Lyudmila Larina
Valentin Lopyrev

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Nitroazoles

Synthesis, Structure and Applications

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Nitroazoles: Synthesis, Structure and Applications

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Preface

The present monograph is devoted to the chemistry of nitroazoles, one of the most interesting series of heteroaromatic compounds. The azoles hold a special position in the chemistry of heterocycles. Their unique properties and specific biological activity attract much attention of research chemists all over the world. During the last years the interest in the chemistry of nitroazoles has increasing. The nitro derivatives of azoles have found a wide application in various fields of industrial chemistry, agriculture, and medicine. Medical products developed by nitroazoles incluce azomycin, metronidazole, misonidazole, tinidazole, nitazole, etc., ionic liquids, high-energy materials, synthons for nanocompounds, universal bases in peptide nucleic acids, plant growth regulators, and intermediates for organic synthesis.

The investigations in the field of energetic compounds have received enormous interest in recent years. Energetic materials on the base nitroazoles – explosives, propellants, and pyrotechnics – are widely used for both civilian and military applications. Nitroazoles, especially polynitroazoles, possess higher heat of formation, density, and oxygen balance than their carbocyclic analogs. A number of ongoing research programs worldwide are aimed for the development of new explosives and propellants with higher performance characteristics or enhanced insensitivity to thermal or shock insults and pyrotechnics with reduced smoke. The preparation of nitroazoles demonstrates its great synthetic potential. At the same time, feasibility and availability of the starting molecules make this strategy a powerful method for high-energy material construction. The introduction of electron-withdrawing nitro groups into azole cycle tends to produce energetic materials with high density, low sensitivity, and good thermal stability. Synthesis, molecular design, and explosive characteristics of new energetic compounds based on nitroazole have been studied in the famous Lawrence Livermore National Laboratory (USA). The investigations of research teams of A. Katritzky, A. Pozharskii, J. Elguero, S. Shevelev, V. Semenov, A. Sheremetev and so on, unveil the wide synthetic possibility of producing nitroazoles.

We consider azoles as five-membered heteroaromatic compounds and their annelated derivatives containing at least two endocyclic heteroatoms, one of which is nitrogen (pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, thiazole, selenazoles, tetrazole, indazole, benzimidazole, benzoxazole, benzothiazole, benzoselenazoles, benzotriazole, etc.).

A large body of information on the methods of synthesis, application, structure, and properties of all known five-membered nitroazoles – pyrazoles, imidazoles, triazoles, tetrazoles, oxazoles, isoxazoles, oxadiazoles, thiazoles, isothiazoles, thiadiazoles, selenazoles, selenadiazoles, and their benzo analogs – indazoles, benzimidazoles, benzoxazoles, benzisoxazoles, benzoxadiazoles, benzothiazoles, benzoisothiazoles, benzothiadiazoles, benzotriazoles, benzoselenazoles, and benzoselenadiazoles has been systematized, summarized, and critically discussed in this monograph.

Chapters 1 and 2 give comprehensive data on the preparation methods of all known *C*- and *N*-nitroderivatives of five-membered azoles and their condensed analogs. This book focuses on the nitration reaction, one of the main synthetic routes to nitroazoles. General information on the theory of nitration is given prior to the chapter covering synthetic methods. A separate section in the monograph is given to the special class of nitroazoles – polynitroazoles.

The critical evaluation of a large body of the information on the study of nitroazoles by physical/chemical methods (NMR, NQR, ESR, UV, IR- spectroscopy, X-ray, mass spectrometry, polarography, dipole moments, and other methods) is presented in Chap. 3.

Chapter 4 is devoted to the application of nitroazoles, many of which are important building blocks in drug discovery, well-known medicines, and hypoxic cell radiosensitizers.

Special attention is paid to those nitroimidazole derivatives among which are medicines with a vividly expressed therapeutical activity (azomycine, metronidazole, ipronidazole, carnidazole, dimetridazole, secnidazole, and many others) and to nitrotriazoles, nitrotetrazoles, and polynitroazoles used as high-energy compounds.

Our extensive investigations of the tautomerism, reactivity, electrochemistry, and structure of nitro derivatives of azoles are also included. Enormous number of facts are covered in the book.

This treatise constitutes the first complete collection of information on the chemistry of azoles containing a nitro group in the cycle. The monograph of Prof. Boyer (1986) on nitroazoles deals with only the *C*-nitro derivatives of *N*- and *N*,*O*-containing five-membered heterocycles, whereas the *N*-nitro derivatives presenting a new class of the oxide nitrogen generators (in particular, *N*-nitropyrazoles), as well as also thia- and selenazoles and all benzazoles remained unheeded. Prof. J.H. Boyer has noted that "that 'rapid development' of the chemistry of the nitroazoles in the Soviet Union began about 1960 and has provided more journal publications of research in the area than were found for any other country" and "the Russian emphasis on investigating" nitroazoles "has been outstanding."

This monograph provides comprehensive systematization of data on *C*- and *N*-nitroazole chemistry with in-depth information on structure and preparation, that is, nitration reactions and heterocyclization.

The monograph is mainly addressed to research professionals, research scientists (chemists, physicists, pharmaceutics, biochemists, chemical technologists), engineers, and "physicians—especially those dealing with oncology". This book can

be used as a textbook for postdoctorals and graduate students in chemistry, biochemistry, medical pharmacology, agricultural bioapplications, and for all who want to get acquainted with the chemistry and structure of nitroazoles.

The book may be of interest for the specialists dealing with the production of high-energy compounds (gas generators for air-bags, explosives, propellants, and pyrotechnics), nanomaterials, polymers, fibers, superelectrophiles, nonlinear optical materials, dyes (including fluorescent and cyanine dyes), and inhibitors of metal corrosion. It is also useful for people working in pharmaceutical industry.

We hope that it will be an invaluable reference for professionals in the field of heterocyclic chemistry, and that this book will initiate new investigations in this area.

The recent nature of the material and a large number of references (~2,200) make the book interesting for a wide range of specialists.

The authors would greatly appreciate receiving from readers any suggestions, comments, and recommendations.

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Contents

Introduction

Vigorous development of the chemistry of nitro compounds can be explained in terms of the practical and theoretical significance of these compounds. It can be said with assurance that the chemistry of nitro compounds has transformed into an independent area of organic chemistry. Many nitro compounds are used as explosives, ignition mixtures, and rocket fuels. Nitro aromatics serve as initial compounds for numerous dyers and pharmaceutical preparations. Nitro group-containing substances are constituents of many medicines. There are known nitro-containing pesticides and anticorrosion additives, technical solvents, etc.

From the theoretical viewpoint, compounds containing the nitro group are of interest due to their peculiar reactivity. They are very convenient in the investigation of structure–composition relationships. The reaction of electrophilic nitration is one of the most important and popular directions in organic chemistry.

Nitro compounds were the objective of much research. Certain aspects of this field of organic chemistry are discussed in many monographs and reviews. Well known treatise is a monograph on the chemistry of nitro and nitroso groups edited by Feuer [1]. The chemistry and technology of aromatic nitro compounds is considered in monographs [2–4]. Much attention has been given to unsaturated [5], aliphatic and alicyclic nitro compounds [6].

A great number of publications deal with the reaction of nitration [7–20]. At the same time, volumes literature on nitro heterocycles has not been systematized until the present time. Direct nitration of some five-membered heterocycles such as pyrroles, furans, thiophenes, pyrazoles, imidazoles, and thiazoles has been discussed by Katritzky [21, 22]. Some synthetic routes to nitrated six-membered nitrogen-containing aromatic heterocycles [23], as well as the nitration of oxo-pyrimidines and -imidazoles [24], and quantum-chemical studies of the nitration of benzazoles [25] have been reported.

The present monograph is devoted to the chemistry of a fascinating class of heterocyclic compounds, that of nitroazoles. The presence of the nitro group in the heterocyclic ring containing two or more hetero atoms points to a unique character of this cycle.

Some little data on the nitroazoles have been published in monographs and reviews dealing with the derivatives of pyrazole [26, 27], oxazole [28], thiazole [29], 1,2,4-triazole [30], 1,2,3-triazole [31], tetrazoles [32], benzimidazole [33], and benzotriazole [34]. Some representatives of nitroazoles are described in a comprehensive and

excellent book on heterocycles by Katritzky and Pozharskii [35] and in reviews on five-membered ring systems with two and more heteroatoms [36–39]. Recently Elguero and colleagues have surveyed some problems on tautomerism investigation of azoles [40]. Special monographs and reviews are dedicated to the chemistry, biological properties, and clinical application of nitroimidazoles [41–43]. In a monograph devoted to nitroazoles [44], only five-membered heterocycles with *N*- and *N*,*O*-endocyclic heteroatoms have been considered, whereas thia- and selenazoles, *N*-nitroazoles (a new class of the oxide nitrogen generator [45]), and all the nitrobenzoazoles were ignored. We have published some reviews on the synthesis of five-membered nitroazoles [46, 47] and their fused analogs [48, 49], on NMR spectroscopy [50] and mass spectrometry of nitroazoles [51], and on electronic substituent effects in five-membered, nitrogen-containing aromatic heterocycles [52].

Thus, azoles represent five-membered heteroaromatic compounds and they're benzanalogs with two or more heteroatoms of which at least one is nitrogen. According to Albert's classification subdividing all heteroaromatic compounds into π-rich and π-deficient ones, the azoles occupy an intermediate position, as they do not show clearly expressed π-donating or π-deficient properties [53]. It should be noted that this classification reflects the π-electron density distribution in the ground state of a molecule. Though reactivity is determined by the difference in energy of the ground and the transition state of the reaction, in practice a correlation of π-sufficiency change and the facility of electrophilic substitution is frequently observed. Really, as the number of "pyridine" nitrogen atoms increases the π-donating properties of azoles decrease and thus their reactivity in electrophilic substitution reactions is reduced [54]. However, this is not the case sometimes. Thus, 1*H*-imidazo[1,2]benzimidazole, for example, is less active than its 9*H*-isomer in the reactions of this type, though the donating ability of the latter is lower [55].

Nitroazoles possess a very broad array of practical applications. They can be used as anticancer preparations, antiseptics, radiosensitizers, herbicides, fungicides, dyes, ionic liquids, etc. The significant number of applications of nitroazoles makes them rather promising for research and requires deep understanding of their peculiar electronic structure, spectral properties, and chemical and tautomeric transformations [56, 57].

All this provoked us to write a monograph considering from unified positions all the literature available and our own data concerning the methods of synthesis, structure, properties, and application of *C*- and *N*-nitroderivatives of azoles and their condensed analogs.

An extensive volume of literature related to the question under consideration made us exclude a number of references to earlier publications and patents cited in the aforementioned monographs and reviews as well as in later publications.

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Synthesis of Five-Membered Nitroazoles

Abstract Synthesis methods of various *C*- and *N*-nitroderivatives of five-membered azoles – pyrazoles, imidazoles, 1,2,3-triazoles, 1,2,4-triazoles, oxazoles, oxadiazoles, isoxazoles, thiazoles, thiadiazoles, isothiazoles, selenazoles and tetrazoles – are summarized and critically discussed. The special attention focuses on the nitration reaction of azoles with nitric acid or sulfuric–nitric acid mixture, one of the main synthetic routes to nitroazoles. The nitration reactions with such nitrating agents as acetylnitrate, nitric acid/trifluoroacetic anhydride, nitrogen dioxide, nitrogen tetroxide, nitronium tetrafluoroborate, *N*-nitropicolinium tetrafluoroborate are reported. General information on the theory of electrophilic nitration of aromatic compounds is included in the chapter covering synthetic methods. The kinetics and mechanisms of nitration of five-membered azoles are considered. The nitroazole preparation from different cyclic systems or from aminoazoles or based on heterocyclization is the subject of wide speculation. The particular section is devoted to the chemistry of extraordinary class of nitroazoles – polynitroazoles. Vicarious nucleophilic substitution (VNS) reaction in nitroazoles is reviewed in detail.

Electrophilic Nitration of Azoles

The most widespread method of introducing nitro group in aromatic compounds, i.e., electrophilic substitution, is mainly used for the preparation of nitrodiazoles and benzazoles. The accumulation of "pyridine" nitrogen atoms in the cycle reduces the electrophilic substitution ability of compounds. Therefore, some indirect methods of introducing the nitro group are employed for the synthesis of triazole and tetrazole nitro derivatives.

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The ability of azoles to electrophilic substitution reactions is determined by the activity of reagents, the basicity of substrates, and the acidity of media. This caused some uncertainty in the interpretation of results and complicated a comparison of the reactivity of various azoles. The situation has changed after Katritzky and Johnson [1] have reported the criteria allowing, with a sufficient degree of reliance, the establishment in what form (base or conjugative acid) the compound reacts. The information on the mechanism of nitration of azoles was basically borrowed from the extensive literature on the nitration of aromatic hydrocarbons [2–8]; therefore, we have found expedient to discuss briefly some works in this field.

Nitration of aromatic compounds is an immensely important industrial process. The nitroaromatic compounds so produced are themselves widely utilized and act as chemical feedstocks for a great range of useful materials such as dyes, pharmaceuticals, perfumes, and plastics [6, 7].

Electrophilic Nitration Mechanism

As commonly accepted, the nitration of aromatic compounds is a typical reaction of electrophilic substitution, with the NO_2^+ nitronium ion serving as a directly attacking moiety. On nitration by only nitric acid, the nitronium cation is formed via autoprotolysis according to Scheme 1:

$$HNO_3 + HNO_3 \overset{\text{fast}}{\rightleftharpoons} H_2NO_3^+ + NO_3^-$$

$$H_2NO_3^+ \xrightarrow{\text{slowly}} H_2O + NO_2^+$$

$$H_2O + HNO_3 \xrightarrow{\text{fast}} H_3O^+ + NO_3^-$$

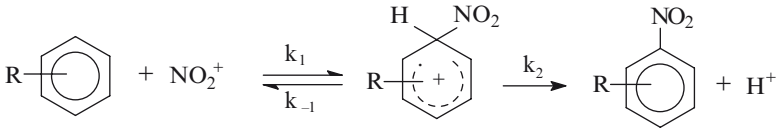
$$3\,HNO_3 \rightleftharpoons NO_2^+ + 2\,NO_3^- + H_3O^+$$

Scheme 1

In a sulfuric–nitric mixture the protonation of nitric acid occurs at the expense of a stronger sulfuric acid.

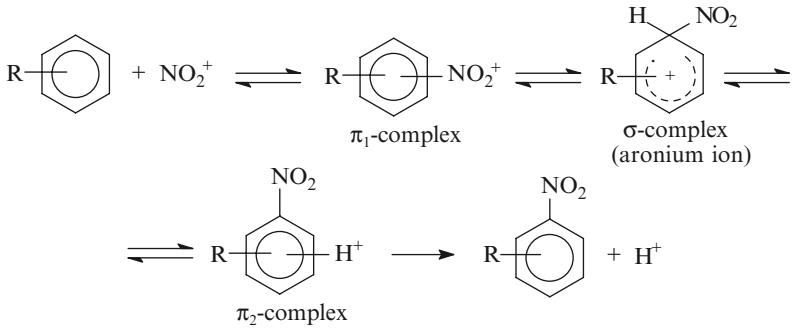
$$HNO_3 + 2H_2SO_4 \rightarrow NO_2^+ + H_3O^+ + 2HSO_4^-$$

There are many kinetic evidences for the fact that the nitronium cation and the aromatic substrate are involved in a reversible bimolecular reaction to form a σ-complex, which, being a strong acid, undergoes fast deprotonation (Scheme 2).



Scheme 2

The nitration pathway of this type was mainly supported by the data reported by Ingold [2]. Later this Scheme has been slightly modified by introducing one more stage, that of the formation of π-complex between the reagent and the substrate (Scheme 3).



Scheme 3

Numerous kinetic investigations of the formation of π-complexes carried out on model compounds have shown a high reaction rate and a low energy of activation of these interactions [3, 9]. As seen from the X-ray available data, the residue of aromatic substrate in π-complexes is structurally similar to the initial compound. All this has allowed a suggestion that in most cases elementary stages with participation of π-complexes do not play an essential role in electrophilic substitution [10]. The limiting stage of the process is the formation of σ-complex that is confirmed, in particular, by correlation of the arene basicity determining the stability of σ-complexes and the reaction rate [9–11]. The energy profile of the reaction is presented in Fig. 1, where ΔE^* is the total energy of activation.

Except for nitric acid and the nitrated mixture, the nitration of aromatic compounds can be carried out with nitronium salts as well [12].

$NO_2^+ \chi^-$, Where $\chi^- = BF_4^-$, ClO_4^- and *etc*

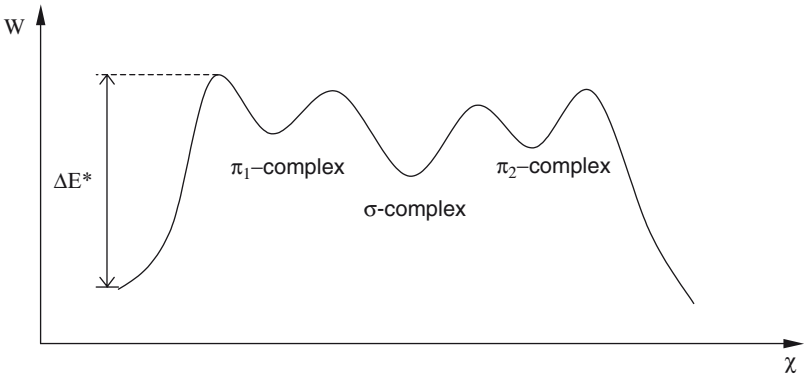


Fig. 1 The energy profile of the reaction of electrophilic substitution: *W* is energy, χ denotes the reaction coordinate

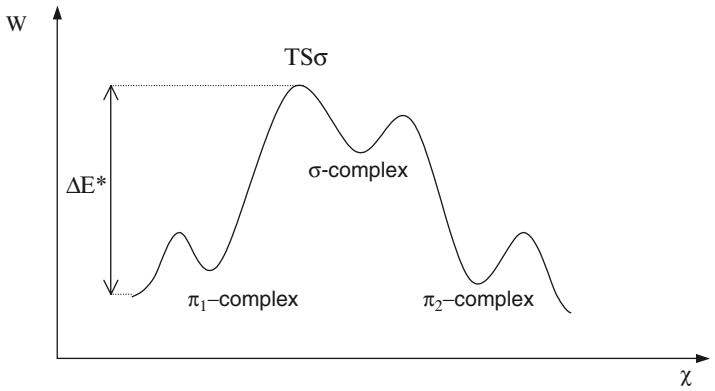
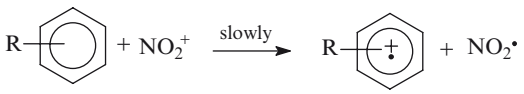


Fig. 2 The energy profile of nitration with nitronium salts: *W* is energy, χ stands for the reaction coordinate, and ΔE^* denotes the total energy of activation

Olah et al. have found out that the reaction rates on the nitration with nitronium salts are in good agreement with the stability of π-complexes [6, 13–16]. On this basis the authors have assumed that the nitronium salts serve as the nitrating agent; the stage limiting the reaction rate is the formation of π-complex (Fig. 2) that is rather uncommon in aromatic substitution.

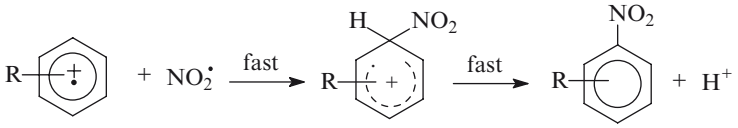
These works have caused intensive polemic discussed in detail in a review [12] and a monograph [24].

Another nitration mechanism has been offered by Perrin for arenes oxidized more easily than toluene [17]. In his opinion, a one-electron transfer from the aromatic substrate to the nitronium cation takes place (Scheme 4).



Scheme 4

The resultant radical cation of aromatic compound reacts with a nitrogen dioxide radical (Scheme 5).



Scheme 5

Ross et al. have reported some discrepancy between the experimental data and generally accepted mechanism of nitration [18–20]. The authors paid special attention to the participation of the radical cation of the aromatic substrate during nitration. It has been shown [20] that in the gas phase the nitronium cation does not act as a nitrating

agent and generates, by means of one-electron transfer, the aromatic radical cations, which react with $NO_2^{\cdot}$ to form nitroaromatic products. Thus, a serious experimental support for the participation of aromatic radical cations in the process of nitration has been provided. The formation of the aromatic radical cation on the initial step of nitration has been considered in a special review by Morkovnikov [21].

Without going into further discussion on the role of one-electron transfer in the mechanism of nitration of aromatic compounds, it should be noted that the nitration mechanism, which seemed to be strictly proved and clear after Ingold's studies [2], now again attracts steadfast attention. The research in this direction is worth further development.

Nitration with Nitric Acid or Sulfuric–Nitric Acid Mixture

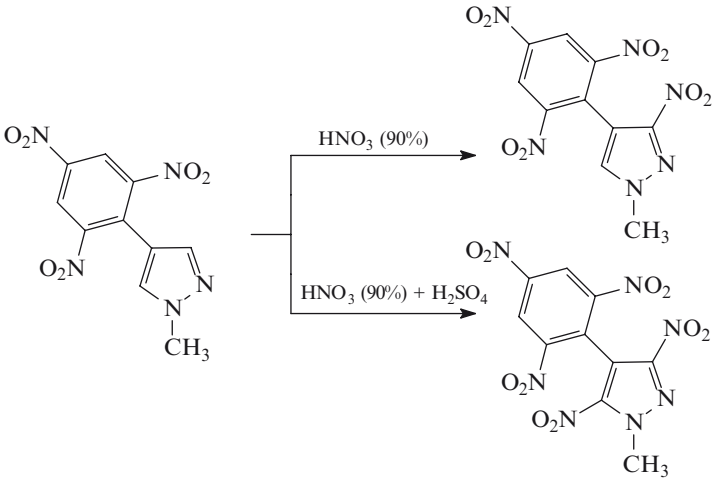
Pyrazoles

In 1893 Büchner and Fritsch [22] obtained 4-nitropyrazole for the first time by heating pyrazole with a mixture of oleum and nitric acid. This method with slight modifications has been used for the synthesis of 4-nitropyrazole up to the present time [23, 24]. During the nitration of substituted pyrazoles the nitro group usually enters at position 4, if it is free [25–53]. Such a process is consistent with the data from quantum-chemical calculations, i.e., the maximum π-electron density at the C-4 atom of the pyrazole ring [54]. The presence of alkyl substituents in the pyrazole ring facilitates the nitration process [25, 26, 39, 51, 52, 55], and here the steric factors are not determining. In fact, the presence of a *tert*-butyl group at position 3 or 5 does not prevent nitration at position 4 [42]. The nitration of 5-chloropyrazoles with a mixture of 100% nitric acid and 65% oleum (or a mixture of 60% nitric acid and polyphosphoric acid) affords substituted 5-chloro-4-nitropyrazoles in 45–91% yield [53].

The nitration of aryl- and thienylpyrazoles leads to the corresponding 4-nitropyrazoles. In this case, however, nitration of the aryl and thienyl substituents also occurs [22, 35, 37, 38, 52]. The nitration of 3-aryl-5-halopyrazoles is accompanied by introduction of a nitro group into the aromatic ring. 4-Chloropyrazoles failed to undergo nitration under these conditions [53]. Thus, 3- and 5-substituted 1-phenylpyrazoles usually form the corresponding 1-(4-nitrophenyl)-4-nitropyrazoles during nitration with a nitrating mixture [35–38]. At the same time nitration with nitric acid or a nitrating mixture under mild conditions leads to the corresponding *para*-nitrophenylpyrazoles [56–61]. 1-(4-Nitropheny)-4-nitropyrazoles are only formed if the concentration of nitric acid in the nitrating mixture is increased (or if the mixture is heated) [33, 34, 61]. 5(3)-Substituted 3(5)-(3-pyridyl)pyrazoles are nitrated at position 4 of the pyrazole ring [27–29]. During the nitration of 3(5)-methylpyrazole [51, 52], 3(5)-trimethylsilylpyrazole [43], 3(5)-halogeno-5(3)-methylpyrazole [44, 48, 49], pyrazole-3-carboxylic acid [30, 62], and 3(5)-nitropyrazole [29, 63] the corresponding 4-nitro derivatives are obtained.

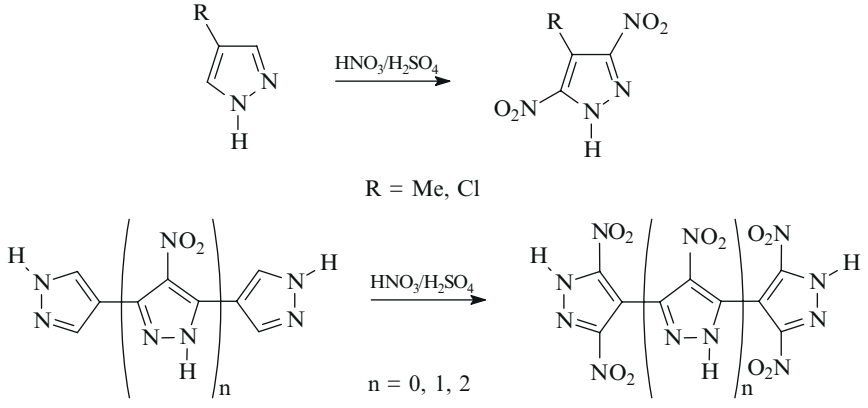
The introduction of such electron-withdrawing groups as 2,4-dinitrophenyl, picryl, or nitroguanidyl at position 1 of pyrazole does not hinder the nitration of pyrazole at position 4 [32, 41, 64].

The nitration of 3-hydroxy- or 5-hydroxypyrazoles (pyrazolones) also takes place at position 4 [65–67]. Although it was considered for a long time that pyrazoles are only nitrated at position 4, in rare cases the nitro group enters at position 3 or 5 [41, 45–47, 63, 68–72]. This usually occurs when position 4 is already occupied. Thus, for example, 1-methyl-3-nitro-4-(2,4,6-trinitrophenyl)pyrazole is formed when 1-methyl-4-(2,4,6-trinitrophenyl)pyrazole is heated in nitric acid (Scheme 6).



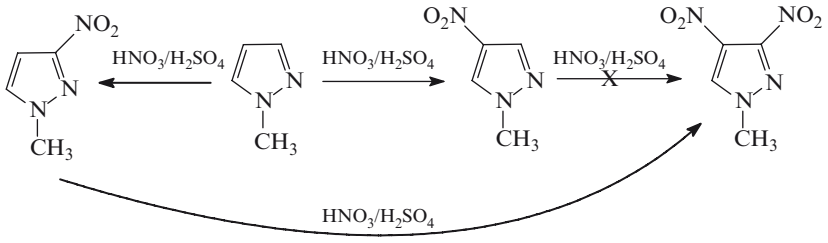
Scheme 6

At the same time the use of a sulfuric–nitric acid mixture leads to the 3,5-dinitro derivative [68]. Analogically dinitro compounds with high yield (70–80%) are observed on the nitration of 4-methyl-, 4-cloropyrazole and polypyrazoles [71, 73] (Scheme 7).



Scheme 7

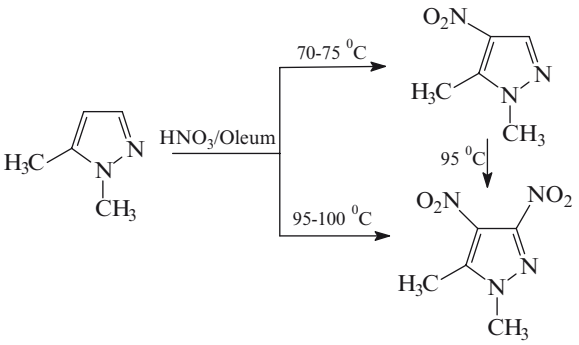
When 1-methylpyrazole is heated for a long time with a sulfuric–nitric acid mixture, 1-methyl-4-nitropyrazole and 1-methyl-3,4-dinitropyrazole are formed in a ratio of 4:1. Here the dinitro derivative is formed as a result of further nitration of 1-methyl-3-nitropyrazole [45] (Scheme 8).



Scheme 8

The introduction of electron-donating substituents into the pyrazole ring facilitates the nitration process, while the introduction of electron-withdrawing substituents retards it. In fact, 4-nitropyrazole, 1-methyl-4-nitropyrazole, 1,3-dimethyl-4-nitropyrazole, and 1-methyl-4-nitro-5-pyrazole carboxylic acid are not nitrated to the dinitro-substituted compounds [47, 63]. However, when heated with a mixture of nitric acid and oleum, 1,5-dimethyl-4-nitropyrazole changes to the 1,5-dimethyl-3,4-dinitro derivative [47].

The simultaneous introduction of two nitro groups into the pyrazole ring is rarely observed [29, 45–47, 63, 68]. This occurs under considerably more rigorous conditions than mononitration. Thus, 1-alkyl-4-bromo-3,5-dinitropyrazoles are also formed together with 1-alkyl-4-nitropyrazoles (as a result of *ipso*-substitution) during the nitration of l-alkyl-4-bromopyrazoles [46]. Here, it was assumed that the nitro group enters first at position 3. However, it was established more recently that the nitration rate of 4-bromo- and 4-chloro-1-methylpyrazoles with the sulfuric–nitric acid mixture is higher at position 5 than at position 3 [74] (Scheme 9)

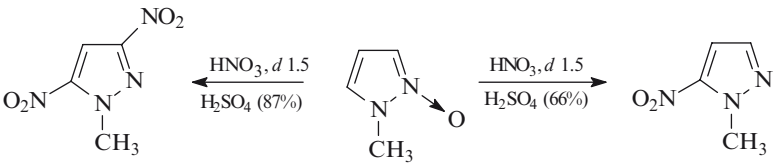


Scheme 9

The "pyrrole" nitrogen atom activates the pyrazole ring toward electrophilic reagents to a greater degree than the "pyridine" nitrogen atom deactivates it. This is confirmed by the higher rate constant for substitution of the hydrogen atom at position 3 of

1,4-dimethylpyrazole than the rate constant for the substitution of hydrogen at the ortho position of toluene [64].

Some examples of the nitration of pyrazole N-oxides are known [75, 76]. The result of nitration is determined by the ratio of the components in the nitrating mixture (Scheme 10).



Scheme 10

In some cases 1-methyl-5-nitro- and 1-methyl-3,5-dinitropyrazole can form as a result of deoxygenation [76]. Nevetheless, the nitration of 2-benzylpyrazole 1-oxide by sulfuric–nitric acid mixture leads to 2-benzyl-3-nitropyrazole 1-oxide in quantitative yield. Further nitration takes place in the phenyl 4-position forming 3-nitro-2-(4-nitrobenzyl)pyrazole 1-oxide and then in the pyrazole 5-position to give 3,5-dinitro-2-(4-nitrobenzyl)pyrazole 1-oxide as the final product [77].

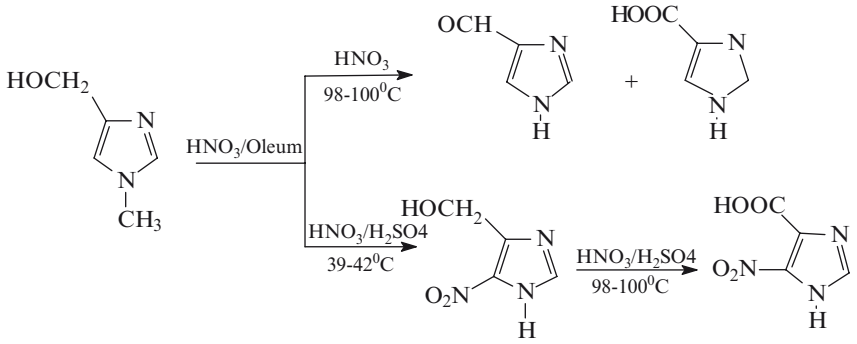
Imidazoles

In spite of extensive investigations into the electrophilic substitution of imidazoles, no rational explanation has yet been found for certain features of the reaction [78]. The nitration of imidazoles takes place exclusively at position 4 or 5. In reaction with the sulfuric–nitric acid mixture imidazole itself forms the 4(5)-nitro derivative [79–85]. A large number of papers have been devoted to the production of 2-methyl-4(5)-nitroimidazole by the nitration of 2-methylimidazole [79, 82, 86–94]. This is due to the fact that 2-methyl-4(5)-nitroimidazole is an important intermediate product in the synthesis of highly effective medical products (metronidazole, tinidazole, dimetridazole, etc.).

The nitration of other 2-alkyl-substituted imidazoles takes place similarly: 2-ethylimidazole [86, 87, 92, 95], 2-propylimidazole [87], 2-isopropylimidazole [87, 89–92, 96], and 2-butylimidazole [87, 89]. During the nitration of 2-phenylimidazole with the sulfuric–nitric acid mixture the nitro group enters first at position 4 of the benzene ring [97, 98], and nitration at position 4(5) of the imidazole ring only takes place under more rigorous conditions [82, 91]. In cases where the aryl group is passivated by electron-withdrawing substituents the nitration takes place exclusively in the imidazole ring [86, 99–102]. The presence of other substituents at position 2 does not change the direction of nitration [88, 93, 103–108].

The presence of a substituent at position 4(5) of the imidazole ring does not prevent entry of the nitro group at position 5(4) [87, 95, 109–121]. The size of the substituent does not play a part (isopropyl, cyclopentyl, and cyclohexyl) [113].

