) X = S, Y = O
(203) X = Y = S

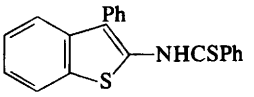


(204) X = Y = O
(205) X = S, Y = O
(206) X = Y = S

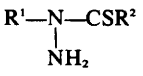
respectively, with the thionation agent. The heterocyclic compounds (207) reacted with phosphorus pentasulphide to form the same rearrangement product (208).[225] *N*-Thioacylhydrazines (209) have been obtained by the



(207) X = O, S



(208)

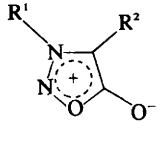


(209)

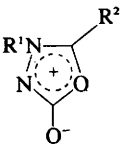
reaction of the sydnones (210) with phosphorus pentasulphide,[226] and by treatment of the isosydnones (211) with hydrogen sulphide in the presence of pyridine.[227] Carbostyril and *N*-methylcarbostyril have been transformed into their thio-analogues by *OO*-dialkyl and *OO*-diphenyl dithiophosphoric acids.[228]

The thiocarbonyl sulphur atom has been introduced into several cyclic thioamides by the reaction of the appropriate cyclic chloro-imines with nucleophiles such as thiourea[229–232] and the hydrogen sulphide anion.[48,233] Some selenopyrrolones (212) have been prepared from the corresponding 3-formyl-2-chloropyrrole by successive treatment of the latter with potassium hydrogen selenide and secondary amines.[233] A reinvestigation of the

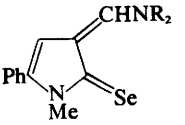
[222] V. K. Khairullin and M. A. Vasyanina, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 2059.
[223] C. Trebaul, *Bull. Soc. chim. France*, 1972, 1840.
[224] C. Trebaul, *Bull. Soc. chim. France*, 1973, 721.
[225] E. Koltai, J. Nyitrai, K. Lempert, G. Horwath, A. Kalman, and G. Argay, *Tetrahedron*, 1973, **29**, 2783; E. Koltai and K. Lempert, *ibid.*, 1973, **29**, 2795.
[226] K. Sugimoto and M. Ohta, *Bull. Chem. Soc. Japan*, 1973, **46**, 2921.
[227] A. R. McCarthy, W. D. Ollis, and C. A. Ramsden, *J.C.S. Perkin I*, 1974, 627,
[228] A. Nakanishi and S. Oae, *Tetrahedron*, 1973, **29**, 2023.
[229] A. Attar, H. Wamhoff, and F. Korte, *Chem. Ber.*, 1973, **106**, 3524.
[230] M. Robba, P. Touzot, and R.-M. Riquelme, *Compt. rend.*, 1973, **276**, *C*, 93.
[231] G. Doré, M. Bonhomme, and M. Robba, *Tetrahedron*, 1972, **28**, 3277.
[232] A. Yamazaki, T. Furukawa, M. Akiyama, M. Okutsu, I. Kumashiro, and M. Ikehara, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 692.
[233] I. Y. Kvitko and N. B. Sokolova, *Khim. geterotsikl. Soedinenii*, 1973, 565.



(210)



(211)



(212)

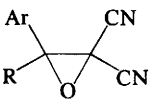
reaction of simple acyclic imidoyl chlorides with hydrogen sulphide revealed that simple *N*-substituted alkyl- and aryl-thioamides are formed in excellent yields if the reaction is carried out in the presence of catalytic amounts of phosphorus pentasulphide.[234]

The base-catalysed reaction of nitriles with hydrogen sulphide constitutes a classic method of preparation of *N*-unsubstituted thioamides. Recent papers dealing with this reaction report the preparation of thioformamide,[235] 2-thiocarbamoyl-1,10-phenanthroline,[236] thiocarbamoylthiophens,[237] and thiocarbamoylselenophens.[238] 2-Selenocarbamoylselenophen and 3-selenocarbamoylselenophen have been synthesized by treatment of the corresponding cyanoselenophens with hydrogen selenide.[238] Some aliphatic and aromatic primary thioamides have also been obtained by the reaction of their related nitriles with *OO*-dialkyl dithiophosphoric acids.[239] Whereas 2-aryl-1,1-dicyanoepoxides (213; R = H) reacted with thiourea to form 2-aminothiazolin-4-ones, 2,2-disubstituted 1,1-dicyano-epoxides (213; R = Ph or alkyl) gave the thioamides (214) under similar reaction conditions.[240] Thiobenzamide has been reported to be formed in low yield by the reaction of benzamidine with carbon disulphide.[241]

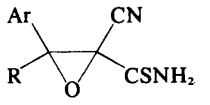
Several papers have reported on the application of the Willgerodt–Kindler reaction in the synthesis of thioamides.[242–244] In an investigation of a modified form of this reaction, Ried and his co-workers[245] treated some 2,4,6-trimethylphenyl alkyl ketones with dimorpholinodisulphide (215). Only the methyl ketone afforded a normal Willgerodt–Kindler product (216), but otherwise a clear relationship between the nature of the product and the nature of the ketone alkyl group, *i.e.* the number of

[234] K. Jakopcic and B. Karaman, *Bull. Sci., Cons. Acad. Sci. Arts R.S.F. Yougoslavie, Sect. A*, 1973, **18**, 65 (*Chem. Abs.*, 1973, **79**, 78 050).
[235] E. H. Axelrod, *Ann. N.Y. Acad. Sci.*, 1973, **214**, 14.
[236] H. A. Goodwin, F. E. Smith, E. König, and G. Ritter, *Austral. J. Chem.*, 1973, **26**, 521; H. A. Goodwin, D. W. Mather, and F. E. Smith, *ibid.*, p. 2623.
[237] K. Gewald, M. Hentschel, and R. Heikel, *J. prakt. Chem.*, 1973, **315**, 539.
[238] P. Chauvin, J. Morel, C. Paulmier, and P. Pastour, *Compt. rend.*, 1972, **274**, *C*, 1347.
[239] A. Nakanishi and S. Oae, *Chem. and Ind.*, 1973, 274.
[240] M. Ferrey, A. Robert, and A. Foucaud, *Compt. rend.*, 1973, **277**, *C*, 1153.
[241] Y. E. Moharir, *Indian J. Chem.*, 1972, **10**, 315.
[242] T. Hisano and Y. Yabuta, *Org. Prep. Proced. Internat.*, 1972, **4**, 105; T. Hisano and Y. Yabuta, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 511.
[243] W. Ried and E. Nyiondi-Bonguen, *Annalen*, 1973, 134; Y. N. Zafranskii, A. N. Semenova, K. E. Zhukova, and N. I. Baganov, *Khim. Prom. (Moscow)*, 1972, **48**, 631 (*Chem. Abs.*, 1972, **77**, 151 631; 1973, **78**, 29 395).
[244] K. Gewald, M. Kleinert, B. Thiele, and M. Hentschel, *J. prakt. Chem.*, 1972, **314**, 303.
[245] W. Ried, W. Ochs, H. Liebig, and K. Wagner, *Annalen*, 1972, **757**, 147.

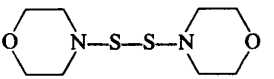
α-hydrogen atoms present, could be demonstrated. The dissociation of dimorpholinodisulphide into (217) and (218) was suggested as the key step in the reactions.[245] The reactions between *N*-substituted isothiazolium salts that are unsubstituted in the 3-position and elemental sulphur in boiling pyridine afforded isothiazoline-3-thiones.[246]



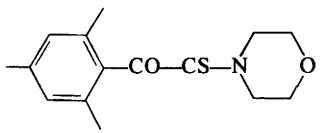
(213)



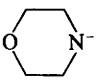
(214)



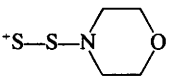
(215)



(216)



(217)

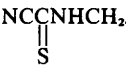


(218)

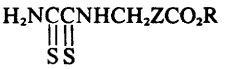
The applicability of isothiocyanates as reagents in the synthesis of thioamides has been amply demonstrated. Thus a series of aliphatic *N*-arylthioamides has been synthesized by the reaction of aryl isothiocyanates with alkyl magnesium iodides.[247] In their search for suitable methods for the preparation of *N*-acylthioamides, Walter and Krohn[248] allowed benzoyl isothiocyanate to react with several alkyl magnesium bromides at −60 °C, and obtained in most cases the desired *N*-benzoylthioamides in moderate to good yields. Thioamides have been obtained by the base-promoted reactions of isothiocyanates with arylsulphonylacetamides,[249] arylsulphonylacetophenones,[250] 1-cyano-isochromane,[251] and 1-cyano-isothiochromane.[251] The action of potassium cyanide on 5-isothiocyanatohexanoic or *p*-(isothiocyanatomethyl)benzoic acid, or their esters, gave compounds of the type (219), which on treatment with hydrogen sulphide yielded dithio-oxamides (220).[252] Dimethoxycarbene reacted with 2 equivalents of aryl isothiocyanate to yield the dithiohydantoin (221).[253] This reaction was found to proceed eleven times slower than the similar reaction of dimethoxycarbene with aryl isocyanates, and was believed to involve the dipole (222) as an intermediate.[253] Several new thioamides have been reported to be synthesized by Michael-type reactions of enamines with the

[246] G. E. Bachers, D. M. McKinnon, and J. M. Buchshriber, *Canad. J. Chem.*, 1972, **50**, 2568.
[247] K. K. Ginwala and J. P. Trivedi, *J. Indian Chem. Soc.*, 1971, **48**, 791.
[248] W. Walter and J. Krohn, *Annalen*, 1973, 476.
[249] V. M. Neplyuev, M. G. Lekar, R. G. Dubenko, and P. S. Pel'kis, *Zhur. org. Khim.*, 1971, **7**, 2352.
[250] V. M. Neplyuev, T. A. Sinenko, R. G. Dubenko, and P. S. Pel'kis, *Zhur. org. Khim.*, 1973, **9**, 347.
[251] H. Böhme and F. Ziegler, *Synthesis*, 1973, 297.
[252] A. F. Grabenko, M. N. Danchenko, and P. S. Pel'kis, *Zhur. org. Khim.*, 1972, **8**, 528.
[253] R. W. Hoffmann, K. Steinbach, and B. Dittrich, *Chem. Ber.*, 1973, **106**, 2174.

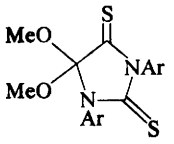
appropriate isothiocyanates.[203,254–256] 2,3,3-Trimethyl-3*H*-indoles also yielded formal Michael adducts (223) upon treatment with isothiocyanates, but this reaction was shown to proceed *via* the unstable thioureas (224).[257,258] *N*-Substituted pyrrole-2-thiocarboxamides (225) and (226) have been obtained in high yields by the reaction of appropriate isothiocyanates with pyrroles that are unsubstituted in the 2-position.[259,260] However, the thiocarboxamide group may also be introduced into the 3-position of the pyrrole ring, if both the 2- and the 5-position are occupied, as demonstrated by the formation of (227) in the reaction of 2-ethoxycarbonyl-3,5-dimethylpyrrole



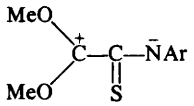
(219) $Z = -(CH_2)_4-$ or C_6H_4
$R = H$, Me, or Et



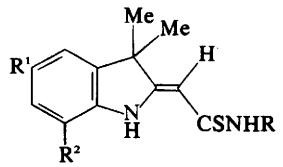
(220)



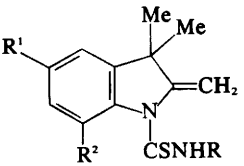
(221)



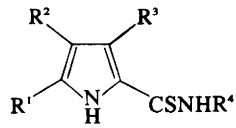
(222)



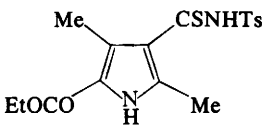
(223)



(224)



(225) $R^1 = R^2 = R^3 = H$: $R^4 = CO_2Et$
(226) $R^1 = R^3 = Me$; $R^4 = Ts$;
$R^2 = H$ or CO_2Et

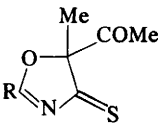


(227)

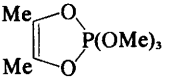
with tosyl isothiocyanate.[260] *o*-Isothiocyanato-*trans*-cinnamaldehyde underwent an intramolecular ring-closure reaction, yielding 3-formylquinolone-2(1*H*)-thione, on treatment with base,[261] and the Δ^2-oxazoline-4-thiones (228) were the products in the reaction of acyl isothiocyanates with the 1,3,2-dioxaphospholen (229).[262] Thiobutyrolactams (230) were produced as

[254] J. Gordeler and M. Bischoff, *Chem. Ber.*, 1972, **105**, 3566.
[255] O. Tsuge and A. Inaba, *Bull. Chem. Soc. Japan*, 1973, **46**, 2221.
[256] M. Dzurilla, P. Kristian, and E. Demjanova, *Chem. Zvesti*, 1973, **27**, 488.
[257] L. Capuano and H. J. Schrepfer, *Chem. Ber.*, 1972, **105**, 2539.
[258] L. Capuano, H. J. Schrepfer, K. Müller, and H. Roos, *Chem. Ber.*, 1974, **107**, 929.
[259] E. P. Papadopoulos, *J. Org. Chem.*, 1973, **38**, 667.
[260] A. Treibs, L. Schulze, F.-H. Kreuzer, and H.-G. Holm, *Annalen*, 1973, 207.
[261] R. Hull, *J.C.S. Perkin I*, 1973, 2911.
[262] F. Ramirez, V. A. V. Prasad, and H. J. Bauer, *Phosphorus*, 1973, **2**, 185.

the result of an elimination of aryl isocyanate from the unstable intermediate adducts (231) formed initially in the reaction of aryl isothiocyanates with the nitrones (232).[263] Bicyclic compounds containing the thiolactam grouping have been obtained by the reaction of phenyl isothiocyanate with the pyrylium betaine (113)[140] and the meso-ionic compound (233), [264] respectively.



(228)



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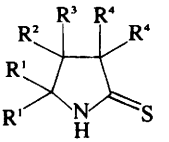

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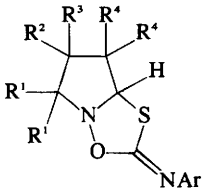
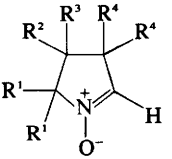


(231)



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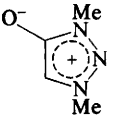
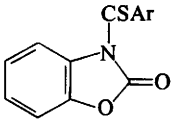


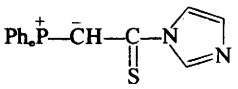
(233)

A variety of thioamides and heterocyclic compounds containing the thiolactam grouping have been synthesized by thioacylation of amines by means of thioketens,[58,166] thioacyl chlorides,[265–267] ethyl thionoformate,[268] dithio-acids,[266,269] 3,1(4*H*)-benzothiazine-4-thiones,[63,270] 2,4-dithioxodihydro-3,1(4*H*)-benzothiazine,[270] *N*-thiobenzoyltriazoles,[266] and 3-thioaroyl-1,3-benzoxazolinones (234).[271] The thiocarbonyl-stabilized phosphonium ylide (235) has been obtained by the reaction of triphenylphosphonium methylide with di(imidazol-1-yl) thioketone (236).[266] Monothio-oxamides (237) were produced by the action of primary amines on the compounds (238),[272] and the betaine (117) was found to be ring-opened by benzylamine and pyrrolidine, yielding the thioamides (239) and (240), respectively.[142] Some selenoformamides have been obtained by the reaction of primary and secondary amines with dialkyl triselenocarbonates.[273]

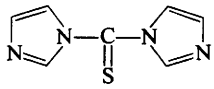
[263] D. St. C. Black and K. G. Watson, *Tetrahedron Letters*, 1972, 4191; *Austral. J. Chem.*, 1973, **26**, 2473.
[264] K. T. Potts and S. Husain, *J. Org. Chem.*, 1972, **37**, 2049.
[265] N. M. Oleinik, L. M. Litvinenko, and L. P. Kurchenko, *Zhur. org. Khim.*, 1972, **8**, 1632.
[266] W. Walter and M. Radke, *Annalen*, 1973, 636.
[267] W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, 1972, **37**, 1526.
[268] R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Letters*, 1973, 4645.
[269] D. Nardi, A. Tajana, and S. Rossi, *J. Heterocyclic Chem.*, 1973, **10**, 815.
[270] S. Leistner and G. Wagner, *Z. Chem.*, 1973, **13**, 135.
[271] G. Wagner and S. Leistner, *Pharmazie*, 1972, **27**, 631.
[272] H. Oediger and N. Joop, *Annalen*, 1972, **758**, 1.
[273] L. Henriksen and E. S. S. Kristiansen, *Ann. N.Y. Acad. Sci.*, 1972, **192**, 101.



(234)

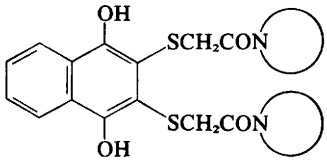


(235)

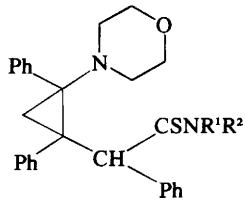


(236)

(237)



(238)



(239) $R^1 = H$, $R^2 = CH_2Ph$
(240) $R^1R^2 = -(CH_2)_4-$

Nilsson and his co-workers have reported on the applicability of *C*-sulphonylthioformamides (241) as excellent thiocarbamoylation agents towards nucleophiles such as the cyanide anion and anions of active-methylene compounds.[274] The first thioacylthiophosphinylimides (242) have been synthesized by the reaction of dimethylthiophosphinic acid chloride with thioamide anions.[275] The reaction of acetophenones with sulphur chloride afforded light brown resinous materials that on subsequent treatment with aqueous sodium hydroxide in DMF were converted into arylglyoxyldimethylthioamides (243).[276] Some thioaroyl isothiocyanates have been obtained by thermal rearrangement of the corresponding

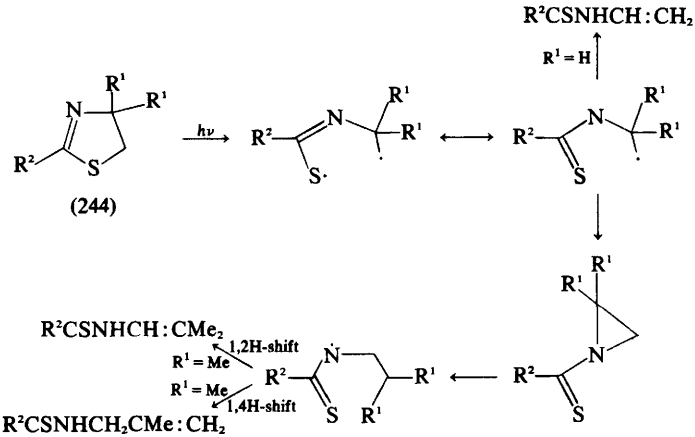
(241) (242) R = Ph or CH_2Ph (243)

thiocyanates.[277] The formation of *N*-thioacylketimines (136) by the photolysis of thioketones in acetonitrile solution should also be mentioned.[163]

Among the several papers[227,278–281] reporting on the formation of thioamides by ring-opening reactions of heterocyclic compounds is one[281] which describes the formation of *N*-alkenylthioamides by photoisomerization of Δ^2-thiazolines (244). The isomerization was considered to proceed *via* biradicals generated as the result of an initial homolytic cleavage of the

[274] N. H. Nilsson, A. Senning, S. Karlsen, and J. Sandstrøm, *Synthesis*, 1972, 314.
[275] J. Bödeker and H. Zärtner, *Z. Chem.*, 1974, **14**, 56.
[276] T. Matsuda and Y. Takeda, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 89.
[277] J. Goerdeler and W. Teller, *Tetrahedron Letters*, 1972, 1513.
[278] A. Alemagna and T. Bacchetti, *Gazzetta*, 1972, **102**, 1068, 1077.
[279] R. M. Christie, A. S. Ingram, D. H. Reid, and R. G. Webster, *J.C.S. Perkin I*, 1974, 722.
[280] G. Wagner and S. Leistner, *Pharmazie*, 1973, **28**, 25.
[281] T. Matsuura and Y. Ito, *J.C.S. Chem. Comm.*, 1972, 896.

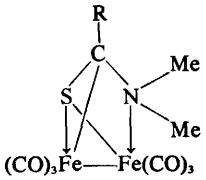
C—S bond in (244) (Scheme 10).[281] Some other recent papers, describing the synthesis of heterocyclic compounds containing the thiolactam[258,282–288] or the selenolactam[289] grouping, also deserve attention.



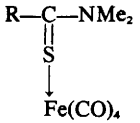
Scheme 10

Metal Complexes.—In order to determine the effect of the presence of a nitrogen donor on the *ortho*-metallation of the thiobenzoyl function, Alper and Chan[290,291] treated *NN*-dimethylthiobenzamide with di-iron enneacarbonyl. However, no sulphur-donor ligand *ortho*-metallated complex was obtained, as happens in the case of thiobenzophenone,[92] but instead the complexes (245) and (246) were formed.[290,291] *NN*-Dimethylthioacetamide similarly yielded the complexes (247) and (248),[291] whereas the unsubstituted thiobenzamide on treatment with di-iron enneacarbonyl gave the complexes (249) and (250).[291] The synthesis and properties of metal complexes of dithio-oxamides,[292] dithiomalonamides,[293] 2-thiocarbamoyl-1,10-phenanthrolines,[236] thiomorpholine-3-thione,[212] and 2,4-dithiouracil[294] have also been described recently.

[282] C. O. Okafor, *J. Org. Chem.*, 1973, **38**, 4383.
[283] H.-J. Kabbe, *Synthesis*, 1972, 268.
[284] W. Abraham and G. Barnikow, *Tetrahedron*, 1973, **29**, 691.
[285] D. E. Horning and J. M. Muchowski, *Canad. J. Chem.*, 1973, **51**, 2349.
[286] D. St. C. Black and K. G. Watson, *Austral. J. Chem.*, 1973, **26**, 2177.
[287] W. Ried and W. Merkel, *Annalen*, 1973, 122.
[288] T. Hino, T. Suzuki, S. Takeda, N. Kano, Y. Ishii, A. Sasaki, and M. Nakagawa, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2739.
[289] Y. N. Koshelov, I. Y. Kvitko, and E. D. Samartseva, *Zhur. org. Khim.*, 1972, **8**, 2204.
[290] H. Alper and A. S. K. Chan, *J.C.S. Chem. Comm.*, 1973, 724.
[291] H. Alper and A. S. K. Chan, *Inorg. Chem.*, 1974, **13**, 225.
[292] G. C. Pellacani, G. Peyronel, and A. C. Fabretti, *Gazzetta*, 1972, **102**, 11; G. C. Pellacani, G. Peyronel, and A. Pignedoli, *ibid.*, p. 835.
[293] G. Peyronel, G. C. Pellacani, G. Benetti, and G. Pollacci, *J.C.S. Dalton*, 1973, 879.
[294] J. S. Dwivedi and U. Agarwala, *Z. anorg. Chem.*, 1973, **397**, 74.

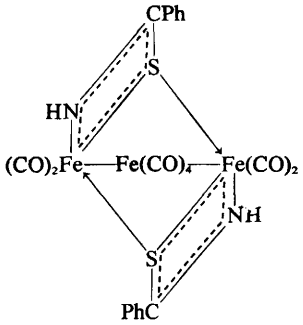


(245) R = Ph
(247) R = Me



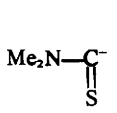
(246) R = Ph
(248) R = Me

$(PhCSNH_2)_2Fe(CO)_3$
(249)

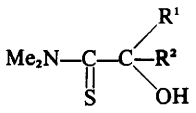


(250)

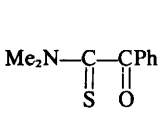
Reactions.—In contrast to the compounds described in the foregoing sections, thioamides constitute a class of compounds for which the principles of reactivity are rather well established on the basis of the experience of several decades. This is clearly reflected by the fact that only a minority of the very many recent papers dealing with the chemistry of compounds containing the thioamide moiety actually report on the reactivity of simple thioamide systems. Among these are two papers[295,296] describing the formation of the anion (251) by the action of lithium di-isopropylamide on *NN*-dimethylformamide at low temperatures. The applicability of (251) as an efficient nucleophilic thiocarbamoylation agent was demonstrated by the ready formation of α-hydroxythioamides (252) in high yields on addition of ketones[295,296] or aldehydes[296] to the yellow THF solution of (251). With methyl benzoate and methyl iodide, (251) similarly gave the phenylglyoxylic thioamide (253) and *NN*-dimethylthioacetamide,



(251)



(252)

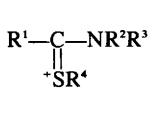


(253)

respectively.[296] The sites of protonation in [^{15}N]thioacetamide and [^{15}N]thiobenzamide have been the subject of a recent n.m.r. spectroscopic study, resulting in the conclusion that *S*-protonation is the predominant process, if not the only form of protonation.[297] The alkylation reactions of several thioamides, acyclic as well as cyclic, with diazomethane,[220,298] alkyl

[295] B. Banhidai and U. Schöllkopf, *Angew. Chem.*, 1973, **85**, 861.
[296] D. Enders and D. Seebach, *Angew. Chem.*, 1973, **85**, 1104.
[297] W. Walter, M. F. Sieveking, and E. Schaumann, *Tetrahedron Letters*, 1974, 839.
[298] N. A. Kassab, M. H. Elnagdy, N. A. Messeha, and H. A. R. Ead, *J. prakt. Chem.*, 1972, **314**, 799; N. A. Kassab, M. H. Elnagdy, and H. A. R. Ead, *ibid.*, 1973, **315**, 265; N. A. Kassab and N. A. Messeha, *ibid.*, p. 1017.

halides,[213,299–302] and triethyloxonium tetrafluoroborate[303] have been extensively studied. Two papers reporting on the synthesis of new heterocyclic systems by means of thioamide alkylation reactions should be mentioned in this connection; the first one[299] describes the formation of 1,5-dihydro-1,2,3,4-thia(S^{IV})triazoles (255) by the reaction of quaternary salts of *N,N*-disubstituted thioamides (254) with sodium azide, the other[304] the formation of 1,3-benzo[*e*]thiazepines (256) by the reaction of simple thioamides with 2-bromomethylbenzyl or 2-bromomethylbenzoyl bromide. Some new thiazoles and selenazoles have been synthesized by Hantzsch-type reactions of the thio- and seleno-amides (257) with α-chlorocarbonyl compounds.[238,305] The thiazines (258), which are important precursors in the synthesis of cephems, were prepared by the reaction of the thioformamide



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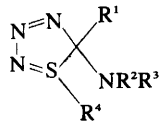
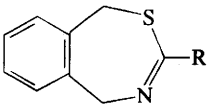


(255)



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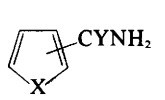
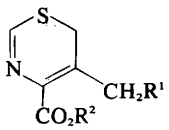
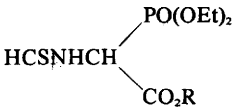


(257) X = O, S, or Se
Y = S or Se



(258)



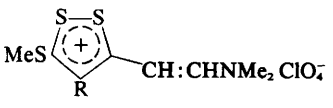
(259)

derivative (259) with suitable α-chloro-ketones.[306] A new route to 2,4-disubstituted thiazines has been found in the reaction of primary thioamides with β,β-dichlorovinyl aryl ketones.[307] Several other heterocyclic compounds have been produced by treatment of appropriate thioamides[308,309] or thiohydrazides[310,311] with reagents such as acid chlorides,[308] phenyl esters,[309] phosgene,[310] and isocyanide dichlorides.[311] *NN*-Dimethylthioformamide

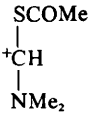
[299] S. I. Mathew and F. Stansfield, *J.C.S. Perkin I*, 1974, 540.
[300] W. Walter and J. Krohn, *Annalen*, 1973, 443.
[301] M. I. Ali, A. A. El-Sayad, and H. A. Hammouda, *J. prakt. Chem.*, 1973, **315**, 1090.
[302] M. Kleiner. *J.C.S. Perkin I*, 1973, 739.
[303] J. E. Oliver and P. E. Sonnet, *J. Org. Chem.*, 1973, **38**, 1437.
[304] D. N. Reinhoudt, *Rec. Trav. chim.*, 1973, **92**, 20.
[305] P. Chauvin, J. Morel, and P. Pastour, *Compt. rend.*, 1973, **276**, *C*, 1453.
[306] R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Letters*, 1973, 4649.
[307] W. Schroth, G. Dill, N. T. K. Dung, N. T. M. Khoi, P. T. Binh, H.-J. Waskiewicz, and A. Hildebrandt, *Z. Chem.*, 1974, **14**, 52.
[308] T. Kappe and W. Golser, *Synthesis*, 1972, 312.
[309] R. Ketcham, T. Kappe, and E. Ziegler, *J. Heterocyclic Chem.*, 1973, **10**, 223.
[310] K. Rüfenacht, *Helv. Chim. Acta*, 1973, **56**, 162.
[311] W. D. Ollis and C. A. Ramsden, *J.C.S. Perkin I*, 1974, 633.

reacted with 4-substituted 5-methyl-3-methylthio-1,2-dithiolylium perchlorates in the presence of acetic anhydride to yield the condensation products (260).[312] The formation of (260) was interpreted in terms of the attack of an intermediate 5-methylene-1,2-dithiole on acetylated thioformamide (261).[312] The action of sulphenyl chlorides on secondary thioamides afforded the disulphides (262).[313]

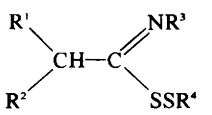
Several new examples of the reactivity of thioamides towards compounds containing activated carbon–carbon double or triple bonds have appeared.[56,314–318] Thus little-known thiazine derivatives have been synthesized by treatment of primary thioamides with $\alpha\beta$-unsaturated ketones;[314,315] pyridine-2-thiones afforded, on treatment with α-bromo-$\alpha\beta$-unsaturated acids[316] or acetylenedicarboxylic acid,[317] dihydrothiazolo[3,2-*a*]pyridinium salts, whereas the vinyl sulphides (263) were the products obtained in their reactions with propiolic or phenylpropiolic acid;[317] a Diels–Alder adduct was produced by the reaction of the thioamide (264) with dimethyl acetylenedicarboxylate.[318] *NN'*-Disubstituted phenylpropiolamidines (265),



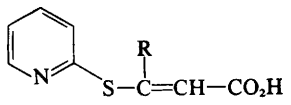
(260)



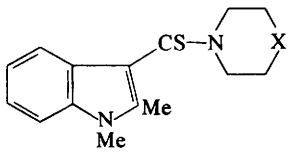
(261)



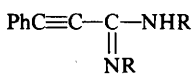
(262)



(263) R = H or Ph



(264) X = O or CH_2



(265)

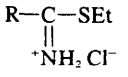
however, reacted with primary thioamides as a desulphurization agent, affording nitriles in excellent yields together with β-mercaptocinnamamidines (34).[56] Thiobenzamide has been desulphurated to benzonitrile by phosphorus tris(diethylamide).[319]

Recent studies of the reactivity of thioamides towards amine derivatives

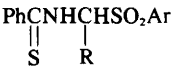
[312] C. Metayer, G. Duguay, and H. Quiniou, *Bull. Soc. chim. France*, 1972, 4576.
[313] W. Walter and H.-W. Meyer, *Annalen*, 1973, 462.
[314] S. Hoff and A. P. Blok, *Rec. Trav. chim.*, 1973, **92**, 631.
[315] H. Hartmann, *Tetrahedron Letters*, 1972, 3977.
[316] K. Undheim and R. Lie, *Acta Chem. Scand.*, 1973, **27**, 1749.
[317] R. Lie and K. Undheim, *Acta Chem. Scand.*, 1973, **27**, 1756.
[318] Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2770.
[319] T. Sodeyama, M. Kodomari, and K. Itabashi, *Chem. Letters*, 1973, 577.

deal mainly with heterocyclic compounds containing the thiolactam grouping.[320–322] However, one exceptional paper reports[323] that the aminolysis of *N*-acylthiobenzamides always proceeds by a nucleophilic attack of the amine on the carbon atom of the carbonyl group, a thiobenzamide and an amide containing the attacking amino-group being formed. In contrast to the corresponding amides, simple alkyl- and aryl-thioamides reacted spontaneously with ethyl thiochloroformate to produce the thioimino-ester hydrochlorides (266).[324]

Thiobenzamide has been reported to undergo a Mannich-type reaction on simultaneous treatment with aldehydes and arylsulphinic acids, yielding the compounds (267).[325] 2-, 3-, and 4-thiocarbamoylpyridines similarly gave the *N*-(aminomethyl)thioamides (268) by reaction with a variety of amines in the presence of formaldehyde.[326] A new stereospecific synthesis of 5,6-dihydro-4*H*-1,3-thiazines (269) depends on the reaction of thioamides with aldehydes and alkenes;[327] it was considered likely that (270) is an intermediate in this reaction.

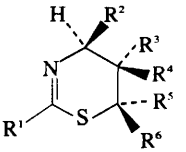


(266)

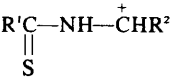


(267)

(268)



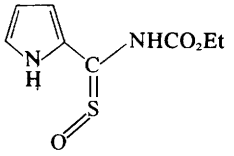
(269)



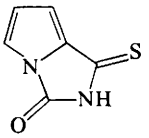
(270)

The hydrogen peroxide oxidation of *N*-(ethoxycarbonyl)pyrrole-2-thiocarboxamide (225) has been the subject of a recent study by Papadopoulos,[259] who found that in basic media (225) is converted into the corresponding amide, whereas in acidic solution the sulphine (271) is formed. The thiocarbonyl group in (272) [the cyclization product obtained by heating (225) in quinoline] behaved similarly.[259] Several examples of the formation of heterocyclic compounds, especially isothiazole derivatives, by oxidative treatment of appropriate thioamides have appeared.[60,150,237,328] The

[320] P. G. Sekachev, *Khim. geterotsikl. Soedinenii*, 1973, 1351.
[321] F. Asinger, D. Neuray, W. Leuchtenberger, A. Saus, and F. A. Dagga, *Annalen*, 1972, **761**, 95.
[322] F. Asinger, D. Neuray, W. Leuchtenberger, and U. Lames, *Annalen*, 1973, 879; F. Asinger and W. Leuchtenberger, *ibid.*, 1974, 157.
[323] G. Wagner and S. Leistner, *Pharmazie*, 1972, **27**, 59.
[324] S. L. Razniak, E. M. Flagg, and F. Siebenthall, *J. Org. Chem.*, 1973, **38**, 2242.
[325] H. Meijer, R. M. Tel, J. Strating, and J. B. F. N. Engberts, *Rec. Trav. chim.*, 1973, **92**, 72.
[326] H. Foks and J. Sawlewicz, *Rozpr. Gdansk. Tow. Nauk, Wydz. 3*, 1973, 109 (*Chem. Abs.*, 1974, **80**, 47 794).
[327] L. Abis and C. Giordano, *J.C.S. Perkin I*, 1973, 771.
[328] H. Kunzek and G. Barnikow, *Z. Chem.*, 1973, **13**, 175.



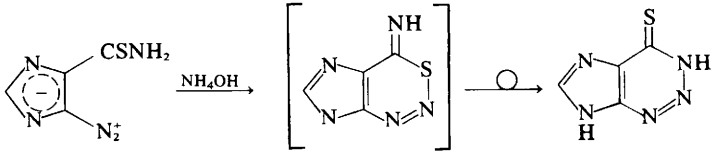
(271)



(272)

iodine oxidation of 1-phenyl-2,3-dimethyl-Δ^3-pyrazoline-5-thione afforded a disulphide.[329]

Among the several papers reporting on the applicability of thioamides[330–337] and thiohydrazides[338–342] in the synthesis of heterocyclic compounds, the most interesting paper is perhaps that of Ofitserov and his co-workers,[330] describing the formation of (275) by the action of aqueous ammonia on the meso-ionic thioamide (273); the formation of (275) was explained on the basis of a mechanism involving (274) as a spontaneously rearranging intermediate.[330]

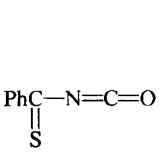


(273) (274) (275)

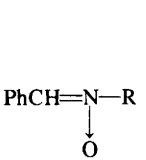
A series of recent papers documents solid advance within the chemistry of thioacyl isocyanates. Thus a variety of heterocyclic compounds have been obtained in (4+2) cycloaddition reactions of thiobenzoyl isocyanate (276) with aldehydes,[343] diarylketens,[344] ketenimines,[344] benzylideneamines,[345]

[329] M. Orban, E. Koros, and K. Vargha, *Magyar Kém. Folyóirat*, 1973, **79**, 452 (*Chem. Abs.*, 1974, **80**, 14 872).
[330] V. I. Ofitserov, Z. V. Pushkareva, V. S. Mokrushin, and K. V. Aglitskaya, *Khim. geterotsikl. Soedinenii*, 1973, 1292.
[331] J. Meijer and L. Brandsma, *Rec. Trav. chim.*, 1973, **92**, 1331.
[332] J. Nyitrai and K. Lempert, *Acta Chim. Acad. Sci. Hung.*, 1972, **73**, 43.
[333] M. Yokoyama, Y. Sawachi, and T. Isso, *J. Org. Chem.*, 1973, **38**, 802.
[334] M. Jancevska and V. Prisaganec, *God. Zb., Prir.-Mat. Fak. Univ. Skopje, Mat. Fiz. Hem.*, 1971, **21**, 59 (*Chem. Abs.*, 1972, **76**, 140 627).
[335] R. L. N. Harris, *Austral. J. Chem.*, 1972, **25**, 993.
[336] M. Takahashi, S. Shirahashi, and N. Sugawara, *Nippon Kagaku Kaishi*, 1973, 1519.
[337] D. A. Tomalia and J. N. Paige, *J. Org. Chem.*, 1973, **38**, 3949.
[338] A. M. Barghash, A.-M. M. E. Omar, A. M. Farghaly, and M. S. Ragab, *Pharmazie*, 1973, **28**, 482.
[339] A. M. Barghash, A.-M. M. E. Omar, A. M. Farghaly, and M. S. Ragab, *Pharmazie*, 1973, **28**, 407.
[340] R. Grashey, M. Baumann, and R. Hamprecht, *Tetrahedron Letters*, 1972, 2939.
[341] P. Thieme, M. Patsch, and H. König, *Annalen*, 1972, **764**, 94.
[342] A. Y. Lazaris, S. M. Shmuilovich, and A. N. Egorochkin, *Khim. geterotsikl. Soedinenii*, 1973, 1345.
[343] A. Schulze and J. Goerdeler, *Tetrahedron Letters*, 1974, 221.
[344] J. Goerdeler, R. Schimpf, and M.-L. Tiedt, *Chem. Ber.*, 1972, **105**, 3322.
[345] O. Tsuge and S. Kanemasa, *Bull. Chem. Soc. Japan*, 1972, **45**, 2877.

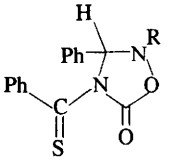
dianils,[345] cinnamylideneanilines,[345] carbodi-imides,[346] and benzaldazines.[347] Goerdeler and Schimpf have reported[348] that (276) reacts with the nitrone (277) to form the (2 + 3) cycloadduct (278), whereas an open-chain thioamide (279) is formed by the reaction of (276) with diphenylnitrone (280). The statement that the formation of (279) proceeds *via* the (2 + 3) cycloadduct intermediate (281) was nicely supported by the observation that (278), on heating with ethanolic sodium methoxide, easily released carbon dioxide to form (282).[348] The reactivity of thiobenzoyl isocyanate



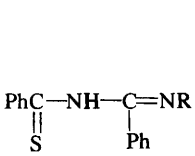
(276)



(277) R = Me
(280) R = Ph



(278) R = Me
(281) R = Ph



(279) R = Ph
(282) R = Me

(276) towards phenylhydrazine,[349] hydrazobenzenes,[349] nitrosobenzene,[348] diazoalkanes,[348,350] sulphonium ylides,[350] Δ^2-thiazolines,[351] and Δ^2-oxazolines[351] has also been studied.

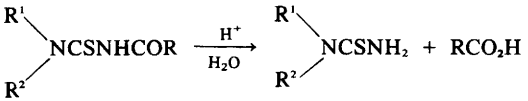
Limitations of space preclude a discussion of other recent papers[66,261,352–361] dealing with the chemistry of heterocyclic compounds containing the thiolactam grouping.

9 Thioureas and Selenoureas

Synthesis.—The most common method for the preparation of thioureas is based on the reaction of isothiocyanates with amines, and, not unexpectedly, the majority of the papers dealing with the preparation of new

[346] O. Tsuge and K. Sakai, *Bull. Chem. Soc. Japan*, 1972, **45**, 1534.
[347] O. Tsuge and S. Kanemasa, *Bull. Chem. Soc. Japan*, 1972, **45**, 3591.
[348] J. Goerdeler and R. Schimpf. *Chem. Ber.*, 1973, **106**, 1496.
[349] O. Tsuge and S. Kanemasa, *J. Org. Chem.*, 1973, **38**, 2972.
[350] O. Tsuge, K. Sakai, and M. Tashiro, *Tetrahedron*, 1973, **29**, 1983.
[351] O. Tsuge and S. Kanemasa, *Tetrahedron*, 1972, **28**, 4737.
[352] J. Fetter, J. Nyitrai, and K. Lempert, *Acta Chim. Acad. Sci. Hung.*, 1973, **79**, 197.
[353] E. Koltai, J. Nyitrai, and K. Lempert, *Tetrahedron*, 1973, **29**, 2781.
[354] F. Asinger, D. Neuray, A. Saus, J. Gräber, and U. Lames, *Monatsh.*, 1972, **103**, 406.
[355] E. Götschi, W. Hunkeler, H.-J. Wild, P. Schneider, W. Fuhrer, J. Gleason, and A. Eschenmoser, *Angew. Chem.*, 1973, **85**, 950; E. Götschi and A. Eschenmoser, *ibid.*, p. 952.
[356] R. Lie and K. Undheim, *J.C.S. Perkin I*, 1973, 2049; K. Undheim and P. E. Fjeldstad, *ibid.*, p. 829.
[357] H. Tomisawa, K. Kosaka, H. Hongo, R. Fugita, H. Kato, and C. H. Wang, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2590; H. Tomisawa and C. H. Wang, *ibid.*, p. 2607.
[358] C. O. Okafor, *J. Org. Chem.*, 1973, **38**, 4386; K. Gewald, M. Buchwalder, and M. Peukert, *J. prakt. Chem.*, 1973, **315**, 679; M. Robba, G. Dore, and M. Bonhomme, *J. Heterocyclic Chem.*, 1973, **10**, 579.
[359] S. Kobayashi, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 941.
[360] G. Wagner and S. Leistner, *Z. Chem.*, 1972, **12**, 175.
[361] G. Wagner and S. Leistner, *Pharmazie*, 1973, **28**, 633; F. Yoneda, Y. Sakuma, M. Ueno, and S. Nishigaki, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 926; J. L. Fourrey and P. Jouin, *Tetrahedron Letters*, 1973, 3225; J. L. Fourrey, P. Jouin, and J. Moron, *ibid.*, p. 3229.

thioureas report on the application of this particular method. Primary[304,362–373] and secondary[304,373–377] amines, as well as hydroxylamines,[378,379] have been the amine participants most frequently employed, but ammonia[380] and some heterocyclic compounds with an incorporated imine function[381–383] have also been used. Hartmann and Reuther[377] have indicated a novel route to the otherwise synthetically difficultly accessible 1,1-disubstituted thioureas (284) in the reaction of secondary amines with benzoyl isothiocyanate or ethoxycarbonyl isothiocyanate, as the products (283) thus obtained easily decomposed to (284) in acidic surroundings. Worthy of mention also is the



(283) R = Ph or OEt (284)

observation that the heterocyclic compound (285) reacts in different ways with phenyl isocyanate and phenyl isothiocyanate, yielding (286) in the

[362] A. Kreutzberger and H.-H. Schröders. *Arch. Pharm.* 1972, **305**, 907; *Tetrahedron Letters*, 1973, 687; N. B. Galstukhova, M. N. Shchukina, T. N. Zykova, G. N. Pershin, and K. Antos, *Khim.-Farm. Zhur.*, 1972, **6**, 14; N. B. Galstukhova, I. M. Berzina, M. N. Shchukina, T. N. Zykova, and G. N. Pershin, *ibid.*, 1973, **7**, 3; T. R. Ovsepyan, P. R. Akopyan, and A. A. Aroyan, *Armyan. khim. Zhur.*, 1972, **25**, 42; P. R. Akopyan, T. R. Ovsepyan, and A. A. Aroyan, *ibid.*, 1972, **26**, 234; E. N. Karanov and G. N. Vasilev, *Doklady Akad. Sel'skokhoz. Nauk Bolg.*, 1971, **4**, 129 (*Chem. Abs.*, 1972, **77**, 74 993); P. N. Bhargava and J. Singh, *Current Sci.*, 1972, **41**, 60; A. Nayak and T. E. Acharya, *ibid.*, p. 892; T. E. Acharya, P. N. Dhal, and A. Nayak, *J. Inst. Chem., Calcutta*, 1972, **44**, 166 (*Chem. Abs.*, 1973, **79**, 5 296); V. J. Ram, H. N. Pandey, and S. N. Singh, *Indian J. Pharm.*, 1973, **35**, 30; *J. Indian Chem. Soc.*, 1972, **49**, 181; H. Oehme and R. Thamm, *J. prakt. Chem.*, 1973, **315**, 526.

[363] M. O. Lozinskii, A. F. Shivanyuk, and P. S. Pel'kis, *Khim. geterotsikl. Soedinenii*, 1971, 176.

[364] H. J. Schrepfer, L. Capuano, and H.-L. Schmidt, *Chem. Ber.*, 1973, **106**, 2925.

[365] P. L. Ovechkin, L. A. Ignatova, A. E. Gekhman, and B. Unkovskii, *Khim. geterotsikl. Soedinenii*, 1972, 937.

[366] B. Stanovnik and M. Tišler, *Synthesis*, 1972, 308.

[367] (*a*) A.-M. M. E. Omar, *Pharmazie*, 1972, **27**, 798; (*b*) A. A. B. Hazzaa, A.-M. M. E. Omar, and M. E. Ragab, *ibid.*, 1973, **28**, 364.

[368] I. V. Smolanka and A. A. Dobosh, *Ukrain. khim. Zhur.*, 1973, 39, 402.

[369] K. Harsanyi, D. Korbonitz, and P. Kiss, *Acta Chim. Acad. Sci. Hung.*, 1973, **77**, 333.

[370] B. Stanovnik and M. Tišler, *Monatsh.*, 1973, **104**, 1034.

[371] J. Goerdeler and H. Hohage, *Chem. Ber.*, 1973, **106**, 1487.

[372] I. N. Azerbaev, A. B. Asmanova, L. A. Tsoi, and V. S. Bazalitskaya, *Khim. Atsetilena Tekhnol. Karbid Kal'tsiya*, 1972, 106 (*Chem. Abs.*, 1973, **79**, 104 892).

[373] W. Abraham and G. Barnikow, *Tetrahedron*, 1973, **29**, 699.

[374] T. T. Dustmukhamedov and S. R. Tulyaganov, *Uzbek. khim. Zhur.*, 1973, **17**, 52 (*Chem. Abs.*, 1973, **79**, 52 972).

[375] S. M. Khripak, A. A. Dobosh, and I. V. Smolanka, *Khim. geterotsikl. Soedinenii*, 1973, 567.

[376] K. Hasegawa and S. Hirooka, *Nippon Kagaku Kaishi*, 1972, 1098.

[377] H. Hartmann and I. Reuther, *J. prakt. Chem.*, 1973, **315**, 144.

[378] F. Grambal, J. Mollin, and M. Hejsek, *Acta Univ. Palacki. Olomuc., Fac. Rerum Natur.*, 1971, 351 (*Chem. Abs.*, 1973, **79**, 104 893); R. Stoffel and H.-J. Bresse, *Chem. Ber.*, 1972, **105**, 3115.

[379] R. Stoffel and H.-J. Bresse, *Arch. Pharm.*, 1973, **306**, 579.

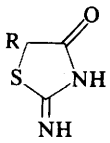
[380] M. A. Kaldrikyan and A. A. Aroyan, *Armyan. khim. Zhur.*, 1971, **24**, 913.

[381] F. G. Weber and K. Brosche, *Z. Chem.*, 1972, **12**, 132.

[382] D. Prelica, E. Kleczek, and H. Siaglo, *Pol. J. Pharmacol. Pharm.*, 1973, **25**, 163.

[383] T. Hirata, H. B. Wood, and J. S. Driscoll, *J.C.S. Perkin I*, 1973, 1209.

former and (287) in the latter case.[382] Hirata and his co-workers have pointed out[383] that the product formed primarily in the reaction of the aminotriazole (288) with ethoxycarbonyl isothiocyanate is (289), which, however, on standing rearranges to (290); the latter compound was previously regarded as the primary product. The thiourea (291) has been prepared by the reaction of the potassium salt of pyrrole with ethoxycarbonyl isothiocyanate.[259] A new synthesis of thiobiuret (293) has been developed on the basis of the reaction of urea with benzoyl isothiocyanate, as the subsequent acidic methanolysis of the product (292) afforded (293) in 75%



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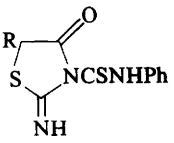

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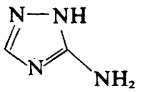
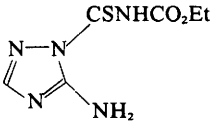
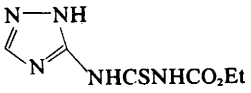


(288)



(289)



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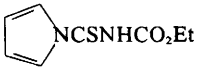

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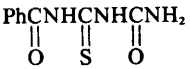
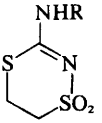


(292)

(293)

yield.[384] The formation of the 1,4,2-dithiazine 1,1-dioxides (294) and (295) in the reaction of vinylsulphonamide with isothiocyanates was interpreted in terms of a spontaneous cyclization reaction of the intermediate thioureas (296).[385] The formation of the heterocyclic thioureas (297) by the reaction of *SS'*-dialkyl dithioxaldi-imidates (298) with thiocyanic acid was considered to proceed *via* a spontaneous ring-closure reaction of the intermediate isothiocyanate (299), taking place simultaneously with the migration of an alkylmercapto-group.[386] A miscellany of heterocyclic compounds containing the thiourea moiety have been obtained by means of the reaction between isothiocyanates and amines in cases where one or both of the reactants have other reactive groups (refs. 304, 365, 366, 368, 375, 379,

[384] D. L. Klayman, R. J. Shine, and J. D. Bower, *J. Org. Chem.*, 1972, **37**, 1532.
[385] K. Nakahashi, S. Hirooka, and K. Hasegawa, *Bull. Chem. Soc. Japan*, 1972, **45**, 3217.
[386] V. P. Shah, R. Ketcham, K. J. Palmer, and R. Y. Wong, *J. Org. Chem.*, 1972, **37**, 2155.



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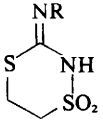

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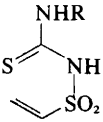

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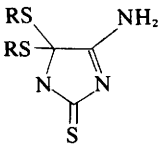

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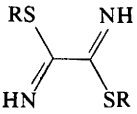

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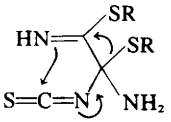


(299)

387—389). More exotic thioureas were the products of interesting reactions of isothiocyanates with ketimines,[390] enamines,[391] imino-esters,[392] amidines,[392,393] amidrazones,[394] and substituted ammonium salts.[395] Some selenoureas have been synthesized by the reaction of isoselenocyanates with amines,[372,396] and the phosphorus compounds (300) were obtained analogously by treatment of ω-mercaptoalkylphenylphosphines with phenyl isothiocyanate.[397] The action of primary amines on (300) resulted in the formation of *N*-alkyl-*N'*-phenylthioureas in high yields with simultaneous regeneration of the ω-mercaptoalkylphenylphosphine.[397]

Abel and Dunster have reported[398] that dimethyl(trimethylstannyl)amine, on treatment with phenyl isothiocyanate, yields the trimethylstannylthiourea (301). On the other hand, Matsuda and his co-workers found that the related reaction of *N*-trimethylsilyl(diphenylmethylene)amines with isothiocyanates affords equilibrium mixtures of the two rapidly interconvertible tautomeric compounds (302) and (303).[399]

[387] V. Knoppova and L. Drobnica, *Chem. Zvesti*, 1972, **26**, 533.
[388] M. Nagano, J. Tobitsuka, T. Matsui, and K. Oyamada, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2618; M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *ibid.*, 1972, **20**, 2626; R. A. Coburn and B. Bhooshan, *J. Org. Chem.*, 1973, **38**, 3863; G. Barnikow and H. Ebeling, *Z. Chem.*, 1973, **13**, 468.
[389] A. Butt and R. Parvenn, *Pakistan J. Sci. Ind. Res.*, 1972, **15**, 243; J. Lehmann and H. Wamhoff, *Chem. Ber.*, 1973, **106**, 3533.
[390] T. Takeshima, T. Miyauchi, N. Fukada, S. Koshizawa, and M. Muraoka, *J.C.S. Perkin I*, 1973, 1009.
[391] H. Singh and S. Singh, *Austral. J. Chem.*, 1973, **26**, 2453.
[392] G. Barnikow and H. Ebeling, *Z. Chem.*, 1973, **13**, 424.
[393] J. Neuffer and J. Goerdeler, *Chem. Ber.*, 1972, **105**, 3138.
[394] W. Walter and H. Weiss, *Annalen*, 1973, 1294.
[395] N. J. Cusack, B. J. Hildick, D. H. Robinson, P. W. Rugg, and G. Shaw, *J.C.S. Perkin I*, 1973, 1720.
[396] N. Sonoda, G. Yamamoto, and S. Tsutsumi, *Bull. Chem. Soc. Japan*, 1972, **45**, 2937.
[397] K. Issleib and K.-D. Franze, *J. prakt. Chem.*, 1973, **315**, 471.
[398] E. W. Abel and M. O. Dunster, *J.C.S. Dalton*, 1973, **98**.
[399] I. Matsuda, K. Itoh, and Y. Ishii, *J.C.S. Perkin I*, 1972, 1678.

$PhNHCSPPhCH_2CH_2SR$ $Me_3SnNPhCSNMe_2$

(300) R = H or Et (301)

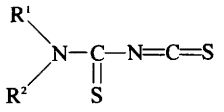
$Ph_2C{=}NCSNRSiMe_3$ $Ph_2C{=}NC(S{-}SiMe_3){=}NR$

(302) (303)

Several thioureas have been synthesized by ring-opening reactions of heterocyclic compounds such as 1,3-dithiolan-2-thiones,[400] 5-arylimino-1,2,4-dithiazolidine-3-thiones,[401] benzoxazole-2-thiones,[402] and 3,1-benzothiazine-4-thione derivatives.[270] Similarly, the action of triphenylphosphine on 5-amino-1,2,4-dithiazolo-3-thiones gave thiocarbamoyl isothiocyanates (304).[403] Other thioureas have been obtained by thermolytic decarbonylation of 2-amino-5(4*H*)-thiazolones[404] and by treatment of 4,5,6,7-tetrahydrocyclopenta-1,3-dioxin-4-one[405] and 3-nitrophthalic anhydride with thiourea.[406]

As a synthetic route to thioureas, the reaction of the corresponding urea with phosphorus pentasulphide seems to have only little significance. The preparation of (307) from (305) or (306) appears to be the only recent example of the application of this reaction.[259] The cyclic thioureas (308) have been synthesized in high yields by treatment of the corresponding 2-chloronaphth[1,2-*d*]imidazoles with thiourea.[407] The cyanothiourea (309) was obtained in 99% yield by the addition reaction of ethyldicyanamide with hydrogen sulphide.[408] The simultaneous action of hydrogen sulphide and ammonia on the dithiazolium salt (310) afforded the dithiobiuret (311).[409] Some *NN'*-disubstituted thioureas have been synthesized by the reaction of primary amines with carbon disulphide in the presence of diphenyl phosphite.[410] Cyclic thioureas were obtained in related reactions between carbon disulphide and 1,2-diamines[411,412] or 1,4-diamines.[413] Among several

[400] M. Furukawa, K. Nagato, Y. Kojima, and S. Hayashi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1824.
[401] M. G. Paranjpe and A. S. Mahajan, *Indian J. Chem.*, 1972, **10**, 1138.
[402] K. Davidkov and D. Simov, *Doklady Bolg. Akad. Nauk*, 1973, **26**, 777 (*Chem. Abs.*, 1974, **80**, 3224).
[403] J. Goerdeler, J. Haag, C. Lindner, and R. Losch, *Chem. Ber.*, 1974, **107**, 502.
[404] M. Kato, A. Kobayashi, and S. Umemoto, *Chem. Letters*, 1972, 1129.
[405] G. Jäger, *Chem. Ber.*, 1972, **105**, 137.
[406] J. Ciba, E. Bobrowska, and Z. Gregorowicz, *Roczniki Chem.*, 1973, **47**, 1275.
[407] E. G. Knysh, A. N. Krasovskii, and P. M. Kochergin, *Khim. geterotsikl. Soedinenii*, 1972, 33.
[408] P. H. Benders, *Tetrahedron Letters*, 1973, 3653.
[409] I. Iwataki, *Bull. Chem. Soc. Japan*, 1972, **45**, 3572.
[410] N. Yamazaki, F. Higashi, and T. Iguchi, *Tetrahedron Letters*, 1974, 1191.
[411] I. G. Il'ina, N. B. Kazennova, V. G. Bakhmutskaya, and A. P. Terent'ev, *Khim. geterotsikl. Soedinenii*, 1973, 1112.
[412] E. A. Kuznetsova, S. V. Zhuravlev, T. N. Stepanova, and V. S. Troitskaya, *Khim. geterotsikl. Soedinenii*, 1972, 177.
[413] G. Doleschall, G. Hornyak, B. Agai, G. Simig, J. Fetter, and K. Lempert, *Tetrahedron Letters*, 1973, 5069.



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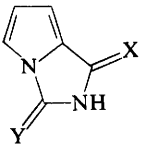
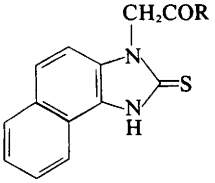


(305) X = Y = O
(306) X = S, Y = O
(307) X = Y = S



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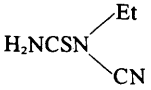

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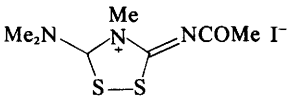
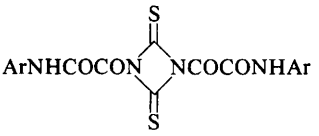


(310)

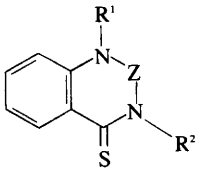
$Me_2NCSNMeCSNH_2$

(311)

recent papers[363,414,415] reporting on the synthesis of thioureas by means of reactions involving thiocyanates as reaction participants, the most interesting is perhaps that[363] describing the formation of 1,3-diazetidine-2,4-dithiones (312) as the result of the action of lead thiocyanate on oxalic acid monochloride monoarylamines. Thiocarbamoyl isothiocyanates (304) were produced by the reaction of thiocarbamoyl chlorides with potassium rhodanide.[416] The action of elemental sulphur on 1,2-dihydro-3,1-benzothiazine-4-thiones (313) at 200 °C afforded the corresponding dithiones (314)



(312)



(313) Z = CH_2
(314) Z = CS

in excellent yields.[417] For the sake of completeness, the many papers describing the syntheses of heterocyclic thiones containing the thiourea moiety are also included in the list of references (refs. 253, 283, 284, 418—431).

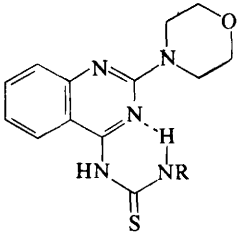
The first examples of thiourea–iron carbonyl complexes have been presented by Alper and Chan.[291] The formation of these complexes was found to depend on the presence or absence of *N*-hydrogen atoms, as in the

[414] A. K. Sen Gupta and A. K. Ramrakhyani, *J. Indian Chem. Soc.*, 1972, **49**, 727; A. A. Popov, I. I. Rozhnyatovskii, V. M. Zaichenko, V. V. Markov, G. A. Lysova, and F. A. Galil-Ogly, *Koks Chim.*, 1973, 43 (*Chem. Abs.*, 1974, **80**, 3 433).
[415] G. Stajer, K. Kottke, and R. Pohloudek-Fabini, *Pharmazie*, 1973, **28**, 433.
[416] P. Kristian, D. Koscik, and J. Bernat, *Chem. Zvesti*, 1973, **27**, 280.
[417] L. Legrand and N. Lozac'h, *Bull. Soc. chim. France*, 1972, 3892, 3905.

case of the related thioamide complexes (see Section 8).[291] The preparation of copper(II) complexes of some 1,5-disubstituted 2,4-dithiobiurets[432] and the preparation and properties of complexes of tetramethylthiourea with organoselenium and organotellurium halides[433] have been the subjects of two other recent papers.

Reactions.—The nucleophilic reactivity of the thiocarbonyl sulphur atom in thioureas has been further exemplified in a series of papers reporting on *S*-alkylation reactions of open-chain[434,435] as well as cyclic[359,415,436] thioureas using alkyl halides. Ried and his co-workers have reported that (4-quinazolyl)thioureas (315) react smoothly with methylene iodide in the presence of triethylamine to yield the 1,3-thiazetidines (316).[437] The ready formation of (316) was attributed to the special effect of the intramolecular hydrogen bonding in (315), as common thioureas usually did not enter into this reaction in a well-defined and profitable way.[437] 5,5-Diphenyl-2-thiohydantoin reacted with symmetrical $\alpha\omega$-dibromo-alkanes to yield the cyclization products (317).[438] The action of excess of methyl iodide on *N'*-substituted *N*-(*o*-aminophenyl)thioureas afforded the benzimidazoles (318),[439] alternatively obtainable by treatment of the same thioureas with mercuric chloride.[367a] In a similar manner, 1-amino-6,7-dimethoxy-3,4-dihydroisoquinolines were formed by the action of mercuric chloride on the thioureas (319)[367b] or their *S*-methyl derivatives (320).[435] A recent paper by Klayman and his co-workers deals with the reactivity of *S*-methiodide derivatives of thioureas that are activated by electron-withdrawing groups towards hydroxylic compounds.[384]

[418] H. Neef, K.-D. Kohnert, and A. Schellenberger, *J. prakt. Chem.*, 1973, **315**, 701.
[419] J. D. Dhake, *J. Indian Chem. Soc.*, 1972, **49**, 1151.
[420] J. D. Dhake, *Indian J. Chem.*, 1971, **9**, 1415.
[421] J. D. Fissekis and F. Sweet, *J. Org. Chem.*, 1973, **38**, 1963.
[422] H. Vorbrüggen and P. Strehlke, *Chem. Ber.*, 1973, **106**, 3039.
[423] R. D. Haugwitz and V. L. Narayanan, *J. Org. Chem.*, 1972, **37**, 2776.
[424] Z. Kazimierczuk, A. Psoda, and D. Shugar, *Acta Biochim. Polon.*, 1973, **20**, 83.
[425] S. Landa, J. Burhard, and J. Vais, *Coll. Czech. Chem. Comm.*, 1973, **38**, 2947.
[426] R. Neidlein and G. Menche, *Arch. Pharm.*, 1972, **305**, 596.
[427] J. P. Gawlowski and J. Mirek, *Roczniki Chem.*, 1972, **46**, 421.
[428] V. G. Vodop'yanov, V. G. Golov, and N. I. Romanova, *Zhur. Vsesoyuz. Khim. obshch. im D.I. Mendeleeva*, 1972, **17**, 351 (*Chem. Abs.*, 1972, **77**, 101 513).
[429] D. E. Bergstrom, I. Inoue, and N. J. Leonard, *J. Org. Chem.*, 1972, **37**, 3902.
[430] J. A. Gautier, M. Miocque, C. Combet-Farnoux, and J. F. Girardeau, *Bull. Soc. chim. France*, 1972, 682.
[431] M. Hubert-Habart, C. Pene, and R. Royer, *Chim. Ther.*, 1973, **8**, 194 (*Chem. Abs.*, 1973, **79**, 78 720).
[432] K. P. Srivastava and N. K. Agarwal, *Z. anorg. Chem.*, 1972, **393**, 168.
[433] K. J. Wynne, *Ann. N.Y. Acad. Sci.*, 1972, **192**, 107.
[434] M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 74.
[435] A.-M. M. E. Omar, *Pharmazie*, 1972, **27**, 552.
[436] L. A. Ignatova, G. L. Ovechkina, and B. V. Unkovskii, *Reakts. Spos. org. Soedinenii*, 1973, **10**, 73 (*Chem. Abs.*, 1973, **79**, 114 789).
[437] W. Ried, W. Merkel, and O. Mösinger, *Annalen*, 1973, 1362.
[438] Z. Cichon and A. Zejc, *Pol. J. Pharmacol. Pharm.*, 1973, **25**, 187 (*Chem. Abs.*, 1973, **79**, 78 691).
[439] A.-M. M. E. Omar, *Synthesis*, 1974, 41.



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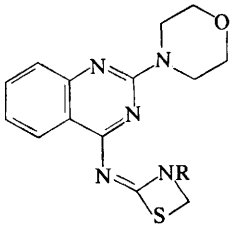

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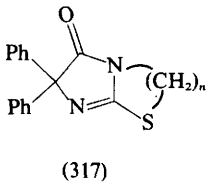

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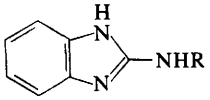

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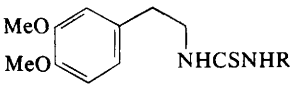

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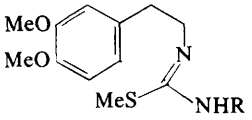
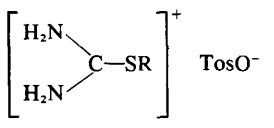


(320)

Thiourea has been *S*-alkylated by alcohols. By refluxing mixtures of thiourea and a primary or secondary alcohol with toluene-*p*-sulphonic acid in dioxan, Nakano and his co-workers obtained salts of the type (321).[440] Thiols were produced by the basic hydrolysis of these salts.[440]

The kinetics of the reaction of phenacyl bromide with phenylthioureas have been investigated by conductance techniques.[441] The reaction was found to be both energy- and entropy-controlled, and the rate was found to be enhanced by electron-donating phenyl-substituents. The authors suggested a reaction mechanism involving the transition state (322), but



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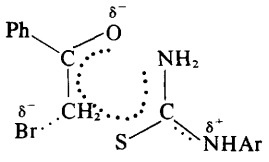


(322)

pointed out that the reaction may be initiated by NH-attack rather than S-attack on the phenacyl bromide molecule.[441] Several further examples of the synthesis of thiazoles or thiazolines by the reaction of thioureas with different types of α-halogenocarbonyls have appeared.[363,369,442] Achary and

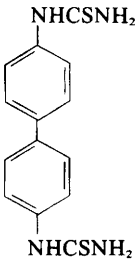
[440] K. Nakano, T. Takido, and K. Itabashi, *Yuki Gosei Kagaku Kyokai Shi*, 1972, **30**, 63 (*Chem. Abs.*, 1972, **76**, 126 349).

[441] G. B. Behera, R. C. Acharya, and M. K. Rout, *Indian J. Chem.*, 1973, **11**, 81.

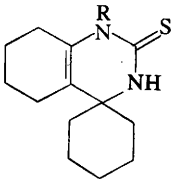
[442] D. Suciu, *Arch. Pharm.*, 1973, **306**, 152, C. P. Joshua and P. N. K. Nambisan, *Indian J. Chem.*, 1973, **11**, 118; D.-I. Schütze, H. Timmler, and F. Kröhnke, *Chem. Ber.*, 1972, **105**, 3121; A.-M. M. E. Omar, *Pharmazie*, 1973, **28**, 110; L. Y. Ladnaya and L. I. Maslova, *Farm. Zhur. (Kiev)*, 1973, **28**, 12; H. Tripathy, P. N. Dhal, and G. N. Mahapatra, *J. Indian Chem. Soc.*, 1973, **50**, 135.

Nayak observed[443] that 1-(2-pyridyl)thiourea reacted with chloroacetic acid in ethanolic solution in the presence of sodium acetate to yield 2-(2-pyridylimino)thiazolidin-4-one, whereas the same reaction afforded 3-(2-pyridyl)-thiohydantoin when performed in pyridine solution. On treatment with chloroacetic acid in pyridine, *p*-bis(thioureido)biphenyl (323) similarly yielded *p*-bis(thiohydantoin-3-yl)biphenyl.[444] The reactions of monosubstituted thioureas with $\alpha\beta$-unsaturated $\beta\beta$-dichlorocarbonyl compounds[307] and 2-(1-chlorocyclohexyl)cyclohexanone[427] afforded 1,3-thiazine-6-thiones and the spiro-compounds (324), respectively.

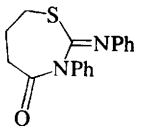
A series of 1,3-benzo[*e*]thiazepines, a new class of heterocyclic compounds, have been synthesized by Reinhoudt[304] by the reaction of 2-bromomethylbenzyl or 2-bromomethylbenzoyl bromide with thioureas. Compound (325) was obtained in a similar way from *NN'*-diphenylthiourea and 4-bromobutyryl chloride.[304] Reinhoudt also found[304] that the thioureas (326), on heating in acetone, underwent a ring-closure reaction to form either (327) or (328) (for $R^1 = H$). The formation of (328) was considered to be a result of



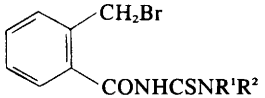
(323)



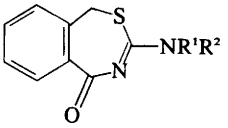
(324)



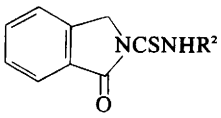
(325)



(326)



(327)

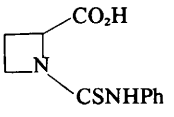


(328)

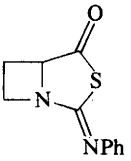
a spontaneous 1,4-transannular reaction of an intermediate thiazepine (327; $R^1 = H$). A convenient synthetic route to 1,3-disubstituted 4,5-dioxo-2-thioxoimidazolidines has been found in the reaction of 1,3-disubstituted thioureas with oxalyl chloride.[445] The conversion of the thiocarbamoylazetidine (329) into the hydantoin derivative (331), induced by the action of DCC on the former, was rationalized in terms of an initial internal

[443] T. E. Achary and A. Nayak, *Current Sci.*, 1972, **41**, 539.
[444] B. Mahapatra, P. N. Dhal, and A. Nayak, *J. Inst. Chemists (India)*, 1973, **45**, 17 (*Chem. Abs.*, 1973, **79**, 42 408).
[445] M. Augustin and K. H. Jankowski, *Wiss. Z. Martin-Luther-Univ., Halle-Wittenberg, Math.-Naturwiss. Reihe*, 1972, **21**, 43 (*Chem. Abs.*, 1973, **78**, 159 515).

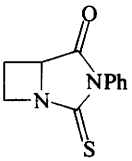
nuclophilic attack of the thiocarbonyl sulphur atom on the neighbouring carboxylic carbon atom leading to (330), which subsequently rearranges to (331).[446] Thiocarbamoyl isothiocyanates (304) reacted with aldimines, yielding substituted 5,6-dihydro-4*H*-1,3,5-thiadiazine-4-thiones.[416] Some 2-(benzoylimino)-3,5-diaryl-2,3-dihydro-1,3,4-selenadiazoles have been prepared by the reaction of *N*-benzoylselenourea with α-halogenoaldehydrazones.[447]



(329)



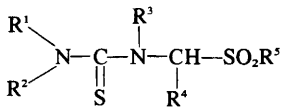
(330)



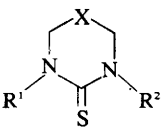
(331)

Three groups of workers have studied the reactivity of thiourea towards αβ-unsaturated ketones.[430,448,449] The notable lability in the reaction course was demonstrated by the simultaneous or alternative formation of different open-chain as well as cyclic products, thus clearly indicating the occurrence of nucleophilic attacks of both the sulphur and the nitrogen atoms of thiourea on both the carbonyl carbon and the β-carbon atom of the αβ-unsaturated ketone. Other papers reporting on the nucleophilic activity of thioureas deal with reactions of the latter with oxirans,[450] oxaziridines,[451] acryloyl chloride,[452] αβ-unsaturated acids,[453] acetylenedicarboxylic acid esters,[370,454] ethyl thiocyanoacetate,[455] and isocyanates.[456]

Thioureas have been employed as the amino-component in Mannich reactions with aldehydes and sulphinic acids, yielding compounds of the type (332).[325] 1,3-Disubstituted thioureas reacted with formaldehyde to yield oxadiazine-4-thiones (333);[457] when carried out in the presence of hydrogen sulphide, the same reactants afforded thiadiazine-4-thiones (334).[457] Several



(332)



(333) X = O

(334) X = S

[446] H. T. Nagasawa, P. S. Fraser, and J. A. Elberling, *J. Org. Chem.*, 1972, **37**, 516.
[447] E. Bulka and D. Ehlers, *J. prakt. Chem.*, 1973, **315**, 510.
[448] R. M. Khachatryan and S. A. Vartanyan, *Armyan. khim. Zhur.*, 1972, **25**, 338.
[449] S. M. Deshpande and A. K. Mukerjee, *Current Sci.*, 1972, **41**, 139.
[450] V. M. Fedoseev and V. S. Churilin, *Zhur. org. Khim.*, 1972, **8**, 205.
[451] S. St. C. Black and K. G. Watson, *Austral. J. Chem.*, 1973, **26**, 2159.
[452] M. Nomura, *Yuki Gosei Kagaku Kyokai Shi*, 1972, **30**, 971 (*Chem. Abs.*, 1973, **78**, 84 342).
[453] K. Takemoto, H. Tahara, Y. Inaki, and N. Ueda, *Chem. Letters*, 1972, 767.
[454] H. Nagase, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 270.
[455] S. Kambe and T. Hayashi, *Bull. Chem. Soc. Japan*, 1972, **45**, 3192.
[456] K. A. Nuridzhanyan and G. V. Kuznetsova, *Khim. geterotsikl. Soedinenii*, 1973, 695.
[457] M. C. Seidel and F. E. Boettner, *J. Heterocyclic Chem.*, 1972, **9**, 231.

further examples of the utility of thioureas in the synthesis of heterocyclic compounds have appeared during the past two years (refs. 308, 314, 315, 380, 424—431, 455, and 458—463). In a series of papers, Iwataki and Ueda have reported on the synthesis of thiazoles[464,465] and 1,2,4-dithiazoles[409,465] by means of cyclization reactions of 2,4-dithiobiurets.

The acidic and the alkaline hydrolyses of *N*-acylthioureas, in both cases leading to the formation of a thiourea and a carboxylic acid, have been the subjects of recent kinetic studies by Congdon and Edward.[466,467] In moderately concentrated acidic medium the hydrolysis was found to proceed in accordance with a bimolecular mechanism involving water as a nucleophile in the rate-determining step. In strong acidic medium, however, the hydrolysis followed a unimolecular mechanism involving an intermediate acyl cation.[466] The fact that the rates of the alkaline hydrolyses of the *N*-acylthioureas were found to be independent of the hydroxide ion concentration when this exceeded *ca.* 0.1 mol l^{-1} led the authors to suggest a mechanism involving the attack of a hydroxide ion on the unionized *N*-acylthiourea molecule.[467] The acidic hydrolysis of 1-acyl-2-thiohydantoins took place in close analogy with that of the *N*-acylthioureas,[468] whereas the alkaline hydrolysis at pH > 11 appeared to involve the attack of a hydroxide ion on the conjugated base of the 1-acyl-2-thiohydantoin.[469] A kinetic study of the desulphurization of ^{35}S-labelled thiourea at 80—100 °C in sodium hydroxide solutions in the pH range 12—13 revealed that the desulphurization most probably takes place in accordance with a second-order reaction:[470]

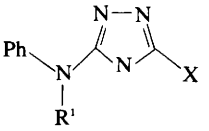
$$NH_2CSNH_2 + OH^- \rightarrow NCNH_2 + SH^- + H_2O$$

The reactivity of thioureas towards nucleophiles has received relatively little attention during the past two years. 1-(2-Methylthio-5-pyrimidinyl)-3-(*p*-butoxyphenyl)thiourea was alcoholysed in boiling ethanol to both possible ethyl thionocarbamates.[471] The action of primary amines on differently substituted *N*-aryl-*N'*-(2-benzothiazolyl)thioureas afforded the corresponding guanidines.[472] Triazoles (335) and/or (336) were produced by

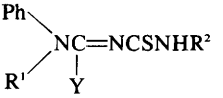
[458] E. Budeanu, *Anal. Sti., Univ. "Al. I. Cuza" Iasi, Sect. 1c*, 1972, **18**, 73 (*Chem. Abs.*, 1973, **78**, 29 704).
[459] D. E. Thurman and H. W. Stollings, *J. Heterocyclic Chem.*, 1973, **10**, 117.
[460] A. E. Kretov, A. P. Momsenko, and Y. A. Levin, *Khim. geterotsikl. Soedinenii*, 1973, 644.
[461] K. S. Dhaka, V. K. Chadka, and H. K. Pujari, *Indian J. Chem.*, 1973, **11**, 554.
[462] W. Ried, R. Oxenius, and W. Merkel, *Angew. Chem.*, 1972, **84**, 535.
[463] W. Ried and R. Oxenius, *Chem. Ber.*, 1973, **106**, 484.
[464] I. Iwataki, *Bull. Chem. Soc. Japan*, 1972, **45**, 3218.
[465] I. Iwataki and A. Ueda, *Bull. Chem. Soc. Japan*, 1972, **45**, 3220.
[466] W. I. Congdon and J. T. Edward, *J. Amer. Chem. Soc.*, 1972, **94**, 6099.
[467] W. I. Congdon and J. T. Edward, *Canad. J. Chem.*, 1974, **52**, 697.
[468] W. I. Congdon and J. T. Edward, *Canad. J. Chem.*, 1972, **50**, 3767.
[469] W. I. Congdon and J. T. Edward, *Canad. J. Chem.*, 1972, **50**, 3780.
[470] G. Marcotrigiano, G. Peyronel, and R. Battistuzzi, *J.C.S. Perkin II*, 1972, 1539.
[471] N. B. Galstukhova, I. M. Berzina, and M. N. Shchukina, *Zhur. org. Khim.*, 1973, **9**, 1070.
[472] P. N. Bhargava and R. Shyam, *Current Sci.*, 1973, **42**, 527.

the hydrazinolysis of the dithio-isobiurets (337), presumably as a result of an internal nucleophilic attack of the hydrazino-group on the thiocarbonyl carbon atom of intermediately formed (338).[473]

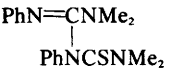
The reactivity of thioureas towards oxidants, however, has been more extensively studied. 1,3-Disubstituted thio- and seleno-ureas have been converted into the corresponding ureas by means of DMSO in the presence of an acidic catalyst.[474] 1,1-Dimethyl-3-phenylthiourea was oxidized by benzenesulphenyl chloride, thionyl chloride, sulphuryl chloride, and sulphur monochloride to the same product, (339).[475] The oxidation of thioureas



(335) $X = NHR^2$
(336) $X = SH$



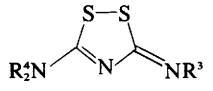
(337) $Y = SMe$
(338) $Y = NHNH_2$



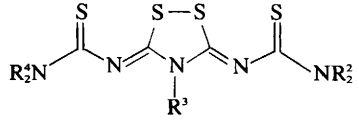
(339)

to the corresponding disulphides by means of iodine or bromine cyanide has been launched as a convenient method for quantitative determination of thioureas.[476] Other recent papers dealing with the oxidative properties of thioureas report on the formation of *S*-trioxides by treatment of thioureas with peroxyacetic acid,[477,478] the permanganate and the bisulphite oxidations of 2-thiouracil to the corresponding uracil-2-sulphonate,[479] and a variety of oxidative cyclization reactions (refs. 335, 409, 465, and 480–483). Goerdeler and Ulmen studied the reaction[482] of some dithiazoles (340), obtainable by oxidative cyclization of 2,4-dithiobiurets (refs. 409, 465, 481, and 482), with thiocarbamoyl isothiocyanates (304; $R^1 = R^2$), and they obtained as products the interesting 3,5-bis(thiocarbamoylimino)-1,2,4-dithiazolidines (341). 3,5-Bis(dimethylthiocarbamoylimino)-1,2,4-dithiazolidine (341; $R^2 = R^4 = Me$) was one of the products in the air oxidation of 1,1,5,5-tetramethyldithiobiuret; *NN*-dimethylthiocarbamoyl isothiocyanate (304; $R^1 = R^2 = Me$) appeared to play an important part in this reaction, as it was considered to be the likely precursor for several of the oxidation products, including (341; $R^2 = R^4 = Me$).[483] Both groups of workers[482,483] suggested the structure (342)

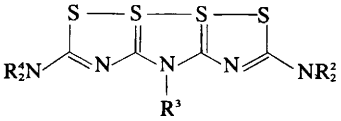
[473] J. S. Davidson, *J. prakt. Chem.*, 1972, **314**, 663.
[474] M. Mikolajczyk and J. Luczak, *Chem. and Ind.*, 1972, 76.
[475] P. Held, M. Gross, and H. Schubert, *Z. Chem.*, 1973, **13**, 341.
[476] R. C. Paul, R. K. Chauhan, and R. Parkash, *Indian J. Chem.*, 1973, **11**, 380.
[477] W. Walter and K.-P. Ruess, *Annalen*, 1974, 225.
[478] W. Walter and K.-P. Ruess, *Annalen*, 1974, 243.
[479] M. Sono and H. Hayatsu, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 995.
[480] G. Barnikow and H. Ebeling, *Z. Chem.*, 1972, **12**, 130.
[481] M. Nagano, M. Oshige, T. Matsui, J. Tubitsuka, and K. Oyamada, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2396; M. Nagano, M. Oshige, T. Kinoshita, T. Matsui, J. Tubitsuka, and K. Oyamada, *ibid.*, p. 2408.
[482] J. Goerdeler and J. Ulmen, *Chem. Ber.*, 1972, **105**, 1568.
[483] J. E. Oliver and J. B. Stokes, *Internat. J. Sulfur Chem. (A)*, 1972, **2**, 105.



(340)



(341)



(342)

as a possible better representation of (341). Later *X*-ray crystallographic investigations[484] actually revealed the existence of a structure with the four sulphur atoms placed collinearly. However, the central S—S bond distance was found to be 2.2 Å, *i.e.* of approximately the same length as that normally found in the 1,2,4-dithiazole ring. On the other hand, the outer S—S distances found (2.8 Å) are too long to represent S—S single bonds, but still considerably shorter than the sum of the van der Waals radii (3.7 Å), and hence they are indicative of the existence of some sort of strong interaction between inner and outer sulphur atoms.

Lack of space precludes a fuller presentation of the many papers reporting on the reactivity of heterocyclic thiones possessing a cyclic thiourea structure (refs. 352, 393, 407, 412, and 485—487).

10 Thiosemicarbazides and Selenosemicarbazides

Synthesis.—The traditional route to thiosemicarbazides is based on the reaction between isothiocyanates and hydrazines, and, obviously, a great number of recent, relevant papers have reported on the application of this reaction in the synthesis of new compounds of this class.[321,488–493] Of

[484] J. E. Oliver, J. L. Flippen, and J. Karle, *J.C.S. Chem. Comm.*, 1972, 1153; J. L. Flippen, *J. Amer. Chem. Soc.*, 1973, **95**, 6073.

[485] A. F. A. Shalaby and H. A. Daboun, *J. prakt. Chem.*, 1971, **313**, 1031.

[486] G. Zigeuner, H. Hamberger, E. Pinter, and R. Ecker, *Monatsh.*, 1973, **104**, 585.

[487] R. J. Badger, D. J. Brown, and J. H. Lister, *J.C.S. Perkin I*, 1973, 1906; J. Bailey and J. A. Elvidge, *ibid.*, p. 823; W. Pendergast, *ibid.*, p. 2759; U. Reichman, F. Bergmann, and D. Lichtenberg, *ibid.*, p. 2647.

[488] H.-J. Jahns, G. Düx, and L. Thielemann, *J. prakt. Chem.*, 1973, **315**, 572; M. Robba, M. Bonhomme, and G. Dore, *Tetrahedron*, 1973, **29**, 2919.

[489] V. S. Dmitrukha and P. S. Pel'kis, *Khim. geterotsikl. Soedinenii*, 1972, 852.

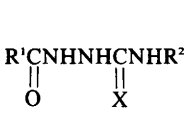
[490] R. Bokaldere and A. Liepina, *Khim. geterotsikl. Soedinenii*, 1973, 276.

[491] C. Budeanu and E. Gheorghe, *Anal. Sti., Univ. "Al. I. Cuza" Iasi, Sect. Ic*, 1973, **19**, 59 (*Chem. Abs.*, 1973, **79**, 126 040).

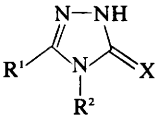
[492] M. Tutoveanu, E. Comanita, and S. Steinberg, *Bul. Inst. Politeh. Iasi*, 1972, **18**, 113 (*Chem. Abs.*, 1973, **79**, 91 739).

[493] M. Tutoveanu, *Bul. Inst. Politeh. Iasi*, 1972, **18**, 103 (*Chem. Abs.*, 1973, **79**, 92 120).

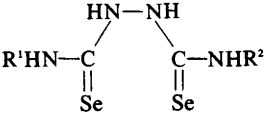
particular interest are the papers[491–493] describing the formation of various 1-acylthiosemicarbazides (343) by the reaction of acylhydrazines with isothiocyanates. The products (343) were generally stable, but rearranged easily in the presence of base to thiazolinethiones (344).[492,493] Bulka and Ehlers obtained[494] stable 1-acylselenocarbazides (345) by the reaction of acylhydrazines with isoselenocyanates. The reaction of benzoyl isoselenocyanate with hydrazine gave the thiazolineselenone (346) directly, evidently as a result of a spontaneous cyclization reaction of primarily formed 3-benzoylselenosemicarbazide.[494] The interesting compounds (347) were in some cases the isolated products in the reaction of isoselenocyanates with 3-substituted selenosemicarbazides, in other cases these were too unstable to allow for isolation, and 2,5-diamino-1,3,4-selenadiazoles (348) were obtained alternatively.[494] 1-Methyl-1-thioaroylhydrazines reacted with phenyl isothiocyanate to give meso-ionic 2-mercapto-1,3,4-thiadiazoles (349),[341] but with aroyl isothiocyanates to yield meso-ionic 2-acylamino-1,3,4-thiadiazoles (350).[341,342] On treatment with lithium aluminium hydride, (350; Ar = R = Ph) underwent a reductive ring-opening reaction, yielding the thiosemicarbazide (351).[342] 3-Amino-3,4-dihydro-2*H*-1,3,5-oxadiazine-4-thiones have been synthesized by the reaction of aroyl isothiocyanates with



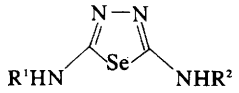
(343) X = S
(345) X = Se



(344) X = S
(346) X = Se
R^1 = Ph, R^2 = H



(347)



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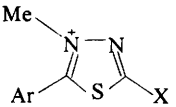


(349) X = S^-
(350) X = $\bar{N}COR$

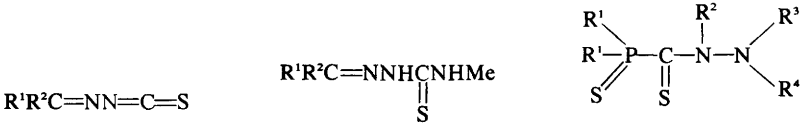
(351)

NN-disubstituted hydrazones.[254] Heterocyclic compounds containing the 1,2,4-triazoline-3-thione structure were formed in reactions between ethoxycarbonyl isothiocyanate and hydrochlorides of amidrazones,[495] phenyl isothiocyanate and anhydro-1-phenylimino-2,4,5-triphenyl-1,2,3-triazoline hydroxide,[496] phenylhydrazones and thiocyanic acid,[497] aroylhydrazines and

[494] E. Bulka and D. Ehlers, *J. prakt. Chem.*, 1973, **315**, 155.
[495] T. Bany and M. Dobosz, *Roczniki Chem.*, 1972, **46**, 1123.
[496] K. B. Sukumaran, C. S. Angadiyavar, and M. V. George, *Tetrahedron*, 1972, **28**, 3987.
[497] H. Schildknecht and G. Renner, *Annalen*, 1972, **761**, 189.

ammonium rhodanide,[492] and hydrazinium thiocyanate and aldehydes or ketones.[498] Several other heterocyclic compounds with incorporated thiosemicarbazide groupings have been prepared by individual routes.[360,490,499,500]

A new route to isothiocyanatoimines (352) has been found in the reaction of triethylammonium 3-alkylidenedithiocarbazate with thiophosgene at 0 °C.[501] The products (352) were, however, rather unstable, and reacted instantly with any methylamine present to produce the thiosemicarbazones (353).[501] Dahl and his co-workers recently described the synthesis of *PP*-disubstituted thiophosphinoylthioformhydrazides (354) by the reaction



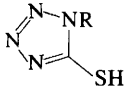
(352) (353) (354)

of the corresponding *PP*-disubstituted methyl thiophosphinoyldithioformates with hydrazines.[502]

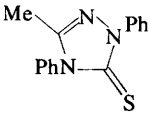
A series of papers dealing with the preparation and properties of metal complexes of 1-coumariloyl-4-arylthiosemicarbazides,[491] *N*-phenylthiocarbamoyl-*N'*-guanylhydrazine,[503] 4-aryl-3-thiourazoles,[504] *S*-methyldithizone,[505] and arylazothioformamides[506] may be of interest to workers in that field.

Reactions.—Recent studies of the nucleophilic reactivity of the thiocarbonyl sulphur atom of thiosemicarbazides have dealt largely with heterocycles containing the thiosemicarbazide or the thiosemicarbazone moiety, and comprise methylation reactions of 3-methyl-1,2,4-triazole-5-thiones[507] and 4-amino-1,2,4-triazolidine-3,5-dithione,[508] reactions of 1-substituted 5-mercaptotetrazoles (355) with arylsulphenyl chlorides to afford the corresponding (5-tetrazolyl)aryl disulphides,[509] and acylation reactions of (355)

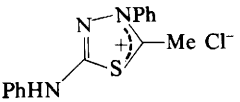
[498] I. Arai, S. Abe, and A. Hagitani, *Bull. Chem. Soc. Japan*, 1973, **46**, 677.
[499] A. B. DeMilo and J. E. Oliver, *J. Heterocyclic Chem.*, 1973, **10**, 231; L. E. Deev, I. B. Lundina, and I. Y. Postovskii, *Khim. geterotsikl. Soedinenii*, 1972, 1292; A. H. Harhash, M. H. Elnagdi, and C. A. S. Elsannib, *J. prakt. Chem.*, 1973, **315**, 211; M. A. Kaldrikyan, A. V. Khekoyan, and A. A. Aroyan, *Armyan. khim. Zhur.*, 1972, **25**, 800.
[500] E. Kranz, J. Kurz, and W. Donner, *Chem. Ber.*, 1972, **105**, 388.
[501] C. Berg, *J.C.S. Chem. Comm.*, 1974, 122.
[502] O. Dahl, J. Andersen, and O. Larsen, *Acta Chem. Scand.*, 1973, **27**, 2503.
[503] A. D. Ahmed. N. R. Chaudhuri, and U. Saha, *Indian J. Chem.*, 1973, **11**, 59.
[504] C. H. Budeanu and A. Gavriliuc, *Anal. Sti., Univ. "Al. I. Cuza" Iasi, Sect. Ic*, 1972, **18**, 183 (*Chem. Abs.*, 1973, **78**, 58 320).
[505] H. M. N. H. Irving, A. H. Nabilsi, and S. S. Sahota, *Analyt. Chim. Acta*, 1973, **67**, 135.
[506] K. A. Jensen, K. Bechgaard, and C. Th. Pedersen, *Acta Chem. Scand.*, 1972, **26**, 2913.
[507] J. L. Barascut, J. Daunis, and R. Jacquier, *Bull. Soc. chim. France*, 1973, 323.
[508] A. D. Sinegibskaya, E. G. Kovalev, and I. Y. Postovskii, *Khim. geterotsikl. Soedinenii*, 1973, 562.
[509] G. Stájer, E. A. Szabó, J. Pintye, F. Klivényi, and P. Sohár, *Chem. Ber.*, 1974, **107**, 299.



(355)



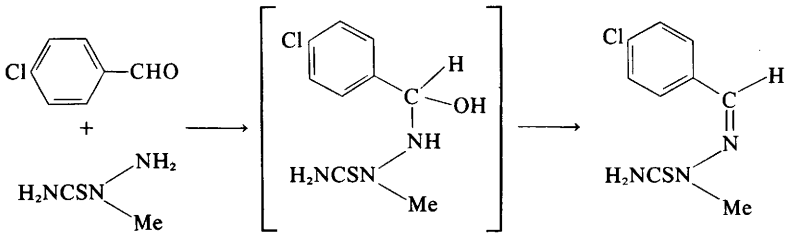
(356)



(357)

using acyl chlorides.[510] In the latter case, *S*-acylation as well as *N*-acylation in the 2- and 4-positions occurred, the product distribution being greatly influenced by the nature of the 1-substituent.[510] A reinvestigation of the reaction of 1,4-diphenylthiosemicarbazide with acetyl chloride revealed that two products, (356) and (357), are formed simultaneously.[511] The action of excess of acrylonitrile on 4-amino-1,2,4-triazolidine-3,5-dithione resulted in simultaneous cyanoethylation of both the nitrogen atom in the 1-position and the thiocarbonyl sulphur atom in the 3-position, whereas *S*-methylated 4-amino-1,2,4-triazolidine-3,5-dithione under the same conditions was cyanoethylated merely in the 1-position.[508] New thiazole derivatives have been synthesized by Hantsch-type reactions of thiosemicarbazides[512,513] or thiosemicarbazones[514] with α-halogenocarbonyl compounds. Thiosemicarbazide has been found to react with carbon disulphide under appropriate conditions to yield 2-amino-5-mercapto-1,3,4-thiadiazole.[515]

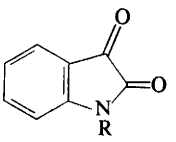
On the basis of a study of the reaction between *p*-chlorobenzaldehyde and 2-methylthiosemicarbazide with special regard to the mechanistic and catalytic aspects, Sayer and Jencks[516] have reported that the reaction in question exhibits a change in rate-determining step at high pH, from rate-determining dehydration of the carbinolamine intermediate to partially rate-determining attack of the nucleophile on the carbonyl group (Scheme 11). Other papers deal with the preparation of thiosemicarbazones derived



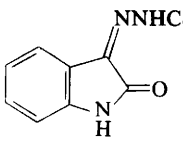
Scheme 11

[510] E. Lippmann, D. Reifegerste, and E. Kleinpeter, *Z. Chem.*, 1973, **13**, 134; *ibid.*, 1974, **14**, 16.
[511] R. Grashey and M. Baumann, *Tetrahedron Letters*, 1972, 2947.
[512] H. J. Jahns, *J. prakt. Chem.*, 1973, **315**, 79.
[513] N. M. Turkevich and V. I. Yakubich, *Khim. geterotsikl. Soedinenii, Sbornik 3*, 1971, 121. (*Chem. Abs.*, 1973, **78**, 71 983).
[514] M. S. Solanki and J. P. Trivedi, *J. Indian Chem. Soc.*, 1972, **49**, 37; I. Simiti and M. Coman, *Ann. Chim. (France)*, 1972, **7**, 33; N. Ergen, O. Altex, and A. Gursoy, *Istanbul Univ. Eczacilik Fak. Mecm.*, 1972, **8**, 3; (*Chem. Abs.*, 1973, **79**, 66 271); I. M. Kazanovskaya, *Farm. Zhur. (Kiev)*, 1972, **27**, 59.
[515] D. Oteleanu, *Farmacia (Bucharest)*, 1972, **20**, 525.
[516] J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, 1973, **95**, 5637.

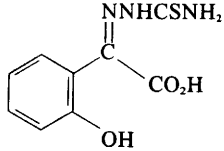
from substituted acetophenones,[517] ethyl acetoacetate,[511,518] and isatins (358),[519,520] and of selenosemicarbazones derived from aromatic aldehydes[521] and isatins (358).[521,522] Mono- and bis-(thiocarbohydrazones) were produced alternatively or simultaneously in the reactions of hexyl methyl ketone[523] and isatin (358; R = H)[524] with thiocarbohydrazide, whereas, of course, the reaction of isatin with 1-phenylthiocarbohydrazide yielded merely the monothiocarbohydrazone (359).[525] 2,3-Coumarandione was ring-opened by thiosemicarbazide to yield either (360) or (361), depending on the pH of the reaction surroundings.[526] Similarly, the thiosemicarbazone (362) was obtained by the action of thiosemicarbazide on the α-phenylimino-derivative of 2,3-coumarandione.[527] The compounds (360), (361), and (362) were useful



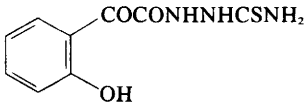
(358) R = H or alkyl



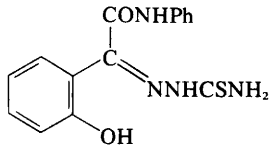
(359)



(360)



(361)

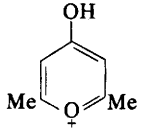


(362)

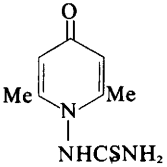
precursors in the synthesis of new heterocyclic compounds.[526,527] The action of thiosemicarbazide on the pyrylium ion (363) resulted in the formation of a new thiosemicarbazide (364).[500] A novel one-step synthesis of *sym*-triazolo-[3,4-*b*]-1,3,4-thiadiazoles (365) is based on the reaction of thiocarbohydrazide with carboxylic acids RCO_2H in the presence of phosphorus oxychloride.[528]

Two papers report on addition reactions of thiosemicarbazides with compounds containing multiple bonds. Thus 2-methyl-4-phenylthiosemicarbazide reacted with β-nitrostyrene to give the open-chain adduct (366),[529]

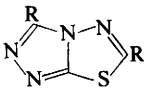
[517] S. S. Tiwari and S. Kumar, *Indian J. Pharm.*, 1972, **34**, 39.
[518] V. K. Rastogi, J. P. Barthwal, N. S. Agarwal, and S. S. Parmar, *Indian J. Pharm.*, 1972, **34**, 114.
[519] A. B. Tomchin, I. S. Ioffe, and G. A. Shirokii, *Zhur. org. Khim.*, 1972, **8**, 400.
[520] L. Heinisch and K. Kramarczyk, *J. prakt. Chem.*, 1972, **314**, 682.
[521] A. A. Tsurkan, V. V. Groshev, V. I. Efremenko, and E. N. Troshenko, *Farm. Zhur. (Kiev)*, 1972, **27**, 69.
[522] J. Krajewski, *Roczniki Chem.*, 1972, **46**, 1177.
[523] A. B. Tomchin, Y. A. Kharit, and A. K. Kutsenko, *Khim.-Farm. Zhur.*, 1973, **7**, 10.
[524] A. B. Tomchin and I. S. Ioffe, *Zhur. org. Khim.*, 1972, **8**, 199.
[525] A. B. Tomchin, V. S. Dmitrukha, T. N. Timofeeva, and P. S. Pel'kis, *Zhur. org. Khim.*, 1973, **9**, 1988.
[526] A. B. Tomchin, I. S. Ioffe, and E. A. Rusakov, *Zhur. org. Khim.*, 1972, **8**, 1295.
[527] A. B. Tomchin, I. S. Ioffe, and E. A. Rusakov, *Zhur. org. Khim.*, 1972, **8**, 1533.
[528] H. Golgolab, I. Lalezari, and L. Hosseini-Gohari, *J. Heterocyclic Chem.*, 1973, **10**, 387.
[529] U. Petersen and H. Heitzer, *Annalen*, 1973, 944.



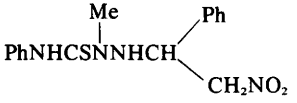
(363)



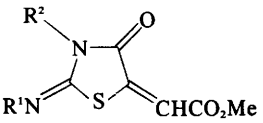
(364)



(365)



(366)



(367)

whereas 4-thiazolidones (367) were obtained in reactions of thiosemicarbazides or acetone thiosemicarbazones with dimethyl acetylenedicarboxylate.[530]

The ability of thiosemicarbazides, thiosemicarbazones, thiocarbohydrazides, and their selenium analogues to undergo a variety of cyclization reactions has been further exemplified in recent syntheses of derivatives of 1,3,4-thiadiazoles,[338,525,531,532] 1,3,4-selenadiazoles,[447,533] 1,3,4-triazole-2-thiones,[311,524,531,534] quinazoline-2-thiones,[458] 1,2,4-triazine-2-thiones,[489] and pyrimido[2,1-*b*]benzothiazoles.[535]

A few papers deal with the reactivity of heterocyclic compounds containing a thiosemicarbazide, a thiosemicarbazone, or a thiocarbohydrazide framework.[504,536]

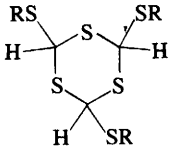
11 Thionocarboxylic and Dithiocarboxylic Acids, their Derivatives, and their Selenium Analogues

Synthesis.—In continuation of their studies of thio-analogues of formic acid, Gattow and his co-workers attempted[537] to synthesize *O*-methyl thioformate

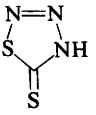
[530] H. Nagase, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 279.
[531] R. A. Coburn, B. Bhooshan, and R. A. Glennon, *J. Org. Chem.*, 1973, **38**, 3947.
[532] I. Simiti and L. Proinov, *Farmacia (Bucharest)*, 1971, **19**, 543; V. Zotta and J. Soare, *ibid.*, 1973, **21**, 215; M. Tutoveanu, E. Comanita, A. Andrei, and I. Mikle, *Bul. Inst. Politeh. Iasi*, 1972, **18**, 95 (*Chem. Abs.*, 1972, **77**, 139 899).
[533] E. Bulka, D. Ehlers, and H. Storm, *J. prakt. Chem.*, 1973, **315**, 164.
[534] M. Tutoveanu, E. Comanita, and A. Andrei, *Bul. Inst. Politeh. Iasi*, 1971, **17**, 89 (*Chem. Abs.*, 1972, **76**, 126 869); A. A. Tsurkan, V. I. Efremenko, and V. V. Groshev, *Farm. Zhur. (Kiev)*, 1972, **27**, 72; C. Demetrescu and I. Saramet, *Rev. Roumaine Chim.*, 1972, **17**, 115 (*Chem. Abs.*, 1972, **76**, 140 655); P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *J. Indian Chem. Soc.*, 1973, **50**, 154; I. Simiti and A. Marie, *Arch. Pharm.*, 1973, **306**, 659.
[535] A. N. Kost, G. A. Golubeva, and L. A. Sviridova, *Khim. geterotsikl. Soedinenii*, 1973, 495.
[536] V. N. Artemov and O. P. Shvaika, *Khim. geterotsikl. Soedinenii*, 1971, **7**, 905; A. B. Tomchin and I. S. Ioffe, *Zhur. org. Khim.*, 1972, **8**, 1287; J. Daunis, Y. Guindo, R. Jacquier, and P. Viallefont, *Bull. Soc. chim. France*, 1972, 1511.
[537] R. Engler and G. Gattow, *Z. anorg. Chem.*, 1972, **388**, 78.

by the action of hydrogen sulphide on trimethyl orthoformate in the presence of catalysts, but obtained only minor amounts of the monomeric thiono-ester. The same authors further showed that dithioformic acid[538] and its methyl and ethyl esters[539] (obtainable by the reaction of potassium sulphide with chloroform and subsequent treatment of the potassium dithioformate thus formed with aqueous hydrogen chloride[538] or the appropriate alkyl halides[539]) are stable as cyclic trimers (368). Both dithioformic acid,[538] cyanodithioformic acid,[540] and azidodithioformic acid[540] were found to be monomeric in the vapour phase. However, in contrast to the two former dithio-acids, solid azidodithioformic acid has crystalline rather than amorphous character, and the possibility cannot be excluded that the latter dithio-acid actually exists as a 1,2,3,4-thiatriazoline (369) in the solid state.[540]

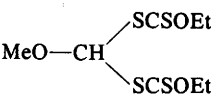
A novel and more profitable route to *O*-methyl thioformate depends on the reaction of dichloromethyl methyl ether with potassium *O*-ethyl dithiocarbonate; the product (370) decomposed thermally at 200—220 °C to



(368) R = H, Me, or Et



(369)



(370)

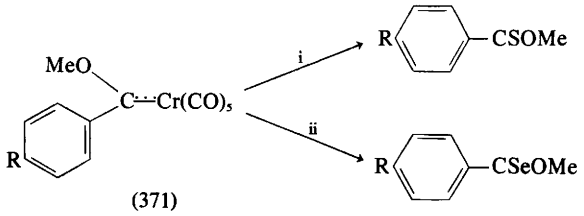
give a mixture of *O*,*S*-diethyl dithiocarbonate and methyl thionoformate, the latter in 56% yield.[541] Mayer and Kröber found a new route to higher thiono-esters in the reaction of ethyl thionoformate with diazo-compounds:[542]

$$H—CS—OEt + R^1R^2CN_2 \rightarrow R^1R^2CH—CS—OEt$$

Some methyl arylthiono- and arylselenono-carboxylates have been synthesized by the reaction of the corresponding pentacarbonyl(methoxyarylcarbene)chromium(o) complexes (371) with elemental sulphur and elemental selenium, respectively (Scheme 12).[543] Successive treatment of β-naphthaldehyde with ammonium polysulphide, hydrogen chloride, sodium hydroxide, and tetraethylammonium iodide afforded tetraethylammonium β-dithionaphthoate.[544]

Several groups of workers have employed the base-catalysed reaction of carbon disulphide with reactive methylene or methine groups in the

[538] R. Engler and G. Gattow, *Z. anorg. Chem.*, 1972, **389**, 145.
[539] R. Engler, G. Gattow, and M. Dräger, *Z. anorg. Chem.*, 1972, **390**, 64.
[540] R. Engler and G. Gattow, *Z. anorg. Chem.*, 1972, **390**, 73.
[541] D. H. Holsboer and H. Kloosterziel, *Rec. Trav. chim.*, 1972, **91**, 1371.
[542] R. Mayer and H. Kröber, *Z. Chem.*, 1973, **13**, 426.
[543] E. O. Fischer and S. Riedmüller, *Chem. Ber.*, 1974, **107**, 915.
[544] G. Mezaraups, L. D. Kulikova, M. Gertners, and E. Jansons, *Khim. Atsetilena Tekhnol. Karbida Kal'tsiya*, 1972, 359 (*Chem. Abs.*, 1974, **80**, 36 894).



(371)

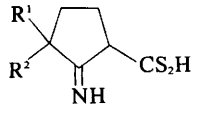
Reagents: i, S_8, ether, 35°C; ii, Se_x, dioxan, 100 °C

Scheme 12

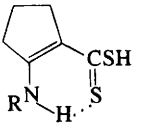
synthesis of dithiocarboxylic acids, their esters, or their keten mercaptal derivatives.[251,545–550] 3-Substituted 2-iminocyclopentanedithiocarboxylic acids (372) were the main products in the reactions of parent cyclopentanones with carbon disulphide and aqueous ammonia.[390] 2-Methylaminocyclopent-1-ene-1-dithiocarboxylic acid (373; R = Me) has been prepared in a similar manner by simultaneous action of carbon disulphide and methylamine on cyclopentanone, but related dithio-acids containing higher alkylamino-groups (373; R ≠ Me) appeared not to be obtainable in this way.[551] Indole-2-carboxylic acid esters and amides gave the dithio-esters (374) on successive treatment with sodium hydride, carbon disulphide, and dimethyl sulphate.[552] Mixtures of dithio-esters (375) and (376) were obtained by the reaction of alkoxybenzenes with carbon disulphide and γ-butyrolactone under Friedel–Crafts conditions in the presence of dimethyl sulphate, but benzene and toluene afforded no dithio-esters under these conditions.[553] Using THF as reaction solvent, Brandsma and his co-workers obtained[554] aliphatic and aromatic dithio-esters in good yields by treatment of Grignard reagents successively with carbon disulphide and alkyl halides. The action of bromoacetonitrile on the magnesium salt of dithiobenzoic acid afforded the dithio-ester (377), also in good yield.[555] An improved technique for the synthesis of carbon diselenide, based on the reaction of methylene chloride with elemental selenium, has been developed by Henriksen and Kristiansen.[556]

Dithio-esters of the type (378) have been synthesized by successive treatment of the parent sulphones with sodium hydride and dimethyl

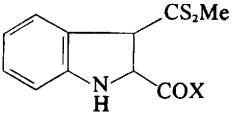
[545] E. J. Corey and R. H. K. Chen, *Tetrahedron Letters*, 1973, 3817.
[546] F. C. V. Larsson and S.-O. Lawesson, *Tetrahedron*, 1972, **28**, 5341.
[547] L. Dalgaard, H. Kolind-Andersen, and S.-O. Lawesson, *Tetrahedron*, 1973, **29**, 2077.
[548] L. Dalgaard, L. Jensen, and S.-O. Lawesson, *Tetrahedron*, 1974, **30**, 93.
[549] I. Shahak and Y. Sasson, *Tetrahedron Letters*, 1973, 4207.
[550] D. Ladurée, P. Rioult, and J. Vialle, *Bull. Soc. chim. France*, 1973, 637.
[551] B. Bordás, P. Sohár, G. Matolcsy, and P. Berencsi, *J. Org. Chem.*, 1972, **37**, 1727.
[552] G. Kobayashi, Y. Matsuda, R. Natuki, and Y. Tominaga, *Yakugaku Zasshi*, 1971, **91**, 1164.
[553] S. R. Ramadas and P. S. Srinivasan, *J.C.S. Chem. Comm.*, 1972, 345.
[554] J. Meijer, P. Vermeer, and L. Brandsma, *Rec. Trav. chim.*, 1973, **92**, 601.
[555] D. H. R. Barton, C. Chavis, M. K. Kaloustian, P. D. Magnus, G. A. Poulton, and P. J. West, *J.C.S. Perkin I*, 1973, 1571.
[556] L. Henriksen and E. S. S. Kristiansen, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 133.



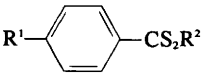
(372)



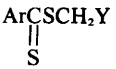
(373)



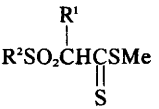
(374) X = OH or NMe_2



(375) $R^2 = Me$
(376) $R^2 = (CH_2)_3CO_2Me$



(377) Y = CN, Ar = Ph
(379) $Y = CO_2H$

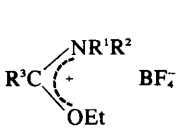


(378)

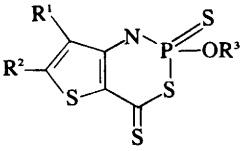
trithiocarbonate.[550] The applicability of (thioaroylthio)acetic acids (379) in the synthesis of aromatic thiono-esters has been the subject of a recent investigation by Barton and his co-workers, who also noticed the inability of the dithio-ester (377) to act as a thiobenzoylation agent.[555] Bis(trifluoromethyl)thioketen (141) reacted with alcohols and thiols to give thiono- and dithio-esters, respectively (see Scheme 8).[58] Various dithio-esters have been produced by ring-opening reactions of 1,2-dithiole-3-thiones,[40] 3-methylthio-1,2-dithiolylium salts,[557,558] 5-alkylmercapto-1,2-dithia-3-cyclopentenimines,[559] isothiazoline-5-thiones,[560] and 2-methylthio-5-t-butyl-1,6,6a-trithiapentalene.[279]

Two groups of workers have synthesized thiono-esters by the action of triethyloxonium fluoroborate on the corresponding amides and successive treatment of the salts (380) thus formed with hydrogen sulphide in pyridine.[555,561] *N*-Acyl-α-amino-dithio-esters have been prepared from the corresponding *N*-acyl-α-amino-nitriles by successive treatment with thiols and hydrogen sulphide under appropriate conditions.[562] A method of choice for preparing thiono- and dithio-esters is to treat the corresponding esters or thiolo-esters with phosphorus pentasulphide, and the advantageous application of polar solvent in such reactions has been suggested recently by Scheeren and his co-workers.[29] Brelivet and Teste treated 3-amino-2-ethoxycarbonylthiophens with phosphorus pentasulphide in xylene and obtained compounds of the type (381), which on treatment with dimethyl sulphate in alcoholic sodium hydroxide easily ring-opened to give dithio-esters (382).[563] Otherwise, phosphorus pentasulphide has been used as a

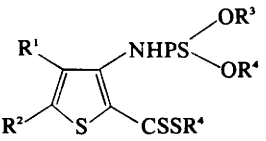
[557] G. Le Coustumer and Y. Mollier, *Compt. rend.*, 1972, **274**, *C*, 1215.
[558] G. Le Coustumer and Y. Mollier, *Bull. Soc. chim. France*, 1973, 3349.
[559] F. Boberg and W. von Gentzkow, *J. prakt. Chem.*, 1973, **315**, 970.
[560] F. Boberg and W. von Gentzkow, *J. prakt. Chem.*, 1973, **315**, 965.
[561] M. Mori, Y. Ban, and T. Oishi, *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 79.
[562] J. Poupart, A. Bruylants, and P. Crooy, *Synthesis*, 1972, 622.
[563] J. Brelivet and J. Teste, *Bull. Soc. chim. France*, 1972, 2289.



(380)



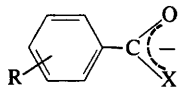
(381)



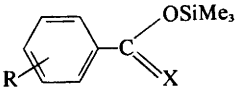
(382)

thionation agent mainly in the synthesis of heterocycles containing the —CS—S— moiety (refs. 126, 223, 224, 564, and 565).

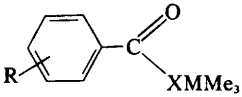
Infrared spectral results combined with Hückel MO calculations led Prangova and his co-workers to conclude[566] that the negative charge of *meta*-substituted thiobenzoate anions is located principally at the oxygen atom. The C—S and C—O bond orders of the thiobenzoate anion were determined as 1.8 and 1.3, respectively, and the authors further pointed out that electron-donating *meta*-substituents increase the C—S bond order. The greater affinity of silicon towards oxygen in preference to sulphur and selenium has been illustrated recently by the reactions of a series of thio- and seleno-benzoates (383) with trimethylsilyl chloride, affording the thiono- and seleno-benzoic esters (384).[567] In contrast, (383) reacted with chlorotrimethyl-germane or -stannane to yield thiolo- or selenolo-esters (385).[567] *S*-Thioaroylhydrosulphamines (386) have been obtained in excellent



(383) X = S or Se



(384) X = S or Se

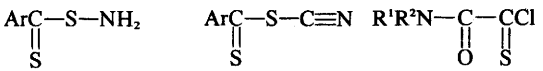


(385) X = S or Se
M = Sn or Ge

yields by the reaction of sodium salts of aromatic dithio-acids with sodium hydroxylamine-*O*-sulphonate.[568] Thioaroyl thiocyanates (387) appear to be more stable than their aroyl analogues, as some representatives of the former actually have been isolated as the products of the reaction of thioaroyl chlorides with sodium thiocyanate.[277] 2-Chloro-2-thioxoacetamides (388) were formed by the reaction of carbamoyl dichlorosulphenyl chlorides (389) with triphenylphosphine.[267]

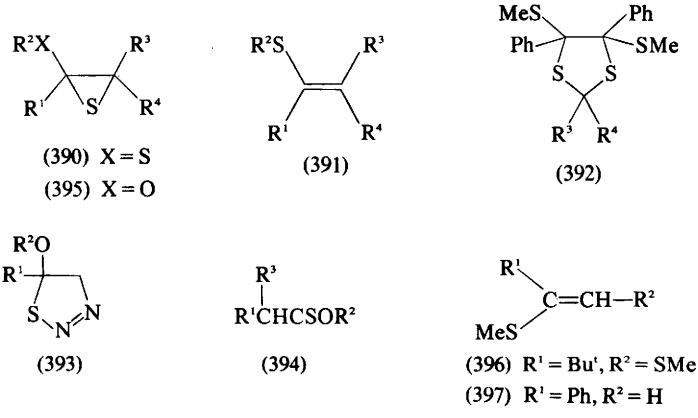
Some papers dealing with the preparation and properties of metal salts and/or metal complexes of thiono- and dithio-acids may be of interest to workers in that field.[290,569–571]

[564] N. K. Son, R. Pinel, and Y. Mollier, *Bull. Soc. chim. France*, 1973, 3334.
[565] M. A. Vasyanina and V. K. Khairullin, *Zhur. obshchei Khim.*, 1972, **42**, 2644.
[566] L. S. Prangova, V. M. Traiger, I. Y. Kvitko, and L. S. Efros, *Doklady Bolg. Akad. Nauk*, 1971, **24**, 1195 (*Chem. Abs.*, 1972, **77**, 87 626).
[567] S. Kato, W. Akada, M. Mizuta, and Y. Ishii, *Bull. Chem. Soc. Japan*, 1973, **46**, 244; H. Ishihara and S. Kato, *Tetrahedron Letters*, 1972, 3751.
[568] M. S. Raasch, *J. Org. Chem.*, 1972, **37**, 3820.
[569] R. Engler, G. Gattow, and M. Dräger, *Z. anorg. Chem.*, 1972, **388**, 229.
[570] A. Ferretti, *Canad. J. Chem.*, 1972, **50**, 4056.
[571] D. Coucouvanis and D. Piltingsrud, *J. Amer. Chem. Soc.*, 1973, **95**, 5556.



(386) (387) (388) (389)

Reactions.—The reactions of thiono- and dithio-esters with diazoalkanes have been studied extensively by French chemists.[117,118] Thus aliphatic dithio-esters, on treatment with diazoalkanes at −5 °C, were found to be converted into thiirans (390) that, however, easily lost sulphur to form olefins (391). Methyl dithiobenzoate reacted anomalously with diazoalkanes, yielding isomeric 1,3-dithiolans (392). The reactions of thiono-esters with diazomethane or diazoethane afforded always two products, in the former case a 1,2,3-thiadiazoline (393) and an insertion product (394; R^3 = H), in the latter case a thiiran (395) and the insertion product (394; R^3 = Me); with 2-diazopropane, only thiirans (395; $R^3 = R^4$ = Me) were formed. Low-temperature experiments suggested[117] that thiadiazolines were general intermediates in these reactions. The same group of workers have also studied the reaction of dithio-esters with dimethylsulphoxonium methylide and report[124] that dithio-esters possessing one or more α-hydrogen atoms underwent *S*-methylation, yielding keten mercaptals, whereas the non-enethiolizable methyl dithiopivalate reacted with two molecules of the ylide to form, *via* a methylthio-group migration, the 1,2-di(methylthio)alkene (396). The formation of α-methylthiostyrene (397)



(390) X = S
(395) X = O

(391)

(392)

(393)

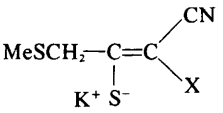
(394)

(396) R^1 = Bu^t, R^2 = SMe
(397) R^1 = Ph, R^2 = H

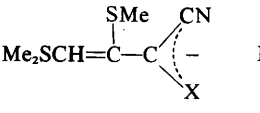
in the reaction of methyl dithiobenzoate with dimethylsulphoxonium methylide was interpreted in terms of an intermediate thiiran (390; R^1 = Ph, R^2 = Me, $R^3 = R^4$ = H).[124]

The reactivity of thiono- and dithio-esters towards nucleophiles such as anions of acetonitrile,[17] the diethyl ester of cyanomethanephosphonic acid,[59] and 2-cyano- and 2-alkoxy-carbonylthioacetamides[60] has been successfully

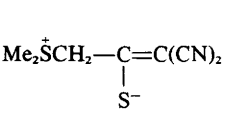
exploited in recent syntheses of new thioketones. Ethyl (methylthio)thionoacetate reacted with malonodinitrile and cyanoacetamide in the presence of potassium ethoxide to yield the salts (398), which on successive treatment with trimethyloxonium fluoroborate and strong base gave new sulphonium ylides (399).[572] The sulphonium betaine (400) has been synthesized by successive treatment of ethyl (methylthio)thionoacetate with



(398) X = CN or $CONH_2$



(399) X = CN or $CONH_2$

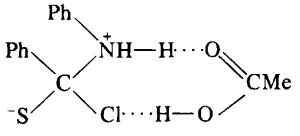


(400)

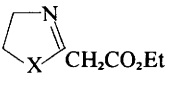
trimethyloxonium fluoroborate, malonodinitrile, and sodium cyanide.[572] Two papers report on the synthesis of ethyl thioacetothionoacetate by base-promoted self-condensation of ethyl thionoacetate.[39,61] The reactions of some representative thiono- and dithio-esters with piperidine proceeded without side-reactions to form thiopiperidides, obeying strictly second-order kinetics,[573] whereas simple aliphatic dithio-esters, on treatment with piperidine, were converted into their piperidinium salts.[574] The reactions between thiobenzoyl chloride and aniline, affording thiobenzanilide, have also been the subject of kinetic studies.[265] In the absence of a catalyst, this reaction was found to proceed in accordance with second-order kinetics; in the presence of acetic acid, however, the reaction appeared to follow third-order kinetics, *i.e.* first-order with respect to each of the reactants as well as to the catalyst. The latter observation led to the conclusion that the acetic-acid-catalysed reaction proceeds *via* a hydrogen-bonded eight-membered cyclic transition state (401).[265] Other recent papers report on the reaction of thiobenzoyl chloride with triazoles, affording thiobenzoyltriazoles,[266] the reactions of $\alpha\beta$-unsaturated β-(methylthio)-dithio-esters with amines affording the corresponding thioamides or enamino-dithio-esters,[575] and the reactions of $\alpha\beta$-unsaturated β-hydroxy-dithio-acids[576] and -dithio-esters[558,576] with amines affording a variety of products, depending on steric and other factors. Aromatically substituted β-hydroxydithiocinnamic acids reacted with *o*-phenylenediamine to form 4-aryl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-thiones,[269] and 2-substituted 4-hydroxy-6-mercaptopyrimidines were obtained in excellent yields by the reaction of methyl ethoxycarbonyldithioacetate with amidines.[577] A reinvestigation of the reaction between diethyl monothionomalonate and 2-aminoethanol revealed[578] that the product formed is ethyl (Δ^2-thiazolin-2-yl)acetate

[572] K. Hartke and G. Gölz, *Chem. Ber.*, 1973, **106**, 2353.
[573] N. S. Tao, S. Scheithauer, and R. Mayer, *Z. Chem.*, 1972, **12**, 133.
[574] S. Kato and M. Mizuta, *Bull. Chem. Soc. Japan*, 1972, **45**, 3492.
[575] J. Maignan and J. Vialle, *Bull. Soc. chim. France*, 1973, 3026.
[576] F. Cleese and H. Quiniou, *Bull. Soc. chim. France*, 1973, 581.
[577] M. Snyers, M. Donnez, D. Isbecque, T. Lakhanisky, and R. Promel, *Bull. Soc. chim. belges*, 1973, **82**, 357.
[578] H. Wamhoff and C. Materne, *Annalen*, 1973, 573.

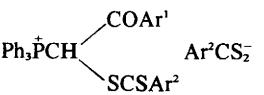
(402), rather than the corresponding oxygen compound (403) as postulated earlier. The reactions of bis(thioaroyl) disulphides with piperidine[579] and phenacylidenetriphenylphosphoranes[580] gave piperidinium salts of the corresponding dithio-acids and salts of the type (404), respectively. The thioanhydrides (405) were found to be cleaved by primary amines to thioamides, ureas, and hydrogen sulphide.[581]



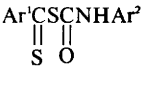
(401)



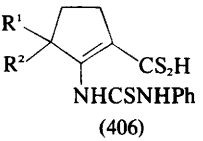
(402) X = S
(403) X = O



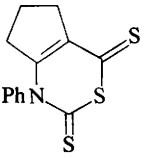
(404)



(405)



(406)



(407)

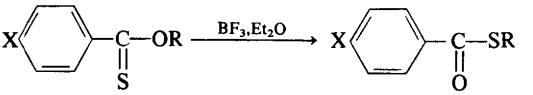
Oae and his co-workers have investigated the reactivity of dithioacetic acid towards olefins, and they found that the reaction takes place either as a Michael-type addition (with olefins bearing an electron-withdrawing group in the α-position to the double bond), or as a Markownikoff-type addition (with olefins bearing an electron-donating group).[582] Dithioacetic acid also underwent addition reactions with vinyl and alkyl sulphoxides, but these reactions were accompanied by a simultaneous reduction of the sulphoxide group.[582] The compounds (405) were formed by the reaction of aryldithio-acids with aryl isocyanates.[581] The dithiocarboxylic group in (372; $R^1 \neq H$), however, was unreactive towards phenyl isothiocyanate, which instead reacted with the imino-group to yield the thiourea derivative (406); (372; $R^1 = R^2 = H$) reacted with phenyl isothiocyanate to give the heterocyclic compound (407).[390]

The utility of thiono- and dithio-esters in the synthesis of heterocyclic compounds has been further demonstrated,[129,318,583–586] and several of the reactions involved, for example the addition reactions with tosylmethyl isocyanide,[583] nitrile ylides,[584] and nitrile oxides,[129] are also of considerable theoretical interest.

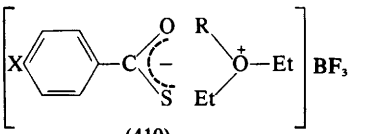
[579] S. Kato and M. Mizuta, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 275.
[580] S. Kato, S. Imamura, and M. Mizuta, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 283.
[581] S. Kato, T. Mitani, and M. Mizuta, *Bull. Chem. Soc. Japan*, 1972, **45**, 3653.
[582] S. Oae, T. Yagihara, and T. Okabe, *Tetrahedron*, 1972, **28**, 3203.
[583] O. H. Oldenziel and A. M. van Leusen, *Tetrahedron Letters*, 1972, 2777.
[584] K. Bunge, R. Huisgen, R. Raab, and H. J. Sturm, *Chem. Ber.*, 1972, **105**, 1307.
[585] K. Hartke and G. Gölz, *Annalen*, 1973, 1644.
[586] W. Schroth and U. Becker, *Z. Chem.*, 1974, **14**, 51.

Recent papers reporting on oxidation reactions of dithio-esters deal with ozonization of aromatic dithio-esters to give the corresponding sulphines,[148] permanganate oxidation of dithio-esters to give the corresponding thiolo-esters,[563] and iodine oxidation of 2-phenyl-3-anilinopropenedithioates to isothiazolium tri-iodides.[246]

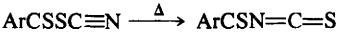
Oishi and his co-workers have reported[561] that aromatic thiono-esters (408), in the presence of boron trifluoride ethyl-etherate, rearrange to the corresponding thiolo-esters (409). The disappearance of the thiono-ester took place in accordance with first-order kinetics, and electron-donating *para*-substituents were found to accelerate the conversion, which was characterized by the Hammett ρ value of -1.38. The mechanism of the rearrangement was considered to involve the intermediate (410), in agreement with the results of cross-over experiments.[561] The thermal rearrangement of thioaroyl thiocyanates (411) to thioaroyl isothiocyanates (412) was also found to be influenced by substituents.[277] Thiono-ester–thiolo-ester



(408) (409)



(410)

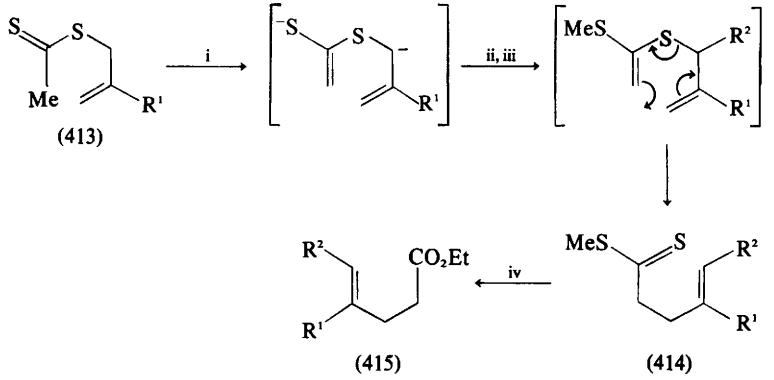


(411) (412)

rearrangement and alkene elimination were the competitive processes that took place in the thermolysis of simple alkyl thionoacetates.[587] Among the several papers[546–548,588,589] reporting on the participation of dithio-esters in the thio-Claisen and related rearrangements, the most significant is perhaps that[589] describing the highly stereoselective rearrangement of the dithio-esters (413) to the γδ-unsaturated dithio-esters (414), which takes place when the former are treated successively with s-butyl-lithium and alkyl halides (Scheme 13). A new route to γδ-unsaturated esters was opened with the discovery of this reaction sequence, as compounds (414), on treatment with an excess of a cupric chloride–cupric oxide mixture in ethanol, were found to be oxidized to the esters (415) in high yields.[589]

The photochemistry of thiono-esters has been studied quite extensively in the past. Rungwerth and Schwetlick pointed out[590] that, besides forming enediol ethers when sulphur is eliminated or yielding olefins in Norrish Type

[587] P. C. Oele, A. Tinkelenberg, and R. Louw, *Tetrahedron Letters*, 1972, 2375.
[588] J. Meijer, P. Vermeer, H. J. T. Bos, and L. Brandsma, *Rec. Trav. chim.*, 1973, **92**, 1067; P. Vermeer, J. Meijer, H. J. T. Bos, and L. Brandsma, *ibid.*, 1974, **93**, 51.
[589] H. Takahashi, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, 1973, **95**, 5803.
[590] D. Rungwerth and K. Schwetlick, *Z. Chem.*, 1974, **14**, 17.



Reagents: i, Bu^{t}Li, −78 °C; ii, R^2X; iii, MeI; iv, $CuCl_2$–CuO, EtOH

Scheme 13

II rearrangement reactions, thiono-esters, on irradiation, may undergo a thiono-ester–thiolo-ester rearrangement, a photo-Fries rearrangement [irradiation of the thiono-ester (416) gave the thioketone (417) in 15% yield], or

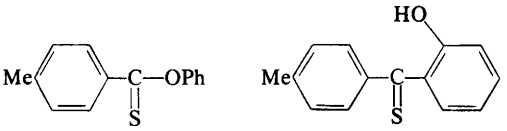


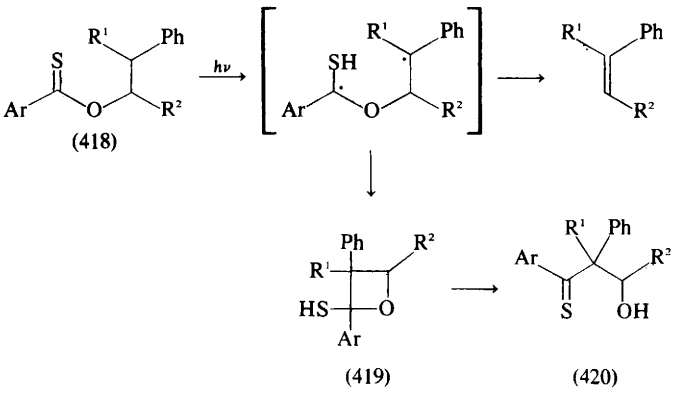
photo-oligomerization, depending on the nature of the thiono-ester. The Norrish Type II photoelimination reaction has been utilized by Barton and his co-workers in the synthesis of a variety of olefins.[71,591,592] Thiobenzoates (418), which have an alkyl group R^2 that is β to the thiocarbonyl group, underwent photocyclization to oxetans (419) in competition with the Type II elimination reaction.[71,72,593] The oxetans were stable at −78 °C, but rearranged rapidly at −20 °C into thiones (420) (Scheme 14).[72] The primary photochemical processes of these reactions have been determined by Wirz[593] on the basis of nanosecond flash photolysis experiments, luminescence measurements, and quantum-yield determinations. Ohno and his co-workers have investigated[594] the photoreaction of *O*-alkyl thiobenzoates with olefins, which gave alkyl phenyl ketones and/or 2-alkoxy-2-phenylthietans. The reaction was interpreted as a photo-cycloaddition, as the latter

[591] D. H. R. Barton, M. Bolton, P. D. Magnus, K. G. Marathe, G. A. Poulton, and P. J. West, *J.C.S. Perkin I*, 1973, 1574.

[592] S. Achmatowicz, D. H. R. Barton, P. D. Magnus, G. A. Poulton, and P. J. West, *J.C.S. Perkin I*, 1973, 1567.

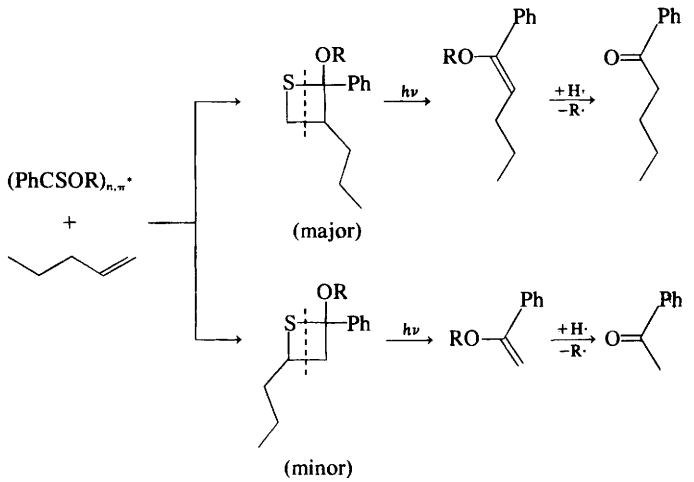
[593] J. Wirz, *J.C.S. Perkin II*, 1973, 1307.

[594] A. Ohno, T. Koizumi, and Y. Akasaki, *Tetrahedron Letters*, 1972, 4993.



Scheme 14

products appeared to be intermediates in the formation of the former. A plausible reaction mechanism (exemplified by pent-1-ene) is outlined in Scheme 15. The intermediate enol ethers were isolable under appropriate



Scheme 15

conditions. Methyl dithiobenzoate reacted with 2,3-diphenylazirine upon irradiation to give a mixture of isomeric 5-methylthio-2,4,5-triphenyl-Δ^2-thiazolines.[595]

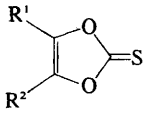
Several papers, dealing with the reactivity of heterocycles containing the

[595] A. Padwa, J. Smolanoff, and S. I. Wetmore, *J. Org. Chem.*, 1973, **38**, 1333.

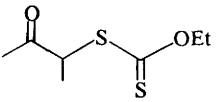
—CS—O—,[596] the —CS—S— (refs. 33, 63, 270, 417, and 597—599), the —CS—S—S— (refs. 403, 486, 600, and 601), or the —CSe—O— moiety[596] have appeared recently.

12 Thionocarbonates, Thionodithiocarbonates, Trithiocarbonates, and their Selenium Analogues

Synthesis.—Fischler and Hartmann have reported[602] that vinylenethionocarbonates (421; R^1, R^2 = H, Me, or Ph) can be synthesized by treatment of the corresponding vinylenecarbonates with phosphorus pentasulphide; the best yields were obtained with disubstituted vinylenecarbonates. The thionodithiocarbonate (422), obtained by the reaction of potassium *O*-alkyl dithiocarbonate with 3-bromo-2-butanone, gave 4,5-dimethyl-1,3-dithiole-2-thione (423) in 72% yield on treatment with phosphorus pentasulphide in boiling decalin.[603] 4,5-Diphenyl-1,3-dithiole-2-thione (424) has been obtained quantitatively by refluxing (425) with elemental sulphur in pyridine for 5 hours.[604] The thionocarbonates (426) and (427) were formed when the corresponding diols (428) were treated with di(imidazol-1-yl) thioketone



(421)



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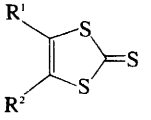
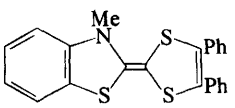


(423) $R^1 = R^2 = Me$

(424) $R^1 = R^2 = Ph$



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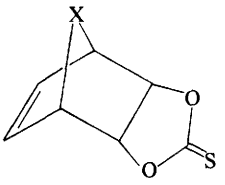
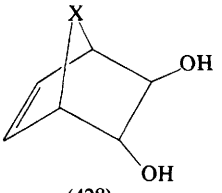


(426) X = O

(427) X = C=CMe$_2$



(428)

[596] I. Y. Kvitko, N. B. Sokolova, and L. S. Efros, *Khim. geterotsikl. Soedinenii*, 1973, 715.

[597] Ya. L. Gol'dfarb and M. A. Kalik, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 2072 (*Chem. Abs.*, 1974, **80**, 27 130).

[598] K. Gewald, M. Buchwalder, and M. Peukert, *J. prakt. Chem.*, 1973, **315**, 679.

[599] S. Leistner, G. Wagner, and E. Iffland, *Z. Chem.*, 1972, **12**, 289.

[600] F. Boberg and W. von Gentzkow, *Annalen*, 1972, **766**, 1; J. L. Burgot and J. Vialle, *Compt. rend.*, 1974, **278**, *C*, 793.

[601] P. de Mayo and H. Y. Ng, *Tetrahedron Letters*, 1973, 1561.

[602] H.-M. Fischler and W. Hartmann, *Chem. Ber.*, 1972, **105**, 2769.

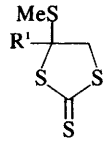
[603] J. P. Ferraris, T. O. Poehler, A. N. Bloch, and D. O. Cowan, *Tetrahedron Letters*, 1973, 2553.

[604] D. Buza and W. Krasuski, *Roczniki Chem.*, 1972, **46**, 2377.

(236).[605,606] Thermolysis of (426) gave vinylenethionocarbonate (421; $R^1 = R^2 = H$).[605]

Several examples of the applicability of carbon disulphide in the synthesis of cyclic as well as open-chain thiono- and trithio-carbonates have appeared. Thus dithallous glycolates reacted with excess of carbon disulphide to form ethylenethionocarbonates together with spiro-orthocarbonates, and the formation of tetramethyl orthocarbonate in the reaction between thallous ethoxide and carbon disulphide evidently proceeded *via* intermediate diethyl thionocarbonate.[607] Klingsberg obtained[608] 5,6-dimethyl-1,3-dithiole-2-thione by the reaction of 4,5-dimethylbenzene-1,2-dithiol with carbon disulphide. The thiirans (390; $R^2 = Me$, $R^3 = R^4 = H$) reacted with carbon disulphide in basic media to yield 4-methylthio-1,3-dithiole-2-thiones (429).[117] Successive treatment of 2,2-diphenylethylenesulphonamide with carbon disulphide and alkyl halides in the presence of a base afforded the unsaturated trithiocarbonate (430),[609] and the symmetrical trithiocarbonate (431) was formed by the simultaneous action of sodium sulphide and carbon disulphide on the oxathiolan derivative (432).[610]

Goerdeler and Hohage have synthesized a series of alkylthio-thiocarbonylthiocyanates (433) by the reaction of the corresponding alkylthio-thiocarbonyl chlorides (434) with sodium rhodanide.[371]



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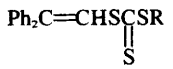

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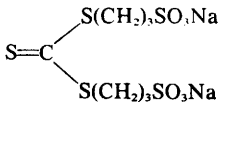

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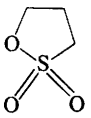

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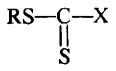
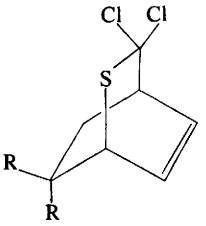


(433) X = SCN
(434) X = Cl

Reactions.—Thiophosgene may be considered as a double acid chloride of thionocarbonic acid, and the several papers reporting on recent progress in the chemistry of thiophosgene are therefore conveniently reviewed in this section. Reports on the utility of thiophosgene in the synthesis of isothiocyanates,[611] tetrachlorothiirans,[116] and 2-thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazines[612] have appeared. However, perhaps more significant

[605] W. K. Anderson and R. H. Dewey, *J. Amer. Chem. Soc.*, 1973, **95**, 7161.
[606] M. Z. Haq, *J. Org. Chem.*, 1972, **37**, 3015.
[607] S. Sakai, Y. Kuroda, and Y. Ishii, *J. Org. Chem.*, 1972, **37**, 4198.
[608] E. Klingsberg, *Synthesis*, 1972, 29.
[609] K. Hasegawa, T. Sasaki, and S. Hirooka, *Bull. Chem. Soc. Japan*, 1973, **46**, 2894.
[610] V. Mozolis and S. Jokubaityte, *Liet. T.S.R. Mokslu Akad. Darb., Ser. B*, 1973, 75 (*Chem. Abs.*, 1974, **80**, 36 682).
[611] S. Sharma, R. Bindra, and R. N. Iyer, *Indian J. Pharm.*, 1973, **35**, 13; M. Uher and J. Jendrichovsky, *Coll. Czech. Chem. Comm.*, 1973, **38**, 620.
[612] P. Kristian, J. Bernat, and M. Novotna, *Coll. Czech. Chem. Comm.*, 1972, **37**, 2972.

are two papers, of which one describes the applicability of thiophosgene as a dienophile towards 1,3-cyclohexadienes in the synthesis of thiabicyclo-[2,2,2]octenes (435),[613] whereas the other reports on the photochemical addition of thiophosgene to olefins.[614] In the latter case 2,2-dichlorothietans are principially formed, but thiophosgene and 2,4-dimethyl-2,3-pentadiene gave a mixture of the thietan (436) and the open-chain adduct (437).[614]



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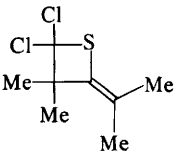

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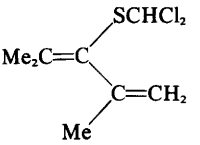
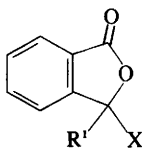


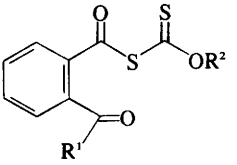
(437)

McKinnon and Queen have studied the influence of structural changes on the rates of hydrolysis of a series of alkyl chlorothionoformates and chlorodithioformates.[615] For both classes of compound, the reactivity was found to be enhanced by increased electron donation of the hydrocarbon group, a fact that, taken together with the solvent isotope effect observed and the activation parameters determined for the hydrolysis, led the authors to conclude that the hydrolysis proceeds in accordance with the S_N1 mechanism.

The synthetic utility of xanthates is well documented, and several recent papers reporting on new results in this field have appeared (refs. 283, 451, 541, 616, and 617). Among these is a paper[617] describing the reaction of the halogenophthalides (438) with potassium *O*-alkyl xanthates, by which *O*-alkyl *S*-phthalidyl xanthates (440) are produced *via* rearrangement of the initially formed compounds (439). Other papers deal with the kinetics of the



(438) R^1 = H or Ph
X = Cl or Br



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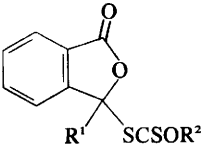
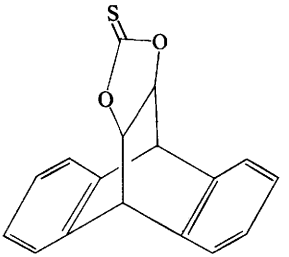


(440)

[613] H. J. Reich and J. E. Trend, *J. Org. Chem.*, 1973, **38**, 2637.
[614] H. Gotthardt, *Tetrahedron Letters*, 1973, 1221.
[615] D. M. McKinnon and A. Queen, *Canad. J. Chem.*, 1972, **50**, 1401.
[616] K. Tomita and M. Nagano, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2302; M. Nagano and K. Tomita, *ibid.*, p. 2308.
[617] S. N. Singh and M. V. George, *J. Org. Chem.*, 1972, **37**, 1375.

hydrogen peroxide oxidation of potassium *O*-ethyl xanthate[618] and with alkylation reactions of trithiocarbonates.[619,620]

Cyclic thionocarbonates have found applicability in olefin syntheses. The Diels–Alder adduct (441), generated by the reaction of anthracene with Δ^4-1,3-dioxolen-2-thione (421; $R^1 = R^2 = H$), gave under conditions of Corey–Winter elimination dibenzobarralene (442).[605] In a similar way, spirohex-4-ene was obtained in 80% yield from (443).[621] Daub and his co-workers have synthesized several uncommon olefins, among these (442), from parent cyclic thionocarbonates, using iron pentacarbonyl as the efficient elimination promoter.[622] Semmelhack and Stauffer have reported that bis-(cyclo-octa-1,5-diene)nickel (444) converts thionocarbonates of *vic*-diols into the corresponding olefins in excellent yields and with a high degree of stereospecificity.[623] In connection with a discussion of the mechanistic pathways of this reaction, the authors presented evidence for the intermediacy of the carbene complex (445).



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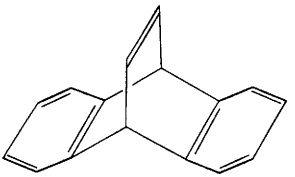

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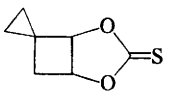

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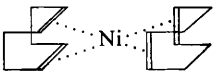

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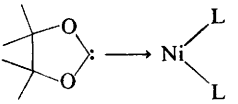
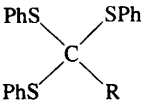


(445) L = cod

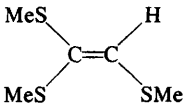
The reaction of diphenyl trithiocarbonate with phenyl-lithium, which takes place at −78 °C to form (446),[624] constitutes a further example of a thiophilic addition to the thiocarbonyl double bond. Compound (446) appeared to be stable in solution below −20 °C, and its structure was confirmed by its reactions with deuterium oxide and methyl iodide, affording (447) and (448), respectively.[624] Dimethyl trithiocarbonate reacted with two equivalents of dimethylsulphoxonium methylide to form

[618] J. Garbacik, J. Najbar, and A. Pomianowski, *Roczniki Chem.*, 1972, **46**, 85.
[619] J. Tuilecki and B. Golus, *Pol. J. Pharmacol. Pharm.*, 1973, **25**, 259.
[620] G. I. Pustoshkin and F. Y. Rachinskii, *Khim. seraorg. Soedinenii, Soderzh. Neftyakhim. Nefteprod.*, 1972, **9**, 290 (*Chem. Abs.*, 1973, **79**, 115 086).
[621] W. Hartmann, L. Schrader, and D. Wendisch, *Chem. Ber.*, 1973, **106**, 1076.
[622] J. Daub, W. Trautz, and U. Erhardt, *Tetrahedron Letters*, 1972, 4435.
[623] M. F. Semmelhack and R. D. Stauffer, *Tetrahedron Letters*, 1973, 2667.
[624] D. Seebach, *Chem. Ber.*, 1972, **105**, 487.

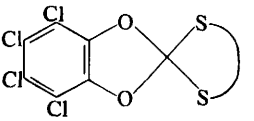
tri(methylthio)ethylene (449) as an indication of a reaction mechanism involving the migration of a methylthio-group.[124] The spiro-compounds (450)



(446) R = Li
(447) R = D
(448) R = Me



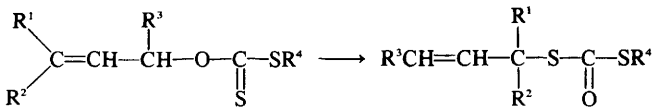
(449)



(450)

have been synthesized by the reaction of various cyclic trithiocarbonates with tetrachloro-1,2-benzoquinone.[625] Other recent papers dealing with the chemistry of trithiocarbonates report on reactions of these with nitrile ylides,[584] nitrile oxides,[129] amines,[400] and triphenylphosphine.[626]

Harano and Taguchi have studied the thermal rearrangement of 2-alkenyl *S*-alkyl xanthates to the corresponding dithiolocarbonates.[627] The rearrangement was shown to be strictly intramolecular and, in the general case, to take place accompanied by an allylic shift (Scheme 16). For sterically more



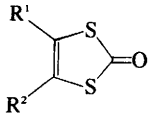
Scheme 16

hindered 2-alkenyl *S*-alkyl xanthates, however, a rearrangement without accompanying allylic shift preferentially occurred.[627]

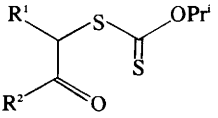
The same group of workers also accounted for the thermal rearrangement reaction of di(ethylthio)propyl *S*-methyl xanthates[628] and the rearrangement of *O,S*-dialkyl dithiocarbonates that occurs under Friedel–Crafts reaction conditions.[629] A new, general synthesis of 1,3-dithiol-2-ones (451) is based on the acid-catalysed ring-closure reaction of the dithiocarbonates (452).[630] The rearrangements of 2-aminoethyl alkyl trithiocarbonates (453) and alkylthiothiocarbonyl thiocyanates (433) into dithiocarbonates (454)[620] and alkylthiothiocarbonyl isothiocyanates (455),[371] respectively, have been described recently.

In close analogy with the behaviour of other thiocarbonyl compounds, thionocarbonates reacted with olefins upon irradiation to form stable thietans.[631] The photolysis of the xanthates (440) afforded biphthalides as the

[625] W. Schroth, H. Bahn, and G. Huck, *Z. Chem.*, 1973, **13**, 465.
[626] H. D. Hartzler, *J. Amer. Chem. Soc.*, 1973, **95**, 4379.
[627] K. Harano and T. Taguchi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2348, 2357.
[628] Y. Kawazoe and T. Taguchi, *Yakugaku Zasshi*, 1972, **92**, 677.
[629] T. Kawata, K. Harano, and T. Taguchi, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 604.
[630] A. K. Bhattacharya and A. G. Hortman, *J. Org. Chem.*, 1974, **39**, 95.
[631] H. Gotthardt and M. Listl, *Tetrahedron Letters*, 1973, 2849.



(451)



(452)

RSCSX

(453) $X = S(CH_2)_2NH_2$

(454) $X = NH(CH_2)_2SH$

(455) $X = N{=}C{=}S$

isolable products.[617] Stilbene trithiocarbonate was desulphurized on irradiation to give phenanthrene.[632] The photodecomposition of ethylene trithiocarbonate, yielding thiiran and carbon disulphide, has been found to proceed unimolecularly from the singlet state without any intervention of the triplet state.[633]

Dialkyl triselenocarbonates have been characterized as ambident electrophiles by Henriksen and Kristiansen on the basis of their study of the reaction of these compounds with amines.[273] In general, this reaction resulted in the formation of various products, a fact that was rationalized by the application of Pearson's principle of hard and soft acids and bases. Thus the selenocarbonyl carbon atom was found to represent the harder centre of acidity, combining principally with the harder amine base added, whereas the selenium atom of the alkylseleno-group appeared to represent a softer centre of acidity, combining preferentially with the softer alkyl selenide ion liberated by the former process.

13 Thionocarbamic and Dithiocarbamic Acids, their Derivatives, and their Selenium Analogues

Synthesis.—A standard method for the preparation of *O*-alkyl thiocarbamates and *S*-alkyl dithiocarbamates depends on the reaction of isothiocyanates with alcohols and thiols, respectively, and several new examples of its applicability have appeared during the past two years (refs. 132, 252, 634, and 635). In special cases the products, either spontaneously or promoted by a catalyst present, underwent a subsequent ring-closure reaction to form heterocycles containing the thionocarbamate or the dithiocarbamate moiety.[132,252,635] Phenols[636] and thiophenols[637,638] reacted with isothiocyanates in a similar way. Some *O*-ethyl selenonocarbamates have been obtained in good yields by ethanolysis of isoselenocyanates,[396] and Mayer and his co-workers have reported on the successful synthesis of the heterocyclic

[632] J. A. Moore and T. Isaacs, *Tetrahedron Letters*, 1973, 5033.

[633] H. Chandra and K. S., Sidhu, *Indian J. Chem.*, 1972, **10**, 1089.

[634] M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 62. Z. Cichon and A. Zejc, *Pol. J. Pharmacol. Pharm.*, 1973, **25**, 263 (*Chem. Abs.*, 1973, **79**, 78 686).

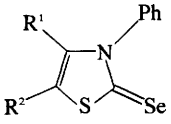
[635] L. Drobnica, V. Knoppova, and E. Komanova, *Chem. Zvesti*, 1972, **26**, 538; V. Knoppova and M. Uher, *ibid.*, 1973, **27**, 399.

[636] L. Capuano, W. Sperling, and R. Zander, *Chem. Ber.*, 1972, **105**, 3055.

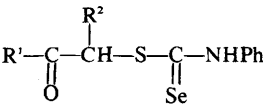
[637] C. Larsen and P. Jakobsen, *Acta Chem. Scand.*, 1973, **27**, 2001.

[638] A. E. Kretov, A. P. Momsenko, A. S. Bespalyi, and Y. A. Levin, *Khim. geterotsikl. Soedinenii*, 1973, 641.

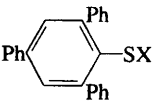
compounds (456) by the reaction of phenyl isoselenocyanate with α-mercaptoketones and subsequent ring-closure of the primarily formed thioselenonocarbamate (457).[639] An alternative, but apparently less profitable, route to (456) was found by the same authors in the reaction of phenyl isoselenocyanate with suitable enamines in the presence of elemental sulphur.[639] Unsubstituted oxazole-2-thione has been synthesized by condensation of glycolic aldehyde with thiocyanic acid.[640] The action of hydrogen sulphide on the thiocyanate (458) at 0 °C and in the presence of triethylamine afforded the dithiocarbamate (459) in 35% yield.[641]



(456)



(457)

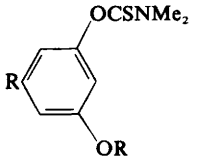


(458) X = CN
(459) X = $CSNH_2$

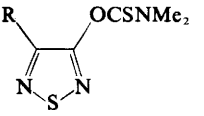
A method of choice for the preparation of thionocarbamates depends on the reactivity of thiocarbamoyl chlorides towards hydroxy-compounds, as demonstrated recently by the syntheses of the compounds (460), (461), and (462) by the reaction of dimethylthiocarbamoyl chloride with resorcines,[642] their monomethyl ethers,[642] and 3-substituted 4-hydroxy-1,2,5-thiadiazoles,[285] respectively. Nilsson and his co-workers have synthesized a series of *C*-sulphonylthioformamides (463) by the reaction of sodium sulphinates with dialkylthiocarbamoyl chlorides.[643] The hydrazide (464) was obtained by a similar reaction of *NN'N'*-trimethylthiocarbazoyl chloride.[643] The authors[643] further reported that compound (463), on treatment with triphenylphosphine in boiling xylene, were reduced to the corresponding dithiocarbamates (465). The action of thiophosgene on *NN'N''*-trisubstituted *N''*-hydroxy-guanidines afforded the heterocyclic compounds (466).[644] The *O*-phenyl thionocarbamate (467) was the isolable product of the reaction of (468) with phenyl chlorothionoformate.[645]

The addition reactions of amines and hydrazines, or derivatives of them, with carbon disulphide constitute common routes to dithiocarbamates[646] and

[639] H. Spies, K. Gewald, and R. Mayer, *J. prakt. Chem.*, 1972, **314**, 646.
[640] G. Lacasse and J. M. Muchowski, *Canad. J. Chem.*, 1972, **50**, 3082.
[641] M. Hedayatullah, T. Bouvet, and L. Deniville, *Compt. rend.*, 1973, **276**, *C*, 1687.
[642] H.-J. Kurth, U. Kraatz, and F. Korte, *Chem. Ber.*, 1973, **106**, 2419.
[643] N. H. Nilsson, C. Jacobsen, O. N. Sørensen, N. K. Haunsø, and A. Senning, *Chem. Ber.*, 1972, **105**, 2854.
[644] G. Voss, E. Fischer, and H. Werchan, *Z. Chem.*, 1973, **13**, 102.
[645] H. R. Kricheldorf, *Annalen*, 1973, 772.
[646] L. P. Zavizion, Y. B. Pyatnova, S. I. Orlov, T. M. Morozova, and T. I. Mel'gunova, *Khim. Prom.*, 1972, **48**, 174; S. I. Zav'yalov and L. L. Zheleznaya, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 2308; G. Wuerbach and H. P. Kloecking, *Pharmazie*, 1973, **28**, 254; S. A. S. El-Dine and O. Clauder, *Acta Chim. Acad. Sci. Hung.*, 1973, **76**, 295; V. V. Dovlatyan and F. V. Avetisyan, *Armyan. khim. Zhur.*, 1973, **26**, 494.

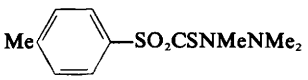


(460) R = $CSNMe_2$
(461) R = Me

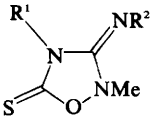


(462)

RXCSNR^{1}R^2
(463) X = SO_2
(465) X = S



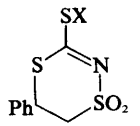
(464)



(466)

$Me_3SiS(CH_2)_2NHY$
(467) Y = CSOPh
(468) Y = $SiMe_3$

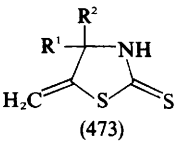
dithiocarbazates,[647] respectively. The sodium salt (469) has been isolated as a primary product (a Michael cyclo-adduct) of the reaction of 2-phenylethene-1-sulphonamide with carbon disulphide in the presence of sodium hydroxide.[648] On treatment with alkyl halides in strongly basic media, (469) underwent a ring-opening reaction to yield the dithiocarbamic ester (470), whereas, in the absence of base, (471) was formed as the result of a simple *S*-alkylation.[648] The acetylenic amines (472) reacted with carbon disulphide in a basic medium to yield the thiazole-thiones (473) *via* intermediate



(469) X = Na
(471) X = alkyl

$PhCH{=}CHSO_2NHCSSR$
(470)

$HC{\equiv}CCR^1R^2NH_2$
(472)

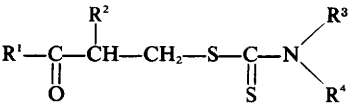


(473)

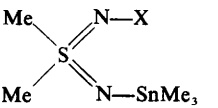
N-carbodithioates.[649] One[651] of the two papers[650,651] reporting on the application of the reaction of aziridines with carbon disulphide in the synthesis of 1,3-thiazolidine-2-thiones also presents an excellent survey of synthetic routes to the latter type of compounds. Dithiocarbamates (474) have been synthesized by insertion of carbon disulphide into ketone Mannich bases.[652] Similar reactions of *N*-(4-hydroxybenzyl)-piperidines and -pyrrolidines with

[647] E. Ajello and C. Arnone, *J. Heterocyclic Chem.*, 1973, **10**, 103; V. V. Dovlatyan and F. V. Avetisyan, *Armyan. khim. Zhur.*, 1973, **26**, 240.
[648] K. Hasegawa, T. Sasaki, and S. Hirooka, *Bull. Chem. Soc. Japan*, 1973, **46**, 696.
[649] I. N. Azerbaev, M. Z. Aitkhozhaeva, and L. A. Tsoi, *Khim. Atsetilena Tekhnol. Karbida Kal'tsiya*, 1972, 154 (*Chem. Abs.*, 1973, **79**, 105 124).
[650] V. I. Markov, S. I. Burmistrov, and D. A. Danileiko, *Khim. Tekhnol. (Kharkov)*, 1971, 97 (*Chem. Abs.*, 1972, **77**, 61 688).
[651] R. A. Bafford, F. Chanon, M. Chanon, and J. Metzger, *Bull. Soc. chim. France*, 1973, 971.
[652] G. Matolcsy and B. Bordas, *Chem. Ber.*, 1973, **106**, 1483.

carbonyl sulphide afforded, however, the corresponding thiolocarbamates.[653] The action of carbon disulphide on *NN'*-bis(trimethylstannyl)-*SS*-dimethylsulphodi-imide (475) resulted in insertion of only one carbon disulphide molecule;[654] the reduced reactivity of the remaining N—Sn function in the product (476) was considered to be connected with the intramolecular pentaco-ordination of the tin atom in question.



(474)



(475) X = $SnMe_3$
(476) X = $CSSnMe_3$

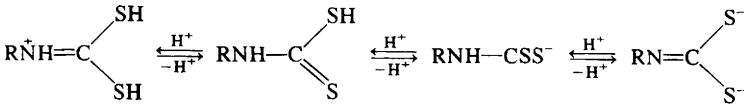
O-Ethyl thionocarbamates have been obtained by ethanolysis of 1,3,4-oxadiazolium-2-thiolates,[227,655] and *S*-alkyl *N*-(ω-mercaptoalkyl)-dithiocarbamates were produced by rearrangement of *S*-alkyl *S'*-(ω-aminoalkyl)trithiocarbonates.[620] Limitations in space preclude a discussion of the many papers reporting on the syntheses of a variety of heterocyclic compounds containing the thionocarbamate[263,656–658] or the dithiocarbamate (refs. 244, 418, 419, 513, 651, and 659—664) grouping.

Some papers dealing with the preparation and properties of metal complexes of thiocarbamoyl chlorides,[665] dithiocarbamates,[398,666] and selenothiocarbamates[667] may be of interest to workers in that field.

Reactions.—The decomposition of dithiocarbamic acids and dithiocarbamates under varied conditions is currently a subject of investigation. In

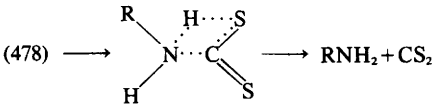
[653] A. O. Fitton and M. Qutob, *J.C.S. Perkin I*, 1972, 2660.
[654] D. Hänssgen and R. Appel, *Chem. Ber.*, 1972, **105**, 3271.
[655] A. Y. Lazaris and A. N. Egorochkin, *Zhur. org. Khim.*, 1972, **8**, 1538.
[656] D. Hoppe, *Angew Chem.*, 1972, **84**, 956; 1973, **85**, 909.
[657] D. E. Horning and J. M. Muchowski, *Canad. J. Chem.*, 1972, **50**, 3079.
[658] S. Petersen and H. Heitzer, *Annalen*, 1972, **764**, 28.
[659] G. Lacasse and J. M. Muchowski, *Canad. J. Chem.*, 1973, **51**, 2353.
[660] T. Takahashi, A. Kaji, and J. Hayami, *Bull. Inst. Chem. Res., Kyoto Univ.*, 1973, **51**, 163 (*Chem. Abs.*, 1973, **79**, 125 590).
[661] C. Gueden and J. Vialle, *Bull. Soc. chim. France*, 1973, 270.
[662] M. Lazovskaya, S. N. Baranov, A. K. Sheinkman, and A. A. Rok, *Khim. geterotsikl. Soedinenii*, 1971, **7**, 599.
[663] J. E. Oliver, R. T. Brown, and N. L. Redfearn, *J. Heterocyclic Chem.*, 1972, **9**, 447.
[664] R. J. S. Beer and A. Naylor, *Tetrahedron Letters*, 1973, 2989.
[665] P. M. Treichel and W. K. Dean, *J.C.S. Chem. Comm.*, 1972, 804.
[666] R. R. Scharfe, V. S. Sastri, and C. L. Chakrabarti, *Canad. J. Chem.*, 1972, **50**, 3384; R. R. Scharfe, V. S. Sastri, C. L. Chakrabarti, and C. H. Langford, *ibid.*, 1973, **51**, 67; R. R. Scharfe, V. S. Sastri, and C. L. Chakrabarti, *Analyt. Chem.*, 1973, **45**, 413; A. Nieuwpoort, J. H. E. Moonen, and J. A. Cras, *Rec. Trav. chim.*, 1973, **92**, 1086; J. P. Fackler, A. Avdeef, and R. G. Fischer, *J. Amer. Chem. Soc.*, 1973, **95**, 774; G. E. Manoussakis and C. A. Tsipis, *J. Inorg. Nuclear Chem.*, 1973, **35**, 743; *Z. anorg. Chem.*, 1973, **398**, 88.
[667] J. Kaiser, E. Hoyer, and E. Höhne, *Z. Chem.*, 1972, **12**, 118; R. Heber, R. Kirmse, and E. Hoyer, *Z. anorg. Chem.*, 1972, **393**, 159; N. Sonoda and T. Tanaka, *J. Inorg. Nuclear Chem.*, 1973, **35**, 1145; G. E. Manoussakis, C. A. Tsipis, and A. G. Christophides, *Inorg. Chem.*, 1973, **12**, 3015.

connection with studies in this field,[668–673] Takami and his co-workers have studied spectrophotometrically the dissociation of *N*-monosubstituted dithiocarbamic acids over a broad pH range.[668] The successive protonations (or deprotonations) were found to take place according to the sequence (477)—(480). The authors further found that the decomposition of monosubstituted dithiocarbamates in acidic surroundings proceeds *via* (478) and not



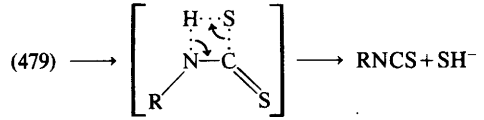
(477) (478) (479) (480)

via (477).[669,670] A kinetic investigation[670] revealed a linear relationship between log k (k = rate constant) and pK_A values of the parent amines, a fact that was interpreted in terms of a decomposition mechanism involving a rate-determining N—C bond cleavage along with a synchronous proton transfer:



A similar mechanism was proposed also for the acid-promoted decomposition of *NN*-disubstituted dithiocarbamates.[671,674] In the latter case, the influence of ionic strength,[674] dielectric constant,[674] temperature,[674] and inductive effects[671,674] was studied. For example, it was found that electron-donating substituents on the nitrogen atom enhance the stability of the dithiocarbamic acid.[671] The existence of an intramolecular hydrogen bonding between the mercapto-proton and the nitrogen atom, which has been postulated in connection with earlier mechanistic interpretations of the decomposition reaction, was questioned.[671] Kinetic studies of the decomposition of *N*-monosubstituted dithiocarbamates in alkaline solution led Takami and his co-workers to conclude[672,673] that the dianions (480) are not directly involved in the decomposition, even in strongly basic surroundings, as stated earlier (see Vol. 2). A mechanism involving the cyclic transition state (481) was considered likely. The decomposition of some metal

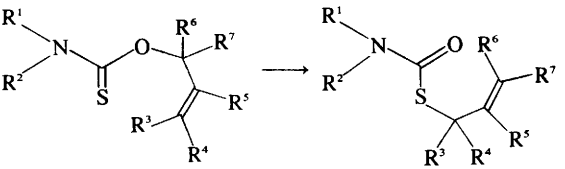
[668] F. Takami, K. Tokuyama, S. Wakahara, and T. Maeda, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 329.
[669] F. Takami, S. Wakahara, and T. Maeda, *Chem. Letters*, 1972, 159.
[670] F. Takami, K. Tokuyama, S. Wakahara, and T. Maeda, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 594.
[671] F. Takami, S. Wakahara, and T. Maeda, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 619.
[672] F. Takami, S. Wakahara, and T. Maeda, *Chem. Letters*, 1972, 409.
[673] F. Takami, K. Tokuyama, S. Wakahara, and T. Maeda, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1311.
[674] D. De Filippo, P. Deplano, F. Devillanova, E. F. Trogu, and G. Verani, *J. Org. Chem.*, 1973, **38**, 560.



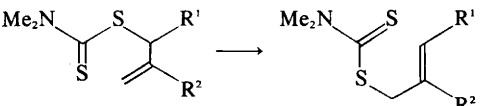
(481)

dithiocarbamates in non-aqueous surroundings has been studied by potentiometry.[675]

Thionocarbamic esters may rearrange thermally to the isomeric thiolocarbamic esters. Two recent papers report on the utility of this particular rearrangement in connection with the synthesis of aromatic thiols.[285,642] The kinetics of the rearrangement of furfuryl *NN*-dimethylthionocarbamates have been studied by Braverman and Goldrath.[676] Hackler and Balko have reported[677] that the allylic dialkylthionocarbamates (482) undergo spontaneously a thermal, 3,3-sigmatropic rearrangement into the isomeric thiolocarbamates (483). The thionocarbamates (482; R^6, $R^7 \neq H$), the formal products of the reaction of dialkylthiocarbamoyl chlorides with appropriate allylic alcohols, were in fact not isolable as such owing to instantaneous rearrangement. The less substituted thionocarbamates (482; $R^6 = H$, $R^7 \neq H$) and (482; $R^6 = R^7 = H$), however, required higher temperatures in order to rearrange completely within a reasonable period of time. Hayashi found[678] that a similar rearrangement of the allylic dithiocarbamates (484) to the isomers (485) takes place gradually on standing, and rapidly at temperatures



(482) (483)



(484) (485)

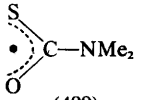
over 100 °C. Kinetic measurements as well as the observation of strong chemically induced dynamic nuclear polarization (CIDNP) effects in connection with the n.m.r. monitoring of the thermal rearrangement of *N*-aroyl-*N*-methyl-*O*-thiocarbamoylhydroxylamines (486) to the corresponding *S*-carbamoylthiohydroxylamines (487) pointed to a mechanism

[675] M. A. Bernard, M.-M. Borel, and G. Chauvenet, *Bull. Soc. chim. France*, 1972, 1663.
[676] S. Braverman and B. Goldrath, *Internat. J. Sulfur Chem.*, 1973, **8**, 55.
[677] R. E. Hackler and T. W. Balko, *J. Org. Chem.*, 1973, **38**, 2106.
[678] T. Hayashi, *Tetrahedron Letters*, 1974, 339.

involving homolytic cleavage of (486) to the radicals (488) and (489), and a subsequent alternative recombination of these.[679] Similarly, the intermediacy of aminyl and $Me_2NCOS\cdot$ radicals in the thermally induced 1,3-rearrangement of oxime thionocarbamates (490), leading to isomeric (491), has been established by observed ^{13}C CIDNP effects.[680]

$ArCONMeXCYNMe_2$
(486) X = O, Y = S
(487) X = S, Y = O

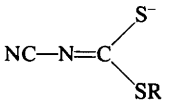
$ArCO\dot{N}Me$
(488)



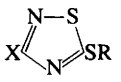
(489)

$Ar_2C{=}NXCYNMe_2$
(490) X = O, Y = S
(491) X = S, Y = O

Several papers report on the nucleophilic reactivity of dithiocarbamate anions towards alkyl halides,[620] 1,2-dibromoalkyl compounds,[681] alkyl and aryl chloroformates,[682] chloroacetic acid,[387,683] chloroacetates,[387,684] 3-halogenophthalides,[617] sulphenyl chlorides,[401,685] sultones,[610] and trialkylammonium compounds.[652] Examples of a similar reactivity of dithiocarbazate anions have also appeared.[501,685–687] A series of papers deal with addition or addition–elimination reactions of dithiocarbamate[57,530,688,689] or dithiocarbazate[529] anions with ω-nitrostyrene,[529] 2-thioxo-, 2-oxo-, and 2-imino-5-methoxycarbonylmethylidene-4-thiazolidones,[688] dimethyl acetylenedicarboxylate,[530,689] and *NN'*-dialkyl phenylpropiolamidines.[57] *S*-Monoalkylated *N*-cyanodithioimidocarbonates (492) underwent oxidative ring-closure to give 3-halogeno-1,2,4-thiadiazole sulphides (493) on treatment with halogenating agents.[690]



(492)



(493) X = Cl, Br, or I

The nucleophilic reactivity of the thiocarbonyl sulphur atom in alkyl thionocarbamates, alkyl dithiocarbamates, and alkyl thionocarbazates has been exemplified recently by the reactions of such compounds with

[679] W. B. Ankers, C. Brown, R. F. Hudson, and A. J. Lawson, *J.C.S. Chem. Comm.*, 1972, 935.
[680] C. Brown, R. F. Hudson, and A. J. Lawson, *J. Amer. Chem., Soc.*, 1973, **95**, 6500.
[681] K. Hiratani, H. Shiono, and M. Okawara, *Chem. Letters*, 1973, 867.
[682] Y. N. Bezobrazov, V. P. Brysova, and R. A. Gukova, *Zhur. org. Khim.*, 1971, **7**, 2282.
[683] V. Knoppova, K. Antos. L. Drobnica, and P. Kristian, *Chem. Zvesti*, 1972, **26**, 527.
[684] A. Y. Lazaris, S. M. Shmuilovich, and A. N. Egorochkin, *Zhur. org. Khim.*, 1972, **8**, 2621.
[685] F. Klivenyi, G. Stajer, A. E. Szabo, and J. Pintye, *Acta Chim. Acad. Sci. Hung.*, 1972, **73**, 63.
[686] F. Klivenyi, G. Stajer, A. E. Szabo, J. Pintye, and E. Vinkler, *Acta Chim. Acad. Sci. Hung.*, 1972, **74**, 87.
[687] N. Kreutzkamp and G. Deicke, *Arch. Pharm.*, 1973, **306**, 321.
[688] H. Nagase, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1132.
[689] C. S. Angadiyavar, M. N. Gudi, and M. V. George, *Indian J. Chem.*, 1972, **10**, 888.
[690] L. S. Wittenbrook, G. L. Smith, and R. J. Timmons, *J. Org. Chem.*, 1973, **38**, 465.

$$Ar^1OCSNHAr^2 \xrightarrow{Ar^3SCl} Ar^1OC(=NAr^2)SSAr^3$$

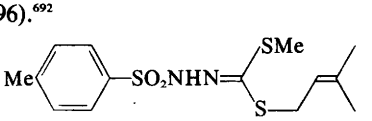
$$PhCH_2SCSNHPh \xrightarrow{Ar^3SCl} PhCH_2SC(=NPh)SSAr^3$$

$$EtOCSNHNHPh \xrightarrow{Ar^3SCl} Ar^3SSCONHNHPh$$

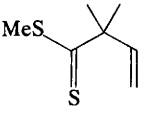
$Ar^3 = p\text{-}MeC_6H_4$

Scheme 17

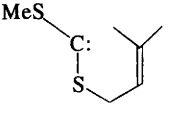
toluene-*p*-sulphenyl chloride (Scheme 17).[685,686] Alkyl thiono- and dithiocarbazates reacted with phosgene to give 1,3,4-thiadiazol-2-ones.[310] Methyl 3-benzoylthionocarbazates and 3-benzoyldithiocarbazates have been *S*-methylated by methyl iodide or dimethyl sulphate in basic media.[691] Treatment of methyl 3-(toluene-*p*-sulphonyl)dithiocarbazate with 3,3-dimethylallyl bromide in the presence of potassium hydroxide afforded (494).[692] The sodium salt of (494) gave on heating the dithio-ester (495) as the result of a 2,3-sigmatropic rearrangement of the initially formed carbene (496).[692]



(494)



(495)



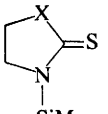
(496)

A miscellany of papers deal with the preparation of quaternary ammonium salts and betaines of thionocarbamates,[693] the reaction of *S*-(dialkylamino)methyl dithiourethanes with CH-acidic compounds,[687] the benzoylation of amines by means of mixed benzoic dithiocarbamic anhydride,[694] the thermal rearrangement of the cyclic thiourethane (497; X = O) to the isothiocyanate (498) [a similar rearrangement did not occur for (497; X = S)],[645] the reactions of dimethyltin bis(*NN*-dimethylthioselenocarbamates) and bis(*NN*-dimethyldiselenocarbamates) with $\alpha\omega$-dibromoalkanes,[695] the utility of *C*-sulphonylthioformamides as thiocarbamoylation reagents,[274] the reactions of ethoxythiocarbonyl isocyanate with aldehydes and ketones leading to 1,3,5-oxathiazines,[343] and the reactivities of alkylthio- and arylthio-thiocarbonyl isothiocyanates towards amines and aldimines.[371] Other papers[376,696] report on applications of thionocarbamic, thionocarbazic, and dithiocarbamic esters in the synthesis of heterocyclic compounds.

Alkyl thionocarbamates have been oxidized to sulphur-free carbamates by iodine in DMSO.[697] Alkyl *N*-(2-pyridyl)dithiocarbamates underwent

[691] K. Rüfenacht, *Helv. Chim. Acta*, 1974, **57**, 23.
[692] J. E. Baldwin and J. A. Walker, *J.C.S. Chem. Comm.*, 1972, 354.
[693] R. A. Bauman, *J. Org. Chem.*, 1972, **37**, 2777.
[694] P. G. Nair and C. P. Joshua, *Tetrahedron Letters*, 1972, 4785.
[695] K. Tanaka and T, Tanaka, *Bull. Chem. Soc. Japan*, 1972, **45**, 489.
[696] I. Z. Siemion, W. Steglich, and L. Wilschowitz, *Roczniki Chem.*, 1972, **46**, 21; K. Rüfenacht, *Helv. Chim. Acta*, 1973, **56**, 2186; K. Hasegawa and S. Hirooka, *Bull. Chem. Soc. Japan*, 1972, **45**, 1567.
[697] Y. Kinoshita, S. Kubota, S. Hashimoto, and H. Ishikawa, *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 701 (*Chem. Abs.*, 1973, **79**, 5113).

oxidative cyclization to 1,2,4-thiazolo[2,3-*a*]pyridinium salts on treatment with bromine or sulphuryl chloride.[335] Oxidation of *C*-sulphonylthioformamides (499) by means of hydrogen peroxide, peracids, or periodates resulted in formation of *S*-sulphonylthiolocarbamates (500).[181,643] In contrast, the oxidation of (499) by ozone afforded *C*-sulphonylformamides (501).[181,643] This difference in reaction course was explained by the occurrence of two different oxidation mechanisms.[181,643] In the former case the oxidation was considered to proceed *via* a dissociation–recombination reaction of an intermediate sulphine (502), whereas the formation of (501) in the latter oxidation reaction was interpreted in terms of a mechanism involving (503) as an intermediate that released sulphur dioxide.



(497)

$Me_3SiO(CH_2)_2NCS$

(498)

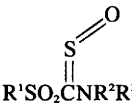
$R^1SO_2CXNR^2R^3$

(499) X = S

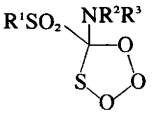
(501) X = O

$R^1SO_2SCONR^2R^3$

(500)



(502)



(503)

The dye-sensitized photo-oxygenation of hexamethyleneammonium hexamethylenedithiocarbamate by xanthene dyes[698] and the photolysis of 4-hydroxybenzyl dithiocarbamates[699] are the subjects of two recent papers. A report on the pyrolysis reactions of aryl *N*-monoalkyldithiocarbamates has also appeared.[637]

Several studies of the reactivity of heterocyclic thiocarbonyl compounds possessing a cyclic thionocarbamate[280,360,700,701] or dithiocarbamate (refs. 66, 353, 420, 661, and 702) structure have been described.

[698] T. Yamase, H. Kokado, and E. Inoue, *Bull. Chem. Soc. Japan*, 1972, **45**, 726.

[699] A. O. Fitton, J. Hill, M. Qutob, and A. Thompson, *J.C.S. Perkin I*, 1972, 2658.

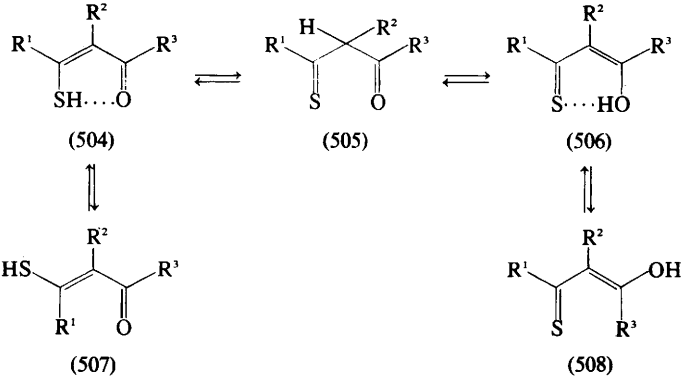
[700] A. Lanzani and G. Jacini, *Riv. Ital. Sostanze Grasse*, 1971, **48**, 471 (*Chem. Abs.*, 1972, **76**, 140 609).

[701] D. Hoppe, *Angew. Chem.*, 1973, **85**, 659, 660.

[702] A. Takamizawa and H. Harada, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 770; G. Wagner and B. Dietzsch, *J. prakt. Chem.*, 1973, **315**, 915; M. V. Konher, *Indian J. Chem.*, 1973, **11**, 321; M. M. Yusupov, R. A. Kozak, and N. K. Rozhkova, *Uzbek. khim. Zhur.*, 1971, **15**, 82 (*Chem. Abs.*, 1972, **76**, 72 445); E. Alimov, A. Sultankulov, N. K. Rozhkova, and S. R. Tulyganov, *ibid.*, 1973, **17**, 52 (*Chem. Abs.*, 1973, **79**, 18 627); M. M. Yusupov, R. A. Kozak, and N. K. Rozhkova, *ibid.*, p. 63 (*Chem. Abs.*, 1973, **79**, 78 667); G. Pfeifer and T. Flora, *Nehezvegyip. Kut. Intez. Kozlem.*, 1972, **4**, 175 (*Chem. Abs.*, 1972, **77**, 125 678); S. Leistner and G. Wagner, *Z. Chem.*, 1973, **13**, 428.

14 Physical Properties

Structure.—*Tautomerism.* The tautomeric properties of monothio-β-dicarbonyl compounds have been extensively studied by several groups of workers in the past two years, and notable progress has been made. In order to clarify the direction of tautomerization in thioacetylacetone (505; $R^1 = R^3 = Me$, $R^2 = H$), Fabian[703] compared the experimental u.v. spectrum of this compound with those derived theoretically for each of the tautomeric forms (504)—(506), and he was able to conclude that thioacetylacetone exists in solution as an equilibrium mixture of the two rapidly interconvertible forms (504) and (506) [in cyclohexane: ~70% (506)]. β-Thioxo-aldehydes (505; R^1 = Ar, R^2 = Me or Ar, $R^3 = H$) appeared to exist in solution as an equilibrium mixture of the two rapidly interconvertible forms (504) and (506), together with the *trans*-enethiol form (507).[51,704] Rather surprisingly, α-alkyl monothiodibenzoylmethanes (505; $R^1 = R^3$ = Ph, R^2 = alkyl) turned out to exist in solution as mixtures of the *trans*-enethiol tautomer (507) and the *trans*-enol tautomer (508).[704] The existence of the forms (507) and (508) is doubtless a consequence of



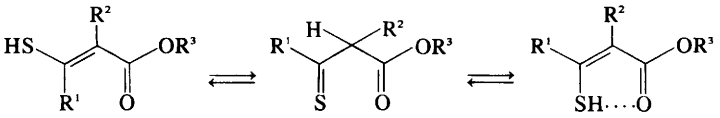
(504) (505) (506)

(507) (508)

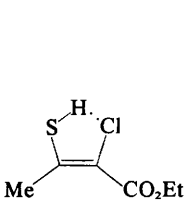
unfavourable steric interactions in the 'classic' structures (504) and (506). The influence of substituents R^1, R^2, and R^3 on the direction of the tautomerization of β-thioxo-esters (510) has been studied by means of n.m.r. and i.r. spectroscopy by Duus,[39] who found that the α-unsubstituted compounds (510; $R^2 = H$) exist in solution as equilibrium mixtures of the predominating *cis*-enethiol form (511) and the *trans*-enethiol form (509) (0–10%). In the case of the α-substituted compounds (510; R^2 = alkyl or Cl), the equilibrium percentages of the latter tautomer in general appeared to be comparable with those of (511), although too bulky α-substituents (for example $R^2 = Pr^i$) gave rise to a prevalence of the thione form (510). The author also presented evidence for the occurrence of restricted rotation of the ester group in the *cis*-enethiol form of the α-substituted compounds, as

[703] J. Fabian, *Tetrahedron*, 1973, **29**, 2449.
[704] G. Klose, K. Arnold, U. Eckelmann, and E. Uhlemann, *Tetrahedron*, 1972, **28**, 6019.