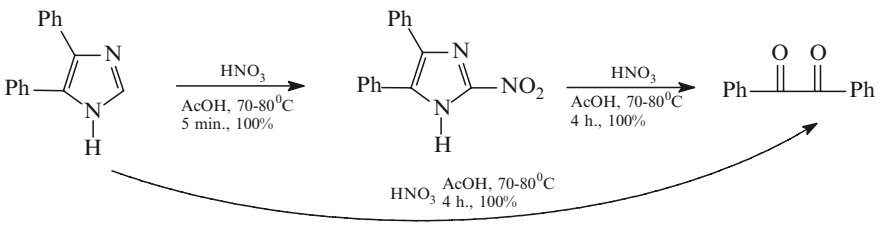
In some cases the nitration is accompanied by oxidation of the side groups [122, 123]. Thus, for example, depending on the conditions, 4(5)-hydroxymethylimidazole is converted by the action of the sulfuric–nitric acid mixture into the corresponding aldehyde [124–126], into 4(5)-imidazolecarboxylic acid [124, 125], or into 4(5)-nitro-5(4)-imidazolecarboxylic acid [122, 123] (Scheme 11).



Scheme 11

The oxidation of the hydroxymethyl group probably takes place more readily than nitration of the ring [124–127]. However, the entry of a nitro group into the imidazole ring without oxidation of the hydroxymethyl group has been reported [107, 110]. Imidazolecarboxylic acids are not nitrated, and their nitro derivatives are therefore obtained by different methods. Nevertheless, the 4- and 5-mononitro-substituted compounds were isolated with the 4,5-dinitro derivative as impurity during the nitration of ethyl 1-methylimidazole-2-carboxylate with a mixture of 100% nitric and sulfuric acids at 95°C [128].

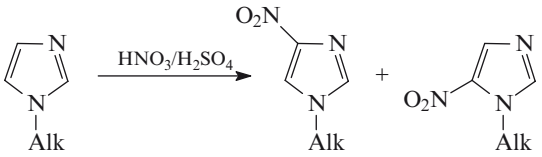
The imidazole ring has high resistance to the destructive action of various oxidizing agents, including nitric acid. It is not possible to introduce the nitro group into the position 2 of imidazole ring, but the reaction 4,5-diphenylimidazole in HNO_3 (1–2 moles) and AcOH with quantitive yield leads to 2-nitro-4,5-diphenylimidazole [129] (Scheme 12).



Scheme 12

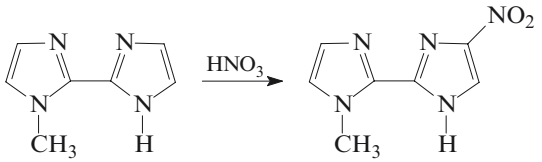
However *N*-acetyl-4,5-diphenylimidazole obtained by boiling in acetic anhydride does not react with excess HNO_3 (1–6 moles) during 4 h [129].

The action of the nitrating mixture on 1-alkylimidazoles gives the 4-and 5-nitro derivatives with a preference for the former [130–132]. The sizes of the substituent have practically no effect on the ratio of the isomers [132]. At the same time this effect is quite noticeable in the series of carbocyclic substrates (Scheme 13).



Scheme 13

The introduction of a substituent at position 1 of the imidazole ring hinders nitration, and most nitro-*N*-methylimidazoles have been prepared by the *N*-methylation of the corresponding nitroimidazoles. Thus, of the two possible nitration products only 1-methyl-2-(4-nitro-2-imidazolyl)imidazole is formed by the action of one equivalent of nitric acid on 1-methyl-2-(2-imidazolyl)imidazole [133] (Scheme 14).



Scheme 14

In this case, probably, nitration takes place through the monocation, and the nitro group attacks the less basic fragment of the molecule.

The nitration of 1,2-disubstituted imidazoles also leads to a mixture of 4-nitro and 5-nitro derivatives [128, 134–139]. The nature of the substituents in the imidazole ring has an effect on the ratio of the isomers. However, specific investigations in this direction have not yet been undertaken. During the nitration of 1,2-disubstituted imidazoles only the 4-nitro [140–143] or the 5-nitro [144–148] derivatives were isolated. It is not impossible that a mixture of isomers was obtained here.

The nitration of 1-methyl-2-(2-furyl)- and 1-methyl-2-(2-thienyl)imidazoles in polyphosphoric acid was described [149, 150]. At room temperature the nitro group enters at position 5 both of the furan and of the thiophene rings. Nitration of the furan derivative by 2 moles of nitric acid leads mainly to the dinitro derivative 1-methyl-2-(5-nitro-2-furyl)-5-nitroimidazole [149]. The introduction of a second nitro group into the thienyl derivative requires more rigorous conditions (80°C, 2 moles of nitric acid). Its position in the imidazole ring was not established [150].

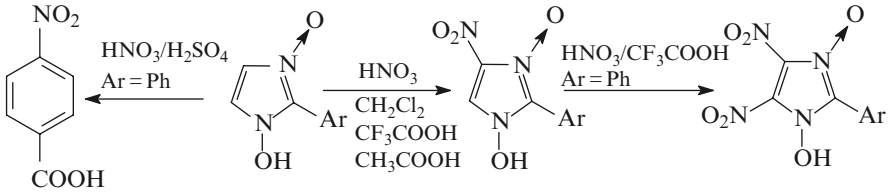
As in the 1,2,4-trisubsrituted derivatives, during the nitration of 1,4-disubstituted imidazoles the nitro group only enters at position 5 [151–154]. If the substituents contain double bonds or hydroxyl groups, a transformation of the side chain can

occur in addition to nitration [152]. On the other hand, during the nitration of 1,5-di- and 1,2,5-trisubstituted imidazoles the nitro group enters at the free position 4 [151, 155–157].

The nitration of 1-alkyl- and 1,2-dialkyl-5-halogenoimidazoles [151, 155, 158], which are used as intermediates in the pharmaceutical chemistry industry, has been investigated in greatest detail. For instance, the immunodepressant azathioprine ("imuran") was obtained from 1-methyl-4-nitro-5-chloroimidazole [158].

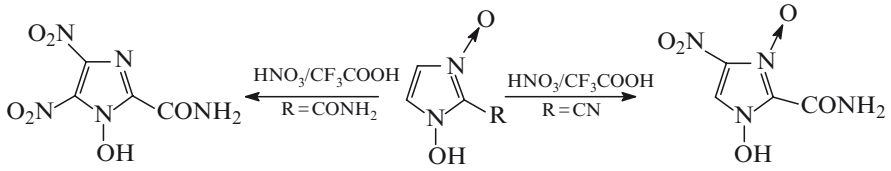
For many years it was not possible to introduce two nitro groups into the imidazole ring [159]. By the use of a somewhat unusual nitration condition (by heating the substrate first with nitric acid and then with the sulfuric–nitric acid mixture) it was possible to obtain 4,5-dinitroimidazole [79]. The method has now also been used for the production of 4,5-dinitroimidazoles [84, 93, 160]. It was also shown that *C*-polynitrobisimidazoles [79] and not *N*-nitroimidazoles, as considered earlier [161], are formed during the nitration of 2,2′-bisimidazole and its bromine derivatives. As already mentioned earlier, during the nitration of ethyl l-methylimidazole-2-carboxylate the 4,5-dinitro derivative was also isolated together with the other nitration products [128]. Increase in the reaction time increases the amount of the dinitro derivative.

The nitration of 1,4,5-trimethylimidazole 3-oxide with the sulfuric–nitric acid mixture leads to the 2-nitro derivative [76, 162]. Both this compound and 1-methylpyrazole 2-oxide enter into reaction in the form of the free base [76]. The nitration of 2-aryl-1-hydroxyimidazole 3-oxides leads either to cleavage of the imidazole ring or to the formation of the 4-nitro or 4,5-dinitro derivatives, depending on the reaction conditions [162] (Scheme 15).



Scheme 15

1-Hydroxyimidazole 3-oxide, which does not have substituents at position 2, is unstable under the conditions of nitration. Uncommon nitration of 1-hydroxy-2-cyanoimidazole 3-oxide and 1-hydroxy-2-carbamoylimidazole 3-oxide was observed in [162] (Scheme 16).

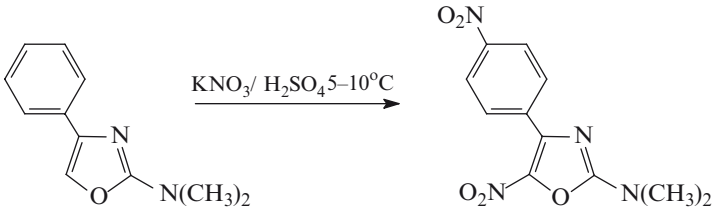


Scheme 16

During the nitration of the cyano derivative the nitrile group is transformed into an amide group, simultaneously with the introduction of the nitro group at position 4, and 1-hydroxy-2-carbamoyl-4-nitroimidazole 3-oxide is formed. During nitration of the corresponding carbamoyl derivative two nitro groups enter the molecule with simultaneous deoxygenation, resulting in the formation of 1-hydroxy-4,5-dinitroimidazole.

Oxazoles and Isoxazoles

The direct entry of a nitro group into the oxazole ring (1,3-oxazole) (exclusively at position 5) has only been reported twice [163, 164]. Thus, 2-dimethylamino-4-(4-nitrophenyl)-5-nitrooxazole was isolated when 2-dimethylamino-4-phenyloxazole was heated [163] (Scheme 17).



Scheme 17

The nitro group probably enters first at the *para*-position of the phenyl ring, after which the oxazole ring is nitrated. The action of nitric acid on 2-phenyloxazole in boiling dichloroethane gives 5-nitro-2-phenyloxazole with a yield of 15% together with the products from nitration of the benzene ring [164]. The nitration of the same compound under certain conditions excluding protonation by the action of *N*-nitropicolinium fluoroborate in acetonitrile gives a 90% yield of 5-nitro-2-phenyloxazole [164].

The isoxazoles (1,2-oxazoles) are nitrated exclusively at position 4. Isoxazole itself is nitrated with difficulty, and the yield of the nitro derivative does not exceed 3.5% [165, 166]. With nitronium tetrafluoroborate as nitrating agent it is possible to increase the yield of 4-nitroisoxazole to 35% [167].

The introduction of electron-donating substituents into the isoxazole ring facilitates the nitration process. Thus, the nitration of 3,5-dialkylisoxazoles [168–171] or bis(3-methylisoxazolyl-5) [172] gave the corresponding 4-nitro derivatives Under the same conditions, however, 3-methyl-5-(2-methoxy-2-phenylethyl)isoxazole was only nitrated in the phenyl ring [173]. Conversely, even at room temperature the nitration of 3-methyl-5-dichloromethyl- and 3-dichloromethyl-5-methylisoxazole gives the corresponding 4-nitro derivatives [174]. The nitration of 3-bromo-5-methylisoxazole is similar [175].

Only the benzene ring is nitrated during the action of the sulfuric–nitric acid mixture on 3-phenylisoxazole. At the same time a mixture of nitric and acetic acids converts it into 3-phenyl-4-nitroisoxazole [176]. Earlier Musante [177] isolated a

compound melting at 174–177°C during the nitration of 3-phenylisoxazole and assigned it the structure of 3-(4-nitrophenyl)isoxazole. More recently, however, it was shown [178] that this compound was 5-(4-nitrophenyl)isoxazole. The latter is formed during the nitration of 5-phenylisoxazole present in the initial reagent as impurity. The fact is that the 3- and 5-phenylisoxazoles have very similar melting points, and the 3- and 5-substituted isomers are formed in the selected method for the synthesis of the initial phenylisoxazole. This explains the error in the interpretation of the results from the nitration of 5-phenylisoxazole [179]. It was considered that a mixture of 5-(4-nitrophenyl)isoxazole (45%) and 4-nitro-5-phenylisoxazole (30%) was formed here. In fact, however, the latter was 4-nitro-3-phenylisoxazole formed as a result of nitration of the other isomer [178].

The contradictory data on the direction of nitration have been checked many times [178, 180–182]. It was shown that small amounts of 5-(3-nitrophenyl)isoxazoles and 4-nitro-5-(4-nitrophenyl)isoxazoles were formed together with the 5-(4-nitrophenyl)isoxazole [178, 180]. The structure of 4-nitro-5-(4-nitrophenyl) isoxazole was demonstrated by the nitration of 5-(4-nitrophenyl)isoxazole [178, 181]. During a more thorough investigation of this process it was found that an equimolar mixture of 5-(2-nitrophenyl)-, 5-(3-nitrophenyl)-, and 5-(4-nitrophenyl) isoxazoles is formed as a result of the reaction [182]. They are accompanied by a small amount of a mixture of difficultly separated 4-nitro-5-(4-nitrophenyl)- and 5-(3-nitrophenyl)isoxazoles.

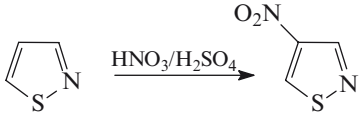
The kinetics of the nitration of 3-methyl-5-phenyl- and 5-methyl-3-phenylisoxazoles [183] and 5,5-dimethylisoxazole [184] were studied. During the nitration of 3,5-diphenylisoxazole by the sulfuric–nitric acid mixture only the phenyl group enters into the reaction [177, 185]. In acetic anhydride, however, the main nitration product is 3,5-diphenyl-4-nitroisoxazole [185].

Initially it was considered that 3-phenylamino-5-phenylisoxazole and 3-phenylamino-5-phenylpyrazole were nitrated exclusively in the phenyl ring [186]. More recently, however, it was shown that the nitro group also enters at position 4 of the heterocycle [187, 188].

Thiazoles and Isothiazoles

The nitration of the isothiazole (1,2-thiazole) ring takes place exclusively at position 4. The 4-substituted isothiazoles are either not nitrated at all [189, 190] or, as in the case of 4-phenylisothiazole, are nitrated in the benzene ring [191].

The action of the sulfuric–nitric acid mixture on isothiazole gives a high yield of the corresponding 4-nitro derivative [190, 192, 193] (Scheme 18).



Scheme 18

Table 1 The relative nitration rates (F) of thiazoles and isothiazoles

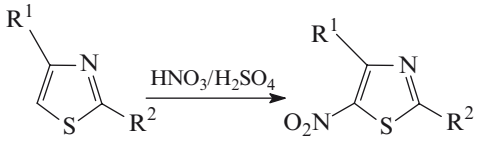
Thiazoles		Isothiazoles	
R	F	R	F
2,4-Me_2	1	3,5-Me_2	0.16
2,5-Me	0.5	5-Me	0.0094
4-Me	0.066	3-Me	0.0055
5-Me	0.04	H	0.0024

The nitration of 3-alkylisothiazoles [190, 193, 194], 5-alkylisothiazoles [190, 193], and other derivatives of isothiazole containing halogen atoms or electron-donating substituents at positions 3 and 5 [183, 193–197] takes place similarly.

Thiazole itself is not nitrated even under fairly rigorous conditions [198, 199]. However, many of its derivatives containing electron-donating substituents are nitrated smoothly.

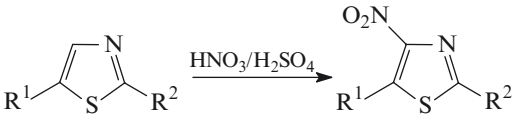
Table 1 gives the relative rate constants for the nitration of thiazoles and isothiazoles. They demonstrate the higher reactivity of the thiazoles during nitration [190, 200]. Such high regioselectivity is not observed during the nitration of thiazoles, as during the nitration of isothiazoles.

Electron-donating substituents at position 2 or positions 2,4 of the thiazole ring direct the entering nitro group toward position 5 of the ring [201–218] (Scheme 19).



Scheme 19

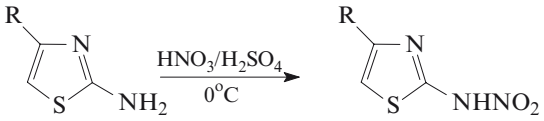
If, however, this position is occupied, e.g., in the case of 5-substituted or 2,5-disubstituted thiazoles, the 4-nitro derivative is formed [201, 202, 205, 207, 208, 210, 211, 219, 220] (Scheme 20).



Scheme 20

Only one example of the nitration of thiazoles at position 2 has been described; the action of the sulfuric–nitric acid mixture on 4,5-dimethylthiazole gave 4,5-dimethyl-2-nitrothiazole [199].

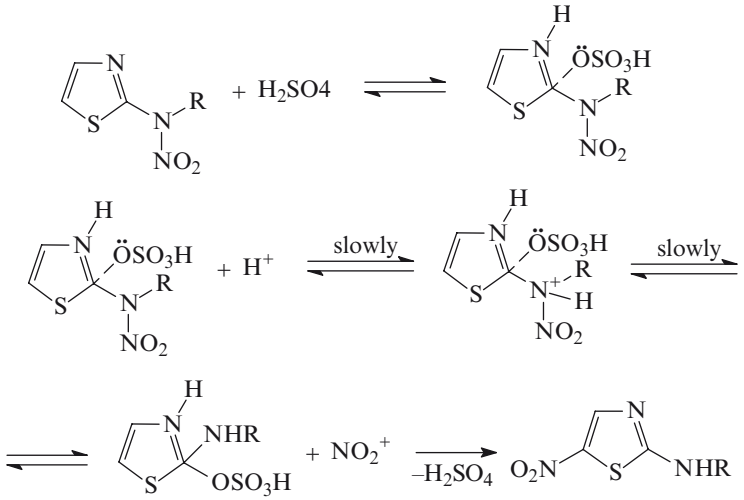
The nitration of 2-amino- and 2-acetamidothiazoles has been studied particularly widely [202–205, 220–226]. This is explained by the wide range of biological activity in the respective nitro derivatives. Here, nitroamines can also form in addition to nitration of the thiazole ring [203, 204, 225] (Scheme 21).



Scheme 21

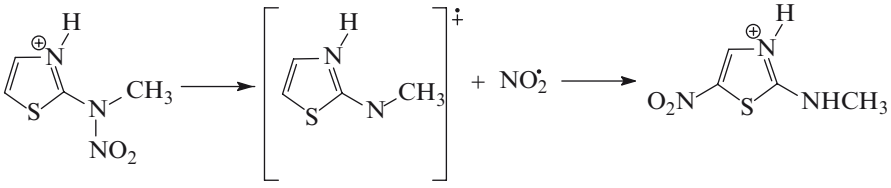
The conditions required for the isolation of such nitroamines have been described [204]. In concentrated sulfuric acid they readily rearrange to 2-amino-5-nitrothiazoles. The isomerization rate depends strongly on the sulfuric acid concentration [204]. Thus, the formation of 2-amino-5-nitrothiazoles may be the result both of direct electrophilic substitution in the thiazole ring and of the aforementioned rearrangement.

A study of the kinetics of isomerization of nitroaminothiazoles [227–229] showed that both intramolecular and intermolecular migration of the nitro group occur [228]. The following reaction mechanism was proposed (Scheme 22).



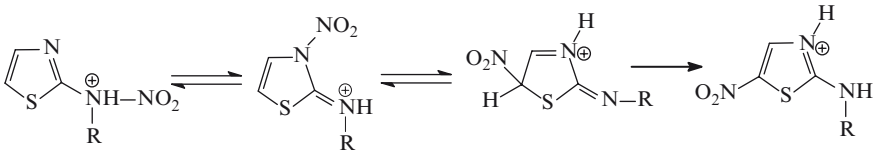
Scheme 22

This gave rise to some objection concerning, in particular, the structure of the intermediates ([230], part 2, p. 73). It would be more logical to suppose the intermediate formation of radical cations according to the following Scheme ([230], part 2, p. 83) (Scheme 23).



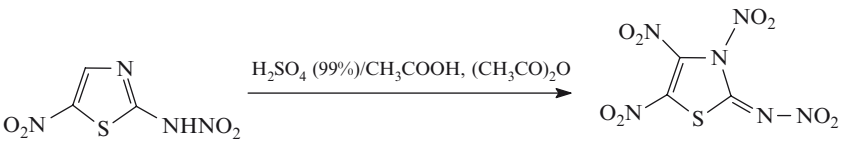
Scheme 23

However, the formation of free radicals in the rearrangement process was denied [231], and this makes it possible to introduce certain corrections into the previously proposed mechanism (Scheme 24).



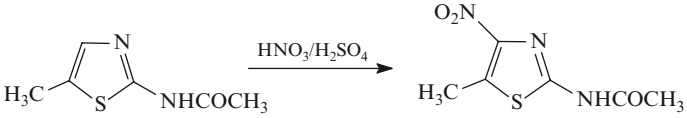
Scheme 24

It would probably be useful to carry out a more detailed investigation of these reactions using ESR and CIDNP techniques. Further nitration of 2-nitroamino-5-nitrothiazole leads to 2-nitroimino-3,4,5-trinitro-3*H*-thiazoline [203] (Scheme 25).



Scheme 25

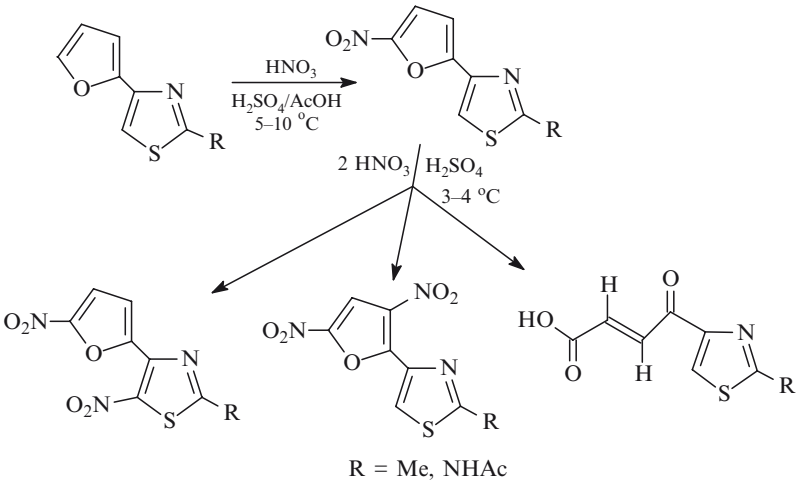
When position 5 is occupied as, for example, in the case of 2-acetamido-5-methylthiazole, the 4-nitro derivative is formed with a small yield [223] (Scheme 26).



Scheme 26

2-Acetamido-4-phenylthiazole is nitrated at position 5 of the thiazole ring [232], in contrast to 2-amino-4-phenylthiazole, which is nitrated in the phenyl ring [233]. This agrees with existing data on the reactivity of thiazoles during electrophilic substitution. N-(2-Thiazolyl)-2-aminopyridine is nitrated exclusively in the thiazole ring [222].

The nitration of 2-, 4- and 5-phenylthiazole with 1 mole of HNO_3 in concentrated H_2SO_4 occurs at *para*-position of the phenyl ring, but not to thiazole cycle [203, 247]. It can be explained then that these compounds react in so-called conjugated acid form (protonated form), but not in base form. Analogically, 2-substituted 4-(2-furyl)thiazole is nitrated into furyl cycle 5 position; however, further nitration with two moles HNO_3 leads to 2-substituted 5-nitro-4-(5-nitro-2-furyl)-thiazoles along with other products [234] (Scheme 27).



Scheme 27

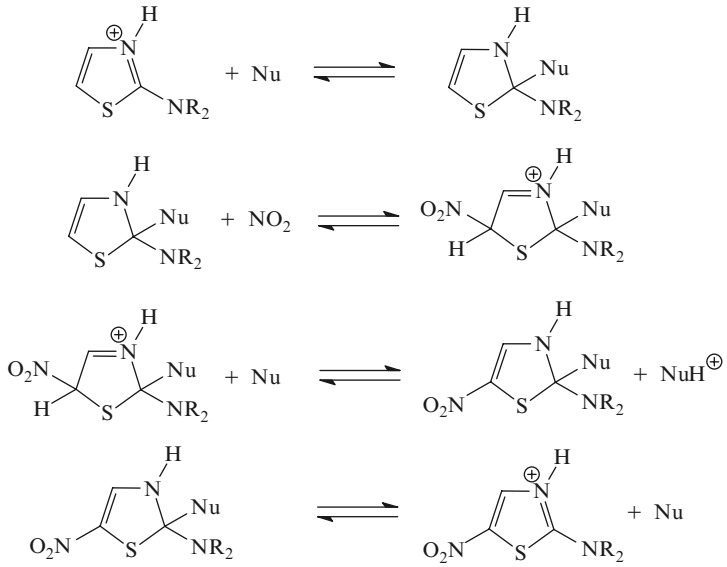
Steric factors also have a specific effect on the nitration process. Thus, 2-amino-4-mesitylthiazole is not nitrated, whereas 2-amino-4-*tert*-butylthiazole forms the corresponding 5-nitro derivative [204]. The 2-amino-, 2-dimethylamino-, 2-piperidino-, and 2-morpholinothiazoles are nitrated at position 5 of the thiazole ring [209, 224]. At the same time 2-dipropylamino-, 2-diallylamino-, and 2-dibutylaminothiazoles are destroyed under these conditions ([230], part 2, p. 72). Such a strong effect from the nature of the substituents at the exocyclic nitrogen atom on the direction of the reaction cannot as yet be explained unambiguously. It was suggested, it is true, that a somewhat unusual nitration mechanism is realized in this case, i.e., that initial nucleophilic attack occurs at the N=C-2 bond of the thiazole ring ([230], part 2, p. 85) (Scheme 28).

However, no evidence for this was given. A thorough kinetic investigation and analysis of the side products would make it possible to check this hypothesis.

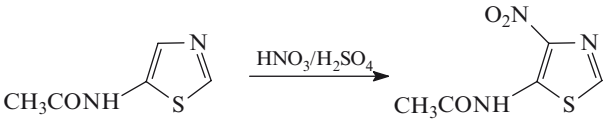
2-Amino-4-phenyl-5-benzoylthiazole is nitrated by nitric acid with the formation of the 2-nitroamino derivative [235]. During the nitration of 5-acetamidothiazole a compound melting at 197–198°C was obtained. It was assigned the structure of 2,4-dinitro-5-acetamidothiazole [221]. In fact, it was the mononitration product 4-nitro-5-acetamidothiazole [201] (Scheme 29).

Selenazoles

Data on the nitration of selenazoles are extremely limited. The 4-methyl- and 2,4-dimethylselenazoles are nitrated more quickly than their thiazole analogs [236].



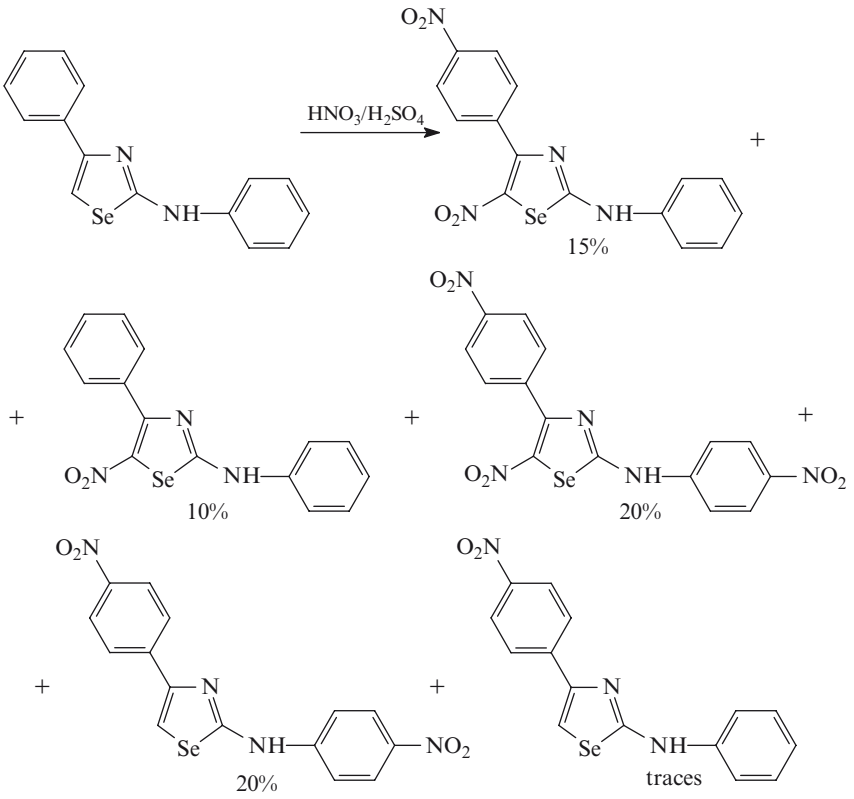
Scheme 28



Scheme 29

Ring opening occurs during the direct nitration of 2-amino-4-methylselenazole [237]. However, protection of the amino group by acylation or alkylation makes it possible to obtain good yields of the corresponding 5-nitro derivatives [237–239].

The nitration of 2-phenylamino-4-phenylselenazole takes place in a more complicated way ([230], part 3). A very vigorous reaction with the formation of several nitration products is observed even with careful addition of this compound to the sulfuric–nitric acid mixture. It was possible to separate and partly to identify the products by column chromatography and thin-layer chromatography. The products from opening of the heterocycle were not detected (Scheme 30).

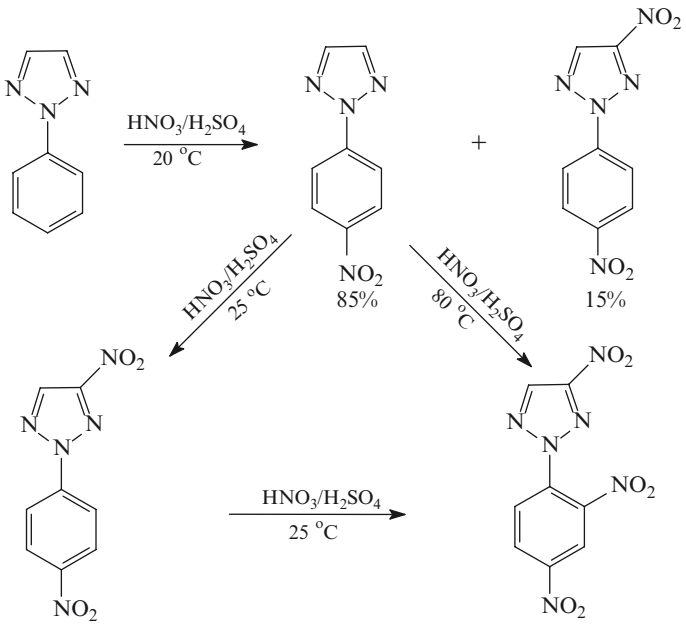


Scheme 30

Triazoles

The presence of three heteroatoms in the azole ring reduces its reactivity in electrophilic substitution reactions more. 1,2,3-Triazole itself could not be nitrated [240]. An attempt to introduce a nitro group into the heterocyclic ring 1-phenyl- and 4-phenyl-1,2,3-triazoles was also unsuccessful. In both cases only the phenyl group was nitrated [241, 242]. Nevertheless, several examples of the entry of a nitro group directly into the triazole ring have been described. Thus, 2-methyl-4-nitro-1,2,3-triazole was formed during the nitration of 2-methyl-1,2,3-triazole with a sulfuric-nitric acid mixture under conditions (20°C). Under harsher nitration conditions (100°C) 2-methyl-4,5-dinitro-1,2,3-triazole was formed [243]. The nitration of 2-phenyl-1,2,3-triazole led to a mixture of the mono- and dinitro derivatives [244] (Scheme 31).

Under mild conditions 2-(4-nitrophenyl)-1,2,3-triazole forms the dinitro derivative, and under harsh conditions it forms the trinitro derivative. In turn, 2-(4-nitrophenyl)-4-nitro-1,2,3-triazole, which was initially assigned the structure of 2-(2-nitrophenyl)-1,2,3-triazole [245], also forms 2-(2,4-dinitrophenyl)-4-nitro-1,2,3-triazole during further nitration [244, 246]. At the same time



Scheme 31

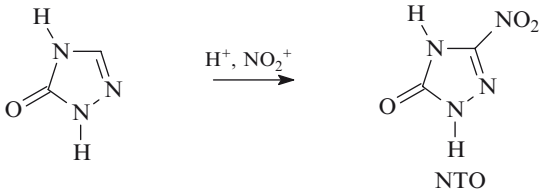
2-(4-bromophenyl)-1,2,3-triazole formed 2-(4-bromo-2-nitrophenyl)-4-nitro-1,2,3-triazole immediately (yield 73%) even under mild conditions (15°C) [240]. In fact, the nature of the substituent and its position in the heterocycle have a significant effect on the process. Thus, for example, 4-methyl-2-phenyl-l ,2,3-triazole is converted by the action of the sulfuric–nitric acid mixture into 4-methyl-5-nitro-2-(2,4-dinitrophenyl)-1,2,3-triazole [246]. 4-Hydroxy-2-phenyl-1,2,3-triazole [247] and 4-picrylamino-1,2,3-triazole [248] are nitrated exclusively in the azole ring with the formation of the corresponding 5-nitro derivatives. 2-(2,4,6-Trinitrophenyl)-1,2,3-triazole is nitrated with a high yield, whereas its 1-isomer does not react with the sulfuric–nitric acid mixture [249].