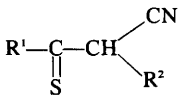
reflected by the equilibrium process (511) ⇄ (512).[39] The existence of appreciable equilibrium concentrations of the *trans*-enethiol form (513) in solutions of ethyl α-chlorothio-acetoacetate was attributed to the occurrence of an intramolecular hydrogen bonding in (513), involving the chlorine atom as the acceptor, rather than to unfavourable steric interactions in the *cis*-enethiol form.[39] Ethyl thioacetothionoacetate exists mainly in the *cis*-enethiol form.[39,61] The α-cyano-thiones and -thials (514) were found to exist as mixtures of the *cis–trans* isomeric enethiols, whereas the thiono- and dithio-esters (515) showed no tendency at all to undergo enethiolization.[17,59]



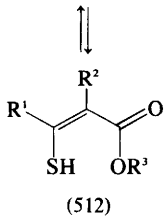
(509) (510) (511)



(513)



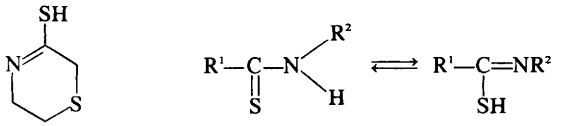
(514) R^1 = H or alkyl
R^2 = H or $PO(OEt)_2$
(515) R^1 = OR or SR
R^2 = H



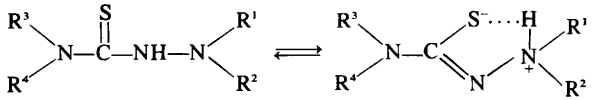
(512)

Cyclic αβ-unsaturated thioketones appeared to exist exclusively in the thione form.[42] A peak at δ = 1.88 p.p.m. in the n.m.r. spectrum of thiomorpholine-3-thione was attributed to the presence of an enethiol tautomer (516).[212] On the basis of a study of the tautomerism of simple thio-amides by means of the basicity method, Kjellin and Sandström found the pK_T values for thioacetamide, *N*-methylthioacetamide, thiobenzamide, and *N*-methylthiobenzamide to be −8.6, −9.6, −8.3, and −8.9, respectively $\{K_T = [(517)]/[(518)]\}$.[705] Walter and Schlichting have reported n.m.r. and i.r. spectral evidence for the occurrence of a betaine–thioacyl tautomerism in solutions of 1,1,4,4-tetrasubstituted thiosemicarbazides (519).[706] Various physical investigations have shown that the thione form predominates for 1-alkylthio-2-carbamoyl-2-cyanoethylene-1-thiols,[707] αβ-unsaturated β-aminodithio-esters,[575] oxazole-2-thiones,[640] 1,3,4-oxadiazole-2-thione,[657]

[705] G. Kjellin and J. Sandström, *Acta Chem. Scand.*, 1973, **27**, 209.
[706] W. Walter and H. Schlichting, *Annalen*, 1973, 1210.
[707] L. Henriksen and B. Baltzer, *Tetrahedron Letters*, 1972, 2485.



(516) (517) (518)



(519)

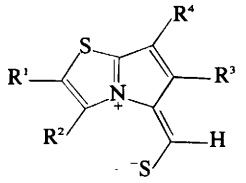
1,2,5-thiadiazole-3-thiones,[285] substituted ammonium salts of benzothiazoline-2-thiones,[708] 3-α-pyridyl-1,2,4-triazoline-5-thiones,[709] 4-mercaptopyrimidine,[710] and 6-thioxanthine.[711] Interesting tautomeric effects have been observed for *N*-acylthioimido-esters,[300] iminoalkyl disulphides,[313] *N*-(diphenylmethylene)-*N'*-alkyl-*N'*-(trimethylsilyl)thioureas (302),[399] 4-quinazolinylthioureas,[712] and 2-methylthio-5,5-pentamethylene-2-imidazoline-4-thiones.[713]

Hydrogen Bonding. The hydrogen-bonding capactity of the thiocarbonyl function has been discussed by several groups of workers in connection with structural studies on αβ-unsaturated β-aminothiones,[714] dithiooxamides,[715] *N*-hydroxythioureas,[716] and 1,3-thiazolidine-2-thiones.[717] An interesting paper by Snyder and his co-workers[718] reports on the application of the Schroeder–Lippincott potential-function model of the hydrogen bond in estimations of the relative strengths of a series of hydrogen-bonded systems with incorporated sulphur atoms.

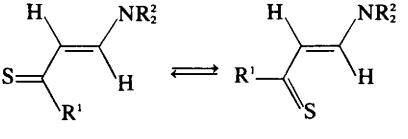
Polarization Effects, Restricted Rotation, and Isomerization Phenomena. The remarkable stability of the thioaldehydes (5) and (6) was regarded by Reid and his co-workers[18] as being due to the conjugation of the thioformyl group with the nitrogen atom, thus admitting of a polarization of the molecule in the direction of a polarized resonance structure such as (520) [in the case of (6)]. In accordance with this interpretation, a restricted rotation about the ring–CHS bond, with its partial double-bond character, could be observed.[18] However, the thials appeared to exist either in the *syn*- or in the *anti*-form, probably under the influence of the neighbouring substituents.

[708] A. F. Halasa and G. E. P. Smith, *J. Org. Chem.*, 1973, **38**, 1353.
[709] S. Kubota and M. Uda, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2096.
[710] M.-T. Mussetta, M. Selim, and N. Q. Trinh, *Compt. rend.*, 1973, **276**, *C*, 1341.
[711] D. Lichtenberg, F. Bergmann, and Z. Neiman, *J.C.S. Perkin II*, 1972, 1676.
[712] W. Merkel and W. Reid, *Chem. Ber.*, 1973, **106**, 471.
[713] J. T. Edward and J. K. Liu, *Canad. J. Chem.*, 1972, **50**, 2423.
[714] U. Dabrowska and J. Dabrowski, *Adv. Mol. Relaxation Processes*, 1973, **5**, 81.
[715] H. O. Desseyn, W. A. Jacob, and M. A. Herman, *Spectrochim. Acta*, 1972, **28A**, 1329.
[716] W. Walter, H. Hühnerfuss, A. Neye, and K.-P. Ruess, *Annalen*, 1973, 821.
[717] P. J. F. Griffiths, G. D. Morgan, and B. Ellis, *Spectrochim. Acta*, 1972, **28A**, 1899.
[718] W. R. Snyder, H. D. Schreiber, and J. N. Spencer, *Spectrochim. Acta*, 1973, **29A**, 1225.

Vinylogous thioamides have been shown[719] to exist in two rotational forms, (521) and (522); the barrier to rotation about the CS—C bond was found to be 2.5—3.1 kcal mol^{-1} higher than that found for corresponding enaminoketones.

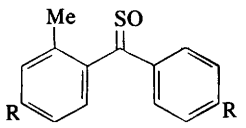


(520)

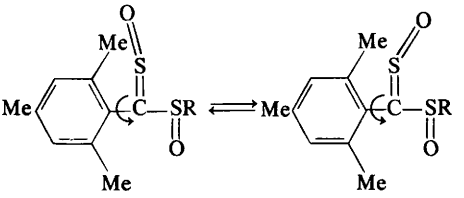


(521) (522)

The *syn–anti* isomerism of the sulphines (523) has been studied by means of n.m.r. spectroscopy by Bonini and his co-workers, who interpreted their results in terms of the occurrence of an isomerization process proceeding by rotation around the C=S bond rather than by inversion about the sulphur atom.[720] The same conclusion was reached by Snyder and Harpp on the basis of an SCF—MO—CNDO investigation of the geometry, the electron distribution, and the *syn–anti* isomerism of sulphine itself and some of its simple derivatives.[721] Tangermann and Zwanenburg have demonstrated[722] that the *ortho*-methyl groups in the sulphoxide sulphines (524) and (525) are



(523)



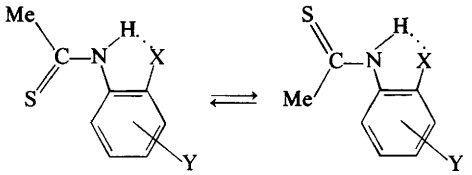
(524) (525)

magnetically non-equivalent owing to restricted rotation around the aryl–sulphine bond; the rotational barrier for (524) was 4.2—4.6 kcal mol^{-1} higher than for the corresponding (*Z*)-isomers, for which ΔF^{*} was found to be 19.1—19.7 kcal mol^{-1}.

Walter and his co-workers have determined ΔF^{*} = 19.4 kcal mol^{-1} for the rotation about the C—N bond in protonated thiobenzamide; this value is 1.5 kcal mol^{-1} higher than that determined for the corresponding rotation in thiobenzamide itself, a fact that lends strong support to the idea that protonation of thioamides takes place preferentially at the S atom.[297] In accordance with expectations, the free energy of activation for rotation about the C—N bond in *NN*-dimethylselenoformamide

[719] J. Dabrowski and K. Kamieńska-Trela, *Org. Magn. Resonance*, 1972, **4**, 421.
[720] B. F. Bonini, L. Lunazzi, G. Maccagnani, and G. Mazzanti, *J.C.S. Perkin I*, 1973, 2314.
[721] J. P. Snyder and D. N. Harpp, *J.C.S. Chem. Comm.*, 1972, 1305.
[722] A. Tangerman and B. Zwanenburg, *Tetrahedron Letters*, 1972, 5329.

($\Delta F^* = 25.8$ kcal mol^{-1}) has been found to be 1.7 kcal mol^{-1} higher than that found for the corresponding thioamide.[723] The influence of substituents on the displacement in the equilibrium system (526) ⇄ (527) has been studied by Walter and Sewekow,[724] who also demonstrated coplanarity of the phenyl



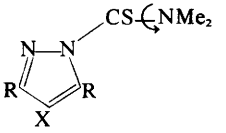
Z-form (526) ⟷ *E*-form (527)

ring and the thioamide moiety in cases where X is a group having the ability of forming a hydrogen bond with the amide hydrogen atom. *ortho*-Substituted *N*-alkylthioformanilides exhibited restricted rotation about the CS—N bond as well as about the N—aryl bond.[725] Evidence has been presented for the occurrence of a conformational 'geared' state in *NN*-di-isopropylthioacetamide, corresponding closely to that found in 5-methyl-3,4-di-isopropyl-1,3-thiazoline-2-thione.[726] Restricted-rotation effects have been observed for large-ring *N*-methylthiolactams,[727] *N*-acylthioamides,[248] *NN*-dimethylthiocarbamoyl cyanide,[728] and *NN'*-di(thioacyl)benzimidazolines.[729]

Several recent papers deal with the restricted C—N rotations in unsubstituted,[730,731] monosubstituted,[731] *NN'*-disubstituted,[731,732] *NN*-disubstituted,[728,731] *N,N,N'*-trisubstituted,[731–733] and tetrasubstituted[734] thioureas, together with the conformational aspects involved. The barriers to C—N rotation of thio- and seleno-urea were equal ($\Delta F^* = 12.8$ kcal mol^{-1}) and above that of urea ($\Delta F^* = 11.0$ kcal mol^{-1}).[730] Restricted-rotation phenomena have been observed for substituted *N*-(tosylmethyl)thioureas,[325] thiourea *S*-trioxides,[477,478,735] and 3-aryl-2-thiohydantoins.[736]

[723] U. Svanholm, *Ann. New York Acad. Sci.*, 1972, **192**, 124.
[724] W. Walter and U. Sewekow, *Annalen*, 1972, **761**, 104.
[725] W. Walter and R. F. Becker, *Tetrahedron*, 1972, **28**, 1705.
[726] C. Roussel, M. Chanon, and J. Metzger, *Tetrahedron Letters*, 1972, 3843.
[727] R. M. Moriarty, E.-L. Yeh, V. A. Curtis, C.-L. Yeh, J. L. Flippen, J. Karle, and K. C. Ramey, *J. Amer. Chem. Soc.*, 1972, **94**, 6871.
[728] R. F. Hobson, L. W. Reeves, and K. N. Shaw, *J. Phys. Chem.*, 1973, **77**, 1228.
[729] W. Walter and U. Sewekow, *Annalen*, 1974, 274.
[730] W. Walter, E. Schaumann, and H. Rose, *Tetrahedron*, 1972, **28**, 3233.
[731] M.-L. Filleux-Blanchard and A. Durand-Couturier, *Bull. Soc. chim. France*, 1972, 4710.
[732] M. V. Andreocci, M. Bossa, G. Ramunni, M. Scazzochio, D. Gattegno, and A. M. Giuliani, *J.C.S. Dalton*, 1974, 41.
[733] D. Gattegno, A. M. Giuliani, M. Bossa, and G. Ramunni, *J.C.S. Dalton*, 1973, 1399.
[734] P. Hanson and D. A. R. Williams, *J.C.S. Perkin II*, 1973, 2162.
[735] W. Walter and K.-P. Ruess, *Annalen*, 1974, 253.
[736] L. D. Colebrook, H. G. Giles, A. Granata, S. Icli, and J. R. Fehlner, *Canad. J. Chem.*, 1973, **51**, 3635; L. D. Colebrook, H. G. Giles, and A. Rosowsky, *Tetrahedron Letters*, 1972, 5239.

The barrier to rotation about the C—N bond for 1,1-dimethylselenosemicarbazide appeared to be slightly higher than that found for its thioanalogue (ΔF^* = 11.6 and 11.2 kcal mol^{-1}, respectively)[723] Other papers report on the influence of the substituents R and X on the barrier to rotation of the dimethylamino-group in the pyrazoles (528),[737] the determination of ΔF^* (21.1 kcal mol^{-1}) for the restricted rotation around the CS—N bond in the thiophosphinoylthioformhydrazide (529),[502] and the *syn–anti* isomerism of isatin β-thiosemicarbazones.[738]



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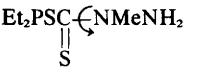

(529)

Lidén and Sandström have studied the CS—N rotation in some *N*-arylthiono- and *N*-aryldithio-carbamates and found that *N*-aryl groups are barrier-lowering compared to *N*-methyl groups.[739] The data obtained by a n.m.r. spectroscopic investigation of some derivatives of dithiocarbazic acids suggested that the rotations about the CS—N and the CS—S bond are sterically hindered.[740] The barrier to rotation around the CS—N bond for dimethylthiocarbamoyl fluoride (ΔF^* = 20.7 kcal mol^{-1}) appeared to be *ca.* 2 kcal mol^{-1} higher than that for the corresponding chloride.[728] Restricted-rotation effects have been observed for carbamoyl- and thiocarbamoyl-ethylthionocarbamates,[208] aryl *N*-alkyldithiocarbamates,[637] metal complexes of dithiocarbamates,[741] tetraethylthiuram disulphide,[742] and some metal complexes of the latter.[742]

Crystal and Molecular Structures. The molecular structure of diphenylcyclopropenethione has been determined by *X*-ray diffraction.[743] The phenyl rings were found to be twisted out of the plane of the cyclopropenyl ring by an average of 4°, probably owing to the steric requirements of the *ortho*-hydrogen atoms. The calculated bond lengths for the C=S (1.630 Å), the C=C (1.338 Å), and the C—C (1.403 Å) bonds suggested that the structure of diphenylcyclopropenethione is not well defined as an aromatic 2π-electron zwitterionic structure. The relatively long C=S bond length (1.696 Å) found for 1,3-dimethylimidazole-2(3*H*)-thione is, however, consistent with a polar structure.[744] By means of *X*-ray crystallographic methods,

[737] L-O. Carlsson, *Acta Chem. Scand.*, 1972, **26**, 21.
[738] A. B. Tomchin, I. S. Ioffe, Y. V. Lepp, and A. I. Kol'tsov, *Zhur. org. Khim.*, 1973, **9**, 1081.
[739] A. Lidén and J. Sandström, *Acta Chem. Scand.*, 1973, **27**, 2567.
[740] D. Gattegno and A. M. Giuliani, *Tetrahedron*, 1974, **30**, 701.
[741] B. L. Edgar, D. J. Duffy, M. C. Palazzotto, and L. H. Pignolet, *J. Amer. Chem. Soc.*, 1973, **95**, 1125.
[742] A. M. Grotens and F. W. Pijpers, *Rec. Trav. chim.*, 1973, **92**, 619.
[743] L. L. Reed and J. P. Schaefer, *J.C.S. Chem. Comm.*, 1972, 528.
[744] G. B. Ansell, *J.C.S. Perkin II*, 1972, 841.

the crystal and molecular structures of 2-isopropylidene-1,1,7,7,9,9-hexamethyl-3,5,10,11-tetrathiadispiro[3,1,3,2]undecane-8-thione,[745] monothiodibenzoylmethane,[746] medium- and large-ring *N*-methylthiolactams,[727] 6-thioguanosine monohydrate,[747] the imidazolethione (297),[386] 3,5-bis(thiocarbamoylimino)-1,2,4-dithiazolidines (341),[484] morpholinothiosemicarbazide,[748] thiocarbonohydrazide hemihydrochloride,[749] diphenylthiocarbazide,[750] 1,3-dithiolan-2-thione,[751] benzoxaline-2-thiones,[752] and bis-(4-morpholinothiocarbonyl) trisulphide[753] have been determined. In addition, *X*-ray crystallographic investigations have been performed on tetraethylammonium cyanodithioformate[754] and metal derivatives of monothiodibenzoylmethane,[755] substituted thioureas,[756] dithioformic acid,[757] and *NN*-dialkyldithiocarbamates.[758]

Spectra.—*Ultraviolet Spectra.* HMO and SCF calculations carried out on tropothione (92) have been interpreted in terms of u.v. data obtained by the assignment of the experimental u.v. spectrum.[759] Using this, the authors were able to conclude that tropothione exhibits polyolefinic rather than aromatic character. The electronic spectrum of diphenylcyclopropenethione has been compared with that derived theoretically.[760] Vialle and his co-workers observed in the u.v. spectra of cycloalkyl thioketones[41] and conjugated cycloalkene thiones[42] three characteristic bands at 475—508 nm, 230—276 nm, and 209—226 nm, which were assigned to (n, π^*), (π, π^*), and (π, σ^*) transitions, respectively. In connection with a study of the enethiol–enol tautomerism of thioacetylacetone and related substances, Fabian[703] compared experimental u.v. spectra with those derived theoretically for the individual tautomers, and, on this background, assignments were made. Thus the intense bands at ~300 nm and ~360 nm in the u.v. spectrum of thioacetylacetone were assigned to (π, π^*) transitions

[745] C. D. Shirrell and D. E. Williams, *Acta Cryst.*, 1973, **B29**, 2128.
[746] J. Sieler, R. Richter, and J. Kaiser, *Z. Chem.*, 1973, **13**, 263.
[747] U. Thewalt and C. E. Bugg, *J. Amer. Chem. Soc.*, 1972, **94**, 8892.
[748] C. H. Koe, H. S. Kim, H. S. Shin, and Y. Lee, *Daehan Hwahak Hwoejee* (*S. Korea*), 1973, **17**, 104 (*Chem. Abs.*, 1973, **78**, 158 741).
[749] A. Braibanti, A. Tiripicchio, and M. T. Camellini, *J.C.S. Perkin II*, 1972, 2116.
[750] M. Harding, M. J. Adams, P. A. Alsop, and H. M. N. H. Irving, *Analyt. Chim. Acta*, 1973, **67**, 204.
[751] B. Klewe and H. M. Seip, *Acta Chem. Scand.*, 1972, **26**, 1860.
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[754] R. Engler, M. Dräger, and G. Gattow, *Z. anorg. Chem.*, 1974, **403**, 81.
[755] S. J. Lippard and S. M. Morehouse, *J. Amer. Chem. Soc.*, 1972, **94**, 6949, 6956.
[756] M. Bonamico, G. Dessy, V. Fares, and L. Scaramuzza, *J.C.S. Dalton*, 1973, 876, S. Esperås, J. W. George, S. Husebye, and Ø. Mikalsen, *Acta Chem. Scand.*, 1973, **27**, 1089.
[757] R. Engler, G. Kiel, and G. Gattow, *Z. anorg. Chem.*, 1974, **404**, 71.
[758] P. Jennische and R. Hesse, *Acta Chem. Scand.*, 1973, **27**, 3531; S. Husebye and S. E. Svaeren, *ibid.*, p. 763; S. Esperås and S. Husebye, *ibid.*, 1972, **26**, 3293; A. Kopwillem, *ibid.*, p. 2941; S. R. Fletcher and A. C. Skapski, *J.C.S. Dalton*, 1974, 486; R. Hesse and P. Jennische, *Acta Chem. Scand.*, 1972, **26**, 3855; S. Esperås and S. Husebye, *ibid.*, 1973, **27**, 706.
[759] T. Machiguchi, T. Hoshi, J. Yoshino, and Y. Kitahara, *Tetrahedron Letters*, 1973, 3873.
[760] Z. Yoshida and H. Miyahara, *Bull. Chem. Soc. Japan*, 1972, **45**, 1919.

in the enethiol tautomer (504) and the enol tautomer (506), respectively. The u.v. spectra of some simple thioamides have been discussed in relation to HMO and PPP calculations.[705] The u.v. spectrum of 2-mercaptopyrazine has been interpreted by means of the PPP method, thus establishing the existence of the tautomeric thione form alone in solution.[761]

Other recent papers report on u.v. spectroscopic studies of 1,5-disubstituted 2,4-dithiobiurets,[762] isatinthiosemicarbazones,[520] 2,4-dihydroxydithiobenzoic acid,[763] thiocarbonyl difluoride,[764] thiophosgene,[765] 3-substituted 2-thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazines,[766] 2- and 4-thioxo-1,3-thiazanes,[767] rhodanine and its *S*- and *N*-methyl derivatives,[768] and cobalt(II) and nickel(II) complexes of *N*-allylthiourea.[769]

Infrared and Raman Spectra. A full paper by Andrieu and Mollier, supplementing a previous short communication (see Vol. 2) in describing their i.r. and Raman spectroscopic investigations of simple aliphatic thioketones, has appeared.[770] For each compound, an intense i.r. band in the region 1243—1270 cm^{-1} could be definitely assigned to the C=S stretching vibration. In the Raman spectra, these bands were very strong and polarized. A linear correlation between ν(C=S) and the sum of the Taft σ^* parameters for the substituents of the —CS— group was demonstrated.[770] An i.r. and Raman spectral study of cyclopropyl alkyl thioketones revealed that a pseudoconjugation between the cyclopropyl group(s) and the C=S bond is unlikely, as the C=S stretching bands for these thioketones appeared at rather high frequencies (1276—1282 cm^{-1}).[771] The i.r. spectra of a series of β-thioxo-esters[39] and of ethyl thioacetothionoacetate[61] have been described and discussed in relation to the tautomerism of these compounds.

The i.r. spectrum of dimethylthioketen, recorded at −70 °C, was characterized by an intense band at 1789 cm^{-1} and two weaker bands at 1813 and 1743 cm^{-1}.[152]

The vibrational spectra of *N*-methylthioacetamide[772] and *NN*-dimethylthioacetamide[773] have been discussed on the basis of normal-co-ordinate treatments. Other papers deal with i.r. and/or Raman spectroscopic

[761] J. S. Kwiatkowski, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1973, **21**, 405.
[762] N. K. Agarwal, A. D. Taneja, and K. P. Srivastava, *J. Inorg. Nuclear Chem.*, 1973, **35**, 3959.
[763] P. Bockans and A. Orupe, *Latv. P.S.R. Zinat. Akad. Vestis, Fiz. Teh. Zinat. Ser.*, 1972, 53 (*Chem. Abs.*, 1972, **77**, 19 012).
[764] C. R. Lessard and D. C. Moule, *Spectrochim. Acta*, 1973, **29A**, 1085.
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[768] K. A. V'yunov, A. I. Ginak, and E. G. Sochilin, *Zhur. priklad. Spektroskopii*, 1972, **16**, 1037.
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[770] C. Andrieu and Y. Mollier, *Spectrochim. Acta*, 1972, **28A**, 785.
[771] C. G. Andrieu, D. Paquer, and Y. Mollier, *Compt. rend.*, 1973, **276**, *C*, 927.
[772] K. V. Ramiah and S. K. Sayee, *Current Sci.*, 1971, **40**, 620.
[773] A. Ray and D. N. Sathyanarayana, *Bull. Chem. Soc. Japan*, 1972, **45**, 2712.

investigations of simple primary[774,775] and secondary[775] thioamides, 3-(aminothiocarbonyl)pyridines,[776] piperazine-2,5-dithiones,[777] thiourea,[778,779] 1-methyl-2-phenylethylthiourea,[780] *N*-hydroxythioureas,[716] *NN'*-diarylthioureas,[781] 2-aryl-2-thiocarbamidoindane-1,3-diones,[782] isatin thiosemicarbazone,[520] and metal complexes of thioureas,[769,783] and thiosemicarbazide derivatives.[784]

Beiner and his co-workers have studied[785] the i.r. spectra of a series of simple aliphatic and alicyclic dithio-acids. A strong band in the region 1190—1245 cm^{-1} was assigned to ν(C=S), and two bands at 2470—2500 cm^{-1} and ~2560 cm^{-1}, respectively, were assigned to the S—H stretching vibrations of a hydrogen-bonded and a free thiolo-group, respectively. In accordance with this interpretation, the intensities of the latter two bands were found to depend strongly on the concentration of the dithio-acid solution.[785] The i.r. spectra of 2,4-dihydroxydithiobenzoic acid,[763] *meta*-substituted potassium thionobenzoates,[566] and metal salts of dithiobenzoic acid[786] have been described and discussed. The force constants *f*(C=S) of some derivatives of thiocarbonic acids have been calculated.[787] The i.r. spectra of thiocarbonyl chlorobromide,[788] ethylene trithiocarbonate,[789] nickel(II) *O*-alkylxanthates,[790] bis-(*NN*-dimethyldithiocarbamato)nickel(II),[791] and bis-(*NN*-dimethyldiselenocarbamato)nickel(II)[791] have been interpreted on the basis of normal-co-ordinate treatments. In addition, i.r. spectroscopic studies have been performed on some heterocyclic compounds[717,766,792] and on miscellaneous metal complexes of dithiocarbamic acids.[793]

[774] K. V. Ramiah and P. U. Bai, *Current Sci.*, 1973, **42**, 194.
[775] W. Walter and H. P. Kubersky, *J. Mol. Structure*, 1972, **11**, 207.
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[792] C. Cogrossi, *Spectrochim. Acta*, 1972, **28A**, 855.
[793] R. Kellner, *Analyt. Chim. Acta*, 1973, **63**, 277; R. Kellner, P. Prokopowski, and H. Malissa *ibid.*, 1974, **68**, 401; E. I. Markova, I. V. Shkhiyants, V. V. Sher, and P. I. Sanin, *Neftekhimiya*, 1973, **13**, 294 (*Chem. Abs.*, 1973, **79**, 65 318).

Rotational Spectra. The rotational spectrum of thioformaldehyde has been investigated in the region 100—250 GHz.[794] The C=S bond length of thioformamide has been determined [r(C=S) = 1.626 Å] on the basis of microwave spectral data.[795]

N.M.R. Spectra. Further documentation of the greater magnetic anisotropy of the C=S bond relative to the C=O bond has been given by Reid and his co-workers, who found[18] that the thioaldehydes (5) and (6) display their thioformyl proton signals in the region δ = 10.09—11.06 p.p.m., *i.e.* at a δ value 0.7—0.8 p.p.m. higher than what is found for the corresponding aldehydes. On this basis, it is surprising to learn that the thioformyl proton signal of methyl thionoformate[537,541] (δ = 9.66 p.p.m.[537]) appears at a higher field than the formyl proton signal of methyl thioloformate (δ = 10.12 p.p.m.[537]). The n.m.r. spectra of alkyl cycloalkyl thioketones,[41] cyclic $\alpha\beta$-unsaturated thioketones,[42], β-oxo-thioketones,[704] β-thioxo-esters,[39] ethyl thioacetothionoacetate,[39,61] and β-thioxo-thioamides[60] have been described and discussed in connection with investigations of the tautomerism of these compounds. Being differently affected by the anisotropy of their thiocarbonyl groups, the *ortho*-hydrogen atoms of the thioamide rotamers (526) and (527) were clearly distinguishable in the n.m.r. spectra.[724] The effect of shift reagents on the n.m.r. spectra of aromatic sulphines allowed for distinction between pairs of isomers[796] and rotamers.[797] ^{1}H n.m.r. spectroscopic studies have been performed on thioacridone;[798] cobalt(III) complexes of α-brominated thioacetylacetone;[799] thiolactams and cyclic thioureas;[800] *N*-methylthiopyridones;[801] 1,2-substituted Δ^4-pyrazoline-3-thiones and Δ^3-triazoline-5-thiones;[802] thiones derived from purines;[803] 4,5-dihydro-1,2,4-triazole-5-thiones and corresponding selenium compounds;[804] dimethyl trithiocarbonate and its mono-, di-, and tri-seleno-analogues;[805] and metal complexes of trimethylthiourea[806] and dithiocarbamic acids.[807]

On the basis of a comparison of the ^{13}C n.m.r. spectra of a series of thiocarbonyl compounds with those of the corresponding carbonyl compounds, Kalinowski and Kessler found[808] the following correlation between

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[795] R. Sugisaki, T. Tanaka, and E. Hirota, *J. Mol. Spectroscopy*, 1974, **49**, 241.
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[801] C. H. Wang, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2760.
[802] M. Begtrup, *Acta Chem. Scand.*, 1974, **B28**, 61.
[803] L.-M. Twanmoh, H. B. Wood, and J. S. Driscoll, *J. Heterocyclic Chem.*, 1973, **10**, 187.
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[805] M. Dräger and G. Gattow, *Spectrochim. Acta*, 1972, **28A**, 425.
[806] D. Gattegno and A. M. Giuliani, *J.C.S. Dalton*, 1973, 1646.
[807] M. C. Palazzotto, D. J. Duffy, B. L. Edgar, L. Que, and L. H. Pignolet, *J. Amer. Chem. Soc.*, 1973, **95**, 4537.
[808] H.-O. Kalinowski and H. Kessler, *Angew. Chem.*, 1974, **86**, 43.

the ^{13}C chemical shifts of thiocarbonyl and carbonyl carbon atoms:

$$\delta(^{13}C{=}S) = 1.45 \times \delta(^{13}C{=}O) - 46.5 \text{ p.p.m.}$$

The ^{13}C n.m.r. spectra of diethyl malonate and all of its possible thio-analogues have been studied by Radeglia and Scheithauer, who stated that the additional displacements of the ^{13}C as well as the ^{1}H shifts brought about by the incorporated sulphur atoms, to a first approximation, are determined by the same interaction effects.[809] Some other papers deal with ^{13}C n.m.r. investigations of thiobarbiturates,[810] ethylenethiuram monosulphide,[811] and azole derivatives containing the thiocarbonyl group.[802]

E.S.R. Spectra. E.s.r. spectroscopic studies have been performed on sodium-reduced aromatic thioketones,[812] and on metal complexes of β-oxo-thioketones,[813] *N*-thiobenzoyl-*N*-phenylhydroxylamine,[814] and *NN*-diethyl-thioselenocarbamic acid.[815]

Photoelectron and E.S.C.A. Spectra. The diselenide structure of thiuram diselenides has been established by means of Röntgenphotoelectron spectroscopy.[816] The photoelectron spectra of thiocarbonyl halides have been studied and interpreted on the basis of CNDO calculations by two groups of workers.[817] ESCA investigations have been performed on dithio-esters derived from active-methylene compounds and carbon disulphide,[818] and on isocoumarins, thioisocoumarins, and isoquinolines containing the thiocarbonyl function.[819]

Mass Spectra. The mass spectra of aromatic sulphines,[820] aryl arylthio sulphines,[821] aryl arylsulphinyl sulphines[821] and aryl arylsulphonyl sulphines[821] have been interpreted. In all cases the occurrence of a rearrangement involving the intermediacy of an oxathiiran could be established. The loss of a sulphydryl radical from the molecular ion appeared to be a characteristic process by the electron-induced fragmentation of thioamides, and this was in some cases taken as evidence for pronounced enethiolization of the molecular ion.[822] The fragmentation

[809] R. Radeglia and S. Scheithauer, *Z. Chem.*, 1974, **14**, 20.
[810] A. Fratiello, M. Mardirossian, and E. Chavez, *J. Magn. Resonance*, 1973, **12**, 221.
[811] M. Alvarez, R. W. Creekmore, and R. T. Rosen, *Tetrahedron Letters*, 1973, 939.
[812] L. J. Aarons and F. C. Adam, *Canad. J. Chem.*, 1972, **50**, 1390.
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[814] D. Rehorek, R. Kirmse, and P. Thomas, *Z. anorg. Chem.*, 1973, **395**, 103.
[815] R. Kirmse, R. Heber, and E. Hoyer, *Z. Chem.*, 1972, **12**, 226.
[816] J. Finster, R. Heber, E. Hoyer, W. I. Nefedow, and J. W. Salyn, *Z. Chem.*, 1974, **14**, 25.
[817] K. Wittel, A. Haas, and H. Bock, *Chem. Ber.*, 1972, **105**, 3865; D. Chadwick, *Canad. J. Chem.*, 1972, **50**, 737.
[818] H. Kolind-Andersen, L. Dalgaard, L. Jensen, and S.-O. Lawesson, *Rec. Trav. chim.*, 1973, **92**, 1169.
[819] J. Escard, G. Mavel, N. Lozac'h, and L. Legrand, *Tetrahedron Letters*, 1973, 249.
[820] A. Tangerman, L. Thijs, A. P. Anker, and B. Zwanenburg, *J.C.S. Perkin II*, 1973, 458.
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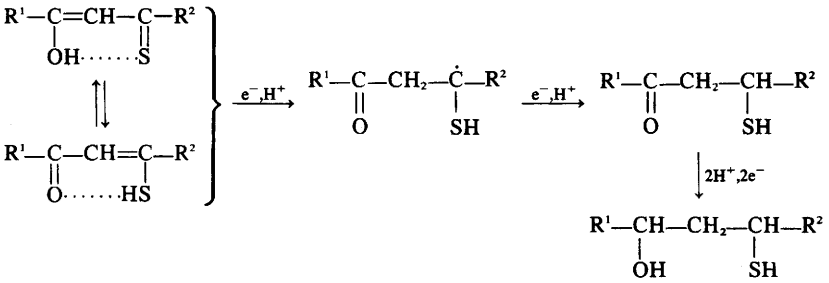
[822] F. C. V. Larsson, S.-O. Lawesson, J. Møller, and G. Schroll, *Acta Chem. Scand.*, 1973, **27**, 747.

routes of substituted selenoureas were found to be similar to those observed for corresponding ureas and thioureas.[823] Isomeric *O,S*- and *S,S*-dialkyl dithiocarbonates were found to be distinguishable by mass spectrometry.[824] Several papers report on mass spectrometric investigations of diphenylcyclopropenethione,[153] 5,5-diphenyldithiohydantoins,[825] 1-(aminothiocarbonyl)benzo[c]pyrrolidines,[304] dithizone,[826] 1-phenyl-5-mercaptotetrazoles,[827] sulphur and selenium isologues of phthalide,[828] dimethyl trithiocarbonate and its selenium analogues,[805] 1,3-dithiole-2-thiones,[829] *S*-(alkoxythiocarbonyl)thiohydroxylamines,[830] aryl *N*-alkyl-dithiocarbamates,[637] *N*-substituted methyl thioselenocarbamates,[823] and 2-thiones of benzothiazole, benzimidazole, and benzoxazole.[831]

Other Physical Properties.—*Electrochemistry.* The polarographic reduction of monothio-β-diketones has been found to proceed by a three-step process, most probably as illustrated in Scheme 18.[832] The polarographic oxidation of monothio-β-diketones was also investigated, but this process could not be so well characterized.[832] Voltammetry of solutions of the

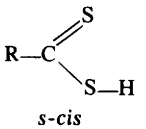


Scheme 18

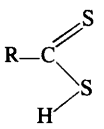
1,3-dithioketonate anion (71) afforded evidence for the occurrence of a further reversible electrochemical reduction of (71) to the corresponding very short-lived dianion radical.[88] A recent paper by Bond and his co-workers deals with the polarographic oxidation and reduction of zinc(II), and mercury(II) complexes of ethyl thioacetothionoacetate.[833]

[823] A. M. Kirkien and R. J. Shine, *Org. Mass Spectrometry*, 1973, **7**, 233.
[824] A. Holm and G. Schroll, *Acta Chem. Scand.*, 1972, **26**, 415.
[825] K. Lempert, K. Zauer, J. Møller, and G. Schroll, *Acta Chem. Scand.*, 1972, **26**, 1542.
[826] P. A. Alsop and H. M. N. H. Irving, *Analyt. Chim. Acta*, 1973, **65**, 202.
[827] A. Antonova, R. Borsdorf, R. Herzschuh, G. Fischer, and H. Engelmann, *J. prakt. Chem.*, 1973, **315**, 313.
[828] W. J. McMurray, S. R. Lipsky, R. J. Cushley, and H. G. Mautner, *J. Heterocyclic Chem.*, 1972, **9**, 1093.
[829] B. Adler and E. Fanghänel, *J. prakt. Chem.*, 1973, **315**, 1139.
[830] A. Holm and G. M. Jensen, *Acta Chem. Scand.*, 1972, **26**, 205.
[831] D. C. DeJongh and M. L. Thomson, *J. Org. Chem.*, 1973, **38**, 1356.
[832] O. Gürtler, P. Thomas, and E. Uhlemann, *J. prakt. Chem.*, 1973, **315**, 73.
[833] A. M. Bond, A. R. Hendrickson, and R. L. Martin, *J. Amer. Chem. Soc.*, 1973, **95**, 1449.

Dipole Moments. The dipole moment of thioformamide ($\mu = 4.01$ D) has been calculated from Stark effect measurements on its microwave spectrum.[795] Dipole-moment measurements of simple aliphatic and alicyclic dithio-acids indicated that these exist mainly in the *s-cis*-form (530) rather than the *s-trans* (531).[785] The conformations of a series of thio-oxamides, dithio-oxamides, and ethyl thio-oxamates have been determined on the



s-cis
(530)



s-trans
(531)

basis of dipole-moment measurements.[834] Dipole moments have been determined for 4-thioxo-1,4-pyrans,[835] 4-mercaptopyrimidines,[710] thiolactams,[800] cyclic thioureas,[800] *N*-hydroxythioureas,[716] and imidazolidine-2-thiones.[836]

Acidity and Basicity Measurements. The dissociation constants of thioformic acid and dithioformic acid have been determined by conductimetry.[837] The K_a values found (8.8×10^{-3} and 0.14, respectively) clearly demonstrate that these sulphur-containing acids are considerably stronger than formic acid. The acidity constants of α-substituted β-thioxo-aldehydes and -ketones appeared to be smaller than those of the corresponding α-unsubstituted compounds, presumably owing to structural differences.[838] pK_a measurements have shown that *N*-acylthioamides are considerably more acidic than common thioamides.[248] The protonation of *N*-acylthioureas in aqueous sulphuric acid has been studied.[839] Various methods have been applied to the determinations of dissociation constants of *N*-substituted β-mercaptocinnamamides,[840] simple thioamides,[705] *PP*-disubstituted thiophosphinoylthioformhydrazides,[502] alkyl *N*-acylthionocarbamates,[841] and *N*-substituted dithiocarbamic acids.[668]

[834] J. Chavigny de Lachevrotière, J. Sandström, and H. Lumbroso, *Compt. rend.*, 1973, **276**, *C*, 1143.
[835] Y. P. Egorov, Y. Y. Borovikov, L. V. Papp, and A. I. Tolmachev, *Teor. i eksp. Khim.*, 1973, **9**, 232.
[836] C. W. N. Cumper and G. D. Pickering, *J.C.S. Perkin II*, 1972, 2045.
[837] R. Engler and G. Gattow, *Z. anorg. Chem.*, 1972, **389**, 151.
[838] E. Uhlemann, U. Eckelmann, and G. Hinsche, *Z. Chem.*, 1973, **13**, 476.
[839] W. I. Congdon and J. T. Edward, *J. Amer. Chem. Soc.*, 1972, **94**, 6096.
[840] A. Yokoyama, M. Chikuma, and H. Tanaka, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2000.
[841] V. I. Ryaboi, V. A. Shenderovich, and N. E. Shchukina, *Zhur. priklad. Khim.*, 1973, **46**, 1095.

6

Ylides of Sulphur, Selenium, and Tellurium, and Related Structures

BY A. Wm. JOHNSON

1 Introduction

This Report covers the literature of the topic appearing since that covered in Volume 2 of this series, and through to the end of 1973. As it will illustrate, sulphur ylides are increasingly being applied in synthetic chemistry, and some evidence is available suggesting their involvement in biochemical processes. Increasing amounts of spectroscopic information and the availability of crystallographic data are facilitating theoretical description of the structure and bonding in sulphur ylides.

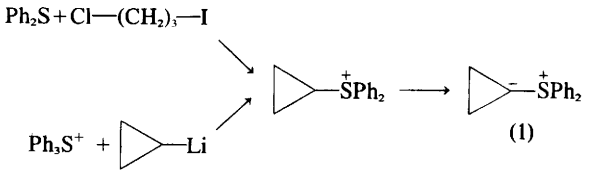
Five review articles have appeared during this biennium, three of which are narrowly focused. The authors and their topics are as follows: Brown, n.m.r. spectra of sulphonium salts and ylides;[1] Wolfe, the *gauche* effect as an explanation for the stereochemistry of the formation of ylides and α-sulphonylcarbanions from their conjugate acids;[2] Trost, the use of sulphoniumcyclopropylides in organic synthesis;[3] Nagai and Tokura, sulphene chemistry;[4] Johnson, the preparation and use of sulphoximine derivatives in organic chemistry.[5]

2 Sulphonium Ylides

Methods of Synthesis.—The salt method, involving the alkylation of a sulphide with an alkyl halide followed by removal of an α-proton with an appropriate base, continues to be of wide applicability, even for complex structures. Adamantyl bromide and methyl ethyl sulphide were smoothly converted into the salt using silver tetrafluoroborate.[6] 1-Iodo-3-chloropropane alkylated diphenyl sulphide with silver tetrafluoroborate assistance,

[1] C. Brown in 'Sulphur in Organic and Inorganic Chemistry,' ed. A. Senning, Marcel Dekker, New York, 1972, Vol. III, Ch. 25. p. 296.
[2] S. Wolfe, *Accounts Chem. Res.*, 1972, **5**, 102.
[3] B. M. Trost, *Accounts Chem. Res.*, 1974, **7**, 85.
[4] T. Nagai and N. Tokura, *Internat. J. Sulfur Chem.* (B), 1972, **7**, 207.
[5] C. R. Johnson, *Accounts Chem. Res.*, 1973, **6**, 341.
[6] B. M. Trost and R. F. Hammen, *J. Amer. Chem. Soc.*, 1973, **95**, 962.

and the resulting sulphonium salt was cyclized to cyclopropyldiphenylsulphonium tetrafluoroborate by treatment with sodium hydride.[7] This proved to be a much more effective route to diphenylsulphoniumcyclopropylide (1)



than the exchange of cyclopropyl-lithium with triphenylsulphonium salts.[8] The use of silver tetrafluoroborate to enhance the reactivity of an alkyl halide as an alkylating agent, first reported by Franzen *et al.*[9] for sulphonium salts, is almost essential if diphenyl sulphide is to be alkylated. Tang and Rapoport,[10] upon detecting both primary and secondary alkyldiphenylsulphonium salts being formed from a primary halide under these conditions, found that diphenyl sulphide could be alkylated with a primary alkyl trifluorosulphonate in carbon tetrachloride solution without rearrangement.

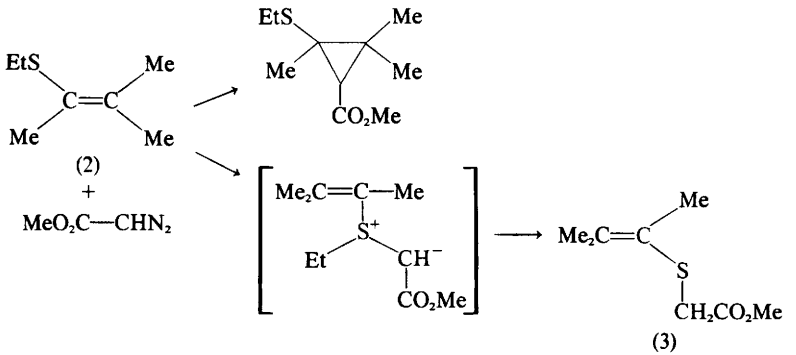
A variety of bases have been used to convert sulphonium salts into ylides. In the case of an unstable ylide such as (1), irreversible generation of the ylide using dimsylsodium in DME resulted in considerable ylide decomposition, whereas the use of a weaker base system, powdered KOH in DMSO, resulted in reversible ylide formation and the maintenance of a lower concentration of ylide.[11] Shono *et al.*[12] now have published full details of the electrochemical conversion of sulphonium salts into ylides. From the corresponding sulphonium salts in aqueous solution at -1.6 to -2.1 V they were able to generate dimethylsulphonium-2-nitrofluorenylide, -benzylide, and -methylide. The former ylide was isolated while the latter two were trapped by reaction with aldehydes, ketones, and diethyl maleate in yields up to 30%. However, they were accompanied by products probably originating from radicals.

Volume 1 of this series contained a detailed discussion on the condensation of active-methylene compounds with sulphoxides to form ylides.[13] The addition of lithium or sodium perchlorate to such reactions now has been found to increase the yields dramatically.[14] In what is undoubtedly a mechanistically analogous reaction, active-methylene carbanions have been

[7] B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, 1973, **95**, 5298.
[8] B. M. Trost, R. LaRochelle, and M. J. Bogdanowicz, *Tetrahedron Letters*, 1970, 3449.
[9] V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, 1961, **94**, 2942.
[10] C. S. F. Tang and H. Rapport, *J. Org. Chem.*, 1973, **38**, 2806.
[11] B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, 1973, **95**, 5307.
[12] T. Shono, T. Akazawa, and M. Mitani, *Tetrahedron*, 1973, **29**, 817.
[13] A. W. Johnson in 'Organic Compounds of Sulphur, Selenium, and Tellurium,' ed. D. H. Reid, (Specialist Periodical Reports), The Chemical Society, London, 1970, Vol. 1, Ch. 6, p. 251.
[14] H. Strzelecka, *Compt. rend.*, 1972, **275**, C, 617.

reported to react with the intermediate formed from the reaction of a sulphide and t-butyl hypochlorite.[15]

Ando *et al.*[16] have published details of the thermal reaction of diazo-compounds with sulphides. For the reaction to be of use, a stabilized diazo-compound and a dialkyl sulphide must be employed, but some aryl sulphides have been used successfully. Thus, diazomalonate and dimethyl sulphide afforded the ylide in 75% yield, and the use of diphenyl sulphide afforded ylide in 85% yield. The use of olefinic sulphides afforded two competitive sites for attack by the carbene presumably formed from the diazo-compound. Diazoacetate and the vinyl sulphide (2) produced a 5% yield of the cyclopropane, resulting from carbene attack at the double bond, and a 39% yield of a rearranged vinyl sulphide (3), resulting from carbene



attack at sulphur to form an ylide followed by intramolecular elimination of ethylene.[17] Grieco *et al.*[18] found that there was exclusive attack at sulphur in a substituted phenyl allyl sulphide to form an ylide, which underwent subsequent rearrangement. On the basis of these experiments, it may be concluded that sulphide sulphur is attacked at least several times more rapidly than a double bond by thermally generated carbenes.

In a preliminary communication, Serratosa and Quintana[19] had found that pivaloyldiazomethane thermally decomposed in the presence of copper-bronze to the olefin dimer, dipivaloylethylene, in high yield, probably *via* a carbene intermediate. The intermediate could be trapped with tetramethylethylene but in the presence of a sulphide, namely thioanisole, a cyclic trimer, tripivaloylcyclopropane (4), was formed in high yield. It was proposed that carbene and sulphide first formed ylide, which then reacted

[15] I. Ikeda, G. F. Whitfield, and D. Swern, Abstracts of the 163rd meeting, American Chemical Society, 1972, Organic Division, paper no. 122.
[16] W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyama, S. Nakaido, and T. Migita, *J. Org. Chem.*, 1972, **37**, 1721.
[17] W. Ando, H. Fujii, T. Takeuchi, H. Higuchi, Y. Saiki, and T. Migita, *Tetrahedron Letters*, 1973, 2117.
[18] P. A. Grieco, D. Boxler, and K. Hiroi, *J. Org. Chem.*, 1973, **38**, 2572.
[19] F. Serratosa and J. Quintana, *Tetrahedron Letters*, 1967, 2245.

with two additional carbene molecules in succession, and that sulphide finally was displaced. In their 1973 full paper, these authors have presented evidence that an alternative proposal, advanced in this Report in 1970,[20] involving ylide formation, attack by carbene to eliminate sulphide and form dimer, and finally Michael addition by ylide on the dimer, accounts for the experimental observations.[21] It is apparent that sulphide and ylide compete for carbene, because the use of more nucleophilic sulphides diminishes the yield of trimer and leads to isolation of ylide. A novel application of the use of sulphide as an intermediary or catalyst to effect trimerization of β-ketodiazo-compounds is the formation of bullvalenetrione (5).[22]

$$RCOCHN_2 \xrightarrow{\text{Cu-bronze}} RCOCH{=}CHCOR$$

$$RCOCHN_2 \xrightarrow[\text{PhSMe}]{\text{Cu-bronze}} \text{RCO-(cyclopropane)-COR, COR}$$

(4)

$$RCOCHN_2 \xrightarrow[\text{MeSMe}]{\text{Cu-bronze}} Me_2S{=}CHCOR$$

$$HC(CH_2COCHN_2)_3 \xrightarrow[\text{PhSMe}]{CuSO_4} \text{(5)}$$

(5)

R = Me_3C

There have been a number of reports on the photochemical reaction between diazo-compounds and sulphides to form either stable or transient ylides. Illger *et al.*[23] reported the isolation of a series of ylides from the reaction of dimethyl sulphide with substituted diazomethanes, such substituents being carbonyl, sulphonyl, or phosphoryl groups. Ando *et al.*[16] described the reaction of diazo dimethylmalonate with a series of sulphides but found that the yields of ylides varied considerably, much more so than for the thermal reaction, with the nucleophilicity of the sulphide. For example, dimethyl sulphide afforded an 88% yield of ylide (6a) while diphenyl sulphide afforded a 12% yield of ylide (6b). Repetition of the reaction with dimethyl sulphide but in the presence of cyclohexene indicated that the sulphide was about six times as reactive as the olefin toward the photochemically generated carbene. These reactions all were assumed to occur by conversion of the diazo-compound into a singlet carbene, which attacked sulphur. However, it was found that (6a) also could

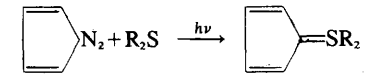
[20] Ref. 13, p. 259.
[21] J. Quintana, M. Torres, and F. Serratosa, *Tetrahedron*, 1973, **29**, 2065.
[22] J. Font, F. Lopez, and F. Serratosa, *Tetrahedron Letters*, 1972, 2589.
[23] W. Illger, A. Liedhegener, and M. Regitz, *Annalen*, 1972, **760**, 1.

$$(MeO_2C)_2CN_2 + R_2S \xrightarrow{h\nu} (MeO_2C)_2C{=}SR_2$$

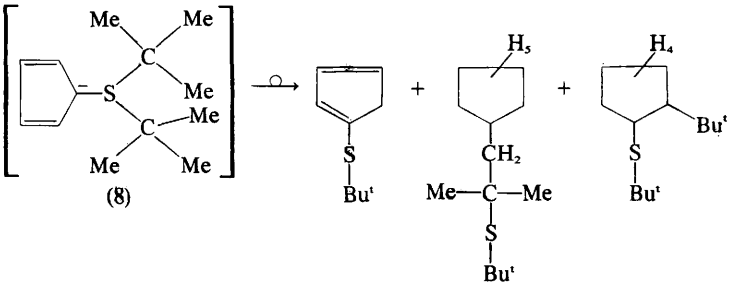
(6) a; R = Me
b; R = Ph

be formed, but in lower yield, in the presence of benzophenone as a sensitizer, a reaction undoubtedly involving the carbene in a triplet state.[16]

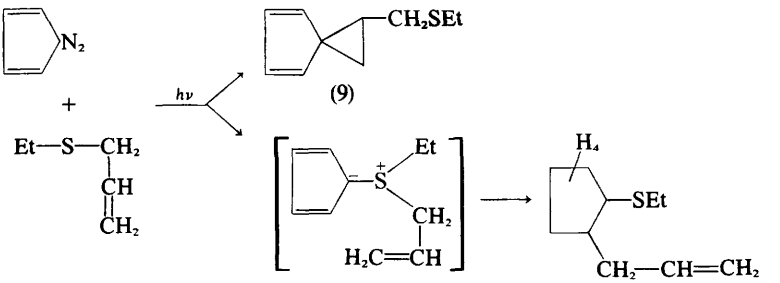
Ando *et al.*[24,25] found the photochemical reaction to be the most useful method to date for the preparation of sulphoniumcyclopentadienylides (7) from diazocyclopentadiene and a variety of dialkyl sulphides. Reaction with di-t-butyl sulphide afforded a mixture of sulphides, which probably resulted from rearrangements of an initially formed ylide (8). With allyl ethyl sulphide, diazocyclopentadiene gave a 13% yield of the addition product (9) and a 31% yield of a product (10) resulting from initial ylide formation



(7)



(8)



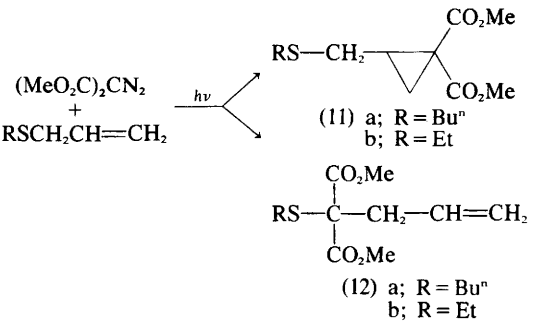
(10)

followed by a sigmatropic rearrangement (insertion product). These authors reported that the ratio of insertion-to-addition products in reactions with allyl ethyl sulphide was as follows: diazoacetate 1.5; diazocyclopentadiene 2.4; diazomalonate 5.1; phenyldiazomethane 8.0; diphenyldiazomethane

[24] W. Ando, J. Suzuki, Y. Saiki, and T. Migita, *J.C.S. Chem. Comm.*, 1973, 365.
[25] W. Ando, Y. Saiki, and T. Migita, *Tetrahedron*, 1973, **29**, 3511.

>26. They concluded that the more stabilized carbene shows greater selectivity for the more nucleophilic reactant (sulphide rather than olefin).[25]

Under photochemical conditions, diazomalonate reacted with allyl n-butyl sulphide to afford an 11% yield of the addition product (11a) and a 57% yield of the insertion product (12a), the latter resulting from initial ylide formation followed by a (2,3)sigmatropic rearrangement.[26] Under thermal conditions in the presence of cupric sulphate, only the insertion product (12a) was obtained, and in 93% yield. Thus, the carbene or carbene–copper complex is more discriminating between sulphide sulphur and double bond as a nucleophilic reaction site. The photochemical reaction between allyl ethyl sulphide and diazomalonate afforded a 51% yield of the insertion product (12b) and a 10% yield of the addition product (11b), but repetition of the reaction in the presence of a benzophenone sensitizer gave an 18% yield of (12b) and a 37% yield of (11b). Thus, the reaction of stabilized



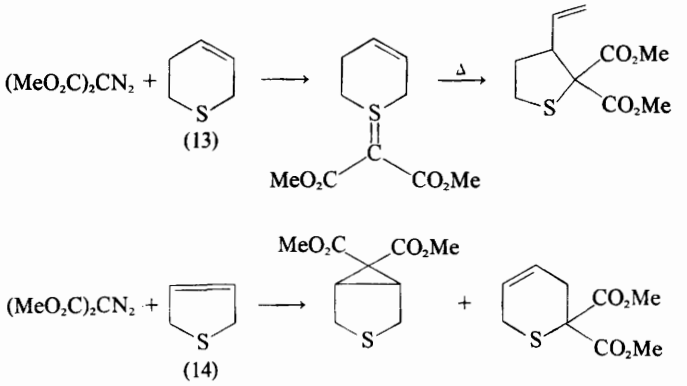
diazo-compounds with sulphides containing olefinic groups may be made to favour attack at sulphur to form a sulphur ylide by using thermal conditions, and to favour attack at the olefin group by using sensitized photochemical conditions.

The reaction of diazomalonate with cyclic olefinic sulphides under photochemical conditions varies depending on ring size. With the six-membered ring system (13) the ylide was isolated. However, on heating it underwent a sigmatropic rearrangement to produce the insertion-type product, the severe conditions presumably being necessitated by strain in the transition state for the rearrangement. With the five-membered-ring system (14) both addition product and insertion product were obtained, the latter by a Stevens rearrangement.[26]

Matsuyama *et al.*[27] found that sulphonium ylide formation from a sulphide and a stabilized diazo-compound could be effectively catalysed by condensation in the presence of a dialkoxy disulphide, and less well in the presence of thiocyanogen. The reaction was thought to involve initial complex

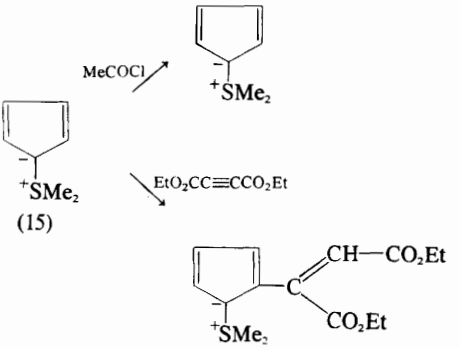
[26] W. Ando, S. Kondo, K. Nakayama, K. Ichibari, H. Kohoda, H. Yamato, I. Imai, S. Nakaido, and T. Migita, *J. Amer. Chem. Soc.*, 1972, **94**, 3870.

[27] H. Matsuyama, H. Minato, and M. Kobayashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 1512.



formation between sulphide and the catalyst, followed by nucleophilic attack of the diazo-compound.

Physical Properties.—Following up on calculations which indicated that the ring system of dimethylsulphoniumcyclopentadienylide (15) possessed aromatic character, Yoshida *et al.*[28] have examined the chemistry of (15).

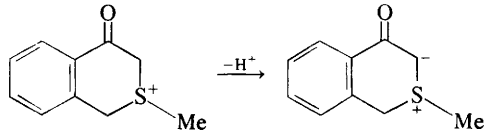


Acylation and alkylation led to 2-substituted ylides, and attempts to effect a Diels–Alder reaction with diethyl acetylenedicarboxylate and other dienophiles led instead to 2-substitution. It is apparent that (15) is more reactive than triphenylphosphoniumcyclopentadienylide and that it undergoes exclusively substitution reactions.

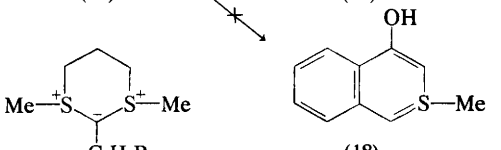
In an attempt to ascertain whether potential involvement of the ylide bond in an aromatic system might provide some driving force for proton removal, the cyclic salt (16) was converted into ylide with a variety of bases. Spectral data and reaction behaviour indicated that a stable ylide (17) had been obtained, rather than a thianaphthol (18).[29] The presence of a second

[28] Z. Yoshida, S. Yoneda, and M. Hazama, *J. Org. Chem.*, 1972, **37**, 1364.
[29] C. Kissel, R. J. Holland, and M. C. Caserio, *J. Org. Chem.*, 1972, **37**, 2720.

sulphonium group apparently is quite effective in stabilizing a sulphonium ylide, as evidenced by the isolation of a series of bis-ylides (19).[30]

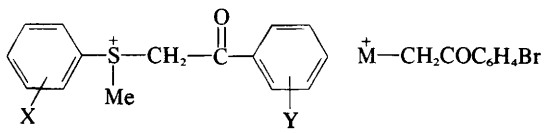


(16) (17)



(18) (19)

Two groups conducted Hammett correlations for pK_a values of the phenacylsulphonium salt (20). For variation of the nature of X, the ρ values found were 1.2[31] and 1.4.[29] For variation of the nature of Y, the ρ values were 2.6[31] and 2.0.[29] These values are comparable to those found for the formation of other phenacylides. It is apparent that there is no special resonance contribution from the *S*-aryl group towards stabilization of the ylide bond, and no 'through conjugation' from the ylide carbanion to the *S*-aryl ring.[29] The electronic effects of the aryl rings are more effectively transmitted by the carbonyl system ($p\pi$–$p\pi$) than by the sulphonium system ($p\pi$–$d\pi$).[31] Ratts[31] studied the pK_a's of a number of phenacylsulphonium salts (21),

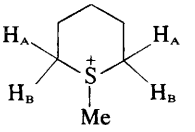


(20) (21)

where M=sulphonium group. Any structural feature in M which tended to delocalize the positive charge (*i.e.* replacement of ethyl by methyl, or increased ring size) would decrease the acidity of the salt because of decreased stabilization of the resultant sulphonium ylide. An increase in the positive charge on sulphur makes it more electronegative and better able to stabilize an adjacent carbanion by both inductive effect and *d*-orbital overlap.

Hofer and Eliel[32] examined the kinetic acidity of the alpha protons in *S*-methylthiapyran (22) by mass spectrometry on the products of deuteroxide-catalysed exchange with D_2O. If there were no discrimination

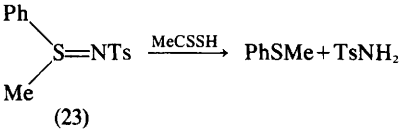
[30] I. Stahl and J. Gosselck, *Tetrahedron*, 1973, **29**, 2323.
[31] K. W. Ratts, *J. Org. Chem.*, 1972, **37**, 848.
[32] O. Hofer and E. Eliel, *J. Amer. Chem. Soc.*, 1973, **95**, 8045.



(22)

between H_A and H_B, the relative rates of incorporation of the four deuterium atoms would be $k_1:k_2:k_3:k_4=4:3:2:1$. The observed rates were 4.4:3.0:1.8:0.8, indicating that only minor preference was shown for any given proton. The *gauche* effect[2] would have predicted a distinct preference for exchange of the equatorial protons, assuming that the *S*-methyl group is equatorial. With the analogous five-membered-ring system the observed relative rates of exchange were 5.6:3.0:0.5:0.2, the wider spread indicating a higher degree of selectivity for certain protons.[32,33]

Chemical Stability.—Oae *et al.*[34,35] have reported three additional methods for the cleavage of sulphonium ylides. Reduction with dithioacetic acid afforded anisole and tosylamide in the case of the sulphidimine (23), but with the ylide (24) the overall effect simply was hydrolysis.[34] With acetic



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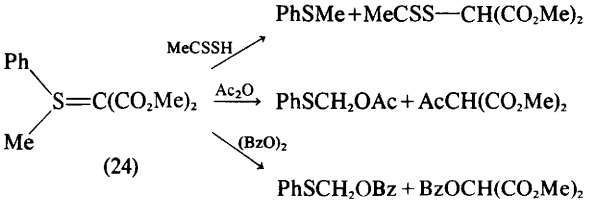


(24)

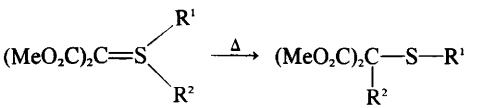
anhydride a Pummerer-type reaction occurred and with benzoyl peroxide an oxidative reaction occurred.[35]

Volume 1 of these Reports contained a detailed review of the conversion of sulphoniumphenacylides into tribenzoylcyclopropane.[36] Earlier in this present Report, it was reported that new evidence, obtained by Quintana *et al.*[21] on the conversion of diazo-ketones into triacylcyclopropanes (4) by

[33] G. Barbarella, A. Garbesi, and A. Fava, *Helv. Chim. Acta*, 1971, **54**, 2297.
[34] S. Oae, T. Yagihara, and T. Okabe, *Tetrahedron*, 1972, **28**, 3203.
[35] T. Yagihara and S. Oae, *Tetrahedron*, 1972, **28**, 2759.
[36] Ref. 13, pp. 258—260.

heating in the presence of copper-bronze and thioanisole, indicated that the reaction proceeded by formation of a diacylethylene and subsequent Michael addition by ylide. The key observation was that after partial completion of the reaction, the reaction mixture contained cyclopropane, dimer and ylide, and as the reaction proceeded further, dimer and ylide vanished. Whereas Trost[37] found that treatment of dimethylsulphonium-phenacylide with cupric sulphate gave high yields of the cyclopropane (4; R=Ph), Sato and Higuchi[38] have found that treatment instead with cupric chloride in methanol afforded a complex $(Me_2\overset{+}{S}—CH_2COPh\ X^-)_2,CuX_2$, which could be isolated as orange plates. The same material was obtainable from the reaction of the conjugate acid of the ylide and cupric chloride. It is possible that ylide simply was protonated and then formed the complex with $CuCl_2$. However, the fact that the complex reacted with diazoacetic ester to afford ethyl β-benzoylacrylate indicates that it must have some 'ylidic' character. In many respects this chemistry is similar to that reported by Nesmeyanov *et al.*[39] for the reaction of triphenylphosphoniumphenacylide with mercuric chloride.

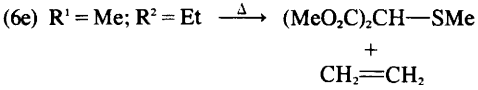
Stabilized ester ylides can undergo several possible reactions on heating. Heating (6a) to 155 °C led to a Steven's rearrangement product (25).[16] Migration preference is shown when one group on sulphur is especially stabilized, in that (6c) afforded (25c) and (6d) afforded (25d). In the latter



(6a) $R^1 = R^2 = Me$ (25)

(6c) $R^1 = Me$; $R^2 = CH_2Ph$

(6d) $R^1 = Et$; $R^2 = CH_2CO_2Et$



case, CIDNP spectra were observed at the migrating methylene group, indicating the probable involvement of a radical-pair mechanism. When R^1 and R^2 both were alkyl groups with no special migratory ability, heating the ylide (6e) resulted in an α′,β-elimination of olefin.[16]

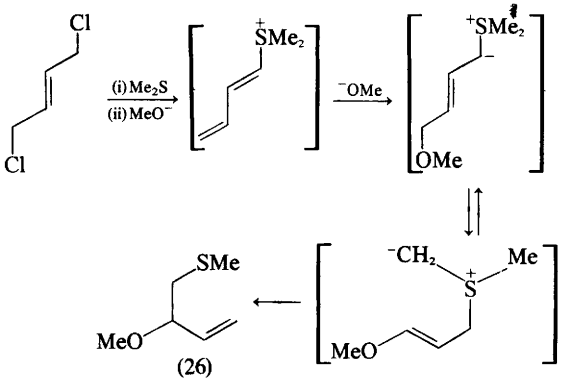
In addition to an elimination reaction and a Steven's rearrangement, the other major alternative for ylide rearrangement, especially with the presence of a point of unsaturation in the molecule, is a cyclic sigmatropic rearrangement, called either a 1,5- or a 2,3-rearrangement, which was

[37] B. M. Trost, *J. Amer. Chem. Soc.*, 1967, **89**, 138.

[38] T. Sato and J. Higuchi, *Tetrahedron Letters*, 1972, 407.

[39] N. A. Nesmeyanov and V. M. Novikov, *Proc. Acad. Sci. U.S.S.R.*, 1965, **162**, 471; N. A. Nesmeyanov, V. M. Novikov, and O. A. Reutov, *J. Organometallic Chem.*, 1965, **4**, 202.

discussed in detail in Volume 2 of these Reports.[40] A number of additional examples have been reported, and this rearrangement mechanism has been proposed to account for a number of additional reactions. As described earlier in this chapter, the ylide (6f; R^1=Ph, R^2=CH_2=CH_2—CH_2) spontaneously was converted into (12; R=Ph).[26] Treatment of 1,4-dichloro-2-butene with dimethyl sulphide and then sodium methoxide afforded (26), which can

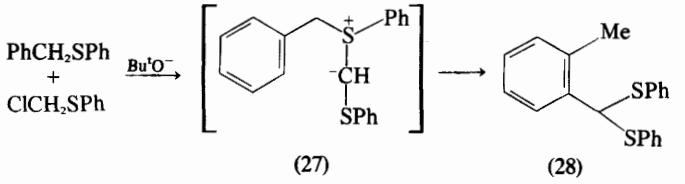


(26)

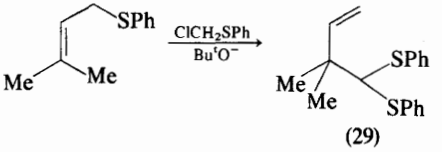
be accounted for as shown and involving a 2,3-rearrangement.[41] The same sequence could be effected starting with the 1-dimethylsulphoniobutadiene, affording (26) in 80% yield,[42] and the initial ylide, dimethylsulphonio-4-methoxy-2-butenylide, could be trapped by its reaction with aldehydes to form oxirans in good yield.[43] The reaction of benzyl phenyl sulphide with α-chlorothioanisole in the presence of potassium t-butoxide in DME gave the thioketal (28) in 70% yield, and probably involved the ylide (27) as an intermediate, which underwent a 2,3-rearrangement (Sommelet rearrangement).[44] The same reaction with γγ-dimethylallyl phenyl sulphide produced an 80% yield of the analogous product (29).

(2,3)-Sigmatropic rearrangements also have been observed in some cyclic systems. The diester ylide (30; R^1=R^2=CO_2Me) required heating to 180 °C in order to rearrange with ring contraction to (31)[26] but the phenacylide (30; R^1=H, R^2=COPh) rearranged at 0 °C to give a 25:1 ratio of *cis*:*trans*-isomers.[45] The five-membered analogue of the diester ylide underwent only a Steven's rearrangement for ring expansion (Scheme 1)[26] while the five-membered analogue of the phenacylide underwent a dimerization reaction.[45] The stereospecificity of the reaction of (30) indicates that an intermediate betaine probably is not involved and a concerted mechanism occurs.

[40] A. W. Johnson in 'Organic Compounds of Sulphur, Selenium, and Tellurium,' ed. D. H. Reid, (Specialist Periodical Reports) The Chemical Society, London, 1973, Vol. 2, Ch. 5, p. 294.
[41] G. Kresze, *Angew. Chem. Internat. Edn.*, 1972, **11**, 1106.
[42] H. Braun, N. Mayer, G. Strobl, and G. Kresze, *Annalen*, 1973, 1317.
[43] H. Braun. G. Huber, and G. Kresze, *Tetrahedron Letters*, 1973, 4033.
[44] S. Julia, C. Huynh, and D. Michelot, *Tetrahedron Letters*, 1972, 3587.
[45] S. Mageswaran, W. D. Ollis, and I. O. Sutherland, *J.C.S. Chem. Comm.*, 1973, 18.



(27) (28)



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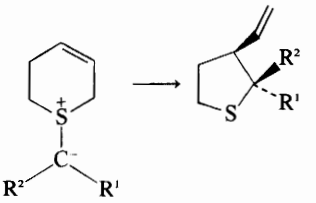
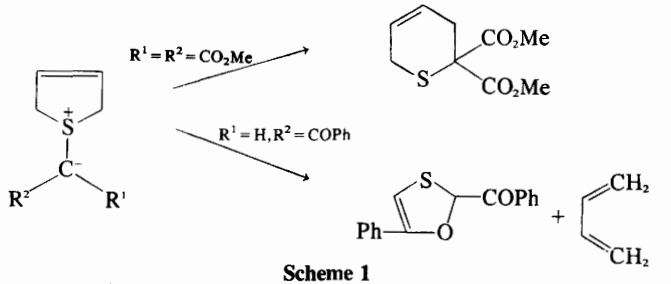


(30) (31)

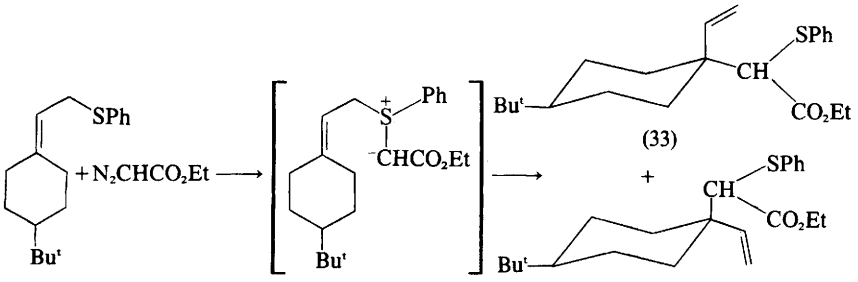


Scheme 1

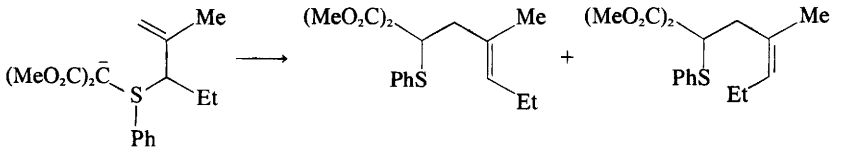
Diazoacetic ester with (32) afforded the intermediate ylide, which spontaneously rearranged in 59% yield to a 91:9 ratio of (33) and (34).[46] The reaction of (32) with dichlorocarbene proceeded analogously, indicating that the carbanion portion of the ylide preferred to attack the exocyclic double bond so as to enter the ring in an equatorial position. After formation from diazomalonate and the sulphide, the ylide (35) rearranged in 70% yield to afford a 90:10 ratio of (36) and (37), the former presumably being the most stable isomer.[18]

Trost and his students have attempted to use the 2,3-sigmatropic rearrangement as a means of transferring chirality. Adamantyl bromide was

[46] G. Andrews and D. A. Evans, *Tetrahedron Letters*, 1972, 5121.

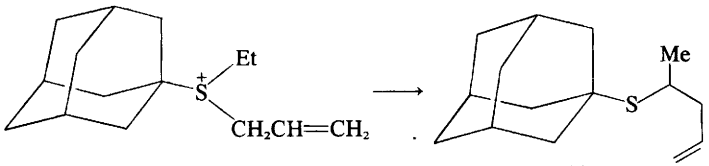


(32) (33) (34)



(35) (36) (37)

converted into an ethylallylsulphonium salt, which was resolved. Treatment with potassium t-butoxide led to three products, two of which were sulphides from displacement of an alkyl group, and the third was the unsaturated sulphide (38), formed in 49% yield. The latter probably was

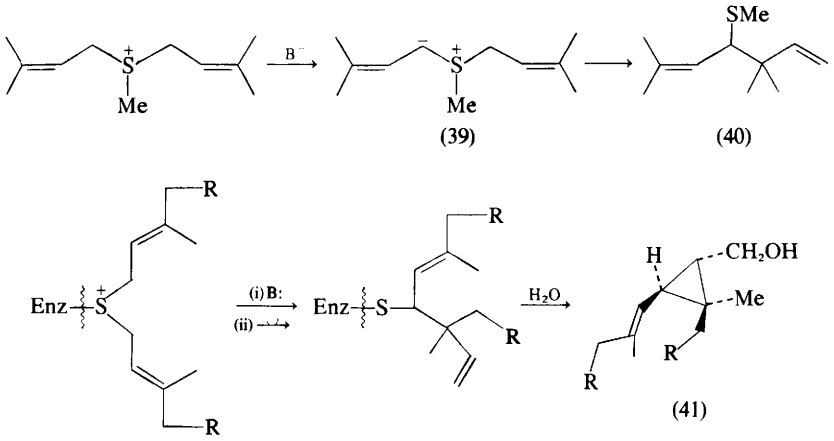


(38)

formed by rearrangement of adamantylallylsulphoniumethylide. The product was optically active, indicating that the reaction occurred with 94% stereospecificity and that chirality was transferred from the ylidic sulphur to carbon.[6] In a related series of experiments, methylbis(γ-dimethylallyl)sulphonium tetrafluoroborate was treated with a series of chiral bases to generate ylide (39), which rearranged to the thioether (40).[47] Most bases employed gave very little or no optical induction but lithium (*R*)(−)-2,2,2-trifluoro-1-phenylethoxide in (*S*,*S*)(+)-1,4-bisdimethylamino-2,3-dimethoxybutane gave (40) with an enantiomeric purity of 12%. The authors suggested that very high optical induction probably could be achieved in an enzymatic environment, and that this type of reaction could serve as a hypothetical model for the biosynthesis of presqualene (41).

As reported in an earlier section of this chapter, ethylallylsulphoniumcyclopentadienylide spontaneously rearranged to the vicinally substituted

[47] B. M. Trost and W. G. Biddlecom, *J. Org. Chem.*, 1973, **38**, 3438.



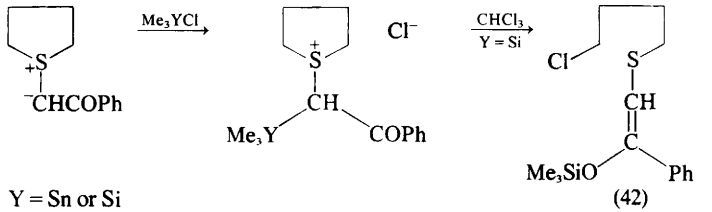
R = geranyl

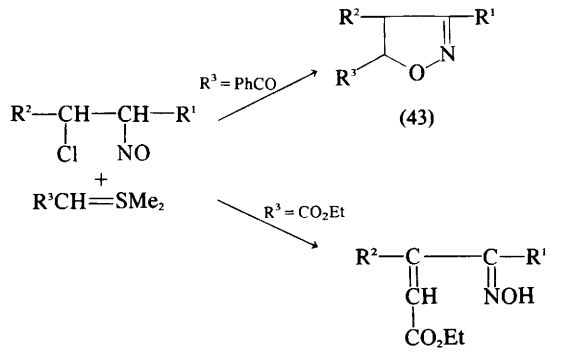
cyclopentadiene (10).[25] A 2,3-rearrangement would have afforded the *gem*-substituted isomer. This is believed to be the first example of what should be classed as a 3,3-rearrangement of a sulphonium ylide.

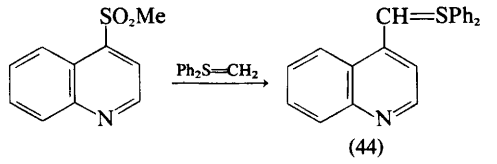
Reactions of Sulphonium Ylides.—Alkylation reactions have been restricted to β-carbonyl ylides. Two additional examples of methylation with trimethyloxonium tetrafluoroborate confirm the earlier conclusion that this reaction occurs to give the *O*-methylated product.[29,48] As reported earlier, phenylsulphenyl chloride effects a *C*-alkylation.[48] Trimethylsilyl chloride and trimethylstannyl chloride *C*-alkylated tetramethylenesulphonium-phenacylide, but in the silyl case the alkylation product rearranged to the *O*-silyl isomer (42), and the sulphur was dealkylated on standing.[49] Dimethylsulphoniumphenacylide underwent *C*-alkylation with α-chloronitroso-compounds, but the product immediately cyclized to an oxazoline (43).[50] With a more basic ylide, dimethylsulphoniumethoxycarbonylmethylide, the alkylation product underwent elimination of the sulphonium group, rather than its displacement. Taylor and Martin[51] reported an unusual example of an alkylation-type reaction in which diphenylsulphoniummethylide displaced the methylsulphonyl group from the quinoline ring to afford a new ylide (44), which was not isolated but was immediately used in a carbonyl-condensation reaction.

Normal *C*-acylations of sulphonium ylides with anhydrides, acyl halides, and isocyanates have been reported by several groups.[48,52,53] However,

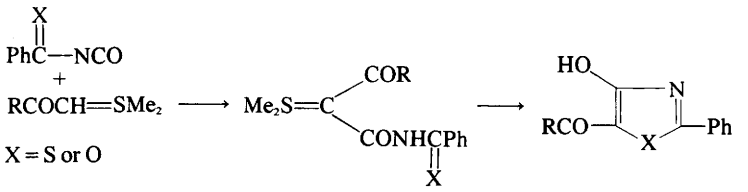
[48] Y. Hayasi and H. Nozaki, *Bull. Chem. Soc. Japan*, 1972, **45**, 198.
[49] K. Itoh, S. Kato, and Y. Ishii, *J. Organometallic Chem.*, 1972, **34**, 293.
[50] P. Bravo, G. Gaudiano, P. P. Ponti, and C. Ticozzi, *Tetrahedron*, 1972, **28**, 3845.
[51] E. C. Taylor and S. F. Martin, *J. Amer. Chem. Soc.*, 1972, **94**, 6218.
[52] D. Jeckel and J. Gosselck, *Tetrahedron Letters*, 1972, 2101.
[53] I. Stahl and J. Gosselck, *Tetrahedron Letters*, 1972, 989.





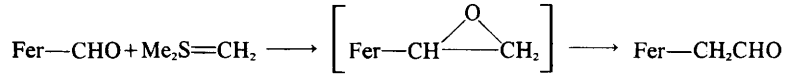


Tsuge *et al.*[54] found that acylation with α-ketoisocyanates, while initially affording the expected amido-ylide, presented the possibility of further intramolecular reaction to afford an oxazole (in the case of benzoyl isocyanate) or a thiazole (in the case of thionobenzoyl isocyanate). In the latter case, the initial acylation product could not be intercepted, the thiazole being obtained, and in the former case the oxazole could be obtained by heating in decalin.

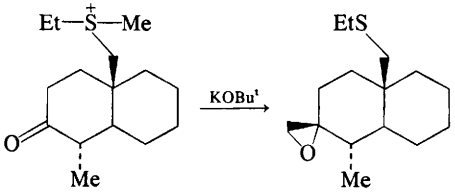


[54] O. Tsuge, K. Sakai, and M. Tashiro, *Tetrahedron*, 1973, **29**, 1983.

The reaction of sulphonium ylides with carbonyl compounds to form oxirans continues to be widely employed in organic synthesis, but ordinary examples will not be catalogued in the Report. Unusual examples will be reported. Ferrocenyloxiran is unknown and could not be obtained from dimethylsulphonium-methylide and ferrocenaldehyde. Instead, ferrocenylacetaldehyde was obtained in 64% yield, presumably *via* initial formation of the oxiran followed by rearrangement.[55] Matthews and Meteyer[56] reported that in the presence of potassium t-butoxide (45) underwent an intramolecular reaction to transfer the methylene group to the carbonyl group, and to the β-side of the ring system (46). The reaction must

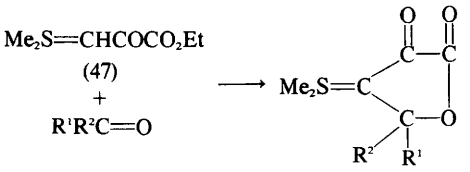


Fer = ferrocenyl



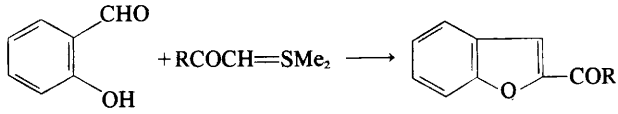
(45) (46)

have been intramolecular because (i) sulphoniumylide attack normally would be from the α-side in the 3-axial position, and (ii) when 10-methyl-2-decalone was added to the reaction mixture, only (46) was formed (*i.e.* no cross-over product). The reaction of ethyl dimethylsulphuranylidenepyruvate (47) with carbonyl compounds proceeded abnormally in that the intermediate betaine oxyanion displaced the ethoxy-group, resulting in a new series of ylides (48).[57] Stabilized sulphonium ylides reacted with a series of salicylaldehydes to afford 2-acylbenzofurans (49) as the sole products.[58]



(48)

[55] J. P. Sevenair, D. H. Lewis, and B. W. Ponder, *J. Org. Chem.*, 1972, **37**, 4061.
[56] R. S. Matthews and T. E. Meteyer, *Synthetic Comm.*, 1972, **2**, 399.
[57] K. Hagio, T. Takai, and T. Mukaiyama, *Chem. Letters*, 1972, 553.
[58] P. Bravo, G. Gaudiano, and C. Ticozzi, *Gazzetta*, 1973, **103**, 95.



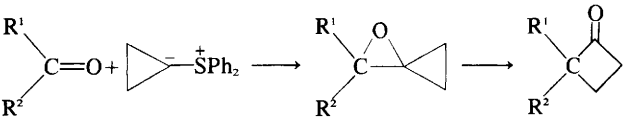
(49)

In two short communications and then in three full papers Trost and his students have extensively reported on the reaction of diphenylsulphonium-cyclopropylide with a variety of carbonyl compounds. The reaction of (1) (in the scrupulous absence of acid) with carbonyls afforded oxaspiropentanes (50). Reaction occurred with benzaldehyde (87%), cyclohexanone (97%), norbornanone (92%), and a wide variety of other carbonyl compounds.[59,60] In the presence of acids the oxaspiropentanes underwent a rearrangement to afford cyclobutanones (51). The reaction of (1) with norbornanone followed by rearrangement afforded an 85:15 ratio of the two isomers (52a) and (52b), with the dominant isomer being that from *exo*-attack of the ylide on the carbonyl group.[61,62] The stereoisomeric mixture of the products (53) obtained from the reaction of t-butylcyclohexanone with (1) followed by rearrangement depended on the acid used in the rearrangement. The a:b ratio for aqueous acid was 82:18, for lithium salts it was 91:9, and for europium salts it was 99:1.[62] Use of 2-methylcyclopropylidenediphenylsulphurane, available in *cis*- or *trans*-forms, afforded stereoisomeric mixtures of oxaspiropentanes,[7] and the rearrangement to cyclobutanes in the presence of lithium salts indicated that the more highly substituted group migrated in the ring expansion.[62]

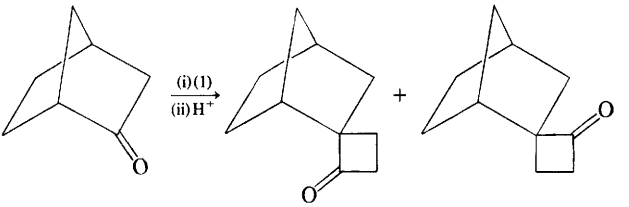
Use of the cyclopropylide (1) has been expanded to permit its use in two ring-forming reactions. In the first, the usual oxaspiropentane was opened with lithium diethylamide and chlorotrimethylsilane, the product being thermally isomerized to a vinyl ether (54). Hydrolysis of the latter afforded a cyclopentanone, the overall result being the addition of a C_3 unit to an α-methyleneketone to form a five-membered ring.[63] The second sequence, called secoalkylation, involved the reaction of (1) with an α-keto-oxiran followed by treatment with fluoroboric acid to afford the expected cyclobutanone (55). Treatment of the latter with methyl-lithium gave a methyl ketone, and treatment of (55) with potassium hydroxide and methanol gave a methyl ester. This reaction provides a ring-fusion geometry complementary to that available through the Robinson annelation reaction.[64]

Several groups have reported some rather unique experimental conditions for the reaction of sulphonium ylides with carbonyl compounds. Shono *et al.*[12] generated the ylide in aqueous solution in the presence of

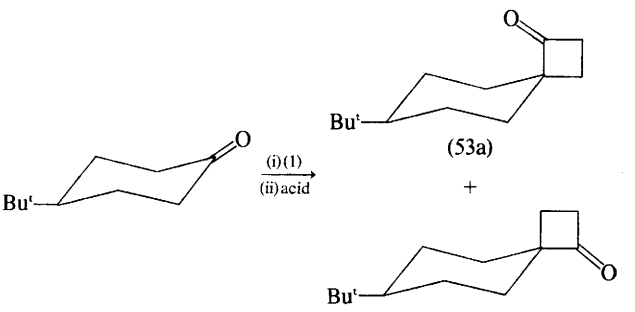
[59] M. J. Bogdanowicz and B. M. Trost, *Tetrahedron Letters*, 1972, 887.
[60] B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, 1973, **95**, 5311.
[61] M. J. Bogdanowicz, T. Ambelang, and B. M. Trost, *Tetrahedron Letters*, 1973, 923.
[62] B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, 1973, **95**, 5321.
[63] B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, 1973, **95**, 289.
[64] B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, 1972, **94**, 4777.



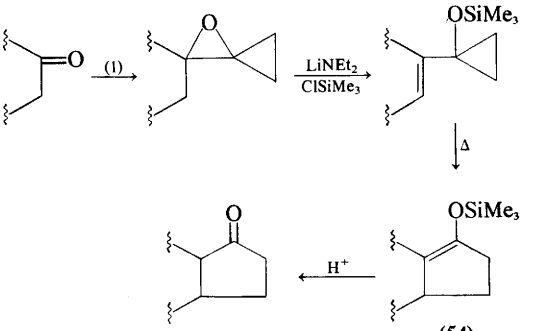
(1) (50) (51)



(52a) (52b)



(53a) (53b)



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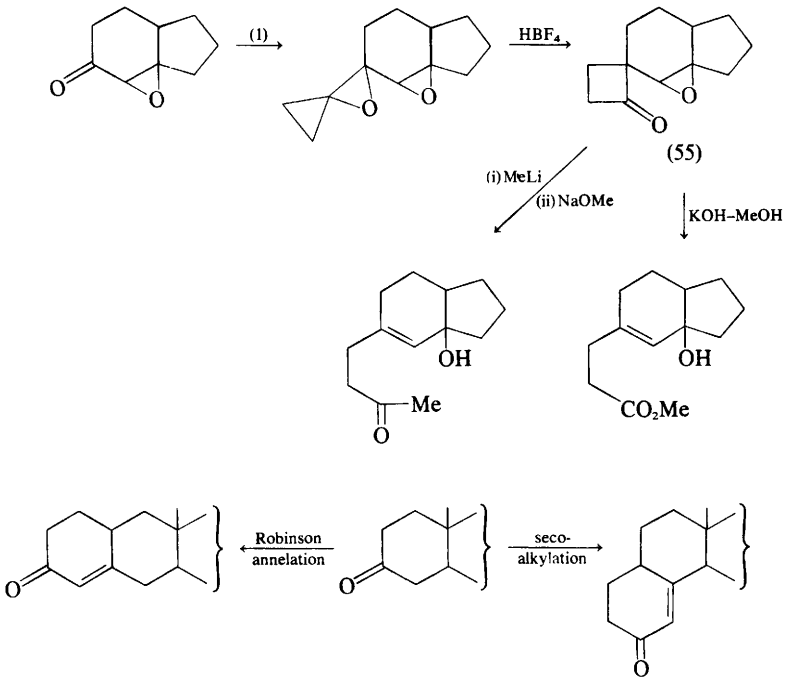
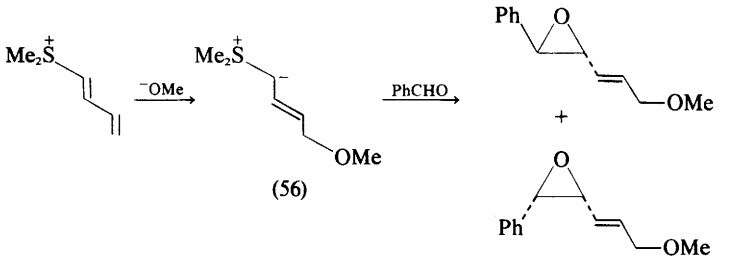


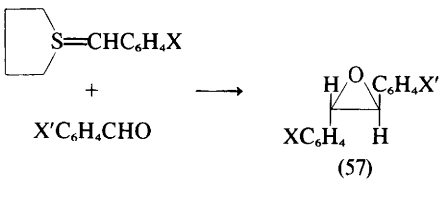
carbonyl compound by electrolysis. Thus, trimethylsulphonium iodide and benzaldehyde afforded a 28% yield of styrene oxide and the same salt with cyclohexanone gave only a 10% yield of oxiran. Braun *et al.*[43] generated ylide (56) *in situ* by addition of methoxide to the diene, and in the presence



of benzaldehyde the two isomeric oxirans were formed, the *trans-trans*-isomer dominating in each case. The reaction of benzaldehyde with lauryldimethylsulphonium salts in the presence of very strong sodium hydroxide (15N) in a 1:3 solvent mixture of benzene and water afforded up to an 81% yield of styrene oxide. These conditions were equally successful with acetophenone and cyclohexanone, with the yields varying with the

halide ion present and the NaOH concentration.[65] Under phase-transfer-catalysed conditions, involving methylene chloride and water solvents, sodium hydroxide as the base, and tetrabutylammonium iodide as a transfer agent, trimethylsulphonium iodide and benzaldehyde afforded a 90% yield of styrene oxide.[66] An equally good yield was obtained with cinnamaldehyde, but low yields were obtained with acetophenone and benzophenone.

The reaction of a substituted ylide with an aldehyde usually leads to dominant or exclusive formation of the *trans*-oxiran. Thus, tetramethylenesulphoniumbenzylides reacted with substituted benzaldehydes to afford only the *trans*-oxirans (57).[67] Townsend and Sharpless[68] demonstrated that the cycle of reactions from *trans*-cyclodecene oxide to the hydroxysulphonium salt (58) and back occurred with less than 3% crossover to the



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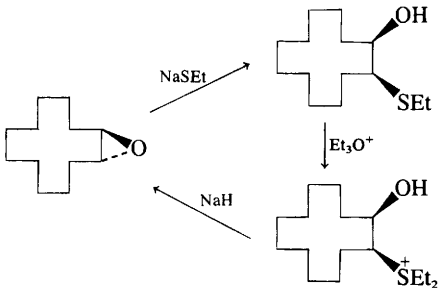


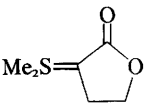
(58)

cis-form. The analogous cycle was effected with the *cis*-cyclodecene oxide, clearly demonstrating that the second step of the ylide–carbonyl reaction to form oxirans occurs with inversion of configuration at the ylide carbon. The reaction of adamantylethylsulphonium-methylide, formed with butyllithium in THF from the optically active salt, with benzaldehyde afforded styrene oxide that was optically inactive. Thus, there was virtually no optical induction.[6]

With many stabilized sulphonium ylides, their reactivity precludes

[65] Y. Yano, T. Okonogi, M. Sunaga, and W. Tagaki, *J.C.S. Chem. Comm.*, 1973, 527.
[66] A. Merz and G. Markl, *Angew. Chem. Internat. Edn.*, 1973, **12**, 845.
[67] M. Hetschko and J. Gosselck, *Chem. Ber.*, 1973, **106**, 996.
[68] J. M. Townsend and K. B. Sharpless, *Tetrahedron Letters*, 1972, 3313.

reactions with some carbonyl compounds. Thus, $PhSCH{=}SMe_2$ would not react with ketones, and only with difficulty with aldehydes.[48] The dimethylsulphuranylidene lactone (59) would not react with benzaldehyde or with cyclohexanone, and neither would the sulphide carbanion (60).[69] In other



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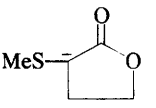
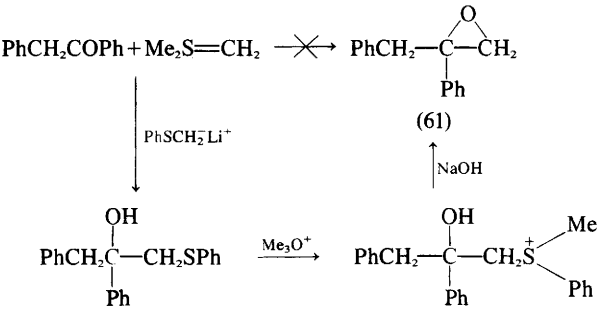


(60)

instances, however, the use of a sulphide carbanion has provided an effective alternative route to oxirans that are unavailable by the direct ylide route. Thus, while desoxybenzoin and dimethylsulphonium-methylide failed to afford the expected oxiran (61), probably owing to enolization, the reaction of desoxybenzoin with thioanisole carbanion, followed by methylation of the sulphide and elimination of the sulphonium group, afforded a 90% yield of (61).[70] In a similar manner di-t-butyl ketone was converted into

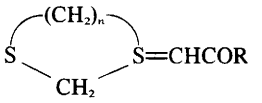


2,2-di-t-butyloxiran in quantitative yield. With 4-t-butylcyclohexanone the carbanion afforded a 25:45 mixture of the isomeric alcohols, with that from axial attack of the carbanion dominating, which were converted into the corresponding oxirans.

Numerous examples have been reported of the reaction of sulphonium ylides with $\alpha\beta$-unsaturated carbonyl compounds whereby the ylide carbanion attacks the β-carbon and the sulphonium group is displaced to afford a cyclopropane. Gruetzmacher[71] reported numerous examples, and Gosselck *et al.*[53,72] reported ordinary addition reactions with the unusual ylides (62) and (63). The *trans*-isomers result from most reactions.[67] The reaction of (64) with methyl acrylate afforded mainly the expected cyclopropane

[69] B. M. Trost and H. C. Arndt, *J. Org. Chem.*, 1973, **38**, 3140.
[70] J. R. Shanklin, C. R. Johnson, J. Ollinger, and R. M. Coates, *J. Amer. Chem. Soc.*, 1973, **95**, 3429.
[71] R. R. Gruetzmacher, *Diss. Abs.*, 1973, **34B**, 134.
[72] M. Hetschko and J. Gosselck, *Tetrahedron Letters*, 1972, 1691.

(*trans*:*cis* = 90:10) in 54% yield, but a major by-product was (65), which undoubtedly resulted from proton transfer in the intermediate to re-form a new substituted ylide (66), which added to another molecule of methyl acrylate.[73] A similar proton migration occurred in the reaction of diethylsulphoniumcyanomethylide with vinyltetramethylenesulphonium bromide, but in this instance a second addition did not occur and the elimination took place directly to afford a sulphonium salt (67).[52] Even though stabilized



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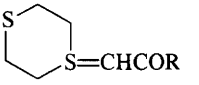

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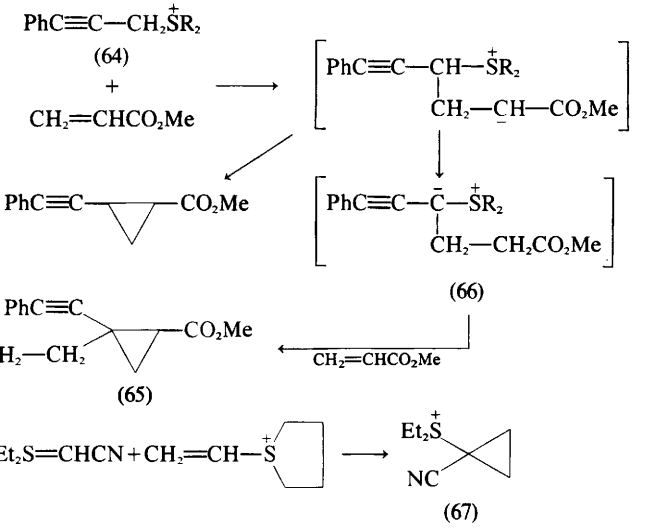


(64)

(65)

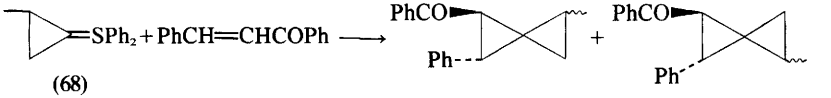
(66)

(67)

ylides are more reactive with $\alpha\beta$-unsaturated carbonyls to form cyclopropanes than they are with carbonyls to form oxirans, too much stabilization will preclude even the former reaction, as evidenced by the fact that dimethylsulphonium(phenylthio)methylide would add to dibenzoylethylene but that dimethylsulphonium(phenylthio)phenacylide would not.[48] Use of diphenylsulphoniumcyclopropylide (1) in the addition reaction afforded spiropentanes in good yield. The reaction of a *cis–trans* mixture of the substituted cyclopropylide (68) with ω-benzoylstyrene afforded a mixture of spiropentanes in about the same *cis*:*trans* ratio.[11] Diphenylsulphoniumisopropylide reacted with the diene ester (69) to give a mixture of $\alpha\beta$-adduct and $\gamma\delta$-adduct. The ratio of the two adducts was 1:4 in DME but 2:1 in THF.

[73] M. Yoshimoto, N. Ishida, and Y. Kishida, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2593.

The same ylide with the open-chain diene ester (70) afforded a 1:4 mixture of the αβ-adduct and the γδ-adduct in both THF and DME. It was suggested that γδ-addition was the normal course of events unless special factors,



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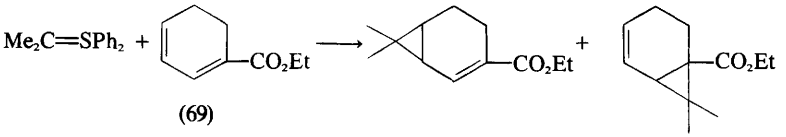

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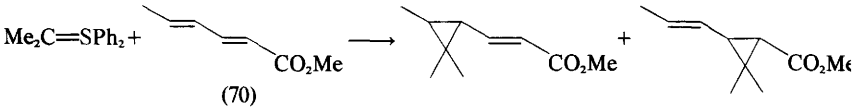
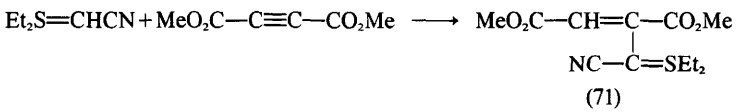


(70)

such as a rigid geometry in (69), favouring complex formation, led to αβ-adduct dominance.[10] The powerful solvating effect of DME would be expected to counterbalance the complexation in the case of (69), thus maintaining the normal dominance of the γδ-adduct.

Additions to conjugated alkynes proceed by initial carbanion addition to the triple bond followed by proton migration to form a new substituted ylide. Thus, diethylsulphoniumcyanomethylide with dimethyl acetylenedicarboxylate afforded the olefinic ylide (71), but the same ylide with an acetylenic sulphonium salt afforded a conjugated ylide (72) with two



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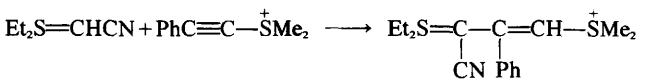
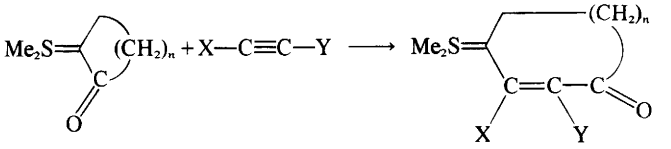


(72)

potential carbanionic sites.[52] Higo *et al.*[74] have published details of the reaction, discussed in Volume 2 of these Reports,[75] between β-keto cyclic ylides (73) and conjugated alkynes to effect a ring expansion by overall insertion of the alkyne group, probably *via* acyl transfer.

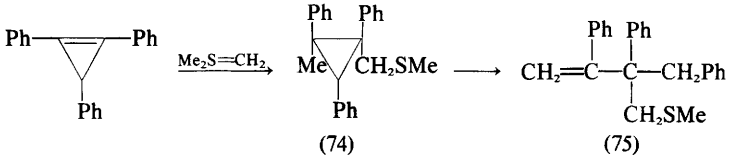
Three separate reactions with the cyclopropene system have been reported. Dimethylsulphonium-methylide with triphenylcyclopropene

[74] M. Higo, T. Sakashita, M. Toyoda, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 1972, **45**, 250.
[75] Ref. 40, p. 303.

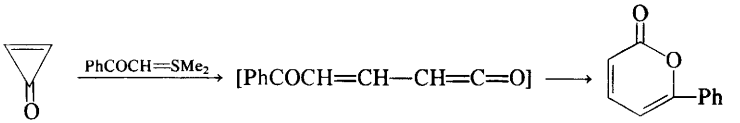


(73)

afforded (75), with the proposed mechanism involving carbanion attack at the olefin group, methyl transfer to form (74), then ring opening.[76] Dimethylsulphoniumphenacylide with cyclopropenone afforded (76), probably *via* attack at the double bond, ring opening to a keten, and cyclization.[77]

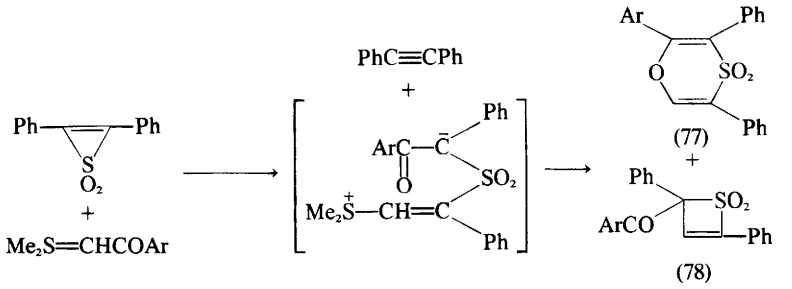


(74) (75)



(76)

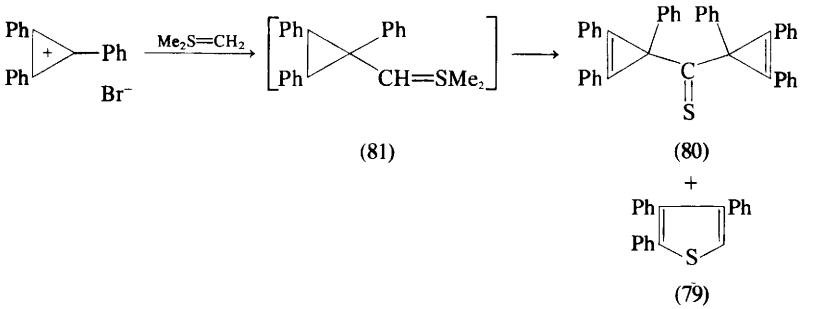
This is analogous to the reaction reported by Hayasi and Nozaki.[78] Dimethylsulphonium(*p*-methyl)phenacylide reacted with diphenylthiiren dioxide to afford mainly diphenylacetylene and a mixture of sulphurous products, mainly (77) and (78), which may have been formed by carbanion attack at the double bond, acyl transfer, ring opening, and then ring closure of an enolate ion.[79]



Ar = *p*-tolyl

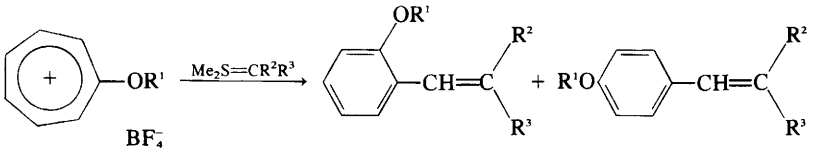
[76] O. A. Nesmeyanova, G. A. Kudryavtseva, and O. S. Chizdov, *Doklady Akad. Nauk S.S.S.R.*, 1973, **210**, 862.
[77] R. Breslow, M. Oda, and J. Pecoraro, *Tetrahedron Letters*, 1972, 4415.
[78] Y. Hayasi and H. Nozaki, *Tetrahedron*, 1971, **27**, 3085.
[79] Y. Hayasi, H. Nakamura, and H. Nozaki, *Bull. Chem. Soc. Japan*, 1973, **46**, 667.

The reaction of dimethylsulphonium-methylide with triphenylcyclopropylium bromide produced a 1:1.7 ratio of the thiophen (79) and the thioketone (80).[80] Formation of a new ylide (81) as an intermediate was proposed, with ring expansion to an *SS*-dimethylthiophen and loss of ethane



(81) (80) + (79)

to account for (79), and attack by a second molecule of cyclopropylium ion and loss of ethane from a resultant ylide to account for (80). The same reaction but with 1-methoxy-1,2,3-trimethylcyclopropene gave a 35% yield of the analogous thiophen.[80] Sugimura *et al.*[81,82] allowed disubstituted stabilized ylides to react with tropylium ion and alkoxytropylium ion (Scheme 2), producing substituted styrenes in each case. Attack of the ylide



Scheme 2

carbanion at C-2 or C-3 would lead to the *ortho*-substituted styrene, while attack at C-4 would afford the *para*-isomer. Both isomers usually were obtained, with the *ortho* usually dominating in the cases studied.

Van Loock *et al.*[83] have published full details of the reaction of sulphonium ylides with azides, a reaction discussed in Volume 2.[84]

3 Oxysulphonium Ylides

Synthesis and Properties.—Oxysulphonium ylide chemistry still suffers from the lack of a variety of simple, high-yield syntheses of the precursor

[80] B. M. Trost, R. C. Atkins, and L. Hoffmann, *J. Amer. Chem. Soc.*, 1973, **95**, 1285.
[81] Y. Sugimura, K. Iino, I. Kawamoto, and Y. Kishida, *Chem. Letters*, 1972, 1085.
[82] Y. Sugimura, K. Iino, I. Kawamoto, and Y. Kishida, *Tetrahedron Letters*, 1972, 4985.
[83] E. Van Loock, G. L'Abbe, and G. Smets, *Tetrahedron*, 1973, **28**, 3061.
[84] Ref. 40, p. 305.

oxysulphonium salts. Kobayashi *et al.*[85] further explored, without success, the possibility of oxidizing sulphonium salts to oxysulphonium salts. They also were unable to discover a general method for alkylating sulphoxides on sulphur. However, later they did report details of the mercuric-iodide-catalysed *S*-methylation with methyl iodide.[86]

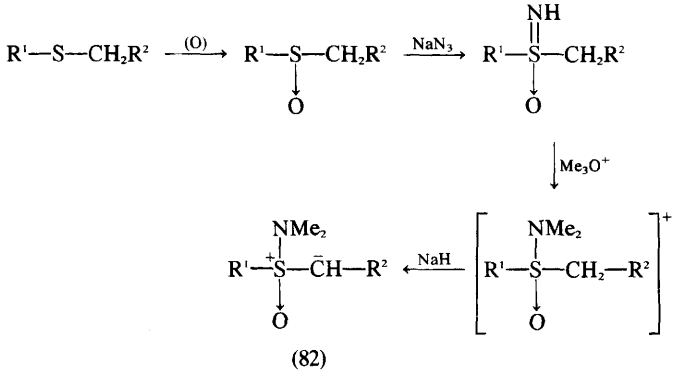
Full details now have appeared regarding the reactions of diazo-compounds with sulphoxides to form oxysulphonium ylides,[87] a method analogous to that employed for sulphonium ylides. The reaction, in the presence of cuprous cyanide, seems effective only with disubstituted diazomethane in which both substituents are strongly electron-withdrawing. Dimethyloxysulphoniumcyclopentadienylide was prepared by this method from diazocyclopentadiene and DMSO.

Additional examples have been reported by C. R. Johnson and his students of the only general method known to date for the preparation of a variety of oxysulphonium ylides. The sequence commences with a sulphide and proceeds by oxidation to sulphoxide, conversion into sulphoximine with sodium azide, exhaustive methylation with trimethyloxonium salt, and finally proton removal, usually with sodium hydride, to afford the ylide (82). Overall yields generally are high so that sulphide-to-ylide yields may be 50—60%. Details have been reported for the preparation of a methylide (82; R^1=Me, R^2=H),[88] an ethylide (82; R^1=*p*-tolyl, R^2=Me),[89] and a series of cyclic ylides (83).[90] In addition, by starting the reaction series with an optically active sulphoxide, readily available from the reaction of a Grignard reagent with a menthyl sulphinate,[86] or by resolution of the intermediate sulphoximine before proceeding further, optically active oxysulphonium ylides have become readily available.[91]

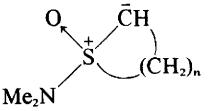
Whereas sulphonium phenacylides are thermally decomposed to cyclopropanes, an oxysulphonium phenacylide gave (84) when heated in the presence of cupric sulphate.[92] Heating (85) in the absence of any catalysts gave (86), probably *via* a 2,3-sigmatropic rearrangement and sulphoxide elimination to afford a diene, which was attacked at the α,β-bond by a second molecule of ylide.[93]

Reactions of Oxysulphonium Ylides.—The reaction of oxysulphonium ylides with carbonyl compounds to form oxirans remains an important synthetic tool. C. R. Johnson and his students have published details of many of the

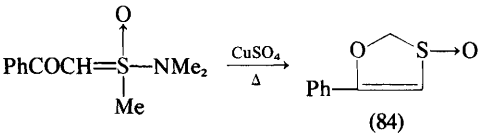
[85] M. Kobayashi, K. Kamiyama, H. Minato, Y. Oishi, Y. Takada, and Y. Hattori, *Bull. Chem. Soc. Japan*, 1972, **45**, 3703.
[86] K. Kamiyama, H. Minato, and M. Kobayashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 3895.
[87] F. Dost and J. Gosselck, *Chem. Ber.*, 1972, **105**, 948.
[88] C. R. Johnson and P. E. Rogers, *J. Org. Chem.*, 1973, **38**, 1793.
[89] C. R. Johnson and E. R. Janiga, *J. Amer. Chem. Soc.*, 1973, **95**, 7692.
[90] C. R. Johnson and L. J. Pepoy, *J. Org. Chem.*, 1972, **37**, 671.
[91] C. R. Johnson and C. W. Schroeck, *J. Amer. Chem. Soc.*, 1973, **95**, 7418.
[92] C. R. Johnson and P. E. Rogers, *J. Org. Chem.*, 1973, **38**, 1798.
[93] Y. Tamura, T. Miyamoto, T. Nishimura, and Y. Kita, *Tetrahedron Letters*, 1973, 2351.



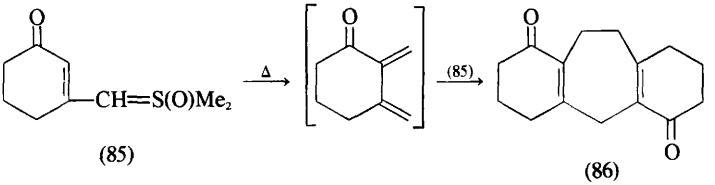
(82)



(83)

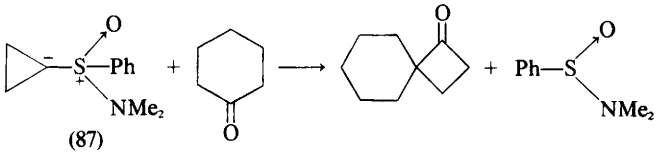


(84)

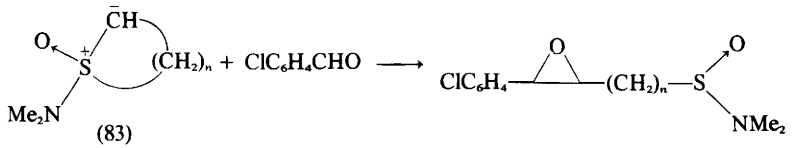


(85) (86)

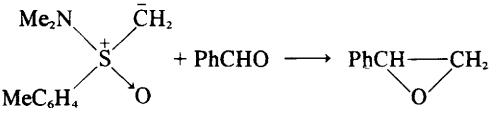
reactions of dimethylamino-oxysulphonium ylides (82) with carbonyl compounds. For the methylide[88] and ethylide,[89] yields were in the 60% range, with aldehydes and ketones being equally reactive. With 4-t-butylcyclohexanone, both the methylide and the ethylide afforded the oxiran resulting from exclusive equatorial attack of the carbanion, the same geometry as exhibited by dimethyloxysulphonium-methylide. The cyclopropylide (87) would not react with benzaldehyde or acetophenone, but it did react with cyclohexanone to afford the cyclobutanone, presumably *via* the intermediacy of the oxiran.[89] The cyclic ylide (83) reacted with *p*-chlorobenzaldehyde to afford good yields of the oxirans in which the *trans*-isomer dominated, exclusively with the five-membered-ring ylide ($n = 3$) but only 66% with the seven-membered ring ($n = 5$).[90] The reaction of the optically active ylide (88)



(87)



(83)



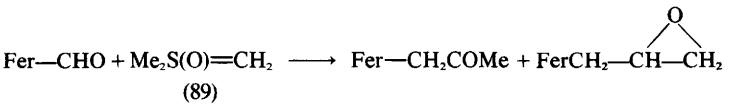
(88)

with benzaldehyde gave styrene oxide in 60% yield, with 20% optical purity.[91]

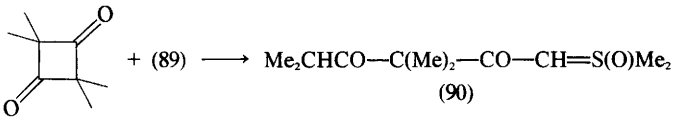
Several unusual examples of the reaction of oxysulphonium ylides with carbonyl compounds have been reported. With ferrocenaldehyde the ylide (89) afforded a mixture of ferrocenylacetone (27%) and 2-ferrocenylmethyloxiran (18%), the former probably from rearrangement of the latter. The oxiran was probably formed from ferrocenylacetaldehyde, a rearrangement product from the initially formed but unstable 2-ferrocenyloxiran.[55] β-Diketones apparently underwent normal initial attack by (89) but the intermediate betaine underwent ring opening to form a new ylide (90).[94] Whereas thioketones with no α-hydrogen underwent normal thiiran formation, enolizable thioketones underwent methylation.[95] The ylide (89) served as a base to remove the proton but the conjugate acid of the ylide, trimethyloxysulphonium ion, then served as a good methylating agent. The same situation prevailed in the reaction with dithio-esters.[95]

Dimethyloxysulphonium-methylide has long been known to add to the olefinic group of αβ-unsaturated carbonyl compounds, and additional examples have been reported.[66,96] Cyclopropane formation also has been reported from stabilized oxysulphonium ylides such as (85)[97] and those carrying two stabilizing groups on the methylide carbon.[87] The dienone (91) underwent double addition with (89) to form the *syn*-isomer only,[98] but the

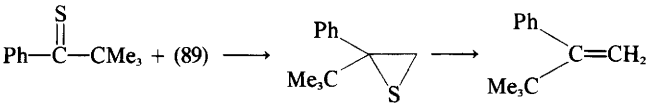
[94] E. Lund, G. E. Palmer, and R. P. Welland, *J.C.S. Chem. Comm.*, 1972, 136.
[95] D. Lecadet, D. Paquera, and A. Thuillier, *Compt. rend.*, 1973, **276**, C, 875.
[96] J. M. Donnelly, P. Bennett, S. O'Brien, and J. O'Grady, *Chem. and Ind.*, 1972, 500.
[97] J. P. Marino and T. Kaneko, *Tetrahedron Letters*, 1973, 3971.
[98] G. L. Buchanan, R. A. Raphael, and R. Taylor, *J.C.S. Perkin I*, 1973, 373.

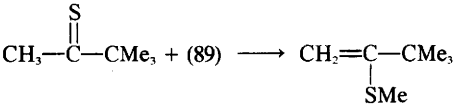


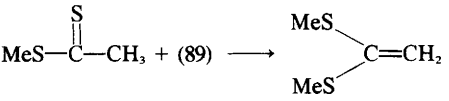
(89)

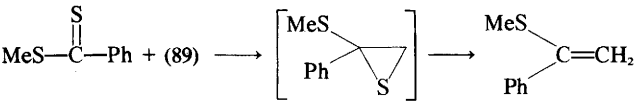


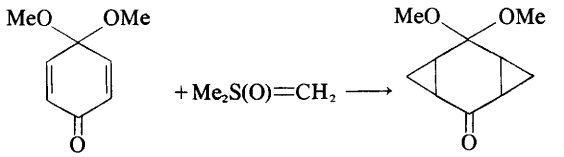
(90)



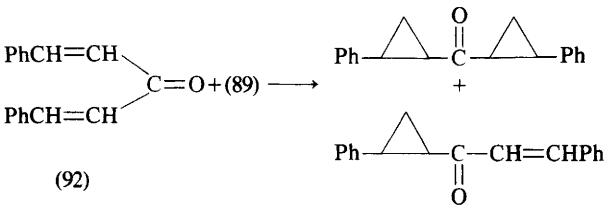








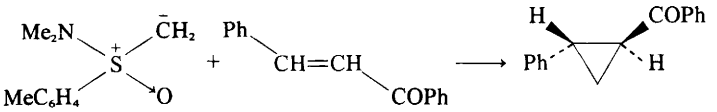
(91) (89)



(92)

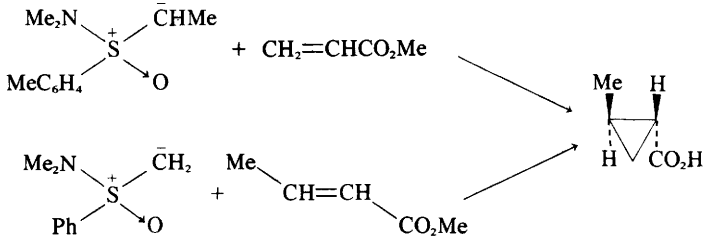
open-chain analogue (92) underwent single or double addition depending on the molar ratio of reactants.[66]

The dimethylamino-oxysulphonium ylides (82) also react with conjugated double bonds to form cyclopropanes. The methylide,[88] ethylide,[89] and isopropylide[89] all gave good yields, with the *trans*-isomers dominating. The methylide with dimethyl maleate gave the *trans*-adduct only when one mole of ylide was used. When two moles of ylide were used the unreacted olefin that could be recovered from the reaction had half isomerized to dimethyl fumarate, indicating that the olefin addition by ylide was reversible.[99] The cyclopropylide (87) also reacted with conjugated olefins to afford spiropentanes in good yield.[89] The cyclic ylides (83) afforded cyclopropanes, as



(88)

expected from similar reactions.[90] The reaction of optically active (*R*)-methylide (88) with *trans*-ω-benzoylstyrene afforded (+)(*S*,*S*)-1-phenyl-2-benzoylcyclopropane in 94% yield and with 35.3% optical purity.[91] Replacement of the dimethylamino-group of the ylide with a diethylamino-group and repeating the reaction gave a lower optical purity, but replacement of the *p*-tolyl group with a mesityl group slightly increased the optical purity of the product. Optically active *trans*-2-methylcyclopropanecarboxylic acid was prepared (Scheme 3) by two routes.[91] The first involved the reaction of

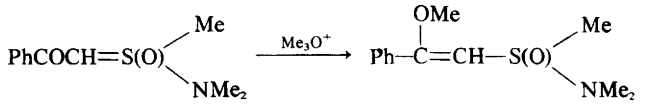


Scheme 3

an ethylide with methyl acrylate and the second involved the reaction of a methylide with methyl methacrylate. The first route gave product with 43% optical purity and the second gave product with 12% optical purity.

In one of the few alkylations known for oxysulphonium ylides, the phenacylide (93) underwent *O*-alkylation with trimethyloxonium ion to give a mixture of stereoisomers.[92] Schmidbaur and Kapp[100] have published

[99] C. R. Johnson, C. W. Schroeck, and J. R. Shanklin, *J. Amer. Chem. Soc.*, 1973, **95**, 7424.
[100] H. Schmidbaur and W. Kapp, *Chem. Ber.*, 1972, **105**, 1203.



(93)

further details of the reaction of (89) with silyl chlorides, demonstrating the ability to replace all chlorines with ylide functions. The monosubstituted silane (94) could be obtained as a crystalline solid, m.p. 25 °C.

$$\underset{(89)}{Me_2S(O){=}CH_2} + Me_3SiCl \longrightarrow \underset{(94)}{Me_2S(O){=}CHSiMe_3}$$

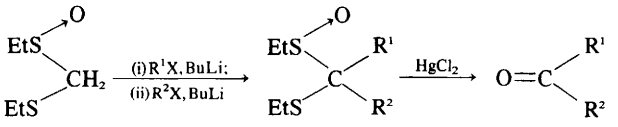
$$\underset{(89)}{Me_2S(O){=}CH_2} + SiCl_4 \xrightarrow{NaH} Si[CH{=}S(O)Me_2]_4$$

Oxysulphonium ylides react with a variety of additional unsaturated functions. Reaction with nitrosobenzene would be expected to form oxaziranes, but instead the isomeric nitrones were obtained,[87] as is well known for sulphonium ylides. Dimethylamino-oxysulphonium ylides react with conjugated alkynes to form new ylides by proton transfer,[92] the same as previously reported for (89) and sulphonium ylides. A number of additional examples of acylation reactions, with acyl halides, anhydrides, sulphonyl halides, and isocyanates, have been reported and have resulted in the formation of new ylides carrying acyl substituents.[54,92] Dimethyloxysulphonium-methylide (89) has been found to react with pyrylium salts and thiopyrylium salts to afford benzenes by replacement of the heteroatom with a methinyl group from the ylide molecule. The mechanism was suggested to involve ring opening by ylide attack, followed eventually by oxyanion transfer to sulphur and ejection of dimethyl sulphone.[101] If such were the case, it would be the first case of Wittig-reaction-like behaviour by a sulphonium ylide.

4 Sulphinyl Ylides

Sulphinyl ylides, the carbanions obtained from sulphoxides by proton abstraction, continue to be of limited use in organic synthesis but of increasing interest in stereochemical studies. The thioacetal monosulphoxide (95) could be dialkylated in the presence of n-butyl-lithium, then cleaved with $HgCl_2$ to afford a ketone. The monoalkylation product could be intercepted readily, thus permitting the effective dialkylation of C=O and a novel 'initiated' synthesis of ketones.[102] The stereochemistry of the methylation of 4-t-butyl-1-thiacyclohexane oxide depends on the orientation of the sulphoxide oxygen. Using methyl iodide or trideuteriomethyl iodide in the

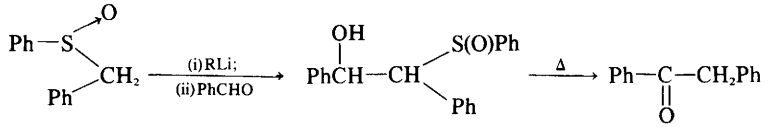
[101] Y. Tamura, K. Sumato, and M. Ikeda, *Chem. and Ind.*, 1972, 498.
[102] J. E. Richman, J. L. Herman, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 3267.



(95)

presence of n-butyl-lithium in THF, the axial sulphoxide afforded mainly axial methylation, and the equatorial sulphoxide afforded equatorial methylation.[103,104] These same preferences held true also when the α-carbons already carried a methyl group, but substitution occurred preferentially on a secondary carbon rather than on a tertiary carbon. These observations are consistent with the '*gauche* effect' proposal of Wolfe,[2] which would predict preferential formation of the sulphinyl carbanion which is *cis* to the lone pair on sulphur (*i.e.* axial sulphoxide has equatorial lone pair and leads to dominant axial methylation, and *vice versa*). Methylsulphinyl carbanion is a typical nucleophile in that reaction with (−)-menthyl toluene-*p*-sulphinate led to sulphination of the carbanion with inversion of configuration at sulphinate sulphur, indicating that the mechanism of the reaction probably was S_N2.[105]

Kingsbury,[106] using phenyl benzyl sulphoxide carbanion generated with organolithium reagents, has shown that condensation of sulphinyl carbanions with benzaldehyde leads predominately to the *threo*-isomer of the 2-sulphinylcarbinol (96). Pyrolysis of the carbinol afforded a ketone,

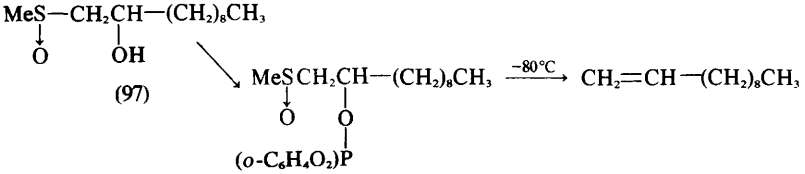


(96)

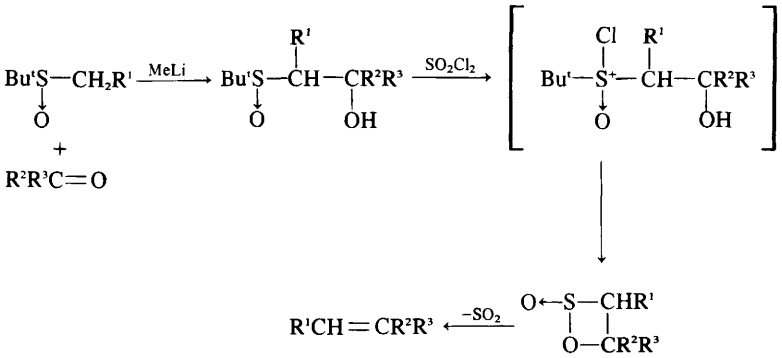
presumably by elimination of PhS(O)H, with the overall result being the replacement of the aldehyde proton with the carbanion portion of the sulphinyl carbanion. The reaction of dimsylsodium with cyclopentanone led to a complex sequence of reactions rather than simple addition.[107] The reaction of optically active (*R*)(+)-methyl *p*-tolyl sulphoxide with benzaldehyde in the presence of diethylamide afforded a mixture of dimers, which were separated by chromatography. Cleavage of the sulphur–carbon bonds with Raney nickel afforded (*S*)(−)-1-phenylethanol and (*R*)(+)-1-phenylethanol, both of very high optical purity.[108] Thus, the readily available optically active sulphoxides can be used for optical induction.[109]

[103] S. Bory, R. Lett, B. Moreau, and A. Marquet. *Tetrahedron Letters*, 1972, 4921.
[104] S. Bory and A. Marquet, *Tetrahedron Letters*, 1973, 4155.
[105] N. Kunieda, J. Nokami, and M. Kinoshita, *Chem. Letters*, 1973, 871.
[106] C. A. Kingsbury, *J. Org. Chem.*, 1972, **37**, 102.
[107] W. T. Comer and D. L. Temple, *J. Org. Chem.*, 1973, **38**, 2121.
[108] G. Tsuchihashi, S, Iriuchijima, and M. Ishihashi, *Tetrahedron Letters*, 1972, 4605.
[109] G. Tsuchihashi, S. Iriuchijima, and K. Maniwa, *Tetrahedron Letters*, 1973, 3389.

Two groups have developed means of extending the condensation of sulphinyl carbanions with carbonyl compounds, such that it becomes an alternative to the Wittig reaction, through conversion of the initial carbinol adducts into olefins. Dimsyl-lithium with benzophenone gave the initial adduct as a lithium salt, which, when treated with a chlorophosphite at −80 °C, afforded a 91% yield of diphenylethylene.[110] The isolated initial adduct (97) could be converted into undecene by reaction first with



methyl-lithium and then the phosphite. The same overall effect was accomplished by chlorinating the carbinol with SO_2Cl_2 or *N*-chlorosuccinimide (Scheme 4), forming a sultine intermediate, and then eliminating SO_2.[111]



Scheme 4

In a wide variety of examples the yields ranged from 53 to 93% under rather mild conditions. The reaction was shown to involve a *cis*-elimination of the hydroxy- and sulphinyl groups.

Investigations of the stereochemistry of proton exchange at the α-carbon of sulphoxides continue to produce conflicting results. For a detailed discussion, readers are referred to the chapter in this Report discussing sulphoxides. Suffice it to mention here that there seems to be general agreement that protonation of α-lithiosulphoxides occurs with retention of configuration.[112–115] However, selectivity in removal of the pro-*R* or the

[110] I. Kuwajima and M. Uchida, *Tetrahedron Letters*, 1972, 649.
[111] J. Jung, N. K. Sharma, and T. Durst, *J. Amer. Chem. Soc.*, 1973, **95**, 3420.
[112] M. B. D'Amore and J. I. Brauman, *J.C.S. Chem. Comm.*, 1973, 398.
[113] R. Viau and T. Durst, *J. Amer. Chem. Soc.*, 1973, **95**, 1346.
[114] K. Nishihata and M. Nishio, *J.C.S. Perkin II*, 1972, 1730.
[115] K. Nishihata and M. Nishio, *Tetrahedron Letters*, 1972, 4839.

pro-*S* proton from sulphoxides is a matter of continuing disagreement.[113,114] There also seems agreement that the *gauche* relationship of the carbanion and the lone pair on sulphur is the most stable configuration.[113,114,116]

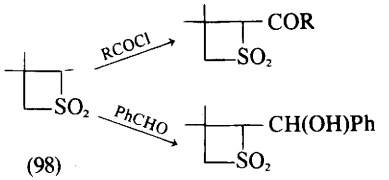
5 Sulphonyl Ylides

Sulphonyl ylides usually are obtained by proton removal from a sulphone. Jarvis and Saukaitis[117] have found that the reaction of an α-bromo- or α-chloro-sulphone with triphenylphosphine resulted in abstraction of the halogen and formation of the sulphonyl ylide as an intermediate, which was trapped by protons from the water present. Benzyl phenyl sulphone was converted into the αα-dilithio-carbanion by treatment with n-butyl-lithium in THF–heptane,[118] and Bosworth and Magnus[119] have reported that a bicyclic phenylsulphone, upon treatment with n-butyl-lithium and then D_2O, was converted into the αα-dideuteriosulphone, and that it was not possible to obtain the mono-deuteriosulphone by that method. Kaiser *et al.*[120] have found that using sodium, lithium, or potassium amide with dimethyl sulphone or with dibenzyl sulphone resulted in formation of the αα′-dicarbanion, as detected by deuteriation or by reaction with benzophenone. Amel and Marek[121] determined the pK_a's of a series of phenylphenacyl sulphones and concluded that the sulphone group provided less stabilization for the phenacylide than did a sulphonium group. The ρ value for substituents on the phenacyl portion was similar to that obtained for sulphonium, phosphonium, arsonium, and pyridinium phenacylides.

The sulphonyl carbanion (98) could be acylated with acyl chlorides.[122] Similar to an earlier report, phenylsulphonylcyclopropylide was arylated by both acridine and anthracene to afford the 9-cyclopropyl derivatives.[123] The acetylenic carbanion (99) was dialkylated by methyl acrylate, and a Dieckmann condensation occurred in the course of the reaction.[124] Apparently the initial carbanionic intermediate resulting from the Michael-type addition underwent a proton transfer to re-form a sulphonyl ylide, which carried out a second addition.

Sulphonyl carbanions usually effect a simple addition to carbonyl compounds to afford carbinols, as exemplified by the reaction of (98) with benzaldehyde.[122] The αα′-dicarbanions of dimethyl sulphone and dibenzyl sulphone reacted with two moles of benzophenone in a similar manner.[120]

[116] R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *J. Amer. Chem. Soc.*, 1972, **94**, 8795.
[117] B. B. Jarvis and J. C. Saukaitis, Abstracts of the 163rd meeting, American Chemical Society, 1972, Organic Division, paper no. 91.
[118] V. Pascali, N. Tangari, and A. Umani-Ronchi, *J.C.S. Perkin I*, 1973, 1166.
[119] N. Bosworth and P. D. Magnus, *J.C.S. Perkin I*, 1973, 2319.
[120] E. M. Kaiser, R. D. Beard, and C. R. Hauser, *J. Organometallic Chem.*, 1973, **59**, 53.
[121] R. T. Amel and P. J. Marek, *J. Org. Chem.*, 1973, **38**, 3513.
[122] J. P. Marino and D. P. Hesson, Abstracts of the 163rd meeting, American Chemical Society, 1972, Organic Division, paper no. 89.
[123] H. Nozaki, T. Nishimura, and Y. Yamamoto, *Bull. Chem. Soc. Japan*, 1972, **45**, 301.
[124] M. Yoshimoto, N. Ishida, and Y. Kishida, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2137.



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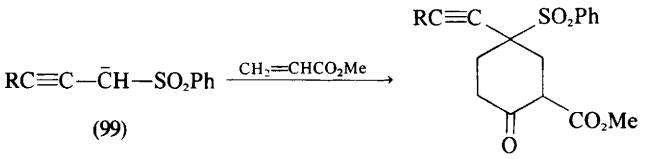
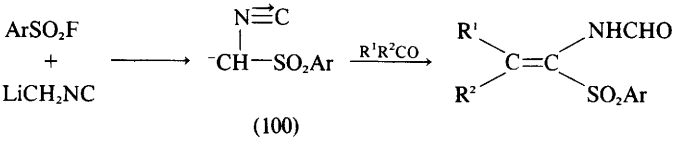
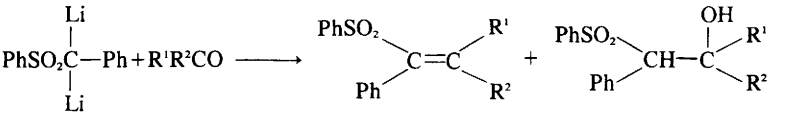


(99)

The unusual isocyanide (100) afforded an olefin directly upon reaction with a series of ketones.[125] In a similar overall reaction, the dilithio-carbanion of phenylbenzyl sulphone reacted with aldehydes or ketones to afford a mixture of olefin and carbinol. Repeating these reactions, but in the



(100)



presence of MgI_2, afforded 50—80% yields of the olefins,[118] the overall effect of the reactions being a dehydration. The phenylsulphonyl group could be removed from these olefins in high yield by treatment with aluminium amalgam.[126]

6 Sulphenes

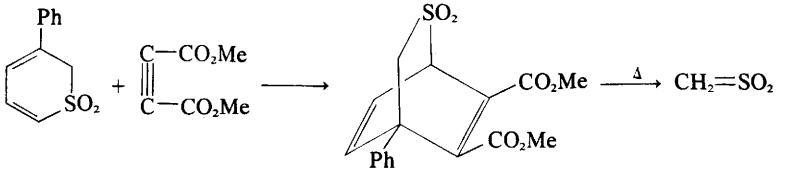
Sulphene chemistry has been reviewed.[4] No sulphene has yet been isolated and purified, but evidence continues to accrue that sulphenes do have a discrete existence. Based on chemical evidence that the carbon end of the sulphene bond C=SO_2 carries a negative charge and acts as a nucleophilic site, the usual approach toward obtaining a stable sulphene has been to attach electron-withdrawing groups to the carbon atom with a hope of dispersing that charge. To date this approach has been unsuccessful. Semi-empirical MO calculations by Snyder[127] now have indicated that the

[125] U. Schollkopf, R. Schroder, and E. Blume, *Annalen*, 1972, **766**, 130.
[126] V. Pascali and A. Umani-Ronchi, *J.C.S. Chem. Comm.*, 1973, 351.
[127] J. P. Snyder, *J. Org. Chem.*, 1973, **38**, 3965.

negative charge on carbon could be dissipated by attachment of electron-donating groups, and that such groups also would reduce the positive charge on sulphur. Both of these charge-density changes would be in a direction to make sulphenes more like sulphines, many of which are stable, isolable species. The well-known thiourea dioxide may be an example verifying Snyder's prediction. The calculated charge densities on sulphene are carbon −0.21 and sulphur +1.2. For thiourea dioxide the calculated densities are carbon +0.65 and sulphur +0.91. The π-bond energy of sulphene has been estimated at 35±5 kcal mol^{-1}.[128]

One of the first methods reported for the preparation of sulphenes was the reaction of sulphonyl chlorides with triethylamine, and a major piece of evidence for specifically sulphene existence was the fact that under such reaction conditions, and in the presence of a deuterium source, only one deuterium atom was incorporated, thereby ruling out a regular exchange reaction. King *et al.*[129] now have reported that in the presence of an unhindered base such as quinuclidine there is a significant amount of di- and tri-deuteriated product formed, and that the amount of such substances decreases as the steric requirements of the nitrogen base are increased. However, it was demonstrated that even in the presence of unhindered bases a sulphene could be trapped in good yield by well-known reactions. On this basis, the authors proposed that the first step in such reactions was sulphene formation, followed by protonation of the sulphene or an amine complex thereof. Christensen[130] found that phenylsulphene could be formed by the reaction of *p*-nitrophenyl phenylsulphonate with potassium t-butoxide.

Two new thermal preparations of sulphenes have been reported, using two different leaving groups. Heating methylsulphonylphthalimide to 600 °C *in vacuo* and bleeding the vapours into a hot mixing zone into which ethylamine was introduced through a capillary gave a 36% yield of *N*-ethyl methylsulphonamide and a quantitative yield of phthalimide.[131] Sulphene also could be trapped, but in lower yield, with methanol, but the reaction also produced formaldehyde as a by-product, probably from the decomposition of sulphene. The bicyclic sulphone (101) afforded sulphene when

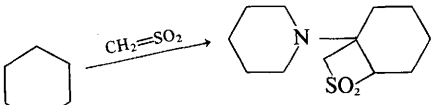


(101)

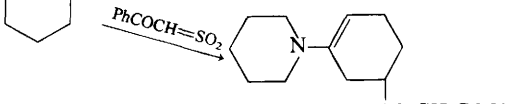
[128] J. F. King and E. G. Lewars, *Canad. J. Chem.*, 1973, **51**, 3044.
[129] J. F. King, E. A. Luinstra, and D. R. K. Harding, *J.C.S. Chem. Comm.*, 1972, 1313.
[130] L. W. Christensen, *Synthesis*, 1973, 534.
[131] W. J. Mijs, J. B. Reesink, and U. E. Wiersum, *J.C.S. Chem. Comm.*, 1972, 412.

heated to 220 °C, as evidenced by trapping experiments.[128,132] When no trapping agent was present, most of the sulphur could be accounted for in the form of sulphur dioxide, but the methylene component could not be accounted for.

Whereas sulphene itself reacts with vinyl amines to afford cyclic adducts [*e.g.* (102)[128]], benzoylsulphene sulphonates the vinyl amine in good yield to afford (103).[133] A common type of zwitterionic intermediate probably is

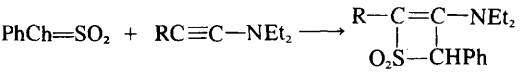


(102)

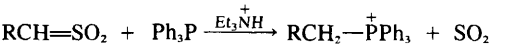


(103)

involved in both instances, the result of olefin attack on the electrophilic SO_2 group. There have been two reports that phenylsulphene reacts with amino-alkynes to afford the cyclic dioxides (104).[130,134] In the presence of



(104)



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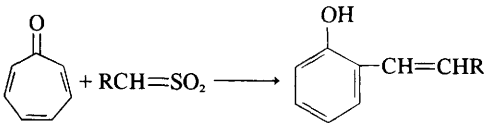


(106)

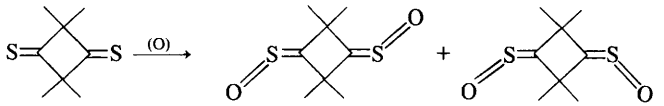
triethylamine, phenylmethylsulphonyl chloride, methanesulphonic anhydride, and 2,4-dinitrophenyl phenylmethanesulphonate all reacted with triphenylphosphine to afford the corresponding phosphonium salt (105). It

[132] J. F. King and E. G. Lewars, *J.C.S. Chem. Comm.*, 1972, 700.
[133] O. Tsuge, S. Iwanami, and S. Hagio, *Bull. Chem. Soc. Japan*, 1972, **45**, 237.
[134] M. E. Kuehne and H. Linde, *J. Org. Chem.*, 1972, **37**, 1846.

was proposed that sulphene formation was involved in each reaction, with the triphenylphosphine adding to the sulphene and displacing SO_2 to afford the phosphonium ylide, which was protonated by the conjugate acid of the amine.[135] Sulphenes have been reported to react with tropone to afford an adduct which rearranged on heating to an *o*-hydroxystyrene (106).[136]

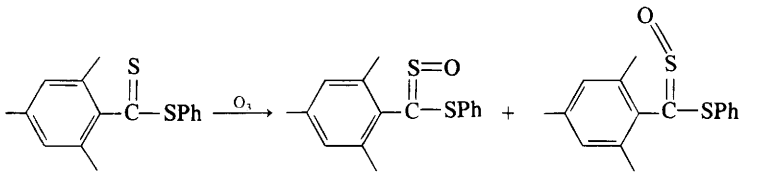
7 Sulphines

To date, sulphines have been prepared by two methods, the dehydrohalogenation of sulphinyl chlorides or the oxidation of thiocarbonyl compounds, but neither has been successful for the preparation of aliphatic sulphines. Zwanenburg *et al.*[137] now have reported that some non-enolizable thiones, such as adamantanethione and the cyclobutanedithione (107), could be



(107) a. *anti* b. *syn*

oxidized to sulphines with *m*-chloroperbenzoic acid. Oxidation of thioketones with ozone is an effective preparative method only if the thioketone is hindered. Thus, thiobenzophenone afforded benzophenone but mesityl phenyl thioketone afforded a 61% yield of the two geometric isomers of the sulphine. Phenyl dithiobenzoate afforded the thiol ester but phenyl dithiomesitoate afforded a 41% yield of the sulphine (108) in a 65:35

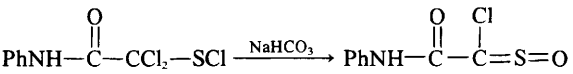


(108)

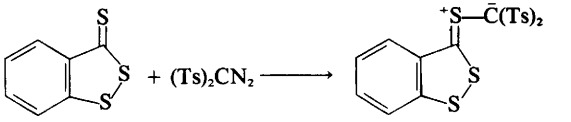
ratio of *syn*:*anti*-isomers.[138] Interestingly, mesityl dithiobenzoate did afford a 23% yield of sulphine. It was shown that diphenylsulphine reacted readily with ozone to afford benzophenone, leading to the conclusion that the synthetic usefulness of the ozone oxidation of thiones is limited by the ease with which unhindered sulphines are further oxidized to ketones and SO_2. In the first example of a new reaction, methyl diphenylmethanesulphinate was

[135] J. F. King, E. G. Lewars, and L. J. Danks, *Canad. J. Chem.*, 1972, **50**, 866.
[136] W. E. Truce and C. I. Li, Abstracts of the 166th meeting, American Chemical Society, 1973, Organic Division, paper no. 105.
[137] B. Zwanenburg, A. Wagenaar, L. Thijs, and J. Strating, *J.C.S. Perkin I*, 1973, 73.
[138] B. Zwanenburg and W. A. J. Janssen, *Synthesis*, 1973, 617.

converted into diphenylsulphine by treatment with sodium methoxide.[139] An oxidative dehalogenation was used to prepare the α-chloro-sulphine (109).[140] In an interesting reaction, diazo(ditosyl)methane reacted with benzotrithione to afford (110), a structure isoelectronic with a sulphine and with sulphur di-imines.[141]



(109)



(110)

Aromatic sulphines are stable isolable compounds. Through semi-empirical MO calculations, Snyder[127] determined the charge density on carbon to be −0.03 and that on sulphur to be +0.51. Tangerman *et al.*[142,143] examined the mass spectra and electron-impact-induced rearrangements of sulphines. The *syn*- and *anti*-isomers of (109) could be detected by i.r. spectroscopy, especially the hydrogen bonding of the NH group with the sulphinyl oxygen.[140] Tangerman and Zwanenburg[144] were able to assign the configuration of the S=O group in a series of diphenylsulphines by use of Eu(dpm)$_3$ as a n.m.r. shift reagent for monitoring the *ortho*- or *meta*-protons. The same results were obtainable using benzene and monitoring solvent-induced shifts in the n.m.r. spectra. By comparison of the n.m.r. chemical shift of the methyl group in *o*-methyl-thiobenzophenone with that for *o*-tolylphenylsulphine, Bonini *et al.*[145] concluded that the methyl group was more shielded in the latter case when the S=O group was *anti*. This conclusion was verified by ^{13}C n.m.r. spectra, aromatic-solvent-induced shifts of the methyl n.m.r. spectra, and by i.r. spectroscopic analysis of the association of sulphine with thiophenol. Equilibration studies of substituted *o*-tolylphenylsulphines gave equilibrium constants (K=*anti*/*syn*) of from 2.3 to 5.3. The activation parameters were quite large, indicating rather high configurational stability. For *o*-tolylphenylsulphine the values were E_a=23.0 kcal mol^{-1}, $\Delta H^{\ddagger}$=22.2 kcal mol^{-1}, and $\Delta S^{\ddagger}$=−26.0 e.u.[145] The mechanism of interconversion from *syn* to *anti* could be rotation about the C=S bond or

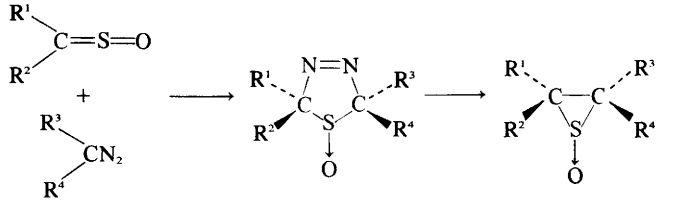
[139] C. G. Gibbs, *Diss. Abs.*, 1973, **34B**, 2521.
[140] W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, 1972, **37**, 3818.
[141] S. Tamagaki and S. Oae, *Tetrahedron Letters*. 1972, 1159.
[142] A. Tangerman, L. Thijs, A. P. Anker, and B. Zwanenburg, *J.C.S. Perkin II*, 1973, 458.
[143] A. Tangerman and B. Zwanenburg, *J.C.S. Perkin II*, 1973, 461.
[144] A. Tangerman and B. Zwanenburg, *Tetrahedron Letters*, 1973, 79.
[145] B. F. Bonini, L. Lunazzi, G. Maccagnani, and G. Mazzanti, *J.C.S. Perkin I*, 1973, 2314.

inversion at sulphur. SCF–MO–CNDO calculations on $CH_2{=}S{=}O$ indicate that the *syn–anti* conversion barrier should be 26.6 kcal mol^{-1} by sulphur inversion and 23.9 kcal mol^{-1} by rotation about the S=O bond.[146] Tangerman and Zwanenburg also were able to detect rotamers due to restricted rotation about the mesityl-carbon bond in a mesitylsulphine, the magnitude of the rotation barrier being larger when the sulphine group was *syn* to the mesityl group.[147] The rotational equilibria were found to be a function of solvent, the more polar rotamer dominating in the more polar solvent.[148]

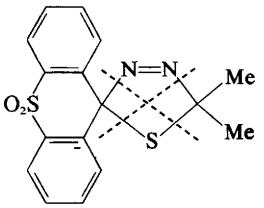
Several groups recently have explored the reaction of sulphines with diazo-compounds. The overall reaction sequence seems to be initial formation of a Δ^3-1,3,4-thiadiazoline 1-oxide adduct (111), elimination of nitrogen to form an episulphoxide (112), and elimination of SO to form olefin (113). The reaction of diphenylsulphine with diazomethane afforded only the olefin according to Venier and Gibbs,[149] but Bonini *et al.*[150] were able to isolate the initial adduct (111). The reaction of the same sulphine with phenyldiazomethane at 0 °C afforded the episulphoxide (112), which was converted into the olefin upon chromatography.[151] Diazoethane[150] and 2-diazopropane[137] afforded only the initial adduct (111) in reaction with a variety of aromatic sulphines and aliphatic sulphines such as (107). With the latter bis-sulphine, 2-diazopropane added to both sulphine groups.[137] With 2-diazopropane, phenyltosylsulphine afforded the adduct (111), but with mesityltosylsulphine only the episulphoxide (112) was obtained.[152] It was proposed that when a sterically crowded diazo-compound and/or sulphine was used in this reaction, the first step was attack of the diazo-carbanion on sulphur, with the resultant carbanion displacing nitrogen. Bonini *et al.*[150] showed that the adduct (114) would dissociate in two directions to form a mixture of the aromatic diazo-compound (presumably together with dimethylsulphine) and the aromatic sulphine (presumably together with diazopropane). Di-*p*-tolyldiazomethane reacted with dichlorosulphine probably to form initially an adduct (111) and then an episulphoxide (112), but the final product was 2-chloro-3-*p*-tolyl-6-methylbenzothiophen 1-oxide.[153]

In their reactions with diazo-compounds, sulphines are behaving in a manner similar to sulphonium ylides, that is with the carbon atom carrying negative charge density and the sulphur atom carrying positive charge density. However, in its reaction with diphenylnitrilimine, diphenylsulphine afforded (115), the result of nucleophilic attack by nitrogen on what must

[146] J. P. Snyder and D. N. Harpp, *J.C.S. Chem. Comm.*, 1972, 1305.
[147] A. Tangerman and B. Zwanenburg, *Tetrahedron Letters*, 1972, 5329.
[148] A. Tangerman and B. Zwanenburg, *Tetrahedron Letters*, 1973, 5195.
[149] C. G. Venier and C. G. Gibbs, *Tetrahedron Letters*, 1972, 2293.
[150] B. F. Bonini, G. Maccagnani, A. Wagenaar, L. Thijs, and B. Zwanenburg, *J.C.S. Perkin I*, 1972, 2490.
[151] B. F. Bonini and G. Maccagnani, *Tetrahedron Letters*, 1973, 3585.
[152] L. Thijs, A. Wagenaar, E. M. M. van Rens, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3589.
[153] L. Thijs, J. Strating, and B. Zwanenburg, *Rec. Trav. chim.*, 1972, **91**, 1345.



(111) (112)



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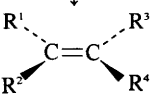
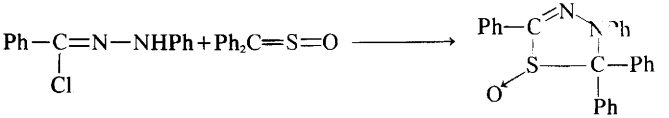


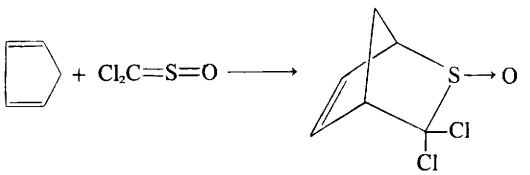
(113)

be a carbon atom with positive charge density.[154] The reaction of diphenylnitrilimine with thiobenzophenone, where the carbon atom clearly has positive character, afforded an adduct which was readily oxidized to (115).

Sulphines previously had been reported to react with polarized olefinic groups, such as in vinylamines, but in those reactions overall substitution occurred.[155] Sulphines now have been found to be dienophiles. A variety of reactions, utilizing several dienes and several sulphines, have been reported.[156] For example, cyclopentadiene and dichlorosulphine afforded (116). The two geometric isomers of phenylchlorosulphine reacted with 2,3-dimethyl-1,4-butadiene to afford the two isomers of the adduct, the



(115)



(116)

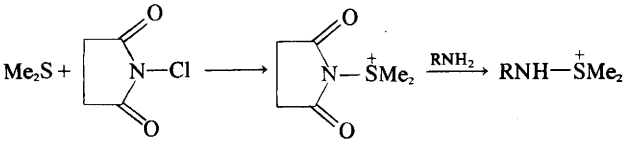
[154] B. F. Bonini, G. Maccagnani, L. Thijs, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3569.
[155] Ref. 13, p. 299.
[156] B. Zwanenburg, L. Thijs, J. B. Boens, and J. Strating, *Rec. Trav. chim.*, 1972, **91**, 443.

dominant isomer being that in which the stereochemical relationships in the sulphine had been maintained in the adduct.

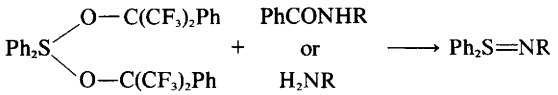
8 Sulphur Imines

Iminosulphuranes.—New results have been reported for four different methods of preparing iminosulphuranes. The reaction of *N*-bromoacetamide with a variety of dialkyl sulphides afforded amidosulphonium salts, which could be deprotonated with triethylamine to the imines.[157] Dialkyl sulphides also afforded imines with *N*-chlorourea.[158] Benzotrithione with chloramine-T gave an interesting and stable thione-imine, which eliminated sulphur on heating to form the carbon-imine.[141] These reactions all are thought to proceed by sulphide attack on halogen, followed by imide attack on sulphur to displace halide. In a similar overall reaction dialkyl, alkyl aryl, and diaryl sulphides reacted with *O*-mesitylenesulphonylhydroxylamine to afford the aminosulphonium salt, which was deprotonated on an ion-exchange resin to afford iminosulphurane.[159,160]

The second method, involving some of the same steps as the first, utilizes a reagent to attach a leaving group to sulphur, such that it may be displaced by a separately added amine or amide. Thus, dimethyl sulphide with *N*-chlorosuccinimide afforded the imidosulphonium salt (117), the imide group being displaceable by a variety of primary amines. The resulting aminosulphonium salts could be converted directly into imines.[161] The reaction of sulphide with t-butyl hypochlorite and then addition of the sodium salt of an amine or amide afforded an imine directly.[162] Similarly, the diphenyldialkoxysulphurane (118) reacted with an amine or its corresponding amide to afford imines in high yield.[163] Lerch and Moffatt[164] have



(117)



(118)

[157] H. Kise, G. F. Whitfield, and D. Swern, *J. Org. Chem.*, 1972, **37**, 1121.
[158] S. Oae, T. Masuda, K. Tsujihara, and N. Furukawa, *Bull. Chem. Soc. Japan*, 1972, **45**, 3586.
[159] Y. Tamura, K. Sumoto, J. Minamikawa, and M. Ikeda, *Tetrahedron Letters*, 1972, 4137.
[160] Y. Tamura, K. Sumoto, H. Matsushima, H. Taniguchi, and M. Ikeda, *J. Org. Chem.*, 1973, **38**, 4324.
[161] E. Vilsmaier and W. Sprugel, *Tetrahedron Letters*, 1972, 625.
[162] D. Swern, I. Ikeda, and G. F. Whitfield, *Tetrahedron Letters*, 1972, 2635.
[163] J. A. Franz and J. C. Martin, *J. Amer. Chem. Soc.*, 1973, **95**, 2017.
[164] U. Lerch and J. G. Moffatt, *J. Org. Chem.*, 1971, **36**, 3391.

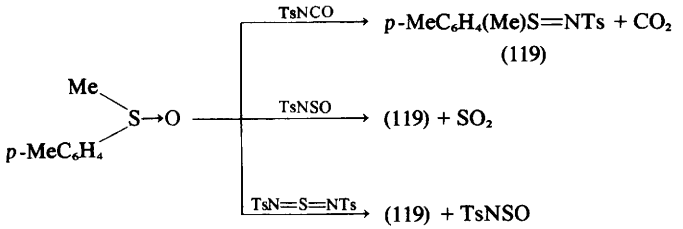
expanded their earlier reports of the reactions of amides with the complexes formed from DMSO–dicyclohexylcarbodi-imide or from DMSO–P_2O_5 to afford imines. In all of these reactions, the first step involves attaching the appropriate leaving group to sulphur.

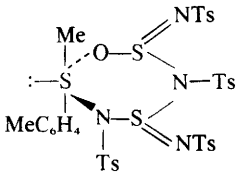
Hayashi and Swern[165] have reported additional examples of the third method, the photochemical coupling of azides with sulphides, which probably occurs through attack of singlet nitrene on sulphur. The earlier reported reaction of a sulphinyl azide with a sulphoxide to afford a *N*-sulphonylimine now has been found to occur with retention of configuration about sulphoxide-sulphur.[166] Okahara *et al.*[167] have reported additional examples of the oxidative coupling of sulphonamides with dimethyl sulphide to afford imines in good yield.

While the previous methods have involved sulphides as starting materials, the fourth involves sulphoxides and their reaction with a deoxygenating nitrogen-containing molecule. For example, methyl *p*-tolyl sulphoxide reacts with tosyl isocyanate,[168] *N*-sulphinyltosyl amide,[169] and bis-tosylsulphur di-imine[169] to afford *N*-tosyliminomethyl-*p*-tolylsulphurane (119). In pyridine solution the (+)(*R*)-sulphoxide reacted with the sulphur di-imine to afford the (−)(*S*)-imine, whereas in benzene or methylene chloride solution the (+)(*R*)-sulphoxide afforded the (+)(*R*)-imine.[169] The former reaction proceeded with inversion, was first-order in sulphoxide and second-order in di-imine, and it was proposed to proceed through the intermediate (120) involving an equatorial–equatorial substitution. The latter reaction proceeded with retention of configuration about sulphur, was first-order in both sulphoxide and di-imine, and was proposed to proceed through the intermediate (121) involving an equatorial–axial substitution.

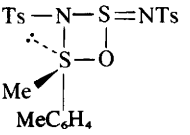
The reaction of methyl *p*-tolyl sulphoxide with tosyl isocyanate has revealed a host of possible individual reactions of a proposed common intermediate (122).[168] The major reaction to form imine (119) was found to proceed with inversion of configuration and to be first-order in sulphoxide and second-order in isocyanate. According to the proposed mechanism, (122) is capable of reacting with isocyanate to afford inverted (119), with sulphoxide to form inverted sulphoxide, and with imine (119) to form racemized (119). The proposed intermediacy of (122) could be verified by interception with several reagents. Addition of *N*-nitrobenzenesulphonyliminotetramethylenesulphurane afforded a mixture of (119) and two new imines resulting from a crossover, *N*-tosyliminotetramethylenesulphurane and *N*-nitrobenzenesulphonyliminomethyl-*p*-tolylsulphurane. Addition of

[165] Y. Hayashi and D. Swern, *Tetrahedron Letters*, 1972, 1921; *J. Amer. Chem. Soc.*, 1973, **95**, 5205.
[166] T. J. Maricich and V. L. Hoffmann, *Tetrahedron Letters*, 1972, 5309.
[167] M. Okahara, K. Matsunaga, and S. Komori, *Synthesis*, 1972, 203.
[168] D. C. Garwood, M. R. Jones, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95**, 1925.
[169] F. G. Yamagishi, D. R. Raynor, E. T. Zwicker, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95**, 1916.

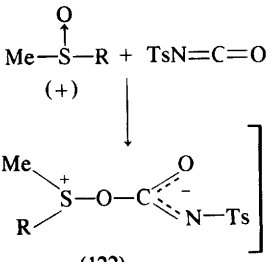

TsNCO
p-MeC6H4(Me)S=NTs + CO2
(119)
Me
S→O
p-MeC6H4
TsNSO
(119) + SO2
TsN=S=NTs
(119) + TsNSO


NTs
Me
O
S
N—Ts
MeC6H4
N
S
NTs
Ts

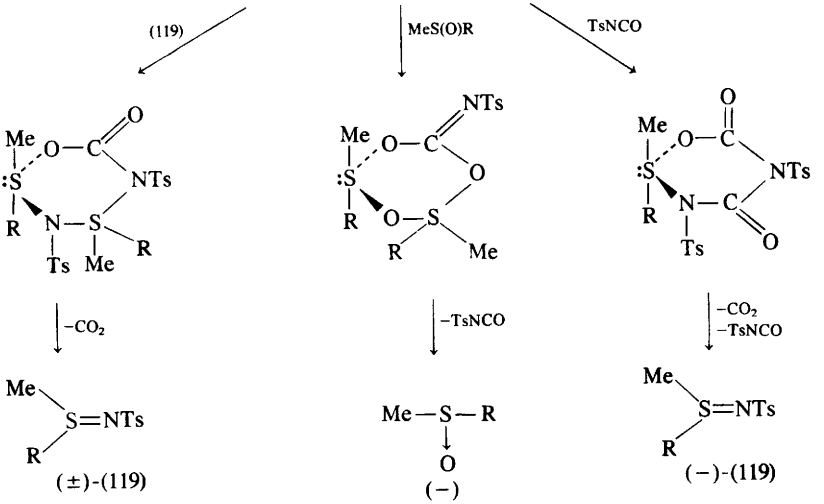
(120)


Ts—N—S=NTs
S—O
Me
MeC6H4

(121)


O
Me—S—R + TsN=C=O
(+)
Me
S
O—C
O
N—Ts
R

(122)


(119)
MeS(O)R
TsNCO
Me
O—C
O
NTs
S
R
N—S
Ts Me
R
-CO2
Me
S=NTs
R
(±)-(119)
NTs
Me
O—C
O
S
R
O—S
R
Me
-TsNCO
Me—S—R
O
(−)
O
Me
O—C
NTs
S
R
N—C
Ts
O
-CO2
-TsNCO
Me
S=NTs
R
(−)-(119)

diethyl sulphide gave *N*-tosyliminodiethylsulphurane and methyl *p*-tolyl sulphide. Thus, a series of interesting and stereospecific ligand transfers, all occurring with inversion of configuration, has been identified.

The pK_a's of a series of *N*-tosyliminomethyl(substituted-phenyl)-sulphuranes and *N*-(substituted-phenylsulphonyl)iminomethylphenylsulphuranes were determined and afforded Hammett correlations with ρ values of +0.89 for the substituted-phenyl sulphonium group and +0.82 for the substituted-phenylsulphonyl group.[170] Thus, electronic effects were transmitted equally effectively by the sulphonium group and the sulphonyl group, and the basicity of the imines was comparable to that of sulphoxides. *X*-Ray analysis of *N*-trichloroacetyliminodimethylsulphurane revealed a S—N bond length of 1.667 Å, about 0.03 Å longer than those earlier reported for the *N*-sulphonyl-imines.[171] Lambert *et al.*[172] examined the configuration of a series of derivatives of thiacyclohexane—the oxide, imine, *N*-tosylimide, and *N*-benzenesulphonylimide, all of which existed in two conformational isomers. For the sulphoxide and imidosulphuranes the axial conformation dominates, but for the iminosulphurane the equatorial conformation dominates. Through n.m.r. spectroscopy such changes in configuration were shown not to be due to sulphur pyramidal inversion or S=N rotation, but instead to conformational changes in the six-membered ring. *N*-Acetyliminomethylethylsulphurane was prepared in optically active form and was found to racemize without dissociation.[173] *N*-Tosyliminomethyl(*p*-substituted-phenyl)-sulphurane also was found to racemize in a unimolecular reaction in which solvent polarity was not a factor and in which the unsubstituted imine racemized faster than either the *p*-methyl- or the *p*-chloro-imine.[174] The activation enthalpy for racemization was found to be 34.1 kcal, compared to 23.3 kcal for a similar ylide and 35—43 kcal for sulphoxides.[173] Thus, there is increasing stability toward racemization as the anionic group attached to tervalent sulphur is changed from carbanion to imino to oxido, perhaps indicating that increasing $p\pi$–$d\pi$ bonding leads to easier racemization by stabilization of the transition state. A comparison of the change in stability toward racemization as ylide is converted into its conjugated acid, the salt being more stable,[175] and when imine is converted into its conjugated acid, the imine being more stable,[173] does not sustain this overall explanation, however.

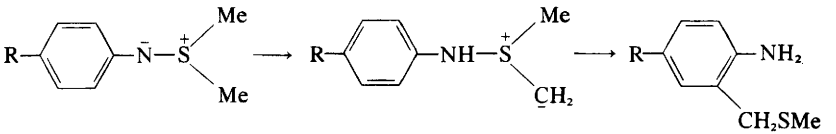
N-Tosyliminosulphuranes could be hydrolysed in concentrated sulphuric acid to afford the free iminosulphurane.[176] However, in dilute acid the hydrolysis proceeded normally to afford a sulphoxide and a

[170] I. Kapovits, F. Ruff, and A. Kucsman, *Tetrahedron*, 1972, **28**, 4413.
[171] A. Kalman, K. Sasvari, and A. Kucsman, *Acta Cryst.*, 1973, **B29**, 1241.
[172] J. B. Lambert, C. E. Mixan, and D. S. Bailey, *J. Amer. Chem. Soc.*, 1972, **94**, 208.
[173] B. C. Menon and D. Darwish, *Tetrahedron Letters*, 1973, 4119.
[174] N. Furukawa, K. Harada, and S. Oae, *Tetrahedron Letters*, 1972, 1377.
[175] D. Darwish and R. L. Tomlinson, *J. Amer. Chem. Soc.*, 1968, **90**, 5938.
[176] N. Furukawa, T. Omata, T. Yoshimura, T. Aida, and S. Oae, *Tetrahedron Letters*, 1972, 1619.

sulphonamide.[177] In the latter reaction the slow step was nucleophilic attack of water on sulphur. The reaction was facilitated by electron-withdrawing groups on an *S*-phenyl group and on a phenylsulphonyl group.

Iminosulphuranes are cleaved by a variety of reagents. Thiophenol effects a reductive cleavage to an amine and a sulphide,[158] as does dithioacetic acid[34] and elemental sulphur.[178] Diphenyl disulphide effects cleavage to a sulphide and a bis-phenylthioamine.[178] Triphenylphosphine with *N*-tosyliminomethylphenylsulphurane afforded thioanisole and *N*-tosyliminotriphenylphosphorane upon heating to 120 °C in DMF.[179] This reaction was found to be first-order each in imine and phosphine, and a detailed study of the effect of substituents indicated that the reaction proceeded by nucleophilic attack of phosphine on sulphur. The introduction of water into the reaction mixture resulted in hydrolysis of the iminophosphorane to a phosphine oxide and tosylamide. A similar imine 'exchange' reaction took place under photochemical conditions when *N*-ethoxycarbonyliminodimethylsulphurane was treated with diethyl sulphide, the product being the diethyl sulphurane.[165] By utilizing ^{14}C labelling, Oae *et al.*[180] were able to verify that the previously reported reaction of *N*-tosyliminodiphenylsulphurane with phenylmagnesium bromide occurred by attack on sulphur to afford triphenylsulphonium ion and tosylamide. In some instances the sulphonium ion was attacked by additional Grignard reagent such that the final products were diphenyl sulphide and biphenyl.

N-Aryliminosulphuranes earlier had been reported to undergo Sommelet-type rearrangements.[181] Claus and Rieder[182] studied the kinetics of the rearrangement of (123) and concluded that the rate was determined by the

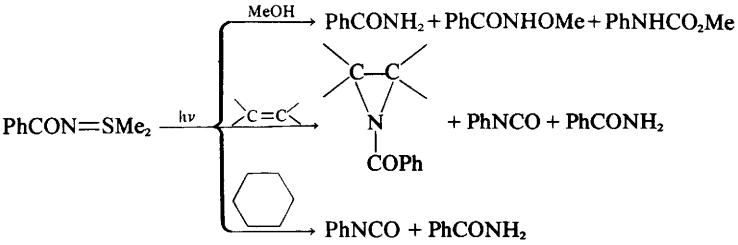


(123)

rate of proton abstraction from the *S*-methyl group (to form an ylide-imine). Furthermore, the rate of rearrangement of the aminosulphonium ylide was greater than its rate of reprotonation. Johnson *et al.*[183] and Gassmann *et al.*[184] both have reported additional examples of such rearrangements, but proceeding from aminosulphonium salts rather than iminosulphuranes.

[177] I. Kapovits, F. Ruff, and A. Kucsman, *Tetrahedron*, 1972, **28**, 4405.
[178] S. Oae, Y. Tsuchida, K. Tsujihara, and N. Furukawa, *Bull. Chem. Soc. Japan*, 1972, **45**, 2856.
[179] T. Aida, N. Furukawa, and S. Oae, *Chem. Letters*, 1973, 805.
[180] S. Oae, T. Yoshimura, and N. Furukawa, *Bull. Chem. Soc. Japan*, 1972, **45**, 2019.
[181] Ref. 40, p. 326.
[182] P. Claus and W. Reider, *Monatsh.*, 1972, **103**, 1163.
[183] C. R. Johnson, C. C. Bacon, and W. D. Kingsbury, *Tetrahedron Letters*, 1972, 501.
[184] P. G. Gassmann, G. Gruetzmacher, and R. H. Smith, *Tetrahedron Letters*, 1972, 497.

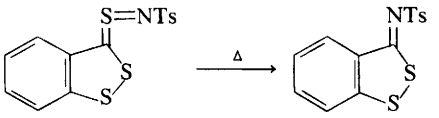
Photolysis of iminosulphuranes apparently proceeds through formation of a nitrene. *N*-Benzoyliminodimethylsulphurane was photolysed in methanol solution (Scheme 5) to afford a mixture of benzamide, *N*-methoxy-



Scheme 5

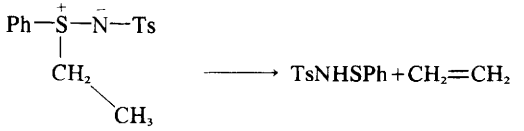
benzamide, and methoxycarbonylaniline, the latter probably being formed from rearrangement of benzoylnitrene to phenyl isocyanate and then addition of methanol.[164] In the presence of a *cis*-olefin, the same imine afforded the *cis*-aziridine, phenyl isocyanate, and benzamide.[165] In the presence of cyclohexane, the imine afforded only benzamide and phenyl isocyanate. It may be concluded that photochemical decomposition of iminosulphuranes proceeds first to the singlet state of a nitrene, which may be trapped by an olefin (stereoselectively), a sulphide, or a protic acid. If not trapped quickly, the singlet state converts into a triplet nitrene, which will not effect an insertion reaction.

There have been a number of reports on the thermolysis of iminosulphuranes. In an unusual case, the imine (124) simply extruded sulphur upon heating to its melting point of 135 °C.[141] Kise *et al.*[185] reported a number of examples of $\alpha'\beta$-eliminations in iminosulphuranes which contain an alkyl group on sulphur. Thus, *N*-acetyliminodiethylsulphurane afforded a 51% yield of ethylene and a 95% yield of *N*-ethylthioacetamide. Oae *et al.*[186] have carried out a detailed kinetic study of such an elimination reaction using *N*-tosyliminophenylethylsulphurane (125). The effect of substituents on the phenyl ring produced a ρ value of +0.90, and the same value was obtained with the α-phenylethylphenyl-imine. The β-hydrogen isotope effect was 3.03, and a similar value of 2.90 was obtained for the α-phenylethylphenyl imine. The relative rates of elimination of ethylene were $1:1.5:10^3$ for (125),



(124)

[185] H. Kise, G. F. Whitfield, and D. Swern, *J. Org. Chem.*, 1972, **37**, 1125.
[186] S. Oae, K. Harada, K. Tsujihara, and N. Furukawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 3482.



(125)

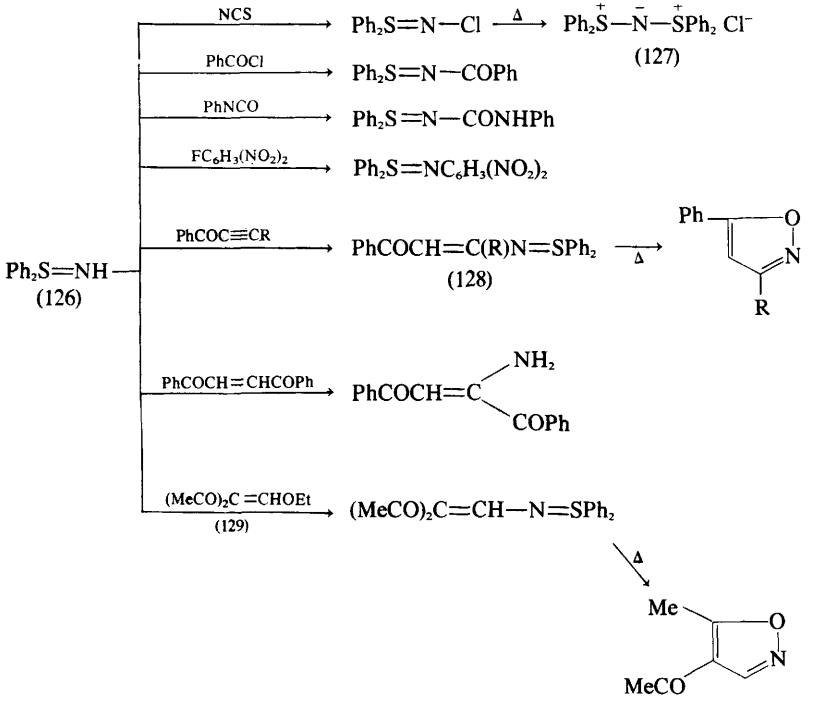
the β-phenylethylphenyl-imine, and the α-phenylethylphenyl-imine. It was concluded that the mechanism of the elimination could not be carbanion-like, and probably was a *cis*-concerted mechanism, with the unusual rate effect of an α-phenyl group being due to stabilization of the transition state.[186]

The unsubstituted imine (126) undergoes a variety of substitution reactions. Halogenation with *N*-chlorosuccinimide and with *N*-bromosuccinimide afforded the *N*-chloro- and *N*-bromo-imines, respectively.[187] The halogeno-imines could be converted into the *N*-cyanoimine by treatment with NaCN, and heating the chloroimine afforded the bis-imine (127).[187] The imine (126) could be acylated with a variety of acylating agents, acyl halides, anhydrides, and isocyanates.[160] In addition, it was sufficiently nucleophilic to displace fluoride from 2,4-dinitrofluorobenzene. The imine (126) would add to benzoylalkynes to form new imines (128), which could be thermally cyclized to isoxazoles. With dibenzoylethylene an addition–substitution was effected and with the vinyl ether (129) a substitution occurred, again to afford an isoxazole.[160]

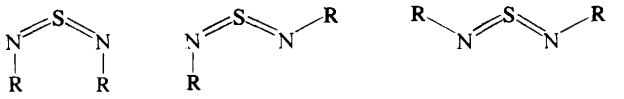
Three examples of imine 'exchange' have been reported in which the basic $p\pi$–$d\pi$ bond of the imine has been maintained but in which either the sulphonium group has been replaced or in which the imino-group has been replaced. Ethoxycarbonyliminodimethylsulphurane reacted with diethyl sulphide under photochemical conditions to afford *N*-ethoxycarbonyliminodiethylsulphurane,[165] the diethyl sulphide replacing dimethyl sulphide. *N*-(2,4-Dinitrophenyl)iminodimethylsulphurane reacted with tosylamide at 90 °C to afford *N*-tosyliminodimethylsulphurane and 2,4-dinitroaniline.[188] Finally, *N*-tosyliminomethylphenylsulphurane with triphenylphosphine at 120 °C afforded *N*-tosyliminotriphenylphosphorane and thioanisole.[179] The oxidation of *N*-benzoyliminodimethylsulphurane with potassium permanganate accomplished the overall effect of an exchange with DMSO, the formation of *N*-benzoyliminodimethyloxysulphurane.[164]

Sulphurdi-imines.—Grunwell and Baker[189] have carried out additional CNDO/2 calculations on the —N=S=N— system based on the u.v. spectra. However, they were unable to demonstrate conclusively that *d*-orbitals were necessary in order to explain the π–π^* electronic transition energies. Previously, *X*-ray analysis had demonstrated that in the solid state

[187] N. Furukawa, T. Yoshimura, and S. Oae, *Tetrahedron Letters*, 1973, 2113.
[188] T. Yamamoto, Y. Hanigaya, and M. Okawara, *Chem. Letters*, 1972, 1009.
[189] J. R. Grunwell and H. S. Baker, *J.C.S. Perkin II*, 1973, 1542.



the di-imine (130; R = *p*-tolyl) existed in the *trans-trans*-configuration.[190] The n.m.r. spectrum of the di-t-butylsulphurdi-imine (130; R = Bu^t) at room temperature showed a sharp singlet which split into a sharp doublet at −40 °C, indicating that at low temperatures either the *cis-trans*-form was the more stable[191] or that an equal mixture of the *cis-cis*- and the *trans-trans*-form existed,[192] and that at room temperature the *trans-trans*-isomer existed. For the dimethylsulphurdi-imine (130; R = methyl) the sharp singlet



(130)

at room temperature separated at −60 °C into two quartets and a weak singlet, indicating that the *trans-trans*-isomer existed at room temperature

[190] G. Leandri, V. Busetti, G. Valle, and M. Mammi, *Chem. Comm.*, 1970, 413.
[191] J. R. Grunwell, C. F. Hoyng, and J. A. Rieck, *Tetrahedron Letters*, 1973, 2421.
[192] J. Kuyper, K. Vrieze, and A. Oskan, *J. Organometallic Chem.*, 1972, **46**, C25.

and that the *cis-trans*-isomer dominated (with a trace of *trans-trans* present) at low temperature.[192]

Ditosylsulphurdi-imine acts as an oxidizing agent, converting hydroquinone into quinone, thiophenol into diphenyl disulphide, hydrazobenzene into azobenzene, and 1,4-dihydronaphthalene into naphthalene.[41] The same di-imine reacted with dimethylaminotrimethylstannane such that the latter reagent added separately across each S=N bond. The same reagent reacted with tetrasulphur tetranitride to form the di-imine (131), which reacted with

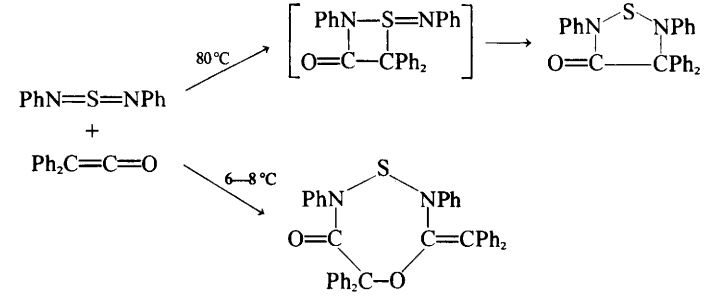
$$S_4N_4 + Me_3SnNMe_2 \longrightarrow \underset{(131)}{Me_3SnN{=}S{=}NSnMe_3} \xrightarrow{Me_3SiCl} Me_3SiN{=}S{=}NSiMe_3$$

trimethylsilyl chloride in a substitution reaction.[193] Di-t-butylsulphurdi-imine reacted with dichloroethyleneplatinum and chlorodicarbonylrhodium to form 1:1 complexes. *X*-Ray analysis of the former complex revealed that the planar di-imine was situated perpendicular to the plane of the platinum group, and indicated the presence of a Pt—N bond. The N=S=N angle of 112° was slightly narrower than the angle in uncomplexed di-imine, and the two t-butyl groups were located *trans* to each other, as in the uncomplexed di-imine.[191]

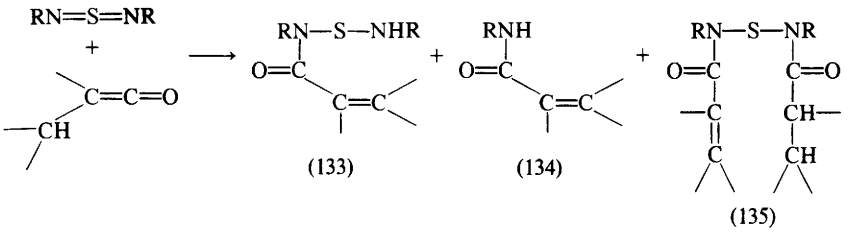
Diphenylsulphurdi-imine previously was reported to react with diphenylketen to afford the 1:1 adduct.[194] It has now been shown that while that reaction does occur at 80 °C, at 6—8 °C a 1:2 adduct (132) is formed.[195] The di-t-butylsulphurdi-imine reacts with the same keten at 0 °C to form first the four-membered 1:1 adduct, which then rearranges at 70 °C to the five-membered 1:1 adduct, the same course as followed by the diphenylsulphurdi-imine. The reaction of either di-imine with a keten having at least one alkyl group led to a different course, apparently resulting from initial attack of the nitrogen on the keten carbonyl group followed by proton transfer to form (133).[195] In some instances this product was accompanied by its hydrolysis product (134) and/or the acylation product (135). With dimethylketen and diphenylsulphurdi-imine a small amount of cyclized product was formed along with (134).

Sulphonedi-imines.—Two groups have carried out theoretical calculations on the sulphonedi-imine system, the nitrogen analogue of sulphone.[196,197] In the isoelectronic series Me_2SO_2, $Me_2S(O)NH$, $Me_2S(NH)_2$ the charge density on sulphur was calculated to increase as follows: −0.35, −0.55, −0.71. Knoll *et al.*[198] determined the rate of exchange of the methyl protons with D_2O in a

[193] D. Hanssgen and W. Roelle, *J. Organometallic Chem.*, 1973, **56**, C14.
[194] Ref. 40, p. 329.
[195] S. Minami, K. Yamataka, Y. Ohshiro, T. Agawa, N. Yasuoka, and N. Kasai, *J. Org. Chem.*, 1972, **37**, 3810.
[196] H. Oberhammer, *Theor. Chim. Acta*, 1972. **26**, 79.
[197] B. Solouki, H. Bock, and R. Appel, *Angew. Chem. Internat. Edn.*, 1972, **11**, 927.
[198] F. Knoll, M. Frank, M. Kalben, J. Kohnke, and R. Appel, *Chem. Ber.*, 1972, **105**, 1922.