It is not possible to introduce a nitro group into the 1,2,4-triazole ring by the action of the sulfuric–nitric acid mixture because of the disactivation of the cycle by two "pyridine" nitrogen atoms; furthermore, their disactivation effect is aggravated by the heterocycle protonation in the acid medium. The only exception is the nitration of 1,2,4-triazolon-5 [250–264]. This is probably due to the specific electronic structure of the substrate (the azolone form) (Scheme 32).

3-Nitro-1,2,4-triazolon-5 (NTO) is one of the popular and widely used in the last time the explore compound [263–268].

In aryl- or amino-substituted 1,2,4-triazols the nitro group enters the side chain [269–271]. An attempt to realize the nitration of 3,5-bisphenylamino-1,2,4-triazole led to opening of the triazole ring. Picrylurea was isolated as the only reaction product [272].

The nitration products of 2-methyl-1,2,3-triazole 1-oxide under mild conditions (20°C) are a mixture of 5-nitro (75%) and 4-nitro (23%) derivatives. Under more



Scheme 32

rigorous conditions (100°C) 4,5-dinitro-2-methyl-1,2,3-triazole 1-oxide (77%) is formed [243, 273]. During the nitration of 5-R-2-methyl-1,2,3-triazole 1-oxide (R = CH_3, Br) the nitro group enters at position 4 of the triazole ring. The bromine atom disactivates the ring, as a result of which rigorous conditions are required for the nitration of 5-bromo-2-methyl-1,2,3-triazole 1-oxide (100°C) [243, 273]. The nitration of 2-phenyl-1,2,3-triazole 1-oxide under the same conditions leads to 2-(2,4-dinitrophenyl)-4-nitro-1,2,3-triazole 1-oxide with a yield of 65% [240].

Oxadiazoles, Thiadiazoles, and Tetrazoles

As a rule, oxadiazoles and thiadiazoles are not nitrated. Reports on the production of 2-nitro-5-amino-1,3,4-thiadiazole during the nitration of 2-amino-l,3,4-thiadiazole [274] proved erroneous [275]. The compound obtained in this case was 2-nitramino-1,3,4-thiadiazole [275]. There is only a single paper on the nitration of derivatives of 1,3,4-oxa- and 1,3,4-thiadiazoles [276]. 2-Dimethylamino-1,3,4-oxa- and 2-dimethylamino-l,3,4-thiadiazoles react with the nitrating mixture with the formation of 2-dimethylamino-5-nitro derivatives. Aryl-substituted oxadiazoles and thiadiazoles are nitrated in the phenyl ring [277, 278].

Until now no example of the nitration of the tetrazole ring by the action of nitrating agents has been described. During the nitration of substituted tetrazoles the nitro group enters exclusively in the side chain [279–281].

Kinetics and Mechanism of Nitration of Azoles by Sulfuric–Nitric Acid Mixture

Determination of the mechanism of nitration of azoles is complicated by the fact that they can be nitrated both in the free form and in the protonated form. The kinetics of the nitration of azoles in media with various acidities is therefore compared with the kinetics of the nitration of related model compounds known to exist in the form of ions (e.g., the quaternary salt of the investigated azole). If nitration takes place through the protonated form, the rate initially increases with increase in the acidity on account of the increase in the concentration of the nitronium ion. After reaching a maximum the rate then remains almost unchanged or decreases slightly.

Table 2 The relative reactivity (F) of alkylthiazoles (compared with benzene, $F = 1$) in nitration (sulfuric–nitric acid mixture, 70°C)

Compound	Reaction center	$F \times 10^3$
5-Methylthiazole	4	6
4-Methylthiazole	5	9
2,5-Dimethylthiazole	4	46
2-Methyl-5-ethylthiazole	4	59
2-Ethyl-5-methylthiazole	4	63
2-*tert*-Butyl-5-methylthiazole	4	83
2,4-Dimethylthiazole	5	150

Table 3 The selectivity of nitration of 2-alkylthiazoles and the yields of nitro products

		Selectivity (%)			
Compound	Nitrating agent	4-NO_2	5-NO_2	Yield (%)	Refs
2-Methylthiazole	$NO_2^+BF_4^-$ or $N_2O_4 \cdot BF_3$	31	69	86	[288]
2-Methylthiazole	H_2SO_4/HNO_3 70°C	23	77	12	[208]
2-*n*-Propylthiazole	H_2SO_4/HNO_3 70°C	29	71	14	[208]

If, however, the free base is nitrated, the increase in the rate before reaching the maximum is less clearly defined. (The increase in the concentration of the nitronium ions is compensated by a decrease in the concentration of the unprotonated molecules.) After reaching the maximum, the curve falls sharply, since further increase in the acidity only reduces the concentration of the free base [184].

The kinetics and mechanism of the nitration of azoles have been studied in a fair amount of detail [56–60, 64, 70, 75, 76, 184, 193, 205, 207, 208, 210, 211, 251, 282–287]. The reactivity of various mono- and dialkylthiazoles compared with benzene was studied by the competing nitration method (Table 2) [207].

It follows from Table 2 that nitration at position 5 of the thiazole ring is realized ~1.5 times more vigorously than at position 4. The presence of the methyl group at position 2 increases the nitration rate at position 5 by approximately 15 times and at the C-4 atom by eight times. These data agree with the selectivity of the nitration of 2-alkylthiazoles (Table 3) [208, 288].

Similar results were obtained during the nitration of 2-methoxythiazole [289].

Katritzky et al. proposed the use of so-called "standardized" rate constants (k_2^0), obtained during the nitration of various aromatic heterocycles by nitric acid in 75% sulfuric acid at 25°C ($H_0 - 6.6$) [59]. These constants make it possible to compare quantitatively the reactivity of various types of heterocyclic compounds in nitration. The calculated "standardized" rate constants for the nitration of azoles are given in Table 4.

Analysis of ~130 reaction profiles for the nitration of various aromatic and heterocyclic compounds made it possible to propose a direct qualitative test for establishing the reaction mechanism from the slope of the $\log k_2 = -aH_0 + b$ relation [59, 290]. If the slope is larger that 1.7, nitration takes place through the protonated form; if it is smaller than 1.7, nitration takes place through the free base. However, there are exceptions from this rule.

Table 4 "Standardized" rate constants for the nitration of azoles

Compound	$d[\lg k_2]/d[-H_0]$	Substrate form[a]	NO_2 position	$-\lg k_2$	Refs
Pyrazole	−0.47	BH^+	4	8.43	[282]
1-Methylpyrazole	2.26	BH^+	4	7.60	[290]
1,5-Dimethylpyrazole	2.25	BH^+	4	6.16	[290]
1,3-Dimethylpyrazole	2.28	BH^+	4	5.94	[290]
1,3,5-Trimethylpyrazole	2.35	BH^+	4	4.79	[184]
1-Phenylpyrazole	2.03	BH^+	4′	3.10	[58]
1-Phenyl-4-nitropyrazole	1.13	B	4′	2.30	[58]
1-(4-Nitrophenyl)pyrazole	1.27	B	4	1.57	[58]
1-Phenyl-3-nitropyrazole	2.21	BH^+	4′	2.76	[56]
1-Phenyl-5-nitropyrazole	2.31	BH^+	4′	4.68	[56]
1-Phenyl-3,5-dimethylpyrazole	2.33	BH^+	4′	3.66	[56]
1-(2-Tolyl)pyrazole	2.37	BH^+	4′	3.41	[56]
1-(2,6-Dimethylphenyl)pyrazole	2.37	BH^+	4′	1.62	[56]
1-Phenyl-3-methyl-5-methoxy-4-nitropyrazole	2.64	BH^+	4′	4.36	[57]
1-(4-Nitrophenyl)-3-methyl-5-methoxypyrazole	1.73	BH^+	4	5.55	[57]
1-Phenyl-3-methyl-4-nitro-5-pyrazolon	1.99	BH^+	4′	0.32	[57]
1-Phenyl-2,3-dimethyl-4-nitro-5-pyrazolon	0.82	B	4′	1.18	[57]
	−0.41	BH^+	4′	5.94	[57]
1-Phenyl-2-methylpyrazolium	1.95	K	4′	5.17	[56]
1,2,3,5-Tetramethylpyrazolium	2.31	K	4	4.93	[184]
1-Methyl-2-phenylpyrazolium	1.99	K	4′	5.56	[58]
1-Methyl-4-nitro-2-phenylpyrazolium	2.19	K	4′	7.51	[58]
1-Methyl-2-(4-nitrophenyl)pyrazolium	2.13	K	4	7.81	[58]
3,5-Dimethylisoxazol	1.05	B	4	2.72	[184]
3-Methyl-5-phenylisoxazol	2.09	BH^+	4′	3.57	[183]
5-Methyl-3-phenylisoxazol	1.47	BH^+	3′	3.70	[183]

(continued)

Table 4 (continued)

Compound	$d[\lg k_2]/d[-H_0]$	Substrate form[a]	NO_2 position	$-\lg k_2$	Refs
2,3-Dimethyl-5-phenylisoxazolium	2.09	K	4′	3.82	[183]
2,5-Dimethyl-3-phenylisoxazolium	1.89	K	3′	3.90	[183]
Isothiazole	1.22	B	4	3.80	[193]
3-Methylisothiazole	1.20	B	4	2.70	[193]
5-Methylisothiazole	1.08	B	4	2.90	[193]
3,5-Dimethylisothiazole	1.74	BH^+	4	9.03	[193]
2,3,5-Trimethylisothiazolium	1.89	K	4	9.03	[193]
2,4-Dimethylthiazole	−1.96	BH^+	5	6.90	[211]
2,5-Dimethylthiazole	−2.05	BH^+	4	7.60	[211]
5-Ethyl-2-*tert*-butylthiazole	−1.94	BH^+	4	6.96	[211]
5-Isopropyl-2-*tert*-butylhtiazole	−1.93	BH^+	4	7.43	[211]
2-Methoxy-4-methylthiazole	−2.31	BH^+	5	4.62	[211]
4-Methyl-2-thiazolone	−1.30	B	5	−1.12	[211]
3,4-Dimethyl-2-thiazolone	−1.05	B	5	−1.82	[211]
2,3,4-Trimethylthiazolium	−2.58	K	5	7.52	[211]
2,3,5-Trimethylthiazolium	−2.00	K	4	7.72	[211]
Imidazole	−0.70	BH^+	4, 5	6.92	[282]
1-Phenylimidazole	2.11	BH^+	4′	3.41	[56]

[a]*K* cation, *B* free base, BH^+ conj. base

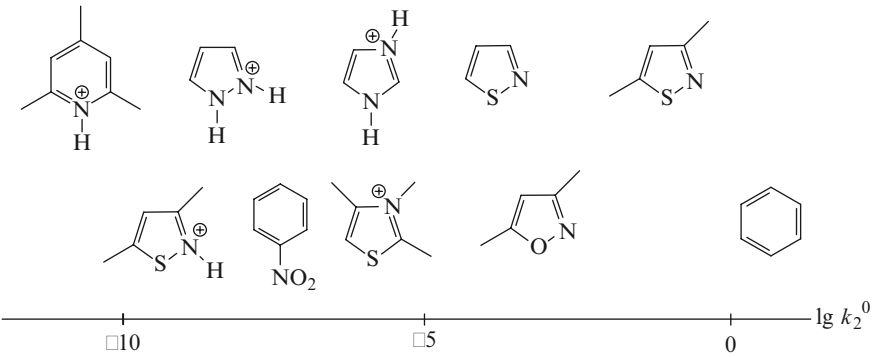


Fig. 3 The "standardized" constants for the nitration (k_2^o) of some heteroaromatic substrates by the sulfuric–nitric acid mixture

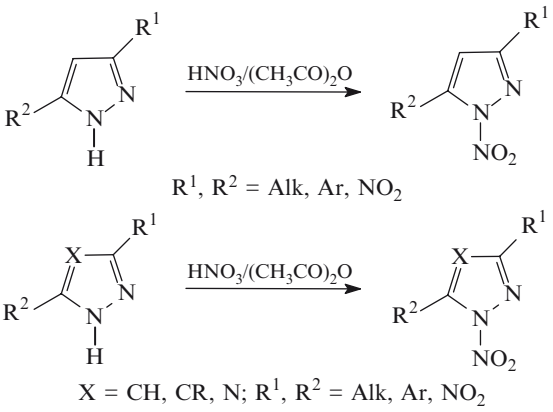
The "standardized" rate constants for the nitration of some azoles and their cations are presented in Fig. 3 for clarity [291]. Here the data for the nitration of benzene (log k_2 0.45) and the pyridinium cation are also given for comparison.

It is quite difficult to compare the reactivity of imidazole and pyrazole during nitration. The fact is that imidazole always enters into nitration in the form of the cation, whereas for pyrazole this only occurs at a sulfuric acid concentration of more than 90% [282, 284]. In fact, in 99% sulfuric acid the nitration rate of pyrazole is rather lower than that of 1,2-dimethylpyrazolium, while in 76% sulfuric acid, on the other hand, the nitration rate of pyrazole is higher [284]. Attempts to draw a correlation between the "standardized" rates of nitration and hydrogen exchange for the same compounds were unsuccessful [285, 290]. It has not yet been possible to create any general scale of reactivity for these compounds during electrophilic substitution.

Nitration by Other Nitrating Agents

In addition to the sulfuric–nitric acid mixture, acetylnitrate (or a mixture of acetic anhydride with nitric acid) is used quite widely for the introduction of a nitro group into the azole ring. Azoles not containing a "pyrrole" nitrogen atom are nitrated by acetylnitrate in the same way as by the sulfuric–nitric acid mixture. Data have been published on the nitration of isoxazoles [176, 181–183, 185, 292, 293] and thiazoles [203, 206, 215] by acetylnitrate. 1-Substituted pyrazoles [48, 61, 294–301], imidazoles [116, 133, 302–305], and isoxazoles [306] are nitrated by the nitric acid–acetic anhydride system in the same way as by the sulfuric–nitric acid mixture.

During the nitration of azoles with an unsubstituted "pyrrole" heteroatom under these conditions it is often possible to isolate the *N*-nitroazoles. Thus, with acetylnitrate in glacial acetic acid it was possible to obtain *N*-nitropyrazoles [63, 307–317], *N*-nitro-1,2,4-triazoles [318, 319], and *N*-nitro-1,2,4-triazolon-5 [264] (Scheme 33).



Scheme 33

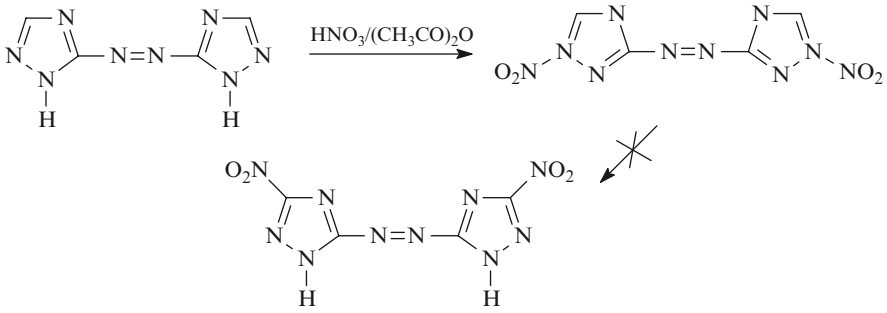
N-nitropyrazoles possess the spazmolitic and antihypertensive activity, compared with mono- and dinitrate isosorbite that is caused by the ability of *N*-nitropyrazoles to generate nitrogen monoxide (NO) at biotransformation in organism [320]. *N*-nitropyrazoles are a new type of a stable source NO; therewith, generation of the NO happens in the reduce conditions. The ease of the elimination of NO depends from the structure of azole: the availability of the neighbouring substituents with N–NO_2-fragment facilitates the ejecting of NO. With connection to this problem the investigation of the influence of the pyrazole structure and reaction condition on the formation of *N*-nitropyrazoles is carried out [321].

For the nitration, the authors [321] had used two known sources of acetylnitrate: mixture of HNO_3 and Ac_2O in AcOH (a) and $Cu(NO_2)_3$ with Ac_2O (b). Usually "acidic" mixture (a) is applied and as a rule the *N*-nitration proceeds on the nitrogen atom more remaining from substituents. Using "unacidic" nitration mixture (b) changes the nitration direction and in case 3(5)-methylpyrazole NO_2-group involved to nitrogen atom neighboured with substituent. Aryl substituent interferes *N*-nitration of neighboured nitrogen atom: 3(5)-methyl-5(3)-phenylpyrazole forms 1-nitro-5-methyl-3-phenylpyrazole; therefore, 3,5-diphenylpyrazole does not form *N*-nitropyrazole [321].

The *N*-nitro derivatives of imidazole can only be isolated in the case where the imidazole ring contains strong electron-withdrawing substituents (e.g., NO_2) [79, 322–329]. In other cases the *C*-nitro derivatives are formed directly [101, 133, 330–335]. It was suggested that the *N*-nitro derivative is formed during the nitration of the intermediate 1,2,3-triazole [336]. However, no evidence was presented for this mechanism.

The kinetics of the nitration of azoles by acetylnitrate has not been studied systematically. Mention has only been made of the complex nature of the reaction kinetics and the low yield of the nitration products, which hinders correct interpretation of the results [56].

The *N*-nitroazoles are extremely reactive compounds and enter into all kinds of sometimes quite unexpected reactions. For this reason they are valuable intermediate products in many syntheses. Thus, for example, the thermal rearrangement of *N*-nitropyrazoles makes it possible to produce the difficultly obtainable 3(5)-nitropyrazoles [63, 310–313, 315]. In addition, *N*-nitropyrazoles [6, 337] and *N*-nitro-1,2,4-triazolon-5 [263, 264] have been used successfully as nitrating agents and this is due to the high lability of the N–NO_2 bond. The length of the N–NO_2 bond is 1.40 A, whereas the bond in other nitroamines is appreciably shorter (1.37 A). The attempt to use the synthesis way of *C*-nitro compound through *N*-nitro compound rearrangement for obtaining 5,5′-dinitro-3,3′-azo-1,2,4-triazole [338, 339] was undertaken. The nitration of 5,5′-azo-1,2,4-triazole by HNO_3/Ac_2O leads to 1,1′-dinitro-3,3′-azo-1,2,4-triazole; however, the rearrangement in *C*-nitro triazole has not happened (Scheme 34).



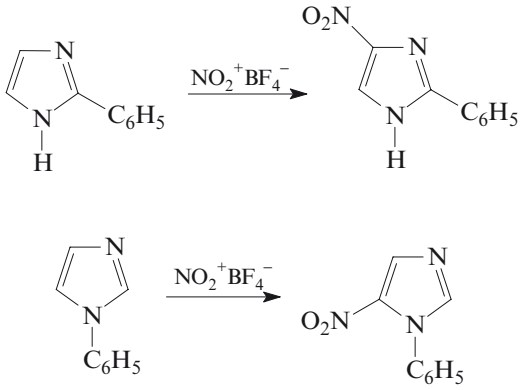
Scheme 34

4-Nitro-5-nitrimino-1*H*-1,2,4-triazole (46%) forms on the nitration of 5-nitrimino-1,4*H*-1,2,4-triazole by HNO_3/Ac_2O only at –8 to –10°C [340]. The following nitration of the product gives 1,1′-dinitro-3,3′-azo-1,2,4-triazole.

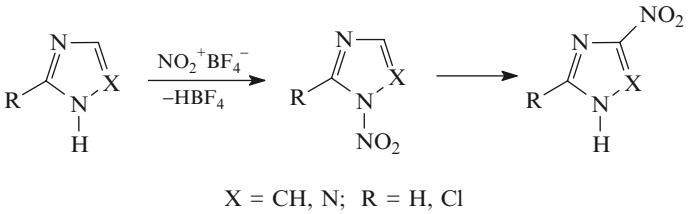
Nitronium tetrafluoroborate is often used to introduce a nitro group into the molecule of azoles. In some cases it is not even isolated in the individual form, but the azole is added to a mixture of concentrated nitric acid and boron trifluoride [334, 341–345]. Nitronium tetrafluoroborate is used particularly often for the selective nitration of a heterocycle in aryl-substituted azoles [101, 102, 164, 346, 347] (Scheme 35).

During the reaction of isoxazole with nitronium tetrafluoroborate 4-nitroisoxazole is isolated with a yield of 35% [167]. With nitronium tetrafluoroborate as nitrating agent it is possible to realize nitration in a neutral medium without protonation of the azole ring. In this case it was possible to isolate *N*-nitroimidazoles [324] and 1,2,4-triazoles [348], or their formation as intermediate products was inferred [349, 350] (Scheme 36).

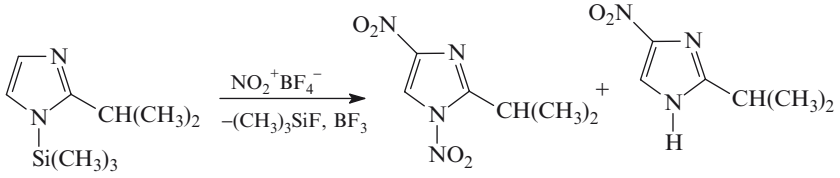
The yields of *C*-nitroazoles are usually low as a result of the denitration of the *N*-nitro compounds by the action of the released fluoroboric acid. To eliminate this undesirable effect it was proposed to use the *N*-trimethylsilyl derivatives of azoles [324, 348] (Scheme 37).



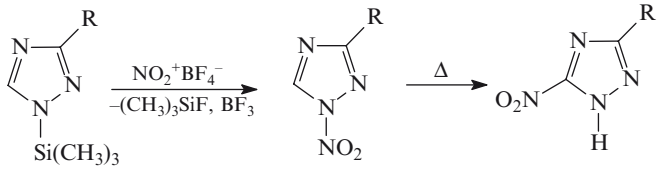
Scheme 35



Scheme 36



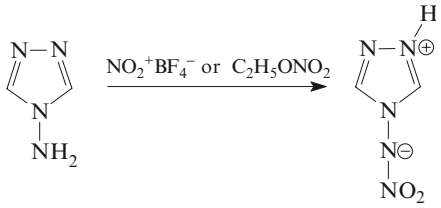
Scheme 37



Scheme 38

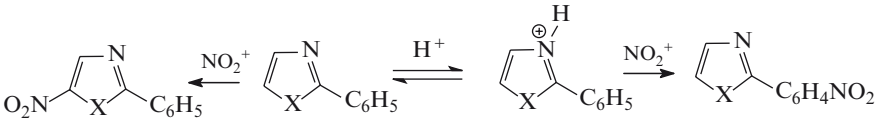
By the nitration of 1-trimethylsilyl-1,2,4-triazoles by nitronium tetrafluoroborate it was possible to obtain the 5-nitro derivative with a yield of up to 90% [348] (Scheme 38).

During nitration with nitronium tetrafluoroborate or ethyl nitrate 4-amino-1,2,4-triazole is converted into the corresponding nitroimide [351] (Scheme 39).



Scheme 39

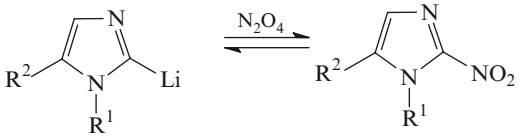
2-Aminothiazole is converted by the action of ethyl nitrate into the 5-nitro derivative [352]. As already mentioned 2-phenyloxazole and 2-phenylthiazole are nitrated into benzene ring by the sulfuric–nitric acid mixture. At the same time their nitration under conditions excluding protonation of the azole ring (with the use of acetylnitrate or *N*-nitropicolinium tetrafluoroborate as nitrating agent) leads to the 5-nitro derivatives [353] (Scheme 40).



X = O, S

Scheme 40

The reaction of the corresponding 2-lithioimidazoles with nitrogen tetroxide has been used for the production of 1-substituted 2-nitroimidazoles [354, 355] (Scheme 41).

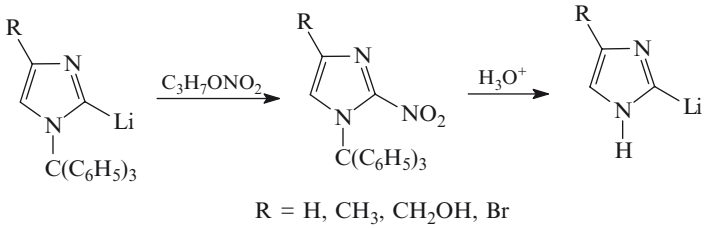


$R^1 = CH_3$, $R^2 = H$; $R^1 = C_6H_5$, $R^2 = H$;
$R^1 = CH_3$, $R^2 = (CH_3)_2CH$

Scheme 41

However, it was not possible to obtain l-trityl-2-nitroimidazole by this method as, for example, also during the nitration of the lithium derivative of 1-tritylimidazole by nitronium tetrafluoroborate [356]. This is probably due to the elimination of the triphenylmethyl group during nitration. However, it was possible to obtain l-trityl-2-nitroimidazole by using propyl nitrate as nitrating agent [356]. The product

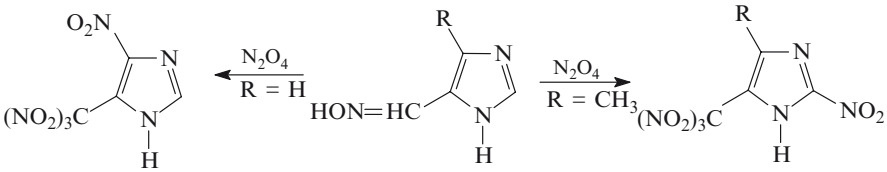
was converted by acid hydrolysis into 2-nitroimidazole with a yield of 30%. 4-Substituted 2-nitroimidazoles were synthesized by a similar method [356–358] (Scheme 42).



R = H, CH_3, CH_2OH, Br

Scheme 42

During the action of dinitrogen tetraoxide (nitrogen dioxide) on the oximes of formylimidazole the nitro group unexpectedly entered at position 2 of the imidazole ring [359, 360] (Scheme 43).



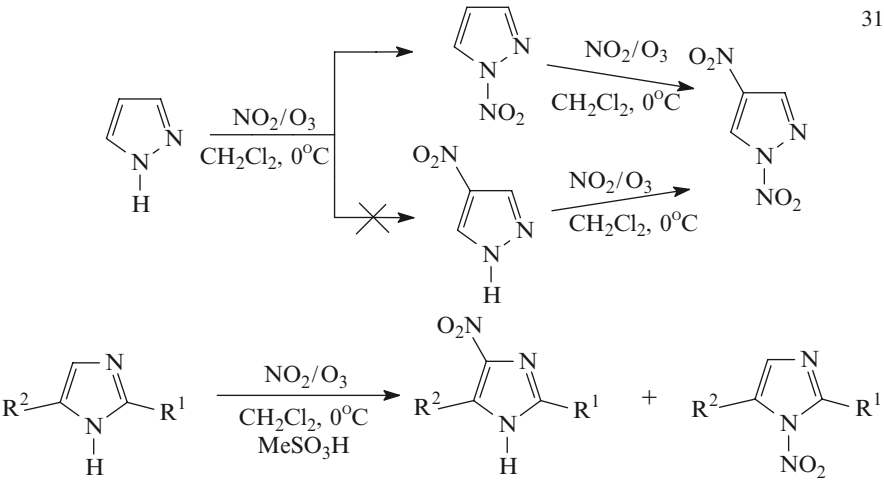
Scheme 43

The nitration of thiazoles can also be conducted in organic solvents (e.g., dichloroethane) with a nitrating mixture consisting of trifluoromethanesulfonic acid, its anhydride, and potassium nitrate. Here the yields of the nitro derivatives are substantially higher than with the sulfuric–nitric acid mixture [361].

A novel methodology for preparative aromatic nitration in which nitrogen dioxide acts a good nitrating agent for aromatic hydrocarbons and derivatives in the presence of ozone ("*kyodai*" nitration) [362] has been applied for azoles [363] (Scheme 44).

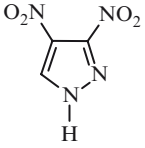
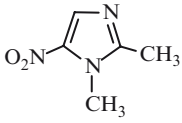
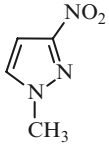
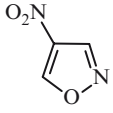
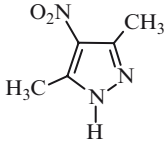
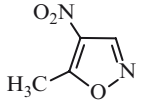
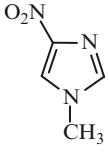
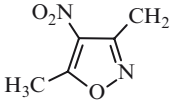
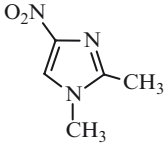
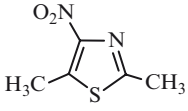
At low temperature pyrazole is easily *N*-nitrated giving 1-nitropyrazole in contrast to classical nitration based on the use of mixed acid; 4-nitropyrazole is not formed. On prolonged reaction, a mixture of 4(5)-nitro- and 1,4-dinitropyrazole is obtained, whereas the last is prepared in the *kyodai* nitration of 4-nitropyrazole [363]. The *kyodai* nitration of imidazoles gave a mixture of 4-nitro- and 1,4-dinitroimidazoles and 1,2,4-triazole – only a few percent of mononitro derivatives even after prolonged reaction [363].

Direct nitration of pyrazoles, imidazoles, isoxazoles, and thiazoles has been carried out by Katritzky et al. with a new nitrating agent – nitric acid/trifluoroacetic anhydride [364, 365]. This method allows obtaining mononitro derivatives of azoles in good yield (Table 5).



Scheme 44

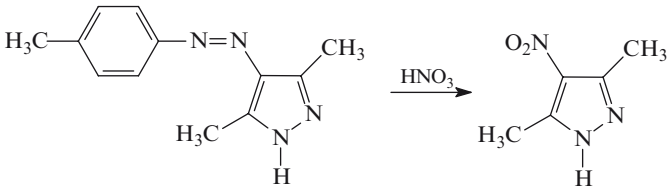
Table 5 Nitration of azoles with $HNO_3/(CF_3CO)_2O$

Product	Yield, %	Product	Yield, %
	41		35
	65		73
	76		64
	61		72
	35		67

Trifluoroacetic anhydride (10 mL) was cooled in an ice bath and the substrate azole (17 mmol) was slowly added. After 1 h, concentrated nitric acid (3 mL) was added dropwise with cooling. After stirring for 12 h at room temperaturte, the excess trifluoroacetic acid and nitric acid were removed under vacuum to get the nitroazole [364]

Ipso-*Nitration of Azoles*

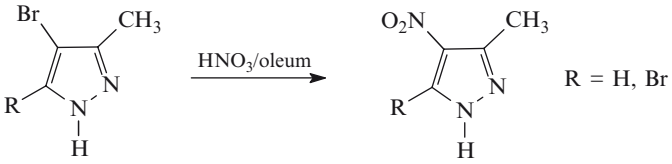
Electrophilic agents and nitrating reagents, in particular, can displace other functional groups apart from hydrogen. Such processes are usually called substitutive nitration or *ipso*-nitration. *Ipso*-nitration has also been used in the chemistry of azoles. The first example of *ipso*-nitration in the pyrazole series was described in 1925. The action of nitric acid on 4-(4-tolylazo)-3,5-dimethylpyrazole led to the formation of 3,5-dimethyl-4-nitropyrazole [366] (Scheme 45).



Scheme 45

The halogen atom acts as a functional group more often than others during substitutive nitration. During the nitration of 4-bromo-3-methylpyrazole with a mixture of nitric acid and oleum 3-methyl-4-nitropyrazole is formed [62] (Scheme 46).

4,5-Dibromo-3-methylpyrazole is nitrated similarly [367, 368].

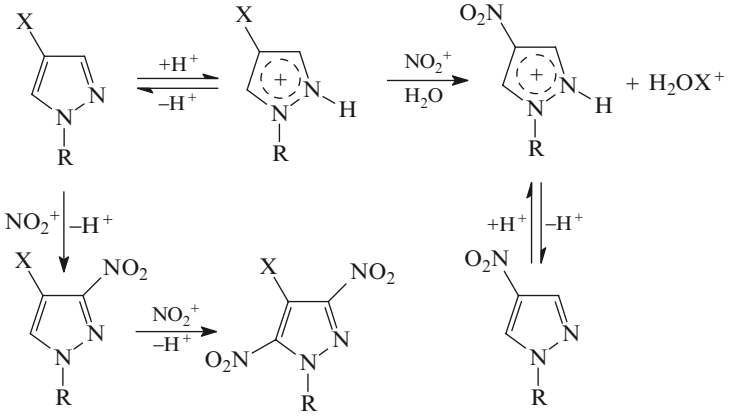


Scheme 46

Ipso-nitration of 4-bromopyrazoles by the sulfuric–nitric acid mixture is approximately 100 times slower than normal nitration of the corresponding unsubstituted pyrazoles [46]. Substitutive nitration of 4-halogeno-1-alkylpyrazoles takes place in parallel with normal nitration at positions 3 and 5 of the heterocycle [46, 74] (Scheme 47).