(132)

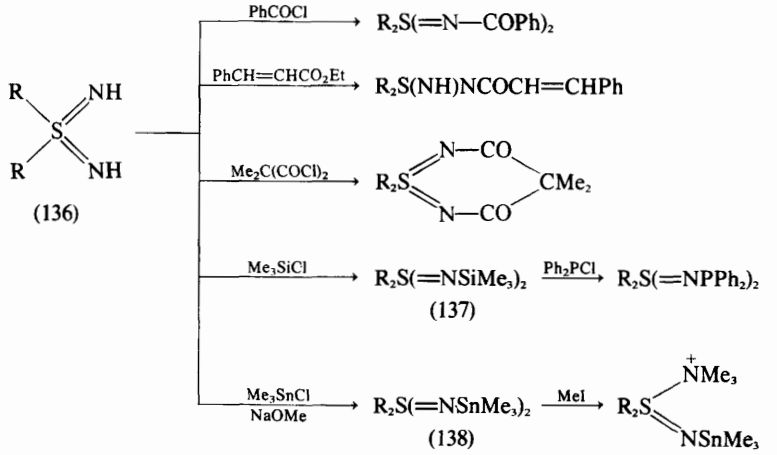


(133) (134) (135)

number of sulphonedi-imine derivatives, and found that in the series Me_2SNH, $Me_2S(NH)_2$, $Me_2S(O)NH$ the pK_a of the *S*-methyl groups decreased from 7.28 to 5.59 and then to 3.10, respectively. All of this evidence indicates that as nitrogen replaces oxygen in iminosulphurane systems a gradual transfer of negative charge takes place *towards* the sulphur atom, making the substituents less nucleophilic and the sulphur atom less electrophilic.

Sulphonedi-imines are nucleophiles and are capable of undergoing acylations. Thus, with reactive acylating agents such as acyl halides, (136) was dibenzoylated with excess benzoyl chloride in the presence of triethylamine.[199] However, with one equivalent of benzoyl chloride the mono-benzoylated imine was obtained. Using esters as the acylating agents generally led to only monoacylation. The reaction of (136) with trimethylsilyl chloride afforded the di-silylated di-imine (137), in which the silyl groups were readily replaced in reaction with other organometallic chlorides.[200] In a similar manner (136; R = Me) formed a complex with trimethylstannyl chloride in the presence of triethylamine, but in the presence of sodium methoxide HCl was eliminated and the di-stannyl di-imine (138) was isolated.[201] The latter compound seemed to be monofunctional in that only one stannyl group could be replaced, such as with methyl

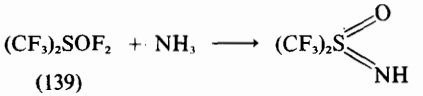
[199] M. Haake, H. Fode, and B. Eichenauer, *Annalen*, 1972, **759**, 107.
[200] W. Wolfsberger and H. Forsterling, *J. Organometallic Chem.*, 1973, **56**, C17.
[201] D. Hanssgen and R. Appel, *Chem. Ber.*, 1972, **105**, 3271.



(136) (137) (138)

iodide. The di-imine (136; R = Me) reacted directly with dimethylamino-alkylstannanes to afford mixtures of polymers, depending on the number of dimethylamino-groups to be replaced; some of the products are network polymers.[201]

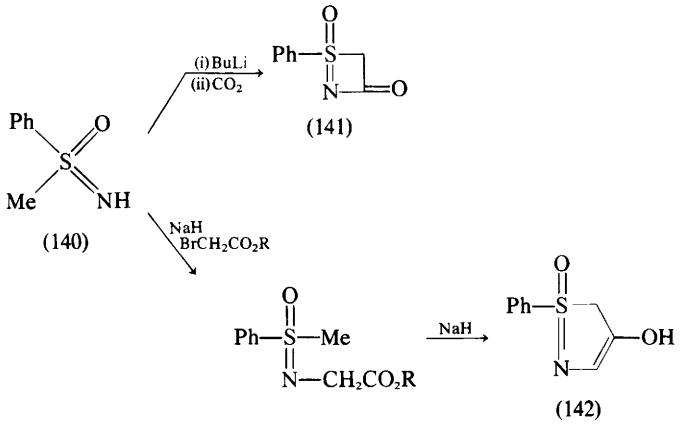
Imino-oxysulphuranes.—No fundamentally new approaches to the preparation of these compounds have been reported. An additional example of the oxidation of an iminosulphurane to an imino-oxysulphurane has been reported.[164] Sulphoxides have been found to displace mesityl sulphonate from *O*-mesitylsulphonylhydroxylamine to form amino-sulphoxides, which could be deprotonated with methoxide.[159] The difluorosulphoxide (139) reacted with liquid ammonia to afford the imino-oxysulphurane.[202]



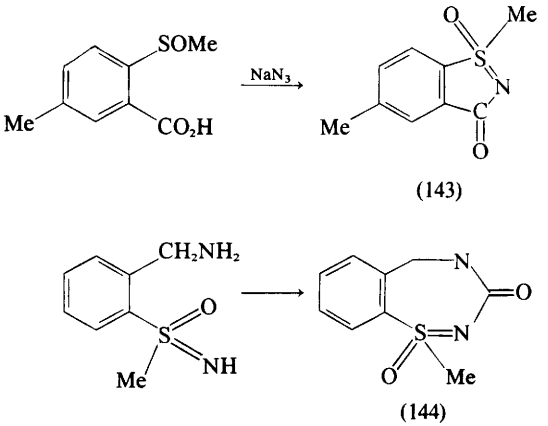
(139)

There has been considerable interest in the preparation of cyclic imino-oxysulphuranes. Treatment of phenylmethylsulphoximine (140) with n-butyl-lithium and then carbonating the reaction product afforded the four-membered system (141).[203] The same starting material with sodium hydride and then bromoacetate gave a new sulphoximine, which underwent internal ylide formation and then intramolecular acylation upon further treatment with sodium hydride to form the five-membered system (142).[203] Johnson *et al.*[204] previously had prepared a saturated non-hydroxylated

[202] D. T. Sauer and J. M. Shreeve, *Inorg. Chem.*, 1972, **11**, 238.
[203] T. R. Williams and D. J. Cram, *J. Org. Chem.*, 1973, **38**, 20.
[204] C. R. Johnson, G. F. Katekar, R. F. Huxol, and E. R. Janiga, *J. Amer. Chem. Soc.*, 1971, **93**, 3771.



analogue of (142) by an intramolecular alkylation. A benzo-fused five-membered system (143) was obtained by treating 2-methylsulphinyl-5-methylbenzoic acid with sodium azide, forming the sulphoximine, which then spontaneously cyclized.[203] The same five-membered-ring system was obtained earlier by the same general route, but using hydrazoic acid and polyphosphoric acid as the reagents.[205] A seven-membered system (144) was

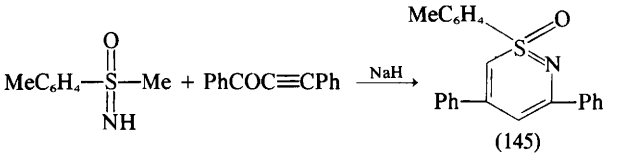


obtained by treating an amino-sulphoximine with a carbonylating agent, *NN'*-carbonyldi-imidazole.[206]

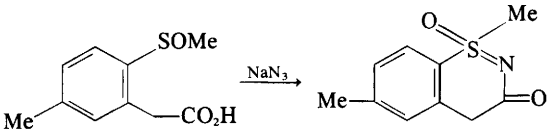
A variety of routes have been employed to produce several different six-membered cyclic imino-oxysulphuranes. The sulphoximine (145) was obtained by conjugate addition of a sulphoximine to phenylbenzoylacetylene.[203] A 3-carbonyl derivative (146) was obtained by employing the

[205] P. Stoss and G. Satzinger, *Angew. Chem. Internat. Edn.*, 1971, **10**, 76.
[206] P. Stoss and G. Satzinger, *Chem. Ber.*, 1972, **105**, 2575.

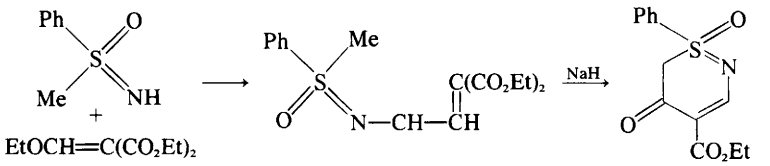
reaction used to prepare (143) on a one-carbon homologue.[203,206] A 5-carbonyl derivative (147) was obtained by addition of a simple sulphoximine to ethoxymethylene malonate to afford a substituted sulphoximine, which was cyclized by treatment with sodium hydride.[207]



(145)



(146)



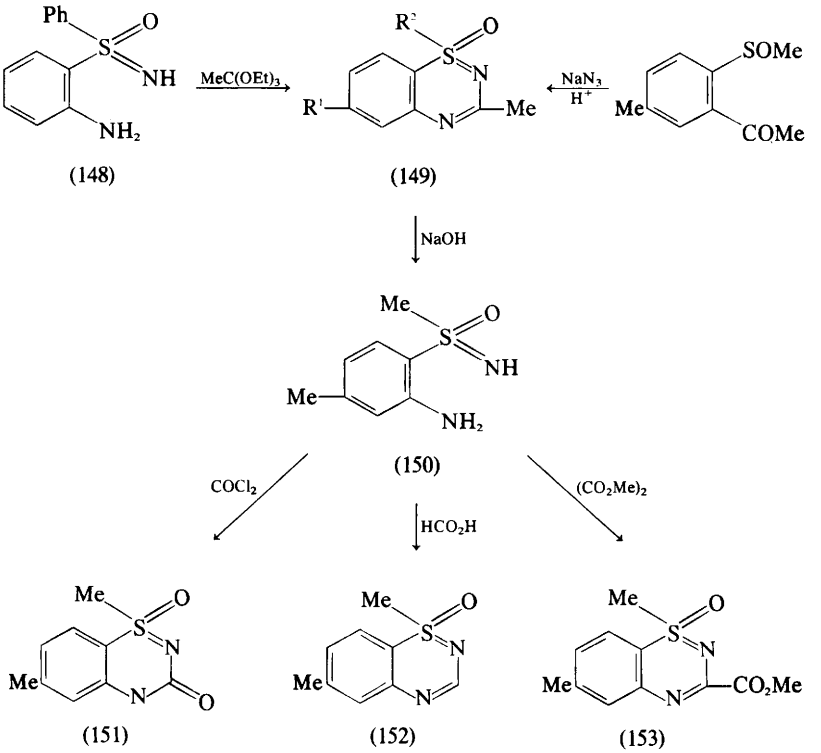
(147)

A series of six-membered cyclic imino-oxysulphuranes with a 4-aza-group also have been prepared. The key intermediate (149) could be obtained by cyclization of an amino-sulphoximine (148)[207] or by effecting a combination imination and Schmidt rearrangement on an *o*-methylsulphinylacetophenone.[203] Base-catalysed hydrolysis of (149) gave the acyclic amino-sulphoximine (150), which subsequently could be closed to three different kinds of cyclic sulphoximines (151), (152), and (153).[203,207]

Imino-oxysulphuranes undergo acylation reactions involving replacement of the =NH group by a =N-acyl group. The already reported reaction of (150) with phosgene is a recent example,[207] while reaction of imino-oxydimethylsulphurane with *N*-chlorosulphonyldialkylamines is exemplary of analogous sulphonation.[167] Imino-oxydiphenylsulphurane reacted with BrCN to afford the *N*-cyanoimine, the cyano-group being capable of partial hydrolysis to an amide function or complete hydrolytic removal and reversion to the parent imine.[208]

In a similar manner, imino-oxysulphuranes undergo alkylation-type reactions. Thus, imino-oxydimethylsulphurane with tritylsulphenyl chloride

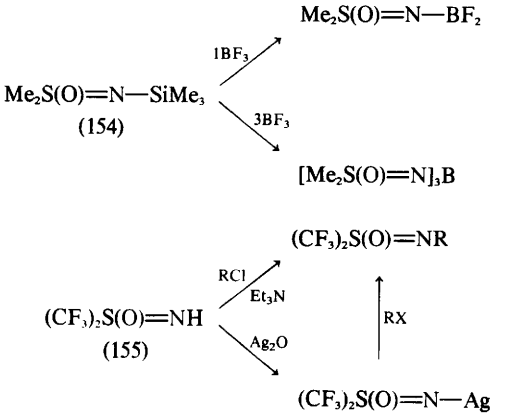
[207] A. C. Barnes, P. D. Kennewell, and J. B. Taylor, *J.C.S. Chem. Comm.*, 1973, 776.
[208] P. Stoss and G. Satzinger, *Tetrahedron Letters*, 1973, 267.



in the presence of triethylamine afforded *N*-tritylsulphenylimino-oxydimethylsulphurane.[209] The reaction of (154) with boron trifluoride led to displacement of the fluorine atoms by one or more imine groups, the number depending on the reactant ratios.[210] The imine (155) would not react directly with alkyl or silyl halides, but would in the presence of tertiary amines.[202] Overall alkylation also could be effected by conversion of the imine into its silver salt and reaction of the latter with an alkyl halide.

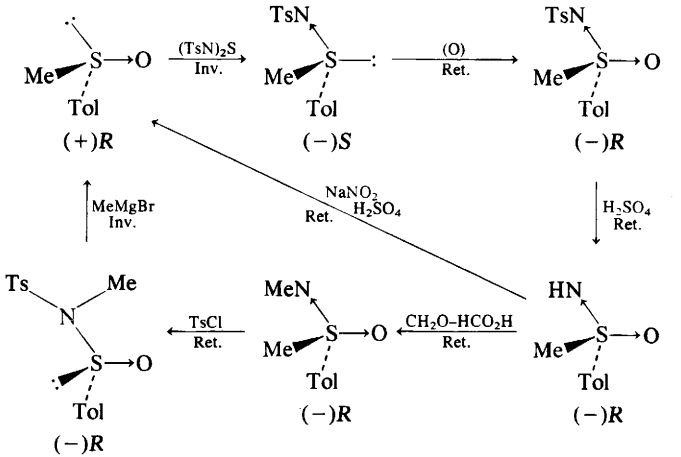
It has previously been demonstrated that the S=N bond of the imino-oxysulphuranes is resistant to acid-catalysed hydrolysis, but an especially significant demonstration is the fact that *N*-cyanoimino-oxysulphurane could be hydrolysed by dilute hydrochloric acid to the *N*-amido-imine and by 50% sulphuric acid to the free imine, probably *via* the *N*-carboxylate, without destroying the S=N bond.[208] Oae *et al.*[178,211] have found that sulphoximines can be cleaved to sulphoxides and a nitrogen fragment by treatment with sulphur or diphenyl disulphide at 160 °C. Using optically active sulphoximines, they were able to obtain optically active

[209] M. Haake, *Tetrahedron Letters*, 1972, 3405.
[210] F. Knoll, M. L. Anagnostopoulous, and R. Appel, *Chem. Ber.*, 1973, **106**, 2089.
[211] S. Oae, Y. Tsuchida, and N. Furukawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 648.



sulphoxides with retained configuration about sulphur in greater than 95% optical purity.

Cram and his students have continued their investigations of stereochemical cycles involving sulphoxides, iminosulphuranes, and imino-oxysulphuranes. In Volume 1 of these Reports the first such cycle was described in detail.[212] More recent work has expanded the cycle to six members, as shown in Scheme 6,[213,214] and the original cycle has been effected with the 2,3-dihydrobenzothiophen oxide series.[169] One of the new observations is that the first step in the cycles, the conversion of sulphoxide into

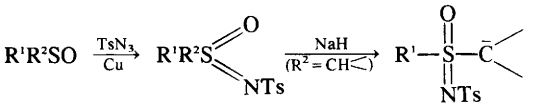


Scheme 6

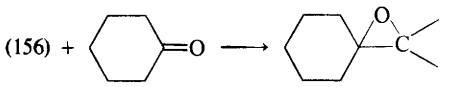
[212] Ref. 13, p. 305.
[213] T. E. Williams, R. E. Booms, and D. J. Cram, *J. Amer. Chem. Soc.*, 1971, **93**, 7338.
[214] T. R. Williams, A. Nudelman, R. E. Booms, and D. J. Cram, *J. Amer. Chem. Soc.*, 1972, **94**, 4684.

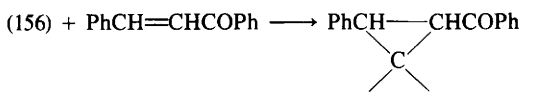
N-tosyliminosulphurane with *NN'*-bistosylsulphurdi-imide, occurs with inversion of configuration of sulphur when conducted in pyridine solution, but occurs with retention of configuration in benzene or methylene chloride solution.[169] The general conclusions from this work are (i) nucleophilic substitution at sulphur generally occurs with inversion of configuration and involves either an axial–axial or equatorial–equatorial displacement, and (ii) electrophilic substitution and desubstitution generally occurs with retention of configuration.[214]

Johnson *et al.*[215] have published details of the conversion of a sulphoxide into an ylide, specifically a sulphoximine ylide (156), by way of the



(156)



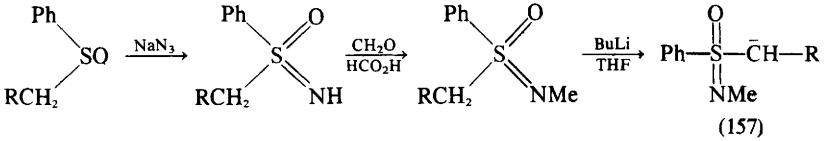


N-tosylimino-oxysulphurane. This ylide reacts in high yield with carbonyl compounds to afford oxirans in a reaction analogous to that effected by sulphonium or oxysulphonium ylides. Optically active phenylmethylsulphoximine could be tosylated and converted into an ylide with sodium hydride in DMSO, and it reacted with acetophenone to afford optically active 1-phenyl-1-methyloxiran. The ylide (156; $R^1 = R^2 = Me$) also effected additions to conjugated carbonyl compounds, such as ω-benzoylstyrene, to afford 1-phenyl-2-benzoylcyclopropane. Johnson[5] recently has reviewed the use of *N*-tosyliminosulphoxonium ylides in organic synthesis.

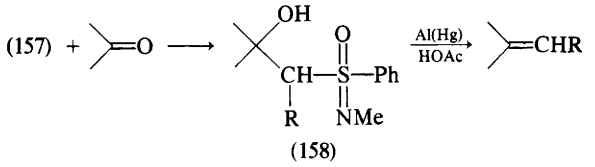
Using a similar system, Johnson *et al.*[216] have been able to effect the overall result of the Wittig reaction but using sulphur ylides. Thus, an alkylphenyl sulphoxide was converted into the sulphoximine with sodium azide, the imine group was methylated with formic acid–formaldehyde, and the *N*-methylimine was converted into the ylide (157) with n-butyl-lithium in THF. The ylide reacted with aldehydes or ketones by adding to the carbonyl group to produce the hydroxysulphoximine (158). The sulphur group could

[215] C. R. Johnson, R. A. Kirchoff, R. J. Reischer, and G. F. Katekar, *J. Amer. Chem. Soc.*, 1973, **95**, 4287.

[216] C. R. Johnson, J. R. Shanklin, and R. A. Kirchoff, *J. Amer. Chem. Soc.*, 1973, **95**, 6462.



(157)

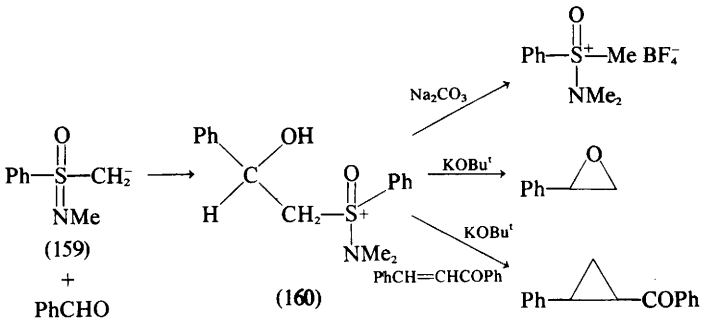


(158)

be removed and water eliminated by treatment with aluminium amalgam in acetic acid, all without rearrangement of the olefin function. Johnson[5] also has reviewed the use of the *N*-methyliminosulphoxonium ylides in organic synthesis.

Johnson *et al.*[99] have used the availability of the above reaction to study further the overall mechanism of the reaction of sulphonium and oxysulphonium ylides with carbonyl compounds and $\alpha\beta$-unsaturated carbonyl compounds. The contrasts between these two types of ylides are well known and can be exemplified as follows: (i) in reactions with cyclic carbonyl compounds, sulphonium ylides attack from the axial position while sulphoxonium ylides attack from the equatorial position; (ii) in reactions with $\alpha\beta$-unsaturated ketones, sulphonium ylides react at the carbonyl group to form oxirans while sulphoxonium ylides react at the olefinic group to form cyclopropanes. These results can be explained by considering the reversibility of the initial step of each ylide reaction and whether the reaction is subject to kinetic or thermodynamic control.

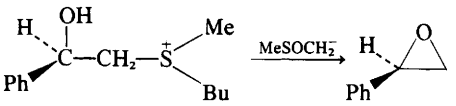
Optically active phenyl-*N*-methyliminosulphoxonium-methylide (159) reacted with benzaldehyde, and the one diastereomer that was isolated was methylated with trimethyloxonium tetrafluoroborate to afford the key intermediate (160). The usual reaction could be continued by treatment with



(159) + PhCHO

(160)

potassium t-butoxide to afford styrene oxide in 71% yield and with 22% optical purity. However, (160) was shown to revert to ylide and carbonyl compound by treatment with sodium carbonate, upon which the sulphonium salt was isolated, or by treatment with potassium t-butoxide in the presence of ω-benzoylstyrene, whereupon re-formed ylide was trapped to afford an 80% yield of 1-phenyl-2-benzoylcyclopropane. It was concluded that (160) must be formed from the reversible reaction of benzaldehyde and a sulphoxonium ylide. The contrasting situation for sulphonium ylides was demonstrated by treatment of the diastereomer (161), obtained from



(161)

optically active n-butylsulphinylmethylide with benzaldehyde followed by conversion of the sulphoxide into a methylsulphonium salt, with dimsyl-sodium to afford the sulphonium alkoxide, which eliminated sulphide to afford styrene oxide in 90% optical purity. Clearly, the intermediate adduct from a sulphonium ylide and an aldehyde proceeds to oxiran faster than it reverts to ylide and aldehyde. Thus, in their reaction with carbonyl compounds, the betaine-forming initial step is reversible with sulphoxonium ylides but not with sulphonium ylides.

The reaction of (159) with 4-t-butylcyclohexanone afforded a mixture of the axial and equatorial adducts. However, methylation of the *N*-methyl-iminosulphoxonium adducts to afford the dimethylaminosulphoxonium salts followed by treatment with dimsylsodium afforded only the oxiran that would have resulted from equatorial attack of a sulphoxonium ylide. In contrast, the reaction of phenylthiomethylide with the same ketone also afforded a mixture of the axial and equatorial adducts but each of these, after methylation and treatment with sodium hydride in THF, separately afforded the oxirans expected from attack of a sulphonium ion at the axial and equatorial positions, respectively. Once again it appears that the initial reaction with a sulphonium ylide was irreversible while that with a sulphoxonium ylide was reversible.

Johnson *et al.*[99] reported additional examples which further illustrate the situations described in the preceding paragraphs. It was concluded that sulphonium ylide reactions generally were subject to kinetic control and were irreversible, thus leading to mixtures of products in some instances. Any alteration in the structure of the ylide to provide increased stabilization would lead to increased reversibility and a shift toward thermodynamic control of the reaction. For example, dimethylsulphonium-methylide reacts with the carbonyl group of cyclohexen-2-one but dimethylsul-phoniumethoxycarbonylmethylide reacts with the olefin group. The product ratios with sulphonium ylides are controlled by the relative rates of the

initial condensation step. In contrast, it was concluded that sulphoxonium ylide reactions generally were subject to thermodynamic control, with the product ratio being determined by the equilibrium among the betaines and the ratio of the rates of the product-producing steps. This particular publication by Johnson, Schroek, and Shanklin[99] is one of the most significant and comprehensive publications to appear regarding the mechanistic basis for the application of sulphur ylides to organic synthesis.

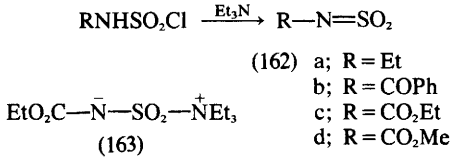
9 Sulphonyl- and Sulphinyl-amines

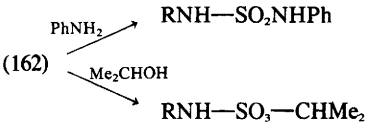
Some new chemistry has been reported for *N*-sulphonylamines, all of it from one laboratory. Atkins and Burgess[217] have published the full details of the work reported briefly in Volumes 1 and 2 of these Reports. The three *N*-sulphonylamines (162; a, R = ethyl; b, R = benzoyl; c, R = ethoxycarbonyl) all were prepared in solution by triethylamine-catalysed removal of the elements of HCl. No *N*-sulphonylamine has been isolated, but in the case of (162c) there was evidence for the existence of the triethylamine complex zwitterion (163), However, this substance participated in reactions as though it were a source of (162c). More recently, (162d; R = methoxycarbonyl) has been prepared by sodium-hydride-catalysed dehydrochlorination followed by complexation with triethylamine and then removal of the triethylamine in THF solution.[218,219]

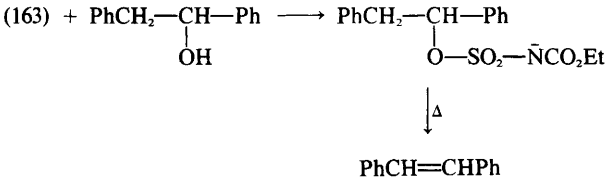
N-Sulphonylamines react with proton sources. Thus, the reaction of (162a) with aniline afforded the amide resulting from nucleophilic attack of nitrogen on sulphur.[217] The reaction with alcohols proceeded analogously. It was found that the initial adduct of (163) with an alcohol carrying a proton on the β-carbon would undergo elimination.[220] A *cis*-elimination was involved but considerable carbonium ion character was thought to be present in view of the occurrence of some rearrangements.

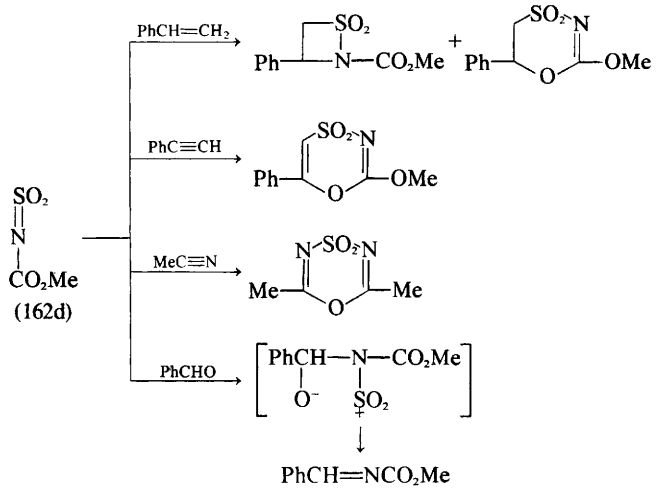
N-Sulphonylamines also react with unsaturated groups. For example, (162d) with styrene afforded a 4:1 mixture of the 1,4- and 1,2-adducts.[218] The reaction was stereospecific and the proportion of 1,2-adduct was increased by increasing the polarity of the solvent and the nucleophilicity of the olefin. Phenylacetylene and acetonitrile also reacted with (162d) to form 1,4-adducts.[218,219] With a vinylamine, (162a) afforded the 1:1 adduct (164), in which the sulphur atom apparently served as the electrophilic site of attack.[217] Similar reactions occurred with vinyl ethers, with 1,4-addition products being observed with *N*-sulphonylamides.[217] Benzaldehyde also reacted with (162d) to afford a benzylideneurethane.[218] In this reaction there is the clearest possible demonstration of the 'ylide-like' character of the *N*-sulphonylamines, with the initial adduct probably being a betaine which

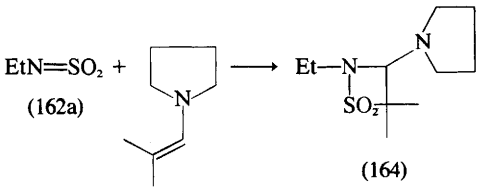
[217] G. M. Atkins, jun., and E. M. Burgess, *J. Amer. Chem. Soc.*, 1972, **94**, 6135.
[218] E. M. Burgess and W. M. Williams, *J. Amer. Chem. Soc.*, 1972, **94**, 4386.
[219] E. M. Burgess and W. M. Williams, *J. Org. Chem.*, 1973, **38**, 1249.
[220] E. M. Burgess, H. R. Penton, and E. A. Taylor, *J. Org. Chem.*, 1973, **38**, 26.


RNHSO2Cl
Et3N
R—N=SO2
(162) a; R = Et
b; R = COPh
c; R = CO2Et
d; R = CO2Me
EtO2C—N—SO2—NEt3
(163)


PhNH2
(162)
Me2CHOH
RNH—SO2NHPh
RNH—SO3—CHMe2


(163) + PhCH2—CH—Ph
OH
PhCH2—CH—Ph
O—SO2—NCO2Et
Δ
PhCH=CHPh


SO2
N
CO2Me
(162d)
PhCH=CH2
PhC≡CH
MeC≡N
PhCHO
Ph
N—CO2Me
SO2
O
OMe
Me
PhCH—N—CO2Me
O⁻
SO2
PhCH=NCO2Me

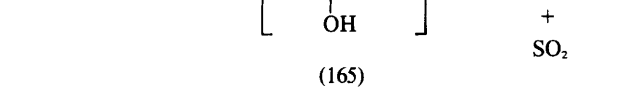

EtN=SO2 +
(162a)
Et—N
SO2
(164)

transfers oxygen from carbon to sulphur in a manner analogous to the Wittig reaction of phosphonium ylides with carbonyl compounds. On the basis of all of this evidence, it seems clear that *N*-sulphonylamines possess a N=S group with at least some of the characteristics of iminosulphuranes.

No new methods for the preparation of *N*-sulphinylamines, R—N=S=O, have been reported. Additional examples of the reaction of thionyl chloride with amines and amides have been reported.[221,222] Oberhammer[196] has reported CNDO/2 calculations on HNSO and ClNSO which predict the N—S—O angle to be 130° and 119°, respectively, and the charge densities for the former to be −0.20 on N and +0.02 on S. Through examination of the mass spectra of *N*-sulphinylamines, Grunwell and Kochan[223] concluded that the *trans* configuration dominated and was more stable, as their calculations had predicted.

Additional examples of the base-catalysed conversion of *N*-sulphinylamines into sulphurdi-imides have been reported[221,222] but the reaction failed with *N*-sulphinylphenylhydrazine.[224] Treatment with hydrogen chloride converts *N*-sulphinylamides into amines and $SOCl_2$, the reverse of the synthesis reaction.[221] Previously it had been reported that *N*-sulphinylamines reacted with carboxylic acids to eliminate SO_2 and form carboxamides,[225] with the mechanism proposed to involve cleavage of the sulphinylamine to an amine and $SOCl_2$, and subsequent reaction of the latter with the carboxylic acid to form an acyl halide, which acylated the amine. Bentz and Nischk[226] reported the reaction to occur using *N*-sulphinyltosylamide, a situation which should preclude the presence of either $SOCl_2$ or HCl. A new report has appeared which examines in detail the mechanism of the reaction between thionylaniline and formic acid, and it is concluded that a bimolecular, second-order reaction prevails, with the formation of an intermediate whose presence can be detected in the n.m.r. spectrum of the reaction mixture. The intermediate is proposed to be (165), with its collapse to afford SO_2 by analogy with other known reactions of sulphinylamines.[227]

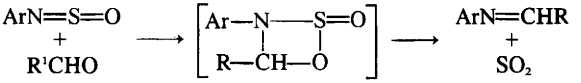
N-Sulphinylamines react with a variety of unsaturated compounds. Reaction with aldehydes appears to proceed *via* an adduct (166), which



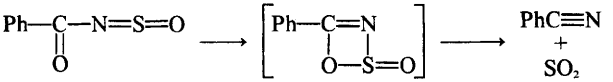
(165)

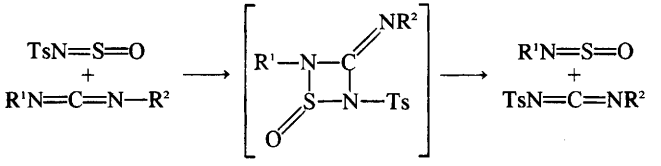
[221] E. S. Levchenko and E. M. Dorokhova, *J. Org. Chem.* (*U.S.S.R.*), 1972, **8**, 2573.
[222] G. Tomaschewski and C. Maniewski, *Tetrahedron Letters*, 1973, 561.
[223] J. R. Grunwell and A. Kochan, *J. Org. Chem.*, 1973, **38**, 1610.
[224] C. Carpanelli, G. Leandri, and G. P. Corallo, *Gazzetta*, 1972, **102**, 539.
[225] W. T. Smith and G. G. King, *J. Org. Chem.*, 1959, **24**, 976.
[226] F. Bentz and G. E. Nischk, *Angew. Chem. Internat. Edn.*, 1970, **9**, 66.
[227] F. Yamada, T. Nishiyama, and T. Emi, *Bull. Chem. Soc. Japan*, 1972, **45**, 271.

loses SO_2 much in the manner of a Wittig-type reaction of iminophosphoranes with aldehydes.[222,228] The pyrolysis of *N*-sulphinylbenzamide to benzonitrile probably occurs by the same route.[221] In a similar manner, nitrosobenzene reacted with thionylaniline to afford azobenzene.[229] Substituted 1,3-butadienes undergo 1,4-addition by sulphinylamines and it has now been reported that the orientation of the addition varies with the location of the substituent.[230] Two groups have reported the reaction of sulphinylamides with carbodi-imides, the net result being the interchange of nitrogen functions, presumably *via* (167) as an intermediate.[231,232] This reaction failed with a sulphinylamine.[232]



(166)

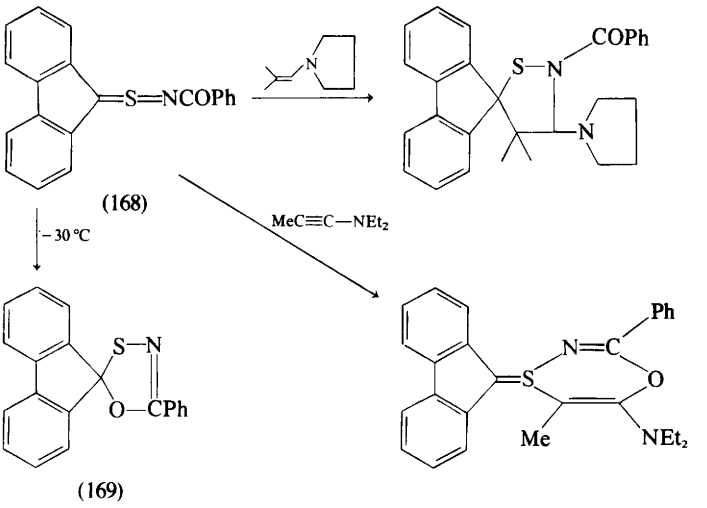




(167)

The unique substance (168) should be mentioned because its structure should reflect some of the characteristics of a sulphine (benzoylimido-group in place of oxygen) and some of the characteristics of a *N*-sulphinylamine (fluorenylidene in place of oxygen). It was obtained by allowing *N*-chlorosulphenylbenzamide to react with diazofluorene and then dehydrohalogenating the reaction product with triethylamine. It spontaneously cyclized to (169) at −30 °C but would react with vinylamines in a manner reminiscent of sulphenes, *N*-sulphonylamines, and *N*-sulphinylamines.[233] A similar structure (124) was obtained from the reaction of chloramine-T with benzotrithione.[141]

[228] N. S. Zefirov and T. M. Pozdnyakova, *J. Org. Chem.* (*U.S.S.R*), 1971, **7**, 966.
[229] T. M. Pozdnyakova and N. S. Zefirov, *J. Org. Chem.* (*U.S.S.R.*), 1972, **8**, 1120.
[230] G. Kresze and U. Wagner, *Annalen*, 1972, **762**, 93.
[231] H. Ulrich, B. Tucker, and A. A. R. Sayigh, *J. Amer. Chem. Soc.*, 1972, **94**, 3484.
[232] T. Minami, M. Fukuda, M. Abe, and T. Agawa, *Bull. Chem. Soc. Japan*, 1973, **46**, 2156.
[233] E. M. Burgess and H. R. Penton, *J. Amer. Chem. Soc.*, 1973, **95**, 279.

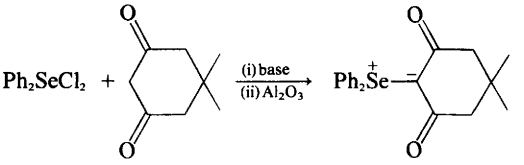


(169)

10 Ylides of Selenium and Tellurium

During the two-year period covered by this Report, no work has appeared on the chemistry of tellurium ylides.

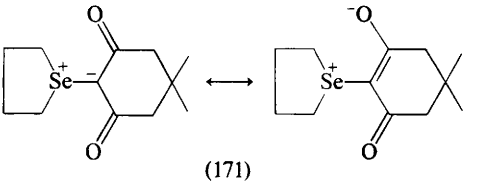
Five separate reports have appeared on the preparation, properties, and reactions of selenium ylides. The reaction of dimedone with dichlorodiphenylselenium afforded a selenonium salt, which was converted into the ylide (170) by chromatography on alumina.[234] Based on this reaction, the



(170)

condensation of a variety of active-methylene compounds with a variety of dichloroselenides in the presence of KOH–MeOH afforded a number of stable, isolable selenonium ylides.[235] The i.r., u.v., and n.m.r. spectra of these ylides were very similar to those of the corresponding sulphonium ylides. With the ready availability of these ylides, (171) was subjected to *X*-ray crystallographic analysis,[236] in which the key findings were as follows: (i) the two ring planes were at an angle of 85° to one another; (ii) the C—Se

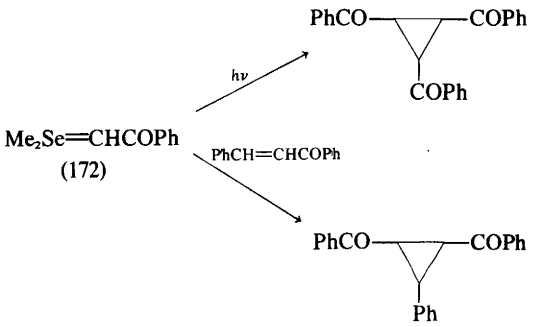
[234] N. N. Magdesieva and R. A. Kyandzhetsian, *J. Org. Chem.* (*U.S.S.R.*), 1971, **7**, 2316.
[235] N. N. Magdesieva, R. A. Kyandzhetsian, and A. A. Ibragimov, *J. Organometallic Chem.*, 1972, **42**, 399.
[236] V. V. Saatsazov, R. A. Kyandzhetsian, S. I. Kuznetsov, and N. N. Magdesieva, *Proc. Acad. Sci. U.S.S.R.*, 1972, **206**, 808.



(171)

bond length was intermediate between typical single bonds (1.90—1.95 Å) and typical double bonds (1.80 Å) at 1.88 Å, indicating some π-bond character; (iii) the C—O bonds (1.29 and 1.30 Å) are intermediate between single-bond (1.40 Å) and double-bond (1.20 Å) length, indicating some enolate character, as identified through the i.r. spectra.

More recently, dimethylselenoniumphenacylide (172) has been prepared



from the conjugate acid and isolated as a crystalline solid.[237] It was found to decompose to tribenzoylcyclopropane on photolysis, just as did the sulphoniumphenacylide. The ylide effected a Michael addition with ω-benzoylstyrene to afford the cyclopropane in high yield, but there was no report of an attempt to make the ylide react with an aldehyde and to detect oxiran formation, as for sulphonium ylides.

The availability of these new synthetic methods and the demonstrable stability of these selenonium ylides should lead to an opening up of the field of selenonium ylides to extensive exploration.

[237] W. W. Lotz and J. Gosselck, *Tetrahedron*, 1973, **29**, 917.

7

Heterocyclic Compounds of Quadricovalent Sulphur

BY D. H. REID

1 Introduction

Much of the work reported in this area during the past two years involves the consolidation or extension of ideas previously reported in preliminary form.[1] A short review of Cava's work on thieno[3,4-*c*]thiophens has been published.[2]

2 Thiabenzenes

2,4,6-Triphenylthiapyrylium salts react with *p*-dimethylaminophenylmagnesium bromide to give[3] a mixture of the thiapyrans (1) and (2). A transient purple coloration indicated the intermediacy of the thiabenzene (3), which had previously been isolated[4] from the reaction of 2,4,6-triphenylthiapyrylium iodide with *p*-dimethylaminophenyl-lithium. The thiabenzene (3) prepared by the latter reaction rearranges to a mixture of the thiapyrans (1) and (2) on being heated in benzene, when treated with hydrogen chloride in ether–benzene, or upon irradiation in sunlight. Whereas 9-phenylthioxanthylium reacts[5] with phenylmagnesium bromide or methylmagnesium iodide to give 9,9-diphenylthioxanthene (4) or 9-methyl-9-phenylthioxanthene (5), reaction with phenyl-lithium occurs at sulphur and affords the thia-anthracene (6). The participation of radicals is suggested.

The thiapyrans (7) and (8) react with sodium amide in liquid ammonia or with t-butyl-lithium in THF to give the stable deep red anion (9).[6] The high acidity of the thiapyran (7) (pK_a *ca.* 20) compared with that of the oxygen analogue (10) (pK_a *ca.* 35) discounts phenyl conjugation as a major source of

[1] (*a*) See 'Organic Compounds of Sulphur, Selenium, and Tellurium', ed. D. H. Reid (Specialist Periodical Reports), The Chemical Society, London, 1970, Vol. 1, Ch. 7; (*b*) *ibid.*, 1973, Vol. 2, Ch. 6.

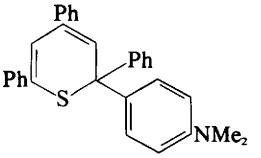
[2] M. P. Cava, *Internat. J. Sulfur Chem.* (*B*), 1972, **7**, 55.

[3] C. C. Price and H. Pirelahi, *J. Org. Chem.*, 1972, **37**, 1718.

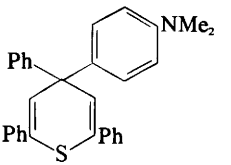
[4] C. C. Price, J. Follweiler, H. Pirelahi, and M. Siskin, *J. Org. Chem.*, 1971, **36**, 791.

[5] M. Hori, T. Kataoka, Y. Asahi, and E. Mizuta, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 1692.

[6] R. R. Schmidt and U. Burkert, *Tetrahedron Letters*, 1973, 4355.



(1)



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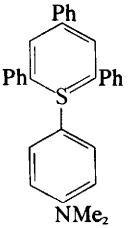

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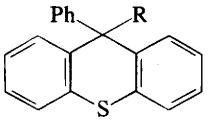
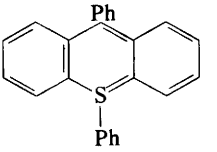
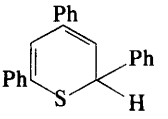


(4) R = Ph
(5) R = Me

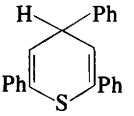


(6)

the stability of the anion (9). It is proposed that the anion (9) is a 6π-electron thiabenzene anion in which the negative charge resides on the sulphur atom and two electrons occupy a low-lying *d*-orbital, rather than an 8π-electron antiaromatic species. The anion (9) reacts with D_2O to give the 2-deuterio-derivative of compound (7) and with alkyl and acyl halides to give 4-substituted thiapyrans (11).



(7)



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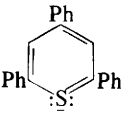
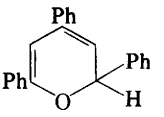


(9)



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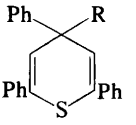
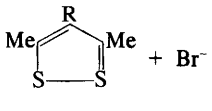


(11) R = alkyl or acyl

The mass spectra of 3,5-dimethyl- (12; R=H) and 3,4,5-trimethyl- (12; R=Me) 1,2-dithiolium bromide show a strong peak arising from the loss of H· from the cation. The dithiabenzene structures (13) are suggested[7] as alternatives to (14) for the ions responsible for these peaks.

The question of the importance of 3*d*-orbitals in supporting electron delocalization through sulphur was examined by studying *inter alia*

[7] C. T. Pedersen and J. Møller, *Tetrahedron*, 1974, **30**, 553.



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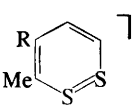
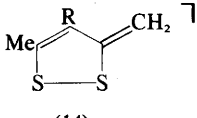


(13)



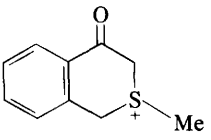
(14)

R = H or Me

2-methyl-2-thianaphthalene derivatives.[8] Deprotonation of the sulphonium salt (15) obtained by methylation of isothiachroman-4-one gave compound (16), for which the β-carbonyl-stabilized sulphonium ylide structure (16a) appears to be the best expression of its properties. Compound (16) is formed reversibly from the salt (15), has $\nu_{(C=O)}$ at 1510 cm^{-1}, and shows a broad temperature-dependent ^1H n.m.r. resonance of δ3.7, which is typical of the exchange-broadened absorption of an ylide proton. The benzylic protons are non-equivalent (J=15.8 Hz), indicating non-planarity of compound (16), and, by implication, pyramidal geometry at the sulphur atom. In contrast to the ylide proton (H-3), which exchanges instantaneously, the benzylic protons do not exchange in [$^2H_6$]DMSO containing D_2O, and no absorption is observed which could be attributed to the thianaphthol structure (17). The benzylic protons in compound (16) and in the open-chain ylide (18) possess comparable acidities and exchange at similar rates in [$^2H_6$]DMSO containing D_2O and NaOD. Also, the chemical shifts of the ylide protons in compounds (16) (δ 3.63) and (18) (δ 4.03) are similar. The significance of delocalization in compound (16) is therefore questionable. Methylation of compound (16) gave the methyl ether (19), which failed to react significantly with sodium methoxide in methanol. Deprotonation of the salt (19) with stronger bases (KOBu^t–DMSO) gave a highly coloured amorphous solid whose n.m.r. spectrum indicated that it is polymeric. The vinylic, benzylic, and SMe protons in the salt (19) exchanged at comparable rates in MeCN–[$^2H_6$]DMSO containing D_2O and NaOD, indicating that the thianaphthalene (20), if formed, is not markedly stable and rapidly reprotonates. It was concluded that there is no evidence to support the concept that conjugation effects are transmitted through sulphur.

A variant of the dimethyloxosulphonium methylide synthesis[9] of thiabenzene 1-oxides has been developed in which 2,2-diacyl-1-alkoxyethylenes (21) are used in place of αβ-ethynyl ketones (Scheme 1).[10] The thiabenzene 1-oxides (22)—(24) were obtained directly, but the stable intermediate (25) was isolated in the synthesis of the derivative (26) using diethyl ethoxymethylenemalonate. The H-2 and H-6 signals in the ^1H n.m.r. spectra of compounds (22)—(24) and (26) occur at relatively high field (H-2,

[8] C. Kissel, R. J. Holland, and M. C. Caserio, *J. Org. Chem.*, 1972, **37**, 2720.
[9] A. G. Hortmann, *J. Amer. Chem. Soc.*, 1965, **87**, 4972; A. G. Hortmann and R. L. Harris, *ibid.*, 1971, **93**, 2471.
[10] Y. Tamura, T. Miyamoto, H. Taniguchi, K. Sumoto, and M. Ikeda, *Tetrahedron Letters*, 1973, 1729.



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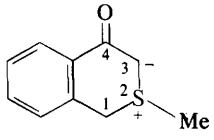
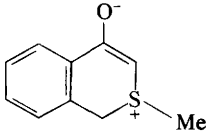
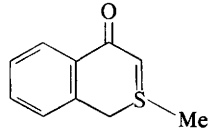


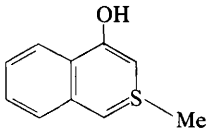
(16a)



(16c)



(16b)



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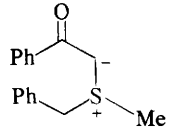

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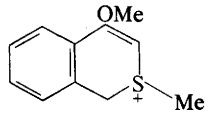
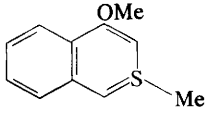


(19)



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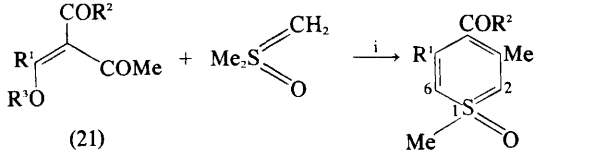
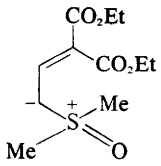


(21)

(22) $R^1 = H, R^2 = Me$
(23) $R^1R^2 = [CH_2]_3$
(24) $R^1 = H, R^2 = OEt$

Reagents: i, NaH–DMSO

Scheme 1



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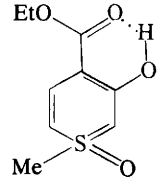
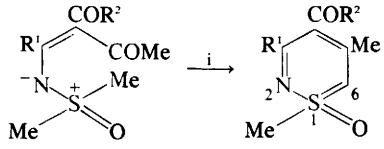


(26)

δ5.19—5.78; H-6, δ5.36—5.80), indicating the absence of a significant diamagnetic ring-current.

3 Azathiabenzenes

The use of dimethylsulphoximine in place of dimethyloxosulphonium methylide in the foregoing synthesis led to the 2-azathiabenzene 1-oxides (29) and (30) *via* the stable isolable ylides (27) and (28) (Scheme 2).[10] The



(27) $R^1 = H, R^2 = Me$ (29) $R^1 = H, R^2 = Me$

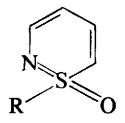
(28) $R^1R^2 = [CH_2]_3$ (30) $R^1R^2 = [CH_2]_3$

Reagents: i, NaH–DMSO

Scheme 2

absence of a significant diamagnetic ring-current in these compounds also is evident from the high-field position of the H-6 signal in their ^1H n.m.r. spectra. Cram has published full details[11] of his synthesis[12] of heterocyclic systems containing carbon, nitrogen, and chiral sulphur. These include the 2-azathiabenzene (1,2-thiazene) 1-oxides (31), the 2-aza-1-thianaphthalene 1-oxides (32), and the 2,4-diaza-1-thianaphthalene 1-oxide derivatives (33) and (34). In a synthetic procedure related to that of Cram, the sulphoxides (35) were converted into the 2,4-diaza-1-thianaphthalene 1-oxides (37) by the action of hydrazoic acid.[13] The intermediate sulphoximines (36) were not isolated, and in certain cases suffered deacylation to give the side-products (38). The 3-chloromethyl derivatives (37; $R=CH_2Cl$) are ring-opened by sodium hydroxide to give the intermediates (39), which re-cyclize to the benzo[*f*]-1,2,5-thiadiazepines (40). In an extension[14] of this work the

[11] T. R. Williams and D. J. Cram, *J. Org. Chem.*, 1973, **38**, 20.
[12] T. R. Williams and D. J. Cram, *J. Amer. Chem. Soc.*, 1971, **93**, 7333; see ref. 1(*b*).
[13] E. Cohnen and J. Mahnke, *Chem. Ber.*, 1972, **105**, 757.
[14] E. Cohnen and J. Mahnke, *Chem. Ber.*, 1973, **106**, 3368.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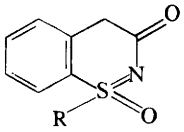
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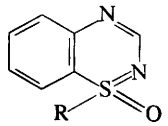
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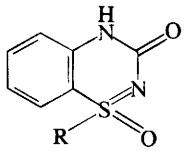

(34)

aminosulphoximines (41) were condensed with aldehydes and ketones to give the 2,4-diaza-1-thianaphthalene 1-oxides (42). The 3-chloromethyl derivative (42; R^1=Cl, R^2=R^3=R^4=H, R^5=CH_2Cl) is rearranged by sodium alkoxide into the benzo[*f*]-1,2,5-thiadiazepine (44) *via*, it is suggested, the aziridine (43).

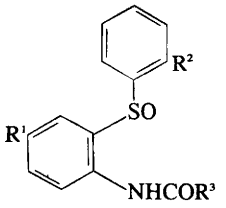
4 Thieno[3,4-c]thiophens and Related Compounds

Thieno[3,4-c]thiophens.—Full details have been published[15] of attempts to synthesize 1,3-dimethylthieno[3,4-*c*]thiophen (45) and of an extension of the method to the preparation of the air- and light-sensitive ester (46). A Pummerer-type reaction of the sulphoxide (47) in boiling acetic anhydride afforded the orange compound (46), which could not be isolated but was trapped as a mixture of the *exo*-(48) and *endo*- adducts with *N*-phenylmaleimide. Cycloaddition of *N*-phenylmaleimide to the transient dimethyl derivative (45) and to the dimethyl ester (46) occurs in the ring of highest electron density [(45):1,3; (46):4,6]. A full account has been given[16] of the preparation and reactivity of tetraphenylthieno[3,4-*c*]thiophen (49), the first stable member of this series of heterocyclic systems. Compound (49) is formed by boiling the sulphoxide (50) in acetic anhydride or by thionation (P_2S_5–xylene) of tetrabenzoylethylene, and in the latter reaction is accompanied by the dihydro-derivative (51). A new synthetic approach[17] to compounds of this type involves the 1,3-dipolar addition of acetylenes to anhydro-azolium hydroxides. Dibenzoylacetylene reacted with the anhydrothiazolium hydroxide (52) to give the diketone (53), which, when thionated (P_2S_5–pyridine), yielded compound (49). Tetraphenylthieno[3,4-*c*]thiophen is a non-polar compound with a singlet ground state,[16] in contrast

[15] M. P. Cava, N. M. Pollack, and G. A. Dieterle, *J. Amer. Chem. Soc.*, 1973, **95**, 2558; M. P. Cava and N. M. Pollack, *ibid.*, 1967, **89**, 3639; see ref. 1(*a*).

[16] M. P. Cava, M. Behfourouz, G. E. M. Husbands, and M. Srinivasan, *J. Amer. Chem. Soc.*, 1973, **95**, 2561; M. P. Cava and G. E. M. Husbands, *ibid.*, 1969, **91**, 3952; see ref. 1(*a*).

[17] K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, 1973, **95**, 2750.



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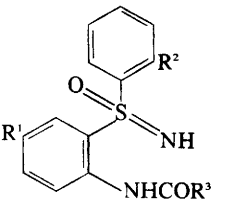

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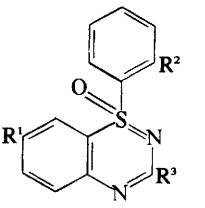

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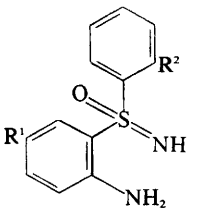
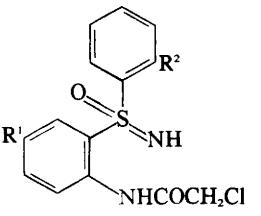


(38)



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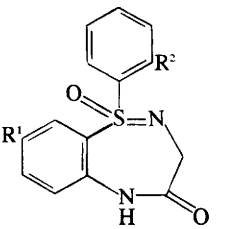

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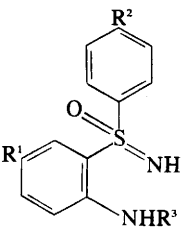

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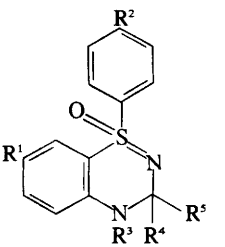

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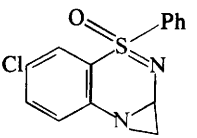

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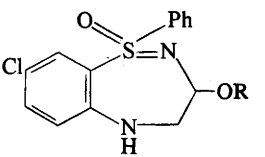
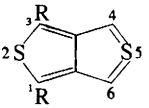
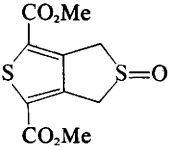


(44) R = Me or Bu^n



(45) R = Me
(46) R = CO_2Me



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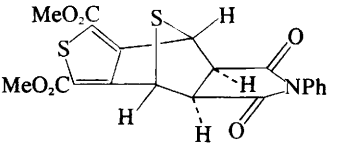
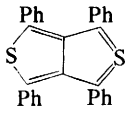


(48)



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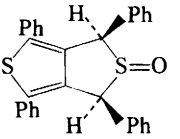

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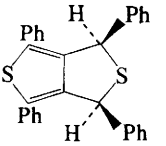

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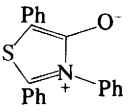

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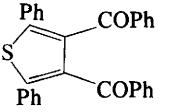
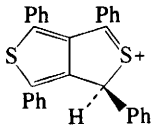


(53)

to the predicted[18] triplet ground state of (unsubstituted) thieno[3,4-*c*]thiophen. It reacts[16] under appropriate conditions by 1,3-addition, with hydrogen (Pd/C) to give the dihydro-derivative (51), with chromic acid to give the diketone (53), and with methanol–acid to give the ether (55) *via* the hypothetical cation (54). Though stable to light, compound (49) is photo-oxidized (by O_2) to a mixture of the diketone (53), the monothione (56), and the sulphine (57), presumably *via* the peroxide (58). Cycloaddition occurs under forcing conditions, *N*-phenylmaleimide giving a mixture of the *exo*-(59) and *endo*-adducts and dimethyl acetylenedicarboxylate with loss of sulphur to give the benzo[*c*]thiophen (60).

An *X*-ray crystal structure determination[19] shows (Figure 1) the heterocyclic part of tetraphenylthieno[3,4-*c*]thiophen (49) to be planar, with the phenyl groups at C-1 and C-4 twisted out of the molecular plane by 39.6° and those at C-3 and C-6 by 58.4°. The lack of coplanarity of the phenyl groups with the heterocyclic system and the fact that the ring–phenyl bond lengths are typical of sp^2–sp^2 single C—C bonds precludes appreciable electronic stabilization by conjugation with the phenyl substituents. A comparison of the C—S and C—C bond lengths in compound (49) with those in thiophen (C-2—S, 1.714; C-2—C-3, 1.37; C-3—C-4, 1.423 Å) and thieno[2,3-*b*]thiophen (61) (C-2—S, 1.73; C-2—C-3, 1.36; C-3—C-3a, 1.41 Å)

[18] D. T. Clark, *Tetrahedron*, 1968, **24**, 2567.
[19] M. D. Glick and R. E. Cook, *Acta Cryst.*, 1972, **B28**, 1336.



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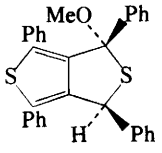

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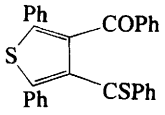
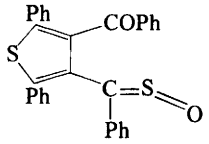


(56)



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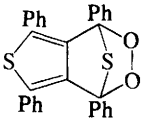

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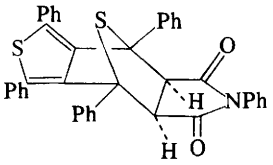

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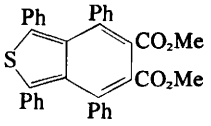

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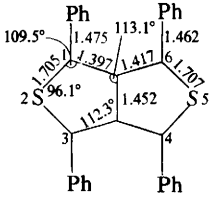
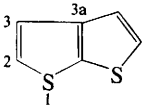


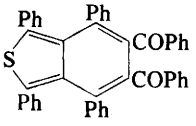
Figure 1 *Molecular dimensions of tetraphenylthieno*[3,4-c]*thiophen* (*lengths*/Å)



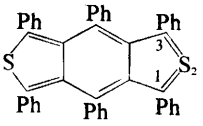
(61)

indicates the occurrence of more extensive peripheral π-electron delocalization in compound (49).

Thionation (P_2S_5–pyridine) of the diketone (62), obtained by the ready cycloaddition of dibenzoylacetylene to tetraphenylthieno[3,4-*c*]thiophen (49), afforded the stable blue hexaphenylthieno[3,4-*f*]benzo[*c*]thiophen (63) (M^+, 100%).[17] Like simple thieno[3,4-*c*]thiophens, compound (63) gives a 1,3-*exo*-adduct with *N*-phenylmaleimide. Thionation of the diketone (62) in xylene gave a blue solution, doubtless containing compound (63), but work-up yielded the dihydro-derivative (64).[16] This is supposed to arise by hydrogen transfer from the solvent to the intermediate (63). Attempted aromatization of the dihydro-compound with DDQ gave the diketone (62), possibly consequent upon the addition of oxygen across positions 1 and 3 of the intermediate dehydrogenation product (63). Thionation of 1,2,4,5-tetrabenzoylbenzene in xylene likewise gave the dihydro-derivative (65) and not the desired compound (66).[16]



(62)



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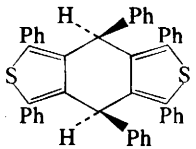

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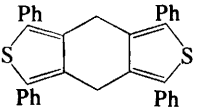

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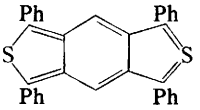
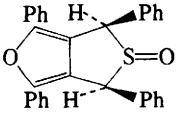


(66)

Thieno[3,4-*c*]furans.—Tetraphenylthieno[3,4-*c*]furan (68), the first reported member of this system, has been prepared in solution by heating the sulphoxide (67) in acetic anhydride.[20] A violet compound, it could not be isolated, but when generated in the presence of dimethyl acetylenedicarboxylate it formed the adduct (69).

Thieno[3,4-*c*]pyrroles.—Two routes to the tetraphenyl derivative (71) have been described. The reaction of tetrabenzoylethylene with methylamine

[20] M. P. Cava and M. A. Sprecker, *J. Amer. Chem. Soc.*, 1972, **94**, 6214.



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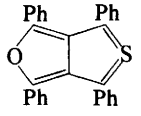
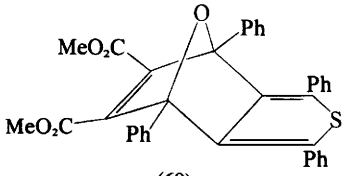
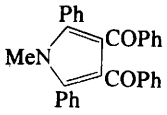


(68)



(69)

gave the pyrrole (70), which, when thionated in toluene, yielded an air-stable red powder consisting principally of the thienopyrrole (71).[20] The presence of this compound was established by formation of the adduct (72) with dimethyl acetylenedicarboxylate. The thienopyrrole (71) thus prepared showed no e.s.r. signal, indicating a singlet ground state for the compound. The pyrrole (70) was also obtained[21] by cyclization of *N*-benzoyl-*N*-phenylsarcosine (73) with acetic anhydride, and 1,3-dipolar addition of



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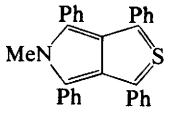
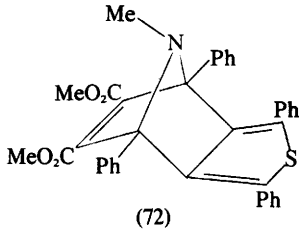


(71)



(72)

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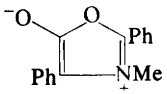

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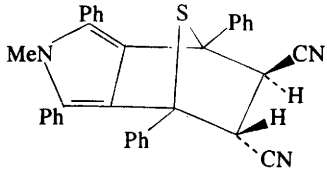

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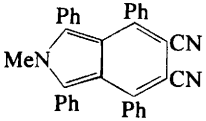

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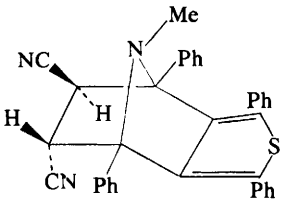
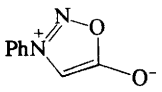


(77)

[21] K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, 1973, **95**, 2749.

dibenzoylacetylene to the resulting anhydro-oxazolium hydroxide (74) with concomitant loss of carbon dioxide. Thionation of the pyrrole (70) (P_2S_5–pyridine) gave the red compound (71), which was stable in the solid state but underwent photochemical decomposition in solution. Compound (71) is a reactive dipolarophile which behaves as a thiocarbonyl and as an azomethine ylide.[21] With fumaronitrile in boiling toluene it gives the thermodynamically more stable thiocarbonyl ylide adduct (75) together with a small amount of the isoindole (76), which is formed irreversibly from the adduct (75) by loss of hydrogen sulphide. In boiling xylene the yield of compound (76) increases at the expense of (75). In contrast, reversible cycloaddition occurs in benzene, involving the azomethine ylide system, and it affords the adduct (77). In boiling xylene the adduct (77) equilibrates with compound (71), which is then converted into the final products (76) and, in small amount, (75).

Thieno[3,4-*c*]pyrazoles.—Cycloaddition of dibenzoylacetylene to *N*-phenylsydnone (78) afforded the pyrazole (79), which, when thionated (P_2S_5–pyridine), gave in high yield the stable triphenylthieno[3,4-*c*]pyrazole (80), the first reported member of this class.[22] Compound (80) enters into cycloaddition reactions, notably with dibenzoylacetylene, with loss of sulphur, giving the diketone (81). Thionation of compound (81) gives, in high yield, the stable blue-black quadricovalent species (82). The mass spectra of



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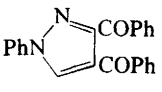

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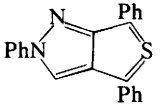
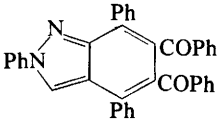


(80)



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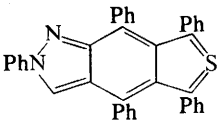


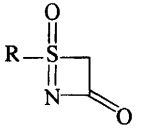
(82)

both compounds (80) and (82) reflect their stability. Both compounds give intense molecular-ion peaks and peaks arising from doubly charged molecular ions [(80): M^+, 100%; M^{2+}, 13%. (82): M^+, 100%; M^{2+}, 17%).

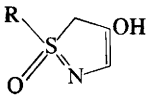
5 Miscellaneous Ring Systems

Full details have been published[11] of the preparation and reactions of the thiazetine 1-oxides (83) and the dihydroisothiazole 1-oxides (84).[12] Sodium

[22] K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, 1972, **94**, 6215.

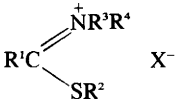


(83)



(84)

azide reacts with the *S*-alkylation products (85) of *NN*-disubstituted thioamides to give colourless products which are formulated as the thiatriazoles (86), rather than simple addition products (87), on the basis of



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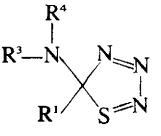

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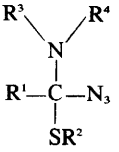
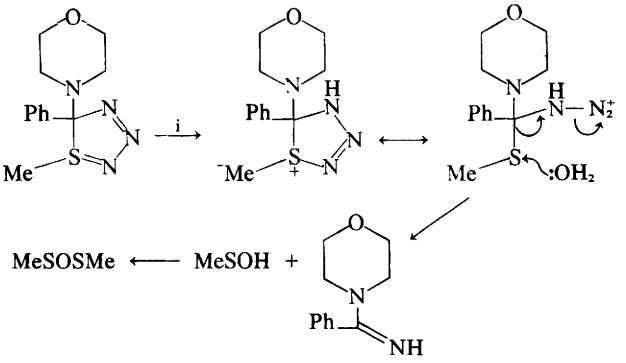


(87)

their spectroscopic and chemical properties.[23] Thus their i.r. spectra show no azide absorption, and their u.v. spectra consist of two intense bands at *ca.* 255 and 314 nm that are not shifted significantly by variation in the nature of the group R.[1] When treated with acid the thiatriazoles evolve nitrogen and give amidines together with thiolsulphinates (Scheme 3). In



Reagents: i, 2M-HCl; room temperature

Scheme 3

boiling toluene the thiatriazole (86; R^1=Ph, NR^3R^4=morpholino) decomposed smoothly with liberation of nitrogen and formation of the corresponding amidine. Benzaldehyde dimethyl dithioacetal was formed concomitantly in an unclarified process involving the solvent.

[23] S. I. Mathew and F. Stansfield, *J.C.S. Perkin I*, 1974, 540.

8

Thiophens and their Selenium and Tellurium Analogues

BY S. GRONOWITZ

1 General

This Report covers the period April 1972—March 1974. The continued interest in thiophen chemistry is evidenced by the fact that the number of references for this two-year period is as large as for the three-year period reviewed in Volume 2.

New cyclization reactions leading to thiophens have been discovered. Especially important is Brandsma's work on the cyclization of unsaturated sulphides.

Strained condensed rings such as thienocyclobutadienes have finally been synthesized. Isomer distributions in electrophilic substitution have been studied in detail by Gol'dfarb and co-workers, especially with deactivated derivatives.

The greatest progress, however, has occurred in the field of fused derivatives. Many methods for the synthesis of the long-sought thienopyrrole system have appeared. Interest is certainly focused on the pharmacological aspects of analogues of active indole derivatives. Interesting effects of thiophen fusion on tropylium ions, on their stability, spectral properties, and chemical reactivities have been found.

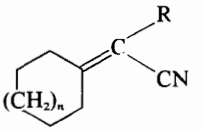
There has also been increasing interest in the chemistry of selenophens, and a paper on ^{77}Se n.m.r. of selenophens has appeared.

2 Monocyclic Thiophens

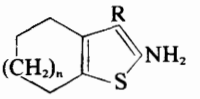
Synthesis of Thiophens by Ring-closure Reactions.—The Hinsberg reaction between α-diketones and dialkyl thiodiacetate has been used for the synthesis of a series of 3,4-disubstituted thiophen-2-carboxylates and -2,5-dicarboxylates.[1] The corresponding condensation of ethyl phenyl glyoxylate and methyl pyruvate with dialkyl thiodiacetate, which yields 3-phenyl- and 3-methyl-4-hydroxythiophen-2,5-dicarboxylates, proceeds through a

[1] C. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin I*, 1972, 2079.

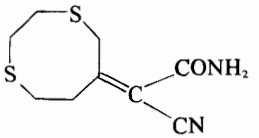
Dieckmann-type reaction mechanism and not through a Stobbe-type reaction mechanism, as is the case in the Hinsberg reaction with α-diketones.[2] The usefulness of the Gewald reaction for the synthesis of 2-amino-3-carbonyl-substituted thiophens, important building-blocks for the synthesis of fused thiophens, has clearly been demonstrated. From the condensation products of cycloalkanones and nitriles (1), the thiophens (2) were obtained through the reaction with sulphur in the presence of diethylamine.[3] Similarly, from the dithiacyclo-octane derivative (3), the thiophen (4) was prepared.[4] In connection with the synthesis of psychopharmaca of the diazepine type, several substituted 2-amino-3-benzoylthiophens (5) were prepared through the reaction of phenacyl cyanides with aldehydes



(1) R = CN, $CONH_2$, or CO_2Et



(2) R = CN, $CONH_2$, or CO_2Et



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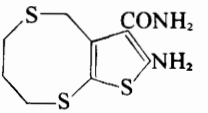

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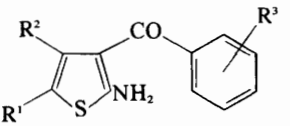
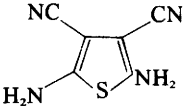


(5)

and sulphur and triethylamine or by means of the other variant of the Gewald reaction, using α-mercapto-aldehydes or -ketones.[5–7] Gewald has recently studied the reaction of nitriles, such as malononitrile, ethyl cyanoacetate, cyanoacetamide, and benzyl cyanide, with sulphur in the presence of bases (Willgerodt conditions). From malononitrile, 2,5-diamino-3,4-dicyanothiophen (6) and 2,4-diamino-3,5-dicyanothiophen were obtained in 30% and 20% yields, respectively.[8] Compound (6) had earlier been

[2] P. P. Paranjpe and G. Bagavant, *Indian J. Chem.*, 1973, **11**, 313.
[3] V. P. Arya, *Indian J. Chem.*, 1972, **10**, 1141.
[4] V. P. Arya, *Indian J. Chem.*, 1972, **10**, 812.
[5] O. Hromatka, D. Binder, and P. Stanetty, *Monatsh.*, 1973, **104**, 709.
[6] O. Hromatka, D. Binder, C. R. Noe, P. Stanetty, and W. Veit, *Monatsh.*, 1973, **104**, 715.
[7] M. Nakanishi, Y. Kato, T. Furuta, N. Arima, and H. Nishimine, *J. Pharm. Soc. Japan*, 1973, **93**, 311.
[8] K. Gewald, M. Kleinert, B. Thiele, and M. Hentschel, *J. prakt. Chem.*, 1972, **314**, 303.

obtained through the reaction of tetracyanoethylene and hydrogen sulphide, and both reactions are assumed to proceed through tetracyanoethane. In the formation of (7), 2-amino-1,1,3-tricyanopropene (8) is assumed to be the



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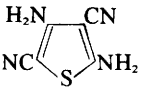

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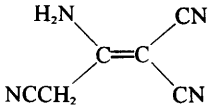
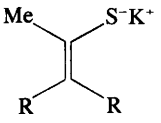


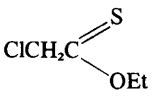
(8)

intermediate. Treating (8) with sulphur and diethylamine in *NN*-dimethylformamide gave 85% of (7). This reaction path is thus another example of the formation of thiophens from derivatives of alkylidenecyanoacetic acids and sulphur.

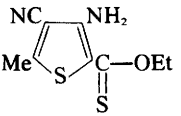
In the reaction of ethyl cyanoacetate with sulphur and base, 2,4-diamino-3,5-di(ethoxycarbonyl)thiophen was only the minor product (20%). The major products were pyrrole derivatives.[8] From cyanoacetamide and benzyl cyanide no thiophen derivatives were obtained.[8] The reaction of (9a) with (10) in the presence of triethylamine yields the aminothiophen (11), while (9b) gives the hydroxythiophen (12). If the salt of ethyl (thiobenzoyl)



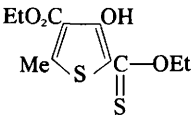
(9) a; R = CN
b; R = CO_2Et



(10)

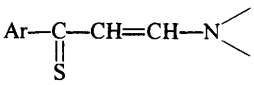


(11)



(12)

cyanoacetate is used, a mixture of amino- and hydroxy-thiophens is obtained.[9] Vinylogous thioamides (13) react with bromoacetone to give 2-acetyl-5-arylthiophens, probably *via* the intermediate (14).[10]



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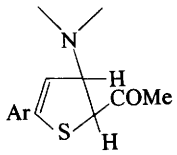
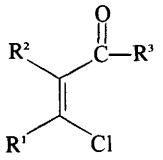


(14)

The reaction between 2-chlorovinylcarbonyl derivatives (15) and thioglycolate (16), leading to substituted thiophen-2-carboxylates (17), and originally described by Fiesselmann only in patents and doctoral theses from

[9] K. Hartke and G. Gölz, *Annalen*, 1973, 1644.
[10] J.-C. Meslin, *Compt. rend.*, 1973, **277**, *C*, 1391.



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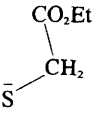

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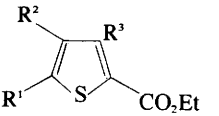
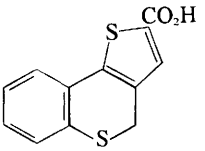
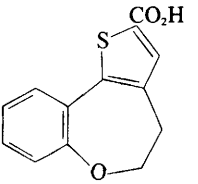


(17)

the University of Erlangen, has been reinvestigated.[11,12] Using this approach, the complex thiophen derivatives (18)—(21) were synthesized. The somewhat similar reaction of the dimer of β-mercaptocinnamic aldehyde with phenacyl bromide leads to 2-benzoyl-5-phenylthiophen.[13]



(18)



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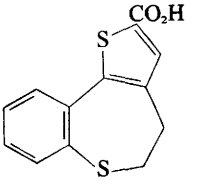

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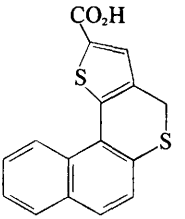
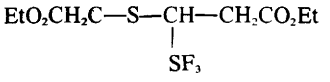


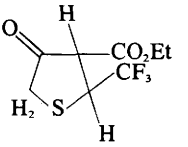
(21)

Dieckmann cyclization of (21a) gave, depending upon conditions, either (21b) or (21c) predominantly. These compounds were transformed into the thiophens (21d) and (21e).[13a] The acid-catalysed reaction of (22) with hydrogen sulphide at −35 °C leads *via* the enethiol to ethyl 2,5-dimethyl thiophen-3-carboxylate as the main product.[14] The monoacetals of substituted succinaldehyde (23), which are conveniently prepared through hydroformylation of αβ-unsaturated aldehyde acetals with *trans*-bis(triphenylphosphine)carbonyl chlororhodium(I) as catalyst, have been used for the synthesis of optically active 3-substituted thiophens (from optically active αβ-unsaturated aldehyde acetals) through the acid-catalysed reaction with

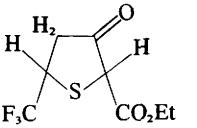
[11] N. D. Trieu and S. Hauptmann, *Z. Chem.*, 1973, **13**, 57.
[12] S. Hauptmann and E.-M. Werner, *J. prakt. Chem.*, 1972, **314**, 499.
[13] M. Pulst, M. Weissenfels, and L. Beyer, *Z. Chem.*, 1973, **13**, 287.
[13a] O. Hromatka, D. Binder, and K. Eichinger, *Monatsh.*, 1974, **105**, 127.
[14] F. Duus, *Acta Chem. Scand.*, 1973, **27**, 466.



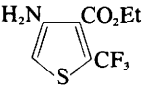
(21a)



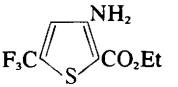
(21b)



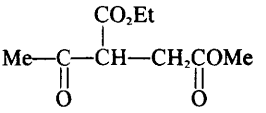
(21c)



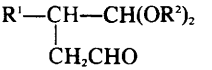
(21d)



(21e)

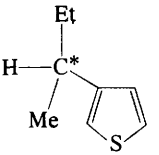


(22)

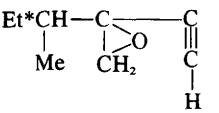


(23)

hydrogen sulphide.[15] Optically active 3-s-butylthiophen (24) was also prepared through the reaction of optically active s-butylsuccinic acid and P_4S_{10} and through the reaction of (25) with barium hydroxide and hydrogen



(24)



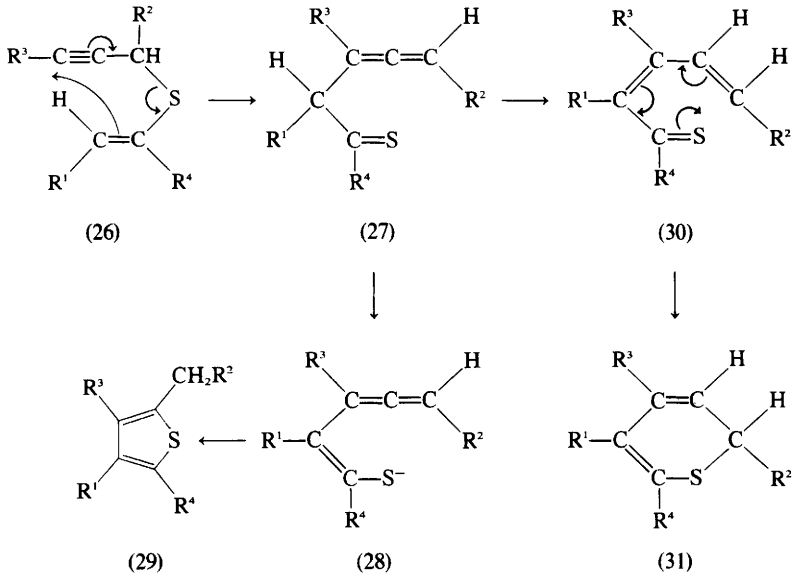
(25)

sulphide.[15] The method *via* the monoacetal gave least racemization and was considered most convenient. Ethers derived from diacetylenes, for instance ferrocenylphenyl ethers of diacetylenic alcohols, as well as diaryl ethers of such alcohols and also some amino-derivatives, have been transformed into 2,5-disubstituted thiophen derivatives through the reaction with sodium hydrogen sulphide.[16–18a] 3,4-Diphenylthiophen was one of the products in the reaction of *cis*- or *trans*-1,4-dibromo-2,3-diphenylbut-2-ene with sodium polysulphide in DMF.[19]

Brandsma has continued his important work on the synthesis of

[15] C. Botteghi, L. Lardicci, and R. Menicagli, *J. Org. Chem.*, 1973, **38**, 2361.
[16] A. G. Makhsumov, T. Yu. Nasriddinov, and A. M. Sladkov, *Zhur. org. Khim.*, 1971, **7**, 1764.
[17] A. G. Makhsumov and E. A. Mirzabaev, *Khim. geterotsikl. Soedinenii*, 1970, **6**, 713.
[18] A. G. Makhsumov, A. Safaev, and E. A. Mirzabaev, *Zhur. org. Khim.*, 1969, **5**, 1510.
[18a] A. S. Zanina, G. N. Khabibulina, V. V. Legkoderya, and I. L. Kotlyarevskii, *Zhur. org. Khim.*, 1972, **8**, 1527.
[19] R. M. Dodson, V. Srinivasan, K. S. Sharma, and R. F. Sauers, *J. Org. Chem.*, 1972, **37**, 2367.

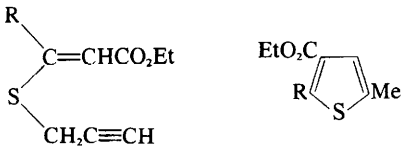
thiophens from acetylenic sulphides. Thiophens, in addition to 2*H*-thiopyrans, are obtained on heating compounds containing the system C≡C–C—S—C=C in HMPA or DMSO in the presence of amines.[20] It is suggested that the acetylenic sulphide (26) rearranges to the allenic thioaldehyde (27), which, in the presence of amines (especially di-isopropylamine), ring-closes *via* the enethiolate (28) to the thiophen (29). In the absence of amine, (27) rearranges to the butadienic thiocarbonyl derivative (30), which ring-closes to the 2*H*-thiopyran (31).[20] Similar results



(26) (27) (30)

(29) (28) (31)

have been obtained with (32), which gave the thiophen (33), along with a 2*H*-thiopyran derivative.[21] When 1-alkynyl propargyl sulphides (34) were

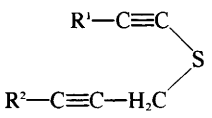


(32) R = Me or Et (33) R = Me or Ph

treated with excess of dialkylamines in DMSO, dialkylaminothiophens (35) were obtained in addition to (36). When no solvent was used, the allenic thioamide (37) was the main product. With dialkylphosphines, thiophens of

[20] D. Schuijl-Laros, P. J. W. Schuijl, and L. Brandsma, *Rec. Trav. chim.*, 1972, **91**, 785.
[21] L. Dalgaard and S.-O. Lawesson, *Tetrahedron*, 1972, **28**, 2051.

the type (38) were obtained in *ca.* 40% yield[22a] (R^1, R^2, and R^3 are alkyl groups). The dialkylaminothiophens were also obtained from acetylenic thioamides[22b] and *NN*-dialkylpenta-2,4-dienethioamides.[22c] The compound (37) is assumed to be intermediate in the formation of the thiophens and is formed through a (3,3)sigmatropic rearrangement *via* the transient thioketen (39).[22a] Heating nitriles of the type (40) in DMSO in the presence of di-isopropylamine leads to 3-cyanothiophens (41).[23]



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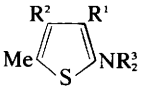

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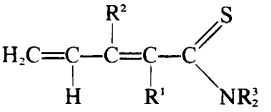

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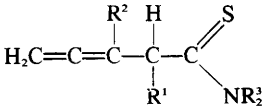

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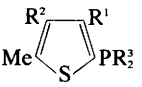

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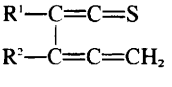

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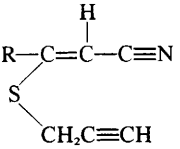

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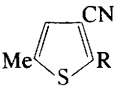
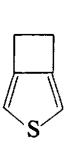


(41)

In connection with work on very strained fused thiophens, compound (42) has been obtained through a Wittig reaction between cyclobutane-1,2-dione (43) and the bis-ylide (44).[24] From the *cis*-form of the diacetylenic thiiran (45), the long-elusive thienocyclobutadiene (46) has been obtained by flow pyrolysis at 250 °C.[25] Compound (46) decomposes immediately on attempted chromatography or exposure to air. In benzene solution at room temperature it dimerizes to (47).

Disulphur dichloride (S_2Cl_2) adds to dimethyl acetylenedicarboxylate to yield (48), which, upon reaction with sodium thiophenolate, gives (49), heating of which leads to extrusion of sulphur, yielding (50).[26]

[22] (*a*) J. Meijer, P. Vermeer, H. J. T. Bos, and L. Brandsma, *Rec. Trav. chim.*, 1974, **93**, 26; (*b*) J. Meijer and L. Brandsma, *ibid.*, 1972, **91**, 578; (*c*) *ibid.*, 1973, **92**, 1331.
[23] R. A. van der Welle and L. Brandsma, *Rec. Trav. chim.*, 1973, **92**, 667.
[24] P. J. Garratt and D. N. Nicolaides, *J.C.S. Chem. Comm.*, 1972, 1014.
[25] K. P. C. Vollhardt and R. G. Bergman, *J. Amer. Chem. Soc.*, 1973, **95**, 7538.
[26] W. Reid and W. Ochs, *Chem. Ber.*, 1972, **105**, 1093.



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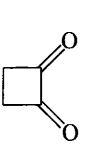
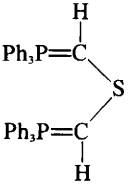


(43)



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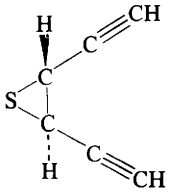
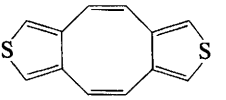
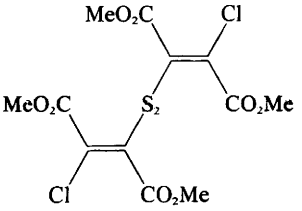


(45)

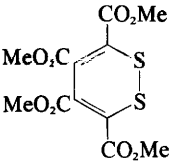
(46)



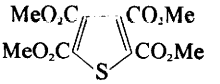
(47)



(48)

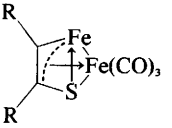


(49)



(50)

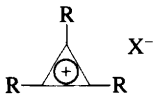
Pyrolysis of the diphenylthioketocarbene complex (51b) at 180 °C gives tetraphenylthiophen as the main product.[27] Reaction of the bis-*p*-methoxy-derivative (51c) with diphenylacetylene produced 2,3-bis-*p*-methoxyphenyl-4,5-diphenylthiophen, demonstrating that the thiophens are formed by addition of the alkyne to the thioketocarbene moiety. The unsubstituted thioketocarbene complex (51a) yields thiophen upon decomposition. In an atmosphere of hexafluorobutyne, 2,3-bistrifluoromethylthiophen is



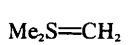
(51) a; R = H
b; R = Ph
c; R = *p*-$MeOC_6H_4$

[27] G. N. Schrauzer and H. Kisch, *J. Amer. Chem. Soc.*, 1973, **95**, 2501.

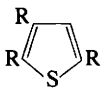
formed.[27] Another very interesting reaction which leads to thiophens (54) is the reaction of triphenylcyclopropenium salts (52) with dimethylsulphonium methylide (53). In addition, thioketones are formed. It is suggested that the reaction proceeds through a σ-sulphurane (55), a species in which sulphur



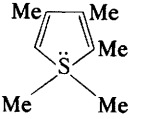
(52) R = Me or Ph



(53)



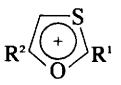
(54) R = Me or Ph



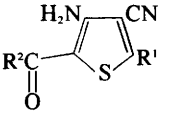
(55)

has expanded its valency shell to ten electrons by formation of four σ-bonds.[28] 4-Acetoxy-2-(acetoxymethyl)thiophen is formed upon treatment of 1,2,3,5-tetra-*O*-acetyl-4-thio-D-ribofuranose with mercuric chloride in DMF.[28a] Convenient methods for the preparation of di- and triphenylthiophens have been worked out through the reaction of phenylbutanes with sulphur.[29]

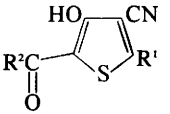
Syntheses of Thiophens from other Ring Systems.—There has been continued interest in the use of 1,3-oxathiazolium salts for the synthesis of thiophens in high yields. From the 2-aryl-substituted derivatives (56), 3-aminothiophens (57) are obtained in the reaction with malononitrile in the presence of base, and 3-hydroxythiophens (58) and (59) with methyl cyanoacetate and



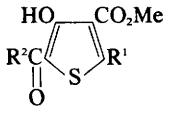
(56)



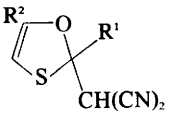
(57)



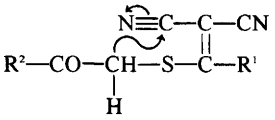
(58)



(59)



(60)



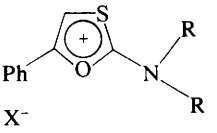
(61)

methyl malonate, respectively.[30] It is assumed that the reaction proceeds *via* nucleophilic attack to give (60) followed by ring-opening to (61) and cyclization, as shown for the reaction with malononitrile.

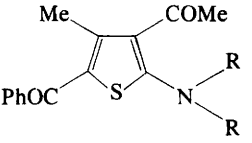
The 2-dialkylamino-1,3-oxathiazolium salts (62) react with β-diketones such as acetylacetone or benzoylacetone, or malononitrile and other active-methylene derivatives in the presence of bases to give thiophens; with

[28] B. M. Trost, R. C. Atkins, and L. Hoffman, *J. Amer. Chem. Soc.*, 1973, **95**, 1285.
[28a] R. L. Whistler and D. J. Hoffman, *Carbohydrate Res.*, 1969, **11**, 137.
[29] M. G. Voronkov, V. É. Udre, and A. O. Taube, *Khim. geterotsikl. Soedinenii*, 1971, 755.
[30] H. Hartmann, H. Schäfer, and K. Gewald, *J. prakt. Chem.*, 1973, **315**, 497.

acetylacetone, (63) is obtained.[31] The Japanese workers suggest a mechanism for these reactions similar to that proposed by Gewald.[30]

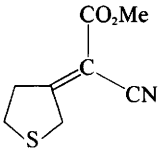


(62)

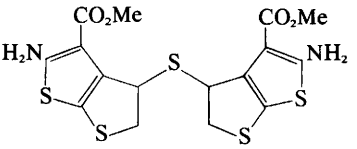


(63)

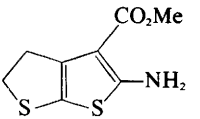
The condensation product from thiacyclopentan-3-one and methyl cyanoacetate (64) yields, in the base-catalysed reaction with sulphur, either (65) or (66) depending upon reaction temperature.[32] Compound (67), prepared through base-catalysed condensation between acrylonitrile and ethyl thioglycolate, was condensed with anilines to (68) and aromatized to (69) with chloranil.[33]



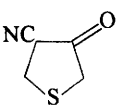
(64)



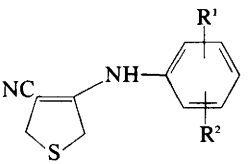
(65)



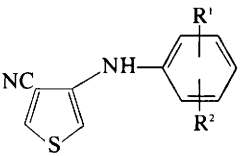
(66)



(67)



(68)

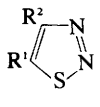


(69)

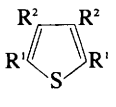
Photolysis of the thiadiazoles (70) leads to the thiophens (71) as main product, in addition to smaller amounts of (72) in the reaction of (70a) and (70c).[34] It was shown that (72) was not formed by photochemical rearrangement of (71). It is assumed that (71) is formed by dimerization of the biradical (73) to (74), followed by sulphur extrusion, while (72) is formed *via* the dimer (75).

Electronic Spectra.—The spectral changes in the u.v. spectra of 31 thiophen-2-sulphonamides were correlated with substituent effects.[35] The u.v. spectra

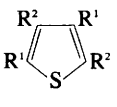
[31] K. Hirai and T. Ishiba, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2384.
[32] K. Gewald and J. Schael, *J. prakt. Chem.*, 1973, **315**, 39.
[33] H. G. Alpermann, H. Ruschig, and W. Meixner, *Arzneim.-Forsch.*, 1972, **22**, 2146.
[34] K.-P. Zeller, H. Meier, and E. Müller, *Annalen.*, 1972, **766**, 32.
[35] A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *Spectrochim. Acta*, 1974, **30A**, 611.



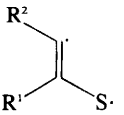
(70) a; $R^1 = H$, $R^2 = COMe$
b; $R^1 = Me$, $R^2 = COMe$
c; $R^1 = Me$, $R^2 = COPh$



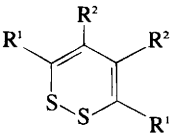
(71)



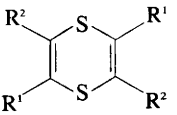
(72)



(73)



(74)

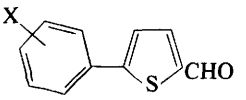


(75)

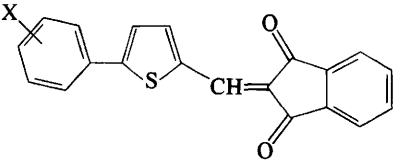
of thienylphenylpropenols in neutral and acidic solutions, as well as of the fluoroborate salts derived from them, have been studied.[36,37] Investigations on the u.v. spectra of heterocyclic chalcogen analogues containing thiophen rings have been continued.[38] The u.v. spectra of substituted methylselenothiophens have been studied and the interaction between substituents has been discussed.[39] The u.v. spectra of some *cis*- and *trans*-2-styrylthiophens,[40] as well as the u.v. and phosphorescence emission of 2- and 3-benzoylthiophen and their *p*-methoxy- and *p*-cyano-derivatives, have been measured[41] and the different transitions discussed.

I.r. Spectra.—The compliance constant matrix of thiophen has been determined on the basis of the experimental frequencies of C_4H_4S and C_4D_4S by the iterative consistency method.[42] The i.r. spectrum of thiophen has been studied in detail at low temperatures (25—90 K).[43] Study of 5-deuteriothiophen-2-aldehyde shows that the multiple i.r. carbonyl absorption is caused by Fermi resonance.[44] I.r. intensities of the ring-stretching bands for 2-substituted thiophens have been correlated with substituent constants. For carbonyl substituents the results were influenced by the conformation of the carbonyl group relative to the ring.[45] In order to study transmission of substituent effects, C=O stretching frequencies have been

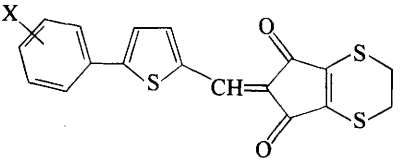
[36] V. F. Lavrushin, R. I. Pogonina, N. S. Pivnenko, and V. P. Izvekov, *Khim. geterotsikl. Soedinenii*, 1970, 1605.
[37] R. I. Pogonina, N. S. Pivnenko, V. P. Izvekov, and V. F. Lavrushin, *Khim. geterotsikl. Soedinenii*, 1971, 27.
[38] S. V. Tsukerman, V. D. Orlov, and V. F. Lavrushin, *Khim. geterotsikl. Soedinenii*, 1969, 67.
[39] V. A. Petukhov, V. P. Litvinov, A. N. Sukiasyan, and Ya. L. Gol'dfarb, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1971, 1700.
[40] A. Arcoria, S. Fisichella, G. Scarlata, and M. Torre, *J. Heterocyclic Chem.*, 1973, **10**, 643.
[41] D. R. Arnold and R. J. Birtwell, *J. Amer. Chem. Soc.*, 1973, **95**, 4599.
[42] C. Tellez and R. Aroca, *J. Mol. Structure*, 1973, **18**, 59.
[43] J. Loisel, J.-P. Pinan-Lucarre, and V. Lorenzelli, *J. Mol. Structure*, 1973, **17**, 341.
[44] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Chem. Comm.*, 1972, 742.
[45] J. M. Angelelli, A. R. Katritzky, R. F. Pinzelli, and R. D. Topsom, *Tetrahedron*, 1972, **28**, 2037.



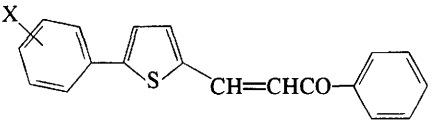
(76)



(77)



(78)



(79)

measured in thiophen derivatives (76)—(79), and correlated with different types of substituent constant.[46-48]

I.r. and n.m.r. spectra of thienylphenylpropenol derivatives indicated them to be *trans*-isomers.[36,37] From i.r. spectroscopic measurements and dipole moments it is concluded that the thiophen-naphthalene analogues of chalcone exist in the *S-cis*-form in solution and have a *trans*-configuration of the substituents at the double bond.[49] The protolytic equilibrium constants in the system H_2SO_4—$MeCO_2H$ and the shifts in frequency of the OH stretching vibrations of phenol and trifluoroacetic acid resulting from the perturbational effects of hydrogen bonding with the carbonyl group of α-alkyl-substituted thiophen analogues of chalcone have been studied.[50] The i.r. stretching frequencies of the NH bond in thiophen-2-sulphonamides have been measured and correlated with Hammett's σ-values.[35]

Dipole Moments.—Electronic charge distribution dipole and second moments have been calculated for thiophen using *ab initio* wavefunctions and the full operators.[51] The structure of thiophen-2-aldehyde in the gas phase has been calculated from dipole-moment data and principal moments of

[46] A. Perjéssy, P. Hrnčiar, R. Frimm, and Ľ. Fišera, *Tetrahedron*, 1972, **28**, 3781.
[47] A. Perjéssy, D. W. Boykin, jun., Ľ. Fišera, A. Krutošiková, and J. Kováč, *J. Org. Chem.*, 1973, **38**, 1807.
[48] A. Perjéssy, P. Hrnčiar, and R. Sokolová, *Coll. Czech. Chem. Comm.*, 1973, **38**, 559.
[49] V. I. Savin, S. A. Flegontov, and Yu. P. Kitaev, *Khim. geterotsikl. Soedinenii*, 1970, 1188.
[50] S. V. Tsukerman, L. A. Kutulya, Yu. N. Surov, and V. F. Lavrushin, *Khim. geterotsikl. Soedinenii*, 1970, 1176.
[51] M. H. Palmer, R. H. Findlay, and A. J. Gaskell, *J.C.S. Perkin II*, 1974, 420.

inertia.[52] Dipole moments have been used for the determination of the conformations of αβ-unsaturated thiophenic ketones.[53] The dipole moments of various thiophen derivatives have been determined.[54]

N.m.r. Spectra.—Interatomic distances and conformations of thiophen-2-aldehyde[55] and 2,2′-bithienyls[56] have been obtained by studying the n.m.r. spectra in a nematic phase. There is continued interest in studying the connection between conformation and long-range couplings in thiophen aldehydes and other heterocyclic aldehydes.[57] The intermolecular interaction of benzene and thiophen with polar solvents has been studied by n.m.r. spectroscopy.[58] The ^{1}H n.m.r. spectra of 62 methyl 3,3′-bithienyls have been investigated. It was found that the resonances of the 2-, 4-, and 5-methyl groups occurred in different intervals.[59] From chemical shifts in the ^{1}H n.m.r. spectra of 2-formyl-, 2-acetyl-, and 2-methoxycarbonyl-thiophen it has been concluded that the order of variation in electron-withdrawing power of the substituent (CHO > COMe > CO_2Me) is retained during formation of the complex with aluminium chloride or protonation of the carbonyl group.[59a] By the use of deuteriated derivatives, assignment of the non-aromatic hydrogen resonances of 2,3-dihalogeno-1,3-di-2-thienyl-propan-1-ones has been carried out.[59b] N.m.r and u.v. spectra have been used for the structure determination of unsymmetrical benzoin analogues containing thiophen rings.[59c]

Various Physical Properties.—Radical cations of 2,5-dialkylthiothiophens have been obtained and their e.s.r. spectra interpreted in terms of unequally populated rotational isomers.[60] The mass spectra of some simple thiophens[61] and some azines derived from 2-acetyl- and 2-formyl-thiophens[62] have been obtained. Molecular ion isomerizations occurring in 3-phenylthiophen and two brominated derivatives have been followed in both slow and fast reactions using ^{13}C-labelling.[62a] Affinities, standard heats, and standard entropies of dyeing of some thiophen-containing azo dyes have been

[52] J. F. Bertran, E. Ortiz, and L. Ballester, *J. Mol. Structure*, 1973, **17**, 161.
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obtained.[63] Polarographic reduction of formyl-2-acetylthiophens has been investigated.[64] The half-wave potentials of (76) and (79) have been correlated with σ-constants.[65] The Mössbauer spectra of μ-oxo-bis[αβγδ-tetrakis(thienyl)]porphinatoiron(III) complexes have been measured at different temperatures.[66] The ground-state aromaticities of furan, thiophen, selenophen, and tellurophen have been compared using seven different criteria.[67]

Electrophilic Substitution.—Rate constants and activation parameters for the Vilsmeier formylation of furan, thiophen, selenophen, and tellurophen have been determined. The results indicate that the differences in ground-state energy play a fundamental role in determining the relative reactivities of the α-positions.[68] The Vilsmeier reaction has been used for the preparation of thiophen-2-[^{2}H]carbaldehydes.[69] Reaction of thiophen with styrene in the presence of palladium(II) acetate leads to *trans*-2-styrylthiophen (13%) and *trans,trans*-2,5-distyrylthiophen.[70] The $SnCl_4$-catalysed reaction of thiophen with tetra-*O*-acetyl-β-D-ribofuranose gives the *C*-glycoside 2-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)thiophen.[70a] Chlorinated 2,3′-bithienyls have been identified as by-products in the reaction of thiophen with sulphuryl chloride and iron powder.[70b] It is suggested that protonated thiophen or chlorothiophen acts as the electrophilic species in the coupling reaction. Aryl-substituted 2-thienyl iodonium halides have been prepared by the reaction of thiophen with substituted phenyliodosoacetates in acetic anhydride–conc. sulphuric acid.[70c,70d]

Gol'dfarb and co-workers have extended their work on isomer distribution in the electrophilic substitution of deactivated thiophens. The quantitative ratio of 4- and 5-nitro-derivatives formed in the nitration of thiophen-2-aldehyde and 2-acetothienone under various conditions has been determined.[71] They found that the *meta*-orienting effect of the protonated acetyl group was stronger than that of the formyl group, while it is approximately the same for the non-protonated forms. The solvent, the nature of the chloromethylating agent, the ratio and order of mixing of the

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reactants have been shown to influence the isomer distribution in the chloromethylation of thiophen-2-aldehyde and 2-acetothienone.[72] In a later paper the dithienylmethane derivatives formed in the $AlCl_3$-catalysed reaction with αα-bischloromethylmethyl ether were reported.[73] 2-Acetothienone reacts with methylene chloride, chloroform, and carbon tetrachloride in the presence of aluminium chloride mainly at position 4 to give substituted di- and tri-thienylmethanes.[74] Bromination of thiophen-2-aldehyde and 2-acetothienone with bromine in conc. sulphuric acid in the presence of silver sulphate gives a mixture of the 4-bromo-, 5-bromo-, and 4,5-dibromo-derivatives. Since the 4-bromo-derivatives are brominated *ca.* 10 times faster than the 5-isomers under the conditions employed, it follows that monobromination occurs predominantly at position 4.[75] English workers have also studied the $AlCl_3$-catalysed bromination of thiophen-2-aldehyde.[76] The $AlCl_3$-catalysed acylation of 2- and 3-acetylthiophen has been studied in detail.[77] Thallation of thiophen-2-aldehyde with thallium(III) trifluoroacetate, followed by reaction with potassium iodide, yields 5-iodothiophen-2-aldehyde.[69] The direction of nitration of 2-acetylthiophen and 2-propionylthiophen oximes has been studied.[78] Reaction of thiophen-2-aldoxime with N_2O_4 affords 2,4-dinitro-5-trinitromethylthiophen in low yield.[78a]

Gol'dfarb and co-workers have also carried out investigations on the directing effect of onium groups. Nitration of trimethyl-(2-thienyl)-ammonium salts occurs almost exclusively at position 5. This is considered to be in agreement with MO calculations.[79] Nitration of dimethyl-(2-thienyl)-sulphonium salts occurs at position 4, whereas bromination gives a mixture of the 4- and 5-monobromo-derivatives and the 4,5-dibromo-derivative.[80] Dimethyl-(3-thienyl)sulphonium salts are nitrated at position 5.[81] Chlorination of 2-nitrothiophen in $CHCl_3$ and $AlCl_3$ gives 4,5-dichloro-2-nitrothiophen.[82]

The directing effect of activating groups has been studied less extensively during this period. Vilsmeier formylation of 2-alkyl-5-methoxy-thiophens at

[72] L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, *Zhur. org. Khim.*, 1971, **7**, 1743.
[73] L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, *Zhur. org. Khim.*, 1973, **9**, 1514.
[74] A. P. Yakubov, Yu. K. Sudarushkin, L. I. Belen'kii, and Ya. L. Gol'dfarb, *Zhur. org. Khim.*, 1973, **9**, 1521.
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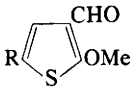
20 °C leads, as expected, to the 4-substituted derivative (80). However, at 50—70 °C, dealkylation occurs, leading to N-substituted 5-alkyl-3-aminomethylene-Δ^4-thiolen-2-ones (81).[83]



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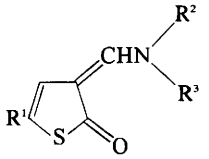
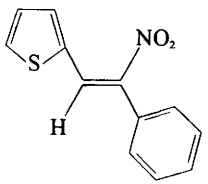


(81)

2-Alkylthio-5-alkylthiophens are chloromethylated at position 3 by chloromethyl methyl ether.[84] 3-Methylthiothiophen has been nitrated at position 2.[81] The influence of the reaction conditions on the isomer distribution in the acylation of 2-methoxy-, 2-methylthio-, and 2-dimethylamino-thiophen has been studied.[85] Azo-coupling and aminomethylation occur at position 3 of some 4,5-disubstituted 2-acylaminothiophens.[86] 3-Acetylamino-2-benzoylthiophen yields the 4,5-dichloro-derivative with sulphuryl chloride,[87] while 3-acetylamino- or 3-benzoylamino-4-carbonylthiophen derivatives are chlorinated at position 2.[88]

Nitration of 2-benzylthiophen with nitric acid in acetic anhydride gave 5-nitro-2-benzylthiophen as the main product together with smaller amounts of the 3- and 4-nitro-isomers.[89] Formylation and acetylation of 2-(2-thenyl)-selenophen occurs to *ca.* 80% in the free α-position of the selenophen ring.[90] In the nitration of *trans*-2-styrylthiophen the main product was β-nitro-2-styrylthiophen (82). Smaller amounts of 3-nitro- and 5-nitro-2-styrylthiophen were also formed.[91] The isomer distributions in some electrophilic



(82)

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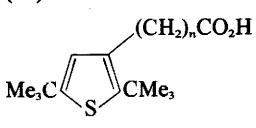
[91] A. Arcoria, E. Maccarone, and G. A. Tomaselli, *J. Heterocyclic Chem.*, 1973, **10**, 191.

substitutions of 2-phenylthiophen have been studied.[92] Some 2-arylthiophens have been formylated at position 5.[93] Interesting results concerning steric and electronic influences have been obtained in the acylation of 2-methyl-5-phenylthiophen. Depending upon catalyst and solvent, acylation occurs predominantly at position 3 or 4.[94,95] Acetylation in benzene with $SnCl_4$ as catalyst yields 88% of the 3-acetyl and 12% of the 4-acetyl derivative, whereas $AlCl_3$ as catalyst yields 28% of the 3-isomer and 72% of the 4-isomer.[94] Nitration of 5-formyl-2,2'-bithienyl with copper nitrate in acetic acid yields mixtures of the 5'- and 3'-nitro-derivatives.[96] Many substituents are easily removed under electrophilic conditions. Additional examples are provided by the deacylation of 2,5-di-t-butyl-3-acyl derivatives by prolonged refluxing with a mixture of hydrochloric and formic acid.[97] The methylseleno-group is split off in the reaction of 2-methylselenothiophen with bromine, yielding 2,5-dibromothiophen.[98] Removal of t-butyl groups[99] during electrophilic ring-closures (*cf.* below) has also been observed.

Electrophilic Ring-closure.—Acids of the type (83), in toluene and polyphosphoric acid, ring-close to position 4 and eliminate a t-butyl group when $n = 2$ (84), and ring-close to position 2, when $n = 3$ or 4, yielding (85).[99,100]



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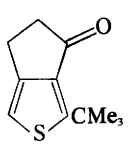

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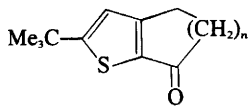

(85)

Ring-closure of the 2,5-dichloro-3-thienyl-substituted acids (86) to (87) is best achieved by using the acid chlorides and $AlCl_3$ as catalyst.[101] Many different methods for the dechlorination of (87) were tried. Total dechlorination was achieved in only one case. The chlorine *ortho* to the carbonyl group could, however, be removed in various ways.[102] A mixture of isomers corresponding to ring-closure at the 3- (20%) and 4-position (80%) of the

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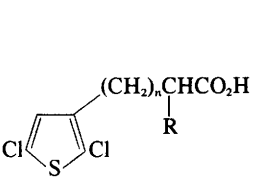
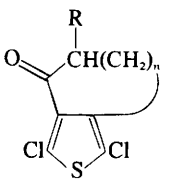
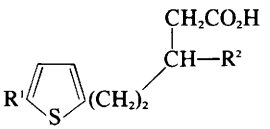


(86) $n = 1$—3



(87) $n = 1$—3

thiophen ring was obtained during intramolecular acylation of 12-(5-methyl-2-thienyl)lauryl chloride. In connection with work on thienotropones (89), the acid (88) has been ring-closed *via* the acid chloride using $SnCl_4$ as catalyst.[103]



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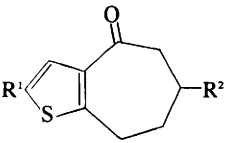

(89)

In connection with work on dithieno- and thienofuro-fused tropylium derivatives, electrophilic ring-closure of (90)—(94) to the ketones (95)—(99) was achieved in quantitative yields by treating the acids with PCl_5 followed by $SnCl_4$ in benzene.[104,105] In order to obtain (98) and (99), it was found essential to carry out the ring-closure from a carboxylic function on the furan ring onto the thiophen ring.[105] The above-mentioned ring-closure could also be carried out with the *cis*-forms (100) and (101) to give the dithienotropones (102) and (103).[106] Some thenylthio-acids have been ring-closed to (104) and (105) using PPA as reagent.[107]

Radical Reactions.—The reaction of α-chloro ethers with zinc in the presence of thiophen yields di-2-thienyl alkanes (106).[108] Photolysis of 3-iodopyridine in the presence of thiophen yields a mixture of 3-(2-thienyl)-pyridine and 3-(3-thienyl)pyridine in a 7:1 ratio.[109] The synthesis and rate of decomposition of 2- and 3-thenoyl peroxides and of mixed thenoylfuroyl peroxides have been described.[110] Aryl 2-thenoates were obtained in high yields by the reaction of substituted benzenes with 2-thenoyl peroxide in the

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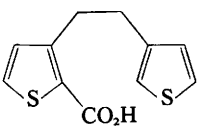

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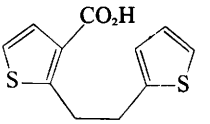

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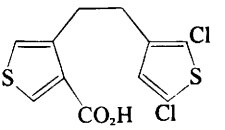

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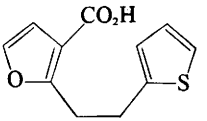

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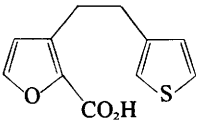

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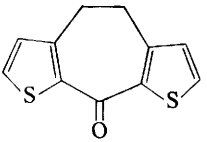

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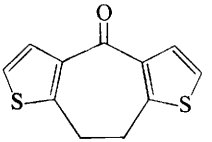
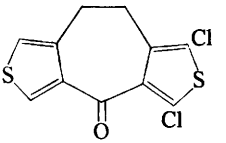


(96)



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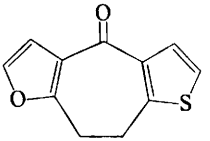

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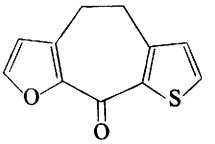

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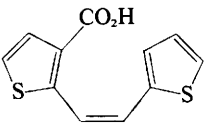

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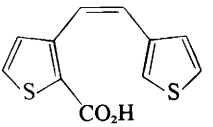
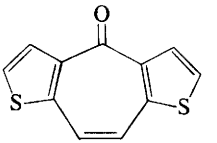
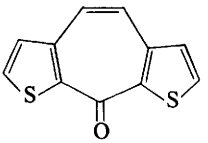


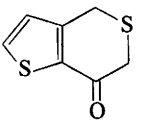
(101)



(102)



(103)



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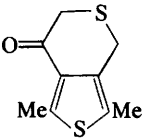
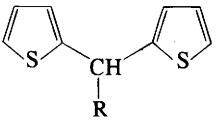


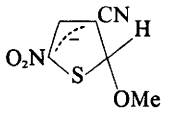
(105)



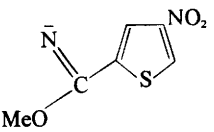
(106)

presence of cupric chloride at 80 °C. The ratios of isomers and the relative rates for aromatic substrates indicated that 2-thenoyloxylation was brought about by 2-thenoyloxyl radicals possessing electrophilic properties.[111,112] It is suggested that the function of the copper(II) chloride is to oxidize the intermediate cyclohexadienyl radical. In the absence of cupric chloride, substitution of iodine by the thenoyloxy-group took place, yielding phenyl 2-thenoate, when iodobenzene was used as substrate.[112]

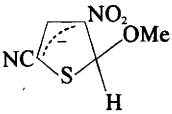
Nucleophilic Substitutions.—The rates of nucleophilic substitution of bromine in 3-bromo-2-nitrothiophen with *o*-, *m*-, and *p*-substituted thiophenoxide ions in methanol are faster than those of 2-bromo-3-nitrothiophen with the same nucleophiles.[113] Somewhat unexpectedly, 2,3-dibromo-4-methyl-5-nitrothiophen reacts faster with nucleophiles such as piperidine and phenylthiolate at position 2 than does 2,3-dibromo-5-nitrothiophen.[114] 4-Cyano-2-nitrothiophen reacts with sodium methoxide in methanol to give the Meisenheimer adduct (107), whereas 2-cyano-4-nitrothiophen gives the sodium salt of the carboxyimidate (108), from which methyl 4-nitrothiophen-2-carboxyimidate can be isolated upon acidification.[115] If, however, 2-cyano-4-nitrothiophen is treated with sodium methoxide in [$^2H_6$]DMSO, formation of the Meisenheimer complex (109) is



(107)



(108)

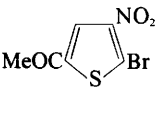


(109)

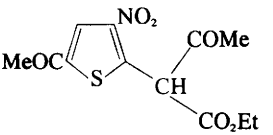
observed.[115,116] This complex is also formed when (108) is dissolved in DMSO.[115] 2-Chloro-3,5-dinitrothiophen reacts with α-amino-acids to give *N*-(3,5-dinitro-2-thienyl)amino-acids.[117] Doubly activated 2-bromothiophens such as (110) react with the sodium enolate of ethyl acetoacetate to give

[111] S. Hashimoto, W. Koike, and M. Oyama, *J. Chem. Soc. Japan, Chem. Ind. Chem.*, 1972, 375.
[112] S. Hashimoto, W. Koike, and Y. Okahata, *J. Chem. Soc. Japan, Chem. Ind. Chem.*, 1973, 1139.
[113] G. Guanti, C. Dell'Erba, and P. Macera, *J. Heterocyclic Chem.*, 1973, **10**, 1007.
[114] D. Spinelli, G. Consiglio, and A. Corrao, *Tetrahedron Letters*, 1972, 4021.
[115] G. Doddi, G. Illuminati, and F. Stegel, *Tetrahedron Letters*, 1973, 3221.
[116] C. Paulmier, M. P. Simonnin, A. P. Chatrousse, and F. Terrier, *Tetrahedron Letters*, 1973, 1123.
[117] L. H. Hellberg, M. J. Prodanovich, and F. Stults, *J. Heterocyclic Chem.*, 1972, **9**, 401.

(111).[118] In the reaction of aryl 2-thienyliodonium ions with nucleophiles (Br^- or Cl^-) by pyrolysis or in solution, the nucleophile preferentially



(110)



(111)

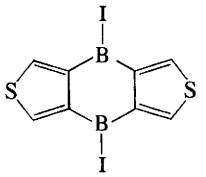
attacks the aryl group.[10c,70d] This is rather unexpected, as the thiophen ring is normally more susceptible to nucleophilic substitution. It is therefore probable that the mechanism for these reactions is not the normal bimolecular nucleophilic aromatic substitution. A convenient method for the synthesis of nitrothiophens consists in the reaction of dithienyliodonium salts with sodium nitrite in DMF.[119] The iodonium salts are conveniently obtained through reaction of thienyl-lithium derivatives with *trans*-chlorovinyliodosodichloride at −70 °C. Deuterium-substituted thiophen-2-carboxylic acids are conveniently prepared by heating the corresponding protio acid with NaOD in D_2O.[120] It is suggested that the mechanism involves nucleophilic addition–elimination.

Further investigations of the rearrangements and aminations of 2-bromothiophen and dibromothiophens have been carried out. On treatment of these compounds with potassium amide in liquid ammonia at −75 °C, a bromine migration from the α-position to the β-position takes place. At −33 °C, amination to 3-aminothiophen, in addition to α- to β-bromine rearrangement, was observed.[121] The mechanism of the trans-bromination was assumed to be intermolecular, involving dibromo- and tribromo-thiophens. Formation of 3-aminothiophen does not occur *via* a dehydrothiophen, but is the result of amination of a polybromothiophen, yielding an aminobromothiophen, which is debrominated by reaction with amide ion or a thiophen anion.[121] Debrominations also occur in the reaction of di-, tri-, and tetra-bromothiophens with sodium alkoxides in DMSO.[122]

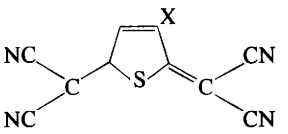
The reaction between iodothiophens and copper acetylides has been of great use for the preparation of naturally occurring thiophens.[123–125] Reaction of 2,5-dimethyl-3,4-iodothiophen with boron tri-iodide opens the route to

[118] V. I. Shvedov, V. K. Vasileva, Y. I. Trofimkin, and A. N. Grinev, *Khim. geterotsikl. Soedinenii*, 1973, 1628.
[119] S. Gronowitz and B. Holm, *Chem. Scripta*, 1972, **2**, 245.
[120] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin I*, 1973, 201.
[121] H. C. van der Plas, D. A. de Bie, G. Geurtsen, M. G. Reinecke, and H. W. Adickes, *Rec. Trav. chim.*, 1974, **93**, 33.
[122] J. M. Barker, I. G. C. Coutts, and P. R. Huddleston, *J.C.S. Chem. Comm.*, 1972, 615.
[123] F. Bohlmann and W. Skuballa, *Chem. Ber.*, 1973, **106**, 497.
[124] F. Bohlmann and P.-D. Hopf, *Chem. Ber.*, 1973, **106**, 3621.
[125] F. Bohlmann, C. Zdero, and H. Kapteyn, *Chem. Ber.*, 1973, **106**, 2755.

tricyclic boron-containing heterocycles (112).[126] Reaction of 2,3,5-tribromothiophen with tetracyanoethylene oxide gives (113a), which was hydrogenolysed to (113b), the structure of which was determined by *X*-ray crystallography.[127]

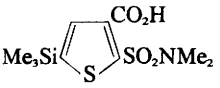


(112)

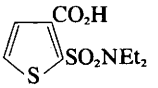


(113) a; X = Br
b; X = H

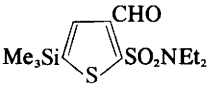
Metallation and Halogen–Metal Exchange.—Lithiation of thiophens, either by metallation or by halogen–metal exchange, continues to play an important role in the synthesis of thiophen derivatives. Quite interesting results were obtained in the metallation of substituted thiophen-2-sulphonamides. 5-Trimethylsilyl-*NN*-dimethylthiophen-2-sulphonamide gave, as expected, metallation at position 3, yielding (114) after reaction with carbon dioxide. In the same reaction of the diethyl amide, the acid (115) was obtained. Removal of the trimethylsilyl group occurred during carbonation or work-up, as reaction with DMF yielded (116). The most unexpected result was obtained when 5-trimethylsilyl-*NN*-dimethylthiophen-2-sulphonamide was treated with the butyl-lithium–*NNN'N'*-tetramethylethylenediamine complex in order to increase the yields. In this case the dimethylamino-derivative (117) was obtained in 39% yield. Curiously enough, the



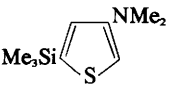
(114)



(115)



(116)

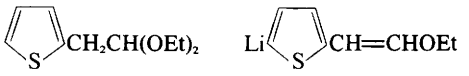


(117)

diethyl analogue did not react thus.[128] Metallation of 2-thienylacetylene with butyl-lithium gave 2-thienylpropiolic acid after reaction with carbon dioxide. Competitive metallation between 2-thienylacetylene and

[126] B. Asgarouladi, R. Full. K.-J. Schaper, and W. Siebert, *Chem. Ber.*, 1974, **107**, 34.
[127] B. Aurivillius, *Acta Chem. Scand.*, 1972, **26**, 3612.
[128] D. W. Slocum and P. J. Gierer, *J. Org. Chem.*, 1973, **38**, 4189.

phenylacetylene indicated the former compound to be more acidic.[128a] 2-(Trialkylsilyl)-5-thienylphosphonates and thiophosphonates were prepared by metallation of 2-(trialkylsilyl)thiophens followed by treatment with dialkyl chlorophosphate and dialkyl chlorothiophosphate, respectively.[129] Ketimines and ketones have been prepared from 2-trimethylsilyl-5-thienyllithium and nitriles.[130] Reaction of thienyl-lithium derivatives with trichloroacetonitrile[130] or hexachloroethane[131] yields chlorothiophens.[130] Reaction of 2-thienyl-lithium with bromoacetaldehyde diethyl acetal gave (118) in 40% yield. Reaction of (118) with two equivalents of butyl-lithium yielded the thienyl-lithium derivative (119), which was transformed into various derivatives.[132]



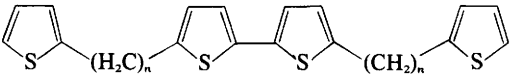
(118) (119)

Metallation of 2′-(2-pyridyl)thiophen occurs almost exclusively at position 5 using butyl-lithium–THF or lithium di-isopropylamide, but predominantly at position 3 when ethereal butyl-lithium and short reaction times are used.[133] This unusual and interesting β-metallation of a thiophen with a free α-position most probably depends on the chelating properties of the pyridinic nitrogen, and was also observed with 2′-(2-quinolyl)thiophen.

Thienyl-lithium derivatives prepared through halogen–metal exchange and containing acetal-protected carbonyl groups have been used in the synthesis of di- and tri-formyl derivatives of thiophen,[134] t-butoxy-substituted thiophen aldehydes,[135] and formylacetylthiophens.[64,136] Symmetrical thienyl-substituted ketones have been obtained from thienyl-lithium derivatives and carbamates.[105,137] Mixed heterocyclic carbinols have been obtained through the reaction of thienyl-lithium derivatives with heterocyclic aldehydes.[138] Thienyl-lithium derivatives react with cyclohexanone, and various phenylthiophens have been made by aromatization of the intermediate cyclohexenyl derivative.[92,139] The reaction of thienyl-lithium derivatives with *NN*-dimethylacetamide, which has been used for the synthesis of

[128a] T. B. Patrick, J. M. Disher, and W. J. Probst, *J. Org. Chem.*, 1972, **37**, 4467.
[129] S. F. Thames, L. H. Edwards, T. N. Jacobs, P. L. Grube and F. H. Pinkerton, *J. Heterocyclic Chem.*, 1972, **9**, 1259.
[130] F. H. Pinkerton and S. F. Thames, *J. Heterocyclic Chem.*, 1972, **9**, 725.
[131] S. Gronowitz, A.-B. Hörnfeldt, and K. Pettersson, *Synthetic Comm.*, 1973, **3**, 213.
[132] P. L. Kelly, S. F. Thames, and J. E. McCleskey, *J. Heterocyclic Chem.*, 1972, **9**, 141.
[133] T. Kauffmann and A. Mitschker, *Tetrahedron Letters*, 1973, 4039.
[134] B. Decroix, J. Morel, C. Paulmier, and P. Pastour, *Bull. Soc. chim. France*, 1972, 1848.
[135] C. Paulmier, J. Morel, D. Semard, and P. Pastour, *Bull. Soc. chim. France*, 1973, 2434.
[136] E. Sandberg, *Chem. Scripta*, 1972, **2**, 241.
[137] T. M. Cresp and M. V. Sargent, *J.C.S. Perkin I*, 1973, 2961.
[138] C. Maletras, B. Decroix, J. Morel, and C. Paulmier, *Compt. rend.*, 1973, **276**, *C*, 1305.
[139] S. Gronowitz, J. Rehnö, K. Titlestad, M. Vadzis, B. Sjöberg, P. Bamberg, B. Ekström, and U. Forsgren, *Acta Pharm. Suecica*, 1972, **9**, 381.

acetylthiophens, fails with sterically hindered thienyl-lithium derivatives owing to enolization.[92] Thienyl-lithium derivatives have of course been used for the synthesis of thiophencarboxylic acids,[104–106] and thiophenboronic acid derivatives.[140] In connection with work on optically active 3,3′-bithienyls, the coupling of 3-thienyl-lithium derivatives with cupric chloride is of key synthetic importance.[141,142] This reaction has also been used for the synthesis of complex bithienyls such as (120) and (121).[143,144,144a] A new



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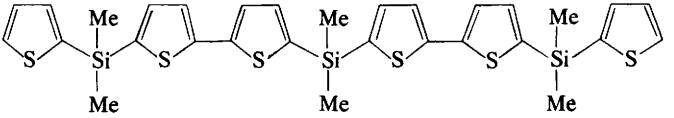
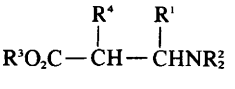
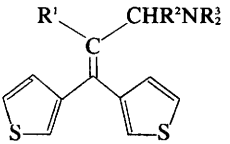


(121)

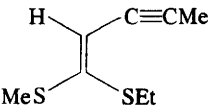
mechanism of racemization has been suggested in order to explain the facile racemization of 2,2′- and 4,4′-dilithium-3,3′-bithienyls.[145] Trichloro-2-thienyl-lithium, prepared by halogen–metal exchange of tetrachlorothiophen, reacts with hexafluorobenzene in THF to give tetrakis(trichloro-2-thienyl)difluoro-benzene in good yield.[146] The addition of thienyl-lithium over the azo-methine bond in pyridines and quinolines has been used in the syntheses of polyheterocycles,[147] as has the coupling between thienyl-lithium and 2-chloropyridines.[148] 3-Thienyl-lithium reacts with (122) to give potentially pharmacologically active compounds (123),[149] and ring-opening of 2-methyl-5-methylthio-3-thienyl-lithium has been used in the synthesis of the unsymmetrical acetylenic ketenthioacetal (124).[150]



(122)



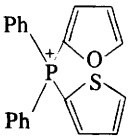
(123)



(124)

[140] R. Lantz and A.-B. Hörnfeldt, *Chem. Scripta*, 1972, **2**, 9.
[141] R. Håkansson, A. Ask, and A. Almquist, *Chem. Scripta*, 1972, **2**, 72.
[142] E. Wiklund and R. Håkansson, *Chem. Scripta*, 1973, **3**, 220.
[143] T. Kauffmann, J. Jackisch, A. Woltermann, and P. Röwemeier, *Angew. Chem.*, 1972, **84**, 826.
[144] T. Kauffmann, J. Legler, E. Ludorff, and H. Fischer, *Angew. Chem.*, 1972, **84**, 828.
[144a] T. Kauffmann and H.-H. Kniese, *Tetrahedron Letters*, 1973, 4043.
[145] R. Håkansson, *Chem. Scripta*, 1972, **2**, 109.
[146] M. R. Smith, jun., B. B. Singh, and H. Gilman, *J. Organometallic Chem.*, 1973, **61**, 1.
[147] T. Kauffmann and A. Woltermann, *Angew. Chem.*, 1972, **84**, 824.
[148] T. Kaufmann, A. Mitschker, and H.-J. Straitberger, *Angew. Chem.*, 1972, **84**, 829.
[149] M. Robba and D. Duval, *Chim. Thérap.*, 1973, **8**, 22.
[150] S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, 1973, **27**, 2242.

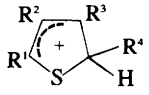
The carbonylation of 2-chloromercury-thiophen in methanol with CO at 100 °C and 50 atm in the presence of lithium chloropalladite yields 2,2′-dithienyl ketone (40%), 2-methoxycarbonylthiophen (35%), and 2,2′-bithienyl (10%). 2,5-Dichloromercury-thiophen gave 5,5′-dimethoxycarbonyl-2,2′-diethienyl ketone (36%) and 2,5-dimethoxycarbonylthiophen (40%).[151] Alkaline hydrolysis of the phosphonium salt (125) gave furan and



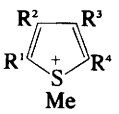
(125)

thiophen in a 1:3 ratio, indicating that the forming 2-thienyl carbanion is more stable than the 2-furyl analogue and implying stabilization of the nascent negative charge in the former by sulphur *d*-orbital participation.[152] This reaction is paralleled by the faster metallation of thiophen than furan by butyl-lithium.

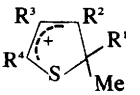
Photochemistry of Thiophens.—A model for the photochemically induced valence-bond isomerizations of thiophens has been proposed.[153] Irradiation of the thiophenium ion (126), obtained by protonation of thiophens with fluorosulphonic acid at low temperature, led to no reaction. However, irradiation of the *S*-methylated derivatives (127) smoothly gave migration to (128).[154] Both thiophen and 2,5-dimethylthiophen give photocycloaddition



(126)



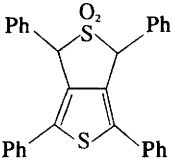
(127)



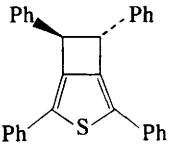
(128)

with dimethyl acetylenedicarboxylate. The labile 1,4-adduct could not be isolated, but split off sulphur to give derivatives of dimethyl phthalate.[155] The Pyrex-filtered u.v. irradiation of some 1-aryl-2-(2-thienyl)ethenes, which leads to cyclobutane derivatives, has been studied in benzene solution and in the crystalline state. The solid-state behaviour was found to be crystal-lattice-controlled.[156] Photolysis of either *cis*- or *trans*-(129) yields primarily the thienocyclobutene (130), while (131) gives (132). Both (130) and (132) give naphtho[c]thiophen derivatives upon thermolysis.[157]

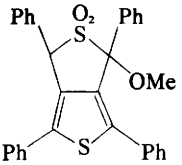
[151] T. Izumi, T. Iino, and A. Kasahara, *Bull. Chem. Soc. Japan*, 1973, **46**, 2251.
[152] D. W. Allen, S. J. Grayson, I. Harness, B. G. Hutley, and I. W. Mowat, *J.C.S. Perkin II*, 1973, 1912.
[153] R. M. Kellogg, *Tetrahedron Letters*, 1972, 1429.
[154] H. Hogeveen, R. M. Kellogg, and K. A. Kuindersma, *Tetrahedron Letters*, 1973, 3929.
[155] H. J. Kuhn and K. Gollnick, *Tetrahedron Letters*, 1972, 1909.
[156] B. S. Green and L. Heller, *J. Org. Chem.*, 1974, **39**, 196.
[157] M. P. Cava, M. V. Lakshmikantham, and M. Behforouz, *J. Org. Chem.*, 1974, **39**, 206.



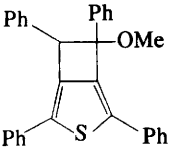
(129)



(130)



(131)

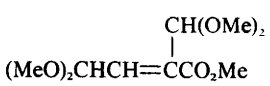


(132)

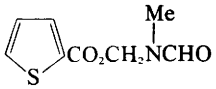
Electrochemical Reactions.—The electrochemical oxidation of 2- and 3-methylthiophens with methanolic ammonium bromide as electrolyte on a carbon or platinum anode gives 5-bromo-2-methylthiophen and 2-bromo-3-methylthiophen as main products.[158] Electrochemical oxidation of methyl thiophen-2-carboxylate on a graphite anode in methanolic sulphuric acid gives the *cis* and *trans* forms of (133). Methyl thiophen-3-carboxylate yields (134).[159] On the other hand, electrolysis of thiophen-2-carboxylic acid in DMF on platinum electrodes gives (135).[160]

$$MeO_2CHC{=}CHC(OMe)_2CO_2Me$$

(133)



(134)

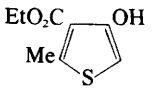


(135)

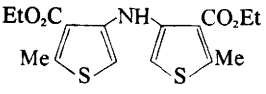
The Structure and Reactions of Hydroxy- and Mercapto-thiophens.—Some tautomeric 2,5-dialkyl-3-hydroxythiophen systems have been prepared and characterized as acetoxy-derivatives. The equilibration between the two tautomeric forms of these systems is very rapid and the influence of substituents and solvent on the equilibrium has been determined.[140] 2,5-Diformyl-3-hydroxythiophen has been synthesized by dealkylation of the t-butoxy-derivative and exists exclusively in the hydroxy form.[135] The product distribution in the alkylation of the thallium salt of the

[158] M. Němec, M. Janda, and J. Šrogl, *Coll. Czech. Chem. Comm.*, 1973, **38**, 3857.
[159] M. Janda, J. Šrogl, M. Němec, and A. Janoušová, *Coll. Czech. Chem. Comm.*, 1973, **38**, 1221.
[160] P. A. Konstantinov, I. V. Shelepin, and N. M. Koloskova, *Khim. geterotsikl. Soedinenii*, 1971, 915.

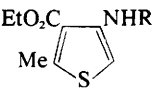
2-hydroxythiophen system has been determined.[161] 3-Ethoxycarbonyl-4-hydroxy-2-methylthiophen has been nitrated at position 5.[161a] The hydroxythiophen (136) reacts with excess ammonium acetate to give (137),[162] with alkylammonium acetate to give (138),[163] and with hydrazine to give (139).[162,163a] An interesting ring-transformation occurs upon reaction of (136) with hydrazine acetate, yielding the pyrazole (139a).[163a] Vilsmeier reaction of (138) gives (140).[164] The reaction of primary amines with (141)[83] yields the



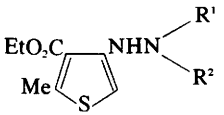
(136)



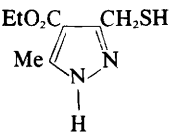
(137)



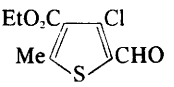
(138)



(139)

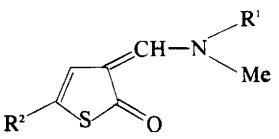


(139a)

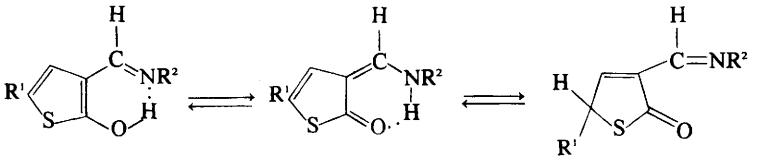


(140)

tautomeric N-monosubstituted 5-alkyl-3-aminomethylene-Δ^4-thiolen-2-ones (142)—(144).[165] ^{1}H n.m.r. studies of this system indicate that in solution and



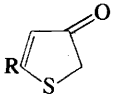
(141)



(142) (143) (144)

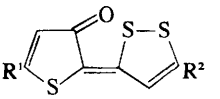
[161] E. B. Pedersen and S.-O. Lawesson, *Tetrahedron*, 1972, **28**, 2479.
[161a] V. I. Shvedov, V. K. Vasil'eva, O. B. Romanova, and A. N. Grinev, *Khim. geterotsikl. Soedinenii*, 1973, 1024.
[162] V. I. Shvedov, V. K. Vasil'eva, and A. N. Grinev, *Khim. geterotsikl. Soedinenii*, 1969, 567.
[163] V. I. Shvedov, V. K. Vasil'eva, and A. N. Grinev, *Khim. geterotsikl. Soedinenii*, 1970, 1602.
[163a] V. I. Shvedov, V. K. Vasil'eva, A. N. Grinev, and N. P. Kostyuchenko, *Khim. geterotsikl. Soedinenii*, 1971, 759.
[164] V. I. Shvedov, V. K. Vasil'eva, and A. N. Grinev, *Khim. geterotsikl. Soedinenii*, 1972, 427.
[165] Ya. L. Gol'dfarb and M. A. Kalik, *Khim. geterotsikl. Soedinenii*, 1971, 178.

in the molten state it exists as (143). In DMSO the intramolecular hydrogen-bond breaks, and associates with the solvent are formed.[166] The reaction of the 3-hydroxythiophens (145) with (146) in the presence of triethylamine yields (147).[167]



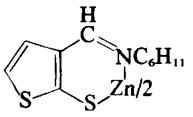
(145)

(146)

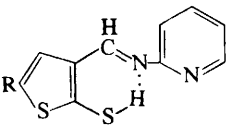


(147)

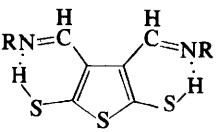
The reactions of bromine, acetyl chloride, and butyl-lithium with the zinc chelate (148) have been studied,[168] as has the action of methyl iodide on some chelates derived from (149).[169] Chelates derived from 2,5-dimercaptothiophens such as (150) have been prepared.[170] Interaction of dipotassium



(148)



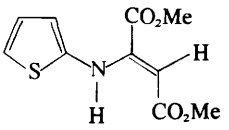
(149)



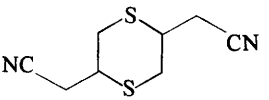
(150)

cyclo-octatetraenate with thiophenic disulphides and thiocyanates leads to mercaptothiophens.[171] 2- and 3- mercaptothiophens have been alkylated with propargylic bromides.[20]

Aminothiophens and their Reactions.—The Michael reaction of 2-aminothiophen with dimethyl acetylenedicarboxylate yields (151) as the main product. As a by-product, (152) is obtained *via* ring-opening and



(151)

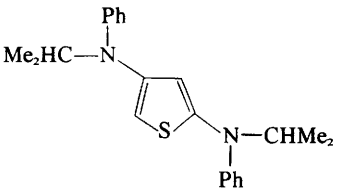


(152)

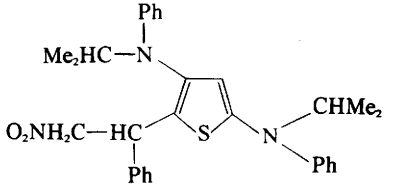
dimerization of the imino form. Alkylation of (151) with allyl halides in hexametapol in the presence of sodium hydride occurred on the nitrogen. The *N*-allylthiophenamines were transformed into various tricyclic

[166] V. S. Bogdanov, M. A. Kalik, G. M. Zhidomirov, N. D. Chuvylkin, and Ya. L. Gol'dfarb, *Zhur. org. Khim.*, 1971, **7**, 1953.
[167] C. Lemarie-Retour, M. Stavaux, and N. Lozac'h, *Bull. Soc. chim. France*, 1973, 1659.
[168] Ya. L. Gol'dfarb and M. A. Kalik, *Khim. geterotsikl. Soedinenii*, 1969, 475.
[169] Ya. L. Gol'dfarb and M. A. Kalik, *Khim. geterotsikl. Soedinenii*, 1972, 902.
[170] Ya. L. Gol'dfarb and M. A. Kalik, *Khim. geterotsikl. Soedinenii*, 1970, 1323.
[171] Z. V. Todres, F. M. Stoyanovich, Ya. L. Gol'dfarb, and D. N. Kursanov, *Khim. geterotsikl. Soedinenii*, 1973, **9**, 632.

thiophen derivatives *via* hetero-Cope rearrangements.[172] The diaminothiophen (153) behaves as an enamine and undergoes Michael-type addition at position 5 with β-nitrostyrene, dimethyl acetylenedicarboxylate, and related compounds to yield (154), with the first-mentioned reagent.

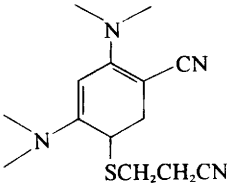


(153)



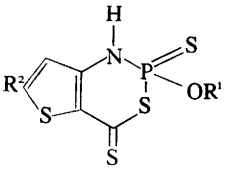
(154)

Dienophiles such as acrylonitrile and *N*-phenylmaleimide give novel cyclic structures, such as (155) with acrylonitrile. It is considered that this product

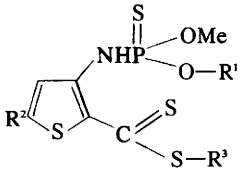


(155)

is not necessarily formed from a simple Diels–Alder reaction, and alternative mechanisms are discussed.[173] 3-Aminothiophen has been isolated and characterized.[174] Analogues of styryl dyes as well as simple azo-dyes have been prepared by coupling with 2-(diethyl)aminothiophen.[175] The reaction of 3-aminothiophen-2-carboxylates with P_4S_{10} in xylene gives (156), which upon treatment with base and alkyl halide can be transformed into (157).[176] The reaction of *o*-acylaminothiophencarboxylates such as (158a) and (158b) with



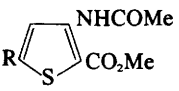
(156)



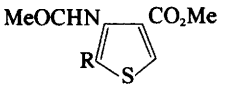
(157)

[172] S. Blechert, R. Gericke, and E. Winterfeldt, *Chem. Ber.*, 1973, **106**, 368.
[173] J. P. Chupp, *J. Heterocyclic Chem.*, 1972, **9**, 1033.
[174] E. W. Brunett, D. M. Altwein, and W. C. McCarthy, *J. Heterocyclic Chem.*, 1973, **10**, 1067.
[175] F. A. Mikhailenko, L. I. Shevchuk, and A. I. Kiprianov, *Khim. geterotsikl. Soedinenii*, 1973, 923.
[176] J. Brelivet and J. Teste, *Bull. Soc. chim. France*, 1972, 2289.

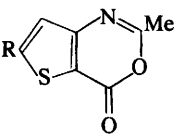
PCl_5 leads to (159a) and (159b), respectively. The compounds (159a) and (159b) were converted into *o*-acylaminoaryl ketones (160a) and (160b) by



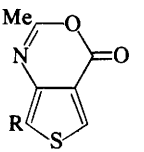
(158a)



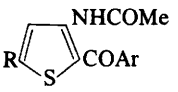
(158b)



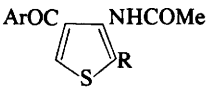
(159a)



(159b)

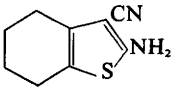


(160a)

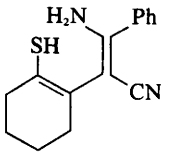


(160b)

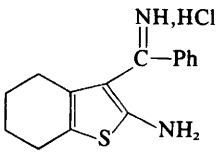
reaction with arylmagnesium bromides.[88,177–180] The reaction of the 2-amino-3-cyanothiophen (161) leads to the ring-opened product (162). Upon standing in methanol solution, (162) ring-closed to (163). A mechanism for



(161)



(162)



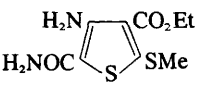
(163)

the formation of (162) was suggested. Thermolysis of (162) led to complex condensed thiophens.[181] N-Monoalkylation of *o*-aminocyano- and *o*-amino-methoxycarbonyl-thiophens can conveniently be carried out with trialkyl orthocarboxylates and sodium borohydride.[182]

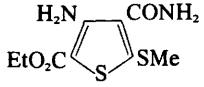
o-Aminocyanothiophen and *o*-aminocarbonyl-substituted thiophens have been diazotized, and the diazonium salts reduced with hypophosphoric

[177] O. Hromatka and D. Binder, *Monatsh.*, 1973, **104**, 1343.
[178] O. Hromatka, D. Binder, and K. Eichinger, *Monatsh.*, 1973, **104**, 1513.
[179] O. Hromatka, D. Binder, and K. Eichinger, *Monatsh.*, 1974, **105**, 135.
[180] O. Hromatka, D. Binder, and K. Eichinger, *Monatsh.*, 1974, **105**, 138.
[181] R. Heckendorn and A. R. Gagneux, *Tetrahedron Letters*, 1973, 2279.
[182] R. A. Crochet, jun. and C. DeWitt Blanton, jun., *Synthesis*, 1974, 55.

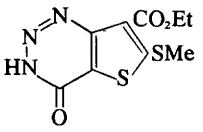
acid.[3,88,183] Diazotization of (164a) and (164b) led to (165a) and (165b), respectively.[183a]



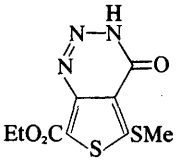
(164a)



(164b)

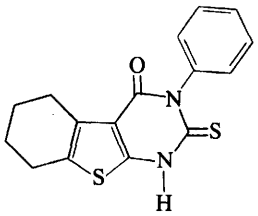


(165a)



(165b)

A 2-amino-3-ethoxycarbonylthiophen, when treated with phenyl isothiocyanate, gave a thiourea derivative which ring-closed to (166).[183b]



(166)

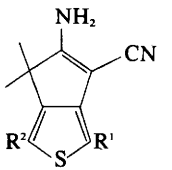
The reactions of some compounds containing thiophen–phosphorus bonds have been studied.[184,185]

Side-chain Reactivities.—Several papers quantitatively treating the influence of the thiophen ring on side-chain reactivity have appeared. The reaction of 5-substituted 2-thenoyl chlorides with aniline in benzene follows second-order kinetics. The values of the Hammett ρ-constants are greater than that for the benzoylation reaction, indicating that the thiophen nucleus is more efficient than the benzene ring in relaying the electronic effects of the substituent to the reaction centre.[186] The rate of the reaction of 3-thenoyl chloride[187] and of thiophen-2-sulphonyl chloride with substituted anilines[188] has also been studied, and the Hammett equation applied to the rate

[183] O. Hromatka and D. Binder, *Monatsh.*, 1973, **104**, 1105.
[183a] L. Henriksen and H. Autrup, *Acta Chem. Scand.*, 1972, **26**, 3342.
[183b] S. M. Khripak, A. A. Dobosh, and I. V. Smolanka, *Khim. geterotsikl. Soedinenii*, 1973, 567.
[184] V. K. Khairullin and R. Z. Aliev, *Zhur. obshchei Khim.*, 1973, **43**, 1921.
[185] V. K. Khairullin and R. Z. Aliev, *Zhur. obshchei Khim.*, 1973, **43**, 2165.
[186] G. Alberghina, A. Arcoria, S. Fisichella, and G. Scarlata, *Gazzetta*, 1973, **103**, 319.
[187] A. Arcoria and S. Fisichella, *J. Org. Chem.*, 1973, **38**, 3774.
[188] A. Arcoria, E. Maccarone, G. Musumarra, and G. A. Tomaselli, *J. Org. Chem.*, 1973, **38**, 2457.

constants. The solvolytic rearrangement of 2-(2-thienyl)ethyl tosylate and 2-(5-methyl-2-thienyl)ethyl tosylate has been studied in trifluoroethanol and acetic acid. The thienyl isomer reacts only 3—6 times faster than the benzene analogue, depending upon solvent. Isotope labelling showed that scrambling was essentially complete in trifluoroethanol. Support for the concept that the transition state is an unsymmetrically bridged system was obtained.[189] The rates of solvolysis of nine substituted 1-(2-thienyl)ethyl *p*-nitrobenzoates in 80% ethanol were correlated with the substituent constants σ_m^+ and σ_p^+.[190] Other correlations of physical and chemical properties with reactivity parameters are given in refs. 35, 45—48, and 65.

Chloromethyl Derivatives.—Halogenomethylthiophens, prepared by direct chloromethylation,[191–194] by side-chain bromination[104–106] or *via* the formyl and hydroxymethyl derivatives,[195] still play an important role as intermediates in the synthesis of thiophen derivatives. They have been transformed into triphenylphosphonium salts[105,106,137,196,197] and diethyl thenylphosphonates[104] for use in the Wittig reaction. From the rates of alkaline hydrolysis of mixed arylmethyldiphenylphosphonium salts, such as 2-furylmethyl-2-thenyl- and 2-benzyl-2-thenyl-diphenylphosphonium salts, it was concluded that the relative stabilities of the resulting carbanions are 2-furylmethyl > 2-thenyl > benzyl.[152] (2-Thenoylmethyl)triphenylphosphonium salt has been used in the reaction with phenyl glyoxal for the preparation of 1-(2-thienyl)-4-phenylbut-2-ene-1,4-dione.[197a] The chloromethyl derivatives have been transformed into cyanomethyl derivatives,[84,192,193,195] which in the case of 3,4-dicyanomethyl derivatives were transformed by Thorpe cyclization into the bicyclic derivative (167) or *via* the 3,4-dimethoxycarbonylmethyl derivatives and Dieckmann cyclization into (168).[195,198] The chloromethyl derivatives have been used in ethyl



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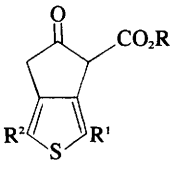
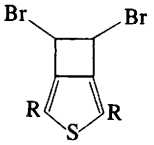


(168)

[189] D. S. Noyce and R. L. Castenson, *J. Amer. Chem. Soc.*, 1973, **95**, 1247.
[190] D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *J. Org. Chem.*, 1972, **37**, 2615.
[191] G. Muraro and P. Cagniant, *Bull. Soc. chim. France*, 1973, 310.
[192] R. Helmers, *Annalen*, 1973, 181.
[193] I. B. Karmanova, Y. B. Volkenshtein, and L. I. Belen'kii, *Khim. geterotsikl. Soedinenii*, 1973, 490.
[194] S. W. Longworth and J. F. W. McOmie, *J.C.S. Chem. Comm.*, 1972, 623.
[195] R. Helmers, *J. prakt. Chem.*, 1972, **314**, 334.
[196] W. Carruthers and M. G. Pellatt, *J.C.S. Perkin I*, 1973, 1136.
[197] G. Manecke and M. Härtel, *Chem. Ber.*, 1973, **106**, 655.
[197a] M. I. Shevchuk, A. F. Tolochko, M. S. Vaisberg, and A. V. Dombrovskii, *Zhur. org. Khim.*, 1969, **5**, 523.
[198] R. Helmers, *Annalen*, 1973, 890.

malonate synthesis in connection with preparation of ω-(2,5-dichloro-3-thienyl)- and ω-(2,5-di-t-butyl)-aliphatic acids,[191] and also treated with other nucleophiles, for instance butanethiolate.[193] On heating 2-chloromethylthiophen with sulphur in *o*-dichlorobenzene at 180—185 °C, 1,2-dithienylethylene is obtained, probably *via* the di-2-thenyl sulphide.[199] 2,5-Dihalogeno-3,4-bis(dibromomethyl)thiophens have been used in the synthesis of the strained *cis*- and *trans*-3,4-dibromocyclobutane derivatives (169).[194] (For similar syntheses see refs. 24 and 25.) Attempts to prepare a thiophen analogue of biphenylene from (170) failed.[200]



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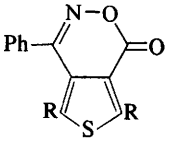
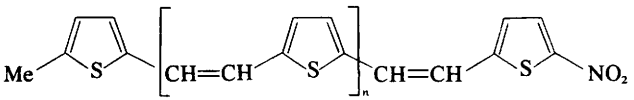


(170)

Reactions of Thiophen Aldehydes and Ketones.—Thiophen aldehydes have been extensively used as components in the Wittig reaction.[40,104–106,196,197,201] It was found that *o*-halogeno-substituted thiophen aldehydes with *o*-halogeno-substituted thenyltriphenylphosphonium salts gave especially high proportions of substituted *cis*-1,2-dithienylethenes,[105,106] and also in the phosphonate modification unusually much *cis*-isomer was found.[104] Some oligomeric αα-unsymmetrically disubstituted dithienylenevinylenes (171) were pre-



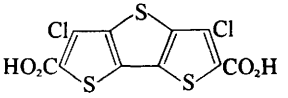
(171)

pared by the Wittig reaction. The relationship between their chemical structure, spectral behaviour, and electrical conductivity was investigated.[197] In connection with attempts to prepare macrocyclic derivatives, the reaction between 3,4-diformyl-2,5-dimethylthiophen and the bis-ylide from 2,5-dimethylthiophen-3,4-diylbis-methylenetriphenylphosphonium chloride was studied.[196] The reaction between thiophen aldehydes and triethyl phosphonoacetate has been used for the synthesis of ethyl thienylacrylates.[201] The Wittig reaction between cyclopropyl 2-thienyl ketone and methylene-triphenylphosphorane gives (172), which reacted differently than the benzene analogue with butyl-lithium, giving a mixture of *cis*- and *trans*-(173).[202] Thienylacrylic acid derivatives have also been prepared

[199] M. G. Voronkov, A. N. Pereferkovich, M. P. Gavar, and G. V. Ozolin', *Khim. geterotsikl. Soedinenii*, 1970, 1183.
[200] M. P. David and J. F. W. McOmie, *Tetrahedron Letters*, 1973, 1361,
[201] B. Capron, C. Paulmier, and P. Pastour, *Compt. rend.*, 1973, **277**, C, 167.
[202] S. Brenner and E. Dunkelblum, *Tetrahedron Letters*, 1973, 2487.

3 Thienothiophens, their Benzo-derivatives, and Analogous Compounds

Synthesis.—The reactions of thiophen-2- and 3-acrylic acid with thionyl chloride in the presence of pyridine yield a mixture of chlorinated derivatives of thieno[3,2-*b*]thiophen-2-carboxylic acid and thieno[2,3-*b*]-thiophen-2-acrylic acid.[201,340,341] From thiophen-2,5-diacrylic acid, (241) was obtained.[201] Aromatization of (66) gives thieno[2,3-*b*]thiophens.[31] Reaction of (242) with methyl thioglycolate yielded (243).[164] Ethylthiophen was



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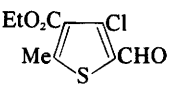
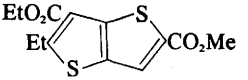
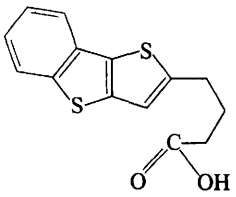


(242)



(243)

converted into thieno[3,2-*b*]thiophen in 13.5% yield through the reaction with hydrogen sulphide over aluminochromium and aluminoiron catalysts at 450 °C.[342] Heating of (244) with P_2O_5 somewhat unexpectedly gives (245) in high yield.[343]



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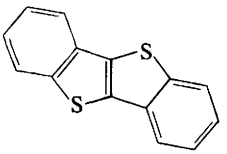


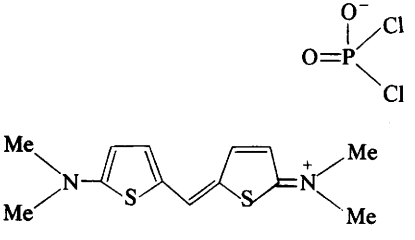
(245)

Theoretical Studies and Physical Properties.—Quantum chemical calculations on the reactivity of thienothiophens have been carried out.[344] The e.s.r. spectra of the radical anions of carbonyl, nitro, and cyano derivatives of the two [*b*]-fused thiophens have been studied.[345] The proton chemical shifts of 2-substituted thieno[2,3-*b*]thiophens have been correlated with the two-parameter equation of Swain and Lupton.[346]

The interaction of the sulphonyl group with an adjacent unsaturated centre has been studied in the sulphone (246) and in its differently fused isomers.[347]

Substitution Reactions.—The reactivities of thieno[3,2-*b*]thiophen and thieno[2,3-*b*]thiophen, relative to thiophen, in electrophilic formylation,

[340] W. B. Wright, jun., *J. Heterocyclic Chem.*, 1972, **9**, 879.
[341] S. Gronowitz and B. Maltesson, *Acad. Chem. Scand.*, 1972, **26**, 2982.
[342] V. P. Litvinov and É. G. Ostapenko, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1971, 1683.
[343] A. Ricci, D. Balucani, and B. Berardo, *Compt. rend.*, 1972, **275**, *C*, 139.
[344] Ya. L. Gol'dfarb, V. P. Litvinov, G. M. Zhidomirov, I. A. Abronin, and R. Z. Zakharyan, *Chem. Scripta*, 1974, **5**, 49.
[345] G. F. Pedulli, M. Tiecco, A. Alberti, and G. Martelli, *J.C.S. Perkin II*, 1973, 1816.
[346] A. Bugge, *Chem. Scripta*, 1973, **3**, 190.
[347] F. de Jong and M. J. Janssen, *Rec. Trav. chim.*, 1973, **92**, 1073.



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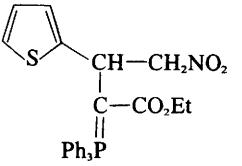
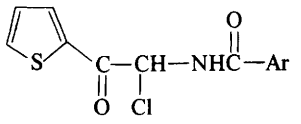


(175)

The condensation of the diethyl acetal of thiophen-2-aldehyde with substituted dioxolanium salts gives 2-thienylacryl-1,3-dioxalonium salts, which can be hydrolysed to 2-thienylacrylic acids.[217] Treatment of the *gem*-dimorpholide of thiophen-2-aldehyde with benzamide or acetamide in the presence of sulphuric acid yields the *gem*-(di-*N*-acylamino) derivative.[218]

3-Thienyl analogues of ephedrine and psi-ephedrine have been prepared by side-chain bromination of 3-propionylthiophen followed by reaction with methylamine and reduction. The diastereomers were separated by treatment with picric acid in ether.[219] The basic condensation of methyl 2-thienyl and phenyl 2-thienyl ketones with dimethyl succinate gave predominantly the (*E*)-half esters.[220] The Leuckart reaction with 2-propionylthiophen gives, in addition to the expected 1-(2-thienyl)-1-aminopropane, 4-(2-thienyl)-5-methylpyrimidine as by-product.[221] The i.r. and n.m.r. spectra of 3-thenoyl-2-oxo-propionate prepared through base-catalysed condensation of 2-acetylthiophen and diethyl oxalate have been studied.[222] There has been continued interest in the metal complexes derived from thenoyltrifluoroacetone.[223,224] The *N*-acyl-α-chloroglycine derivative (176) has been prepared from 2-thienylglyoxal[225] and treated with different nitrogen and sulphur nucleophiles.[226] The imidazole derivative was used as a model for amidoalkylating therapeutics. From 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophen, the steroidal system (177) has been synthesized.[227] 2-Thenoic reacted with DMF–$POCl_3$ to give (178), while the corresponding glycol gave (179) with the same reagent.[228] In connection with work on macrocyclic compounds, the intramolecular cyclization of 2-(ω-haloalkyl)-5-ethoxycarbonylthiophens such as (180) under basic conditions has been

[217] G. N. Dorofeenko, L. V. Mezheritskaya, and Yu. I. Ryabukhin, *Zhur. org. Khim.*, 1973, **9**, 390.
[218] Y. Le Floc'h, A. Brault, and M. Kerfanto, *Compt. rend.*, 1972, **275**, *C*, 1545.
[219] J. M. Barker and P. R. Huddleston, *J.C.S. Perkin I*, 1973, 1200.
[220] N. R. El-Rayyes, *J. prakt. Chem.*, 1973, **315**, 300.
[221] D. T. Hill and B. Loev, *J. Org. Chem.*, 1973, **38**, 2102.
[222] P.-J. Bargnoux, J. Paris, and J. Couquelet, *Compt. rend.*, 1973, **276**, *C*, 1041.
[223] L. I. Kononenko and T. P. Piontkovskaya, *Zhur. analit. Khim.*, 1969, **24**, 379.
[224] M. P. Noskova, L. A. Gribov, and Yu. A. Zolotov, *Zhur. strukt. Khim.*, 1969, **10**, 474.
[225] D. Matthies, *Synthesis*, 1972, 380.
[226] D. Matthies and R. Wolff, *Pharm. Acta Helv.*, 1973, **48**, 44.
[227] I. R. Trehan, D. K. Sharma, and D. V. Rewal, *Indian J. Chem.*, 1973, **11**, 827.
[228] S. Pennanen, *Acta Chem. Scand.*, 1973, **27**, 3133.



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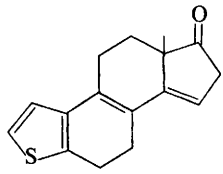

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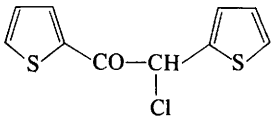

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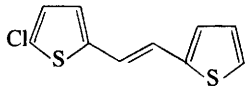
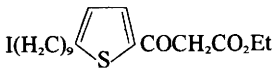
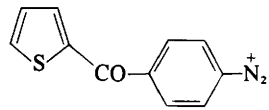


(179)

studied in detail.[229] The coupling of diazonium salts such as (181) with different naphthalene derivatives has been studied.[230]

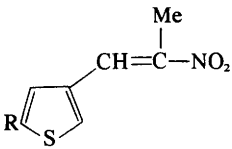


(180)

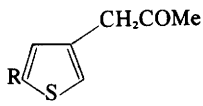


(181)

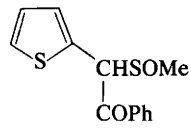
Various Side-chain Reactions.—The condensation product between 2-methyl- and 2-ethyl-thiophen-4-aldehyde and nitroethane (182) was transformed into (183) by treatment with iron and hydrochloric acid.[231] The carbanion from methyl 2-thenylsulphoxide reacts with ethyl benzoate to give (184), which by aluminium amalgam was reduced to 2-thenyl phenyl



(182)



(183)



(184)

ketone.[232] When ethyl thiophen-2-carboxylate was treated with propionyl chloride or butyryl chloride in the presence of $FeCl_3$, (185) was obtained as the main product with a by-product believed to be (186) [from (185b)]. Also

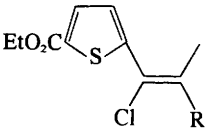
[229] S. Z. Taits, É. A. Krasnyanskaya, and Ya. L. Gol'dfarb, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1970, 2228.

[230] A. Arcoria, S. Fisichella, G. Scarlata, and M. Torre, *Chimica e Industria*, 1973, **55**, 789.

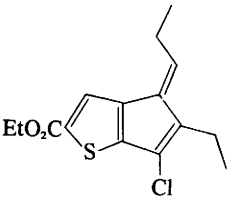
[231] L. V. Dulenko, G. N. Dorofeenko, S. N. Baranov, I. G. Katts, and V. I. Dulenko, *Khim. geterotsikl. Soedinenii*, 1971, **7**, 320.

[232] Ya. L. Gol'dfarb, A. P. Yakubov, and L. N. Belen'kii, *Khim. geterotsikl. Soedinenii*, 1971, 910.

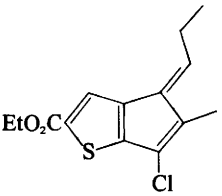
the reaction of 5-butyryl-2-ethoxycarbonylthiophen with propionyl chloride and $FeCl_3$ gave (185b). From 4-butyryl-2-ethoxycarbonylthiophen, on the other hand, (187) is obtained. A possible mechanism for the formation of the thienofulvenes is discussed.[233] The reaction of (188) with acetic anhydride and



(185) a; R = Me
b; R = Et

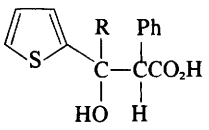


(186)

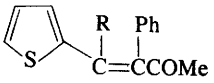


(187)

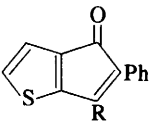
catalytic amounts of zinc chloride leads to the unsaturated methyl ketones (189). Only when R = Ph was the formation of the condensed derivative (190) observed.[234] The products obtained from the reaction of thiophen-3,4-dicarbonyl chloride with $AlCl_3$ and benzene have been carefully



(188)

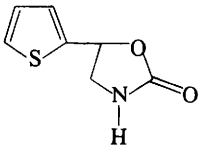


(189)



(190)

characterized.[235] In a study of dihydroisoquinoline rearrangements, the Reissert compound from isoquinolines and thiophen-2-carbonyl chloride was used.[236] A convenient synthesis of 2-thienylacetylene consists in the conversion of 3-hydroxy-3-(2-thienyl)propionic acid hydrazide to 5-(2-thienyl)-2-oxazolidone (191), which *via* the *N*-nitroso-derivative was trans-

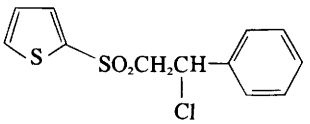


(191)

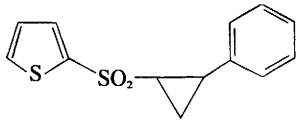
formed into 2-thienylacetylene.[128a] A method for selective reduction of aromatic carboxy-groups to methyl groups has been applied to 5-methoxycarbonyl-2-thiophencarboxylic acid.[237] Cobalt(II) acetate in conjunction with

[233] S. Pennanen, *Acta Chem. Scand.*, 1972, **26**, 2907.
[234] T. P. Ivanov and D. M. Mondeshka, *J. prakt. Chem.*, 1973, **315**, 993.
[235] D. W. H. MacDowell, R. A. Jourdenais, R. W. Naylor, and J. C. Wisowaty, *J. Org. Chem.*, 1972, **37**, 4406.
[236] J. Knabe and A. Frie, *Arch. Pharm.*, 1973, **306**, 648.
[237] R. A. Benkeser and D. F. Ehler, *J. Org. Chem.*, 1973, **38**, 3660.

9,10-dibromoanthracene is an efficient catalyst for the oxidation of 2-methylthiophen. From 2,5-dimethylthiophen the dicarboxylic acid is obtained in 91% yield.[238] Both 2-methyl-3-nitrothiophen and 3-methyl-2-nitrothiophen have been condensed to styryl derivatives with benzaldehydes in the presence of catalytic amounts of pyrrolidine.[239] The copper-catalysed reaction of thiophen-2-sulphonyl chloride with styrene gives (192), which through elimination of hydrogen chloride with triethylamine and reaction with dimethylsulphonium methylide was transformed into (193).[240] A method for the synthesis of esters of thiophen-2,5-

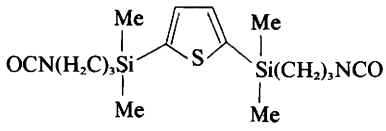


(192)

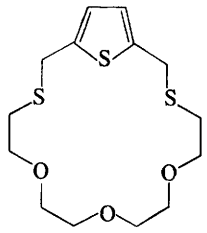


(193)

diglyoxylic acid from the iodomagnesium derivatives of thiophen-2,5-dicarbinols has been developed.[241] The reaction between 2-thienylacrylic acid and ethyl dichlorophosphine has been studied.[242] 2,5-Bis(γ-isocyanatopropyldimethylsilyl)thiophen (194) has been prepared.[243] In connection with a study of the reductive fission of substituted 1-phenyl-1-ethanols by potassium metal in t-butyl alcohol, 1-(2-thienyl)-1-ethanol was also studied and proved to be the most reactive compound.[244] A new complex ligand system of the crown-type (195) has been synthesized.[245] Polyamides have been prepared from thiophen-2,5-dicarboxylic acid and piperazine.[246]



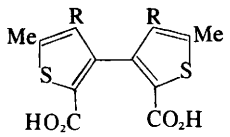
(194)



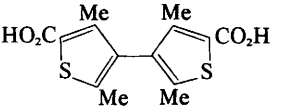
(195)

[238] P. A. Konstantinov, T. V. Shchedrinskaya, I. V. Zakharov, and M. N. Volkov, *Zhur. org. Khim.*, 1972, **8**, 2590.
[239] K. Srinivasan, K. G. Srinivasan, K. K. Balasubramanian, and S. Swaminathan, *Synthesis*, 1973, 313.
[240] C. T. Goralski, *J. Org. Chem.*, 1972, **37**, 2354.
[241] I. I. Lapkin and Yu. P. Dormidontov, *Khim. geterotsikl. Soedinenii*, 1970, **6**, 898.
[242] M. A. Vasyanina and V. K. Khairullin, *Zhur. obshchei Khim.*, 1974, **44**, 48.
[243] I. A. Vostokov, Yu. I. Dergunov, V. P. Kozyukov, V. D. Sheludyakov, V. F. Mironov, and V. Z. Anisimova, *Zhur. obshchei Khim.*, 1973, **43**, 623.
[244] C. H. Wang and C. A. Kingsbury, *J. Org. Chem.*, 1972, **37**, 2489.
[245] F. Vögtle and E. Weber, *Angew. Chem.*, 1974, **86**, 126.
[246] V. P. Sarzhevskaya, K. A. Koranev, and S. E. Smirnova-Zamkova, *Ukrain. khim. Zhur.*, 1969, **35**, 390.

Bi- and Poly-heterocycles.—There has been increasing interest in optically active 3,3′-bithienyls.[141,142,145,247,248] The absolute configuration of (196a) has been determined by relating it by chemical methods to hexabromo-3,3′-bithienyl.[141] The racemization of some bridged derivatives of (196a) has also been studied. The compound (196b) has been resolved into antipodes and sterically related to (196a) and its racemization studied.[247] The c.d. spectra of (196b) and its carboxylic-acid-modified derivatives, as well as of some other 2,2′-dicarboxy-3,3′-bithienyls, have been investigated in detail.[248] The diacid



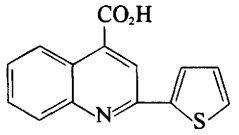
(196) a; R = Br
b; R = Me



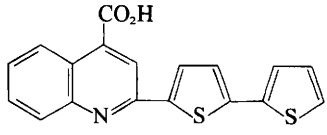
(197)

(197) has been resolved into antipodes and its configuration was determined.[142] The direction of moments and assignments of $\pi \rightarrow \pi^*$ transitions in some bithienyls have been determined from polarized spectroscopy on oriented films.[249] The chemical and electrochemical reductions of 3,3′-dinitro-2,2′-bithienyl and 2,2′-dinitro-3,3′-dithienyl lead to bithienylamino-derivatives and to *N*-oxides of dithienopyridazines.[250] Some azomethine bases derived from 2,2′-bithienyls have been prepared.[251] A series of Russian articles treats the synthesis, derivatization, and electrophilic substitution reactions of combinations of thiophen and quinoline rings, such as in compounds (198),[252–254] (199),[255,256,256a] and (200).[256] Kauffmann has continued his work on the synthesis and chemical properties of polyheterocycles containing thiophen, pyridine, pyrimidine, and imidazole rings.[133,144,147,148] Different 1,4-(dithienyl)benzenes have been synthesized and their acetylation and metallation have been studied.[257] Through the reaction of 2-thienyl-lithium derivatives with 2,4,6-trichloro-*sym*-triazine, 2,4-dichloro-6-(thienyl)-*sym*-triazines were obtained, and their nitration and bromination investigated.[258] Thienyl-1,3-oxazoles and the corresponding

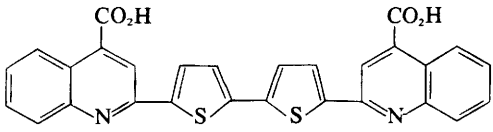
[247] R. Håkansson, *Chem. Scripta*, 1973, **3**, 177.
[248] R. Håkansson, *Chem. Scripta*, 1973, **3**, 212.
[249] B. Nordén, R. Håkansson, and M. Sundbom, *Acta Chem. Scand.*, 1972, **26**, 429.
[250] J.-C. Nonciaux, R. Guilard, and E. Laviron, *Bull. Soc. chim. France*, 1973, 3318.
[251] K. I. Vakhreeva, A. E. Lipkin, T. B. Ryskina, and N. I. Skachkova, *Khim.-farm. Zhur.*, 1973, **7**, 24.
[252] M. N. Zemtsova and A. E. Lipkin, *Khim. geterotsikl. Soedinenii*, 1973, **9**, 183.
[253] R. S. Belenkaya, A. E. Lipkin, and V. M. Ostryakov, *Khim.-farm. Zhur.*, 1972, **6**, 13.
[254] B. I. Ardashev, A. S. Zarifyan, and G. G. Glukhovets, *Khim. geterotsikl. Soedinenii*, 1972, 525.
[255] M. N. Semtsova, P. L. Trakhtenberg, A. E. Lipkin, and T. B. Ryskina, *Khim.-farm. Zhur.*, 1973, **7**, 13.
[256] P. L. Trakhtenberg, A. E. Lipkin, and Z. I. Nuzhdina, *Khim. geterotsikl. Soedinenii*, 1972, **8**, 773.
[256a] P. L. Trakhtenberg and A. E. Lipkin, *Khim. geterotsikl. Soedinenii*, 1974, 61.
[257] P. Ribereau, G. Queguiner, and P. Pastour, *Bull. Soc. chim. France*, 1972, 1581.
[258] J. K. Chakrabarti, R. W. Goulding, and A. Todd, *J.C.S. Perkin I*, 1973, 2499.



(198)



(199)

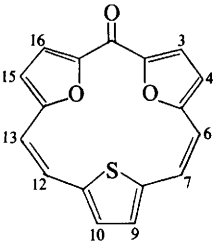


(200)

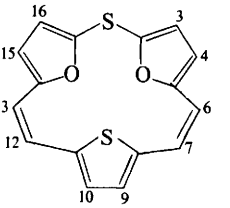
thiazoles and selenazoles have been synthesized.[259] Many examples of compounds can be found in which the thiophen is connected to more or less exotic other rings, such as the 1,2-dithiolylium ring,[260–262] the thiazolo[2,3-*b*]-1,3,4-thiadiazole ring,[263] the pyrimido[4,5-*d*]pyridazine ring,[264,265] the pyrazine ring,[266] the chromone ring,[267,268] 1,2,4-oxadiazole ring,[269] the 1,3,4-oxadiazole ring,[270] the imidazole ring[271] and the benzimidazole ring.[272]

Thiophen Analogues of Porphyrins.—Interest in macrocyclic compounds containing thiophen rings is continuing. The [17]annulenone (201) has been synthesized, and by comparison of its n.m.r. spectrum with that of the homo-annulene it was found that it did not support a paramagnetic ring current.[137] Another 17-membered macrocyclic system (202) was also found to be atropic.[273] Both in the synthesis of (201) and (202) and in the 16-membered macrocycle (203),[196] the Wittig reaction played a key role. The 22π-electron macrocycle (204) has also been prepared[274] and the reaction of 2,5-dimethylthiophen with formaldehyde and zinc chloride in acetic acid gives (205) (major product) and (206).[275]

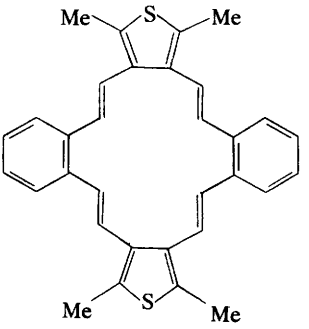
[259] P. Chauvin, J. Morel, and P. Pastour, *Compt. rend.*, 1973, **276**, C, 1453.
[260] G. Duguay and H. Quiniou, *Bull. Soc. chim. France*, 1972, 637.
[261] J.-P. Guemas and H. Quiniou, *Bull. Soc. chim. France*, 1973, 592.
[262] F. Clesse, J.-P. Pradera, and H. Quiniou, *Bull. Soc. chim. France*, 1973, 586.
[263] M. M. Kochhar, M. Salahi-Asbahi, and B. B. Williams, *J. Pharm. Sci.*, 1973, **62**, 336.
[264] S. Yurugi, M. Hieda, T. Fushimi, Y. Kawamatsu, H. Sugihara, and M. Tomimoto, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1528.
[265] S. Yurugi, T. Fushimi, and M. Hieda, *J. Pharm. Soc. Japan*, 1972, **92**, 1316.
[266] Y. Nakatani and Y. Yanatori, *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 1509.
[267] K. A. Thakar and G. D. Deshpande, *J. Indian Chem. Soc.*, 1972, **49**, 1029.
[268] V. P. Khilya, L. G. Grishko, and V. Sabo, *Khim. geterotsikl. Soedinenii*, 1972, **8**, 1321.
[269] S. Yurugi, A. Miyake, M. Tomimoto, H. Matsumura, and Y. Imai, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1885.
[270] H. Saikachi, N. Shimojo, and Y. Uehara, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1663.
[271] K. Akagane, G. G. Allan, C. S. Chopra, T. Friberg, T. Mattila, S. Omuircheartaigh, and J. B. Thomson, *Suomen Kem.*, 1972, **45**, 223.
[272] A. Jurasek, M. Breza, and R. Kada, *Coll. Czech. Chem. Comm.*, 1972, **37**, 2246.
[273] T. M. Cresp and M. V. Sargent, *J.C.S. Perkin I*, 1973, 1786.
[274] M. J. Broadhurst, R. Grigg, and A. W. Johnson, *J.C.S. Perkin I*, 1972, 2111.
[275] O. Meth-Cohn, *Tetrahedron Letters*, 1973, 91.



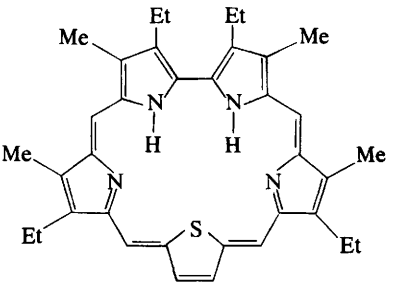
(201)



(202)



(203)



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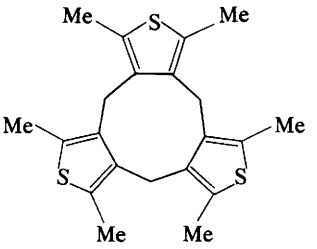

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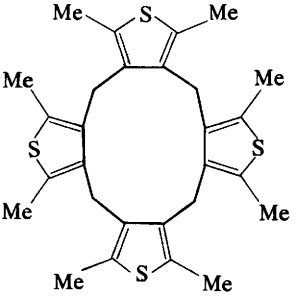


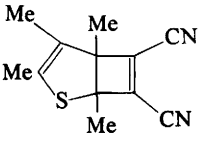
(206)

Reactions Leading to Destruction of the Thiophen Ring.—The product formed in the reaction between tetramethylthiophen and dicyanoacetylene in the presence of $AlCl_3$, and believed to be a thiepin derivative,[276] was later shown to be a cyclobutene derivative (207) formed by a [2 + 2] cycloaddition.[277] Thermally, (207) is rearranged to (208) by a [3,3]

[276] H. Wynberg and R. Helder, *Tetrahedron Letters*, 1972, 3647.

[277] D. N. Reinhoudt, H. C. Volger, C. G. Kouwenhoven, H. Wynberg, and R. Helder, *Tetrahedron Letters*, 1972, 5269.

antara–antara Cope rearrangement.[276,277] However, the cycloaddition of dimethyl acetylenedicarboxylate to the aminothiophen (209) at −30 °C gave the cyclobutene (210), which at that temperature isomerized to the thiepin (211).[278] On heating, sulphur was extruded from (211), yielding (212).[278] As



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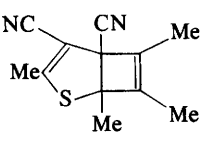

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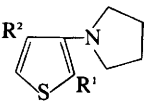
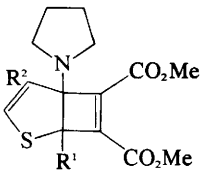


(209) R^1, R^2 = H, Me



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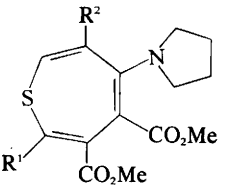
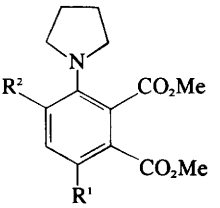


(211)



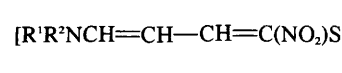
(212)

mentioned above, it has been suggested that the formation of benzene derivatives in the photochemical reaction between thiophens and acetylenes proceeds *via* a [2 + 4] cycloaddition.[155] On the other hand, photoaddition of carbonyl compounds to 2,5-dimethylthiophen is of the [2 + 2] type, yielding oxetan derivatives.[279]

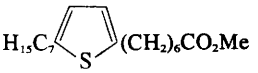
Convenient methods for the *S*-alkylation of thiophens with the methyl or ethyl esters of fluorosulphonic acid, or with methyl iodide and $AgBF_4$, have been worked out. The ylide from the methyl derivative has been obtained.[280]

The reaction between 2-nitrothiophen and secondary aliphatic amines leads most probably to the ring-opened product (213).[281] Raney-Nickel desulphurization continues to play an important role in the structure determination of thiophen derivatives,[100] and for the synthesis of macrocyclic compounds, such as α-alkylcycloalkanones,[102a,282] amino-lactams of aliphatic diaminocarboxylic acids,[283] and of dethiobiotin.[284] The nickel boride catalyst (NiBo), prepared from nickel(II) chloride and sodium borohydride in methanol, gives olefins in 50—55% yield. From (214) a mixture of methyl

[278] D. N. Reinhoudt and C. G. Kouwenhoven, *J.C.S. Chem. Comm.*, 1972, 1233.
[279] C. Rivas and R. A. Bolivar, *J. Heterocyclic Chem.*, 1973, **10**, 967.
[280] R. F. Heldeweg and H. Hogeveen, *Tetrahedron Letters*, 1974, 75.
[281] G. Guanti, C. Dell'Erba, and G. Leandri, *J.C.S. Chem. Comm.*, 1972, 1060.
[282] S. Z. Taits, V. N. Bulgakova, and Ya. L. Gol'dfarb, *Khim. geterotsikl. Soedinenii*, 1973, 16.
[283] B. P. Fabrichnyi, I. F. Shalavina, S. M. Kostrova, and Ya. L. Gol'dfarb, *Zhur. org. Khim.*, 1972, **8**, 187.
[284] B. P. Fabrichnyi, I. F. Shalavina, S. M. Kostrova, and Ya. L. Gol'dfarb, *Khim. geterotsikl. Soedinenii*, 1972, 315.



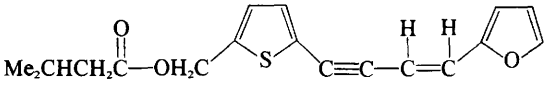
(213)



(214)

oleate and methyl elaidate was obtained.[285] For complete reduction of thiophens NiBo appears, however, to be inferior to Raney-Nickel.[286]

Naturally occurring Thiophens.—New acetylenic thiophen derivatives are still found in Nature, especially by Bohlmann and his group. From *Santolina rosmarinifolia* L., the compound (215) was isolated.[287] From the South African family Arctotideae, genus *Berkheya*, twelve new thiophen-containing derivatives were isolated.[288] One of these was believed to have structure (216), but by elegant synthesis of both (216) and an alternative structure (217), the latter was proved to be correct.[123] Biosynthetic pathways



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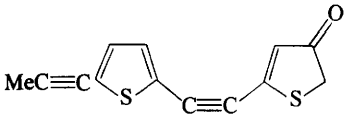

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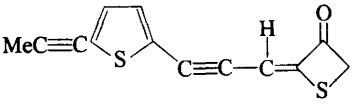
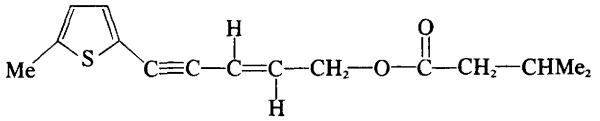


(217)

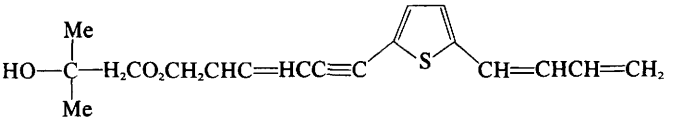
are discussed.[288] From the South African Composite *Osmitopsis asteriscordes* (L.) Cass., the ester (218) was isolated and the structure confirmed by



(218)

synthesis.[289] Several other naturally occurring thiophens such as (219),[124] (220), and (221)[125] have also been synthesized. Coupling of iodothiophens with acetylenic copper salts plays an important role in the synthesis of these compounds. A thiophen derivative has also been isolated from Japanese mugwort.[290] A great number of simple thiophen derivatives and condensed thiophens have been found in sulphur-rich shale oils.[291,292]

[285] J. Schut, J. B. F. N. Engberts, and H. Wynberg, *Synthetic Comm.*, 1972, **2**, 415.
[286] R. B. Boar, D. W. Hawkins, J. F. McGhie, and D. H. R. Barton, *J.C.S. Perkin I*, 1973, 654.
[287] F. Bohlmann and C. Zdero, *Chem. Ber.*, 1973, **106**, 845.
[288] F. Bohlmann and C. Zdero, *Chem. Ber.*, 1972, **105**, 1245.
[289] F. Bohlmann and C. Zdero, *Chem. Ber.*, 1972, **105**, 1919.
[290] K. Yano, S. Takahashi, and T. Furukawa, *Phytochemistry*, 1972, **11**, 2577.
[291] M. Pailer and H. Grünhaus, *Monatsh.*, 1973, **104**, 312.
[292] M. Pailer and L. Berner-Fenz, *Monatsh.*, 1973, **104**, 339.



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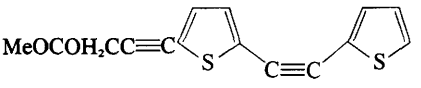

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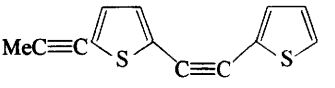
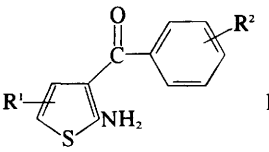


(221)

Thiophens of Pharmacological Interest.—There has been a marked increase in interest in pharmacologically active thiophens. There has been extensive work by several groups on the thiophen analogues of the psychopharmacologically active 1,4-benzodiazepines. The synthetic route used was the same as for diazepam. 2-Amino-3-aroylthiophens (222), prepared by the Gewald reaction or by the reaction of *o*-amino-esters or derivatives thereof with Grignard reagents, were chloroacetylated, transformed into the iodoacetyl derivative (223), aminated to (224), and ring-closed by refluxing in ethanol to the 1,4-diazepine ring, which was alkylated on nitrogen to (226).[5,6,82,87,177,180,183,293,294] The R group on thiophen has been Cl, Br, Me, Et, CO_2Me, CF_3, and NO_2. The 4-*N*-oxide of (225) has also been obtained.[177,293] C-Annelated thieno-1,4-diazepines (227) have been similarly prepared.[88,178,179,295] The derivative (226; R^1 = 2-Et, R^1 = *o*-Cl) is probably



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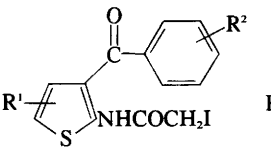

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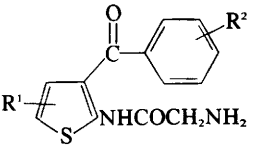

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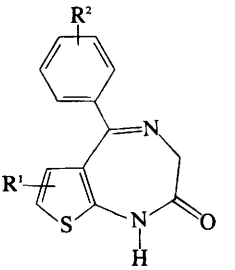

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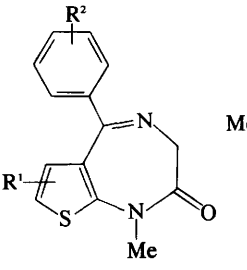

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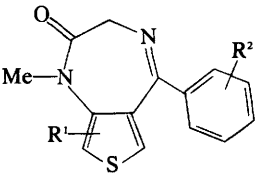
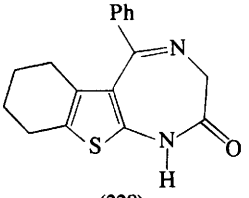


(227)

[293] O. Hromatka and D. Binder, *Monatsh.*, 1973, **104**, 704.
[294] O. Hromatka, D. Binder, and W. Veit, *Monatsh.*, 1973, **104**, 973.
[295] O. Hromatka, D. Binder, and K. Eichinger, *Monatsh.*, 1974, **105**, 123.

already in use in Japan[296,297,297a] and its metabolism has been studied.[7] Compound (228) was obtained from compound (165) *via* reaction with glycine ethyl ester hydrochloride in pyridine.[181]

Semisynthetic penicillins containing side-chains related to those in oxacillin and cloxacillin, such as (229)—(232),[139] and to ampicillin, such as (233),[298] have been prepared. In connection with studies on the synthesis and chemistry of cephalosporin antibiotics, thiophen-2-acetic acid is used as side-chain.[299–310]



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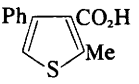

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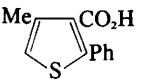

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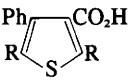
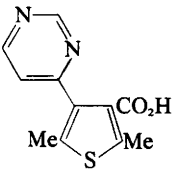
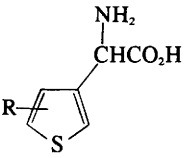


(231) R = Me or Bu^t

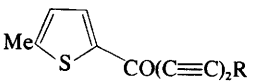


(232)



(233) R = H or Me

The compounds (234) have been synthesized as analogues of the antibiotic capillin.[311] New 2-nitrothiophen derivatives having antimicrobial



(234)

[296] M. Nakanishi, T. Tsumagari, Y. Takigawa, S. Shuto, T. Kenjo, and T. Fukuda, *Arzneim.-Forsch.*, 1972, **22**, 1905.

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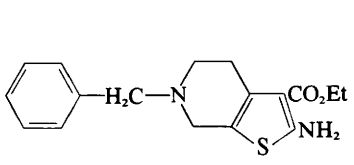
[308] T. Jen, B. Dienel, J. Frazee, and J. Weisbach, *J. Medicin. Chem.*, 1972, **15**, 1172.

[309] D. Willner, A. M. Jelenevsky, and L. C. Cheney, *J. Medicin. Chem.*, 1972, **15**, 948.

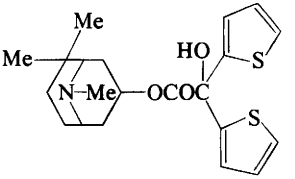
[310] J. R. E. Hoover, G. L. Dunn, D. R. Jakas, L. L. Lam, J. J. Taggart, J. R. Guarini, and L. Phillips, *J. Medicin. Chem.*, 1974, **17**, 34.

[311] V. I. Knutov and A. S. Nakhmanovich, *Izvest. Akad. Nauk. S.S.S.R., Ser. khim.*, 1971, 2069.

and antischistosomal properties have been synthesized.[312,313,313a] Some thiosemicarbazones of thiophen-2-aldehydes, especially 5-cyanothiophen-2-aldehyde thiosemicarbazone, show tuberculostatic activity[314] both *in vitro* and *in vivo*, and high antiviral effects against pox viruses.[315,316] Metabolites from the anti-inflammatory compound (234a) have been identified. The metabolic fate, as well as the absorption, distribution, and excretion, of the potent anti-parkinsonian drug (235) have been studied by ^{14}C-labelling.[317,318]



(234a)



(235)

The pharmacological properties of other basic derivatives of dithienylglycolic acid and phenylthienylglycolic acid have been investigated.[319,320] The metabolism of the new anticholinergic drug (236)[321] and of the analogous compound (237),[322] as well as the synthesis of (238) and (239), have been described.[323] The synthesis and pharmacological properties of a series of N-substituted 2-amino-1-(2-thienyl)ethanols have been described. Strong β-adrenergic blocking activity has been observed in *N*-isopropyl- or *N*-t-butyl-substituted ring-chlorinated compounds.[324] A highly active anti-phlogistic compound was found in (240).[32] The microbial metabolism of thiophen-2-carboxylic acid has been studied in detail.[325] Many potential pharmacologically active compounds have been prepared where the thiophen ring represents just one of many different substituents tested.

[312] E. Szarvasi, L. Fontaine, and A. Betbeder-Matibet, *J. Medicin. Chem.*, 1973, **16**, 281.
[313] D. W. Henry, V. H. Brown, M. Cory, J. G. Johansson, and E. Bueding, *J. Medicin. Chem.*, 1973, **16**, 1287.
[313a] C. Rufer, H.-J. Kessler, and A. Damerius, *Chim. Thérap.*, 1972, **7**, 122.
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[317] T. Meshi, S. Nakamura, and Y. Sato, *Chem. and Pharm. Bull. (Japan)* 1972, **20**, 1687.
[318] M. Otsuka, S. Nakamura, and Y. Sato, *J. Pharm. Soc. Japan*, 1972, **92**, 986.
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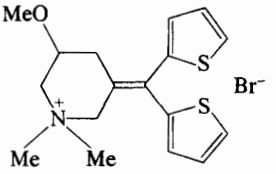
[325] R. E. Cripps, *Biochem. J.*, 1973, **134**, 353.



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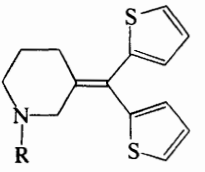

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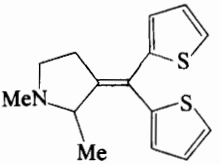

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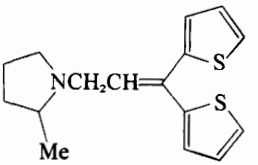

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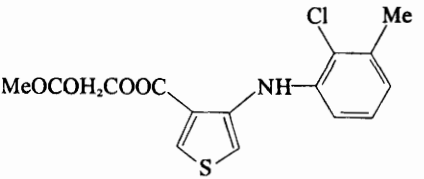


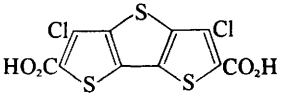
(240)

Thiophen-ring-containing compounds with anticoagulant properties,[326] anti-inflammatory properties,[327] psychotropic activity,[328] diuretic action,[329,330] hypocholesteremic activity,[269,331] antimitotic,[332] bacteriostatic,[333,334] anthelmintic,[335–337] antispasmodic,[338] and antiradiation activity[339] have thus been prepared.

[326] E. Boschetti, D. Molho, J. Chabert, M. Grand, and L. Fontaine, *Chim. Thérap.*, 1972, **7**, 20.
[327] M. Miocque, H. Moskowitz, J. Blanc-Guenee, A. M. Saint-Marc, G. Raynaud, J. Thomas, C. Gouret, and B. Pourrias, *Chim. Thérap.*, 1972, **7**, 283.
[328] K.-H. Weber, A. Bauer, and K.-H. Hauptmann, *Annalen*, 1972, **756**, 128.
[329] M. M. Kochhar, M. Salahi-Asbahi, and B. B. Williams, *J. Pharm. Sci.*, 1973, **62**, 336.
[330] C. Fauran, J. Eberle, D. Berthon, G. Huguet, M. Sergant, B. Pourrias, G. Raynaud, M. Garrivet, and V. Hecaen, *Chim. Thérap.*, 1971, **6**, 453.
[331] H. Saikachi, N. Shimojo, and Y. Uehara, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1663.
[332] J.-P. Marquet, L. Montagnier, J. Gruest, J.-D. Bourzat, J. Andre-Louisfert, and E. Bisagni, *Chim. Thérap.*, 1971, **6**, 427.
[333] A. F. Cockerill, M. F. Ellis, D. M. Rackham, and E. Wildsmith, *J.C.S. Perkin II*, 1973, 173.
[334] G. Kempter, J. Spindler, H.-J. Fiebig, and G. Sarodnick, *J. prakt. Chem.*, 1971, **313**, 977.
[335] J. G. Morales, R. R. Whetstone, D. W. Stoutamire, and D. K. Hass, *J. Medicin. Chem.*, 1972, **15**, 1225.
[336] A. F. Cockerill, D. M. Rackham, and N. C. Franklin, *J.C.S. Perkin II*, 1973, 509.
[337] J. A. Claisse, M. W. Foxton, G. I. Gregory, A. H. Sheppard, E. P. Tiley, W. K. Warburton, and M. J. Wilson, *J.C.S. Perkin I*, 1973, 2241.
[338] H. Igarashi and T. Kurihara, *J. Pharm. Soc. Japan*, 1973, **93**, 554.
[339] R. D. Westland, M. L. Mouk, J. L. Holmes, R. A. Cooley, jun., J. S. Hong, and M. M. Grenan, *J. Medicin. Chem.*, 1972, **15**, 968.

3 Thienothiophens, their Benzo-derivatives, and Analogous Compounds

Synthesis.—The reactions of thiophen-2- and 3-acrylic acid with thionyl chloride in the presence of pyridine yield a mixture of chlorinated derivatives of thieno[3,2-*b*]thiophen-2-carboxylic acid and thieno[2,3-*b*]-thiophen-2-acrylic acid.[201,340,341] From thiophen-2,5-diacrylic acid, (241) was obtained.[201] Aromatization of (66) gives thieno[2,3-*b*]thiophens.[31] Reaction of (242) with methyl thioglycolate yielded (243).[164] Ethylthiophen was



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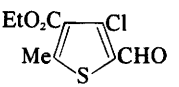

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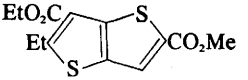
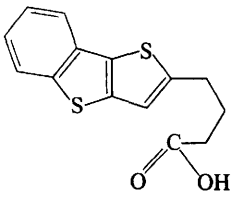


(243)

converted into thieno[3,2-*b*]thiophen in 13.5% yield through the reaction with hydrogen sulphide over aluminochromium and aluminoiron catalysts at 450 °C.[342] Heating of (244) with P_2O_5 somewhat unexpectedly gives (245) in high yield.[343]



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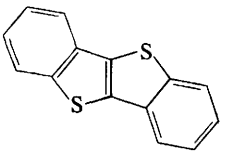


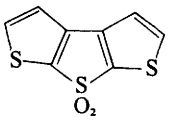
(245)

Theoretical Studies and Physical Properties.—Quantum chemical calculations on the reactivity of thienothiophens have been carried out.[344] The e.s.r. spectra of the radical anions of carbonyl, nitro, and cyano derivatives of the two [*b*]-fused thiophens have been studied.[345] The proton chemical shifts of 2-substituted thieno[2,3-*b*]thiophens have been correlated with the two-parameter equation of Swain and Lupton.[346]

The interaction of the sulphonyl group with an adjacent unsaturated centre has been studied in the sulphone (246) and in its differently fused isomers.[347]

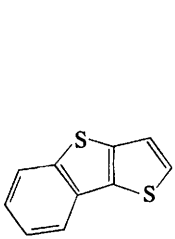
Substitution Reactions.—The reactivities of thieno[3,2-*b*]thiophen and thieno[2,3-*b*]thiophen, relative to thiophen, in electrophilic formylation,

[340] W. B. Wright, jun., *J. Heterocyclic Chem.*, 1972, **9**, 879.
[341] S. Gronowitz and B. Maltesson, *Acad. Chem. Scand.*, 1972, **26**, 2982.
[342] V. P. Litvinov and É. G. Ostapenko, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1971, 1683.
[343] A. Ricci, D. Balucani, and B. Berardo, *Compt. rend.*, 1972, **275**, *C*, 139.
[344] Ya. L. Gol'dfarb, V. P. Litvinov, G. M. Zhidomirov, I. A. Abronin, and R. Z. Zakharyan, *Chem. Scripta*, 1974, **5**, 49.
[345] G. F. Pedulli, M. Tiecco, A. Alberti, and G. Martelli, *J.C.S. Perkin II*, 1973, 1816.
[346] A. Bugge, *Chem. Scripta*, 1973, **3**, 190.
[347] F. de Jong and M. J. Janssen, *Rec. Trav. chim.*, 1973, **92**, 1073.



(246)

acetylation, and chlorination have been studied by means of competitive experiments.[348] The benzothiophen (247) underwent Friedel–Crafts benzoylation at position 2. The ketones obtained from methyl-substituted benzoic acids underwent the Elb reaction in low yield to give derivatives of (248).[349]



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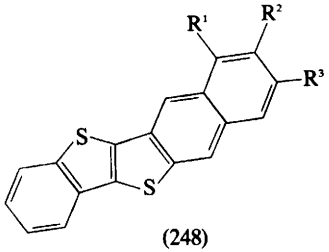
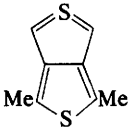


(248)

2,5-Diformylthieno[2,3-*b*]thiophen prepared by metallation of thieno[2,3-*b*]-thiophen with excess butyl-lithium and DMF has been used as a building-block for heterohelicene syntheses.[350]

Non-classical Thienothiophens.—Detailed papers on the synthesis and chemical reactions of 1,3-disubstituted thieno[3,4-*c*]thiophens, *e.g.* (249) and (250),[351] and on the stable tetraphenyl derivative (251), have appeared.[352]



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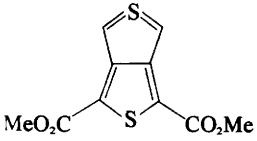
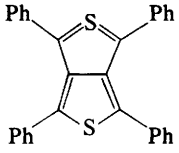


(250)

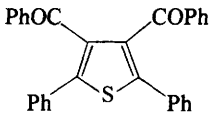


(251)

Compound (251) is non-polar, gives no e.s.r. signal, and thus appears to contain sulphur atoms with considerable quadricovalent character. An *X*-ray study indicates that the four phenyl groups are not coplanar with the ring system.[353] A convenient synthesis of 3,4-dibenzoyl-2,5-diphenylthiophen (252), a useful starting material for (251), has been described in the

[348] A. Bugge, *Chem. Scripta*, 1972, **2**, 137.
[349] P. Jacquignon, A. Croisy, A. Ricci, and D. Balucani, *J.C.S. Perkin I*, 1973, 734.
[350] J. H. Dopper, D. Oudman, and H. Wynberg, *J. Amer. Chem. Soc.*, 1973, **95**, 3692.
[351] M. P. Cava, N. M. Pollack, and G. A. Dieterle, *J. Amer. Chem. Soc.*, 1973, **95**, 2558.
[352] M. P. Cava, M. Behforouz, G. E. M. Husbands, and M. Srinivasan, *J. Amer. Chem. Soc.*, 1973, **95**, 2561.
[353] M. D. Glück and R. E. Cook, *Acta Cryst.*, 1972, **B28**, 1336.

reaction of (253) with dibenzoylacetylene.[354] The reaction of (251) with this reagent gives (254), which with P_2S_5 in pyridine yields (255). When (254) reacted with P_2S_5 in xylene, the 4,8-dihydro-derivative of (255) was obtained instead.[355]



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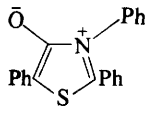

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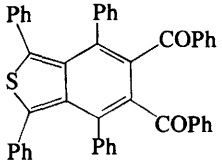

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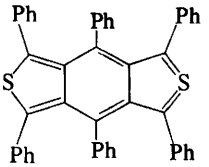
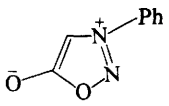
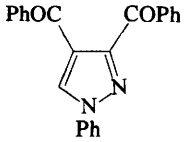


(255)

Reaction of phenylsydnone (256) with dibenzoylacetylene gave (257), which again could be converted into (258) by reaction with P_2S_5 in pyridine. The brick-red (258) easily underwent cycloadditions with acetylenic and



(256)



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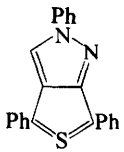


(258)

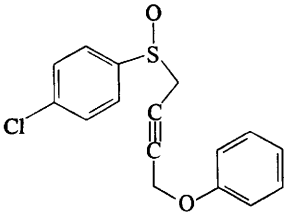
olefinic dipolarophiles.[356] The thieno[3,4-*c*]furan and thieno[3,4-*c*]pyrrole systems have been synthesized similarly from the corresponding 3,4-dibenzoyl-2,5-diphenylfurans and pyrroles.[357,358] It is claimed that the pyrrole system shows both azomethine ylide and thiocarbonyl ylide dipolar characteristics.[358] A review concerning covalent condensed thiophens has appeared.[359]

4 Benzothiophens and their Benzo-fused Systems

Synthesis of Benzothiophens by Ring-closure Reactions.—Thiophenols react slowly (5–22 days) with dimethyl acetylenedicarboxylate in methanol to

[354] K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, 1973, **95**, 2750.
[355] M. P. Cava and M. A. Sprecker, *J. Org. Chem.*, 1973, **38**, 3975.
[356] K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, 1972, **94**, 6215.
[357] M. P. Cava and M. A. Sprecker, *J. Amer. Chem. Soc.*, 1972, **94**, 6214.
[358] K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, 1973, **95**, 2749.
[359] M. P. Cava, *Internat. J. Sulfur Chem.* (C), 1972, **7**, 55.

give dimethyl benzo[*b*]thiophen-2,3-dicarboxylate in acceptable yields.[360] Between lithium pentafluorobenzenethiolate and diethyl acetylenedicarboxylate a fast reaction with displacement of fluorine is observed at −70 °C, leading to diethyl 4,5,6,7-tetrafluorobenzo[*b*]thiophen-2,3-dicarboxylate.[361] Ethylbenzene has been converted into benzo[*b*]thiophen by reaction with hydrogen sulphide over aluminochromium oxide at 500 °C.[342] 3-Hydroxy-2-methoxycarbonylbenzo[*b*]thiophens have been prepared in one step by the reaction of methyl *o*-nitrobenzoates (nitro displacement) with lithium methyl thioglycolate in DMF at 0 °C.[362] The mechanism of the formation of chlorinated 2-benzo[*b*]thiophencarboxylic acids from cinnamic acids and thionyl chloride in the presence of pyridine has been studied.[363] Heating of the acetylenic sulphoxide (259) leads *via* allylic rearrangement of (260) to the benzo[*b*] derivatives (261), which were treated with different amines.[364] Ring-contraction occurs in the cyclodehydration of (262), giving the benzo[*b*]thiophen (263) as the main product, especially at higher



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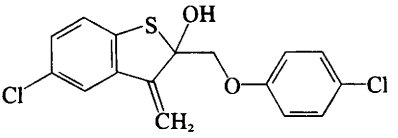

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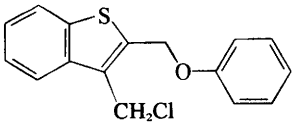

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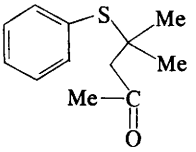

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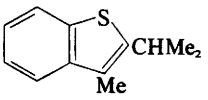
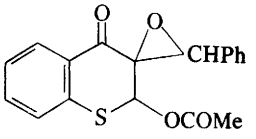


(263)

temperatures.[365] In the alkaline hydrolysis of (264), the hydroxy-aldehydes (265) and (266) are formed with ring-contraction.[366] The reaction of substituted butyrophenones and valerophenones (267) with chlorosulphonic acid is found to give 3-chloro-2-substituted benzo[*b*]thiophen 1,1-dioxides (268).[367] Irradiation of (269) in benzene solution gave (270), which was unambiguously prepared by PPA cyclodehydration of the appropriate

[360] K. Undheim and R. Lie, *Acta Chem. Scand.*, 1973, **27**, 595.
[361] G. M. Brooke and M. A. Quasem, *J.C.S. Perkin I*, 1973, 429.
[362] J. R. Beck, *J. Org. Chem.*, 1973, **38**, 4086.
[363] A. J. Krubsack and T. Higa, *Tetrahedron Letters*, 1973, 125.
[364] B. El-Osta, K. C. Majumdar, and B. S. Thyagarajan, *J. Heterocyclic Chem.*, 1973, **10**, 107.
[365] D. D. MacNicol and J. J. McKendrick, *Tetrahedron Letters*, 1973, 2593.
[366] H. Hofmann, H. Westernacher, and H. -J. Haberstroh, *Chem. Ber.*, 1973, **106**, 349.
[367] V. P. Arya and S. J. Shenoy, *Indian J. Chem.*, 1973, **11**, 628.



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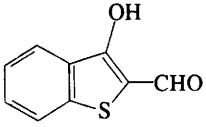

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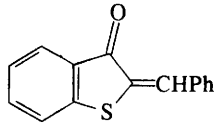

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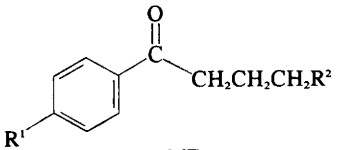

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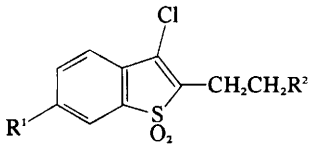

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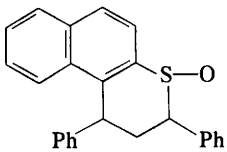

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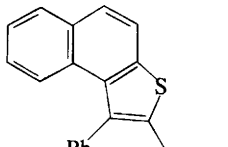
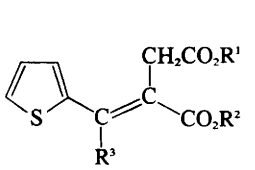


(270)

naphthyl β-ketosulphide.[368] The mechanism has been studied in detail.[368,369] Some methoxy-substituted 3-benzo[*b*]thiophencarboxylic acids were prepared through the reaction of methoxythiophenolate with ethyl bromopyruvate, followed by PPA cyclization.[370,371]

Some benzo[*b*] derivatives have been synthesized starting from thiophen derivatives. The condensation of methyl 2-thienyl and phenyl 2-thienyl ketones with dimethyl succinate in the presence of potassium t-butoxide gave predominantly the *E*-half ester (271), which upon treatment with sodium acetate–acetic anhydride gave the benzo[*b*]thiophen (272).[220] The reaction of alkyl 2-thienyl ketones with the Grignard reagent (273) gives the acetals (274), which upon treatment with 10% refluxing H_2SO_4 hydrolyse and cyclize to (275).[372] Photocyclization–oxidation of 1-phenyl-4-(2′-thienyl)buta-1,3-diene gave 4-phenylbenzo[*b*]thiophen.[373] Irradiation of the 1,2-dithiol-3-thione (276) gave the benzothiophen (277).[374] The reaction of thienopyrylium salts with dialkylamines gives 5-dialkylaminobenzo[*b*]thiophens.[375]

[368] A. G. Schultz and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 4787.
[369] A. G. Schultz and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 4791.
[370] R. L. Titus and C. F. Titus, *J. Heterocyclic Chem.*, 1973, **10**, 679.
[371] E. Campaigne, R. B. Rogers, A. Donelson, and T. R. Bosin, *J. Heterocyclic Chem.*, 1973, **10**, 979.
[372] H. J. J. Loozen and E. F. Godefroi, *J. Org. Chem.*, 1973, **38**, 1056.
[373] C. C. Leznoff, W. Lilie, and C. Manning, *Canad. J. Chem.*, 1974, **52**, 132.
[374] P. de Mayo and H. Y. Ng, *Tetrahedron Letters*, 1973, 1561.
[375] V. I. Dulenko and N. N. Alekseev, *Doklady Akad. Nauk S.S.S.R.*, 1972, **206**, 351.



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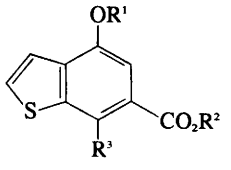
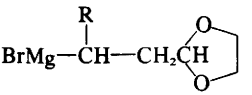


(272)



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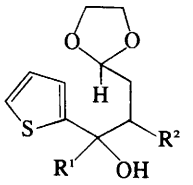

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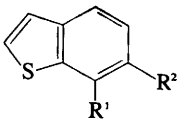

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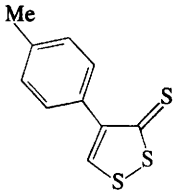

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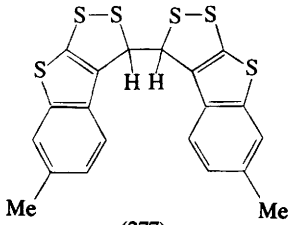
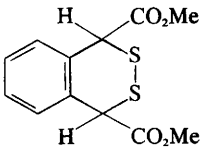


(277)

A new important route to the benzo[c]thiophen series was found in the reaction of (278) with alkali, yielding (279).[376] Complexes obtained from



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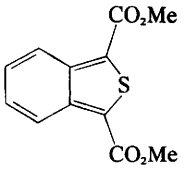


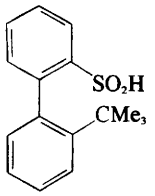
(279)

thiobenzophenone and $Fe_2(CO)_9$ could be transformed into derivatives of benzo[c]thiophen.[377]

Heating of (280) with acetic anhydride proceeds with elimination of the t-butyl group, giving dibenzothiophen.[378] Condensation of (281) with (282)

[376] G. Cignarella and G. Cordella, *Tetrahedron Letters*, 1973, 1871.
[377] H. Alper and A. S. K. Chan, *J. Amer. Chem. Soc.*, 1973, **95**, 4905.
[378] F. M. Stoyanovich, R. G. Karpenko, G. I. Gorushkina, and Ya. L. Gol'dfarb, *Tetrahedron*, 1972, **28**, 5017.

gave (283), which was cyclized to the benzo[*b*]thiophen (284) and aromatized to the dibenzothiophen (285).[379] The reaction of (286) with ethyl dichloroethoxyacetate yields the dibenzothiophen (287), from which the bridged derivative (288) was prepared in several steps.[380] Naphtho[1,2-*b*]-thiophens and naphtho[2,1-*b*]thiophens have been prepared by oxidative



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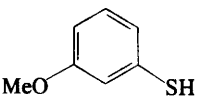

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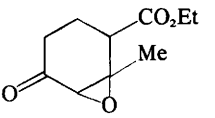

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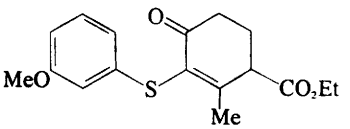

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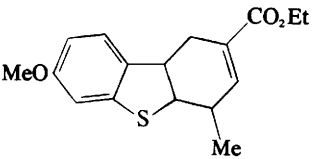

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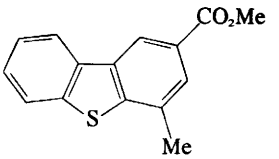

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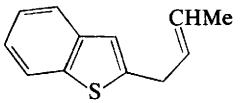

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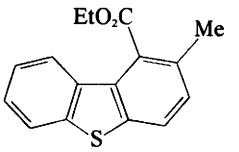

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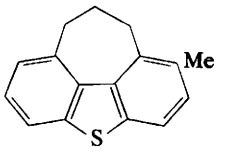


(288)

photochemical ring-closure of 1-aryl-2-(2-thienyl)- and 1-aryl-2-(3-thienyl)-ethylenes, respectively.[204,205]

Physical Properties.—Spin-density distributions in benzo[*b*]thiophen have been determined by n.m.r. contact shift measurements on a nickel(II)–aminotropone iminate derivative.[381] The relation between chemical structure

[379] R. R. Crenshaw, G. M. Luke, T. A. Jenks, G. Bialy, and M. E. Bierwagen, *J. Medicin. Chem.*, 1972, **15**, 1162.

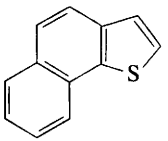
[380] P. Cagniant, N. Bellinger, and D. Cagniant, *Compt. rend.*, 1973, **277**, *C*, 383.

[381] D. R. Eaton, R. E. Benson, C. G. Bottomley, and A. D. Josey, *J. Amer. Chem. Soc.*, 1972, **94**, 5996.

and absorption spectra of monoazo dyes containing the benzo[*b*]thiophen nucleus and its derivatives has been studied,[382] as well as the spectra of 3-keto-2,3-dihydrobenzo[*b*]thiophens.[383] Mass spectra of some phenyl- and chloro-substituted benzo[*b*]thiophens have been investigated.[384]

Electrophilic Substitution.—The great interest in electrophilic substitution of benzo[*b*]thiophen derivatives is continuing. The t-butylation of benzo[*b*]thiophen has been reinvestigated.[385] Isomers and other products obtained in the nitration of 3-t-butyl-2-benzo[*b*]thiophencarboxylic acid,[385] and in the bromination, nitration, Vilsmeier formylation, and Friedel–Crafts acetylation of 4-methoxybenzo[*b*]thiophen and its 3-methyl derivative have been carefully determined.[386] Similarly, electrophilic substitution of 4-hydroxybenzo[*b*]thiophen and its 3-methyl derivative,[387] of 7-hydroxy- and 7-mercapto-3-methylbenzo[*b*]thiophen,[388] and of 7-chloro-3-methylbenzo[*b*]thiophen[389] has been studied. The Mannich reaction of 5-hydroxybenzo[*b*]thiophen with formaldehyde and secondary amines gives 4-aminomethyl derivatives; the nature of the products with primary amines depends largely on the experimental conditions.[390] Partial rate factors for electrophilic reactions of benzo[*b*]thiophen and naphthalene have been compared. No straight plots were obtained when log(partial rate factors) was plotted against ρ (extended selectivity treatment), implying a variable σ^+-parameter for these benzo-fused systems.[391]

The synthesis of a new naphtho[1,2-*b*]thiophen (289), starting from 3,4-



(289)

dihydronaphthalen-1(2*H*)-one and going *via* 1-chloro-3,4-dihydronaphthalene-2-carbaldehyde, has been worked out.[392] Bromination, formylation, acetylation, and lithiation of (289) occur at position 2, while nitration gave a

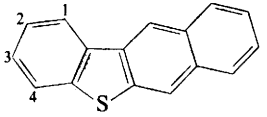
[382] M. Kamel, M. A. Allam, R. M. Issa, A. T. El-Aref, and S. T. El-Aref, *J. prakt. Chem.*, 1971, **313**, 1131.
[383] G. A. Yugai, M. A. Mostoslavskii, and T. V. Denisova, *Khim. geterotsikl. Soedinenii*, 1970, 1326.
[384] V. S. Fal'ko, V. I. Khvostenko, V. É. Udre, and M. G. Voronkov, *Khim. geterotsikl. Soedinenii*, 1971, 326.
[385] J. Cooper and R. M. Scrowston, *J.C.S. Perkin I*, 1972, 414.
[386] K. Clarke, R. M. Scrowston, and T. M. Sutton, *J.C.S. Perkin I*, 1973, 623.
[387] K. Clarke, R. M. Scrowston, and T. M. Sutton, *J.C.S. Perkin I*, 1973, 1196.
[388] N. B. Chapman, K. Clarke, and A. Manolis, *J.C.S. Perkin I*, 1972, 2593.
[389] N. B. Chapman, K. Clarke, and A. Manolis, *J.C.S. Perkin I*, 1972, 1404.
[390] S. M. A. D. Zayed, M. M. Sidky, and A. Emran, *J. prakt. Chem.*, 1973, **315**, 244.
[391] S. Clementi, P. Linda, and C. D. Johnson, *J.C.S. Perkin II*, 1973, 1250.
[392] K. Clarke, D. N. Gregory, and R. M. Scrowston, *J.C.S. Perkin I*, 1973, 2956.

mixture of the 2- and 5-isomer. When position 2 is blocked with an ethoxycarbonyl group, bromination and nitration occur at position 5.

Nucleophilic Substitution, Metallation, and Halogen–Metal Exchange.—Direct nucleophilic displacement of the 7-chloro-group of 7-chloro-3-methylbenzo[*b*]thiophen has been achieved.[389] 3-Bromobenzo[*b*]thiophen was reduced to the 3-deuterio-derivative by the reaction with sodium borodeuteride and palladium chloride.[393] Meisenheimer complexes were formed in the reaction of methoxide ion with 2-methoxy-3-nitro- and 3-methoxy-2-nitrobenzo[*b*]thiophen.[394] Rate and equilibrium data were determined in methanol at 25 °C. On treatment of 2-bromobenzo[*b*]thiophen with potassium amide in liquid ammonia, bromine migration to the adjacent carbon atom was observed. Considerable evidence for the occurrence of an intermolecular transbromination was obtained.[395] The reaction of 3-bromobenzo[*b*]thiophen with piperidine has been reinvestigated and found to give primarily the normal, but also some of the cine-substitution product, which is the only product obtained in the reaction of 2-bromobenzo[*b*]thiophen. Possible mechanisms for some of these reactions are suggested.[396]

Some benzo[*b*]thiophen derivatives of biological interest have been selectively deuteriated or tritiated at position 2 by reaction with butyl-lithium and ^2H_2O or ^3H_2O.[397]

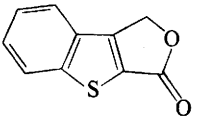
2-Benzo[*b*]thienyl-lithium reacts with *o*-nitrofluorobenzene to give 2-(*o*-nitrophenyl)benzo[*b*]thiophen, with pentafluoropyridine to give 2,4,6-tri-(2-benzo[*b*]thienyl)difluoropyridine, and with 2-fluoropyridine to give 2-(2-pyridyl)benzo[*b*]thiophen as main products.[398] 2,3-Diformyl- and 2,3-dicarboxy-benzo[*b*]thiophen are obtained by treating 3-bromo- or 2,3-dibromobenzo[*b*]thiophen with two equivalents of butyl-lithium followed by the appropriate reagent.[399] By stepwise reaction followed by protection of the first introduced carbonyl group by acetal formation, 2,3-ketones, aldehydes, and acid aldehydes of benzo[*b*]thiophen were obtained.[399] Benzo[*b*]naphtho[2,3-*d*]thiophen (290) is metallated at position 4 by butyl-lithium.[400]



(290)

[393] T. R. Bosin, M. G. Raymond, and A. R. Buckpitt, *Tetrahedron Letters*, 1973, 4699.
[394] F. de Santis and F. Stegel, *Gazzetta*, 1973, **103**, 649.
[395] D. A. de Bie, H. C. van der Plas, G. Geurtsen, and K. Nijdam, *Rec. Trav. chim.*, 1973, **92**, 245.
[396] M. G. Reinecke, W. B. Mohr, H. W. Adickes, D. A. de Bie, H. C. van der Plas, and K. Nijdam, *J. Org. Chem.*, 1973, **38**, 1365.
[397] T. R. Bosin and R. B. Rogers, *J. Labelled Compounds*, 1973, **9**, 395.
[398] K. E. Chippendale, B. Iddon, and H. Suschitzky, *J.C.S. Perkin I*, 1972, 2023.
[399] G. Dore, M. Bonhomme, and M. Robba, *Tetrahedron* 1972, **28**, 2553.
[400] V. P. Litvinov, D. D. Gverdtsiteli, and E. D. Lubuzh, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1972, 79.

Side-chain Reactions.—On heating to 325—400 °C 2- and 3-methylbenzo[*b*]thiophen disproportionate to 2,3-dimethylbenzo[*b*]thiophen and benzo[*b*]thiophen.[401] 2-Ethoxycarbonyl-3-methylbenzo[*b*]thiophen was brominated in the side-chain, and *via* the hydroxymethyl derivative was transformed into the lactone (291). The isomeric lactone (292) was prepared *via* the nitrile alcohol.[402] Thermolysis and electron-impact fragmentation of some aldazines and ketazines of the benzo[*b*]thiophen series have been studied.[403] The structure of the *syn*- and *anti*-isomers of (293) has been determined. Their toluene-*p*-sulphonates rearrange to the lactam (294),[404]



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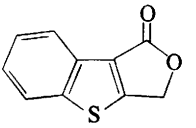

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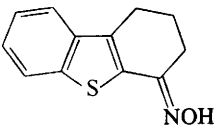

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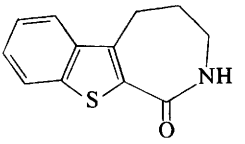
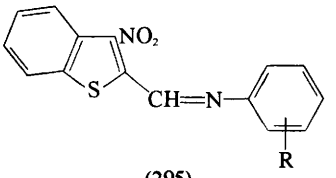


(294)

which was further transformed into *N*-sulphonyl amidrazones and tetracyclic triazole derivatives of pharmacological interest.

The reduction of anils derived from 3-nitrobenzo[*b*]thiophen-2-carbaldehydes (295) with triethyl phosphite gave the indazole analogue (296) in moderate yield.[405] Higher yields of (296) were obtained by thermal decomposition of the corresponding azido-derivative, which was prepared by reduction of 2-formyl-3-nitrobenzo[*b*]thiophen to the amino-derivative, followed by diazotization and reaction with sodium azide. On the other hand, reduction of isomeric anils (297) with triethyl phosphite gave a mixture of (298) and benzo[*b*]thiophen-3-carbonitrile, while pyrolysis of the corresponding azide gave (298) and (299).[405] Possible reaction mechanisms are suggested. It has been shown that polyphosphoric acid is a more convenient cyclodehydration agent than concentrated sulphuric acid in the Beyer–Combes synthesis of 2,4-dimethylquinolines, and this was used in the transformation of (300) into (301).[406] Intramolecular cyclizations of

[401] A. N. Korepanov, T. A. Danilova, and E. A. Viktorova, *Zhur. org. Khim.*, 1973, **9**, 641.
[402] L. Christiaens and M. Renson, *Bull. Soc. chim. belges*, 1972, **81**, 609.
[403] G. Saint-Ruf and L. Christiaens, *Bull. Soc. chim. France*, 1972, 4375.
[404] R. Neidlein and M. Ziegler, *Arch. Pharm.*, 1973, **306**, 531.
[405] K. E. Chippendale, B. Iddon, and H. Suschitzky, *J.C.S. Perkin I*, 1973, 129.
[406] G. Saint-Ruf, A. De, and J. C. Perche, *Bull. Soc. chim. France*, 1973, 2514.



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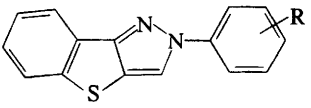

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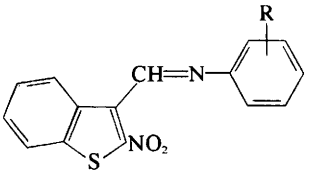

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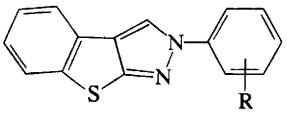

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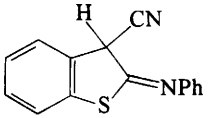

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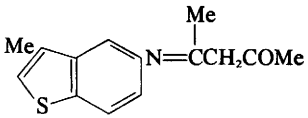

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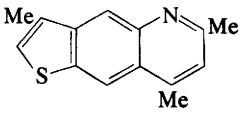
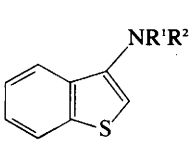


(301)

1-(pent-4-enyl)dibenzothiophens and of 2,3-bis-(2-methylpent-4-enyl)-dibenzothiophen have been carried out.[407] Cycloaddition of dimethyl acetylenedicarboxylate to (302) gives the benzo[*b*]thiepin (303), which upon heating is transformed into naphthalenes.[408]



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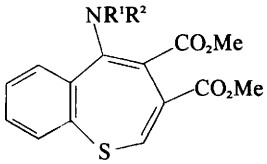
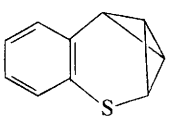


(303)

Photochemistry.—Benzo[*b*]thiophen-3-carbaldehydes and -carboxylic acid have been obtained *via* light-catalysed *N*-bromosuccinimide bromination of 3-methylbenzo[*b*]thiophen.[409] The photochemical behaviour of benzo[*b*]thiophen was found to differ from that of thiophen. It does not undergo photoisomerization and is not converted into an indole when irradiated in the presence of a primary amine. Its photochemical behaviour resembles that of naphthalene.[410] Photolysis of various

[407] J. Gourier and P. Canonne, *Bull. Soc. chim. France*, 1973, 3110.
[408] D. N. Reinhoudt and C. G. Kouwenhoven, *J.C.S. Chem. Comm.*, 1972, 1232.
[409] H. J. Brabander, *J. Heterocyclic Chem.*, 1973, **10**, 127.
[410] P. Grandclaudon, A. Lablache-Combier, and C. Párkányi, *Tetrahedron*, 1973, **29**, 651.

5-azidobenzo[*b*]thiophens in secondary amines unexpectedly gave a 4-amino-5-*NN*-dialkylaminobenzo[*b*]thiophen, whereas 4-azidobenzo[*b*]-thiophen gave no rearranged products.[411] Photochemical as well as thermal and silver-promoted reactions of (304) lead to (305), which was also prepared by photochemical addition of *cis*-dichloroethylene to benzo[*b*]thiophen using acetophenone as sensitizer followed by dechlorination of the adduct with sodium–phenanthrene in THF.[412]



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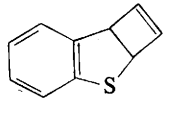
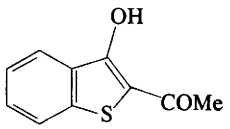
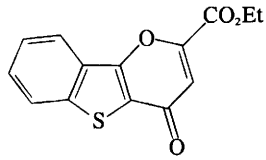


(305)

2- and 3-Hydroxybenzo[*b*]thiophen Systems.—Benzo[*b*]thiophen-2(3*H*)-one has been prepared from 2-t-butoxybenzo[*b*]thiophen by dealkylation. Alkylation of sodium, thallium, and tetrabutylammonium salts of the 2-hydroxybenzo[*b*]thiophen system led to both *C*- and *O*-alkylation, along with products due to ring-opening. At elevated temperatures, benzo[*b*]thiophen-2(3*H*)-one reacted with HMPA to give 2-dimethylaminobenzo[*b*]thiophen. Other 2-aminobenzo[*b*]thiophens were formed on refluxing in the presence of an excess of the corresponding amine.[413] The tautomerism in anils of 3-hydroxybenzo[*b*]thiophen-2-aldehydes has been investigated.[414] Through the condensation of (306) with diethyl oxalate, (307), which was of interest as an anti-asthma agent, was synthesized.[415] Some iodothioindoxyls have been condensed with aromatic aldehydes and their dyeing properties studied.[416]



(306)



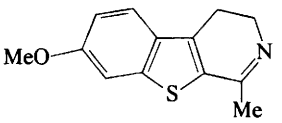
(307)

Reaction at Sulphur.—By the use of ^{35}S-tracer it was shown that dibenzothiophen does not exchange sulphur on heating.[417] Methods for the synthesis of 5-aryl- or 5-alkyl-dibenzothiophenium salts have been worked out.[418] The reaction of *S*-aryldibenzothiophenium fluoroborates with aryllithium was shown to proceed according to two routes, leading to biaryl and

[411] B. Iddon, H. Suschitzky, and D. S. Taylor, *J.C.S. Chem. Comm.*, 1972, 879.
[412] I. Murata, T. Tatsuoka, and Y. Sugihara, *Tetrahedron Letters*, 1974, 199.
[413] N. O. Vesterager, E. B. Pedersen, and S.-O. Lawesson, *Tetrahedron*, 1973, **29**, 321.
[414] V. A. Bren, V. I. Usacheva, and V. I. Minkin, *Khim. geterotsikl. Soedinenii*, 1972, **8**, 620.
[415] J. B. Wright and H. G. Johnson, *J. Medicin. Chem.*, 1973, **16**, 861.
[416] A. K. Das and A. K. Sinha, *J. Indian Chem. Soc.*, 1972, **49**, 993.
[417] S. Oae, S. Makino, and Y. Tsuchida, *Bull. Chem. Soc. Japan*, 1973, **46**, 650.
[418] M. Hori, T. Kataoka, H. Shimizu, and M. Miyagaki, *J. Pharm. Soc. Japan*, 1973, **93**, 476.

dibenzothiophen or to 2-arylthio-*o*-terphenyl formation. Electron-withdrawing substituents favour the former, whereas electron-donating substituents favour the latter route. The mechanisms of these reactions were discussed and interpreted in terms of tetra-arylsulphuranes as intermediates.[419] The synthesis and reactions of 2,3-dichlorobenzo[*b*]thiophen 1-oxide have been described.[420]

Pharmacologically Active Compounds.—Interest in preparing benzo[*b*]thiophen analogues of various types of pharmacologically active indole derivative is continuing. Two groups of workers have described the synthesis of 3-(β-dimethylaminoethyl)-4-hydroxybenzo[*b*]thiophen, the analogue of the hallucinogen psilocin and of related compounds. The key step in Campaigne's synthesis was halogen–metal exchange of 3-bromo-4-methoxybenzo[*b*]thiophen with butyl-lithium, followed by reaction with *NNN'N'*-tetramethyloxamide and subsequent reduction of the keto-amide.[421,422] Chapman's route starts from 4-methoxy-3-methylbenzo[*b*]thiophen-2-carboxylic acid, and the crucial step is the conversion of the methyl substituent into a bromomethyl group.[423] Some 2- and 3-dialkylaminomethyl-5-methoxybenzo[*b*]thiophens have been prepared from the appropriate bromomethyl compounds and secondary amines as serotonin analogues.[424] The benzo[*b*]thiophen analogues of harmalin (308) and harmine (309) have been synthesized[425] and tested as MAO inhibitors.[426] The yohimbane analogue (310) was prepared by reaction of (311) with $POCl_3$ and $NaBH_4$. The compound (311) was prepared through the reaction of 3-(β-aminoethyl)benzo[*b*]thiophen with isochroman-3-one.[427] 4-(*p*-Methoxyphenyl)-2-methylcyclohexane-carboxylic acids (312) and related compounds, which are potential antifertility agents, were prepared by desulphurization of the benzo[*b*]thiophen (313).[428] A large number of derivatives



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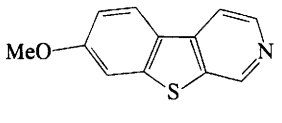
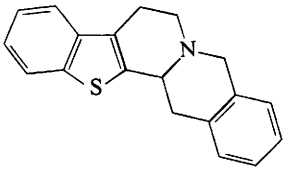


(309)

[419] B. M. Trost and H. C. Arndt, *J. Amer. Chem. Soc.*, 1973, **95**, 5288.
[420] V. I. Dronov, G. M. Prokhorov, and N. S. Lyubopytova, *Khim. geterotsikl. Soedinenii*, 1970, **6**, 1192.
[421] E. Campaigne and R. B. Rogers, *J. Heterocyclic Chem.*, 1973, **10**, 297.
[422] E. Campaigne and R. B. Rogers, *J. Heterocyclic Chem.*, 1973, **10**, 963.
[423] N. B. Chapman, R. M. Scrowston, and T. M. Sutton, *J.C.S. Perkin I*, 1972, 3011.
[424] N. B. Chapman, K. Clarke, B. A. Gore, A. Manolis, H. Porter, and T. M. Sutton, *J.C.S. Perkin I*, 1973, 750.
[425] T. R. Bosin, R. P. Maickel, A. Dinner, A. Snell, and E. Campaigne, *J. Heterocyclic Chem.*, 1972, **9**, 1265.
[426] T. R. Bosin, E. Campaigne, and R. P. Maickel, *Life Sciences*, 1972, **11**, 685.
[427] G. Wolf, W. Meise, and F. Zymalkowski, *Tetrahedron Letters*, 1972, 3223.
[428] R. R. Crenshaw, G. M. Luke, T. A. Jenks, R. A. Partyka, G. Bialy, and M. E. Bierwagen, *J. Medicin. Chem.*, 1973, **16**, 813.



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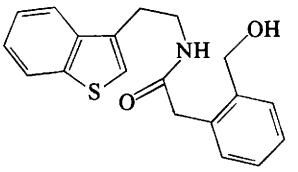

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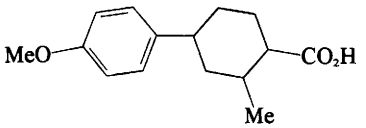

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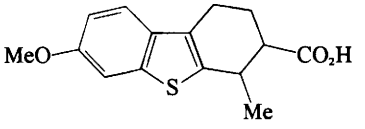
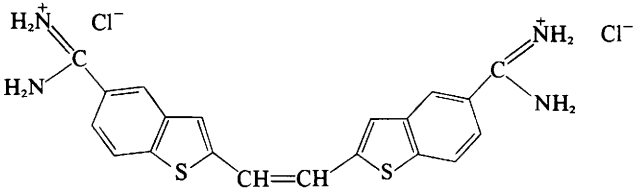


(313)

of 4-methyldibenzothiophen-3-carboxylic acids have also been synthesized and tested as antifertility agents.[379] In connection with very extensive work on trypanocidal diamidines with three rings in two isolated ring systems and with four rings in one or two rings systems, the benzo[*b*]thiophen ring system has been used as a component, for instance as in (314).[429,430] In connection with work on antiparasitic compounds, (315) has been synthesized.[431] Compounds of the type (316), which were prepared by acylation of 2-alkyl-substituted benzo[*b*]thiophens with *p*-methoxybenzoyl chloride followed by demethylation, halogenation, and alkylation of the phenolic OH group, had valuable anti-anginal properties.[432]



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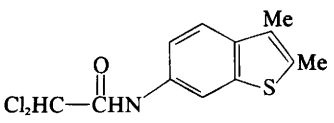

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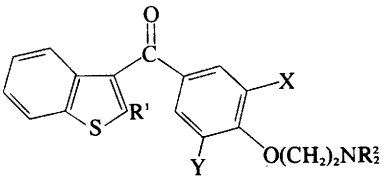

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[429] O. Dann, R. Fernbach, W. Pfeifer, E. Demant, G. Bergen, S. Lang, and G. Lürding, *Annalen*, 1972, **760**, 37.

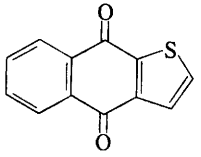
[430] O. Dann, G. Volz, E. Demant, W. Pfeifer, G. Bergen, H. Fick, and E. Walkenhorst, *Annalen*, 1973, 1112.

[431] L. Rene, R. Royer, R. Cavier, and J. Cenac, *Chim. Thérap.*, 1973, **8**, 364.

[432] N. Claeys, C. Goldenberg, R. Wandestrick, E. Deray, M. Descamps, G. Delaunois, J. Bauthier, and R. Charlier, *Chim. Thérap.*, 1972, **7**, 377.

5 Thiophen Analogues of Polycyclic Aromatic Hydrocarbons

Thiophen Analogues of Anthracene and Phenanthrene.—The six possible isomers (317)—(322) resulting from the replacement of one or both benzene



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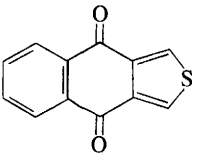

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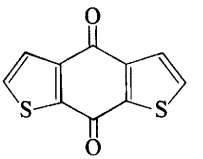

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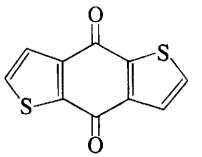

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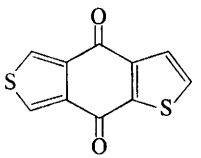

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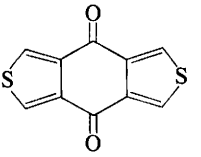
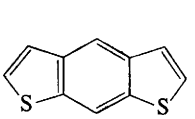


(322)

rings in 9,10-anthraquinone with thiophen rings have been synthesized.[433] Some of the compounds were prepared through Friedel–Crafts reaction between thiophen-3,4-dicarboxylic acid derivatives and benzene (318) or thiophen (321), or with 2,5-dichlorothiophen followed by reduction of the chlorine (322). Compounds (319) and (320) were obtained by oxidation of the known 8-acetoxybenzo[1,2-*b*:5,4-*b*']dithiophen and 4-acetoxybenzo[1,2-*b*:4,5-*b*']dithiophen. The mode of fusion had great influence on the reduction with an equimolar mixture of aluminium chloride–lithium aluminium hydride. Compounds (319) and (320) were reduced to the hydroquinone stage, whereas (318) and the dichloro-derivative of (322) were reduced in high yield, and (317) and (321) in low yield, to dihydroaromatic systems.[433] The reaction of dichloromethyl alkyl ethers and $SnCl_4$ with dithienylmethanes or benzo[*b*]thienylmethanes (Bradsher reaction) has been successfully applied to the synthesis of anthracene analogues such as (323)—(325).[434] The chiral triptycene analogue (326) was resolved *via* the dehydroabietyl amine salt and decarboxylated to optically active (327), which in turn was desulphurized with Raney-nickel to (328). Comparison of c.d. data for (327) and (328) led to the conclusion that $\pi\pi$ interactions exist among all three rings in triptycene systems.[435] Compound (327) was prepared through the reaction of (329) with triphenylphosphonium dibromide.[436] Derivatives of thiophen analogues of phenanthrene such as (330)[204,206] and (331)[205] have been synthesized and found to have antimalarial activity. The DNA-binding power of some derivatives has been studied.[437]

[433] D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, 1972, **37**, 1712.
[434] M. Ahmed, J. Ashby, M. Ayad, and O. Meth-Cohn, *J.C.S. Perkin I*, 1973, 1099.
[435] J. de Wit and H. Wynberg, *Tetrahedron*, 1972, **28**, 4617.
[436] J. de Wit and H. Wynberg, *Rec. Trav. chim.*, 1973, **92**, 281.
[437] J. W. Panter, D. W. Boykin, jun., and W. D. Wilson, *J. Medicin. Chem.*, 1973, **16**, 1366.



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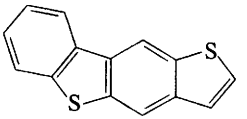

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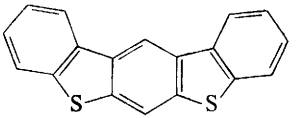

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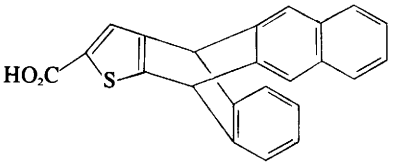

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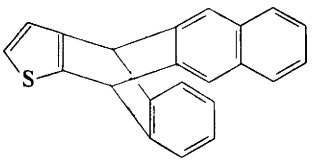

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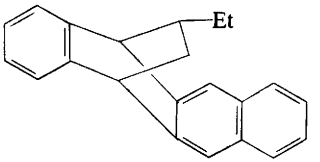

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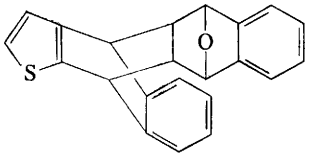

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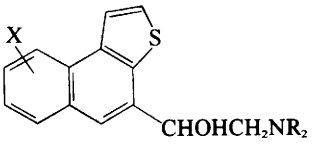

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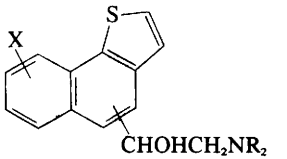
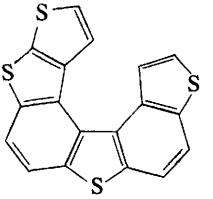


(331)

Thiophen Analogues of Helicenes.—By the use of thieno[2,3-*b*]thiophen as building block and by the use of double photocyclization, the heterohexahelicenes (332)—(335) were prepared and their n.m.r. and u.v. spectra discussed.[350] New heterohelicenes containing seven-membered rings have been synthesized. From the compound (336), the azepine derivative (337) was obtained by treatment with benzylamine and sodium dithionite. The helical nature of the azepine was revealed by the non-equivalence of the geminal protons.[438]

Thiophen Analogues of Indene and Fluorene.—The syntheses of the two [*b*]-annelated thiophen isosteres of 2-nitroindene (338) and (339) have been achieved by the intramolecular base-catalysed condensation of (340) and (341), respectively. The compounds (338) and (339) undergo fast tautomerism also in the absence of added base. The position of the equilibrium was determined by n.m.r., and the importance of certain specific long-range

[438] H. Wynberg and M. Cabell, *J. Org. Chem.*, 1973, **38**, 2814.



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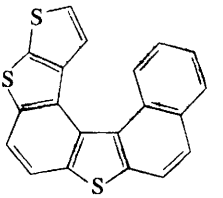

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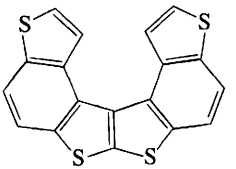

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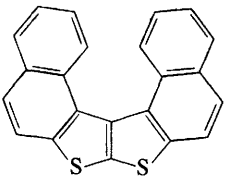
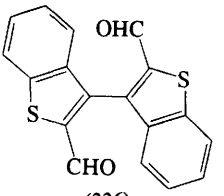


(335)



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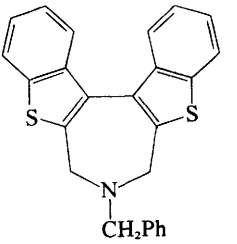

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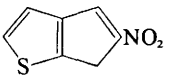

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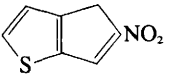

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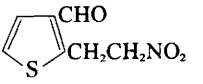

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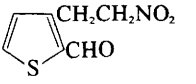


(341)

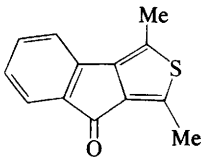
couplings is pointed out.[439] The parent 4*H*-cyclopenta[*c*]thiophen (342) has been synthesized by dechlorination of the 1,3-dichloro-derivative.[440] The 100 MHz spectra of (342) and its 1,3-dichloro-derivative have been analysed in detail, and the small value of the 1,3-coupling constant in (342) was taken as evidence for partial bond fixation.[441] The reaction of (342) and of its 1,3-dichloro-derivative with butyl-lithium has been studied. HMO calculations of bond orders and charge distribution on the 4*H*-cyclopenta[*c*]-thiophen anion have been carried out. A good correlation between

[439] J. Skramstad, *Acta Chem. Scand.*, 1972, **26**, 556.
[440] J. Skramstad, *Acta Chem. Scand.*, 1969, **23**, 703.
[441] J. Skramstad, *Chem. Scripta*, 1973, **4**, 77.

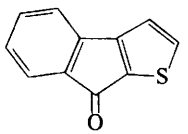
(342)

calculated charge distribution and relative chemical shifts of the anion was obtained.[442]

The interest in the thiophen analogues of fluorene is continuing. A detailed paper on the synthesis of (343) and (344) and the nitration of the latter has now appeared.[443] On treatment of (343) and (344) with $Mo(CO)_6$ or $W(CO)_6$, (345) and (346) are obtained.[444] From (347) and (348), the thiophen–selenophen fluorenone analogues (349) and (350) were obtained by Ullmann coupling.[138]



(343)



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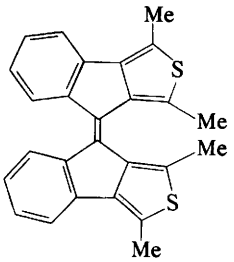

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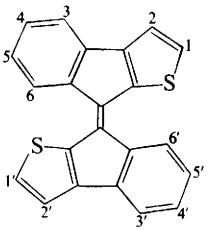

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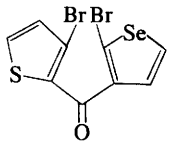

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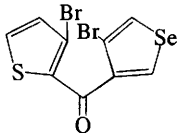

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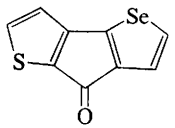

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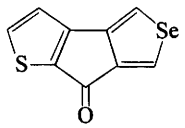
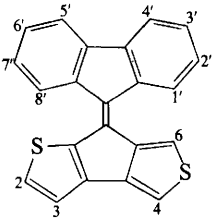


(350)

Fulvalene analogues such as (345) and (346) were also prepared in the more classical way, by treating the fluorenyl-lithium analogue with the fluorenone

[442] J. Skramstad, *Chem. Scripta*, 1973, **4**, 81.
[443] R. Dabard and J.-Y. Le Bihan, *Bull. Soc. chim. France*, 1972, 4280.
[444] G. Brule and J.-Y. Le Bihan, *Compt. rend.*, 1972, **274**, C, 1218.

analogue, followed by dehydration. In this way Wynberg *et al.* prepared the compounds (351)—(357). Great differences in the reactivity of the intermediate carbinols in the dehydration were observed.[445] Thiophen analogues



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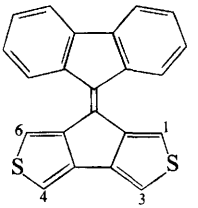

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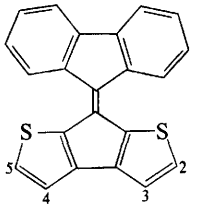

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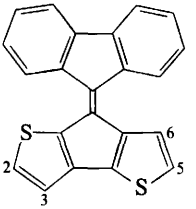

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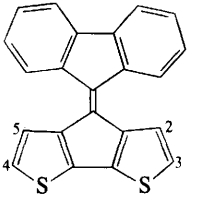

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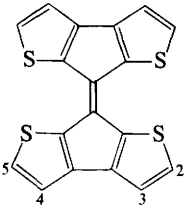

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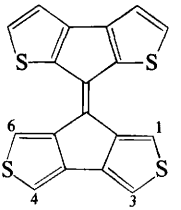
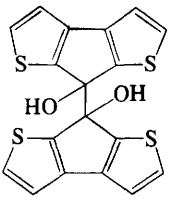


(357)

of fluorenone could be reduced to the pinacols (358)—(360). Only (360), however, was formed in high yield. Pinacol rearrangement of (360) in boiling acetic acid with a catalytic amount of iodine gave (361) in high yield. Reduction of (361) with $LiAlH_4$ gave (362), which was rearranged in boiling acetic acid containing a catalytic amount of iodine to the thiophen analogue (363) of dibenzo[*g*,*p*]chrysene.[446]

Thiophen-fused Tropylium Ions and Related Compounds.—Interest in thiophen-fused tropylium ions is continuing. Bromination of (364) with bromine in CCl_4 gave the tribromo-derivative (365), whereas phenyl trimethylammonium tribromide only dibrominated α to the carbonyl group. Dehydrobromination of the latter gave the thienotropones (366) in high

[445] G. J. Heeres and H. Wynberg, *Tetrahedron*, 1972, **28**, 5237.
[446] G. J. Heeres and H. Wynberg, *Synthetic Comm.*, 1972, **2**, 335.



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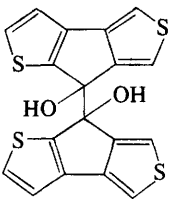

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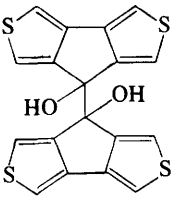

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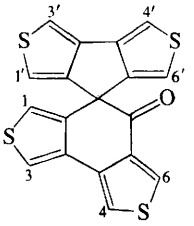

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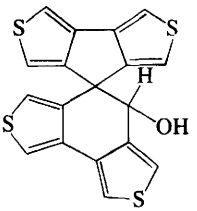

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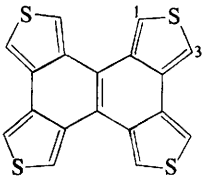
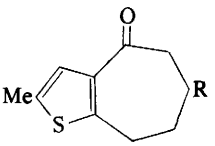
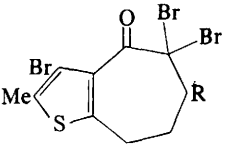


(363)

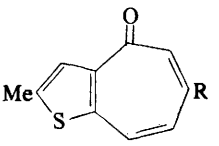
yield.[103] The 1,1-dihalogenocyclopropanes (367) were prepared from 6,7-dihydrobenzo[*b*]thiophens. These compounds rearranged thermally even in the absence of base to (368).[447] Attempts to prepare the tropylium ion from



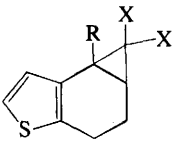
(364) R = H or Me



(365) R = H or Me



(366) R = H or Me



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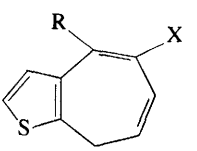
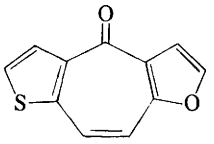


(368)

(368) have hitherto failed. From the ketones (95) and (96), the dithienotropones (102) and (103) were prepared by side-chain bromination–dehydrobromination,[106] as were the furothienotropones (369) and (370) from (98) and (99).[448] A characteristic dependence of the C=O stretching frequencies of these tropones on the mode of fusion was observed. The unsaturated ketones were directly reduced by $LiAlH_4$ to the methylene derivatives, which upon hydride exchange with trityl perchlorate gave the tropylium

[447] C. V. Greco and V. G. Grosso, *J. Org. Chem.*, 1973, **38**, 146.
[448] S. Gronowitz, B. Yom-Tov, and U. Michael, *Acta Chem. Scand.*, 1973, **27**, 2257.



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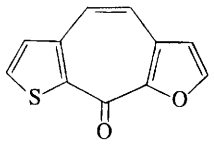
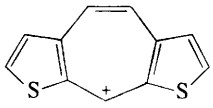


(370)

ions (371)—(374).[106,448] These tropylium ions were very stable, in contrast to the dibenzotropylium analogue ($pK_{R^+} = -1.9$), with pK_{R^+} values between 5.4



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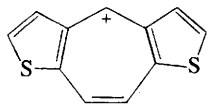

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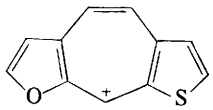

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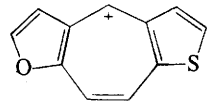


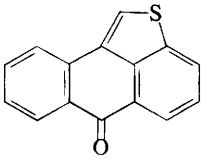
(374)

and 6.9. Attempts were made to explain these differences. It was found that (371)—(373) smoothly underwent deuterium exchange with concentrated deuteriosulphuric acids in the heterocyclic β-position. This was proven in the case of (371) and (372) by the synthesis of authentic 3-deuterio-derivatives. MO calculations indicated the β-positions to be most reactive in electrophilic substitution.[448] The u.v. spectra of the above-mentioned tropones and tropylium ions have been measured, and good agreement with spectra calculated by the PPP method was obtained.[449] The thiophanthrone (375) could also be reduced to the methylene derivative with $LiAlH_4$, which by treatment with trityl perchlorate was transformed into the thiophen analogue of the benzo[2,3]phenalenium cation (376). By reaction of (375) with *NN*-dimethylaniline in the presence of phosphorus oxychloride, the 6-aryl derivative (377) was obtained.[450] The u.v. spectral data were compared with those of the parent benzene derivatives.

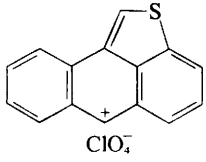
6 Thiophens Fused to Five-membered Aromatic Heterocyclic Rings

Pyrrole- and Furan-fused Thiophens and Related Compounds.—During recent years there has been a great interest in the thiophen analogues of indole, the thienopyrroles, especially among Russian workers, and several

[449] T. Liljefors, U. Michael, B. Yom-Tov, and S. Gronowitz, *Acta Chem. Scand.*, 1973, **27**, 2485.
[450] A. L. Cherian, P. Y. Pandit, and S. Seshadri, *Indian J. Chem.*, 1972, **10**, 361.



(375)



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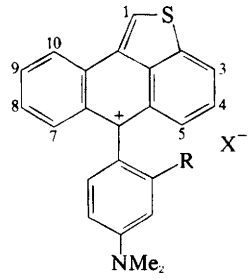
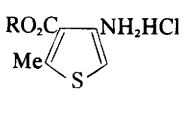
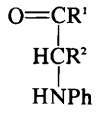


(377)

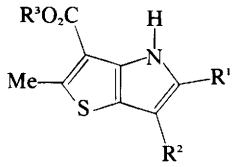
new methods have been worked out. By heating the amine (378) with α-anilinoacetophenones (379) for 10 min at 140—160 °C, (380) is formed.[451]



(378)

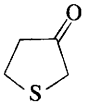


(379)

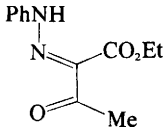


(380)

Through the reaction of (381) with (382), the thienopyrrole (383) was obtained.[452] From the pyrrole (384) the thienopyrrole (388) was prepared *via* (385)—(387).[453] Heating the azido derivatives (389) and (390), obtained by



(381)



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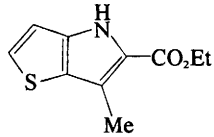
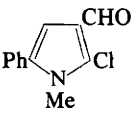


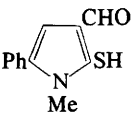
(383)

condensation of 3,4-diformylthiophen with one and two equivalents of ethyl azidoacetate, respectively, gave the thienopyrroles (391) and (392). The formylation of 6*H*-thieno[2,3-*b*]pyrrole has been studied.[454] Thermolysis of azides such as (393) and (394) has been used for the synthesis of (395).[398] Reductive cyclization of the analogous nitro-derivatives with triethyl phosphate has been used in the synthesis of (395).[398] Another example of this method is the transformation of (396) and (397) into (398) and (399), respectively.[455] Some electrophilic substitution reactions of (398; R = H)

[451] V. I. Shvedov, A. N. Grinev, and V. K. Vasil'eva, *Khim. geterotsikl. Soedinenii*, 1970, 276.
[452] V. I. Shvedov, L. B. Altukhova, Y. I. Trofimkin, and A. N. Grinev, *Khim. geterotsikl. Soedinenii*, 1972, 1577.
[453] I. Y. Kvitko and N. B. Sokolova, *Khim. geterotsikl. Soedinenii*, 1973, 565.
[454] M. Farnier, S. Soth, and P. Fournari, *Compt. rend.*, 1973, **277**, *C*, 1149.
[455] K. E. Chippendale, B. Iddon, and H. Suschitzky, *J.C.S. Perkin I*, 1973, 125.



(384)



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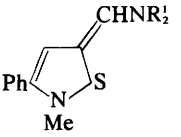

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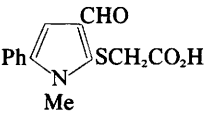

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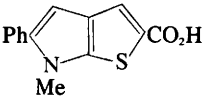

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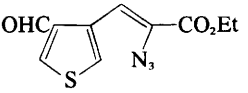

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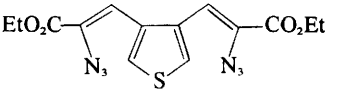

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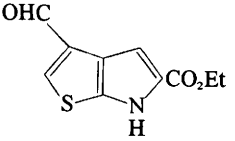
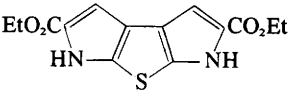


(391)



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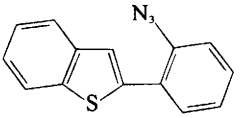

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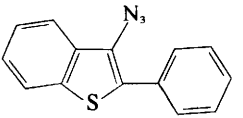

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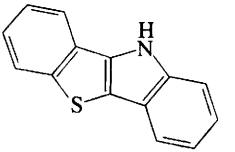

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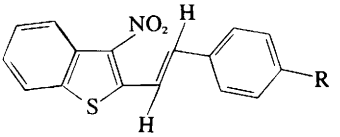

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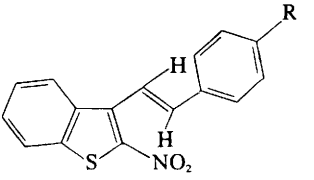

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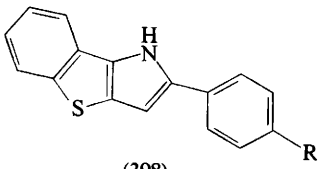

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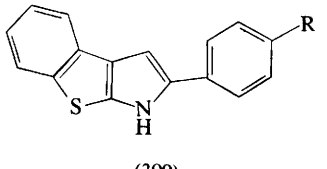
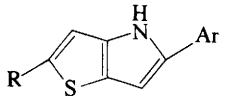
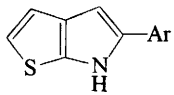


(399)

have also been carried out.[455] Compounds (400) and (401) have also been prepared by reductive cyclization of the appropriate *o*-nitrovinylthiophen.[456]

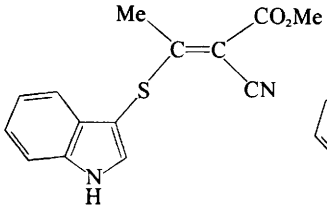


(400)

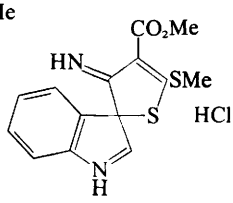


(401)

Refluxing of (402) with 10% hydrochloric acid for 10 min gave (403), which upon continued reflux for 5 h gave (404) in 60—80% yield.[457] The path of this interesting reaction is discussed.



(402)



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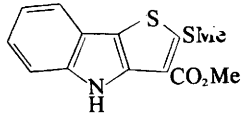


(404)

Conversion of 6-piperidinomethylthieno[3,2-*b*]pyrrole into analogues of tryptophan, tryptamine, and indoleacetic acid has been described.[458] Through the reaction of 5-hydrazinobenzo[*b*]thiophen with methyl isopropyl ketone in the presence of dilute sulphuric acid, (405) was obtained.[459]

Through the $NaHCO_3$-catalysed reaction of 3-chloro-2-formylbenzo[*b*]-furan with thioglycolic acids, (406) was obtained, which was transformed into (407) by decarboxylative ring-closure.[460] Through the same steps as described for the synthesis of (388) from (384), the furan (408) was transformed into (409).[461]

[456] K. Srinivasan, K. G. Srinivasan, K. K. Balasubramanian, and S. Swaminathan, *Synthesis*, 1973, 313.

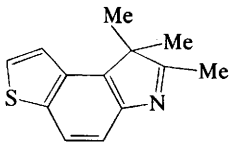
[457] G. Kobayashi, Y. Tominaga, S. Kisaki, M. Sone, and S. Ueno, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 2344.

[458] A. J. Humphries, R. L. Keener, K. Yano, F. S. Skelton, E. Freiter, and H. R. Snyder, *J. Org. Chem.*, 1972, **37**, 3626.

[459] P. I. Abramenko and V. G. Zhiryakov, *Khim. geterotsikl. Soedinenii*, 1971, 187.

[460] P. Cagniant, G. Kirsch, and L. Perrin, *Compt. rend.*, 1973, **276**, *C*, 1561.

[461] I. Y. Kvitko, N. B. Sokolova, and L. S. Éfros, *Khim. geterotsikl. Soedinenii*, 1973, 715.



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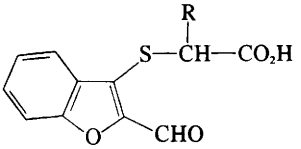
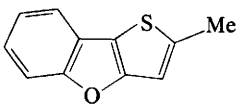


(406)



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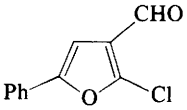

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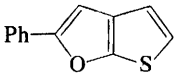
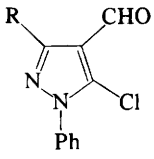
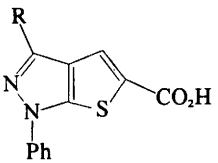


(409)

Pyrazole-, Thiazole-, and Imidazole-fused Thiophens.—Starting from (410) and carrying out nucleophilic substitution with thioglycolate followed by ring-closure, as described for (384) and (408), the thieno[2,3-*d*]pyrazole system (411) was synthesized. Their ionization constants have been determined and the transmission of the influence of the substituents R has been studied and found to be more feeble than in naphthalene and benzo[*b*]thiophen.[462] From the cyano-derivative (412), thiophen-fused derivatives such as (413) and (414) have been synthesized.[463] Electrophilic



(410)



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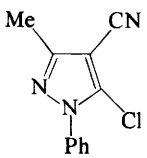

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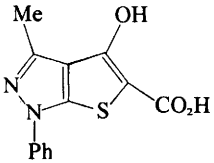
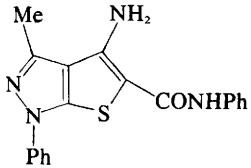


(413)

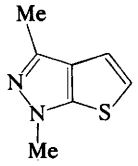


(414)

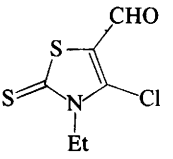
substitution of (415) has been studied.[464] The synthesis of benzothieno[3,2-*c*]pyrazoles (296) and benzothieno[2,3-*c*]pyrazoles (298) has been mentioned earlier in this report.[405]

[462] Yu. N. Koshelev, I. Y. Kvitko, and L. S. Éfros, *Zhur. org. Khim.*, 1972, **8**, 1750.
[463] L. N. Zakharov, I. Y. Kvitko, and A. V. Eltsov, *Zhur. org. Khim.*, 1973, **9**, 2416.
[464] Yu. N. Koshelev, A. V. Reznichenko, L. S. Efros, and I. Y. Kvitko, *Zhur. org. Khim.*, 1973, **9**, 2201.

From (416) the thieno[2,3-*d*]thiazolidine system (417) was prepared by the same method as that used for (411).[465] 2-Aminothiophen hydrochlorides



(415)



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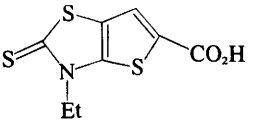

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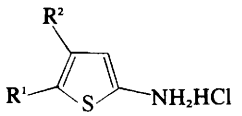
blocked at position 5 (418) were thiocyanated at position 3 to give (419) by reaction with potassium thiocyanate and bromine in acetic acid, or with



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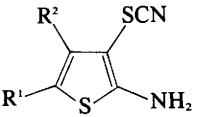
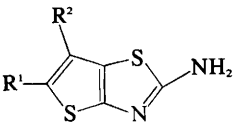


(419)

same method as that used for (411).[465] 2-Aminothiophen hydrochlorides with blocked at position 5 were thiocyanated at position 3 to give (419) by reaction with potassium thiocyanate and bromine in acetic acid, or with potassium thiocyanate and hydrogen peroxide in alcohol. The thiocyano-derivatives smoothly ring-closed on treatment with acetic anhydride or with hydrochloric acid in ethanol to the thiazole-fused derivative (420). The 3-aminothieno[2,3-*c*]isothiazole system was also prepared by Gewald. Starting from the 2-amino-3-cyano derivatives, (421) yields the thioamides (422) upon reaction with hydrogen sulphide, which in turn upon oxidation with hydrogen peroxide in ethanol–pyridine gives (423).[466] Complexes of the isothiazole-fused systems (424) have been prepared.[168]



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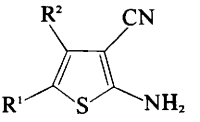

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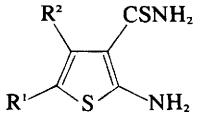

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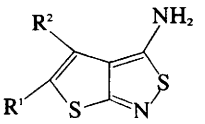

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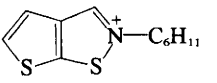


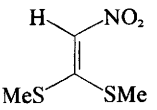
(424)

[465] I. Y. Kvitko, *Khim. geterotsikl. Soedinenii*, 1969, 760.
[466] K. Gewald, M. Hentschel, and R. Heikel, *J. prakt. Chem.*, 1973, **315**, 539.

7 Thiophens Fused to Six-membered Aromatic Heterocyclic Rings

Thiophen Analogues of Quinoline.—Interest in the chemistry of thienopyridines is continuing. Thieno[3,2-*b*]pyridine has been prepared in 80% yield through the zinc-chloride-catalysed condensation of 3-aminothiophen hydrochloride with malonic aldehyde acetal.[467] Reaction of the 2-amino-3-benzylthiophen (425) with 1-nitro-2,2-bis(methylmercapto)ethylene (426) gave the thieno[2,3-*b*]pyridine derivative (427) in 29% yield.[468] 5-Ethylthieno-

(425)



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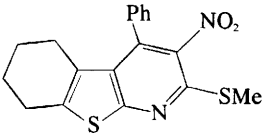

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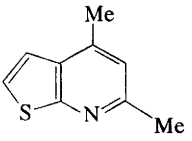
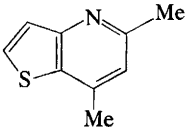
[2,3-*b*]pyridine has been nitrated.[469] (428) Has been prepared by the Combes reaction from 2-aminothiophen hydrochloride and acetylacetone in conc.



(428)

sulphuric acid. Compounds (429)—(431) were prepared similarly from the appropriate amines.[470] Bicyclic and tricyclic thienopyridines are converted



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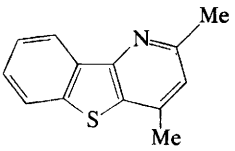

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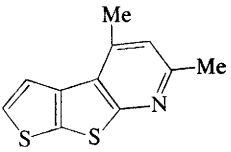
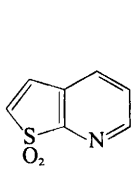


(431)

into sulphones by means of acid hypochlorite. The sulphone (432) undergoes Diels–Alder reaction with furan, giving both the *exo* (433) and *endo* forms (434), as well as with anthracene and naphthacene. Self condensation of (432) occurred with the elimination of sulphur dioxide, yielding 8-(3-pyridyl)quinoline.[471] The u.v., ^{1}H n.m.r., and mass spectral data of the sulphones were discussed. Heating of the azido-derivative (435) in trichlorobenzene to 190 °C gave only 5% of (436), besides much tar and other

[467] F. Outurquin, G. Ahkow, and C. Paulmier, *Compt. rend.*, 1973, **277**, *C*, 29.
[468] H. Schäfer, B. Bartho, and K. Gewald, *Z. Chem.*, 1973, **13**, 294.
[469] L. H. Klemm and H. Lund, *J. Heterocyclic Chem.*, 1973, **10**, 871.
[470] P. I. Abramenko, *Khim. geterotsikl. Soedinenii*, 1971, 468.
[471] L. H. Klemm and R. E. Merrill, *J. Heterocyclic Chem.*, 1972, **9**, 293.



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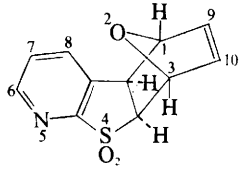

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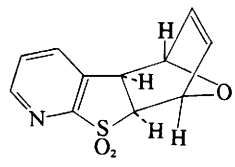
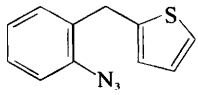


(434)

minor products. On the other hand, the 2,5-dimethyl derivative (437) gave, besides the corresponding amine, 34% of the compound (438). The



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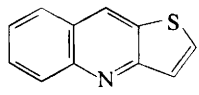

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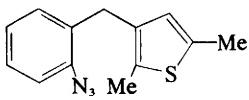

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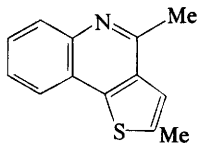
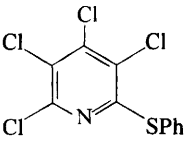


(438)

mechanism of formation of this unexpected product was discussed.[472] Irradiation of appropriately substituted polyhalogenopyridines led to fused polyhalogeno-heterocycles. Thus, from (439), the thieno[2,3-*b*]pyridine (440) was obtained.[473] *o*-Isothiocyanato-*trans*-cinnamaldehyde (441), obtained from quinoline and thiophosgene, gives (442) upon reaction with diethyl sodiomalonate. Subsequent alkylation with methyl chloroacetate gave thieno[2,3-*b*]quinolines (443).[474] Compounds such as (444) and (445) were obtained by heating (446) to 210—250 °C.[172] The acylaminoaldehyde derivatives (446a) could be converted into the thienopyridine (446b).[475] Thieno[3,4-*b*]pyridine (447) has been prepared from 2,3-dimethylpyridine by side-chain chlorination followed by reaction of the 2,3-dichloromethyl derivative with sodium sulphide, oxidation of the sulphide to the sulphoxide, followed by catalytic dehydration over alumina. The *c*-annelated system (447), although markedly more unstable than the *b*-annelated system, appears to be more stable than benzo[*c*]thiophen.[476]

Thiophen Analogues of Isoquinoline.—The methyl derivatives (448) and (449) were prepared by principally new routes. Starting from the lithium

[472] G. R. Cliff, G. Jones, and J. M. Woollard, *Tetrahedron Letters*, 1973, 2401.
[473] J. Bratt and H. Suschitzky, *J.C.S. Chem. Comm.*, 1972, 949.
[474] R. Hull, *J.C.S. Perkin I*, 1973, 2911.
[475] V. I. Shvedov, I. A. Kharizomenova, and A. N. Grinev, *Khim. geterotsikl. Soedinenii*, 1974, 58.
[476] L. H. Klemm, W. O. Johnson, and D. V. White, *J. Heterocyclic Chem.*, 1972, **9**, 843.



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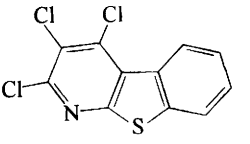

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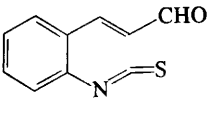

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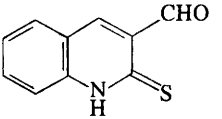

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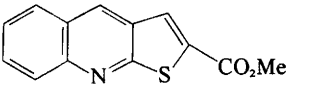

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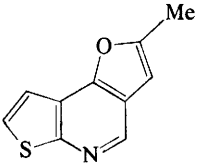

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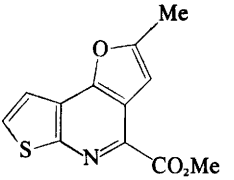

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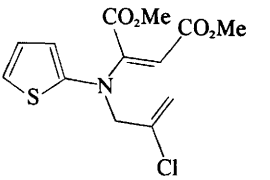

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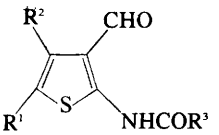

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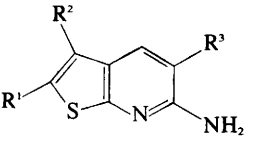

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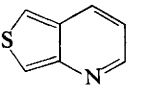

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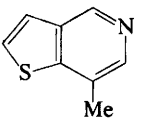

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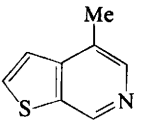

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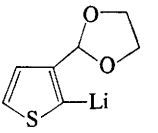
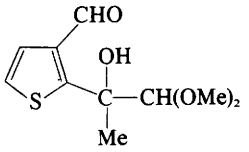


(450)

derivative (450), the compound (451) was obtained by reaction with methylglyoxal dimethylacetal followed by hydrolysis with 2N-HCl in ether. Oximation of (451) followed by $LiAlH_4$ reduction gave the amine (452), which upon acidic hydrolysis gave (448) in 71% yield; carrying out the same steps with (453) gave (449).[136] Reaction of the thieno[2,3-*c*]pyrylium salts (454) with ammonia gives the thieno[2,3-*c*]pyridine derivatives (455).[231] Irradiation of (456) gave the benzo-fused derivative (457).[473] The *c*-annelated thiophen analogue of isoquinoline was prepared analogously to the quinoline analogue starting from 3,4-dimethylpyridine.[476] Thiophen



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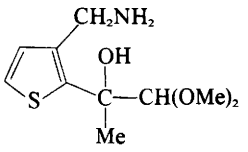

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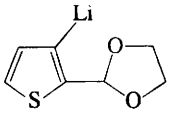

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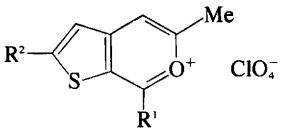

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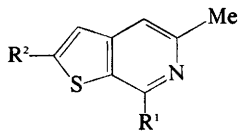

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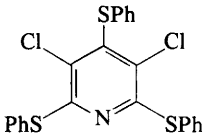

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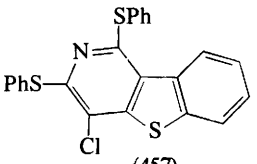
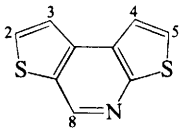


(457)

analogues (458)—(460) of phenanthridine were prepared by treatment of the appropriate dithienopyridones with $LiAlH_4$–$AlCl_3$ in THF. The u.v. spectra



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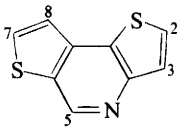

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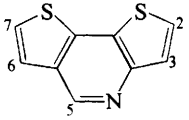
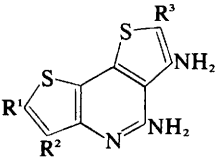
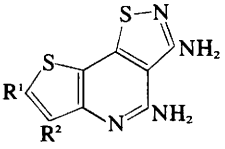


(460)

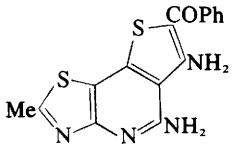
of these compounds were discussed.[477] Complex tricyclic heterocyclic systems, *e.g.* (461)—(463), have been synthesized.[9]



(461)



(462)

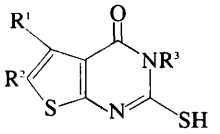


(463)

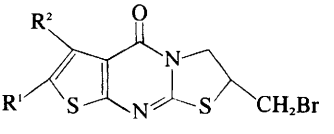
Pyrimidine-fused Systems.—*o*-Aminothiophencarboxylic acid derivatives have been extensively used for the synthesis of thienopyrimidine derivatives. Thus the mercapto-derivatives (464) have been synthesized by

[477] G. J. Heeres and H. Wynberg, *Synthetic Comm.*, 1972, **2**, 365.

cyclization of esters or amides of the corresponding 2-aminothiophen-3-carboxylic acids, either by direct reaction with thiourea or by reaction with methyl or allyl isothiocyanate *via* the corresponding NN-disubstituted thioureas as intermediates.[478,479] The halogenation of the *N*-allyl derivative yields (465).[479] The compound (465) was also obtained through the reaction

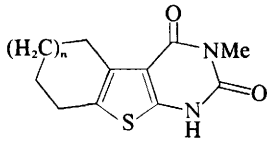


(464)

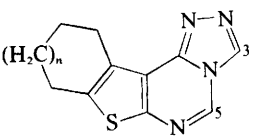


(465)

of 2-amino-3-ethoxycarbonylthiophen with 2,3-dibromopropylisothiocyanate.[480] Through reaction of 2-amino-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen with methyl isocyanate followed by cyclization of the resulting urea, the compound (466; $n = 1$) was obtained, which was converted into chloro- and hydrazino-derivatives.[3] On the other hand, the seven-membered analogue (466; $n = 2$) was prepared by the reaction of cycloheptanone with *N*-cyanoacetylurethane and sulphur in the presence of diethylamine followed by methylation of the NH derivative. The derivative (466; $n = 3$) was prepared similarly from cyclo-octanone.[3] The derivatives (466) were further converted into new tetracyclic heterocycles, *e.g.* (467)—(471).[3] The compounds were prepared for pharmaceutical testing.



(466)



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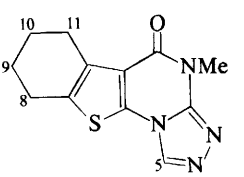

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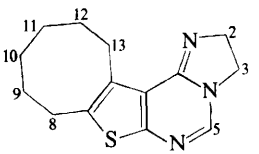
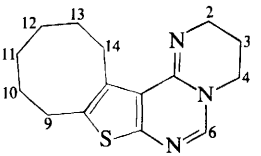
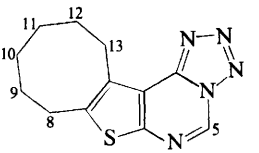


(469)



(470)

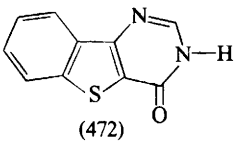


(471)

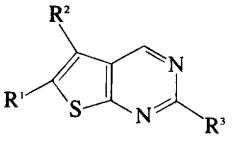
The demethyl derivative of (466; $n = 1$) has been transformed into aromatic thienopyrimidine and derivatives.[481] From 3-amino-2-ethoxycarbonylbenzo-[*b*]thiophen through reaction with formamide, (472) was obtained, which

[478] F. Sauter and W. Deinhammer, *Monatsh.*, 1973, **104**, 1593.
[479] I. V. Smolanka, A. A. Dobosh, and S. M. Khripak, *Khim. geterotsikl. Soedinenii*, 1973, 1289.
[480] A. A. Dobosh, I. V. Smolanka, and S. M. Khripak, *Khim. geterotsikl. Soedinenii*, 1974, 134.
[481] M. Robba, P. Touzot, and R. M. Riquelme, *Compt. rend.*, 1973, **276**, *C*, 93.

was converted into a number of derivatives by transformation of the nitrogen-containing ring or by aromatic substitution in the benzene ring.[482,483] From (466a) the thienopyrimidines (473) were synthesized.[475] Through the reaction of 2,4-diamino-3,4-dicyanothiophen with formamide, (474) was



(472)



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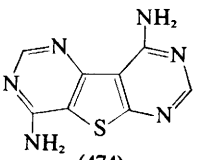
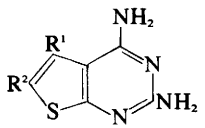
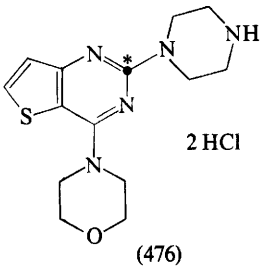


(474)

obtained.[8] 2-Amino-3-cyanothiophens, prepared by the Gewald reaction, were used in the synthesis of a large number of substituted 2,4-diaminothieno[2,3-*d*]pyrimidines (475) through the reaction with chloroformamidine hydrochloride. R^1 and R^2 symbolize many different substituents, and also fused carbocyclic heterocyclic rings.[484–487] Many of the synthesized compounds showed antifolate and antimalarial effects. ^{13}C- and ^{14}C-labelled (476), which is an inhibitor of thrombocyte agglutination, were prepared starting from 3-amino-2-methoxycarbonylthiophen and marked potassium thiocyanate and ethyl bromide, which leads to (477). The metabolism of

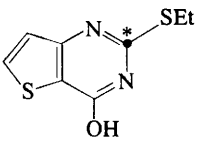


(475)



2 HCl

(476)

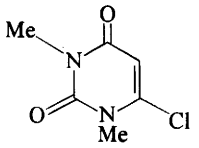


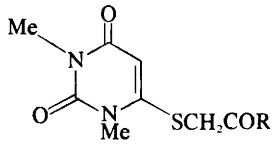
(477)

(476) was studied in detail.[488] A quite different approach to the thieno[2,3-*d*]-pyrimidine system was used by Japanese workers, who started from (478), transformed it into (479), which was ring-closed by PPA treatment to (480), and then converted into (481).[489]

Pyridazine-fused Systems.—The extensive work of Robba and co-workers on the synthesis and chemistry of 1-benzothieno[2,3-*d*]pyridazines (482), earlier published as short communications and reviewed in Volume 2, has

[482] M. Robba, P. Touzot, and R. M. Riquelme, *Tetrahedron Letters*, 1972, 4549.
[483] M. Robba, P. Touzot, and R. M. Riquelme, *Compt. rend.*, 1973, **276**, *C*, 1591.
[484] A. Rosowsky, M. Chaykovsky, K. K. N. Chen, M. Lin, and E. J. Modest, *J. Medicin. Chem.*, 1973, **16**, 185.
[485] M. Chaykovsky, M. Lin, A. Rosowsky, and E. J. Modest, *J. Medicin. Chem.*, 1973, **16**, 188.
[486] A. Rosowsky, K. K. N. Chen, and M. Lin, *J. Medicin. Chem.*, 1973, **16**, 191.
[487] E. F. Elslager, P. Jacob, and L. M. Werbel, *J. Heterocyclic Chem.*, 1972, **9**, 775.
[488] A. Zimmer, A. Prox, H. Pelzer, and R. Hankwitz, *Biochem. Pharmacol.*, 1973, **22**, 2213.
[489] H. Ogura, M. Sakaguchi, and K. Takeda, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 404.


(478)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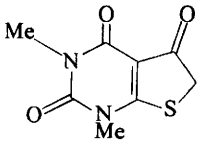
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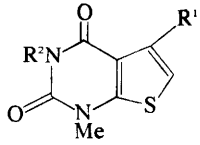
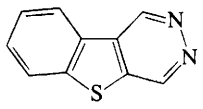
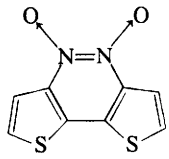

(481)

now resulted in six lengthy papers.[399,490–494] The system is reached through the reaction of benzo[*b*]thiophen-2,3-dialdehydes, ketone-aldehydes, or acid-aldehydes with hydrazine.[399] Electrophilic substitution on the benzothienopyridazines allows introduction of substituents in the benzene ring.[490] The benzothienopyridazines have been used for the introduction of different substituents in the pyridazine ring[492,493] and for the fusion of additional heterocyclic rings.[493,494] The chemical and electrochemical reduction of 3,3′-dinitro-2,2′-bithienyl and 2,2′-dinitro-3,3′-bithienyl led to *N*-oxides of dithienopyridazines (483) and (484). Controlled reduction of these compounds gave the corresponding dithienopyridazines.[250] 1-Benzothieno-[3,2-*c*]cinnoline (485) and some of its derivatives were obtained in good


(482)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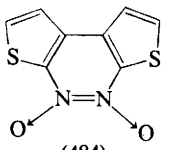
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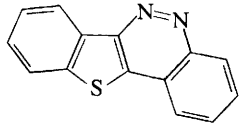
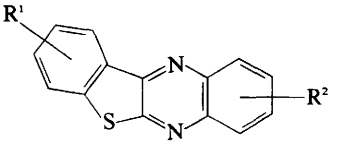

(485)

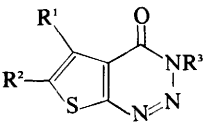
[490] G. Dore, M. Bonhomme, and M. Robba, *Tetrahedron*, 1972, **28**, 3277.
[491] G. Dore, M. Bonhomme, and M. Robba, *Bull. Soc. chim. France*, 1972, 4629.
[492] G. Dore, M. Bonhomme, and M. Robba, *Bull. Soc. chim. France*, 1973, 1132.
[493] M. Robba, G. Dore, and M. Bonhomme, *J. Heterocyclic Chem.*, 1973, **10**, 579.
[494] M. Robba, M. Bonhomme, and G. Dore, *Tetrahedron*, 1973, **29**, 2919.

yield when aqueous solutions of the diazonium chlorides derived from 2-(*o*-aminophenyl)benzo[*b*]thiophens were kept at room temperature.[495]

Thiophens Fused with other Nitrogen-containing Heterocycles.—Thionaphthenophenazines (486) have been prepared by the condensation of thionaphthaquinones with *o*-phenylenediamines.[496] Thieno[2,3-*d*]-1,2,3-triazines (487) were obtained by intramolecular cyclizations of diazonium compounds prepared from derivatives of 2-aminothiophen-3-carboxamides.[497] In a similar way (488) gave (489).[463]



(486)



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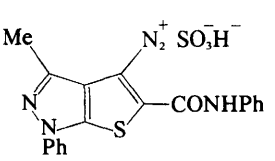

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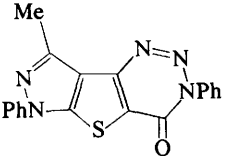
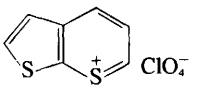
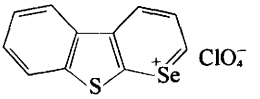


(489)

Miscellaneous Fused Systems.—The oxidation of thieno[2,3-*b*]thiapyrylium perchlorate (490) with MnO_2 gave, among other products, 2-thieno[2,3-*b*]-thiophenaldehyde and 2*H*-thieno[2,3-*b*]thiopyran-2-one.[498] Similar results were obtained with the isomeric thieno[3,2-*b*]thiopyrylium perchlorate. The 1-benzothieno-[3,2-*b*]- and -[2,3-*b*]-selenopyrylium salts (491) and (492)



(490)



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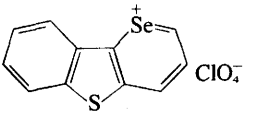
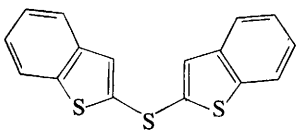


(492)

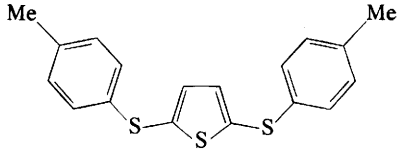
have been synthesized and their spectral data and reactivity towards nucleophiles studied.[499] Thieno[2,3-c]pyrylium salts have been used for the synthesis of benzo[*b*]thiophen derivatives.[500] The action of dichloromethyl ether and tin tetrachloride on diheterocyclic sulphides in ethers led to

[495] K. E. Chippendale, B. Iddon, and H. Suschitzky, *J.C.S. Perkin I*, 1972, 2030.
[496] K. D. Banerji, A. K. D. Mazumdar, and K. K. Sen, *J. Indian Chem. Soc.*, 1973, **50**, 268.
[497] F. Sauter and W. Deinhammar, *Monatsh.*, 1973, **104**, 1586.
[498] F. Boccuzzi, I. Degani, and R. Fochi, *Ann. Chim. (Italy)*, 1972. **62**, 528.
[499] A. Tadino, L. Christiaens, M. Renson, and P. Cagniant, *Bull. Soc. chim. belges*, 1972, **81**, 595.
[500] V. I. Dulenko, I. G. Katts, L. V. Dulenko, and G. N. Dorofeenko, *Khim. geterotsikl. Soedinenii*, 1970, 134.

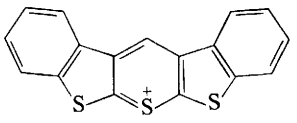
the corresponding thiapyrylium and pyrylium salts. For instance, (493) and (494) gave (495) and (496), respectively.[501] Reaction of 2-hydroxyaceto-



(493)

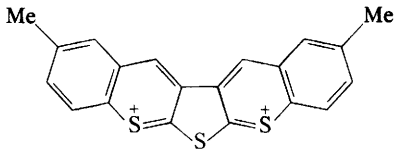


(494)



$SnCl_5^-$

(495)

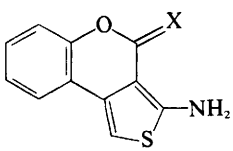


$SnCl_6^{2-}$

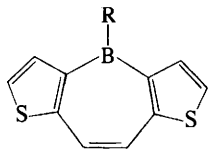
(496)

phenones with sulphur and active methylene nitriles (cyanoacetate, malononitrile) led to 4-oxo- or 4-imino-derivatives of 3-amino-4*H*-thieno[3,4-*c*]-1-benzopyran (497). Other products from this reaction were identified and further reactions were studied.[502]

A convenient method for the synthesis of the borepino[3,2-*b*;6,7-*b*]dithiophen system (498) has been worked out. By comparing its spectral properties with those of the corresponding dihydro-derivative and with the isoelectronic dithienotropylium ions, some evidence for aromatic stabilization was obtained.[503] The chemistry of another boron-containing fused thiophen system (499) has been studied.[126]



(497) X = O or NH



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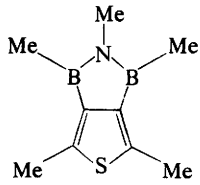


(499)

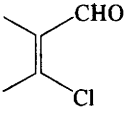
8 Selenophens and Tellurophens

General.—During the past two years a marked increase in interest in selenophen chemistry can be noticed, and especially many differently fused

[501] J. Ashby, M. Ayad, and O. Meth-Cohn, *J.C.S. Perkin I*, 1973, 1104.
[502] W. Ried and E. Nyiondi-bonguen, *Annalen*, 1973, 134.
[503] A. T. Jeffries and S. Gronowitz, *Chem. Scripta*, 1973, **4**, 183.

systems have been studied. An increased interest in pharmacologically active derivatives can also be noticed, after the realization that the toxicity of at least certain types of selenium derivatives is not as high as generally believed earlier.

Monocyclic Selenophens.—*Ring-closures.* The Fiesselmann reaction has been applied to the synthesis of selenophens. The reaction of (500) with sodium selenide and ethyl bromoacetate thus gave (501).[504] Also the Gewald reaction is successful; cyclohexanone reacts with ethyl cyanoacetate and selenium in the presence of base to give (502).[505] 2,5-Diarylselenophens are obtained, together with small amounts of the 2,4-isomer, on heating 4-aryl-1,2,3-selenadiazoles.[506] Upon pyrolysis of (503) at 250 °C the selenophen derivative (504) is formed.[507]



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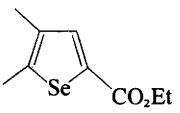

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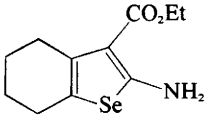

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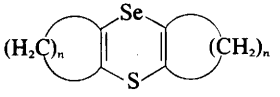
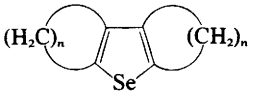


(503)



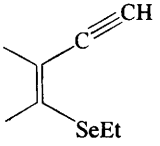
(504)

Physical Properties. ^{1}H n.m.r. spectra of some selenophen derivatives have been studied[508] and used for conformational analysis of selenophen-2-aldehyde. ^{77}Se n.m.r. spectra of 2-substituted selenophens have been obtained, showing large substituent effects. Correlation with some other n.m.r. parameters, such as ^{13}C n.m.r. shifts and the electronegativity of the halogens are reported.[509] The i.r. spectra[510] and u.v. spectra[511] of a large number of chalcogen analogues containing the selenophen nucleus have been studied, and correlations with Hammett's σ-parameters have been attempted.

[504] P. Cagniant, P. Perkin, G. Kirsch, and D. Cagniant, *Compt. rend.*, 1973, **277**, C, 37.
[505] S. M. Khripak, A. A. Dobosh, I. V. Smolanka, and A. S. Mikitchin, *Khim. geterotsikl. Soedinenii*, 1973, 326.
[506] I. Lalezari, A. Shafiee, F. Rabet, and M. Yalpani, *J. Heterocyclic Chem.*, 1973, **10**, 953.
[507] I. Lalezari, A. Shafiee, and M. Yalpani, *J. Heterocyclic Chem.*, 1972, **9**, 1411.
[508] S. V. Tsukerman, A. I. Yatsenko, V. D. Orlov, and V. F. Lavrushin, *Str. Mol. Kvantovaya Khim.*, 1970, 20.
[509] S. Gronowitz, I. Johnson, and A.-B. Hörnfeldt, *Chem. Scripta*, 1973, **3**, 94.
[510] S. V. Tsukerman, V. D. Orlov, Yu. S. Rozwa, and V. F. Lavrushin, *Chem. Heterocyclic Compounds*, 1969, **5**, 461.
[511] S. V. Tsukerman, V. D. Orlov, and V. F. Lavrushin, *Khim. geterotsikl. Soedinenii*, 1969, 67.

Electrophilic Substitution. The rate constants and activation parameters for the formylation of selenophen by the DMF–phosgene complex in chloroform have been determined and compared with those of the other five-membered heterocycles.[68] Acylation of 2-benzylselenophen occurs exclusively in the α-position of the selenophen ring. Formylation and acetylation of 2-(2-thienyl)selenophen went predominantly (80 and 75%, respectively) in the α-position of the selenophen ring and 20% in the α-position of the thiophen ring.[90] 2,5-Dimethylselenophen-3-carboxylic acid could be iodinated at position 4 with iodine–iodic acid.[512] Bromination of 2-formylselenophen in $AlCl_3$ yielded the 4-isomer.[513] Bromination of 2-methylselenophen with *N*-bromosuccinimide in acetic acid gave 3,5-dibromo-2-methylselenophen.[150]

Nucleophilic Substitution, Metallation and Halogen–Metal Exchange. A Meisenheimer complex has been obtained from 2-methoxy-3,5-dinitroselenophen.[514] 3-Selenienyl-lithium derivatives obtained through halogen–metal exchange between 3-bromoselenophens and alkyl-lithium derivatives at low temperatures ring-open easily at higher temperatures. It was found that 3-selenienyl-lithium at room temperature gave *Z*-1-ethylselenobut-1-en-3-yne (505) in 70% yield in the presence of ethyl bromide.[515] This ring-opening reaction is of great preparative use for the synthesis of acetylenic mixed ketenthioselenoacetals.[150] From (506), compound (507)



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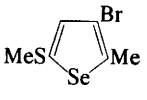

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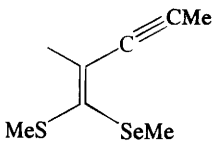


(507)

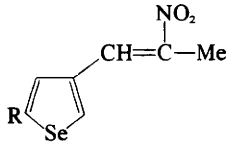
was obtained upon halogen–metal exchange with ethyl-lithium followed by reaction with ethyl bromide.[150] However, by working rapidly, between −50 and −100 °C, 3-selenienyl-lithium can be used for the synthesis of 3-substituted selenophen derivatives. In this way 3-chloroselenophen has been obtained by reaction with hexachloroethane,[131] and selenophen-3-aldehyde with DMF.[513] Both 2- and 3-selenienyl-lithium derivatives have been extensively used for the synthesis of di- and tri-formylselenophens,[134] and for the synthesis of t-butylselenophens[135,516] through reaction with t-butyl perbenzoate. From these compounds hydroxyselenophenaldehydes were obtained in some cases. Different diselenienylcarbinols have been

[512] S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, 1972, **26**, 2279.
[513] V. I. Dulenko and N. N. Alekseev, *Khim. geterotsikl. Soedinenii*, 1973, 918.
[514] F. Terrier, A. P. Chatrousse, R. Schaal, C. Paulmier, and P. Pastour, *Tetrahedron Letters*, 1972, 1961.
[515] S. Gronowitz and T. Frejd, *Internat. J. Sulfur. Chem.* (*A*), 1972, **2**, 165.
[516] J. Morel, C. Paulmier, and P. Pastour, *J. Heterocyclic Chem.*, 1972, **9**, 355.

obtained through the reaction of selenienyl-lithium derivatives with selenophenaldehydes.[138] 4,4′-Dimethoxycarbonyl-2,2′,5,5′-tetramethyl-3,3′-biselenienyl has been prepared by Ullmann coupling.[512]

Side-chain Reactivities. 2,5-Dimethylselenophen has been oxidized to the 2,5-dicarboxylic acid.[517] 2-Selenienylethylene oxide has been prepared by side-chain bromination of 2-acetylselenophen with dioxan dibromide followed by reduction to the bromohydrin and cyclization.[518] Substituted ω-(2-selenienyl)ethylamines have been synthesized by the reduction of the corresponding αβ-unsaturated nitro-compounds.[519] 2-(ω-Nitrovinyl)selenophen was also alkoxylated and aminated. 2-Thienyl-2-selenienylmethane was obtained through reaction of 2-chloromethylselenophen with 2-thienyllithium.[520] Reaction of acetylenes with 2-formylselenophen and its derivatives gave selenienylalkynyl alcohols, which were oxidized to the corresponding ketones by MnO_2. The latter, upon reaction with hydroxylamine and hydrazine, gave selenienyl-substituted isoxazoles and pyrazoles.[521] Side-chain bromination of 3-methylselenophen, as well as the Sommelet reaction with 3-chloromethylselenophen, were unsuccessful.[522] The benzylimines of 3-formylselenophen were condensed with nitroethane to (508), which was reduced to (509), a useful starting material for fused systems.[513] From 3-acetylselenophen a number of β-diketones have been synthesized by condensation with esters, and transformed into 3-(3-selenienyl)pyrazoles.[523] The direction of enolization of these β-diketones has also been studied.[522] By the condensation of selenophencarboxamide with ω-chlorinated ketones, 2-(selenienyl)oxazoles have been prepared. Similarly, 2-selenienylthiazoles and 2-selenienylselenazoles were prepared from the selenophen thio- and seleno-amides.[259,524] Dicyanoselenophens have been converted into other carboxylic acid derivatives.[524] α-Amino-alcohols of the selenophen series have been prepared by nitrosation of 2-acylselenophens followed by reduction of the resulting α-keto-oximes.[525] 4,4′-Dicarboxy-2,2′,5,5′-tetramethyl-3,3′-biselenienyl has been resolved into antipodes, and its configuration relative to the analogous thiophen derivative was determined. It racemizes *ca.* 90 times slower than the thiophen analogue.[512] The complex selenophen (510) has been synthesized.[526]

[517] P. A. Konstantinov, T. V. Shchedrinskaya, and I. V. Zakharov, *Khim. geterotsikl. Soedinenii*, 1972, 1605.
[518] N. N. Magdesieva and T. A. Balashova, *Khim. geterotsikl. Soedinenii*, 1970, 716.
[519] N. N. Magdesieva and T. A. Balashova, *Khim. geterotsikl. Soedinenii*, 1971, 184.
[520] P. A. Konstantinov, N. M. Koloskova, F. D. Kireeva, and E. M. Malakhaev, *Zhur. obshchei Khim.*, 1972, **42**, 1780.
[521] A. S. Nakhmanovich, V. N. Elokhina, and R. V. Karnaukhova, *Khim. geterotsikl. Soedinenii*, 1971, 920.
[522] Yu. K. Yur'ev, N. N. Magdesieva, and A. T. Monakhova, *Khim. geterotsikl. Soedinenii*, 1968, 645.
[523] Yu. K. Yur'ev, N. N. Magdesieva, and A. T. Monakhova, *Khim. geterotsikl. Soedinenii*, 1968, 650.
[524] P. Chuvin, J. Morel, C. Paulmier, and P. Pastour, *Compt. rend.*, 1972, **274**, *C*, 1347.
[525] N. N. Magdesieva, T. A. Balashova, and G. M. Demyanova, *Khim. geterotsikl. Soedinenii*, 1972, 626.
[526] A. K. Sheinkman, T. V. Stupnikova, and A. A. Deikalo, *Khim. geterotsikl. Soedinenii*, 1973, 1147.



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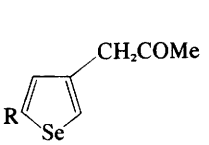

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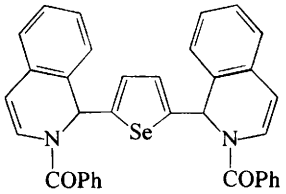
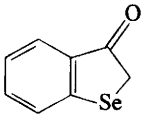


(510)

Benzo[*b*]selenophens and their Benzo-fused Derivatives.—The oxo-derivative (511) is a key intermediate in the synthesis of benzo[*b*]selenophens. Through reduction with sodium borohydride the parent compound is obtained, while reaction with methyl magnesium iodide yields the 3-methyl derivative.[527] Under Vilsmeier formylation conditions, (511) was transformed into 3-chloro-2-formylbenzo[*b*]selenophen, a useful compound for the fusion of further rings.[528] Compound (511) can also be condensed with aromatic aldehydes to compounds (512), some of them with antibacterial



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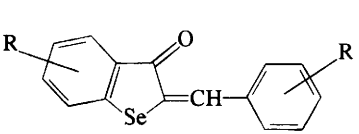
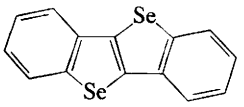


(512)

activity.[529] A simple method for the synthesis of benzo[*b*]selenophen derivatives consists of heating *o*-methylselenobenzaldehyde or *o*-methylselenoacetophenone in the presence of chloroacetone, leading to 2-acetyl- and 2-acetyl-3-methyl-selenophen, respectively.[530] Reaction of bromoacetic acid with *o*-methylselenobenzaldehyde gave (513), besides the 2-benzo[*b*]-selenophencarboxylic acid. The mechanism for the formation of (513) was discussed.[530]

Russian workers have worked out another approach to benzo-[*b*]selenophens starting from selenophen derivatives. Acylation of (514) gave (515), which upon treatment with perchloric acid gave the pyrylium salts (516).[531] Upon treatment with secondary amines, (516) gave amino-substituted benzo[*b*]selenophens, *e.g.* (517).[531] From the pyrylium salt (518), only (519) was obtained.[375] On treatment of (518) with aqueous hydroxide, (520) was obtained.[532] Other benzo[*b*]selenophens hydroxylated in the benzene ring have been prepared similarly.[532] Through the condensation of

[527] N. N. Magdesieva and V. A. Vdovin, *Khim. geterotsikl. Soedinenii*, 1970, 1475.
[528] P. Cagniant and G. Kirsch, *Compt. rend.*, 1972, **274**, *C*, 1394.
[529] G. Kirsch and P. Cagniant, *Compt. rend.*, 1972, **275**, *C*, 1029.
[530] P. Faller and F. Mantovani, *Bull. Soc. chim France*, 1972, 1643.
[531] V. I. Dulenko and N. N. Alekseev, *Khim. geterotsikl. Soedinenii*, 1973, 1212.
[532] V. I. Dulenko, N. N. Alekseev, and L. M. Kapkan, *Khim. geterotsikl. Soedinenii*, 1973, 1342.



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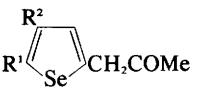

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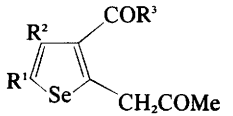

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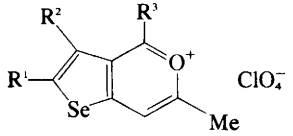

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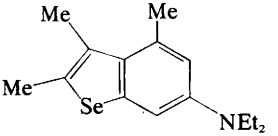

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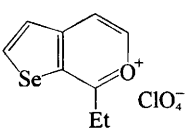

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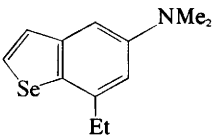

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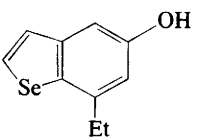
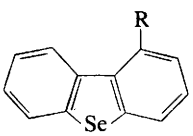


(520)

2-alkylbenzo[*b*]selenophens with ethyl dichloroethoxyacetate, dibenzoselenophens were prepared.[380] From 1-ethoxycarbonyldibenzoselenophen, compounds (521) were synthesized and the acids ring-closed to the ketones (522) and (523). The latter was reduced to the alcohol and aromatized to (524).[533]



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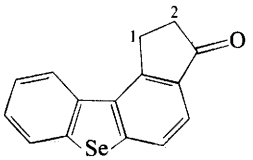

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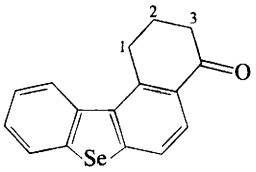

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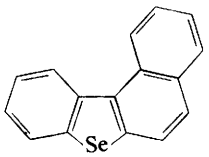
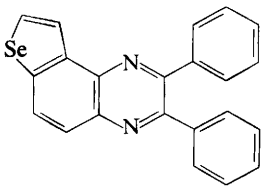


(524)

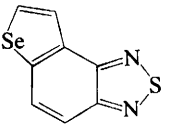
[533] P. Cagniant, N. Bellinger, and D. Cagniant, *Compt. rend.*, 1973, **277**, C, 779.

The ^{1}H n.m.r. spectrum of benzo[*b*]selenophen has been analysed.[534] The thermolysis and electron cleavage of aldazines and ketazines of the benzo[*b*]selenophen series have been studied.[403]

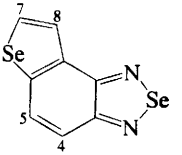
Contrary to benzo[*b*]thiophen, benzo[*b*]selenophen is acylated at position 2.[534] 2-Bromobenzo[*b*]selenophen, prepared from the 2-lithium derivative and bromine, is acylated at position 3, and from this derivative the 3-isomers could be synthesized.[535] A large number of 2- and 3-aroylbenzo[*b*]selenophens were synthesized, either by Friedel–Crafts reaction of benzo[*b*]selenophencarboxylic acid chlorides and benzenes or from benzo[*b*]selenophens and benzoic acid chlorides. Also the reaction between Grignard reagents and nitriles was used for the synthesis of aroylbenzo[*b*]selenophens.[536] 4,5-Diaminobenzo[*b*]selenophen has been synthesized *via* nitration of 5-aminobenzo[*b*]selenophen or *via* the reaction of the diazonium salt derived from the 5-amino-derivative with *p*-sulphanilic acid.[537] From the diamino-derivative, several fused benzo[*b*]selenophens, *e.g.* (525), (526), and (527), were prepared.[537] Reaction of the phenyl-



(525)



(526)

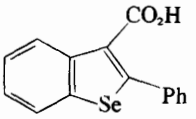


(527)

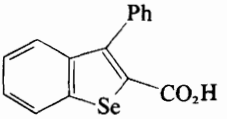
benzo[*b*]selenophencarboxylic acids (528) and (529) with thionyl chloride and $AlCl_3$ gave (530) and (531), respectively. However, treatment of (529) with PPA gave (532), which was also obtained on treatment of (531) with PPA.[538] Reduction of (512) with sodium borohydride in ethanol followed by treatment with hydrogen chloride in ethanol gave 2-arylmethylselenophens (533). Treatment of such compounds with butyl dichloroformate and $SnCl_4$ in methylene chloride (Rieche reagent) gave, through formylation followed by cyclodehydration, the benzo-fused systems (534)—(536).[539] Lactones derived from 3-hydroxymethyl-2-benzo[*b*]selenophencarboxylic acids have been prepared.[402] Through Ullmann coupling of (537a) and (537b), the selenophen analogues of fluorenone (538a) and (538b) were prepared.[138]

Selenophens Fused to Five-membered Rings.—Reaction of 3-(3-selenienyl)-acrylic acid with thionyl chloride and pyridine gives a complex mixture of

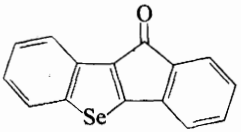
[534] P. Faller and J. Weber, *Bull. Soc. chim. France*, 1972, 3193.
[535] T. Q. Minh, F. Mantovani, P. Faller, L. Christiaens, and M. Renson, *Bull. Soc. chim. France*, 1972, 3955.
[536] F. Mantovani, L. Christiaens, and P. Faller, *Bull. Soc. chim. France*, 1972, 1595.
[537] P. Jacquignon, G. Marechal, M. Renson, A. Ruwet, and D. P. Hien, *Bull. Soc. chim. France*, 1973, 677.
[538] E. Iteke, L. Christiaens, and M. Renson, *Compt. rend.*, 1972, **275**, *C*, 277.
[539] F. Girardin, L. Christiaens, and P. Faller, *Compt. rend.*, 1973, **277**, *C*, 113.



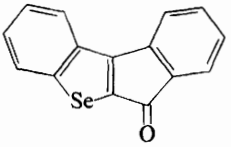
(528)



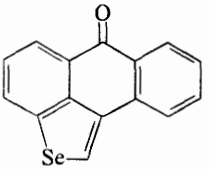
(529)



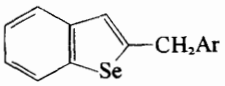
(530)



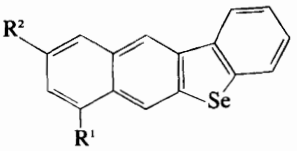
(531)



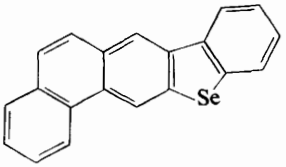
(532)



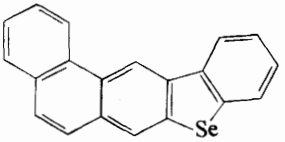
(533)



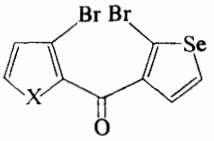
(534)



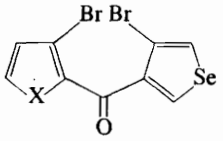
(535)



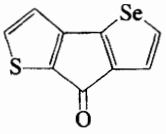
(536)



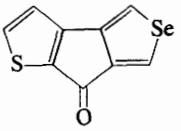
(537a)



(537b)

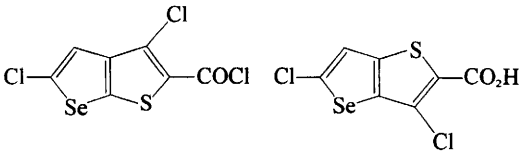


(538a)



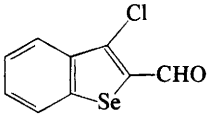
(538b)

chlorinated seleno[2,3-*b*]thiophencarboxylic acid chlorides, the main product being (539a).[341] Similarly, from the 2-substituted acrylic acid, (539b) was

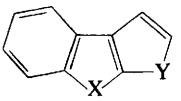


(539a) (539b)

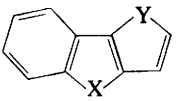
obtained.[201]- Starting from the chloroaldehyde (540), easily prepared from (511), the tricyclic system (542b) was obtained by nucleophilic substitution with thioglycolate followed by ring-closure.[540] The benzo-fused analogues of selenolothiophen and selenoloselenophen, (541) and (542), isosteric with anthracene, have been synthesized. The key intermediate in the preparation of (541) was the aldehyde (543), which by reaction with bromoacetic acid and acetic anhydride in pyridine was directly transformed into the acid (544). This acid was also obtained *via* condensation of (543) with malonic acid and esterification to (545) followed by ring-closure with bromine in pyridine, giving upon hydrolysis (544). Alternatively, (546) could be used as starting material, being formylated by the Rieche method to give (547), and then ring-closed to (544). The acid (548) was used for the synthesis of (542b).



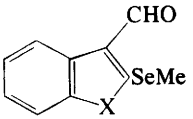
(540)



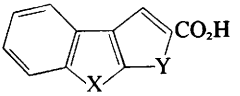
(541) a; X = S, Y = Se
b; X = Se, Y = S
c; X = Y = Se



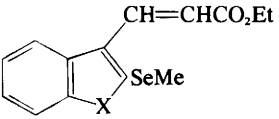
(542) a; X = S, Y = Se
b; X = Se, Y = S
c; X = Y = Se



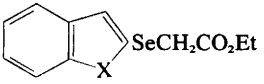
(543)



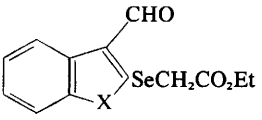
(544)



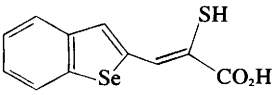
(545)



(546)



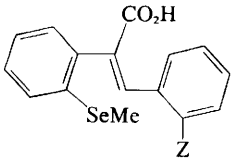
(547)



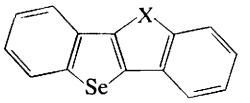
(548)

[540] G. Kirsch and P. Cagniant, *Compt. rend.*, 1972, **274**, *C*, 2179.

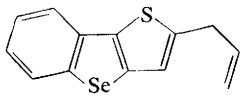
Decarboxylation of the acids gave the parent compounds (541) and (542).[541] The product of condensation between *o*-(methylseleno)phenylacetic acid and *o*-methylthio- or *o*-methylseleno-benzaldehydes (549) gave the tetracyclic derivatives (550). These were also obtained by Rieche formylation of (551).[538] The pyrrole-fused selenophen (552) was prepared similarly to the



(549) a; Z = SMe
b; Z = SeMe

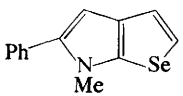


(550) X = S or Se

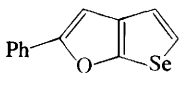


(551)

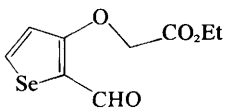
thiophen analogue *via* (384)—(388), using selenide instead of sulphide in the appropriate step.[453] In the same way the furan-fused system (553) was prepared, by allowing (408) to react with sodium selenide. Another route to the furo-fused system was the alkylation of 3-hydroxyselenophen-2-aldehyde with ethyl bromoacetate to (554) followed by ring-closure with sodium ethoxide in ethanol to (555).[135] The pyrazole-fused selenophen (556) was prepared similarly to the thiophen analogue starting from (410), which after reaction with potassium hydrogen selenide, imine formation, and alkylation at the selenium atom was converted into (557). Ring-closure then led to the 2-carboxylic acid of (556).[542] Some electrophilic substitution reactions of (556) have been studied.[464] New polymethine dyes derived from selenonaphtheno[2,3-*d*]thiazole derivatives (558) have been synthesized.[543]



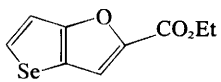
(552)



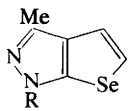
(553)



(554)



(555)



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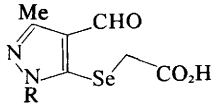

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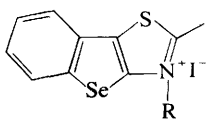
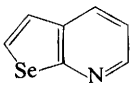


(558)

[541] E. Iteke, L. Christiaens, and M. Renson, *Bull. Soc. chim France*, 1972, 4767.
[542] Y. N. Koshelev, I. Y. Kvitko, and E. D. Samartseva, *Zhur. org. Khim.*, 1972, 2204.
[543] P. I. Abramenko, *Khim. geterotsikl. Soedinenii*, 1971, 459.

Selenophens Fused to Six-membered Heterocyclic Aromatic Rings.—As mentioned previously, the synthesis of selenophenopyrylium cations useful for the synthesis of many fused selenophen derivatives has been described.[375,513,531,544] Pyridine-fused selenophens (559) and (560) have been prepared from 2- and 3-aminoselenophen by condensation with malonaldehyde acetal.[467] The isomer (559) was also prepared, starting from ethyl 2-chloronicotinate, which was transformed into (561) *via* the corresponding carbinol. Wittig condensation with ethoxycarbonylmethylenetriphenylphosphorane gave the expected ethyl acrylate (562). Successive bromination and



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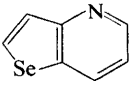

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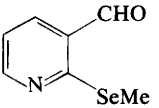

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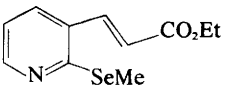
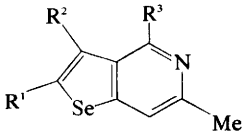


(562)

cyclization of (562) gave the 2-ethoxycarbonyl derivative of (559), which was saponified and decarboxylated with copper chromite under high vacuum.[545] Selenophen analogues of isoquinoline, such as (563) and (564),



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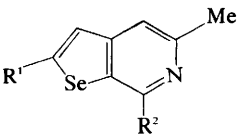
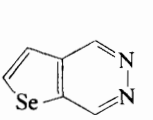


(564)

have been obtained by reaction of the pyrylium salts (516) and (518) with ammonia.[513,531,544] Derivatives of (563) and (564) have also been prepared by applying the Pomeranz–Fritsch reaction (condensation of carbonyl derivatives with the dimethyl acetal of aminoacetaldehyde with PPA) to selenophen-2- and -3-aldehydes and 2- and 3-acetylselenophens.[546] In an extensive investigation, the synthesis of selenopyridazines (565) and (566) and derivatives from diformylselenophens has been described and their n.m.r. spectra have been discussed.[135,547] Allyl isothiocyanate gave, upon reaction with (502) followed by alkaline cyclization, the pyrimidine-fused selenophen derivative (567), which was alkylated to (568) with methyl chloroacetate.[505]

Tellurophens.—The dipole moments of tellurophen, tetrahydrotellurophen, and some α-carbonyl derivatives have been determined, and from these data the mesomeric moment of tellurophen and the conformation of the

[544] V. I. Dulenko, N. N. Alekseev, and S. N. Baranov, *Khim. geterotsikl. Soedinenii*, 1971, 997.
[545] P. Pirson and L. Christiaens, *Bull. Soc. chim. France*, 1973, 704.
[546] F. Outurquin, C. Paulmier, J. Morel, and P. Pastour, *Compt. rend.*, 1972, **274**, C, 1696.
[547] B. Decroix, J. Morel, C. Paulmier, and P. Pastour, *Bull. Soc. chim. France*, 1972, 3453.



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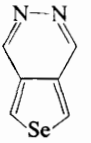

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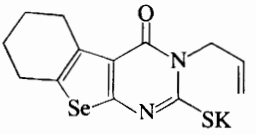

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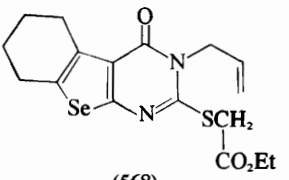
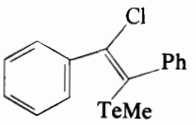


(568)

acetyl derivative can be estimated.[548] Rate constants and activation parameters in the Vilsmeier formylation of tellurophen have been compared with those of the other five-membered heterocycles. It reacts 37 times faster than thiophen but three times slower than furan.[68] The substituent constant σ^+ for the tellurophen ring (α-position) has been determined from the reactivity data of tellurophen in three electrophilic substitutions and from the solvolysis of 1-arylethyl acetates ($\sigma^+ = -0.92$).[549] On heating (569) hydrogen chloride is split off and (570) formed, which by reduction with sodium sulphide is transformed into the benzo[*b*]tellurophen (571).[550] 2-Substituted derivatives of benzo[*b*]tellurophen were prepared in high



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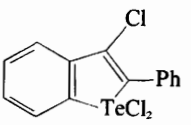

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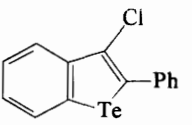

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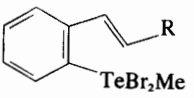

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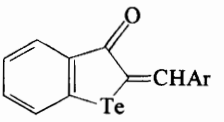


(573)

[548] H. Lumbroso, D. M. Bertin, F. Fringuelli, and A. Taticchi, *Compt. rend*, 1973, **277**, *C*, 203.
[549] F. Fringuelli, G. Marino, and A. Taticchi, *Gazzetta*, 1972, **102**, 534.
[550] I. D. Sadekov and V. I. Minkin, *Khim. geterotsikl. Soedinenii*, 1971, 138.

yields by the Wittig reaction of *o*-methyltellurobenzaldehyde, followed by the cyclization of the tellurium salts dihalogenated on the tellurium atom (572) by pyridine. Ring-closure to benzo[*b*]tellurophen occurs with elimination of methyl bromide.[551] 2-Formyl and 2-methyl derivatives were prepared *via* the lithium derivative obtained by metallation. Reaction of *o*-(methyltelluro)-acetophenone with aromatic aldehydes in the presence of piperidine gave compounds (573), which, as in the benzoselenophen series, should be useful starting materials for more complex benzo[*b*]tellurophens.[552] The ^{1}H n.m.r. spectrum of benzo[*b*]tellurophen has been analysed.[534]

[551] J. L. Piette, J. M. Talbot, J. C. Genard, and M. Renson, *Bull. Soc. chim. France*, 1973, 2468.
[552] J. L. Piette, A. Petit, and M. Renson, *Compt. rend.*, 1973, **276**, *C*, 1035.

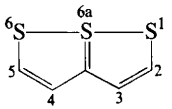
9

6a-Thiathiophthens and Related Compounds

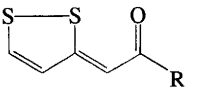
BY R. J. S. BEER

1 Introduction

The name, 6a-thiathiophthen, and the conventional representation (1) will be retained for the parent series of compounds, and selenium-containing analogues will be named and formulated similarly. Structures in which one of the terminal sulphur atoms of 6a-thiathiophthen is replaced by oxygen will be named as 1,2-dithiolylidene aldehydes or ketones (2), but, for



(1)

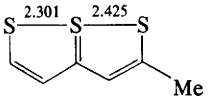


(2)

convenience, other analogues of the thiathiophthens will be given names based on the pentalene system (see Section 8).

2 Structural and Theoretical Studies

The detailed examination of 6a-thiathiophthens by *X*-ray crystallography has been continued. A new study of the parent compound confirms that the molecule is symmetric, but with revised S—S distances of 2.363 Å.[1] In 2-methyl-6a-thiathiophthen (3) the S-1—S-6a distance is lengthened,[2] in accordance with CNDO/2 calculations,[3] and the shortening of the S-1—S-6a bond in 3-methyl-2,5-diphenyl-6a-thiathiophthen (4)[4] is also in agreement



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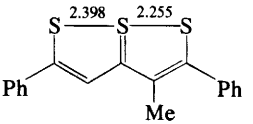
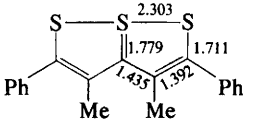


(4)

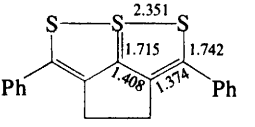
[1] L. K. Hansen and A. Hordvik, *Acta Chem. Scand.*, 1973 **27**, 411.
[2] A. Hordvik and L. J. Saethre, *Acta Chem. Scand.*, 1972, **26**, 1729.
[3] See 'Organic Compounds of Sulphur, Selenium, and Tellurium', ed. D. H. Reid (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 2.
[4] A. Hordvik, O. Sjølset, and L. J. Saethre, *Acta Chem. Scand.*, 1972, **26**, 1297.

with prediction. 3,4-Dimethyl-2,5-diphenyl-6a-thiathiophthen (5) shows mirror symmetry, and is of interest in having a particularly long C-3a—S-6a bond.[5]

The closely related ethano- and propano-6a-thiathiophthens (6) and (7) have been compared,[6] and significant features (notably the unusually short C-3a—S-6a bond) in the structure of the ethano-compound have been attributed to strain produced by the ethylene bridge between C-3 and C-4. In the much more complex 3,4-propano-6a-thiathiophthen (8), the S—S



(5)



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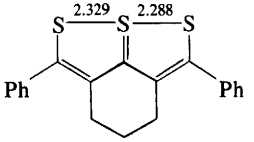

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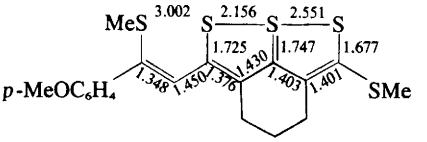
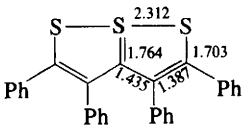


(8)

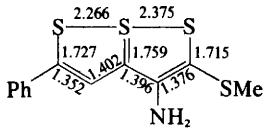
distances are markedly unequal.[7] Although the sulphur atom of the methylthio-group is well separated from its neighbour (by 3.002 Å), the array of four sulphur atoms is approximately linear.

Rather surprisingly, in view of earlier work, 2,3,4,5-tetraphenyl-6a-thiathiophthen (9) shows mirror symmetry.[8] Full details have appeared[9] of the structural work on 2-*p*-dimethylaminophenyl-4-phenyl-6a-thiathiophthen, previously reported briefly,[3] and a preliminary account has been given[10] of the *X*-ray crystal structure of 3-amino-2-methylthio-5-phenyl-6a-thiathiophthen (10).

An electron diffraction study of 6a-thiathiophthen (in the gaseous state) supports the view that the molecule has C_{2v} symmetry, with bond orders of 1.25—1.40[S-6a—C-3a], 1.45[S-1—C-2, S-6—C-5], and 1.47—1.75[C—C].[11]



(9)



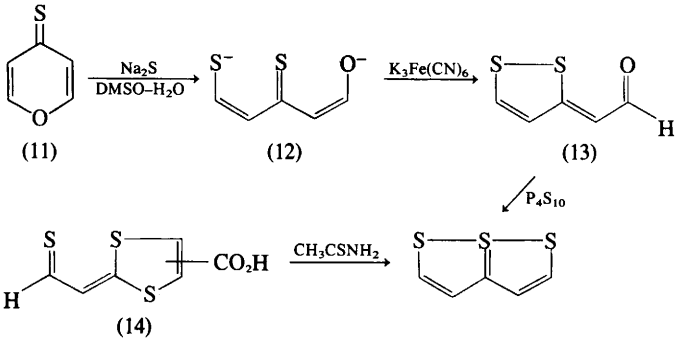
(10)

[5] A. Hordvik, O. Sjølset, and L. J. Saethre, *Acta Chem. Scand.*, 1973, **27**, 379.
[6] B. Birknes, A. Hordvik, and L. J. Saethre, *Acta Chem. Scand.*, 1972, **26**, 2140; 1973, **27**, 382.
[7] J. Sletten, *Acta Chem. Scand.*, 1973, **27**, 229.
[8] O. Hjellum and A. Hordvik, *Acta Chem. Scand.*, 1973, **27**, 2666.
[9] A. Hordvik and L. J. Saethre, *Acta Chem. Scand.*, 1972, **26**, 3114.
[10] A. J. Barnett, R. J. S. Beer, B. V. Karaoghlanian, E. C. Llaguno, and I. C, Paul, *J.C.S. Chem. Comm.*, 1972, 836.
[11] Q. Shen and K. Hedberg, *J. Amer. Chem. Soc.*, 1974, **96**, 289.

The question of symmetry in 6a-thiathiophthens, in relation to the interpretation of various physical studies previously reported[3] and to theoretical studies, is reviewed in a paper dealing with CNDO calculations of ionization and excitation energies, for the parent compound and its 2,5-dimethyl derivative.[12] 6a-Thiathiophthen is included in a further theoretical study,[13] which covers a range of heterocyclic sulphur compounds.

3 Synthesis of 6a-Thiathiophthens

Two methods have been recommended for the preparation of the parent member of the series. γ-Pyrone is converted, *via* the thione (11) and the dianion (12), into the dithiolylidene aldehyde, 1-oxa-6,6a-dithiapentalene (13), and the sequence is completed by treatment with phosphorus pentasulphide (overall yield from the readily accessible γ-pyrone is 12%).[14] In the second method,[15] the mixture of acids (14), obtained by addition of

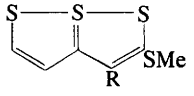


(11) (12) (13) (14)

propiolic acid to 1,2-dithiole-3-thione, is heated with thioacetamide, when rearrangement and decarboxylation to 6a-thiathiophthen take place (overall yield from the thione is 45%); using methyl propiolate in the addition reaction, the rearrangement reaction with thioacetamide yields both 2-methoxycarbonyl- and 3-methoxycarbonyl-6a-thiathiophthen.

The Vilsmeier salt synthesis has been extended to the preparation of 2-methylthio-6a-thiathiophthens (15; R = H or Me).[16] Full details have been published[17] of the route to dithiolylidene ketones and thiathiophthens by way of 3-phenacylthio-1,2-dithiolium salts[3] and related compounds. The 2-dimethylamino-6a-thiathiophthen (16), prepared by this method, is also obtained when the dithiolium salt (17) is treated with phosphorus pentasulphide, and the resulting mixture of isothiathiophthens (18; $R^1 = H$, $R^2 = Ph$) and (18; $R^1 = Ph$, $R^2 = H$) heated with thioacetamide.

[12] J. Kroner and D. Proch, *Tetrahedron Letters*, 1972, 2537.
[13] M. H. Palmer and R. H. Findlay, *Tetrahedron Letters*, 1972, 4165.
[14] D. H. Reid and R. G. Webster, *J.C.S. Perkin I*, 1972, 1447.
[15] H. Davy and J. Vialle, *Compt. rend.*, 1972, **275**, *C*, 625.
[16] C. Metayer, G. Duguay, and H. Quiniou, *Bull. Soc. chim. France*, 1972, 4576.
[17] G. Caillaud and Y. Mollier, *Bull. Soc. chim. France*, 1972, 147, 151.



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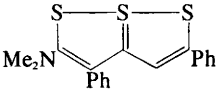

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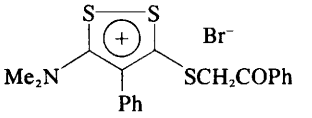

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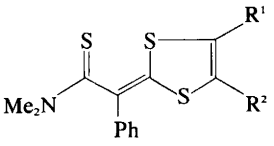
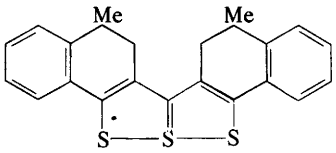


(18)

Difficulties have been encountered in attempts to prepare dibenzo- and dinaphtho-6a-thiathiophthens.[18] The tetrahydro-derivative (19) could not be dehydrogenated, and the dithiolylidene ketone (20) was not converted into the corresponding thiathiophthen with phosphorus pentasulphide. Compounds (21; R = Me or Ph) and (22), in which the thiathiophthen system is



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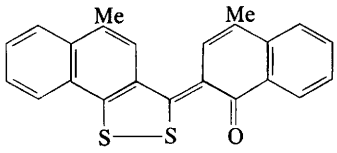

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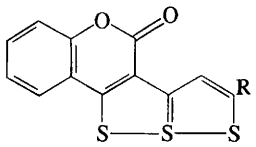

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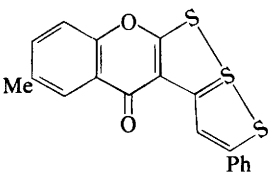
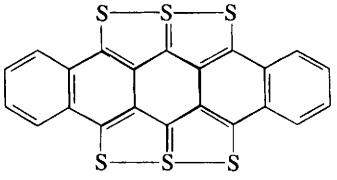


(22)

fused to coumarin and chromone rings, have, however, been prepared,[19] and the insoluble, highly coloured products obtained by heating pentacene and hexacene with sulphur have been formulated as the *peri*-fused thiathiophthens (23) and (24).[20]

Perhaps the most intriguing of the new structures which have been reported is the tris-dithiolethione (26),[21] with the molecular formula C_9S_9. This structure is assigned to the highly insoluble product obtained when the mesitylene derivative (25) is heated with sulphur in dimethylformamide.

[18] E. Klingsberg, *J. Org. Chem.*, 1972, **37**, 3226.
[19] F. M. Dean, J. Goodchild, and A. W. Hill, *J.C.S. Perkin I*, 1973, 1022.
[20] E. P. Goodings, D. A. Mitchard, and G. Owen, *J.C.S. Perkin I*, 1972, 1310; see also *Chem. Abs.*, 1973, **78**, 159 696.
[21] J. P. Brown and T. B. Gay, *J.C.S. Perkin I*, 1974, 866.



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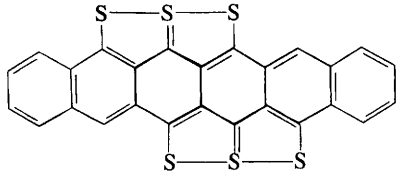

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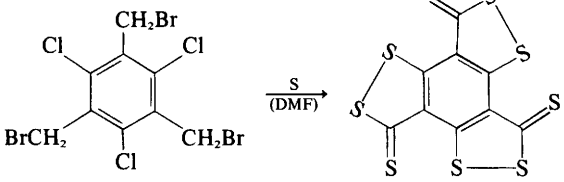


(25) (26)

4 Properties and Reactions of 6a-Thiathiophthens

A systematic study has been made of the mass spectra of 6a-thiathiophthens.[22] Common features are the appearance of intense molecular ion peaks, and prominent peaks corresponding to the loss of hydrogen, and of sulphur and hydrogen.

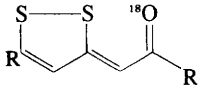
The preparation of ^{18}O-enriched dithiolylidene ketones (27; R = Me or Ph) from thiathiophthens, by the sulphuric acid method, has been described,[23] and the same method applied to the coumarin derivative (21; R = Me).[19] Peracetic acid in acetone is reported to be a more effective reagent than mercuric acetate for the conversion of 3-formyl-2,5-diaryl-6a-thiathiophthens (28) into the corresponding dithiolylidene ketones.[24]

Certain substitution reactions of thiathiophthens have been studied in considerable detail by Reid and his co-workers.[25,26] As previously observed,[3] nitration and nitrosation lead to rearranged, and sometimes desulphurized, products containing the 1-oxa-6,6a-dithia-2-azapentalene system (29; R^1 = Bu^t or Ph, R^2 = CHO, CS_2Me *etc.*) (see Section 8). The coupling of 2-t-butyl-6a-thiathiophthen with *p*-nitrobenzenediazonium fluoroborate also brings about a rearrangement, which here leads to a 1,6a-dithia-5,6-diazapentalene (30).[27]

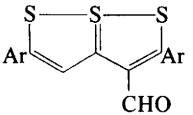
The S—S bonds in the thiathiophthen system can survive treatment with conventional reducing agents (*e.g.* stannous chloride).[10] Thus, it is possible

[22] C. Th. Pedersen, N. L. Huaman, and J. Møller, *Acta Chem. Scand.*, 1972, **26**, 565.
[23] R. Pinel and Y. Mollier, *Bull. Soc. chim. France*, 1972, 1385.
[24] J. Bignebat and H. Quiniou, *Bull. Soc. chim. France*, 1972, 4181.
[25] J. G. Dingwall, A. R. Dunn, D. H. Reid, and K. O. Wade, *J.C.S. Perkin I*, 1972, 1360.
[26] R. M. Christie, A. S. Ingram, D. H. Reid, and R. G. Webster, *J.C.S. Perkin I*, 1974, 722.
[27] R. M. Christie, A. S. Ingram, D. H. Reid, and R. G. Webster, *J.C.S. Chem. Comm.*, 1973, 92.

to reduce the nitro-groups in 2-methylthio-3-nitro-5-phenyl-6a-thiathiophthen, and in 3-nitro-2,5-diphenyl-6a-thiathiophthen to amino-groups. The products (31; R = Ph or MeS) absorb at longer wavelengths than do normal thiathiophthens and show basic properties, in contrast to the 2-amino-compounds, which are acidic rather than basic.



(27)



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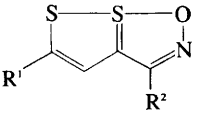

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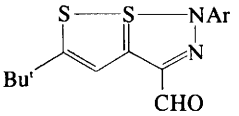
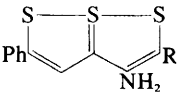


(30)

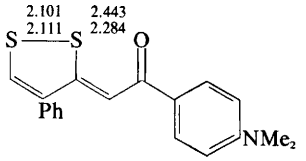


(31)

5 1,2-Dithiolylidene Aldehydes and Ketones

The mass spectra of a series of dithiolylidene aldehydes and ketones have been reported, and discussed in detail.[28] All the compounds studied show intense molecular-ion peaks, and peaks corresponding to loss of oxygen and hydrogen, and to loss of sulphur and hydrogen, are commonly observed.

A preliminary account has been given[29] of the *X*-ray crystal structure of the *p*-dimethylaminophenyl ketone (32). Two crystallographically independent molecules are involved, with S—S distances of 2.101 and 2.111 Å, and

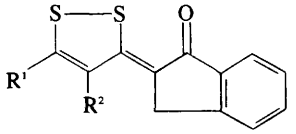


(32)

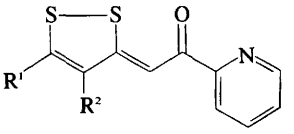
S—O distances of 2.443 and 2.284 Å, respectively. Significantly, the longer S—S distance corresponds with the shorter S—O contact.

In a continued study of dithiolylidene ketones,[30,23] compounds of types (33) and (34) have been prepared, and the behaviour of various members of the series on protonation has been examined. With the pyridyl ketones, protonation and methylation occur on nitrogen rather than on oxygen. Spectroscopic data on formyl compounds (35; R^1 = Ar, R^2 = H) suggest they exist in solution as mixtures with the geometrical isomers (35; R^1 = H,

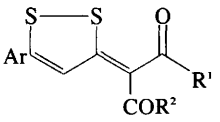
[28] C. Th. Pedersen, N. L. Huaman, R. Pinel, and J. Møller, *Acta Chem. Scand.*, 1972, **26**, 1305.
[29] A. Hordvik and L. J. Saethre, *Acta Chem. Scand.*, 1972, **26**, 849.
[30] D. Festal, J. Tison, K. S. N'Guyen, R. Pinel, and Y. Mollier, *Bull. Soc. chim. France*, 1973, 3339.



(33)



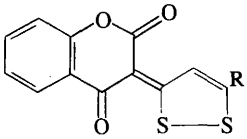
(34)



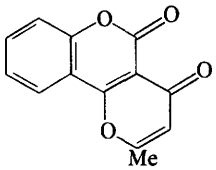
(35)

R^2 = Ar), the major components having the ketonic oxygen associated with the disulphide group.[24]

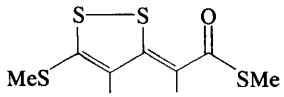
4-Hydroxycoumarin condenses with 3-methylthio-5-phenyl-1,2-dithiolium salts to give the complex dithiolylidene ketone (36; R = Ph), required for comparison with the product (36; R = Me) obtained by treatment of the pyranocoumarin (37) with boron sulphide.[19] The base-catalysed reaction of 5-methylene-1,2-dithiole-3-thiones with carbon oxysulphide leads, after methylation of the intermediates, to mixtures of two types of product, (38) and (39).[31]



(36)



(37)



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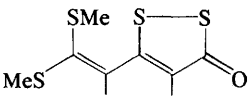


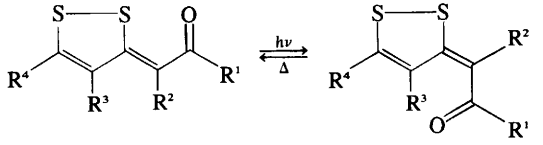
(39)

The photoproducts obtained by irradiation of dithiolylidene ketones (40) have been identified as *trans*-isomers (41),[32,33] some of which survive long enough to allow spectroscopic measurements to be made. The ketone [40; $R^1 = R^4$ = Et, $R^2R^3 = (CH_2)_3$] is not affected by irradiation.[32] When (40; $R^1 = R^4$ = Ph, $R^2 = R^3$ = H) is irradiated in a poly(methacrylate) matrix, the photoproduct is stable at room temperature, and only reverts slowly to

[31] J-L Burgot, *Bull. Soc. chim. France*, 1974, 140.

[32] R. Gleiter, K-H Knauer, E. Schmidt, Y. Mollier, and R. Pinel, *Tetrahedron Letters*, 1973, 1257; G. Calzaferri, R. Gleiter, K-H Knauer, E. Rommel, E. Schmidt, and H. Behringer, *Helv. Chim. Acta*, 1973, **56**, 597.

[33] C. Th. Pedersen and C. Lohse, *J.C.S. Chem. Comm.*, 1973, 123.

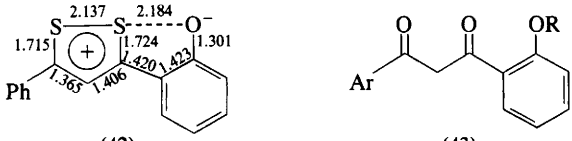


(40) (41)

starting material at 110 °C, the inference being that the matrix retards the rotational process required for reversion.[33] As would be expected, (40; $R^1 = R^4 = Ph$, $R^2 = COPh$, $R^3 = H$) shows no change on irradiation. The effects of varying substitution patterns on the rate of the reversion process have been discussed in detail.[34]

X-Ray data have been reported[35] for the dithiolium phenolate (42). This compound differs from dithiolylidene ketones in showing no carbonyl absorption, even of a modified kind, in the i.r. spectrum, a consequence of increased bonding between oxygen and sulphur, as indicated by the relatively short S—O distance (2.184 Å) and the relatively long S—S distance (2.137 Å).

An improved method of synthesis of phenolates of type (42) has been described.[36] The phenolic group in the normal starting material (43; R = H)



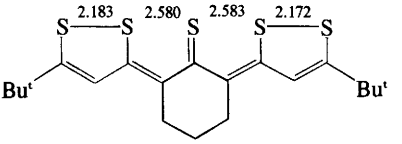
(42) (43)

is protected by methylation before treatment with phosphorus pentasulphide; alternatively, treatment of the methyl ether (43; R = Me) with hydrogen disulphide and hydrogen chloride yields a 3-(*o*-methoxyphenyl)-1,2-dithiolium salt, which undergoes demethylation to the phenolate when heated with pyridine.

6 Multisulphur Systems

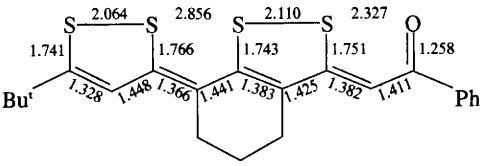
Systems containing more than three sulphur atoms feature in a number of reports. Full details have been published of structural work on the S_5 compound (44).[37] The molecule appears to consist of two fused thiathiophthen systems, with an approximately linear array of sulphur atoms, although there is some bending of the molecule about the central C—S bond.

[34] C. Th. Pedersen and C. Lohse, *J.C.S. Perkin I*, 1973, 2837.
[35] E. C. Llaguno, I. C. Paul, R. Pinel, and Y. Mollier, *Tetrahedron Letters*, 1972, 4687.
[36] D. Barrillier, C. Gy, P. Rioult, and J. Vialle, *Bull. Soc. chim. France*, 1973, 277.
[37] R. Kristensen and J. Sletten, *Acta Chem. Scand.*, 1973, **27**, 2517.



(44)

The related structure (45)[38] is probably best regarded as a 1,2-dithiolylidene ketone with a short S—O contact, and marked bond alternation in the long carbon chain. Compound (46) is effectively a 5-dithiolylidenemethyl-1,2-dithiole-3-thione.[39]



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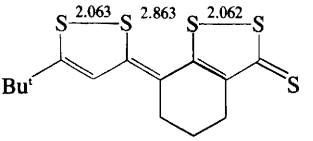
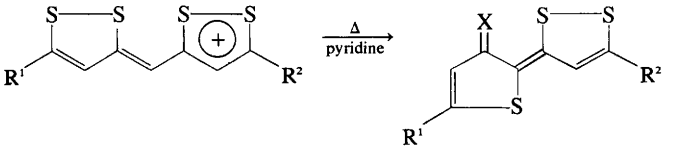


(46)

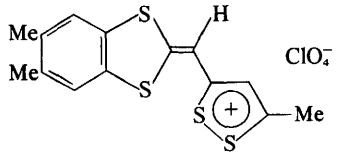
The mass spectra of a number of multisulphur systems have been examined.[40] Although reproducible, the spectra are not particularly characteristic. Under appropriate conditions, strong molecular-ion peaks are observed, indicating that these compounds have considerable thermal stability.

The conversion of methine salts (47) into thiathiophthen-like products (48; X = S)[3] has been described in detail,[41] and the structures assigned have



(47) (48)

[38] J. Sletten and M. Velsvik, *Acta Chem. Scand.*, 1973, **27**, 3881.
[39] J. Sletten, *Acta Chem. Scand.*, 1972, **26**, 873.
[40] C. Th. Pedersen, M. Stavaux, and J. Møller, *Acta Chem. Scand.*, 1972, **26**, 3875.
[41] C. Lemarie-Retour, M. Stavaux, and N. Lozac'h, *Bull. Soc. chim. France*, 1973, 1659.



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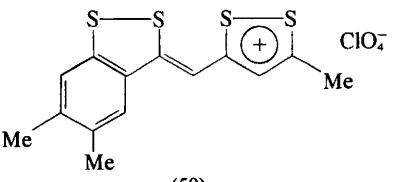
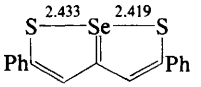


(50)

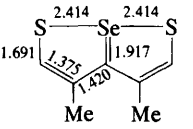
been confirmed by independent syntheses *via* the oxygen analogues (48; X = O). Methine salts of types (49) and (50) have been synthesized.[42]

7 6a-Selenathiophthens

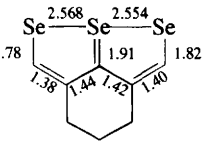
Structural data have been reported for three selenium-containing analogues of 6a-thiathiophthen. 2,5-Diphenyl-6a-selenathiophthen (51)[43] has S—Se bonds that are nearly equal in length, whilst 3,4-dimethyl-6a-selenathiophthen (52)[44] shows C_{2v} symmetry. The propano-bridge in the Se_3 compound (53) causes a slight shortening of the Se—Se bonds.[45]



(51)



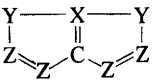
(52)



(53)

8 Other Analogues of 6a-Thiathiophthen

Many of the compounds to be discussed in this section are conveniently (although perhaps not correctly) named as derivatives of pentalene, and are represented by the general formula (54). In principle, the Y and Z positions

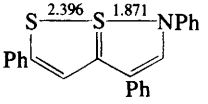


(54) X = S, Se, or Te
Y = O, S, Se, or NR
Z = N or CR(sp^2)

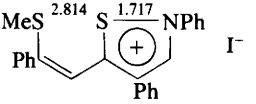
can be occupied by any of the atoms or groups shown, and the molecules need not have mirror symmetry, so that the number of possible combinations is very large, although considerations of stability obviously impose some limitations in practice. The assumption is made that these are bicyclic systems and, in many examples, this assumption is justified by spectroscopic and *X*-ray crystallographic data.

[42] E. Klingsberg, *Synthesis*, 1972, 29.
[43] A. Hordvik, T. S. Rimala, and L. J. Saethre, *Acta Chem. Scand.*, 1972, **26**, 2139.
[44] A. Hordvik, T. S. Rimala, and L. J. Saethre, *Acta Chem. Scand.*, 1973, **27**, 360.
[45] A. Hordvik and J. A. Porten, *Acta Chem. Scand.*, 1973, **27**, 485.

Most closely related to the 6a-thiathiophthens, and to dithiolylidene ketones, are the 1,6a-dithia-6-azapentalenes, which have been discussed previously.[3] A new *X*-ray study in this series provides data for the triphenyl compound (55) and its *S*-methyl derivative (56).[46] Comparison of the S—S and S—N distances in the two compounds is instructive.

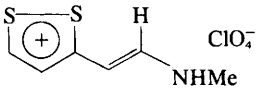


(55)



(56)

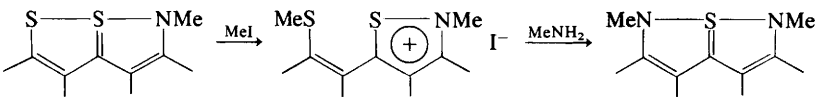
Two general methods have been described for the synthesis of 1,6a-dithia-6-azapentalenes, one involving the treatment of Vilsmeier salts with primary amines in dimethylformamide,[47,48] the second a direct conversion of 6a-thiathiophthens with ethanolic methylamine in acetonitrile,[47] a reaction which proceeds with surprising ease. These methods have provided a range of compounds for detailed study.[47] Basic properties are indicated by the formation of stable perchlorates, protonation normally occurring on nitrogen and giving probably the *trans*-form, for example (57), although there is



(57)

some evidence for partial *C*-protonation. N.m.r. studies show that the ring protons in the aza-compounds are more deshielded than those in the analogous oxa-compounds (dithiolylidene ketones), but less deshielded than those in 6a-thiathiophthens.

Methylation of the aza-compounds occurs on sulphur, yielding isothiazolium salts (58). Treatment of these salts with methylamine leads to 6a-thia-1,6-diazapentalenes (59),[3] a detailed account of which has now



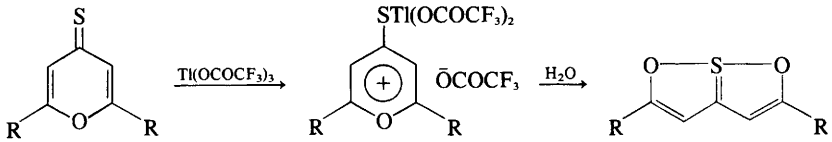
(58) (59)

appeared.[49] Members of this series resemble enamines or pyrroles; they are unstable, and n.m.r. studies indicate marked shielding of the protons at the 3- and 4-positions.

One of the most interesting developments in the area covered by this

[46] F. Leung and S. C. Nyburg, *Canad. J. Chem.*, 1972, **50**, 324.
[47] J. G. Dingwall, A. S. Ingram, D. H. Reid, and J. D. Symon, *J.C.S. Perkin I*, 1973, 2351.
[48] C. Metayer, G. Duguay, and H. Quiniou, *Bull. Soc. chim. France*, 1974, 163.
[49] A. S. Ingram, D. H. Reid, and J. D. Symon, *J.C.S. Perkin I*, 1974, 242.

chapter is the discovery of a simple and elegant method for the preparation of 1,6-dioxa-6a-thiapentalenes,[50] previously known only in complex structures.[3,51] 4*H*-Pyran-4-thione (60; R = H) is treated with thallium(III) trifluoroacetate in acetonitrile, and the resulting pyrylium salt converted into the dioxathiapentalene (61; R = H) by the action of water. The method



(60) (61)

is less successful with 2,6-dimethyl-4*H*-pyran-4-thione, but can be applied to the 2,6-diethoxycarbonyl derivative (60; R = CO_2Et). Preliminary studies with 1,6-dioxa-6a-thiapentalene indicate facile bromination to the 3,4-dibromo-derivative, and iodination to mono- and di-iodo-derivatives.

A minor product isolated in studies of the sulphurization of the pyrano-coumarin (37) is thought to be a member of the dioxathiapentalene series.[19]

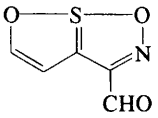
1-Oxa-6,6a-dithia-2-azapentalenes (62; X = S), originally named as 3-nitrosomethylene-1,2-dithioles,[3] are obtained in excellent yields by the action of nitrous acid on 3-methyl (or methylene)-1,2-dithiolium salts,[25] and the selenium analogues (62; X = Se) are made by the same method. Treatment of 6a-thiathiophthens with tetranitromethane in pyridine can produce 3-formyl-1-oxa-6,6a-dithia-2-azapentalenes (62; X = S, R^1 = Bu^t or Ph, R^2 = H, R^3 = CHO); these reactions probably involve oxidative desulphurization as a first step, and subsequent *nitrosation* of dithiolylidene aldehydes. Spectroscopic comparison of the 1-oxa-6,6a-dithia-2-azapentalenes with the corresponding nitro-compounds (63), and earlier *X*-ray crystallographic work,[3] suggest that the 'nitroso-compounds' are best regarded as bicyclic systems.

(62) (63)

Further studies of nitrosation reactions are described in a recent paper,[26] which shows that the same products of type (62; R^3 = CHO) can be obtained from suitably substituted 6a-thiathiophthens, dithiolylidene aldehydes, and 1,6a-dithia-6-azapentalenes. 1,6-Dioxa-6a-thiapentalene (61; R = H) is sensitive to acids, and is destroyed by nitrous acid in acetic acid, but is

[50] D. H. Reid and R. G. Webster, *J.C.S. Chem. Comm.*, 1972, 1283.
[51] I. H. Pomerantz, L. J. Miller, R. Barron, E. Hansen, D. Mastbrook, and I. Egry, *Tetrahedron*, 1972, **28**, 2183.

successfully nitrosated with nitrosyl hexafluorophosphate to give the 3-formyl derivative (64) of a new system, 1,6-dioxa-6a-thia-2-aza-pentalene. A general mechanism for electrophilic substitutions of this kind, involving rearrangements, has been proposed.



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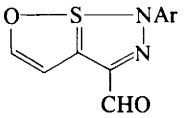
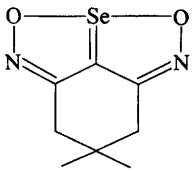


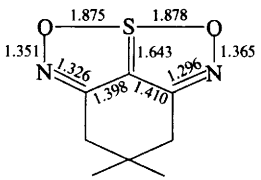
(65)

The formation of the 1,6a-dithia-5,6-diazapentalene (30) by attempted diazo-coupling with 2-t-butyl-6a-thiathiophthen has been mentioned earlier in this chapter. 5,6-Diaza-compounds have also been obtained from dithiolylidene aldehydes and from 1,6a-dithia-6-azapentalenes, suggesting that the N-6—S-6a bond must be relatively strong, like the O-1—S-6a bond in 1-oxa-6,6a-dithia-2-azapentalenes. Members of the 1,6a-dithia-5,6-diaza series can also be obtained by the reaction of 3-methyl-1,2-dithiolium salts with *p*-nitrobenzenediazonium fluoroborate in ethanol.[27] Coupling of diazonium salts with 1,6-dioxa-6a-thiapentalene (61; R = H) leads to yet another new system (65).

Full details have appeared of the *X*-ray crystallographic study of the 1,6-dioxa-6a-selena-2,5-diazapentalene (66),[52] previously reported briefly,[3] and a preliminary note[53] gives structural data for the sulphur analogue (67),



(66)

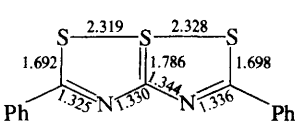


(67)

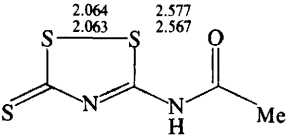
in which the S—O distances have the expected values[3] of *ca.* 1.88 Å. The C—S distance (1.643 Å) is one of the shortest yet recorded.

Several interesting structures incorporating the 1,2,4-dithiazole ring have been described. Of these, the only one which is clearly a member of the 'pentalene' series is the 1,6,6a-trithia-3,4-diaza-compound (68),[3] for which full structural details have been given.[54] In the 5-acetamido-1,2,4-dithiazole derivative (69),[55] the oxygen–sulphur contacts (2.577 and 2.567 Å, in the two crystallographically independent molecules) do not produce any stretching of the S—S bonds (2.064 and 2.063 Å).

[52] E. C. Llaguno and I. C. Paul, *J.C.S. Perkin II*, 1972, 2001.
[53] E. C. Llaguno and I. C. Paul, *Tetrahedron Letters*, 1973, 1565.
[54] A. Hordvik and L. M. Milje, *Acta Chem. Scand.*, 1973, **27**, 511.
[55] G. Eide, A. Hordvik, and L. J. Saethre, *Acta Chem. Scand.*, 1972, **26**, 2140.

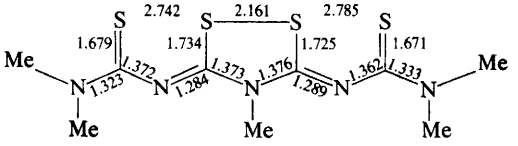


(68)

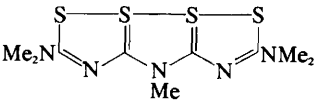


(69)

Routes to 1,2,4-dithiazole systems of type (70) have been published.[56] The *X*-ray structural data on two representatives[57] clearly support the conventional structures, rather than structures with four linked sulphur atoms (71),



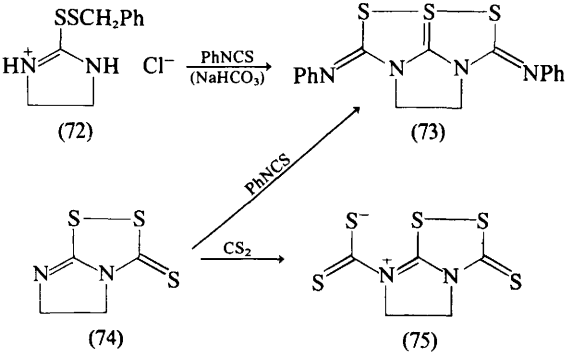
(70)



(71)

although some interaction between the outer pairs of sulphur atoms is possible.

A new variation on the thiathiophthen theme is provided by the symmetrical structure (73), assigned to the product obtained by the action of phenyl isothiocyanate on the disulphide (72), or on the thione (74).[58] This



(72) (73)

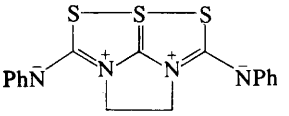
(74) (75)

[56] J. Goerdeler and J. Ulmen, *Chem. Ber.*, 1972, **105**, 1568; J. E. Oliver and J. B. Stokes, *Internat. J. Sulfur Chem.* (*A*), 1972, **2**, 105.

[57] J. E. Oliver, J. L. Flippen, and J. Karle, *J.C.S. Chem. Comm.*, 1972, 1153; J. L. Flippen, *J. Amer. Chem. Soc.*, 1973, **95**, 6073.

[58] R. J. S. Beer and A. Naylor, *Tetrahedron Letters*, 1973, 2989.

product, which incorporates two fused 1,2,4-dithiazole systems, and which differs in physical properties and in stability from the previously described,[59] loose, adduct (75) of the thione (74) and carbon disulphide, cannot easily be formulated as a thiathiophthen analogue, since this would require a substantial contribution from the highly polarized form (76). The



(76)

alternative is to regard it as the first well-defined example of a new series of compounds, which are effectively reduced forms of thiathiophthen-type structures, lacking a complete peripheral π-system of electrons, and therefore not depending on stabilization of the usual aromatic kind.

[59] C. W. Pluijgers, J. W. Vonk, and G. D. Thorn, *Tetrahedron Letters*, 1971, 1317.

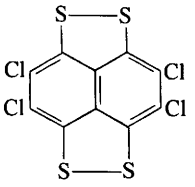
10
1,2- and 1,3-Dithioles

BY R. J. S. BEER

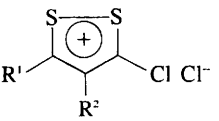
1 1,2-Dithioles and Related Compounds

Fusion of octachloronaphthalene with sulphur gives the *peri*-fused bis-dithiole (1) in good yield. When sulphur is replaced by selenium, only one diselenide bridge is introduced.[1]

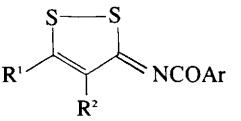
1,2-Dithiole-3-imine derivatives feature in a number of papers. 3-Acylimines (3), for example, are obtained from 3-chloro-1,2-dithiolium



(1)



(2)



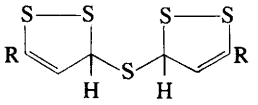
(3)

chlorides (2; $R^1 = R^2 = Cl$; $R^1 = Ph$, $R^2 = H$)[2] and *NN*-dichloronitrobenzamides.[3] Although 5-aryl-3-bromo-1,2-dithiolium bromides yield 3-arylimines when treated with aromatic amines, 4-aryl-3-bromodithiolium salts are converted into isothiazolinethiones,[4] contrary to an earlier report. 5-Aryl-1,2-dithiole-3-thiones and the corresponding 3-imines are amongst the products formed, although only in minor proportions, by the reaction between aroyldithioacetic esters and aromatic amines.[5]

The reaction of isothiazolium salts with sulphur in hot pyridine has been studied in detail. If the nitrogen atom carries an aryl substituent, the products can include 1,2-dithiole-3-imines.[6] 2-Alkylisothiazolium salts lacking a substituent in the 3-position react with aqueous hydrogen sulphide to

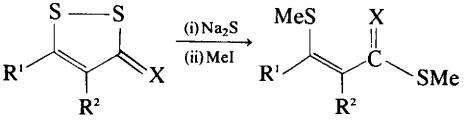
[1] E. Klingsberg, *Tetrahedron*, 1972, **28**, 963.
[2] F. Boberg and W. Gentzkow, *Annalen*, 1972, **766**, 1.
[3] F. Boberg and G.-J. Wentrup, *Annalen*, 1973, 241.
[4] F. Boberg and W. Gentzkow, *J. prakt. Chem.*, 1973, **315**, 965.
[5] F. Clesse and H. Quiniou, *Bull. Soc. chim. France*, 1973, 581.
[6] G. E. Bachers, D. M. McKinnon, and J. M. Buchshriber, *Canad. J. Chem.*, 1972, **50**, 2568.

give bis-1,2-dithiolyl sulphides (4)[7] but further investigation of this reaction has shown that 1,2-dithiole-3-thiones can also be formed.[8]



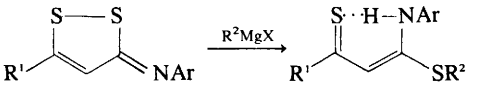
(4)

Ring-opening reactions occur when 1,2-dithiole-3-ones and -3-thiones are treated with sodium sulphide;[9] after methylation, products of type (5; X = O



(5)

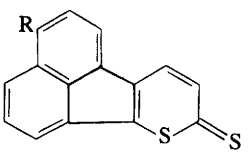
or S) are obtained. Studies of ring cleavage of 1,2-dithiole derivatives with Grignard reagents have been extended to 3-arylimines (6); the products (7) have been used to synthesize various heterocyclic systems.[10]



(6) (7)

The mechanism of the base-catalysed condensation reaction between 1,2-dithiole-3-thiones and ketones of the acenaphthene series, which leads to thiopyran derivatives (8), has been discussed in detail,[11] and is thought to involve carbanion attack at the 5-position, leading to ring-opening and consequent changes.

Acid chlorides derived from carboxylic acids of the 1,2-dithiole-3-one series (9; R^1 = Ar, R^2 = CO_2H) or (9; R^1 = CO_2H, R^2 = Ar) behave normally



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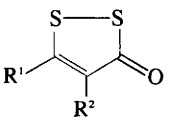
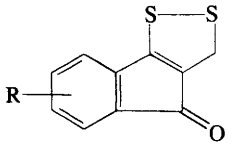


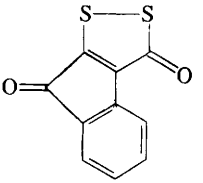
(9)

[7] P. Sykes and H. Ullah, *J.C.S. Perkin I*, 1972, 2305.
[8] D. M. McKinnon and M. E. Hassan, *Canad. J. Chem.*, 1973, **51**, 3081.
[9] J. Maignan and J. Vialle, *Bull. Soc. chim. France*, 1973, 1973.
[10] F. Boberg and W. Gentzkow, *Annalen*, 1973, 247, 256.
[11] K. S. N'Guyen, R. Pinel, and Y. Mollier, *Bull. Soc. chim. France*, 1973, 3334.

with alcohols and amines. Friedel–Crafts reactions can occur either internally, leading to products of type (10) and (11), or with added reactant, such as anisole, to give, for example, the ketone (12).[12]



(10)



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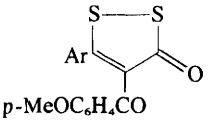
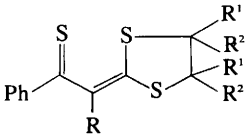


(12)

The addition of methyl propiolate and of propiolic acid to 1,2-dithiole-3-thione[13,14] produces mixtures of 'isothiathiophthens' (see Chapter 9). Photocatalysed addition of olefins to 1,2-dithiole-3-thiones has been studied by two groups; 5-phenyl- and 4,5-diphenyl-1,2-dithiole-3-thione give products of type (13; R = H or Ph),[15] whilst the 4-*p*-tolyl compound, with 1,1-diphenylethylene, is converted into the 3-vinylthio-dithiole (14).[16]



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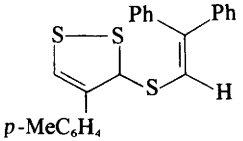
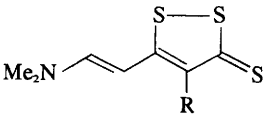


(14)

Several papers deal with condensation reactions of 'active' 5-methyl or methylene groups in 1,2-dithiole-3-thiones. Thus, 5-dimethylaminovinyl-1,2-dithiole-3-thiones (15) are made in this way, using the diethyl 'acetal' of

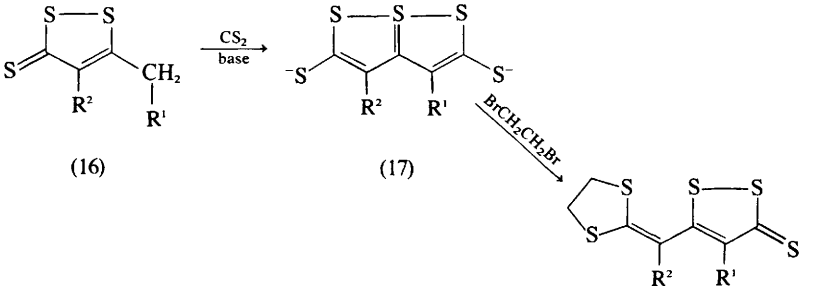


(15)

dimethylformamide as the reactant.[17] The products are identical with those obtained previously from 5-dimethylaminovinyl-3-methylthio-1,2-dithiolium perchlorates by the action of pyridine. The base-catalysed condensation of carbon oxysulphide with 5-alkyl-1,2-dithiole-3-thiones has been referred to in Chapter 9. Condensation of carbon

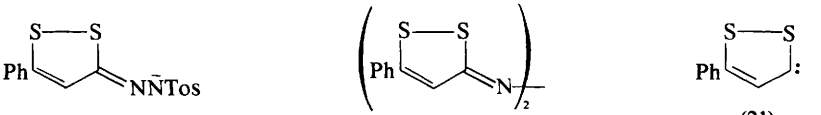
[12] C. Trebaul, *Bull. Soc. chim. France*, 1972, 1840; 1973, 721.
[13] H. Davy and J. Vialle, *Compt. rend.*, 1972, **275**, C, 625.
[14] See 'Organic Compounds of Sulphur, Selenium, and Tellurium', ed. D. H. Reid (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 2.
[15] R. Okazaki, F. Ishii, K. Ozawa, and N. Inamoto, *Chem. Letters*, 1972, 9.
[16] P. de Mayo and H. Y. Ng, *Tetrahedron Letters*, 1973, 1561.
[17] C. Métayer, G. Duguay, and H. Quiniou, *Bull. Soc. chim. France*, 1974, 163.

disulphide with the dithiolethione (16), and reaction of the intermediate dianion (17) with 1,2-dibromoethane, can lead to two products, *viz.* (18) and its isomer with R^1, R^2 substituents interchanged.[18]



(16) (17) (18)

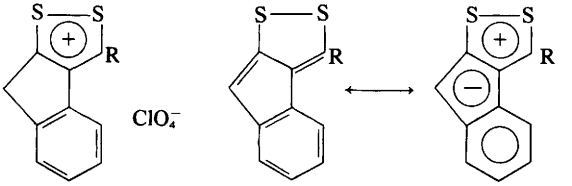
Thermolysis of the tosylhydrazone anion (19) gives a mixture of the 1,2-dithiole-3-thione and the azine (20).[19] No evidence was obtained of formation of the bi-dithiole, which might have resulted from a carbenoid intermediate of type (21).