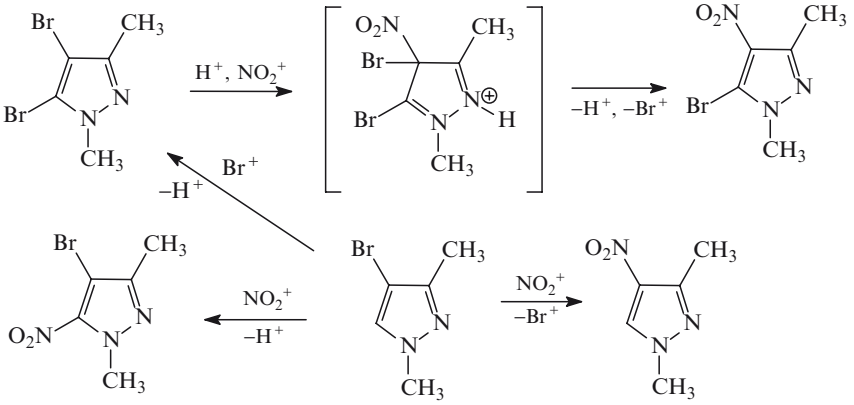
Parallel *ipso*-nitration at position 4 and nitration at position 5 of the pyrazole ring were also observed during the action of the sulfuric–nitric acid mixture on 1,3-dimethyl-4-bromopyrazole [369]. The released bromine cation partly brominates the initial reagent with the formation of 1,3-dimethyl-4,5-dibromopyrazole. The latter is subsequently transformed into 1,3-dimethyl-5-bromo-4-nitropyrazole (see the Scheme later). The nitration of 1,3-dimethyl-4,5-dibromopyrazole leads to the formation of 1,3-dimethyl-5-bromo-4-nitropyrazole and 1,3-dimethyl-4-nitropyrazole [369] (Scheme 48).

A convenient synthetic procedure for the preparation of 4-nitroiodopyrazoles (useful synthons) – nitrodeiodination of polyiodopyrazoles with sulfuric-nitric acid mixture – has been proposed [370] (Scheme 49).

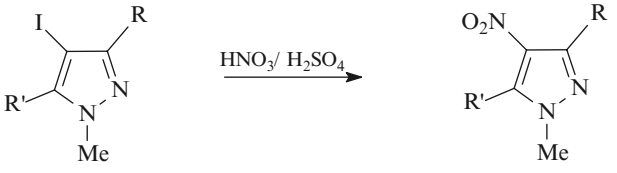


X = Hal, R = CH_3, C_2H_5

Scheme 47



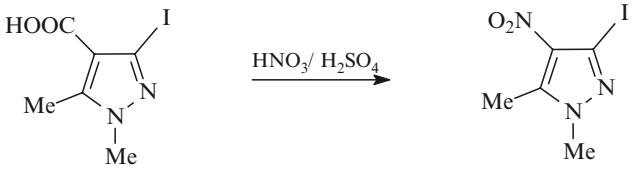
Scheme 48



R, R' = Me,I; I, Me; I, CO_2H; CO_2H, I; NO_2, I; I, I:

Scheme 49

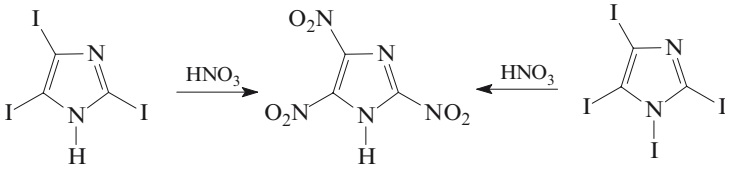
Interestingly that the *ipso*-nitration of the pyrazole in the presence of a carboxylic group takes place, whereas 3-iodo-4-nitro-1,5-dimethylpyrazole has also obtained by nitrodecarboxylation of 3-iodo-1,5-dimethylpyrazole-4-carboxylic acid [370] (Scheme 50).



Scheme 50

The *ipso*-nitration of substituted azoles can also take place during the action of acetylnitrate [46]. The substitutive nitration of halogenopyrazoles was investigated comprehensively, and the important role of the electronic effect of the substituents on the process was established [44, 46, 369–374]. Thus, during the nitration of 4-halogenopyrazolecarboxylic acids containing carboxyl groups at positions 3 or 5 of the pyrazole ring the nitro group enters at positions 5 and 3, respectively. Thus, substitutive nitration cannot occur in this case [373]. During the nitration of l-methyl-3-nitro-4-halogenopyrazole-5-carboxylic acids the halogen atom is retained, while the nitro group displaces the carboxyl group, leading to l-methyl-3,5-dinitro-4-halogenopyrazoles [373]. The nitration of 3-nitro-4-cyanopyrazole by the sulfuric–nitric acid mixture at 100°C leads to 3,4-dinitropyrazole. In the opinion of the authors direct substitution of the nitrile group does not occur, but it undergoes preliminary hydrolysis followed by nitrodecarboxylation [375]. The rate of nitrodecarboxylation of 5-substituted 4-bromo-l-methylpyrazole-3-carboxylic acids is determined by the nature of the substituent at position 5, being accelerated with decrease in the electron-withdrawing characteristics of the substituent [374]. Examples of the *ipso*-nitration of halogenopyrazoles are not restricted to those described earlier [50, 371, 372].

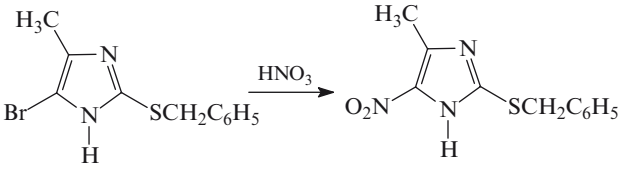
The substitutive nitration of iodoimidazoles has been described in detail [376–382]. However, the structure assigned to the obtained nitro imidazoles proved erroneous [367, 377, 379, 382]. The correct structure was established later [140, 141]. The error was due to the fact that the initial compound was assigned the structure of 2,4-diiodoimidazole. In fact, 4,5-diiodoimidazole undergoes nitration and is converted into 4,5-dinitroimidazole. 2,4,5-Triiodoimidazole and 1,2,4,5-tetraiodoimidazole are nitrated to 2,4,5-trinitroimidazole by the action of nitric acid [383] (Scheme 51).



Scheme 51

Substitutive nitration of halogenoimidazoles has been widely used for the synthesis of various nitroimidazoles [40, 378–385]. When 2-benzylthio-5(4)-bromo-4(5)-

methylimidazole is boiled with dilute nitric acid, oxidation of the benzylthio group with the formation of the corresponding sulfoxide takes place in addition to *ipso*-nitration [386] (Scheme 52).



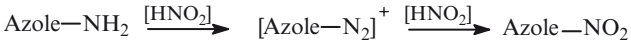
Scheme 52

3,5-Dimethyl-4-halogenoisoxazoles also enter into substitutive nitration. Here, only the iodine derivatives react with the sulfuric–nitric acid mixture. Both the bromine and the chlorine derivatives react slowly with a mixture of acetic anhydride and nitric acid [169].

Examples of the *ipso*-nitration of halogen-substituted isothiazoles [387] and thiazoles [388–390] are known. 2,4-Disubstituted 5-bromo- and 5-iodooxazoles react with nitrogen tetroxide to form the 5-nitro derivatives [391].

Synthesis from Aminoazoles

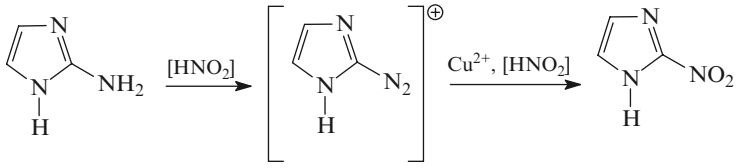
In cases where it is not necessary to introduce the nitro group directly at a position of the azole ring poorly susceptible to electrophilic attack it is possible to use the Sandmeyer reaction or its modifications (Scheme 53). The use of copper salts as catalysts is not essential in a number of cases [392, 393].



Scheme 53

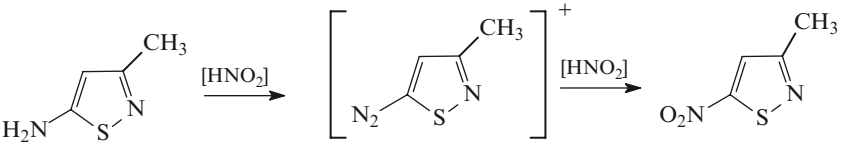
Derivatives of pyrazole containing a nitro group at position 3 or 5 were obtained in this way [393–400]. Nevertheless, the diazotiation of 3,5-dimethyl-4-aminopyrazole does not lead to the formation of nitro derivatives [398].

2-Nitroimidazole (the natural antibiotic azomycin) was synthesized from 2-aminoimidazole [401–405] (Scheme 54).



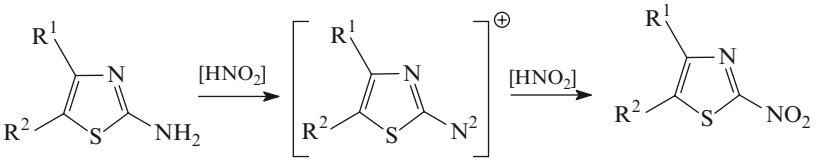
Scheme 54

The Sandmeyer's reaction has been used many times for the synthesis of 2-nitroimidazole and many of its derivatives [335, 395, 406–413]. Nucleophilic substitution of the diazo group has been used for the synthesis of derivatives of 5-nitroisothiazole [414] (Scheme 55).



Scheme 55

2-Nitrothiazole and also 4- and 5-substituted 2-nitrothiazoles were obtained from the corresponding 2-amino derivatives [415–420] (Scheme 56).



$R_1 = R_2 =$ Alk, Ar

Scheme 56

2-Methyl-5-(2-furyl)-4-nitrothiazole and 2-methyl-4-nitrothiazole were isolated from the mixture of products from the reaction of 5-amino-2-methylthiazole-4-carboxylic acid with isoamyl nitrite in the presence of furan [421].

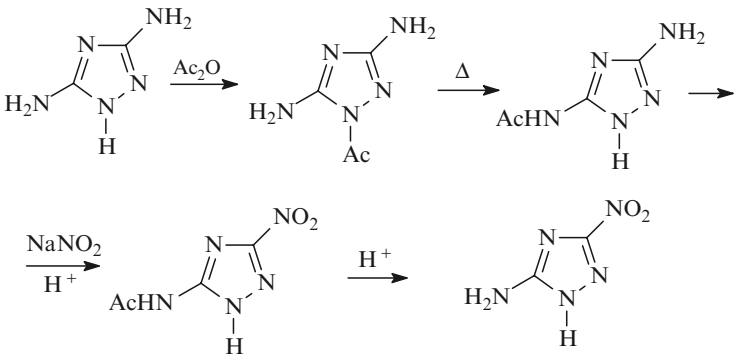
The nitro derivatives of 1,2,4-triazole [262, 269, 392, 422–427], 1,3,4-oxadiazole [392], 1,2,5-oxadiazole [428, 429], 1,2,3-thiadiazole [430], and 1,3,4-thiadiazole [392, 417, 431–435] were obtained by the reaction of the corresponding diazonium salts with sodium nitrite.

Nucleophilic substitution of the diazo group is practically the only method for the production of nitro derivatives of tetrazole [392, 436–443]. 5-Nitrotetrazole itself was isolated and identified in the form of metallic salts [436–440, 442, 443].

The mechanism of substitution of the diazo group by a nitro group in heterocyclic compounds has not been studied specially. As already mentioned, in many cases the reaction takes place as catalytic nucleophilic substitution and does not require the use of a catalyst (copper salts) [392, 444]. The results from investigation of the kinetics of the substitution of the diazonium group by the nitro group in compounds of the benzene series make it possible to suppose that the diazonitrite is formed intermediately and quickly reacts with a second nitrite anion [392, 444]. Some difference between the kinetics of the reaction of 3-diazonium-5-carboxy-1,2,4-triazole and 3-diazonium-5-methoxycarbonyl-1,2,4-triazole with sodium nitrite in hydrochloric acid and the analogous process in the benzene series is probably due to prototropic

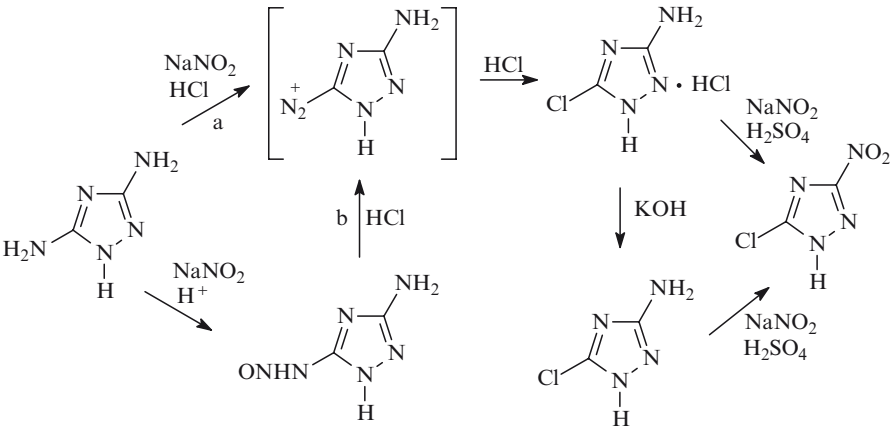
processes in the triazoles [444]. However, it is not possible to obtain 2-nitroimidazole from 2-aminoimidazole in the absence of the copper salts [392]. The normal Sandmeyer's reaction can probably be used in this and in certain other cases.

Diazotiation 3-amino-5-acetamido-1,2,4-triazole and following substitution diazo group on nitro group on the method [392] leads to corresponding nitrotriazole [445], which on the acyl protection relieving gives 5-amino-3-nitro-1,2,4-triazole [262, 446] (Scheme 57).



Scheme 57

The convenient method of 3-nitro-5-cloro-1,2,4-triazole synthesis from corresponding 3-aminoderivative [447] was worked out. The aforementioned way [348] is very laborious and dangerous (Scheme 58).

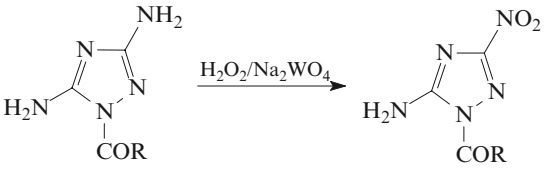


Scheme 58

3-Amino-5-cloro-1,2,4-triazole is obtained from guanazol (3,5-dinitro-1,2,4-triazole) by the direction diazotiation in hydrochloric acid (a), but at first it more rationally is the guanazol mononitrosation with treatment followed by heated HCl (b).

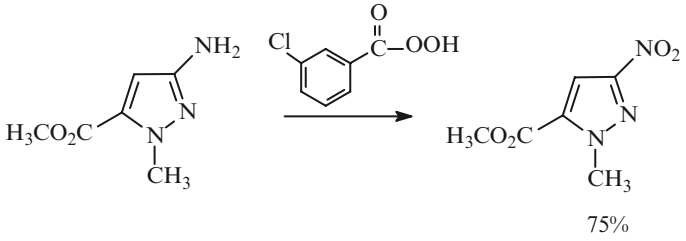
Another method of transforming aminoazoles into nitroazoles, i.e., oxidation, is significantly less widely used. 1-Phenyl-3- and l-phenyl-5-aminopyrazoles are oxidized to nitro derivatives by peroxytrifluoroacetic acid (CF_3CO_3H) [448]. Under these conditions unsubstituted 3(5)-aminopyrazole is oxidized more extensively with opening of the pyrazole ring, while l-methyl-5-aminopyrazole forms a small yield of the *N*-oxide of the corresponding nitro derivative [448]. Another example of the use of peroxytrifluoroacetic acid in the synthesis of nitropyrazoles is the oxidation of 3-amino-4-cyanopyrazole [375]. Here, 3-nitro-4-cyanopyrazole is formed with a yield of 90%, whereas the authors were unable to obtain it by the Sandmeyer's reaction. The amino group in 2-amino-4,5-imidazoledicarboxylic acid is easily oxidized, being converted into a nitro group by the action of hydrogen peroxide in oleum (Caro's acid) [449]. It is assumed that 2-aminoimidazole is a precursor of azomycin during its microbiological synthesis [450].

3(5)-Nitro-1,2,4-triazole (45%) [451] and 1-methyl-4-cyano-5-nitropyrazole (42%) [452] were isolated during the oxidation of corresponding aminoazole derivatives by a solution of hydrogen peroxide in trifluoroacetic acid. One of the amino groups in l-acyl-3,5-diamino-1,2,4-triazole is oxidized by hydrogen peroxide in the presence of sodium tungstate [453] (Scheme 59).



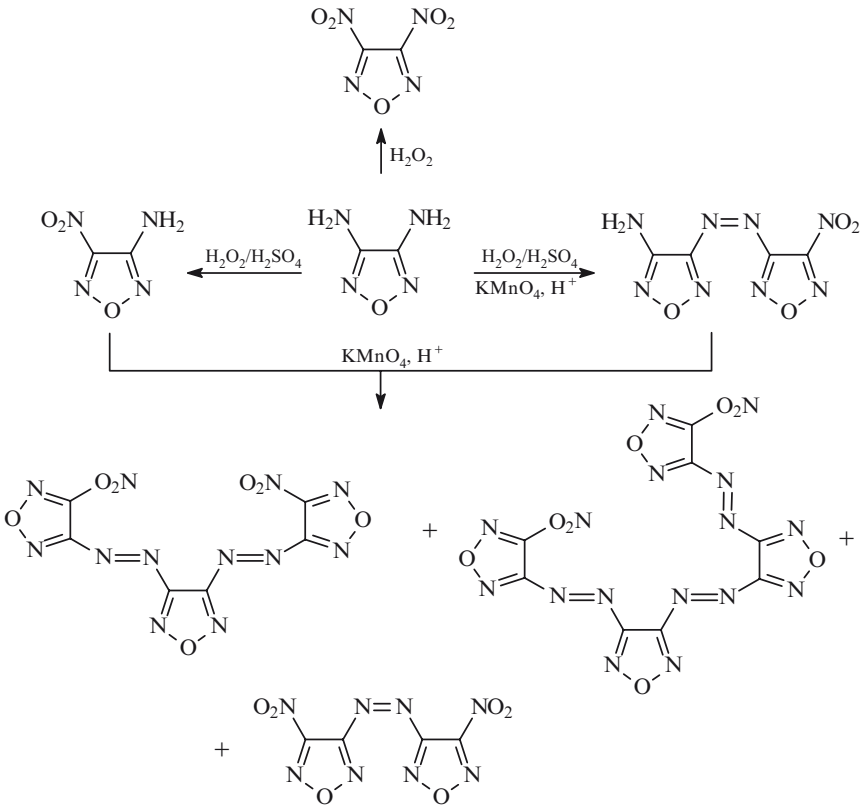
Scheme 59

1-Methyl-3-nitro-5-methoxycarbonyl pyrazole was prepared by the addition of *meta*-chloro-perbenzoic acid to 1-methyl-5-methoxycarbonyl pyrazole [454] (Scheme 60).



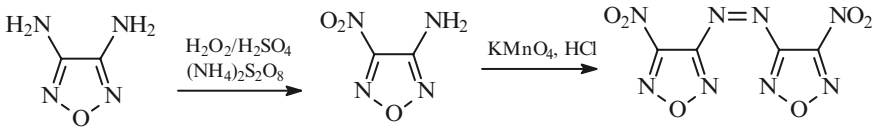
Scheme 60

Nitrofurazans and -furoxans – high-density energetic compounds – have been obtained by oxidation of the corresponding aminooxadiazoles mainly in the presence of H_2O_2/H_2SO_4 [455–465]. For example, the series of Sheremetev's work opens the widespread possibility of the preparation of new energetic compounds on the base of nitrofurazans and nitrotriazoles [460–464, 466, 467] (Scheme 61).



Scheme 61

It should be noted that dinitroazofurazan has resulted from available diaminofurazan in two steps in practically same conditions and on X-ray data exist in two modifications [457] (Scheme 62).



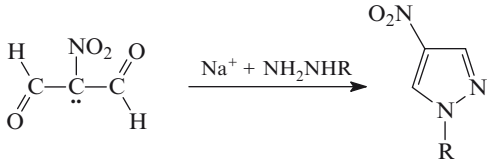
Scheme 62

Nonselective attacks at the carbon combined with a nitro group and carbon combined with the N(O) atom of the azoxy group were observed in the reaction of 4,4′-dinitroazoxyfurazan with bases and nucleophiles [468]. The preparation of dinitro polyfurazans shows the great synthetic potential of the construction sequence. The simplicity and availability of the starting substances (compounds) makes this strategy a powerful method for high energetic material construction.

5-Nitrotetrazole has been obtained by the diazotiation of 5-aminotetrazole with following addition of 20% H_2SO_4 [469]. 2-Methyl-5-nitrotetrazole has been prepared by the oxidation of the 5-amino derivative by dinitrogen peroxide [470].

Synthesis Based on Heterocyclization

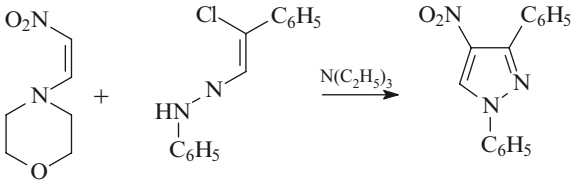
The construction of a heterocyclic ring from two reagents, one of which contains a nitro group, is widely used in the synthesis of the nitro derivatives of pyrazole, isoxazole, and 1,2,3-triazole. Thus, for example, the reaction of sodionitromalonaldehyde with substituted hydrazines leads to the corresponding derivatives of 4-nitropyrazole [33, 61, 471–473] (Scheme 63).



Scheme 63

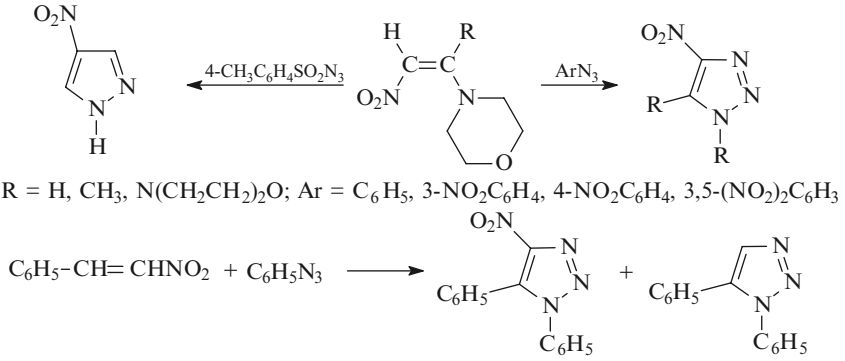
This reaction was extended to other β-dicarbonyl compounds containing a nitro group [474–476]. The mechanism of the reaction of hydrazine with 1,3-dicarbonyl compounds is still largely unclear. Nevertheless, important evidence was obtained to indicate that a dihydroxypyrazolidine intermediate is formed in this reaction [477]. If hydroxylamine is used instead of free hydrazine in the reaction with nitromalonaldehyde, the product is 4-nitroisoxazole [471]. When a mixture of nitrocyanoacetic ester with one equivalent of hydrazine hydrate and a small amount of water is boiled, 5-amino-4-nitro-3-pyrazolone is formed [478].

Nitroalkenes are valuable starting reagents for the synthesis of nitroazoles [479]. Thus, l,3-diphenyl-4-nitropyrazole is formed in the reaction of l-nitro-2-morpholinoethene with *a*-chlorobenzylidenephenylhydrazine [480]. However, the yield is not greater than 20% (Scheme 64).



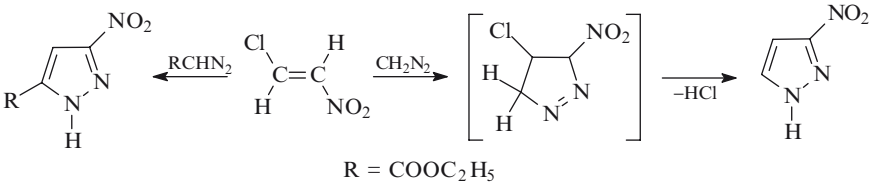
Scheme 64

Certain other α-chlorohydrazones react similarly with nitromorpholinoethene [480]. The reaction of aryl azides with 1-nitro-2-organoethenes leads to *C*-nitro-1,2,3-triazoles [249, 480–484] (Scheme 65).



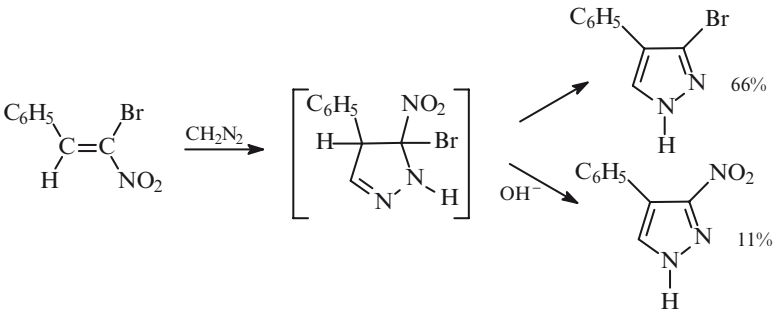
Scheme 65

Even wider possibilities for the production of various nitroazoles are presented by 1-nitro-2-halogenoethenes. Thus, the product from the cycloaddition of diazomethane to trans-1-nitro-2-chloroethene is 3-nitropyrazole (yield 65%) [485] (Scheme 66).



Scheme 66

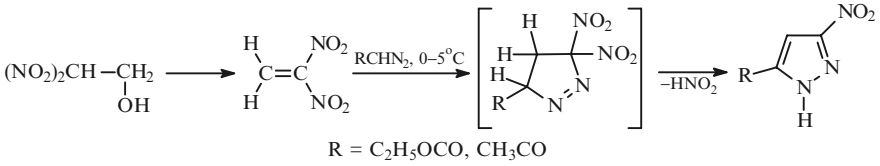
trans-1-Nitro-2-chloroethene also reacts with diazoacetic acid at room temperature to form 3-nitro-5-ethoxycarbonylpyrazole (yield 43%) [485]. 1-Bromo-1-nitro-2-phenylethene is converted by the action of diazomethane into 3-bromo-3-nitro-4-phenylpyrazoline, which is converted either into 3-bromo-4-phenylpyrazole or into 3-nitro-4-phenylpyrazole, depending on the pH of the medium [486] (Scheme 67).



Scheme 67

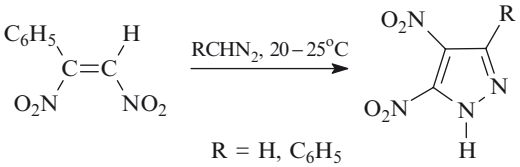
The reaction of sodium azide with l-bromo-l-nitro-2-arylethenes takes place by a formal 1,3-cycloaddition Scheme leading to 4(5)-aryl-5(4)-nitro-1,2,3-triazoles [487–489]. During the synthesis of nitrotriazoles the bromonitroarylethenes can be replaced successfully by the more readily obtainable 1,2-dibromo-l-nitro-2-arylethanes [489].

The intermediate product in the synthesis of 3-nitropyrazoles from 2,2-dinitroethanol and diazo ketones or diazoacetic ester is 1,1-dinitroethene [490, 491] (Scheme 68).



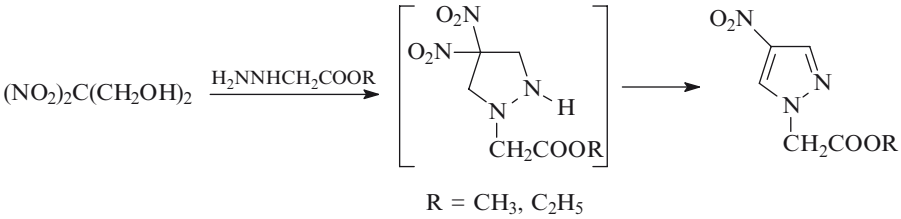
Scheme 68

In certain cases 1,2-dinitro-2-phenylethene also forms the corresponding nitropyrazoles in reaction with diazoalkanes [492–494] (Scheme 69).



Scheme 69

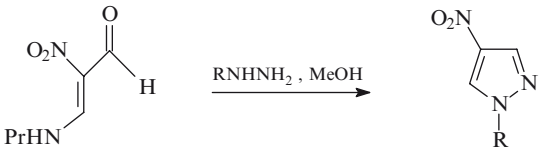
The products from the reaction of 2,2-dinitro-1,3-propanedione with hydrazinoacetic esters are derivatives of 4-nitropyrazole [495] (Scheme 70).



Scheme 70

1-Organyl-4-nitropyrazoles have been prepared by the reaction of β-nitroenamines having a formyl group at the β-position and hydrazines in methanol [496] (Scheme 71).

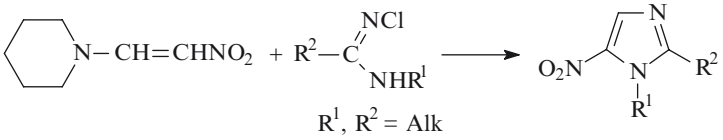
Analogically, the interaction of the same nitroenamine with hydroxylamine hydrochloride in methanol gives 4-nitroisoxazole [496].



R	t, °C	time, h	yield, %
Me	rt	3	96
H	rt	3	87
t-Bu	rt	24	29
t-Bu	80	3	59
CH_2CO_2Et	Rt	24	90
Ph	80	3	35
p-MeC_6H_4	80	3	47
p-$NO_2C_6H_4$	80	3	0

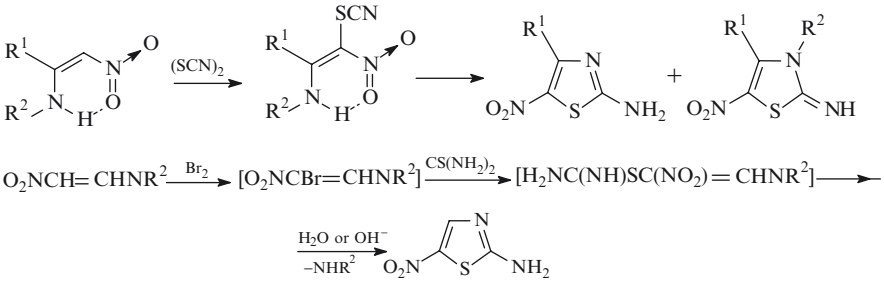
Scheme 71

Nitroenamines have also been used for the synthesis of nitroimidazoles [497] (Scheme 72).



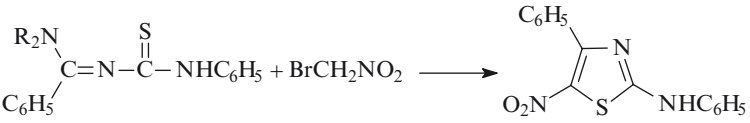
Scheme 72

5-Nitrothiazoles can be obtained by the reaction of nitroaminoethenes with dithiocyanogen [498] or thiourea [499] (Scheme 73).



Scheme 73

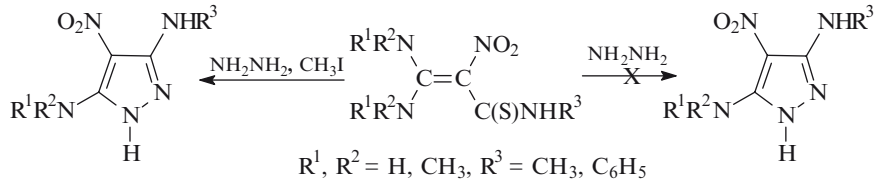
The yields of the products from the reaction of phenylthiourea derivatives with bromonitromethane depend largely on the nature of substitution at the nitrogen atom [500] (Scheme 74).



Scheme 74

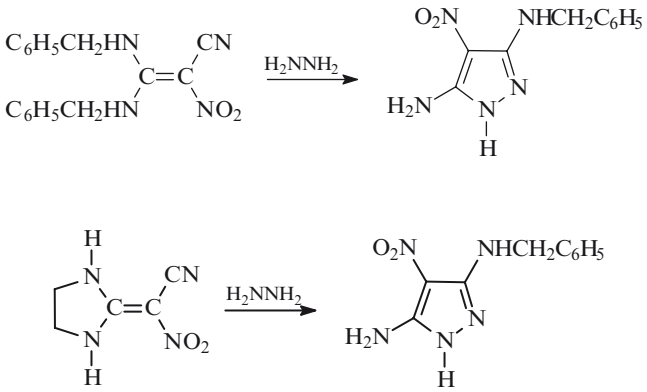
It was possible to obtain 2-amino-5-nitrothiazole while avoiding the risk of explosion at the nitration stage [499]. The nitroaminoethene used for this purpose cannot be isolated in the pure form and is generated from nitromethane and dimethylformamide during the reaction.

Nitroketene aminals react with organic thiocyanates to form the amides of β,β-bis-amino-α-nitrothioacrylic acid [501]. The latter proved valuable starting compounds for the synthesis of various heterocycles [502]. It was not possible to obtain nitropyrazoles by the direct action of hydrazine hydrate on these amides [502, 503]. However, the corresponding derivatives of 3,5-diamino-4-nitropyrazole were synthesized after previous methylation of the hydrazine hydrate with methyl iodide or dimethyl sulfate (without isolating the *S*-methyl intermediate) [504] (Scheme 75).



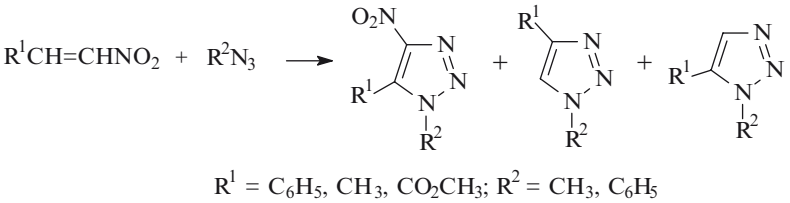
Scheme 75

3,3-Di(benzylammo)-2-nitroacrylonitrile is converted by the action of hydrazine into 3(5)-benzylamino-5(3)-amino-4-nitropyrazole [502, 503] (Scheme 76). Cyclic nitroenamines react similarly with hydrazine [502] (Scheme 76).



Scheme 76

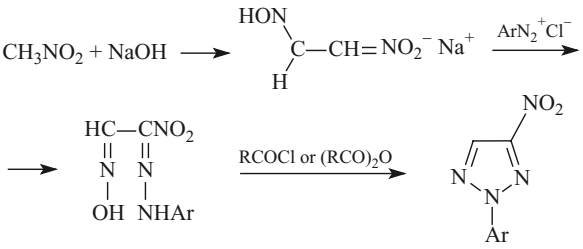
By using nitroenamines as initial reagents it is possible to obtain the quaternary salts of 4-nitroisothiazoles [502, 505] and 4-nitro-1,2,3-triazoles [506]. Phenylazide and methylazide react with olefines and form corresponding 4-nitro-1,2,3-triazole and also two isomeric triazoles [507] (Scheme 77).



$R^1 = C_6H_5, CH_3, CO_2CH_3; R^2 = CH_3, C_6H_5$

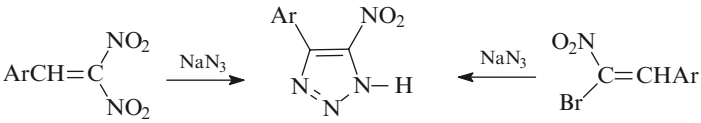
Scheme 77

A convenient preparative method for the synthesis of 2-substituted 4-nitro-1,2,3-triazoles is based on the condensation of diazonium salts with metazonic acid. The latter is in turn synthesized by the action of alkali on nitromethane [423, 508–510] (Scheme 78).



Scheme 78

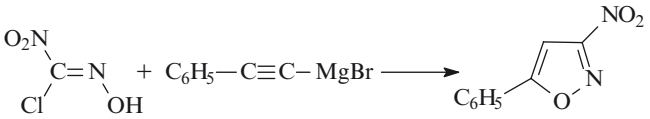
4-Aryl-5-nitro-1,2,3-triazoles with high yield in mild conditions (room temperature, 2.5–4.5 h) were prepared by the reaction β,β-dinitrostyroles with NaN_3 in acetonitrile or interaction of β-brom-β-nitrostyroles with NaN_3 in DMF [511] (Scheme 79).



Ar = C_6H_5, 4–$CH_3C_6H_4$, 4–ClC_6H_4

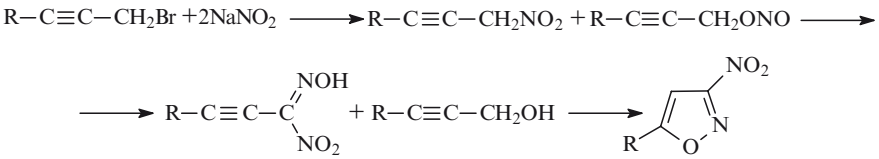
Scheme 79

The first representative of 3-nitroisoxazoles – 3-nitro-5-phenylisoxazole – was obtained by the condensation of the magnesium derivative of β-bromophenylacetylene with chloronitroformaldehyde oxime [512, 513] (Scheme 80).



Scheme 80

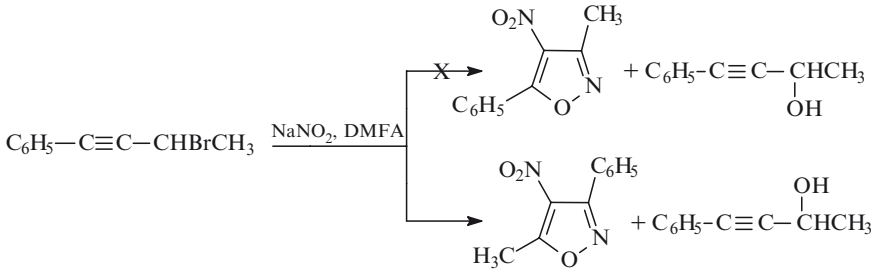
It is much easier to obtain 3-nitroisoxazole and its derivatives by the action of sodium or silver nitrites on the corresponding derivatives of propargyl bromide [514–517] (Scheme 81).



R = H, Alk, Ar

Scheme 81

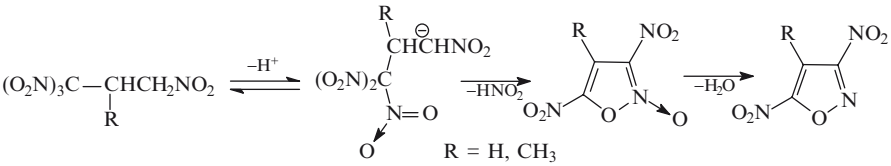
The use of secondary alkynyl bromides such as 3-bromo-1-phenyl-1-butyne in this reaction leads to 5-methyl-3-phenyl-4-nitroisoxazole [518] and not 3-methyl-5-phenyl-4-nitroisoxazole [515] (Scheme 82).



Scheme 82

Such a reaction path is explained by regiospecific reaction of the intermediately formed ambident anion with the esters of nitrous acid [518].

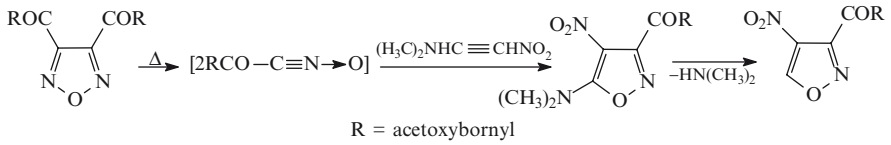
When boiled with water or dilute mineral acids, 1,1,1,3-tetranitroalkanes undergo cyclization to 3,5-dinitroisoxazoles [519]. The intermediate products of this reaction are probably the *N*-oxides of 3,5-dinitroisoxazolines, which are easily dehydrated to the corresponding nitroisoxazoles (Scheme 83).



Scheme 83

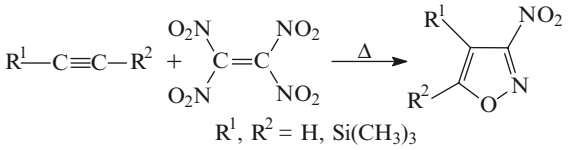
The cycloaddition of 1-halogeno-1-nitroethene with nitrile *N*-oxides leads to the nitro derivatives of isoxazole [520–524]. Thus, for example, the reaction of equimolar amounts of 1-chloro- or 1-bromonitroethene with benzonitrile *N*-oxide gave 5-nitro-3-phenylisoxazole [520]. The same compound is formed in the reaction of nitrile *N*-oxides with *trans*-2-chloro-1-nitroethene [485]. The formation of nitroisoxazoles in these reactions can be explained by the fact that the initial products from the cycloaddition of halogenonitro-Δ^2-isoxazolines more readily eliminate a molecule of hydrogen halide and not HNO_2.

During thermolysis diacylfuroxans are transformed into the *N*-oxides of α-keto nitriles, which form cyclic adducts in situ with various dipolarophiles [525]. This method was used for the production of 4-nitro-3-(2-acetoxybornyl-2-carbonyl) isoxazole (yield 50%) by boiling bis(2-acetoxybornyl-2-carbonyl)furoxan with an excess of trans-β-dimethylammonitroethene in toluene (Scheme 84).



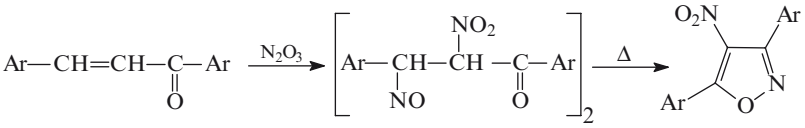
Scheme 84

The reaction of tetranitroethene with acetylene and its trimethylsilyl derivatives leads to 3-nitroisoxazoles [526] (Scheme 85).



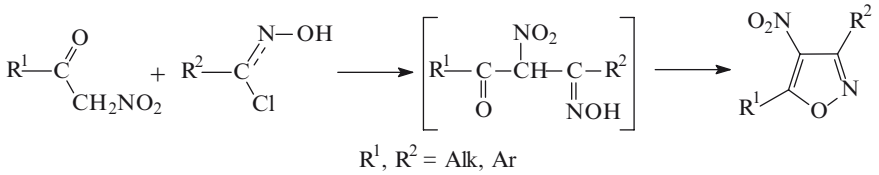
Scheme 85

With dinitrogen trioxide unsaturated ketones form dimeric vicinal nitronitroso derivatives, which are converted into 4-nitroisoxazoles when heated [527] (Scheme 86).



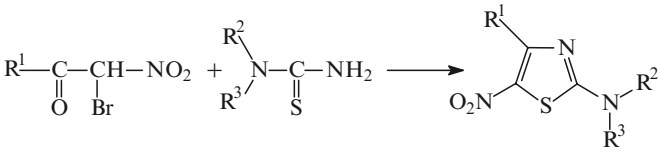
Scheme 86

Another path to such vicinal nitronitroso derivatives and then to 4-nitroisoxazoles is based on the treatment of a-nitro ketones with hydroxamoyl chlorides [528] (Scheme 87).



Scheme 87

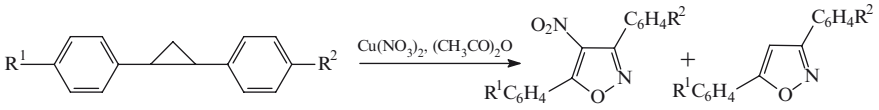
This reaction is convenient for preparative synthesis, since it can be conducted in a single stage [529]. α-Halogeno-α-nitro ketones are also used for the synthesis of 5-nitrothiazoles [213] (Scheme 88).



Scheme 1.88

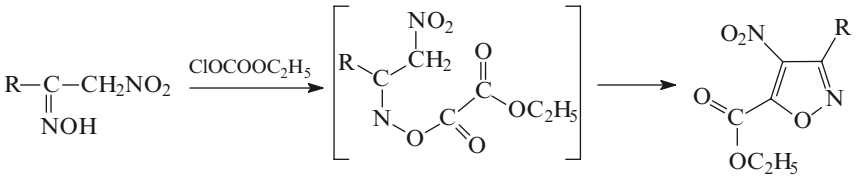
Certain 2-aminoaryl-4-phenyl-5-nitroselenazoles were obtained from these ketones [530].

4-Nitro-3,5-diarylisoxazoles were isolated with low yields during the nitration of 1,2-diarylcyclopropanes with copper nitrate [531–533] (Scheme 89).



Scheme 1.89

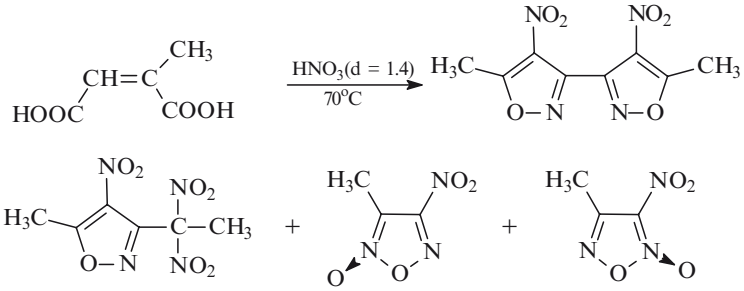
Finally, it is necessary to mention another method for the production of 4-nitroisoxazoles according to the following Scheme [534] (Scheme 90).



Scheme 90

In this way it was possible to obtain 4-nitroisoxazoles with extremely reactive furanosyl substituents [534].

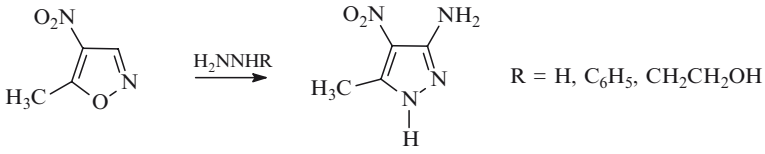
Interaction of methylmalein acid with HNO_3 leads to next nitrated isoxazoles and oxadiazoles [535] (Scheme 91).



Scheme 91

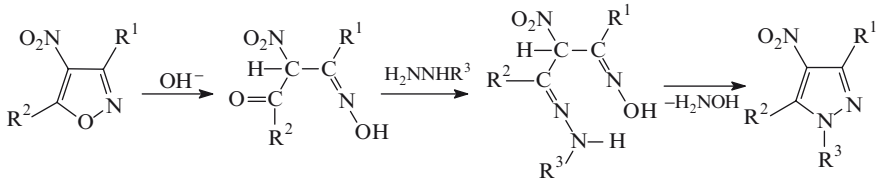
Synthesis from Various Cyclic Systems

The mutual transitions of various types of hetero cycles (recyclizations) are fairly widespread in the chemistry of azoles. Reaction of 1,4-dinitropyrazole with hydroxylamine liberated from corresponding salt in the presence of sodium methoxide resulted in 4-nitroisoxazole (77%) and a small amount of 5-methoxy-4-nitropyrazole [535]. 4-Nitroisoxazoles, like incidentally their unnitrated analogs, are transformed into derivatives of 4-nitropyrazole by the hydrazine or its monosubstituted derivatives. Thus, 3(5)-amino-5(3)-methyl-4-nitropyrazole or its 1-organo derivative was obtained from 5-methyl-4-nitroisoxazole [28, 34, 35, 536] (Scheme 92).



Scheme 92

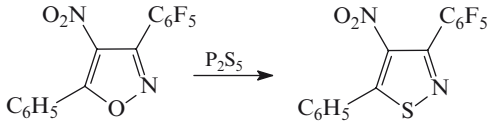
During the reaction of 3,5-disubstituted 4-nitroisoxazoles with hydrazine the isoxazole ring is opened initially. The obtained monoxime of the β-diketone then undergoes cyclization again with an excess of the hydrazine with the elimination of the hydroxylamine and the corresponding pyrazole [174, 536, 537] (Scheme 93).



Scheme 93

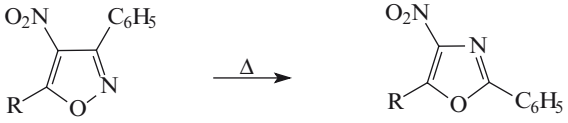
New oligonucleotides containing 5-guanidino-4-nitroimidazole were obtained from deoxyguanosine with peroxynitrite [538].

3-Pentafluorophenyl-5-phenyl-4-nitroisoxazole reacts with phosphorus pentasulfide to form 3-pentafluorophenyl-5-phenyl-4-nitroisothiazole [539] (Scheme 94).



Scheme 94

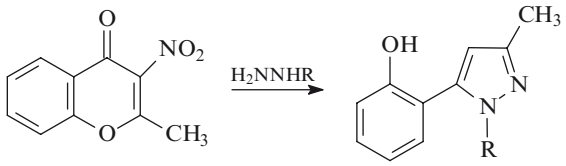
5-Substituted 3-phenyl-4-nitroisoxazoles unexpectedly undergo thermal isomerization (with mild heating in an inert solvent), leading to the previously unknown 4-nitrooxazole derivatives [540–542] (Scheme 95).



R = H, CO_2Me, COPh

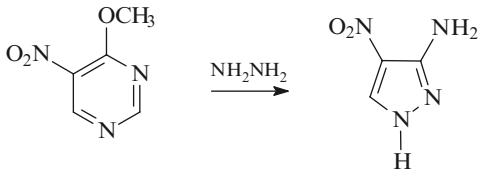
Scheme 95

Recyclization can also take place with a change in the ring size. Thus, 3(5)-methyl-5(3)-(2-hydroxyphenyl)-4-nitropyrazole is obtained with a high yield in the reaction of 2-methyl-3-nitrochromone with hydrazine [543, 544]. Instead of hydrazine it is possible to use its alkyl or aryl derivatives. In this case 1-substituted 4-nitropyrazoles are isolated [543, 545] (Scheme 96).



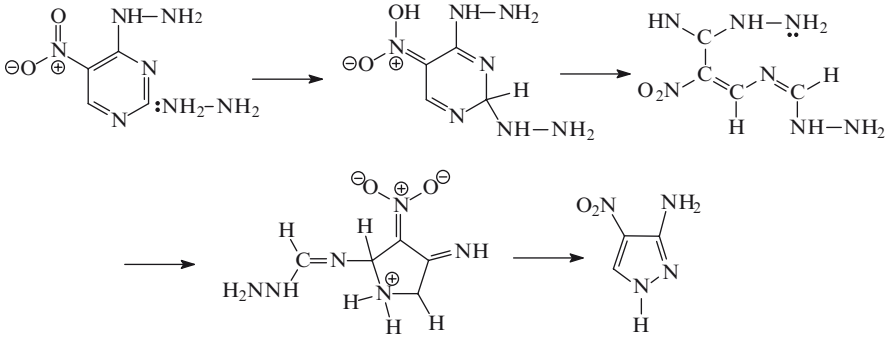
Scheme 96

4-Methoxy-5-nitropyrimidines react with hydrazine hydrate, being converted into 3-amino-4-nitropyrazoles [546, 547] (Scheme 97).



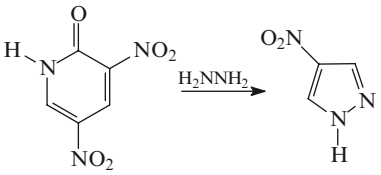
Scheme 97

5-Nitropyrimidine itself is converted by the action of hydrazine into 4-nitropyrazole. In this case the hydrazine initially attacks the pyrimidine ring at position 4 [548]. The following mechanism is proposed for this rearrangement [547] (Scheme 98).



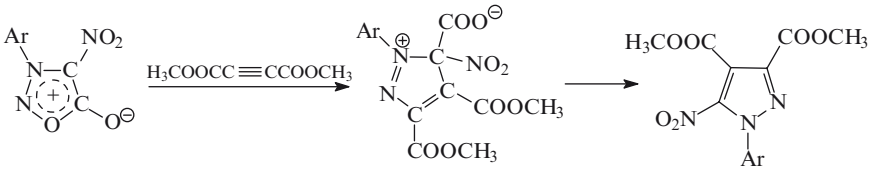
Scheme 98

The action of hydrazine or hydroxylamine on certain other nitropyrimidine systems leads to 4-nitropyrazoles and 4-nitrooxazoles [549]. When 1,5-disubstituted 4-nitro-6-pyridazinone derivatives are heated in an alkaline medium the derivatives of 4-nitropyrazole are formed with high yields. 1-Substituted 4-nitropyrazole-5-carboxyiic acids [550, 551] or 1-substituted 4-nitropyrazoles [552–554] can be obtained, depending on the conditions. Another promising method of synthesis has been opened up for the production of 4-nitropyrazole derivatives. 4-Nitropyrazole is obtained with a high yield in the reaction of 3,5-dinitro-2-pyridone with hydrazine [555] (Scheme 99).



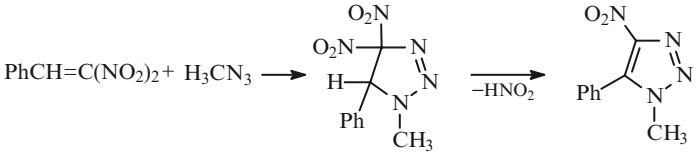
Scheme 99

3-Aryl-4-nitrosydnones react with acetylenedicarboxylic esters with the formation of l-aryl-3-nitro-4,5-pyrazoledicarboxylate [556] (Scheme 100).



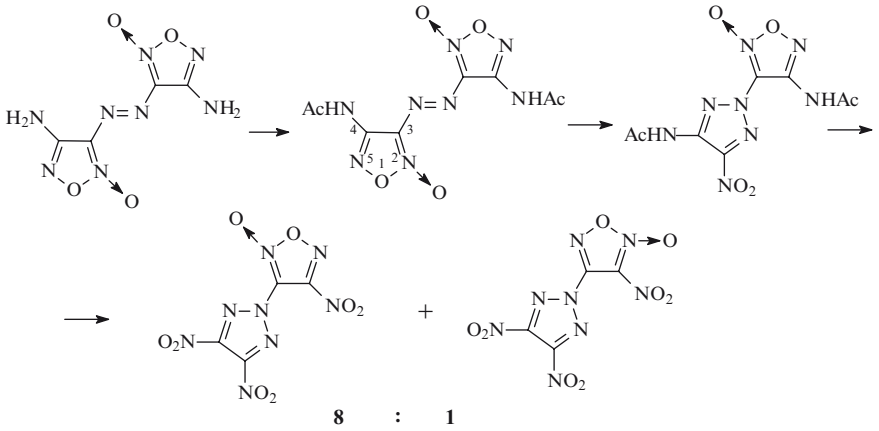
Scheme 100

In contrast to reactions with alkynes [507] that are nonregioseletive, methylazide reacts regiospecifically with α-nitro-olefines and forms only 4-nitro-5-phenyl-1,2,3-triazole after elimination of HNO_2 [557] (Scheme 101).



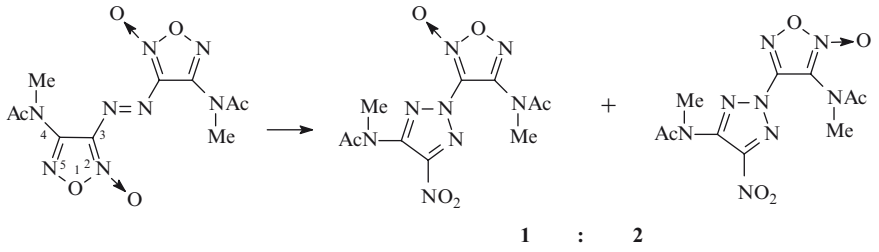
Scheme 101

Thermal recyclization of the 4,4′-bis(acetamido)-3,3′-azofuroxan leads to 4-acetamido-3-(5-acetamido-4-nitro-1,2,3-triazol-2-yl)furoxan [558]. This transformation is probably initiated by the nucleophilic attack of an amide anion or amine on the nitrogen atom of the furoxan. The oxidation of the latter results in two isomers 4-nitro-3- and 3-nitro-4-(4,5-dinitro-1,2,3-triazol-2-yl)furoxan in the 8:1 ratio, which were separated by chromatography on SiO_2 (Scheme 102).



Scheme 102

Bis(acetamido) derivative of furoxan undergoes the aforementioned rearrangement to form a mixture of two isomeric nitrotriazolylfuroxans in the 1:2 ratio [558] (Scheme 103).



Scheme 103

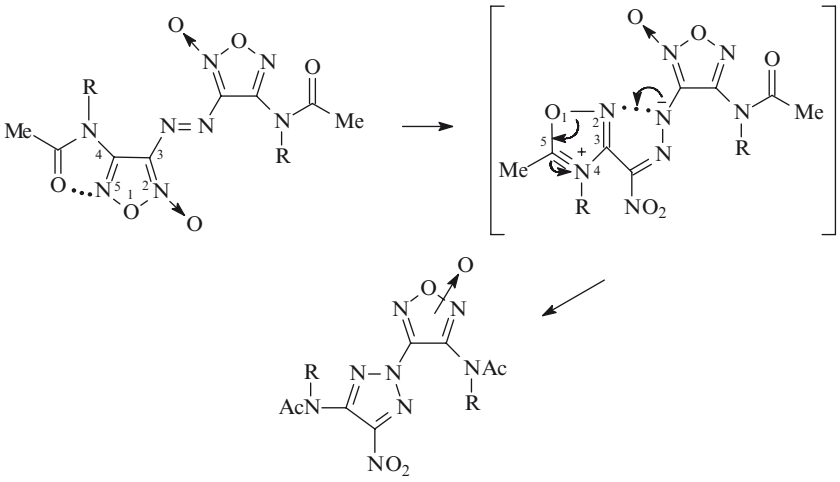
The rearrangement is the transformation of one of the acetamidofuroxan cycles into the 1,2,4-oxadiazole ring with the cleavage of the O(1)-N(5) bond of the furoxan and the formation of a nitromethylene fragment [558] (Scheme 104).

The thermal cleavage of O(1)-N(1) bond under the action of nucleophiles leading to, in particular, 1,2,3-triazole is the typical reaction of 1,2,4-oxadiazoles, including intramolecular reaction [558].

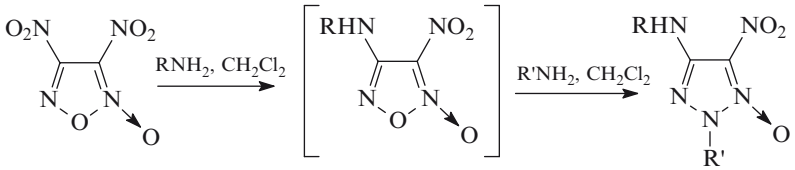
Various 1-aryl(hetaryl)-4-nitro-1,2,3-triazoles are obtained in result of heterocyclic rearrangements of uncondenced furoxans with the use of ionic liquids as reaction media [559–564].

5-Nitro-1,2,3-triazole 1-oxide derivatives may be obtained directly from furoxans [565] (Scheme 105).

It has been supposed [565] that the primary amine attacks the nitrogen atom of the *N*-oxide fragment to open the furoxan cycle, then dehydrative cyclization follows to form the 1,2,3-triazole 1-oxide ring (Scheme 106).

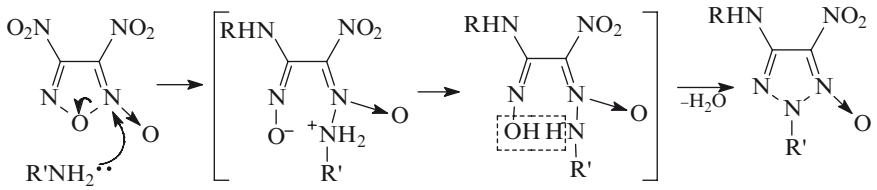


Scheme 104



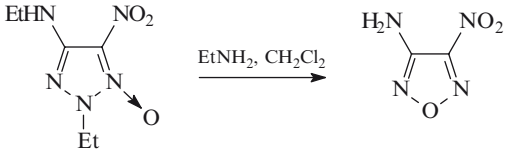
R = H, Alk, $HOCH_2CH_2$, $NCCH_2CH_2$; R' = Alk, vinyl

Scheme 105



Scheme 106

It should be noted that 3-amino-4-nitrofurazan has been isolated as a side product of 1,2,3-triazole 1-oxide in all cases of this reaction. For example, 2-ethyl-4-ethylamine-5-nitro-1,2,3-triazole 1-oxide with excess ethylamine transforms quantitatively into nitroaminofurazan [565] (Scheme 107).

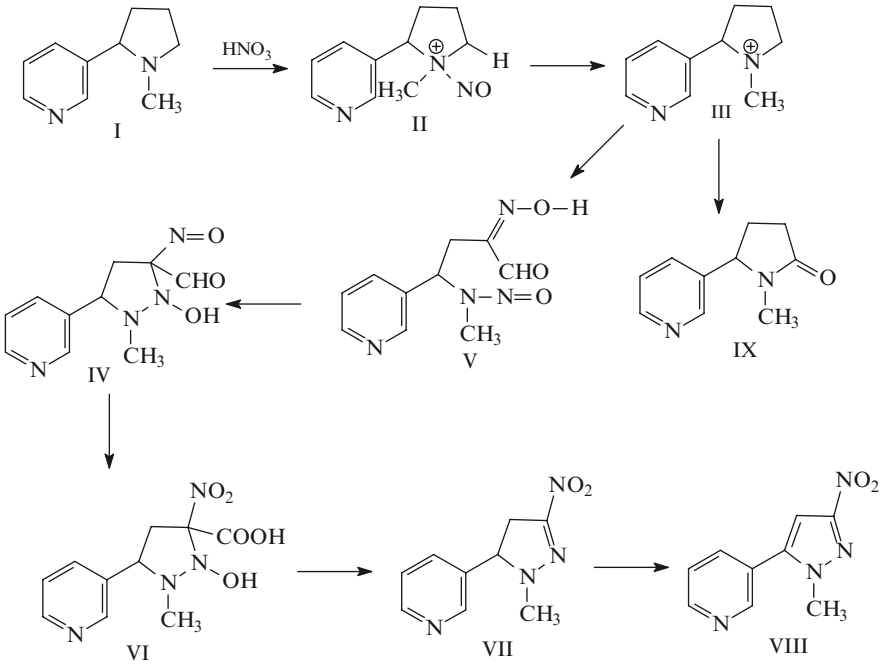


Scheme 107

The chemistry of nitrofuroxans has been presented in detail in monograph [566] and review [567]; therefore, here we consider works published after.

Other Methods of Preparation

The oxidation of nicotine by nitric acid gave a product that was initially assigned the structure of 4-nitro-3(5)-(3-pyridyl)pyrazole [568, 569]. Later on, however, it was established that this substance was 3(5)-nitro-5(3)-(3-pyridyl)pyrazole [27–29]. The mechanism of this reaction can be represented by the following Scheme [570] (Scheme 108).



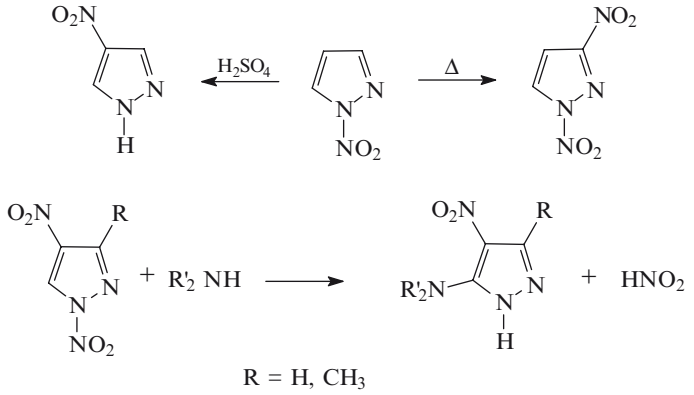
Scheme 108

It is assumed that the elimination of HNO from the nitrosium salt of nicotine (II) leads to the formation of the pyrrolium salt (III). Hydration of this imine salt and oxidation of the obtained carbinolamine give cotinine (IX). *C*-Nitrosation of the imine salt (III) at the C-4′ atom and *N*-nitrosation at the secondary amine can lead to the formation of the intermediate (IV), which then undergoes cyclization to the pyrazolidine derivative (V). The nitroso group is then oxidized to a nitro group, while the aldehyde group is oxidized to a carboxyl group, forming compound (VI). Decarboxylation and dehydration of the latter lead to the formation of the pyrazoline (VII). Dehydrogenation of the pyrazoline ring gives the final product (VIII), the yield of which amounts to 8–9%.

3-Substituted 1,5-diphenyl-4-nitropyrazoles are obtained from corresponding 3-pyrazolines, which slowly oxidize on standing in air [571].

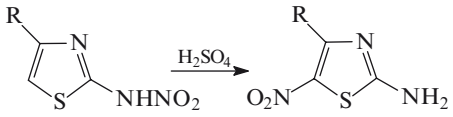
The 3- and 4-nitrosopyrazoles are easily oxidized to the corresponding nitro derivatives [22, 572, 573]. 1-Aryl substituted 4-dimethylaminopyrazoles are converted into the 5-nitro derivatives by the action of nitrous acid [574, 575].

As already mentioned, a convenient method for the synthesis of 3- and 4-nitropyrazoles is isomerization of *N*-nitropyrazoles [63, 309, 310, 313, 314, 576] (Scheme 109).



Scheme 109

This reaction acquires special significance as a result of the fact that it is possible to introduce a nitro group at position 3(5) of the pyrazole ring. This is impossible during direct nitration. *N*-Nitroimidazoles [323, 326] and 1,2,4-triazoles [318, 577] enter into such a rearrangement. In a similar way *N*-nitroaminothiazoles isomerize to 2-amino-5-nitrothiazoles [231] (Scheme 110).

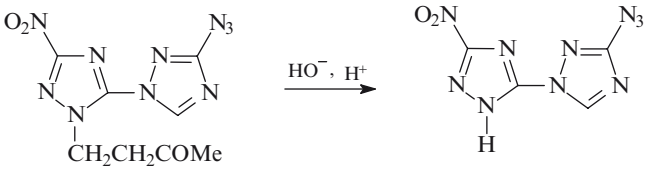


Scheme 110

2-(*N*-Methylamino)-5-nitro-4-phenylthiazole has been prepared by interaction of 2-(*N*-methyl-*N*-nitroamino)-4-phenylthiazole with 50% sulfuric acid [578]. The result indicates that migration of the *N*-nitro group occurs on the intramolecular path; however, in concentrated sulfuric acid, formation of nitronium ion and ring nitration also takes place [578]. 4-Nitro-5-azidoimidazole has been obtained from corresponding 5-diazo compound, and hydrazone steroids passed anticancer and antibacterial activity [579].

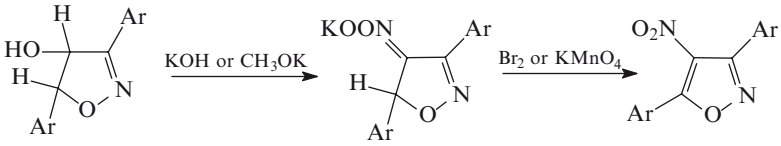
Azido derivatives nitro-bis-1,2,4-triazoles a perspective hight energetic compounds have been prepared by functionalization or defunctionalization of (relative)

corresponding compounds [580]. For examples, 5-(3-azido-1,2,4-triazol-1-yl)-3-nitro-1,2,4-triazole forms as the result of hydrolysis in alkaline medium of bis-triazole ketone [580] (Scheme 111).