(19) (20) (21)

2 1,2-Dithiolium Salts

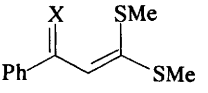
Details have been given[20] of methods for the preparation of 1,2-dithiolium tri-iodides and iodides by the action of hydrogen sulphide and iodine on 1,3-diketones, and the diacetyl disulphide method[14] has been applied to 1-acylindan-2-ones, yielding indeno-1,2-dithiolium salts (22), which can be deprotonated to indeno-1,2-dithioles (23).[21] A mechanistic study has been



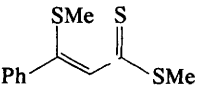
(22) (23)

[18] J.-L. Burgot, *Bull. Soc. chim. France*, 1974, 140; J. Burgot and J. Vialle, *ibid.*, p. 137.
[19] H. Behringer and E. Meinetsberger, *Tetrahedron Letters*, 1973, 1915.
[20] J.-P. Guemas and H. Quiniou, *Bull. Soc. chim. France*, 1973, 592; A. R. Hendrickson and R. L. Martin, *J. Org. Chem.*, 1973, **38**, 2548.
[21] K. Hartke and D. Krampitz, *Chem. Ber.*, 1974, **107**, 739.

made[22] of the previously reported reaction[14] in which 3-methylthio-1,2-dithiolium salts are prepared from keten mercaptals, *e.g.* (24; X = O), by treatment with phosphorus pentasulphide. The intermediates involved are probably the thione (24; X = S) and the dithio-ester (25).

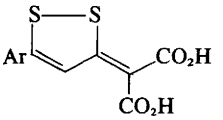


(24)



(25)

1,2-Dithiolylidene derivatives of malonic acid (26) decarboxylate in perchloric acid–acetic acid to give 5-aryl-1,2-dithiolium perchlorates.[23] Vilsmeier salts of type (27) are produced by condensation of 5-methyl-1,2-dithiolium salts with dimethylthioformamide,[24] and a similar *trans*-structure (28) is formed[25] when 6-methyl-1,6a-dithia-6-azapentalene (see Chapter 9) is protonated.



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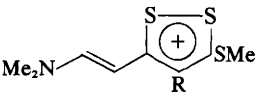

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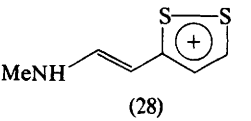
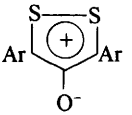
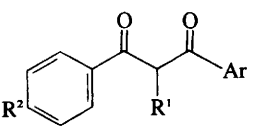


(28)

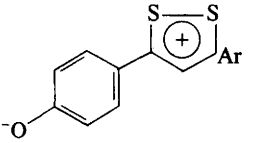
The material formed when 1,3-diphenylpropane-1,2,3-trione is treated with hydrogen sulphide and hydrogen chloride,[14] and which on treatment with triethylamine gives the meso-ionic compound (29; Ar = Ph), has now been recognized as a mixture containing the hydrochloride of compound (29) and 3,5-diphenyl-1,2-dithiolium chloride.[26] Another approach[27] to meso-ionic compounds of type (29) involves treatment of 2-acetoxy-1,3-diketones (30; R^1 = OAc) with hydrogen disulphide and hydrogen chloride, leading to the 4-hydroxy-1,2-dithiolium chloride; the meso-ionic compound is then generated by deprotonation with pyridine. *p*-Hydroxyphenyl-dithiolium salts, prepared from the diketones (30; R^1 = H, R^2 = OH), yield phenolates (31) on treatment with triethylamine.



(29)



(30)

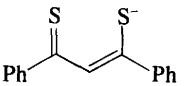


(31)

[22] J. Maignan and J. Vialle, *Bull. Soc. chim. France*, 1973, 2388.
[23] M. Bard and G. Duguay, *Compt. rend.*, 1972, **275**, *C*, 905.
[24] C. Métayer, G. Duguay, and H. Quiniou, *Bull. Soc. chim. France*, 1972, 4576.
[25] J. G. Dingwall, A. S. Ingram, D. H. Reid, and J. D. Symon, *J.C.S. Perkin I*, 1973, 2351.
[26] A. Chinone, K. Inouye, and M. Ohta, *Bull. Chem. Soc. Japan*, 1972, **45**, 213.
[27] D. Barrillier, P. Rioult, and J. Vialle, *Bull. Soc. chim. France*, 1973, 3031.

Non-empirical MO calculations for 1,2- and 1,3-dithiolium cations suggest that the *d*-orbitals are involved in bonding only to a trivial extent.[28] A series of papers has appeared[29] describing CNDO calculations of the electronic spectra of 1,2-dithiolium cations, and presenting a theoretical treatment of the species produced by cathodic reduction of dithiolium salts,[30] particularly the radical form (32).[14] Flash photolysis of 2,5-diphenyl-1,2-dithiolium salts in ethanol yields two products,[31] of which the less stable has the absorption spectrum of the radical (32; R = Ph), and the longer-lived product appears to be the ring-opened anion (33); thus, the reaction is a photoreduction involving solvent.

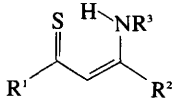
(32)



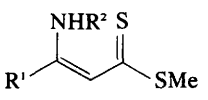
(33)

S(2p) Binding energies for 3,5-dimethyl-, 3,5-diphenyl-, and 3-methyl-5-phenyl-dithiolium cations have been measured by *X*-ray photoelectron spectroscopy,[32] and some mass spectral data for the thermolysis products of 1,2-dithiolium salts have been recorded.[33]

Ring-opening reactions[14] of 1,2-dithiolium salts feature in several reports. 3-Phenyl- and 3,5-diphenyl-1,2-dithiolium perchlorates react with 2-mercaptoethylamine to give the thiones (34; $R^1 = Ph$, $R^2 = H$, $R^3 = CH_2CH_2SH$) and (34; $R^1 = R^2 = Ph$, $R^3 = CH_2CH_2SH$),[7] and 3-phenylvinyl-1,2-dithiolium perchlorate reacts similarly with aromatic primary amines, yielding thiones (34; $R^1 = PhCH{:}CH$, $R^2 = H$, $R^3 = Ar$).[34] Studies on the behaviour of 3-methylthio-1,2-dithiolium salts with amines[14] have been continued; 5-alkyl-substituted compounds react with primary aliphatic amines to give β-alkylaminodithioacrylates (35).[35]



(34)

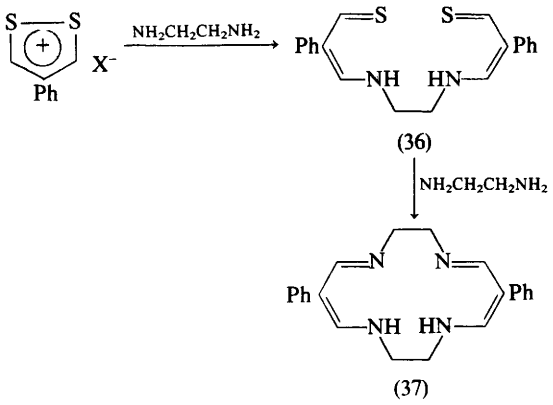


(35)

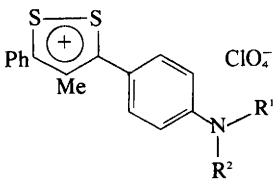
Interesting applications of the amine ring-opening reactions have been reported.[36] With ethylenediamine, 4-phenyl-1,2-dithiolium salts yield the

[28] M. H. Palmer and R. H. Findlay, *Tetrahedron Letters*, 1972, 4165.
[29] C. Guimou, D. Gonbeau, and G. Pfister-Guillouzo, *Tetrahedron*, 1973, **29**, 3399.
[30] K. Bechgaard, V. D. Parker, and C. Th. Pedersen, *J. Amer. Chem. Soc.*, 1973, **95**, 4373.
[31] C. Th. Pedersen and C. Lohse, *Tetrahedron Letters*, 1972, 5213.
[32] S. W. Schneller and W. E. Swartz, *J. Heterocyclic Chem.*, 1974, **11**, 105.
[33] C. Th. Pedersen and J. Møller, *Tetrahedron*, 1974, **30**, 553.
[34] C. Métayer and G. Duguay, *Compt. rend.*, 1971, **273**, *C*, 1457.
[35] G. Le Coustumer and Y. Mollier, *Bull. Soc. chim. France*, 1973, 3349.
[36] S. C. Taug, G. N. Weinstein, and R. H. Holm, *J. Amer. Chem. Soc.*, 1973, **95**, 613.

dithione (36), which, on further treatment with ethylenediamine, is converted into the macrocycle (37). Related structures with trimethylene bridges between the nitrogen atoms have been prepared similarly.



Tertiary aromatic amines are known to undergo electrophilic substitution with 1,2-dithiolium cations; this reaction has now been extended to cover secondary and even primary aromatic amines.[37] The products are dithiolium salts of type (38; R^1, R^2 = H or alkyl).

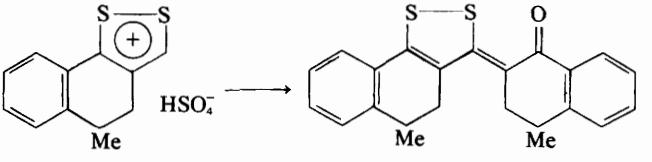


(38)

Details have been given of some previously described condensations of 3-aryl-1,2-dithiolium salts; with carbanions derived from β-keto-aldehydes, 1,2-dithiolylidene ketones are produced;[38] the carbanion from methyl benzoyldithioacetate gives rise to 6a-thiathiophthens and thiopyran derivatives.[39] The dithiolium salt (39) combines with 4-methyltetralone to give the dithiolylidene ketone (40).[40]

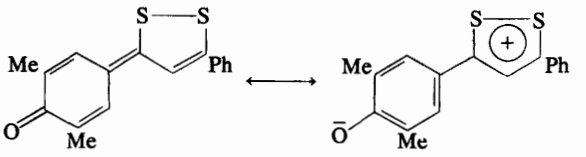
Condensations involving 3-methylthio-1,2-dithiolium salts have been used to prepare compounds (41) and (42).[41] The spectroscopic properties of the former suggest that the quinonoid form (41a) makes a more important

[37] A. Reliquet and F. Reliquet-Clesse, *Compt. rend.*, 1972, **275**, *C*, 689.
[38] J. Bignebat and H. Quiniou, *Bull. Soc. chim. France*, 1972, 4181.
[39] F. Clesse, J. P. Pradere, and H. Quiniou, *Bull. Soc. chim. France*, 1973, 586.
[40] E. Klingsberg, *J. Org. Chem.*, 1972, **37**, 3226.
[41] R. Pinel and Y. Mollier, *Bull. Soc. chim. France*, 1973, 608, 1032.

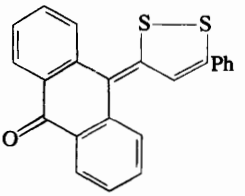


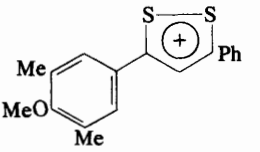
(39) (40)

contribution to the hybrid than does the dithiolium phenolate form (41b); methylation gives the salt (43), which is easily demethylated by treatment with triethylamine. In the crowded structure (42), the dithiole ring is probably twisted out of the plane of the anthrone ring.



(41a) (41b)

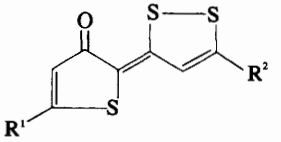


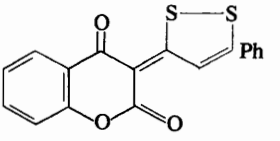


(42) (43)

Other synthetic applications of 3-methylthio-1,2-dithiolium salts are illustrated by the preparation of dithiolylidene ketones of types (44)[42] and (45).[43] The previously reported route to dithiolylidene ketones,[14] from 3-phenacylthio-1,2-dithiolium salts, has been described in detail.[44]

The reactivity of methyl or methylene groups attached at the 3- and 5-positions of the 1,2-dithiolium nucleus has been exploited in various ways. Thus, the known condensation with dimethylthioformamide has been

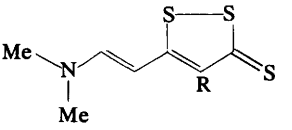




(44) (45)

[42] C. Lemarie-Retour, M. Stavaux, and N. Lozac'h, *Bull. Soc. chim. France*, 1973, 1659.
[43] F. M. Dean, J. Goodchild, and A. W. Hill, *J.C.S. Perkin I*, 1973, 1022.
[44] G. Caillaud and Y. Mollier, *Bull. Soc. chim. France*, 1972, 147.

employed to synthesize compounds of type (27); these products lose the *S*-methyl group when heated in pyridine, giving *trans*-5-dimethylaminovinyl-1,2-dithiole-3-thiones (46).[24] Nitrosation of dithiolium salts (47) produces 1-oxa-6,6a-dithia-2-azapentalenes (48) in excellent yield,[45] and similar reactions with diazonium salts give rise to 1,6a-dithia-5,6-diazapentalenes (49).[46] These products are discussed with related substances in Chapter 9, Section 8.



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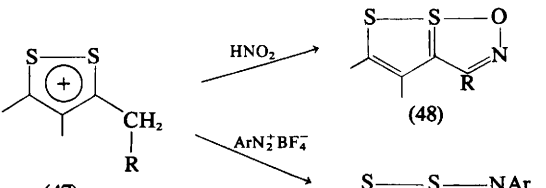
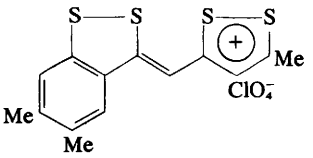
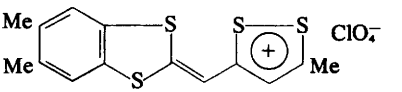


(47) (48) (49)

Condensation of 3,5-dimethyl-1,2-dithiolium perchlorate with methylthio-1,2- or -1,3-dithiolium cations has also been reported and leads to the intensely coloured methine salts (50) and (51).[47]



(50)

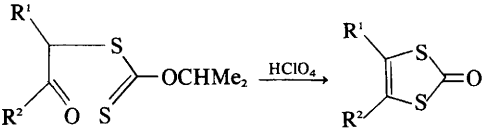


(51)

3 1,3-Dithioles and Related Compounds

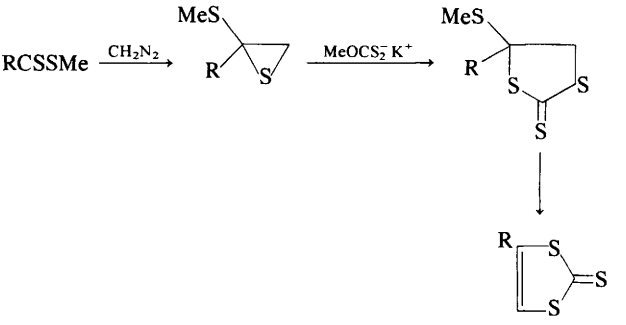
A useful general method has been described for the synthesis of 1,3-dithiole-2-ones from easily available starting materials;[48] xanthate esters of type (52) undergo cyclization with loss of the isopropyl group when treated

[45] J. G. Dingwall, A. R. Dunn, D. H. Reid, and K. O. Wade, *J.C.S. Perkin I*, 1972, 1360.
[46] R. M. Christie, A. S. Ingram, D. H. Reid, and R. G. Webster, *J.C.S. Chem. Comm.*, 1973, 92.
[47] E. Klingsberg, *Synthesis*, 1972, 29.
[48] A. K. Bhattacharya and A. G. Hortmann, *J. Org. Chem.*, 1974, **39**, 95.



(52) (53)

with perchloric acid, giving the dithiole-ones (53) in good yield. 1,3-Dithiole-2-thiones (54) have been obtained[49] by the route shown, and 2-arylimines (56) are produced by addition of phenylacetylene to thiadiazole derivatives (55).[50]



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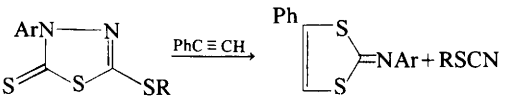
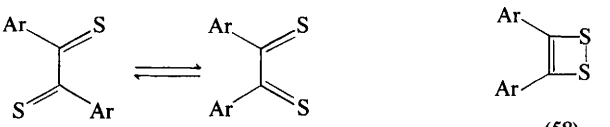


(55) (56)

Irradiation of 4,5-bis-*p*-dimethylaminophenyl-1,3-dithiole-2-one in benzene yields the dark red, stable, α-dithione (57; Ar = *p*-$Me_2NC_6H_4$), which appears to exist, in solution, partly in the cyclized form (58).[51]

The stereospecific conversion of selenadiazoles (59) into diselenafulvenes (60) by the action of bases is thought to proceed *via* a selenaketen.[52] A



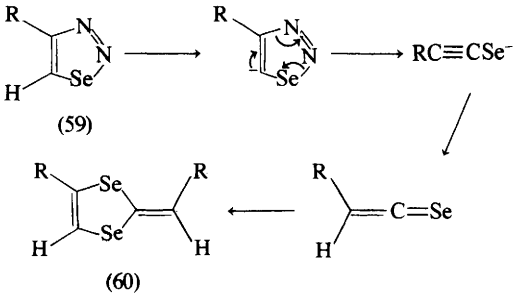
(57) (58)

[49] J. M. Beiner, D. Lecadet, D. Paquer, A. Thuillier, and J. Vialle, *Bull. Soc. chim. France*, 1973, 1979.

[50] C. Gueden and J. Vialle, *Bull. Soc. chim. France*, 1973, 270.

[51] W. Küsters and P. de Mayo, *J. Amer. Chem. Soc.*, 1973, **95**, 2383.

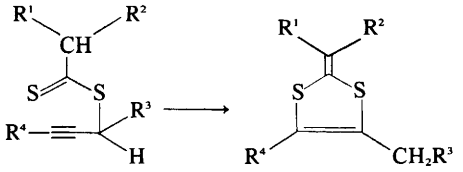
[52] I. Lalezari, A. Shafiee, and M. Yalpani, *J. Org. Chem.*, 1973, **38**, 338.



(59)

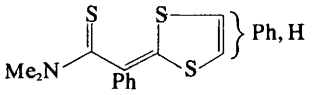
(60)

re-examination of the similar reaction with thiadiazoles shows that the initially formed dithiafulvenes have the same geometry as the selenium compounds (60).[53] Dithiafulvenes (62) are also obtained when alkynylalkanedithioates of structure (61) are heated in the presence of ethyldi-isopropylamine.[54]



(61) (62)

Isothiathiophthen-like structures (63) are produced when 3-dimethylamino-5-phenacylthio-4-phenyl-1,2-dithiolium bromide is heated with phosphorus pentasulphide in pyridine.[44]

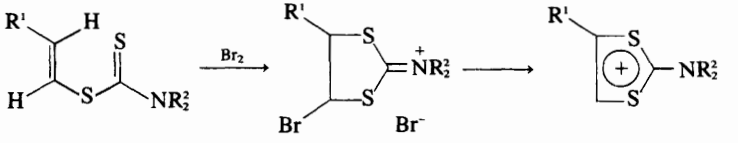


(63)

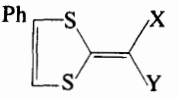
4 1,3-Dithiolium Salts

Addition of bromine to readily available intermediates of type (64) gives the cyclized salts (65), which lose hydrogen bromide when heated, producing 2-dialkylamino-1,3-dithiolium bromides (66) in good yield.[55] The piperidine derivative [66; R^1 = Ph, $R^2_2 = (CH_2)_5$] condenses readily with active methylene groups, giving rise to a range of products of general structure (67; X, Y = CN,CO_2Et,COMe *etc.*).[56]

[53] A. Shafiee and I. Lalezari, *J. Heterocyclic Chem.*, 1973, **10**, 11.
[54] J. Meijer, P. Vermeer, H. J. T. Bos, and L. Brandsma, *Rec. Trav. chim.*, 1973, **92**, 1067.
[55] K. Hiratani, H. Shiono, and M. Okawara, *Chem. Letters* 1973, 867.
[56] K. Hirai, T. Ishiba, and H. Sugimoto, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1711.

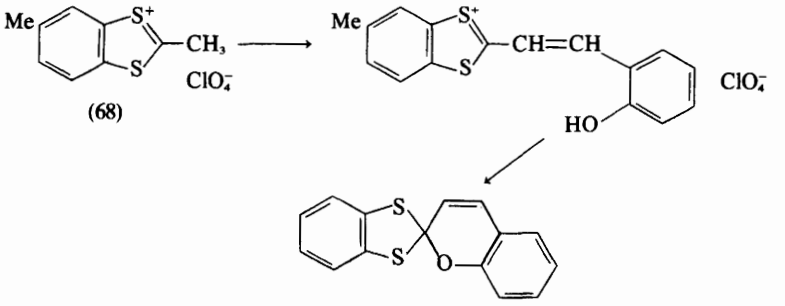


(64) (65) (66)



(67)

o-Hydroxybenzaldehydes condense at the 2-methyl group in the benzo-1,3-dithiolium perchlorate (68); the products cyclize in the presence of bases to spiropyran derivatives (69).[57]



(68) (69)

1,3-Dithiolium systems are included in a theoretical (LCAO–MO) treatment of sulphur-containing methine dyestuffs; the observed and calculated electronic absorption spectra are compared.[58]

5 1,3-Dithiole Carbene Reactions and Bi-1,3-dithioles

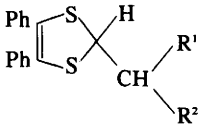
The reactions of 4,5-diphenyl-2-piperidino-1,3-dithiole with a wide range of compounds have been described.[59] Amongst the products, which arise from insertion reactions of the carbenoid species (70; R = Ph), are, for example, (71; $R^1 = R^2 = COMe$), (71; $R^1 = COMe$, $R^2 = CO_2Et$), (71; $R^1 = Et$, $R^2 = CHO$), (72; R = COPh), and (72; $R = CH_2COCH{:}CHPh$). The product obtained with 1-methylbenzothiazolium methosulphate is the electron-rich

[57] L. E. Nivorozhkin, N. S. Loseva, and V. I. Minkin, *Khim. geterotsikl. Soedinenii*, 1972, 318 (*Chem. Abs.*, 1972, **77**, 61 907).

[58] J. Fabian and H. Hartmann, *Tetrahedron*, 1973, **29**, 2597; J. Fabian, H. Hartmann, and K. Fabian, *ibid.*, p. 2609.

[59] K. M. Pazdro and W. Polaczkowa, *Roczniki Chem.*, 1971, **45**, 1487; 1972, **46**, 889.

(70)



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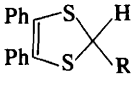
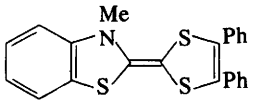


(72)

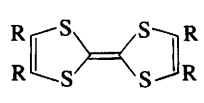
olefin (73),[60] which, when heated with sulphur in pyridine, gives 4,5-diphenyl-1,3-dithiole-2-thione quantitatively.



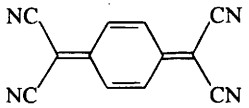
(73)

Carbene reactions are also involved when electron-deficient acetylenes are heated with carbon disulphide.[14] Full details have now been published[61] for these addition reactions, in which intermediates of type (70; R = CF_3 or CO_2Me) are postulated. Generation of benzyne, from 1-aminobenzotriazole and lead tetra-acetate, in the presence of carbon disulphide, also leads to a 1,3-dithiole carbene, and hence to a variety of complex products.[62]

One of the most interesting developments in 1,3-dithiole chemistry is the discovery[63] that the complex formed between the 2,2′-bi-1,3-dithiole (74; R = H) and tetracyanoquinodimethane (75) has remarkable electrical properties, behaving like a metal over a large temperature range. This intensely



(74)



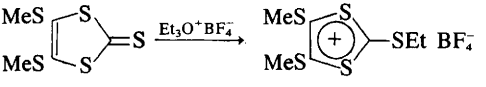
(75)

coloured product is reported to have by far the largest maximum conductivity of any known organic compound. U.v. measurements suggest that the complex consists of radical cations derived from the dithiole component, and radical anions from the quinomethane. *X*-Ray crystallographic studies indicate that the crystals contain segregated columnar stacks of cations and anions.[64]

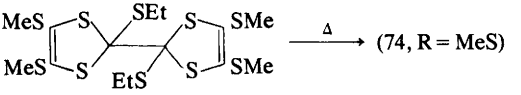
A similar highly conducting complex has been obtained from the tetramethylbidithiole (74; R = Me), itself prepared by deprotonation of

[60] D. Buza and W. Krasuski, *Roczniki Chem.*, 1972, **46**, 2377.
[61] H. D. Hartzler, *J. Amer. Chem. Soc.*, 1973, **95**, 4379.
[62] J. Nakayama, *J.C.S. Chem. Comm.*, 1974, 166.
[63] J. Ferraris, D. O. Cowan, V. Walatka, and J. H. Perlstein, *J. Amer. Chem. Soc.*, 1973, **95**, 949.
[64] T. E. Phillips, T. J. Kistenmacher, J. P. Ferraris, and D. O. Cowan, *J.C.S. Chem. Comm.*, 1973, 471.

4,5-dimethyl-1,3-dithiolium perchlorate.[65,14] Very recently, the tetrakis-methylthio-compound (74; R = MeS) has been reported.[66] The preparation, which is also applicable to the parent dithiole, apparently with advantage, involves conversion of the dithiolethione (76)[67] into the corresponding 2-ethylthio-1,3-dithiolium fluoroborate, bimolecular electrochemical reduction to (77), and a final pyrolysis stage.



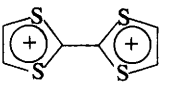
(76)



(77)

A detailed discussion has appeared[68] of reversible redox systems[14] based on the bi-dithiole (74; R = H) and the related cyclohexeno- and benzo-compounds, the last of which is best prepared by the action of ethyl phosphite on benzo-1,3-dithiole-2-thione.

The 2,2'-bi-1,3-dithiolium cation (78) has been combined with a complex chelated nickel anion to give a highly conducting salt, which probably contains the radical cation (79).[69]



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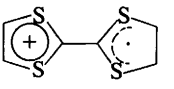


(79)

[65] J. P. Ferraris, T. O. Poehler, A. N. Bloch, and D. O. Cowan, *Tetrahedron Letters*, 1973, 2553.
[66] P. R. Moses and J. Q. Chambers, *J. Amer. Chem. Soc.*, 1974, **96**, 945.
[67] S. Wawzonek and S. M. Heilmann, *J. Org. Chem.*, 1974, **39**, 511.
[68] S. Hünig, G. Kiesslich, H. Quast, and D. Schentzow, *Annalen*, 1973, 310.
[69] F. Wudl, C. H. Ho, and A. Nagel, *J.C.S. Chem. Comm.*, 1973, 923.

11
Thiopyrans and Related Compounds

BY R. J. S. BEER

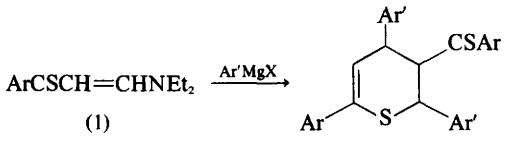
1 Introduction

As in Volume 2, monocyclic thiopyran derivatives (Sections 2—6) have been separated from benzothiopyrans (Sections 7—10). Some aspects of the chemistry of thiopyran 1,1-dioxides are discussed in Section 5. Compounds in which the thiopyran ring is fused to other heterocyclic systems appear in Section 11.

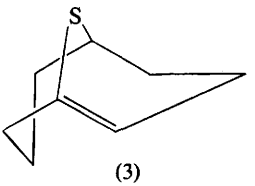
It has not been possible to include the many references to thiopyrans in the patent literature.

2 Dihydrothiopyrans

Δ^2-Dihydrothiopyrans (2) are produced by the action of Grignard reagents on diethylaminovinylthiones (1).[1] The spectroscopic properties of the bicyclic compound (3) are not those of a typical vinyl sulphide; the structure of its adduct with 1,3-diphenylisobenzofuran has been discussed.[2] A new preparation of the diketone (4)[3] has appeared.[4]



(1) (2)



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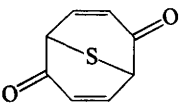
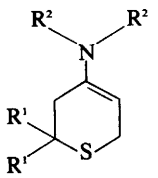


(4)

[1] J.-P. Pradère, G. Bouet, and H. Quiniou, *Tetrahedron Letters*, 1972, 3471.
[2] C. B. Quin and J. R. Wiseman, *J. Amer. Chem. Soc.*, 1973, **95**, 6120; C. B. Quin, J. R. Wiseman, and J. C. Calabrese, *ibid.*, p. 6121.
[3] See 'Organic Compounds of Sulphur, Selenium, and Tellurium' ed. D. H. Reid (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 2.
[4] D. D. MacNicol, P. H. McCabe, and R. A. Raphael, *Synth. Comm.*, 1972, **2**, 185.

The 4-pyrrolidino-Δ^3-dihydropyran [5; R^1 = Me, $R^2_2 = (CH_2)_4$] reacts normally with methyl acrylate,[5] and the related enamine [5; R^1 = H, $R^2_2 = (CH_2)_5$] adds dimethyl acetylenedicarboxylate to give two isomeric 3,8-dihydro-2*H*-thiocins, presumably *via* the intermediate (6).[6] 4-Methoxy-Δ^3-dihydrothiopyran has been suggested[7] as a reagent for the protection of alcohol groups without introduction of a new chiral centre.



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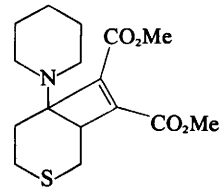
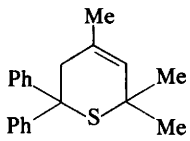


(6)

The heavily substituted Δ^3-dihydrothiopyran (7) results from Diels–Alder addition of thiobenzophenone and 1,1,3-trimethyl-1,3-butadiene, and related spiro-compounds have been obtained from cyclic thioketones.[8] The equilibria between tautomers (8; R^1 = Me, Et, *etc.*) and (9) have been studied;[9] under acidic conditions, form (8) is always the major component.



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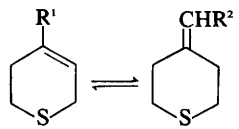
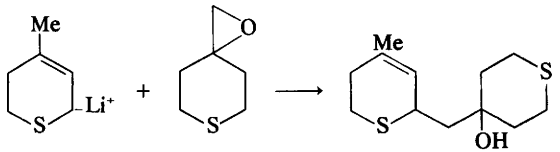


(8) (9)

Ingenious use has been made of the lithium derivative (10) in the preparation of intermediates for the synthesis of *Cecropia* juvenile hormone; a typical reaction is that with the epoxide (11) to give the alcohol (12), from which, after dehydration, another reactive carbanion can be

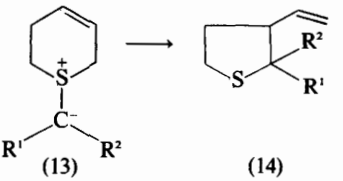


(10) (11) (12)

[5] S. A. Vartanyan and E. A. Abgaryan, *Armyan. Khim. Zhur.*, 1972, **25**, 609 (*Chem. Abs.*, 1973, **78**, 84 186).
[6] D. N. Reinhoudt and C. G. Kouwenhoven, *Tetrahedron Letters*, 1973, 3751.
[7] J. H. van Boom, P. van Deursen, and J. Meeuwse, *J.C.S. Chem. Comm.*, 1972, 766.
[8] H. Gotthardt, *Chem. Ber.*, 1972, **105**, 2008.
[9] R. Borsdorf, H. Remane, E. Kleinpeter, and M. Gallus, *Z. Chem.*, 1973, **13**, 220.

generated.[10] Desulphurization of appropriate compounds of this general type produces the required long carbon chain, with branching ethyl groups.

Ylides of type (13) undergo rearrangements to thiophan derivatives (14).

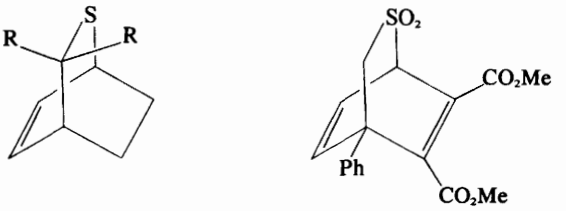


(13) (14)

When both groups (R^1 and R^2) attached to the negative centre are electron-attracting, the ylide is stable and requires vigorous conditions for rearrangement,[11] but when R^1 is hydrogen, rearrangement occurs stereoselectively at 0 °C.[12] The possibility of generating a transient ylide of type (15) has been investigated. Pyrolysis of sodium salts of tetrahydrothiopyran-4-one tosylhydrazones gives Δ^3-dihydrothiopyrans, for example the bicyclic compound (16).[13]

(15) (16)

Thiophosgene reacts with cyclohexa-1,3-diene to yield the adduct (17; R = Cl), which can be hydrolysed to the ketone or reduced with lithium aluminium hydride to the bicyclo[2,2,2]oct-5-ene.[14] The related sulphone (18), made by addition of dimethyl acetylenedicarboxylate to 3-phenyl-2*H*-thiopyran 1,1-dioxide, undergoes a reverse Diels–Alder reaction at 220 °C,



(17) (18)

[10] K. Kondo, A. Negishi, K. Matsui, and D. Tunemoto, *J.C.S. Chem. Comm.*, 1972, 1311; P. L. Stotter and R. E. Hornish, *J. Amer. Chem. Soc.*, 1973, **95**, 4444.

[11] W. Ando, S. Kondo, K. Nakayama, K. Ichibori, H. Kohoda, H. Yamato, I. Imai, S. Nakaido, and T. Migita, *J. Amer. Chem. Soc.*, 1972, **94**, 3870.

[12] S. Mageswaran, W. D. Ollis, and I. O. Sutherland, *J.C.S. Chem. Comm.*, 1973, 656.

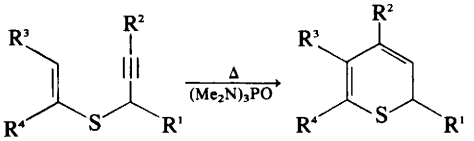
[13] P. Y. Johnson, E. Koza, and R. E. Kohrman, *J. Org. Chem.* 1973, **38**, 2967.

[14] H. J. Reich and J. E. Trend, *J. Org. Chem.*, 1973, **38**, 2637.

generating sulphene, the formation of which may be proved by trapping with enamines, or amines.[15] The reaction of thiobenzophenone with cyclohepatriene leads to an unsaturated bicyclic structure similar to compound (17).[16] Other complex dihydrothiopyrans are obtained by reaction of hexafluorothioacetone dimer with styrene,[17] and by addition of sulphines to conjugated dienes.[18]

3 2*H*-Thiopyrans and Related Compounds

Acetylenic vinyl sulphides of structure (19) undergo cyclization when heated in hexamethylphosphortriamide, giving 2*H*-thiopyrans (20).[19]

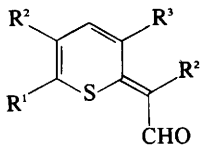


(19) (20)

Another route involves the addition of activated olefins to enaminothiones.[20] Symmetrical bis-β-formylvinyl sulphides cyclize with base to 2*H*-thiopyran derivatives of type (21).[21]

Addition of keten to β-dialkylaminovinylthiones provides a route to 4,6-diaryl- or 6-aryl-2*H*-thiopyran-2-ones,[22] whilst 5,6-diaryl-3-cyano-derivatives can be prepared from β-mercapto- or β-chloro-acroleins (22; R = SH or Cl).[23] Full details have been published of the formation of 2*H*-thiopyran-2-thiones in condensation reactions between 1,2-dithiolium salts and aroyldithioacetic esters.[24]

The structure of products of type (23), obtained in decarboxylation



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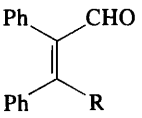

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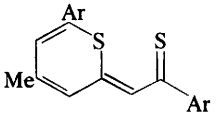


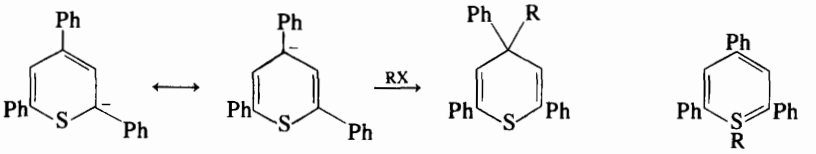
(23)

[15] J. F. King and E. G. Lewars, *J.C.S. Chem. Comm.*, 1972, 700; *Canad. J. Chem.*, 1973, **51**, 3044.
[16] Y. Ohnishi, Y. Akasaki, and A. Ohno, *Bull. Chem. Soc. Japan*, 1973, **46**, 3307.
[17] T. Kitazume and N. Ishikawa, *Chem. Letters*, 1973, 267.
[18] B. Zwanenburg, L. Thijs, J. B. Broens, and J. Strating, *Rec. Trav. chim.*, 1972, **91**, 443.
[19] D. Schuijl-Laros, P. J. W. Schuijl, and L. Brandsma, *Rec. Trav. chim.*, 1972, **91**, 785; R. A. van der Welle and L. Brandsma, *ibid.*, 1973, **92**, 667.
[20] J.-P. Pradère and H. Quiniou, *Compt. rend.*, 1972, **275**, *C*, 677.
[21] M. Weissenfels and M. Pulst, *Tetrahedron*, 1972, **28**, 5197.
[22] J.-C. Meslin and H. Quiniou, *Bull. Soc. chim. France*, 1972, 2517.
[23] M. Weissenfels and S. Illing, *Z. Chem.*, 1973, **13**, 130.
[24] F. Clesse, J.-P. Pradère, and H. Quiniou, *Bull. Soc. chim. France*, 1973, 586.

reactions of 1,2-dithiolylidenemalonic acids, has been re-examined,[25] as has the mechanism of formation of annelated thiopyranthiones in condensations of acenaphthenones with 1,2-dithiole-3-thiones.[26] Other reports[27,28] mention 2*H*-thiopyran derivatives incidentally.

4 4*H*-Thiopyran Derivatives

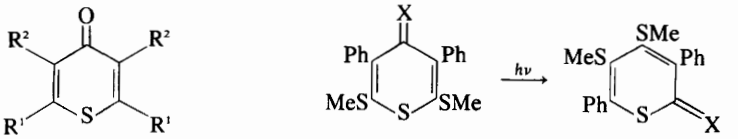
The same, relatively stable, carbanionic species (24) is produced by the action of bases on 2,4,6-triphenyl-2*H*- and -4*H*-thiopyrans;[29] methylation and acetylation of the anion lead to 4,4-disubstituted 4*H*-thiopyrans (25). Products with this substitution pattern (25; R = *p*-$Me_2NC_6H_4$) are also obtained, with the similar 2*H*-thiopyran derivatives, from the supposed thiabenzene (26; R = *p*-$Me_2NC_6H_4$).[30]



(24) (25) (26)

A direct method for the preparation of keten mercaptals, when applied to dibenzyl ketone, is reported to give the 4*H*-thiopyran-4-one (27; R^1 = MeS, R^2 = Ph).[31] 2,6-Diphenyl-4*H*-thiopyran-4-one, under Reformatskii conditions, yields a 4-methoxycarbonylmethyl-thiopyrylium salt.[32]

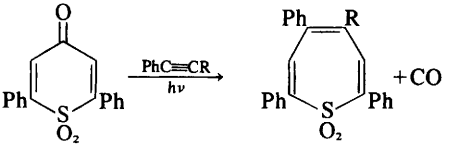
The photochemistry of 4*H*-thiopyran derivatives[3] has been explored further, by an examination of the behaviour of compound (28; X = Ph_2C), which on irradiation changes to the 2*H*-derivative (29; X = Ph_2C); photooxidation of this product yields benzophenone and the 2*H*-thiopyran-2-one (29; X = O).[33] Full details have been published of earlier work[3] on (28; X = O) and related structures.[34]



(27) (28) (29)

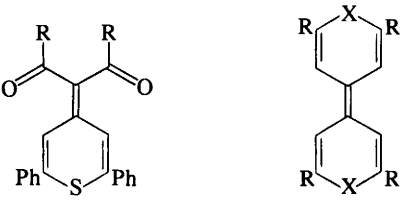
[25] M. Bard and G. Duguay, *Compt. rend.*, 1972, **275**, *C*, 905.
[26] K. S. N'Guyen, R. Pinel, and Y. Mollier, *Bull. Soc. chim. France*, 1973, 3334.
[27] C. Gueden and J. Vialle, *Bull. Soc. chim. France*, 1973, 270.
[28] P. J. Garratt, A. B. Holmes, F. Sondheimer, and K. P. C. Vollhardt, *J.C.S. Perkin I*, 1973, 2253.
[29] R. R. Schmidt and V. Burkert, *Tetrahedron Letters*, 1973, 4355.
[30] C. C. Price and H. Pirelahi, *J. Org. Chem.*, 1972, **37**, 1718.
[31] I. Shahak and Y. Sasson, *Tetrahedron Letters*, 1973, 4207.
[32] S. V. Krivun, A. I. Buryak, and S. N. Baranov, *Khim. geterotsikl. Soedinenii*, 1973, 1317 (*Chem. Abs.*, 1974, **80**, 47 782).
[33] N. Ishibe and M. Tamura, *J.C.S. Chem. Comm.*, 1974, 48.
[34] N. Ishibe, M. Odani, and R. Tanuma, *J.C.S. Perkin I*, 1972, 1203; N. Ishibe, M. Sunami, and M. Odani, *Tetrahedron*, 1973, **29**, 2005.

Irradiation of mixtures of 2,6-diphenyl-4*H*-thiopyran-4-one 1,1-dioxide (30) and arylacetylenes brings about addition with loss of carbon monoxide; the products are thiepin 1,1-dioxides (31; R = H, Me, or Ph).[35] Various



(30) (31)

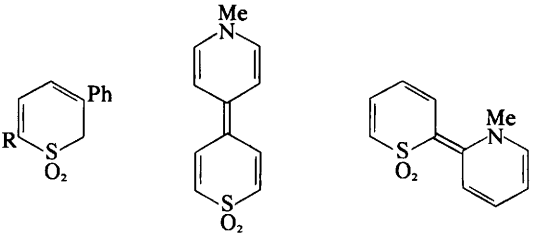
structures incorporating the generalized system (32) have been reported, and the redox properties of compounds of types (33; X = S, O, or NR) have been discussed.[36]



(32) (33)

5 Thiopyran 1,1-Dioxides

Sulphones of the thiopyran series continue to receive attention. The acidities of compounds (34; R = H) and (34; R = Me) have been measured; the former is a stronger acid than the acyclic disulphone $MeSO_2CH_2SO_2Me$, but a weaker acid than the keto-sulphone $MeCOCH_2SO_2Me$.[37] Several conjugated systems of types (35) and (36) have been prepared.[38] The electronic situation in the thiopyran rings of these compounds should



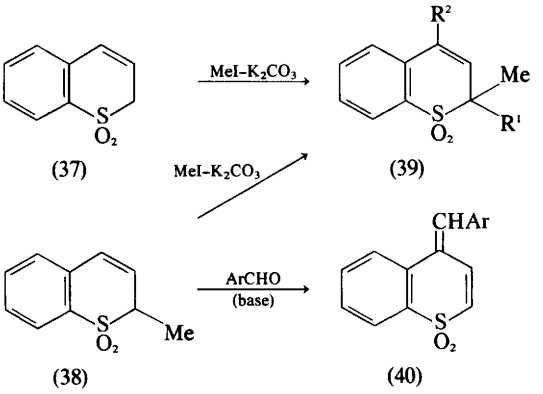
(34) (35) (36)

[35] N. Ishibe, K. Hashimoto, and M. Sunami, *J. Org. Chem.*, 1974, **39**, 103.
[36] H. Mönnighoff and G. Seitz, *Arch. Pharm.*, 1972, **305**, 259; *ibid.*, 1973, **306**, 794; S. Hünig, B. J. Garner, G. Ruider, and W. Schenk, *Annalen*, 1973, 1036.
[37] G. Gaviraghi and G. Pagani, *J.C.S. Perkin II*, 1973, 50.
[38] G. Pagani, *J.C.S. Perkin II*, 1973, 1184.

resemble that of thiopyran dioxide anions,[3] and spectral similarities are discussed in detail. Protonation and methylation studies indicate the nucleophilic character of the sulphone rings at the 2- and 6- positions.

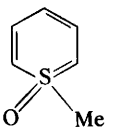
X-Ray crystallographic data have been reported for two compounds of this series,[39] one of each type. In both examples, the thiopyran ring is not planar but is boat-shaped; the bond lengths indicate appreciable contributions from the dipolar structures, and suggest that the sulphone groups are involved in the π-electron delocalization.

Substitution and condensation reactions of a series of benzo- and dibenzo-thiopyran dioxides have been studied.[40] Methylation of compounds (37) and (38) leads to the same mixture of products, (39; R^1 = Me, R^2 = H), (39; R^1 = R^2 = Me), and (39; R^1 = H, R^2 = Me). Condensation of sulphone (38) with aromatic aldehydes gives 4-arylidene derivatives (40).



A different aspect of thiopyran dioxide chemistry is reflected in the Diels–Alder addition which leads to compound (18) (see p. 525).

Although not a sulphone, the (formally) sexivalent sulphur compound (41) is included here; a new synthesis for 'thiabenzene oxides' of this type has been reported.[41]



(41)

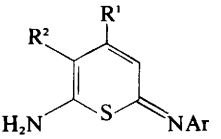
[39] G. D. Andreetti, G. Bocelli, and P. Sgarabotto, *J.C.S. Perkin II*, 1973, 1189.
[40] S. Bradamante and G. Pagani, *J.C.S. Perkin I*, 1973, 163.
[41] Y. Tamura, T. Miyamoto, H. Taniguchi, K. Sumoto, and M. Ikeda, *Tetrahedron Letters*, 1973, 1729.

6 Thiopyrylium Salts

Many further examples have been given[42] of the preparation of mixtures of thiopyrylium salts and the corresponding tetrahydrothiopyrans, by the action of hydrogen sulphide and various acids on 1,5-diketones.[3] Selenopyrylium salts have also been prepared by this method.[43]

2-Amino-6-methylthio-thiopyrylium salts, obtained by methylation of the related 2*H*-thiopyran-2-thiones, react with aromatic amines to give 2-arylimines (42).[44] 2-Amino-6-arylthiopyrylium salts have also been prepared, from β-mercaptovinylacrylonitriles, by an extension of a reaction previously used for the synthesis of 2-aminopyrylium and pyridinium salts.[45]

Several theoretical treatments have appeared. Non-empirical calculations suggest that the 3*d* orbitals are used only to a trivial extent,[46] but, in another study,[47] the conclusion is reached that involvement of the *d*-orbitals may be important, and that contributions of forms of type (43) to the hybrid



(42)

(43)

structure could help to explain some interesting differences between the n.m.r. spectra of thiopyrylium cations and those of the oxygen and nitrogen analogues; the signals for β- and γ-protons in the thiopyrylium cation are virtually superimposed, whereas in the pyrylium and pyridinium salts, these signals are well separated.

Methine salts, based on the thiopyran system, are included in an extensive theoretical and spectroscopic investigation of sulphur-containing dyestuffs.[48]

Ring-opening reactions occur when thiopyrylium fluoroborate is treated

[42] V. G. Kharchenko, M. E. Stankevich, N. M. Krupanets, A. R. Yakoreva, V. I. Kleimenova, and S. K. Klimenko, *Zhur. org. Khim.*, 1972, **8**, 193; V. G. Kharchenko, N. M. Krupanets, S. K. Klimenko, and M. N. Berezhnaya, *ibid.*, p. 390; V. G. Kharchenko, N. M. Yartseva, and M. N. Berezhnaya, *ibid.*, p. 2619; V. G. Kharchenko and A. A. Rassudova, *ibid.*, 1973, **9**, 2177; V. G. Kharchenko, S. K. Klimenko, T. V. Stolbova, and N. S. Smirnova, *ibid.*, p. 2434; V. G. Kharchenko, M. E. Stankevich, A. R. Yakoreva, A. A. Rassudova, and N. M. Yartseva, *Khim. geterotsikl. Soedinenii*, 1972, 916; V. G. Kharchenko, T. I. Krupina, S. K. Klimenko, and A. A. Rassudova, *ibid.*, p. 1196; V. G. Kharchenko and A. A. Rassudova, *ibid.*, 1973, 196 (*Chem. Abs.*, 1972, **76**, 113 023, 140 419; **77**, 151 822; 1973, **78**, 4 081, 84 201, 136 006; 1974, **80**, 36 959, 47 789).

[43] M. A. Kudinova, S. V. Krivun, and A. I. Tolmachev, *Khim. geterotsikl. Soedinenii*, 1973, 857 (*Chem. Abs.* 1973, **79**, 105 056).

[44] K. Gewald, M. Buchwalder, and M. Penkert, *J. prakt. Chem.*, 1973, **315**, 679.

[45] J. Liebscher and H. Hartmann, *Z. Chem.*, 1973, **13**, 342.

[46] M. H. Palmer and R. H. Findlay, *Tetrahedron Letters*, 1972, 4165.

[47] S. Yoneda, T. Sugimoto, and Z. Yoshida, *Tetrahedron*, 1973, **29**, 2009.

[48] J. Fabian and H. Hartmann, *Tetrahedron*, 1973, **29**, 2597; J. Fabian, H. Hartmann, and K. Fabian, *ibid.*, p. 2609.

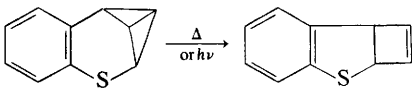
with primary amines; with the 2,4,6-triphenyl cation, no reaction is observed with aromatic amines, but methylamine converts it into the pyridinium salts.[49] Secondary amines are reported to convert 4-chloro-2,6-diphenylthiopyrylium salts to the 4-dialkylamino-compounds.[50]

A further example[3] has been reported[51] of the formation of a benzene derivative (44) from the 2,4,6-triphenylthiopyrylium cation and a reactive carbanion, in this case dimethyloxosulphonium methylide.

(44)

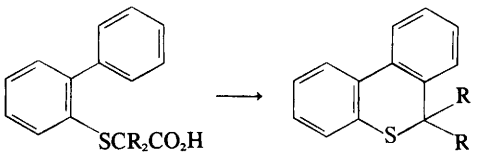
7 Thiochromans and Thiochromenes

Dehydrogenation of thiochroman is accompanied by rearrangement to 2-methylbenzo[*b*]thiophen.[52] The thiochroman derivative (45) also rearranges, thermally and photochemically, to a benzothiophen (46).[53] Diben-



(45) (46)

zothiopyrans (48; R = H or Me) are produced by persulphate oxidation of thioglycollic acids of type (47; R = H or Me).[54]



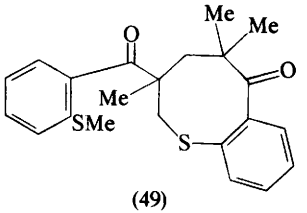
(47) (48)

The intramolecular rotation of the aldehyde group of benzaldehyde has been studied in the clathrate compound formed with 4-*p*-hydroxyphenyl-2,2,4-trimethylthiochroman.[55] This thiochroman can also be used to store

[49] Z. Yoshida, H. Sugimoto, T. Sugimoto, and S. Yoneda, *J. Org. Chem.*, 1973, **38**, 3990.
[50] S. V. Krivun, A. I. Buryak, and S. N. Baranov, *Dopovidi Akad. Nauk Ukrain., R.S.R., Ser. B*, 1972, **34**, 931 (*Chem. Abs.*, 1973, **78**, 159 364).
[51] Y. Tamura, K. Sumoto, and M. Ikeda, *Chem. and Ind.*, 1972, 498.
[52] E. A. Viktorova, A. A. Freger, A. V. Egorov, and L. M. Petrova, *Khim. geterotsikl. Soedinenii*, 1973, 141 (*Chem. Abs.*, 1973, **78**, 111 067).
[53] I. Murata, T. Tatsuoka, and Y. Sugihara, *Tetrahedron Letters*, 1973, 4261; 1974, 199.
[54] P. S. Dewar, A. R. Forrester, and R. H. Thompson, *J.C.S. Perkin I*, 1972, 2857.
[55] D. D. MacNicol, *J.C.S. Chem. Comm.*, 1973, 621.

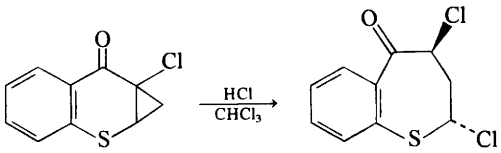
dimethylmercury.[56] In both examples, the ratio of host to guest is 6:1, corresponding to one guest molecule in each cavity.

A previous report that 3-bromothiochroman-4-one is reduced by sodium borohydride to the *cis*-3-bromo-4-hydroxy-compound has been confirmed.[57] Attempts to methylate 3-methylthiochroman-4-one with methyl iodide–potassium t-butoxide failed to produce the expected 3,3-dimethyl derivative; instead, the much more complex product (49) is formed.[58] Methylation with other bases present, however, does proceed normally.



(49)

The cyclopropanothiochromanone (50) undergoes stereoselective ring opening when treated with hydrogen chloride in chloroform.[59] 3-Cyanothiochroman-4-one has been synthesized conventionally from methyl



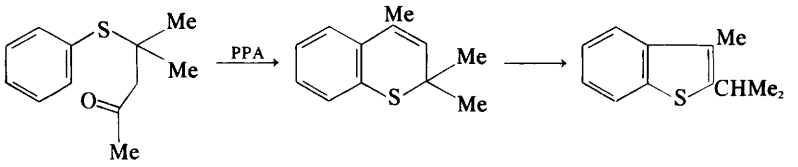
(50)

thiosalicylate,[60] and 3-aryl derivatives have been prepared by treating thiochromanone with diazonium salts.[61]

Cyclodehydration of the ketone (51) with polyphosphoric acid gives only a small amount of the Δ^3-thiochromene (52). The major volatile product is the benzo[*b*]thiophen (53), probably formed from the thiochromene *via* a thiiranium intermediate.[62] Irradiation of Δ^3-selenochromene at low temperature is reported to give the selenoketone (54). The reaction is reversed thermally.[63]

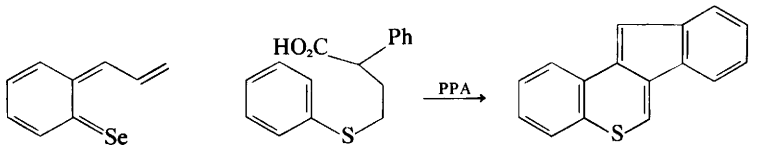
Attempted cyclodehydration of the acid (55) does not give the expected

[56] R. J. Cross, J. J. McKendrick, and D. D. MacNicol, *Nature*, 1973, **245**, 146.
[57] A. Chatterjee and B. Bandyopadhyay, *Indian J. Chem.*, 1973, **11**, 446.
[58] I. W. J. Still, M. S. Chauhan, and M. T. Thomas, *Canad. J. Chem.*, 1973, **51**, 839.
[59] V. J. Traynelis, J. C. Sih, Y. Yoshikawa, R. F. Love, and D. M. Borgnaes, *J. Org. Chem.*, 1973, **38**, 2623; V. J. Traynelis, J. C. Sih, and D. M. Borgnaes, *ibid.*, p. 2629.
[60] A. P. Momsenko, *Zhur. org. Khim.*, 1973, **9**, 775 (*Chem. Abs.*, 1973, **79**, 31 797).
[61] A. K. Panigrahi and M. K. Rout, *J. Indian Chem. Soc.*, 1972, **49**, 23.
[62] D. D. MacNicol and J. J. McKendrick, *Tetrahedron Letters*, 1973, 2593.
[63] B. S. Lukjanow, M. I. Knjazschanski, J. W. Rewinski, L. E. Niworozschkin, and W. I. Minkin, *Tetrahedron Letters*, 1973, 2007.



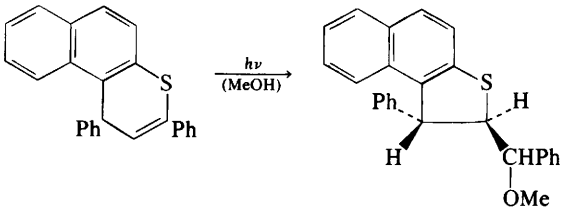
(51) (52) (53)

thiaheptane derivative. On the basis of spectroscopic evidence, the orange product is assigned structure (56).[64]



(54) (55) (56)

Pummerer reactions with thiochroman 1-oxides normally yield Δ^2-chromenes,[65,66] except when the 2-position is blocked.[67] The thiochromene (57), produced in this way, undergoes the photochemical rearrangement shown.[66] A different stereoisomeric form of compound (58) is produced

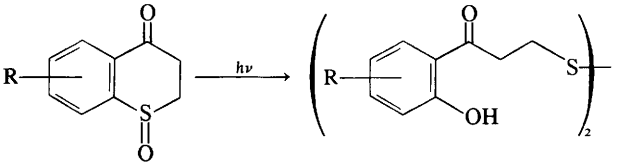


(57) (58)

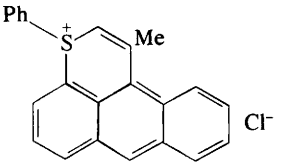
from the original sulphoxide by irradiation, first in benzene to yield a benzo[*b*]thiophen, and then in benzene–methanol.[68] Irradiation of thiochromanone 1-oxides (59) yields disulphides (60).[69]

Complex indigoid dyestuffs based on *peri*-fused naphthothiopyran-3-ones have been described,[70] and the thiochromene derivative (61) is mentioned in an interesting paper on degenerate interconversions of sulphonium salts.[71]

[64] F. Kvis, E. Svátek, R. Zahradnik, and M. Protiva, *Coll. Czech. Chem. Comm.*, 1972, **37**, 3808.
[65] E. N. Karaulova, G. D. Gal'pern, V. D. Nikitina, I. V. Cherepanova, and L. R. Barykina, *Neftekhimiya*, 1972, **12**, 104 (*Chem. Abs.*, 1972, **76**, 153 506).
[66] A. G. Schultz and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 4791.
[67] D. O. Spry, *J.C.S. Chem. Comm.*, 1973, 259.
[68] A. G. Schultz and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 4787.
[69] I. W. J. Still, M. S. Chauhan, and M. T. Thomas, *Tetrahedron Letters*, 1973, 1311.
[70] M. A. Mostoslavskii, S. I. Saenko, and V. L. Belyaev, *Khim. geterotsikl. Soedinenii*, 1973, 1034 (*Chem. Abs.*, 1974, **80**, 28 436).
[71] R. J. Basalay and J. C. Martin, *J. Amer. Chem. Soc.*, 1973, **95**, 2565, 2572.



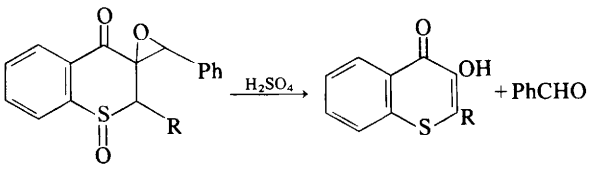
(59) (60)



(61)

8 Thiochromones and Thiocoumarins

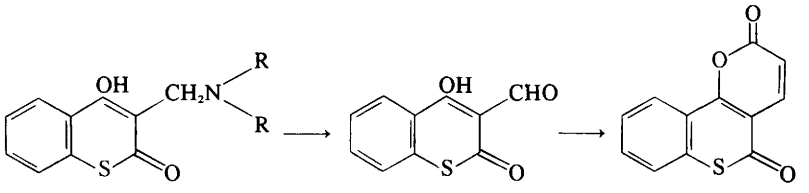
Some thioflavones[72] and isothioflavones[73] have been reported. α-Epoxyketones of type (62; R = H or Me) yield 3-hydroxy-Δ^2-thiochromen-4-ones (63) on treatment with sulphuric acid.[74]



(62) (63)

4-Methylthiocoumarin has been prepared by treating thiophenol with diketen followed by cyclization of the resulting thiol ester with polyphosphoric acid.[75] 4-Hydroxythiocoumarins undergo Michael additions with αβ-unsaturated ketones,[76] and also form Mannich bases (64), from which the pyranothiocoumarin derivative (65) has been prepared.[77]

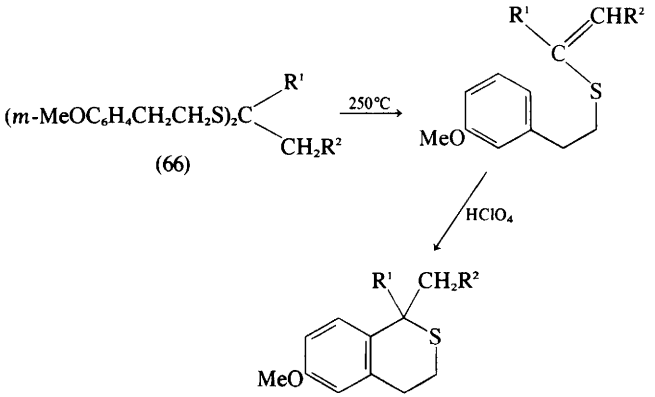
[72] M. von Strandtmann, S. Klutchko, M. P. Cohen, and J. Shavel, *J. Heterocyclic Chem.*, 1972, **9**, 171.
[73] G. F. Katekar and R. M. Thomson, *Austral. J. Chem.*, 1972, **25**, 647.
[74] H. Hofmann, H. Westernacher, and H.-J. Haberstroh, *Chem. Ber.*, 1973, **106**, 349.
[75] K. Konishi, H. Umemoto, M. Yamamoto, and T. Kitao, *Nippon Kagaku Kaishi*, 1973, 118 (*Chem. Abs.*, 1973, **78**, 84 200).
[76] P. S. Jamkhandi and S. Rajagopal, *Indian J. Chem.*, 1972, **10**, 1114.
[77] P. S. Jamkhandi and S. Rajagopal, *Indian J. Chem.*, 1973, **11**, 708.



(64) (65)

9 Thioisochromans and Related Compounds

A new route to thioisochromans has been described.[78] Thioacetals of type (66) eliminate one thiol residue when heated, and the products cyclize quantitatively on treatment with perchloric acid at room temperature.

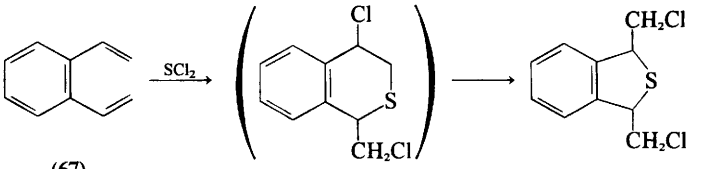


(66)

Insertion reactions of diazomethane with 1-chlorothioisochroman lead to 2-chloro-1,2,4,5-tetrahydro-3-benzothiepin and 1-chloromethylthioisochroman.[79] Other thioisochroman derivatives have been prepared by condensation reactions with the carbanion derived from 1-cyanothioisochroman.[80] A 1,4-disubstituted thioisochroman is postulated as the unstable intermediate involved in the conversion of *o*-divinylbenzene (67) into the benzo[*c*]thiophen derivative (68).[81]

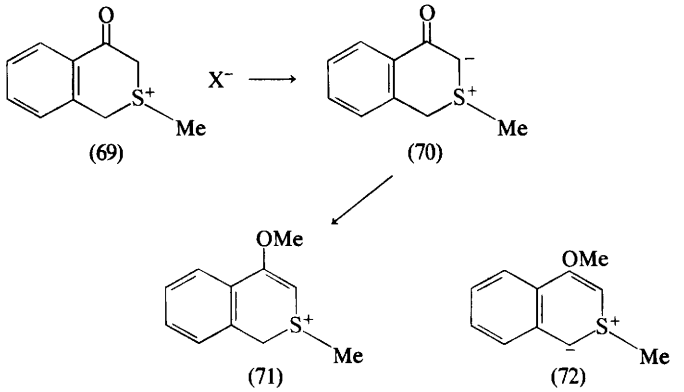
Beckmann reactions of the oxime of thioisochroman-4-one proceed normally, except with sulphuryl chloride, when ring-opening occurs, and a benzonitrile derivative is obtained.[82] The sulphonium salt (69) forms the stabilized ylide (70) on treatment with base. Methylation of the ylide occurs

[78] E. R. de Waard, H. R. Reus, and H. O. Huisman, *Tetrahedron Letters*, 1973, 4315.
[79] H. Böhme and F. Ziegler, *Chem. Ber.*, 1974, **107**, 605.
[80] H. Böhme and F. Ziegler, *Synthesis*, 1973, 297.
[81] T. J. Barton and R. C. Kippenhan, *J. Org. Chem.*, 1972, **37**, 4194.
[82] R. K. Hill and D. A. Cullison, *J. Amer. Chem. Soc.*, 1973, **95**, 2923.



(67) (68)

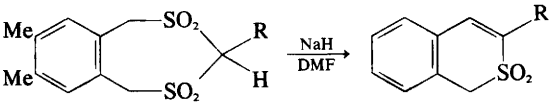
on oxygen to give compound (71), but attempts to convert this into the interesting structure (72) were inconclusive.[83]



(69) (70) (71) (72)

Stereoselective syntheses of *cis*-1,4- and *cis*-1,3-dimethylthioisochromans have been achieved by hydrogenation of appropriately substituted Δ^3-thioisochromenes.[84] The stereochemistry of the products and of the related sulphones, which exist in boat forms, is discussed in detail.

Disulphones of type (73) undergo an unusual reaction when treated with

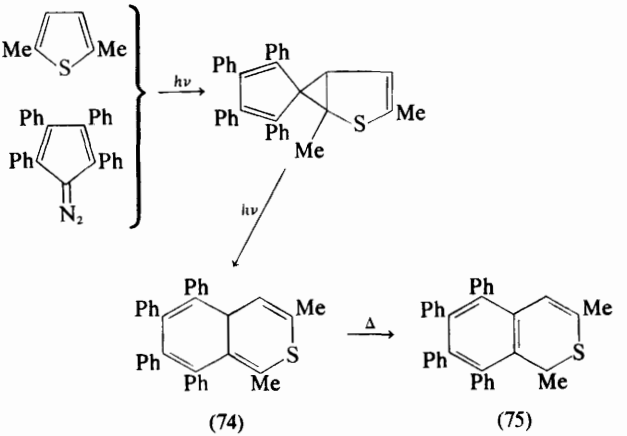


(73)

sodium hydride in DMF,[85] and the non-aromatic 4*H*-thiopyran (74) is involved in a sequence of reactions leading finally to the Δ^3-thioisochromene (75).[86]

Thio- and dithio-isocoumarins have been studied by the ESCA method,[87]

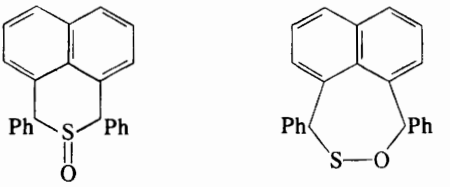
[83] C. Kissel, R. J. Holland, and M. C. Caserio, *J. Org. Chem.*, 1972, **37**, 2720.
[84] D. A. Pulman and D. A. Whiting, *J.C.S. Perkin I*, 1973, 410.
[85] S. Rozen, I. Shahak, and E. D. Bergmann, *Internat. J. Sulfur Chem.* (A), 1972, **2**, 287.
[86] H. Dürr, B. Heu, B. Ruge, and G. Scheppers, *J.C.S. Chem. Comm.*, 1972, 1257.
[87] J. Escard, G. Mavel, N. Lozac'h, and L. Legrand, *Tetrahedron Letters*, 1973, 249.



(74) (75)

and syntheses of 3-mercapto- and 3-methylthio-thioisocoumarins have been reported.[88]

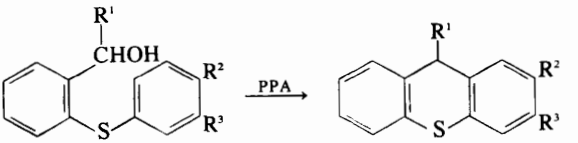
The photochemical transformation of *peri*-fused thiopyran *S*-oxides (76) into related pyrans and ring-opened products probably involves sulphenate esters of type (77).[89]



(76) (77)

10 Thioxanthenes, Thioxanthones, and Related Compounds

The synthesis of thioxanthenes (79; R^3 = H) by acid-catalysed dehydration of alcohols of type (78; R^3 = H) can lead to rearranged products [79; R^2 = H, R^3 = R^2 of (78)].[90] Irradiation of the thiolactone (80) in deoxygenated

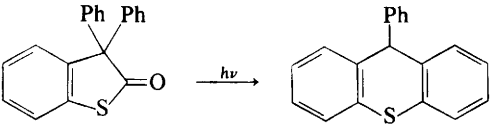


(78) (79)

[88] G. Kobayashi, Y. Matsuda, R. Natsuki, H. Yamaguchi, and Y. Tominaga, *Yakugaku Zasshi*, 1972, **92**, 449 (*Chem. Abs.*, 1972, **77**, 61 747).

[89] A. G. Schultz and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 3605.

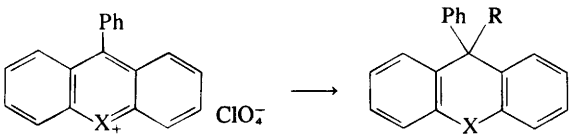
[90] G. Capozzi, G. Melloni, and G. Modena, *J.C.S. Perkin I*, 1973, 2250.



(80)

solvents gives thioxanthene derivatives;[91] in the presence of oxygen, thioxanthone is one of the products. Diarylvinylthioxanthenes[92] and urethane derivatives[93] have been reported. Several papers deal with the synthesis of thioxanthones as potential schistosomicidal agents.[94]

The thioxanthylium salt (81; X = S) reacts with nucleophiles to form thioxanthene derivatives of type [82; X = S, R = CN, $CH(CN)_2$, *etc.*];[95]



(81) (82)

nitration occurs in the *meta-* and *para-* positions of the substituent phenyl group.[96] The reactions of the analogous selenoxanthylium salt (81; X = Se) with phenyl-lithium, phenylmagnesium bromide, and other reagents have been investigated.[97] Thioxanthylium salts are reported to form coloured charge-transfer complexes with various heterocyclic bases.[98]

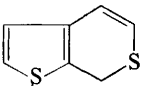
An *X*-ray crystallographic study of 9-isobutylthioxanthene 10,10-dioxide has been reported;[99] the central ring exists in a boat conformation, with the molecule folded about the S—C-9 axis.

The action of alkalis on a series of thioxanthone 10,10-dioxides has been investigated; the products include xanthones and the hydroxybenzophenone-sulphonic acids from which they are derived.[100]

[91] J. Nasielski and G. Jacqmin, *Tetrahedron*, 1972, **28**, 597; G. Jacqmin, J. Nasielski, G. Billy, and M. Remy, *Tetrahedron Letters*, 1973, 3655.
[92] W. Tadros, A. B. Sakla, S. B. Awad, and N. F. Abdul-Malik, *Helv. Chim. Acta*, 1973, **56**, 1829.
[93] I. Okabayashi, F. Miyoshi, and M. Arimoto, *Yakugaku Zasshi*, 1972, **92**, 1390 (*Chem. Abs.*, 1973, **78**, 58 200).
[94] I. Okabayashi, F. Miyoshi, and M. Arimoto, *Yakugaku Zasshi*, 1972, **92**, 1386 (*Chem. Abs.*, 1973, **78**, 58 199); G. M. Laidlaw, J. C. Collins, S. Archer, D. Rosi, and J. W. Schulenberg, *J. Org. Chem.*, 1973, **38**, 1743; I. Nabih and A. Zayed, *J. Pharm. Sci.*, 1973, **62**, 1547.
[95] M. Hori, T. Kataoka, Y. Asahi, and E. Mizuta, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1415.
[96] M. Hori, T. Kataoka, K. Ohno, and T. Toyoda, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1272, 1282.
[97] M. Hori, T. Kataoka, H. Shimizu, and C-F. Hsü, *Chem. Letters*, 1973, 391.
[98] G. E. Ivanov, *Khim. geterotsikl. Soedinenii*, 1973, 663 (*Chem. Abs.*, 1973, **79**, 66 145).
[99] S. S. C. Chu and B. Chung, *Acta Cryst.*, 1973, **B29**, 2253.
[100] O. F. Bennett, M. J. Bouchard, R. Malloy, P. Dervin, and G. Saluti, *J. Org. Chem.*, 1972, **37**, 1356.

11 Complex Thiopyran Derivatives

Synthetic work on thienothiopyran derivatives continues. Amongst the systems reported are compounds (83) and (84), related to benzo[*b*]thiophen



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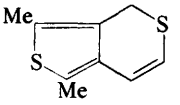
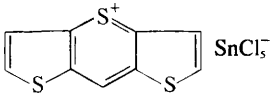


(84)

and benzo[*c*]thiophen,[101] various thiopyrylium salts, including the thieno-compounds (85) and (86), obtained by applications of the 'direct Bradsher



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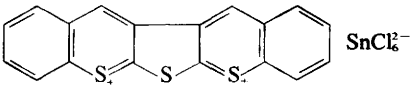
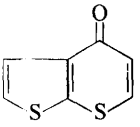


(86)

reaction',[102] and the thiochromone and thiocoumarin analogues (87) and (88).[103] Complex selenopyrylium salts (89) and (90) have also been prepared.[104]



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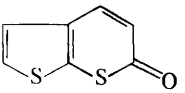

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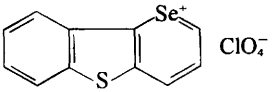

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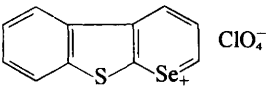
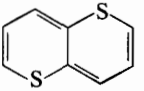


(90)

Attempts to synthesize thiopyranothiopyrans (91) and (92) from the reduced forms, for example (93), have not been completely successful, although some evidence has been obtained for the existence of compound (92).[105] Systems of this type are included in a theoretical (HMO) treatment of various sulphur heterocycles.[106]

[101] I. Alam and G. Thyagarajan, *Tetrahedron*, 1973, **29**, 1829.
[102] J. Ashby, M. Ayad, and O. Meth-Cohn, *J.C.S. Perkin I*, 1973, 1104.
[103] F. Boccuzzi, I. Degani, and R. Fochi, *Ann. Chim.* (*Italy*) 1972, **62**, 528.
[104] A. Tadino, L. Christiaens, M. Renson, and P. Cagniant, *Bull. Soc. chim. belges*, 1972, **81**, 595.
[105] T. E. Young and L. J. Heitz, *J. Org. Chem.*, 1973, **38**, 1562; T. E. Young, L. J. Heitz, and D. J. Steklenski, *ibid.*, p. 1567.
[106] B. A. Hess and L. J. Schaad, *J. Amer. Chem. Soc.*, 1973, **95**, 3907.



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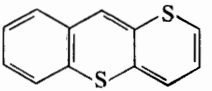

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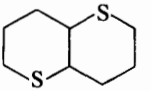
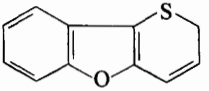


(93)

Systems in which oxygen-containing rings are involved are represented by compounds (94) and related structures,[107] and by more complicated examples (95)[108] and (96).[109]



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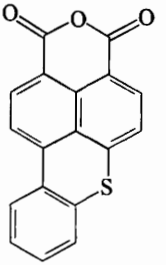

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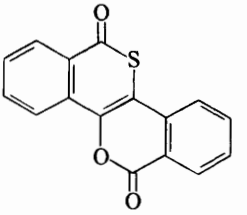
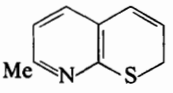


(96)

Pyridine and pyridazinone rings appear in compounds (97)[110] and (98),[111] the indole ring features in a series of compounds of type (99),[112] and a diazepinone ring in the thiopyran (100).[113]



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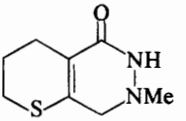

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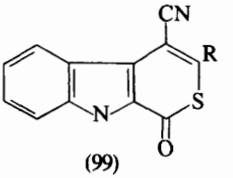

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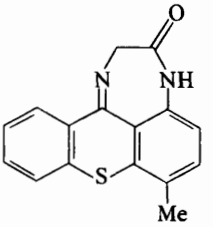


(100)

[107] M. Perrin and D. Cagniant, *Compt. rend.*, 1971, **273**, C, 1441.
[108] P. H. Grayshan, A. M. Kadhim, and A. T. Peters, *J. Heterocyclic Chem.*, 1974, **11**, 33.
[109] M. Kodomari and K. Itabashi, *Yuki Gosei Kagaku Kyokai Shi*, 1972, **30**, 629 (*Chem. Abs.*, 1972, **77**, 151 820).
[110] P. I. Abramenko and V. G. Zhiryakov, *Khim. geterotsikl. Soedinenii*, 1972, 1539 (*Chem. Abs.*, 1973, **78**, 58 265).
[111] M. Baues, U. Kraatz, and F. Korte, *Annalen*, 1973, 1310.
[112] Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1973, **93**, 1523 (*Chem. Abs.*, 1974, **80**, 59 885).
[113] F. Eiden and J. Dusemund, *Arch. Pharm.*, 1972, **305**, 324.

12
Isothiazoles

BY F. KURZER

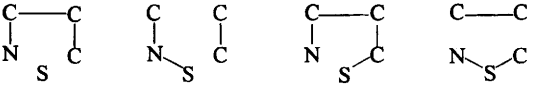
1 Introduction

The intensified activity in the study of the chemistry of isothiazole, noted in the previous Report, has been sustained, possibly with an emphasized interest in condensed ring-systems. Now that numerous syntheses of isothiazoles are available, the careful and detailed investigation of both the physical and chemical properties of this ring-system, and its correlation with related structures, are particularly timely. The possible involvement of isothiazole derivatives in the biosynthetic pathway to penicillins and cephalosporins is a suggestion of exceptional interest (see ref. 43, below) that will no doubt stimulate further significant work.

Slack and Wooldridge's authoritative review of 1965 on isothiazoles (see these Reports, Vol. 1, p. 369) has been supplemented by one of the authors,[1] so that concise up-to-date information on this ring system is now available from these two sources. A useful brief survey of routes to alkylisothiazoles is incorporated in a paper[2] dealing with their synthesis.

2 Synthesis

As new synthetic routes to isothiazoles are reported, additional modes of constructing the isothiazole nucleus (types D, E, and F) need to be added to those previously listed in formally classifying isothiazole syntheses. Ring-closures of type C continue to provide the more important synthetic



Type A Type B Type C Type D

Type E Type F

[1] K. R. H. Wooldridge in 'Advances in Heterocyclic Chemistry', ed. A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1972, Vol. 14, p. 2.

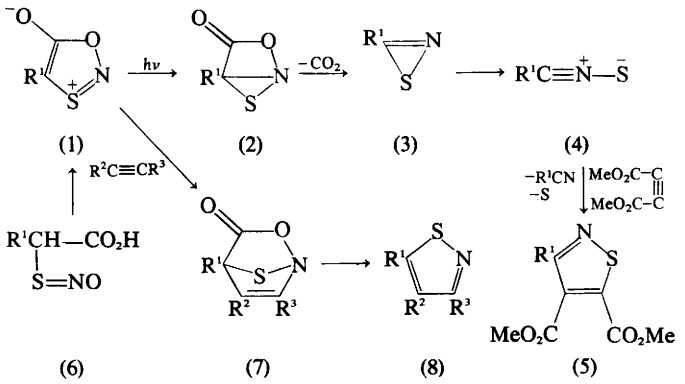
[2] A. Perichaud, J. C. Poite, G. Mille, and J. P. Roggero, *Bull. Soc. chim. France*, 1972, 3830.

methods (see these Reports, Vol. 2, p. 556). Wherever the mode of cyclization is not established with certainty, the most likely reaction path is selected to provide a basis for a provisional classification.

From Oxathiazolones (Type B).—A kinetic examination of the synthesis of 3-phenylisothiazole-4,5-dicarboxylate from 5-phenyl-1,3,4-oxathiazol-2-one and dimethyl acetylenedicarboxylate (these Reports, Vol. 2, p. 558) supports the intermediacy of benzonitrile sulphide. The method is also applicable to alkyl analogues.[3]

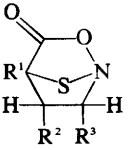
From Meso-ionic 1,3,2-oxathiazolium-5-olates (Type B).—The photolysis (at 4045—4078 Å) of the meso-ionic 4-phenyl-1,3,2-oxathiazolium-5-olate (1) yields, as the final products, benzonitrile, sulphur, and carbon dioxide. The suggested mechanism (1) → (2) → (3) → (4) receives experimental support from the fact that the ultimate intermediate (4) can be trapped (10%) as the substituted isothiazole (5) by means of dimethyl acetylenedicarboxylate, the alkyne undergoing 1,3-dipolar cycloaddition to the intermediate benzonitrile sulphide.[4]

Since the meso-ionic reactants (1) are readily accessible from (6) (and ultimately from mercaptoarylacetic acids), their conversion into isothiazoles (8) has been successfully developed as a synthetic route. They are treated with acetylene-mono- or -di-carboxylic acid esters in toluene at 60—100 °C, and afford, with loss of carbon dioxide, good yields of isothiazoles (8), probably by way of labile intermediates of type (7).



Activated alkenes (*e.g.* dimethyl maleate, methyl cinnamate) react analogously; the isothiazoles arise probably from the hypothetical bicyclic intermediate (9) by loss of carbon dioxide and dehydrogenation.[5]

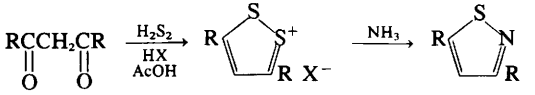
[3] R. K. Howe and J. E. Franz, *J.C.S., Chem. Comm.*, 1973, 524.
[4] H. Gotthardt, *Tetrahedron Letters*, 1971, 1277; *Chem. Ber.*, 1972, **105**, 188.
[5] H. Gotthardt, *Tetrahedron Letters*, 1971, 1281; *Chem. Ber.*, 1972, **105**, 196.



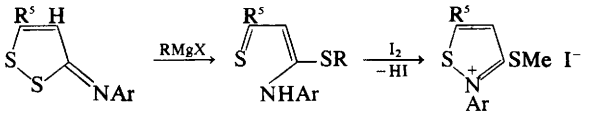
(9)

From Isoxazoles (Type C).—Further examples have been given of the conversion of isoxazoles into the corresponding isothiazoles,[6,7] including 1-methyl-4-[3(or 5)-methyl-5(or 3)-isothiazolyl]pyridinium salts,[7] by the method of McGregor *et al.* (see this Report, Vol. 1, p. 369).

From 1,2-Dithiolans (Type C).—Several variations of the general synthesis of isothiazoles from 1,2-dithiolans (see these Reports, Vol. 2, p. 563) have been employed in the production of further series of isothiazole derivatives.[8–10] In a comparative study, this route has been described as the most generally applicable method of preparing di- and tri-alkylisothiazoles.[2]



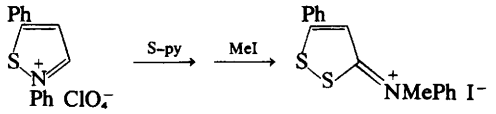
The action of Grignard reagents on *N*-(5-aryl-3*H*-1,2-dithiol-3-ylidene)-arylamines (10) provides the 1,3-bifunctional reagents (11),[11] which have proved to be versatile starting materials in heterocyclic syntheses. Their oxidation with iodine produces isothiazolium iodides (12) in 29—34% yield.



(10) (11) (12)

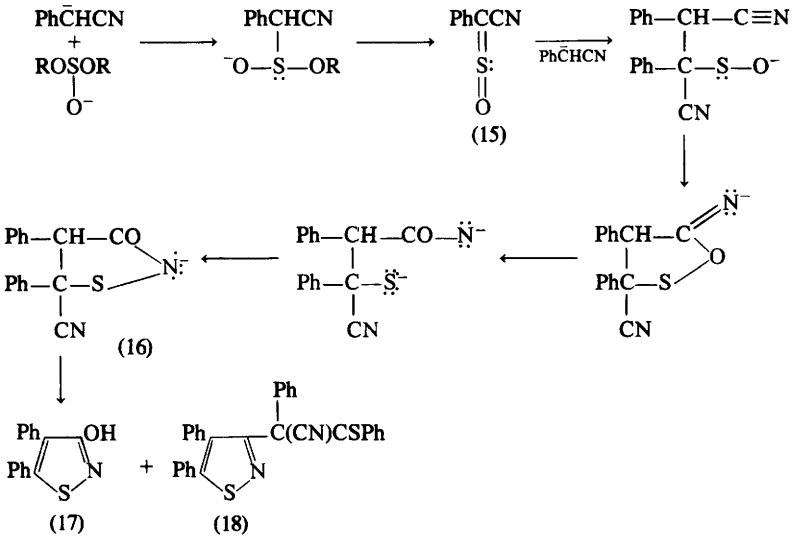
The work, incidentally, disproves a previous assignment[12] of the structure (12; Ar = R^5 = Ph) to the product of the successive sulphurization and quaternization of 2,5-diphenylisothiazolium perchlorate (13); this compound is non-identical with authentic material now obtained, and is in fact the dithiolan derivative (14).[13]

[6] J. W. Scott and A. Boris, *J. Medicin. Chem.*, 1973, **16**, 512.
[7] G. E. Wiegand, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *J. Medicin. Chem.*, 1971, **14**, 1015.
[8] J. C. Poite, S. Coen, and J. Roggero, *Bull. Soc. chim. France*, 1971, 4373.
[9] P. Sykes and H. Ullah, *J.C.S. Perkin I*, 1972, 2305.
[10] G. E. Bachers, D. M. McKinnon, and J. M. Buchshriber, *Canad. J. Chem.*, 1972, **50**, 2568.
[11] F. Boberg and W. von Gentzkow, *Annalen*, 1973, 247.
[12] D. M. McKinnon and E. A. Robak, *Canad. J. Chem.*, 1968, **46**, 1855.
[13] F. Boberg and W. von Gentzkow, *Annalen*, 1973, 256.



(13) (14)

Condensation of Nitriles and Dialkyl Sulphites. (Type C).—A novel isothiazole synthesis involves the interaction of phenylacetonitrile anion, generated in the presence of sodamide, and diethyl sulphite. The main product of the reaction, 4,5-diphenylisothiazol-3-ol (17) (47%), is accompanied by α-cyano-α-(4,5-diphenylisothiazol-3-yl)benzyl phenyl thione (18) (up to 15%). The use of other dialkyl sulphites produces the same isothiazolol (17), but in much reduced yields (9—18%). The reaction may possibly proceed by way of the sulphine intermediate (15), as outlined in Scheme 1, terminating with loss of hydrogen cyanide from (16).[14]

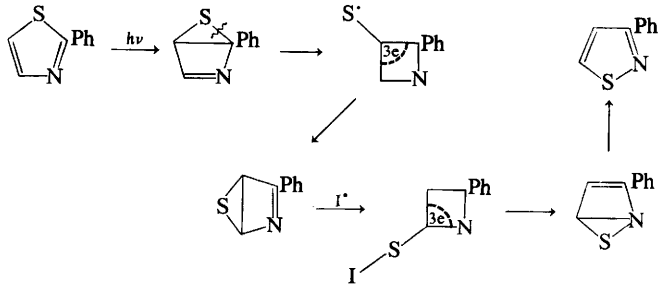


Scheme 1

Photoisomerization of Thiazoles (Type C).—Much new information has been provided concerning photolytic reactions involving isothiazoles[15,16] (see these Reports, Vol. 2, p. 563). 2-Phenylthiazoles bearing deuterium or a methyl group in position 4 or 5 are isomerized photolytically in the presence of iodine to 3-phenylisothiazoles.[15] 5-Phenylthiazole similarly yields principally 4-phenylisothiazole (21%).[16] For additional examples, physical data

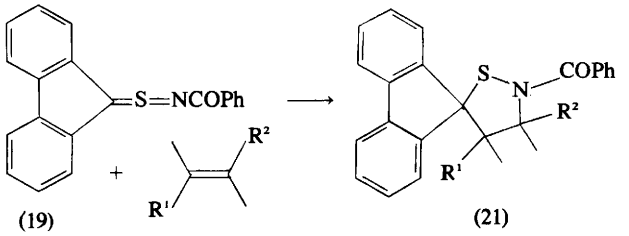
[14] M. D. Scott, *J.C.S. Perkin I*, 1972, 1432.
[15] C. Riou, G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. chim. France*, 1972, 2673.
[16] G. Vernin, C. Riou, H. J. M. Dou, L. Boucasse, J. Metzger, and G. Loridan, *Bull. Soc. chim. France*, 1973, 1743.

(including calculated electron densities and bond orders), and detailed discussion, the extensive original papers must be consulted.[15,16] Of five possible mechanisms from published data that were considered, those best fitting the results are a valence-isomerization process, with or without preliminary opening of weaker bonds in the first excited state, or a mechanism involving torsion of bonds adjacent to sulphur.[16] The stages are exemplified, for 2-phenylisothiazole, in Scheme 2.[15]



Scheme 2

From Thione-*S*-imides (Type D).—The first synthesis of compounds incorporating the thione-*S*-imide ($R^1_2C{:}S{:}NR^2$) system has been announced, and some of their novel reactions have been enumerated. Amongst them, the cycloaddition of *N*-isobutenylpyrrolidine (20) to (19) yields a 1:1 adduct, formulated as the isothiazolidine (21).[17]

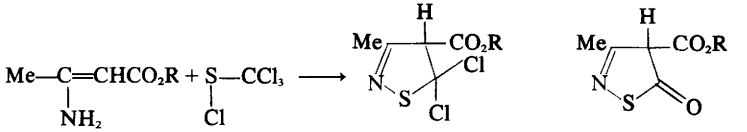


(20) $R^1 = Me$, $R^2 = N(CH_2)_4$

From β-Aminocrotonic Esters (Type E).—A novel direct ring synthesis of 5-hydroxyisothiazoles involves the condensation of a β-aminocrotonic ester (22) with perchloromethanethiol in the presence of base: the heterocyclic products (23) are obtained directly (30—40%), presumably by the reaction sequence shown.[18]

Type F Synthesis.—The substituted 5-ethoxythiocarbonylthiophen (24) functions as a thioacylating agent, converting malonic dinitrile into the

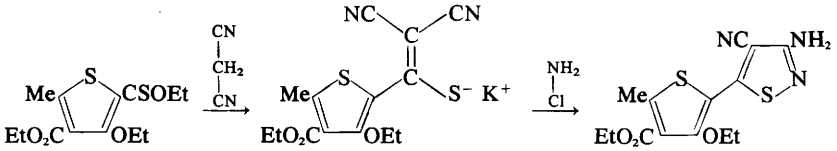
[17] E. M. Burgess and H. R. Penton, jun., *J. Amer. Chem. Soc.*, 1973, **95**, 279.
[18] J. A. Waite and K. R. H. Wooldridge, *Tetrahedron Letters*, 1972, 327.



(22) (23)

potassium salt (25). Under the influence of chloramine, this is cyclized to the 5-substituted 3-amino-4-cyanoisothiazole (26) in excellent yield.[19]

Further examples of isothiazoles have been produced by well-established syntheses. A comparative study examining four distinct routes has provided mono-, di-, and tri-methylisothiazoles.[2] Directions have been given[9] for the synthesis of the parent compound of the series, isothiazole, from propynal[20] in improved yield.



(24) (25) (26)

3 Physical Properties

Theoretical calculations, by the HMO and PPP methods, have provided information concerning electron densities, bond orders, and polarization energies of 3-, 4-, and 5-phenylisothiazoles.[16,21]

The u.v. spectra of 4-nitroisothiazole and its homologues feature maxima at 209—220 nm (ε 10 000) and 263—275 nm (ε 8 500).[22] N.m.r. spectra have been recorded and discussed in respect of dimethyl- and trimethyl-isothiazoles,[2] 3,5-dialkylisothiazoles,[8] as well as 4-nitroisothiazole and its methyl and dimethyl homologues, including some halogenated derivatives.[22]

A study of the mass spectra of 4-substituted 3,5-di(alkylthio)isothiazoles shows that the decomposition may occur along two competing routes, details of which were given.[23,24] Fragmentation patterns were also provided and discussed for dimethyl- and trimethyl-[2] and 4-phenyl-isothiazoles.[21]

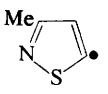
A number of properties of 4,5-diphenylisothiazol-3-ol are in accord with those reported for other hydroxyisothiazoles. The compound appears to exist almost wholly as the enolic tautomer, forming a sodium salt, giving a

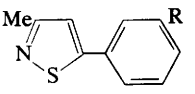
[19] K. Hartke and G. Golz, *Annalen*, 1973, 1644.
[20] F. Wille, *Angew. Chem. Internat. Edn.*, 1962, **1**, 335; R. Raap, *Canad. J. Chem.*, 1966, **44**, 1324.
[21] M. Baule, R. Vivaldi, J. C. Poite, H. J. M. Dou, G. Vernin, and J. Metzger, *Bull. Soc. chim. France*, 1971, 4310.
[22] J. C. Poite, J. Roggero, H. J. M. Dou, G. Vernin, and J. Metzger, *Bull. Soc. chim. France*, 1972, 162.
[23] J. Julien, J. C. Poite, G. Salmona, and E. J. Vincent, *Compt. rend.*, 1972, **274**, *C*, 1871.
[24] J. Julien, E. J. Vincent, J. C. Poite, and J. Roggero, *Org. Mass Spectrometry*, 1973, **7**, 463.

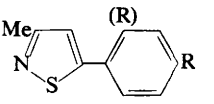
purple colour with ferric chloride, and showing no significant absorption above 1630 cm^{-1}.[14]

4 Chemical Properties

Free-radical Reactions.—Metzger and his co-workers have continued to contribute to the existing knowledge of radical processes involving isothiazoles, by substantial and detailed studies of selected reactions.[25,26] The 3-methylthiazol-5-yl radical (27), produced photolytically (20—65%) from the corresponding 5-iodo-compound, reacts with aromatic substrates PhR (R = $CHMe_2$, CMe_3, OMe, Cl, Br, Me, or CN) to give mixtures of *meta*-, *para*-, and *ortho*-isomers (28), (29), as well as secondary products [*e.g.* (30)] arising by photoisomerization. The isomer ratio (28)/(29) resulting


(27)


(28)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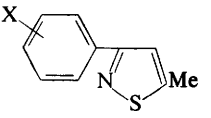
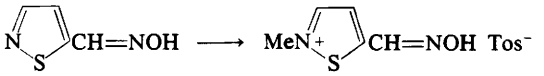

(30)

from the 3-methylthiazol-5-yl radical (27) is generally lower than that of phenyl radicals reacting with the same substrate. The difficult separation and identification of the isomer mixtures was achieved by an elaborate combination of chromatographic and spectroscopic techniques.[25] A further investigation dealing with isothiazol-4(or 5)-yl and 3-methylisothiazol-4-yl radicals led to analogous conclusions.[26] The three radicals acting upon nine different substrates give *ca.* 100 products, the nature and relative proportions of which show that the action of the heteroaryl radicals resembles essentially that of the phenyl radical.[26]

Alkylation and Quaternization.—4-Bromo-5-hydroxy-3-methylisothiazole is *O*-methylated by diazomethane: in contrast, 3-hydroxy-5-phenylisothiazole is *N*-methylated, and equimolar mixtures of the *O*- and *N*-methyl derivatives are produced from 3-hydroxyisothiazoles.[27] *N*-Methylation also prevails when 3-hydroxy-4,5-diphenylisothiazole is alkylated by dimethyl sulphate.[14]

[25] G. Vernin, J. C. Poite, H. J. M. Dou, J. Metzger, and G. Vernin, *Bull. Soc. chim. France*, 1972, 3157.
[26] G. Vernin, J. C. Poite, C. Riou, H. J. M. Dou, J. Metzger, and G. Vernin, *Bull. Soc. chim. France*, 1973, 1822.
[27] I. D. H. Stocks, J. A. Waite, and K. R. H. Wooldridge *J. Chem. Soc.* (*C*), 1971, 1314.

Isothiazole-3(or 5)-carboxaldoxime (31) (but not its 4-isomer) reacts with methyl tosylate, albeit with difficulty, affording 3(or 5)-hydroxyiminomethyl-2-methylisothiazolium tosylate (32) in low yield (8—9%).[28]



(31) (32)

Nitration.—Isothiazole and its 3- and 5-methyl and 3,5-dimethyl homologues are nitrated exclusively in their 4-position. Quantitative experiments under standard conditions demonstrate the lower relative reactivities of isothiazoles compared with those of the corresponding thiazoles (see Table 1).[22]

Table 1 *Relative rates of nitration*[22]

Thiazoles		*Isothiazoles*	
2,4-Dimethyl	1	3,5-Dimethyl	0.16
2,5-Dimethyl	0.5	5-Methyl	0.0094
4-Methyl	0.066	3-Methyl	0.0055
5-Methyl	0.04	Isothiazole	0.0024

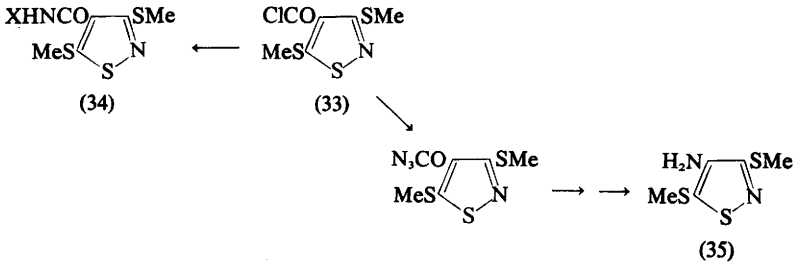
A study of the nitration of 3-, 4-, and 5-phenylisothiazoles reveals a strong deactivation of the benzene nucleus by the heterocyclic ring. The calculated electron densities of the phenylisothiazoles are not in entire agreement with the observed orientation of the nitro-groups in the resulting mixtures of mono-nitro-derivatives.[21]

5-Amino-3-methylisothiazole has been converted, by way of the diazonium salt, into 3-methyl-5-nitroisothiazole. Treatment of 3,5-dichloroisothiazole-4-carbonitrile with sodium or silver nitrite yields the 5-hydroxy-compound, presumably *via* an unstable nitrite ester; a nitro-compound is not obtained.[29]

Nucleophilic Reactions.—Nucleophilic substitution in the isothiazole nucleus, as well as a variety of nucleophilic ring fissions, continue to attract a good deal of attention. The methylsulphonyl group is particularly prone to nucleophilic replacement: 3,5-bis(methylsulphonyl)isothiazole-4-carbonitrile, readily accessible from malononitrile and carbon disulphide,[30] yields the 5-(substituted)amino-compounds on treatment with ammonia, amines, or hydrazine, and the 5-ethoxy-compound when treated with ethanol in the presence of sodium carbonate. The electron-attracting cyano-group appears to promote the nucleophilic displacement, since 3,5-bis(methylsulphonyl)-4-phenylisothiazole displays reduced reactivity.[31]

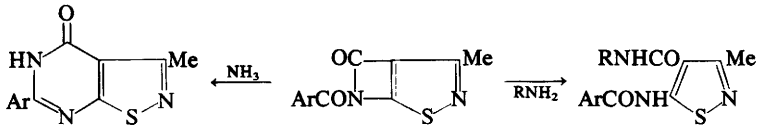
[28] H. P. Benschop, A. M. van Oosten, D. H. J. M. Platenburg, and C. van Hooidonk, *J. Medicin. Chem.*, 1970, **13**, 1208.
[29] R. J. A. Walsh and K. R. H. Wooldridge, *J.C.S. Perkin I*, 1972, 1247.
[30] W. R. Hatchard, *J. Org. Chem.*, 1964, **29**, 665.
[31] M. Davis and J. A. Gordon, *J.C.S. Perkin I*, 1972, 638.

4-Chloroformyl-3,5-bis(methylthio)isothiazole (33), produced from the corresponding 4-nitrile,[30,32] is a useful source of 4-amido- (34), 4-amino- (35), and other isothiazole derivatives, which are accessible by conventional interconversions.[33]



(34) (33) (35)

Thionyl chloride converts 5-aroylamino-3-methylisothiazole-4-carboxylic acids into lactams (36), which are cleaved to the amides (37) by aliphatic and aromatic amines, and converted into isothiazolo[5,4-*d*]pyrimidines (38) by ammonia.[34]



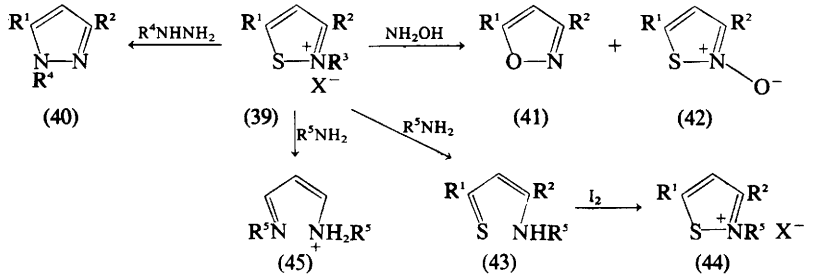
(38) (36) (37)

2-Alkylisothiazolium salts are generally stable to oxidizing agents such as hydrogen peroxide and sodium periodate. They are rapidly decomposed by warm alkalis, but no identifiable products were isolable from the resulting tars. They are particularly sensitive towards nucleophilic attack.[35]

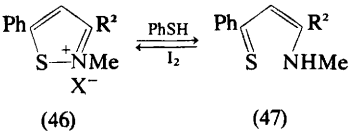
Their interaction with nitrogen nucleophiles, first described by Olofson *et al.*,[36] has been further studied.[9]

The action on (39) of ethanolic ammonia, hydrazine hydrate, and phenylhydrazine yields the corresponding isothiazole, pyrazole, and 1-phenylpyrazole (40), respectively. Hydroxylamine produces isoxazoles (41) and isothiazole *N*-oxides (42) side by side. Primary amines yield principally the linear amino-thiones (43), reconvertible by oxidation with iodine into the isothiazolium salts (44), but dianil salts (45) arise from isothiazolium salts lacking 3-, 4-, or 5-substituents. Secondary and tertiary amines cause far-reaching decomposition, with deposition of sulphur, but certain examples are without effect.[9]

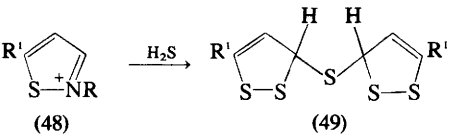
[32] E. Soederbaeck, *Acta Chem. Scand.*, 1963, **17**, 362.
[33] J. C. Poite, J. Julien, E. J. Vincent, and J. Roggero, *Bull. Soc. chim. France*, 1972, 2296.
[34] Z. Machon and L. Kuczynski, *Diss. Pharm. Pharmacol.*, 1970, **22**, 395 (*Chem. Abs.*, 1971, **74**, 87 882p).
[35] J. M. Landesberg and R. A. Olofson, *Tetrahedron*, 1966, **22**, 2135.
[36] R. A. Olofson, J. M. Landesberg, R. O. Berry, D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *Tetrahedron*, 1966, **22**, 2119.



Amongst sulphur nucleophiles, benzenethiol cleaves the nucleus of the salts (46), yielding methylamino-thiones (47), in which the 2-methyl group of

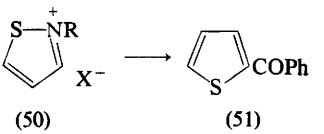


the starting materials is retained. Hydrogen sulphide reacts extremely readily with isothiazolium salts lacking 3-substituents (48; $R^2 = H$) to yield bis-1,2-dithiolyl sulphides (49), the original 2-substituent being lost as the corresponding amine.[9]



The observations are compatible with a mechanism involving the initial attack of the nitrogen nucleophile on the 3-position of the isothiazolium cation, followed by ring-opening (*i.e.* mechanism C of Landsberg and Olofson[35]); whether or not cyclization takes place subsequently depends on the nature of R in the nucleophile RNH_2. The structure of some of the products suggests that the initial nucleophilic attack occurs on C-5 in certain examples.[9]

The nucleophilic attack of sodium benzoylacetate on a variety of isothiazolium salts (50) yields, in all cases examined, 2-benzoylthiophens (51). Here the reaction is probably best accounted for by a mechanism

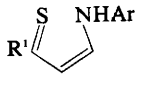


involving the nucleophilic attack of a phenacyl ion (actual or potential) on the ring sulphur, resulting in ring cleavage, followed by recyclization to

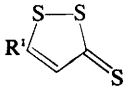
thiophen with loss of amine, as a result of the attack of the activated methylene on the imine function.[37]

The action of hydrogen sulphide on (50) proceeds differently, depending on whether an *N*-aryl or -alkyl group is present in the isothiazolium structure.

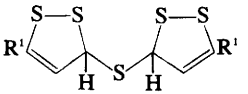
The former yield principally β-aminopropenethiones (52), but the latter produce 1,2-dithiole-3-thiones (53) or bis-1,2-dithiol-3-yl sulphides (54). A mechanism accounting for the observations was suggested.[37]



(52)

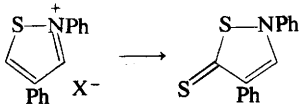


(53)



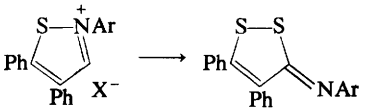
(54)

The interaction of isothiazolium salts and sulphur in boiling pyridine, previously examined in isolated cases,[38,39] has been studied more systematically. 5-Unsubstituted isothiazolium salts (55) appear to give the corresponding isothiazoline-5-thiones (56). 3-Unsubstituted *N*-alkylisothiazolium



(55) (56)

salts give the isothiazoline-3-thiones, but *N*-aryl analogues (57) produce 1,2-dithiole-3-imines (58). The yields are generally low.[10] The reaction, proceeding by ring-opening and recyclization, may occur by the mechanism

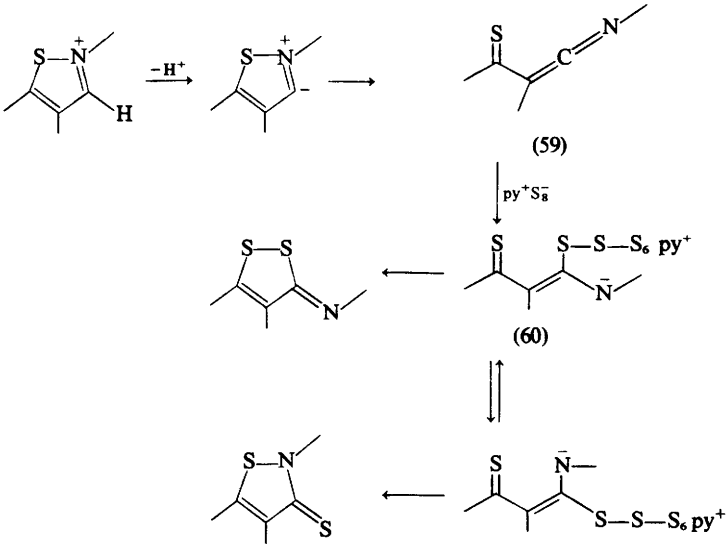


(57) (58)

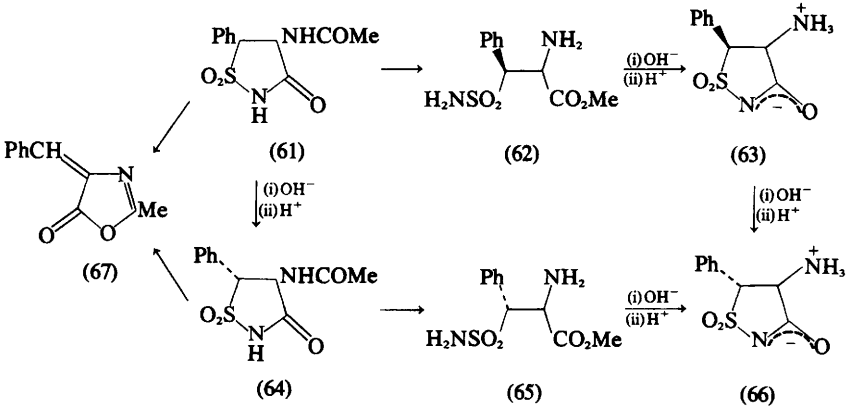
involving the thioketimine (59), which reacts with a polysulphide-chain (formed from sulphur and pyridine) to produce the intermediate (60), which may cyclize to the observed products.[10]

Further Rearrangements.—Acetic anhydride–pyridine rearranges both *cis*- and *trans*-4-acetamido-5-phenylisothiazolidin-3-one 1,1-dioxide [(61) and (64)] to 4-benzylidene-2-methyl-2-oxazolin-5-one (67).[40] The isomers are convertible stereospecifically into the corresponding *cis*- and *trans*- parent

[37] D. M. McKinnon and M. E. Hassan, *Canad. J. Chem.*, 1973, **51**, 3081.
[38] D. M. McKinnon and E. A. Robak, *Canad. J. Chem.*, 1968, **46**, 1855.
[39] G. Le Coustumer and Y. Mollier, *Compt. rend.*, 1970, **270**, *C*, 433; *Bull. Soc. chim. France*, 1970, 3076 (see these Reports, Vol. 2, p. 563).
[40] J. C. Howard, *J. Org. Chem.*, 1971, **36**, 1073 (see these Reports, Vol. 2, p. 561).



amines (63) and (66), which are cyclic analogues of phenylalanine. This process consists of the preliminary methanolysis of the 4-acetamido-compounds (61) and (64) to the 3-sulphamylphenylalanine methyl esters (62) and (65), followed by alkaline cyclization.[41] The products (63) and (66) are inner

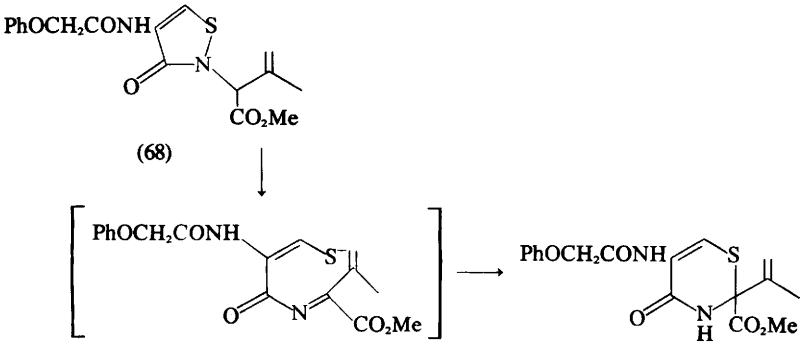


salts, as shown by their high decomposition points, insolubility in non-polar solvents, and spectral and titration data. An excess of alkali epimerizes the *cis*- forms of both the acetamido- (61) and amino-compounds (63) readily and irreversibly to the less restricted *trans*-isomers (64) and (66) by a second-order reaction. The results require the reversal of the previous[40]

[41] J. C. Howard, *J. Org. Chem.*, 1972, **37**, 3781.

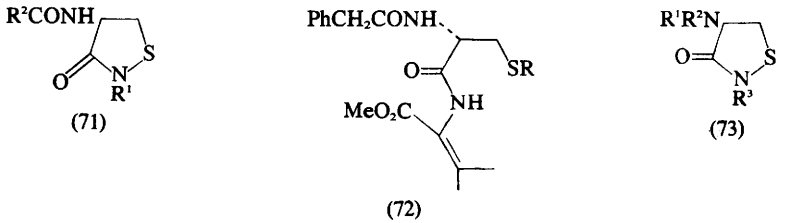
tentative configurational assignments to the starting materials (61) and (64), based on n.m.r. measurements.[41]

The isothiazolone (68) undergoes base-catalysed rearrangement in dimethyl-acetamide or -formamide, yielding (70), presumably by way of the intermediate acylimine (69). The observation is of significance in penicillin chemistry, since compounds (68) and (70), amongst others, are by-products of the transformation of penicillin V sulphoxide methyl esters into cephalosporin derivatives.[42]



Complex Formation.—Suitably substituted 2-alkylisothiazolium salts yield crystalline complexes with heavy-metal salts, including mercury(II) chloride, lead nitrate, and antimony trichloride.[9]

Biochemical.—In the course of wider studies connected with the biosynthesis of β-lactam antibiotics, the oxidation of a number of cysteinylpeptides has been found to yield products incorporating the isothiazolidinone residue (71). Cysteinyldehydrovaline (72; R = H), for example, reacts with phenylselenyl bromide, yielding the thioselenide (72; R = SePh), which is cyclized oxidatively to the corresponding isothiazolidinone (73; R^1 = H,

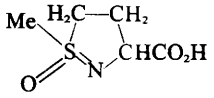


R^2 = phenylacetyl; R^3 = α-methyl-β-methylcrotonyl). The ease with which substituted isothiazolidinones arise under these circumstances suggests

[42] R. B. Morin, E. M. Gordon, T. McGrath, and R. Shuman, *Tetrahedron Letters*, 1973, 2159.

their possible involvement in the biosynthetic pathway to penicillins and cephalosporins.[43]

L(or D)-Methionine sulphone are reversible inhibitors of glutamine synthetase. Incubation of L(or D)-[*methyl*-^{14}C]methionine sulphone with glutamine synthetase in the presence of ATP yields a ^{14}C-containing product that is tentatively formulated as the isothiazole derivative (74). The assigned



(74)

structure is as yet unconfirmed, but its synthesis is analogous to the established conversion[44] of glutamate into pyrrolidonecarboxylate under the catalytic influence of the same enzyme.[45]

1-Methyl-4-(3-methyl-5-isothiazolyl)pyridinium iodide and its 5-methyl-3-isothiazolyl isomer are active hypoglycaemic agents, reducing the blood glucose concentration by 33—90% in mice.[7]

5 1,2-Benzisothiazoles

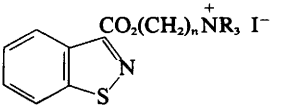
The chemistry of both 1,2- and 2,1-benzisothiazoles (benzo-[*d*]- and -[*c*]-isothiazoles) has been the subject of a comprehensive review.[46] Developments of the past 20 years were emphasized for 1,2-benzisothiazoles, previous work having been covered by Bambas' monograph of 1952.[47] Little was known concerning 2,1-benzisothiazoles before that time, so that the new account is the first definitive review of this subject. The section on saccharin (3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide) in Bambas' book[47] has also been updated by the appearance of a detailed review[48] on the chemistry of this and related compounds, thus providing a complete survey of this section of the chemistry of 1,2-benzisothiazole.

The majority of the contributions during the present period of review have dealt with the application and extension of existing synthetic methods.

Extensive series of 1,2-benzisothiazole-3-carboxylic acid derivatives of type (75),[49,50] (76),[50] and (77),[51] as well as naphtho[2,3-*d*]isothiazolyl-3-acetic

[43] J. E. Baldwin, S. B. Haber, and J. Kitchin, *J.C.S. Chem. Comm.*, 1973, 790.
[44] A. Meister, M. W. Bukenberger, and M. Strassburger, *Biochem. Z.*, 1963, **338**, 217.
[45] W. B. Rowe and A. Meister, *Biochemistry*, 1973, **12**, 1578.
[46] M. Davis in 'Advances in Heterocyclic Chemistry', ed. A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1972, Vol. 14, p. 43.
[47] L. L. Bambas, 'The Chemistry of Heterocyclic Compounds', Interscience, New York, 1952, vol. IV, pp. 225–378.
[48] H. Hettler in 'Advances in Heterocyclic Chemistry', ed. A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1973, Vol. 15, p. 233.
[49] L. Amoretti and P. Mantovani, *Farmaco, Edn. Sci.*, 1973, **28**, 183.
[50] L. Amoretti, P. L. Catellani, M. Impicciatore, and A. Cavaggioni, *Farmaco, Edn. Sci.*, 1972, **27**, 855.
[51] T. Vitali, M. R. Mingiardi, and C. A. Maggiali, *Farmaco, Edn. Sci.*, 1973, **28**, 8.

acids (78)[51] have been produced by conventional methods[49–52] for biological screening, particularly as local anaesthetics.[49,50] Substituted 1,2-benzisothiazol-3-ylacetic acids, synthesized from the preformed ring-system, are potent selective phytocides.[53] Quaternary ammonium salts (79) derived from 3-aminoalkoxy-1,2-benzisothiazoles possess acetylcholine- and nicotine-like properties both *in vivo* and *in vitro*.[52,54]



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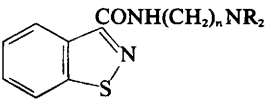

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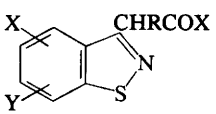

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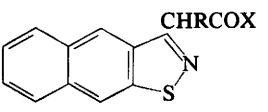

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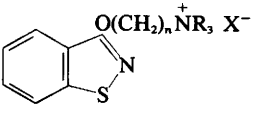


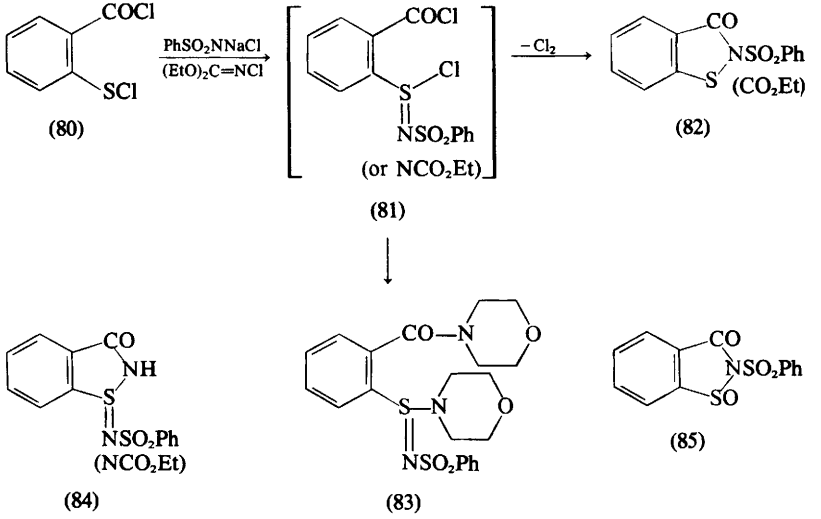
(79)

In view of the versatility of 3-methylbenzothiazol-2-one hydrazone as a starting material for producing heterocyclic azo-compounds by oxidative coupling,[55] the isomeric 2-methyl-1,2-benzisothiazol-3-one hydrazone has been synthesized (from the corresponding 3-chloro-derivative), and its coupling with dimethylaniline and 1-hydroxy-2-naphthoic acid anilide has been examined.[56]

The oxidative imination of *o*-chlorocarbonyl benzenesulphenyl chloride (80) by *N*-chloro-amines yields, in the first instance, unstable substituted iminosulphinyl chlorides (81); their existence is confirmed by their conversion into the stable dimorpholides [*e.g.* (83)]. The intermediates (81) are readily cyclized, with loss of chlorine, to the benzisothiazolone derivatives (82). Analogous cyclic sulphoxides (85) are similarly obtainable from sulphinyl chlorides corresponding to (80). The use of diethyl *N*-chloroiminocarbonate further extends the scope of this synthesis (see Scheme 3); *o*-carboxybenzene acyliminosulphinimides [*e.g.* (84)] are accessible from the preformed ring-system by the same reagents.[57]

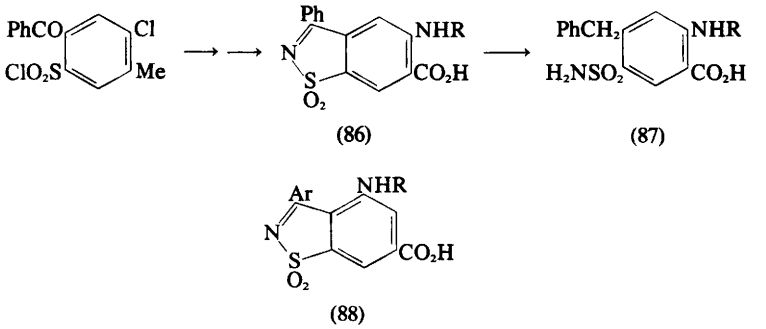
1,2-Benzisothiazole 1,1-Dioxides.—A series of 5-amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides (86) have been synthesized[58] by the method

[52] G. L. Piccinin, G. Bertaccini, and F. Mossini, *Farmaco, Edn. Sci.*, 1971, **26**, 40.
[53] T. Vitali, V. Plazzi, and C. F. Laureri, *Farmaco, Edn. Sci.*, 1972, **27**, 773.
[54] M. Impicciatore, G. L. Piccinin, F. Mossini, and C. F. Laureri, *Farmaco, Edn. Sci.*, 1972, **27**, 109.
[55] For Summary see S. Hünig, W. Brenninger, H. Geiger, G. Kaupp, W. Kniese, W. Lampe, H. Quast, R. D. Rauschenbach, and A. Schütz, *Angew Chem.*, 1968, **80**, 343.
[56] S. Hünig, G. Kiesslich, K. H. Oette, and H. Quast, *Annalen*, 1971, **754**, 46.
[57] E. S. Levchenko and I. N. Berzina, *Zhur. org. Khim.*, 1970, **6**, 2273.
[58] P. W. Feit, O. B. T. Nielsen, and N. Rastrup-Andersen, *J. Medicin, Chem.*, 1973, **16**, 127.



Scheme 3

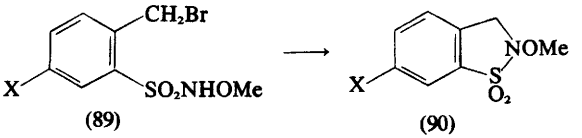
of Wright.[59] Isomers (88) were produced by similar conventional routes.[60] Wolff–Kishner reduction cleaves the heterocyclic ring of (86), yielding (87).[58]



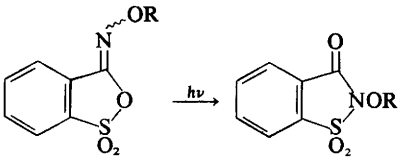
2-Methoxybenzisothiazoline 1,1-dioxides (90) are formed by cyclization, in DMF–triethylamine, of the corresponding sulphonhydroxamic acids (89), *e.g.* α-bromo-*N*-methoxy-*o*-toluenesulphonamide (89; X = H).[61]

The photoisomerization of *N*-alkoxyisosulphobenzimides (91) to the corresponding 1,2-benzisothiazole derivatives (92) (*N*-alkoxysaccharins) has been briefly reported.[62]

[59] J. B. Wright, *J. Heterocyclic Chem.*, 1968, **5**, 453.
[60] O. B. T. Nielsen, C. K. Nielsen, and P. W. Feit, *J. Medicin. Chem.*, 1973, **16**, 1170.
[61] L. A. Levy, *J. Heterocyclic Chem.*, 1971, **8**, 873.
[62] L. A. Levy, *Tetrahedron Letters*, 1972, 3289.

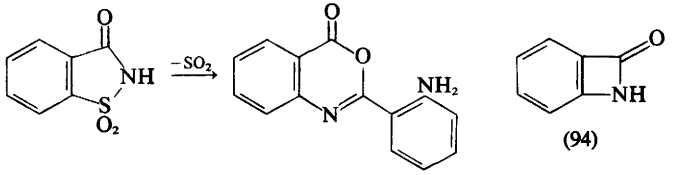


(89) (90)



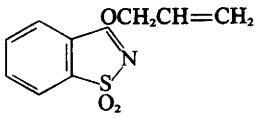
(91) (92) R = Me or CH_2Ph

Thermolysis of 1,2-benzisothiazol-3-one 1,1-dioxide (saccharin) in boiling diethyl phthalate (b.p. 298 °C) produces 5% yields of (93), the formation of which is rationalized by postulating the intermediate formation of benzoazetidinone (94).[63]



(93) (94)

3-Allyloxy-1,2-benzisothiazole 1,1-dioxide ['Oryzemate', (95)] prevents infection and development of rice blast fungus under field conditions. Its



(95)

distribution and metabolic fate has been studied by the use of the ^{35}S-labelled compound. It is taken up preferentially by the leaves of the plant; identified metabolites include allyl *o*-sulphamoylbenzoate, saccharin, and *N*-D-glucopyranosyl-saccharin.[64]

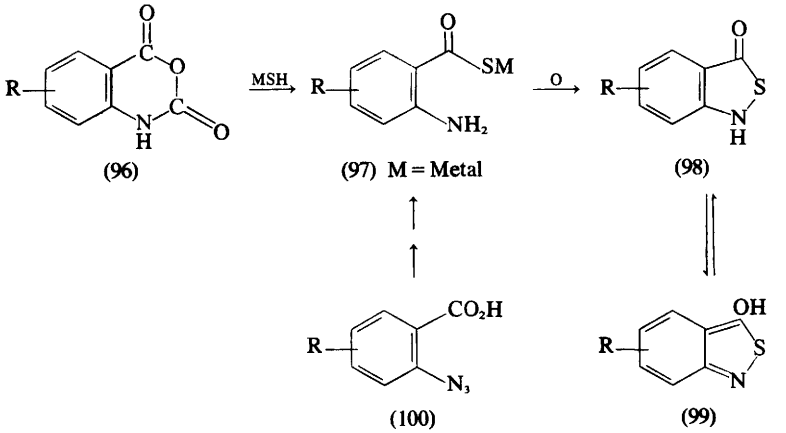
6 2,1-Benzisothiazoles

3-Hydroxy-2,1-benzisothiazoles (99) are accessible by the general oxidative cyclization involving suitably placed amino- and mercapto-groups. Thus,

[63] A. J. Barker and R. K. Smalley, *Tetrahedron Letters*, 1971, 4629.

[64] M. Uchiyama, H. Abe, R. Sato, M. Shimura, and T. Watanabe, *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 737.

treatment of thioanthranilic acid (97) with hydrogen peroxide produces the bicyclic products in satisfactory yield.[65,66] The required intermediates (97) are obtained from isatoic anhydride (96)[66,67] or 2-azidobenzoic acids (100).[65] The oxy-2,1-benzisothiazoles are pale-yellow alkali-soluble solids, which exist, according to their i.r. spectra, in the ketonic form (98).[65]



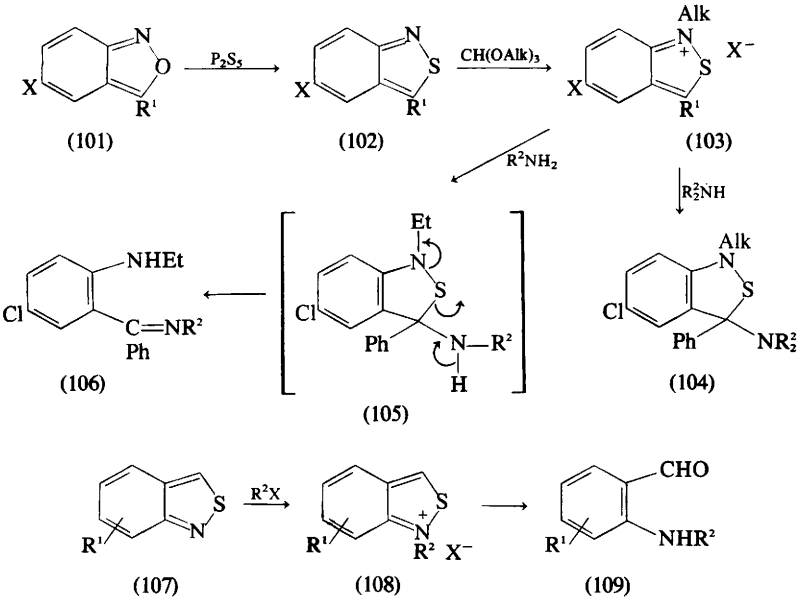
(96) (97) M = Metal (98) (100) (99)

2,1-Benzisothiazoles (102) may be prepared from the corresponding 2,1-benzisoxazoles (101) by the action of phosphorus pentasulphide. The reaction fails in the conventional media, including pyridine, normally employed in this method, but proceeds in yields of up to 54% in imidazole or 2-methylimidazole; however, the nature of the influence of these solvents is as yet unexplained.[68]

Alkylation of 2,1-benzisothiazoles (102) with trialkyl orthoformates in the presence of Lewis acids such as boron trifluoride etherate affords the quaternary salts (103). Their treatment with secondary amines produces the expected 1-alkyl-3-aryl-3-dialkylamino-2,1-benzisothiazoline derivatives (104). In contrast, the presumed intermediates (105) arising from primary amines (including glycine methyl ester) are cleaved, with extrusion of sulphur, to the azomethines (106).[68]

2,1-Benzisothiazole itself and its simple derivatives (107) also yield quaternary salts (108) on treatment with dialkyl sulphates, alkyl bromides, or alkyl toluene-*p*-sulphonates. The salts are rapidly ring-cleaved to *o*-aminobenzaldehydes (109) by aqueous acids and bases. 1-Methyl-5-nitro-2,1-benzisothiazolium toluene-*p*-sulphonate (108; $R^1 = 5\text{-}NO_2$, $R^2 = Me$, X = Ts) reacts particularly readily, the aldehyde being obtained directly upon attempted crystallization of the quaternary salt from water or aqueous

[65] H. Böshagen and W. Geiger, *Chem. Ber.*, 1973, **106**, 376.
[66] A. H. Albert, R. K. Robins, and D. E. O'Brien, *J. Heterocyclic Chem.*, 1973, **10**, 413.
[67] A. T. Fanning and T. D. Roberts, *Tetrahedron Letters*, 1971, 805.
[68] O. Aki, Y. Nakagawa, and K. Sirakawa, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2372.



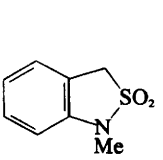
ethanol. The reaction is thus of additional practical utility in making available otherwise difficultly accessible *o*-aminobenzaldehydes (109), which are themselves useful synthetic intermediates.[69]

1-Mono- (110) and 1,3-di-substituted (114) 2,1-benzisothiazoline 2,2-dioxides have been synthesized by existing methods.[70] The former compounds undergo the aldol condensation, aminoalkylation, and cyanoethylation at the methylene-carbon, though not without difficulty, yielding (111), (112), and (113). The 1,3-dialkyl analogue (114) reacts with methyl vinyl ketone, acrylamide, and acrylonitrile, and affords the 3,3-disubstituted compounds (115), (116), and (117), respectively.[71]

Under the action of electrophiles, 1-methyl- and 1,3-dimethyl-2,1-benzisothiazoline 2,2-dioxides undergo substitution in their 5-position, affording 5-nitro-, 5-halogeno-, and 5-bromoacetyl derivatives (the last by Friedel–Crafts acylation). The 5-substituents may be modified by conventional processes (Scheme 4).[72]

The readily available 3-amino-2,1-benzisothiazole is convertible, by way of the diazonium salt (isolable as fluoroborate), into other 3-functional derivatives by the Sandmeyer reaction. It yields a mono- and a di-acetyl derivative, depending on the conditions.[73]

[69] M. Davis, E. Homfeld, and K. S. L. Srivastava, *J.C.S. Perkin I*, 1973, 1863.
[70] J. Bunnett, T. Kato, R. R. Flynn, and J. A. Skorcz, *J. Org. Chem.*, 1963, **28**, 1.
[71] J. A. Skorcz and T. Suh, *J. Heterocyclic Chem.*, 1972, **9**, 219.
[72] J. A. Skorcz, J. T. Suh, and R. L. Germershausen, *J. Heterocyclic Chem.*, 1973, **10**, 249.
[73] R. K. Buckley, M. Davis, and K. S. L. Srivastava, *Austral. J. Chem.*, 1971, **24**, 2405.



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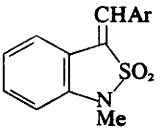

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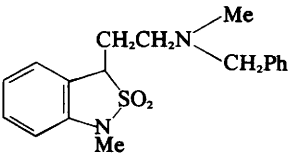

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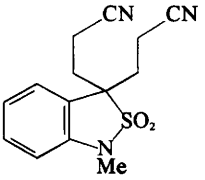
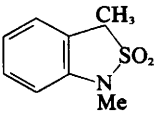
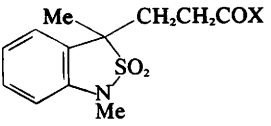


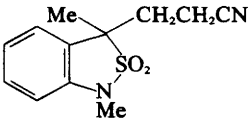
(113)



(114)



(115) X = Me
(116) X = NH_2



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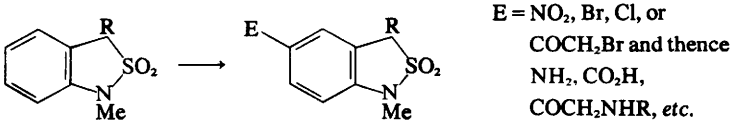


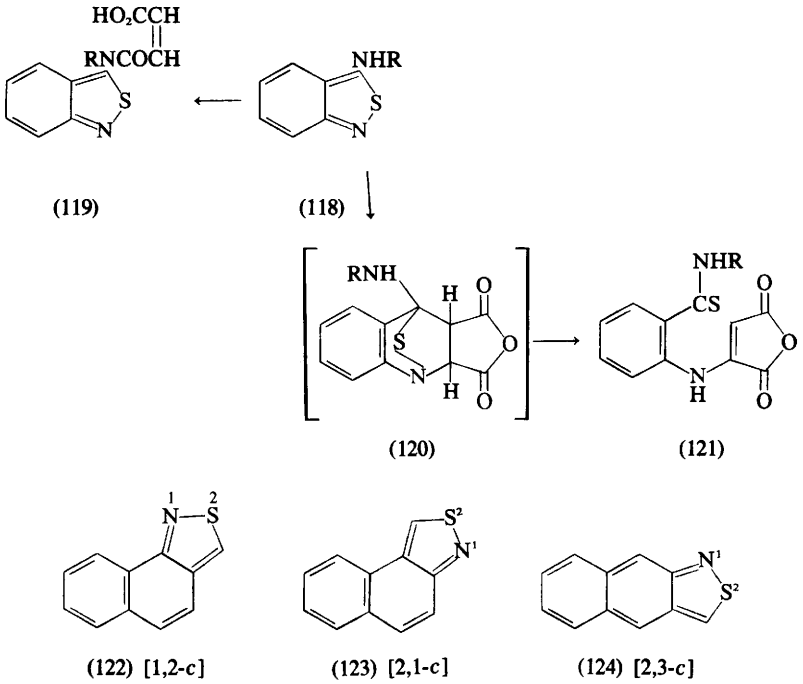
Scheme 4

Unlike 2,1-benzisoxazoles, 2,1-benzisothiazole (and its 5-methoxy-derivative) does not undergo the Diels–Alder reaction. 3-Amino-2,1-benzisothiazole (118; R = H) reacts with maleic anhydride in boiling benzene to yield simply the maleamic acid (119; R = H). 3-Methyl(and ethyl)amino-2,1-benzisothiazole (118; R = Me or Et), on the other hand, produce the thioamide (121), possibly by way of the intermediate (non-isolable) Diels–Alder adduct (120).[74]

7 Naphthisothiazoles and Isothiazolanthrene

Of the three possible isomeric naphth[c]isothiazoles (122)—(124), the angular isomers (122) and (123) have been synthesized by the reaction of the

[74] M. Davis and K. S. L. Srivastava, *J.C.S. Perkin I*, 1972, 935.



(119) (118) (120) (121)

(122) [1,2-c] (123) [2,1-c] (124) [2,3-c]

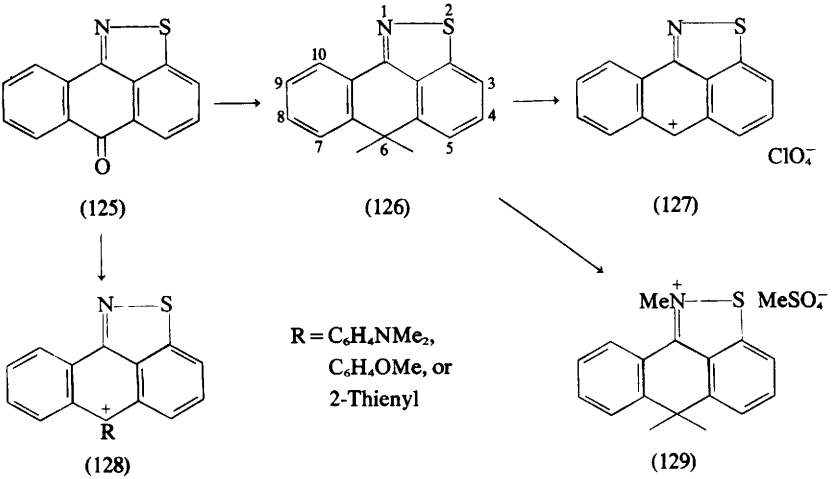
appropriate methylnaphthylamine with thionyl chloride (see these Reports, Vol. 2, p. 576), but attempts to obtain the linear isomer by this method failed. A side-reaction, probably occurring before cyclization, leads to the production of 5-chlorinated (122).[75]

Isothiazolanthrone (125) reacts with dimethylaniline, anisole, or thiophen in the presence of phosphorus oxychloride to yield 6-arylisothiazolanthrenium salts [*e.g.* perchlorates, (128)]. The unsubstituted isothiazolanthrenium perchlorate (127), forming a brown solid, is obtainable by reduction of isothiazolanthrone (125) by aluminium isopropoxide, and dehydrogenation of the resulting isothiazolanthrene (126) with trityl perchlorate. Addition of dimethyl sulphate to the isothiazolanthrene (126) yields the quaternary salts (129). U.v. spectral data were provided.[76]

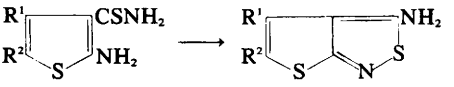
8 Other Condensed Ring Systems incorporating Isothiazole

Thieno[2,3-c]isothiazoles.—3-Aminothieno[2,3-c]isothiazoles are accessible by the oxidation of 2-aminothiophenthioamides. They undergo diazotization

[75] M. Davis, G. C. Ramsay, and L. J. Stevens, *Austral. J. Chem.*, 1972, **25**, 1355.
[76] A. L. Cherian, P. Y. Pandit, and S. Seshadri, *Indian J. Chem.*, 1972, **10**, 361.



and coupling to azo-dyes as expected:[77]



Isothiazolopyridines.—A general synthesis of isothiazolo[2,3-*a*]pyridinium salts involves a cyclization by the formation of an S—N bond as the final step. Thus, oxidation of the substituted thioacetamide (130) with hydrogen peroxide–perchloric acid or bromine, yields 2-dimethylaminoisothiazolo-[2,3-*a*]pyridinium perchlorate (131) or its 3-bromo-derivative, respectively. Applied to suitable thioketones, *e.g.* (132), the method affords a 2-alkyl-compound, *e.g.* (133), but is of restricted applicability because of the lack of efficient routes to the starting thiones (132).[78]

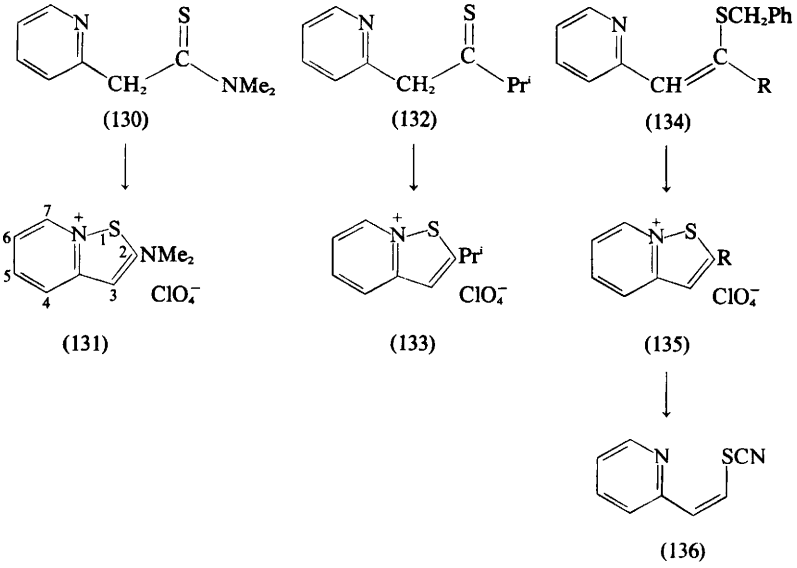
In another variant of the synthesis, the base-catalysed addition of phenylmethanethiol to 2-ethynylpyridine provides 2-(2-benzylthiovinyl)-pyridines (134), which are oxidized [to (135)] by bromine in 25—35% overall yield. The assigned structures of the condensed heterocycles agree with their n.m.r. spectra.[78]

The parent compound (135; R = H) is cleaved to *cis*-2-(2-thiocyanovinyl)-pyridine (136), but other nucleophiles cause complete decomposition to intractable products.[78]

Four additional isomeric isothiazolo-pyridine ring-systems have been synthesized by annelating the isothiazole ring to the pre-formed pyridine ring.

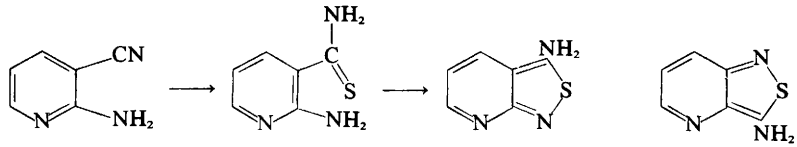
3-Aminoisothiazolo[3,4-*b*]pyridine (138) is formed from 2-aminonicotino-nitrile (137) by its successive conversion into the thioamide and oxidative

[77] K. Gewald, M. Hentschel, and R. Heikel, *J. prakt. Chem.*, 1973, **315**, 539.
[78] G. G. Abott and D. Leaver, *J.C.S. Chem. Comm.*, 1973, 150.



(130) (131) (132) (133) (134) (135) (136)

cyclization by hydrogen peroxide in pyridine. Its amino-group undergoes the expected reactions, including diazotization; its removal produces the parent base of the series. 3-Aminoisothiazolo[4,3-*b*]pyridine (139) is obtained by the same general method from 3-aminopicolinonitrile, but its attempted deamination failed.[79]

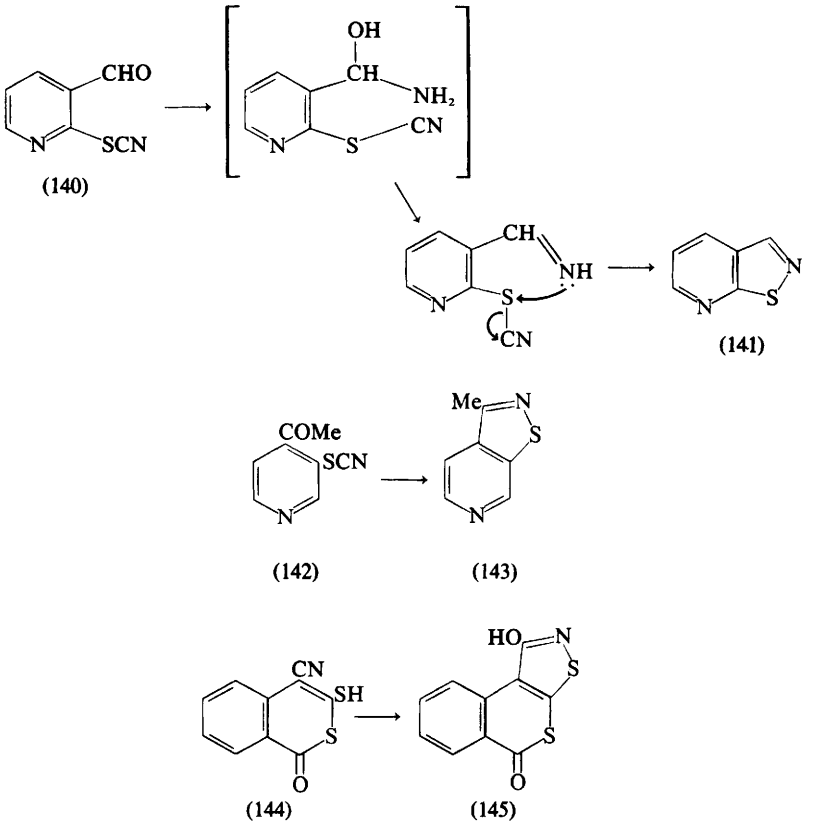


(137) (138) (139)

Isothiazolo[5,4-*b*]pyridine (141) is produced by the prolonged action of liquid ammonia at −50 °C on *o*-thiocyanatoformylpyridine (140). Finally, 3-methylisothiazolo[5,4-*c*]pyridine (143) is similarly accessible from 4-acetyl-3-thiocyanatopyridine (142). The spectral properties (n.m.r., u.v.) of each of the four series of compounds were determined and discussed.[79]

Isothiazolo[4,3-*d*]thioisocoumarin.—The cyclization of 3-thio-4-cyanothioisocoumarin (144) to the corresponding isothiazolo-compound (145) is on record.[80]

[79] A. Taurins and V. T. Khouw, *Canad. J. Chem.*, 1973, **51**, 1741.
[80] G. Kobayashi, Y. Matsuda, R. Natsuki, H. Yamaguchi, and Y. Tominaga, *Yakugaku Zasshi*, 1972, **92**, 449 (*Chem. Abs.*, 1972, **77**, 61 747k).



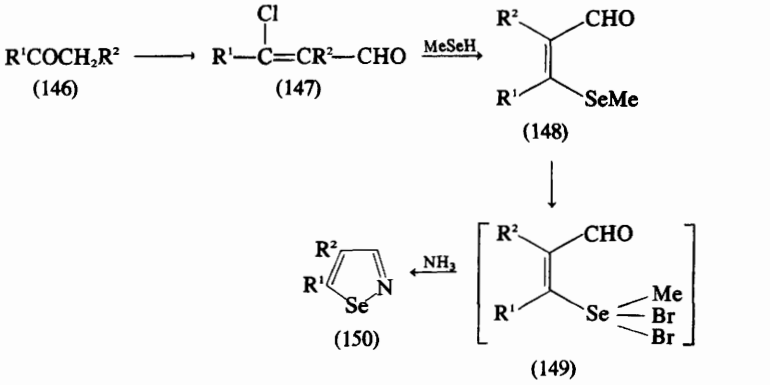
(140) (141) (142) (143) (144) (145)

9 Isoselenazoles

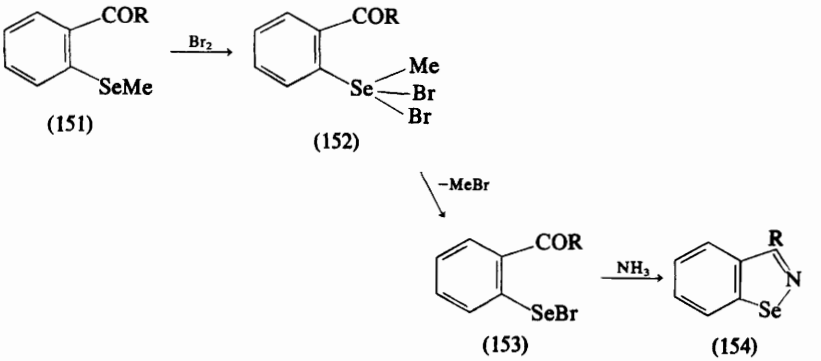
A novel synthesis of isoselenazoles (150), using bromoseleno-intermediates in the final cyclization stage, comprises the successive treatment, at −80 °C, of selenoethers of type (148), *e.g.* *cis*-β-methylseleno-2-propenal, with bromine and ammonia; it generally affords the desired heterocycles in very good yield. The precursors (148) are ultimately derived from the appropriate ketones (146), which are first converted into the chloro-aldehydes (147) by the Vilsmeier–Haack reaction, and then treated with methaneselenol in pyridine–triethylamine. They arise as mixtures of *cis*- and *trans*-isomers, separable by spinning-band fractional distillation. The u.v. and n.m.r. spectra of the isoselenazoles were recorded and discussed.[81]

1,2-Benzisoselenazoles (154) arise similarly by the action of ammonia on *o*-bromoseleno-derivatives of benzaldehyde, acetophenone, or benzophenone (153; R = H, Me, or Ph).[81] The intermediates (153) are readily

[81] R. Weber and M. Renson, *J. Heterocyclic Chem.*, 1973, **10**, 267.



accessible *via* (152) by the action of bromine on the appropriate methyl selenoethers (151)[82] and are employed *in situ*, affording the desired condensed heterocycles (154) in 55—70% overall yield. The route formally



resembles a synthesis of 1,2-benzisothiazoles from comparable o-sulphenyl halides.[83] It has the advantage of not employing the unstable selenocyanic acid needed in the more conventional cyclization routes.

[82] A. Ruwet and M. Renson, *Bull. Soc. chim. belges*, 1970, **79**, 593.
[83] K. Fries, K. Eishold, and B. Vahlberg, *Annalen*, 1927, **454**, 264.

13
Thiazoles and Related Compounds

BY F. KURZER

1 Introduction

During the current period of review, the study of the chemistry of thiazoles has attracted the same steady attention as in previous years. A comprehensive and unifying survey of the subject as a whole is still lacking. A summary of the synthesis of 2-thiazolines and thiazolidines by the ring-expansion of aziridines[1] forms a useful introduction to Wohl and Headley's study of the stereochemistry of this reaction.

In contrast, the existing knowledge of selenazoles and related selenium-containing nitrogen heterocycles is well documented, both within the framework of a large monograph on selenium compounds[2,3] and in a specialized review discussing the chemistry of selenazoles.[4]

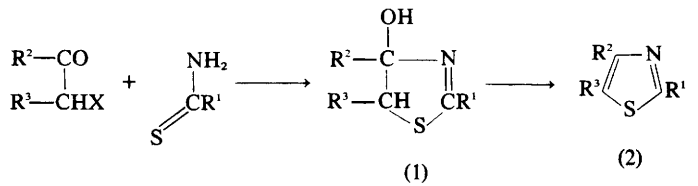
Table 1 *Production of thiazoles by Hantzsch's synthesis*

Compound Type	*Reference*
4-Substituted 2-furyl(thienyl)thiazoles	6, 7
4,5-Disubstituted 2-methylthiothiazolium salts	8
β-Phenyl-β-(4-phenylthiazol-2-yl)ethylamine	9
Substituted 2-aminothiazoles	10
2-Amino-4-arylthiazoles	11, 12
2-Amino-4-(2-thienyl)thiazoles	13, 14
2-Amino-4-arylthiazole-5-carboxyanilides	15
2-Amino-5-isonitrosomethylthiazole	16
5-Acylamino-2-methyl-4-phenylthiazoles	17
2-Amino-4-methylthiazole-5-anilide	18
2-Benzylidenehydrazinothiazol-4-ylacetic acid esters	19
(4-Substituted-2-thiazolyl)hydrazones	20
2-Thioureidothiazoles	21

[1] R. A. Wohl and D. F. Headley, *J. Org. Chem.*, 1972, **37**, 4401.
[2] E. Bulka in 'Organic Selenium Compounds', ed. D. L. Klayman and W. H. H. Günther, Wiley–Interscience, New York, 1973, pp. 449–496.
[3] L. G. S. Brooker, J. A. Ford, and E. J. van Lare, in 'Organic Selenium Compounds', ed. D. L. Klayman and W. H. H. Günther, Wiley–Interscience, New York, 1973, p. 507.
[4] E. Bulka in 'Advances in Heterocyclic Chemistry', ed. A. R. Katritzky, Academic Press, New York and London, Vol. 2, 1963, pp. 344–364.

2 Synthesis[5] of Thiazoles

Hantzsch's Synthesis (Type A, S—C—N + C—C).—The bulk of the preparative work in the thiazole field continues to be based on Hantzsch's synthesis (*cf.* Table 1[6–21]). The intermediate formation of 4-hydroxy-2-thiazolines in this reaction has once again been demonstrated[6,22] (*cf.* these Reports, Vol. 1, p. 379), this time in respect of thiazoles unsubstituted at their hetero-nitrogen atom (2).[22] Some kinetic data concerning the conversion (1) → (2), based on u.v. spectral measurements, are on record.[23]

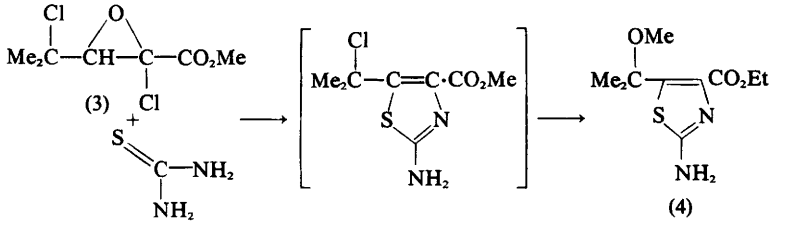


(1) (2)

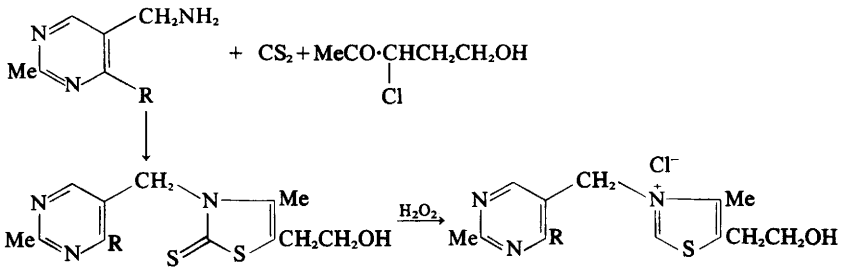
Other Type A (S—C—N + C—C) Syntheses.—2,4-Dichloro-2,3-epoxyalkanoates (3), (obtainable by the reaction of aliphatic α-halogenoaldehydes with methyl dichloroacetate) react with thiourea in methanol to yield 2-amino-4-methoxycarbonyl-5-(1-methoxyalkyl)thiazoles (4) as shown.[24]

Desaminothiamine (6; R = H) and other 2′-, 4′-, and *S*-variants of thiamine, have been prepared by attaching the thiazole moiety, derived from carbon disulphide and 3-chloropentan-1-ol-4-one, to the appropriate pyrimidine, followed by oxidative desulphurization of the resulting thiazolinethiones (5) with hydrogen peroxide.[25]

[5] For the system of classification, see J. M. Sprague and H. Land, in 'Heterocyclic Compounds', ed. R. C. Elderfield, Wiley, New York, 1957, Vol. 5, pp. 484, 496.
[6] P. Chauvin, J. Morel, and P. Pastour, *Compt. rend.*, 1973, **276**, *C*, 1453.
[7] P. Chauvin, J. Morel, C. Paulmier, and P. Pastour, *Compt. rend.*, 1972, **274**, *C*, 1347.
[8] E. D. Sych and E. K. Mikitenko, *Khim. geterotsikl. Soedinenii*, 1971, 857 (*Chem. Abs.*, 1972, **76**, 25 154k).
[9] F. Eiden and J. Iwan, *Arch. Pharm.*, 1973, **306**, 470.
[10] G. Y. Sarkis and S. Al-Azawe, *J. Chem. and Eng. Data*, 1973, **18**, 99.
[11] U. Stauss, H. P. Härter, and O. Schindler, *Chimia (Switz.)*, 1973, **27**, 99.
[12] C. P. Joshua and P. N. K. Nambisan, *Indian J. Chem.*, 1973, **11**, 118.
[13] V. A. Smirnov and A. E. Lipkin, *Khim. geterotsikl. Soedinenii*, 1971, 1369 (*Chem. Abs.*, 1972, **76**, 46 129w).
[14] V. A. Smirnov, A. E. Lipkin, and T. B. Ryskina, *Khim. Farm. Zhur.*, 1972, **6**, 24 (*Chem. Abs.*, 1972, **77**, 109 860w).
[15] A. S. Shawali, M. I. Ali, and A. A. Fahmi, *Bull. Chem. Soc. Japan*, 1973, **46**, 1798.
[16] E. C. Taylor and R. C. Portnoy, *J. Org. Chem.*, 1973, **38**, 806.
[17] B. S. Drach, I. Y. Dolgushina, and A. V. Kirsanov, *Zhur. org. Khim.*, 1973, **9**, 414.
[18] M. I. Ali, M. A. Abou-State, and N. M. Hassan, *Indian J. Chem.*, 1973, **11**, 4.
[19] I. Simiti and M. Coman, *Ann. Chim. (France)*, 1972, **7**, 33.
[20] M. S. Solanki and J. P. Trivedi, *J. Indian Chem. Soc.*, 1972, **49**, 37.
[21] I. Iwataki, *Bull. Chem. Soc. Japan*, 1972, **45**, 3218.
[22] K. Arakawa, T. Miyasaka, and H. Ohtsuka, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1041.
[23] I. Simiti, M. Coman, and I. Schwartz, *Rev. Roumaine Chim.*, 1973, **18**, 685.
[24] A. Takeda, S. Tsuboi, S. Wada, and H. Kato, *Bull. Chem. Soc. Japan*, 1972, **45**, 1217.
[25] H. Neef, K. D. Kohnert, and A. Schellenberger, *J. prakt. Chem.*, 1973, **315**, 701; see also H. Nakao, M. Ito, and S. Muramatsu, *Ann. Sankyo Res. Lab.*, 1966, **18**, 33 (*Chem. Abs.*, 1967, **66**, 115 678).

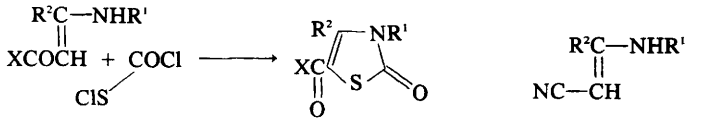


(3) (4)



(5) (6)

Type B (C—C—N + C—S) Syntheses.—Primary and secondary enamines and chlorocarbonyl sulphenyl chloride undergo a cycloacylation to thiazolones. Ethyl β-aminoacrylate (7; X = OR^2), for example, produces the 2-oxothiazole-5-carboxylic acid esters (8; X = COR^2) in 60—80% yields. β-Aminocrotonic nitriles (9) similarly afford the corresponding 5-cyano-heterocycles.[26]



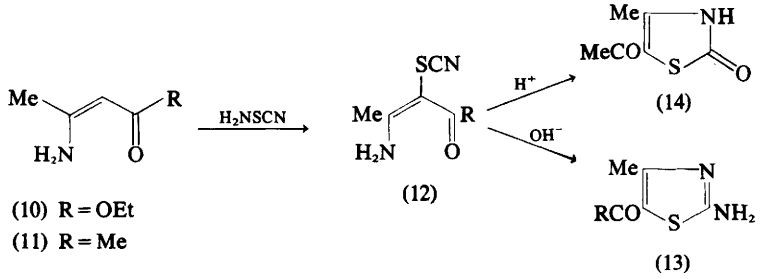
(7) (8) (9)

X = OR^3 or R^3NH R^1 = H, Alk, or Ph

The synthesis of the thiazole nucleus from aminothiocyanogen and ketones (these Reports, Vol. 2, p. 589) is also applicable to enamines derived from β-dicarbonyl compounds. Thus, β-aminocrotonic ester (10) or 2-aminopent-2-en-4-one (11) yield the intermediate enamines (12), which are cyclized to 2-aminothiazoles (13) under the influence of alkalis, and to Δ^4-thiazol-2-ones (14) by acids.[27]

The intermediate formation of substituted thioureas (15) in Heilbron's

[26] K. Grohe and H. Heitzer, *Annalen*, 1973, 1018.
[27] E. Schmitz and H. Striegler, *J. prakt. Chem.*, 1971, **313**, 1125.



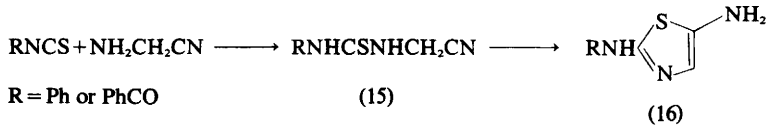
(10) R = OEt
(11) R = Me

(12)

(13)

(14)

synthesis of thiazoles (16)[28] from aminoacetonitrile and isothiocyanates has been demonstrated.[29]

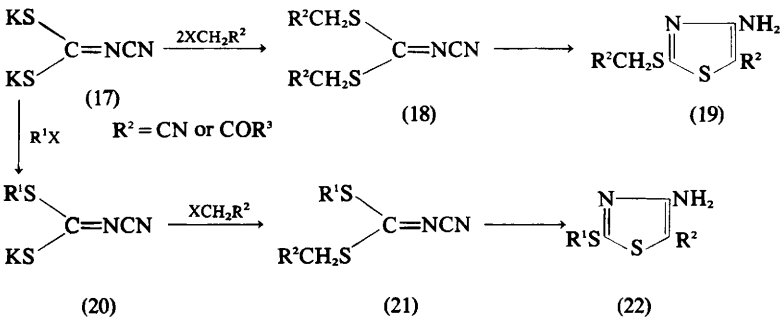


R = Ph or PhCO

(15)

(16)

Type F (C—N—C—S + C) Syntheses.—Potassium salts of cyanodithioiminocarbonates (17) react with two moles of α-halogeno-ketones or chloroacetonitrile in basic media to yield substituted 4-aminothiazoles (19).[30] By first alkylating the reactants (17), thiazoles (22) bearing unlike substituents in positions 2 and 5 may be obtained by this route. In suitable examples, the postulated intermediates (18) and (21) may be isolated.[31]



(17)

R^2 = CN or COR^3

(18)

(19)

(20)

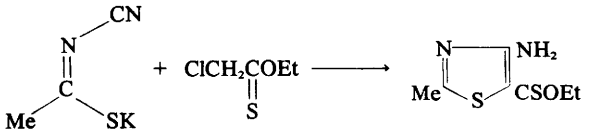
(21)

(22)

O-Ethyl α-chlorothioacetate (24), readily accessible from ethyl α-chloroorthoacetate and hydrogen sulphide in the presence of ferric chloride,[32] is a bifunctional thioacylating agent of great usefulness in the synthesis of sulphur heterocycles. Its condensation with the potassium salt of

[28] A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 1948, 1262.
[29] J. M. Balquist and F. Goetz, *J. Heterocyclic Chem.*, 1972, **9**, 937.
[30] K. Gewald, P. Blauschmidt, and R. Mayer, *J. prakt. Chem.*, 1967, **35**, 97; K. A. Jensen and L. Henriksen, *Acta Chem. Scand.*, 1968, **22**, 1107.
[31] D. Wobig, *Annalen*, 1972, **764**, 125.
[32] A. Ohno, T. Koizumi, and G. Tsuchihashi, *Tetrahedron Letters*, 1968, 2083.

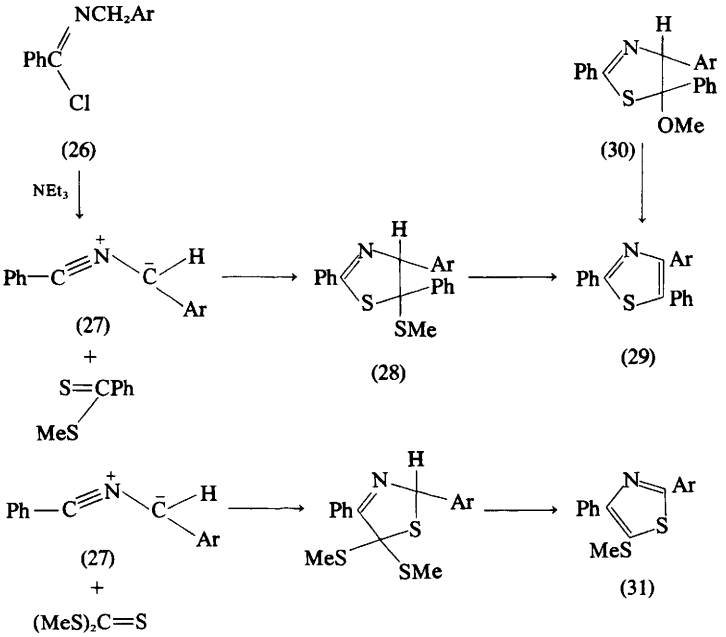
(thioacetyl)cyanamide (23) produces the substituted 4-aminothiazole (25) in 79% yield.[33]



(23) (24) (25)

Type H (C—N—C + C—S) Syntheses.—In the course of their detailed studies of nitrile-ylides, Huisgen and his co-workers[34] have examined cycloadditions of benzonitrile 4-nitrobenzylide (27) [arising from *N*-(4-nitrobenzyl)benzimidoyl chloride, (26; Ar = *p*-$C_6H_4NO_2$)] to a variety of carbon–heteroatom multiple bonds.[34] Thus, the interaction of (26) with an excess of methyl dithiobenzoate in triethylamine gave 85% yields of 2,5-diphenyl-4-(4-nitrophenyl)thiazole (29), with loss of methanethiol, two stereoisomeric Δ^2-thiazolines (28) being formed intermediately. The same thiazole arose by the use of monothiobenzoate from the primarily formed 5-methoxythiazoline (30) by spontaneous loss of methanol.[34]

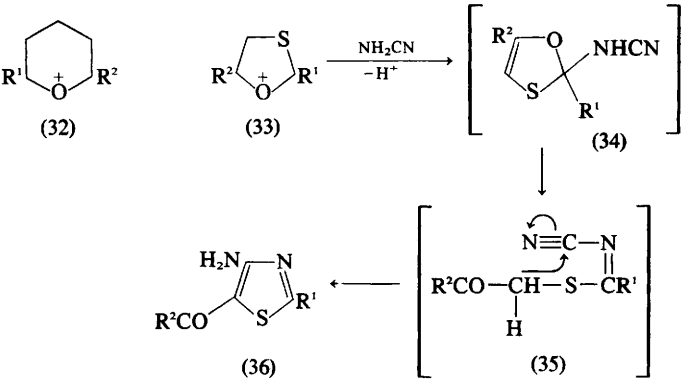
The cycloaddition of (27) to dimethyl trithiocarbonate occurs readily in the cold in a direction *opposite* to that of (di)thiobenzoates, yielding (31); the



[33] K. Hartke and G. Golz, *Annalen*, 1973, 1644.
[34] K. Bunge, R. Huisgen, R. Raab, and H. J. Sturm, *Chem. Ber.*, 1972, **105**, 1307.

intermediate thiazoline is not isolable. The direction of the cycloaddition of nitrile ylides, nitrile imines, and diazoalkanes was compared and the possible factors controlling it were discussed.[34]

Type J (C—S—C—N—C) Syntheses.—In common with their π-isoelectronic pyrylium analogues (32), 1,3-oxathiazolium salts (33)[35] are convertible into other ring-systems under the influence of nucleophiles. Their reaction with cyanamide in the presence of sodium ethoxide produces substituted 4-aminothiazoles (36); it probably involves the initial addition of the nitrile moiety at C-2, followed by ring-scission to (35), and recyclization to (36).[36]



Syntheses from the Pre-formed Thiazole Ring.—Large numbers of thiazole derivatives are produced by modifying the substituents in the pre-formed heterocycle (see Table 2[37–50]).

The preparation of the parent base from the readily accessible

[35] H. Hartmann, *J. prakt. Chem.*, 1971, **313**, 730.
[36] H. Hartmann, H. Schäfer, and K. Gewald, *J. prakt. Chem.*, 1973, **315**, 497; see also H. Hartmann, *Z. Chem.*, 1971, **11**, 421.
[37] N. Saldabols, S. Hillers, L. N. Alekseeva, and L. Kruzmetra, *Khim. Farm. Zhur.*, 1971, **5**, 15 (*Chem. Abs.*, 1972, **76**, 14 410q).
[38] S. Kano, *J. Pharm. Soc. Japan*, 1971, **91**, 1342 (*Chem. Abs.*, 1972, **76**, 99 549q).
[39] R. J. A. Walsh and K. R. H. Wooldridge, *Chim. Thérapie*, 1973, **8**, 199.
[40] I. Nabih and H. Zoorob, *J. Pharm. Sci.*, 1972, **61**, 967.
[41] P. Strehlke, *Chem. Ber.*, 1973, **106**, 721.
[42] P. J. Islip, M. D. Closier, and J. E. Weale, *J. Medicin. Chem.*, 1973, **16**, 1027.
[43] I. Simiti and G. Hintz, *Pharmazie*, 1972, **27**, 146.
[44] S. Minami, M. Tomita, and K. Kawaguchi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1716.
[45] P. J. Islip, M. D. Closier, M. R. Johnson, and M. C. Neville, *J. Medicin. Chem.*, 1972, **15**, 101.
[46] K. A. Nuridzhanyan and G. V. Kuznetsova, *Khim. geterotsikl. Soedinenii*, 1972, 1626 (*Chem. Abs.*, 1973, **78**, 71 989a).
[47] H. Tripathy, D. G. Pradhan, B. C. Dash, and G. N. Mahapatra, *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 1375.
[48] M. D. Aptekar, E. P. Trailina, L. K. Gulchenko, and I. A. Savich, *Khim. Farm. Zhur.*, 1972, **6**, 19 (*Chem. Abs.*, 1973, **78**, 38 507).
[49] M. A. Portnov, T. A. Veselitskaya, and V. A. Zasasov, *Khim. Farm. Zhur.*, 1971, **5**, 24 (*Chem. Abs.*, 1971, **75**, 48 964t).
[50] E. C. Roberts and Y. F. Shealy, *J. Medicin. Chem.*, 1972, **15**, 1310.

Table 2 *Production of thiazoles from the pre-formed heterocycle by conventional reactions.*

Compound	*Reference*
4-(2-Furylvinyl)thiazoles	37
2-Alkylamino(alkylthio, hydroxy)-5-thiocyanatothiazoles	38
Ethyl 2-nitrothiazole-4-carboxylate	39
2-*N*-(2′-Methyl-4′-hydroxy-5′-pyrimidoyl)amino-5-nitrothiazole	40
5-Nitrothiazol-2-ylcarboxylic acid	41
3-[(5-Nitro-2-thiazolyl)amino]propionitrile	42
2-Benzyl-4-formylthiazoles	43
Thiazol-2-yl-β-mercaptocinnamamides	44
1-Acyl-3-(thiazol-2-yl)ureas	45, 46
1-Substituted-2-(thiazolyl)hydrouracils	45
N-Thiazolyl-substituted salicylic and other hydroxy-acid amides	47
N^4-Benzylidene-N^1-(2-thiazolyl)sulphanilamides	48
2-(*p*-Aminobenzenesulphonamido)thiazole	49
Folic acid, thiazole analogue	50

2-bromothiazole is noteworthy. It is performed nearly quantitatively by electrolytic reduction at −0.7 V (*vs.* Ag|AgCl) in hydrochloric acid.[51] The process is based on the polarographic data concerning halogenothiazoles due to Laviron;[52] thiazole shows no polarographic wave in acid solution and is not further reduced under the experimental conditions.

3 Physical Properties of Thiazoles

Metzger and his co-workers[53] have continued to provide theoretical calculations, based on HMO and PPP methods, of the magnitudes of electron densities, bond orders, and negative polarization energies of thiazole derivatives, including 2-, 4-, and 5-phenylthiazoles.[53]

A detailed study of n.m.r. spectra[54] has provided extensive data on chemical shifts and coupling constants in respect of a series of monophenylthiazoles, and their derivatives bearing alkyl and functional substituents in their hetero-rings. The chemical shifts were correlated with the net π-charges derived theoretically from electron density and energy diagrams, and the overall results were compared with those previously[55] obtained in respect of thiazole and its methyl derivatives.

The pK_a values of 2-amino-4(and 5)-(*p*-substituted)arylthiazoles, determined spectrometrically, are linearly related to the Hammett σ_{para} values of

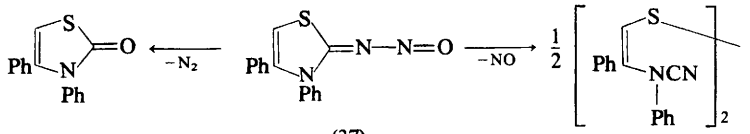
[51] P. E. Iversen, *Synthesis*, 1972, 484.
[52] E. Laviron, *Bull. Soc. chim. France*, 1961, 2350.
[53] M. Baule, R. Vivaldi, J. C. Poite, H. J. M. Dou, G. Vernin, and J. Metzger, *Bull. Soc. chim. France*, 1971, 4310.
[54] J. P. Aune, R. P. T. Luu, E. J. Vincent, and J. Metzger, *Bull. Soc. chim. France*, 1972, 2679.
[55] E. J. Vincent, R. P. T. Luu, and J. Metzger, *Bull. Soc. chim. France*, 1966, 87.

the substituted-phenyl substituents. In agreement with the greater electronegativity of oxygen compared with that of sulphur, the thiazoles are more basic than their 2-amino-4-aryloxazole analogues.[11]

4 Chemical Properties of Thiazoles

Photolytic and Related Reactions.—The photoisomerization of 2-phenylthiazole has been elucidated by marking the 4- or 5-position of this structure with deuterium or with a methyl group. 5-Deuterio-2-phenylthiazole, for example, is isomerized principally to 5-deuterio-4-phenylthiazole, or to 4-deuterio-3-phenylisothiazole, in the absence or presence, respectively, of iodine. Supplementary studies employing 2-, 5-, and 4-phenylthiazole gave comparable results. Possible mechanisms of these reactions were considered in detail: those best fitting the observations are valence-isomerization processes, with or without preliminary opening of weaker bonds in the first excited state, involving torsion of bonds adjacent to sulphur.[56]

N-Nitroso-imines are generally unstable, decomposing to the corresponding carbonyl compounds and nitrogen. Although a few heteroaromatic compounds bearing a nitroso-imino-group stabilized by conjugation have been isolated, they also decompose to carbonyl compounds and nitrogen in boiling toluene. Thus, 3,4-diphenyl-2-nitroso-imino-2,3-dihydrothiazole (37) yields the thiazolone (38) as the product of its thermolysis; its photolysis proceeds differently, cleaving the hetero-ring and producing bis-[(2-phenyl-2-*N*-phenylcyanamino)vinyl] disulphide (39). More detailed experiments were carried out in the benzothiazole series (see p. 626).[57]



(38) (37) (39)

Thiazol-2-yl radicals, generated by the aprotic diazotization of 2-aminothiazole, interact with alkylbenzenes to yield principally 2-arylthiazoles. The relative rates and partial rate factors of this homolytic thiazolylation process have been measured. The influence of substituents on the radicals is related to their polar character, but is much smaller than that of substituents in aromatic substrates.[58]

Quaternization and Alkylation.—The rates of quaternization of a number of thiazoles[59,60] and benzothiazoles[60] have been measured by kinetic,[59]

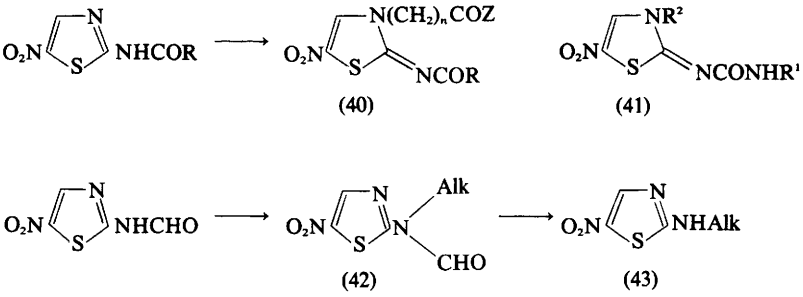
[56] C. Riou, G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. chim. France*, 1972, 2673; G. Vernin, C. Riou, H. J. M. Dou, L. Boucasse, J. Metzger, and G. Loridan, *ibid.*, 1973, 1743.
[57] K. Akiba, I. Fukawa, N. Nomura, and N. Inamoto, *Bull. Chem. Soc. Japan*, 1972, **45**, 1867.
[58] G. Vernin, H. J. M. Dou, and J. Metzger, *J.C.S. Perkin II*, 1973, 1093.
[59] R. Gallo, M. Chanon, H. Lund, and J. Metzger, *Tetrahedron Letters*, 1972, 3857.
[60] G. B. Behera, J. N. Kar, R. C. Acharya, and M. K. Rout, *J. Org. Chem.*, 1973, **38**, 2164.

spectrometric,[59] and conductometric[60] techniques, and the entropies of activation of the reactions calculated.[60]

A study of the quaternization of 2-alkyl- and 2,4-dialkyl-thiazoles and 2-alkyl-1,3,4-thiadiazoles has served to elucidate the applicability of the Taft steric parameters, E_s.[61] It appears that E_s values from the Taft scale will correlate structural or reactivity data, provided that the groups concerned are in a structural environment which does not induce a significant conformational preference of the group.[62]

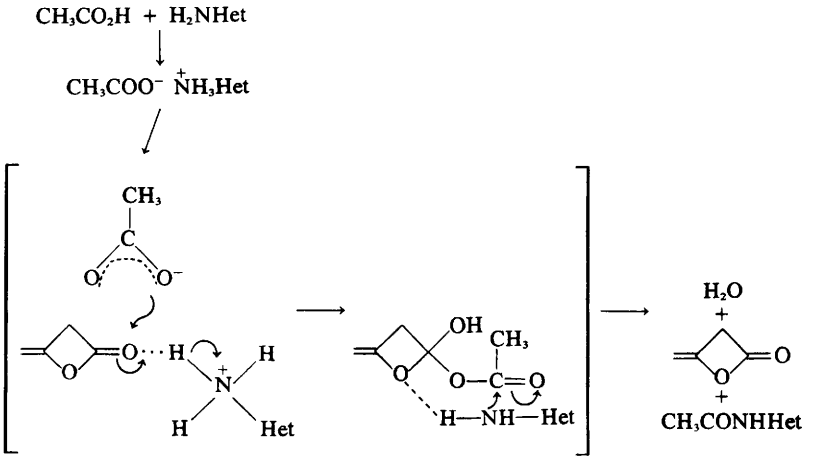
The alkylation of 2-amino-4-ethylthiazole with secondary alcohols gives 60—70% yields of 2-alkylamino-derivatives. t-Butyl alcohol in sulphuric acid produces 2-amino-4-ethyl-5-t-butylthiazole.[63]

The alkylation of 2-acetamido-5-nitrothiazole with bromoacetic acid or bromoacetamide[64] in DMF, or with other alkyl halides,[65] occurs predominantly on the hetero-ring nitrogen, furnishing iminothiazolines of type (40)[64] and (41).[65] In contrast, alkylation of the sodium salt of 2-formamido-5-nitrothiazole produces exclusively exocyclically *N*-alkylated products (42). Subsequent removal of the formyl group by hydrolysis or hydrazinolysis affords good yields of the aminothiazoles (43), which are convertible into functional derivatives by conventional procedures.[65]



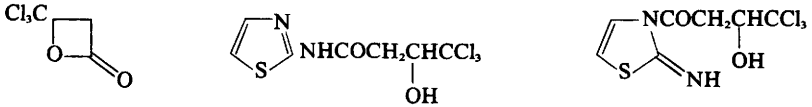
Acylation.—The conversion of 2-aminothiazole into the 2-acetamido-derivative by boiling acetic acid is greatly promoted by the catalytic action of diketen, possibly by a mechanism involving a six-centred cyclic transition state stabilized by at least two hydrogen bonds (Scheme 1).[67]

[61] R. W. Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 3120; and in 'Steric Effects in Organic Chemistry', ed. M. S. Newman, Wiley, New York, 1956, Ch. 13.
[62] A. Babadjamian, M. Chanon, R. Gallo, and J. Metzger, *J. Amer. Chem. Soc.*, 1973, **95**, 3807.
[63] V. A. Krasovskii and S. I. Burmistrov, *Khim. geterotsikl. Soedinenii*, 1971, 1188 (*Chem. Abs.*, 1972, **76**, 25 147k).
[64] P. J. Islip, M. D. Closier, M. C. Neville, L. M. Werbel, and D. B. Capps, *J. Medicin. Chem.*, 1972, **15**, 951.
[65] L. M. Werbel, M. B. Degnan, G. F. Harger, D. B. Capps, P. J. Islip, and M. D. Closier, *J. Medicin. Chem.*, 1972, **15**, 955.
[66] P. J. Islip, M. D. Closier, and M. C. Neville, *J. Medicin. Chem.*, 1973, **16**, 1030.
[67] F. I. Luknitskii, *Zhur. org. Khim.*, 1971, **7**, 1247.



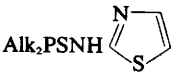
Scheme 1

β-Trichloromethyl-β-propiolactone (44) similarly acylates 2-amino-thiazole (as well as 2-amino-1,3,4-thiadiazoles) at the nuclear and exocyclic nitrogen, yielding (45) and (46).[68]



(44) (45) (46)

Sodium borohydride reduces 2-acylamino-5-acylthiazoles preferably at the 5-acyl-group, to the corresponding 5-α-hydroxyalkyl derivatives.[69] Dialkylphosphinothioyl derivatives (47) of 2-aminothiazole have been described.[70]



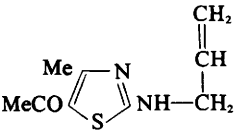
(47)

Electrophilic Substitution.—The nitration of a series of phenyl-, benzyl-, and phenethyl-thiazoles has been studied under standard conditions suitable for the mono-nitration of the most reactive example, *viz.* 4,5-dimethyl-2-phenethylthiazole. The results show that the heterocyclic ring exerts a strong

[68] F. I. Luknitskii and F. P. Shvartsman, *Khim. geterotsikl. Soedinenii*, 1972, 260 (*Chem. Abs.*, 1972, **76**, 140 733k).
[69] D. Suciu, *J. prakt. Chem.*, 1972, **314**, 961.
[70] J. Bödeker and R. John-Schenk, *Z. Chem.*, 1972, **12**, 137.

deactivating effect on the benzene nucleus. It promotes predominant *meta*- and *para*-nitration in the 2-benzylthiazoles and *para*-nitration in the 2-phenethylthiazoles. The calculated electron densities of the reactants are not in good agreement with the experimental observations, and reasons for the discrepancies have been discussed.[53]

Bromination of the substituted 2-amino-thiazole (48) yields, in two stages, the tribromo-derivative (49) as final product. Its further interaction with thioureas yields bi-thiazoles of type (50).[71]



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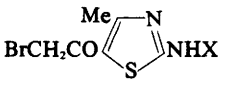

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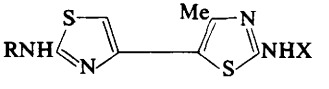


(50)

X = $CH_2CHBrCH_2Br$

A quantitative study of the solvolysis of α-arylethanol derivatives has been developed as an approach to the estimation of aromatic reactivity;[72] the concept has been extended with success to heterocyclic systems and provides a useful set of σ constants for the (hetero)aryl moiety, designated σ^+ by Streitwieser.[72] The quantitative solvolysis of the three isomeric 1-(thiazolyl)ethyl chlorides (and of 1-phenethyl chloride) has given the following replacement σ^+_{Ar} values for the thiazole moieties: 5-, 4-, 2-thiazolyl; −0.18, −0.01, +0.26, respectively. They show that the susceptibility to *electrophilic* aromatic substitution is in the order 5-thiazolyl > 4-thiazolyl > phenyl > 2-thiazolyl, a conclusion that is in agreement with the results of other theoretical approaches to this problem.[73]

The extension[74] of this work to several substituted 1-(5-thiazolyl)ethanol derivatives has provided information on the transmission of substituent effects in this heterocyclic system. For the series 1-(2-X-5-thiazolyl)ethyl and 1-(5-X-2-thiazolyl)ethyl chlorides, reaction rates are well correlated by Brown's[75] substituent constants σ_p^+ for the substituents X. The results suggest that in situations where direct conjugation, in a classical valence-bond sense, is permissible, substituent constants from benzene appear applicable to substituted thiazoles.

[71] D. Suciu, *Arch. Pharm.*, 1973, **306**, 152.
[72] A. Streitwieser, A. Lewis, I. Schwager, R. W. Fish, and S. Labana, *J. Amer. Chem. Soc.*, 1970, **92**, 6525, and subsequent papers.
[73] D. S. Noyce and S. A. Fike, *J. Org. Chem.*, 1973, **38**, 3316.
[74] D. S. Noyce and S. A. Fike, *J. Org. Chem.*, 1973, **38**, 3318.
[75] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4079.