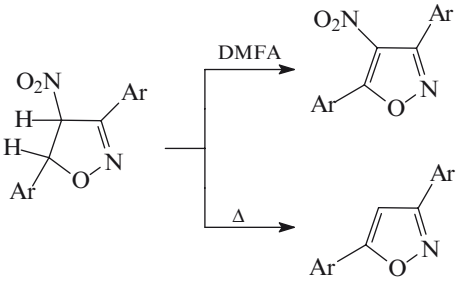
Scheme 111

The salts of 3,5-diaryl-Δ_2-isoxazolinyl-4-nitronic acids are readily transformed into 4-nitroisoxazoles during oxidation with bromine [581] or potassium permanganate [582, 583] (Scheme 112).



Scheme 112

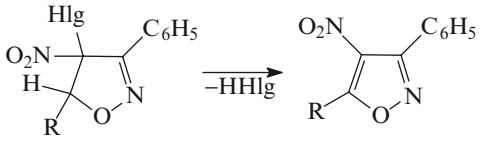
4-Nitroisoxazolines are also aromatized by the action of other oxidizing agents (MnO_2, [584], CrC_3 [540], HSO_3F [540], and $C(NO_2)_4$ [585]). In some cases 4-nitroisoxazoles can be obtained by the thermolysis of the respective isoxazolines. Thus, 3,5-disubstituted 4-nitroisoxazolines form 4-nitroisoxazoles when heated in DMF. At the same time nitrous acid is eliminated during the thermolysis of the 4-nitroisoxazolines in the absence of a solvent [586] (Scheme 113).



Ar = C_6H_5, 3-FC_6H_4

Scheme 113

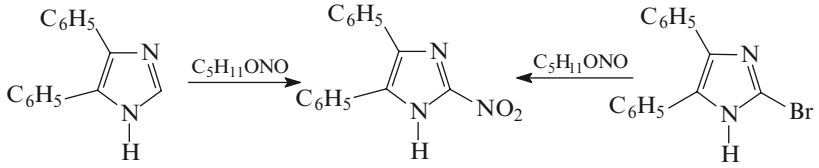
4-Chloro- and 4-bromo-4-nitroisoxazolines are converted into the corresponding nitroisoxazoles by the action of bases while 4-iodo-4-nitrooxazoline is converted spontaneously during storage [587] (Scheme 114).



Scheme 114

The product from the reaction of citraconic acid (or its anhydride) with nitric acid was initially assigned the structure of 3-methyl-5-(1,1,2-trinitroethyl)isoxazole [588]. However, it was subsequently established that this compound was 5-methyl-4-nitro-3-(1,1-dinitroethyl)isoxazole [589]. As mentioned earlier, the antibiotic azomycin (2-nitroimidazole) and some of its derivatives can be obtained by microbiological synthesis [331, 450, 590, 591].

2,5-Diphenyl-4-nitrosoimidazole is oxidized by amyl nitrate to the corresponding 4-nitro derivative [592]. An unusual reaction is observed when 4,5-diphenylimidazole and 2-bromo-4,5-diphenylimidazole are boiled with amyl nitrite. Instead of nitrosation the substrate undergoes nitration with the formation of 2-nitro-4,5-diphenylimidazole [593] (Scheme 115).



Scheme 115

The reaction of 1-methoxy-2-phenyl-1,2,3-triazole tetrafluoroborate with alkali-metal nitrites or silver nitrite gives 5-nitro-2-phenyl-1,2,3-triazole [594].

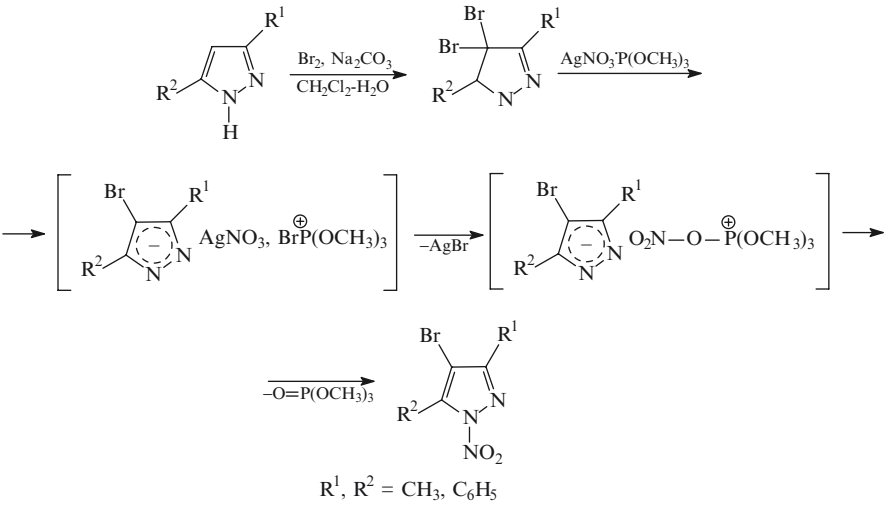
For a long time it was considered that the only method for the production of *N*-nitroazoles was the nitration of azoles with acetylnitrate. Comparatively recently it was found that 4,4-dibromo-4*H*-pyrazoles form 3,5-disubstituted 4-bromo-1-nitropyrazoles with the complex of silver nitrate and trimethyl phosfite. 4-Bromopyrazole derivatives are formed as impurities [595] (Scheme 116).

4-Nitrofuroxans can be obtained by oxidation of 4-dimethylsulfuliminofuroxans by treatment of trifluoroperacetic acid [596] (Scheme 117).

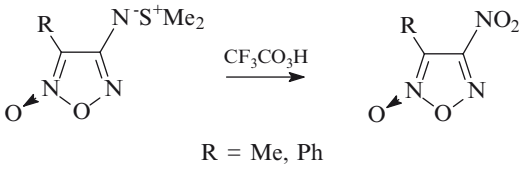
The yield of the nitrofuroxans is 70%.

Transformation of bis(3-nitrofurazan-4-yl) disulfide by oxidation-destructive nitration with nitric acid leads to 3,4-dinitrofurazan and 4,4′-dinitroazoxyfurazan [597] (Scheme 118).

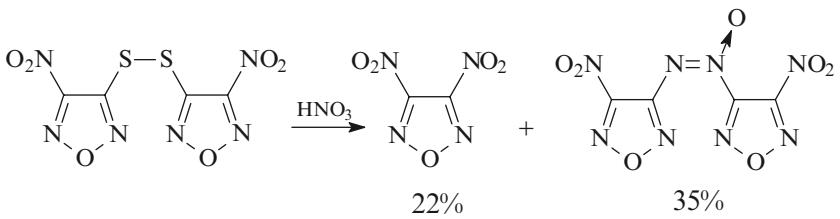
The first act in the process is the cleavage of S–S bond; in contrast to this, decomposition of bis(3-nitrofurazan-4-yl) sulfide does not occur in these conditions [597].



Scheme 116



Scheme 117



Scheme 118

1,4-Dimethoxy-2-(3-nitro-1,2,4-triazol-1-yl)benzene and 1,1,4-trimethoxy-4-(3-nitro-1,2,4-triazol-1-yl)cyclohexane-2,5-diene have been prepared by indirect electrochemical method [598].

1-Methyl-3-nitro- and 1-methyl-5-nitro-1,2,4-triazole derivatives with high yield (50–90%) have been obtained by the alkylation of corresponding triazoles [599].

Polynitroazoles

Polynitroazoles have attracted major attention of chemists all over the world due to their antibiotic, radiosensitizing, antiprotozoan, and, mainly, energetic properties [364, 365, 600–608]. In recent years, the investigations in the field of energetic heterocyclic compounds have received considerable interest. Energetic materials – explosives, propellants, and pyrotechnics – are widely used for both civilian and military purposes. A number of ongoing research programs worldwide are aimed to the development of new explosives and propellants with higher performance characteristics or enhanced insensitivity to thermal or shock insults and pyrotechnics with reduced smoke. Polynitroazoles and nitroazoles, as heterocycles as a whole, possess higher heat of formation, density, and oxygen balance than their carbocyclic analogs.

Synthesis, molecular design, and explosive performance prediction codes to guide the synthesis of new energetic compounds based on nitroazole or polynitroazole and other systems have been studied in the famous Lawrence Livermore National Laboratory (USA) [604].

The synthesis and chemical properties of 1,4-dinitroimidazoles [363], 4,5-dinitroimidazoles [383, 609–611], 2,4-dinitro-, and 2,4,5-trinitroimidazoles and their 1-substituted derivatives [84, 383, 612–617] have been described. 1-Substituted 2,4-dinitroimidazoles have been synthesized and tested as potential radiosensitizing agents for selective sensitizing of hypoxic mammalian cells to the lethal effect of radiation. The reaction of 2,4(5)-dinitroimidazole with oxirane derivatives upon heating in absolute ethanol affords the expected 1-substituted 2,4-dinitroimidazoles as well as results in a novel class of isomeric nitroimidazo(2,1b)oxazoles due to the intramolecular cyclization. The study of radiosensitizing activity of these agents against hypoxic Chinese hamster cells (V-79) indicates that 2,4-dinitroimidazoles are better sensitizers than the other nitroimidazoles, thus suggesting the necessity of the 2-nitro function in the molecule. The 1-(2-hydroxy-3-methoxypropyl)-2,4-dinitroimidazole is found to be the most effective radiosensitizer of this series [615]. At the same time dinitroimidazoles (DNI) are powerful insensitive highly explosive compounds with explosive force greater than that of triamino-trinitrobenzene (TATB) or trinitrotoluene. DNI has both excellent thermal sensitivity and impact insensitivity, and yet it is still a powerful high-performance explosive. DNI exists as three isomers, 1,4-dinitroimidazole, 2,4-dinitroimidazole, and 4,5-dinitroimidazole, while 2,4-dinitroimidazole delivers the best explosive performance. DNI is considered as a replacement for TATB as the initiating explosive in nuclear warheads.

1-Methyl-2,4,5-trinitroimidazole has been synthesized from 4-nitroimidazole using stepwise nitration and further methylation by dimethylsulfate or from commercially available imidazole. 1-Methyl-2,4,5-trinitroimidazole is relatively insensitive to impact, and its thermal stability is excellent. The calculated detonation properties point to the fact that its performance is about 30% better than that of TATB. The data of impact sensitivity, friction sensitivity, time-to-explosion tem-

perature, vacuum stability tests, good oxygen balance, and measured heat of formation of this material denote that its propellant performance should be good [616].

Energetic salts on the base of 3,5-dinitropyrazole, 2,4-dinitroimidazole, 4,5-dinitroimidazole, 2,4,5-trinitroimidazole, 3,5-dinitro-1,2,4-triazole (azolium cations and azolate anions), and their mononitro analogs have been synthesized and characterized [161, 613, 618–637]. Azolyl salts exhibit good physical properties including relatively high densities (1.38–1.75 g/cm) and high positive heats of formation as well as moderate detonation properties. To design salts with the most potent energetic properties, both cation and anion should have the highest nitrogen content, which in turn enhances the density and detonation characteristics [636]. The synthesis and application of new members of heterocyclic-based energetic, low-melting salts are of special interest. Energetic materials, i.e., salt-based, often hold advantages over nonionic molecules since these salts tend to exhibit lower vapor pressure and higher densities than their atomically similar nonionic analogs. The cation is generally a bulky organic nitrogen-containing heterocycle with low symmetry. The anions are usually inorganic, such as nitrates, perchlorates or organic, such as pyrazolate, imidazolate, triazolate, and tetrazolate [623, 637]. The standard enthalpies of formation of hexamethylenetetrammonium salts composed of energetic anions 3,5-dinitropyrazolate, 4,5-dinitroimidazolate, 3,5-dinitro-1,2,4-triazolate, and 5-nitrotetrazolate were calculated by the computationally feasible DFT(B3LYP) and MP2 methods along with an empirical approach based on the densities of the salts [628]. Most of the salts possess such physical properties as good hydrolytic stabilities, relatively high densities (>1.50 g/cm^3), and high positive heats of formation [623, 628, 636]. 2,4,5-Trinitroimidazolate salts with "high-nitrogen" cations are prone to be highly hydrogen bonded and have the formation heats in the range of 616 kJ/mol. Thermostability, density, and oxygen balance are improved by the presence of 2,4,5-trinitroimidazolate. Theoretical calculations show that all of the new salts are promising propellants [633].

Novel energetic salts, alkylimidazolium cations paired with 3,5-dinitro-1,2,4-triazolate, 4-nitro-1,2,3-triazolate, 2,4-dinitroimidazolate, 4,5-dinitroimidazolate, 4-nitroimidazolate, and tetrazolate anions have been prepared and studied by single crystal X-ray diffraction, differential scanning calorimetry, and thermogravimetry method [161, 626, 627]. The effects of cation and anion type as well as structure on the physicochemical properties of the resulting salts, including several ionic liquids (defined as having m.p. < 100°C), have been examined and discussed. The ionic liquid, 1-butyl-3-methylimidazolium 3,5-dinitro-1,2,4-triazolate with relatively large, rigid heterocyclic anion has unexpectedly low melting point (35°C) [626]. The presence of electron-withdrawing nitro-substituents in the triazole ring favors the formation of stable aromatic charge delocalized anions, compared with unsubstituted triazoles, which interact only weakly through hydrogen bonding with the cation [626].

Thermal decomposition of energetic compounds, 1,4-dinitroimidazole [638–640], 1-nitro-3-(β,β,β-trinitro-ethyl)-4,5-dinitroiminoimidazolidine-2-one [641] and its 4-nitroiminoimidazole [642], 1-dinitromethyl-3-nitro-1,2,4-triazole derivatives [643], and *C*-nitro- and *N*-nitro-1,2,4-triazoles [644–646], has been studied. The critical temperature of thermal explosion of imidazole derivative is 155.7°C [641].

The kinetics of hydrolysis of energetic material precursors – mono- and dinitro derivatives of pyrazole, imidazole, 1,2,4-triazole, and isoxazole has been studied by the polarographic and photometric methods [647]. The alkaline hydrolysis rate constants experimentally determined depend on the nature of the heterocycle. A possible mechanism for hydrolytic transformations of nitroazoles is proposed on the basis of the calculated thermodynamic parameters of the reaction.

Investigations of new energetic materials of oxazole series of azoles have been carried out [429, 648–653]. Detonation characteristics including heats of detonation, heats of formation in gas phase, detonation velocities and pressures, and crystal densities of dinitrofurazans and -furoxans – so-called *high energy density materials* (HEDM) were calculated by quantum chemistry, molecular mechanics, and Monte Carlo methods [648]. 3,4-Dinitrofurazan and 3-nitro-4-nitroaminofurazan are recommended to be promising energetic compounds. The crystal densities, specific impulses, detonation properties, and sensitivities of most nitrofurazans and -furoxans are quite high. The author [648] supposes that it is not an efficient way to augment detonation properties by increasing molecules. Therefore, the smaller molecules are preferentially recommended, and the type, order, and quantities of the linking groups in polyfurazans and polyfuroxans can affect the detonation properties. Computational correlation approach to predict impact sensitivity of dinitrofurazans, nitroimidazoles, nitropyrazoles, nitrotriazoles, etc. has been proposed [652]. The approach is based on elemental composition and two structural parameters of $C_aH_bN_cO_d$ energetic nitroazoles. The results obtained for compounds mentioned are compared with complex neural network computations, which use compositional and topological descriptors [652].

Mono- and dinitrofurazans and -furoxans are the important objects in designing and synthesizing HEDM. As it is shown earlier, they can be prepared by oxidation of the corresponding aminooxadiazoles in the presence of H_2O_2/H_2SO_4 [455–465]. For instance, the Sheremetev's works report the great synthetic possibility of producing energetic materials on the base of dinitrofurazans and -triazoles [429, 460–464, 466, 467, 644, 653] (see Scheme 61). The preparation of dinitro polyfurazans unveils the wide synthetic potential of the energetic compounds construction.

The chemical properties of 1,4-dinitropyrazole [654] and 1,4-dimethyl-3,5-dinitropyrazole obtained by the nitration of 1,4-dimethylpyrazole [655], nitrotriazoles [656–663], and other nitroazoles [662, 664–666] have been studied. 1,4-Dinitropyrazole undergoes ring transformation reactions with primary amines, hydrazines, hydroxylamine, and amidines [654]. Acid hydrolysis of dinitropyrazole leads to (1-methyl-3,5-dinitropyrazol-4-yl)acetaldehyde, and the reaction with sodium nitrite in hydrochloric acid furnishes 2-hydroxymino-2-(1-methyl-3,5-dinitropyrazol-4-yl)acetaldehyde [655].

3,5-Dinitro-1,2,4-triazole has been synthesized from 3,5-diamino derivative with sodium nitrite excess [667], and the protocol was proposed for the preparation of 3,5-dinitro-1,2,4-triazole from dicyanodiamide and hydrazine without isolation of 3,5-diamino-1,2,4-triazole.

The design and synthesis of 1,4-dinitropyrazole C-nucleosides possessing antitumor, antibacterial, antifungal, and antiviral activity have been reported [668–670].

The use of 2,7-dimethyl-3,8-dinitrodipyrazolo[1,5-a,1′,5′-d]pyrazine-4,9-dione – a new labeling reagent for liquid chromatographic analysis of amino acids – is offered [671]. Application of the method to quality control of commercially available oral polyaminoacid formulations is described. 1,2-Diacetyl-4,4-dinitropyrazolidine and products of its further nitration have been obtained [672].

The structure of 4,4′-dinitro-2,2′-biimidazole dimethylformamide solvate [673] and 1-(4-chlorophenacyl)-2-methyl-4,5-dinitro-1H-imidazole [674] has been determined by X-ray diffraction analysis. Both nitro groups in the latter product are deviated significantly from the imidazole plane, and the C4–NO_2 bond length is only slightly shorter than the value for a normal single $C_{sp}2$–NO_2 bond, and the C5–NO_2 bond length is much shorter than C4–NO_2 [674]. The C-4-nitro group is easily replaced by morpholine, while the C-5-nitro group shows a high stability on treatment with the amine. In the crystal structure, the molecules are coupled via C–(HO)–O–hydrogen bonds.

The structure of 1,2,5-trinitroimidazole and 1,2,4,5-tetranitroimidazole has been studied with various levels of ab initio and density functional (DF) theories [675, 676]. The second-order perturbation method (MP2) with the 6-31G** basis set has predicted considerably long N–N bond lengths in nitroimidazoles that is 1.737 and 1.824 Å, respectively. According to the analyses with bonding natures and CHELPG charges at the MP2 level, the N–N bonds of 1,2,5-trinitro- and 1,2,4,5-tetranitroimidazole appear to have ionic nature, and the 1-nitro group bears some positive charge and has attractive electrostatic interactions with O atoms of adjacent nitro groups. Although all the theories utilized in this study predict that both compounds are stable in their potential-energy surfaces, significantly long N–N bond lengths calculated with MP2 and DF theories imply a strong hyperconjugation effect, which the authors explain for the tendency to form a salt in these compounds easily [675].

The electrochemical reduction of dinitroazoles [677–680] has been investigated by polarography and ESR spectroscopy. Upon electrochemical reduction in acetonitrile, all *N*-alkylnitroazoles form stable radical anions and all *N*-unsubstituted nitroazoles give stable radical dianions. 1-Nitro- and 1,4-dinitropyrazoles are reduced upon splitting the NO_2 anion [678], while the electrochemical reduction of 1,4-dinitropyrazole allows to observe the well-resoluted ESR spectrum, and the splitting character proves a dimeric radical product [678]. The presence of two nitro groups in the azole molecule substantially changes the electrochemical behavior as compared with the behavior of its mononitro analogs [678–681]. The electrochemical reduction of 1-methyl-3,5-dinitro-1,2,4-triazole proceeds unusually [679]. The latter in acetonitrile is reduced to deliver radical trianion with well-resoluted ESR spectrum [679].

The neutron inelastic scattering spectra of 2,4-dinitroimidazole have been registered and calculated by solid-slate calculation methods at BLYP/dnd, BP/dnd, and PWC/dnd theory levels [682]. Comparison of the observed and calculated neutron spectra reveals that the BLYP/dnd calculations provide the best description of the experimental spectrum.

In conclusion, the preparation of polynitroazoles shows the great synthetic potential. Advantageous approaches for the syntheses of polynitro derivatives of five-

membered heterocycles broaden the range of their utility [683, 684]. The feasibility and availability of the starting compounds make this strategy a powerful method for high energetic material construction. The presence of electron-withdrawing nitro groups in the azole ring tends to produce energetic materials with high energy, high density, low sensitivity, and good heat resistance, while the enhancement of ring aromaticity can also increase thermal stability. The ongoing works in the field of energetic salts will extend the range of anions, develop systems with higher density heterocyclic cations, and evaluate the properties of these materials.

Conclusions

The basic procedure of the preparation of nitroazoles is the nitration reaction. The nitration of organic compounds, known for a century and a half, is still very enigmatic and attracts the attention of many researchers due to the interest in the nitration of heterocyclic compounds, in particular, of azoles. The reaction mechanism is the subject of heated discussions; the methods of nitration are being constantly developed and modified, and the range of nitrating agents is ever expanding.

Therefore, in spite of the great number of studies devoted to the nitration of azoles, the interest in this issue has never waned. This is mainly because many nitroazoles are of great practical value. Mechanistic aspects of the *ipso*-nitration of azoles remained poorly understood until recently. Further extensive research of the kinetics and mechanism of the nitration of azoles, especially with novel nitrating agents, is desired. It should be expected that the *N*-nitropyrazoles will find ever increasing use as nitrating agents.

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Synthesis of Nitrobenzazoles

Abstract A great deal of information on the methods of synthesis of nitrated benzo analogs – indazoles, benzimidazoles, benzoxazoles, benzisoxazoles, benzoxadiazoles, benzothiazoles, benzoisothiazoles, benzothiadiazoles, benzotriazoles, benzoselenazoles, benzoselenadiazoles – is systematized, summarized, and critically discussed. Major attention is paid to electrophilic nitration, a much used and convenient method for the preparation of nitrobenzazoles. The nitration of benzazoles is a complex process in which the experimental conditions can modify the product orientation. The existence of an annelated benzene ring in the benzazole molecule influences much of its ability for electrophilic substitution – all benzazoles are more easily nitrated than their five-membered analogs, and the nitro group is generally introduced into the arylene fragment of the molecule. Vicarious nucleophilic *C*-amination of benzazoles, practically, the single method of direct introduction of the amino group into nitro compounds is presented.

Introduction

The nitro derivatives of benzazoles have found wide applications in various branches of medicine, technology, and agriculture. For a long time they were used as radiosensitizers, anesthetics, anticancer medications, dyes, plasticizers, ionic liquids, pesticides, herbicides, and plant growth regulators. The nitrobenzazoles are convenient synthons and intermediates in organic synthesis. Benzotriazole, in particular, is a useful synthetic auxiliary: it is easily introduced, activates molecules toward numerous transformations, and can be removed readily at the end of the reaction sequence [1].

The syntheses of nitrobenzazoles have been critically discussed in our reviews [2]. Some representatives of nitrobenzazoles are described in Katritzky's works [3, 4] and reviews [6–8].

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The enormous amount of literature related to this topic made it necessary to exclude a series of references on earlier investigations and patents cited in the aforementioned reviews and monographs and also in more recent publications.

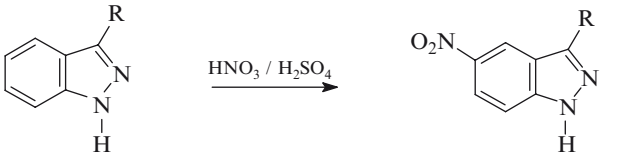
Some pioneering papers dealing with the synthesis of nitrated benzazoles have been included in the present chapter.

The most widespread and convenient method for the preparation of nitrobenzazoles is the reaction of nitration. Electrophilic substitution of azoles is a complex reaction in which the experimental conditions can modify the product orientation. The ability of azoles to electrophilic substitution is determined by the activity of reagents, the basicity of substrates, and the acidity of medium. This caused some uncertainty in interpreting the results and complicated comparison of the reactivity of various azoles among them. The situation has changed after Katritzky and Johnson [7] had reported the criteria allowing, with a sufficient degree of reliance, the establishment in what form (base or conjugative acid) the compound reacts. The information on the mechanism of nitration of azoles is basically borrowed from the extensive literature on the nitration of aromatic and heteroaromatic compounds [8]; therefore, it does not make sense to discuss this point in the review.

The existence of an annelated benzene ring in the benzazole molecule influences much its ability for electrophilic substitution. All benzazoles are more easily nitrated than their five-membered analogs, and the nitro group is generally introduced into the arylene fragment of the molecule.

Nitration of Benzazoles

Indazoles



R = H, CH_3, CH_2COOH, Cl, COOH, $COOCH_3$, CN

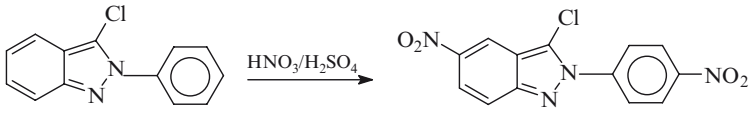
Scheme 2.1

Indazoles are nitrated, mainly into the position 5 by a mixture of sulfuric and nitric acids or just by nitric acid (Scheme 2.1) with formation of 5-nitroindazole derivatives that are a part of so-called universal nucleosides [9].

The presence of substituents mainly affects the direction of the process and not its rate. 1-Phenylindazole with 86% nitric acid gives a tetranitro derivative, which has one nitro group in the position 5; the second nitro group is in the *para*-position of the phenyl ring, with the position of the other two being not determined reasonably well [10]. If the nitration is performed by potassium nitrate in sulfuric acid, 1-(4-nitrophenyl)-5-nitroindazole is formed. Both the electron-donating and electron-withdrawing substituents at the indazole cycle C-3 atom direct the coming nitro

group to the position 5 in the nitration by nitric acid or by the mixture of sulfuric and nitric acids (Scheme 2.1) [10–16].

As mentioned in a patent [17], the nitration of 3-trifluoromethylindazole results in a mixture of 5-nitro- and 7-nitro-isomers. If the mixture of nitric and sulfuric acids is used as a nitrating agent, the formation of 3-methyl-7-nitroindazole as a by-product is observed [11]. Nitration of 3-chloro-2-phenylindazole with a mixture



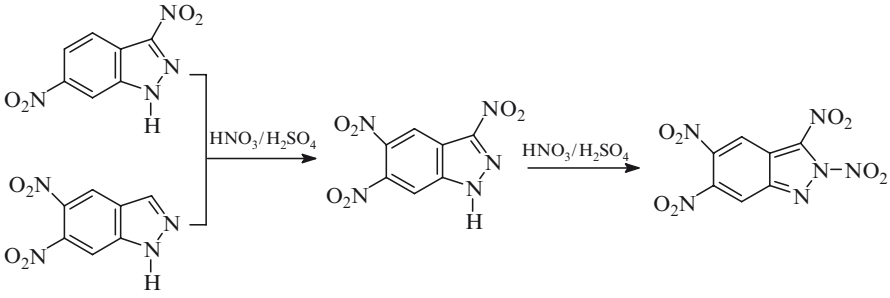
Scheme 2.2

of fuming nitric acid and concentrated sulfuric acid at 0°C gives 3-chloro-5-nitro-2-(4-nitrophenyl)indazole in yield 73% (Scheme 2.2) [18].

The nitration of 2-phenylindazole at 0°C with sulfuric–nitric acid mixture leads to 5-nitro-2-phenylindazole and 7-nitro-2-phenylindazole. These compounds have been identified using NMR spectroscopy [19]. In spite of the fact that the indazole positions 5 and 7 are most reactive with respect to electrophilic substitution [20] it is difficult to know beforehand the competition between the aromatic positions of the indazole ring (C-4, C-5, C-6, C-7) and the *N*-phenyl ring.

Electron-donating substituents in the indazole cycle positions 5 and 7 direct the coming nitro group to the position 4 [21, 22], and 6-acetylaminoindazole is nitrated to the position 7 [21]. It is known that 7-nitroindazoles are potent building blocks in divergent syntheses of bioactive compounds [23]. Under further nitration of mononitroindazoles the site of introduction of the second nitro group depends on both the position of the already present one and reaction conditions. For example, 5-nitroindazole is nitrated by the sulfuric–nitric acid mixture into 5,7-dinitro derivative, whereas in 6-nitroindazole the second nitro group enters into the position 5 [24]. After the nitration 7-nitroindazole forms 5,7-dinitro derivative [25].

The information about indazoles containing three or more nitro groups is rather scarce [26, 27]. Tetranitroindazole has been first assigned a wrong structure [26], but then it has been established to be 2,3,5,6-tetranitroindazole (Scheme 2.3) [27].



Scheme 2.3

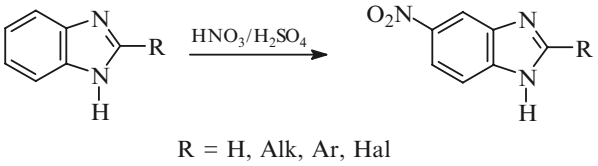
The formation of *N*-nitroazoles under the effect of sulfuric–nitric mixture is a rather seldom phenomenon [15, 27], since the *N*–NO_2 bond is unstable in acids. The most convenient way to *N*-nitroindazoles is nitration by acetyl nitrate [15, 27–37].

2-Nitroindazoles, the products of nitration with nitric acid in acetic anhydride, are easily rearranged to 3-nitro derivatives that make these isomers fairly accessible [28]. This method has been modified by Pozharskii [38] with a main goal to increase the yield of the reaction product. So 3-nitroindazole has been obtained without the intermediate 2-nitroindazole.

Kinetics and mechanism of nitration of indazoles with acetyl nitrate have not been specially investigated. In the sulfuric–nitric mixture indazoles are nitrated in the cation form [39].

Benzimidazoles

Benzimidazole is nitrated to the position 5(6) [40–44]. The same orientation is observed

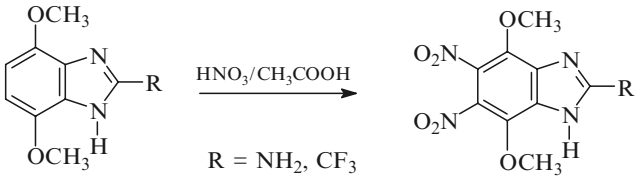


Scheme 2.4

in the nitration of different 2-substituted benzimidazoles (Scheme 2.4) [45–67].

In a boiling mixture of nitric (*d* 1.50) and concentrated sulfuric acids 2-chlorobenzimidazole gives 2-chloro-5,6-dinitrobenzimidazole in a 75–80% yield [67]. In analogous conditions, benzimidazole and 2-alkyl substituted benzimidazoles are also transformed into 5,6-dinitro derivatives; however, in this case simultaneous formation of 4,6-dinitro isomers, which can be separated by fractional crystallization, has been fixed [48, 68]. 5(6)-Nitro-2-heterylbenzimidazoles (thiazolyl-4-, furyl-4-, and pyrrolyl-4-) having antihelminthic activity were obtained by nitration with sulfuric–nitric mixture on cooling [69].

2-Trifluoromethyl- and 2-amino-4,7-dimetoxybenzimidazoles are nitrated to 5,6-dinitro derivatives already at 0°C (Scheme 2.5) [70].

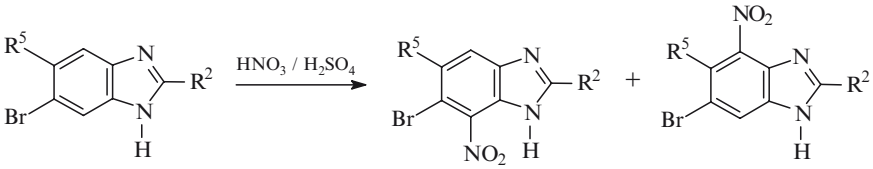


Scheme 2.5

The nitration of 5-nitrobenzimidazole under severe conditions gives two isomeric 5,6-dinitro- and 4,6(5,7)-dinitrobenzimidazoles. The structures of these products are identified only spectroscopically in the solution. The solid state structure of the major isomer 5,6-dinitrobenzimidazole has been determined by X-ray diffraction [71].

The nitration of 5-substituted benzimidazoles affords both mono- and dinitro derivatives. The two nitro groups occupy exclusively the positions 4 and 6 to form 5-substituted 4,6-dinitrobenzimidazoles [72–75]. It is interesting to note if in the nitration of 5-hydroxybenzimidazole the nitro group enters into the 4 position [74], whereas in the nitration of 5-chloro-, 5-ethyl-, and 5-ethoxybenzimidazole [73] and also 5-chloro- and 5-methyl-2-alkylbenzimidazoles [76, 77] it will occupy the 6 position. These data indicate that under the influence of electronic effects of the substituent in the position 5, the reactivity of C-4 and C-6 atoms of the benzimidazole ring is slightly equalized. That is why among the products of mononitration of 5-substituted benzimidazoles one can find 5-substituted 6-nitrobenzimidazoles [49, 75–80], 5-substituted 4-nitrobenzimidazoles [74, 75], and a mixture of these isomers [54, 75, 81, 82].

The nitration of 2-alkyl-5(6)-chloro(or methyl)-6(5)-halobenzimidazoles with excess nitric acid (~3 equivalents) in sulfuric acid leads to a mixture of 4-nitro- and 7-nitrobenzimidazoles except for 2-methyl-5,6-dibromobenzimidazole [76], as shown in Scheme 2.6. It is natural that 2-methyl-5,6-dibromobenzimidazole in the nitration under the same conditions gives 4(7)-nitro-2-methyl-5,6-dibromobenzimidazole in good yield.

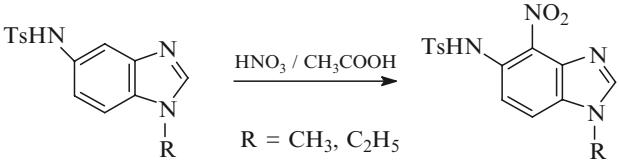


R^2 = Alk, R^5 = Hal, Me

Scheme 2.6

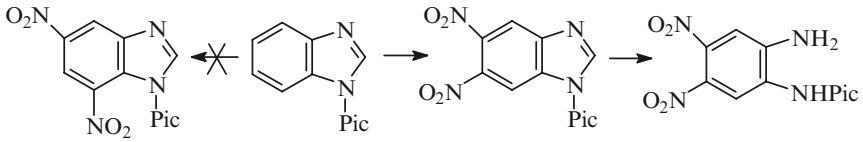
Preparation of 2,5(6)-dimethyl-4(7)-nitrobenzimidazole by nitration of 2,5(6)-dimethyl derivative has been reported in a patent [83], but there is no supporting evidence for the correctness of the assigned structures.

On nitration of 1-substituted benzimidazoles 5- and 6-nitro isomers [84–91] are formed. At the same time the nitration of 1-alkyl-5-tosylaminobenzimidazole with nitric acid in a solution of acetic acid leads to the formation of one isomer, the nitro group being involved in the position 4 (Scheme 2.7) [92].



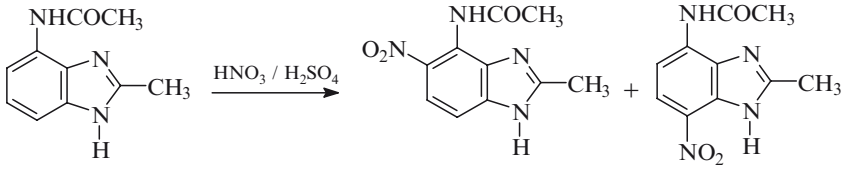
Scheme 2.7

The nitration of 1-picrylbenzimidazole with 100% nitric acid and 96% sulfuric acid gives, instead of the expected 5,7-dinitro derivative, the hydrolytically unstable 5,6-dinitro-1-picrylbenzimidazole that opens to the correspondent amine, as shown in Scheme 2.8 [93].



Scheme 2.8

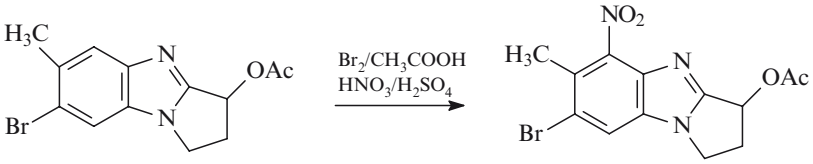
On nitration of 2-methyl-4(7)-acetylaminobenzimidazole two isomeric nitro products were obtained; the amount of 2-methyl-4(7)-acetylamino-7(4)-nitro isomer was twice as large (Scheme 2.9) [94].



Scheme 2.9

Prevailing formation of the 7-nitro derivative was observed in the nitration of 4-fluoro- [95] and 4-*tert*-butylbenzimidazole [96, 97]. When the benzimidazole ring has its 4 and 6 positions substituted, the nitration proceeds across the C-4 or C-7 atom [98–101].

In a medium of bromine in acetic acid and nitric–sulfuric mixture the benzimidazole derivatives are nitrated only to position 4 [102]. In this case the bromine is introduced into the position 5 or 6 (Scheme 2.10).



Scheme 2.10

Mechanism of the nitration of benzimidazoles has not been studied much, but there are weighty arguments to conclude that they are nitrated as conjugated acids [51, 103]. Kinetic studies of the nitration of benzimidazole and some of its 2-substituted derivatives have confirmed that the protonated form is involved in the process [104]. Recent results of quantum chemical studies of the nitration of benzazoles indicate the importance of the protonated benzimidazolium cations in the nitration process [43].

It has been noted that in the nitration of 2-phenylbenzimidazole, the rate of nitration into the benzimidazole 5 position is about three orders of magnitude higher than that of the phenyl ring [51].

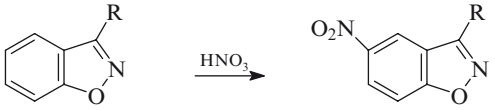
Benzimidazolone-2 and benzimidazolthione-2 derivatives are more prone to nitration [105, 106], and in this case the nitro group enters the position 5(6). It should be noted that depending on the reaction conditions, it is possible to obtain benzimidazolone dinitro, trinitro, or tetranitro derivatives [103, 107]. 5-Nitrobenzimidazolone-2 is nitrated with concentrated nitric acid on heating (80–90°C) only to the position 6 to give 5,6-dinitrobenzimidazolone-2 [108].

In the reaction of nitronium tetrafluoroborate with 1-aminobenzimidazole the nitro group enters the side chain with the formation of *N*-nitroimides [109]. In some cases the nitration of benzimidazoles with acetylnitrate leads to 1-nitrobenzimidazoles [110].

Some examples of the nitration of benzimidazole derivatives have been reported [110–114].

Benzisoxazoles, Benzoxazoles, and Benzoxadiazoles

1,2-Benzisoxazole and its 3-substituted derivatives are nitrated into the position 5 (Scheme 2.11) [115–125].



R = H, Alk, COOR'

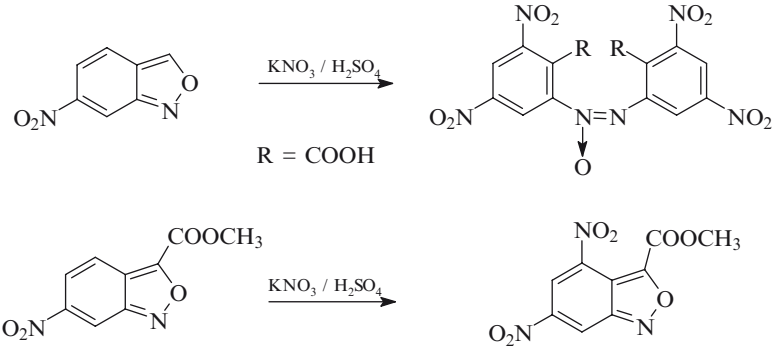
Scheme 2.11

The nature of substituent in the arylene fragment significantly influences the nitration direction. For example, 3,5-dialkyl-1,2-benzisoxazoles are nitrated into the position 4 (the data about the formation of 3,5-dimethyl-7-nitro-1,2-benzisoxazole presented in [115] turned out to be wrong [119], whereas 3-alkyl-5-nitro derivatives occupy the position 7 [119]). The nitration of 7-methoxy-2-phenylbenzisoxazole affords 7-methoxy-2-phenyl-4-nitro derivative [126].

The mechanism of the nitration of benzisoxazoles in sulfuric–nitric acid mixture has been studied with 3-methyl-1,2-benzisoxazole [121]. It has been found that at a sulfuric acid concentration of about 80–90% the substrate reacts as a free base, and at a higher concentration the conjugated acid undergoes nitration. It is worth mentioning that in 1,2-benzisoxazole and its 3-methyl derivative the higher electron density is concentrated on the C-7 atom and in the case of charge-controlled reactions the nitration would lead to 7-nitro isomers. Since 5-nitro derivatives are formed, the process of nitration seems to be of orbital-controlled character [121].

The nitration of 2,1-benzisoxazoles (anthranils) and their thioanalogs is poorly understood. Unsubstituted anthranil and its 3-methyl and 3-chloro derivatives are nitrated, generally, on the C-5 atom (in the first two cases, along with the main product small amounts of 7-nitro isomer were obtained) [127, 128]. When heated, 6-chloro-2,1-benzoxazole (6-chloranthranil) forms only 7-nitro derivative [129]. The nature of substituent significantly influences the site of the nitro group introduction. For example, on heating 5-chloroanthranil forms 5-chloro-4-nitroanthranil, but its 3-phenyl derivative is nitrated into the position 7 (along with the nitro group entering into the phenyl ring) [130].

It was impossible to introduce the second nitro group into 6-nitroanthranil because of the heterocycle ring opening, as shown in Scheme 2.12; however, 3-carbomethoxy-6-nitro-2,1-benzisoxazole is more easily nitrated to 4,6-dinitro derivative [130].

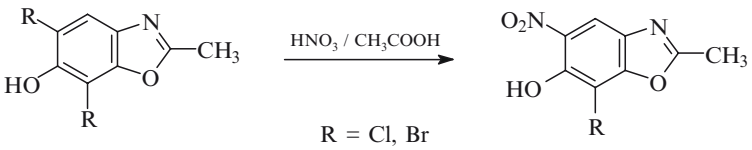


Scheme 2.12

In benzoxazoles and their 2-substituted derivatives the nitro group is presumably introduced into the position 6 [131–135]. In the nitration of 2-methylbenzoxazole a mixture of 80% of 6-nitro- and 20% of 5-nitro isomer was isolated. 2-Phenylbenzoxazole is first nitrated to the position 6 [136, 137]. The nitration of benzoxazolones-2 and benzoxazolthiones-2 proceeds in an analogous way [138–141].

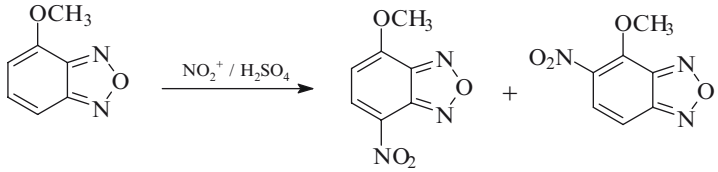
The reaction of cooled nitric acid with benzoxazole results in the formation of a mixture of 2-hydroxy-4-nitro- and 2-hydroxy-5-nitroformylanilines. On heating the same reaction gives a mixture of 5- and 6-nitrobenzoxazoles – the latter being prevailing [131]. Here, a question arises whether the formation of nitrohydroxyformylaniline results from the hydrolysis of the nitrobenzoxazole formed or it is due to the nitration of hydroxyformylaniline (the product of benzoxazole hydrolysis). The authors have shown the nitration precedes to the hydrolysis [131]. If the position 6 in benzoxazole is occupied, the nitration goes into the position 5 [142]. In the same work an example of nitrolysis (substituting nitration, *ipso*-nitration) of 2-methyl-5,7-dihalogeno-6-hydroxybenzoxazoles is given (Scheme 2.13).

Substituted benzoxazoles are also nitrated with nitric–sulfuric mixture into the 6 position, if it is vacant [143, 144]. In earlier publications it has been stated that benzofurazans (2,1,3-benzoxadiazoles) are nitrated exclusively to the 4(7) position



Scheme 2.13

[145–147]. If the 4 and 7 positions are occupied, as in 4,7-dichloro-2,1,3-benzoxadiazoles, for example, the nitration is impossible. At the same time, 4,6-dichloro-7-nitrobenzofurazan was obtained in good yield from 4,6-dichlorobenzofurazan [148]. Later it has been shown that in the presence of strong electron-donating substituents (like OCH_3) and along with nitration to the position 7 the addition of the nitro group to the C-5 atom takes place (Scheme 2.14) [149].



Scheme 2.14

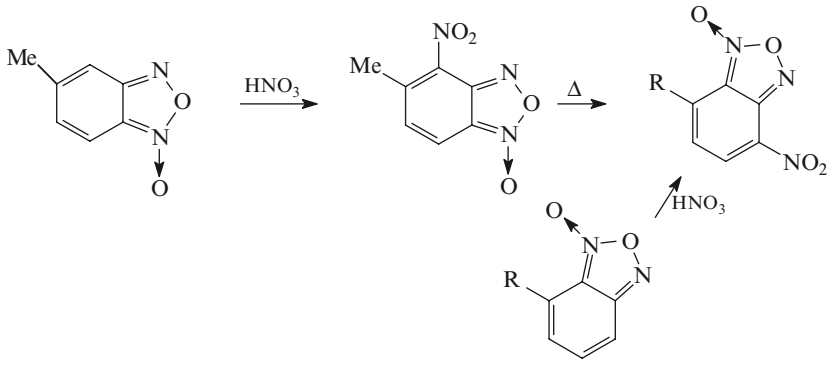
As expected, strong electron-deficient substituents in the position 5 orient the incoming nitro group exclusively to the position 7 [150, 151]. 7-Nitrobenzofurazans possess fluorescent properties and may be useful as biochemical fluorescent probes [152]. Some examples of obtaining dinitrobenzofurazans by nitration are described in references [153, 154].

The benzofuroxan phenylene ring is subjected to electrophilic substitution, in particular, nitration reaction. If the nitro group is introduced into the position neighboring to the heterocycle, the nitro compound formed undergoes the so-called Boulton–Katritzky rearrangement [155–161].

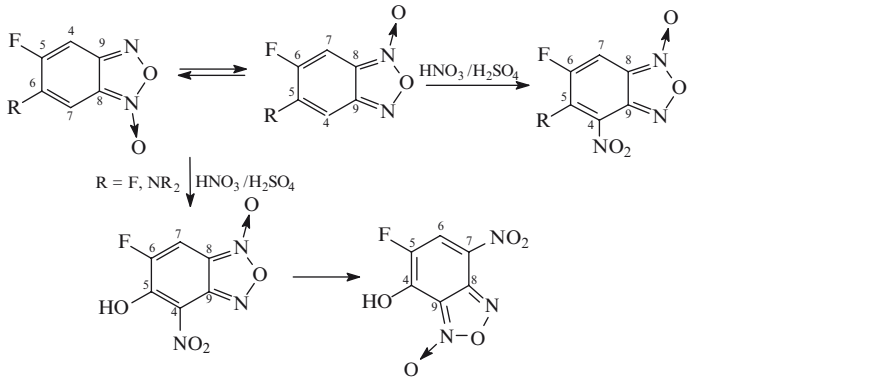
The nitration of 5-methylbenzofuroxan results in a 4-nitro derivative, which on heating is transformed to a more stable 7-methyl isomer according to the Boulton–Katritzky rearrangement. As shown in Scheme 2.15, the latter compound is obtained by direct nitration of 4-methylbenzofuroxan [159].

Similarly, 5-chloro-4,6-dinitrobenzofuroxan prepared by the nitration of 5-chlorobenzofuroxan by HNO_3/H_2SO_4, 0→21°C [162] undergoes the Boulton–Katritzky rearrangement (28°C, 51 h, $CHCl_3$) to give 7-chloro-4,6-dinitrobenzofuroxan.

It has been pointed out [155] that in the presence of fluorine atom in the position 5 in 4-nitrobenzofuroxan no Boulton–Katritzky rearrangement occurs. Later it has been established [161] that fluoro-containing benzofuroxans are fairly easily nitrated; however, not all nitration products are involved in the Boulton–Katritzky rearrangement. 5,6-Difluorobenzofuroxan and 5(6)-amino substituted 6(5)-fluorobenzofuroxans are nitrated with HNO_3 (*d* 1.54) and H_2SO_4 acids on cooling to form 4-nitro-5-hydroxy-6-fluorobenzofuroxan (Scheme 2.16) [161].



Scheme 2.15



R = F, $N(CH_3)_2$, morpholino, thiomorpholin-4-yl, pyrrolidin-1-yl, OCH_3, OC_2H_5, tetrahydrofuran-2-yl methoxy

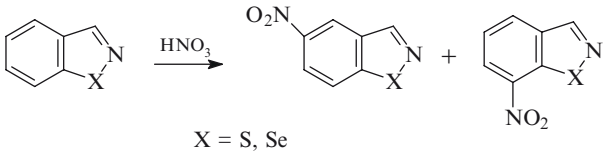
Scheme 2.16

Under nitration conditions the substituted fluorine (or the amine group) in the position 5 is easily hydrolyzed to hydroxy group. 4-Nitro-5-hydroxy-6-fluorobenzofuroxan, on dissolving in a polar solvent (DMSO), partly transforms to 4-hydroxy-5-fluoro-7-nitrobenzofuroxan as a result of the Boulton–Katritzky rearrangement (Scheme 2.16) [161]. Under nitration of 5(6)-alkoxy-6(5)-fluorobenzofuroxans the corresponding 4-nitrobenzofuroxans were obtained. In this reaction the C-4 atom in the *ortho*-position to the electron-donating substituent and remote from the *N*-oxide group is also the center of electrophilic attack. In this case, however, no products of the Boulton–Katritzky rearrangement are formed.

4,6-Dichlorobenzofuroxan is nitrated by HNO_3 and oleum 30% to form 4,6-dichloro-5,7-dinitrobenzofuroxan, one of the most perspective precursors of explosive compounds [162].

Benzisothiazoles, Benzothiazoles, and Benzothiadiazoles

Like 1,2-benzoselenazole [163], 1,2-benzothiazole [164–166] on heating forms a mixture of 5-nitro- and 7-nitro isomers (Scheme 2.17).



Scheme 2.17

The introduction of substituents into the position 3 does not change the reaction course [165, 167–169]. 4-Amino-7-nitrobenzisothiazole in the sulfuric–nitric mixture forms 5,7-dinitro derivative in low yield [170]. 4-Chloro-7-nitro-1,2-benzisothiazole was obtained as a result of the nitration of 4-chloro-1,2-benzisothiazole [171, 172]. 5-Hydroxy-1,2-benzothiazole is nitrated to the position 4, and in case of 5-hydroxy-4,6-dibromo-1,2-benzisothiazole a substitutive nitration to form 5-hydroxy-6-bromo-4-nitro isomer occurs [173].

The main product of the nitration of 2,1-benzisothiazole (thioanthranil) is 5-nitro-2,1-benzisothiazole (57%); however, alongside significant amounts of other isomers such as 7-nitro- (26%) and 4-nitro-2,1-benzisothiazole (17%) are formed [174]. The nitration of several other substituted thioanthranils has also been carried out [128, 174–176].

6-Nitrobenzothiazole is the main product of the nitration of benzothiazoles [177–183]. In several works it has been noted that along with this product some other hardly separable isomers are formed. Ward and Poshe [177] have developed a method to separate mixtures of isomers and showed that on nitration four isomers can be formed (Table 2.1).

2-Substituted derivatives of benzothiazole are also nitrated principally into the position 6 [134, 184–192]. Nevertheless, nitration of 2-aryl-4,7-dimethoxy benzothiazoles results in a mixture of 5- and 6-nitrobenzothiazoles [193]. In 2-phenyl substituted benzothiazoles the nitro group first enters into the benzothiazole cycle [178, 187, 194]. Like 2-aminothiazoles, 2-aminobenzothiazoles first form with the sulfuric–nitric mixture nitramines, which later are rearranged to 2-amino-6-nitrobenzothiazoles. If the benzothiazole position 6 is already occupied by a rather strong electron-withdrawing substituent (NO_2, RSO_2), the nitro group enters into

Table 1 Isomers ratio in the nitration of benzothiazole with sulfuric–nitric mixture

		Yield of isomeric nitrobenzothiazoles (%)			
t (°C)	Total yield (%)	4-NO_2	5-NO_2	6-NO_2	7-NO_2
10±2	83.0	22.6	6.4	49.6	21.3
35±2	91.6	21.4	8.5	50.1	20.0

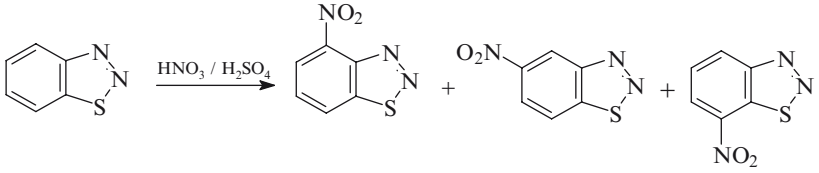
the position 4. Strong electron-donating substituents at the C-6 atom (NH_2, OCH_3) orient the incoming nitro group mainly to the position 7 [194–197]. Nitration of other benzothiazole derivatives has also been carried out [134, 198–202].

As a result of the nitration of benzothiazolones-2 [136, 203, 204] and benzothiazolylthiones-2 [205, 206] with the sulfuric–nitric mixture 6-nitro isomers are obtained.

The nitration of benzothiazoles with ethyl nitrate [207] is analogous to that with the sulfuric–nitric mixture.

Unlike 1,2,3-benzoxadiazoles the existence of which is open to question [208–210], 1,2,3-benzothiadiazoles are well known and their nitration has been described in the literature. On nitration of 1,2,3-benzothiadiazoles with sulfuric–nitric mixture Overberger et al. [211] have obtained 4-nitro-1,2,3-benzothiadiazole.

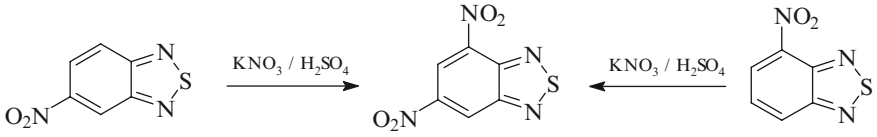
Freis and Reitz, using potassium nitrate in sulfuric acid on heating, have obtained two mononitrated products and assigned to them the structures of 4- and 7-nitro isomers [212]. Later, this structure has been proved by a secondary synthesis [213], and the other isomer turned out to be 5-nitro-1,2,3-benzothiadiazole [214, 215]. On a more careful study all three isomers were found among the reaction products, as shown in Scheme 2.18 [216].



Scheme 2.18

Substituted 1,2,3-benzothiadiazoles are nitrated to the position 5 or 7 if they are vacant [197, 217–219]. The data [218] on the synthesis of 4-nitro-substituted 1,2,3-benzothiadiazoles need to be checked.

Like benzofurazan, 2,1,3-benzothiadiazole is also nitrated to the position 4(7) [220, 221]. If there are electron-donating substituents (CH_3, OH, OCH_3) at the C-5 atom, 4-nitro derivatives are readily obtained in high yield [222–229]. The electron-withdrawing substituents (nitro group) at the same carbon atom direct the incoming nitro group to the 7(4) position [230]. So, on heating 5-nitro- and 7-nitro-2,1,3-benzothiadiazoles turn into 5,7-dinitro-2,1,3-benzothiadiazole (Scheme 2.19).



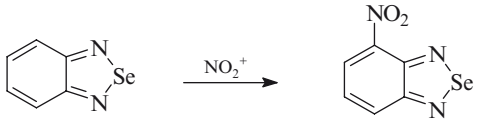
Scheme 2.19

Electron-donating substituents at the C-4 atom direct the incoming nitro group to the position 5 or 7; however, the amount of 7-nitro isomer is higher than that of 4-nitro isomer [222–234]. The direction of the nitration of di- and tri-substituted 2,1,3-benzothiadiazoles is determined by the position and electron nature of substituents [223, 227, 229, 230, 232, 235–239]. *Ipso*-nitration of 4,7-dibromo-2,1,3-benzothiadiazole to form 4-bromo-7-nitroderivative has been reported [235].

Benzoselenazoles and Benzoselenodiazoles

Benzoselenazoles and their derivatives are also nitrated at the position 6 [240, 241]. The nitration can be accompanied by the oxidation of the azole ring, and 6-nitrobenzoselenazolone-2 can be isolated as a by-product.

The nitration of 2,1,3-benzoselenodiazoles proceeds in the same way as with their thio analogs. For example, 2,1,3-benzoselenodiazole, in the sulfuric–nitric mixture, is transformed into a 4-nitro derivative with a yield of 90–98% (Scheme 2.20) [223, 230, 242–245].



Scheme 2.20

From the preparative point of view, especially when working with small amounts of the substrate, it is reasonable to use nitration with a mixture of sodium nitrate and sulfuric acid [245, 246]. This method allows simultaneous introduction of two nitro groups into 4 and 7 positions of the annelated benzene ring. Under nitration of 5,6-disubstituted 2,1,3-benzothia- and 2,1,3-benzoselenodiazoles a regular enhancement of deactivating effect of the substituent on the reactivity of 2,1,3-benzothia- and 2,1,3-benzoselenodiazole is observed (in the following order: $CH_3 < Cl < NO_2$). Under these conditions neither 5,6-dinitro-2,1,3-benzoselenodiazole or its thio analog undergo nitration [246].

The direction of substitution upon nitration of 2,1,3-benzoselenodiazole derivatives [230, 247–249] is the same as that for their thio analogs.

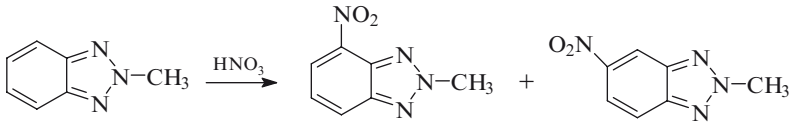
Benzotriazoles

On nitration of unsubstituted benzotriazole the nitro group enters into the position 4(7) [43, 250–254]. 6(5)-Methyl-5,7(4,6)-dinitrobenzotriazole has been synthesized by nitration of 6(5)-methyl-7(4)-nitrobenzotriazole under thermal conditions

and by novel mode – microwave irradiation [255]. Advantages of the microwave irradiation method are shown.

Earlier the nitration of 1-methylbenzotriazole was considered to lead to 7-nitro isomer [250, 252], but later the formation of 1-methyl-4-nitrobenzotriazole was proved [256]. Other 1-substituted benzotriazoles are also nitrated to the position 4 [257–261]. Arguments of Feldman and Usovskii in favor of their synthesis of 5-alkoxy-6-nitrobenzotriazoles turned out to be incorrect [262]; actually, the authors obtained 4-nitro isomers [263]. On boiling in the mixture of sulfuric and nitric acids 1-picrylbenzotriazole is nitrated into 5,7-dinitro-1-picrylbenzotriazole [264]. It is interesting to note that 6-nitro-1-picrylbenzotriazole in nitric acid gives 5,6-dinitro derivative, whereas in sulfuric–nitric mixture 5,6,7-trinitro derivative is formed. In fact, we can prove the formation of the latter only indirectly, since one of the nitro groups is easily substituted by the methoxy group on dissolving the reaction product in methanol [264]. At the same time 1-(2,4-dinitrophenyl)-5-nitrobenzotriazole was obtained from 1-(2,4-dinitrophenyl)benzotriazole with sulfuric–nitric mixture [265]. The main product of the nitration of 5-R-benzotriazole is 5-R-4-nitrobenzotriazole [250, 255, 266, 267].

Previously it was believed that only one 4-nitro isomer was obtained on nitration of 2-methylbenzotriazole [268]; however, later it was shown that the authors dealt with a mixture of 4- and 5-nitro isomers (Scheme 2.21) [269].



Scheme 2.21

Under nitration, benzotriazolyl-2 acetic acid gave only one 4-nitro isomer [270]. The same results were achieved with the nitration of 2-(4-nitrophenyl)benzotriazole [271]. Structure of the nitration products of some benzotriazoles has not been determined till the present time [272].

The use of acetyl nitrate in place of sulfuric–nitric mixture as a nitrating agent leads to 1-nitro derivatives [28]. These compounds have also been obtained by the nitration of 1-chlorobenzotriazole with a silver nitrate complex with trimethylphosphite [273].

1-Hydroxybenzotriazole is nitrated with nitric acid in glacial acetic acid to give 6-nitro derivative, whereas the use of sulfuric–nitric mixture does not lead to positive results [274]. 1- and 2-Aminobenzotriazoles react with nitronium boron fluoride to form nitroimides isolated as alkali metal salts, involving no nitro group in the phenylene fragment [109].

Quantum chemical studies (MP2/cc-pVDZ treatment) of the reactivity of benzazoles indicate the preferred nitration of benzotriazoles and their protonated cations into the 4- and/or 7-position that is in good agreement with the experiment [43].

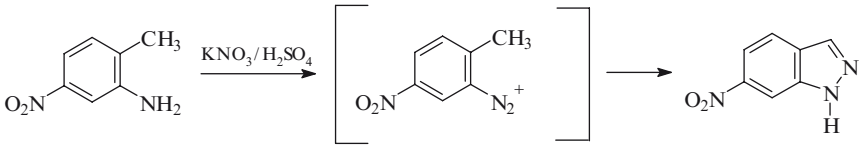
So-called *Kyodai* nitration – a novel methodology of nitration with nitrogen dioxide and ozone – has been applied to several benzimidazoles with formation of 1-nitrobenzimidazoles and following conversion to 1-nitrobenzotriazoles [275].

The nitration of benzotriazole *N*-oxide with dilute nitric acid gives the 7-nitro derivatives, whereas nitration with a mixture of nitric and acetic acids leads to 5-nitro- and 7-nitro isomers in a ratio of 1:9 [276].

Synthesis of Nitrobenzazoles via Heterocyclization

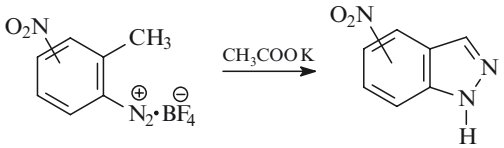
Nitroindazoles

The reactions of heterocyclization also have a wide preparative usage in the synthesis of nitrobenzazoles. Here, the nitro group first enters into one of the fragments from which the heterocyclic system is being built. In this case the presence of the nitro group often influences much of the course of the process. The diazotization of *ortho*-toluidine results in the formation of indazole in a yield not more than 5%. At the same time, 4-nitro-2-aminotoluene under the same conditions transforms to 6-nitroindazole in high yield, as shown in Scheme 2.22 [277–279].



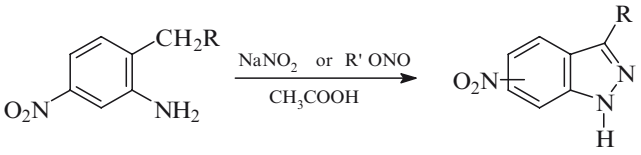
Scheme 2.22

4-Nitro- [280], 5-nitro- [277, 278, 281], and 7-nitroindazoles [278, 280, 282–285] are obtained in an analogous manner. The diazonium salt, obtained from 2-amino-6-nitro-*meta*-xylole, gives a mixture of 7-methyl-4-nitro- and 7-methyl-6-nitroindazole. It should be noted that the reaction of diazotization of *ortho*-toluidines, having other substituents apart from the nitro group, is often used to obtain different nitroindazoles [11, 18–22, 24, 25, 279, 280, 286, 287]. An original method of the synthesis of nitroindazoles involves the reaction of *ortho*-tolyldiazonium tetrafluoroborate with potassium acetate in the presence of crown ethers (18-crown-6) (Scheme 2.23) [288–290]. The reaction of cyclization has a high rate at room temperature (yield 60–90%).



Scheme 2.23

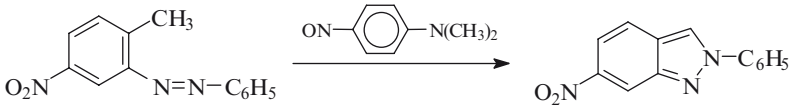
The diazotization of 2-alkylaminoanilines containing the nitro group in the phenyl ring leads to 3-substituted indazoles (Scheme 2.24) [11, 17, 282, 291, 292].



R = CH_3, CF_3, R' = Alk

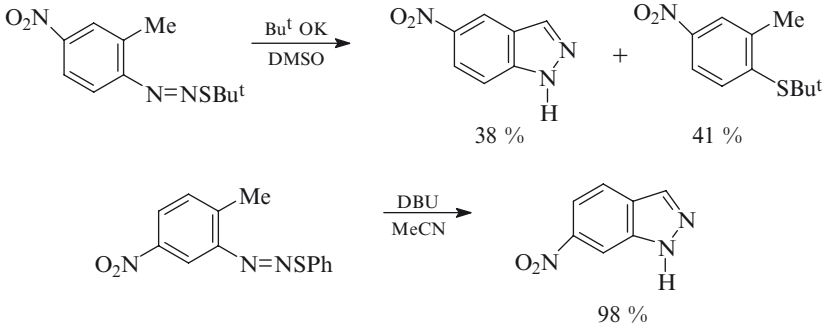
Scheme 2.24

Diazoamino compounds are formed, and sometimes they can be obtained as intermediates [282]. In some cases nitroindazoles as by-products are determined on diazonation of nonnitrated *ortho*-toluidines with isoalkylnitrite [293]. 2-Phenylazo-4-nitrotoluene gives 2-phenyl-6-nitroindazole on boiling with *para*-nitrosodimethylaminobenzene (Scheme 2.25) [294].



Scheme 2.25

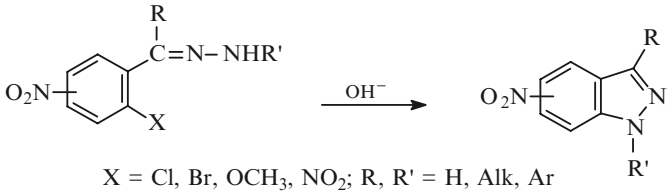
In this case the activation of the methyl group by the nitro group is a necessary reaction condition. Moreover, the nitro group has to be in the *ortho*- or *para*-position to the methyl group [294, 295]. If it is in the *meta*-position, no indazole is formed. This is in good agreement with larger yields of 6-nitroindazole in comparison with the ones of 5-nitroindazole (Scheme 2.26) [296].



Scheme 2.26

It means that more drastic reaction conditions are necessary for the cyclization with a methyl group in the *meta*-position.