In contrast, neither electrophilic substituent constants[75] σ_m^+ nor σ_m constants provide a suitable basis for correlating the relative rates of solvolysis of 1-(2-substituted 4-thiazolyl)ethyl chlorides, recalling similar poor correlations in several other heterocyclic systems. An alternative working model, based on a comparison of appropriately substituted pyridines and thiazoles, provides an adequate treatment of the substituent effects in these instances.[76]

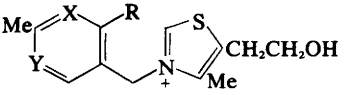
The rate of solvolysis of 1-(2-phenyl-5-thiazolyl)ethyl chloride is consistent with the substituent having an electrophilic substituent constant value of $\sigma_p^+ = -0.34$. This result is accounted for satisfactorily in terms of the coplanarity of the triazole and phenyl rings in this structure.[77]

Nucleophilic Substitution.—The replacement of halogen in 2-bromo-5-carboxy-4-methylthiazoles (51; R = EtO or PhNH) by a wide variety of nucleophiles (including phenols, thiophenols, dithiocarbamic acids, and sulphinic acids) has provided the appropriate derivatives (52) in high yields, but some anomalies were observed. The products included examples incorporating 1,3,4-thiadiazole or benzothiazole nuclei in the 2-position of (52).[78]

(51) (52)

Nucleophilic replacement of nitro- by fluoro-groups, by the action of potassium fluoride in *N*-methyl-2-pyrrolidone, provides 2-fluorothiazole, which is difficultly accessible by other means.[79]

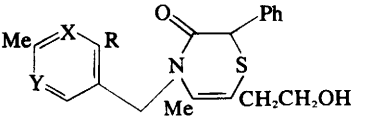
Ring Expansion to 1,4-Thiazines.—Takamizawa's ring expansion of thiazolium salts to 1,4-thiazines by the use of dialkyl acylphosphonates (these Reports, Vol. 2, p. 605) has been extended to analogues (53)—(55) of thiamine. The synthesis of each of the model compounds was described in detail; they gave, in general, the expected 1,4-thiazines (56) as the main products. For the extensive data, the original paper must be consulted.[80]



(53) X = Y = N

(54) X = N, Y = CH

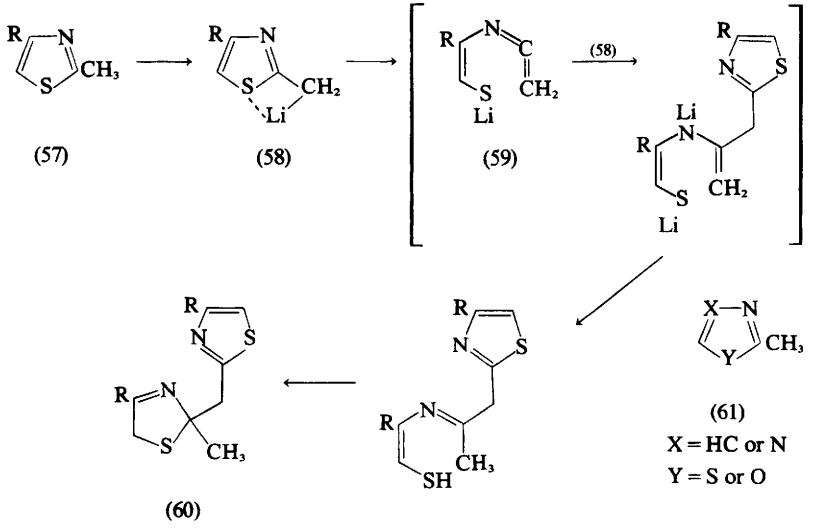
(55) X = Y = CH; R = NH_2



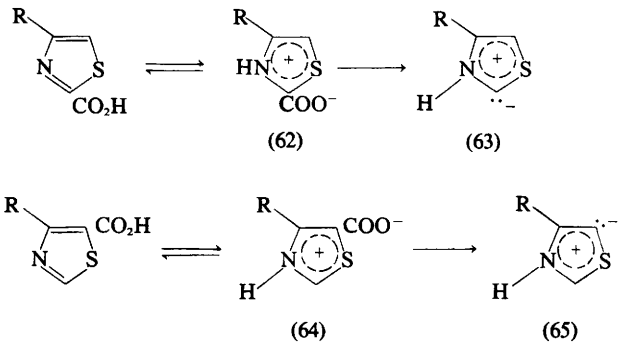
(56)

[76] D. S. Noyce and S. A. Fike, *J. Org. Chem.*, 1973, **38**, 3321.
[77] D. S. Noyce and S. A. Fike, *J. Org. Chem.*, 1973, **38**, 2433.
[78] M. F. A. Abdel-Lateef and Z. Eckstein, *Roczniki Chem.*, 1972, **46**, 1647.
[79] G. Bartoli, A. Latrofa, F. Naso, and P. E. Todesco, *J.C.S. Perkin I*, 1972, 2671.
[80] A. Takamizawa and H. Harada, *Chem. and Pharm. Bull (Japan)*, 1973, **21**, 770.

Dimerization.—The lithio-salts of thiazoles[*e.g.* (58)], though stable at low temperatures, rearrange and dimerize to (60) at room temperature, by way of ketenimines (59), in 90% yield. The dimers (60) are reconverted into the starting material (57) above 150 °C. The reaction is general to heteroaryl systems of type (61), and has also been performed using 2-methyl-5-phenyl-1,3,4-thiadiazole.[81]



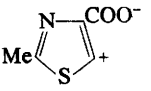
Ylides of Thiazolium Ions.—The decarboxylation of thiazolium carboxylates (62) and (64), and parallel work on oxazolium and imidazolium analogues, has been employed for measuring the rate of generation of heterocyclic ylides (63), (65), with the object of studying the effect of the sulphur atom on ylide stability. The kinetic data suggest that the 5-ylides are generated at approximate relative rates of $10^{5.4}:10^{3}:1$ for the oxazolium, thiazolium, and



[81] A. I. Meyers and G. N. Knaus, *J. Amer. Chem. Soc.*, 1973, **95**, 3408.

imidazolium rings. Since potential acidities in the ground state predict similar rates for the thiazole and imidazole analogues, the large difference between them is ascribed to a transition-state effect, and reflects the special bonding properties of sulphur in an azolium ring. The bearing of these and other conclusions on the structure of thiamine ylide was discussed.[82]

Dehydrothiazole.—The established ready generation of benzyne by the decomposition of benzenediazonium-2-carboxylate has stimulated attempts to produce 4,5-dehydrothiazole analogously, by diazotization of 5-amino-2-methylthiazole-4-carboxylic acid. In the presence of furan, 5-(2′-furyl)-2-methylthiazole-4-carboxylic acid is indeed formed, but the preliminary evidence suggests that 4,5-dehydro-2-methylthiazole in the polar form is unlikely to be involved as an intermediate in this reaction, the product arising more probably from (66).[83]



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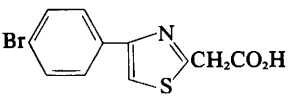
Miscellaneous Reactions.—In a study aimed at the elucidation of the mechanism of the decarboxylation of heterocyclic acetic and related acids, compounds (67)—(69) were included in the quantitative experiments. The



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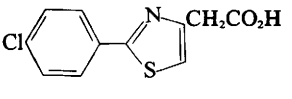

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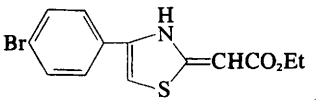
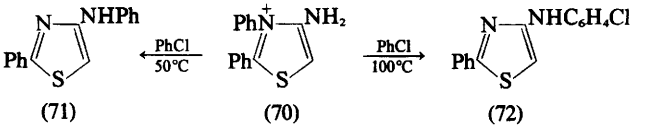


(69)

observations favour the participation of zwitterions rather than cyclic transition states as intermediates of the decarboxylation.[84]

Further examples of the aminolysis of 4-amino-2,3-diarylthiazolium chlorides have been examined [*e.g.* (70) → (71) and (72) at 50 °C, (70) → (72) at 100 °C]. Taken as a whole, the observations have not sustained the mechanism previously suggested (these Reports, Vol. 2, p. 601), and other proposals have accordingly been made.[85]

[82] P. Haake, L. P. Bausher, and J. P. McNeal, *J. Amer. Chem. Soc.*, 1971, **93**, 7045.
[83] Y. Tamura, T. Miyamoto, and M. Ikeda, *Chem. and Ind.*, 1971, 1439.
[84] P. J. Taylor, *J.C.S. Perkin II*, 1972, 1077; R. G. Button and P. J. Taylor, *ibid.*, 1973, 557.
[85] A. Chinone, M. Maruyama, and M. Ohta, *Bull. Chem. Soc. Japan*, 1972, **45**, 2222.

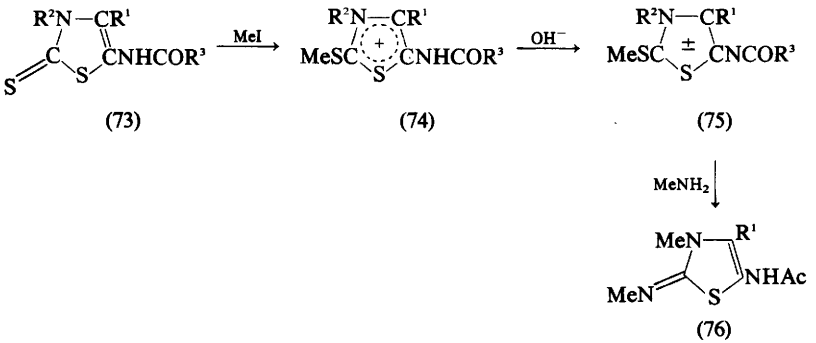


(71) (70) (72)

Cyanine Dyes.—The thiazole ring may function as the heterocyclic moiety in cyanine dyes. (compare Chap. 14, p. 636).[86–89]

Analytical.—The mass spectra of 24 alkylthiazoles have been tabulated.[90] The data are of potential analytical use, in that alkylthiazoles have been found in several foods, including roasted filberts,[91] roasted peanuts,[91] and roasted coffee,[92] while related 2-thiazolines have been identified in beef broth.[93]

Meso-ionic Thiazoles.—Successive treatment of 5-acylamino-Δ^4-thiazoline-2-thiones (73) with methyl iodide and alkali yields products that have been recognized as meso-ionic 5-acylimino-2-methylthio-thiazoles (75) (see also these Reports, Vol. 2, p. 614).[94] This formulation supersedes the thiazolium salt structure by which certain members of this series have previously been represented.[95] The methylthio-group of (75) is readily replaced on treatment with nucleophilic reagents such as potassium hydrosulphide, dicyanomethide ion, amines, *etc.*, with formation of 2-substituted 5-acylamino-Δ^4-thiazolines [*e.g.* (76)].[94]

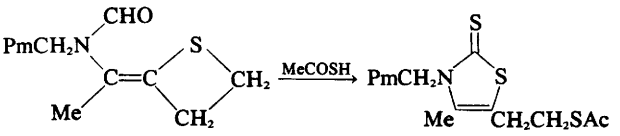


(73) (74) (75) (76)

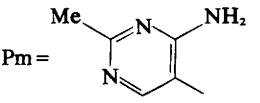
[86] E. D. Sych and O. V. Moreiko, *Khim. geterotsikl. Soedinenii*, 1972, 933 (*Chem. Abs.*, 1972, **77**, 166 138r).
[87] A. V. Kazymov and L. P. Shchelkina, *Khim. geterotsikl. Soedinenii*, 1971, 693 (*Chem. Abs.*, 1972, **76**, 114 813s).
[88] E. D. Korotkaya and V. Y. Pochinok, *Khim. geterotsikl. Soedinenii*, 1972, 786 (*Chem. Abs.*, 1972, **77**, 141 472g).
[89] A. I. Kiprianov, S. G. Fridman, and F. A. Mikhailenko, *Zhur. org. Khim.*, 1973, **9**, 1253.
[90] R. G. Buttery, L. C. Ling, and R. E. Lundin, *J. Agric. Food Chem.*, 1973, **21**, 488.
[91] T. E. Kinlin, R. Muralidhara, A. O. Pittet, A. Sanderson, and J. P. Walradt, *J. Agric. Food Chem.*, 1971, **19**, 972; *ibid.*, 1972, **20**, 1021.
[92] M. Stoll, M. Winter, F. Gautschi, I. Flament, and B. Wilhalm, *Helv. Chim. Acta*, 1967, **50**, 628.
[93] C. H. T. Tonsbeek, H. Copier, and A. J. Planken, *J. Agric. Food Chem.*, 1971, **19**, 1014.
[94] T. Shiba and H. Kato, *Bull. Chem. Soc. Japan*, 1973, **46**, 964.
[95] A. H. Cook and S. F. Cox, *J. Chem. Soc.*, 1949, 2337.

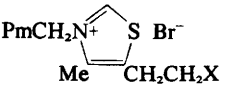
5 Biochemical Aspects of Thiazoles

Thiamine anhydride (77) is a useful source of sulphur analogues of thiamine. Thus, it reacts with thioacetic acid to give the thiazolinethione (78), which on successive desulphurization by the action of hydrogen peroxide and treatment with barium chloride affords acetylthioethylthiamine (79); hydrolysis finally produces mercaptoethylthiamine (80), the sulphur analogue of thiamine. This is convertible into further derivatives,[96] particularly by replacement of the mercapto-group of the 5-side-chain by amino-, sulphenyl-, sulphinyl-, and sulphonyl-residues [*e.g.* (81), (82)].[97]



(77) (78)





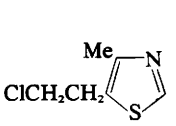
(79) X = SAc
(80) X = SH
(81) X = SO_2OH
(82) X = SO_2Me

2-(4-Chlorophenyl)thiazol-4-ylacetic acid ('Myalex', see these Reports, Vol. 1, p. 386) is a potent anti-inflammatory agent in animals, but it causes cholestatic jaundice in patients with rheumatoid arthritis, and has consequently not become an established remedy. Its metabolism by microorganisms yields at least eleven (identified) metabolites. Attack occurs at its acetic acid side-chain, which is modified in a number of ways, in contrast to the hydroxylation of the chlorophenyl ring effected by mammals (see these Reports, Vol. 1, p. 392, and Vol. 2, p. 613).[98]

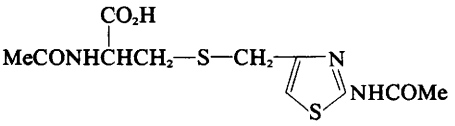
'Chloromethiazole' (83) is metabolized in rat mainly to 2-hydroxy-4-methylthiazole-5-acetylglycine. Liver, brain, and kidney homogenates convert it into 2-hydroxy-4-methylthiazole-5-acetic acid and its non-hydroxylated analogue.[99] 2-Acetamidothiazoles are metabolized (in rat) with fission of the thiazole ring, chiefly to the corresponding acetylhydantoic acids. The predominating metabolite of 2-acetamido-4-chloromethylthiazole

[96] A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2222.
[97] A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2229.
[98] R. Howe, R. H. Moore, B. S. Rao, and A. H. Wood, *J. Medicin. Chem.*, 1972, **15**, 1040.
[99] G. Herbertz and H. Reinauer, *Naunyn-Schmiedeberg's Arch. Pharmakol.*, 1971, **270**, 192 (*Chem. Abs.*, 1971, **75**, 107 943k).

is its conjugate with mercapturic acid [*i.e.* (84)], and 2-acetamidothiazole-4-carboxylic acid.[100] A number of 4,5-dialkyl(or -aryl)-2-halogenoacetylamino(and 2-sulphonamido)thiazoles show promising mitostatic properties.[101]



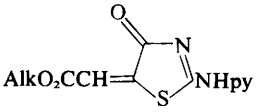
(83)



(84)

6 Synthesis of Δ^2-Thiazolines

Type A (S—C—N + C—C) Syntheses.—4-Hydroxy-Δ^2-thiazolines have been produced by Hantzsch's method.[22] The synthesis of Δ^2-thiazolines by the interaction of substituted thioureas and diethyl acetylenedicarboxylate (see these Reports, Vol. 2, p. 617) has been applied to the production of 5-alkoxycarbonylmethylene-2-(2-pyridylamino)-Δ^2-thiazolin-4-ones (85).[102]



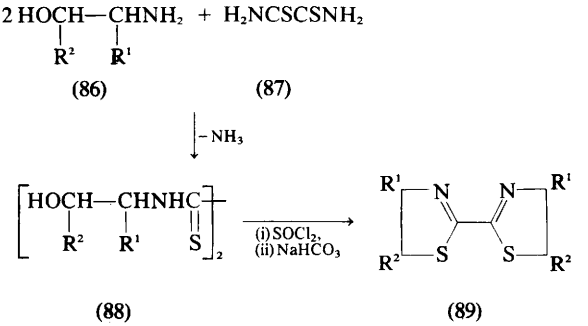
(85)

The synthesis of Δ^2-thiazolin-4-ones from glycidic esters and thiourea, first reported by Culvenor *et al.*,[103] has been reinvestigated by modern spectroscopic methods, and the mechanism originally proposed has been confirmed experimentally.[104] Phenyl dithiocarbamate reacts analogously.

Type B (C—C—N + C—S) Syntheses.—A facile synthesis of 2,2′-bis-Δ^2-thiazolines (89) from readily available starting materials involves the condensation of amino-alcohols (86) and dithio-oxamide (rubeanic acid) (87) to *NN*′-bis(hydroxyalkyl)dithio-oxamides (88). These are converted, by successive treatment with thionyl chloride and bicarbonate, into the desired bicyclic products (89).[105]

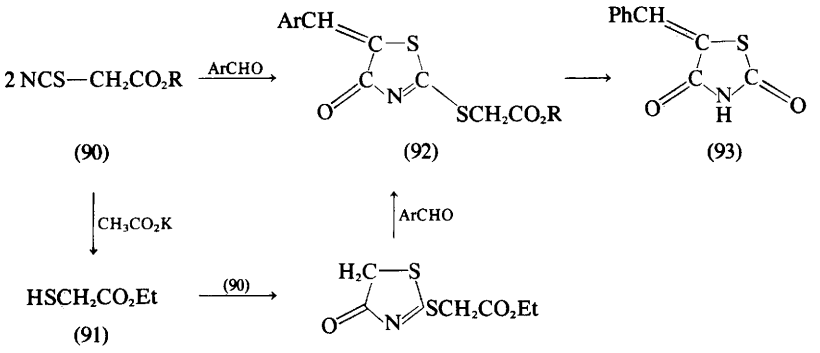
Type D (C—C—S + C—N) Syntheses.—The interaction of thiocyanoacetic ester (90) with aldehyde in the presence of potassium acetate–acetic acid unexpectedly yields 5-arylidene-2-ethoxycarbonylmethylthio-Δ^2-thiazolin-4-ones (92). Reaction in acetic acid alone gives only poor yields of

[100] S. H. Chatfield and W. H. Hunter, *Biochem. J.*, 1973, **134**, 869, 879.
[101] F. Gagiu, A. Cacoveanu, C. Nistor, and G. Todor, *Pharmazie*, 1972, **27**, 164, 166.
[102] B, Stanovnik and M. Tišler, *Monatsh.*, 1973, **104**, 1034.
[103] C. C. J. Culvenor, W. Davies, J. A. Maclaren, P. F. Nelson, and W. E. Savige, *J. Chem. Soc.*, 1949, 2573.
[104] J. Roggero and M. Audibert, *Bull. Soc. chim. France*, 1971, 4021.
[105] D. A. Tomalia and J. N. Paige, *J. Org. Chem.*, 1973, **38**, 3949.



(86) (87) (88) (89)

5-arylidenethiazolidine-2,4-dione (93). The formation of (92) is visualized to involve the preliminary conversion of the thiocyanoacetic ester (90) into mercaptoacetate (91) by the potassium acetate, followed by its successive condensation with more (90) and aldehyde to give the final product (92).[106]

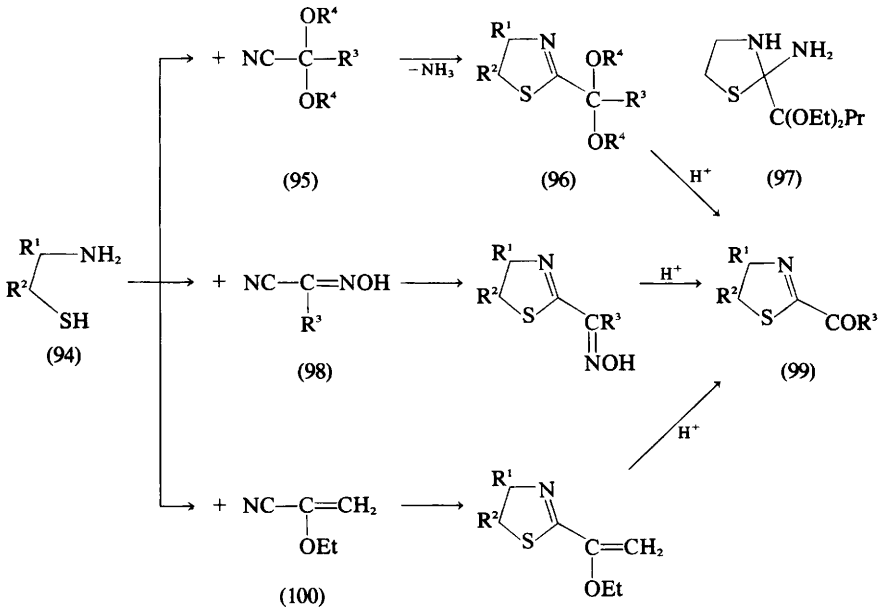


(90) (92) (93) (91)

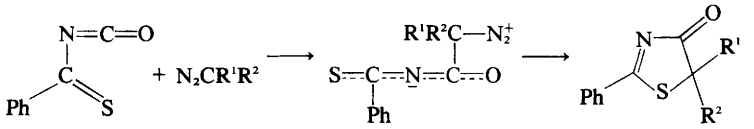
Type E (N—C—C—S + C) Syntheses.—2-Acyl-Δ^2-thiazolines (99) are accessible by the adaptation of known reactions,[107] by the condensation of cysteamine (94; $R^1 = R^2 = H$) and 2,2-dialkoxyalkanenitrile, followed by hydrolysis of the resulting 2-(1,1-dialkoxyalkyl)-Δ^2-thiazoline (96) by 96% sulphuric acid. The intermediate adduct (97) was isolated in one example. The use of 2-hydroxyalkane-iminonitriles (98) and 2-ethoxyacrylonitrile (100) affords 2-acyl-Δ^2-thiazolines similarly.[108] The synthetic work was stimulated in some measure by the observation[109] that a substance with a bread-like odour, isolated from beef-broth, was very probably 2-acetyl-Δ^2-thiazoline.

Type F (C—N—C—S + C) Syntheses.—The condensation of thiobenzoyl isocyanate and diazoalkanes, with loss of nitrogen from the latter, affords

[106] S. Kambe, *Bull. Chem. Soc. Japan*, 1973, **46**, 2926.
[107] H. Baganz and L. Domaschke, *Chem. Ber.*, 1962, **95**, 1842.
[108] T. Doornbos and H. G. Peer, *Rec. Trav. chim.*, 1972, **91**, 711.
[109] C. H. T. Tonsbeck, H. Copier, and A. J. Plancken, *J. Agric. Food Chem.*, 1971, **19**, 1014.



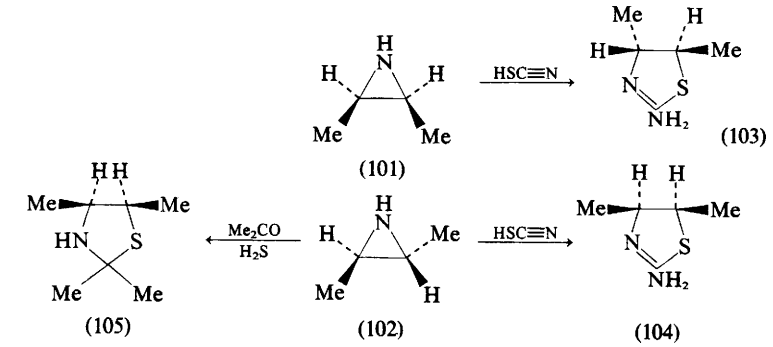
Δ^2-thiazolin-4-ones in variable yield. A dipolar adduct may function as the primary stage in this reaction (Scheme 2).[110]



Scheme 2

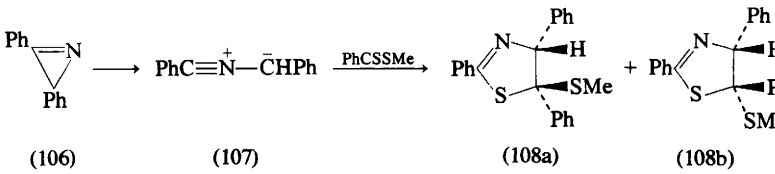
Type H (C—N—C + C—S) Syntheses.—*Ring Expansion of Aziridines.* The stereochemistry of the well-established synthesis of Δ^2-thiazolines and thiazolidines by ring-enlargement of aziridines (these Reports, Vol. 1, p. 397; Vol. 2., pp. 620, 636) has been studied for the first time. The interaction of aziridines with thiocyanic acid, producing 2-amino-Δ^2-thiazolines, or with acetone–hydrogen sulphide, yielding 2,2-dimethylthiazolidines, proceeds stereospecifically with 100% Walden inversion. Thus, for example, *cis*- and *trans*-2,3-dimethylaziridine (101) and (102) give exclusively *trans*- and *cis*-2-amino-4,5-dimethyl-Δ^2-thiazolines (103) and (104), respectively. According to its i.r. spectrum, 2-amino-Δ^2-thiazoline exists wholly as the 2-amino-tautomer, incorporating an endocyclic double bond, and all other members of this series are represented accordingly. The *trans*-aziridine (102) similarly produces exclusively *cis*-2,2,4,5-tetramethylthiazolidine (105)

[110] J. Goerdeler and R. Schimpf, *Chem. Ber.*, 1973, **106**, 1496.



on treatment with acetone in the presence of hydrogen sulphide. The stereochemical assignments are based on n.m.r. spectral data. Detailed mechanisms for both ring-expansions were proposed.[1]

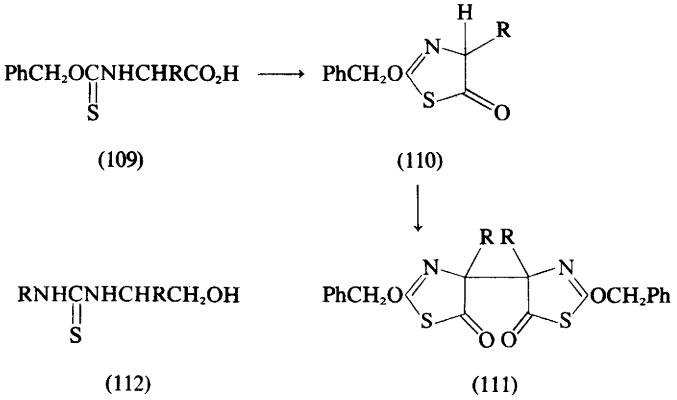
The photochemically induced addition of the dipolarophile methyl dithiobenzoate to 2,3-diphenylaziridine (106) in benzene produces, *via* the nitrile ylide (107), a mixture of the two stereoisomeric Δ^2-thiazolines (108a) and (108b), the latter as the major product (total 25%).[111]



Type K (C—C—N—C—S) Syntheses.—Further examples of the dehydrative cyclization, by means of dicyclohexylcarbodi-imide, of *N*-benzyloxythiocarbonylamino-acids (109) to 2-benzyloxy-Δ^2-thiazolin-5-ones (110) have been reported. Compared with 2-phenyl-Δ^2-thiazolin-5-ones, the products show a greatly diminished tendency to enolization, probably attributable to the inductive effect of their benzyloxy-group.[112] Their oxidation by iodine produces the corresponding 4,4′-bis-(2-benzyloxy-Δ^2-thiazolin-5-ones) (111); the formation of the possible stereoisomers was indicated by n.m.r. spectroscopy.[113] Dehydrative cyclization of the thiocarbonylamino-alcohols (112) yields Δ^2-thiazolines analogously.[114]

Type N (N—C—C—S—C) Syntheses.—The well-known cyclization of the radioprotective *S*-aminomethylisothiouronium bromide hydrobromide (AET) into 2-amino-Δ^2-thiazoline (2-AT)[115] has been studied kinetically by

[111] A. Padwa, D. Dean, and J. Smolanoff, *Tetrahedron Letters*, 1972, 4087.
[112] A. Siemion, W. Steglich, and L. Wilschowitz, *Roczniki Chem.*, 1972, **46**, 21.
[113] A. Siemion, W. Steglich, and L. Wilschowitz, *Roczniki Chem.*, 1972, **46**, 29.
[114] K. Harsanyi, D. Korbonits, and P. Kiss, *Magyar. Kém. Folyóirat*, 1973, **79**, 109.
[115] D. G. Doherty, R. Shapira, and W. T. Burnett, *J. Amer. Chem. Soc.*, 1957, **79**, 5667.

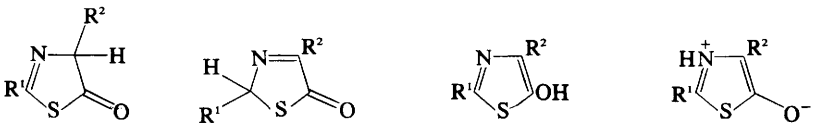


(109) (110) (112) (111)

the use of ^{14}C-labelled starting material. The reaction is essentially monomolecular; its activation energy, determined from the Arrhenius equation, is 17.5 kcal mol^{-1} and its rate constant 11.7×10^{-4} min^{-1} at 37 °C.[116] The cyclization of the corresponding selenium compound (prepared from [^{75}Se]selenourea) proceeds slightly more slowly.[117]

7 Physical Properties of Δ^2-Thiazolines

2,4-Disubstituted thiazolin-5-ones may have one of structures (113)—(116). According to its spectral properties, 4-isopropyl-2-phenylthiazolinone must be represented by (113) rather than (114).[118] I.r. and n.m.r. measurements



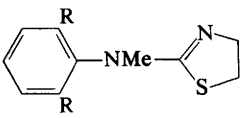
(113) (114) (115) (116)

show that 2-alkyl(and aryl)thiazolin-5-ones exist in the keto-form in chloroform, but are enolized to various degrees in polar solvents such as dimethyl sulphoxide; they are also readily acylated on their oxygen. In contrast, 2-alkoxythiazolin-5-ones do not enolize in polar solvents and are only acylated in low yield in the presence of a strong base (*e.g.* sodium hydride).[119]

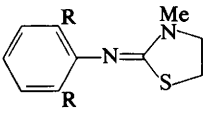
The structures of the isomeric 2-arylamino-Δ^2-thiazolines bearing a methyl group on their extranuclear or ring nitrogen, (117) and (118), may be assigned on the basis of their n.m.r. spectra, specifically by the signals of

[116] L. Kronrad and I. Kozak, *J. Labelled Compounds*, 1973, **9**, 107.
[117] L. Kronrad and I. Kozak, *J. Labelled Compounds*, 1973, **9**, 117.
[118] E. Glotter and M. D. Bachi, *Israel J. Chem.*, 1970, **8**, 633.
[119] J. H. Davies, R. H. Davis, and R. A. G. Carrington, *J.C.S. Perkin I*, 1972, 1983.

their 2,6-symmetrically substituted aryl group. The AB_2 multiplet of the aromatic protons is displaced considerably towards the AX_2 pattern in the ring-methylated structures incorporating a conjugated C=N bond (118), compared with the isomeric Δ^2-thiazoline structures (117).[120]



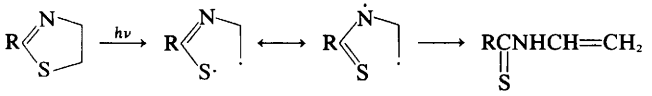
(117)



(118)

8 Chemical Properties of Δ^2-Thiazolines

The photoisomerization of Δ^2-thiazolines to *N*-alkenylthioamides (119) has been briefly reported. 2,4,4-Trimethyl-Δ^2-thiazoline, as well as its

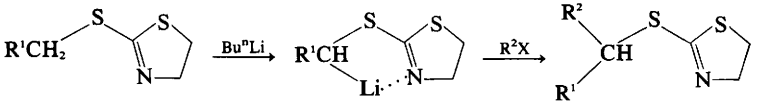


R = Me, Et, or Ph

(119)

2,5,5-isomer, produces a mixture of $MeCSNHCH{=}CMe_2$ and $MeCSNHCH_2CMe{=}CH_2$. Feasible mechanisms for each of the processes were considered.[121]

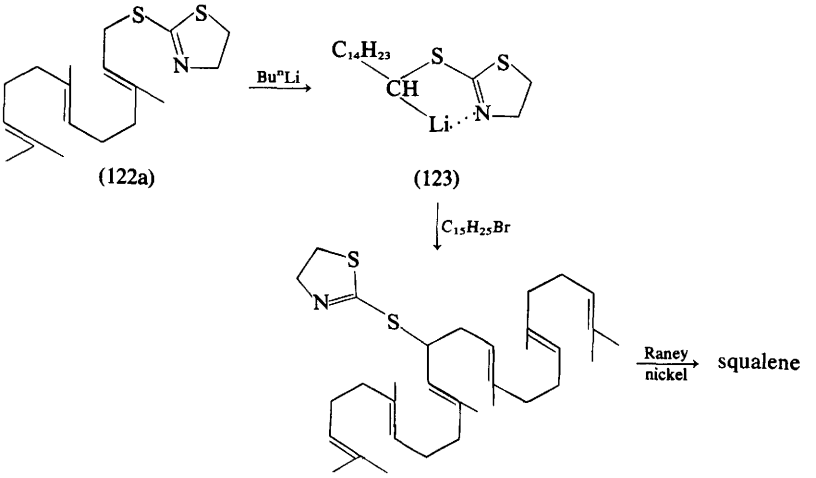
A preliminary report has outlined a novel interesting synthesis of squalene using 2-alkenylthio-Δ^2-thiazoline lithium derivatives. Compounds of this type (122) are obtainable by treatment of alkylthiothiazolines (120) with n-butyl-lithium, and alkylation of the resulting lithium salt (121) with



(120) (121) (122)

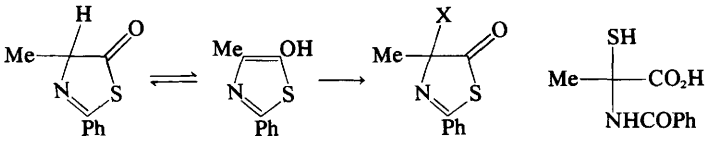
alkyl halide. The use of 2-(farnesylthio)thiazoline (122a) in this sequence yields, on metallation [to (123)] and successive treatment with farnesyl bromide and Raney nickel, squalene (80%) that is identical with the natural product.[122] The method is also applicable to the synthesis of other unsaturated systems, including, for example, 1,5-diynes, by the dilithiation of 2-propargylthiothiazoline.[123]

[120] P. Sohar and L. Toldy, *Magyar Kém. Folyóirat*, 1972, **78**, 539.
[121] T. Matsuura and Y. Ito, *J.C.S. Chem. Comm.*, 1972, 896.
[122] K. Hirai, H. Matsuda, and Y. Kishida, *Tetrahedron Letters*, 1971, 4359.
[123] K. Hirai and Y. Kishida, *Tetrahedron Letters*, 1972, 2117.



(122a) (123) (124)

4-Methyl-2-phenyl-Δ^2-thiazolin-5-one[124] exists as an equilibrium of the keto (125) and enol (126) forms (see these Reports, Vol. 2, p. 624). Successive treatment with sulphuryl chloride and thiolacetic acid yields the acetylthio-compound (127); however, on attempted deacetylation, desulphurization occurs with regeneration of the thiazolinone (125).[125] The route is therefore not suitable for the preparation of thionamides analogous to (128), which are accessible from the corresponding oxazolinone.[126]



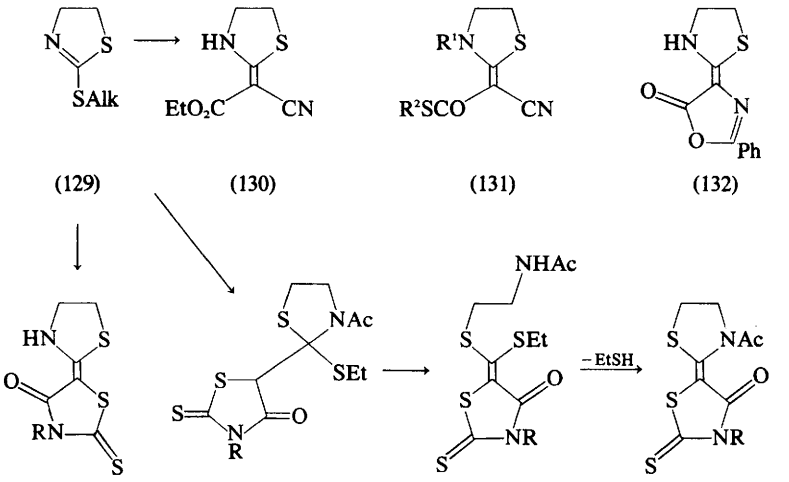
(125) (126) (127) X = SAc (128)

Amongst examples of reactions of 2-thiothiazolines with active methylene groups, their interactions with cyanoacetic ester[127,128] (see also these Reports, Vol. 1, p. 408) and rhodanines[129] have been studied. 2-Alkylthio-Δ^2-thiazolines[127,128] (129) or their quaternary salts[128] are converted by the former reagents into 2-(ethoxycarbonylcyanomethylene)thiazolidine (130). Their tetrasubstituted double bond resists catalytic

[124] G. C. Barrett and A. R. Khokhar, *J. Chem. Soc.* (*C*), 1969, 1117.
[125] I. D. Rae and B. N. Umbrasas, *Austral. J. Chem.*, 1971, **24**, 2729.
[126] P. M. Pojer and I. D. Rae, *Tetrahedron Letters*, 1971, 3077.
[127] K. Hirai, H. Matsuda, and Y. Kishida, *Chem. and Pharm. Bull.* (*Japan*), 1971, **20**, 97.
[128] Y. Sakurai, M. Kurumi, T. Okutome, S. Sato, and K. Yamaguchi, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 1426.
[129] M. Kurumi, T. Okutome, Y. Sakurai, S. Sato, and K. Yamaguchi, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 1431.

hydrogenation[127] and hydrolysis.[128] The *N*-acetylthiol esters (131)[128] and the lactone (132)[127] are similarly accessible.

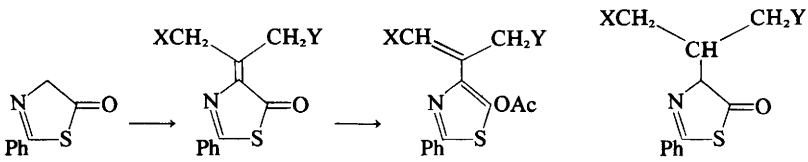
The condensation with rhodanine in boiling acetic acid gives (133) in high yield. The corresponding thiazolinium salts, having their 2-position activated towards nucleophiles, react identically under much milder conditions. In acetic anhydride, the reaction proceeds differently, producing, by way of the isolable intermediates (134) and (135), the acetylated condensed product (136).[129]



(129) (130) (131) (132)

(133) (134) (135) (136)

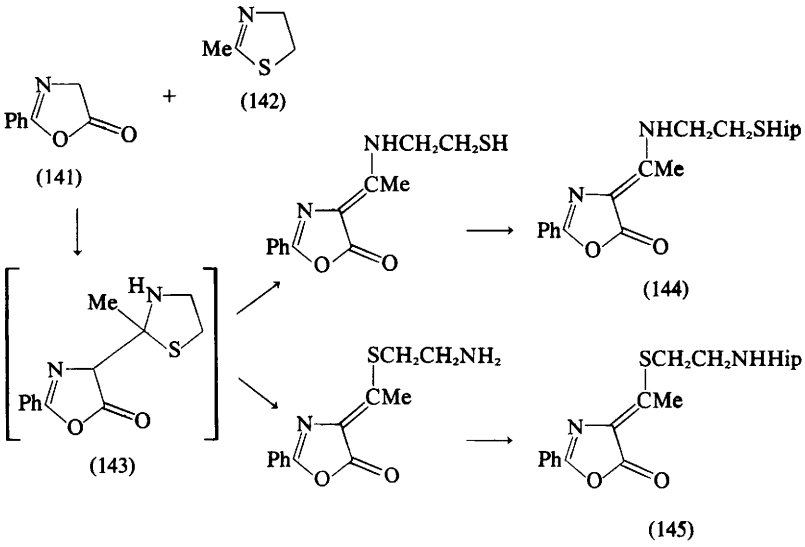
The condensation of 2-phenyl-Δ^2-thiazolin-5-one (137) and ketones in the presence of a basic catalyst (*e.g.* benzylamine) affords 4-alkylidene-2-phenyl-Δ^2-thiazolin-5-ones (138). The use of 1-acetoxypropan-2-one gives a mixture of the two isomeric thiazolinones (138; X = OAc, Y = H) and (138; X = H, Y = OAc); their configurations were elucidated by means of their n.m.r. spectra, (138; X = OAc, Y = H) being assigned to the isomer bearing a deshielded methyl group. Acylation of (138) affords 5-acyloxy-4-alkenyl-2-phenylthiazoles, *e.g.* (139), and reduction produces the appropriate 4-alkyl derivatives (140).[130]



(137) (138) (139) (140)

[130] M. D. Bachi, *J.C.S. Perkin I*, 1972, 310.

The action of 2-phenyl-Δ^2-oxazolin-5-one (141) on 2-alkyl-Δ^2-thiazolines (142) proceeds by the nucleophilic attack on C-2 of the latter. Subsequent fission of the thiadiazolidine ring of the presumed intermediate (143) occurs at either the 1,2- or 2,3-bond, yielding the two products (144) and (145) side by side. The compounds (144) are obtained exclusively, in high yield, when the reaction is performed in pyridine at room temperature.

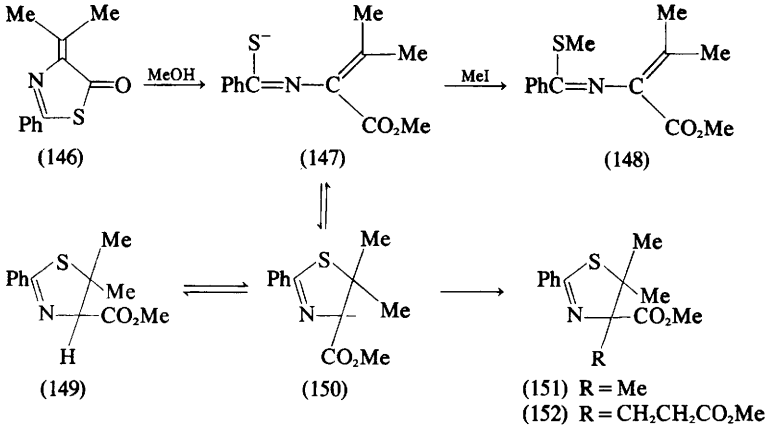


The use, in this reaction, of a system containing an active methylene group, but devoid of acylating power (*e.g.* 3-phenyl-Δ^2-isoxazolin-5-one), was also studied. Attack takes place again at the 2-position of the 2-alkyl-Δ^2-thiazolines, and terminates with the production of thiols corresponding to (144). The configuration of these products about the alkylidene group is not known with certainty.[131]

In approaches to the biogenetic synthesis of penicillin, Bachi and Rothfield[132] have studied the use of thiobenzimidate derivatives of α-amino-acids for the synthesis of β-lactams, and observed in the course of this work a scission and recyclization of Δ^2-thiazolines. Attempts to prepare thiobenzoyldidehydrovaline methyl ester by methanolysis of the isopropylidenethiazolinone (146) gave 5,5-dimethyl-2-phenyl-Δ^2-thiazoline-4-carboxylate (149) *via* the thienolate ion (147); in the presence of an excess of methyl iodide this intermediate gives rise to the thioimidate (148). Another approach to (147) is by the ring-cleavage of the Δ^2-thiazoline (149) at -10 °C in a suspension of sodium hydride in THF–methyl iodide. The carbanion (150)

[131] D. C. Cook and A. Lawson, *J.C.S. Perkin I*, 1973, 465.
[132] M. D. Bachi and M. Rothfield, *J.C.S. Perkin I*, 1972, 2326.

thus formed is trapped by the alkylating agent, giving the trimethylthiazoline (151) (67%). At room temperature in the absence of an alkylating agent, however, the carbanion (150) rearranges to the thioenolate (147), which on ring closure and simultaneous displacement of methoxide ion regenerates the thiazolinone (146), thus effectively reversing the reaction.[132]



(146) (147) (148)

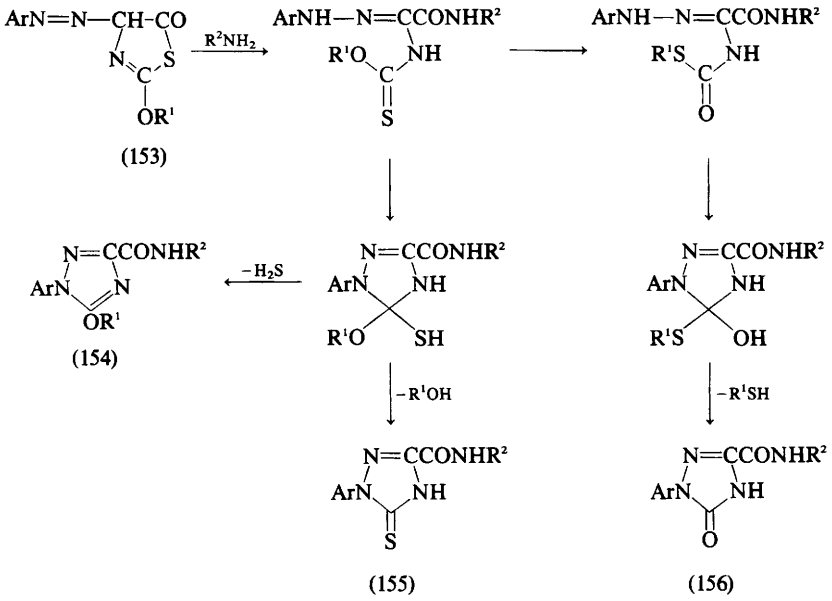
(149) (150) (151) R = Me
(152) R = $CH_2CH_2CO_2Me$

The aminolysis of substituted 4-arylazo-Δ^2-thiazolin-5-ones has been investigated, with the results shown in Scheme 3. Treatment of 2-alkoxy-4-arylazo-Δ^2-thiazolin-5-ones (153) with strongly basic amines yields, depending on the nature of the 2-alkyloxy-groups [in (153)], the 1,2,4-triazolin-5-ones (156) or -5-thiones (155). Aromatic amines yield the 1,2,4-triazoles (154). Probable common intermediate stages of these reactions are shown.[133,134]

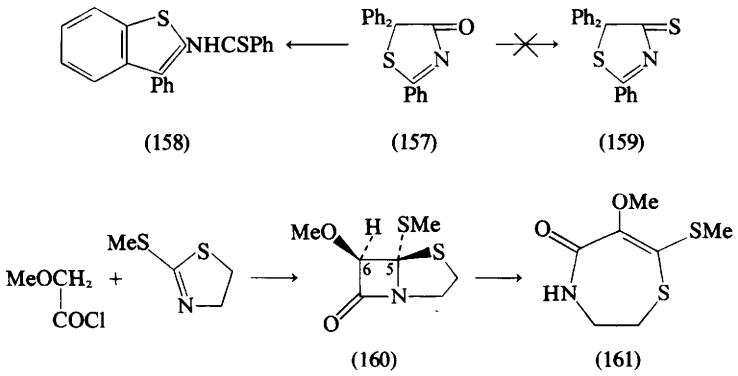
The action of phosphorus pentasulphide on 2,5,5-triphenyl-Δ^2-thiazolin-4-one (157) yields, instead of the expected 4-thione (159), the thiophen derivative (158).[135] The structure of this compound, suggested by its spectral properties, was confirmed by *X*-ray analysis. Analogues of (157) incorporating chlorinated aryl residues react analogously. The reaction proceeds by simultaneous cleavage of the thiazole ring at the S—C-5 bond, and re-cyclization involving the *ortho*-position of one of the aryl groups.[135]

The action of methoxyacetyl chloride on 2-methylthio-Δ^2-thiazoline leads to the stereospecific formation of 6-methoxy-5-methylthiopenam (160) (73%). The n.m.r. spectrum of the corresponding 5-methylsulphoxide shows that the substituents at C-5 and C-6 are in *cis*-configuration to each other. The product (160) is stable, but rearranges under the influence of trifluoroacetic acid to a product formulated as the 1,4-thiazepine (161).[136]

[133] A. H. Harhash, M. H. Elnagdi, and E. A. Hafez, *J. prakt. Chem.*, 1971, **313**, 706.
[134] A. H. Harhash, M. H. Elnagdi, and C. A. S. Elsannib, *J. prakt. Chem.*, 1973, **315**, 211.
[135] E. Koltai, J. Nyitrai, K. Lempert, G. Horvath, A. Kalman, and G. Argay, *Tetrahedron*, 1973, **29**, 2783.
[136] A. K. Bose, J. L. Fahey, and M. S. Manhas, *J. Heterocyclic Chem.*, 1973, **10**, 791.



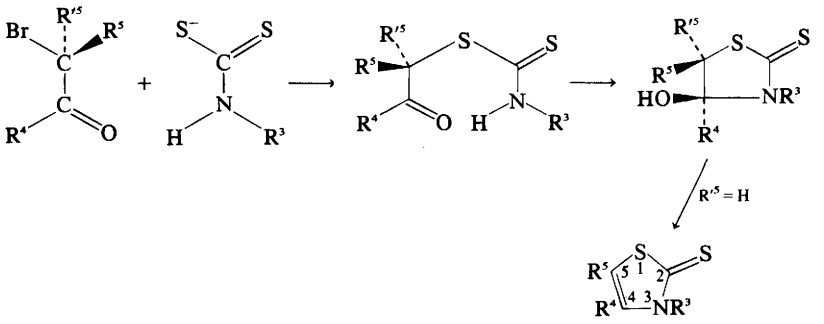
Scheme 3



9 Synthesis of Δ^4-Thiazolines

Hantzsch's synthesis of Δ^4-thiazolines, like that of thiazoles (see this vol., p. 567), has been shown to involve isolable intermediate 4-hydroxy-heterocycles. A series of 3,4-dialkyl-Δ^4-thiazoline-2-thiones (162) were prepared from *N*-alkyldithiocarbamates and α-halogeno-ketones or -aldehydes in this work; the stereochemical course of this reaction was elucidated (see

Scheme 4; superscripts on the R's refer to the positions in the final product to which they are attached).[137]

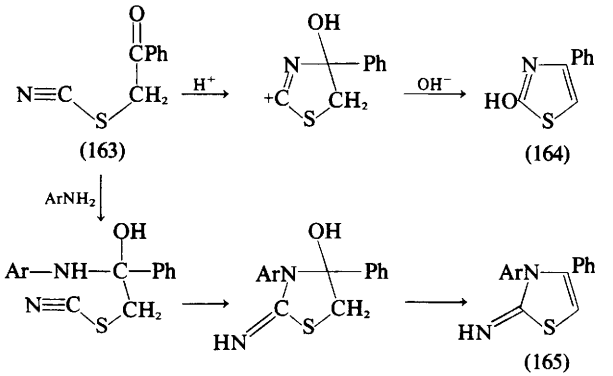


(162)

Scheme 4

Further classes of Δ^4-thiazolines have been produced by Hantzsch's synthesis; they include 3,4,5-trisubstituted 2-thio-Δ^4-thiazolines,[138] 2-arylimino-3-aryl-4-methyl-Δ^4-thiazolines,[139] 2-arylimino-3-diphenylphosphinylamino-Δ^4-thiazolines,[140] 3,4-diaryl-2-[(arylsulphonyl)cyanomethylene]-Δ^4-thiazolines,[141] and their 2-[(carbonamido)cyanomethylene] analogues.[142]

The interaction of phenacyl thiocyanate (163) and arylamines yields 2-imino-3-aryl-4-phenyl-Δ^4-thiazolines (165). The parallel intramolecular cyclization of (163) to 2-hydroxy-4-phenylthiazole (164) is not significant

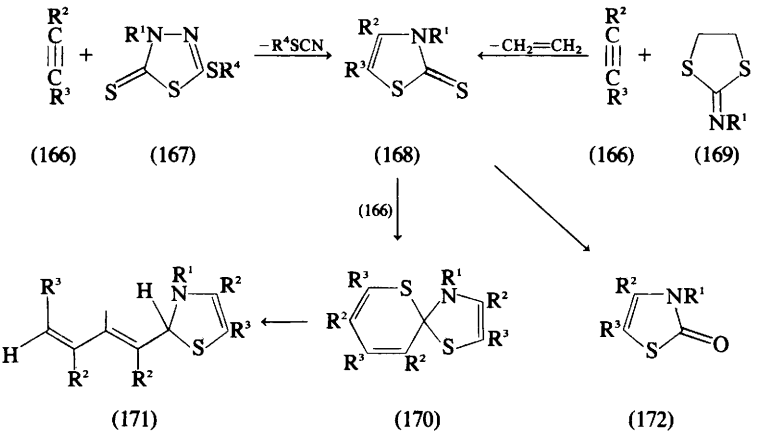


(163) (164) (165)

[137] C. M. Roussel, R. Gallo, M. Chanon, and J. Metzger, *Bull. Soc. chim. France*, 1971, 1902.
[138] H. Tripathy, M. K. Das, B. Sahu, B. C. Dash, and G. N. Mahapatra, *J. Indian Chem. Soc.*, 1973, **50**, 417.
[139] H. Tripathy, P. N. Dahl, and G. N. Mahapatra, *J. Indian Chem. Soc.*, 1973, **50**, 135.
[140] H. J. Jahns, *J. prakt. Chem.*, 1973, **315**, 79.
[141] V. M. Neplyuev, Y. N. Usenko, R. G. Dubenko, and P. S. Pelkis, *Khim. geterotsikl. Soedinenii*, 1970, 1194 (*Chem. Abs.*, 1971, **75**, 5775q).
[142] V. M. Neplyuev, R. G. Dubenko, and P. S. Pelkis, *Khim. geterotsikl. Soedinenii*, 1971, 1186 (*Chem. Abs.*, 1972, **76**, 25 150f).

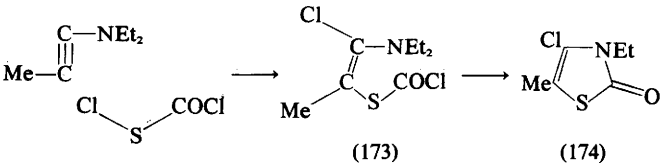
when strongly basic arylamines are used, and it may be suppressed in the case of weak bases by the addition of mineral acid.[143]

Equimolar quantities of acetylenedicarboxylic acid esters (166) and 2-*N*-substituted 1,3-dithiolan-2-imines (169) undergo a 1,3-dipolar cycloaddition, with elimination of ethylene, to yield Δ^4-thiazoline-2-thiones (168). The same products result from 2-alkylthio-1,3,4-thiadiazoline-5-thiones (167), with loss of alkyl thiocyanate as shown. They are desulphurized to the corresponding thiazolinones (172) by the action of mercuric acetate in acetone–acetic acid. They react with two further moles of the acetylenic reagent (166) to produce the spiranes (170; *e.g.* $R^2 = R^3 = CO_2Me$), which are in turn desulphurized and cleaved by Raney nickel to the Δ^4-thiazoline derivatives (171). An analogous series of reactions was carried out using propiolic acid esters.[144]



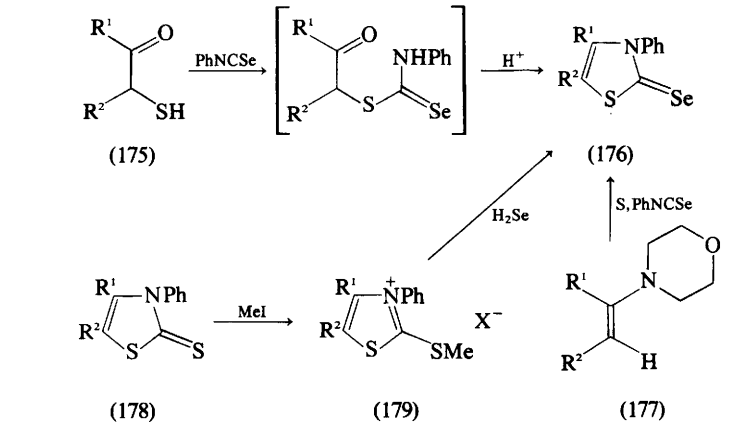
Diethylaminopropyne and chlorocarbonylsulphenyl chloride react additively to form the intermediate adduct (173) as a *cis–trans* mixture. On distillation this loses chloroethane, giving 4-chloro-3-ethyl-4-methyl-Δ^4-thiazolin-2-one (174); since only the *trans*-isomer is cyclizable, the yields are moderate.[145]

The condensation of α-oxo-thiols (175) with isothiocyanates[146] has been extended, by the use of phenyl isoselenocyanate, to the synthesis of



[143] M. P. Mahajan, S. K. Vasudeva, and N. K. Ralhan, *Indian J. Chem.*, 1972, **10**, 318.
[144] C. Gueden and J. Vialle, *Bull. Soc. chim. France*, 1973, 270.
[145] N. Schindler, *Synthesis*, 1971, 656.
[146] K. Rühlmann, A. Grosalski, and U. Schräpler, *J. prakt. Chem.*, 1960, **11**, 54.

3-phenyl-4,5-dialkyl-Δ^4-thiazoline-2-selenones (176). In selected cases, the α-oxo-thiols may be replaced by enamines of type (177) in conjunction with sulphur, but yields are low. The structure of the selenones (176) is confirmed by their unequivocal synthesis as shown, (178) → (179) → (176).[147]

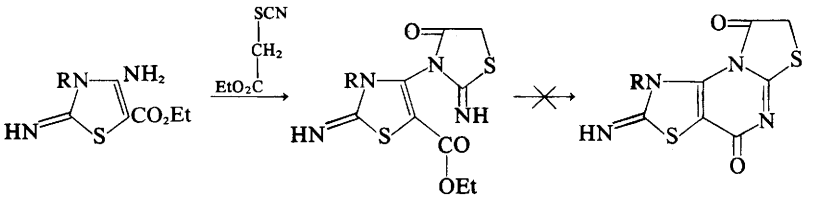


(175) (176) (178) (179) (177)

1-Alkyl-3-(3-alkyl-5-nitro-Δ^4-thiazolin-2-ylidene)ureas have been produced from the pre-formed heterocyclic system by conventional reactions.[65]

10 Properties of Δ^4-Thiazolines

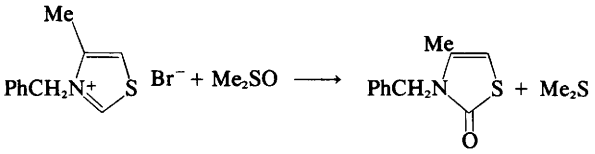
4-Amino-5-ethoxycarbonyl-Δ^4-thiazolines (180) are convertible, by two routes, into thiazolidin-3-yl-Δ^4-thiazolines (181), but their attempted further cyclization [to (182)] was not successful.[148]



(180) (181) (182)

The isolation of traces (less than 1%) of 3-benzyl-4-methyl-Δ^4-thiazolin-2-one as a product of the oxidation of 3-benzyl-4-methylthiazolium bromide by DMSO in the absence of oxygen (Scheme 5) has been taken as the basis for discussing the mechanism of this reaction in terms of carbene intermediates, and of its relevance to reactions of thiamine.[149]

[147] H. Spies, K. Gewald, and R. Mayer, *J. prakt. Chem.*, 1972, **314**, 646.
[148] A. Singh, H. Singh, and K. S. Narang, *Austral. J. Chem.*, 1972, **25**, 1351.
[149] H. C. Sorensen and L. L. Ingraham, *Arch. Biochem. Biophys.*, 1969, **134**, 214.



Scheme 5

A number of 2-imino-5-nitro-Δ^4-thiazolin-3-acetamides (40) and analogous ureas (41) possess appreciable schistosomicidal activity, effecting a 50—100% reduction of adult *Schistosoma mansoni* in mice at daily doses of less than 400 mg kg^{-1} for 14 days.[64,65]

11 Synthesis[5] of Thiazolidines

Type A (S—C—N + C—C) Syntheses.—The versatile condensation of suitable two-carbon systems with thioamido-, thiocyanato-, and related compounds continues, in a variety of forms, to serve as the most widely used route to thiazolidines.

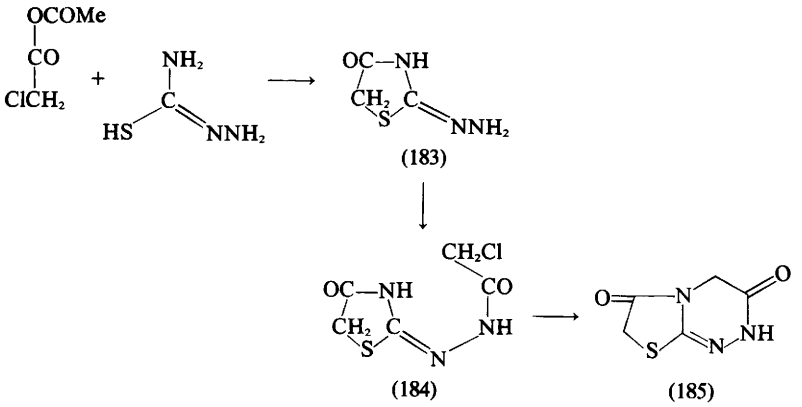
Hantzsch's synthesis, prominent amongst these, has provided the following series of compounds: 3-aryl-2-aryliminothiazolidin-4-ones[150,151] and 3-phenethyl analogues,[152,153] 2-hydrazonothiazolidin-4-ones,[154] 3-aryl-2-[(arylsulphonyl)cyanomethylene]-5*H*-thiazolidin-4-ones,[141] and substituted thiazolidine-2-thiones.[155]

Acetic chloroacetic anhydride may be employed in the Hantzsch synthesis, yielding, for example, 2-hydrazonothiazolidin-4-one (183) with thiosemicarbazide. Further action of the anhydride yields the 2-chloroacetylhydrazono-derivative (184), which readily cyclizes to the thiazolo[2,3-*c*][1,2,4]triazine (185).[156]

Phenylimino-oxalic acid dichloride (prepared from oxalic acid, phosphorus pentachloride, and aniline in benzene) is likewise a suitable starting material in this synthesis of both thiazolidines and condensed ring-systems incorporating the thiazole system (see Chapter 14, imidazo[2,1-*b*]benzothiazoles and thiazolo[3,2-*a*]benzimidazole). Its interaction with diphenylthiourea produces 3-phenyl-2,5-bis(phenylimino)thiazolidin-4-one (Scheme 6).[157]

Amides of acetylthioacetic acid react with maleic anhydride at *ca.* 100 °C

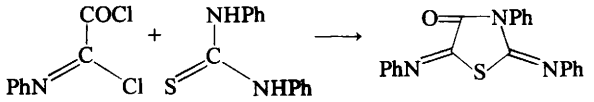
[150] H. N. Pandey and V. J. Ram, *J. Indian Chem. Soc.*, 1972, **49**, 171.
[151] V. J. Ram, H. N. Pandey, and S. N. Singh, *J. Indian Chem. Soc.*, 1972, **49**, 181.
[152] S. S. Parmar, C. Dwivedi, A. Chaudhari, and T. K. Gupta, *J. Medicin. Chem.*, 1972, **15**, 99.
[153] C. Dwivedi, T. K. Gupta, and S. S. Parmar, *J. Medicin. Chem.*, 1972, **15**, 553.
[154] Y. V. Svetkin and A. N. Minlibaeva, *Zhur. org. Khim.*, 1971, **7**, 1301.
[155] R. A. Bafford, F. Chanon, M. Chanon, and J. Metzger, *Bull. Soc. chim. France*, 1973, 971.
[156] Y. V. Svetkin, A. N. Minlibaeva, and A. G. Mansurova, *Zhur. org. Khim.*, 1972, **8**, 1722.
[157] M. O. Lozinskii, A. F. Shivanyuk, and P. S. Pelkis, *Khim. geterotsikl. Soedinenii*, 1971, 471 (*Chem. Abs.*, 1972, **76**, 25 184v).



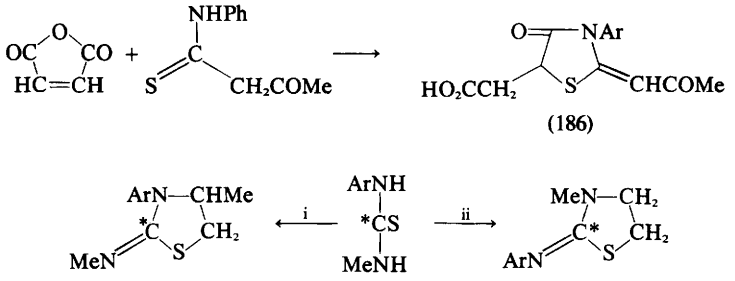
(183)

(184) (185)

to yield the substituted thiazolidine (186).[158] Details have been provided for preparing ^{14}C-labelled thiazolidines from labelled aryl isothiocyanates, by the routes shown in Scheme 7.[159]



Scheme 6



(186)

Reagents: i, $BrCH_2CHBrMe$; ii, $MeNHCH_2CH_2OH$

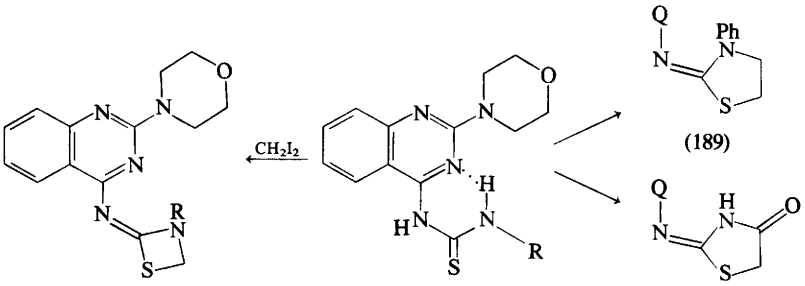
Scheme 7

4-Quinazolylthioureas of type (187), incorporating strong intramolecular N···H—N hydrogen bonds, react correspondingly readily with diiodomethane to form 1,3-thiazetidines (188) in good yield. The use of other

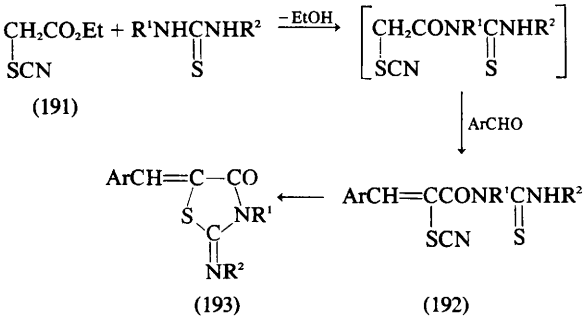
[158] A. N. Borisevich and P. S. Pelkis, *Khim. geterotsikl. Soedinenii*, 1971, 1001 (*Chem. Abs.*, 1972, **76**, 14 415v).

[159] G. Zolyomi, L. Toldy, and D. Banfi, *J. Labelled Compounds.*, 1973, **9**, 243.

bifunctional alkylating agents produces the appropriate cyclic analogues. Thus, the action of 1,2-dibromoethane on (187; R = Ph), and that of ethyl chloroacetate on (187; R = H), yields the thiazolidines (189) and (190), respectively.[160]



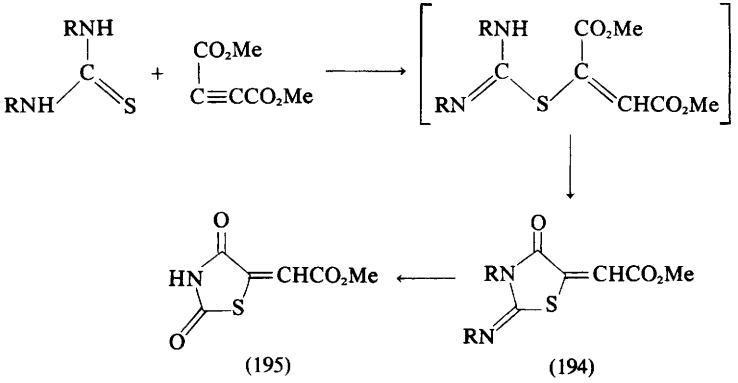
The interaction of ethyl thiocyanoacetate (191) with aromatic aldehydes and *NN'*-dialkylthioureas yields the linear condensation products (192). With thiourea or *N*-methylthiourea, reaction continues with cyclization, yielding 5-benzylidene-2-imino-4-thiazolidinone [(193) from thiourea]. The suggested reaction sequence is supported by the isolation of the intermediates in selected instances.[161,162]



The structure of the products of the condensation of thiourea or 1,3-disubstituted thioureas with acetylenedicarboxylate esters has been in dispute (see these Reports, Vol. 2, pp. 617, 760). The compounds have now been shown, by *X*-ray studies[163] and chemical evidence,[164] to be 2-imino-4-thiazolidinones (194), and *not* the six-membered alternatives. Hydrolysis of

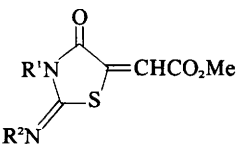
[160] W. Ried, W. Merkel, and O. Mösinger, *Annalen*, 1973, 1362.
[161] S. Kambe, T. Hayashi, H. Yasuda, and A. Sakurai, *Nippon Kagaku Zasshi*, 1971, **92**, 867 (*Chem. Abs.*, 1972, **77**, 5397j).
[162] S. Kambe and T. Hayashi, *Bull. Chem. Soc. Japan*, 1972, **45**, 3192.
[163] J. F. B. Mercer, G. M. Priestley, R. N. Warrener, E. Adman, and L. H. Jensen, *Synthetic Comm.*, 1972, **2**, 35.
[164] H. Nagase, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 270.

the products [*e.g.* (194; R = H)] with methanolic hydrogen chloride gave the substituted 2,4-dioxothiazolidine (195), identical with authentic material derived from 2,4-dioxothiazolidine-5-acetic acid. Extensive spectral evidence supports the formulation.[164]

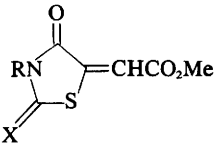


(195) (194)

Monosubstituted thioureas give, in this reaction, a mixture of the isomeric 2-imino-4-thiazolidinones (196) and (197), the former predominating.[164] Similarly, dithiocarbamates, thiocarbamates, thiosemicarbazides, and thiosemicarbazones give analogous 4-thiazolidinones of type (198) and (199), which were further studied.[165]



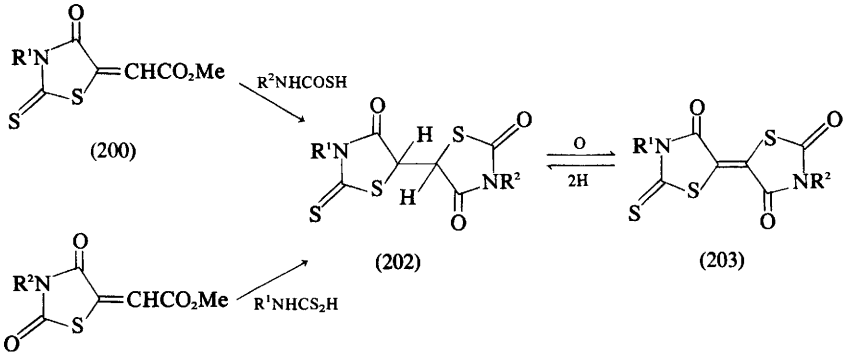
(196) $R^1 = H$
(197) $R^2 = H$
(198) R^1 = Ph or $Me_2C{=}N$;
R^2 = H, Me, or NH_2



(199) X = O or S

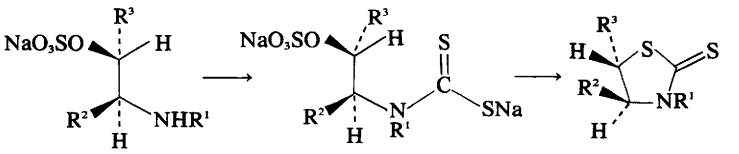
Thus, 2-thiono-5-methoxycarbonylmethylidene-4-thiazolidinones (200) and their 2-oxo-analogues (201) react with thio- and dithio-carbamates to yield the identical bicyclic adducts (202), which are autoxidized in the presence of triethylamine to the $\Delta^{5,5'}$-bis-thiazolidin-4-ones (203). The intermediates (202) are too readily oxidized to be isolated from the reaction mixture, but they are obtainable by the reduction of (203) by zinc and acetic acid. 2-Imino-analogues of (200) react similarly. The configuration of (203) is supported by the observed displacement of their CO bands in the i.r. spectra under irradiation, similar to that of thioindigo.[165,166]

[165] H. Nagase, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 279.
[166] H. Nagase, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1132.



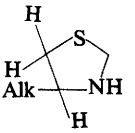
(200) (201) (202) (203)

Type B (C—C—N + C—S) Syntheses.—The interaction of aminoalkyl hydrogen sulphates and carbon disulphide[167] in alkaline media provides a most useful route to thiazolidine-2-thiones, which has been applied to the preparation of a further range of examples, *e.g.* (205). Cyclization occurs most rapidly at pH 5—6, but the linear intermediates (204) are isolable under



(204) (205)

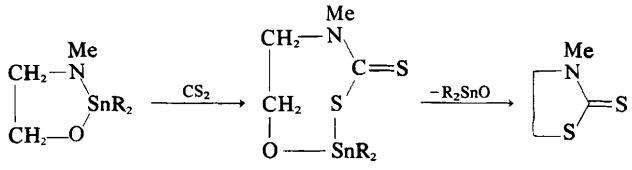
appropriate conditions. *erythro*-3-Aminobutyl-2-sulphate yields exclusively *trans*-4,5-dimethylthiazolidine-2-thione. By employing asymmetric amino-alcohols ($RCHNH_2CH_2OH$), optically active examples of the heterocycles (206; Alk = Me or Et) are obtained.[168]



(206)

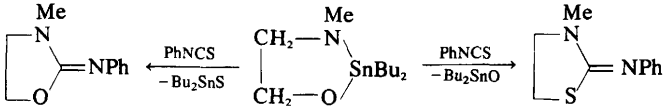
N-Substituted 2,2-dialkyl-1-oxa-3-aza-2-stannacyclopentanes (207) react additively at 0 °C at their Sn—N bond with carbon disulphide, giving stable 1:1 adducts (208). At moderate temperatures, reaction occurs with loss of dialkyltin oxide, resulting in 3-methylthiazolidine-2-thione (209) (together

[167] C. S. Dewey and R. A. Bafford, *J. Org. Chem.*, 1965, **30**, 491, 495.
[168] R. A. Bafford, F. Chanon, M. Chanon, and J. Metzger, *Bull. Soc. chim. France*, 1973, 971.



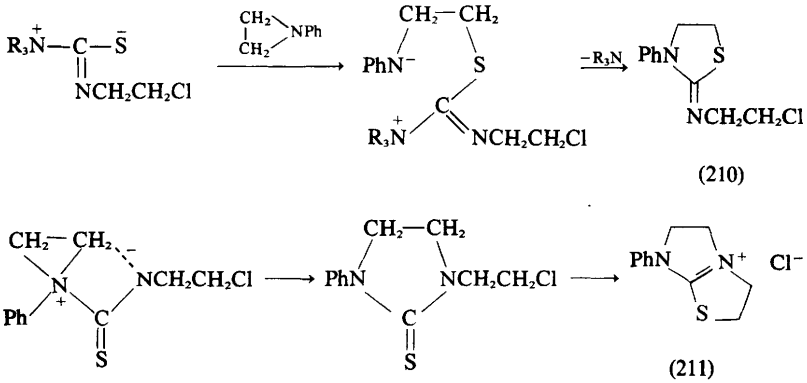
(207) (208) (209)

with the corresponding oxazolidine-2-thione). An analogous reaction involving phenyl isothiocyanate is also shown, in Scheme 8.[169]



Scheme 8

The interaction of 2-chloroethyl isothiocyanate and *N*-phenylethylenimine in triethylamine yields the substituted 2-iminothiazolidine (210). In the absence of the tertiary base, the reduced imidazo[2,1-*b*]thiazole (211) is formed as a by-product, possibly by the mechanism shown.[170]



(210)

(211)

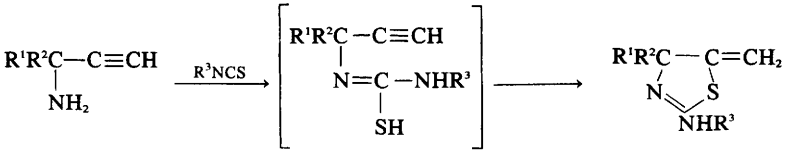
Isothiocyanate esters undergo an addition–cyclization with 3-amino-3-alkyl-1-butynes at 50 °C to form 2-amino-Δ^2-thiazolines (Scheme 9); 3-alkylamino-3-alkyl-1-butynes produce the corresponding iminothiazolidines (212).[171]

Type D (C—C—S + C—N) Syntheses.—β-Aryl-α-mercaptoacrylic acids exist in the thiol (213) rather than the thiopyruvic acid form and are suitable

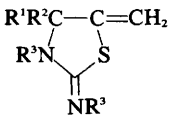
[169] S. Sakai, Y. Fujimura, and Y. Ishii, *J. Organometallic Chem.*, 1973, **50**, 113.

[170] A. P. Sineokov and V. S. Kutyreva, *Khim. geterotsikl. Soedinenii*, 1971, 1651, (*Chem. Abs.*, 1972, **77**, 5396h).

[171] I. N. Azerbaev, L. T. Kalkabaeva, M. Z. Aitkhozhaeva, and L. A. Tsoi, *Khim. geterotsikl. Soedinenii*, 1972, 471 (*Chem. Abs.*, 1972, **77**, 61 864).



Scheme 9



(212)

starting materials for synthesizing thiazolidines. They are readily added to the C=N bond of Schiff's bases; simultaneous cyclodehydration results in thiazolidin-4-ones (214).[172] The condensation of thioglycolic acid and *N*-arylhexafluoroisopropylideneimines, forming 2,2-bis(trifluoromethyl)-3-aryl-4-thiazolidinones (215) in good yields, is another example of this reaction.[173]

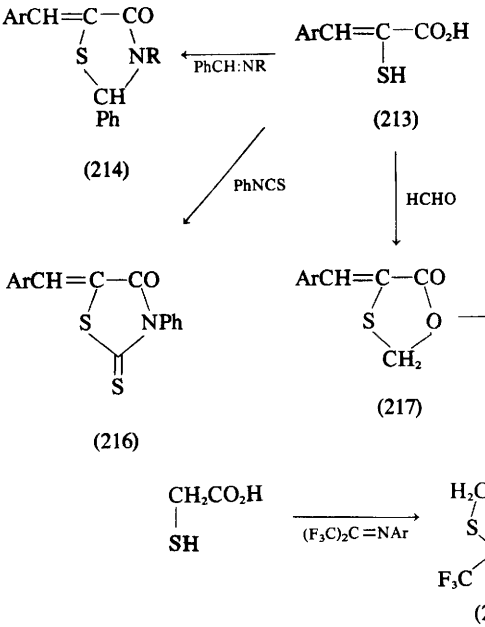
Addition [of (213)] to the C=N bond of phenyl isothiocyanate and cyclization affords 5-arylidene-1-phenylrhodanines (216). The reaction of acrylic acids (213) with formaldehyde in acetic acid produces 4-arylidene-1,3-oxathiolan-5-ones (217), which are in their turn convertible by concentrated ammonia into 5-arylidenethiazolidin-4-ones (218).[172]

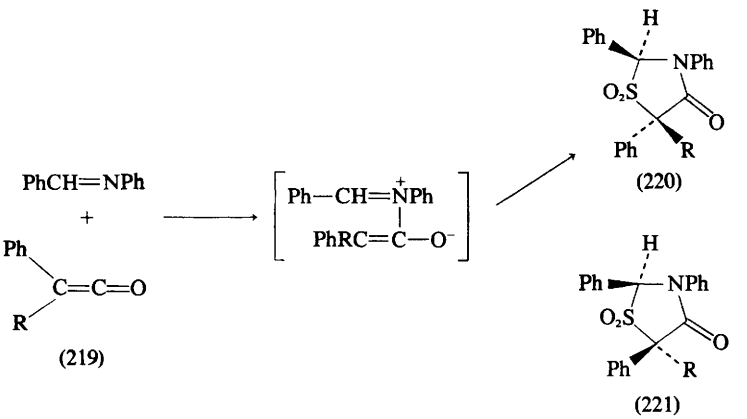
The condensation of benzalaniline and keten to a thiazolidinone 1,1-dioxide in liquid sulphur dioxide (see these Reports, Vol. 1, p. 405) has been extended to keto-ketens (219); of the two theoretically possible isomers (220) and (221), only the *trans*-form is produced. The configuration was determined by an *X*-ray analysis in one case (R = i-C_3H_7), and full structural details were given.[174]

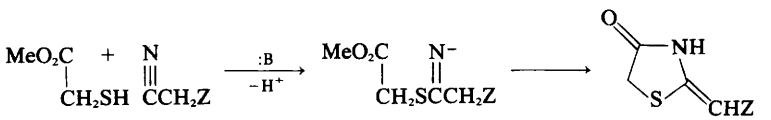
The interaction of α-mercapto-esters with ethyl cyanoacetate or analogous nitriles incorporating active methylene groups yields 2-carboxymethylene-4-thiazolidinones (222). They are visualized to arise by the attack of the sulphur at the nitrile carbon, followed by lactam formation.[175]

Type E (N—C—C—S + C) Syntheses.—Syntheses of thiazolidines in which one reactant participating in the cyclization supplies only the carbon atom at position 2 of the hetero-ring have long been a preferred route, and this continues to provide a variety of compounds of this series.

[172] A. H. Harhash, M. H. Elnagdi, and S. O. Abdallah, *Indian J. Chem.*, 1973, **11**, 128.
[173] N. Ishikawa and T. Kitazuma, *Bull. Chem. Soc. Japan*, 1973, **46**, 3260.
[174] J. M. Decazes, J. L. Luche, H. B. Kagan, R. Parthasarathy, and J. Ohrt, *Tetrahedron Letters*, 1972, 3633.
[175] J. L. Isidor and R. L. McKee, *J. Org. Chem.*, 1973, **38**, 3615.

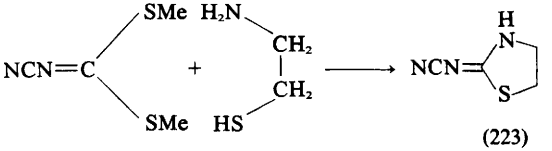






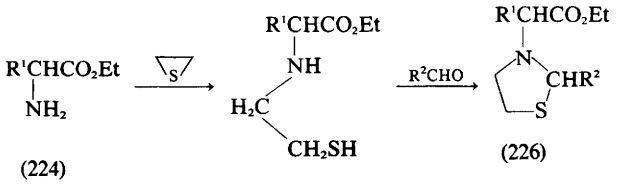
(222) Z = CO_2Et, CN, or, $CONH_2$

The condensation of dimethyl cyanodithioimidocarbonate and cysteamine in ethanol produces 2-cyaniminothiazolidine (223) in 70% yield.[176]



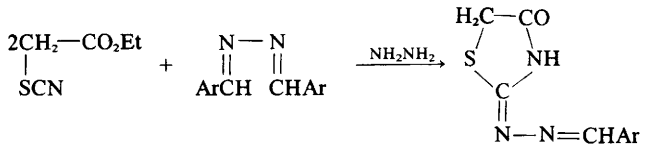
(223)

In Bulavin's synthesis, α-amino-acid ethyl esters (224) are converted by means of thiiran into the corresponding α-(2-mercaptoethyl)amino-acid esters (225). Their condensation with a variety of aldehydes affords excellent yields of 2-substituted 3-(1-ethoxycarbonylalkyl)thiazolidines (226).[177]



(224) (225) (226)

2-Hydrazono-4-thiazolidin-4-ones (227) are conveniently obtainable in a one-stage process by the interaction of ethyl thiocyanoacetate, arylideneazines, and hydrazine (2:1:1).[178]



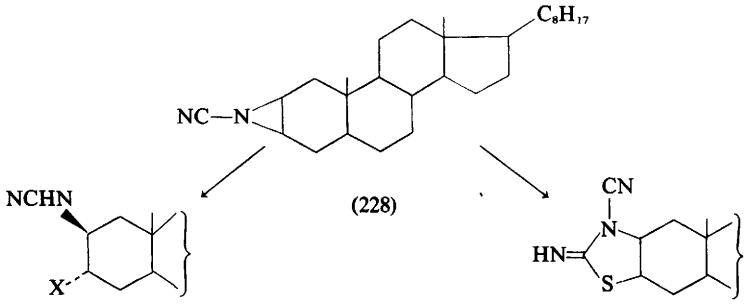
(227)

The stereochemical course of the ring-expansion of aziridines to thiazolidines is described together with that leading to Δ^2-thiazolines (see p. 583).[1] Further examples of this well-established synthesis have been given.[155,179]

The *N*-cyanaziridine ring of 2,3β-cyaniminocholestane (228) is opened by a variety of nucleophilic reagents, yielding 2β-cyanamino-3α-substituted cholestanes (229). The reaction with potassium thiocyanate is exceptional in

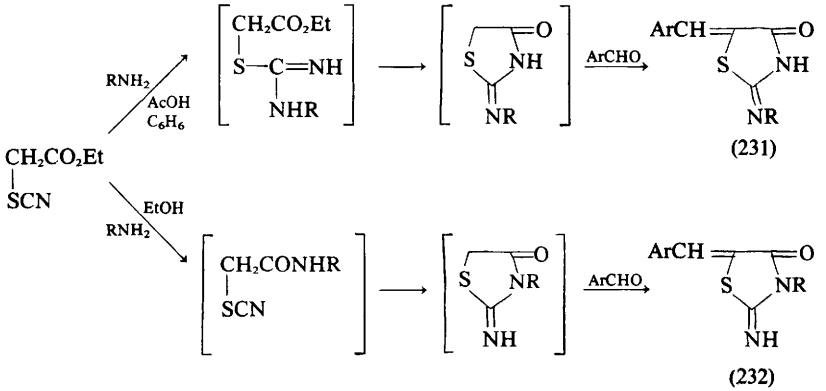
[176] R. Neidlein and H. Reuter, *Arch. Pharm.*, 1972, **305**, 731.
[177] L. G. Bulavin, *Zhur. org. Khim.*, 1971, **7**, 2086.
[178] S. Kambe and T. Hayashi, *Bull. Chem. Soc. Japan*, 1972, **45**, 952.
[179] R. D. Westland, R. A. Cooley, J. L. Holmes, J. S. Hong, M. H. Lin, and M. L. Zwiesler, *J. Medicin. Chem.*, 1973, **16**, 319.

that immediate recyclization of the primary cleavage product results in 2′-imino-3′-cyanothiazolidinocholestane (230).[180]



(229) (230)

Type G (C—C—S—C—N) Syntheses.—The reaction of ethyl thiocyanoacetate with an amine and aromatic aldehyde produces variously substituted 5-arylidene-2-iminothiazolidin-4-one derivatives (231) and (232). Condensation proceeds differently in benzene–acetic acid and ethanol, with the results shown.[181]



In conclusion, brief reference is made to numerous thiazolidines that have been synthesized in the course of biological screening programmes, by well-established cyclization reactions. They include 2,2-dialkyl- and 2-spirothiazolidines,[182] 2-alkyl(or aryl)-2-ethoxycarbonylthiazolidines,[183] and 3-substituted 2-imino-5-carboxymethylthiazolidin-4-ones.[184] Substituted

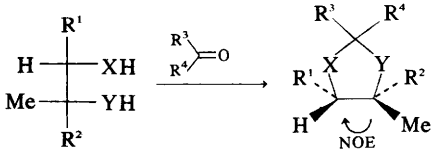
[180] K. Ponsold and W. Ihn, *Tetrahedron Letters*, 1972, 4121.
[181] S. Kambe, T. Hayashi, H. Yasuda, and A. Sakurai, *Nippon Kagaku Zasshi*, 1971, **92**, 867 (*Chem. Abs.*, 1972, **77**, 5397j).
[182] M. Fatome, P. Poutrain, R. Granger, H. Orzalesi, Y. Robbe, and M. Randon, *Chim. Thérapie*, 1970, **5**, 312.
[183] P. S. Farmer, C. C. Leung, and E. M. K. Lui, *J. Medicin. Chem.*, 1973, **16**, 411.
[184] S. Nagar, H. H. Singh, J. N. Sinha, and S. S. Parmar, *J. Medicin. Chem.*, 1973, **16**, 178.

2-{[(3-thiazolidinyl)alkyl]thio} pyridines have been prepared from the preformed hetero-nucleus.[185]

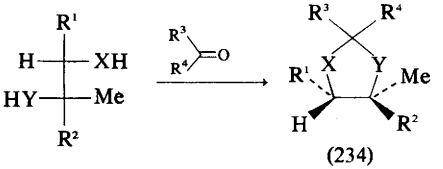
12 Properties of Thiazolidines

Spectra.—The i.r. spectra of Δ^2-thiazolin-5-ones and thiazolidine-2,5-diones feature carbonyl absorption bands that are displaced (by *ca.* 100 cm^{-1}) towards the lower frequencies in comparison with the corresponding oxazole derivatives.[186]

Stereoisomers of the *threo-* and *erythro*-type may be distinguished by their conversion into five-membered cyclic derivatives, including thiazolidines: *erythro*-Compounds give rise to derivatives (233), which on irradiation of the methyl group exhibit an intramolecular nuclear Overhauser effect (NOE)[187] on the adjacent methine-proton. In contrast, *threo*-compounds produce derivatives (234), which do not exhibit this effect, but show instead a long-range W-type coupling between the methyl group and the adjacent proton.[188]



(233)

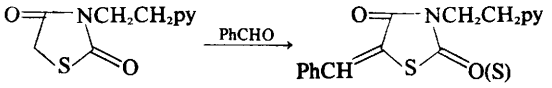


(234)

N-Alkylation.—The action of alkyl halides on thiazolidine-2,4-dione in DMF–potassium carbonate yields, in addition to the expected 3-alkyl derivatives, up to 38% of the corresponding *NN'*-dialkylureas.[189]

Thiazolidine-2,4-dione and rhodanines undergo pyridylethylation on treatment with freshly distilled 2-vinylpyridine, yielding *N*-[β-(2-pyridyl)-ethyl]thiazolidine-2,4-dione (235) and analogues. Further action of benzaldehyde produces benzylidene derivatives (236).[190]

[185] R. D. Westland, M. H. Lin, R. A. Cooley, M. Zwiesler, and M. Grenan, *J. Medicin. Chem.*, 1973, **16**, 328.
[186] D. Konopinska, I. Z. Siemon, and L. Wilschowitz, *Roczniki Chem.*, 1973, **47**, 35.
[187] J. H. Noggle and R. E. Schirmer, 'The Nuclear Overhauser Effect', Academic Press, New York, 1971.
[188] K. Nakanishi, D. A. Schooley, M. Koreeda, and I. Miura, *J. Amer. Chem. Soc.*, 1972, **94**, 2865.
[189] G. Irick, *J. Heterocyclic Chem.*, 1971, **8**, 847.
[190] M. A. Lazovskaya, S. N. Baranov, A. K. Sheinkman, and A. A. Rok, *Khim. geterotsikl. Soedinenii*, 1971, 599 (*Chem. Abs.*, 1972, **76**, 126 846t).

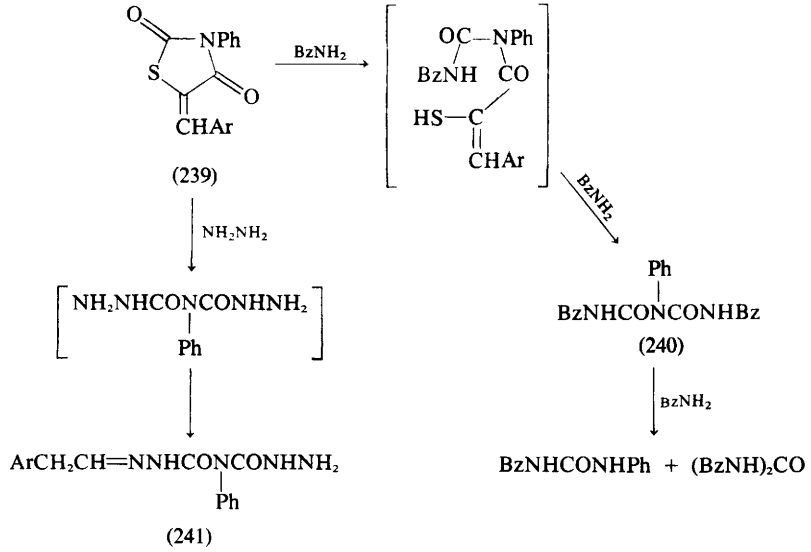


(235) (236)

Thiazolidine-2,4-dione and its derivatives undergo the Mannich reaction; aminomethylation occurs at the hetero-nitrogen atom, yielding products of type (237) and (238). Selenazolidine-2,4-diones react analogously.[191]

(237) (238)

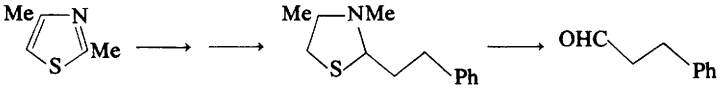
Ring Scission.—Aminolysis of 5-arylidene-3-phenylthiazolidine-2,4-diones (239) with an excess of benzylamine results in nucleophilic ring scission, giving equimolar quantities of phenylbenzylurea and dibenzylurea; the intermediate 1,5-dibenzyl-3-phenylbiuret (240) is isolable (up to 25%) under controlled conditions. Hydrazinolysis gives biuret derivatives of type (241).[192]



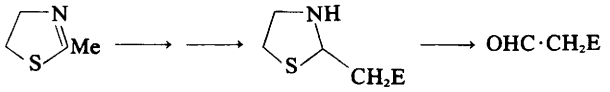
The hydrolytic ring-opening of suitable thiazolidine derivatives in 20% aqueous acetonitrile catalysed by mercuric chloride provides a route to

[191] V. E. Konenko, B. E. Zhitar, and S. N. Baranov, *Zhur. org. Khim.*, 1973, **9**, 61.
[192] A. R. A. Raouf, M. T. Omar, and M. M. Habashy, *J. prakt. Chem.*, 1973, **315**, 492.

aldehydes of practical utility because of the neutral conditions under which the aldehyde is released.[193,194] The required heterocyclic reactants may be obtained from a thiazole, *e.g.* (242),[193] or a Δ^2-thiazoline, *e.g.* (243),[194] by way of their lithio-salts, followed by condensation with electrophiles and subsequent reduction.

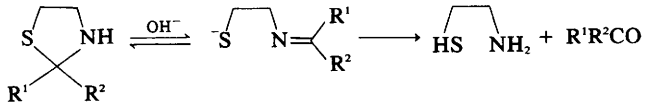


(242)



(243)

Silver ion greatly accelerates the rate of hydrolytic ring scission in alkaline media of suitably substituted thiazolidines. The mechanism (Scheme 10) is thought to involve Schiff's bases as intermediates.[195]

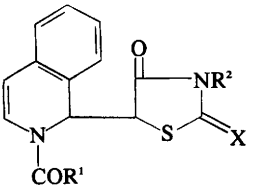


Scheme 10

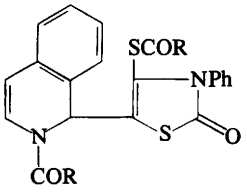
Condensations at the 5-Methylene Group.—Thiazolidinones undergo direct heteroarylation under the influence of *N*-acyl salts of six-membered nitrogen heterocycles. Thus, *N*-acylisoquinolinium salts convert the appropriate thiazolidinone into products of type (244), or 3-phenylisorhodanine into (245). Several other heterocyclic patterns (including quinolinium, pyridinium, and acridinium salts) were employed successfully in the production of analogous structures.[196,197] 5-(2-Oxo-3-indolinylidene)-3-aryl-2-phenyliminothiazolidin-4-ones (246), of thioindigoid character, are formed by the condensation of thiazolidin-4-ones and isatin.[198]

Grignard Reagents.—5-Arylidene-4-aryliminothiazolidin-2-ones (247) undergo a 1,4-addition with alkylmagnesium halides, yielding adducts of

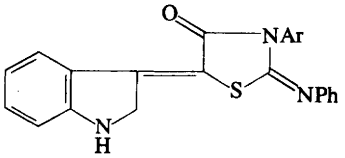
[193] L. J. Altman and S. Richheimer, *Tetrahedron Letters*, 1971, 4709.
[194] A. I. Meyers, R. Munavu, and J. Durandetta, *Tetrahedron Letters*, 1972, 3929.
[195] R. R. Luhowy, R. F. W. Cieciuch, and F. Meneghini, *Tetrahedron Letters*, 1973, 1285.
[196] A. K. Sheinkman, A. A. Deikalo, and S. N. Baranov, *Khim. geterotsikl. Soedinenii*, 1970, 130 (*Chem. Abs.*, 1970, **72**, 90 355h).
[197] A. A. Deikalo, A. K. Sheinkman, and S. N. Baranov, *Khim. geterotsikl. Soedinenii*, 1972, 1359 (*Chem. Abs.*, 1973, **78**, 43 343s).
[198] R. P. Rao and S. Raj, *J. Indian Chem. Soc.*, 1973, **50**, 366.



(244) X = O, S, or NPh

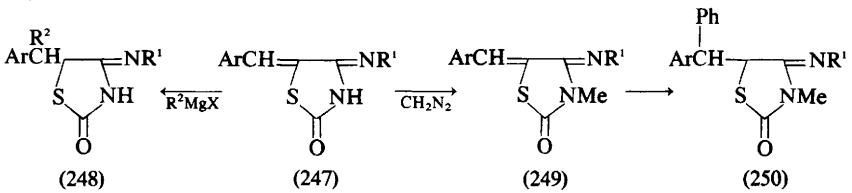


(245)



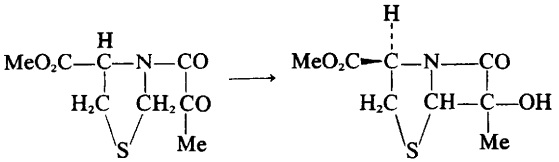
(246)

structure (248). The coloured *N*-methyl derivatives (249), obtainable by *N*-methylation of (247) by diazomethane, react analogously, yielding (250).[199]



(248) (247) (249) (250)

Penicillins.—The condensation of L-4-methoxycarbonylthiazolidine and pyruvic acid in the presence of dicyclohexylcarbodi-imide yields (50%) 3-pyruvoyl-4-methoxycarbonylthiazolidine (251). This may be photolytically cyclized to 3-methoxycarbonyl-6-hydroxy-6-methylpenam (252),[200] *i.e.*



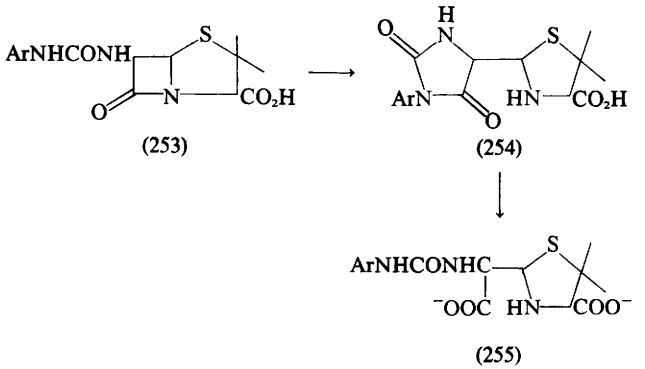
(251) (252)

a 6-oxygen analogue of the penicillins. The corresponding cyclic sulphoxide and sulphone [of (251)] undergo the same reactions.[201]

In neutral and alkaline aqueous solution, 6-(*N*-phenylureido)penicillanic

[199] N. A. L. Kassab, M. H. Elnagdy, and H. A. R. Ead, *J. prakt. Chem.*, 1973, **315**, 265.
[200] For nomenclature, see J. C. Sheehan, K. R. Henery-Logan, and D. A. Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 3292.
[201] K. R. Henery-Logan and C. G. Chen, *Tetrahedron Letters*, 1973, 1103.

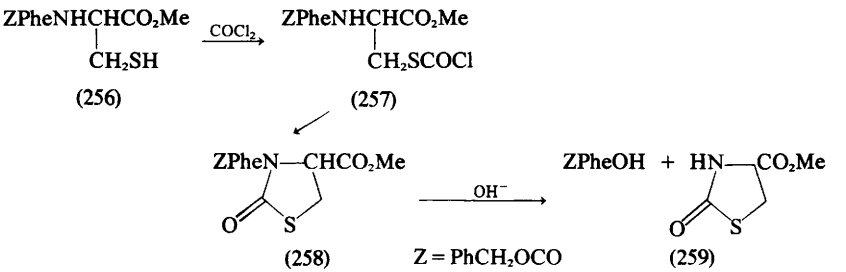
acids (253) are rapidly rearranged to the isomeric 3-phenylhydantoin-thiazolidines (254). The kinetics of the process are consistent with a mechanism involving an intramolecular nucleophilic attack of the terminal ureido-nitrogen anion on the β-lactam carbonyl-carbon, resulting in the scission of the four-membered ring. The product is rapidly hydrolysed further at pH 11 to the penicilloic acid (255).[202]



(253) (254) (255)

Peptides.—A method of selectively cleaving peptides at a cysteine residue by way of thiazolidine intermediates has been described.[203] It closely resembles the reaction sequence employing analogous oxazolidine peptides derived from phosgene and serine or threonine residues in peptide chains.[204]

The peptide (256), incorporating cysteine, is converted, by treatment with phosgene followed by mild pyrolysis in boiling xylene, into the thiazolidinone peptide (258). Alkaline hydrolysis at room temperature selectively cleaves it at the peptide linkage involving the amino-group of the cysteine residue, generally without racemization, and in good yield, liberating (259). The method fails in examples where the initial *S*-chlorocarbonyl intermediate (257) decomposes completely before cyclization to (258) has occurred.[203]



(256) (257) (258) (259)

Z = $PhCH_2OCO$

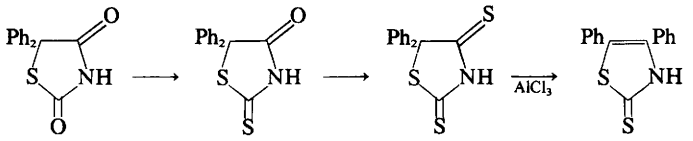
[202] H. Bundgaard, *Acta Pharm. Suecica*, 1973, **10**, 309.
[203] T. Inui, *Bull. Chem. Soc. Japan*, 1971, **44**, 2515.
[204] T. Kaneko, I. Takeuchi and T. Inui, *Bull. Chem. Soc. Japan*, 1968, **41**, 974; T. Kaneko, S. Kusumoto, T. Inui, and T. Shiba, *ibid.*, 1968, **41**, 2155.

In a study of nona- and deca-peptide analogues of bradykinin, thiazolidine-4-carboxylic acid was successfully incorporated into the peptide chain in place of proline at position 3 by solid-phase synthesis. The analogues were in general less active than bradykinin.[205]

Biochemical and Physiological Properties.—2-Arylimino-3-(*p*-chlorophenethyl)thiazolidin-4-ones inhibit the oxidation of 2-oxoglutarate, citrate, 3-hydroxybutyrate, and pyruvate, but have no inhibitory effect on the respiratory activity of rat brain homogenate with sodium succinate used as substrate. They thus appear to exert selective inhibition of NAD^+-dependent oxidations.[152]

The radioprotective properties of thiazolidines continue to be a subject of considerable interest (*cf.* ref. 183 for a brief list of the relevant literature).[183,206,207] Activity has been found in simple derivatives such as 2,2-dimethyl-, 2-methyl-2-ethyl-, and 2-phenyl-thiazolidines.[182] Thiazolidines substituted in their 3-position with 5-halogeno-2-pyridyloxy-pentyl or -hexyl groups possess relatively high radioprotective action when administered orally.[179] Promising activity is also shown by their thio-analogues.[185]

Rhodanine, Isorhodanine, and Thiorhodanine.—Phosphorus pentasulphide converts 5,5-diphenylthiazolidine-2,4-dione (260) successively into the monothione (261) and 2,4-dithione (262), in refluxing dioxan and tetralin (b.p. 180 °C), respectively. Treatment of the 2,4-dithione (262) with aluminium chloride in boiling toluene causes simultaneous desulphurization and rearrangement, with formation of 4,5-diphenyl-Δ^4-thiazoline-2-thione (263).[208] The reaction resembles that previously established[209] in respect of the comparable 5,5-diphenyldithiohydantoin.



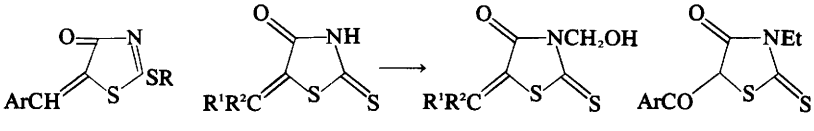
(260) (261) (262) (263)

5-Benzylidenethiorhodanines are accessible from the corresponding rhodanines by the action of phosphorus pentasulphide in anhydrous dioxan.[210]

The action of alkyl halides on rhodanine and its 5-benzylidene derivatives

[205] A. M. Felix, M. H. Jimenez, R. Vergona, and M. R. Cohen, *Internat. J. Peptide Protein Res.*, 1973, **5**, 201.
[206] R. D. Westland, M. L. Mouk, J. L. Holmes, R. A. Cooley, J. S. Hong, and M. M. Grenan, *J. Medicin. Chem.*, 1972, **15**, 968.
[207] R. D. Westland and J. L. Holmes, *J. Medicin. Chem.*, 1972, **15**, 976.
[208] E. Koltai, J. Nyitrai, and K. Lempert, *Tetrahedron*, 1973, **29**, 2781.
[209] K. Lempert and J. Nyitrai, *Tetrahedron Letters*, 1965, 2927; *Acta Chim. Acad. Sci. Hung.*, 1967, **51**, 95.
[210] K. A. Vyunov, A. I. Ginak, and E. G. Sochilin, *Khim. geterotsikl. Soedinenii*, 1971, 192 (*Chem. Abs.*, 1971, **75**, 35 863j).

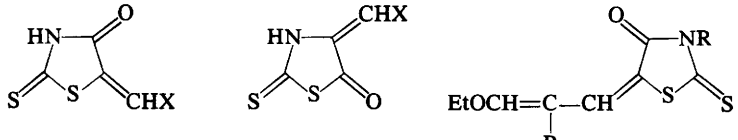
yields 2-alkylated products (264).[211] Formaldehyde in ethanol or acetone at 50 °C converts rhodanine and its 5-substituted derivatives of type (265) into pale-yellow β-hydroxymethyl compounds (266). The alternative 2-*S*-hydroxymethyl structure is excluded by the spectral evidence.[212] 3-Ethylrhodanine is *C*-acylated to the 5-aroyl derivatives (267) by the action of aroyl halides in high yield.[213]



(264) (265) (266) (267)

$R^1, R^2 = H$, Alk, or Ar

A wide range of condensation products of type (268) and (269), derived from aldehydes and rhodanine or 5-oxothiazolidine-2-thione, has been produced by conventional methods, with a view to determining their antimicrobial activities.[214] Bromomalonaldehyde tetraethylacetal reacts at the active 5-methylene group of 3-substituted rhodanines, yielding products of structure (270).[215]

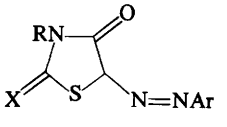


(268) (269) (270)

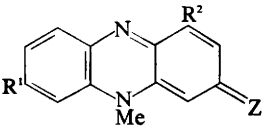
The action of diazonium salts on thiazolidine-2,4-diones and rhodanines yields 5-arylazo-2,4-diones (271) resembling azo-rhodanines in spectral and other properties.[216] Condensation products of phenazine and rhodanine of type (272) are formed in good yield by the nucleophilic attack of *N*-methylrhodanine on the appropriate phenazinium perchlorate. A benzothiazole residue may be similarly incorporated.[217]

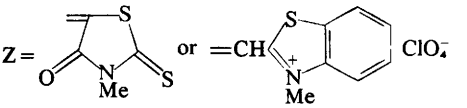
Grignard reagents react with 5-arylideneisorhodanines (273), with preservation of the heterocyclic nucleus and formation of the 5-substituted products (274). Reaction proceeds by the attack of the carbanion of the reagent on the exocyclic electrophilic carbon atom. As in other isorhodanines (see these Reports, Vol. 2, p. 648), the thiono-group in both

[211] A. I. Ginak, K. A. Vyunov, V. V. Barmina, and E. G. Sochilin, *Khim. geterotsikl. Soedinenii*, 1971, 189 (*Chem. Abs.*, 1971, **75**, 35 864k).
[212] M. A. Borisova, A. I. Ginak, T. L. Ivanova, and E. G. Sochilin, *Zhur. org. Khim.*, 1971, **7**, 1498.
[213] I. Y. Kvitko, S. V. Bolkhovets, and A. M. Kokurina, *Khim. geterotsikl. Soedinenii*, 1972, 1491.
[214] M. Gasha, A. Tsuji, Y. Sakurai, M. Kurumi, T. Endo, S. Sato, and K. Yamaguchi, *J. Pharm. Soc. Japan*, 1972, **92**, 490.
[215] E. P. Shelkina and A. V. Kazymov, *Zhur. org. Khim.*, 1972, **8**, 635.
[216] P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *J. Indian Chem. Soc.*, 1971, **48**, 719.
[217] A. Y. Ilchenko and V. N. Rudenko, *Khim. geterotsikl. Soedinenii*, 1972, 1425.

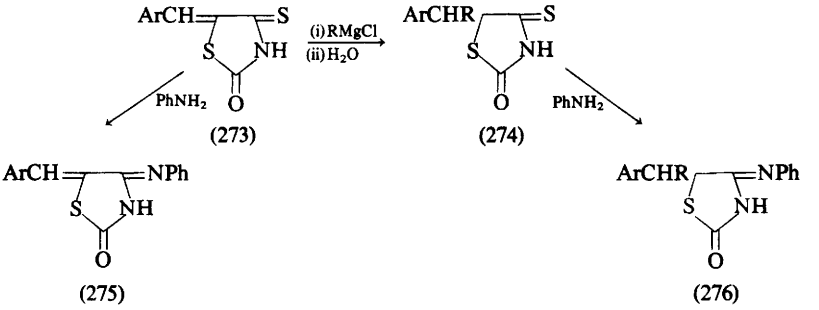


(271)

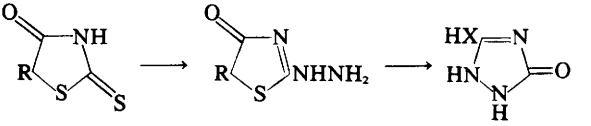


(272) 

the reagents (273) and products (274) is readily replaced upon aminolysis, giving, for example, 5-phenylimino-analogues of type (275) and (276). 5-*S*-Alkylthio-derivatives of (273) and (274) are accessible by the action of both alkyl halides and diazomethane; *N*-alkylation is not observed.[218]



Shvaika *et al.*[219] have continued their study of the ring-cleavage and recyclization of thiazolidinones under the influence of hydrazines. Rhodanine and its 5-ethyl homologue (277) furnish 2-hydrazino-Δ^2-thiazolin-4-ones (278), further convertible into 1,2,4-triazole derivatives (279). At



(277) (278) R = H or Et (279)

room temperature in ethanol, hydrazine cleaves thiazolidine-2,4-dione to $HSCH_2CONHCONHNH_2$, and rhodanine to $HSCH_2CONHCSNHNH_2$.[220]

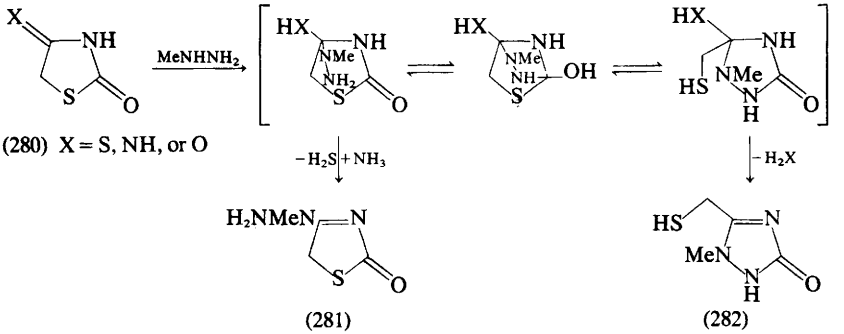
Methylhydrazine reacts with the heterocycles (280) by addition of its

[218] N. A. L. Kassab, M. H. Elnagdy, N. A. Messieha, and H. A. R. Ead, *J. prakt. Chem.*, 1972, **314**, 799.

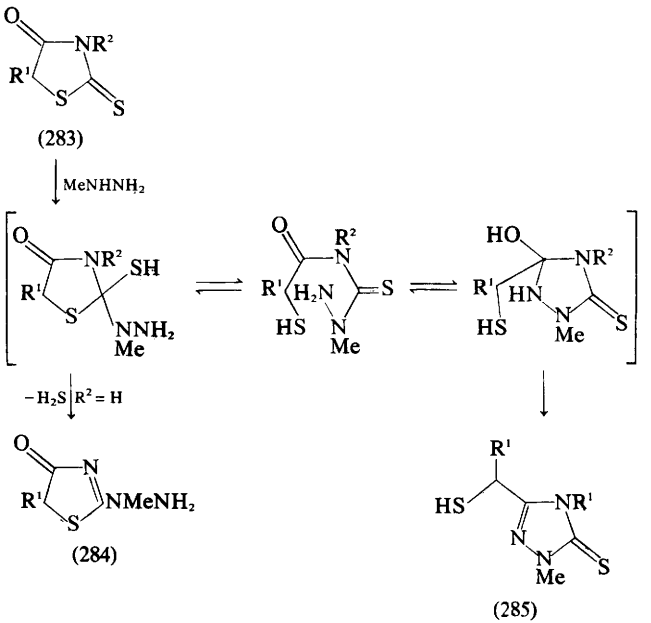
[219] O. P. Shvaika, V. N. Artemov, and S. N. Baranov, *Khim. geterotsikl. Soedinenii*, 1971, 39 (*Chem. Abs.*, 1971, **75**, 35 882q). See also these Reports, Vol. 2, p. 648.

[220] V. N. Artemov, N. I. Geonya, S. N. Baranov, L. R. Kolomoitsev, and O. P. Shvaika, *Khim. Farm. Zhur.*, 1971, **5**, 6 (*Chem. Abs.*, 1972, **76**, 34 220f).

methylamino-moiety to their 4-position; simultaneous fission and cyclization results in the substituted triazolones (282). Intermediates of structure (281) may be isolated; they yield benzylidene derivatives, confirming the assigned position [in (281) and hence in (282)] of the methyl group



originating from the methylhydrazine. Rhodanines (283) yield, in this reaction, hydrazinothiazolinones (284) in non-aqueous and triazolethiones (285) in aqueous media; the probable course of these interconversions is outlined in Scheme 11.[221]



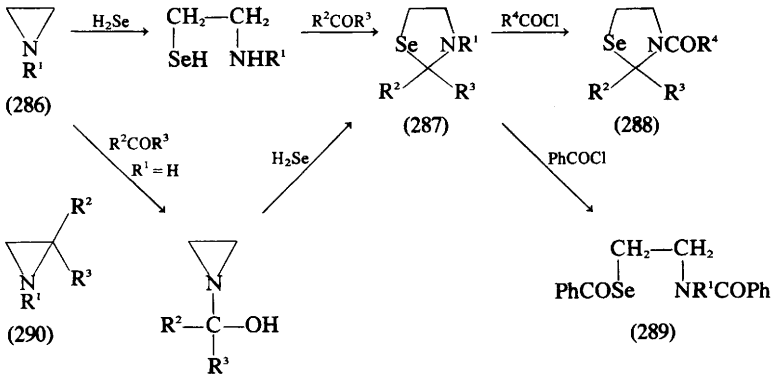
Scheme 11

[221] O. P. Shvaika, V. N. Artemov, and S. N. Baranov, *Zhur. org. Khim.*, 1971, **7**, 1968.

13 Selenazoles

Reference has already been made to recent reviews on selenazoles.[3,4] Relatively little new work has appeared during the past two years. The Hantzsch synthesis has been adapted to the production of 2-thienyl (and furyl)selenazoles from the appropriate selenamides.[6,7]

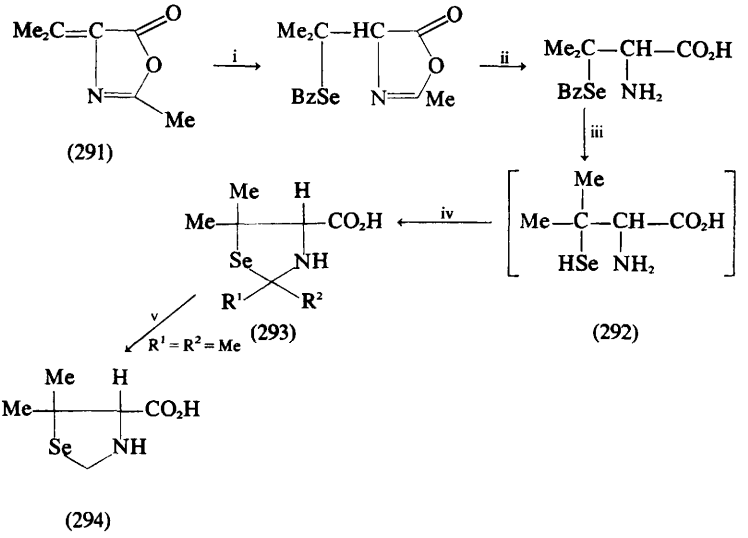
Selenazolidines have become accessible by an adaptation of the well-known thiazolidine synthesis from aziridines. The interaction of aziridines (286) with aldehydes or ketones in conjunction with hydrogen selenide produces the appropriate selenazolidines (287) in satisfactory yields.[222] More highly substituted examples arise analogously from (290).[223] The compounds yield stable *N*-acyl derivatives (288); however, benzoylation of 2-monosubstituted or 2-unsubstituted selenazolidines results in ring-opening and formation of *N*,*Se*-dibenzoylselenocysteamine (289; $R^1 = H$).[224]



Other ring-scissions, *e.g.* under the influence of Raney nickel, and the oxidation of the resulting linear products to diselenides were also described.[223] The spectral properties of representative compounds were discussed in detail.

In another, but related, approach selenazolidines (293) and (294) were derived from selenocysteine and selenopenicillamine (292) by the route shown in Scheme 12, starting with 2-methyl-4-isopropylideneoxazol-5-one (291). In the last stage, the 2-methyl groups of the heterocycle (293; $R^1 = R^2 = Me$) are displaced by an exchange reaction employing formaldehyde.[225]

[222] C. Draguet and M. Renson, *Bull. Soc. chim. belges*, 1972, **81**, 279.
[223] C. Draguet and M. Renson, *Bull. Soc. chim. belges*, 1972, **81**, 295.
[224] C. Draguet and M. Renson, *Bull. Soc. chim. belges*, 1972, **81**, 284.
[225] C. Draguet and M. Renson, *Bull. Soc. chim. belges*, 1972, **81**, 303.

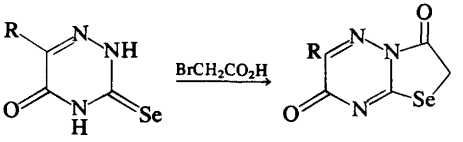


(291) (292) (293) (294)

Reagents: i, BzSeH; ii, HBr–HAc; iii, Na–NH_3; iv, R^1COR^2; v, HCHO

Scheme 12

Representatives of the selenazolo[3,2-*b*]-1,2,4-triazine system (296) are accessible from 6-substituted 2,3,4,5-tetrahydro-*as*-triazin-5-one-3-selenones (295) by successive condensation with bromoacetic ester and ring-closure of the primary substitution products with acetic anhydride.[226]



(295) (296)

[226] A. Shafiee and I. Lalezari, *J. Heterocyclic Chem.*, 1971, **8**, 1011.

14

Condensed Ring Systems Incorporating Thiazole

BY F. KURZER

1 Introduction

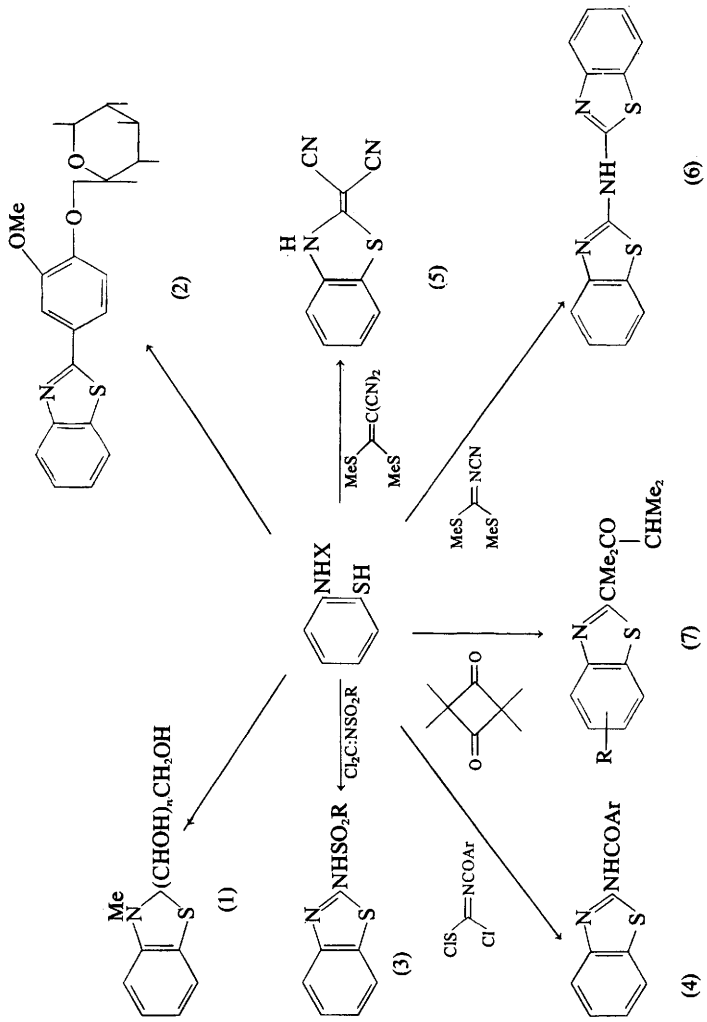
This chapter deals with benzothiazole, followed by all other fused structures incorporating thiazole, in their order of increasing ring-complexity. The pattern of the previous Reports is closely followed, in the hope of providing a measure of continuity, and with the aim of presenting the material in an increasingly condensed form.

Consolidating rather than innovating progress has been recorded over the past two years, but advances of significance continue to be reported. In the benzothiazole field, work aimed at the understanding of chemiluminescence and bioluminescence of firefly luciferin deals with a most interesting aspect of the subject. In the almost limitless area of condensed heterothiazoles, thiazolopyridines and thiazolopyrimidines are the ring systems that continue to attract the greatest attention.

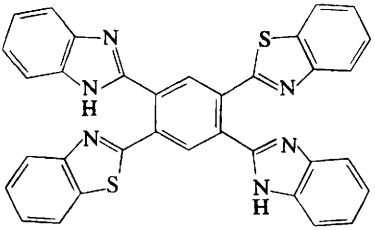
2 Synthesis of Benzothiazole

From *o*-Aminothiophenols (Type A, S—C_6H_4—N + C).—*o*-Aminothiophenols continue to be widely used as starting materials in benzothiazole synthesis. Their interaction with monosaccharides or glucosides yields products of type (1)[1] or (2).[2] *N*-(Dichloromethylene)sulphonamides or *N*-aroyl-*S*-chloroisothiocarbamoyl chloride furnish 2-acylamido-derivatives (3)[3] and (4).[4] 1,1-Bis(methylthio)-2,2-dicyanoethylene, dimethyl cyanimidodithioate, and 2,2,4,4-tetramethylcyclobutane-1,3-dione (*i.e.* the dimer of dimethylketen) produce benzothiazole derivatives of types (5),[5] (6),[6] and (7),[7] respectively.

[1] L. Szilagyi and R. Bognar, *Carbohydrate Res.*, 1970, **15**, 371.
[2] Z. Kolodynska and W. Wieniawski, *Acta Polon. Pharm.*, 1972, **29**, 372; *ibid.*, 1973, **30**, 15.
[3] R. Neidlein and H. Krüll, *Arch. Pharm.*, 1971, **304**, 763.
[4] R. Neidlein and H. Reuter, *Arch. Pharm.*, 1972, **305**, 183.
[5] R. Neidlein and H. Reuter, *Arch. Pharm.*, 1972, **305**, 731.
[6] R. Neidlein and H. Reuter, *Synthesis*, 1971, 540.
[7] S. Linke, *J. Heterocyclic Chem.*, 1973, **10**, 721.

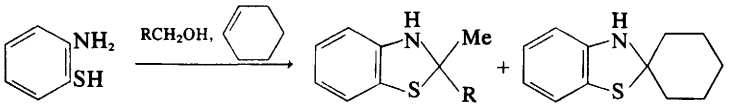

OMe
(2)
CN
CN
H
(5)
(6)
MeS
C(CN)2
MeS
MeS
NCN
MeS
NHX
SH
CMe2CO
CHMe2
(7)
R
Me
(CHOH)nCH2OH
(1)
Cl2C:NSO2R
NHSO2R
(3)
ClS
NCOAr
Cl
NHCOAr
(4)

The condensation of *o*-aminothiophenol and terephthaloylenebis(benzimidazole) in polyphosphoric acid at 140—200 °C yields the bis-benzothiazolyl derivative (8); related structures are similarly accessible.[8]



(8)

Photolysis of simple primary alcohols in the presence of 2-aminothiophenol and cyclohexene produces the spiro-benzothiazoline (10) (2—6%), and (mainly) 2-alkyl-2-methylbenzothiazolines (9) (5—55%); the methyl group of the latter may arise from a carbon atom of the cyclohexene.[9]

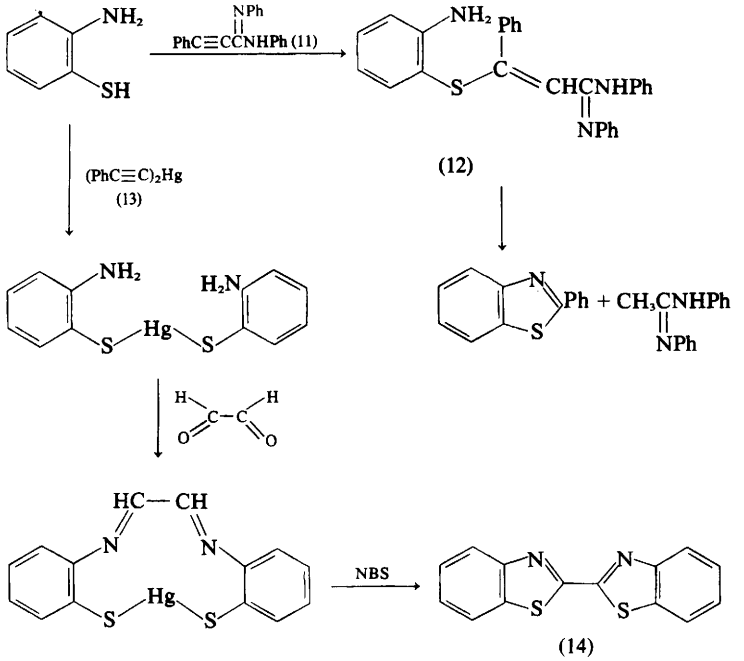


(9) (10)

The interaction of *o*-aminothiophenol with *NN'*-diphenylphenylpropiolamidine (11) occurs by nucleophilic addition at the β-carbon of the acetylenic bond, yielding the adduct (12). This is rapidly cyclized to 2-phenylbenzothiazole in boiling DMF, with elimination of *NN'*-diphenylacetamidine. The overall reaction constitutes a novel cleavage of the acetylene triple bond, the mechanism of which was considered in some detail.[10] In the course of a wider study of the conversion of thiocarbonamido-compounds into mercaptides by means of mercury bis(phenylacetylide),[11] 2-aminothiophenol gave 2,2'-bis(benzothiazolyl) (14) by the sequence of reactions shown.[12]

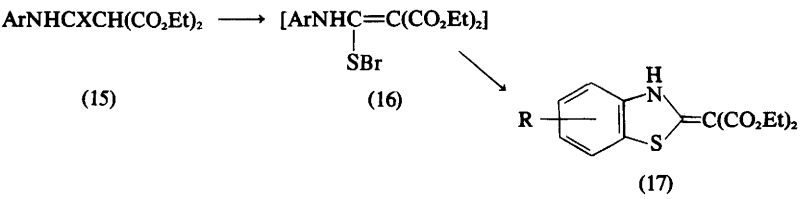
Jacobson–Hugershoff Synthesis (Type B, C_6H_5—N—C—S).—A variety of benzothiazoles continue to be produced by this old-established synthesis.

[8] V. V. Korshak, E. S. Krongauz, A. P. Travnikova, and A. L. Rusanov, *Khim. geterotsikl. Soedinenii*, 1972, 247; (*Chem. Abs.*, 1972, **76**, 140 644g).
[9] Y. Maki, M. Suzuki, Y. Masada, and K. Hashimoto, *J.C.S. Chem. Comm.*, 1972, 209.
[10] H. Fujita, R. Endo, K. Murayama, and T. Ichii, *Bull. Chem. Soc. Japan*, 1972, **45**, 1581.
[11] L. M. Shegal and I. L. Shegal, *Khim. geterotsikl. Soedinenii*, 1970, 1330 (*Chem. Abs.*, 1971, **75**, 5777s).
[12] W. Ried and R. Oxenius, *Chem. Ber.*, 1973, **106**, 484.



Recent examples include 2-(ω-arylhydrazino)benzothiazoles,[13] 2-benzothiazolylhydrazones of 4-arylthiosemicarbazides,[11] and 2-[(arylsulphonyl)-cyanomethyl]benzothiazoles.[14]

The oxidation of thioanilides of diethyl methanetricarboxylate (15; X = S) by bromine in polar solvents, especially formic acid, yields the corresponding benzothiazoles (17). An examination of the reaction under a variety of conditions suggests that sulphenyl bromides (16) function as intermediates. In non-polar solvents, desulphurization to the amides (15; X = O) becomes the predominating reaction.[15]

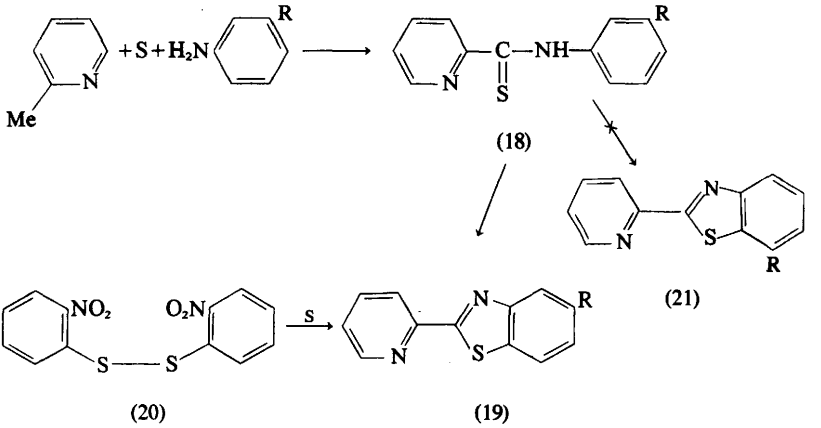


[13] M. Z. Peretyazhko and P. S. Pelkis, *Khim. geterotsikl. Soedinenii*, 1971, 765 (*Chem. Abs.*, 1972, **76**, 25 153j).

[14] V. M. Neplyuev, Y. N. Usenko, R. G. Dubenko, and P. S. Pelkis, *Khim. geterotsikl. Soedinenii*, 1970, 1194 (*Chem. Abs.*, 1971, **75**, 5775q).

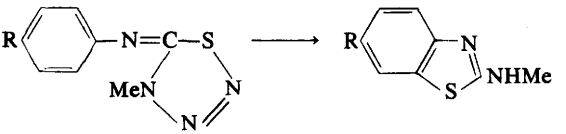
[15] H. Kunzek and G. Barnikow, *Z. Chem.*, 1973, **13**, 176.

Other Type B Syntheses.—The prolonged interaction of 2-picoline with *meta*-substituted anilines in the presence of sulphur at 170 °C under Willgerodt–Kindler conditions gives, apart from the thioanilides (18), only one of the two possible isomers, namely 5-substituted benzothiazoles (19), the structure of which was confirmed by their unequivocal synthesis from (20). In contrast, both isomers (19) and (21) are obtained by the oxidative cyclization of the thioanilides (18) by the modified Jacobson reaction; the two reactions clearly occur by distinct mechanisms.[16]



(18) (21) (20) (19)

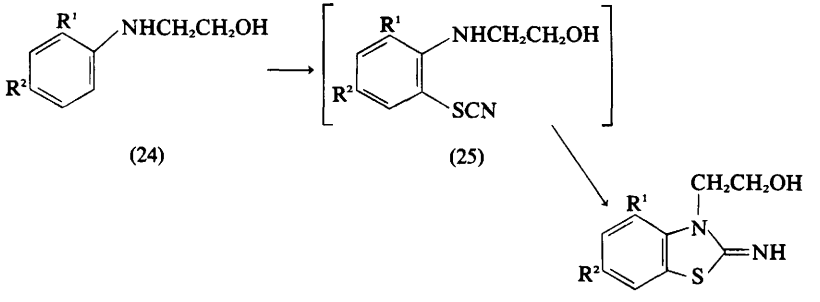
5-Arylimino-4-methyl-1,2,3,4-thiatriazoles (22), obtainable by methylation of the parent heterocycles with diazomethane, undergo ring contraction at 120—130 °C, with loss of nitrogen, to afford the corresponding benzothiazoles (23) in 50% yield.[17]



(22) (23)

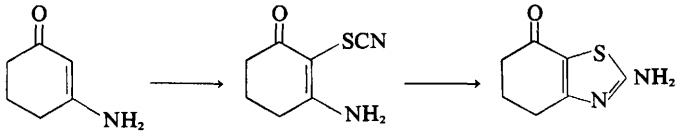
Type C Syntheses (N—C_6H_4—S—C).—The thiocyanation of *para*-substituted alkanolanilines (24) by sodium thiocyanate and bromine in glacial acetic acid at room temperature results in the immediate cyclization of the primary substitution products (25) to 2-imino-3-hydroxyethyl-2,3-dihydrobenzothiazoles (26). The assigned structures, supported by the spectral evidence, were confirmed by the alternative synthesis of (26) from appropriately substituted thioureas by Hugershoff's method.[18]

[16] T. Hisano and Y. Yabuta, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 511.
[17] R. Neidlein and J. Tauber, *Arch. Pharm.*, 1971, **304**, 687.
[18] R. F. Ambartsumova and S. R. Tulyaganov, *Zhur. org. Khim.*, 1971, **7**, 1962.



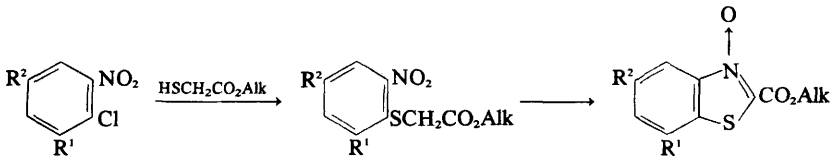
(24) (25) (26)

Aminothiocyanogen may take the place of the more commonly employed dithiocyanogen in introducing the thiocyanato-group into aromatic nuclei. *p*-Toluidine is converted by this reaction into 2-amino-6-methylbenzothiazole in 94% yield. 1-Aminocyclohex-1-en-3-one (27) similarly affords the substituted 4,5,6,7-tetrahydrobenzothiazole (28).[19]



(27) (28)

The interaction of *o*-chloronitrobenzenes (29) and thioglycolic esters (30) in ethanol in the presence of triethylamine (1.1 mole) produces substituted 2-alkoxycarbonylbenzothiazole *N*-oxides (32), generally in excellent yields. The reaction proceeds exothermally in one stage, but in suitable cases, the intermediate arylthioglycolic esters (31) are isolable, and are in fact occasionally the final products. The resulting hetero-*N*-oxides are yellow, crystalline, relatively sparingly soluble compounds of considerable reactivity (*cf.* properties, p. 629). Spectral data confirmed the attachment of the oxygen at the nitrogen, *i.e.* the non-occurrence of its possible migration to the sulphur atom [in (32)].[20]



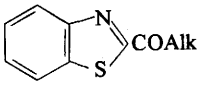
(29) (30) (31) (32)

[19] E. Schmitz and H. Striegler, *J. prakt. Chem.*, 1971, **313**, 1125.
[20] K. Wagner, H. Heitzer, and L. Oehlmann, *Chem. Ber.*, 1973, **106**, 640.

Table 1 *Production of benzothiazoles from the pre-formed ring-system*

Type of Compound	*Reference*
Substituted 2-anilinobenzothiazoles	22
Benzothiazol-2-ylbenzylamines	23
2-(Adamantylacylamino)benzothiazoles (34)	24
3-Methyl-2-benzothiazolinone [1-^{15}N]hydrazones (and [2-^{15}N])	25
2-Aminobenzothiazole, dialkylphosphinothioyl derivatives (35)	26
Benzothiazoles, 2-azo-dyes (36)	27
α-Benzothiazol-2-yl-α,β-diarylhydrazyl radicals	28
Benzothiazol-2-ylformazans	29
Benzothiazol-2-yl disulphides	30
5-Alkyl-6-hydroxy-4,7-dioxobenzothiazoles	31
1-(*S*-Benzothiazole-2-thionyl)-1-alkylmercapto-*al*-D-galactose penta-*O*-acetate (37)	32
2-Substituted 5-(or 6)benzothiazoleacetic acids	33
2-(1,2,4-Triazolyl)benzothiazoles	34
2-(1-Piperazinyl)benzothiazoles	35

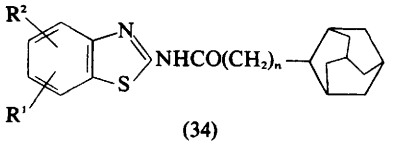
The interaction of azobenzene-2-sulphenyl bromide and methyl alkyl ketones in aqueous ethanol yields benzothiazol-2-yl alkyl ketones (33), by way of intermediate sulphides.[21]



(33)

Numerous benzothiazoles are being produced from the pre-formed ring-system by replacement reactions, and by standard modifications of existing substituents. Compounds so formed are listed in Table 1.[22–35]

[21] A. Chaudhuri and P. K. Sarma, *Indian J. Chem.*, 1973, **11**, 315; see also A. Burawoy and A. Chaudhuri, *J. Chem. Soc.*, 1956, 648.
[22] C. J. Sharpe, P. J. Palmer, D. E. Evans, G. R. Brown, G. King, R. S. Shadbolt, R. B. Trigg, R. J. Ward, A. Ashford, and J. W. Ross, *J. Medicin. Chem.*, 1972, **15**, 523.
[23] P. J. Palmer, G. Hall, R. B. Trigg, and J. V. Warrington, *J. Medicin. Chem.*, 1971, **14**, 1223; P. J. Palmer, R. J. Ward, and J. V. Warrington, *ibid.*, p. 1226; P. J. Palmer, R. B. Trigg, and J. V. Warrington, *ibid.*, p. 1228.
[24] E. Costakis and P. Canonne, *J. Medicin. Chem.*, 1971, **14**, 1222.
[25] R. A. Bartsch, S. Hünig, and H. Quast, *J. Org. Chem.*, 1972, **37**, 3604.
[26] J. Bödeker and R. John-Schenk, *Z. Chem.*, 1972, **12**, 137.
[27] M. A. Abbadi, O. F. Ginzburg, and B. A. Porai-Koshits, *Zhur. org. Khim.*, 1972, **8**, 2412.
[28] N. I. Abramova, R. O. Matevosyan, Y. A. Abramov, V. N. Yakovleva, A. K. Chirkov, L. A. Perelyaeva, V. A. Gubanov, and V. I. Koryakov, *Khim. geterotsikl. Soedinenii*, 1971, 1484 (*Chem. Abs.*, 1972, **77**, 34 409).
[29] L. M. Shegal, I. L. Shegal, and N. P. Bednyagina, *Khim. geterotsikl. Soedinenii*, 1972, 35 (*Chem. Abs.*, 1972, **76**, 153 659r).
[30] K. Sirakawa, O. Aki, T. Tsujikawa, and T. Tsuda, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 235.
[31] M. D. Friedman, P. L. Stotter, T. H. Porter, and K. Folkers, *J. Medicin. Chem.*, 1973, **16**, 1314.
[32] H. Zinner and M. Schlutt, *J. prakt. Chem.*, 1971, **313**, 1181.
[33] J. Wada, T. Suzuki, M. Iwasaki, H. Miyamatsu, S. Ueno, and M. Shimizu, *J. Medicin. Chem.*, 1973, **16**, 930.
[34] F. Russo, M. Santagati, and G. Pappalardo, *Ann. Chim. (Italy)*, 1972, **62**, 351.
[35] M. Verderame, *J. Medicin. Chem.*, 1972, **15**, 693.



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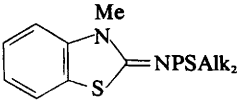

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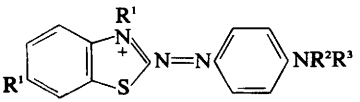

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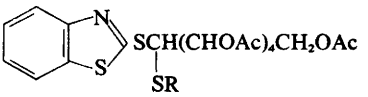


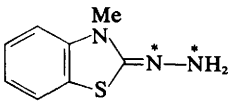
(37)

3 Physical Properties of Benzothiazoles

Spectral properties[36] and dissociation constants[37] of a series of phenols carrying in their *ortho-* or *para*-position a heterocyclic substituent (including the benzothiazolyl group) have been determined. The linear relation of dissociation constants with Hammett σ_p constants was used to calculate substitution constants for the heterocyclic residues. Owing to their electron-withdrawing effect, the hetero-substituents invariably enhance the acidity of the phenolic hydroxy-group.

The availability of ^{15}N-labelled benzothiazole derivatives (38)—(40) has occasioned a detailed study of the i.r. spectra of corresponding pairs of labelled and unlabelled compounds. The results provide evidence, *inter alia*, for the existence of 2-nitrosoimino-3-methylbenzothiazoline as the two geometrical isomerides (40) and (41).[25]

Information derived from i.r. spectra is available concerning the tautomerism and intramolecular hydrogen bonding of the azohydrazone group in 1-benzothiazolyl-3-methyl-5-naphthylformazans of type (42).[38]



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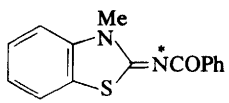

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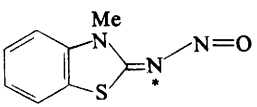

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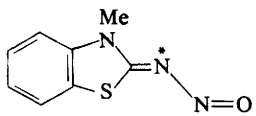
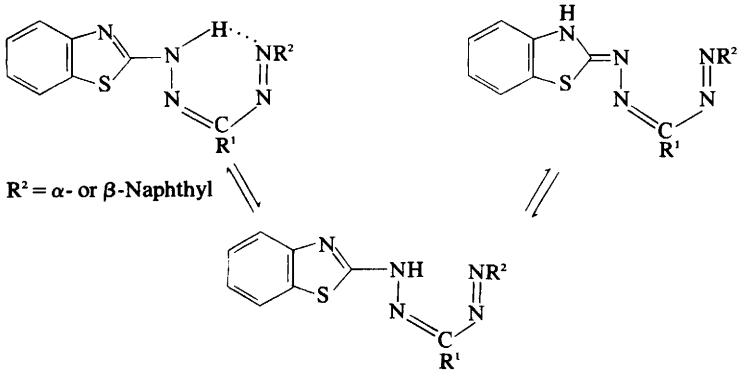


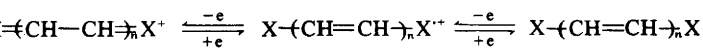
(41)

[36] J. Durmis, M. Karvas, and Z. Manasek, *Coll. Czech. Chem. Comm.*, 1973, **38**, 224, 243.
[37] J. Durmis, M. Karvas, and Z. Manasek, *Coll. Czech. Chem. Comm.*, 1973, **38**, 215.
[38] G. N. Lipunova, E. P. Motyleva, and N. P. Bednyagina, *Khim. geterotsikl. Soedinenii*, 1971, 831 (*Chem. Abs.*, 1972, **76**, 25 175t).

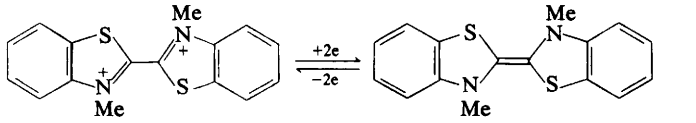


(42)

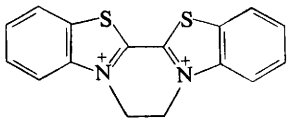
The polarographic behaviour and u.v. spectra of 2,2′-bis-(3-methyl-3-benzothiazolium) salts (44) and the analogous bridged structures (45) show that such hetero-substituted ethylenes form redox systems of type (43).[39]



(43, ox.) (43, semi.) (43, red.)



(44, ox.) (44, red.)



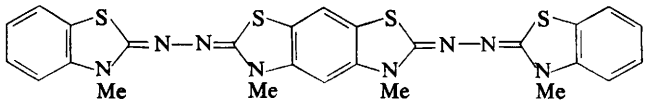
(45, ox.)

Their semiquinone formation constants are derived from their two-step polarograms. Their preparation, chiefly by quaternization of 2,2′-bis-benzothiazole, was described in detail.[40]

The synthesis of bis-azins of type (46) and related compounds has been briefly described and their oxidation stages have been examined.[41]

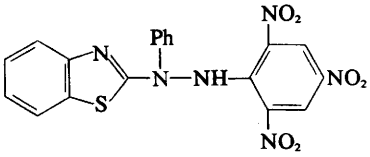
Spectral and physical methods have been employed to examine the structures of the two stable radicals α-(6-methyl-2-benzothiazolyl)-α-phenyl-β-picrylhydrazyl, its isomer, and their hydrazines (47a) and (47b), as

[39] S. Hünig, D. Scheutzow, and H. Schlaf, *Annalen*, 1972, **765**, 126.
[40] S. Hünig, D. Scheutzow, H. Schlaf, and H. Quast, *Annalen*, 1972, **765**, 110.
[41] G. Manecke and J. Kautz, *Tetrahedron Letters*, 1972, 629.

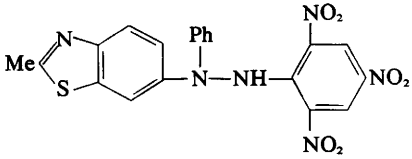


(46)

well as their charge-transfer complexes with piperidine.[42] The former (47a), obtained in 70% yield by treating α-2-benzothiazolyl-α-phenylhydrazine with 2,4,6-trinitroanisole, exhibits polymorphism, existing in the monoclinic and triclinic form. Detailed crystallographic data, as well as the results of an *X*-ray analysis, are on record.[43]



(47a)



(47b)

4 Chemical Properties of Benzothiazoles

Homolysis, Oxidation, and Reduction.—Photolysis converts 2-nitrosoimino-3-phenyl-2,3-dihydrobenzothiazole (48; R = Ph), with loss of nitric oxide, into bis[*o*-(*N*-phenylcyanamino)phenyl] disulphide in 74% yield. Under varied conditions, 2-imino-3-phenyl-2,3-dihydrobenzothiazole is also formed (20%). The relative rates of the photolysis of (48) were measured in a number of different solvents. An interpretation of the results in terms of a free-radical mechanism involving the biradical (49) was proposed.[44]

In an extensive study of the selective homolytic amidation of heteroaromatic bases, the behaviour of benzothiazole has been described.[45] Carbamoyl and α-*N*-amidoalkyl radicals (generated from formamide or *N*-alkylacetamides) attack its 2-position, producing 2-carboxamido- or 2-acetamidomethyl-benzothiazoles, generally in satisfactory yields.[45]

The action of peracids on substituted 2-(2-pyridyl)benzothiazoles attacks their pyridine ring preferentially; subsequent cleavage of the thiazole ring results in 2-(1-oxido-2-picolinamido)benzenesulphonic acids. In contrast, pertrifluoroacetic acid oxygenates the nitrogen of the thiazole ring.[46]

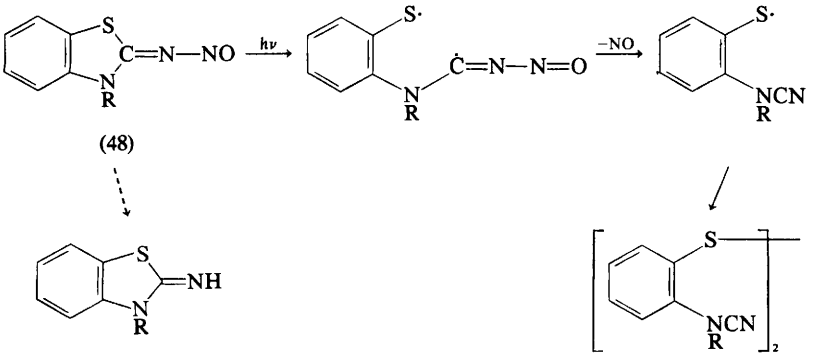
[42] R. O. Matevosyan, N. I. Abramova, Y. A. Abramov, V. N. Yakovleva, A. K. Chirkov, L. A. Perelyaeva, V. A. Gubanov, V. I. Koryakov, and O. B. Donskikh, *Khim. geterotsikl. Soedinenii*, 1971, 462 (*Chem. Abs.*, 1972, **76**, 24 503m).

[43] L. A. Petrov, O. B. Donskikh, V. D. Galyaminskikh, B. P. Manannikov, R. O. Matevosyan, and A. K. Chirkov, *Khim. geterotsikl. Soedinenii*, 1973, 322 (*Chem. Abs.*, 1973, **78**, 159 504).

[44] K. Akiba, I. Fukawa, N. Nomura, and N. Inamoto, *Bull. Chem. Soc. Japan*, 1972, **45**, 1867.

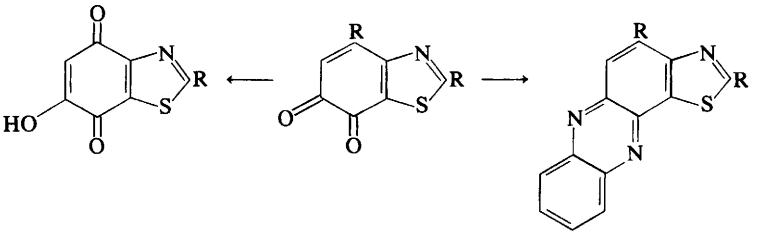
[45] A. Arnone, M. Cecere, R. Galli, F. Minisci, M. Perchinunno, O. Porta, and G. Gardini, *Gazzetta.*, 1973, **103**, 13.

[46] T. Hisano and H. Koga, *J. Pharm. Soc. Japan*, 1971, **91**, 1013.



(48)

The oxidation of 6-hydroxybenzothiazole by oxygen in the presence of a secondary amine–copper(II) complex yields 2,4-bis(dialkylamino)benzothiazolequinones. Their further treatment with *o*-phenylenediamine or alkali produces the corresponding phenazines or 6-hydroxy-4,7-quinones, respectively (Scheme 1).[47]

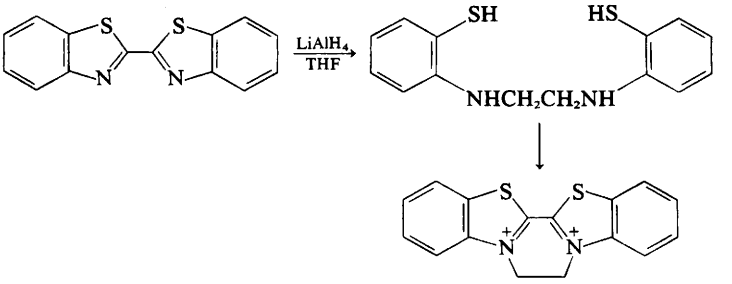


Scheme 1

Reduction of benzothiazole by lithium aluminium hydride produces *o*-(methylamino)thiophenol; applied to 2,2′-bibenzothiazole, the method affords the stable diamine (82%); this compound is of interest in that it is recyclized by oxalyl chloride to a bridged quaternary salt (Scheme 2), which has featured in a wider investigation of heterocyclic redox systems.[40]

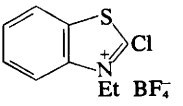
Nucleophilic Substitution.—Approaching nucleophiles induce partial positive charges on the carbon skeleton of heterocycles and are generally regarded to react at the carbon atom having the highest charge density. This view has been disputed on the basis of observations made concerning transfer reactions of the nitromethane anion to cations of various nitrogen heterocycles (including benzothiazole). The reactivities show no correlation with the charge densities, but are directly related to the energies of the lowest unoccupied antibonding orbitals of the cations.[48]

[47] A. V. Lukyanov, V. G. Voronin, and Y. S. Tsizin, *Khim. geterotsikl. Soedinenii*, 1971, 196 (*Chem. Abs.*, 1971, **75**, 35 925f); see also these Reports, Vol. 2, p. 665.
[48] W. Kiel, F. Kröhnke, and G. Schneider, *Annalen*, 1972, **766**, 45.

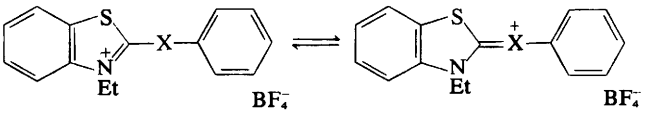


Scheme 2

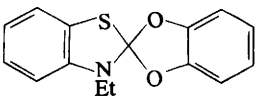
N-Alkyl-2-chlorobenzothiazolium tetrafluoroborates (50) are attacked by the heteroatom of nucleophiles such as (thio)phenols or *N*-alkylanilines to yield salts of type (51). Catechol affords the spiran (52), arising by loss of HBF_4 from the salt (51) first formed. Dimethylaniline cannot produce a quaternary salt (51) by loss of hydrogen chloride; it therefore undergoes condensation instead, with formation of (53). The structures were assigned on the basis of u.v. and n.m.r. spectra.[49]



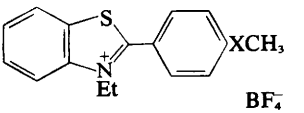
(50)



(51; X = NMe, O, or S)



(52)



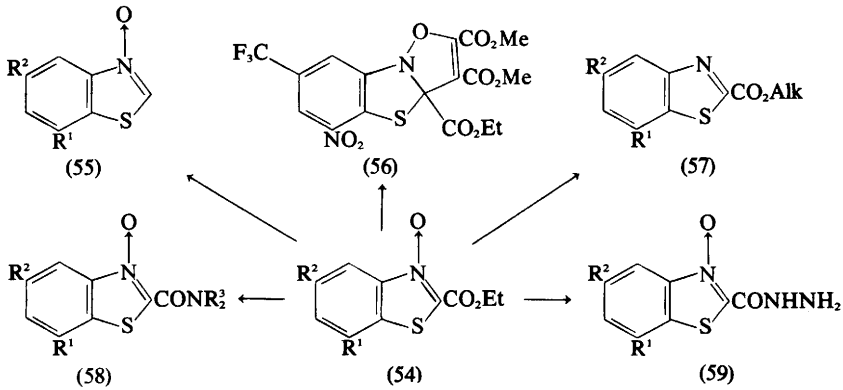
(53)

The electrophilic character of the C-2 position in benzothiazole *N*-oxide is enhanced in comparison with that of N-oxygen-free analogues; as a result, reactions with nucleophiles, and 1,3-dipolar cycloadditions, occur readily under the mildest conditions.[20]

Alkaline hydrolysis of (54) at 0—5 °C is attended by decarboxylation,

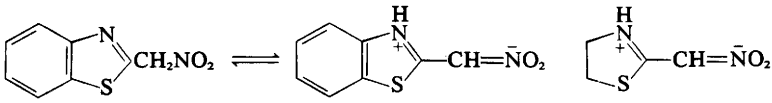
[49] K. Dimroth and K. Severin, *Annalen*, 1973, 380.

yielding (55). Dimethyl acetylenedicarboxylate is added at the potential 1,3-dipolar centres, furnishing the stable tricyclic adduct (56).[20] Ammonia, mono- and di-alkylamines,[20,50] hydrazine, and hydroxylamine react particularly readily, yielding the appropriate 2-carbonamido-compounds (58) and (59), without affecting the *N*-oxygen.[20] As in other heteroaromatic *N*-oxides, the *N*-oxygen of (54) is smoothly removed by reduction, preferably by the use of trialkyl phosphites in ethanol, furnishing good yields of substituted 2-alkoxycarbonylbenzothiazoles (57) that may be difficultly accessible by other routes. A distinction between the *N*-oxides (54) and their parent compounds (57) by i.r. spectroscopy was not practicable because of the



overlap of the NO_2 and *N*-oxide bands, and the rather wide and partly coinciding ranges of the CO peaks of both series of compounds.[20]

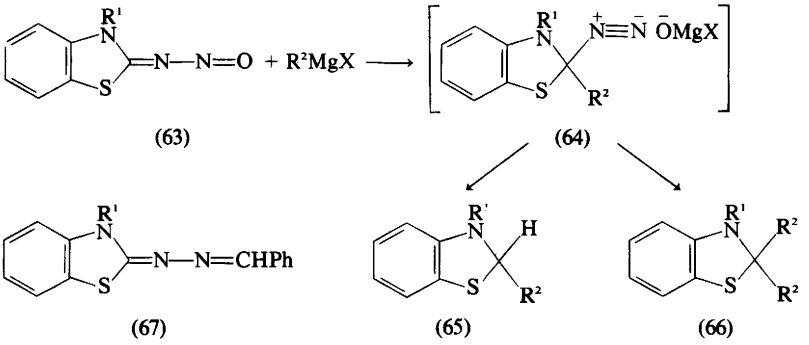
Nitration.—In common with comparable heterocycles, 2-methylbenzothiazole is readily nitrated in its exocyclic methyl group by a novel technique employing sodium amide–alkyl nitrate in liquid ammonia. According to its spectral properties, the resulting α-nitromethyl compound (60) is in equilibrium with its dipolar form (61). The non-aromatic 2-methylthiazoline similarly yields the somewhat labile nitro-derivative (62). The method is of practical utility, because nitro-compounds of this type were hitherto only obtainable in low yield by multi-stage syntheses.[51]



Organometallic Reagents.—3-Substituted 2-nitrosoiminobenzothiazolines (63) are unusually stable by virtue of their high resonance stabilization.

[50] S. Takahashi, S. Hashimoto, and H. Kano, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 287.
[51] H. Feuer and J. P. Lawrence, *J. Org. Chem.*, 1972, **37**, 3662.

Their reaction with Grignard reagents (which attack their C-2 carbon or nitroso-nitrogen) yields one of three major products, depending on the nature of the reagents. Thus, arylmagnesium bromides produce, with extrusion of the nitrosoimino-group, the corresponding 2,2-diarylbenzothiazolines (66), but 'bulky' Grignard reagents (*e.g.* Bu^{t}MgCl) introduce only one alkyl group, producing (65); the reaction may proceed by way of intermediates of type (64). Benzylmagnesium chloride produces, with retention of the nitrogenous moiety, the azine (67) as main product.[52]



(63) (64) (67) (65) (66)

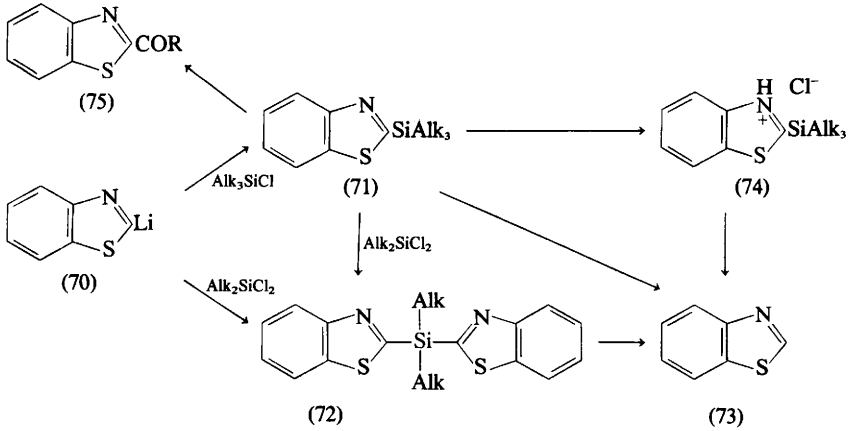
Benzothiazolyl-triazenes of type (68) and (69) are formed by the interaction of the appropriate azide and Grignard reagents. Their photochemical decomposition was studied kinetically.[53]

(68) (69)

2-Benzothiazolyl-lithium (70), prepared from benzothiazole and n-butyllithium in THF at −80 °C, reacts *in situ* with the appropriate chlorosilanes to afford mono- (71) and di-(2-benzothiazolyl)silanes (72) (see also these Reports, Vol. 2, p. 672).[54] The latter are also formed in higher yields from (71) by a novel trans-silylation reaction.[55] The assigned structures of the silylbenzothiazoles are in agreement with their observed n.m.r. spectra. The compounds are colourless, stable substances, of considerable reactivity.

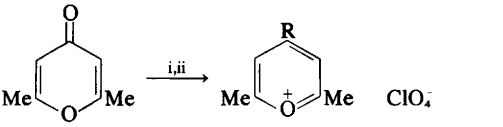
Thus, both (71) and (72) are rapidly cleaved to benzothiazole (73) by the action of water. Imonium salts (74), obtained from (71) and hydrogen halides in ether, are thermolabile, giving (73) on storage, and quaternary salts are obtainable in special cases. The low stability of the carbon–silicon

[52] K. Akiba, T. Kawamura, M. Hisaoka, and N. Inamoto, *Chem. Letters*, 1973, 201.
[53] L. I. Skripnik, V. Pochinok, and T. F. Prikhodko, *Khim. geterotsikl. Soedinenii*, 1971, 201 (*Chem. Abs.*, 1971, **75**, 48 111n).
[54] P. Jutzi and H. J. Hoffmann, *Chem. Ber.*, 1973, **106**, 594.
[55] P. Jutzi and H. J. Hoffmann, *J. Organometallic Chem.*, 1972, **40**, C61.



bond in the silyl-benzothiazoles may be exploited in electrophilic substitution reactions in position 2: acid chlorides, for example, displace the leaving group under mild conditions, giving high yields of 2-benzothiazolyl ketones (75).[54]

2-Benzothiazolyl-lithium reacts with 2,6-dimethyl-γ-pyrone at −75 °C, yielding the pyrilium perchlorates (Scheme 3).[56]



R = Benzothiazolyl

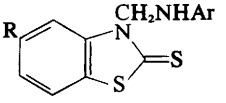
Reagents: i, RLi; ii, $HClO_4$

Scheme 3

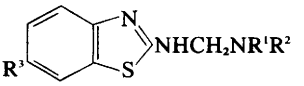
Condensations.—Aminoalkylation of the appropriate benzothiazoles has provided a series of 3-aminomethylbenzothiazoline-2-thiones (76)[57] and methylenediamines (77)[58] (see these Reports, Vol. 2, p. 668).

2-Aminobenzothiazoles are convertible into 'dehydro-*N*-Mannich bases' (79), *e.g.* piperidinoformimidoylbenzothiazole, by the action of a secondary base (*e.g.* piperidine or morpholine), with *sym*-triazine as the source of the central methine group. The mechanism is thought to involve aminomethinyl intermediates of type (78). Other amino-heterocycles (*e.g.* 1,3,4-thiadiazoles) react similarly, affording products such as (80).[59]

[56] G. N. Dorofeenko, A. V. Koblik, B. A. Tertov, and T. I. Polyakova, *Khim. geterotsikl. Soedinenii*, 1972, 1580 (*Chem. Abs.*, 1973, **78**, 58 189v).
[57] R. S. Varma, *J. prakt. Chem.*, 1972, **314**, 955.
[58] J. Paris, J. Couquelet, and P. Tronche, *Bull. Soc. chim. France*, 1973, 672.
[59] A. Kreutzberger and M. U. Uzbek, *Arch. Pharm.*, 1973, **306**, 28.



(76)



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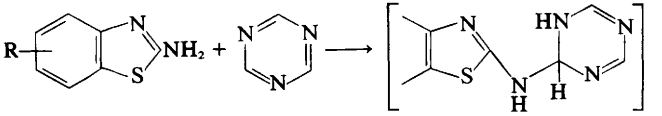
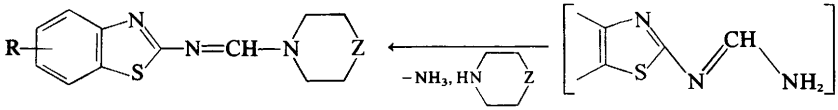
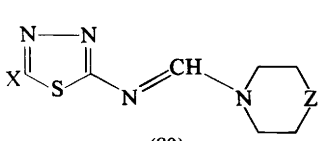


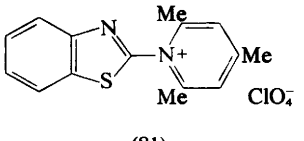


(79) (78)

The interaction of 2-aminobenzothiazole and 2,4,6-trimethylpyrilium perchlorate in boiling acetic acid gives condensation products of type (81).[60]



(80)



(81)

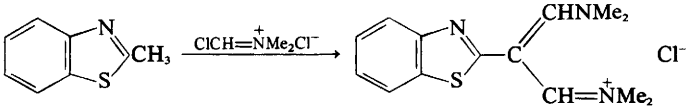
The formylation of 2-methylbenzothiazole by the Vilsmeier–Haack reaction using dimethylchloroformiminium chloride (82) in DMF yields the 1,3-bis-dimethylamino-2-(2-benzothiazolyl)propenium salt (83), which is hydrolysed by alkali to 2-benzothiazolylmalonic dialdehyde (84). The corresponding quaternary salt (85) reacts similarly in DMF, yielding (86) as the final product. In chloroform, however, its formylation followed by hydrolysis affords the trimethine dyes (87; R = H or CHO) and (88). Their formation is ascribed to the condensation of the primary formylation products with an excess of quaternary salt.[61] A series of reactions based on 3-methylbenzoselenazole take an entirely parallel course.[61]

Quaternary salts of 2-methylbenzothiazole react with benzoylacetaldehyde tetraethylacetal (89) to yield the ethoxybutadienyl-substituted derivatives (90), which are in turn converted, by the action of potassium carbonate, into 2-(β-phenyl-γ-formylallylidene)benzothiazolines (91).[62]

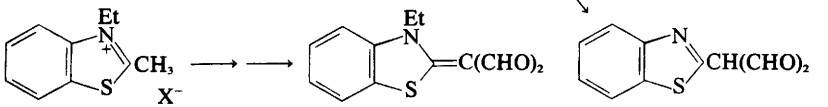
[60] G. N. Dorofeenko, A. N. Narkevich, Y. A. Zhdanov, and T. G. Soroka, *Khim. geterotsikl. Soedinenii*, 1970, 315 (*Chem. Abs.*, 1970, **73**, 66 502d).

[61] J. Ciernik, *Coll. Czech. Chem. Comm.*, 1972, **37**, 2273.

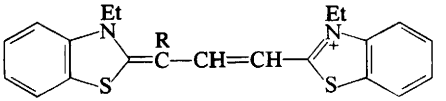
[62] A. V. Kazymov and E. P. Shchelkina, *Khim. geterotsikl. Soedinenii*, 1971, 1378 (*Chem. Abs.*, 1972, **76**, 59 511q).



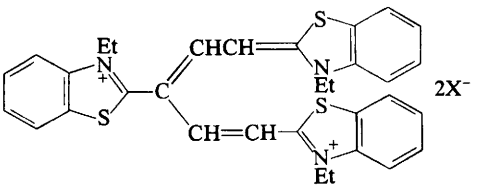
(82) (83)



(85) (86) (84)



(87)



(88)

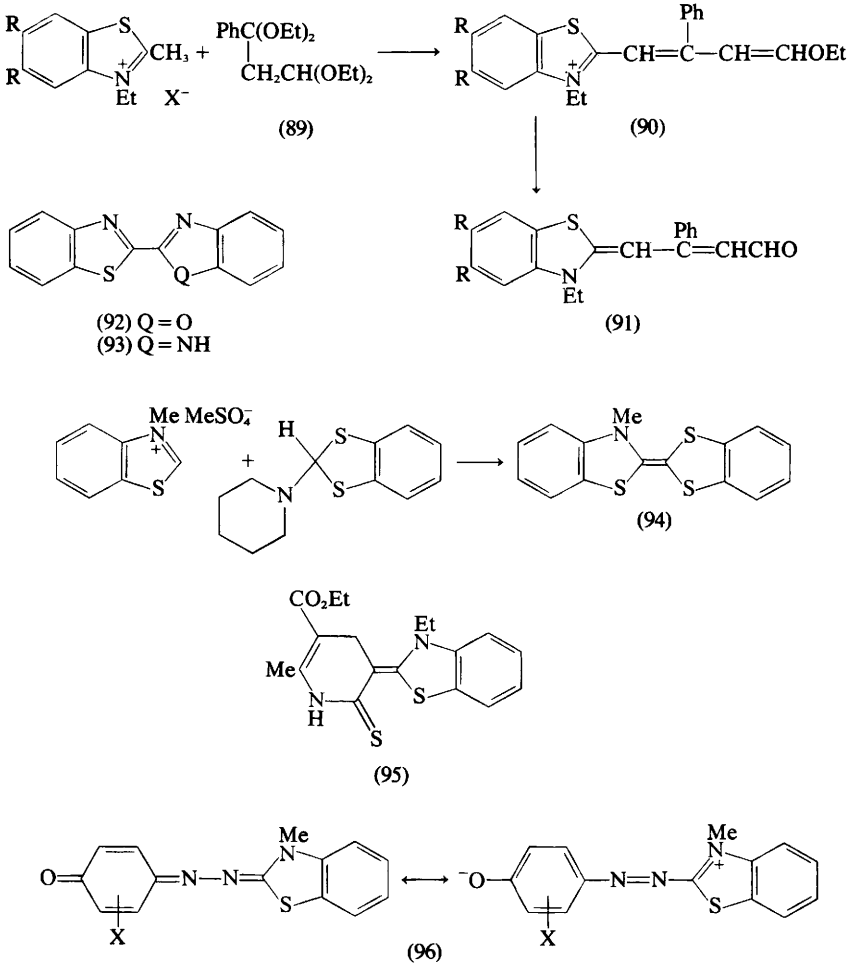
Comparable thiazoles and benzoselenazoles undergo the same reaction sequence.[62]

In the course of a wider study of the reaction between active methyl groups and *ortho*-substituted bifunctional molecules in the presence of sulphur, 2-methylbenzothiazole gave, with phenylenediamine or *o*-aminophenol, the 2-substituted benzazoles (92) and (93).[63]

The synthesis of unsymmetrical ethylenic condensation products (94) of substituted benzothiazoles and 1,3-dithiols has been briefly reported.[64] Substituted 2-(tetrahydro-5-pyridylene)benzothiazole (95) and analogues have been obtained from the appropriate components for the examination of their dyeing properties.[65]

The condensation of 3-methylbenzothiazolinone hydrazone with phenols in the presence of potassium ferricyanide yields coloured products of type (96) and provides the basis for a sensitive colour-test superior to that

[63] T. Hisano and H. Koga, *Yakugaku Zasshi*, 1971, **91**, 180. (*Chem. Abs.*, 1971, **74**, 125 559y).
[64] D. Buza and W. Krasuski, *Roczniki Chem.*, 1972, **46**, 2377.
[65] E. D. Sych and L. T. Gorb, *Khim. geterotsikl. Soedinenii*, 1971, 225 (*Chem. Abs.*, 1971, **75**, 119 187e).

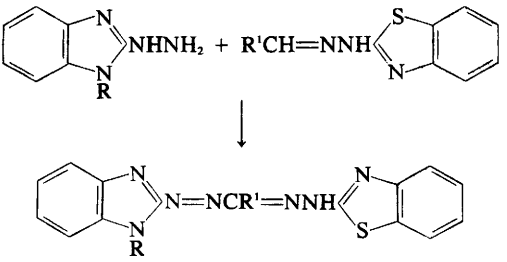


involving aminoantipyrine. Chromatographic techniques may serve for the separation and identification of individual phenols.[66]

Benzimidazolylformazans of type (97) are obtainable by the oxidative condensation of the appropriate hydrazine and hydrazone as shown.[67]

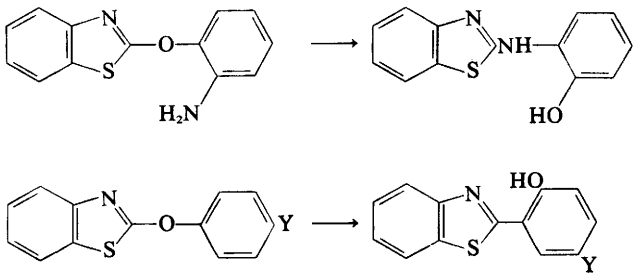
Rearrangement.—In a general study of rearrangements of 2-aryloxybenzazoles, members of the benzothiazole series were found to undergo the Smiles or Fries rearrangement under the influence of Lewis acids, or on

[66] K. Yasuda, *Nippon Kagaku Zasshi*, 1971, **92**, 974 (*Chem. Abs.*, 1972, **76**, 80 859u).
[67] N. P. Bednyagina, Y. A. Sedov, G. M. Petrova, and I. Y. Postovskii, *Khim. geterotsikl. Soedinenii*, 1972, 390 (*Chem. Abs.*, 1972, **77**, 61 885d).



(97)

photolysis, depending on the nature of the reactant and conditions. Two examples are shown in Scheme 4.[68]



Scheme 4

Schiff's bases derived from benzothiazole-2-carbaldehyde and primary amines undergo base-catalysed prototropic rearrangement and hydrolysis to afford high yields of the carbonyl compound corresponding to the original amine. Because of the practical advantages of the procedure, benzothiazole carbaldehydes are especially convenient reagents for transaminations of this kind.[69] A rearrangement of benzothiazoles to 1,2,3-benzothiadiazoles is described in Chapter 15 (p. 675).[70]

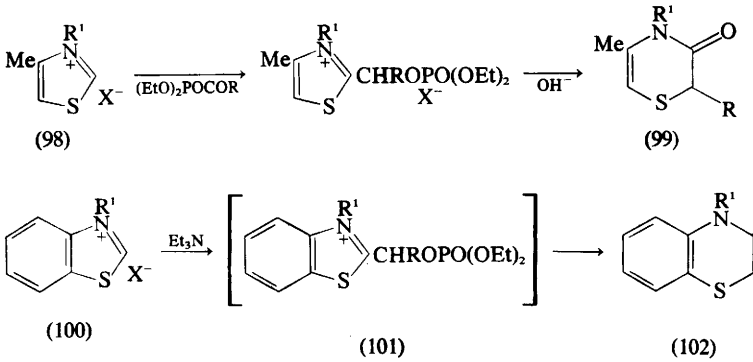
Ring Expansion to 1,4-Thiazines.—Further examples have been given of the Takamizawa ring-expansion of thiazoles (98) to 1,4-thiazines (99) (see these Reports, Vol. 2, p. 605), and its applicability to benzothiazoles has been demonstrated. Thus, the reaction of simple benzothiazolium salts (100) with diethyl acylphosphonates under the established conditions gave 1,4-benzothiazines of type (102), the structure of which was confirmed by an unequivocal synthesis. In contrast to the monocyclic adducts (99), the presumed intermediates (101) were not isolable.[71]

[68] T. Nagai, Y. Fukushima, T. K. Kuroda, H. Shimizu, S. Sekiguchi, and K. Matsui, *Bull. Chem. Soc. Japan*, 1973, **46**, 2600.

[69] V. Calo, L. Lopez, and P. E. Todesco, *J.C.S. Perkin I*, 1972, 1652. See also E. J. Corey and K. Achiwa, *J. Amer. Chem. Soc.*, 1969, **91**, 1429.

[70] E. Haddock, P. Kirby, and A. W. Johnson, *J. Chem. Soc.* (*C*), 1971, 3642.

[71] A. Takamizawa, H. Sato, and Y. Sato, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 892.



(98) (99)

(100) (101) (102)

Polymethine and other Dyes.—Merocyanine, carbocyanine, and monomethine dyes incorporating the benzothiazole structure (see these Reports, Vol. 2, p. 673) continue to be reported in great profusion in the Russian literature, usually with information concerning their light-absorbing and photosensitizing properties.[72-87] Benzoselenazoles may take the place of their sulphur analogues in these dye-structures.[81]

Sulphur-containing polymethine dyes, including those incorporating thiazolidine and benzothiazole residues, exhibit certain anomalous chromophoric properties (*e.g.* abnormal vinylene shifts), which have been traced to an interannular non-bonded S–S interaction in the monomethine ion. The conclusion is supported both by a detailed examination of the

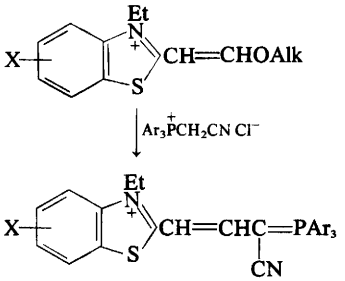
[72] A. V. Kazymov and E. P. Shchelkina, *Zhur. org. Khim.*, 1971, **7**, 1966.
[73] E. D. Sych and I. V. Fesenko, *Khim. geterotsikl. Soedinenii*, 1971, 228 (*Chem. Abs.*, 1971, **75**, 119 191b).
[74] A. V. Kazymov and L. P. Shchelkina, *Khim. geterotsikl. Soedinenii*, 1971, 693 (*Chem. Abs.*, 1972, **76**, 114 813s).
[75] M. O. Lozinskii, S. N. Kukota, and P. S. Pelkis, *Khim. geterotsikl. Soedinenii*, 1971, 1048 (*Chem. Abs.*, 1972, **76**, 87 119m).
[76] A. I. Tolmachev and M. A. Kudinova, *Khim. geterotsikl. Soedinenii*, 1971, 1177 (*Chem. Abs.*, 1972, **76**, 34 086s).
[77] M. V. Deichmeister and A. Z. Pinkhazova, *Khim. geterotsikl. Soedinenii*, 1971, 1387 (*Chem. Abs.*, 1972, **76**, 87 124j).
[78] A. V. Kazymov, L. P. Shchelkina, N. G. Kabirova, and A. F. Vompe, *Khim. geterotsikl. Soedinenii*, 1971, 1561 (*Chem. Abs.* 1972, **77**, 7277u).
[79] E. P. Shchelkina and A. V. Kazymov, *Zhur. org. Khim.*, 1972, **8**, 635.
[80] L. M. Yagupolskii, M. M. Kulchitskii, and A. Y. Ilchenko, *Zhur. org. Khim.*, 1972, **8**, 2182, 2447.
[81] A. V. Kazymov and E. P. Shchelkina, *Khim. geterotsikl. Soedinenii*, 1972, 780 (*Chem. Abs.*, 1972, **77**, 153 899q).
[82] E. D. Korotkaya and V. Y. Pochinok, *Khim. geterotsikl. Soedinenii*, 1972, 786 (*Chem. Abs.*, 1972, **77**, 141 472g).
[83] Z. I. Moskalenko, *Khim. geterotsikl. Soedinenii*, 1972, 1182 (*Chem. Abs.*, 1973, **78**, 85 898g).
[84] V. M. Zubarovskii, *Khim. geterotsikl. Soedinenii*, 1972, 1579, (*Index Chemicus*, 1973, **48**, 199 848).
[85] A. V. Kazymov and L. P. Shchelkina, *Khim. geterotsikl. Soedinenii*, 1972, 1615 (*Chem. Abs.*, 1973, **78**, 125 815u).
[86] M. M. Kulchitskii, A. Y. Ilchenko, and L. M. Yagupolskii, *Zhur. org. Khim.*, 1973, **9**, 827.
[87] A. I. Kiprianov, S. G. Fridman, and F. A. Mikhailenko, *Zhur. org. Khim.*, 1973, **9**, 1253.

spectra of appropriately substituted dyes and by theoretical LCAO–MO calculations.[88]

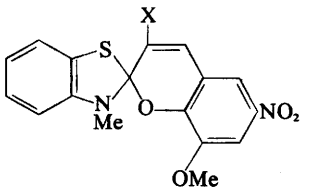
The half-wave potentials of a number of benzothi(and selen)azole dyes have been correlated with their electronic spectra.[89]

Phosphorus-containing polymethine cyanine dyes of type (103) are accessible by the condensation of 2-alkoxyvinyl (or 4-alkoxybutadienyl)-benzothiazolium and cyanomethylphosphonium salts.[90]

A comprehensive reinvestigation of the known synthesis of photochromic benzothiazole spiranes (104) (see these Reports, Vol. 1, p. 417) has



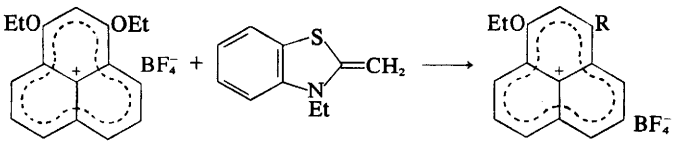
(103)



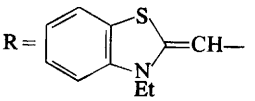
(104)

further defined its scope and limitations and established the spectral properties of compounds of this and closely related structures.[91]

The reaction of di- and tri-alkoxy-phenalenium fluoroborates [*e.g.* (105)][92] with the methylene-base (106) of 3-ethyl-2-methylbenzothiazolium salts and analogues produces a variety of dyes [*e.g.* (107) and higher



(105) (106) (107)



[88] J. Fabian and H. Hartmann, *Tetrahedron*, 1973, **29**, 2597, J. Fabian, H. Hartmann, and K. Fabian, *ibid.*, p. 2609.

[89] O. Gurtler, B. Konieczny, J. V. Grossmann, and G. Bach, *J. prakt. Chem.*, 1973, **315**, 323.

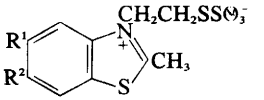
[90] A. V. Kazymov, E. B. Sumskaya, K. M. Kirillova, and E. P. Shchelkina, *Zhur. obshchei Khim.*, 1971, **41**, 2434.

[91] A. Samat, R. Guglielmetti, and J. Metzger, *Helv. Chim. Acta*, 1972, **55**, 1782.

[92] D. H. Reid, *Quart. Rev.*, 1965, **19**, 274.

degree of substitution by R], of potential photographic interest.[93,94] Their electronic spectra were determined and discussed in detail.[95]

S-[2-(Benzothiazolium-3-yl)ethyl]thiosulphates (108) have been prepared for incorporation into cyanine dyes of the Bunte-salt type.[96]



(108)

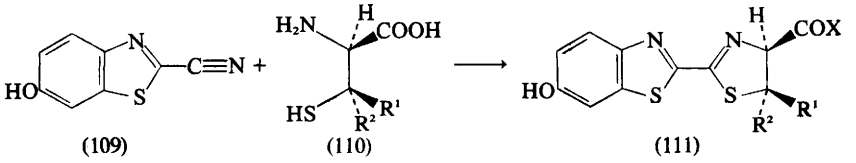
Metal Complexes.—A variety of benzothiazole derivatives continue to serve as ligands in the preparation of metal complexes.[97–102]

Chemiluminescence and Bioluminescence.—The function of thiazole and benzothiazole derivatives in the processes of bioluminescence and chemiluminescence continues to form the subject of significant investigations.[103] Extensive contributions have been provided by White *et al.*,[104] who have reviewed this interesting and active field. They have shown that the luminescence of firefly luciferins involves intermediates having dioxetan structures.

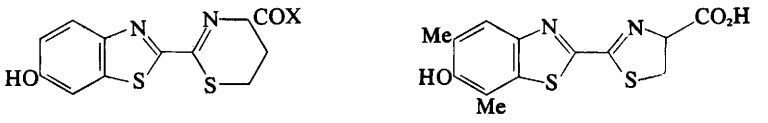
Firefly luciferin (111; $R^1 = R^2 = H$, $X = OH$) and a number of its analogues were synthesized by previously established reaction sequences[105] from a variety of substituted 2-cyanobenzothiazoles (109) and cysteines (110). Amongst others, homoluciferin (112) and 5′,7′-dimethyl-luciferin (113) are accessible in this way. Their adenylates were produced by the condensation of the free acids with adenosine monophosphate in the presence of dicyclohexylcarbodi-imide. These were used in detailed spectrophotometric studies of their chemiluminescence (initiated by bases), their fluorescence, and their bioluminescence under the influence of luciferase; the possible mechanisms of these processes were discussed.[104]

The suggested mechanism for the red light emission by firefly luciferyl

[93] S. Hünig and E. Wolff, *Chimia (Switz.)*, 1968, **22**, 33; *Annalen*, 1970, **732**, 7, 26.
[94] J. K. Elwood, *J. Org. Chem.*, 1973, **38**, 2425.
[95] J. K. Elwood, *J. Org. Chem.*, 1973, **38**, 2430.
[96] M. Yamamoto, S. Nakamura, K. Yoshimura, M. Yuge, S. Morosawa, and A. Yokoo, *Bull. Chem. Soc. Japan*, 1973, **40**, 1509.
[97] W. W. Fee, J. D. Pulsford, and P. D. Vowles, *Austral. J. Chem.*, 1973, **26**, 675.
[98] N. Shimidzu and T. Uno, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 184.
[99] V. Armeanu and E. Dragusin, *Rev. Roumaine Chim.*, 1971, **16**, 1357; *ibid.*, 1973, **18**, 1475.
[100] K. M. Yunusov, A. D. Garnovskii, O. A. Osipov, and Y. V. Kolodyazhnyi, *Zhur. obshchei Khim.*, 1971, **41**, 1320.
[101] A. D. Garnovskii, V. A. Kogan, O. A. Osipov, S. G. Kochin, L. I. Kuznetsova, and G. K. Mitina, *Zhur. obshchei Khim.*, 1971, **41**, 1370.
[102] A. D. Garnovskii, L. S. Minkina, L. V. Sakhashchik, V. P. Kurbatov, and O. A. Osipov, *Zhur. obshchei Khim.*, 1971, **41**, 1884.
[103] See also M. J. Cormier, J. E. Wampler, and K. Hori, in 'Progress in the Chemistry of Organic Natural Products', Springer, Wien and New York, 1973, Vol. 30, p. 1.
[104] E. H. White, E. Rapaport, H. H. Seliger, and T. A. Hopkins, *Bio-organic Chem.*, 1971, **1**, 92—122.
[105] E. H. White, F. McCapra, and G. F. Field, *J. Amer. Chem. Soc.*, 1963, **85**, 337.

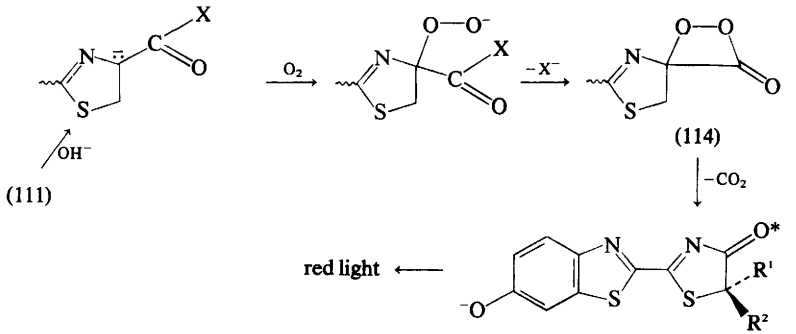


(109) (110) (111)



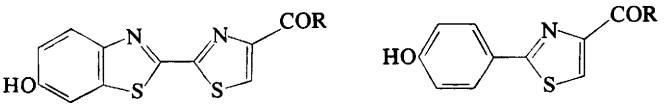
(112) (113)

adenylate (111; R = H, X = AMP) involves the intermediate dioxetan (114); it is essentially the same as one previously outlined for the phenyl ester of



5,5-dimethyl-luciferin[106] and is shown below. A similar pathway for the enzymatic light emission is consistent with the experimental findings.[104]

Hydrazines (115a, b) and (116a, b) derived from dehydroluciferin (115c) or 2-(4′-hydroxyphenyl)thiazole-4-carboxylic acid (116c) act as chemiluminescent materials in aprotic media, a strong base and oxygen being the only



(115) (a) R = $NHNH_2$
(b) R = NHNHMe
(c) R = OH

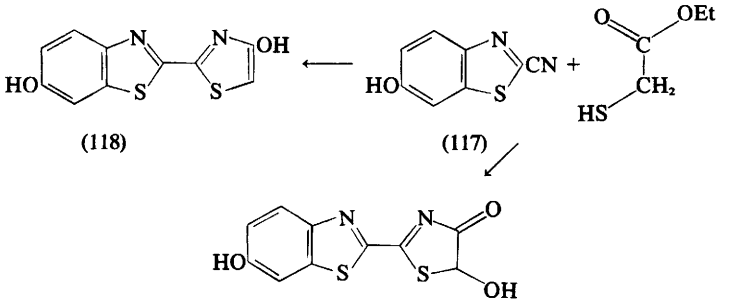
(116)

requirements for light emission.[107] Here the mechanism is likely to be a base-catalysed autoxidation, followed by electron transfer,[108] and the

[106] F. McCapra, Y. C. Chang, and V. P. Francois, *Chem. Comm.*, 1968, 22.
[107] E. Rapaport, M. W. Cass, and E. H. White, *J. Amer. Chem. Soc.*, 1972, **94**, 3153.
[108] *Cf*. D. M. Hercules, *Accounts Chem. Res.*, 1969, **2**, 301.

corresponding acid anion appears to be the light emitter. The unsubstituted hydrazides provide the highest quantum yield for emission in each series.[107]

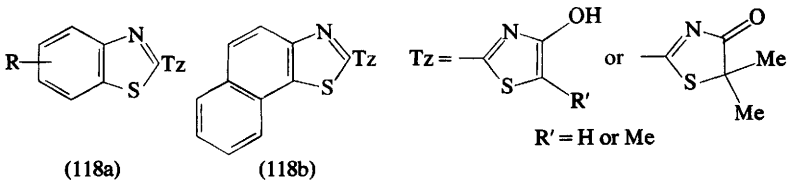
2-(6'-Hydroxybenzothiazol-2'-yl)-4-hydroxythiazole ['firefly oxyluciferin', (118)], in the form of its dianion, has been identified as an emitter in the yellow-green chemiluminescence and bioluminescence of the firefly, both *in vitro*[109] and *in vivo*.[110] It has been synthesized by the condensation of 2-cyano-6-hydroxybenzothiazole (117) and ethyl thioglycolate at 0 °C during 2 minutes under nitrogen,[109] a method that had previously failed[111] under less mild conditions. In the presence of oxygen, the product of the reaction contains an additional oxygen atom and has been formulated as 'dioxyluciferin' (119). Oxyluciferin (118) is converted into firefly luciferin (111;



(118) (117) (119)

$R^1 = R^2 = H$, X = OH) on being heated with cysteine in basic media, and may function in this fashion in firefly lanterns[109] (see these Reports, Vol. 2, p. 613).

The foregoing synthesis of oxyluciferin is applicable to the production of analogues, chiefly by the use of variously substituted 2-cyano-benzothiazoles or -naphthothiazoles. The presence of α-methyl groups in ethyl thioglycolate retards the rate of the condensation, but the analogues (118a) and (118b) are, in general, more stable, and more easily synthesized than the parent oxyluciferin.[112]



(118a) (118b)

R' = H or Me

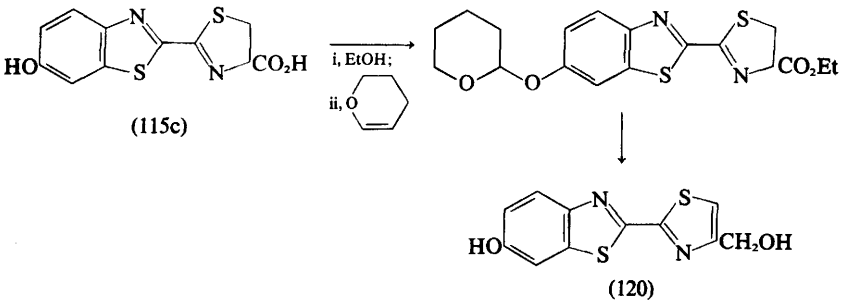
[109] N. Suzuki, M. Sato, K. Okada, and T. Goto, *Tetrahedron*, 1972, **28**, 4065; *Tetrahedron Letters*, 1969, 4683.

[110] N. Suzuki and T. Goto, *Tetrahedron*, 1972, **28**, 4075; *Tetrahedron Letters*, 1971, 2021.

[111] P. J. Plant, E. H. White, and W. D. McElroy, *Biochem. Biophys. Res. Comm.*, 1968, **31**, 98.

[112] N. Suzuki and T. Goto, *Agric. and Biol. Chem. (Japan)*, 1972, **36**, 2213.

Dehydroluciferin (115c) has been converted into the corresponding alcohol by reduction of the suitably protected molecule. The resulting 'dehydroluciferol' (120), 2-(6'-hydroxy-2'-benzothiazolyl)-4-hydroxymethylthiazole, is highly fluorescent, and exhibits excitation and emission spectra

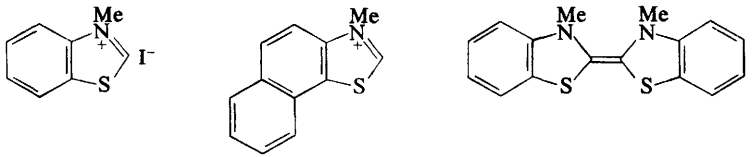


(115c) (120)

similar to those of dehydroluciferin. It is enzymatically unreactive, as it cannot form an acyl adenylate, which precludes its participation in the light-emitting step.[113] Its availability has prompted experiments that have shed further light on the mechanism of action of firefly luciferase.[114]

Biochemical and Miscellaneous.—3-Methyl-2-benzothiazolone hydrazone is incorporated quantitatively into the anticodon loop of t-RNA^{Phe} from yeast. Reaction occurs by Schiff's base formation with the ribose aldehyde group remaining after excision of the base Y from the nucleotide. The reaction provides a method of chemically modifying the natural polymer, with retention of its biochemical activity.[115]

N-Methylbenzothiazolone hydrazone hydrochloride (MBTH) is suitable for characterizing steroids such as 17-hydroxy-3,20-dioxopregn-4-en-21-al as osazones.[116] *N*-Methylbenzothiazolium and naphtho[2,1-*d*]thiazolium salts (121) and (122) and certain dimers, *e.g.* (123), promote catalytically the acyloin condensation of benzaldehyde to benzoin.[117]

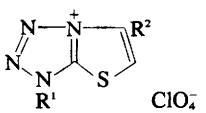


(121) (122) (123)

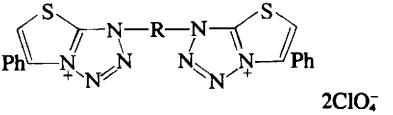
[113] L. J. Bowie, V. Horak, and M. Deluca, *Biochemistry*, 1973, **12**, 1845.
[114] L. J. Bowie, R. Irwin, M. Loken, M. Deluca, and L. Brand, *Biochemistry*, 1973, **12**, 1852.
[115] W. Freist, A. Maelicke, M. Sprinzl, and F. Cramer, *European J. Biochem.*, 1972, **31**, 215.
[116] E. S. Szymanski, C. S. Furfine, and C. F. Hammer, *Steroids*, 1972, **19**, 243.
[117] B. Lachmann, H. Steinmaus, and H. W. Wanzlick, *Tetrahedron*, 1971, **27**, 4085.

5 Structures comprising Two Five-membered Rings (5, 5)

Thiazolo[3,2-*d*]tetrazoles (CN_4-C_3NS).—Further examples of thiazolo[3,2-*d*]-tetrazolium salts (124)[118] and (125)[119] have been prepared by Hantzsch's



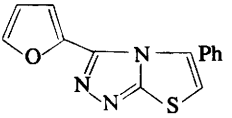
(124)



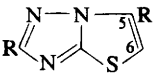
(125)

synthesis from 5-mercapto-1-phenyl-1,2,3,4-tetrazole (see these Reports, Vol. 1, p. 425). This does not rearrange to 5-anilino-1,2,3,4-thiatriazole under the conditions of the condensation; the intermediate tetrazolyl β-keto-sulphides are readily cyclized by concentrated sulphuric acid to (124), which are best isolated as the non-hygroscopic perchlorates.[118]

Thiazolo-[2,3-*c*]- and -[3,2-*b*]-*sym*-triazoles (C_2N_3-C_3NS).—3-(2-Furyl)-5-phenylthiazolo[2,3-*c*]-*sym*-triazole (126) is obtainable from the appropriate triazole-5-thiol and phenacyl bromide by Hantzsch's synthesis.[120] Members of the isomeric [3,2-*b*]-ring system (127) have been obtained by annelating



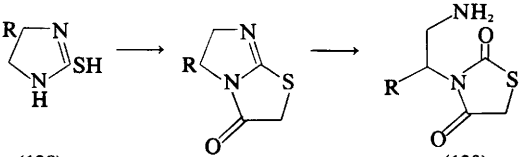
(126)



(127)

the thiazole ring to 3-mercapto-1,2,4-triazole by two distinct methods. The products resist thiocyanation, but are brominated in their 6-position.[121]

Imidazo[2,1-*b*]thiazoles (C_3NS-C_3N_2).—The reaction of 2-mercaptoimidazoline (128; R = H) with ethyl chloroacetate yields the expected 5,6-dihydro-4*H*-imidazo[2,1-*b*]thiazol-3(2*H*)-one (129; R = H).[122] In the same reaction, 4-methyl-2-mercaptoimidazoline (128; R = Me) affords the substituted thiazolidine-2,4-dione (130; R = Me), presumably by ring-cleavage of the

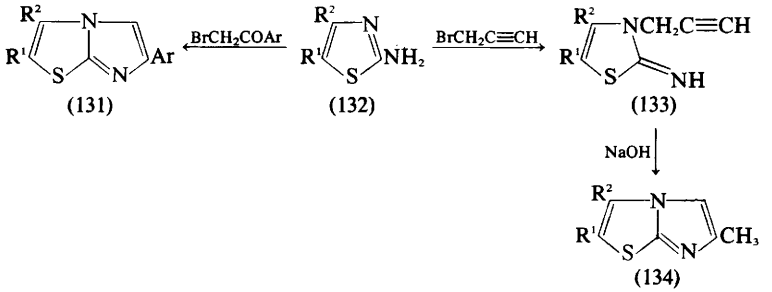


(128) (129) (130)

[118] H. Alper and R. Stout, *J. Heterocyclic Chem.*, 1973, **10**, 5.
[119] U. Askani, R. Neidlein, and J. Tauber, *Pharmazie*, 1971, **26**, 463.
[120] M. M. Kochhar and B. B. Williams, *J. Medicin. Chem.*, 1972, **15**, 332.
[121] S. Kano, *J. Pharm. Soc. Japan*, 1972, **92**, 935.
[122] H. S. Chaudhary and H. K. Pujari, *J. Indian Chem. Soc.*, 1968, **45**, 710.

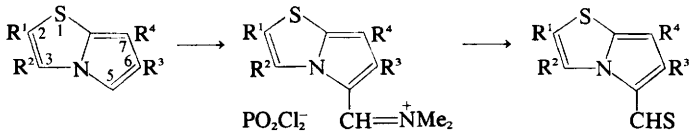
bicyclic intermediate (129; R = Me).[123] The use of 2-mercaptoimidazoline (128; R = H) in conjunction with ethyl α-bromopropionate, which introduces a methyl group into the thiazole moiety of the primary product (129), again leads to cleavage, with formation of 3-(β-aminoethyl)-5-methylthiazolidine-2,4-dione. Insufficient information is as yet available to account for the variable stability of the bicyclic compounds.[124] 2-Mercapto-4,5-diphenylimidazole has also served as starting material in syntheses of this type.[125]

Imidazo[2,1-*b*]thiazoles (132) are further obtainable in good yield from 2-aminothiazoles (131) by the action of phenylacyl bromide,[126,127] or from 2-imino-3-(2-propynyl)-Δ^4-thiazolines (133) by alkaline cyclization.[127] Thiocyanation of (132) and (134) yields the corresponding 5-thiocyanato-derivatives. The synthesis by established routes of further examples of this ring-system has been recorded.[128]



(131) (132) (133) (134)

Pyrrolo[2,1-*b*]thiazoles (C_3NS-C_4N).—Pyrrolo[2,1-*b*]thiazoles have been thioformylated by a novel application[129] of the Vilsmeier reaction.[130] Treatment of the reactants (135) with phosphoryl chloride in DMF produces the Vilsmeier salts (136), which are convertible into the orange or red pyrrolo[2,1-*b*]thiazole-5-thioaldehydes (137) by thiohydrolysis, using sodium hydrogen sulphide. The isomeric 7-thioaldehydes (138) are similarly



(135) (136) (137)

(138) H in place of CHS
R^4 = CHS

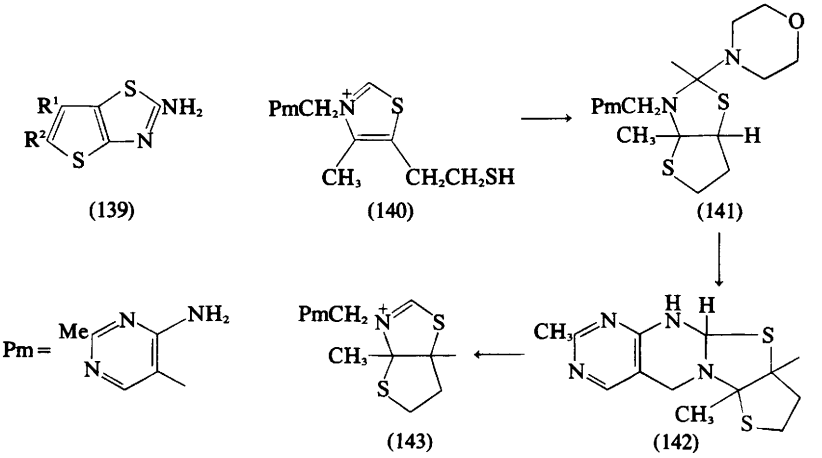
[123] V. K. Chadha, H. S. Chaudhary, and H. K. Pujari, *Indian J. Chem.*, 1970, **8**, 885.
[124] H. S. Chaudhary and H. K. Pujari, *Indian J. Chem.*, 1972, **10**, 766.
[125] J. Mohan, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.*, 1973, **11**, 747.
[126] G. Kempter, J. Spindler, H. J. Fiebig, and G. Sarodnik, *J. prakt. Chem.*, 1971, **313**, 977.
[127] S. Kano, *J. Pharm. Soc. Japan*, 1972, **92**, 51.
[128] V. P. Arya, F. Fernandes, and V. Sudarsanam, *Indian J. Chem.*, 1972, **10**, 598.
[129] S. McKenzie and D. H. Reid, *Chem. Comm.*, 1966, 401; *J. Chem. Soc.* (*C*), 1970, 145.
[130] R. K. Mackie, S. McKenzie, D. H. Reid, and R. G. Webster, *J.C.S. Perkin I*, 1973, 657.

accessible. 5-[^{2}H]Thiocarbaldehydes were obtained by the use of [$^2H_7$]dimethylformamide in the Vilsmeier stage.[130] In establishing the structures of the new thioaldehydes (137) and (138), a number of authentic pyrrolo[2,1-*b*]thiazoles were required for comparison, and they were obtained by procedures previously established.[131]

The results are of wider significance, since previous attempts to isolate alkyl or aryl thioaldehydes have always given cyclic or linear polymers by opening of the transient C=S bond. In the present heterocyclic examples, the conjugation of the thioformyl group with the nitrogen atom results in polarization of the C=S bond, thus decreasing the tendency to polymerization. Furthermore, the polarization sets up a barrier to rotation about the ring—CHS bond, leading to the possible existence of *syn*- and *anti*-geometrical isomers. The configuration of the thioaldehyde group in these compounds was established by n.m.r. spectral studies.[130]

Thieno[2,3-*d*]thiazoles (C_3NS-C_4S).—2-Aminothieno[2,3-*d*]thiazoles (139) are accessible from 2-aminothiophen by way of 3-thiocyanato-derivatives, followed by cyclization.[132]

Mercaptoethylthiamine (140)[133] is converted, on treatment with morpholine in DMF, into the substituted perhydrothieno[2,3-*d*]thiazole (141) (*i.e.* '2-morpholinodihydrothiamine'), cyclized by bicarbonate to (142), and thence cleaved by ethanolic hydrogen chloride to the thiazolium salt (143).[134]

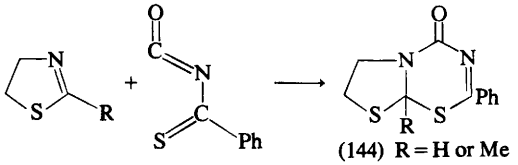


6 Structures comprising One Five-membered and One Six-membered Ring (5, 6)

Thiazolo[2,3-*b*][1,3,5]thiadiazines (C_3NS-C_3N_2S).—Thiobenzoyl isocyanate reacts with Δ^2-thiazoline at −70 °C or with 2-methyl-Δ^2-thiazoline at room

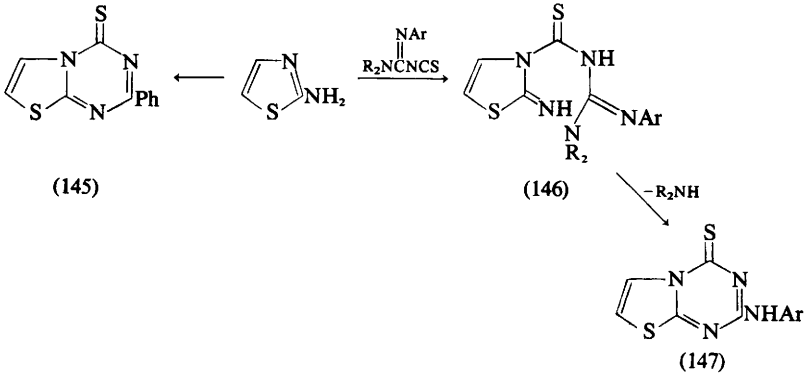
[131] B. B. Molloy, D. H. Reid, and F. S. Skelton, *J. Chem. Soc.*, 1965, 65.
[132] K. Gewald, M. Hentschel, and R. Heikel, *J. prakt. Chem.*, 1973, **315**, 539.
[133] F. Schultz, *Z. physiol. Chem.*, 1940, **265**, 113.
[134] A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2222.

temperature to give the (4 + 2) cycloadducts, *viz.* 6,7-dihydro-2-phenyl-(8a-methyl)thiazolo[2,3-*b*][1,3,5]thiadiazin-4-ones (144). Under different conditions, 2:1 adducts are formed with loss of water, resulting in the thiazolo-[3,2-*c*]pyrimidine ring-system (see p. 651).[135]



(144) R = H or Me

Thiazolo[3,2-*a*]-*sym*-triazines (C_3NS-C_3N_3).—Benzoyl isothiocyanate reacts additively at the ring-nitrogen of 2-aminothiazole, to yield (22%) 5-thioxo-7-phenyl-5*H*-thiazolo[3,2-*a*][1,3,5]triazine (145).[136] The action of formamidinoyl isothiocyanates similarly produces, by way of the intermediate adducts (146), the corresponding 7-arylamino-analogues (147).[137]

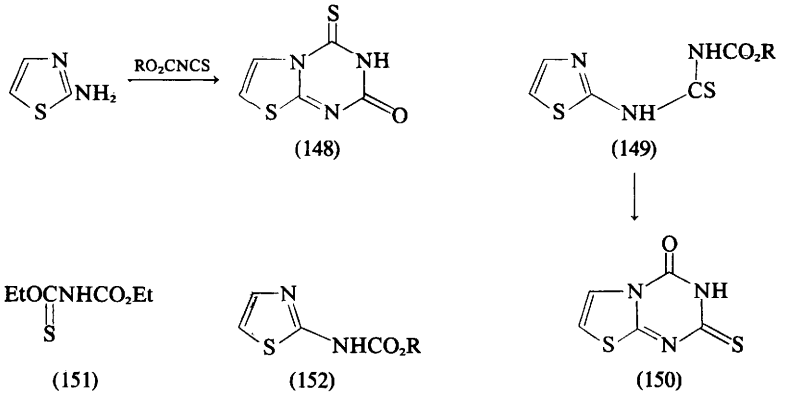


(145) (146) (147)

The interaction of 2-aminothiazole and ethoxycarbonyl isothiocyanate in ethyl acetate gives no less than four products, separable by chromatography. The *N*-ethoxycarbonyl-*N'*-(2-thiazolyl)thioureas (149), which predominate amongst them (*ca.* 40—50%), appear not to undergo further cyclization spontaneously to the bicyclic products (150) except in one case (when R = Ph), but this ring closure does occur at 180 °C. In each case, thiazolo[3,2-*a*]-*sym*-triazine-4-thione-2-one (148) was isolated in 20—40% yield, while (151) and (152) arose as minor products.[138]

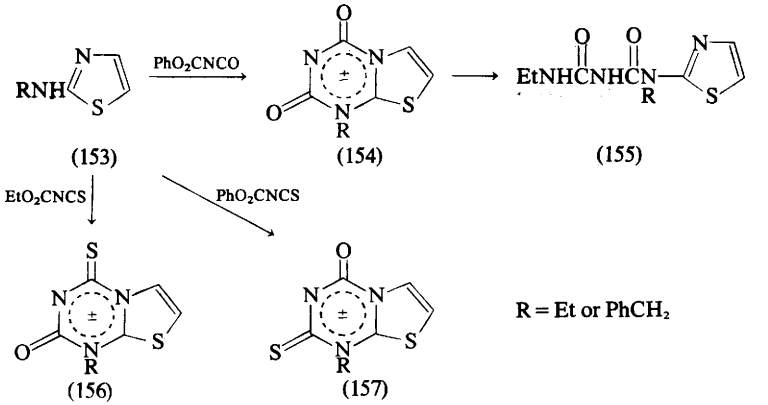
The use of 4- or 5-mono- and 4,5-di-substituted thiazoles gave similar results, but the experimental material is too extensive to be fully reported.[139]

[135] O. Tsuge and S. Kanemasa, *Tetrahedron*, 1972, **28**, 4737.
[136] G. Barnikow and J. Bödeker, *J. prakt. Chem.*, 1971, **313**, 1148.
[137] W. Abrahams and G. Barnikow, *Tetrahedron*, 1973, **29**, 699.
[138] M. Nagano, J. Tobitsuka, T. Matsui, and K. Oyamada, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2618.
[139] M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2626; *ibid.*, 1973, **21**, 74.



Thiazoles having pK_a values lower than that of 2-aminothiazole (p*K* 5.35), or bearing certain 4-substituents, fail to yield bicyclic condensed products of type (148). The cyclization rate appears to be governed by the basicity of the aminothiazoles employed, as well as steric factors.[139]

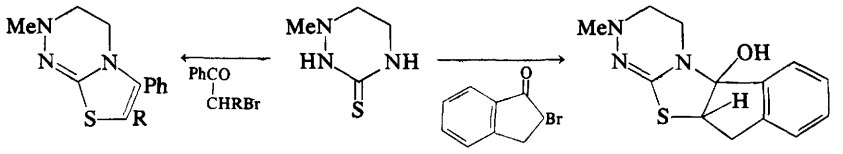
Meso-ionic Thiazolo[3,2-a]-sym-*triazine*-5,7-*diones*. 2-Alkylaminothiazoles (153) react with phenoxycarbonyl isocyanate to produce meso-ionic 8-substituted thiazolo[3,2-*a*]-*sym*-triazine-5,7-diones (154), but the action of ethoxycarbonyl isocyanate results merely in acylation. These meso-ionic xanthine analogues (154) are sparingly soluble labile solids which are ring-cleaved by ethylamine to (155). The use of phenoxy(or ethoxy)carbonyl isothiocyanate in this reaction affords monothiones of the isomeric series (157) and (156), respectively.[140]



Thiazolo[2,3-*c*][1,2,4]triazines (C_3NS-C_3N_3).—Continued work on the condensation of 1,4,5,6-tetrahydro-1-methyl-*as*-triazine-3(2*H*)-thione (158) with

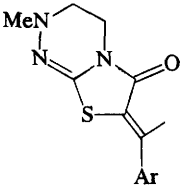
[140] R. A. Coburn and B. Bhoosan, *J. Org. Chem.*, 1973, **38**, 3868.

α-halogenoketones (*e.g.* phenacyl bromide, desyl bromide) (compare these Reports, Vol. 2, p. 685) has provided further examples of substituted thiazolo[2,3-*c*][1,2,4]triazines (159; R = H or Ph). The use of 2-bromo-1-indanone rapidly yields 1*H*,6*H*-indeno[1′2′:4, 5]thiazolo[2,3-c][1,2,4]triazin-10b-(5a*H*)-ol (160) (and its 10b-ethoxy-homologue). This is the only case in



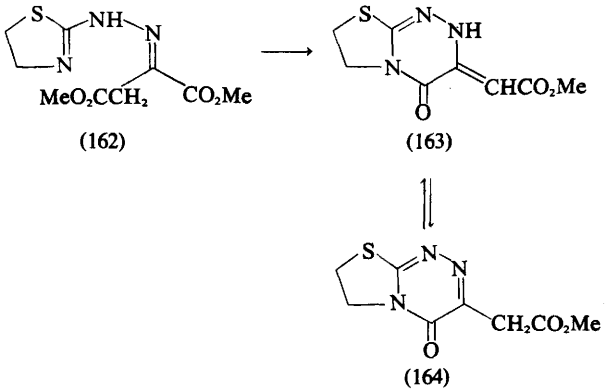
(159) (158) (160)

which simultaneous dehydration was not observed, a fact that was ascribed to the *cis*-configuration of the 5a-H and 10b-OH groups [in (160)].[141] 3,4-Dihydro-2-methyl-2*H*-thiazolo[2,3-*c*][1,2,4]triazin-6(7*H*)-one undergoes condensation with a variety of aromatic aldehydes, yielding (161).[141]



(161)

The tautomeric enamine (163) and endocyclic (164) forms of the substituted thiazolo[2,3-*c*][1,2,4]triazine have been isolated in the solid state. Thus, on stirring (162) in cold methanol containing triethylamine, the



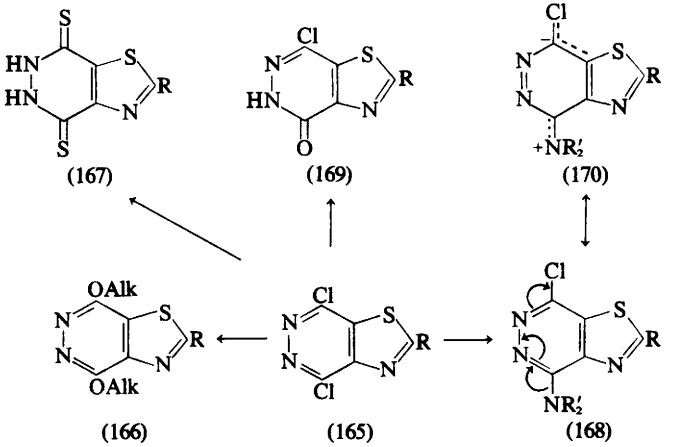
(162) (163)

(164)

[141] D. L. Trepanier and P. E. Krieger, *J. Heterocyclic Chem.*, 1972, **9**, 1385.

triazinone (163) is precipitated. It is sufficiently stable to be recovered unchanged from cold chloroform on addition of light petroleum, but is converted into the endocyclic tautomer (164) on warming.[142]

Thiazolo[4,5-*d*]pyridazines (C_3NS-C_4N_2).—The electron-attracting effects of both the halogen substituents and the pyridazine-nitrogens in 4,7-dichlorothiazolo[4,5-*d*]pyridazines (165) act in the same sense in reducing the electron density of carbons 4 and 7, thus promoting attack by nucleophiles. The action of alkoxide produces 4,7-dialkoxy-derivatives (166), while successive treatment with thiourea and alkali affords the 4,7-dithioxo-4,5,6,7-tetrahydro-compounds (167). Ammonolysis and aminolysis terminate at the mono-substitution stage, however, affording 7-chloro-4-(substituted)aminothiazolo[4,5-*d*]pyridazines (168). This exclusive mono-substitution, even under severe conditions, is ascribed to the strong electron-releasing properties of the amino-groups; once the 4-position has been so substituted, the increased electron-density at position 7 [*cf.* (170)] prevents further nucleophilic attack at this centre. The greater reactivity of the 4-

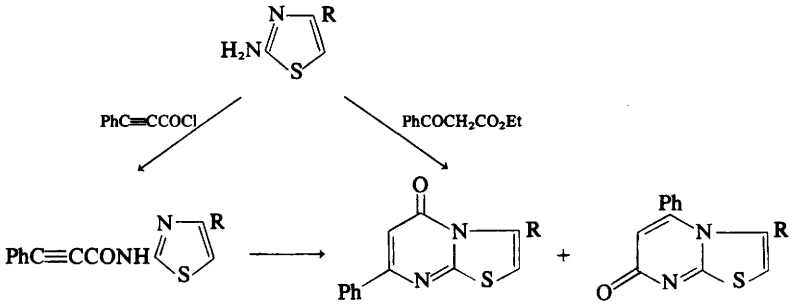


position [in (165)] is also illustrated by the results of their acidic hydrolysis, which yields the 4,5-dihydro-7-chloro-4-oxo-derivatives (169); according to the spectral evidence, the products exist as lactams. Unlike other halogenodiazines, which are generally readily converted by catalytic hydrogenation into the dehalogenated parent bases, 2-substituted 4,7-dichlorothiazolo[4,5-*d*]pyridazines do not undergo this reaction under the influence of a variety of catalysts, even under fairly severe conditions.[143]

Thiazolo[3,2-*a*]pyrimidines (C_3NS-C_4N_2).—The interaction of 2-aminothiazole and phenylpropiolyl chloride yields, in addition to the expected

[142] D. J. Le Count and A. T. Greer, *Tetrahedron Letters*, 1973, 2905.
[143] M. Robba and Y. Leguen, *Bull. Soc. chim. France*, 1971, 3537.

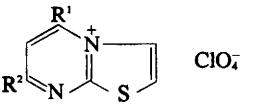
propiolamides (171), up to 58% of 5-oxo-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine (172; R = H). 2-Amino-4-methylthiazole gives rise to both possible isomers (172) and (173).[144] The structure of (172; R = H), based on its



(171) (172) (173)

spectral properties, is confirmed by its alternative synthesis from the 2-amino-heterocycle and ethyl benzoylacetate according to the method of Allen *et al.*[145] The cyclization (171) → (172) + (173) occurs in concentrated sulphuric acid at 55 °C.[144]

Other members of this ring-system, *e.g.* (174), are obtained by the

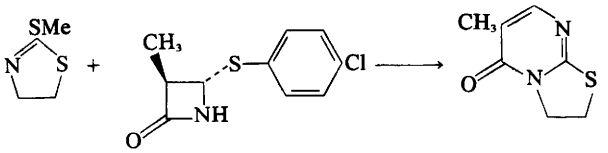


(174)

condensation of 2-aminothiazoles with β-chlorovinyl ketones,[146,147] β-keto-aldehydes, and β-diketones.[147,148] 2-Aminobenzothiazole gives rise to the corresponding trinuclear fused structures.[146,147]

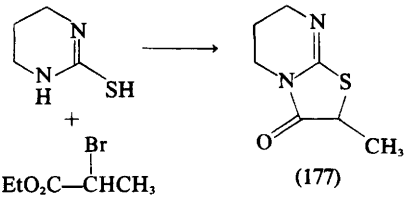
The interaction of 2-alkylthio-Δ^2-thiazoline and 3-methyl-4-*p*-chlorophenylthio-2-azetidinone (175) (in the presence of catalytic amounts of 1,4-diazabicyclo[2,2,2]octane) at 120 °C under nitrogen affords 16% yields of 6-methyl-5-oxo-5*H*-2,3-dihydrothiazolo[3,2-*a*]pyrimidine (176). This and analogous reactions of the azetidinone are promoted by the good leaving properties of its arylthio-group.[149]

[144] S. Minami, M. Tomita, and K. Kawaguchi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1716.
[145] C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, 1959, **24**, 779.
[146] S. I. Shulga and V. A. Chuiguk, *Khim. geterotsikl. Soedinenii*, 1972, 632 (*Chem. Abs.*, 1972, **77**, 126 482*s*).
[147] S. I. Shulga, N. F. Fursaeva, and V. A. Chuiguk, *Khim. geterotsikl. Soedinenii*, 1972, 629 (*Chem. Abs.*, 1972, **77**, 126 559*x*).
[148] S. I. Shulga and V. A. Chuiguk, *Khim. geterotsikl. Soedinenii*, 1972, 637 (*Chem. Abs.*, 1972, **77**, 126 484*u*).
[149] K. Hirai, H. Matsuda, and Y. Kishida, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1305.



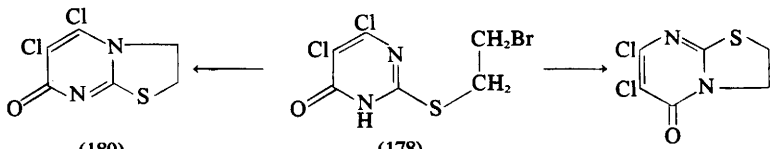
(175) (176)

The condensation of 2-mercapto-3,4,5,6-tetrahydropyrimidine and ethyl α-bromopropionate at 160 °C yields 2-methyl-4,5,6,7-tetrahydrothiazolo[3,2-*a*]pyrimidin-3(2*H*)-one (177) nearly quantitatively.[124] 2-(2-Bromoethylthio)-



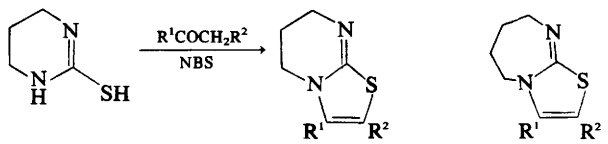
(177)

4,5-dichloropyrimidin-6-one (178) is cyclized in 4% yield to the isomeric thiazolo[3,2-*a*]pyrimidines (179) and (180), by the action of DMF or acetone, respectively.[150]



(180) (178) (179)

The use of *N*-bromosuccinimide in conjunction with ketones provides an improved technique for annelating a thiazole ring to a heterocyclic thiol. Thiazolo[3,2-*a*]pyrimidines (181) and thiazolo[3,2-*a*][1,3]diazepines (182) have been obtained advantageously by this procedure.[151]

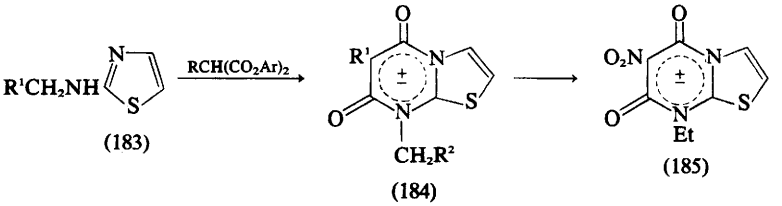


(181) (182)

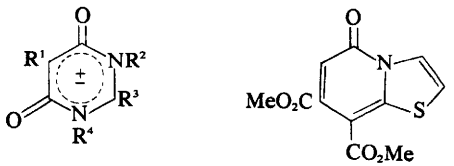
Meso-ionic Thiazolo[3,2-a]*pyrimidine-5,7-diones.* The interaction of 2-alkylaminothiazoles (183) and bis-(2,4,6-trichlorophenyl)malonate esters at

[150] K. Berg-Nielsen, T. Stensrud, and E. Bernatek, *Acta Chem. Scand.*, 1972, **26**, 947.
[151] K. S. Dhaka, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.*, 1973, **11**, 554.

160 °C affords a series of stable anhydro-5-hydroxy-8-alkylthiazolo[3,2-*a*]-pyridinium-7-one hydroxides (184) in good yield. These meso-ionic xanthines may be regarded as products of the fusion of the electron-rich thiazole ring with the electron-deficient portion of the known meso-ionic 1,3-dimethylpyrimidine-4,6-dione (187). Information was provided on their spectral properties, and their ring-cleavage in acid and alkaline media.[152] Further examples, including an adamantyl derivative, of this ring system, and their antibacterial activity, were separately reported.[153]



(183) (184) (185)



(187) (186)

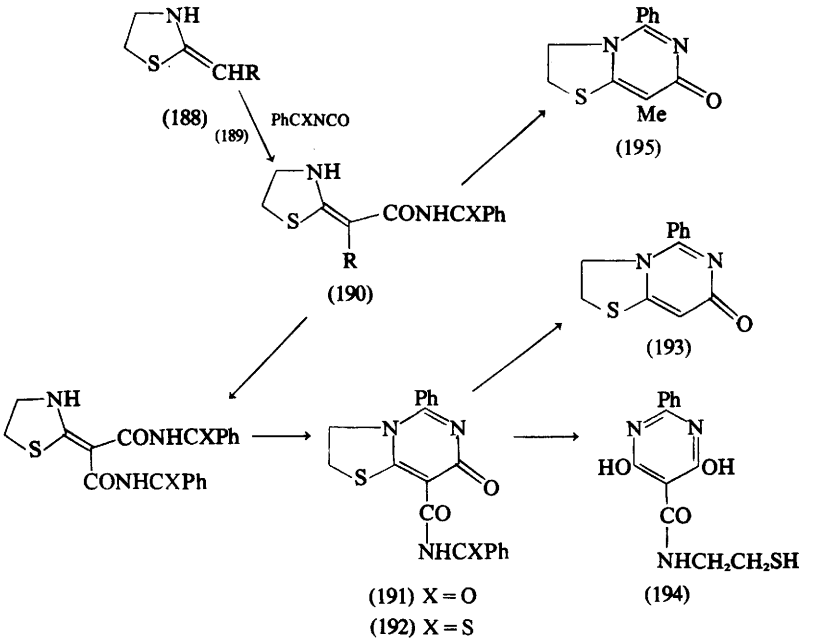
Molecular orbital calculations point to the 6-position of (184; R^1 = H, R^2 = Et) as the most likely site of electrophilic attack. Conformably to this expectation, nitration at 0 °C produces the 6-nitro-derivative (185) nearly quantitatively, and bromination and chloromercuration proceed analogously. Like monocyclic meso-ionic pyrimidines, the meso-ionic thiazolo[3,2-*a*]pyrimidines react with dipolarophiles, such as dimethyl acetylenedicarboxylate, to give 7,8-dimethoxycarbonylthiazolo[3,2-*a*]pyridin-5-one (186).[152]

The paper includes a useful classification and brief discussion of other possible meso-ionic purinone analogues, which possess π-electron systems isoelectronic with those of purinones.[152]

Thiazolo[3,2-*c*]pyrimidines (C_3NS-C_4N_2).—The interaction of 2-methyl-Δ^2-thiazoline (188; R = H) with (thio)benzoyl isocyanate (189; X = O or S) at 90—95 °C produces 2:1 adducts, *viz.* 2,3-dihydro-5-phenyl-8-benzoyl(thio)-carbamoylthiazolo[3,2-*c*]pyrimidin-7-ones (191) and (192). Acid hydrolysis

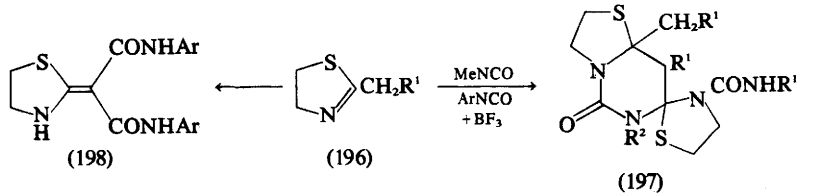
[152] R. A. Coburn and R. A. Glennon, *J. Heterocyclic Chem.*, 1973, **10**, 487.
[153] R. A. Coburn and R. A. Glennon, *J. Pharm. Sci.*, 1973, **62**, 1785.

and decarboxylation yields (193), while alkaline hydrolysis cleaves the thiazole moiety and produces, with transient ring-opening of the six-membered ring, the pyrimidine derivative (194). 2-Ethyl-Δ^2-thiazoline (188; R = Me) reacts with benzoyl isocyanate to yield, amongst other products, the thiazolo[3,2-*c*]pyrimidine (195). Its formation from (190) fits into the



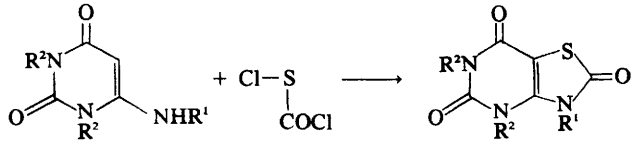
framework of the overall mechanism, involving the reactant in its enamine form (188) (see reaction scheme).[135]

The interaction of 2-alkyl-Δ^2-thiazolines (196) and aryl isocyanates in the presence of catalytic amounts of boron trifluoride etherate, or methyl isocyanate, produces cyclic 2:2 adducts (197), *e.g.* 6′,8a′-dimethyl-3-methylcarbamoyl-5′-oxospiro(thiazolidine-2,7′-perhydrothiazolo[3,2-*c*]pyrimidine). This contrasts with the formation of the simple 2:1 adducts (198) in the absence of the catalyst (see these Reports, Vol. 2, p. 627). The 2:2 adducts may have one of several possible structures; their formulation as (197) is based on their spectral properties and the results of their



degradation. Possible mechanisms of their formation were briefly considered.[154]

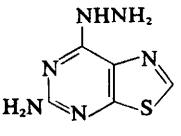
Thiazolo[4,5-*d*]pyrimidines (C_3NS-C_4N_2).—Like linear enamines (see Ch. 13, Type B syntheses), heterocyclic enamines react with chlorocarbonyl sulphenyl chloride, with formation of an annelated thiazole ring. Members of the thiazolo[4,5-*d*]pyrimidine series (199) are readily accessible by this route.[155]



(199)

Thiazolo[5,4-*d*]pyrimidines (C_3NS-C_4N_2).—In continuation of studies of rearrangements of thiazolo[5,4-*d*]pyrimidines,[156] condensed *as*-triazines and purines have been obtained from further examples, *e.g.* (200), of this ring system.[157]

The first thiazolo[5,4-*d*]pyrimidine nucleoside (201), bearing the ribose moiety in the 4-position, (isolated both as the α- and β-anomeric forms), has been obtained from thiazolo[5,4-*d*]pyrimidine-5,7-dione.[158]



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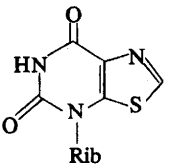
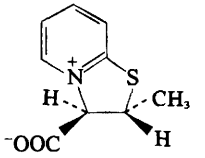


(201)

Thiazolo[3,2-*a*]pyridines (C_3NS-C_5N).—The established synthesis of thiazolo[3,2-*a*]pyridines from pyridine-2-thiones and α-bromo-αβ-unsaturated carbonyl compounds (these Reports, Vol. 1, p. 432; Vol. 2, p. 698) has been further studied. The use of the isomeric α-bromocrotonic acids yields the expected bicyclic products (202), exclusively of the 2,3-*trans*-configuration, owing to the concurrent isomerization of the *cis*- to the *trans*-acid.[159]

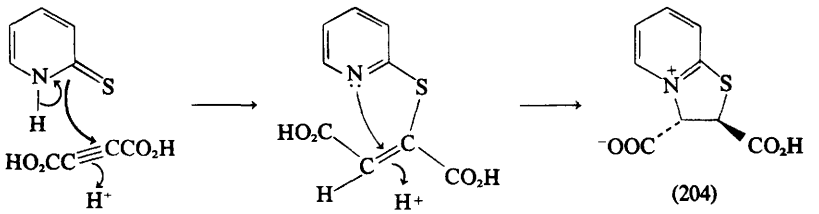
Activated acetylenes undergo a comparable Michael-addition–cyclization process. Thus, acetylenedicarboxylic acid affords *trans*-2,3-dicarboxydihydrothiazolo[3,2-*a*]pyridinium salts (204). The intermediate vinyl

[154] R. Richter and H. Ulrich, *Chem. Ber.*, 1973, **106**, 1501.
[155] K. Grohe and H. Heitzer, *Annalen*, 1973, 1018.
[156] C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, 1969, **34**, 3161.
[157] C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, 1971, **36**, 3502.
[158] C. L. Schmidt, W. J. Rusho, and L. B. Townsend, *Chem. Comm.*, 1971, 1515.
[159] K. Undheim and R. Lie, *Acta Chem. Scand.*, 1973, **27**, 1749.



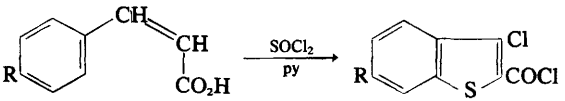
(202)

thioethers (203) are isolable from the reaction of propiolic and phenylpropiolic acids and are cyclizable to (204) by bromine. The stereochemistry of this reaction was examined and its mechanism discussed.[160]

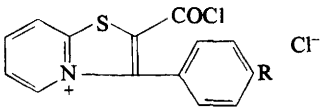


(203) (204)

The interaction of cinnamic acid with an excess of thionyl chloride in the presence of 0.1 molar proportions of pyridine yields, in addition to the main products (205), 3-aryl-2-chloroformylthiazolo[3,2-*a*]pyridinium chlorides



(205)



(206)

(206) consistently as by-products. The yields of (206) are nearly quantitative in terms of the pyridine used, but cannot be appreciably increased by raising the pyridine:cinnamic acid ratio.[161]

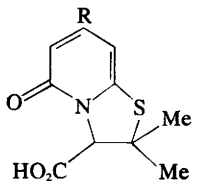
Solutions of penicillamine in aqueous citric acid give rise to very small quantities (maximum 0.05%) of fluorescing products that have been identified as derivatives (207) of thiazolo[3,2-*a*]pyridine. Above pH 6 the yields are minimal, suggesting that the use of citrates as buffer systems for dissolved penicillins does not affect the stability of the preparations. The

[160] R. Lie and K. Undheim, *Acta Chem. Scand.*, 1973, **27**, 1756.
[161] W. B. Wright and H. J. Brabander, *J. Heterocyclic Chem.*, 1972, **9**, 1017.

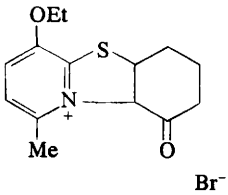
reaction might form the basis for an assay of penicillamine, and hence penicillins.[162]

The structure of 2,3-(3′-cyclohexanon-1′,2′-ylene)-5-methyl-8-ethoxydihydrothiazolo[3,2-*a*]pyridinium bromide (208), that had previously not been assignable with certainty from n.m.r. spectroscopic measurements, has been confirmed by *X*-ray analysis.[163]

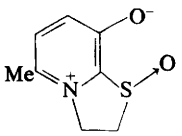
Extensive data and exhaustive discussions are available on the fragmentation patterns of thiazolo[3,2-*a*]pyridinium derivatives[164] in the mass spectrometer. Individual studies have dealt with 3-oxides,[165] 8-oxides,[166] and 3-carboxylates.[167] Information is available concerning the chiroptical properties of the (1*S*)-sulphoxide of 5-methyldihydrothiazolo[3,2-*a*]pyridinium 8-oxide (209), which shows positive Cotton effects at 355 and 229 nm in alkaline, and at 315 and 223 nm in acid solution.[168]



(207) R = H or CO_2H



(208)

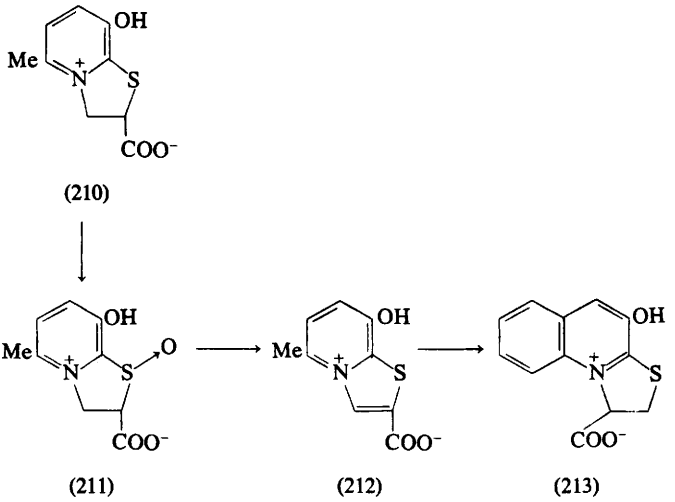


(209)

The oxidation of 8-hydroxy-5-methyldihydrothiazolo[3,2-*a*]pyridinium-3-carboxylate by a variety of oxidizing agents produces the *cis*-sulphoxide, precisely as previously outlined for the action of peracids (see these Reports, Vol. 1, p. 432). The corresponding 2-carboxylate (210) yields, in this reaction, the thiazole (212) by loss of water from (211), as well as minor products formed by fission of the thiazole ring. Oxidation of the *trans*-2,6-dicarboxy-derivative corresponding to (210) yields the same thiazole (212) with simultaneous decarboxylation.[169]

The oxidation of (210) (and more highly substituted analogues) was subsequently studied in detail at 4.5 °C in the n.m.r. apparatus, revealing relative oxidation rates and the diastereoisomer ratio of the sulphoxides. The use of performic acid gave the sulphoxide (211) in the diastereoisomer ratio 1:1, but 35% hydrogen peroxide gave principally the thiazole (212). The presence of substituents in the pyridine ring of (210) has a significant influence on the reaction rates. Comparable observations concerning quinoline analogues (213) were also recorded.[170]

[162] U. Olthoff, R. Hüttenrauch, and K. Matthey, *Pharmazie*, 1970, **25**, 789.
[163] P. Groth, *Acta Chem. Scand.*, 1972, **26**, 3131.
[164] K. Undheim and T. Hurum, *Acta Chem. Scand.*, 1972, **26**, 2385.
[165] K. Undheim, P. E. Fjeldstad, and P. O. Tveita, *Acta Chem. Scand.*, 1971, **25**, 2943.
[166] K. R. Reistad and K. Undheim, *Acta Chem. Scand.*, 1971, **25**, 2954.
[167] R. Lie and K. Undheim, *Acta Chem. Scand.*, 1972, **26**, 3459.
[168] T. Greibrokk and K. Undheim, *Tetrahedron*, 1972, **28**, 1223.
[169] T. Greibrokk and K. Undheim, *Acta Chem. Scand.*, 1971, **25**, 2251.
[170] T. Greibrokk, *Acta Chem. Scand.*, 1972, **26**, 3347.



(210) (211) (212) (213)

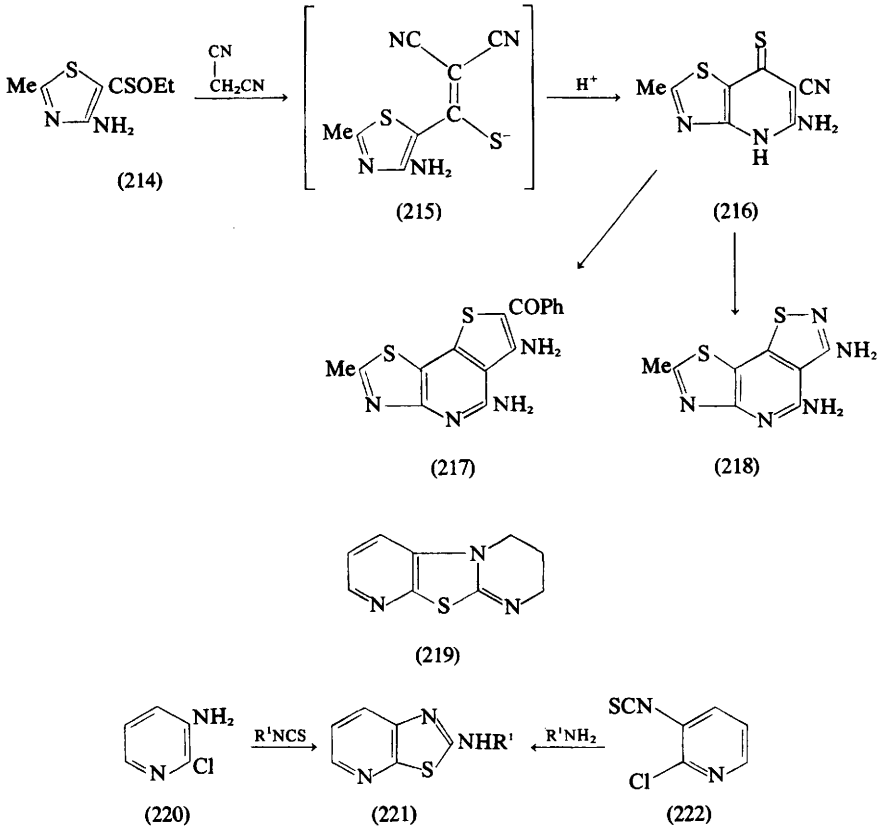
The solvolysis of 2-arylthiazolo[3,2-*a*]pyridinium 3-oxides (these Reports, Vol. 2, p. 699) has been reinvestigated in detail, using a series of new members of this structure. Acid hydrolysis is accelerated by the presence of electron-releasing substituents. The less ready alkaline hydrolysis appears to involve initial pseudo-base formation.[171]

3,7-Dimethylthiazolo[3,2-*a*]pyridinium perchlorate undergoes condensation with 3-methyl-2-formylmethylenebenzothiazoline, though with some difficulty, yielding the appropriate trimethinecyanine dye.[172]

Thiazolo[4,5-*b*]pyridines **(C_3NS-C_5N).**—4-Amino-5-ethoxythiocarbonyl-2-methylthiazole (214) acts as a thioacylating agent of moderate effectiveness, converting malonic dinitrile into the adduct (215), which ring-closes spontaneously to the dihydrothiazolo[4,5-*b*]pyridine derivative (216) in acid solution. Its further interaction with chloramine or bromoacetophenone produces good yields of members of the thieno[2,3-*d*]thiazolo[4,5-*b*]-pyridine (217) and isothiazolo[5,4-*d*]thiazolo[4,5-*b*]pyridine (218) ring-systems, respectively.[173]

Thiazolo[5,4-*b*]pyridines **[C_3NS-C_5N].**—2-Substituted thiazolo[5,4-*b*]-pyridines (221) are formed from 3-amino-2-chloro- (220) or 2-chloro-3-isothiocyanatopyridine (222) as shown. Pyrolysis of the 2-(3-chloropropylamino)-compound [221; R = $(CH_2)_3Cl$] thus obtained yields the substituted pyrimido[2,3-*b*]thiazolo[5,4-*b*]pyridine (219).[174]

[171] P. E. Fjeldstad and K. Undheim, *Acta Chem. Scand.*, 1973, **27**, 1763.
[172] A. V. Eltsov and M. L. Aleksandrova, *Zhur. org. Khim.*, 1972, **8**, 2437.
[173] K. Hartke and G. Golz, *Annalen*, 1973, 1644.
[174] V. P. Arya, K. G. Dave, S. J. Shenoy, V. G. Khadse, and R. H. Nayak, *Indian J. Chem.* 1973, **11**, 744.

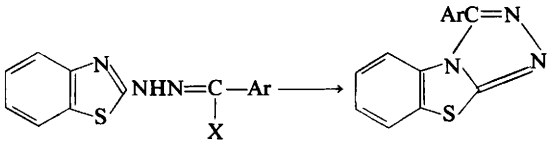


7 Structures comprising Two Five-membered and One Six-membered Ring (5,5,6)

***sym*-Triazolo[3,4-*b*]benzothiazoles** (C_2N_3-C_3NS-C_6).—The action of bromine converts benzaldehyde benzothiazol-2-ylhydrazones (223) into *sym*-triazolo-[3,4-*b*]benzothiazoles (225). Various types of molecular complexes of the reactants with bromine are formed under other conditions, and are isolable in suitable cases. Hydrazonyl bromides (224) are likely to be concerned as intermediates in the cyclization, being themselves convertible into (225) in high yield (85—95%).[175]

Thiazolo[3,2-*e*]purines (C_3NS-C_3N_2-C_4N_2).—A general synthesis, of the Hantzsch type, of thiazolo[3,2-*e*]purines is of interest because it makes available a series of thiazolo[3,2-*e*]adenines of potential physiological

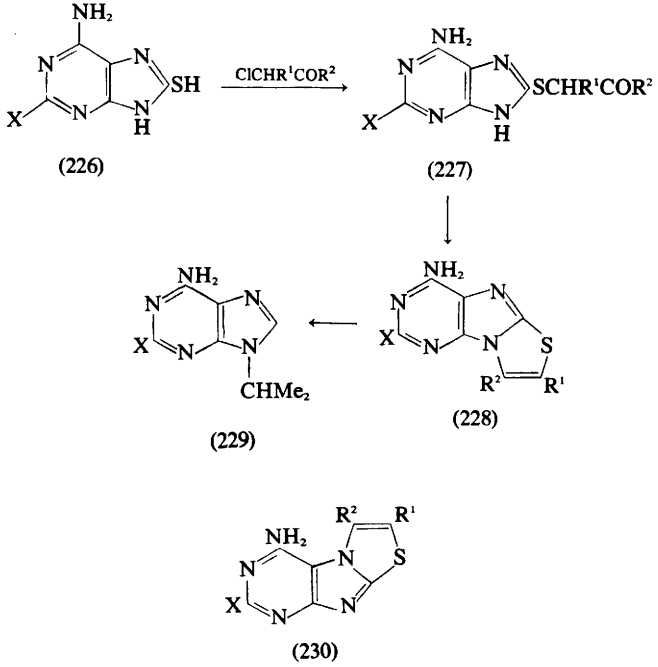
[175] R. N. Butler, P. O'Sullivan, and F. L. Scott, *J.C.S. Perkin I*, 1972, 1519.



(223) X = H
(224) X = Br

(225)

significance. 8-Thioadenines (226) serve as starting materials: their condensation with α-halogenocarbonyl compounds produces the isolable intermediates (227), which are cyclized by polyphosphoric acid at 140—150 °C or by ethanolic hydrogen chloride to yield the desired thiazolo-adenines (228). Their possible alternative formulation as thiazolo[2,3-*f*]purines (230) is excluded by their desulphurization by Raney nickel to 9-isopropyladenine (229), and not its 7-isopropyl isomer, which would have arisen from the alternative cyclized structure (230).[176]



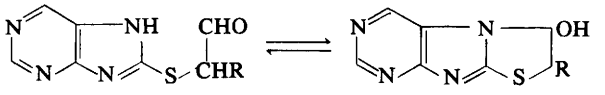
(226) (227) (228) (229)

(230)

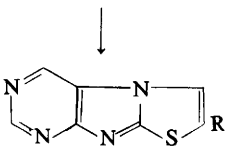
Thiazolo[2,3-*f*]purines (C_3NS-C_3N_2-C_4N_2).—8-Purinylthioacetaldehydes (231) exist, in the solid state, as the tautomeric thiazolinopurines (232), which are

[176] H. Uno, A. Irie, and K. Hino, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 34.

converted into thiazolo[2,3-*f*]purines (233) on dehydration. The corresponding theophylline analogues undergo the same reaction sequence.[177]

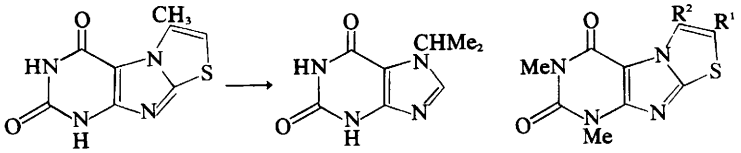


(231) (232)



(233)

The interaction of 8-thiolxanthine and monochloroacetone yields 6-methylthiazolo[2,3-*f*]xanthine (234). Its desulphurization to 7-isopropylxanthine (235) confirms the formulation originally proposed by Todd and Bergel,[178] in their work on thiochrome. Thiazolo[2,3-*f*]-hypoxanthine[179] and thiazolo[2,3-*f*]theophyllines[180] of type (236) are similarly



(234) (235) (236)

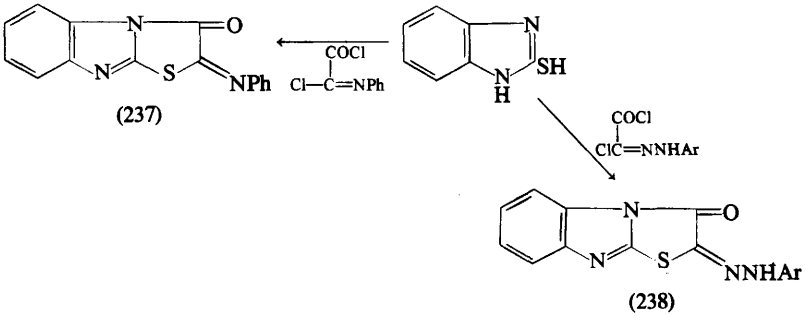
accessible. The cyclization [to (234)] thus proceeds in the opposite sense to that of 8-thioladenine (see above), which yields thiazolo[3,2-*e*]purines. The tricyclic structures show the usual reactions of purines, the enolizable keto-groups being replaceable successively by chloro-, amino-, and mercapto-groupings.[179]

Imidazo[2,1-*b*]thiazolo[5,4-*b*]pyridines (C_3NS-C_3N_2-C_5N).—See Pyrido[2,3-*d*]-imidazo[2,1-*b*]thiazolo[5,4-*b*]pyridines, below.

Thiazolo[3,2-*a*]benzimidazoles (C_3NS-C_3N_2-C_6).—Members of this ring system have been prepared from 2-mercaptobenzimidazole by conventional routes,[181,182] the direction of cyclization being confirmed by n.m.r. spectral data.[182] Condensation with (phenylimino)oxalic acid dichloride produces

[177] M. I. Yurchenko, B. V. Kurmaz, and P. M. Kochergin, *Khim. geterotsikl. Soedinenii*, 1972, 996 (*Chem. Abs.*, 1973, **78**, 43 424u).
[178] A. R. Todd and F. Bergel, *J. Chem. Soc.*, 1936, 1559.
[179] H. Uno, A. Irie, and K. Hino, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 256.
[180] H. Uno, A. Irie, and K. Hino, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2603.
[181] S. Kano, *J. Pharm. Soc. Japan*, 1972, **92**, 927.
[182] J. Mohan and H. K. Pujari, *Indian J. Chem.*, 1972, **10**, 274.

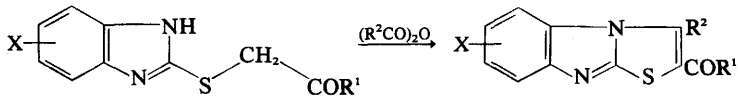
2-phenylimino-3-oxothiazolo[3,2-*a*]benzimidazole (237),[183] and 2-arylhydrazino-analogues (238) are similarly accessible.[184] The cyclization



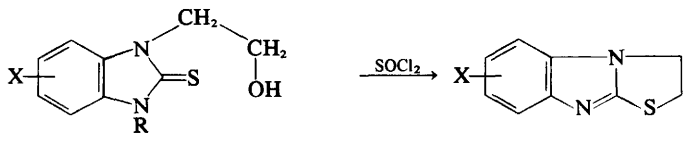
(237)

(238)

of 2-(acylmethylthio)benzimidazoles (239) with acyl anhydrides,[185] and of 1-(β-hydroxyethyl)benzimidazole-2-thiones (241) with thionyl chloride,[186] provide further examples of this ring-system, (240) and (242).



(239) (240)



(241) (242)

Thiazolo[4,5-*f*]indazoles (C_3NS-C_3N_2-C_6).—The thiocyanation of 6-aminoindazole and simultaneous cyclization of the intermediate affords good yields of 6-aminothiazolo[4,5-*f*]indazole (243), the spectral properties of which were examined. The product yields azo-compounds suitable for dyeing polyacrylonitrile fibres.[187]

Imidazo[2,1-*b*]benzothiazoles (C_3NS-C_3N_2-C_6).—The condensation of (phenylimino)oxalic acid dichloride and 2-aminobenzothiazole affords

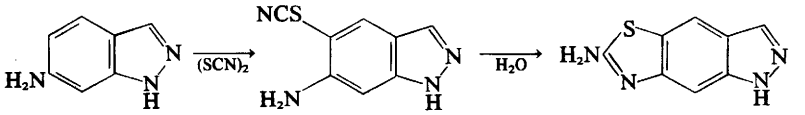
[183] M. O. Lozinskii, A. F. Shivanyuk, and P. S. Pelkis, *Khim. geterotsikl. Soedinenii*, 1971, 471 (*Chem. Abs.*, 1972, **76**, 25 184v).

[184] M. O. Lozinskii, A. F. Shivanyuk, and P. S. Pelkis, *Khim. geterotsikl. Soedinenii*, 1971, 930 (*Chem. Abs.*, 1972, **76**, 34 200z).

[185] A. N. Krasovskii, P. M. Kochergin, and T. E. Kozlovskaya, *Khim. geterotsikl. Soedinenii*, 1971, 393 (*Chem. Abs.*, 1972, **76**, 144 333).

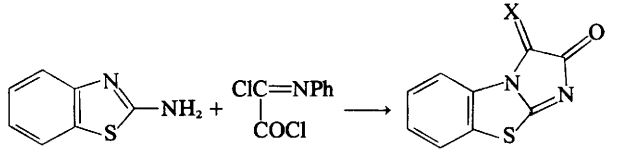
[186] E. A. Kuznetsova, S. V. Zhuravlev, T. N. Stepanova, and V. S. Troitskaya, *Khim. geterotsikl. Soedinenii*, 1972, 177 (*Chem. Abs.*, 1972, **76**, 153 674s).

[187] C. Tarabasanu-Mihaila, L. Floru, E. Balta, and A. Predescu, *Rev. Roumaine Chim.*, 1973, **18**, 889.



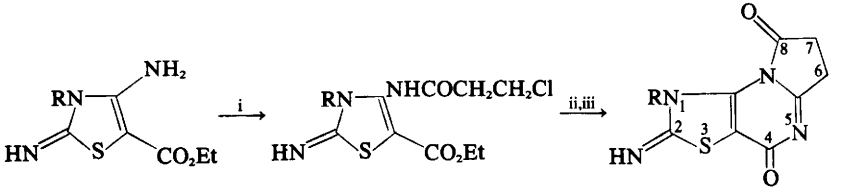
(243)

3-(phenylimino)-2-oxoimidazo[2,1-*b*]benzothiazole (244).[183] The arylhydrazino-compound (245) arises similarly by the use of the analogous reagent Cl(ClCO)C:NNHAr.[184] The synthesis by established methods of further examples of this ring-system has been reported.[128,181,188]



(244) X = NPh
(245) X = NNHPh

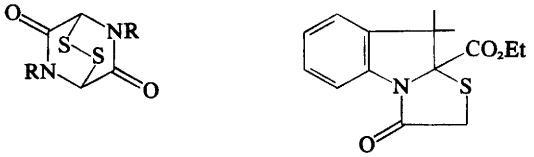
Pyrrolo[1,2-*a*]thiazolo[5,4-*e*]pyrimidines (C_3NS-C_4N-C_4N_2).—A representative of this ring system has been produced from 4-amino-5-ethoxycarbonyl-3-*o*-tolyl-Δ^4-thiazoline by the reaction sequence shown in Scheme 5.[189]



Reagents: i, $ClCH_2CH_2COCl$; ii, KCN: iii, H_3PO_4

Scheme 5

Indolino[2,1-*b*]thiazoles (C_3NS-C_4N-C_6).—A number of indolino[2,1-*b*]thiazolidines, *e.g.* (247), have been prepared in the course of a comprehensive study of synthetic approaches to gliotoxin analogues, the simplest of the natural products containing the epidithiodiketopiperazine ring (246). The details given in the original account are extensive.[190]

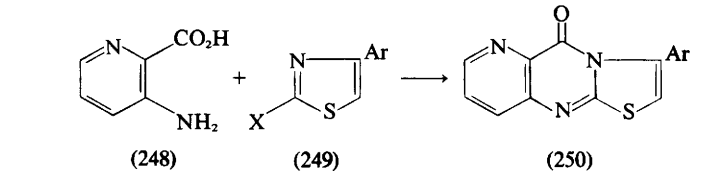


(246) (247)

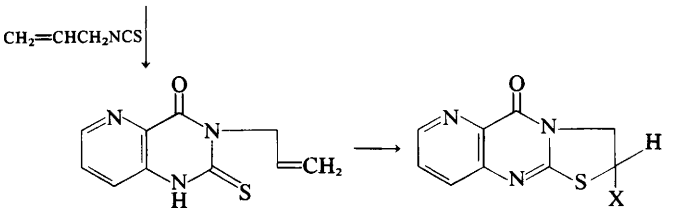
[188] N. P. Grin, A. N. Krasovskii, and P. M. Kochergin, *Khim. geterotsikl. Soedinenii*, 1972, 1271 (*Chem. Abs.*, 1972, **77**, 164 598s).
[189] A. Singh, H. Singh, and K. S. Narang, *Austral. J. Chem.*, 1972, **25**, 1351.
[190] H. C. J. Ottenheym, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, 1973, **95**, 1989.

8 Structures comprising One Five-membered and Two Six-membered Rings (5,6,6)

Pyrido[3,2-*d*]thiazolo[3,2-*a*]pyrimidines (C_3NS-C_4N_2-C_5N).—3-Aryl-5*H*-pyrido[3,2-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones (250) are formed by the condensation of 3-aminopicolinic acid (248) and 4-aryl-2-bromothiazole (249), and by another route. The addition of allyl isothiocyanate to 3-aminopicolinic acid (248) yields the intermediate (251), which affords reduced forms of the fused ring-system (252) and (253) on treatment with hydrogen chloride and bromine, respectively.[191]

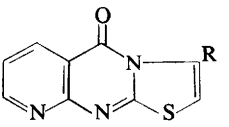


(248) (249) (250)



(251) (252) X = CH_3; (253) X = CH_2Br

The isomeric ring-system (254) is synthesized by the analogous condensation of 2-chloronicotinic acid and 2-aminothiazole, resulting in 3-phenyl-5*H*-pyrido[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one (254).[191]

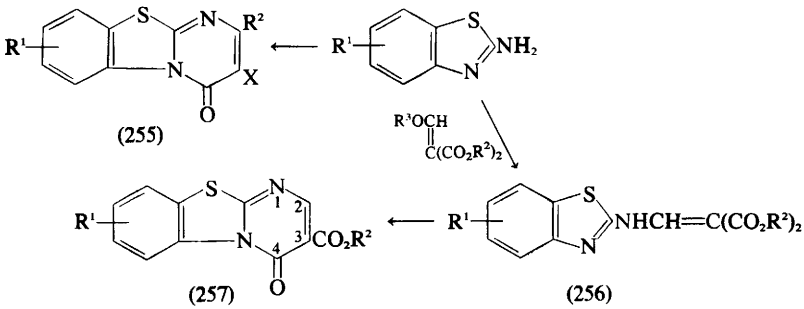


(254)

Pyrimido[2,3-*b*]thiazolo[5,4-*b*]pyridines (C_3NS-C_4N_2-C_5N).—See thiazolo[5,4-*b*]pyridines and pyrimido[2,1-*b*]benzothiazoles.

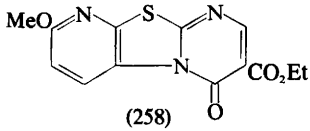
Pyrimido[2,1-*b*]benzothiazoles (C_3NS-C_4N_2-C_6).—The condensation of 2-aminobenzothiazole and ethyl aceto(or benzoyl)acetate in polyphosphoric acid at 140 °C yields 2-substituted pyrimido[2,1-*b*]benzothiazoles (255).[192] Diethyl ethoxymethylenemalonate yields substituted 4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylic acids (257), by way of the linear

[191] A. S. Narang, A. N. Kaushal, S. Singh, and K. S. Narang, *Indian J. Chem.*, 1972, **10**, 602.
[192] T. Okabe, K. Maekawa, and E. Taniguchi, *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 1197.



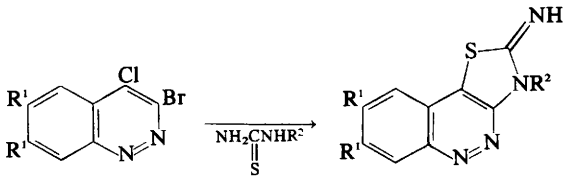
(255) (256) (257)

intermediates (256). A 9-aza-analogue (258), similarly prepared, is an example of the pyrimido[2,3-*b*]thiazolo[5,4-*b*]pyridine ring-system.[193]



(258)

Thiazolo[4,5-*c*]cinnolines (C_3NS-C_4N_2-C_6).—The condensation of 3-bromo-4-chloro-6,7-dimethoxycinnoline (259; R = MeO) with thiourea gives merely the corresponding 4-mercapto-compound, but phenylthiourea produces the substituted thiazolo[4,5-*c*]cinnolines (260).[194]

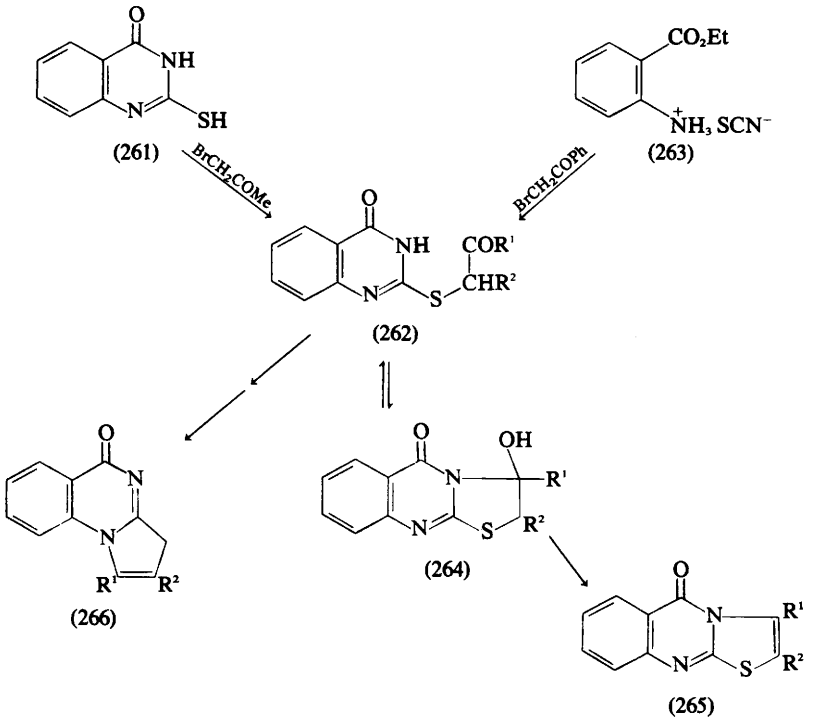


(259) (260)

Thiazolo[2,3-*b*]quinazolines (C_3NS-C_4N_2-C_6).—The interaction of 4-keto-2-thiotetrahydroquinazoline (261) with bromoacetone yields principally (90%) the thiazolo[2,3-*b*]quinazoline derivative (264), which is dehydrated by polyphosphoric acid at 130—140 °C to 3-methyl-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (265). The isomeric thiazolo[3,2-*a*]quinazolin-5-one (266) arises as minor by-product (10%) by the alternative mode of cyclization.[195]

The condensation of *o*-ethoxycarbonylanilinium thiocyanate (263) and bromoacetophenone yields, in the first place, 4-ketotetrahydroquinazolyl-2-thioacetophenone (262), which is progressively ring-closed to (266) on prolonged reaction.[195]

[193] R. J. Alaimo, *J. Heterocyclic Chem.*, 1973, **10**, 769.
[194] A. N. Kaushal and K. S. Narang, *Indian J. Chem.*, 1972, **10**, 675.
[195] H. Singh, K. B. Lal, and S. Singh, *Chem. and Ind.*, 1972, 255; *Indian J. Chem.*, 1973, **11**, 750.

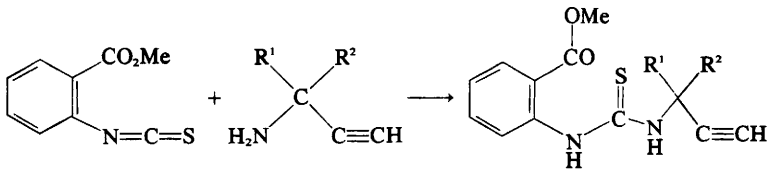


A three-stage synthesis, involving the condensation of methyl 2-isothiocyanatobenzoate (267) and propargylamines (268), followed by two successive cyclizations, provides access to 2-methylene-5-oxo-5*H*-thiazolo[2,3-*b*]quinazolines (271) in overall yields of 50—80%. In suitable cases, the intermediates (269) and (270) may be isolated.[196]

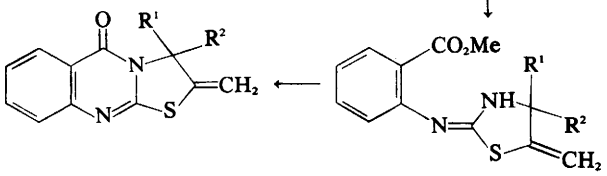
Thiazolo[4,5-*b*]quinoxalines (C_3NS-C_4N_2-C_6).—2,3-Dichloroquinoxalines condense with *NN'*-diarylthioureas to furnish good yields of the substituted thiazolo[4,5-*b*]quinoxalines (272).[197]

Thiazolo[3,2-*a*]quinolines (and isoquinolines) (C_3NS-C_5N-C_6).—The synthetic routes to thiazolo[3,2-*a*]pyridines developed by Undheim and his coworkers (these Reports, Vol. 1 p. 431, Vol. 2, p. 695) are readily extended to the production of systems incorporating additional fused rings, *e.g.* dihydrothiazolo[3,2-*a*]pyridinium compounds (274). Their synthesis from quinoline-2-thione (273) by two established reaction sequences is outlined in Scheme 6. The electronegativity of the additional phenyl ring in quinoline deactivates the resulting structure in comparison with pyridine, and causes greatly

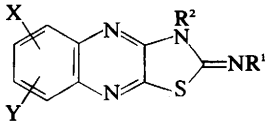
[196] P. Thieme and H. König, *Synthesis*, 1973, 426.
[197] S. Singh and C. Singh, *J. Indian Chem. Soc.*, 1971, **48**, 925.



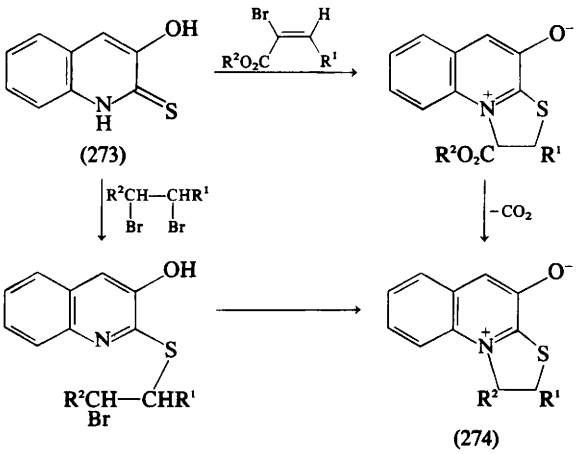
(267) (268) (269)



(271) (270)



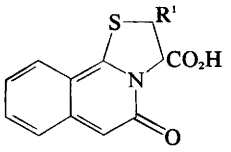
(272)



(273) (274)

Scheme 6

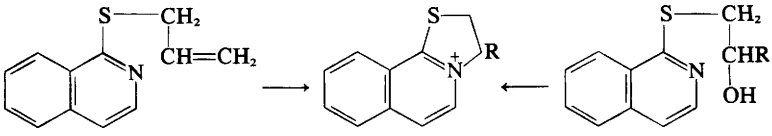
reduced reaction rates. Electrophilic substitution in (274) attacks the position *ortho* to the phenolic oxygen. Full spectral data of the new compounds were provided and discussed.[198] Thiazolo[3,2-*a*]isoquinoline analogues (275) are accessible by the same route from 3-hydroxy-1-mercaptoisoquinoline.[199]



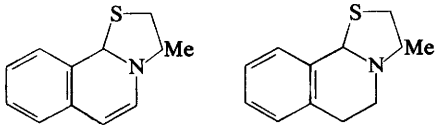
(275)

Thiazolo-[4,5-*f*]- and -[5,4-*f*]-quinolines (C_3NS-C_5N-C_6).—The behaviour under electron impact of members of these series has been studied, and fragmentation patterns have been proposed.[200]

Thiazolo[2,3-*a*]isoquinoline (C_3NS-C_5N-C_6).—3-Substituted 2,3-dihydrothiazolo[2,3-*a*]isoquinolinium salts (277) have been synthesized (*a*) by cyclizing 1-allylthioisoquinoline (276) by means of polyphosphoric acid at 140 °C,[201] (*b*) by similarly cyclizing β-hydroxyethylthioisoquinoline (278),[201,202] and (*c*) by the interaction of ethylene dibromide and 1-mercaptoisoquinoline.[201] The reduction of (277; R = Me) with sodium borohydride or lithium aluminium hydride yields a difficultly separable mixture of (279) and (280), the latter predominating.[201]



(276) (277) (278)

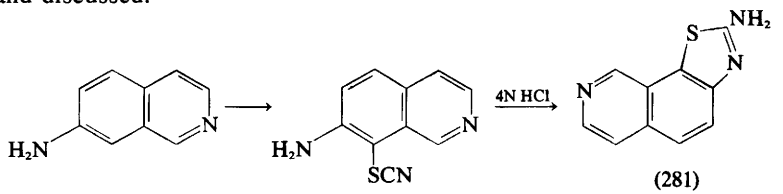


(279) (280)

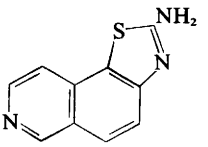
Thiazolo-[4,5-*h*]-, -[5,4-*f*]-, and -[5,4-*h*]-isoquinolines (C_3NS-C_5N-C_6).—In their programme[203] aiming at the synthesis of eight isomeric thiazoloisoquinolines, Taurins and his co-workers have synthesized representatives

[198] T. Greibrokk and K. Undheim, *Acta Chem. Scand.*, 1971, **25**, 2935.
[199] K. R. Reistad and K. Undheim, *Acta Chem. Scand.*, 1972, **26**, 1620.
[200] E. Barni, *J. Heterocyclic Chem.*, 1972, **9**, 501.
[201] H. Singh and K. Lal, *J.C.S. Perkin I*, 1972, 1799.
[202] H. Singh and K. Lal, *Indian J. Chem.*, 1972, **10**, 247.
[203] C. E. Hall and A. Taurins, *Canad. J. Chem.*, 1966, **44**, 2465, 2473; *ibid.*, 1968, **46**, 691.

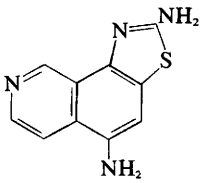
of the [4,5-*h*]- (281), [5,4-*f*]- (282), and [5,4-*h*]- (283) series. The general route involved the *ortho*-thiocyanation of the appropriate aminoisoquinoline, followed by cyclization (and removal of the amino-group), and it is exemplified by the synthesis of (281). Full spectral details were recorded and discussed.[204]



(281)



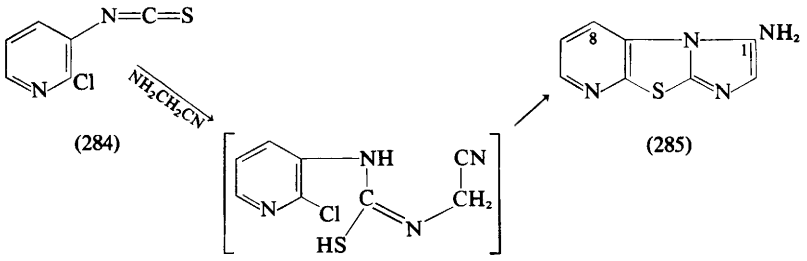
(282)



(283)

9 Structures comprising Two Five-membered and Two Six-membered Rings (5,5,6,6)

Pyrido[2,3-*d*]imidazo[2,1-*b*]thiazolo[5,4-*b*]pyridine (C_3NS-C_3N_2-C_5N-C_5N) and Related Systems.—The readily available 2-chloro-3-isothiocyanatopyridine (284) reacts with compounds containing both electrophilic and nucleophilic centres to form a variety of condensed thiazolopyridines. Its interaction with aminoacetonitrile, for example, furnishes 56% yields of 1-amino-imidazo[2,1-*b*]thiazolo[5,4-*b*]pyridine (285). Its condensation with methyl-

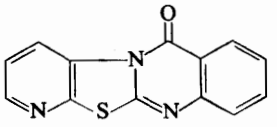


(284)

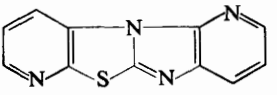
(285)

anthranilate yields 12-oxo-12*H*-pyrido[3,2-*a*]thiazolo[2,3-*b*]quinazoline (286), and that with *o*-chloroaniline pyrido[2,3-*d*]imidazo[2,1-*b*]thiazolo-[5,4-*b*]pyridine (287). Another ring system thus accessible is the 1,2,4-triazolo[2,1-*b*]thiazolo[5,4-*b*]pyridine structure (288).[174]

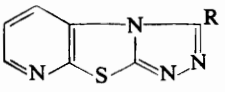
[204] A. Taurins and R. K. C. Hsia, *Canad. J. Chem.*, 1971, **49**, 4054.



(286)



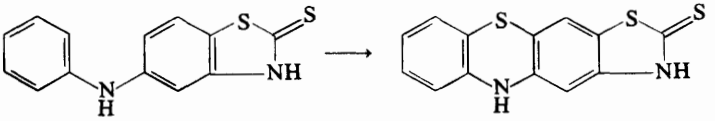
(287)



(288)

10 Structures comprising One Five-membered and Three Six-membered Rings (5,6,6,6)

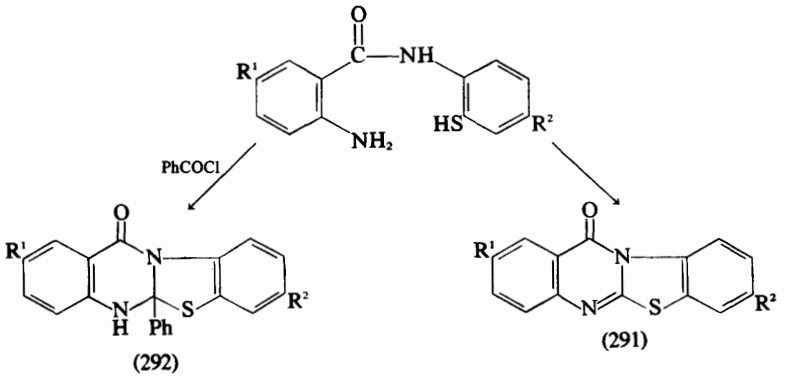
Thiazolo[4,5-*b*]phenothiazine (C_3NS-C_4NS-C_6-C_6).—2,3-Dihydrothiazolo[4,5-*b*]phenothiazine-2-thione (290) is formed when 2-aminophenothiazine[205] or 5-anilino-2,3-dihydrobenzothiazole-2-thione (289)[206] is heated with sulphur and carbon disulphide at 170—200 °C under pressure. It undergoes methylation and quaternization as expected.[205]



(289) (290)

Pyrido[3,2-*a*]thiazolo[2,3-*b*]quinazolines (C_3NS-C_4N_2-C_5N-C_6).—See Pyrido-[2,3-*d*]imidazo[2,1-*b*]thiazolo[5,4-*b*]pyridine, above.

Benzothiazolo-[2,3-*b*]- and -[3,2-*a*]-quinazolines (C_3NS-C_5N-C_6-C_6).—2-Mercapto-2′-aminobenzanilides, accessible from isatoic anhydride and

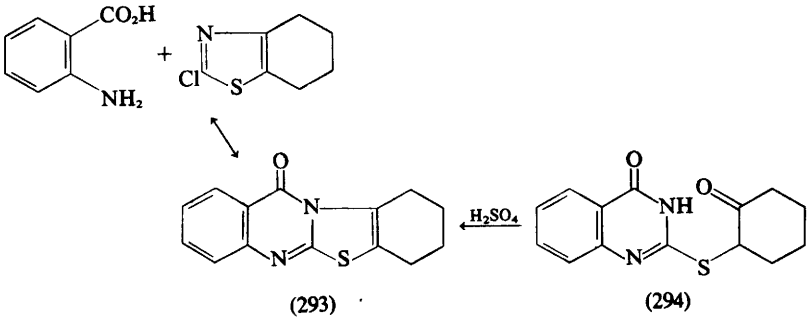


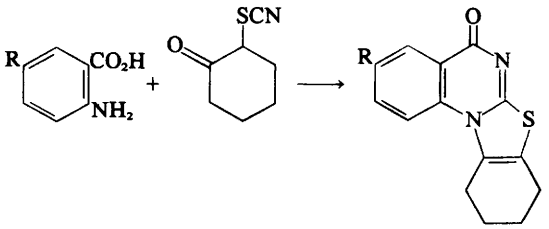
(292) (291)

[205] V. V. Shavyrina and S. V. Zhuravlev, *Khim. geterotsikl. Soedinenii*, 1971, 42 (*Chem. Abs.*, 1971, **75**, 20 322h).

[206] V. V. Shavyrina and S. V. Zhuravlev, *Khim. geterotsikl. Soedinenii*, 1972, 38 (*Chem. Abs.*, 1972, **77**, 34 440y).

2-amino-5-substituted thiophenols, react with ethyl chloroformate to yield 12*H*-benzothiazolo[2,3-*b*]quinazolin-12-ones of type (291). The action of benzoyl chloride similarly affords derivatives of the same ring-system, *e.g.* (292).[207] The synthesis of partially reduced examples of this ring system was undertaken in order to study the effect of such structural changes on their chemical and biological properties. Tetrahydro-12*H*-benzothiazolo[2,3-*b*]-quinazolines (293) are produced by the condensation of anthranilic acid and 2-chlorotetrahydrobenzothiazole, or by the cyclodehydration of the condensation product (294) of 2-chlorocyclohexanone and 4-keto-2-thiotetrahydroquinazoline.





(295)

The angular isomers, *viz.* tetrahydro-5*H*-benzothiazolo[3,2-*a*]quinazolines (295), arise in the condensation of 2-thiocyanatocyclohexanone and anthranilic acid.[208]

[207] A. N. Kaushal, S. Singh, A. P. Taneja, and K. S. Narang, *Indian J. Chem.*, 1972, **10**, 476.
[208] S. K. Modi, S. Singh, and K. S. Narang, *Indian J. Chem.*, 1972, **10**, 605.

15

Thiadiazoles and Selenadiazoles

BY F. KURZER

1 Introduction

Activity continues in the investigation of all four isomeric series of thiadiazoles, and an increased interest in the selenadiazole analogues is discernible. The material is presented in the sequence established in the previous Reports.

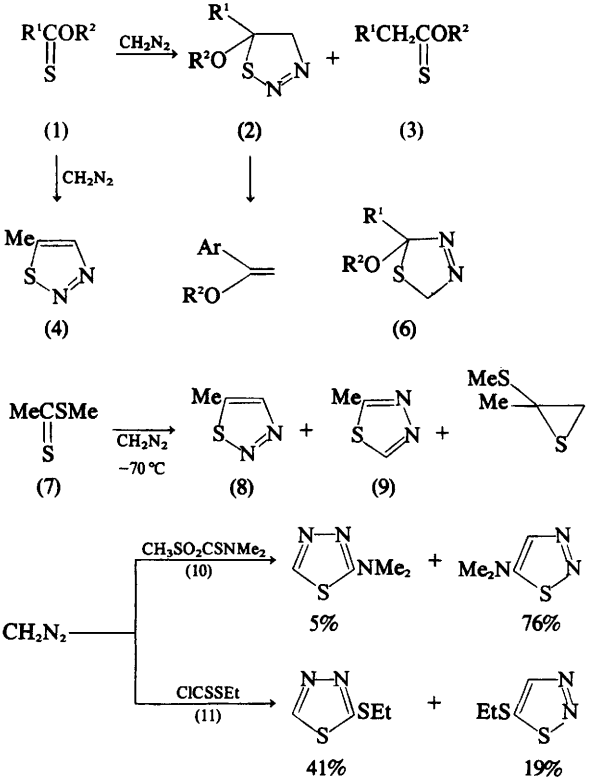
2 Synthesis of 1,2,3-Thiadiazoles

Pechmann's Synthesis.—The use of diazoalkanes in the production of 1,2,3-thiadiazoles has been further developed; these routes may be regarded as extensions of Pechmann's old-established synthesis.

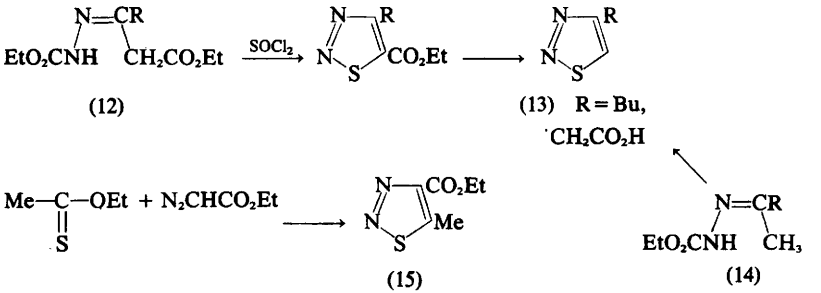
The action of diazoalkanes on thiocarbonyl compounds provides a versatile route to thiirans; 1,2,3-thiadiazole derivatives, which function as intermediates, are isolable in suitable cases. Thus, diazomethane reacts with thionesters (1) yielding 5-alkoxy-5-methyl-Δ^2-1,2,3-thiadiazolines (2) (*ca.* 60%) together with the next higher homologous thionester (3) (*ca.* 30%). Aromatic members (2; R = Ar) decompose readily to the alkenes (5). Ethyl thioformate (1; R^1 = H, R^2 = Et) gives rise, by methylation and aromatization, to (4), and to linear products.[1] Comparable observations involving diazoethane and diazopropane are also on record.[2] The formulation of the products as 1,2,3-thiadiazolines (2) in preference to the possible Δ^3-1,3,4-thiadiazoline structures (6) is supported by the results of n.m.r. studies. However, both isomers, (8) (20%) and (9) (45%), are obtained when diazomethane acts on methyl dithioacetate (7) at −70 °C (compare also these Reports, Vol. 1. p. 450).[1]

In a study of the interaction of electron-depleted thiocarbonyl compounds with diazoalkanes, the *C*-sulphonylthioformamide derivative (10) and ethyl chlorodithioformate (11) were found to yield mixtures of products that have been provisionally formulated as 1,2,3- and 1,3,4-thiadiazoles.[3]

[1] J. M. Beiner, D. Lecadet, D. Paquer, A. Thullier, and J. Vialle, *Bull. Soc. chim. France*, 1973, 1979.
[2] J. M. Beiner, D. Lecadet, D. Paquer, and A. Thullier, *Bull. Soc. chim. France*, 1973, 1983.
[3] S. Holm and A. Senning, *Tetrahedron Letters*, 1973, 2389.



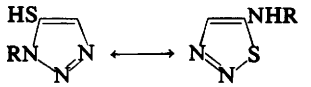
From Hydrazones.—Raap and Micetich's[4] synthesis of 1,2,3-thiadiazoles [from (12)] has been applied to the production of further examples (13). The use of the readily accessible hydrazone (14) provides the desired compounds directly in one step. The condensation of diazoacetate with *O*-ethyl thionoacetate affords the substituted 1,2,3-thiadiazole (15).[5]



[4]. R. Raap and R. G. Micetich, *Canad. J. Chem.*, 1968, **46**, 1057.

[5] S. I. Rämsby, S. O. Ogren, S. B. Ross, and N. E. Stjernstrom, *Acta Pharm. Suecica*, 1973, **10**, 285.

By Other Reactions.—The well-known rearrangement of 1-aryl-5-mercapto-1,2,3-triazoles to 5-anilino-1,2,3-thiadiazoles[6] (Scheme 1) occurs more slowly and reversibly in the aliphatic series.[7]

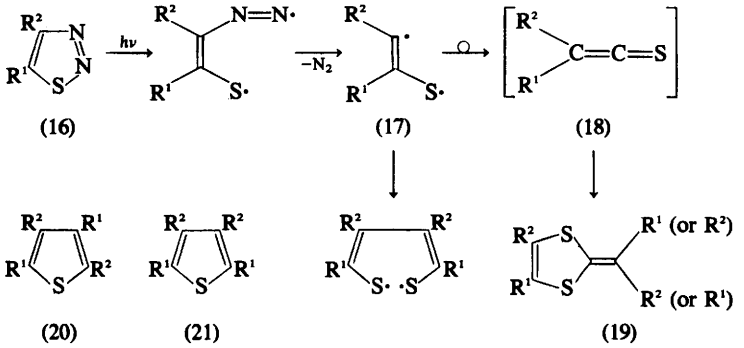


Scheme 1

3 Properties of 1,2,3-Thiadiazoles

The study of the fragmentation of 1,2,3-thiadiazoles under electron impact has been further extended (*cf.* these Reports, Vol. 2, p. 718), and likely mechanisms of the processes have been discussed.[8]

The photolysis of substituted 1,2,3-thiadiazoles (16) in benzene proceeds with quantitative loss of nitrogen, and primary formation of 1,3-biradicals (17). Depending on the nature of the substituents, they give rise to 1:1 mixtures of *cis*- and *trans*-1,3-dithiol derivatives (19), or symmetrical or unsymmetrical thiophens (20) and (21). Photolysis in the gaseous phase



occurs analogously: 4-ethoxycarbonyl-5-methyl-1,2,3-thiadiazole, for example, yields (19; R^1 = Me, R^2 = CO_2Et) as main product.[9] The formation of the dithiol derivatives (19) is visualized to proceed by way of the thioketens (18),[10] formed by a reaction resembling the Wolff rearrangement of α-diazo-ketones; it provides indirect evidence for the existence, at least as intermediates, of the thioketens that were sought by Staudinger[11] as early as 1916.

[6] C. Pedersen and T. Kindt-Larsen, *Acta Chem. Scand.*, 1962, **16**, 1800; M. Reglitz and A. Liedhegener, *Annalen*, 1967, **710**, 118; M. Reglitz and H. Scherer, *Chem. Ber.*, 1969, **102**, 417.

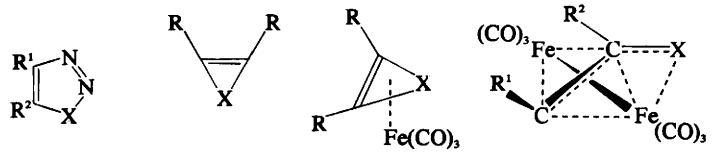
[7] M. Begtrup, *Acta Chem. Scand.*, 1972, **26**, 1243.

[8] K. P. Zeller, H. Meier, and E. Müller, *Org. Mass Spectrometry*, 1971, **5**, 373; *Tetrahedron*, 1972, **28**, 1353.

[9] K. P. Zeller, H. Meier, and E. Müller, *Annalen*, 1972, **766**, 32.

[10] W. Kirmse and L. Horner, *Annalen*, 1958, **614**, 4.

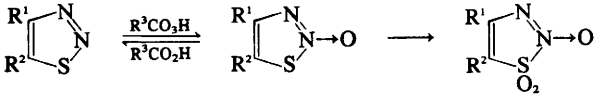
[11] H. Staudinger and J. Siegwart, *Chem. Ber.*, 1916, **49**, 1918.



(22) (23) (24) (25)

4,5-Disubstituted 1,2,3-thiadiazoles and their selenium analogues (22; X = S or Se) serve as sources of the heterocyclic systems of general structure (23; X = S or Se), which have so far been known only as intermediates. Attempts to stabilize and trap them as complexes of type (24) have in fact given different complexes, but it is thought that the complexes (24) function as intermediates. Thus, nonacarbonyldi-iron, which is known to catalyse the elimination of nitrogen from organic azides, reacts with the thiadiazoles (22; X = S) and more rapidly with the selenadiazoles (22; X = Se) to yield red crystalline carbene complexes of type (25). When the 4- and 5-substituents in (22) are non-identical, two isomeric carbene complexes are produced, the minor isomer being in each case a rearrangement product.[12]

The oxidation of 1,2,3-thiadiazoles (26) with peracetic or *m*-chloroperbenzoic acid yields the corresponding 2-oxides (27) reversibly; further action may result in 1,1,2-trioxides (28). The preferential oxidation at N-2



(26) (27) (28)

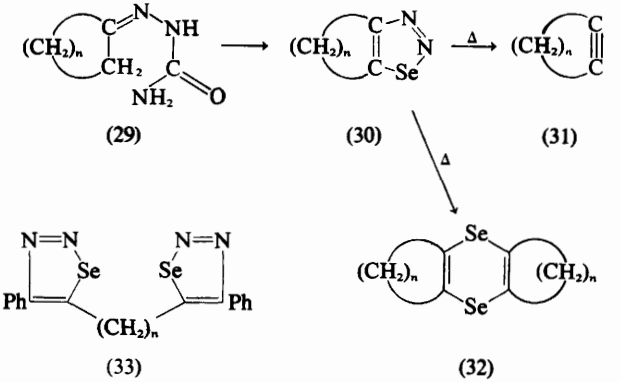
rather than N-3 is in accordance with its higher electron density due to the adjacent sulphur atom, and this is confirmed by MO calculations. The dipole moments and spectral properties of the *N*-oxides agree with the structural assignments and suggest a high degree of double-bond character of the N—O link.[13]

4 Synthesis and Properties of 1,2,3-Selenadiazoles

Lalezari's synthesis of 1,2,3-selenadiazoles (these Reports, Vol. 2, p. 720) has been extended to the production of cycloalka-1,2,3-selenadiazoles (30; $n = 3$—6 or 10) from cyclic ketone semicarbazones (29). Their pyrolysis yields the acetylenes (31) (*e.g.* cyclo-octyne) and dimeric selenohydrocarbons of type (32).[14] Almost identical results were reported independently by another group.[15] The method is also applicable to the synthesis of

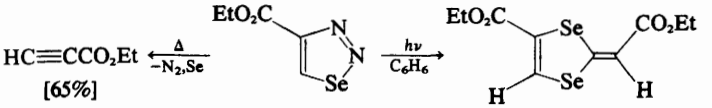
[12] T. L. Gilchrist, P. G. Mente, and C. W. Rees, *J.C.S. Perkin I*, 1972, 2165.
[13] P. Braun, K. P. Zeller, H. Meier, and E. Müller, *Tetrahedron*, 1972, **28**, 5655.
[14] I. Lalezari, A. Shafiee, and M. Yalpani, *J. Heterocyclic Chem.*, 1972, **9**, 1411.
[15] H. Meier and E. Voigt, *Tetrahedron*, 1972, **28**, 187.

di-1,2,3-selenadiazoles *e.g.* (33), which afford good yields of dialkynes on pyrolysis.[16]



(29) (30) (31) (33) (32)

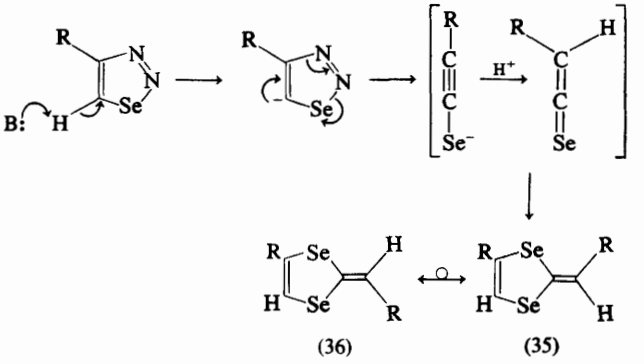
The thermolysis and photolysis of 4-ethoxycarbonyl-1,2,3-selenadiazole (34) and its 5-methyl derivatives have been briefly reported and their



(34) [18%] (1:1 *cis*:*trans*)

mechanisms accounted for in terms of radical processes involving intermediate selenoketens.[17]

Alkalis convert 4-substituted 1,2,3-selenadiazoles, with evolution of nitrogen, into equilibrium mixtures of *cis*- (35) and *trans*- (36) 2, ω-disubstituted 1,4-diselenafulvenes, presumably by the mechanism shown. The



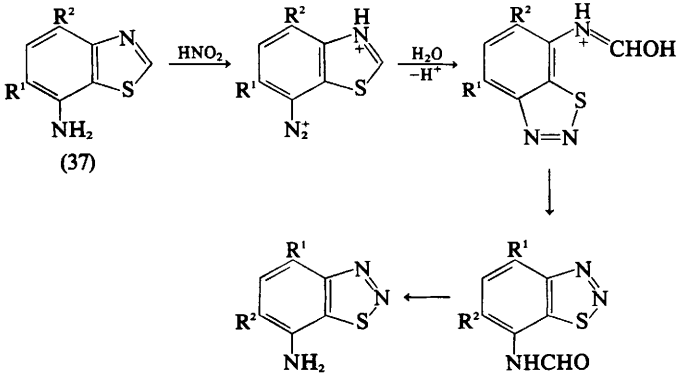
(36) (35)

[16] I. Lalezari, A. Shafiee, and H. Golgolab, *J. Heterocyclic Chem.*, 1973, **10**, 655.
[17] H. Meier and I. Menzel, *Tetrahedron Letters*, 1972, 445.

intermediate acetylene derivative is trapped as the insoluble potassium salt by conducting the reaction in dioxan–potassium ethoxide.[18]

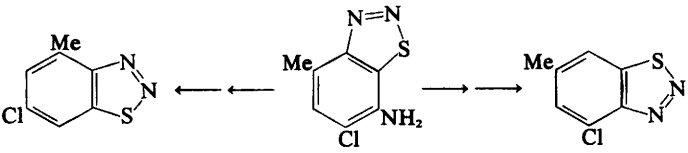
5 Synthesis of 1,2,3-Benzothiadiazoles

Diazotization of 7-aminobenzothiazole (37), followed by hydrolysis, yields 7-amino-1,2,3-benzothiadiazole (39), presumably by the electrophilic intramolecular attack of the diazonium cation at the sulphur.[19] 7-Amino-6-halogenobenzothiazoles react analogously.[20] The isolation (95%) of intermediate 7-formamido-1,2,3-benzothiadiazoles (38) suggests that the mechanism may be depicted as in Scheme 2.[21]



Scheme 2

7-Amino-1,2,3-benzothiadiazoles can themselves undergo this rearrangement. Thus, diazotization followed by reduction with hypophosphorous acid converts 7-amino-6-chloro-4-methyl-1,2,3-benzothiadiazole (40) into the rearranged 4-chloro-6-methyl compound (41); a small but significant quantity of non-rearranged product (42) is also obtained. When C-4 is

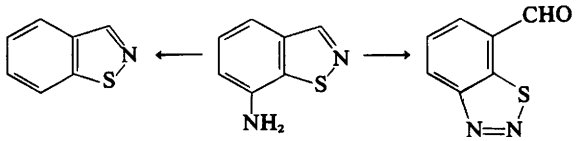


(42) 10—12% (40) (41) 88—90%

unsubstituted, the presence of any substituent (of *either* electronic effect) at C-6 causes predominant rearrangement, which therefore appears to be governed chiefly by steric factors.[20]

[18] I. Lalezari, A. Shafiee, and M. Yalpani, *J. Org. Chem.*, 1973, **38**, 338.
[19] J. H. Davies and P. Kirby, *J. Chem. Soc.* (C), 1967, 321.
[20] E. Haddock, P. Kirby, and A. W. Johnson, *J. Chem. Soc.* (C), 1970, 2514.
[21] E. Haddock, P. Kirby, and A. W. Johnson, *J. Chem. Soc.* (C), 1971, 3642.

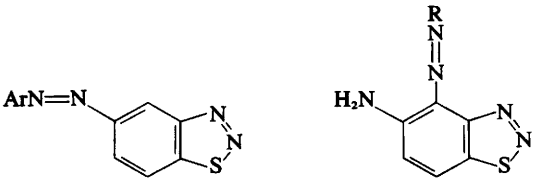
Diazonium salts derived from 7-aminobenzisothiazole (43) similarly yield 1,2,3-benzothiadiazole-7-carbaldehyde and analogues (44) on decomposition under Sandmeyer conditions. Reduction of the diazonium group by hypophosphorous acid produces, without rearrangement, the benzisothiazole (45).[22]



(45) (43) (44)

Benzothiaza-thiolium salts, obtainable from primary arylamines by the Herz reaction,[23] are ring-opened by bases to *o*-amino-thiols, which yield 1,2,3-benzothiadiazoles on diazotization. The method has now been simplified as a one-stage procedure, but yields are variable.[24] It has been applied with success to the production of 1,2,3-benzothiadiazole-6-carboxylic acid (methyl ester) in 60% overall yield.[25]

A series of azo-dyes (46), (47) incorporating the benzo-1,2,3-thiadiazole structure have been produced from the 5-amino-heterocycle by conventional methods, and their properties as dyes evaluated.[26]



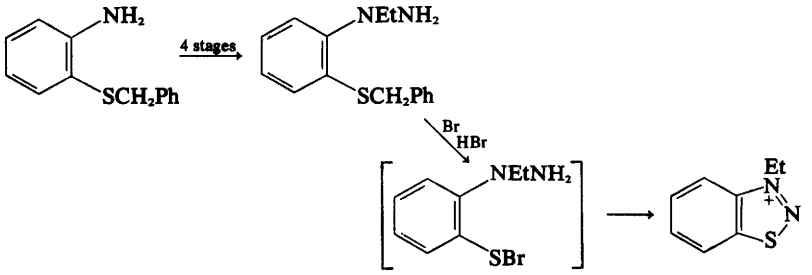
(46) (47)

6 Properties of 1,2,3-Benzothiadiazoles

An unequivocal synthesis has established that quaternization of 1,2,3-benzothiadiazole yields *N*-3(and not *N*-2)-alkyl derivatives. 3-Ethyl-1,2,3-benzothiadiazolium bromide, used as a reference compound, was synthesized from 2-aminophenyl benzyl sulphide as shown in Scheme 3, and it was identical with the compound obtained by quaternization.[27]

A number of 1,2,3-benzoselenadiazoles were quaternized successfully with alkyl 2,4-dinitrobenzenesulphonates in nitrobenzene. The reactivity

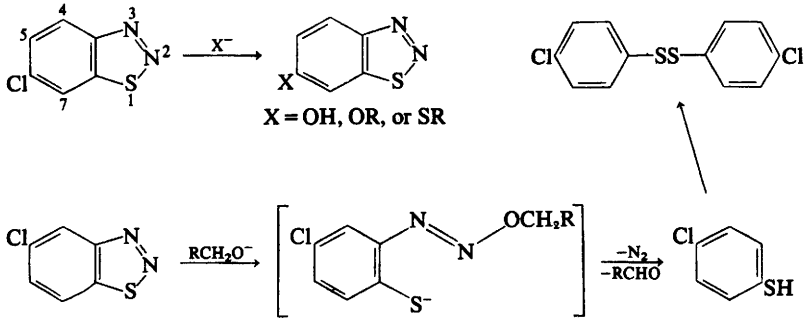
[22] E. Haddock, P. Kirby, and A. W. Johnson, *J. Chem. Soc.* (*C*), 1971, 3994.
[23] W. K. Warburton, *Chem. Rev.*, 1957, **57**, 1011.
[24] P. Kirby, S. B. Soloway, J. H. Davies, and S. B. Webb, *J. Chem. Soc.* (*C*), 1970, 2250.
[25] J. B. Carr, *J. Heterocyclic Chem.*, 1972, **9**, 1149.
[26] M. Kamel, I. B. Hannout, and A. Z. Morsi, *J. prakt. Chem.*, 1971, **313**, 129.
[27] G. A. Jaffari, A. J. Nunn, and J. T. Ralph, *J. Chem. Soc.* (*C*), 1970, 2060.



Scheme 3

of the parent bases decreases in the order: 1,2,3-benzoselenadiazole > 2,1,3-benzoselenadiazole > 1,2,3-benzothiadiazole > 2,1,3-benzothiadiazole, which follows closely the magnitude of the pK_a values of their first ionization constants ($-2.25 > -2.7 > -3.1 > -4.5$).[27]

The halogen of mono- and di-halogeno-1,2,3-benzothiadiazoles may be replaced nucleophilically, with formation of products that vary with the nature of the nucleophile, with the halogen, and with its position in the ring. 6-Chloro-1,2,3-benzothiadiazole reacts readily with hydroxide, alkoxide, and thiolate anions in aqueous DMSO to give the appropriate substituted products (Scheme 4). In contrast, 5-chloro-1,2,3-benzothiadiazole yields



Scheme 4

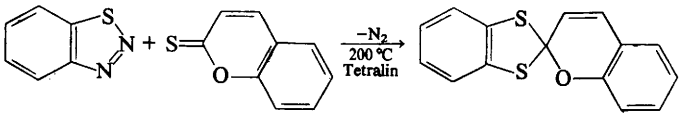
bis-*p*-chlorophenyl disulphide, at least under the influence of alkoxide ion; the initial product is probably the thiol, which is then oxidized by the DMSO. The different behaviour of the 5- and 6-chloro-compounds may be due to the lower electron density on the 2-nitrogen in the former isomer. A number of canonical forms can be written for the 6-chloro-compound (but not for the 5-isomer) involving positively charged chlorine and a negative charge delocalized over the whole ring system.[28]

The action of phenyl radicals (generated from *N*-nitrosoacetanilide) on

[28] J. H. Davies, E. Haddock, P. Kirby, and S. B. Webb, *J. Chem. Soc.* (*C*), 1971, 2843.

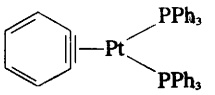
1,2,3-benzothiadiazole in ethyl acetate at room temperature proceeds with total loss of nitrogen, and formation of diphenyl sulphide, thianthrene, and dibenzothiophen. A mechanism for this reaction was briefly considered.[29]

1,2,3-Benzothiadiazole (48) is known to decompose above 200 °C with loss of nitrogen and formation of a reactive 1,3-dipolar species, which reacts particularly readily with C=S groups.[30] Its interaction with substituted 2-thiocoumarins (49) under these conditions furnishes a series of spiropyrans of structure (50); spectroscopic (u.v., n.m.r.) data support the formulation.[31]

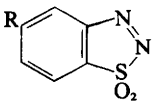


(48) (49) (50)

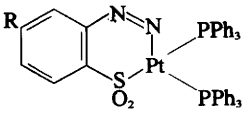
In experiments aimed at the preparation of stable benzyne complexes of platinum of type (51), 1,2,3-benzothiadiazole 1,1-dioxides (52; R = H or Me), which are known to fragment under mild conditions, were used as a potential source of benzyne. However, their interaction with tetrakis-(triphenylphosphine)platinum in benzene did not give the required benzyne complexes, but resulted in excellent yields of yellow crystalline azo-complexes of structure (53) or possibly (54; R = H or Me).[32]



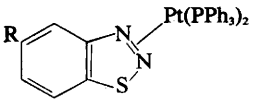
(51)



(52)



(53)



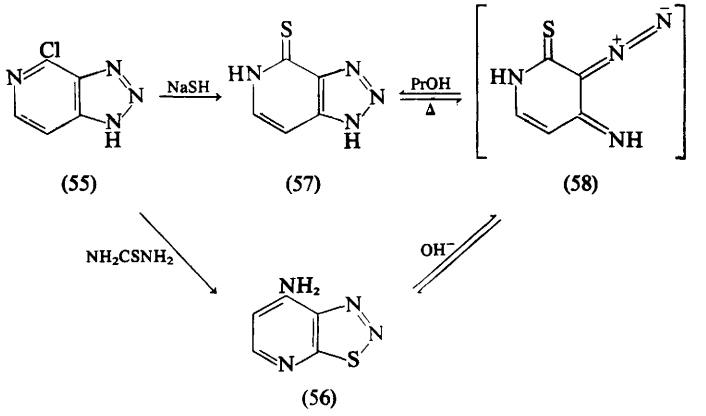
(54)

1,2,3-Benzothiadiazole and its derivatives exert an appreciable synergistic effect on insecticides.[33]

[29] L. Benati, A. Tundo, and G. Zenardi, *J.C.S. Chem. Comm.*, 1972, 590.
[30] R. Huisgen and V. Weberndörfer, *Experientia*, 1961, **17**, 566.
[31] P. Appriou and R. Guglielmetti, *Compt. rend.*, 1972, **275**, *C*, 57.
[32] T. L. Gilchrist, F. J. Graveling, and C. W. Rees, *J. Chem. Soc.* (*C*), 1971, 977; *Chem. Comm.*, 1968, 821; see also C. D. Cook and G. S. Jauhal, *J. Amer. Chem. Soc.*, 1968, **90**, 1464.
[33] J. C. Felton, D. W. Jenner, and P. Kirby, *J. Agric. Food Chem.*, 1970, **18**, 671.

7 Synthesis of [1,2,3]Thiadiazolo[5,4-*b*]pyridine

The interaction of 4-chloro-1*H*-*vic*-triazolo[4,5-*c*]pyridine (55) and thiourea in propanol produces, in addition to the 4-propylthio-substitution product (18%), moderate yields (30%) of 7-amino-[1,2,3]thiadiazolo[5,4-*b*]pyridine (56).[34] This probably arises from the intermediate (58) by ring opening of the *vic*-triazole ring, as is suggested by the observation that 1,5-dihydro-4*H*-*vic*-triazolo[4,5-*c*]pyridine-4-thione (57) in refluxing propanol gives rise to an equilibrium mixture of (56) and (57). The reconversion (70%) of (56) into (57) occurs in alkaline media, apparently by ring-opening of the thiadiazole ring of (56) and formation of the electron-releasing anion of the pyridinethione intermediate (58).[34] The reaction resembles the rearrangement of thiadiazolopyrimidines into 8-azapurinethiones[35] and thiazolopyrimidines into purinethiones.[36]

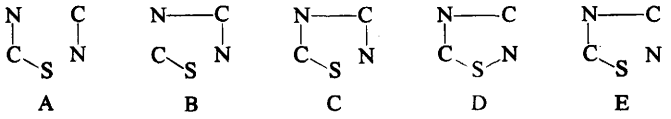


(55) (57) (58)

(56)

8 Synthesis of 1,2,4-Thiadiazoles

In accordance with previous practice,[37] the synthetic routes to 1,2,4-thiadiazoles are formally classified according to the nature of the fragments from which the heterocyclic ring is ultimately constructed. Types D and E are added to those previously given.[37]

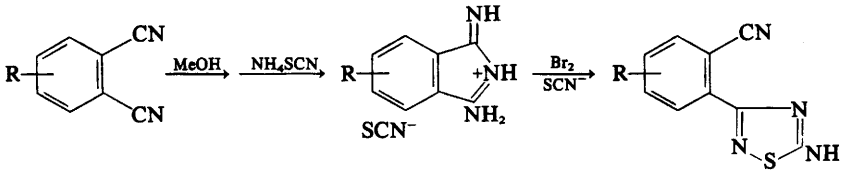


A B C D E

[34] C. Temple, B. H. Smith, and J. A. Montgomery, *J. Org. Chem.*, 1972, **37**, 3601.
[35] A. Albert and K. Tratt, *Angew. Chem. Internat. Edn.*, 1966, **5**, 587.
[36] D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 1957, 682.
[37] F. Kurzer, 'Advances in Heterocyclic Chemistry', ed. A. R. Katritzky, Academic Press, New York, 1965, Vol. 5, pp. 119, 122.

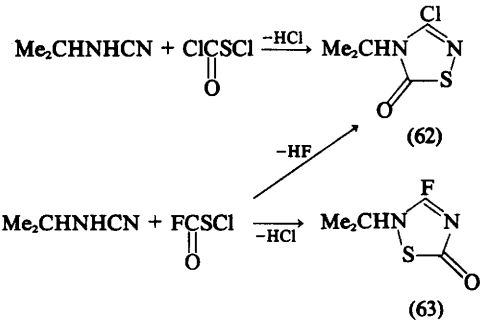
The direct exploitation of known reactions has provided 1,2,4-thiadiazole-5-thiones,[38] substituted 5-amino-3-mercapto-1,2,4-thiadiazoles,[39] and 5-(substituted)amino-3-trichloromethyl-1,2,4-thiadiazoles.[40]

Type B Syntheses [NCN + CS].—1-Amino-3-imino-isoindoleninium thiocyanates (60), which are accessible from *o*-dinitriles (59), are convertible into 3-substituted 5-amino-1,2,4-thiadiazoles (61) by the simultaneous action of bromine and sodium methoxide. The reactants (60) thus play the role of the linear amidines in Goerdeler's[41] synthesis, of which the present modification is a useful extension.[42]



(59) (60) (61)

In a wider investigation of the interaction of methanesulphenyl halides and cyanamides, 1,2,4-thiadiazoles were obtained as the main products in certain cases. Thus, isopropylcyanamide undergoes an addition–substitution with chlorocarbonosulphenyl chloride (ClCOSCl), yielding 3-chloro-4-isopropyl-Δ^2-1,2,4-thiadiazolin-5-one (62). The use of the fluorocarbono-analogue produces (62) and (63) side by side, involving respectively its S—Cl or COF group in the addition to the triple bond of the cyanamide.[43]

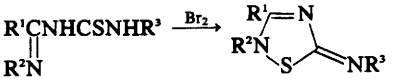


(62) (63)

Type C Syntheses [NCNCS].—The oxidative cyclization of compounds incorporating the amidinothiono-group [C(:NH)NHCS] continues to provide the most versatile route to 1,2,4-thiadiazoles.

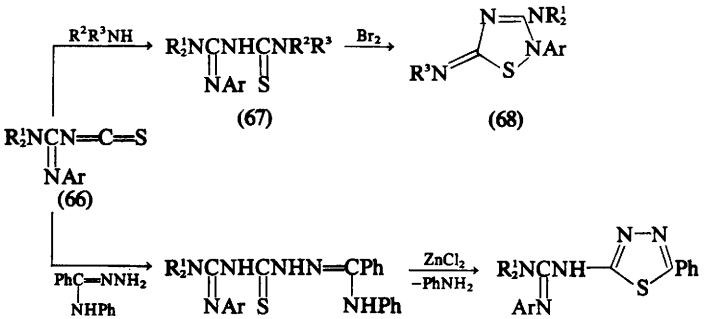
[38] G. Lacasse and J. M. Muchowski, *Canad. J. Chem.*, 1973, **51**, 2353.
[39] M. Zbirovsky, J. Myska, and J. Stanek, *Coll. Czech. Chem. Comm.*, 1971, **36**, 4087, 4091.
[40] E. F. Elslager, J. Johnson, and L. M. Werbel, *J. Heterocyclic Chem.*, 1973, **10**, 611.
[41] J. Goerdeler, K. Wember, and G. Worsch, *Chem. Ber.*, 1954, **87**, 57.
[42] K. Leverenz, *Angew. Chem.*, 1973, **85**, 226.
[43] A. Haas and V. Plass, *Chem. Ber.*, 1973, **106**, 3391.

A further variant of this synthesis is the conversion of imidoylthioureas (64) into 2,3-disubstituted 5-imino-Δ^3-1,2,4-thiadiazolines[44] (65) under the usual conditions.[45]



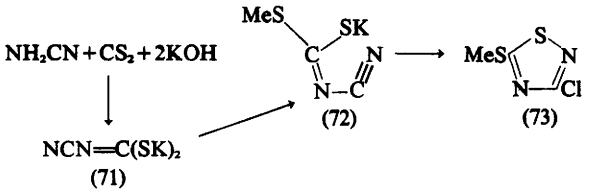
(64) (65)

Formamidinoyl isothiocyanates (66) react additively with amines to yield amidinothioureas (67), which are cyclized by bromine to yield substituted 1,2,4-thiadiazoles (68). The comparable adducts (69) derived from amidrazones are rather unstable, and are ring-closed, with loss of aniline, to 1,3,4-thiadiazoles (70) by the action of zinc chloride in acetonitrile.[46]



(66) (67) (68) (69) (70)

A direct route to 5-alkylthio-3-chloro-1,2,4-thiadiazoles (73) involves the monoalkylation of the readily accessible dipotassium cyanodithioimidocarbonate (71), followed by oxidative cyclization with sulphuryl chloride.[47] The



(71) (72) (73)

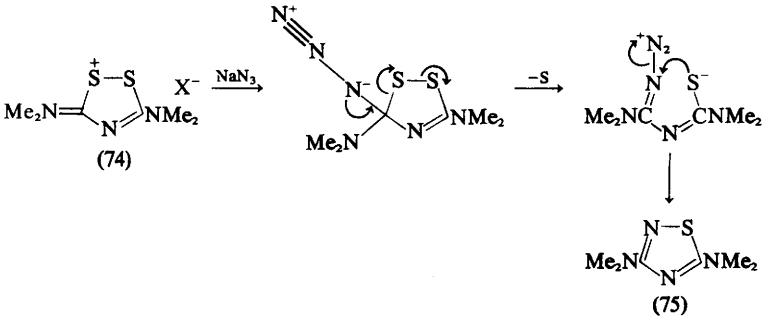
synthesis has been extended to the production of numerous examples, employing a variety of primary and secondary alkyl halides in the first step, and halogens as well as sulphuryl chloride in the cyclization.[48]

The interaction of benzamidine and carbon disulphide in alkaline media

[44] G. Barnikow and H. Ebeling, *Z. Chem.*, 1972, **12**, 130.
[45] F. Kurzer, *J. Chem. Soc.*, 1956, 2345.
[46] W. Abraham and G. Barnikow, *Tetrahedron*, 1973, **29**, 699.
[47] R. J. Timmons and L. S. Wittenbrook, *J. Org. Chem.*, 1967, **32**, 1566.
[48] L. S. Wittenbrook, G. L. Smith, and R. J. Timmons, *J. Org. Chem.*, 1973, **38**, 465.

produces, amongst other products, small yields of 3-phenyl-5-mercapto-1,2,4-thiadiazole. This probably arises by oxidation of the substituted dithiocarbamate initially formed.[49]

3,5-Bis(dimethylamino)-1,2,4-dithiazolium chloride (74) reacts with sodium azide in DMF, yielding the 1,2,4-thiadiazole (75) (75%), possibly by

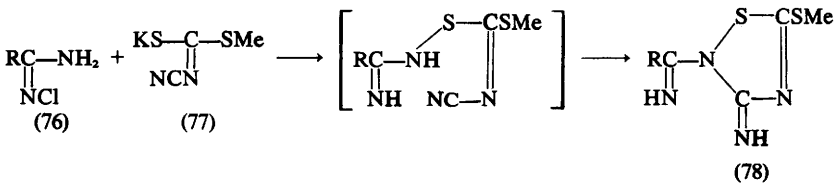


(74) (75)

the mechanism shown. Reactants (74) bearing non-identical substituents may give rise to pairs of isomeric 1,2,4-thiadiazoles, but usually produce only the one arising by attack of the azide ion at the carbon bearing the less highly substituted amino-group.[50] The action of potassium cyanate in this reaction generally yields the expected 4,6-bis(dialkylamino)-2*H*-1,3,5-thiadiazin-2-ones, but 1,2,4-thiadiazoles arise again in anomalous cases, with simultaneous loss of carbon monoxide.[51]

Thaler and McDivitt's synthesis of 3-chloro-1,2,4-thiadiazol-5-yl sulphenyl chloride (these Reports, Vol. 2, p. 721) has been described independently by another group of workers.[52]

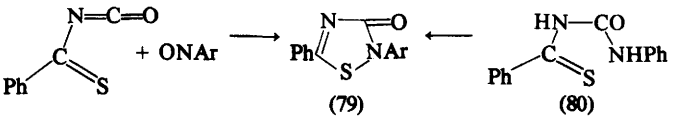
Type D Syntheses [CNCSN].—The condensation of *N*-chloro-amidines (76) and potassium methyl cyanoiminodithiocarbonate (77) in chloroform below 5 °C yields 2-imidoyl-3-imino-5-methylthio-Δ^4-1,2,4-thiadiazolines (78) in one stage. The reductive and hydrolytic ring cleavage of the products was briefly outlined.[53]



(76) (77) (78)

[49] Y. E. Moharir, *Indian J. Chem.*, 1972, **10**, 315.
[50] J. E. Oliver, *J. Org. Chem.*, 1971, **36**, 3465.
[51] J. E. Oliver, B. A. Bierl, and J. M. Ruth, *J. Org. Chem.*, 1972, **37**, 131.
[52] R. Neidlein and H. Reuter, *Arch. Pharm.*, 1972, **305**, 373.
[53] T. Fuchigami and K. Odo, *Chem. Letters*, 1973, 917.

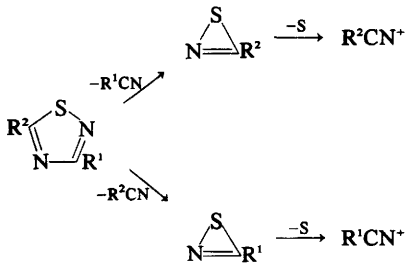
Type E Syntheses [CNCS + N].—The interaction of thiobenzoyl isocyanate and nitrosobenzene yields, surprisingly, the 1,2,4-thiadiazolin-3-ones (79) (58%), with elimination of oxygen, the fate of which is as yet not elucidated. The formulation of the products is confirmed by their unequivocal synthesis by the oxidative cyclization of (80).[54]



(79) (80)

9 Properties of 1,2,4-Thiadiazoles

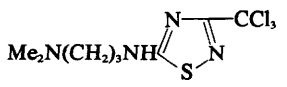
An examination of the mass spectra of substituted 1,2,4-thiadiazoles supplements and extends previous studies[55] in this field. Fragmentation occurs with loss of RCN from the molecular ion, followed by extrusion of sulphur and formation of a nitrilium ion (Scheme 5).[56]



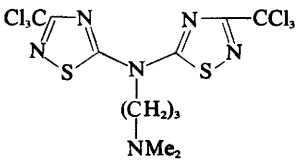
Scheme 5

Diquaternary salts of 1,2,4- and 1,3,4-thiadiazoles are dealt with under the latter heading.

The action of *NN*-dimethylpropane-1,3-diamine on 5-chloro-3-trichloromethyl-1,2,4-thiadiazole gives moderate yields of three substitution products, (81), (82), and (83), the last being apparently formed by an unusual replacement of the distal methyl group of (82). This bis-thiadiazole (82)

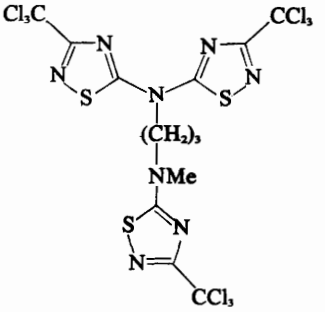


(81)



(82)

[54] J. Goerdeler and R. Schimpf, *Chem. Ber.*, 1973, **106**, 1496.
[55] A. H. Miller and R. J. Pancirow, *J. Heterocyclic Chem.*, 1971, **8**, 163.
[56] K. T. Potts and R. Armbruster, *J. Heterocyclic Chem.*, 1972, **9**, 651.

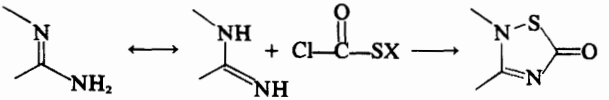


(83)

is the most promising member of a series of effective antimalarial compounds.[40]

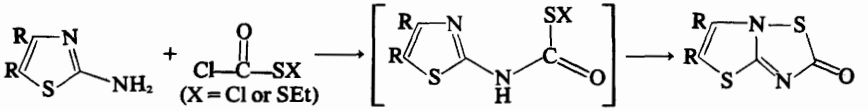
10 Condensed Systems incorporating 1,2,4-Thiadiazoles

A general synthetic route to N-bridgehead condensed heterocyclic structures incorporating a 1,2,4-thiadiazole ring consists of the interaction of an α-amino-heterocyclic compound with chlorothioformyl chloride (84) or ethyldithiocarbonyl chloride (85). The reaction is widely applicable, as shown.



(84) X = Cl
(85) X = SEt

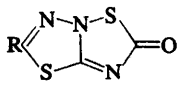
2-Aminothiazoles (86) react with chlorothioformyl chloride (84) to give tars, from which 2*H*-thiazolo[3,2-*b*][1,2,4]thiadiazol-2-one (87) is isolable in 3% yield; the use of ethyldithiocarbonyl chloride (85) raises the yields to 25%.[57]



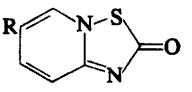
(86) (87)

More favourable results are obtained in analogous syntheses, which afford the following types of compounds: 6*H*-[1,3,4]thiadiazolo[3,2-*b*]-[1,2,4]thiadiazol-6-ones (10—53%) (88); 2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyridin-2-ones (48%) (89); 2*H*-[1,2,4]thiadiazolo[2,3-*b*]pyridazin-2-ones (90), and 5,6-dihydro-2*H*-[1,2,4]thiadiazolo[3,2-*b*]thiazin-2-one (91). The i.r. spectra

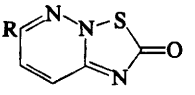
[57] K. Pilgram and R. D. Skiles, *J. Org. Chem.*, 1973, **38**, 1575.



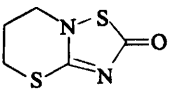
(88)



(89)



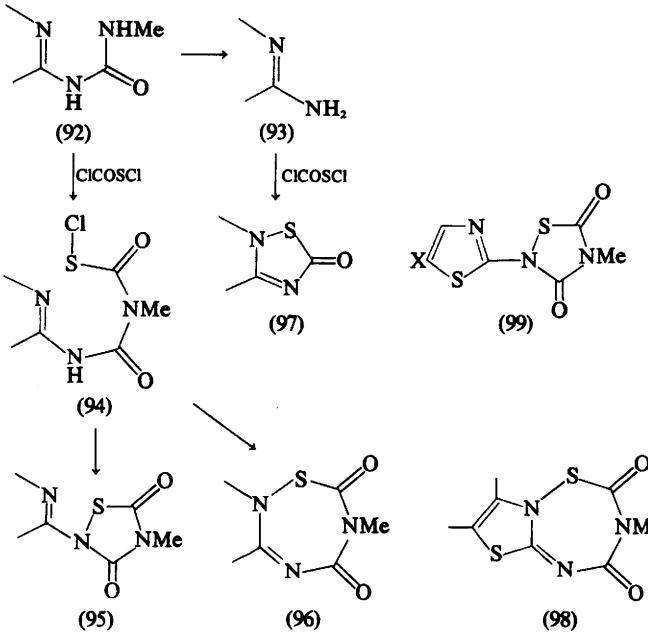
(90)



(91)

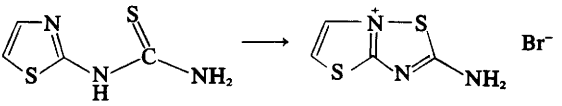
of all these condensed heterocycles include a carbonyl band at 1700 cm^{-1}, and one due to the —C=N grouping in the 1640—1670 cm^{-1} range.[57]

The interaction of chlorothioformyl chloride and comparable heterocyclic methylureas (92) proceeds partly with identical results. Loss of methyl isocyanate from (92) yields the parent amine (93) and thence the condensed bicyclic products (97), as described immediately above. Simultaneous direct condensation of the urea (92) affords, by way of the hypothetical intermediate (94), the fused thiatriazepinediones (96) as well as 1,2,4-thiadiazolidinediones (95), generally in moderate yields. The observations on record are too varied to be adequately summarized; examples of the structures obtained are 2*H*-thiazolo[3,2-*b*][1,2,4,6]thiatriazepine-2,4(3*H*)-diones (98) and 2-(thiazol-2-yl)-4-methyl-1,2,4-thiadiazolidine-3,5-diones (99).[58]

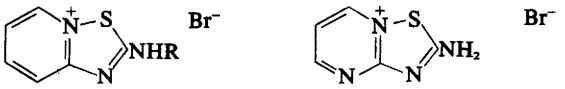


[58] K. Pilgram and R. D. Skiles, *J. Org. Chem.*, 1973, **38**, 1578.

Representatives of the 1,2,4-thiadiazolo[3,2-*b*]thiazole (101),[59] 1,2,4-thiadiazolo[2,3-*a*]pyridine (102),[59,60] and 1,2,4-thiadiazolo[2,3-*a*]pyrimidine (103)[59] ring-system are accessible in high yield by the action of bromine in chloroform on the appropriate heterocyclic thiourea, *e.g.* (100).[59]

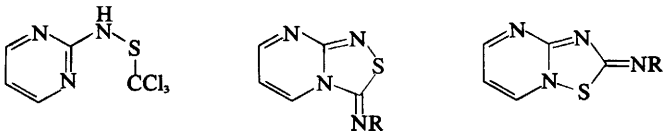


(100) (101)



(102) (103)

2-(Trichloromethylthioamino)pyrimidine (104), obtainable from 2-aminopyrimidine and trichloromethanethiol,[61] reacts with a variety of primary aryl amines in chloroform, giving moderate yields of the 3*H*-[1,2,4]-thiadiazolo[4,3-*a*]pyrimidine derivatives (105). The alternative possible formulation (106) was excluded on the basis of spectral data.



(104) (105) (106)

The same approach gave members of the following ring systems: 3*H*-[1,2,4]thiadiazolo[4,3-*c*]pyrimidines (from 4-aminopyrimidine); 3*H*-[1,2,4]-thiadiazolo[4,3-*a*]pyrazine (from 2-aminopyrazine); 3*H*-[1,2,4]thiadiazolo-[4,3-*b*]pyridazine (from 2-amino-6-chloropyridazine).[62]

11 Synthesis of 1,3,4-Thiadiazoles

The great majority of new 1,3,4-thiadiazoles have been produced by well-tried routes. These include known cyclizations of compounds related

[59] G. Barnikow and J. Bödeker, *J. prakt. Chem.*, 1971, **313**, 1148.
[60] R. L. N. Harris, *Austral. J. Chem.*, 1972, **25**, 993.
[61] J. Goerdeler and E. R. Erbach, *Chem. Ber.*, 1962, **95**, 1637.
[62] K. T. Potts and J. Kane, *J. Org. Chem.*, 1973, **38**, 3087.

Table 1 *Production of* 1,3,4-*thiadiazoles by conventional cyclizations*

Type of Compound	*Reference*
2,5-Diaryl-1,3,4-thiadiazoles	46, 63, 64
2-Mercapto-5-(pyrazin-2-yl)-1,3,4-thiadiazoles	65
2-Alkoxy(or alkylthio)-5-chloromethyl-1,3,4-thiadiazoles	66
2-Alkoxy(or alkylthio)-1,3,4-thiadiazol-5-(3*H*)-ones (and -thiones)	67, 68
2-Amino-5-vinyl-1,3,4-thiadiazoles	69
2-Substituted 5-(3,3-diphenylpropylamino)-1,3,4-thiadiazoles	70
5-Phenylamino-2-[ethyl-2'-(phenothiazin-10-yl)]-1,3,4-thiadiazole	71
2-Aryl-5-(*p*-fluorophenylsulphonyl)phenyl-1,3,4-thiadiazoles	72
2-Amino-5-(arylsulphonyl)phenyl-1,3,4-thiadiazoles	73

to thiosemicarbazides, dithiocarbazates, *etc.* (see Table 1[63–73]), and conventional methods that modify substituents in the pre-formed ring-system (see Table 2[74–81]).

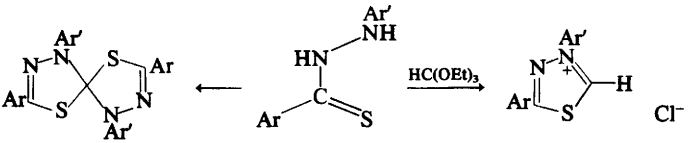
A series of 2,4-diaryl-1,3,4-thiadiazolium salts (108) have been synthesized by the condensation of thiobenzoylphenylhydrazine hydrochloride and triethyl orthoformate in ether at 0 °C, for a study of the influence of the 2- and 4-substituents on the acidity of the hetero-proton by deuterium exchange. At 90 °C, the free hydrazine base (107) reacts differently, and produces the spiro-compound (109) as the main product.[82]

An improvement is effected in the synthesis of 5-unsubstituted

[63] A. M. Barghash, A. M. M. E. Omar, A. M. Farghaly, and M. S. Ragab, *Pharmazie*, 1973, **28**, 407.
[64] L. M. Shegal and I. L. Shegal, *Khim. geterotsikl. Soedinenii*, 1970, 1330 (*Chem. Abs.*, 1971, **75**, 5777).
[65] V. Ambrogi, K. Bloch, S. Daturi, W. Logemann, and M. A. Parenti, *J. Pharm. Sci.*, 1972, **61**, 1483.
[66] K. Rufenacht, *Helv. Chim. Acta*, 1972, **55**, 1979.
[67] K. Rufenacht, *Helv. Chim. Acta*, 1972, **55**, 1178.
[68] K. Rufenacht, *Helv. Chim. Acta*, 1972, **55**, 1187.
[69] I. Hirao and Y. Kato, *Bull. Chem. Soc. Japan*, 1971, **44**, 3136.
[70] K. Harsanyi, D. Korbonits, and P. Kiss, *Magyar Kém. Folyóirat*, 1973, **79**, 109.
[71] B. Albrecht and H. Brauniger, *Pharmazie*, 1972, **27**, 282.
[72] C. Demetrescu, *Rev. Roumaine Chim.*, 1972, **17**, 1013.
[73] C. Demetrescu and V. Manu, *Pharmazie*, 1972, **27**, 439.
[74] S. Giri and H. Singh, *J. Indian Chem. Soc.*, 1972, **49**, 175.
[75] G. Asato and G. Berkelhammer, *J. Medicin. Chem.*, 1972, **15**, 1086.
[76] G. H. Hamor and F. Rubessa, *J. Medicin. Chem.*, 1972, **15**, 470.
[77] A. M. Grant, S. V. Krees, A. B. Mauger, W. J. Rzeszotarski, and F. W. Wolff, *J. Medicin. Chem.*, 1972, **15**, 1082.
[78] S. Minami, M. Tomita, and K. Kawaguchi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1716.
[79] M. D. Aptekar, E. P. Trailina, L. K. Gulchenko, and I. A. Savich, *Khim. Farm. Zhur.*, 1972, **6**, 19 (*Chem. Abs.*, 1973, **78**, 38 507).
[80] T. N. Nikulina, V. S. Onoprienko, K. S. Bushueva, and V. A. Zasosov, *Khim. Farm. Zhur.* 1971, **5**, 32 (*Chem. Abs.*, 1972, **76**, 25 191v).
[81] P. J. Islip and M. R. Johnson, *J. Medicin. Chem.*, 1973, **16**, 1308.
[82] G. Scherowsky, *Tetrahedron Letters*, 1971, 4985.

Table 2 *Production of 1,3,4-thiadiazoles from the pre-formed ring-system*

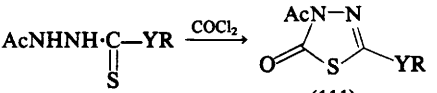
Type of Compound	*Reference*
2-Alkylthio-1,3,4-thiadiazole-5(4*H*)-thiones	67
3-(5-Substituted-1,3,4-thiadiazol-2-yl)-4-quinazolones	74
2-Amino-5-(1-methyl-2-nitro-5-imidazolyl)-1,3,4-thiadiazole	75
2-Anilino-5-(amino-oxy)methyl-1,3,4-thiadiazole	76
Substituted 2-acylamino-1,3,4-thiadiazoles	77
1,3,4-Thiadiazol-2-yl-β-mercaptocinnamamides	78
N-(2-Anilino-1,3,4-thiadiazol-5-ylmethoxy)phthalimide	76
N^1-(1,3,4-Thiadiazol-2-yl)-N^4-benzylidenesulphanilamides	79
2-*p*-Aminobenzenesulphonamido-5-ethyl-1,3,4-thiadiazole ('Ethasol')	80
2-(5-Nitro-2-furyl)-5-ureido-1,3,4-thiadiazoles	81



(109) (107) (108)

2-alkylamino-1,3,4-thiadiazoles by the condensation of 4-alkylthiosemicarbazides and orthoformate esters by the addition of a little mineral acid; this suppresses the parallel formation of the isomeric 4-alkyl-1,2,4-triazoline-3-thiones that are otherwise invariably formed.[83]

The synthesis of 1,3,4-thiadiazolinones from dithiocarbazic esters and phosgene [(110) → (111; Ac = H)] is applicable to 3-acylated thio- and



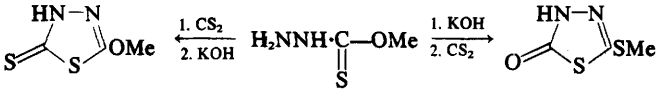
(110) (111)

dithio-carbazic esters (110), in spite of their enhanced acidic properties and their lack of a free amino-group. Reaction occurs spontaneously, even in the absence of acid-binding reagents, to afford a wide range of 3-acyl-5-alkoxy-(or alkylthio)-Δ^4-1,3,4-thiadiazolin-2-ones, including examples incorporating variously substituted phosphoric acid residues [111; Y = O or S; Ac = PhCO, $PhSO_2$, EtO_2C, Me_2NCO, or $(R^1O)R^2PX$].[84]

The synthesis of 5-methoxy-1,3,4-thiadiazole-2(3*H*)-thione (114) by the successive treatment of *O*-methyl thiocarbazate (112) with carbon disulphide and alkali proceeds normally. However, addition of the reagents in the inverse order results in the isomeric 5-methylthio-compound (113) by a transmethylation process, for which a possible mechanism was proposed.[67]

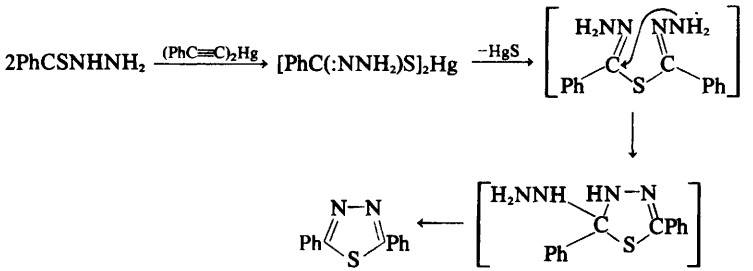
Thiobenzoylhydrazine reacts with mercury bis(phenylacetylide) to yield the labile mercaptide, which cyclizes in boiling chloroform with the

[83] R. A. Coburn, B. Bhoosan, and R. A. Glennon, *J. Org. Chem.*, 1973, **38**, 3947.
[84] K. Rufenacht, *Helv. Chim. Acta*, 1973, **56**, 162.



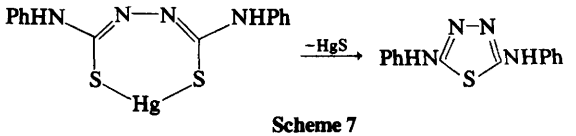
(114) (112) (113)

elimination of mercuric sulphide, to give 2,5-diphenyl-1,3,4-thiadiazole (*ca.* 40%), together with 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine (Scheme 6).



Scheme 6

Pyrolysis of the mercaptide derived from diphenylbithiourea similarly affords 2,5-di(anilino)-1,3,4-thiadiazole (71%) as shown in Scheme 7.[85]



Scheme 7

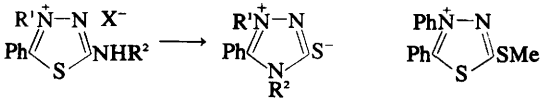
12 Properties of 1,3,4-Thiadiazoles

The n.m.r. spectra of a series of 2-amino-1,3,4-thiadiazoles have been compared with those of the selena-analogues. The dependence of the chemical shifts of the NH protons on temperature and concentration reflects their participation in intermolecular hydrogen-bonding.[86]

The quaternization by methyl iodide of a series of 2-alkyl-5-methyl-1,3,4-thiadiazoles has been studied quantitatively by a spectrometric method.[87] The product distribution due to quaternization at N-3 and N-4 in a series of 2,5-disubstituted 1,3,4-thiadiazoles has been determined. The observed influence of alkyl substituents on product distribution is almost the same as in comparable thiazoles, but is less pronounced than in the pyridazine series, probably owing to differences in the geometry of their respective transition states.[88]

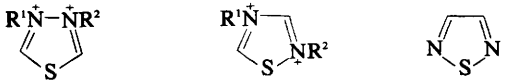
[85] W. Ried and R. Oxenius, *Chem. Ber.*, 1973, **106**, 484.
[86] U. Svanholm, *Acta Chem. Scand.*, 1972, **26**, 459.
[87] R. Gallo, M. Chanon, H. Lund, and J. Metzger, *Tetrahedron Letters*, 1972, 3857.
[88] H. Lund, *Acta Chem. Scand.*, 1973, **27**, 391.

In the course of their work on meso-ionic five-membered heterocyclic systems, Grashey *et al.*[89] described the production, by several routes, of 2-amino-1,3,4-thiadiazolium salts (115), and their ready conversion, by alkalis, into the meso-ionic 1,2,4-triazole-3-thiones (116) (see also these Reports, Vol. 2, p. 746, ref. 105). It probably occurs by deprotonation of (115), attack by the nucleophile at position 5, followed by ring-cleavage and recyclization to (116).[89] Transformations involving 2-mercapto-analogues (117) have been described and their mechanism discussed.[90]



(115) (116) (117)

While diaza-heteroaromatic compounds (*e.g.* pyrimidines, diazoles) can, in principle, form diquaternary salts without loss of aromaticity, the introduction of the second alkyl group is difficult, undoubtedly because of the reduction in nucleophilicity of the second ring-nitrogen resulting from the quaternization of the first. Diquaternary salts of thiadiazoles of type (118) and (119), and of other diazoles, have been prepared for the first time by using more effective alkylating agents, *viz.* trialkyloxonium salts. The ease with which the reaction occurs is subject to steric influences; specially favourable results are obtained by fusing the bases with trimethyloxonium tetraborates. However, 1,2,5-thiadiazole (120) has so far failed to undergo diquaternization. The proposed structures are supported by a combination of spectroscopic and chemical data.[91]



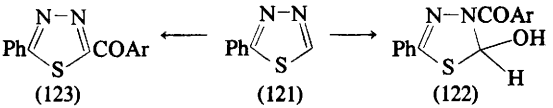
(118) (119) (120)

The (exocyclic) acetylation of 2-amino-1,3,4-thiadiazole and its 5-ethyl homologue by boiling acetic acid is greatly accelerated by the catalytic influence of diketen. A suggested general mechanism of this catalyst action is given in the appropriate section on 2-aminothiazoles (this volume, Chap. 13, p. 574).[92]

Treatment of 2-phenyl-1,3,4-thiadiazole (121) with aroyl achlorides in aqueous sodium carbonate, bicarbonate, or cyanide has been claimed to yield 4-aroyl-5-hydroxy-2-phenyl-Δ^2-1,3,4-thiadiazolines (122).[93] Analogous pseudobases derived from benzimidazole and dihydroisoquinoline have

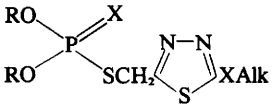
[89] R. Grashey, M. Baumann, and R. Hamprecht, *Tetrahedron Letters*, 1972, 2939.
[90] P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *Indian J. Chem.*, 1973, **11**, 753.
[91] T. J. Curphey and K. S. Prasad, *J. Org. Chem.*, 1972, **37**, 2259.
[92] F. I. Luknitskii, *Zhur. org. Khim.*, 1971, **7**, 1247.
[93] A. Alemagna and T. Bacchetti, *Gazzetta*, 1972, **102**, 1068, 1077, 1084.

been described, in which electron-withdrawing groups stabilize the C—OH bond by enhancing its covalent character.[94] The products, exemplified by (122; Ar = Ph), are reconverted into the starting materials hydrolytically and pyrolytically, and yield chiefly 2,5-diphenyl-1,3,4-thiadiazole in alkaline media. The action of carbodi-imide produces the corresponding ether. In contrast, the prolonged action of acyl halides on (121) at 190—200 °C effects *C*-acylation, yielding chiefly (123). The possible mechanism of these reactions was discussed.[93]



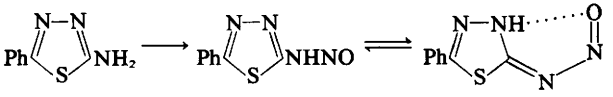
(123) (121) (122)

2-Substituted 5-chloromethyl-1,3,4-thiadiazoles react readily with salts of thio- and dithio-phosphoric acids to form *OO*-dialkyl-*S*-[(2-substituted 1,3,4-thiadiazol-5-yl)methyl]thio- and dithio-phosphates (124); they are oils, often decomposing on attempted distillation.[66]

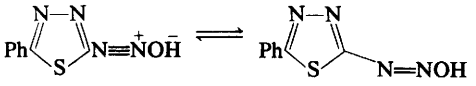


(124) X = O or S

Heterocyclic amines containing a C=N system adjacent to the amino-group, but lacking labile hydrogen atoms, yield stable primary nitrosamines on treatment with nitrous acid. 2-Amino-5-phenyl-1,3,4-thiadiazole conforms to this generalization.[95] Chemical and spectral data suggest that the predominant tautomeric forms of the possible alternatives (126)—(129) are (126) and (129). Stabilization by hydrogen bonding [as in (127)], though an attractive explanation for the stability of the products, is not borne out by the experimental observations. The action of boiling benzene causes homolytic displacement of the nitrosamino-group, with formation of 2,5-diphenyl-1,3,4-thiadiazole; it is regarded as an example of a



(125) (126) (127)



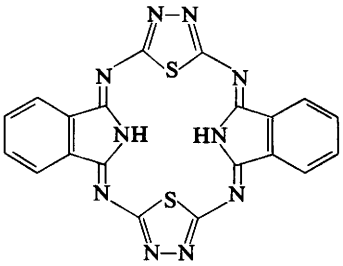
(128) (129)

[94] D. Beke in 'Advances in Heterocyclic Chemistry', ed. A. R. Katritzky, Academic Press, New York, 1963, Vol. 1., p. 167.

[95] R. N. Butler, T. M. Lambe, J. C. Tobin, and F. L. Scott, *J.C.S. Perkin I*, 1973, 1357.

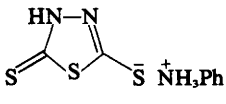
Gomberg–Bachman process, involving the initial homolysis of the diazohydroxide form (129) into $R^{\cdot}$, N_2, and $OH^{\cdot}$.[95]

The symmetrical macroheterocyclic product (130) is formed (81%) by condensing 2,5-diamino-1,3,4-thiadiazole and phthalonitrile in ethylene glycol at 120 °C.[96]

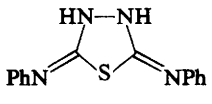


(130)

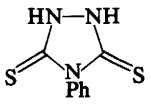
2,5-Dithiono-1,3,4-thiadiazolidine reacts with equimolar quantities of arylamines at 100—160 °C to yield amine salts (131); at higher temperatures (180 °C), five main products (132)—(136) are formed, with loss of hydrogen sulphide (see these Reports, Vol. 2, p. 740).[97]



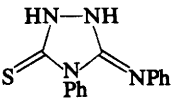
(131)



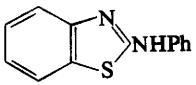
(132)



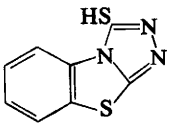
(133)



(134)



(135)



(136)

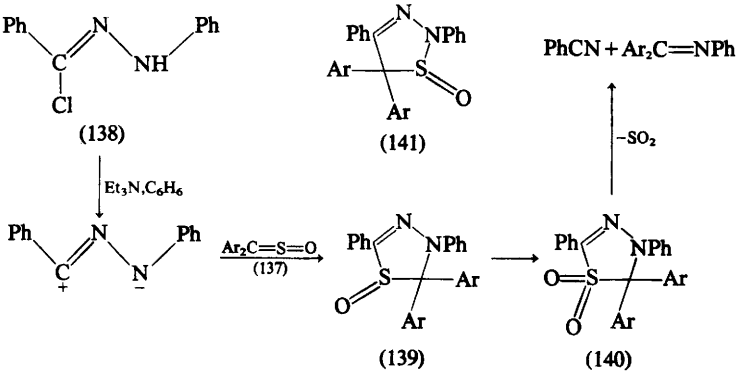
The ring-scission of 1,3,4-thiadiazoles, at their N—N bond, in alkaline media, has been examined and discussed. 2-Phenyl-1,3,4-thiadiazole, for example, produces benzonitrile and thiocyanate ions in high yield.[98]

The binding of 2-acetamido-5-*N*-(bromoacetyl)sulphonamido-1,3,4-thiadiazole ('*N*-Bromoacetyl-Acetazolamide') at histidine sites in human carbonic anhydrase B has been studied by the use of the *acetyl*-^{14}C-labelled drug. The results suggest that the histidine sites reacting with this compound are possibly also concerned in the catalytic action of the enzyme.[99]

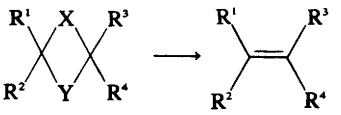
[96] V. F. Borodkin and N. A. Kolesnikov, *Khim. geterotsikl. Soedinenii*, 1971, 194 (*Chem. Abs.*, 1971, **75**, 35 981w).
[97] M. V. Konher, *Indian J. Chem.*, 1973, **11**, 321.
[98] A. Alemagna, T. Bacchetti, and C. Rizzi, *Gazzetta*, 1972, **102**, 311.
[99] S. C. C. Wong, S. I. Kandel, M. Kandel, and A. G. Gornall, *J. Biol. Chem.*, 1972, **247**, 3810.

Δ^2-1,3,4-Thiadiazolines.—The cycloaddition of aromatic sulphines to nitrilimines is a regiospecific non-stereospecific reaction resulting in the formation of Δ^2-1,3,4-thiadiazoline derivatives. Interaction of the sulphines (137) and diphenylnitrilimine [generated *in situ* by the action of triethylamine on *N*-α-chlorobenzylidene-*N'*-phenylhydrazine (138) in boiling benzene] gave uniform 1:1 adducts that were identified as the Δ^2-1,3,4-thiadiazoline *S*-oxides (139), the alternative 1,2,3-thiadiazoline structure (141) being conclusively eliminated on the basis of chemical and spectroscopic evidence. The non-stereospecific nature of the reaction was demonstrated and its significance discussed.[100]

The *S*-oxides (139) are readily oxidized to the sulphones (140), which are in turn pyrolysed with loss of sulphur dioxide as shown. This twofold extrusion-process confirms the sites of bond-formation in the original cycloaddition.[100]



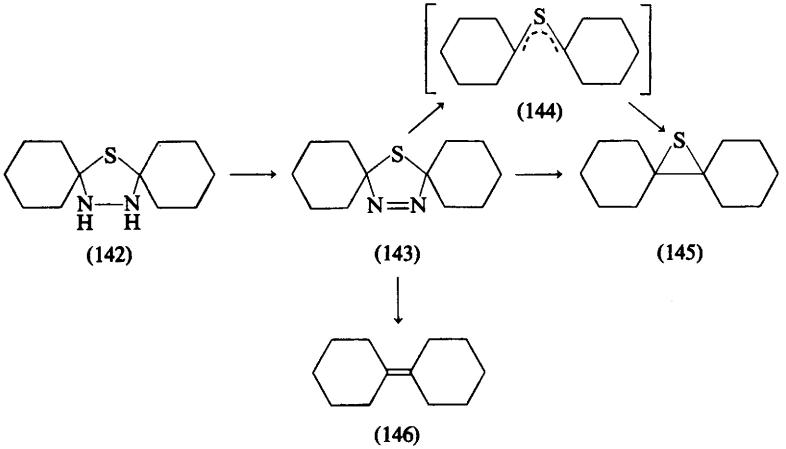
Δ^3-1,3,4-Thiadiazolines.—A novel synthesis of highly hindered olefins is based on the principle of a two-fold extrusion process (Scheme 8).[101,102]



Scheme 8

1,3,4-Thiadiazolidine derivatives, amongst other structures, have proved suitable as starting materials for this purpose. Thus, the azo-sulphide (143), accessible by the oxidation of the spirane (142), is converted into the thiiran (145) at 100 °C, but it affords high yields of the bis-cyclohexylidene (146) on thermolysis in the presence of triphenylphosphine. The required

[100] B. F. Bonini, G. Maccagnani, L. Thijs, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3569.
[101] D. H. R. Barton and B. J. Willis, *Chem. Comm.*, 1970, 1225; D. H. R. Barton, E. H. Smith, and B. J. Willis, *ibid.* p. 1226, D. H. R. Barton and B. J. Willis, *J.C.S. Perkin I*, 1972, 305.
[102] R. M. Kellogg and S. Wassenaar, *Tetrahedron Letters*, 1970, 1987.



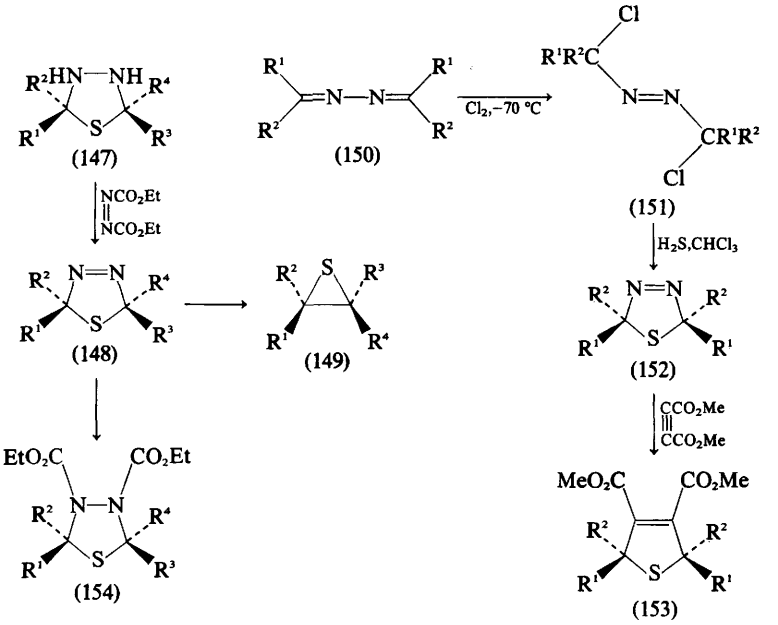
thiadiazolidine (142) is obtainable by treatment of cyclohexanone with hydrazine and hydrogen sulphide, or from cyclohexanone azine by the action of hydrogen sulphide.[101,102] The method has been applied to the synthesis of bicyclobutylidene.[103]

In a comprehensive investigation[104] concerned with thiocarbonyl ylides, Δ^3-1,3,4-thiadiazolines (148) have served as precursors of this type of structure, and their synthesis has therefore been studied in further detail (see also these Reports, Vol. 1, p. 449). They are accessible by dehydrogenation of the corresponding 1,3,4-thiadiazolidines [(147) → (148)], using diethyl azodicarboxylate as the hydrogen acceptor. A more generally applicable route is the action of hydrogen sulphide on the addition products (151) of chlorine and azines (150). This synthesis of (152) deliberately avoids the unstable thiadiazolidine stage by the 'dehydrogenation' of the azine *before* ring-closure.[104]

The pyrolytic conversion of 2,2,5,5-bis(pentamethylene)-Δ^3-1,3,4-thiadiazoline (143) into the episulphide (145) proceeds, according to kinetic evidence, *via* the primarily formed ylide (144). Detailed observations, made with *cis*- and *trans*-2,5-diethyl (and di-t-butyl)-Δ^3-1,3,4-thiadiazoline (148), show that the process proceeds sterically, in agreement with orbital-symmetry considerations, by conrotatory ring-closure [to (149)].

The Δ^3-1,3,4-thiadiazolidines (148) undergo cycloaddition with diethyl azodicarboxylate stereospecifically, forming 2,5-dialkyl-3,4-diethoxycarbonyl-1,3,4-thiadiazolidines (154) with complete retention of configuration. The comparable stereospecific cycloaddition involving dimethyl acetylenedicarboxylate, (152) → (153), yields the corresponding 2,5-dihydrothiophens.[104]

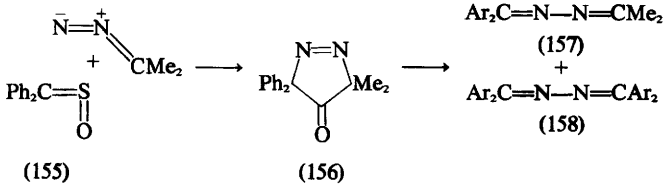
[103] J. W. Everett and P. J. Garratt, *J.C.S. Chem. Comm.*, 1972, 642.
[104] J. Butler, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, 1972, **37**, 4045.



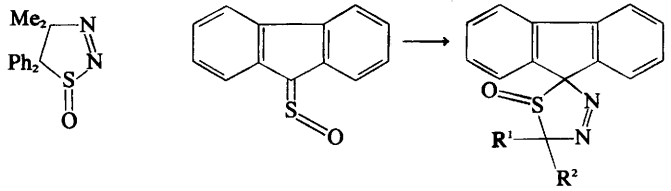
The cycloaddition of 2-diazoalkanes to aromatic sulphines (thione *S*-oxides), readily accessible by peroxy-acid oxidation of thienes,[105] provides yet another efficient route to Δ^3-1,3,4-thiadiazolines (156). Thiobenzophenone *S*-oxide (155) and 2-diazopropane, for example, afford 2,2-dimethyl-5,5-diphenyl-1,3,4-thiadiazoline 1-oxide (156). Photolysis to the azines (157) and (158) establishes the orientation of the cycloaddition, and excludes the alternative formulation (159).[106] Thiofluorenone *S*-oxide (160) similarly yields spiro-compounds of type (161).[106,107]

The steric course of this cycloaddition has been studied[108] by an examination of the interaction of 2-diazopropane with the geometrical isomers of sulphines in ether at −20 °C. In all examples, each of the geometrical isomers yields a single distinct product. The sum of the observations shows that the spatial arrangement of the S=O group and the substituents R^1 and R^2 is retained in the product. The cycloaddition is therefore a stereospecific process, involving most probably a concerted process in the formation of product. The presence of bulky substituents in *either* of the reactants sterically hinders the cycloaddition to the five-membered ring-system, and favours alternative reaction paths, of which the

[105] B. Zwanenburg, L. Thijs, and J. Strating, *Rec. Trav. chim.*, 1967, **86**, 577.
[106] B. F. Bonini, G. Maccagnani, A. Wagenaar, L. Thijs, and B. Zwanenburg, *J.C.S. Perkin I*, 1972, 2490.
[107] C. G. Venier and C. G. Gibbs, *Tetrahedron Letters*, 1972, 2293.
[108] L. Thijs, A. Wagenaar, E. M. M. van Rens, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3589.

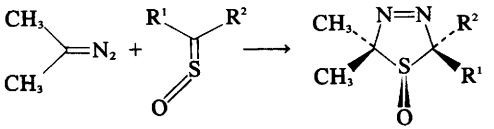


(155) (156) (157) + (158)



(159) (160) (161)

non-stereospecific formation of episulphoxides (Scheme 9) is the most interesting example.[108]



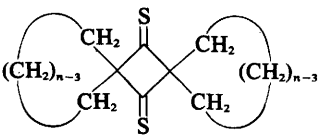
Scheme 9

Analogous observations concerning bis-Δ^3-1,3,4-thiadiazolines are also on record.[109] Thus, treatment of tetramethylcyclobutane-1,3-dithione (162), dispiro[4,1,4,1]dodecane-6,12-dithione (163; $n = 5$), and dispiro[5,1,5,1]-tetradecane-7,14-dithione (163; $n = 6$) with diazomethane at 0 °C immediately discharges their red colour, to produce near-quantitative yields of bis-adducts, formulated as stereoisomeric bis-Δ^3-1,3,4-thiadiazolines (164) and (165; $n = 5$ or 6). They are reasonably stable, but gradually change, with loss of nitrogen, to stereoisomeric mixtures of the diepisulphides. The conversion of adamantanethione into (166) and (167) was also mentioned.[109]

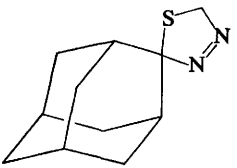
Δ^3-1,3,4-Thiadiazoline-2,5-dione (169), obtained by the oxidation of (168) with lead tetra-acetate at −78 °C, is a highly reactive dienophile. By performing the oxidation in the presence of a 1,3-diene, good yields of Diels–Alder products (170) are obtained. Alkaline hydrolysis of (170; $R^1 + R^2 = CH_2CH_2$; $R^3 = R^4 = H$) gives cyclohexadiene and nitrogen, while catalytic hydrogenation produces the dihydro-derivative (171).[110]

[109] A. P. Krapcho, D. R. Rao, M. P. Silvon, and B. Abegaz, *J. Org. Chem.*, 1971, **36**, 3885.
[110] E. J. Corey and B. B. Snider, *J. Org. Chem.*, 1973, **38**, 3632.

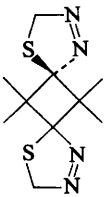
(162)



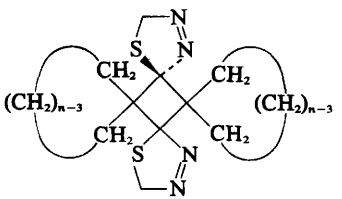
(163)



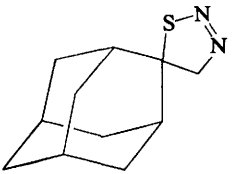
(166)



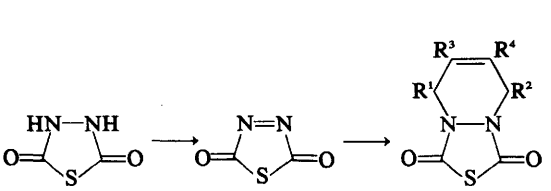
(164)



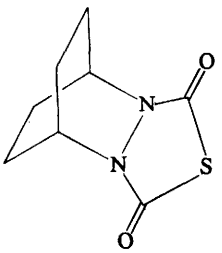
(165)



(167)



(168) (169) (170)

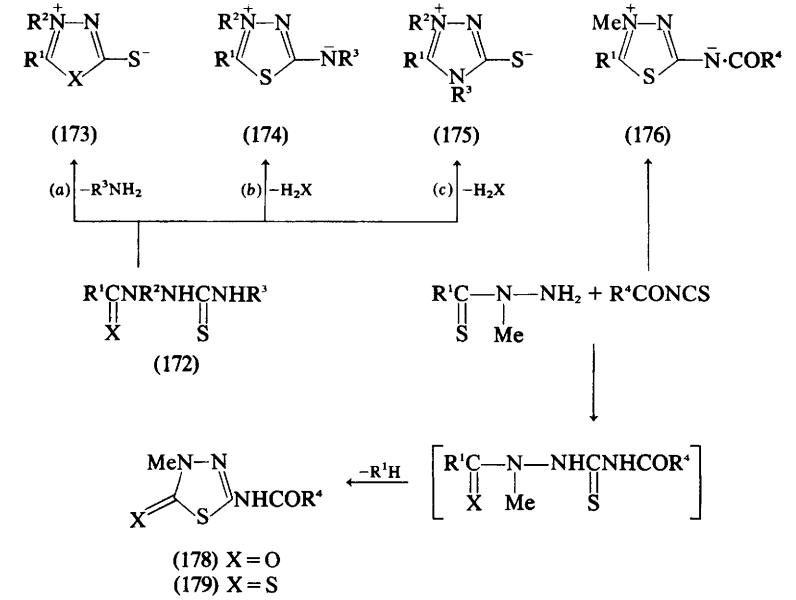


(171)

Meso-ionic 1,3,4-Thiadiazoles.—It is well known that acylated thiosemicarbazides are readily cyclizable to five-membered heterocycles, especially oxadiazoles, thiadiazoles, and triazoles. Reactants (172) incorporating at N-1 an additional firmly held substituent react analogously, but give rise to the corresponding meso-ionic heterocycles (173)—(176).

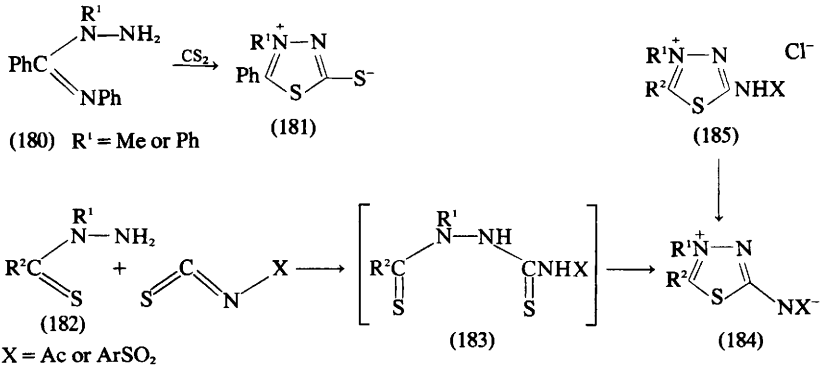
Thus, *N*-methyl-*N*-thiobenzhydrazide reacts with isothiocyanate esters in alkaline media to produce moderate yields of meso-ionic 2-mercapto-1,3,4-thiadiazoles, *e.g.* (173; R^1 = Ph, R^2 = Me), directly. Acyl isothiocyanates similarly furnish the meso-ionic 2-acylamino-1,3,4-thiadiazoles (176) smoothly in excellent yields. Intermediate acylthiosemicarbazides (177) containing a readily eliminated group R^1 (*e.g.* Me_2N, PhO) cyclize differently: nucleophilic attack of the thiono-sulphur at the acyl group occurs initially as in reaction path (*b*), but proceeds with loss of RH instead of H_2X, resulting in 1,3,4-thiadiazolin-2-ones (178) or -2-thiones (179), instead of meso-ionic products.[111]

[111] P. Thieme, M. Patsch, and H. König, *Annalen*, 1972, **764**, 94.



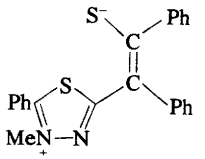
The action of carbon disulphide on substituted amidrazones (180) furnishes the meso-ionic 1,3,4-thiadiazole-2-thiones (181) nearly quantitatively.[89] Substituted thioacylhydrazides (182) react with acyl or arylsulphonyl isothiocyanates, yielding stable crystalline meso-ionic 1,3,4-thiadiazole-imines (184), also formed by the deprotonation of (185).[112]

The acetylation of 1,4-diphenylthiosemicarbazide has been carefully reinvestigated, and the controversial structures of the products have been established as 5-methyl-4-phenyl-2-anilino-1,3,4-thiadiazolium chloride and meso-ionic 1,4-diphenyl-1,2,4-triazole-3-thione.[113]



[112] R. Grashey, R. Hamprecht, N. Keramaris, and M. Baumann, *Tetrahedron Letters*, 1972, 2943.
[113] R. Grashey and M. Baumann, *Tetrahedron Letters*, 1972, 2947.

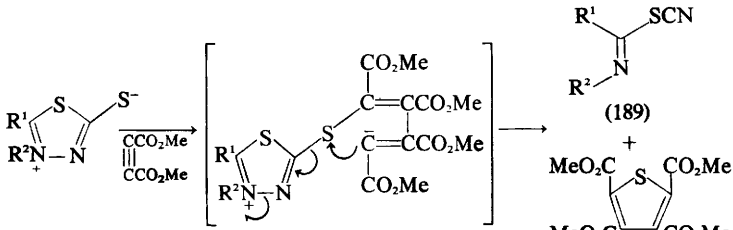
The meso-ionic 1,3,4-thiadiazole (186) arises from 1-thiobenzoyl-1-methylhydrazine and carboxymethyl benzyldithioate (*cf.* these Reports,



(186)

Vol. 2, p. 749). Its structure is confirmed by *X*-ray analysis, which shows the two sulphur atoms to be arranged in *syn*-configuration with respect to each other.[114]

Meso-ionic 1,3,4-thiadiazoles (187) condense with dimethyl acetylenedicarboxylate in boiling benzene, forming *S*-cyanothioimidates (189) and the thiophen derivative (190) in 50 and 30% yield, possibly by way of the hypothetical intermediates (188).[115]



(187) (188) (189) (190)

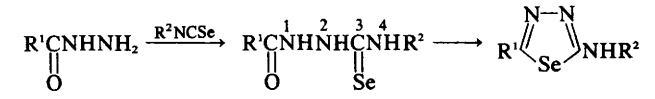
13 Synthesis and Properties of 1,3,4-Selenadiazoles

Examples of well-established 1,3,4-thiadiazole syntheses have been extended to the production and study of their selenium analogues.[116,117] 1,4-Disubstituted selenosemicarbazides (191; R^2 = Alk, Ar, or Ac) are readily accessible in good yield by the addition of isoselenocyanate esters (including benzoyl isoselenocyanate) to acylhydrazines.[116] Their cyclization in acidic media affords the stable crystalline 1,3,4-selenadiazoles (192; R^2 = Alk, Ar, or Ac);[117] the members of the aroylamino-series are stable to alkalis, but are hydrolysable by acids to the parent amines (192; R^2 = H); these are convertible into conventional derivatives, as expected.[117]

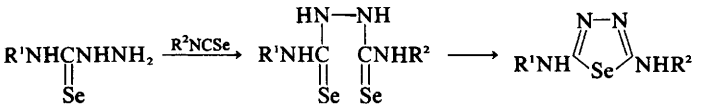
Bis-selenoureas of type (194) are similarly accessible, but usually cyclize spontaneously to the substituted 2,5-dianilino-1,3,4-selenadiazoles (195). The action of acetic anhydride on (194) yields diacetyl derivatives of (195)

[114] R. M. Moriarty, R. Mukherjee, J. L. Flippen, and J. Karle, *Chem. Comm.*, 1971, 1436.
[115] R. M. Moriarty and A. Chin, *J.C.S. Chem. Comm.*, 1972, 1300.
[116] E. Bulka and D. Ehlers, *J. prakt. Chem.*, 1973, **315**, 155.
[117] E. Bulka, D. Ehlers, and H. Storm, *J. prakt. Chem.*, 1973, **315**, 164.

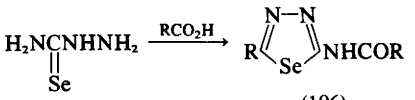
directly.[116] Yet another variation of this synthesis involves the condensation of selenosemicarbazide with carboxylic acids, yielding (196).[118,119]



(191) (192)



(193) (194) (195)



(196)

The n.m.r. spectra of a series of 2-amino-1,3,4-selenadiazoles have been studied and compared with those of the corresponding sulphur heterocycles.[86]

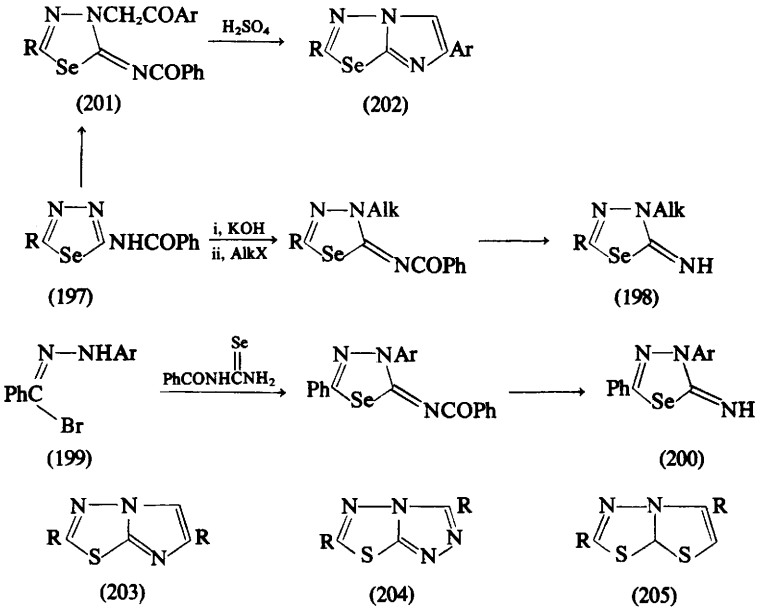
Alkylation of 2-benzamido-1,3,4-selenadiazoles (197) occurs on their ring-nitrogen, yielding, after prolonged acid hydrolysis, 3-alkyl-2-imino-2,3-dihydro-1,3,4-selenadiazoles (198).[120] The behaviour of the selenium compounds thus resembles that of their sulphur analogues, but differs from that of 2-acylamino-1,3,4-oxadiazoles, which are alkylated at their exocyclic nitrogen. 3-Aryl derivatives (200), which are not accessible by this method, are formed by the condensation of α-halogenated aldehyde hydrazones (199) with selenoureas (or semicarbazides) as shown (compare ref. 121).[120]

Successive treatment of (197) with ω-halogenoacetophenone, and cyclization by 60% sulphuric acid, produces the substituted imidazo[2,1-*b*][1,3,4]-selenadiazoles (202).[118,120]

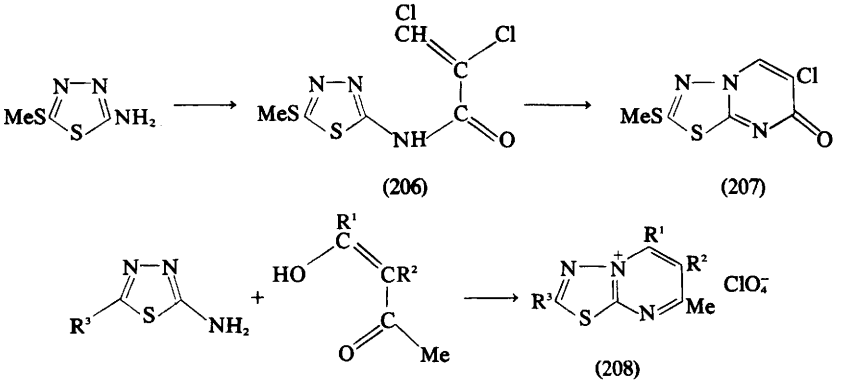
14 Condensed 1,3,4-Thiadiazoles

Members of the imidazo[2,1-*b*]- (203),[122,123] *sym*-triazolo[3,4-*b*]- (204),[124] and thiazolo[2,3-*b*]-1,3,4-thiadiazole (205)[125,126] ring systems have been produced by variations of conventional syntheses.

[118] I. Lalezari and A. Shafiee, *J. Heterocyclic Chem.*, 1971, **8**, 835.
[119] A. Shafiee, I. Lalezari, S. Yazdany, and A. Pournorouz, *J. Pharm. Sci.*, 1973, **62**, 839.
[120] E. Bulka and D. Ehlers, *J. prakt. Chem.*, 1973, **315**, 510.
[121] R. Fusco and C. Musante, *Gazzetta*, 1938, **68**, 665.
[122] S. Kano, *Yakugaku Zasshi*, 1972, **92**, 935.
[123] V. P. Arya, F. Fernandes, and V. Sudarsanam, *Indian J. Chem.*, 1972, **10**, 598.
[124] H. Golgolab, I. Lalezari, and L. Hosseini-Gohari, *J. Heterocyclic Chem.*, 1973, **10**, 387.
[125] M. M. Kochhar, M. Salahi-Asbahi, and B. B. Williams, *J. Pharm. Sci.*, 1973, **62**, 336.
[126] U. Askani, R. Neidlein, and J. Tauber, *Pharmazie*, 1971, **26**, 463.

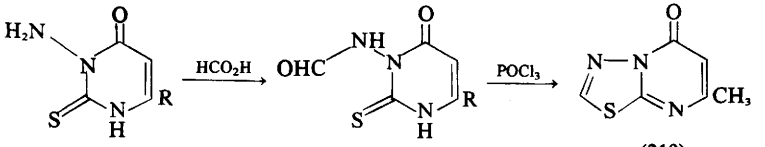


The general synthesis of 1,3,4-thiadiazolo[3,2-*a*]pyrimidines from 2-amino-1,3,4-thiadiazoles[127] has been varied by the use of 2,3-dichloroacryloyl chloride; the intermediate (206) is cyclized thermally to the final product (207) in 35% yield.[128] A similar route [to (208)] is the condensation of 2-amino-1,3,4-thiadiazoles with the appropriate β-diketones.[129–131]



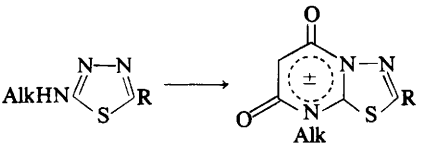
[127] T. Okabe, K. Maekawa, and E. Taniguchi, *Agric. and Biol. Chem. (Japan)*, 1973, **37**, 1197.
[128] J. G. Kuderna, R. D. Skiles, and K. Pilgram, *J. Org. Chem.*, 1971, **36**, 3506.
[129] H. Hartmann, *Z. Chem.*, 1971, **11**, 460.
[130] M. K. Pordeli and V. A. Chuiguk, *Khim geterotsikl. Soedinenii*, 1973, 199 (*Chem. Abs.*, 1973, **78**, 124 530c).
[131] H. Paul and A. Sitte, *Monatsh.*, 1971, **102**, 550.

In the opposite approach, 7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (210) is formed from the *N*-aminopyrimidinone (209) by successive formylation and cyclization with phosphorus oxychloride.[132]



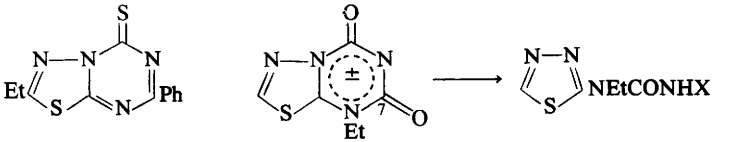
(209) (210)

Anhydro-8-ethyl-5-hydroxythiadiazolo[3,2-*a*]pyrimidinium-7-one hydroxide (211) and homologues are meso-ionic members of this ring system that are accessible in good yield by the condensation of 2-amino-1,3,4-thiadiazoles and bis-(2,4,6-trichlorophenyl)malonate esters.[133,134]



(211)

The interaction, in boiling acetone, of 2-amino-5-ethyl-1,3,4-thiadiazole and benzoyl isothiocyanate produces, in addition to the expected thiourea formed by simple addition, small yields of 2-ethyl-5-thioxo-7-phenyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]-*sym*-triazine (212).[135] 2-Ethylamino-1,3,4-thiadiazole reacts with phenoxycarbonyl isocyanate to produce meso-ionic 8-ethyl-1,3,4-thiadiazolo[3,2-*a*]-*sym*-triazine-5,7-dione (213). Its six-membered ring is readily cleaved by ethylamine or water, with formation of the substituted biuret (214; X = EtNHCO) or urea (214; X = H), respectively. The use of



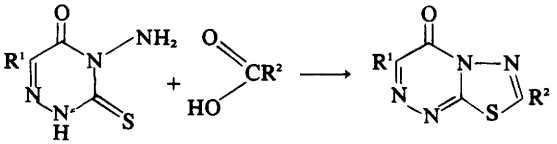
(212) (213) (214)

phenoxycarbonyl isothiocyanate in this synthesis affords the 7-thiono-analogue of (213).[136]

6-Substituted 4-amino-2,3,4,5-tetrahydro-*as*-triazin-5-one-3-thiones react

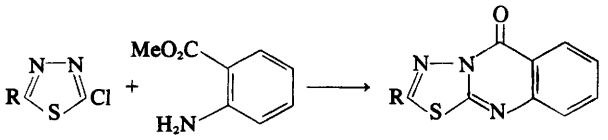
[132] T. Tsuji and T. Ueda, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2530.
[133] R. A. Coburn and R. A. Glennon, *J. Heterocyclic Chem.*, 1973, **10**, 487.
[134] R. A. Coburn and R. A. Glennon, *J. Pharm. Sci.*, 1973, **62**, 1785.
[135] G. Barnikow and J. Bödeker, *J. prakt. Chem.*, 1971, **313**, 1148.
[136] R. A. Coburn and B. Bhoosan, *J. Org. Chem.*, 1973, **38**, 3868.

with aromatic acids in boiling phosphorus oxychloride to yield 2,6-disubstituted 7-oxo-7*H*-1,3,4-thiadiazolo[2,3-*c*]-*as*-triazines (215) in excellent yields.[124]



(215)

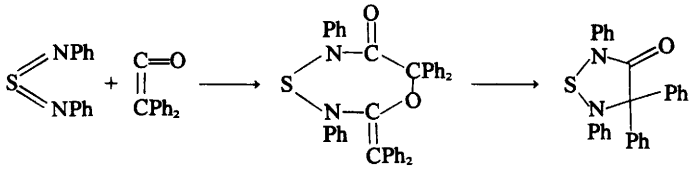
2-Aryl-5*H*-1,3,4-thiadiazolo[2,3-*b*]quinazolin-5-ones (216) are accessible in moderate yield by the condensation of 2-chloro-1,3,4-thiadiazoles and methyl anthranilate in boiling acetic acid.[137]



(216)

15 Synthesis of 1,2,5-Thiadiazoles

The synthesis of 1,2,5-thiadiazoles from sulphur di-imides and ketens (these Reports, Vol. 1, p. 453, Vol. 2, p. 752) has been more closely studied. The course of the cycloaddition is temperature-dependent, resulting in the labile 1:2 adduct (217) at 6—8 °C, and in the 1:1 adduct (218), *i.e.* the

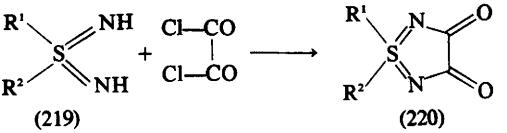


(217) (218)

thiadiazolidine, at 80 °C; the former is converted into the latter in boiling benzene. The applicability of the route may be somewhat limited: although di-t-butylsulphur di-imide and diphenylketen afford the expected 4,4-diphenyl-2,5-di-t-butyl-1,2,5-thiadiazolidin-3-one, other pairs of reactants give rise to other ring systems, as well as to linear structures.[138]

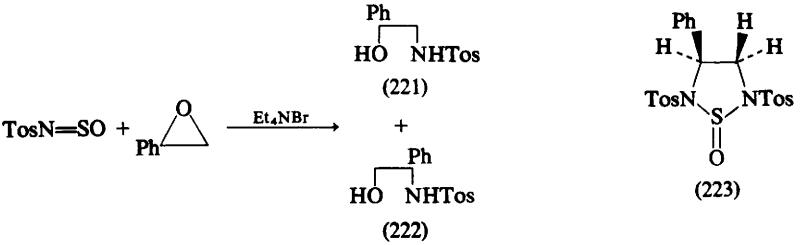
SS-Disubstituted sulphur di-imides (219) are attracting increasing attention as synthetic reagents. Their interaction, in dilute solution, with the difunctional oxalyl chloride, in the presence of triethylamine, affords the substituted 1,2,5-thiadiazole-3,5-diones (220) almost quantitatively.[139]

[137] T. R. Vakula, V. R. Rao, and V. R. Srinivasan, *J. prakt. Chem.*, 1973, **315**, 185.
[138] T. Minami, K. Yamataka, Y. Ohshiro, T. Agawa, N. Yasuoka, and N. Kasai, *J. Org. Chem.*, 1972, **37**, 3810.
[139] M. Haake, H. Fode, and B. Eichenauer, *Annalen*, 1972, **759**, 107.



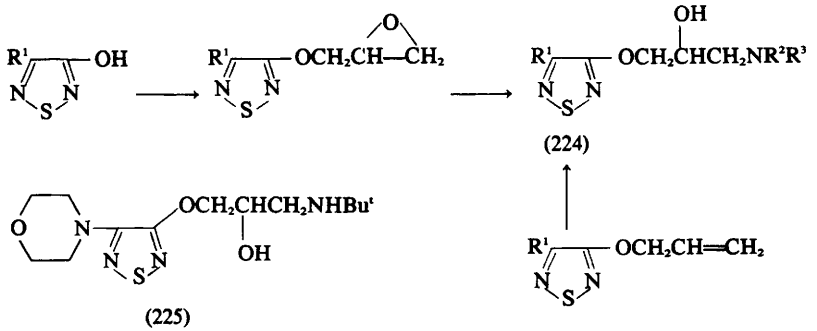
(219) (220)

The reaction of *N*-sulphinyltoluene-*p*-sulphonamide with styrene oxide gives, in addition to the linear products (221) and (222), small yields (6%) of 3-phenyl-2,5-di(toluene-*p*-sulphonyl)-1,2,5-thiadiazolidine 1-oxide (223), consistent with the formation of a 2:1 adduct with loss of sulphur dioxide.[140]



(221) (222) (223)

A number of substituted 1,2,5-thiadiazoles (224) have been produced from the pre-formed ring-system by conventional modifications of its substituents; some of these are exemplified in the reaction scheme. Compound (225) was resolved, and the pure enantiomeric bases were isolated for pharmacological evaluation.[141]

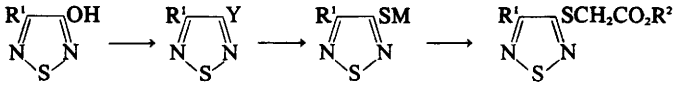


(224) (225)

3-Mercapto-1,2,5-thiadiazoles are obtainable by a procedure based on the rearrangement of thiono- into thiol-carbamates. It comprises the thioacylation of (226) with thiocarbamoyl chloride, then rearrangement of the resulting thionocarbamate (227) at 130 °C into (228), followed by hydrolysis. The resulting labile thiol is stabilized as the potassium or mercury salt (229), or as the 4-methoxycarbonylmethyl derivative (230). The i.r. spectrum (in

[140] O. Tsuge and S. Mataka, *J. Chem. Soc. Japan (Pure Chem. Sect.)*, 1971, **92**, 543 (*Chem. Abs.*, 1972, **76**, 99 574u).

[141] B. K. Wasson, W. K. Gibson, R. S. Stuart, H. W. R. Williams, and C. H. Yates, *J. Medicin. Chem.*, 1972, **15**, 651.



(226) (227) Y = $OCSNMe_2$ (228) Y = $SCONMe_2$ (229) M = K or $\frac{Hg}{2}$ (230) R^1 = H or CN

chloroform) of 3-mercapto-4-carbonamido-1,2,5-thiadiazole contains no peaks in the 2600—2500 cm^{-1} region, suggesting the presence of the thione tautomer under these conditions.[142]

16 Properties of 1,2,5-Thiadiazoles

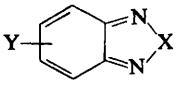
The u.v. vapour-phase absorption spectra of 1,2,5-thiadiazole,[143] and the i.r. and Raman spectra of 3-chloro-[144] and 3,4-dichloro-1,2,5-thiadiazole,[145] have been recorded and interpreted in great detail. In the case of the dichloro-compound, for example, assignments have been made for all 15 fundamental vibrations; they are consistent with the molecule being planar and having C_{2v} symmetry, and are supported by a good correlation with those of the parent 1,2,5-thiadiazole and its 3-monochloro-derivative.

17 Properties of 2,1,3-Benzothiadiazoles

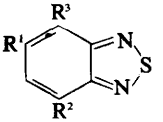
A number of physical and chemical properties of 2,1,3-benzothiadiazoles have been described. Dipole-moment measurements have provided information concerning the polar nature of a variety of 2,1,3-benzodiazoles (231). A comparison of the observed and calculated values of the dipole moments (using the value for the parent compound as a group moment) provides some insight into the relative importance of the possible mesomeric structures. The mesomeric charge transfer increases regularly from the oxygen to the selenium structures, being nearly undetected in 2,1,3-benzoxadiazoles, and very pronounced in the 2,1,3-benzoselenadiazoles. The 2,1,3-benzoxadiazoles appear to assume *ortho*-quinonoid structures, with resonance occurring with the five-membered ring. The S and Se analogues show increasing aromatic character.[146] pK_a Values of 2,1,3-benzothiadiazole and its hydroxy- and nitro-derivatives (232) are available.[147]

The bromination of melted 2,1,3-benzothiadiazole in the presence of reduced iron powder provides an improved procedure for the exclusive production of the 4,5,6,7-tetrabromo-derivative, in 53% yield.[148] Sulphonation of 7-bromo-2,1,3-benzothiadiazole yields the 4-sulphonic acid (233),

[142] D. E. Horning and J. M. Muchowski, *Canad. J. Chem.*, 1973, **51**, 2349.
[143] E. F. Firkins and A. W. Richardson, *Chem. Comm.*, 1971, 1368.
[144] A. W. Richardson, *Canad. J. Chem.*, 1972, **50**, 627.
[145] A. W. Richardson, *Canad. J. Chem.*, 1973, **51**, 680.
[146] F. L. Tobiason, L. Huestis, C. Chandler, S. E. Pedersen, and P. Peters, *J. Heterocyclic Chem.*, 1973, **10**, 773.
[147] D. Dalmonte, E. Sandri, and W. Cere, *Ann. Chim.* (*Italy*), 1970, **60**, 801.
[148] D. E. Bublitz, *J. Heterocyclic Chem.*, 1972, **9**, 539.



(231) X = O, S, or Se
Y = H, Me, Cl, NO_2, or NH_2



(232) R^1, R^3 = H or OH
R^2 = H or NO_2

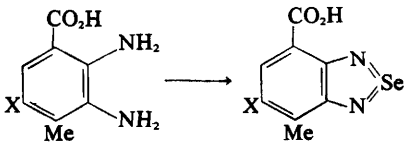
(233)

from which the usual functional derivatives are accessible by conventional methods.[149]

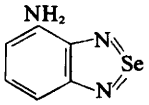
18 Synthesis and Properties of 2,1,3-Benzoselenadiazoles

Examples of the production of 2,1,3-benzoselenadiazoles (235) from *o*-diamines, *e.g.* (234; X = H or Br), by the action of selenium dioxide have been described.[150,151]

Benzoselenadiazoles are aminated by treatment with equimolar quantities of hydroxylamine sulphate in concentrated sulphuric acid in the presence of vanadium pentoxide as catalyst; the appropriate amines, *e.g.* (236), are isolated in moderate yields (9—37%).[152]



(234) (235)



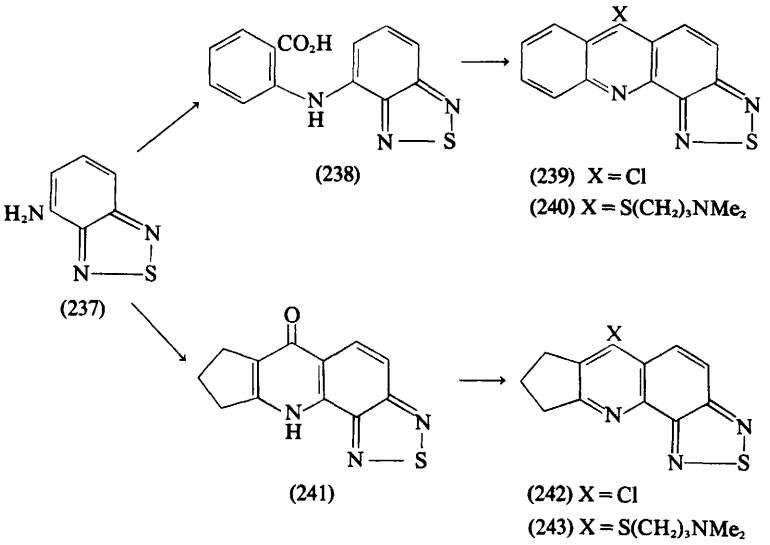
(236)

19 Condensed 1,2,5-Thiadiazoles

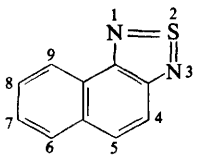
4-Amino-2,1,3-benzothiadiazole (237) is convertible into its anthranilic acid derivative (238), which is cyclized by phosphorus oxychloride to 6-chloro-[1,2,5]thiadiazolo[3,4-*c*]acridine (239). Replacement of its 6-halogeno-substituent produces derivatives such as (240). An analogous series of reactions provides 7,8,9,10-tetrahydro-analogues. The condensation of (237) and alkyl 2-oxocyclopentanecarboxylate yields derivatives of the [1,2,5]-thiadiazolo[3,4-*h*]quinoline ring system such as (241)—(243).[153]

Electrophilic substitutions of naphtho[1,2-*d*][2,1,3]thiadiazole (244) have been studied in some detail. Nitration[154] produces a mixture of the 6- and

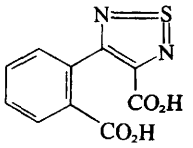
[149] F. S. Mikhailitsyn, *Khim. geterotsikl. Soedinenii*, 1973, 319, (*Chem. Abs.*, 1973, **78**, 147 925z).
[150] T. F. Stepanova, D. P. Sevbo, and O. F. Ginzburg, *Zhur. org. Khim.*, 1971, **7**, 1921.
[151] T. F. Stepanova, D. P. Sevbo, O. F. Ginzburg, G. A. Labutina, and B. R. Shteiman, *Zhur. org. Khim.*, 1972, **8**, 1745.
[152] V. A. Sergeev, V. G. Pesin, and N. M. Kotikova, *Khim. geterotsikl. Soedinenii*, 1972, 328 (*Chem. Abs.*, 1972, **77**, 61 898k).
[153] E. F. Elslager and N. F. Haley, *J. Heterocyclic Chem.*, 1972, **9**, 1109.
[154] V. G. Pesin and L. A. Kaukhova, *Khim. geterotsikl. Soedinenii*, 1972, 1496 (*Chem. Abs.*, 1973, **78**, 43 382d).



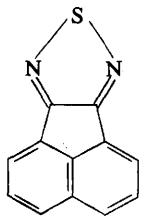
9-nitro-derivatives, which are convertible into amino- and hydroxy-compounds as expected. Halogenation[155] by chlorine–sulphur dioxide, bromine–lead tetra-acetate, or *N*-bromosuccinimide occurs in the 5-position, but other isomers and dihalogeno-derivatives are obtainable under selected conditions. The oxidation[154] by chromic acid cleaves the central benzene ring, yielding the dicarboxylic acid (245).



(244)



(245)



(246)

Precise structural details, obtained by *X*-ray diffraction measurements, are available concerning acenaphtho[1,2-*c*][1,2,5]thiadiazole (246).[156]

[155] V. G. Pesin and L. A. Kaukhova, *Khim. geterotsikl. Soedinenii*, 1972, 1503 (*Chem. Abs.*, 1973, **78**, 43 380b).

[156] J. P. Schaefer and S. K. Arora, *Chem. Comm.*, 1971, 1623.

16
Thiazines

BY G. PROTA

1 Introduction

Progress in the field of thiazines has been well sustained, the major concentration of effort being concerned, as usual, with the 1,3- and 1,4-isomers of this ring system. A number of new synthetic routes have improved and diversified the accessibility of compounds of these heterocycles, and several novel reactions have been described.

With respect to the organization of reviewing the material, the present Chapter follows quite closely Chapter 16 in Volume 2 of these Reports. Aspects of the chemistry of 1,3-thiazines arising from work on the cephalosporins and related compounds are reviewed in Chapter 3, and those concerning 2-azathiabenzenes are discussed in Chapter 6 in connection with other heterocyclic systems containing sexivalent sulphur.

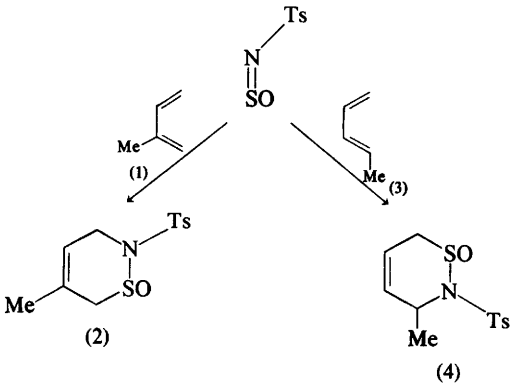
2 1,2-Thiazines

Simple 1,2-Thiazines.—Remarkably little activity has been evident in this area during the past two years. Kresze and Wagner[1] have made a detailed study on the orientation in the synthesis of 3,6-dihydro-2*H*-1,2-thiazine 1-oxides by [4 + 2] cycloaddition of dienes and *N*-sulphinyltosylamide. As a rule, the electrophilic sulphur atom of the dienophile attacks C-1 of 2-substituted dienes, *e.g.* (1), to give the adduct (2), while in the case of 1-substituted dienes, *e.g.* (3), it adds usually to C-4 with the formation of the isomeric thiazine (4), provided that the reaction may be kinetically controlled (Scheme 1).

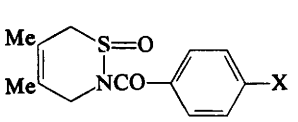
Various thiazine 1-oxides (5) and 1-*N*-imines (6) have also been obtained[2] by cycloaddition of 2,3-dimethylbutadiene to the appropriate *N*-sulphinylamides and symmetrical sulphur di-imides, respectively.

Benzo-1,2-thiazines.—A novel route to benzothiazine dioxides, *e.g.* (8), is based upon the facile cyclization of *o*-diazoacetylbenzenesulphonamide (7)

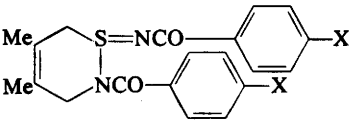
[1] G. Kresze and U. Wagner, *Annalen*, 1972, **762**, 93.
[2] E. S. Levchenko and E. M. Dorokhova, *Zhur. org. Khim.*, 1972, **8**, 2526 (*Chem. Abs.*, 1973, **78**, 72 033w).



Scheme 1



(5) X = H, Cl, Br, Me, or MeO

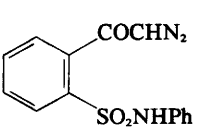


(6) X = H, Cl, or Br

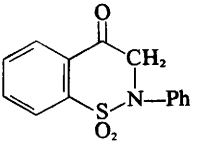
with formic acid at room temperature.[3] Use of toluene-*p*-sulphonic acid as the catalyst for the reaction gives (8) in lower yields, together with the benzisothiazole (9), originating probably by ring-contraction of the thiazine product, as outlined in (10). This view is supported by the observation that (8) combines readily with toluene-*p*-sulphonic acid to give the benzisothiazole dioxide (9) in good yields. Thermal cyclization of the diazo-ketone (7) in boiling chlorobenzene[3] also proceeds differently to give, in addition to the benzothiazine dioxide (8), its 3-oxo-isomer (13), which may be regarded as originating from the keten (12), derived by Wolff rearrangement of the expected acylcarbene intermediate (11).

An attempt to achieve the ring-expansion of the benzothiazine epoxide (14) *via* benzoyl migration[4] with boron trifluoride etherate in dichloromethane is reported[5] to yield, instead of the desired β-diketone (15), the keto-aldehyde (16), arising apparently by phenyl migration; this is an alternative pathway that has already been observed.[6] Existing syntheses[7] of the 2,1-benzothiazine dioxide (18) have been supplemented by an improved

[3] G. Heyes, G. Holt, and A. Lewis, *J.C.S. Perkin I*, 1972, 2351.
[4] H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, 1956, **78**, 4394; H. Hofman and H. Wasternacher, *Chem. Ber.*, 1969, **102**, 205, and refs. therein.
[5] H. Zinnes and J. Shavel jun., *J. Heterocyclic Chem.*, 1973, **10**, 95.
[6] G. L. Buchanam and D. B. Jhaveri, *J. Org. Chem.*, 1961, **26**, 4295; J. W. Ager, F. A. Eastwood, and R. Robinson, *Tetrahedron Supplement*, 1966, **7**, 277.
[7] B. Loev, M. R. Kormendy, and K. M. Snader, *J. Org. Chem.*, 1966, **31**, 3531; B. Loev and K. M. Snader, *J. Heterocyclic Chem.*, 1967, **4**, 403; S. Rossi and G. Pagani, *Ann. Chim. (Italy)*, 1966, **56**, 741.



(7)



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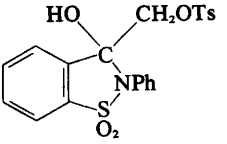

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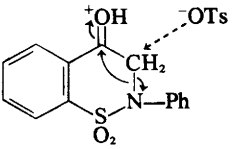

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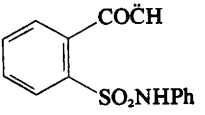

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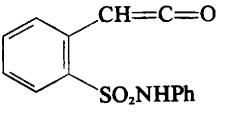

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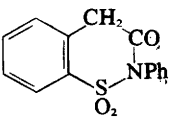
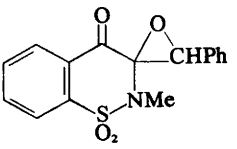


(13)

route that is based upon the ring-closure of the readily available *N*-methylsulphonamide (17) with sodium hydride in dry DMF.[8]



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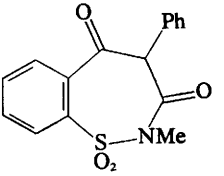
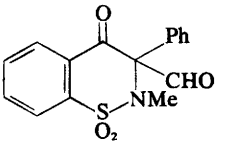


(15)



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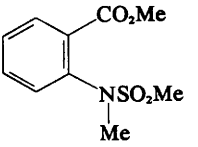
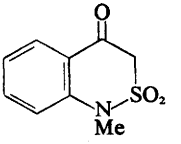


(17)



(18)

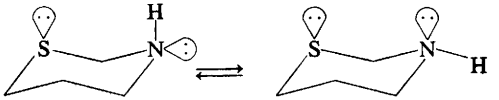
In the course of biological screening programmes, numerous benzothiazine dioxide derivatives[9,10] have been produced by variations of

[8] J. G. Lombardino, *J. Heterocyclic Chem.*, 1972, **9**, 315.
[9] E. Sianesi, R. Redaelli, M. J. Magistretti, and E. Massarani, *J. Medicin. Chem.*, 1973, **16**, 1133.
[10] H. Zinnes, N. A. Lindo, J. C. Sircar, M. L. Schwartz, J. Shavel, jun., and G. Dipasquale, *J. Medicin. Chem.*, 1973, **16**, 44.

established syntheses or by appropriate modifications from a pre-formed thiazine structure.

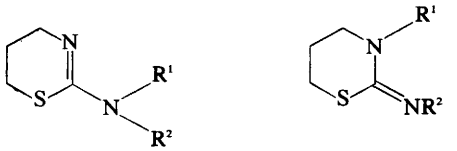
3 1,3-Thiazines

Simple 1,3-Thiazines.—In connection with a study on the NH conformation in the analogues of piperidine in which a ring CH_2 group is replaced by a hetero-atom, the equilibrium position of tetrahydro-1,3-thiazine [(19a) ⇄ (19b)] has been examined.[11] I.r. measurements of the ν(NH) first overtone and electric dipole moments indicate that the predominant conformer is that with the NH axial. This preference, which applies also for tetrahydro-1,3-oxazine, may be interpreted in terms of attractive forces between the lone pair of the sulphur atom and axial NH in the conformer (19a), and repulsive 'rabbit ear' forces between the two axial lone pairs in the conformer (19b).



(19a) (19b)

As an extension of early studies (see Vol. 2, p. 761), Sohar and Toldy[12] have checked the reliability of i.r. and n.m.r. data in assigning tautomeric structures (20a) or (20b) to 2-arylamino-1,3-thiazines and to their *N*-substituted derivatives by examining the spectral features of several isomer pairs (21a) and (21b), synthesized by unambiguous routes. The original papers[12] contain a wealth of details, to which the reader is referred.



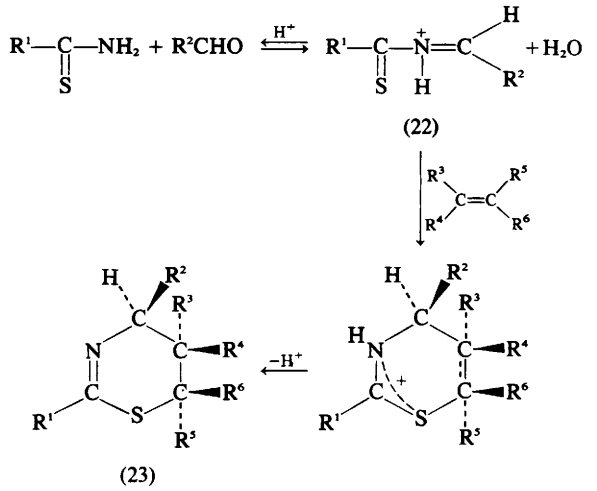
(20a) $R^1 = H$, R^2 = aryl (20b) $R^1 = H$, R^2 = aryl
(21a) R^1 = Me, R^2 = aryl (21b) R^1 = Me, R^2 = aryl

Several new approaches to the synthesis of 1,3-thiazines have been explored. Particularly interesting in this context is the one-step condensation of a thioamide, an aldehyde, and an olefin in the presence of an acid catalyst, leading to 5,6-dihydro-4*H*-1,3-thiazines (23) with a wide variety of substituents[13] (Scheme 2). Configurational n.m.r. analysis of the products

[11] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, S. Saba, A. J. Sparrow, and D. L. Trepanier, *J.C.S. Chem. Comm.*, 1972, 673; M. J. Cook, R. A. Y. Jones, A. R. Katritzky, M. Moreno Manas, A. C. Richards, A. J. Sparrow, and D. L. Trepanier, *J.C.S. Perkin II*, 1973, 326.

[12] P. Sohár and L. Toldy, *Acta Chim. Acad. Sci. Hung.*, 1973, **75**, 99; *Org. Magn. Resonance*, 1972, **4**, 779.

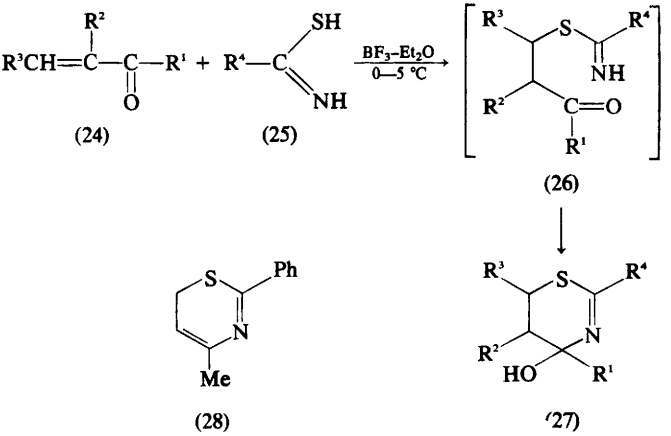
[13] L. Abis and C. Giordano, *J.C.S. Perkin I*, 1973, 771.



Scheme 2

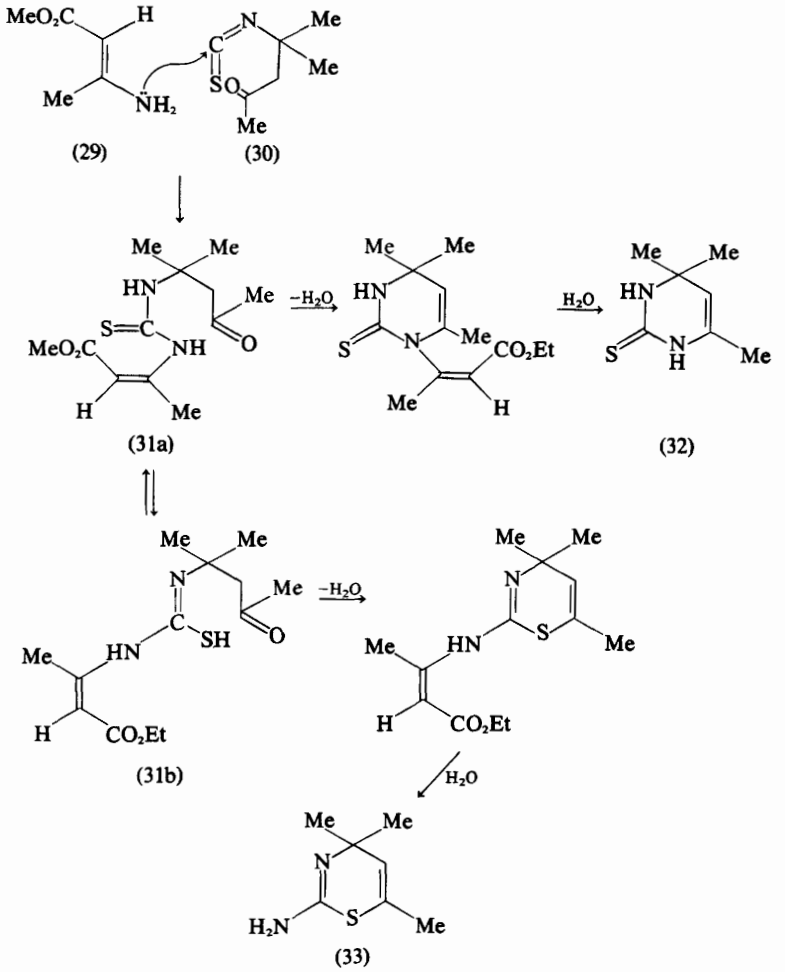
provides evidence that the reaction is stereospecific and regiospecific, thus proceeding probably through a *cis* electrophilic cycloaddition of the thioamidoalkyl ion (22), generated *in situ*, to the olefin.

Substituted 4,5-dihydro-6*H*-1,3-thiazines (27) are formed[14] in high yields by Michael addition of thioamides, thioureas, or thiocarbamates (25) to the double bond of $\alpha\beta$-unsaturated aldehydes, ketones, or ketols (24) in the presence of boron trifluoride etherate and subsequent spontaneous ring-closure of the resulting intermediate (26). In some instances the products (27) can be converted into the corresponding 6*H*-1,3-thiazines, *e.g.* (28), with $POCl_3$ in pyridine or with acid in aprotic solvents.



[14] S. Hoff and A. P. Blok, *Rec. Trav. chim.*, 1973, **92**, 631.

Condensation of ethyl β-aminocrotonate (29) with the β-keto-isothiocyanate (30) in hydrocarbon solvents results in the formation of the 2-thiolo-pyrimidine (32) as the major product and the 2-amino-1,3-thiazine (33) as the minor component. However, the use of ether, chloroform, or acetonitrile as solvents reverses the product ratio.[15] This observation points towards the feasibility of formation of the tautomeric intermediate (31), which through attack of nitrogen (31a) or sulphur (31b) at the carbonyl followed by dehydration and enamine hydrolysis leads to (32) and (33), respectively (*cf.* Scheme 3). Thus, in solvents of higher dielectric constant,

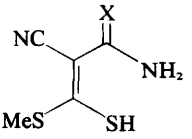


Scheme 3

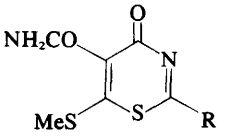
[15] H. Singh and S. Singh, *Austral. J. Chem.*, 1973, **26**, 2453.

the more polar thiol structure (31b) is favoured, and thereby (33) is formed, whereas in hydrocarbon solvents the prevailing thione tautomer leads to the pyrimidinethione (32).

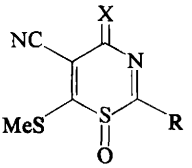
The utility of the cyanoamide (34a) and cyanothioamide (34b) as intermediates for synthesizing 1,3-thiazine derivatives (see Vol. 2, p. 762) has been further examined.[16] Condensation of (34a) with an aromatic acid in the presence of polyphosphate ester in refluxing chloroform affords the 5-carbamoyl-6-methylthio-1,3-thiazin-4-ones (35) in good yields. By contrast, a similar reaction of (34a) with aliphatic acids gives, in low yields, the 5-cyano-1-oxo-derivatives (36), and analogous products (37) are produced from the thioamide (34b) and either aromatic or aliphatic acids.[16] Since these sulphoxides are also formed when the condensation is carried out in an inert atmosphere, it is likely that the S=O group arises by nucleophilic attack of water, resulting from the dehydration step, on a thiazinium intermediate, as outlined in (38).



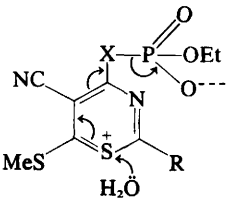
(34a) X = O
(34b) X = S



(35)



(36) X = O
(37) X = S

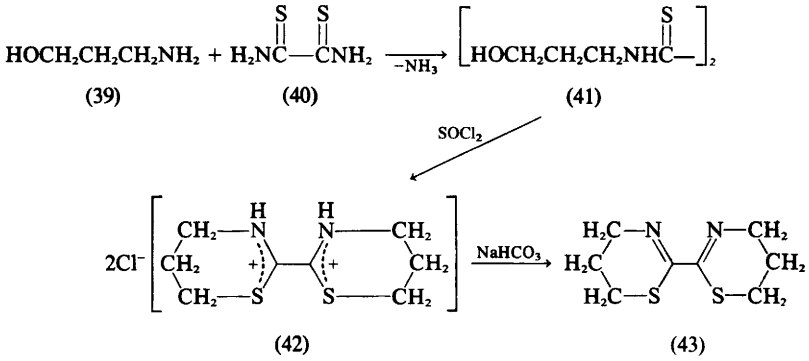


(38)

A facile synthesis of the hitherto unknown 2,2′-bi-Δ^2-thiazinyl from readily available precursors involves[17] the reaction of 3-aminopropanol (39) with rubeanic acid (40), followed by ring-closure of the intermediate (41) with thionyl chloride to give the bithiazinium dication (42), from which the free base (43) is obtained by treatment with sodium bicarbonate (Scheme 4). The method is quite general and has also been adapted to the preparation of 2,2′-bi-Δ^2-thiazolinyl and its homologues, using the appropriate β-amino-alcohols.[17]

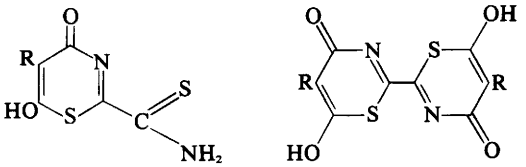
Another route to bithiazinyl systems is exemplified by the thermal condensation of rubeanic acid with 2,4,6-trichlorophenyl malonate, leading

[16] M. Yokoyama, Y. Sawachi, and T. Isso, *J. Org. Chem.*, 1973, **38**, 802.
[17] D. A. Tomalia and J. N. Paige, *J. Org. Chem.*, 1973, **38**, 3949.



Scheme 4

to the 2-thiocarboxamido-thiazine (44), which is converted into the bicyclic product (45) by further reaction with more of the ester.[18] However, in view of the limitations of its applicability, and the low yields obtained, the synthetic value of this reaction appears to be rather circumscribed.

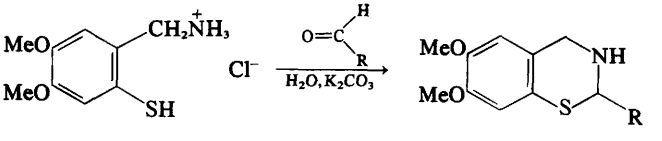


(44) (45)

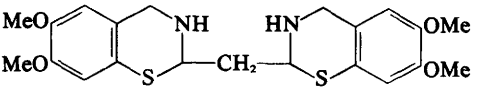
Benzo-1,3-thiazines.—A direct procedure for preparing 2,3-dehydro-4*H*-1,3-benzothiazines is afforded[19] by the condensation of 2-mercaptobenzylamine and its derivatives with ketones or aldehydes in alkaline medium. Thus, for example, (46) reacts with acetaldehyde to give (47; R = Me) in excellent yields. A somewhat different course is observed in the condensation of (46) with formaldehyde, which gives the methylene bis-derivative (48), resulting from the fast reaction of the primary product (47; R = H) with more of the aldehyde.

In connection with studies on the thermolysis of oxazolin-5-ones, the 2-arylthio-substituted derivative (49) has been observed to undergo thermally induced cycloelimination of carbon dioxide to give the 2*H*-1,3-benzothiazine (52), presumably *via* the ylide intermediates (50) and (51).[20] Like 2-ethoxybenzoxazin-4-one,[21] the sulphur analogue (53) undergoes ethanol elimination under the influence of an acid catalyst to give the unstable cyclic acylamine (54), which can be trapped as Diels–Alder adducts

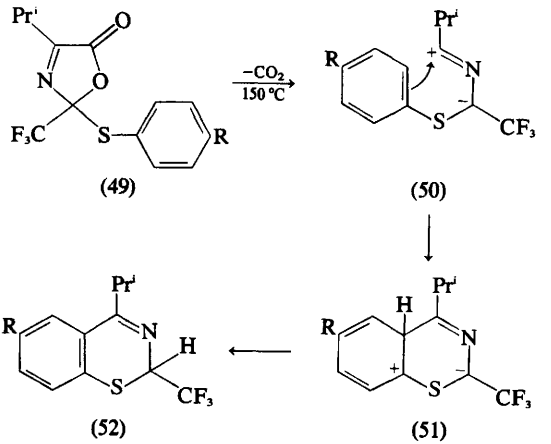
[18] R. Ketcham, T. Kappe, and E. Ziegler, *J. Heterocyclic Chem.*, 1973, **10**, 223.
[19] J. Szabó, I. Varga, E. Vinkler, and E. Barthos, *Acta Chim. Acad. Sci. Hung.*, 1972, **72**, 213.
[20] P. Gruber, L. Muller, and W. Steglich, *Chem. Ber.*, 1973, **106**, 2863.
[21] D. Ben-Ishai and A. Warshansky, *J. Heterocyclic Chem.*, 1971, **8**, 865.



(46) (47)

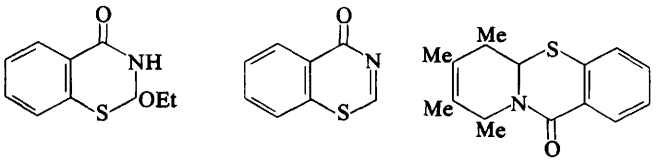


(48)



(49) (50) (51) (52)

with dienes.[22] Thus, the reaction of (53) with 1,2,3,4-tetramethylbutadiene, catalysed by boron trifluoride etherate, leads to the *cis*-adduct (55) in 50% yield.

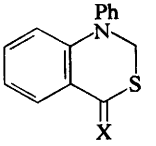


(53) (54) (55)

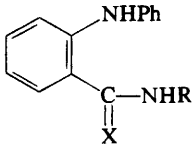
Some aspects of the chemistry of 3,1-benzothiazine derivatives have also been examined recently. Treatment of the benzothiazinones (56) with aliphatic primary amines in boiling ethanol results in ring-opening, and formation of the aminobenzamides (57) by loss of a CH_2S fragment.[23] With

[22] D. Ben-Ishai, I. Gillon, and A. Warshansky, *J. Heterocyclic Chem.*, 1973, **10**, 149.
[23] L. Legrand and N. Lozach, *Bull. Soc. chim. France*, 1973, 1665.

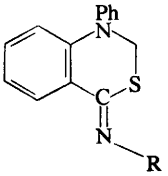
the thione analogues (58) the reaction gives either the thiobenzamides (59), or the imino-derivatives (60), or a mixture of (59) and (60), depending on the solvent and the amine used.[24] Notably, on heating at *ca.* 200 °C, the compounds (60) are converted into the corresponding quinazolinethiones (61), and a similar process probably accounts for the formation of (63), in place of the expected (62), in the reaction of the benzothiazinethiones (58) with aromatic primary amines, carried out at 200 °C.



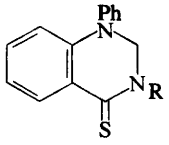
(56) X = O
(58) X = S



(57) X = O
(59) X = S

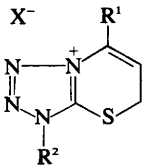


(60) R = alkyl
(62) R = aryl

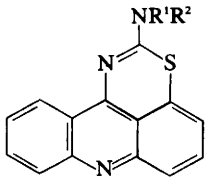


(61) R = alkyl
(63) R = aryl

Further examples of fused-ring systems incorporating the 1,3-thiazine structure have been obtained by adaptations or extensions of conventional cyclization reactions; they include the new tetrazolo[5,4-*b*][1,3]thiazinium salts (64),[25] some highly fluorescent 1,3-thiazino[4,5,6-*kl*]acridines (65)



(64)



(65)

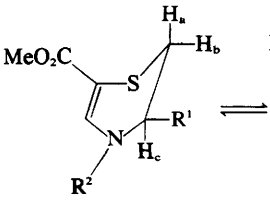
derived from isothiourea derivatives and 9-isothiocyanatoacridine,[26] and

[24] L. Legrand and N. Lozach, *Bull. Soc. chim. France*, 1972, 3892, 3905.
[25] H. Alper and R. W. Stout, *J. Heterocyclic Chem.*, 1973, **10**, 569.
[26] J. E. Sinsheimer, A. Deleenheer, and J. H. Burckhalter, *J. Pharm. Sci.*, 1973, **62**, 1370.

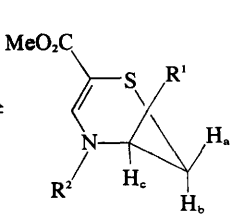
other structures in which the thiazine system is annelated to imidazole,[27] pyridine,[28] quinoline,[29] and quinazoline[30] rings.

4 1,4-Thiazines

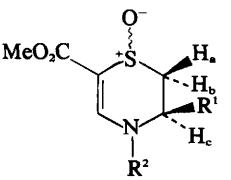
Monocyclic 1,4-Thiazines.—Full details have appeared[31] of the synthesis and conformational equilibria [(66a) ⇄ (66b)] of some dihydrothiazines, previously reported (see Vol. 1, p. 463). In further studies of this system, Kitchin and Stoodley[32] have synthesized a series of (*R*)- and (*S*)-sulphoxide derivatives (67)—(72) and examined their conformational behaviour by n.m.r. spectroscopy. The results illustrate a marked preference of 2,3-dihydro-6-methoxycarbonyl-1,4-thiazine 1-oxides to adopt the conformer which possesses an axial oxide group. Thus, the (*R*)-sulphoxides exist predominantly as (73), and the (*S*)-sulphoxides show an overwhelming preference for (74). This behaviour is presumably associated with the higher free-energy of those conformers with an equatorial oxide formation, which are destabilized by a severe $A^{(1,2)}$ interaction between the sulphinyl and methoxycarbonyl groups.



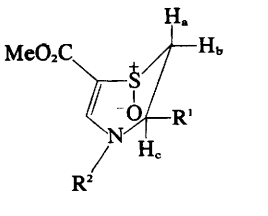
(66a)



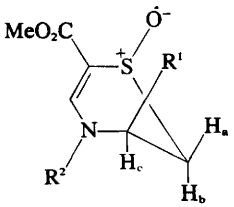
(66b)



	R¹	R²
(67)	CH_2OH	H
(68)	H	H
(69)	CO_2H	H
(70)	CH_2OAc	H
(71)	CH_2OMs	H
(72)	CH_2OH	Pr^i



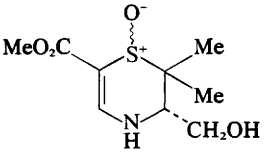
(73)



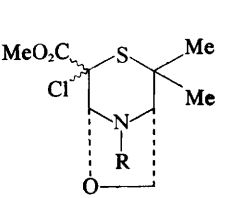
(74)

[27] J. Mohan, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.*, 1973, **11**, 747.
[28] T. Zawisza and S. Respond, *Pol. J. Pharmacol. Pharm.*, 1973, **25**, 385, (*Chem. Abs.*, 1974, **80**, 27 185c).
[29] A. E. Kretov, A. P. Momsenko, A. S. Bespalyi, and Yu. A. Levin, *Khim. geterotsikl. Soedinenii*, 1973, 641 (*Chem. Abs.*, 1973, **79**, 42 431c); A. E. Kretov, A. P. Momsenko, and Yu. A. Levin, *ibid.* p. 644 (*Chem. Abs.*, 1973, **79**, 42 434f).
[30] T. Jen, B. Daniel, F. Dowald, H. Vanhdeven, P. Bender, and B. Loev, *J. Medicin. Chem.*, 1973, **16**, 633.
[31] A. R. Dunn and R. J. Stoodley, *Tetrahedron*, 1972, **28**, 3315.
[32] J. Kitchin and R. J. Stoodley, *Tetrahedron*, 1973, **29**, 3023.

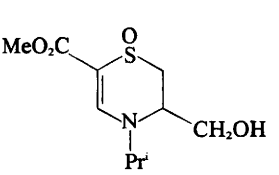
Other interesting developments in the chemistry of these systems have been reported. Treatment[33] of a 6:1 mixture of the alcohol sulphoxides (75) with acetyl chloride in acetonitrile results in the formation of the bicyclic amine (76), which affords the corresponding amide (77). A detailed study of the analogous conversions of the diastereoisomers (78) and (79) leading to the same chloro-amine (82) suggests that the process is promoted by the rapid formation of the acetoxysulphonium salt (80), which may undergo an intramolecular conjugated addition to give the bicyclic salt (81); this then affords the product by a normal Pummerer reaction.



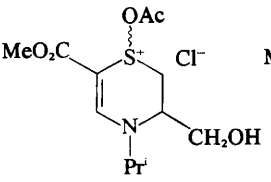
(75)



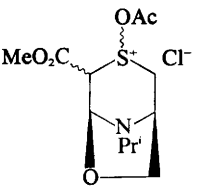
(76) R = H
(77) R = Ac



(78) 1*R*
(79) 1*S*



(80)



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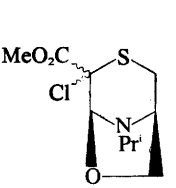
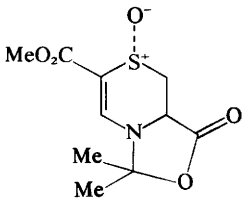
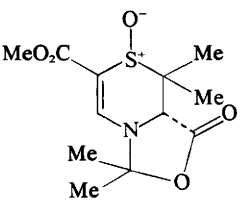


(82)

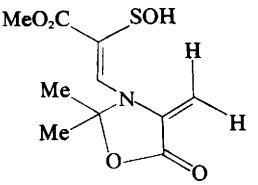
In connection with some other work, the optically active lactone sulphoxides (83) and (84) have been observed[34] to undergo a rapid, thermally induced racemization in boiling chloroform. Deuterium-labelling experiments indicate that the reaction probably involves the intermediacy of the sulphenic acids, *e.g.* (85), that are formed by a concerted hydrogen shift. Such a sigmatropic process finds analogy in the thermal isomerization of



(83)



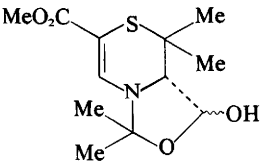
(84)



(85)

[33] J. Kitchin and R. J. Stoodley, *J.C.S. Chem. Comm.*, 1972, 959; *J.C.S. Perkin I*, 1973, **22**, 2464.
[34] A. G. N. Baxter, J. Kitchin, R. J. Stoodley, and R. B. Wilkins, *J.C.S. Chem. Comm.*, 1973, 285.

penam sulphoxides (see Vol. 2, p. 191). Reduction of the lactol (86) with $LiAlH_4$–aluminium chloride gives,[35] instead of the expected ether (90), the pyrrole (89) by loss of two molecules of water. This novel rearrangement, promoted also by aluminium chloride in ether, toluene-*p*-sulphonyl chloride in pyridine, and methanesulphonyl chloride–triethylamine in dichloromethane, is considered to proceed *via* the iminium ion (87), which affords the product by way of the enamine (88). Evidence for the formation of the iminium ion (87) has been obtained by deuterium-incorporation studies of the related conversion of the lactol (86) into the (7*S*)-acetal (91) with methanolic hydrogen chloride.[35]



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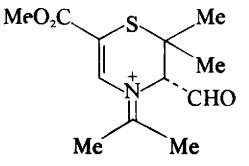

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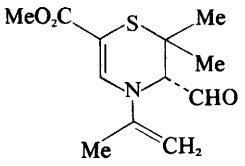

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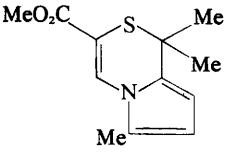
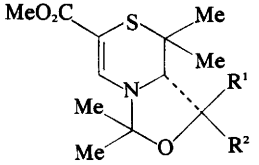


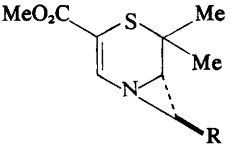
(89)



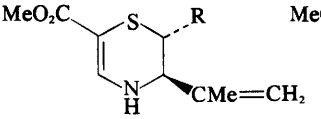
(90) $R^1 = R^2 = H$
(91) $R^1 = OMe$, $R^2 = H$

Rearrangements involving 1,3-sulphur migrations that had been observed in certain 1,4-thiazines[36] [*e.g.* (92) → (93)] have been further explored,[37] using the monodeuteriated aziridine (95), which was synthesized by way of the monodeuteriated thiazinyl alcohol (94) resulting from the reaction of 6α-chloro-[(*S*)-3-*methylene*-^{2}H]penicillanyl alcohol (98) with methanolic sodium methoxide.[38] Thermal isomerization of (95) in boiling toluene proceeds without loss of deuterium to give the isopropenyl derivative (96), indicating that the new carbon–sulphur bond is formed with retention of configuration. This stereochemical result is compatible with a concerted reorganization in which the aziridine (95) reacts in its thermodynamically unfavourable conformation *via* a transition state such as (99) or (100). In the former event, the aziridine (101) is an intermediate in the reaction, which

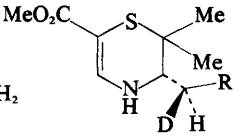
[35] J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 1973, 1985.
[36] A. R. Dunn and R. J. Stoodley, *Chem. Comm.*, 1969, 1169, 1368; *J.C.S. Perkin I*, 1972, 2509.
[37] J. Kitchin and R. J. Stoodley, *J. Amer. Chem. Soc.*, 1973, **95**, 3439; *J.C.S. Perkin I*, 1973, 2460.
[38] J. McMillan and R. J. Stoodley, *Tetrahedron Letters*, 1966, 1266, 1205; *J. Chem. Soc.* (*C*), 1968, 2533.



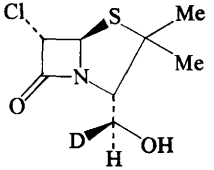
(92) R = H
(95) R = D



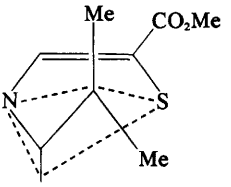
(93) R = H
(96) R = D



(94) R = OH
(97) R = I



(98)



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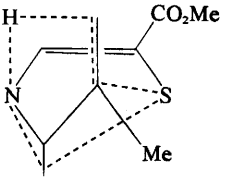
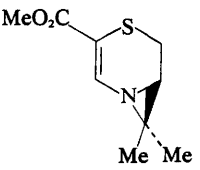
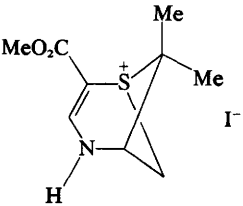


(100)



(101)



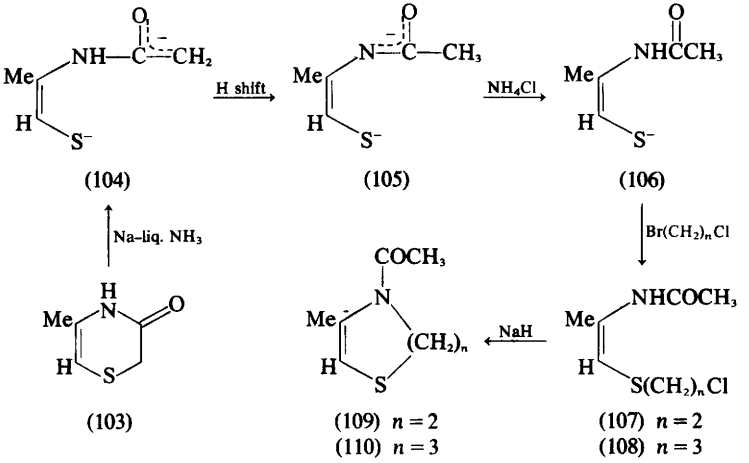
(102)

represents an example of a [4,4] dyotropic shift. A parallel study[37] of the thermal isomerization of the monodeuteriated iodide (97), leading to the isopropenyl derivative (96), has revealed that in this case the 1,3-sulphur shift occurs so that the new carbon–sulphur bond is formed with inversion of configuration. This result may be explained in terms of a reorganization involving the ion pair (102), as had been previously suggested.[36]

According to a recent paper,[39] the reduction of 2,3-dihydro-1,4-thiazin-2-ones, *e.g.* (103), with alkali metals in liquid ammonia results in selective cleavage of the sulphur–carbon sp^3 bond and formation of the dianion (104), which rearranges to the more stable dianion (105). Subsequent addition of one equivalent of ammonium chloride to the solution of (105) in liquid ammonia gives the 2-acetamido-alkenethiolate (106), which can be isolated in nearly quantitative yields and used as an intermediate for the synthesis of new heterocyclic compounds. Thus, for example, alkylation of (106) with 1-bromo-2-chloroethane or 1-chloro-3-bromopropane gives the corresponding *S*-chloroalkylated compounds (107) and (108), which on treatment with

[39] S. Hoff, A. P. Blok, and E. Zwanenburg, *Tetrahedron Letters*, 1972, 5199; *Rec. Trav. chim.*, 1973, **92**, 879.

sodium hydride in boiling toluene are converted into the 1,4-thiazine (109) and the 1,4-thiazepine (110), respectively.

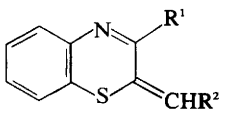


Benzo-1,4-thiazines and Related Compounds.—The chemical behaviour of the Vilsmeier product (111), derived from 1,4-benzothiazin-3(4*H*)-one, has been the subject of detailed studies.[40] Hydrolysis under different conditions affords the acid (112), the aldehyde (114), or the chloro-aldehyde (113), depending on the method of hydrolysis. Treatment of the perchlorate of (111) with DMSO leads to the displacement of the chlorine atom to give the dimethylsulphoxonium derivative (115), while reaction with pyridine proceeds with selective attack at the aminomethylene function, yielding the pyridinium salt (116). This latter reacts readily with aniline in acetic acid medium to give, along with 2-formyl-3-anilino-1,4-benzothiazine (117), the anilinomethylene derivative (120), whose formation probably involves an intramolecular rearrangement of the intermediate pyridinium salt (118), as depicted.

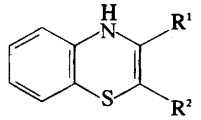
In connection with a study on the reactions of azidoquinones with nucleophiles, the novel benzothiazine quinone (123) has been obtained by the reaction of (121) with ethyl mercaptoacetate in the presence of potassium t-butoxide, followed by the facile ring-closure of the resulting intermediate (122).[41]

The condensation of 1,4-benzoquinone with cysteine ethyl ester was reported[42] to produce the cyclic iminoquinone (124), but new work[43] now provides evidence that the process follows a more complex pathway, which leads to a mixture of two diastereoisomers corresponding to the gross structure (126). The sequence of reactions in Scheme 5 is suggested to

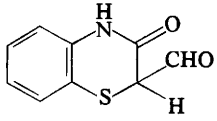
[40] S. R. Shah and S. Seshadri, *Indian J. Chem.*, 1972, **10**, 820, 977.
[41] G. Cajipe, D. Rutolo, and H. W. Moore, *Tetrahedron Letters*, 1973, 4695.
[42] R. Kuhn and H. Beinert, *Ber.*, 1944, **77**, 606; R. Kuhn and H. Hammer, *ibid.*, 1951, **84**, 91.
[43] G. Prota and E. Ponsiglione, *Tetrahedron Letters*, 1972, 1327.



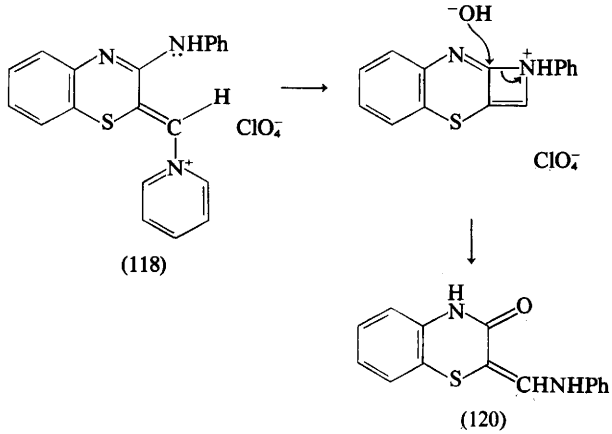
(111) $R^1 = Cl$, $R^2 = NMe_2$
(115) $R^1 = OSMe_2$, $R^2 = NMe_2$
(116) $R^1 = Cl$, $R^2 = py^+ClO_4^-$



(112) $R^1 = H$, $R^2 = CO_2H$
(113) $R^1 = Cl$, $R^2 = CHO$
(117) $R^1 = NHPh$, $R^2 = CHO$

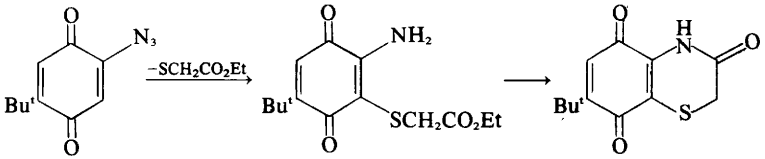


(114)



(118)

(120)

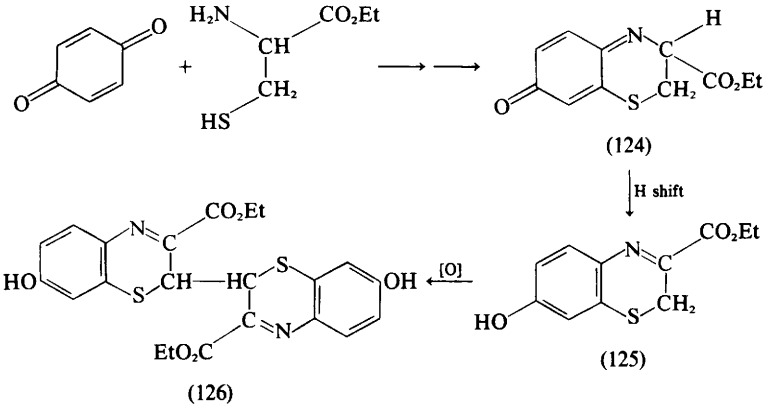


(121) (122) (123)

account for the formation of (126), which involves the oxidative coupling[44] of the 2*H*-1,4-benzothiazine (125), arising from the rearrangement of the primary condensation product (124).

Another structural revision is concerned with the reported[42,45] formation of the thiazine system (127) in the reaction of ninhydrin with cysteine. The chemical and spectroscopic properties of the condensation product are in

[44] D. Sica, C. Santacroce, and G. Prota, *J. Heterocyclic Chem.*, 1970, **7**, 1143.
[45] M. Friedman and C. W. Sigel, *Biochemistry*, 1966, **5**, 478.



(124)

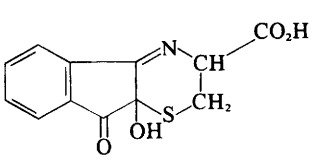
(125)

(126)

Scheme 5

fact consistent with the isomeric spirane structure (129),[46] resulting from the mechanistically more plausible cyclization of the proposed[45] intermediate (128) at the 2-position of the indane skeleton.

A study of the reaction of cysteine and its ethyl ester with adenochrome (130) is also reported[47] to give, along with 5,6-dihydroxy-1-methylindole, the pyrrolo[2,3-*h*][1,4]benzothiazine (132), a member of a novel heterocyclic sytem, which probably arises by the dehydration and oxidative ring-closure of the addition product (131).



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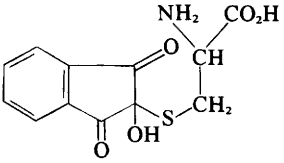

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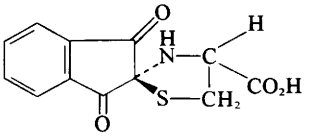

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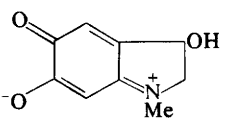
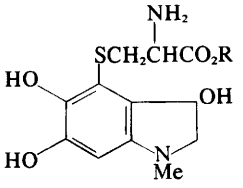


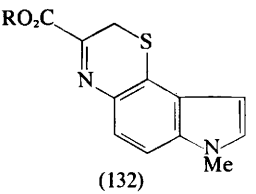
(130)

Phenothiazines (Dibenzo-1,4-thiazines) and Related Compounds.—Further extensive work[48] has appeared on the structure and mode of formation of the green compound that is formed by oxidation of phenothiazine under

[46] G. Prota and E. Ponsiglione, *Tetrahedron*, 1973, **29**, 4271.
[47] C. Santacroce, G. Prota, and D. Sica, *Chimica e Industria*, 1972, **54**, 659.
[48] P. Hanson and R. O. C. Norman, *J.C.S. Perkin II*, 1973, 264.



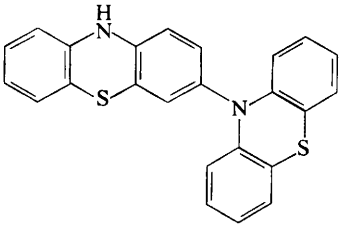
(131)



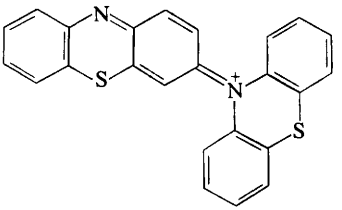
(132)

various conditions (see Vol. 1, p. 467). Direct spectroscopic observations, coupled with a study of the oxidation of the unambiguously prepared 3,10′-biphenothiazinyl (133), lead to the conclusion that the green compound contains the cation (134) and is formed by oxidative dimerization of the neutral radical (135), in accord with an earlier suggestion.[49]

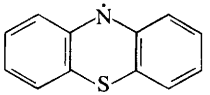
In connection with studies on the chemistry of cation radicals, the stable sulphilimine derivative (136) has been isolated in nearly quantitative yields



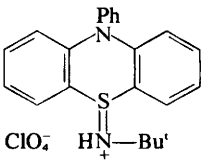
(133)



(134)



(135)



(136)

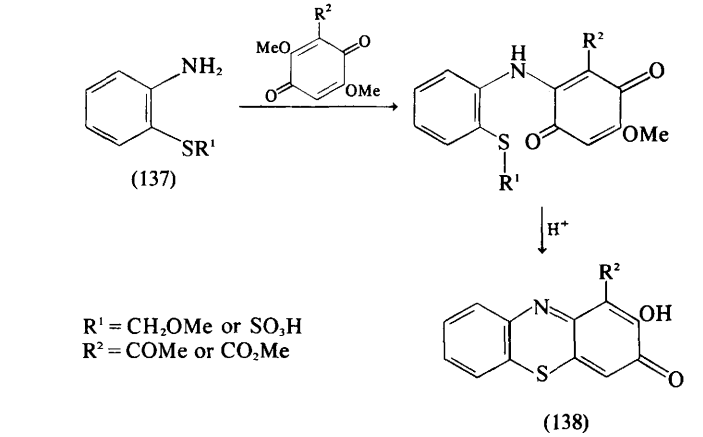
from the reaction of the *N*-phenylphenothiazine cation-radical perchlorate with t-butylamine in acetonitrile solution.[50] An entirely analogous reaction occurs with the thianthrene cation-radical perchlorate.[50]

The synthesis of 2-hydroxy-3*H*-phenoxazinones from *o*-aminophenols and quinones[51] has been successfully adapted to the preparation of the phenothiazine analogues, *e.g.* (138), by condensation of 2,5-dimethoxy-1,4-benzoquinones with SH-protected *o*-aminobenzenethiols (137), followed by

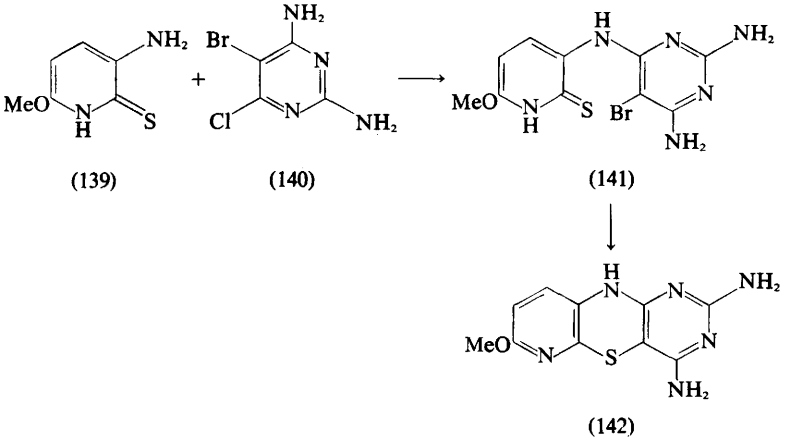
[49] R. Foster and P. Hauson, *Biochim. Biophys. Acta*, 1966, **112**, 482.
[50] H. J. Shine and K. Kim, *Tetrahedron Letters*, 1974, 99.
[51] W. Schäfer and H. Schlude, *Tetrahedron*, 1971, **27**, 4721.

removal of the protective group and ring-closure in acid medium (Scheme 6).[52] Further compounds that have been produced by variations of established routes include 4-aminophenothiazinones,[53] 1- and 4-aminophenothiazine,[54] several 1,2,3,4-tetrahydrophenothiazine derivatives,[55] and some phenothiazine amino-alcohols[56] exhibiting antimalarial activity.

In the realm of azaphenothiazines, Okafor[57] has described the synthesis



Scheme 6



[52] I. Oprean and W. Schäfer, *Annalen*, 1972, **765**, 1.
[53] E. Broser and C. Bodea, *Rev. Roumaine Chim.*, 1972, **17**, 1747.
[54] S. V. Zhuravlev, A. N. Gritsenko and Z. I. Ermakova, *Ref. Zhur. Khim.*, 1972, Abs. No. 7Zh491 and 7Zh492. (*Chem. Abs.*, 1973, **78**, 29 692y and 29 695b).
[55] V. I. Shvedov, L. B. Altukhova, V. M. Lyubchanskaya, and A. N. Grinev, *Khim. geterotsikl. Soedinenii*, 1972, **11**, 1509.
[56] E. A. Nodiff, W. Muller, and T. Yabuuchi, *J. Heterocyclic Chem.*, 1973, **10**, 873.
[57] C. O. Okafor, *J. Org. Chem.*, 1973, **26**, 4386.

of a novel heterocyclic system, *e.g.* (142), by acid-catalysed condensation of suitably substituted 3-aminopyridine-2[1*H*]-thiones (139) with 5,6-dihalogenopyrimidines (140), and subsequent cyclization of the intermediate diarylamine (141). A discussion concerning methods of analysis of phenothiazine drugs in biological material has also appeared.[58] The methods covered include direct screening tests, extraction techniques, thin-layer and gas–liquid chromatography, u.v. spectrophotometry, and spectrofluorometry.

[58] G. Cimbura, *J. Chromatog. Sci.*, 1972, **10**, 287.

17

Theoretical Aspects of Organosulphur and Organoselenium Compounds

BY J. FABIAN

1 Introduction

This Report outlines advances in the quantum chemistry of cyclic conjugated compounds within the period from April 1970 to the beginning of 1974. With respect to problems and advances of the quantum-chemical approximations, this Report is strongly linked to the former.[1]

The development of theoretical methods has led in two obvious directions. A more fundamental understanding of the chemical bond in sulphur compounds and of its properties can only be realized by non-empirical methods. In spite of the remarkable progress in this field and the study of an increasing number of compounds, the applicability of the non-empirical methods is still strongly restricted by high computer expenditure. Semi-empirical methods, however, have turned out to be more reliable in the search for a more general classification and rationalization of experimental data and for an estimation of as-yet-unknown data. Although the fundamental origin of the phenomena cannot be revealed, the experimental chemist can find useful relations between molecular properties of a wide variety of compounds. The fact that experimental chemists are now experienced in using semi-empirical methods has led to a strong overlap between theoretical and experimental studies. However, papers in which the input parameters have been modified in order to reproduce experimentally obtained molecular properties should be regarded critically. The value of these theoretical studies is only convincing where just a few theoretical parameters are introduced to rationalize a large amount of experimental data.

This Report deals with cyclic conjugated compounds which have attached sulphur (selenium)-containing groups, (1), and with compounds which include the heteroatoms within a ring, (2). Since the number of

(1) (2)

[1] D. T. Clark, in 'Organic Compounds of Sulphur, Selenium, and Tellurium,' ed. D. H. Reid (Specialist Periodical Reports), The Chemical Society, London, 1970, Vol. 1, p. 1.

electrons in these systems is relatively large, most of the theoretical studies have been performed by semi-empirical methods at a low level of sophistication. Only those results which were obtained by more refined semi-empirical or non-empirical methods are discussed in detail here.

Recent trends and developments in theoretical methods are outlined in the following section. The aromaticity of sulphur heterocycles is considered separately. The main part of the review concerns theoretical studies of different classes of compounds and these are grouped according to chemical structure. In this way this Report follows previous reviews by Zahradník (to 1964)[2] and by Párkányi (1965—1969).[3] Another survey by the Reporter has covered the quantum chemistry of organic and inorganic sulphur compounds up to 1970.[4a] Some aspects of structure and bonding in organosulphur compounds have been considered more recently by Clark.[4b]

2 Theoretical Methods

Semi-empirical Calculations.—As several excellent descriptions of the semi-empirical methods exist,[5] consideration may be confined to some recent developments, and the modification of these methods in the treatment of organosulphur and organoselenium compounds. In most cases the simple Hückel molecular orbital method (HMO) has been used with the heteroatoms taken into account by the p_π model.[2] One remarkable exception has been the study of Janssen *et al.* on conjugated sulphones;[6] in their paper they offer a simple HMO model for the p_π–d_π interaction of sulphur which is a refinement of the former model of Moffitt and Koch. The inclusion of the $3d_\pi$-orbitals is, in general, not necessary for calculation of compounds with σ-bivalent sulphur.[2] Recent calculations of spin densities have established that their participation worsens the results if one uses the Longuet-Higgins' prescription for sulphur orbitals.[7–9] However, Nanda and Narasimhan have shown, by a careful theoretical study,[7] that poor prediction of spin densities using the Longuet-Higgins model implies the inapplicability and limitation of this model rather than ruling out possible participation of *d*-orbitals on sulphur in bonding.

HMO calculations have been used mostly to discuss or to correlate

[2] R. Zahradník, in 'Advances in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York, 1965, Vol. 5, p. 1.

[3] C. Párkányi, in 'Mechanism of Reactions of Sulfur Compounds,' ed. N. Kharasch, Intra-Science Research Foundation, 1969, Vol. 4, p. 69.

[4] (*a*) J. Fabian, in 'Sulphur in Organic and Inorganic Chemistry,' ed. A. Senning, Marcel Dekker, New York, 1972, Vol. 3, pp. 39—90, 379—390; (*b*) D. T. Clark, *Internat. J. Sulfur Chem.* (*B*), 1972, **7**, 11.

[5] K. Jug, *Theor. Chim. Acta*, 1969, **14**, 91; G. Klopman and B. O.'Leary, *Fortschr. Chem. Forsch.*, 1970, **15**, 445; W. Kutzelnigg, G. Del Re, and G. Berthier, *ibid.*, 1971, **22**, 1; M. J. S. Dewar, *ibid.*, 1971, **23**, 1.

[6] F. De Jong and M. J. Janssen, *J.C.S., Perkin II*, 1972, 572.

[7] D. N. Nanda and P. T. Narasimhan, *Mol. Phys.*, 1972, **24**, 1341.

[8] L. Lunazzi, G. Placucci, and M. Tiecco, *Tetrahedron Letters*, 1972, 3847.

[9] L. Lunazzi, A. Mangini, G. Placucci, P. Spagnolo, and M. Tiecco, *J.C.S. Perkin II*, 1972, 192.

quantities of chemical reactivity, redox potentials, n.m.r. chemical shifts, e.s.r. hyperfine splitting constants, and u.v.—visible excitation energies (see below). (A derivation of optimal parameters by a contour approach is given in ref. 10.) Extended Hückel theory (EHT) has been applied in the standard procedure (see ref. 1). The Pariser–Parr–Pople (PPP) method has been modified and used in calculations of sulphur organic compounds. Skancke *et al.* have extended their parametrization to sulphur-containing heteroatomic molecules.[11]

Attempts to obtain relations for the derivation of core and electron repulsion integrals have been reported. Yoshida *et al.*[12] have published equations in which the Coulomb repulsion and core resonance integrals depend on the calculated π-charges; the integrals are thus optimized within the iterative self-consistent-field (SCF) calculation. For molecules having a localized σ-charge or strongly polar groups the assumption of a non-polarizable core is open to question, and procedures have been proposed for the evaluation of the core charges for these molecules, using Mulliken electronegativities.[13,14] Relations have been published which allow calculation of the core charges in sulphur, selenium, and tellurium compounds.[13] The core charges for some ionic and meso-ionic sulphur heterocycles have been derived from the corresponding CNDO/2 all-valence-electron distribution.[15] Starting from the core charge, the valence state ionization potentials and one-centre Coulomb integrals may be calculated by parabolic[13,15] or linear equations,[13] or by means of the interpolation formula of Nishimoto.[14] The paper by Zahradník *et al.* contains the necessary constants for calculations on sulphur, selenium, and tellurium compounds. Another modified PPP method for treating sulphur organic compounds in which the variable π-electronegativity as well as the σ-polarization effect are taken into account has been described by Hammond.[16] The core and repulsion integrals were adjusted by means of relations between valence-state ionization potentials and Slater effective nuclear charges.

Compared to the PPP procedure with fixed core parameters, the refined methods do not offer much improvement in the calculation of transition energies or molecular ionization potentials.[17] A similar conclusion was drawn following a comparison of results from different approximations.[15] Zahradník *et al.*[18] have shown that the fixed parameter derived in reference 17 also permits discussion of the spectral data of sulphur-containing radicals by open-shell SCF calculation in the Longuet-Higgins–Pople treatment.

[10] D. M. Sturmer and W. S. Gaugh, *Photogr. Sci. Eng.*, 1973, **17**, 146.
[11] A. Skancke and P. N. Skancke, *Acta Chem. Scand.*, 1970, **24**, 23.
[12] Z. Yoshida and T. Kobayashi, *Theor. Chim. Acta*, 1970, **19**, 377; *ibid.*, 1971, **20**, 216.
[13] J. Pancíř, I. Matoušek, and R. Zahradník, *Coll. Czech. Chem. Comm.*, 1973, **38**, 3039.
[14] Y. Ferré, É.-J. Vincent, H. Larivé, and J. Metzger, *Bull. Soc. chim. France*, 1972, 3862.
[15] J. Fabian, *J. prakt. Chem.*, 1973, **315**, 690.
[16] H. A. Hammond, *Theor. Chim. Acta*, 1970, **18**, 239.
[17] J. Fabian, A. Mehlhorn, and R. Zahradník, *J. Phys. Chem.*, 1968, **72**, 3975.
[18] R. Zahradník, P. Čarsky, S. Hünig, G. Kiesslich, and D. Scheutzow, *Internat. J. Sulfur Chem. (C)*, 1971, **6**, 109.

As Dewar has pointed out,[19,20] PPP parameters derived from electronic excitation energies are unsuited for calculation of thermochemical data; calculation of the heat of atomization requires lower core resonance integrals. Consequently, two different sets of parameters were employed for the quantum chemical calculations of π systems. In connection with this, the recent paper of Pancíř and Zahradník is worthy of mention.[13] An appropriate choice of the core parameters permitted calculation of ground-state and excited-state properties; this careful study embraces a variety of compounds, including thiophenol and some sulphur heterocycles.

Some efforts have been made to incorporate the $3d_\pi$-orbitals into the PPP formalism. Pioneering work was done by Bielefeld and Fitts on thiophen and the participation of these orbitals in sulphur-containing radicals has been taken into account by Nanda and Narasimhan[7] using the unrestricted Hartree–Fock (URHF) formalism of Amos and Snyder, using orthogonalized atomic orbitals (OAO): in order to preserve molecular symmetry and rotational invariance, the repulsion integrals in the OAO basis involving *d*-orbitals were averaged. A roughly approximated *pd* model with a completely empirical parametrization has been used in calculating heterocyclic closed-shell systems;[15,21] the effect of the *d*-orbitals on the electron distribution and transition energies was found to be small. However, a more fundamental discussion requires more refined theoretical methods.

Some attempts have also been made to include the orbital of the lone-pair electrons in the linear combination of the p_π-orbitals;[21] this would allow the $\pi^* \leftarrow n$ transitions of thioketones to be considered.

Although electronic transition energies are mainly obtained by semi-empirical SCF methods with limited configuration interaction (LCI) based on delocalized orbitals, the use of localized orbitals has some advantages for the interpretation of data. The latter procedure is known as the 'Molecules-in-Molecule' (MIM) method. An extension of this method to π-electron systems with heteroatoms has been given and exemplified for sulphur-containing compounds.[22] Differences in the calculated spectral data between the PPP and MIM methods are small where the participating localized π systems are weakly coupled.[23]

The main applications of the PPP method are in the predictions of electronic excitation energies, ionization potentials, and bond lengths, and (where contributions of the σ system and even dipole moments are taken into account) predictions of molecular geometries and heats of atomization.

[19] M. J. S. Dewar, 'The Molecular Orbital Theory of Organic Chemistry,' McGraw-Hill, New York, 1969.
[20] M. J. S. Dewar and N. Trinajstić, *J. Amer. Chem. Soc.*, 1970, **92**, 1453.
[21] J. Fabian, *Z. phys. Chem.* (*Leipzig*), 1972, **250**, 377.
[22] K. H. Giovanelli, G. Hohlneicher and P. A. Straub, *Ber. Bunsengesellschaft phys. Chem.*, 1971, **75**, 857; K. H. Giovanelli, J. Dehler, and G. Hohlneicher, *ibid.*, p. 864.
[23] J. Fabian and H. Keiper, *Wiss. Z. Tech. Univ. Dresden*, 1973, **22**, 769.

More experience is now available in the field of semi-empirical all-valence-electron calculation. The CNDO/2 procedure ('complete neglect of differential overlap') has mainly found application using the *pd* model of sulphur in the parametrization of Santry and Segal,[24] which strongly exaggerates *d*-orbital participation. A later modification by Santry[25] has been shown not to be rotationally invariant[26] and so it is unreliable for the theoretical investigation of molecular conformations and related problems. The CNDO/2 method has been invoked mostly for discussions of electron distribution (dipole moments), bond strength, and molecular geometry. Unfortunately, in general the energy-minimized configurations of compounds having second- and higher-row elements were not derived by appropriate computer programs, and so some results may be questionable. In many cases conformational studies by the CNDO/2 method have yielded insufficient results. In this respect the PCILO method ('perturbative configuration interaction with localized orbitals') seems to be more reliable; results for some sulphur-containing structures have been published recently.[27,28]

Some modifications of the standard CNDO/2 procedure[24] have been made to obtain better values for the barriers to pyramidal inversion[29] and the electronic transition energies (CNDO/S method).[30,31] Exaggerated intermingling of π- and σ-electronic transitions was avoided by differentiation of the π- and σ-type overlap by an appropriate factor. Although SCF ground-state properties seem to be little influenced by *d*-orbitals, the situation for the excited states might be expected to be different because singly excited configurations involving excitation to 3*d* AO's lie close in energy to low-lying excited valence states. Therefore some attempts have been made recently to include S-3*d* orbitals in calculations of electronic spectral data.[32–34]

Calculations on selenium compounds of the type (1) and (2) have not been reported, although the CNDO/2 parameters for selenium which are now available make these possible.[35]

The INDO ('intermediate neglect of differential overlap') formulation and parametrization have been extended for calculations of compounds with

[24] D. P. Santry and G. A. Segal, *J. Chem. Phys.*, 1967, **47**, 158.
[25] D. P. Santry, *J. Amer. Chem. Soc.*, 1968, **90**, 3309.
[26] J. R. Sabin, D. P. Santry, and K. Weiss, *J. Amer. Chem. Soc.*, 1972, **94**, 6651.
[27] R. Arnaud, D. Faramond-Baud, and M. Gelius, *Theor. Chim. Acta*, 1973, **31**, 335.
[28] J. L. Coubeils and B. Pullman, *Theor. Chim. Acta*, 1972, **24**, 35.
[29] A. Rauk, J. D. Andose, W. G. Frick, R. Tang, and K. Mislow, *J. Amer. Chem. Soc.*, 1971, **93**, 6507.
[30] A. Tajiri, T. Asano, and T. Nakajima, *Tetrahedron Letters*, 1971, 1785.
[31] G. Pfister-Guillouzo, D. Gonbeau, and J. Deschamps, *J. Mol. Structure*, 1972, **14**, 81.
[32] J. Kroner and D. Proch, *Tetrahedron Letters*, 1972, 2537.
[33] C. Guimon, D. Gonbeau, and G. Pfister-Guillouzo, *Tetrahedron*, 1973, **29**, 3399.
[34] K.-W. Schulte and A. Schweig, *Theor. Chim. Acta*, 1974, **33**, 19.
[35] H. L. Hase and A. Schweig, *Theor. Chim. Acta*, 1973, **31**, 215.

second-row elements[36] and have been used to predict e.s.r. hyperfine splitting constants.[37]

MINDO/3 ('modified intermediate neglect of differential overlap') calculations were carried out recently by Dewar *et al.* for sulphur-containing reaction intermediates, although the computational details were not specified.[38]

Non-empirical Calculations.—Only a few papers involving non-empirical calculations of heteroaromatic sulphur compounds have been reported. Csizmadia *et al.* have continued their studies on sulphur organic compounds with the computation of the thiirenium ion.[39] Gelius, Roos, and Siegbahn[40] have now published the results of their calculations for thiophen; computational details are given in a previous Report.[1] Thiophen has also been calculated more recently by Palmer and Findlay;[41] in their case the value for total energy was higher than in the former calculations. The linear combination of Gaussians included 10 *s*- and 6 *p*-type functions for sulphur, 7 *s*- and 3 *p*-type functions for carbon, and 3 *s*-type for hydrogen, which were contracted to 1*s*, 2*s*, 2*p*, and 3*p* orbitals. These were then augmented with a single Gaussian for each of the five *d*-orbitals. The authors[41] concluded, in good agreement with Gelius *et al.*,[40] that the inclusion of *d*-orbitals represents a gain in variational flexibility rather than a significant *d*-orbital participation. *d*-Orbital effects of a similar kind were found for other sulphur heterocycles, *e.g.* 1,3- and 1,2-dithiolium cations, thiopyrylium cation, thiadiazoles, and thiathiophthen and hetero-analogues.[4b,41,42]

3 Aromaticity of Organosulphur Compounds

The term 'aromaticity' has been the subject of many discussions in recent years although no definition has been generally accepted. For the experimental chemist a compound may be aromatic if its chemistry is like that of benzene, while for the theoretical chemists a compound is aromatic if it has low ground-state enthalpy and other characteristic ground-state properties such as bond equalization, ring-current effect, Faraday effect *etc.*

Labarre and Crasnier[43] believe that the only way to avoid confusion will be a purely theoretical definition: 'When the theory allows us to predict quantically the experimental signs of aromaticity, it will be possible to

[36] H. G. Benson and A. Hudson, *Theor. Chim. Acta*, 1971, **23**, 259; J. J. Kaufmann and R. Predney, *Internat. J. Quantum Chem.*, 1972, **6**, 231.
[37] V. Galasso, *Chem. Phys. Letters*, 1973, **21**, 54; V. Galasso and N. Trinajstić, *J. Chim. phys.*, 1973, **70**, 1489.
[38] M. J. S. Dewar and C. A. Ramsden, *J.C.S. Chem. Comm.*, 1973, 688.
[39] A. S. Denes, I. G. Csizmadia, and G. Modena, *J.C.S. Chem. Comm.*, 1972, 8.
[40] U. Gelius, B. Roos and P. Siegbahn, *Theor. Chim. Acta*, 1972, **27**, 171.
[41] M. H. Palmer and R. H. Findlay, *Tetrahedron Letters*, 1972, 4165.
[42] M. H. Palmer, R. H. Findlay, and A. J. Gaskell, *J.C.S. Perkin II*, 1974, 420.
[43] J.-F. Labarre and F. Crasnier, *Fortschr. Chem. Forsch.*, 1971, **24**, 33.

approach the unique entity. While awaiting this problematic happy time, it seems that, at the present stage, each group of scientists using a given experimental approach should try to define and to measure whatever is measurable by their own technique, in the hope that the data thus accumulated will eventually fit into a unified theory'.[43] This would mean that any classification would depend upon our experimental knowledge. However, so far as experimental values can be estimated sufficiently theoretically, quantum-chemical calculation may stimulate experimental research and consequently contribute to the further discussion about aromaticity. In line with this point of view, the following studies on sulphur-containing compounds are worthy of mention.

(i) *G*-Values and magneto-optical properties (Faraday-effect) have been calculated for some substituted benzenes and thiophens.[43,44]

(ii) The ring-current effect and proton chemical shifts have been calculated for five-membered heterocycles.[45]

(iii) π-Bond orders and bond lengths have been calculated for thiophenol and several heterocyclic compounds.[20]

(iv) π-Bond orders in the six-membered ring of benzo-condensed heterocycles, and the corresponding vicinal coupling constants, have been calculated, and the electron structures of benzothiepins have been discussed using these experimental values.[46]

(v) Heats of atomization, and stabilization energies relative to olefinic structures ('Dewar' resonance energy') have been calculated. The latter data permitted a classification of the sulphur heterocyclic compounds.[20] The first calculations of resonance energies of cyclic sulphur-containing compounds were performed within the PPP approximation. More recently, Hess and Schaad[47] obtained similar results by HMO calculations and classified a large number of known or as-yet-unknown sulphur heterocycles as aromatic, non-aromatic, or anti-aromatic systems.

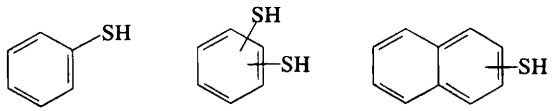
Some of these results are discussed in the following sections.

4 Cyclic π-Systems with Sulphur-containing Groups

Thiols and Sulphides.—Theoretical studies on thiophenol (3) have made important contributions to the knowledge about the substituent effect of the SH group, relative to that of the OH group. Owing to the small resonance integral between the p_π-orbitals of sulphur and carbon, the mercapto-group, is characterized by its weak donor substituent effect. However, because of the low valence-state ionization potential of sulphur, this group exerts a strong shift on the electronic absorption wavelengths and markedly lowers

[44] G. Robinet and J.-F. Labarre, *J. Chim. phys.*, 1970, **67**, 1843.
[45] E. Corradi, P. Lazzeretti, and F. Taddei, *Mol. Phys.*, 1973, **26**, 41.
[46] H. Günther, A. Shyoukh, D. Cremer, and K. H. Frisch, *Tetrahedron Letters*, 1974, 781; D. Cremer and H. Günther, *Annalen*, 1972, **763**, 81.
[47] B. A. Hess and L. J. Schaad, *J. Amer. Chem. Soc.*, 1973, **95**, 3907.

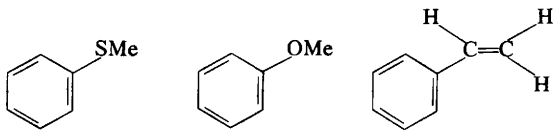
the molecular ionization potential. Good agreement has been obtained by PPP calculations between experimental and theoretical values for (3)—(5)[48] (for calculations on thiocresols see ref. 49). The strong charge-transfer



(3) (4) (5)

character of low-energy $\pi^* \leftarrow \pi$ transitions has been revealed within the MIM model.[50] The absorptions of the deprotonated thiophenols may be described very well if the ionization potential of the sulphur is chosen appropriately.[48]

Discussion about the electronic structures of thiophenol has been revived by the elucidation of the photoelectron (p.e.) spectra.[51,52] Using π-molecular orbitals based on the validity of Koopmans' theorem, Bock *et al.*[51] have nicely visualized the different behaviour of (6) and (7) on ionization. In Figure 1 the qualitative MO schemes are compared with the corresponding



(6) (7) (8)

p.e. spectra. Because of the node properties of the e_{1g} orbitals of benzene, the degeneracy should be removed by a *p*-electron pair extending the π-system. As the ionization energies p_S and p_O, of (6) and (7) respectively, are quite different, splitting patterns should lead to a relatively low first and third ionization potential for (6) in comparison to the O-analogues, but to second ionization potentials of the same order of magnitude. This is just what was observed.

The ionization potentials of *S*-methyl substituted (4) and (5) have been interpreted in a similar way.[51] Agreement between calculated (PPP approximation) and experimental values was excellent. More recently, Johnstone *et al.*[52] have compared the p.e. spectrum of (3) with that of iso-π-electronic styrene (8). The spectra of both are so similar as to be almost superimposable over the whole energy range investigated. This is also in good agreement with results of PPP calculations.

[48] J. S. Kwiatkowski, M. Berndt, and J. Fabian, *Acta Phys. Polon.* (*A*), 1970, **38**, 365.
[49] P. C. Mishra and D. K. Rai, *Indian J. Pure Appl. Phys.*, 1972, **10**, 53.
[50] K. H. Hohlneicher, J. Dehler, and G. Hohlneicher, *Ber. Bunsengesellschaft phys. Chem.*, 1971, **75**, 864.
[51] H. Bock, G. Wagner, and J. Kroner, *Tetrahedron Letters*, 1971, 3713; *Chem. Ber.*, 1972, **105**, 3850.
[52] R. A. Johnstone and F. A. Mellon, *J.C.S. Faraday II*, 1973, 1155.

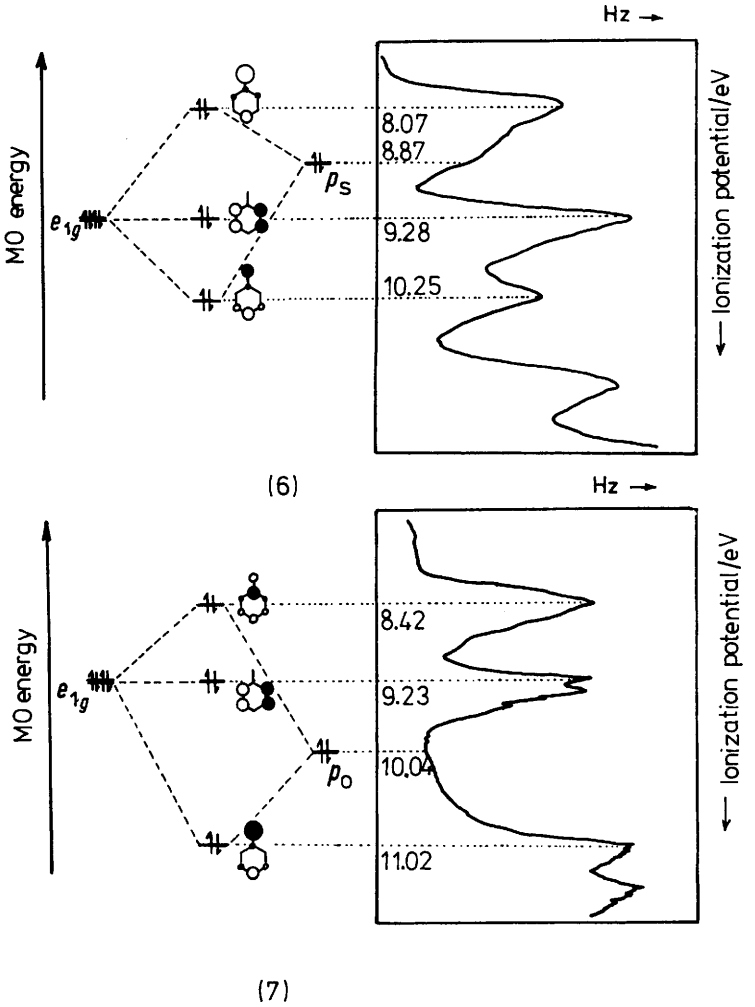


Figure 1 *Qualitative* πMO *schemes for thioanisole* (6) *and anisole* (7) *compared with their photoelectron spectra*
(Adapted from *Tetrahedron Letters*, 1971, 3713)

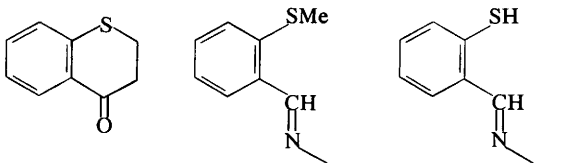
Theoretical studies have been performed on the Faraday effect[44] and the ring-current effect of the SH group.[53] Uncoupled Hartree–Fock perturbation theory was employed for calculation of the ring current. The SCF MO's were obtained by PPP calculations. The SH group as well as other

[53] P. Lazzeretti and F. Taddei, *Mol. Phys.*, 1971, **22**, 941.

hetero-substituents lowers the ring current by an amount that seems to depend on the electronegativity of the substituent. The linear dependence between proton chemical shifts and SCF charges is generally improved when the experimental chemical shifts are corrected for the ring-current contributions.

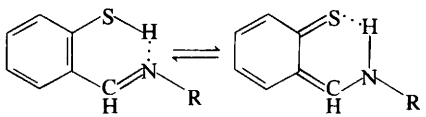
Thiochromanone (9) may be considered a derivative of thiophenol. The spectral excitation energies of (9) have been calculated satisfactorily by the MIM method and interpreted in terms of local excitations on benzene, and the charge-transfer transitions S → benzene, benzene → CO, and S → CO.[50]

Good results were also obtained by PPP calculations for *o*-methylmercaptobenzaldimines (10).[54] However, agreement between theoretical and experimental spectral data could only be achieved for *o*- and



(9) (10) (11)

p-mercapto-compounds and their benzologues when an enethiol–thioketo tautomerism was invoked,[54–56] *i.e.*



(11a) (11b)

The absorption at long wavelength in the visible region was attributed to the quinoid tautomer. Assignment of the electron excitation and discussion of the tautomeric equilibrium have been given with the aid of PPP calculations. A related study[57] [theoretical and experimental, (PPP, CNDO/2)] should also be mentioned; this showed that thioacetylacetone exists as an equilibrium mixture of the enethiol form and the thione form. 3-Arylaminopropene-2-thiones are believed to exist completely in the thione form.[58]

[54] V. I. Minkin, L. P. Olekhnovich, L. E. Nivorozhkin, Yu. A. Zhdanov, and M. Kuyazhanskii, *Zhur. org. Khim.*, 1970, **6**, 348.

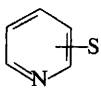
[55] V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, and Yu. A. Ostroumov, *Zhur. org. Khim.*, 1970, **6**, 549.

[56] Yu. A. Zhadnov, V. I. Minkin, L. P. Olekhnovich, and E. N. Malysheva, *Zhur. org. Khim.*, 1970, **6**, 554; V. I. Minkin, L. P. Olekhnovich, and B. Ya. Simkin, *ibid.*, 1971, **7**, 2364; L. E. Nivorozhkin, M. S. Korobov, B. Ya. Simkin, and V. I. Minkin, *ibid.*, 1972, **8**, 1677; V. I. Minkin, B. Ya. Simkin, and L. B. Olekhnovich, *Internat. J. Sulfur Chem.*, 1973, **8**, 249.

[57] J. Fabian, *Tetrahedron*, 1973, **29**, 2449.

[58] M. S. Korobov, L. E. Nivorshkin, and V. I. Minkin, *Zhur. org. Khim.*, 1973, **9**, 1717.

Mercapto-substituted N-heterocycles have been extensively studied by Kwiatkowski *et al.*; PPP-type calculations have been used to predict the $\pi^* \leftarrow \pi$ electronic transition energies, oscillator strengths, and transition polarizations of monomercapto-substituted pyridines (12),[48,59] pyrimidines (13),[48,60] pyrazines (14),[61] purines (15),[62] and 1,3,8-triazaindolizines (16)[63] and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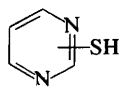
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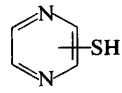
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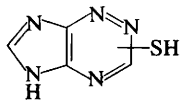
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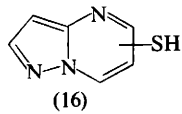
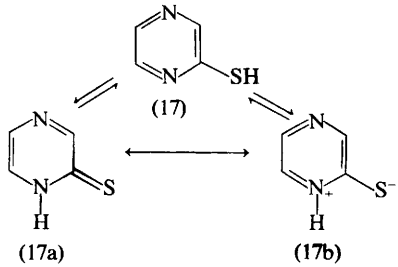

(16)

some of the deprotonated and *S*-methylated derivatives of these compounds (see ref. 64 for calculations on protonated monomethylmercapto-derivatives.) In general, calculated spectra agree well with experimental results.

The treatment of the thiols is more complicated because of their tautomerism:


(17)

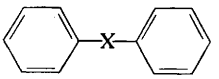
(17a) (17b)

Spectral data of the thiones [*e.g.* (17a)] and of the zwitterionic structures [*e.g.* (17b)] have been calculated.[59-63] The calculations support the results of experimental u.v. analysis in predictions of the most probable tautomeric structures. In general, the thione form is the predominating one. The relevance of zwitterionic structures or at least of polar thione structures is supported by calculations.[59,61] Zwitterionic structures seem to be important for 3-mercapto-pyridine, and 5-mercapto-pyrimidine, which for valency reasons cannot be written in classical thione form. Attempts to analyse the

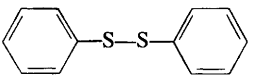
[59] J. S. Kwiatkowski, *J. Mol. Structure*, 1971, **10**, 245.
[60] M. Berndt, M. Ingwer, and J. S. Kwiatkowski, *J. Mol. Structure*, (A), 1973, **19**, 247.
[61] J. S. Kwiatkowski, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1973, **21**, 405.
[62] J. S. Kwiatkowski, *J. Mol. Structure*, 1971, **8**, 471.
[63] C. Glier, F. Dietz, M. Scholz, and G. Fischer, *Tetrahedron*, 1972, **28**, 5779.
[64] J. S. Kwiatkowski, *Acta Phys. Polon.* (A), 1971, **39**, 695.

tautomerism in monosubstituted pyridines and pyrimidines by CNDO/2 calculations have been limited by insufficient knowledge of the molecular geometry.[65] HMO studies on the tautomeric 2,5-dimercapto-1,3,4-triazoles have been mentioned.[66]

Only in a few papers have calculations of cyclic conjugated systems connected by one or more S atom been performed. An attempt has been made to explain the conformations of diphenyl sulphide, diphenyl ether, and diphenyl selenide (18) by investigating the potential surfaces by means of EHT calculations.[67] The butterfly structure was found to be energetically most favoured. The small energy barrier predicted between the principal conformations supports the hypothesis of non-rigid structures for these compounds. By a certain one-electron approximation, among others, the structure of (19) was calculated starting from the experimentally established non-planar geometry.[68] The net charges obtained were compared with charges derived from *X*-ray studies.

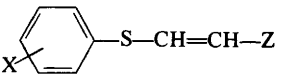


(18) X = O, S, or Se

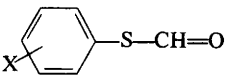


(19)

Another interesting problem concerns the transmission effect through a sulphur bridge. The transmission efficiencies of the sulphur atom in (20; X, Z = heteroatomic groups) were found to be higher than that of oxygen in corresponding ethers; this was interpreted by 'through conjugation'.[69] For this purpose the charge distributions in vinyl methyl and divinyl ethers and sulphur homologues bearing polar substituents at the *trans*-β-position were calculated by the CNDO/2 method (with and without *d*-orbitals). It was concluded that only if the 3*d* orbitals of sulphur can take part in the electron delocalization does the sulphur atom transmit more efficiently than the oxygen atom. The aryl thiolesters (21) have been calculated by the same theoretical



(20)



(21)

approximation.[70] Donor substituents to the thiolester group cause the latter to accept electron density regardless of the *d*-orbital participation. Calculations suggest that the thiolester group withdraws electron density through σ and $2\pi_\pi$–$3d_\pi$ bonding and donates by p_π–p_π bonding.

[65] M. Berndt, J. S. Kwiatkowski, J. Budzinski, and B. Szczodrowska, *Chem. Phys. Letters*, 1973, **19**, 246; J. S. Kwiatkowski and M. Berndt, Preprint of the Institute of Physics, Nicholas Copernicus University Torun, No. 210; J. S. Kwiatkowski, *ibid.*, No. 211.

[66] A. D. Sinegibskaya, E. G. Kovalev, and I. Ya. Postovskii, *Khim. geterotsikl Soedinenii*, 1973, 562, 1708.

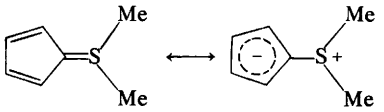
[67] V. Galasso, G. De Alti, and A. Bigotto, *Tetrahedron*, 1971, **27**, 6151.

[68] R. Friedemann and W. Gründler, *Z. Chem.*, 1973, **13**, 308.

[69] O. Kajimoto, M. Kobayashi, and J. Fueno, *Bull. Chem. Soc. Japan*, 1973, **46**, 2316.

[70] J. R. Grunwell and S. I. Hanhan, *Tetrahedron*, 1973, **29**, 1473.

Sulphonium Compounds, Sulphonic Acids, and Sulphones.—Although thorough studies of the conjugation properties of the sulphonium group are not yet available, the electronic structure of the sulphonium cyclopentadienylide (22) has aroused interest.[71-73] π-Bond orders have been calcu-

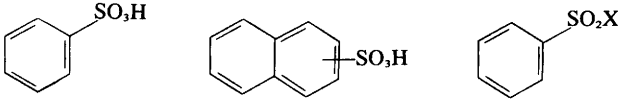


(22) (22a)

lated by the HMO and SCF method and derived from the vicinal n.m.r. coupling constants with the aid of a correlating function; the three sets of values reported are not very different and are in accordance with the ylide-like structure (22a).[71,72] The same conclusion has been drawn from a MIM study, which assumed that the molecule is composed of an electron-donating and an electron-accepting group;[73] the ground state was described as predominantly (22a), with the charge-transfer configuration [corresponding to (22)] contributing only 12%. This led the authors to claim 'aromatic character' for sulphonium cyclopentadienylides, a claim supported by the observed chemical behaviour.[72]

PPP-type calculations, based on simplified models, of the sulphonic acids (23) and (24) have been carried out.[74] In these models conjugation between the sulphonic group and the π electrons of the benzene ring is considered to be due to the presence of a vacant orbital centred on the sulphur atom in the sulphonic group. CNDO/2 calculations for these compounds suggest that the SO_3H group can rotate nearly freely.[75] The C—S bond has a very weak π character with only a small contribution from the *d*-orbitals.

The polarographic reduction potentials of the sulphonic acids and derivatives (25; X = heteroatomic groups)[76] and the carbocyclic (25; X = Ph) and heterocyclic sulphones[6] could be well rationalized by HMO calculations. Mesomeric interaction between the conjugated π systems and the SO_2 group in diaryl sulphones does not affect the S=O bonds; the case of cyclic sulphones derived from thiophens is different, a finding recently established by i.r. data.[77]

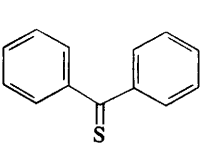


(23) (24) (25)

[71] E. E. Ernstbrunner and D. Lloyd, *Chem. and Ind.*, 1971, 1332.
[72] Z. Yoshida, S. Yoneda, and M. Hazama, *Chem. Comm.*, 1971, 716; *J. Org. Chem.*, 1972, **37**, 1364.
[73] Z. Yoshida, K. Iwata, and S. Yoneda, *Tetrahedron Letters*, 1971, 1519.
[74] V. Em. Sahini and C. I. Ghirvu, *Rev. Roumaine Chim.*, 1970, **15**, 11; 1971, **16**, 149, 321.
[75] C. I. Ghirvu, *Theor. Chim. Acta*, 1973, **30**, 115.
[76] R. Gerdil, *Helv. Chim. Acta*, 1973, **56**, 196.
[77] F. De Jong and M. J. Janssen, *Rec. Trav. chim.*, 1973, **92**, 1073.

Thiones.—PPP-type calculations have been performed which were aimed at interpreting the u.v.—visible spectra of three known cyclic conjugated thiones [(26)—(28)][78,79] and estimating the spectral characteristics of the unknown species [(29)—(32)].[78] Thiobenzaldehyde (29)[80] and thiotropone (32)[81] have since been synthesized, and absorption data were found to be in good agreement with theoretical predictions. Calculations within the PPP approach have been made for (32), tropone, and iminotropone;[81] the bond fixation was found to decrease in the order heptafulvene > thiotropone > iminotropone > tropone, *i.e.* the contribution of the 6π dipolar structure is considerably smaller for thiotropone than for tropone. Bearing in mind the strong bond alternation of tropone recently found by gas electron diffraction,[82] thiotropone should be polyolefinic.

Iso-π-electronic heterocyclic structures may be deduced formally from (32) by replacing one or two double bonds by lone-pair heteroatoms. The nitrogen heterocycle (33) has been studied by means of the HMO method;[83] the sulphur heterocycles are dealt with below.



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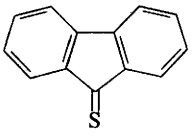

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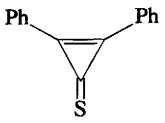
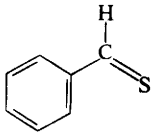


(28)



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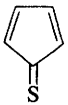

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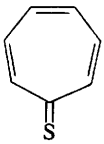

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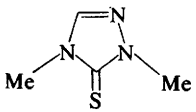


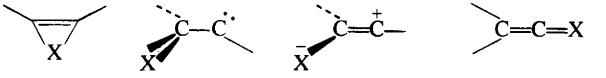
(33)

5 Heterocyclic Sulphur and Selenium Compounds

4π Heterocycles and Derivatives.—From consideration of resonance energy, thiirens (34; X = S) should be anti-aromatic, and their existence consequently highly unfavoured. Nevertheless, their formation in chemical or photochemical reactions has been discussed.[84]

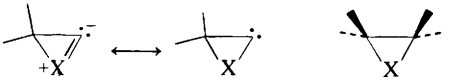
Using the MINDO/3 approach with SIMPLEX energy optimization, Dewar and Ramsden[38] have computed (34) and isomeric structures of (34),

[78] J. Fabian, *Z. phys. Chem. (Leipzig)*, 1972, **250**, 377.
[79] Z. Yoshida and H. Miyahara, *Bull. Chem. Soc. Japan*, 1972, **45**, 1919.
[80] H. G. Giles, R. A. Marty, and P. De Mayo, *J.C.S. Chem. Comm.*, 1974, 409.
[81] T. Machiguchi, T. Hoshi, J. Yoshino, and Y. Kitahara, *Tetrahedron Letters*, 1973, 3873.
[82] M. Ogasawara, T. Jijima, and M. Kimura, *Bull. Chem. Soc. Japan*, 1972, **45**, 3277.
[83] E. G. Kovalev and J. Ya. Postovskii, *Khim. geterotsikl Soedinenii*, 1970, 1138; J. Sandström, *Z. Chem.*, 1970, **10**, 406.
[84] O. P. Strausz, Advances in Chemistry Series, Sulphur Research Trends, No. 110, American Chemical Society, 1972.



X = O, S, or NH

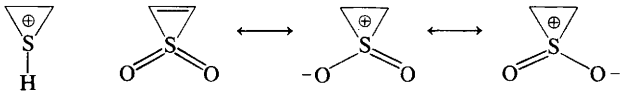
(34) (34a) (34b) (34c)



(34d) X = O, S, or NH (35)

i.e. the carbenes (34a), the zwitterions (34b), the heterocumulenes (34c), and the cyclic carbenes (34d). The structures (34) were calculated to lie in local energy minima, implying that if generated in a chemical reaction they should be stable intermediates. The carbenes (34a) were found to be considerably less stable than the corresponding heterocycles. The calculated heat of hydrogenation for thiiren [(34) + H_2 → (35)] may be considered, if compared with that of cyclopropene, a measure of the anti-aromatic destabilization. As the heats of hydrogenation of both compounds are nearly equal, the anti-aromatic destabilization should be small if not zero (see former discussion[4b,85]). Derivatives of the thiirenium ions (36) may also be intermediates of chemical reactions; non-empirical SCF–MO calculations showed that the thiirenium form is more stable than the $HSCH{=}CH^+$ form.[4b,39]

The role of the sulphur *d*-orbitals in bonding has been discussed for (34) and (36).[4b] If an appropriate d_π orbital participated, a Möbius-type system could arise and a 4π-electron system would be energetically preferred in this case. The relevance of the Möbius-type overlap was recently discussed by Janssen *et al.* in an elucidation of the bonding in thiiren dioxide (37).[86] CNDO/2 calculations revealed that the dipolar structures (37a) and (37b) were not important for the description of the electronic structure (as in the case of cyclopropenone). In good agreement with experimental findings, the bonding in the SO_2 group of (37) was calculated barely to differ from that in aliphatic sulphones.

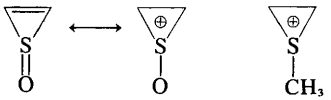


(36) (37) (37a) (37b)

The barriers to pyramidal inversion of methyl-substituted (38) and (39) were calculated to be high, relative to the barrier for thiophen dioxide, and

[85] D. T. Clark, in 'Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry,' ed. E. D. Bergmann, Israel Acad. Science and Humanity, Jerusalem, 1970, Vol. 2, p. 238.

[86] F. De Jong, A. J. Noordin, T. Bouwman, and M. J. Janssen, *Tetrahedron Letters*, 1974, 1209.



(38) (38a) (39)

this has been interpreted as due to the energetically unfavoured planar 4π Hückel-type system.[87]

6π Heterocycles and Derivatives.—*Unsubstituted Thiophens.* Thiophen is energetically favoured;[20] its resonance energy has been calculated to be 6.5 kcal mol^{-1}. This value is higher than that for furan (*ca.* 2 kcal mol^{-1}) but lower than those for pyrrole (*ca.* 9 kcal mol^{-1}) and benzene (*ca.* 20 kcal mol^{-1}). The ring currents of thiophen and furan also suggest that these molecules are less aromatic than pyrrole.[45]

Non-empirical calculations have made important contributions to a better understanding of the electron structure of thiophen.[4b,40] Calculations agreed with semi-empirical π-electron studies in predicting a larger π-electron density on the C_α atom than on the C_β atom; this, however, is more than counterbalanced by the greater accumulation of σ electrons in the β-position. The sulphur atom in thiophen is equally strong as a σ-electron acceptor as a π-electron donor. Only the π-electron distribution seems in agreement with the preferred attack at the α-position of thiophen in electrophilic substitution reactions. To gain more insight into the mechanism of this reaction, Gelius *et al.*[40] have carried out additional calculations; following the method described by Scrocco *et al.*, the electrostatic interaction energy between the molecules and a positive test charge was computed for different plans and mapped. Three distinct minima were found, one in the sulphur-atom region and two over each of the double bonds (Figure 2). The distances from the energy minimum at the double bond to the two carbon nuclei are almost exactly equal. Evidently the preferred α-substitution cannot be explained by a charge-controlled reaction. Gelius *et al.* suggest a frontier-controlled reaction proceeding, perhaps, *via* a π complex. The highest occupied orbital is strongly centred at the α-carbon atom (Figure 2) and consequently the reaction pathway would lead to a preferred α-substitution.

Non-empirical calculations of the *C*-protonated thiophens—the σ complex of the simplest electrophilic substitution reaction—are as yet outstanding. Calculations on the CNDO/2 and PPP levels predict the correct position of electrophilic attack.[88]

A critical examination of the worth of non-empirical calculations for thiophen is possible by comparison with physico-chemical properties. An

[87] J. D. Andose, A. Rauk, R. Tang, and K. Mislow, *Internat. J. Sulfur Chem.* (A), 1971, **1**, 66.
[88] Ya. L. Gol'dfarb, V. P. Litvinov, G. M. Zhidomirov, I. A. Abronin, and R. Z. Zarkharyan, *Chemica Scripta*, 1974, **5**, 49.

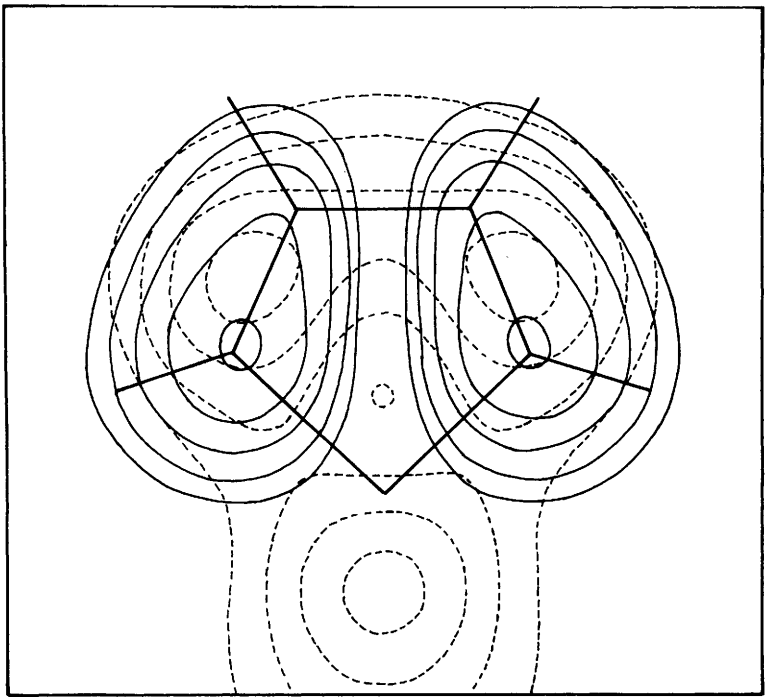


Figure 2 *Molecular potential surface of thiophen in a plane parallel to the molecule at a distance of 1.74 Å (dotted lines) and electron density map for the highest occupied orbital (full lines)*
(Adapted from *Theor. Chim. Acta*, 1972, **27**, 171)

extremely valuable contribution has been provided by p.e. spectroscopy.[52,89,90] U.v. and X-ray excitation lead to the ionization of valence and core electrons, respectively. The ionization potentials (binding energies) of the valence electrons may be equated with the negative value of the molecular orbital energy (within Koopmans' theorem). Although the CNDO/2 approximation provided unsatisfactory values, binding energies and intensities in good agreement with experiment could be computed by non-empirical methods.[40,90] The π-type ionization potentials of thiophen could also be assigned by PPP calculations. The p.e. spectra of selenophen

[89] P. A. Clark, R. Gleiter, and E. Heilbronner, *Tetrahedron*, 1973, **29**, 3085.
[90] U. Gelius, C. J. Allan, G. Johansson, H. Siegbahn, D. A. Allison, and K. Siegbahn, *Physica Scripta*, 1971, **3**, 237; U. Gelius, 'Proceedings of the International Conference on Electron Spectroscopy, 1971,' ed. D. A. Shirley, North Holland, Amsterdam, 1972, *J. Amer. Chem. Soc.*, 1972, **94**, 6298.

and tellurophen revealed that their highest occupied πMO's are in reversed sequence to those of thiophen.[91]

Non-empirical and semi-empirical methods (EHT, CNDO/2) proved to be suited to describing the binding-energy shifts ('chemical shifts') of core electrons when the change of potentials caused by the differences in charge distribution was taken into account.[90,92,93]

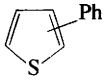
Good agreement has also been achieved between experimental results and theoretical dipole moments, quadrupole moments, diamagnetic susceptibilities, and electronic second moments obtained by non-empirical calculation.[40,42] But, following Bloor *et al.*,[94] the good agreement of the latter values should not be considered as a test for the quality of the molecular wavefunction, as these depend predominantly on the molecular geometry (CNDO/2 calculation of thiophen and other sulphur compounds).

Apart from two exceptions (refs. 30, 34), calculations of electronic transition energies of thiophen have involved PPP π approximations (refs. 11, 13, 16, 95), but results from the latter studies do not differ much from those from the former. (For the role of d_π-orbitals in spin–orbit coupling in thiophen see ref. 96.)

Substituted Thiophens. Aryl-substituted thiophens cannot be planar, and several theoretical studies have been made to predict preferred conformations. EHT computations for 2- and 3-phenylthiophen (40) predict an angle of distortion of 37° between the two planes of the cyclic π-systems:[97] the electron distribution in these conformations was calculated by the CNDO/2-approach and comparison was made between the theoretical and experimental dipole moments. The calculations were later extended to (41) and its hetero-analogues.[98,99] Bond-length calculations predict a very long bond between the heterocycles, which largely preserves the geometries of individual furan and thiophen ring systems.

The planar conformations of (42) have excited strong interest;[100–102] π-type[100] as well as all-valence-electron SCF calculations[101,102] show the S, O-*cis* conformer to be more favoured than the S, O-*trans* form, a finding

[91] W. Schäfer, A. Schweig, S. Gronowitz, A. Taticchi, and F. Fringuelli, *J.C.S. Chem. Comm.*, 1973, 541.
[92] D. T. Clark and D. M. J. Lilley, *Chem. Phys. Letters*, 1971, **9**, 234.
[93] M. E. Schwartz and J. D. Switalski, 'Proceedings of the International Conference on Electron Spectroscopy, 1971,' ed. D. A. Shirley, North Holland, Amsterdam, 1972, *J. Amer. Chem. Soc.*, 1974, **94**, 6298.
[94] Z. B. Maksić and J. E. Bloor, *J. Phys. Chem.*, 1973, **77**, 1520.
[95] A. Julg, M. Bonnet, and Y. Ozias, *Theor. Chim. Acta*, 1970, **17**, 49.
[96] W. R. Wadt and W. R. Moomaw, *Mol. Phys.*, 1973, **25**, 1291.
[97] V. Galasso and G. De Alti, *Tetrahedron*, 1971, **27**, 4947.
[98] V. Galasso and N. Trinajstić, *Tetrahedron*, 1972, **28**, 4419.
[99] L. Klasinc, N. Trinajstić, and E. Pop, *Rev. Roumaine Chim.*, 1973, **18**, 83.
[100] V. I. Minkin, Yu. A. Zhdanov, and E. N. Malysheva, *Teor. i eksp. Khim.*, 1971, **7**, 180.
[101] Ya. L. Gol'dfarb, G. M. Zhidomirov, N. D. Chuvylkin, and L. I. Belen'kii, *Khim. geterotsikl Soedinenii*, 1972, 155.
[102] L. Lunazzi and C. A. Veracini, *J.C.S. Perkin II*, 1973, 1739; S. Nagata, T. Yamabe, K. Yoshikawa, and H. Kato, *Tetrahedron*, 1973, **29**, 2545.



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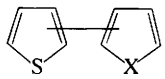
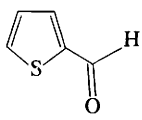


(41) X = O, S, or Se



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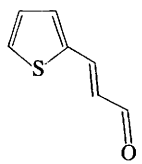
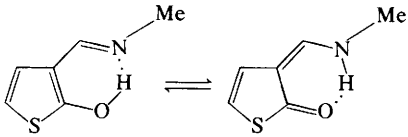


(43)

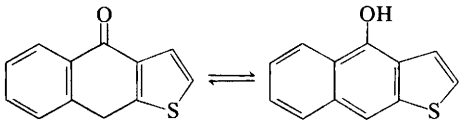
in agreement with experimental results. The attractive interaction between the 3*d* orbitals and the carbonyl oxygen lone pair accounts for the greater stability of the S, O-*cis* form. The calculated value for the barrier to rotation was in good agreement with the experimental value only when the *d*-orbitals were included.

A PPP study of (43) has shown that the unsaturated side chain should be energetically preferred in the *s-trans* arrangement.[103]

Theoretical methods have been applied to elucidate tautomeric equilibria. In agreement with the experimental finding, the Δ^4-thiolen-2-one (44a) was calculated to be more stable than the hydroxythiophen (44).[104] Tautomerization of thiophen analogues of anthrone, *e.g.* (45), was discussed in the light of the differences in HMO energies.[105]



(44) (44a)

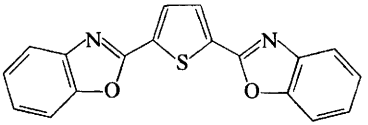


(45) (45a)

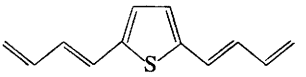
PPP calculations of substituted thiophens have yielded electronic spectral data in good agreement with experiment. Calculations for the weakly coupled phenylthiophens (40) gave nearly the same results by the PPP and MIM approximations;[23] the intense long-wavelength absorption of 2-phenylthiophen may be interpreted by the strong participation of charge-transfer configurations. Spectral data of (46) and other compounds, which have application as brighteners, have been calculated.[106] With the aid of PPP

[103] V. V. Zverev and Yu. P. Kitaev, *Zhur. org. Khim.*, 1974, **10**, 417.
[104] V. S. Bogdanov, M. A. Kalik, G. M. Zhidomirov, N. D. Chuvylkin, and Ya. L. Gol'dfarb, *Zhur. org. Khim.*, 1971, **7**, 1953.
[105] D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, 1971, **36**, 3999, 4004.
[106] H. Frühbeis, *Melliand Textilber.*, 1973, **9**, 955.

calculations, the spectra of the 2,5-polyenyl-substituted thiophens, *e.g.* (47), were rationalized as from substituted polyenes rather than thiophens.[107] An interpretation of the spectra of heterocyclic triptycenes [*e.g.* (48)] involved the assumption of interannular interactions.[108] Satisfactory results have been achieved in calculations of ^1H chemical shifts (by a modified HMO approach)[109] and ring proton–proton coupling constants of thiophens and



(46)



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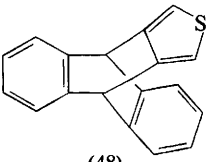


(48)

monosubstituted thiophens (by a perturbed SCF–INDO method).[37] ^{19}F Chemical shifts of fluorothiophens,[110] coupling constants of thiophencarbonylfluoride,[111] p.e. spectra of bromothiophens,[112] and *X*-ray emission $K\beta_1$ spectra of the sulphur in 3-methylthiophens[113] have been discussed, using methods of different levels of sophistication.

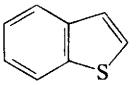
Two papers dealing with HMO calculations of the chemical reactivity of substituted thiophens should be noted; one on the acid-catalysed hydrogen exchange[114] and the other on the transmission of substituent effects across the thiophen ring[115] Gol'dfarb *et al.*[116] have studied another problem in chemical reactivity: electrophilic substitution of thiophen-2-carbaldehyde occurs in the 5-position but at the 4-position when this compound is protonated, and substitution in protonated 2-amino-thiophens occurs at the 5-position despite the *m*-directing property of the ammonium group. They found the chemical reactivity to be related to the CNDO/2 valence-electron densities.[116]

[107] J. W. Van Reijendam and M. J. Janssen, *Tetrahedron*, 1970, **26**, 1291, 1303; M. J. Janssen and J. W. Van Reijendam, *Z. Chem.*, 1970, **10**, 261.
[108] J. De Wit and H. Wynberg, *Tetrahedron*, 1973, **29**, 1379.
[109] B. Kamieński and T. M. Krygowski, *Tetrahedron Letters* 1971, 103.
[110] S. Rodmar, *Mol. Phys.*, 1971, **22**, 123.
[111] K. Schaumburg, *Canad. J. Chem.*, 1971, **49**, 1146.
[112] T. Bergmark, J. Rabalais, J. Wayne, L. O. Werme, L. Karlsson, and K. Siegbahn, 'Proceedings of the International Conference on Electron Spectroscopy, 1971,' ed. D. A. Shirley, North Holland, Amsterdam, 1972, p. 413.
[113] L. N. Mazalov, A. P. Sadovskii, E. A. Gal'tsova, V. V. Murakhtanov, V. G. Torgov, V. M. Bertenev, and A. P. Zeif, *Zhur. strukt. Khim.*, 1973, **14**, 76.
[114] L. Klasinc and K. Humski, *Z. Naturforsch.*, 1970, **25b**, 324.
[115] A. R. Butler, *J. Chem. Soc.* (*B*), 1970, 867.
[116] Ya. L. Gol'dfarb, G. M. Zhidomirov, N. D. Chuvylkin, and L. I. Belen'kii, *Khim. geterotsikl Soedinenii*, 1972, 155; Ya. L. Gol'dfarb, G. M. Zhidomirov, N. D. Chuvylkin, N. S. Ksenzhek, and L. I. Belen'kii, *Zhur. org. Khim.*, 1973, **9**, 1507.

CNDO/2 Wavefunctions of thiophen have been used as a basis in a consideration of the concerted Diels–Alder addition to thiophen, thiophen dioxide, and furan;[117] Lert and Trindle were able to rationalize the observed order of reactivity with the aid of qualitative ideas from perturbation theory.

Annelated Thiophens. PPP Type calculations have made the main contribution to the better understanding of the properties of annelated thiophens. The resonance energies differ clearly between benzo[*b*]thiophen (49) and benzo[*c*]thiophen (50), and between the thieno-thiophens (51)—(54). For thieno[3,4-*c*]thiophen (54) a negative resonance energy has been computed;[20,47] this of course is not surprising, for only zwitterionic structures can be written unless 3*d* AO's are involved. The ring-current effect is different in (49) and (50); a higher electron delocalization was found for the benzene fragment of the more strongly resonance-stabilized (49) than for (50).

U.v.-Photoelectron spectra are available for (49)—(52) and dibenzothiophen (55). On the basis of band shapes and PPP calculations, the first three bands have been assigned to π-ionization potentials.[52,89] The good agreement obtained between measured and calculated ionization potentials suggests that sulphur 3*d* participation must be very small.[89] In contrast, Johnstone *et al.*[52] have explained the striking resemblance of the photoelectron spectra of the annelated thiophens to the iso-π-electronic hydrocarbons naphthalene and anthracene, by the 3*d* participation of the sulphur atoms. This resemblance is well known, and although the usefulness of the PPP model without *d*-orbitals has been confirmed, *e.g.* by calculations of the spectral data of (49)—(53),[11–13,118] of (55) and annelated compounds,[12,13,119]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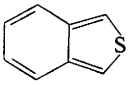
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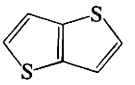
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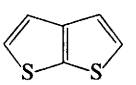
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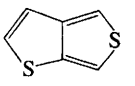
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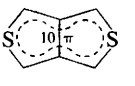

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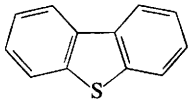
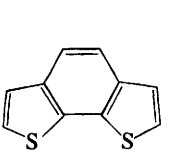

(55)

and of (56),[120] (57),[121] (58),[122] and isomers, a simple explanation of this phenomenon has not been given. At first glance the MIM model should be more appropriate in that it allows separation of sulphur atoms or double

[117] P. W. Lert and C. Trindle, *J. Amer. Chem. Soc.*, 1971, **93**, 6392.
[118] L. Klasinc, E. Pop, N. Trinajstić, and J. V. Knop, *Tetrahedron*, 1972, **28**, 3465.
[119] F. Momicchioli and A. Rastelli, *J. Chem. Soc.* (*B*), 1970, 1353.
[120] L. Klasinc and J. V. Knop, *Z. Naturforsch.*, 1971, **26b**, 1235.
[121] F. De Jong and M. J. Janssen, *J. Org. Chem.*, 1971, **36**, 1645.
[122] M. Scholz, E. Walzel, and H.-J. Hofmann, *J. prakt. Chem.*, 1973, **315**, 1105.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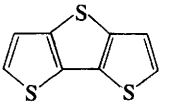
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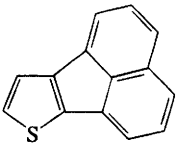
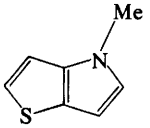

(58)

bonds from the molecular π system. But this model suffers from the strong ground-state depressions which result in cases of strong coupling between the participating π-systems.[23]

PPP calculations have also been carried out for thiophens condensed with N-heterocycles, such as (59), (60),[123] and (61), (62),[124] and isomers. For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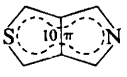
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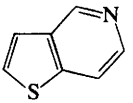
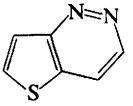
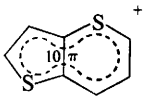

(61)


(62)

the thienopyrroles the $T_1 \leftarrow S_0$ transition energies have been estimated by the half-electron method.[123] Compounds (60) and (54) are expected to be more stable in the triplet state.[123] The electron excitations of thieno[2,3-*c*]thiapyrylium ions [*e.g.* (63)] have been correlated with HMO data.[125]

π-Approximations have also been applied in discussions of the polarographic half-wave potentials of substituted (58)[126] and of the n.m.r. chemical shifts of (58),[127] (64),[128] (61),[129] and isomers. Bond lengths for many of the above-mentioned compounds have been calculated from the π-bond or-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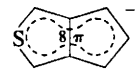
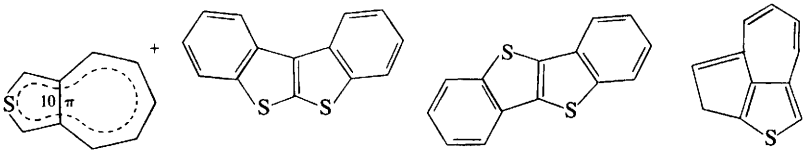

(64)

ders.[11,124,130] An extensive study by Häfelinger also includes other types of conjugated sulphur compounds.[131]

Theoretical studies on chemical reactivity have been mainly restricted to the HMO π-electron distribution and HMO reactivity indices, *e.g.* calculation of (65) and isomers (formation of chromium tricarbonyl complexes);[132]

[123] L. Klasinc and N. Trinajstić, *Tetrahedron*, 1971, **27**, 4045.
[124] A. Helland and P. N. Skancke, *Acta Chem. Scand.*, 1972, **26**, 2601.
[125] T. E. Young and C. R. Hamel, *J. Org. Chem.*, 1970, **35**, 816, 821.
[126] M. Scholz and V. Bachler, *Z. Chem.*, 1973, **13**, 71.
[127] K. D. Bartle, D. W. Jones, R. S. Matthews, A. Birch, and D. A. Crombie, *J. Chem. Soc.* (*B*), 1971, 2092; R. B. Mallion, *J.C.S. Perkin II*, 1973, 235.
[128] J. Skramstad, *Chemica Scripta*, 1973, **4**, 81.
[129] S. Gronowitz and E. Sandberg, *Arkiv. Kemi*, 1971, **32**, 269.
[130] I. Goldberg and U. Shmueli, *Acta Cryst.*, 1971, **B27**, 2164.
[131] G. Häfelinger, *Tetrahedron*, 1971, **27**, 1635.
[132] J. Arriau, J. Deschamps, T. Marey, and J. Tirouflet, *J. Organometallic Chem.*, 1972, **46**, 328.

of substituted (49),[133] of (61), (62), and isomers,[134] of (55), (66), and (67)[135] (electrophilic substitution); and of (68) (isomerization).[136]



(65) (66) (67) (68)

Recently computed CNDO/2 localization energies of electrophilic substitution for thiophen and the thienothiophens (51) and (53) (protonated σ-type complexes without geometry optimization) have provided only a fair correlation with experimental rate constants.[88] The values for localization energies predicted by the CNDO/2 method do not appear to be an improvement over those predicted by the PPP method.

Thiazoles, Isothiazoles, and Selenazoles. The effect of the replacement of C–H group by the more electronegative N atom in going from thiophens to thiazoles (69) or isothiazoles (70) has been examined. The binding energies of core electrons at the ring carbon atoms and at the sulphur have been found to be shifted to higher values by this transition. This has been explained in terms of the charge distributions obtained in CNDO/2 calculations.[92] However, for the interpretation of the u.v.–p.e. spectra the CNDO/2 method was less suitable than the PPP method; the latter method predicts for thiazoles[52] and isothiazoles[137] that one of the first ionization potentials should correspond to the level of the nitrogen lone-pair electron.

Trinajstić *et al.* have concluded from EHT calculations that the most probable conformation of 2-, 4-, and 5-phenylthiazoles (71) is a non-planar one[138] and that the angle of twist about the inter-ring linkage increases in the order $4 < 2 < 5$. The charge distribution for the energetically most favoured geometry was computed by the CNDO/2 method and the calculated dipole moments were found to be consistent with observed values. (For a previous theoretical study of the dipole moments of phenyl-substituted thiazoles, see ref. 139).

The stabilization energies of the donor–acceptor molecular complexes of thiazoles and phenylthiazoles with tetracyanoethylene have been estimated

[133] G. C. Brophy, S. Sternhell, N. M. D. Brown, I. Brown, K. J. Armstrong, and M. Martin-Smith, *J. Chem. Soc.* (*C*), 1970, 933.

[134] L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopfenstein, and D. R. McCoy, *J. Heterocyclic Chem.*, 1970, **7**, 373; L. H. Klemm, W. O. Johnson and D. V. White, *ibid.*, 1972, **9**, 843.

[135] A. Y. Meyer, Z. Rappopart, and D. Elmaleh, *Israel J. Chem.*, 1971, **9**, 135.

[136] H. L. Ammon, L. L. Replogle, P. H. Watts, K. Katsumoto, and J. M. Stewart, *J. Amer. Chem. Soc.*, 1971, **93**, 2196.

[137] G. Salmona, Y. Ferré, and É.-J. Vincent, *J. Chim. phys.*, 1972, 1292.

[138] N. Bodor, M. Farkas, and N. Trinajstić, *Croat. Chem. Acta*, 1971, **43**, 107; V. Galasso and N. Trinajstić, *Tetrahedron*, 1972, **28**, 2799.

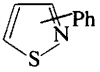
[139] J.-M. Bonnier and M. R. Arnaud, *Compt. rend.*, 1970, **270**, *C*, 885.

by several semi-empirical approaches (EHT, CNDO/2, and PCILO).[27,140] The PCILO method is most suitable and yields results which agree very well with experimental findings.

The *cis–trans* isomerization of 2-formylbenzothiazole (72c) has been studied by Minkin *et al.*[141] in a manner similar to that for the thiophen analogues;[100] (72b) should exist predominantly as the O, S-*cis* isomer. A PPP study of the tautomerism of 2-phenylaminothiazole (72b) has predicted the amino-tautomer to be more stable than the imino-tautomer, a finding in agreement with available experimental data.[142]

(69)

(70)



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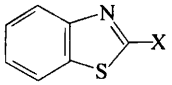
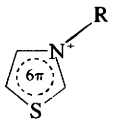


(72) (a) X = H
(b) X = CHO
(c) X = NHPh

An extensive theoretical study of the thiazolium (73),[143] substituted benzothiazolium (74), and benzoselenazolium (75) ions has described well



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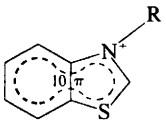

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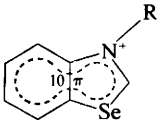


(75)

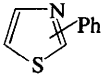
their absorption spectra, their polarographic reduction potentials, and their reactivity.

The following n.m.r. data have been successfully dealt with by various approximations: ^{13}C chemical shifts and J_{CH} of alkyl-substituted-(69) (EHT, CNDO),[144] ^{1}H chemical shifts of (76) (PPP),[145] ^{13}C chemical shifts of 2-methyl-(72a) (EHT, HMO),[146] ^{1}H chemical shifts of (77) (PPP, CNDO/2),[149] and ^{1}H chemical shifts of annelated (77) and isomers (HMO).[147] However, the chemical shift of the ring protons of (70) and (77) could not be correlated

[140] J.-M. Bonnier and M. R. Arnaud, *J. Chim. phys.*, 1971, **68**, 1519.
[141] A. D. Garnowski, Yu. V. Kolodyazhnyi, S. A. Alieva, K. M. Yunusov, I. I. Popov, O. A. Osipov, V. I. Minkin, A. M. Simonov, and I. I. Grandberg, *Zhur. obshchei Khim.*, 1971, **41**, 352.
[142] N. Bodor, I. Schwartz, and N. Trinajstić, *Z. Naturforsch.*, 1971, **26b**, 400.
[143] Y. Ferré and É.-J. Vincent, *Compt. rend.*, 1971, **272**, *C*, 1916; Y. Ferré, É.-J. Vincent, H. Larivé, and J. Metzger, *Bull. Soc. chim. France*, 1972, 3862; 1973, 1003.
[144] R. Garnier, R. Faure, A. Babadjamian, and É.-J. Vincent, *Bull. Soc. chim. France*, 1972, 1040.
[145] J. P. Aune, R. Phan Tan Luu, É.-J. Vincent, and J. Metzger, *Bull. Soc. chim. France*, 1972, 2679.
[146] E. Kleinpeter and R. Borsdorf, *J. prakt. Chem.*, 1973, **315**, 765.
[147] G. G. Dvoryantseva, T. N. Ul'janova, G. P. Syrova, Yu. N. Sheinker, V. M. Aryuzina, T. P. Sycheva, and M. N. Shchukina, *Teor. i eksp. Khim.*, 1970, **6**, 23; G. G. Dvoryantseva, L. M. Alekseeva, T. H. Ul'janova, Yu. H. Sheinker, P. M. Kochergin, and A. H. Krasovskii, *Khim. geterotsikl Soedinenii*, 1971, 937.

with CNDO/2 all-valence-electron densities;[148,149] it is thought that the ring-current effect should be taken into account.[148]

Other subjects of theoretical interest have been the electronic structure of meso-ionic structures [*e.g.* (78) and (79)] (HMO, PPP),[150] the reactivity of (72a) and derivatives towards radical attack (HMO),[151] the reactivity of (71) and (76) towards electrophilic attack and their photochemical ionization



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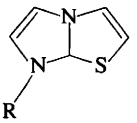

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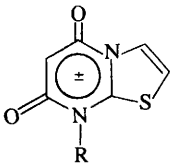

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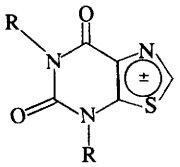


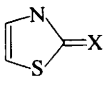
(79)

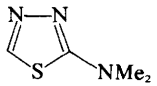
(HMO, PPP, CNDO/2),[151] the reactivity of substituted (73c) and related compounds (HMO),[152] the Hammett σ values of substituted (69) and (73a) (HMO),[153] the basicity of substituted (73a) (HMO, PPP),[154] the H–D exchange of 2-methyl-substituted (75) and (76)[155] (HMO) and of (69)[156] (PPP), and the electron distribution and reactivities of (80a)[157] and (80b)[158] (EHT and PPP, respectively).

Thiadiazoles and Selenathiadiazoles. The u.v.–p.e. spectra of benzo-(81) and benzo-(82)[52,89,159] and the electronic spectra of benzo- and naphtho-(82) and their selenium analogues could be described satisfactorily by PPP calculations which did not take the *d*-orbitals into account. The long-wavelength absorptions of ox-, thi-, and selen-azoles were calculated to be in the order Se > S > O, a result in agreement with experiment. CNDO/2 calculations of the transition energies of (81) and annelated systems did not allow a meaningful judgement about the S 3*d* participation.[160] However, the effect of the *d*-orbitals was demonstrated in results of non-empirical

[148] R. E. Wasylishen, J. B. Rowbotham, and T. Schaefer, *Canad. J. Chem.*, 1974, **52**, 833.
[149] L. Marchetti, L. Pentimalli, P. Lazzeretti, L. Schenetti, and F. Taddei, *J.C.S. Perkin II*, 1973, 1926.
[150] R. A. Coburn, *J. Heterocyclic Chem.*, 1971, **8**, 881; R. A. Coburn and R. A. Glennon, *ibid.*, 1973, **10**, 487.
[151] G. Vernin, H. J. M. Dou, G. Loridan, and J. Metzger, *Bull. Soc. chim. France*, 1970, 2705; M. Baule, R. Vivaldi, J.-C. Poite, H. J. M. Dou, G. Vernin, and J. Metzger, *Bull. Soc. chim. France*, 1971, 4310; G. Vernin, C. Riou, H. J. M. Dou, L. Bouscasse, J. Metzger, and G. Loridan, *ibid.*, 1973, 1743.
[152] I. Schwartz, *Studia Univ. Babes-Bolyai, Ser. Chem.*, 1971, **16**, 51.
[153] D. A. Forsyth and D. S. Noyce, *Tetrahedron Letters*, 1972, 3893.
[154] V. I. Minkin, V. A. Bren, A. D. Garnovski, *Khim. geterotsikl Soedinenii*, 1972, 552.
[155] E. Kleinpeter, R. Borsdorf, and F. Dietz, *J. prakt. Chem.*, 1973, **315**, 600.
[156] H. C. Sorensen and L. L. Ingraham, *J. Heterocyclic Chem.*, 1971, **8**, 551.
[157] V. I. Zaionts, O. V. Maksimova, and M. G. Mints, *Khim. geterotsikl Soedinenii*, 1972, 1622.
[158] L. Bouscasse, M. Chanon, R. Phan Tan Luu, J. E. Vincent, and J. Metzger, *Bull. Soc. chim. France*, 1972, 1055.
[159] A. M. Gyul'machev, I. V. Stankevich, and Z. V. Godres, *Khim. geterotsikl Soedinenii*, 1973, 1473.
[160] J. R. Grunwell and H. S. Baker, *J.C.S. Perkin II*, 1973, 1542.

calculations of the dipole moments of (82) and (83).[42] Calculation of the barrier to rotation of the dimethylamino-group in (84) by the CNDO/2





(80) (a) X = O (81) (82) (83) (84)
(b) X = S

method with and without *d*-orbitals revealed that the *d*-participation has been exaggerated;[161] when a planar dimethylamino-group was assumed, the experimental barriers could be satisfactorily reproduced.

Discussions within the HMO approximation of the electron structures of substituted (83) and of 1,2,5-oxa(thia, selena)diazolo[3,4-*a*]anthraquinones are given in refs. 152 and 162, respectively.

Thiopyrylium and Dithiolium Ions. Nothing has been published on the electronic structure of thiins (85) (for the calculated inversion barrier, though, see ref. 28) although the iso-π-electronic tropylium ions thiopyrylium (86), 1,2-dithiolium (87), and 1,3-dithiolium (88) have been considered in several papers.

(85) (86) (87) (88)

Non-empirical calculations for (86)—(88) by Palmer and Findlay[41] have revealed that *d*-orbitals participate only to a trivial extent. The charge distributions obtained from non-empirical calculations differ considerably from those from all-valence-electron treatments. Nevertheless some semi-empirical calculations gave results in good agreement with experimental data.[163–171] Some arguments for the importance of the S 3*d*-orbitals in (86) have come from an EHT interpretation of the ^{1}H chemical shifts;[165] against

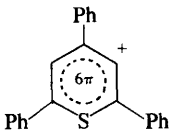
[161] T. Liljefors, J. Sandström, and G. Ribbegard, *J.C.S. Perkin II*, 1973, 1500.
[162] M. V. Gorelik, O. S. Zhdamirov, E. S. Levin, B. E. Saitsev, and L. A. Chetkina, *Zhur. org. Khim.*, 1971, **7**, 1044.
[163] D. Gonbeau, C. Guimon, and G. Pfister-Guillouzo, *Tetrahedron*, 1973, **29**, 3399.
[164] J. Fabian, K. Fabian, and H. Hartmann, *Theor. Chim. Acta*, 1968, **12**, 319; Z. Yoshida, H. Sugimoto, and S. Yoneda, *Tetrahedron*, 1972, **28**, 5873.
[165] S. Yoneda, T. Sugimoto, and Z. Yoshida, *Tetrahedron*, 1973, **29**, 2009.
[166] K. Fabian, H. Hartmann, J. Fabian, and R. Mayer, *Tetrahedron*, 1971, **27**, 4705.
[167] A. Mistr, M. Vávra, J. Skoupý, and R. Zahradník, *Coll. Czech. Chem. Comm.*, 1972, **37**, 1520; A. Mistr and R. Zahradník, *ibid.*, 1973, **38**, 1668.
[168] Z. Yoshida, S. Yoneda, H. Sugimoto, and T. Sugimoto, *Tetrahedron*, 1971, **27**, 6083.
[169] Z. Yoshida, T. Sugimoto, and S. Yoneda, *Tetrahedron Letters*; 1971, 4259.
[170] M. Hori, T. Kataoka, Y. Asahi, and E. Mizuta, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1415.
[171] A. Takamizawa and K. Hirai, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 865.

this, however, is the report that the u.v. spectra may be well reproduced by PPP calculations without *d*-orbitals.[164]

The term-diagrams of the low-energy singlet and triplet $\pi\pi^*$ states of (89) are used to discuss their sensitization efficiency in layers of polyesters.[167]

Pfister-Guillouzo *et al.* have performed CNDO/S calculations (*spd* model) on the 1,2-dithiolium cations (87)[163] and suggested that the spectral absorptions in the u.v. region may be completely interpreted by $\pi^* \leftarrow \pi$ transitions. This is in agreement with a former study involving PPP calculations which provided an adequate description of the absorption spectrum of (87) and rationalized the effects of methyl substituents on (86)—(88) (*i.e.* spectral shifts and changes in the polarographic half-wave potentials).[166] A linear correlation has been found between the reduction potentials and the lowest free MO's (see also ref. 41).

Chemical reactivity has been discussed mainly at the HMO level. Reaction indices such as superdelocalizabilities and localization energies suggest that nucleophilic attack should take place exclusively at the α-carbon.[168] HMO calculations for *p*-localization energy suggest that intermediate (90) may be formed by the photo-oxidation of (89).[169] The reactivity of (91) (electrophilic and nucleophilic substitution) and of 4-*p*-substituted derivatives of (88) (basicity) are discussed in refs. 170 and 171 respectively.



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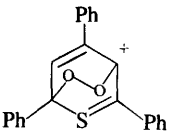

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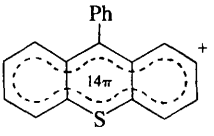
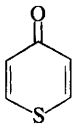


(91)

Thiopyrones, Dithiolones, and Derivatives. The iso-π-electronic tropones and thiotropones (92)—(99) have stimulated much theoretical interest. Although the electronic spectra of the six-membered rings and derivatives



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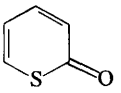

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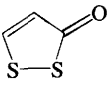
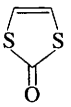


(94)



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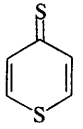

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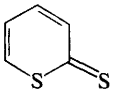

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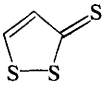

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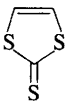


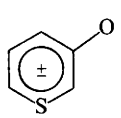
(99)

have been well interpreted,[15,172] the intense absorptions of (98) could not be explained completely by $\pi^* \leftarrow \pi$ transitions.[173,174] Pfister-Guillouzo *et al.*[173] have shown by CNDO/S calculations that the absorption band at about 340 nm results from a $\sigma^* \leftarrow n$ transition and that the longest wavelength absorption results from a $\pi^* \leftarrow n$ transition; the *d*-orbital effect on the long-wavelength transition is negligible.

CNDO/S calculations[175] are in agreement with the observation that protonation of (98) leads to the disappearance of the $\pi^* \leftarrow n$ absorption and to a shift of the $\pi^* \leftarrow \pi$ absorptions to lower wavelengths.[175] The basicities of (92) and (93) and condensed systems have been studied within the π-approximation.[176]

Using only the *p*-model of sulphur, PPP-type calculations[15] of the meso-ionic structures (100)—(102) have given an adequate description of the spectral data; an explanation was also given for the deeper colour of phenyl-substituted (101) and (102) relative to the isomeric structures. An analysis of the population of the *d*-orbital as well as the bond energies of (101) indicated no higher *d*-participation than in (87).

Inserting one double bond between the ring and the C=O (C=S) group leads to (103), with a non-bond interaction between the S and O(S) atoms. These compounds are considered below.



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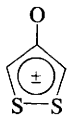

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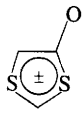

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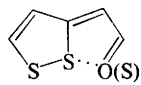
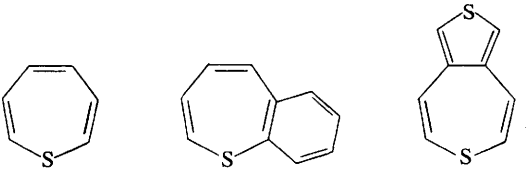


(103)

8π Heterocycles and Derivatives.—*Thiepins.* The resonance energy of the parent compound (104) suggests that it is antiaromatic.[20,47] Predicted C—C bond lengths are nearly equal to those that have been found for single and double bonds in polyenes. There are three benzologues of thiepin; HMO resonance energies suggest structure (105) is most favoured,[49] but whether or not it is planar is open to question. The low stability of synthesized 1-benzothiepin (105) has been reinvestigated recently by means of HMO calculations on a non-planar structure.[177] Among the thienothiepins, compound (106) is predicted to have the highest stability.[47] However, the calculated resonance energy of *ca.* 4 kcal/mol^{-1} (PPP approximation)[20] is of the same order of magnitude as the non-bonded interaction and angle strain in the planar seven-membered ring. CNDO/2 and EHT calculations did not

[172] J. Fabian and G. Laban, *Tetrahedron*, 1969, **25**, 1441; M. Kamiya and Y. Akahori, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 677.
[173] G. Pfister-Guillouzo, D. Gonbeau, and J. Deschamps, *J. Mol. Structure*, 1972, **14**, 81, 95; *Bull. Soc. chim. belges*, 1971, **80**, 311.
[174] J. Fabian, *Z. Chem.*, 1973, **13**, 26.
[175] D. Gonbeau, C. Guimon, and G. Pfister-Guillouzo, *Tetrahedron*, 1973, **29**, 3599.
[176] A. I. Tolmachev, G. G. Dyadyusha, and L. M. Shulezhko, *Teor. i eksp. Khim.*, 1970, **6**, 185.
[177] H. Hofmann, B. Meyer, and P. Hofmann, *Angew. Chem., Internat. Edn.*, 1972, **11**, 423.

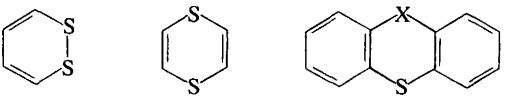


(104) (105) (106)

make a clear-cut revelation of the molecular geometry, but non-planar conformations seem more probable.[178] On the basis of PPP calculations the experimentally observed absorption bands in the u.v. region were assigned to $\pi^* \leftarrow \pi$ transitions.

Dithiins, Oxathiins, and Thiazines. Six-membered cyclic compounds with one or two sulphur atoms have a non-planar structure. Thus, in general, π-type calculations take into account the twisting of the p_π-orbitals. HMO and PPP calculations have provided a negative π-bond order between the sulphur atoms in 1,2-dithiin (107).[179] EHT calculations, however, predicted a σ-bond between the sulphur atoms. Consequently the cyclic structure should be more favoured than acyclic valence tautomers. This was supported by spectral data; the weak long-wavelength absorption is thought to correspond to a $\pi^* \leftarrow \pi$ transition of (107) rather than a $\pi^* \leftarrow n$ transition of acyclic thione structures.[179]

1,4-Dithiin (108), an isomer of (107), has been studied theoretically mainly in the form of its dibenzo-derivatives or their hetero-analogues (109a—c).[180,181] Phenoxathiin (109a), thianthrene (109b), and phenothiazine (109c)



(107) (108) (109) (a) X = O
(b) X = S
(c) X = N—R

have highest occupied molecular orbital (HOMO's) of low energy.[182,183] Consequently these compounds form cations easily. Correlations have been found between the HOMO's and the polarographic oxidation potentials[183] and ionization potentials, obtained by CT complexes.[184] EHT calculations indicate that the all-valence-electron energy of the 'H intra' configuration of

[178] R. Gleiter, E. Schmidt, P. Johnson, and D. O. Cowan, *J. Amer. Chem. Soc.*, 1973, **95**, 2860.
[179] R. Borsdorf, H.-J. Hofmann, H.-J. Köhler, M. Scholz, and J. Fabian, *Tetrahedron*, 1970, **26**, 3227.
[180] M. Kamiya and Y. Akahari, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 117.
[181] M. Kamiya, *Bull. Chem. Soc. Japan*, 1970, **43**, 3929; 1972, **45**, 1589.
[182] N. Tyutyulkov, D. Simov, and S. Stojanov, *Compt. rend. Acad. bulg. Sci.*, 1970, **23**, 1095; A. F. Pozharskii and E. N. Malysheva, *Khim. geterotsikl Soedinenii*, 1970, 103.
[183] W. Schroth, R. Borsdorf, R. Herzschuh, and J. Seidler, *Z. Chem.*, 1970, **10**, 147.
[184] M. Hillebrand, O. Maior, and V. Em. Sahini, *Rev. Roumaine Chim.*, 1970, **15**, 149.

(109c) is 0.2 eV lower than that of the 'H extra' configuration.[180] The calculated electronic excitation energies and ionization potentials are sensitive to the dihedral angle between the two lateral benzene planes. The spatial configurations and electronic properties of (109c) were also studied by Bloor *et al.* from a more biological viewpoint.[185] HMO studies on (109c) and related annelated systems have been performed in a study of the ionization, the electronic excitation, and the reactivity of these compounds.[182] The conformation of the side chain attached to the nitrogen has been investigated by the MO perturbation CI method using the localized orbital method.[28]

Heterocycles with more than Eight π-Electrons.—*Monocyclic Sulphur Compounds.* Calculations of the HMO resonance energy of larger rings with one sulphur atom have revealed that the aromatic, as well as the anti-aromatic, character of these compounds decreases with an increasing number of ring atoms. Consequently these compounds should be polyolefinic, with small or zero electron delocalization. 1,4-Dithiocin (110), a 10π-electron system with

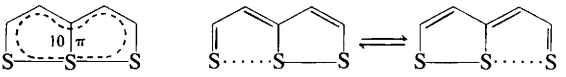
(110)

two sulphur atoms, was predicted to be non-aromatic[52] (see ref. 186, however, for a contrary view). Theoretical studies of heterocycles with more than eight π-electrons have been mainly focused on the fused-ring systems.

Thiathiophthens and Oxygenated Derivatives. Contradictory interpretations of experimental studies of the heterocyclic compound $C_5H_4S_3$ have stimulated a number of theoretical studies. Following the *X*-ray study and radio-frequency spectroscopy, the bicyclic structure of the 6a-thiathiophthen (trithia[1,6,6a]pentalene) (111), with C_{2v} symmetry, seemed to be assured. (For a recent electron-diffraction study see ref. 187). This conclusion was supported by *X*-ray p.e. spectroscopy.[188] A reinvestigation of the *X*-ray and u.v.–p.e. spectra, however, favoured the C_s symmetric structure (111a),[189] and the same conclusion was drawn from a study of the electronic polarization spectrum of the 2,5-dimethyl derivative.[190]

Unfortunately, theoretical studies have not allowed a clear-cut decision to be made between (111) and (111a) as there is little difference in energy

[185] J. E. Bloor, B. R. Gilson, R. J. Haas, and C. L. Zirkle, *J. Medicin. Chem.*, 1970, **13**, 922.
[186] M. O. Riley and J. D. Park, *Tetrahedron Letters*, 1971, 2871.
[187] Q. Shen and K. Hedberg, *J. Amer. Chem. Soc.*, 1974, **96**, 290.
[188] D. T. Clark, D. Kilcast, and D. H. Reid, *Chem. Comm.*, 1971, 638.
[189] R. Gleiter, V. Hornung, B. Lindberg, S. Högberg, and N. Lozac'h, *Chem. Phys. Letters*, 1971, **11**, 401.
[190] R. Gleiter, D. Schmidt, and H. Behringer, *Chem. Comm.*, 1971, 525.



(111) (111a)

between the two.[4b,188,190,191] An extended Hückel calculation has predicted a double minimum for the ground state.[191] The energy barrier between the two minima is reduced if 3*d*-orbitals on sulphur are included a result thought to be mainly due to the considerable interaction between the in-plane 3*p* and 3*d* combination of appropriate symmetry.[191] CNDO/2 calculations, on the other hand, yield a single-minimum potential without taking the 3*d*-orbitals on sulphur into account[188,191] but, due to shortcomings of this method, the result may not be reliable. Perhaps the most plausible explanation of the experimental results has been given by Gleiter,[191] which is that in the case of a valence tautomeric system corresponding to (111a) the experimental methods may 'see' different things, *i.e.* the electronic and p.e. spectra may be compatible with the unsymmetric species since the Franck–Condon principle holds, while an *X*-ray study would provide a symmetrical density map.

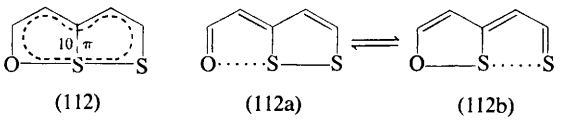
An unequivocal decision between the different potential curves is perhaps only possible by non-empirical calculations with a large basis set and optimized geometries. As yet only minimal-basis-set calculations of (111) are available, with one d_σ and one d_π function for the sulphur atoms.[4b,41,42] The effect of the *d*-orbitals on the binding energy and the ionization potential was low, although the effect on the dipole moment was more pronounced. According to CNDO/2 calculations the σ-framework is strongly polarized and the *d*-orbitals are more important for the central sulphur atom than for the terminal sulphur atoms.[194] All-valence-electron SCF calculations of (111) have also been performed by Yonezawa *et al.*[192] Using an *spd*-model for calculations, Kroner *et al.*[189] found that only the C_s-symmetrical (111a) was consistent with the experimentally found sequence of the ionization potentials (π_1, n, π_2). CNDO/S[193] and PPP calculations[190] also show that (111a) allows better interpretation of the electronic spectrum.

Clark *et al.*[194] have carried out a study on the chemical reactivities of (111) and its methyl-substituted derivatives (PPP approximation). Results for localization energies and charge densities led to certain predictions; that the 3-position is preferred in electrophilic attack, but electrophilic attack at the sulphur may be a competitive reaction, that the 2-position is preferred in nucleophilic attack, and that the 2-methyl-substituted (111) has higher acidity than (111). All these predictions are in good agreement with experimental findings.

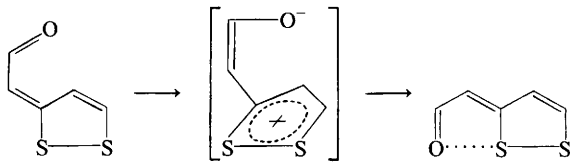
[191] R. Gleiter, D. Werthemann, and H. Behringer, *J. Amer. Chem. Soc.*, 1972, **94**, 651.
[192] H. Yamabe, H. Kato, and T. Yonezawa, *Bull. Chem. Soc. Japan*, 1970, **43**, 3754.
[193] J. Kroner and D. Proch, *Tetrahedron Letters*, 1972, 2537.
[194] D. T. Clark and D. Kilcast, *Tetrahedron*, 1971, **27**, 4367.

CNDO/2-calculations of substituted 6a-thiathiophthens have also been performed to explain the effect of the methyl and phenyl group on the geometry.[195] The calculations indicated that introduction of a 2-methyl or 2-phenyl group lengthened the S-1—S-6a bond of (111), but the introduction of 3-methyl and 6-phenyl groups shortened it. [For a discussion of steric effect on the electronic spectrum of substituted (111) see ref. 174.]

Theoretical studies of the O-analogue dithiofurophthen (112) and related compounds revealed that the O–S interaction is only weak[174,192,196] and that in the ground state the structure (112a) should be clearly favoured. Gleiter has suggested a photochemical valence isomerization between (112a) and (112b);[191] The product of the photoisomerization, however, was identified as the O, S-*trans* form (112*c*), which reverts thermally to the starting material.[197,198] PPP calculations have been carried out for (112a) and (112c) to rationalize the electronic spectral data. Experimental excitation energies and intensities were reproduced satisfactorily from the calculations. The activation energy obtained by the CNDO/2 method for the transition state (112d) is *ca.* 74 kcal mol^{-1}, *cf.* the experimental value of *ca.* 12 kcal mol^{-1}.



(112) (112a) (112b)



(112c) (112d) (112a)

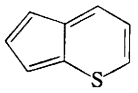
The extended Hückel method provides a better result (*ca.* 6 kcal mol^{-1} less than the experimental value). The O, S-*cis* form (112b) and the O, S-*trans* form [(112c) non-planar] were found to differ in energy by 2.5 kcal mol^{-1}; this difference is attributed to the interaction of the 2*p* lone pair of the oxygen and the *d*-orbitals of the central sulphur.

Cyclopentathiopyrans, Cyclopentadithiols, and Naphthothiopyrans. Fused sulphur heterocyclic ring systems may be separated into two groups. One group consists of molecules formally derived from alternant hydrocarbons

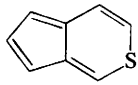
[195] L. K. Hansen, A. Hordvik, and L. J. Saethre, *J.C.S. Chem. Comm.*, 1972, 222.
[196] R. Pinel, Y. Mollier, J.-P. de Barbeyrac, and G. Pfister-Guillouzo, *Compt. rend.*, 1972, **275**, *C*, 909; J. P. Barbeyrac, D. Gonbeau, and G. Pfister-Guillouzo, *J. Mol. Structure*, 1973, **16**, 103, 117.
[197] C. Th. Pederson and C. Lohse, *J.C.S. Chem. Comm.*, 1973, 123.
[198] G. Calzaferri, R. Gleiter, K.-H. Knauer, E. Rommel, E. Schmidt, and H. Behringer, *Helv. Chim. Acta*, 1973, **56**, 597.

by replacing one or several double bonds by sulphur atoms; most of this type have been reviewed among annelated thiophens. The second group embraces sulphur heterocyclic molecules derived from non-alternant hydrocarbons. The cyclopentathiopyrans (113) and (114) belong to the latter group. Electron densities, bond orders, and π-dipole moments have been calculated for the ground state (S_0) and the two lowest excited states (S_1, T_1) of cyclopenta[b]thiopyran.[199] The electron excitation is accompanied by a significant change in the electron distribution. Good agreement between theoretical (PPP)[199] and experimental electronic spectral data enabled the formation of a benzologue of (113) to be verified.[200]

Theoretical spectral data are available for cyclopenta-1,2-dithiol (115), which is as yet unknown.[201] Acenaphtho[5,6-*cd*]thiopyran has been synthesized and claimed to be an example of a stable quadrivalent-sulphur-containing heterocycle corresponding to formula (116). However, this valence state may be questioned; quadrivalent sulphur is not essential to an explanation of the high π resonance energy and stability of this system.[47]



(113)



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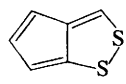

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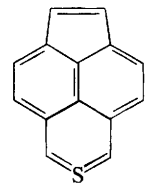


(116)

Bridged Heterocycles.—*Sulphur Heterocycles Bridged by a Single Bond.* Several papers have reported calculations for the isomeric bithienyls (117) which have been aimed at elucidating the molecular structure and electronic transition energies.[11,98,202,203] PPP calculations imply that there should be little interaction between the rings, and resonance energies were calculated to be about twice that of thiophen.[20] According to EHT calculations the barrier difference between the *syn*- and the *anti*-forms decreases sharply over the sequence bifurans, bithiophen, and biselenophen.[98] An easy interconversion should occur between the preferred conformers. The preferred conformers of the bithienyls have been calculated and compared with experimental results.[98,203]

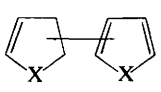
According to PPP calculations the excitation energies of the bithienyls depend little on the conformational arrangement.[204] The blue shift observed for the 2,3′- and 3,3′-isomers relative to the 2,2′-isomer, and reproduced by

[199] R. Zahradník, *Internat. J. Sulfur Chem.* (*B*), 1971, **6**, 147.
[200] F. Kvis, E. Svatek, R. Zahradník, and M. Protiva, *Coll. Czech. Chem. Comm.*, 1972, **37**, 3808.
[201] J. Fabian, *Z. Chem.*, 1972, **12**, 348.
[202] A. Skancke, *Acta Chem. Scand.*, 1970, **24**, 1389.
[203] H. H. Jensen and A. Skancke, *Acta Chem. Scand.*, 1970, **24**, 3766.
[204] M. Milun and N. Trinajstić, *Spectroscopy Letters*, 1973, **6**, 329.

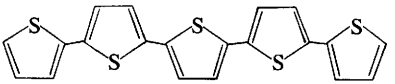
calculations, could be anticipated by simple graph-theoretical thinking, taking into account only progressive branching in the 'polyenic system'.

In the absorption spectrum of quinquethienyl (118) one observes a hypsochromic shift in solution and in a monolayer. Theoretical calculations based on the electron-gas model and an oscillator model have established the polymeric card-model proposed earlier.[205]

The energy gaps for 33 macromolecules, among them (119), have been investigated by the Hückel one-electron approximation.[206]



(117) X = O, S, or Se



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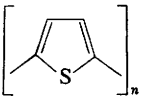
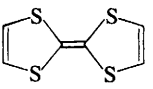
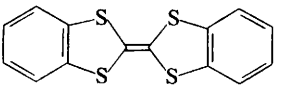


(119) $n \rightarrow \infty$

Sulphur Heterocycles Bridged by a Double Bond. Tetrathiofulvalene (120) has been investigated by various theoretical methods. Coffen *et al.* have discussed the spectra of (120) and hydrogenated analogues by EHT calculations.[207] Their assignment of the weak absorption at 450 nm as a $\sigma^* \leftarrow \pi$ transition was not confirmed by a more recent polarization measurement,[208] and this absorption has now been assigned to a forbidden $\pi^* \leftarrow \pi$ transition which becomes allowed by vibrations.[208] The experimental transition energies are in adequate agreement with those predicted by Zahradník[209] [for calculations on (121) see ref. 209]. The differences between



(120)

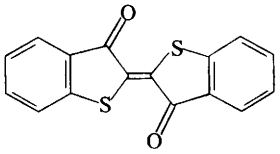


(121)

the first ionization potential obtained by u.v.–p.e. spectroscopy are in good agreement with results of EHT and PPP calculations.[208] Experimentally derived bond distances have been compared with those obtained from CNDO/2 calculations with and without *d*-orbital participation.[210] It was concluded that the *d*-orbitals are necessary to explain the relative lengths of the C=C bonds.

Wild has discussed the colour of thioindigo (122) in the excited S_1 and T_1

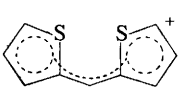
[205] H. J. Nolte and V. Buss, *Chem. Phys. Letters*, 1973, **19**, 395.
[206] I. V. Stankevich and O. B. Tomilin, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1973, 2515.
[207] D. L. Coffen, J. Q. Chambers, D. R. Williams, P. E. Garrett, and N. D. Canfield, *J. Amer. Chem. Soc.*, 1971, **93**, 2258.
[208] R. Gleiter, E. Schmidt, D. O. Cowan, and J. P. Ferraris, *J. Electron Spectroscopy Related Phenomena*, 1973, **2**, 207.
[209] R. Zahradník, P. Carsky, S. Hünig, G. Kiesslich, and D. Scheutzow, *Internat. J. Sulfur Chem.* (*C*), 1971, **6**, 109.
[210] W. F. Cooper, N. C. Kenny, J. W. Edmonds, A. Nagel, F. Wudl, and P. Coppens, *J.C.S. Chem. Comm.*, 1973, 889.



(122)

states ($S_n \leftarrow S_1$ and $T_n \leftarrow T_1$ electronic transitions);[211] in these states the dye should have a deeper colour.

Sulphur and Selenium Heterocycles Bridged by a Polymethinic Chain. Polymethines are chain molecules with small π-bonds alternating along the chain. The deeply coloured compounds containing heterocyclic terminal groups are highly interesting because of their connection with photographic sensitization. The chromophoric properties of many sulphur-containing dyes, *e.g.* (123)—(128) and condensed systems, have been investigated by PPP calculations.[16,212] The long-wavelength absorption mainly depends on the length of polymethinic chain as well as the heterocyclic terminal groups. Annelation has little influence on the low-energy $\pi^* \leftarrow \pi$ transition. The anomalous strong (or low) shift of absorption wavelength between the first two homologues relative to the shift between higher members, and the deviations from the mean-value rule of non-symmetrical dyes, are caused by an interannular no-bond S–S interaction in the monomethine.[213] This conclusion has been confirmed by CNDO/2 calculations on (126). The HMO model enables rationalization of the effect of the S–S interaction. A similar conclusion about the importance of the S–S interaction has been drawn in a



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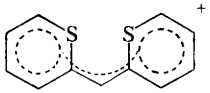

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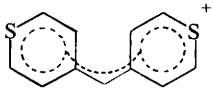

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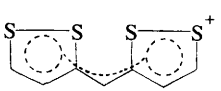

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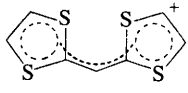

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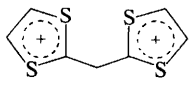

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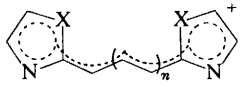


(129) $n = 1, 2 \ldots$
X = O, S, or Se

[211] U. P. Wild, *Chimia (Switz.)*, 1973, **27**, 642.
[212] J. Fabian and H. Hartmann, *Tetrahedron*, 1973, **29**, 2597.
[213] J. Fabian, H. Hartmann, and K. Fabian, *Tetrahedron*, 1973, **29**, 2609.

discussion of the redox potentials of benzo-(129; $n = 0$—7).[214] [For the S–S interaction in protonated dyes, *e.g.* (128), see ref. 215.]

Appropriate HMO parameters were derived for (129) and employed to correlate electronic transition energies and polarographic reduction and oxidation potentials.[10] Tani[216] has shown how to use the HMO method to explain, within a modified electron-transfer mechanism, the capacity of the sulphur and selenium dyes for photosensitization. In this connection, attempts have been made to derive the ionization potential of benzo-(128; X = S, $n = 1$) by calculating the difference in the total π-electronic energy between the ground and ionized states.[217] The value that was calculated was almost twice the measured ionization potential; it was concluded that the dye anion should not be neglected. Recent INDO- and CNDO/2-calculations on the analogue 2,2′-quinocarbocyanine assume that the electron leaves the negative ion.[218]

The HMO π-electron densities and chemical shifts of the methine protons of compounds of the type (129) both decreased as a function of X in the order $N \gg O = S > Se$.[219] In ref. 220 is given a correlation between the lowest HMO transition energies and the long-wavelength absorptions of benzothiazole cyanine dyes that contain the phenalene ring.

The influence of the aggregation of sulphur-containing polymethine dyes [*e.g.* (129; X = S, $n = 1$] upon spectral absorption has been investigated theoretically by a treatment based on the Coulomb interaction between the dye molecules.[221] The energy transfer within the aggregates was computed to be larger for the energetically preferred arrangements than for other ones.[222]

Theoretical studies on some other sulphur-containing polymethines include triarylmethane dyes, phenothiazine dyes, and merocyanine dyes.

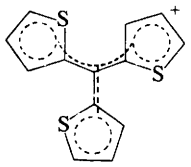
For the triarylmethane dye (130) and isomeric structures a correlation has been found between ^1H chemical shifts and π charges and vicinal coupling constants and π-bond orders;[223] a pronounced charge delocalization is indicated.

HMO and PPP calculations of excited states of methylene blue (131; $R = NMe_2$, X = S) have been performed to derive the site of protonation:[224]

[214] T. Tani, *J. Photogr. Sci.*, 1971, **19**, 161.
[215] J. Fabian and H. Hartmann, *Z. Chem.*, 1972, **12**, 349.
[216] T. Tani, *Photogr. Sci. Eng.*, 1972, **16**, 258; *Denki Kagaku*, 1970, **38**, 531; (*Chem. Abs.*, 1971, **74**, 81 727v.)
[217] R. S. Selsby and R. C. Nelson, *J. Mol. Spectroscopy*, 1970, **33**, 1.
[218] H. Weinstein, B. Apfeldorfer, and R. A. Berg, *Photochem. and Photobiol.*, 1973, **18**, 175.
[219] E. Kleinpeter, R. Borsdorf, G. Bach, and J. V. Grossmann, *J. prakt. Chem.*, 1973, **315**, 587.
[220] J. K. Elwood, *J. Org. Chem.*, 1973, **38**, 2430.
[221] K. Norland, A. Ames, and T. Taylor, *Photogr. Sci. Eng.*, 1970, **14**, 295; V. Czikkely, H. D. Försterling, and H. Kuhn, *Chem. Phys. Letters*, 1970, **6**, 207; R. E. Ballard and B. J. Gardner, *J. Chem. Soc.* (*B*), 1971, 736.
[222] F. Dietz and K.-J. Pässler, *J. Signal AM*, 1973, **1**, 57.
[223] F. Taddei, P. Spagnolo, and M. Tiecco, *Org. Magn. Resonance*, 1970, **2**, 159.
[224] O. Chalvet, J. Haorau, J. Joussot-Dubien, J.-C. Rayez, and J. C. Claude, *J. Chim. phys.*, 1972, **69**, 630; J.-C. Rayez and O. Chalvet, *ibid.*, p. 1545.

this is the intracyclic nitrogen atom for the ground state as well as for the lowest singlet and triplet states. The electronic structures of oxonine, thionine, and selenine dyes (131; X = O, S, or Se; R = NH_2) have also been discussed.[225]

The isomerization of the photochromic spiropyrans leads to coloured merocyanines, *e.g.* (132). An EHT calculation of (132) provides evidence for a twisted *trans*-form.[226] More recent PPP calculations of spectral properties for similar structures are given in ref. 227.



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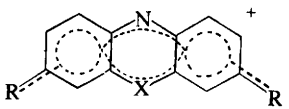

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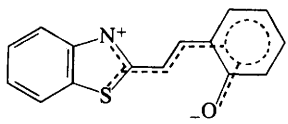

(132)

Sulphur Heterocyclic Radicals.—Most studies in this field have used theoretical methods to derive the spin-density distribution and hyperfine splitting constants. In a few cases the unrestricted Hartree–Fock (UHF) formalism has been applied (PPP approximation).[7,228] (The inclusion of *d*-orbitals slightly improved the spin-density results in the *p*-model.[7])

McLachlan-type spin-density calculations have also been carried out using new Hückel parameters for the *d*-orbital which were obtained by a restricted Hartree–Fock calculation of thiophen. Good results could be achieved for a large number of sulphur-containing radicals by use of the McLachlan perturbation corrections to the HMO method and the sulphur *p*-model. In many cases this method has turned out to be an important tool in the assignment of proton hyperfine coupling constants for the e.s.r. spectrum. Studies have involved radicals of thiophens and derivatives,[7–9,37,229] thiaxanthyl radicals,[230] thiapyryl radicals,[231] 1,2-dithiole radicals,[232] substituted 1,2-dithiet radicals and 1,4-dithiin radicals,[233] the

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thioxoanthren-9-onyl radicals,[234] tetrathiotetracene radicals,[235] phenothiazinyl radicals,[236] the thiadiazine radicals,[7] nitro-substituted benzthiazolohydrazyl radicals,[237] and thioketone radicals.[238]

In some cases comparisons of experimental and theoretical hyperfine splitting constants have been used in investigations of the molecular geometry.[18,230,239,240] In the case of 2,5-dialkylthiothiophen radicals such a study was completed by open-shell CNDO/2 calculations of the stability of the conformers.[240]

Few experimental and theoretical electronic spectra are available for sulphur heterocycles. Zahradník *et al.* have demonstrated the applicability of the open-shell SCF–LCI method of Longuet-Higgins and Pople in calculations of, for example, the cation radicals of (120), (121), and heteroanalogues.[18]

Similar computations have been performed for phenothiazinyl radicals.[241] In general, agreement between theoretical and experimental transition energies is worse than that obtained by use of the closed-shell systems. Absorptions of extremely long wavelength have been predicted for the cation radicals of (49), (50), and (113).[199]

A condition necessary for a radical to be observable is the favourable position of the dismutation equilibrium $Ox + Red \rightleftharpoons 2Sem$. This equilibrium between the oxidized form (Ox) and reduced form (Red) and the radical (Sem) depends on the molecular electronic repulsion integral J_{mm} of the singly occupied molecular orbital of the radical. J_{mm} Values have been computed and listed for a great variety of sulphur heterocyclic radicals.[209] Radicals with extensively conjugated skeletons would be expected to have dismutation constants with lower values, and this has been found. On the other hand, small radicals are likely to dimerize or attack other species. The highest spin density for the unpaired electron is probably at the site of the radical dimerization, *i.e.* the 2-position of the 1,3-dithiole radical. The spin-density distribution may also be responsible for other radicals. The pathway for the polarographic reduction of 1,2-dithiolium cation (87) or trithiones (88) *via* cation radicals has recently been discussed by CNDO/2

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