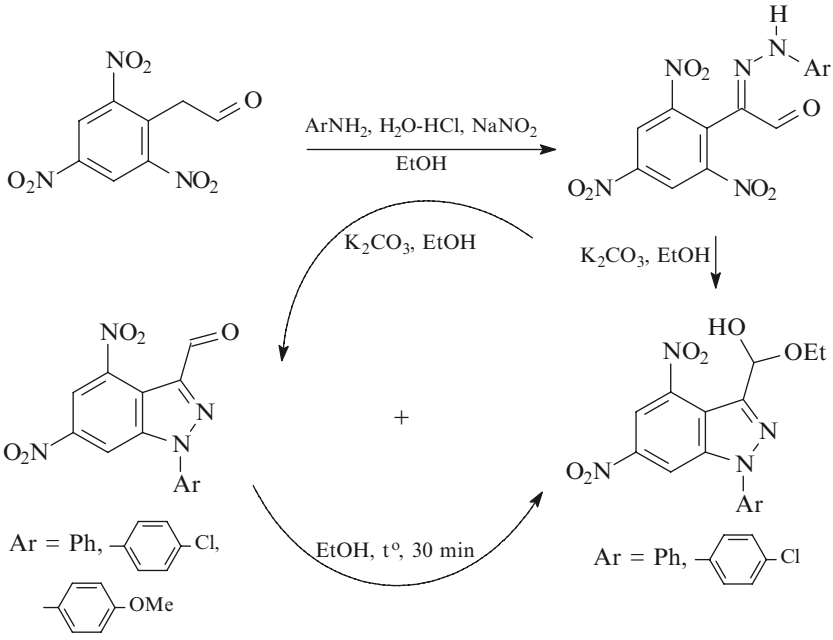
Another widespread synthetic route to nitroindazoles is the reaction of intermolecular cyclization of *ortho*-substituted arylhydrazones, as shown in Scheme 2.27 [10, 297–304].



Scheme 2.27

Besides, in this case the aromatic ring nitro group influences the reaction pathway much. 2-Bromobenzophenone, when heated up to 200°C with hydrazinium hydrate, gives 3-phenylindazole in a very small yield, whereas bromo-5-nitrobenzophenone reacts at 140°C to form 5-nitro-3-phenylindazole in a yield of 65% [298]. In analogous conditions the corresponding indazole is obtained from 2-bromo-3,5-dinitrobenzophenone in high yield [298].

1-Aryl-4,6-dinitroindazoles are obtained by treatment with alkaline metal carbonates of the corresponding hydrazones [302–304]. The latter are formed from picryl acetal aldehydes with aryldiazonium salts. Scheme 2.28 demonstrates that

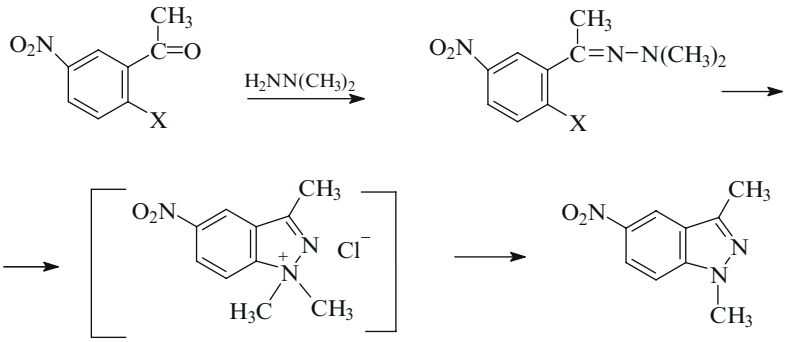


Scheme 2.28

the cyclization of hydrazones occurs due to intramolecular nucleophilic substitution of the nitro group.

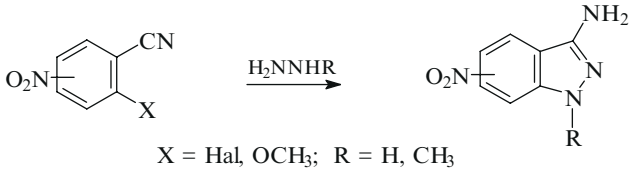
Stable semiacetals can be formed in parallel with dinitroformylindazoles in the absence of electron-donating groups such as 4-MeO-C_6H_4, for example, in the *N*-aryl substituent. Dinitroformylindazoles readily transform to the corresponding semiacetals when boiled in ethanol for 30 min. At the same time, on heating of crystalline semiacetal (Ar = Ph) in the air (80°C, 8 h) an ethanol molecule is abstracted and the corresponding dinitroformyl indazole is regenerated [302, 303].

The pathway of the reaction of 2-chloro-5-nitrobenzophenone with excess *N,N*-dimethylhydrazine is rather interesting (Scheme 2.29). In this case 1,3-dimethyl-5-nitroindazole is formed fast and in high yield [305].



Scheme 2.29

When boiled with hydrazine hydrate, the esters of nitrated *ortho*-halogenobenzene acids transform to corresponding nitroindazolones-3 [306, 307]. 2-Halogeno- or 2-methoxy-X-nitrobenzonitriles are also involved in an analogous reaction (Scheme 2.30) [308–314].

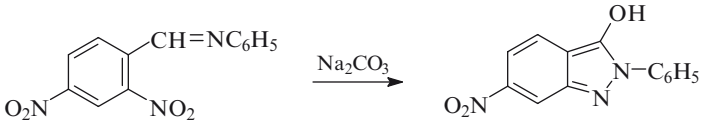


Scheme 2.30

It should be noted that in earlier publications the reaction products were wrongly assigned a structure of 2-cyano-4-nitrophenylhydrazine [308–310] (see [312]).

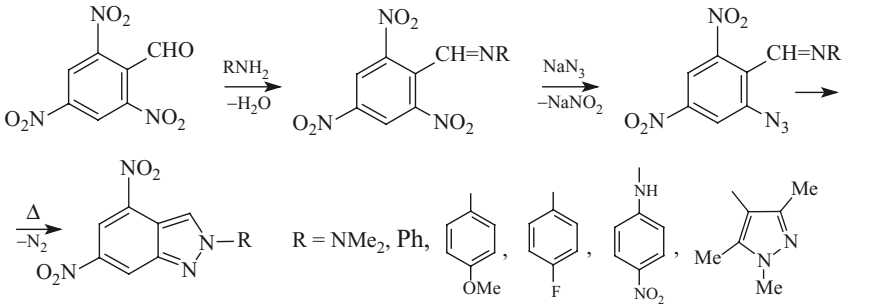
To simplify the synthetic technology of 3-amino-5-nitroindazole and to improve the target product quality it is reasonable to use 2-cyano-4-nitroaniline. The latter is subjected to diazotization, and the azo compound thus formed is reduced with simultaneous closure of the indazole cycle with sulfur dioxide in 5–15% sulfuric acid [315].

There are some ways of preparing nitroindazoles by the reactions of heterocyclization and recyclization. For example, if some Schiff's bases containing a nitro group in the *ortho*-position to the methylene fragment are boiled in an ethanolic sodium carbonate solution, nitro derivatives of indazole are formed (Scheme 2.31) [285, 316–318].



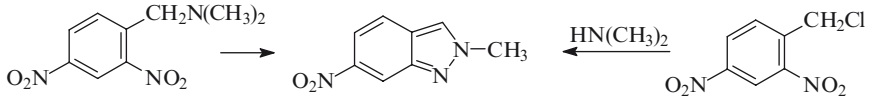
Scheme 2.31

Chemical utilization of explosive 2,4,6-trinitrotoluene (TNT) can lead to 4,6-dinitroindazoles. An original method of preparing 2-substituted 4,6-dinitroindazole involves the formation of *C*-(2,4,6-trinitrophenyl)-*N*-R-azomethines from TNT or the product of its transformation, 2,4,6-trinitrobenzaldehyde with further regiospecific substitution of the nitro group under the action of NaN_3 [319]. Thermolysis of the azides in ethylene glycol at 150–180°C gives the corresponding 4,6-dinitroindazole derivatives in high yields (Scheme 2.32) [319].



Scheme 2.32

An interesting event of intermolecular cyclization has been found on nitrating 4-nitrobenzyldimethylaniline [320]. On standing, the 2,4-dinitro-*N,N*-dimethylbenzylamine formed spontaneously transforms to 2-methyl-6-nitroindazole, which is also obtained in the reaction of dimethylamine with 2,4-dinitrobenzylchloride (Scheme 2.33).

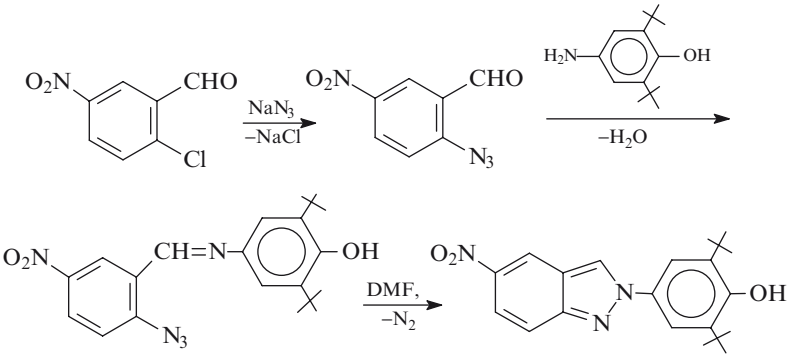


Scheme 2.33

Previously, 2-methyl-6-nitroindazole *N*-oxide was suggested to be the reaction intermediate. However, it was not possible to determine its formation in the

experimental conditions by means of IR and NMR spectroscopy [321]. That is why a more probable reaction pathway seems to be as follows. The reaction is catalyzed with bases and slowed down with acids that prove the suggested Scheme [321].

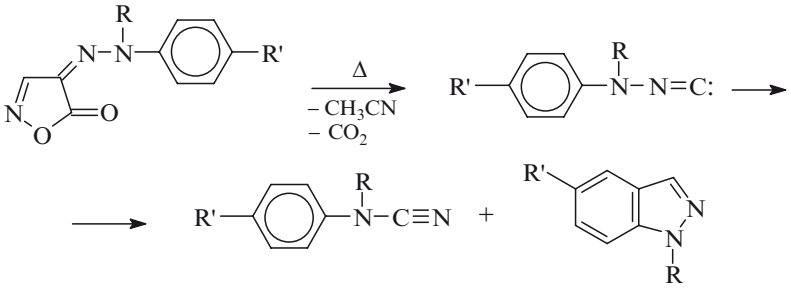
For the synthesis of antioxidants containing fragments of sterically hindered phenol and indazole a method involving thermal decomposition of 2-azidobenzylidenamines to 1,2-dichloro- or 1,2,4-trichlorobenzene and resulting in 2-substituted indazoles was used [321]. So, as seen from Scheme 2.34, 2-chloro-5-nitrobenzaldehyde gives the corresponding azidoaldehyde and then 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-nitroindazole.



Scheme 2.34

Intermediate azomethine could not be isolated. Heating of *N*-(2-azido-5-nitrobenzyliden)aniline in dimethylformamide affords to 2-phenyl-5-nitroindazole, the structure of which has been confirmed by X-ray diffraction [322].

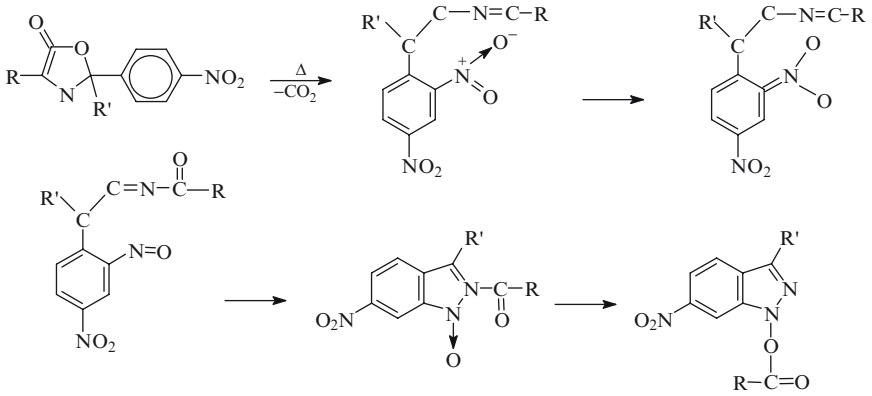
The pyrolysis of 4-arylhydrazono-3-methylisoxazolone-5 forms isocyanoamines, which undergo rearrangement to cyanoamides and corresponding indazoles (Scheme 2.35). Among other compounds 5-nitroindazole was obtained in an analogous way [323].



Scheme 2.35

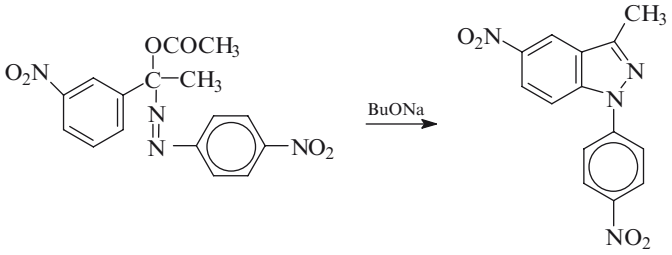
2-(2,4-Dinitrophenyl)-3-oxazolinones-5 behave in a similar way on heating: the elimination of carbon dioxide leads to (2,4-dinitrophenyl)-nitrylimide from which (2-nitrozo-4-nitrophenyl)-*N*-acylimine is formed after intermolecular oxygen

migration. The *N*-acylimine undergoes cyclization to unstable 2-acetyl-6-nitroindazole *N*-oxide with a fast migration of the acyl group to 3-substituted 1-acyloxy-6-nitroindazole (Scheme 2.36) [324].



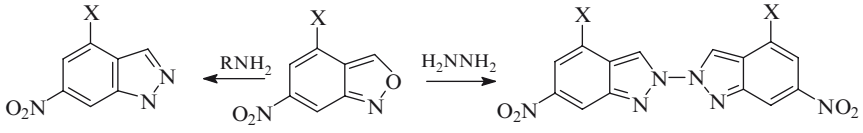
Scheme 2.36

α-Methyl-3-nitro-4-nitrophenylazobenzylacetate on heating with sodium butoxide transforms to 3-methyl-5-nitro-1-(4-nitrophenyl)indazole (Scheme 2.37), but the yield of the final product is 15% in this case [300].



Scheme 2.37

6-Nitroanthranils react with primary amines or with phenylhydrazine to form 2-substituted 6-nitroindazoles [325, 326]. 6,6′-Dinitro-2,2′-bis-indazolyls were obtained in the reaction with hydrazine (Scheme 2.38) [325, 326].

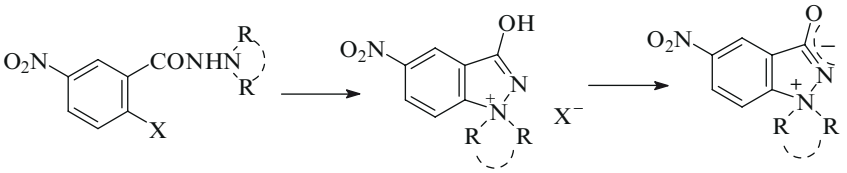


X = H, Cl, Br, I; R = C_6H_5, C_6H_5NH

Scheme 2.38

Nitroindazolones are prepared on heating from the corresponding 2-bromo-3-nitrobenzoates with hydrazine hydrate [327].

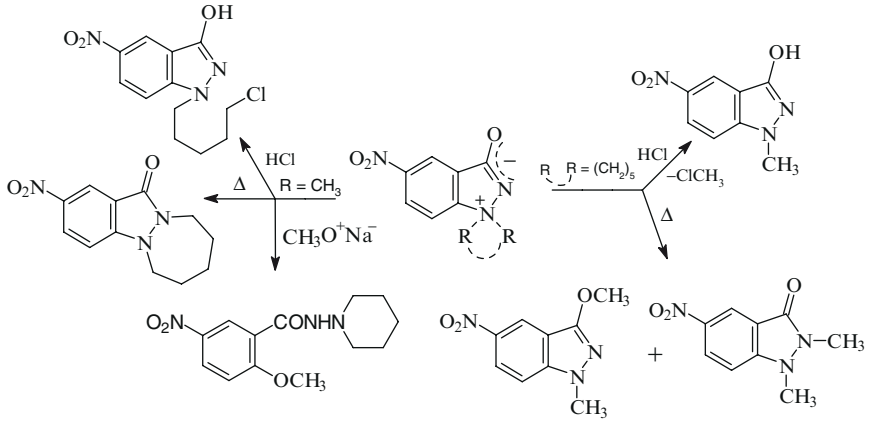
Stable nitroindazolyl-3 oxides (betaines) were obtained in 80–90% yield from the corresponding 2-halogenobenzohydrazides (Scheme 2.39); moreover, from chlorobenzohydrazides betaines are formed in more rigorous conditions [328].



X = F, Cl; R = CH_3, C_2H_5

Scheme 2.39

The treatment of betaines with concentrated sulfuric acid leads to the corresponding derivatives of 5-nitroindazole (products of alkylhalogenides elimination). Heating of betaines results in other nitroindazoles: a product of Steven's rearrangement or a mixture of *N*,*O*- and *N*,*N*-alkyl shift products, as shown in Scheme 2.40 [328].



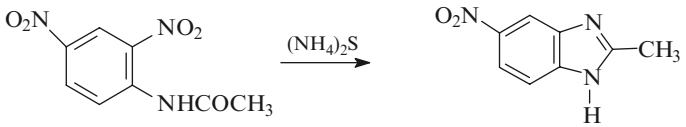
Scheme 2.40

Nitrobenzimidazoles

Benzimidazoles containing nitro group in the arylene fragment are obtained in the reaction of carboxylic acids or their derivatives with nitro-substituted 1,2-diaminobenzenes. This method is especially often used for the synthesis of 4-nitro- and 7-nitrobenzimidazoles, since the latter cannot be obtained by direct nitration of benzimidazoles. In most cases the reaction is carried out in the presence of HCl (the Phillips reaction) [46, 47, 52, 53, 75, 79, 100, 329–340]. Nitrobenzimidazoles

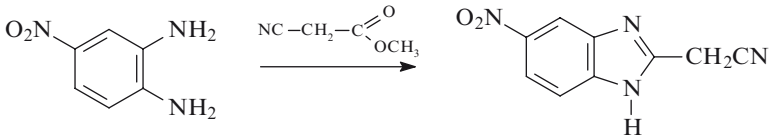
can also be obtained by simple boiling of 1,2-phenylendiamine nitro derivatives with excess lower aliphatic acids (formic or trifluoroacetic acid, for example) [61, 341–344]. Sometimes nitrobenzimidazoles can be obtained by heating the nitrated *ortho*-phenylendiamines, but in this case more rigorous conditions should be applied (the yields are significantly lower) [50, 345–347]. The cyclization is even a more difficult process when aromatic or heterocyclic acids are used [345]. In these conditions polyphosphoric acid is used as a condensing agent [329–340, 348]. Derivatives of acids may be employed in the synthesis of nitrobenzimidazoles in place of the acids themselves. More often anhydrides or chloroanhydrides are used for this purpose [44, 45, 50, 59, 256, 341–344, 349–352]. Usually this reaction is carried out in two stages: acylation of the correspondent 1,2-diaminonitrobenzenes with anhydrides or chloroanhydrides of carboxylic acids followed by cyclization of the forming *ortho*-aminoacylanilines [45, 50, 256, 349–353]. 1,2-Diaminobenzene nitro derivatives react with iminoesters [59, 354–362], nitriles [360, 363], hydrazides [364], and *ortho*-esters [365, 366] to form nitrobenzimidazoles.

A reaction of 4-nitro-1,2-phenylendiamine with benzotrichloride in the presence of sodium methylate [367] has been described. In this case 2-phenyl-5(6)-nitrobenzimidazole is obtained without preliminary extraction of the *ortho*-ester of benzoic acid. Sometimes acylated polynitroanilines, with one of the groups in the *ortho*-position to the amino group, are used as the initial products. On partial reduction of such compounds the cyclization to benzimidazoles takes place [85, 368]. For example, the reduction of 2,4-dinitroacetanilyde with ammonium sulfide has afforded 2-methyl-5(6)-nitrobenzimidazole (Scheme 2.41) [85].



Scheme 2.41

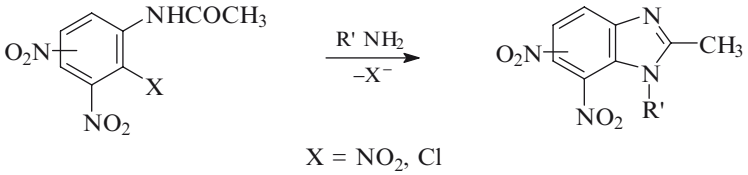
5(6)-Nitro-2-cyanomethylbenzimidazole, an intermediate in the synthesis of cyanine dyes, was prepared from 1,2-diamine-4-nitrobenzene and methyl cyanoacetate in nitrobenzene (Scheme 2.42) [369].



Scheme 2.42

The introduction of the nitro group in azoles leads to a long-wave shift of the visible absorption maximum and an enhancement of the sensitizing properties of cyanine dyes. A long-wave shift of the sensitivity of photographic materials is observed as well [369].

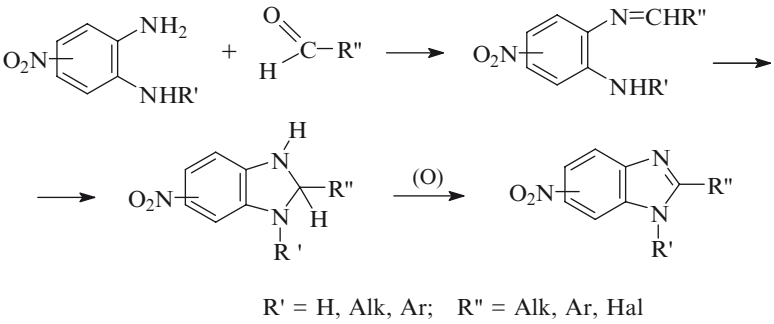
7-Nitrobenzimidazoles can be obtained in the reaction of primary amines with 2-R-3-nitroacetanylides (Scheme 2.43). On nucleophilic substitution the forming 2-NHR-3-nitroacetanylides transform to benzimidazoles without isolation [370].



Scheme 2.43

An interesting reaction has been described by Simonov and his colleagues [371]. Studying the reaction of some aromatic *ortho*-dinitro- and trinitrocompounds with benzylamine they have discovered that under special conditions the reaction of substitution of the nitro group with the benzylamine group is accompanied by reduction of the second nitro group and cyclization into 2-phenylbenzimidazole derivatives. In this case benzyl alcohol forming from benzylamine serves as a reducer. By the way it was obtained 4,5-dimethoxy-7-nitro-2-phenylbenzimidazole in 89% yield from 3,4,5-trinitroveratrole [371].

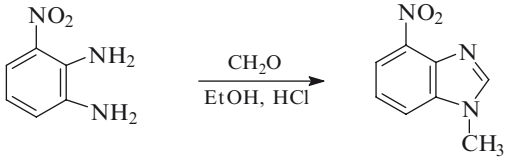
The reaction of 1,2-diaminonitrobenzenes with aldehydes is a widely accepted synthetic route to nitrobenzimidazoles [57, 62, 63, 66, 350, 372–383]. This reaction passes sequentially through a stage of the formation of azomethines (Schiff's base) and benzimidazolines. On oxidation the latter forms the corresponding benzimidazole derivatives (Scheme 2.44).



Scheme 2.44

Copper (II) salts are often used here as an oxidizer [62, 63, 66, 350, 374–379, 381–383], and atmospheric oxygen can also be used for this purpose [383]. For the preparation of nitrobenzimidazole derivatives the corresponding Shiff's bases are often boiled [57, 62, 63, 66, 372, 373, 380].

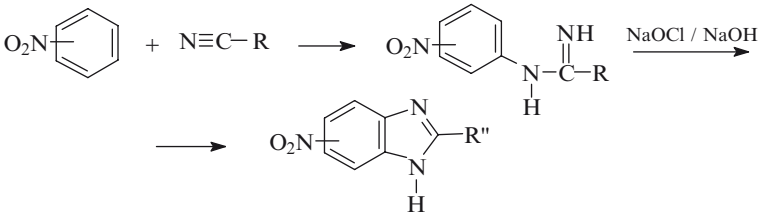
An easy and convenient method has been employed for the synthesis of 1-methyl-4-nitrobenzimidazole (Scheme 2.45) [384].



Scheme 2.45

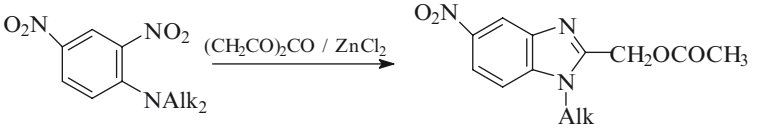
A one-stage reaction of 3-nitro-1,2-phenylendiamine with formaldehyde in an ethanol solution of hydrochloric acid leads to the formation of nitrobenzimidazole in high yield (77%) [384].

Nitroanilines react with organic cyanides in the presence of dry aluminum chloride. Under the influence of sodium hypochlorite in the presence of a base, the resultant amidines undergo cyclization to the corresponding benzimidazoles (Scheme 2.46) [385–388].



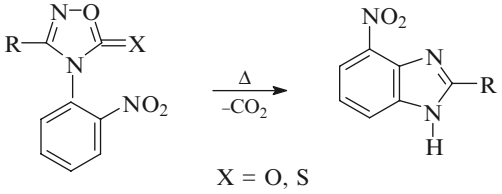
Scheme 2.46

2,4-Dinitroalkylanilines react with acetic anhydride in the presence of zinc chloride to form 2-acetoxymethyl-1-alkyl-5-nitrobenzimidazoles (Scheme 2.47) [389].



Scheme 2.47

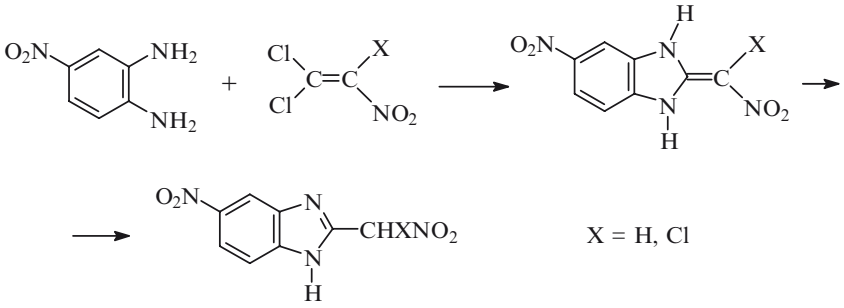
On thermal decomposition 3-substituted-4-nitrophenyl-1,2,4-oxadiazolones-5 form 2-substituted-4-nitrobenzimidazoles (Scheme 2.48) [390–393].



Scheme 2.48

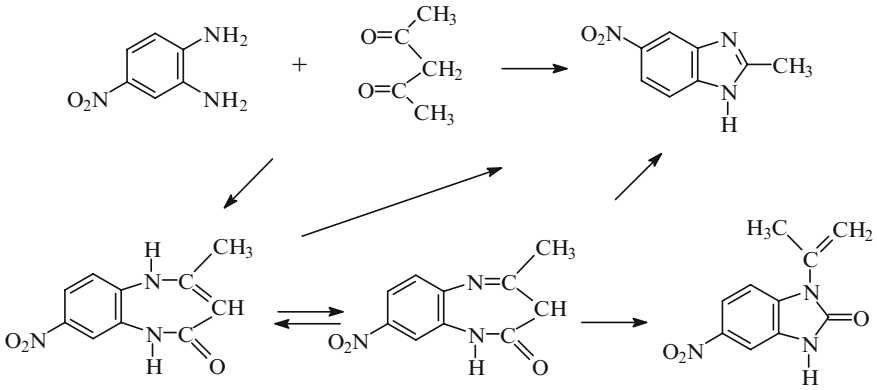
The reaction of *N*-butyl-2,4,6-trinitroaniline with NaOH in 60% 1,4-dioxane/H_2O affords 5,7-dinitro-2-propylbenzimidazole 3-oxide [394].

1,1-Dichloro-2-nitroethylene and trichloronitroethylene react with 4-nitro-1,2-phenyldiamine to afford nitrobenzimidazoles with the nitro group in both the phenylene fragment and side chain [395]. Evidently, the reaction mechanism consists in nucleophilic substitution of halogen atoms at the multiple bonds with subsequent prototropic rearrangement to the benzimidazole system, as shown in Scheme 2.49.



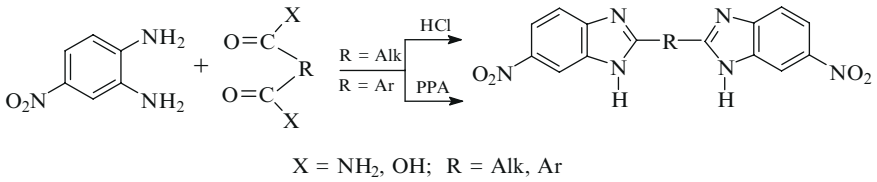
Scheme 2.49

2-Methyl-5-nitrobenzimidazole is formed on heating 4-nitro-1,2-phenylendiamine and its derivatives with the ester of acetoacetic acid (Scheme 2.50) [396, 397]. Depending on the experimental conditions, isomeric 8-nitro-4-methyl-2,5-dihydro-1*H*-1,5-benzodiazepinone-2 and 8-nitro-4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepinone-2 easily transform into each other, and 5-nitro-1-isopropenylbenzimidazolone can be obtained (in this case).



Scheme 2.50

In a similar manner the bis(5-nitrobenzimidazolyl-2) derivatives were obtained (Scheme 2.51) [398].

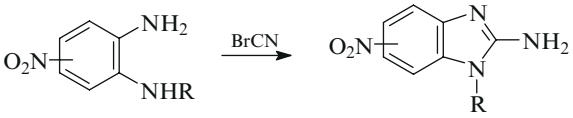


X = NH_2, OH; R = Alk, Ar

Scheme 2.51

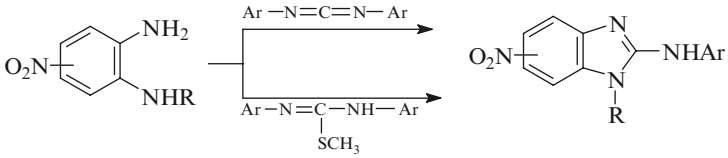
In the synthesis of aromatic derivatives polyphosphoric acid is used [398]. The synthesis of 1-(5-nitrobenzimidazolyl)-3-benzimidazolyl-2-oxapropane by the reaction of 4-(2-benzimidazolyl)-2-oxabutanoic acid hydrochloride and 4-nitro-*ortho*-phenylendiamine has been reported [399].

Like unsubstituted *ortho*-phenylendiamine, its nitro derivatives react with bromocyane to form the corresponding 2-aminobenzimidazoles (Scheme 2.52) [400–403].



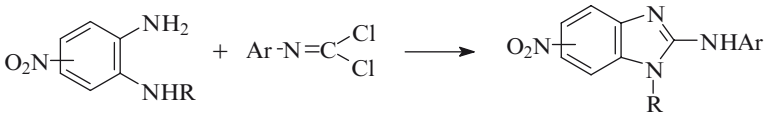
Scheme 2.52

Diarylcarbodiimines or derivatives of *S*-methylurea react with nitrated 1,2-diaminobenzenes in a similar way to lead to 2-arylaminobenzimidazoles (Scheme 2.53) [404, 405].



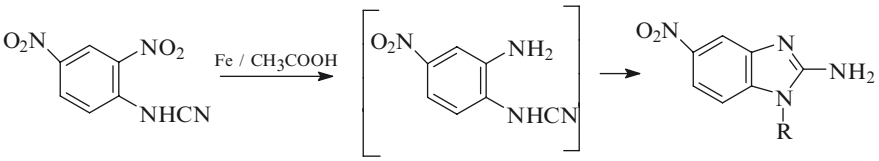
Scheme 2.53

The same products can be obtained with carboimidoyldichlorides as a reagent (Scheme 2.54) [406].



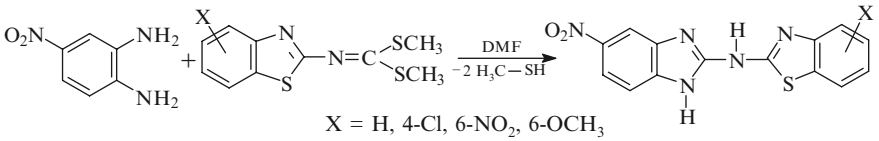
Scheme 2.54

A convenient synthesis of 2-amino-5(6)-nitrobenzimidazole involves reductive cyclization of 2,4-dinitrophenylcyanamide (Scheme 2.55) [407, 408].



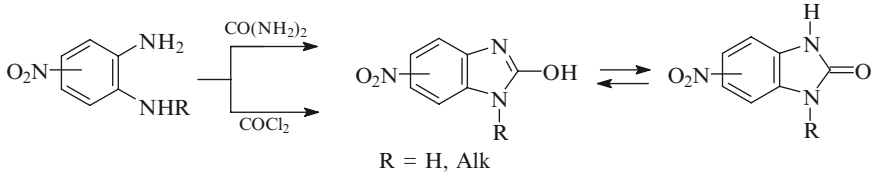
Scheme 2.55

2-(5-Nitrobenzimidazolyl-2-amino)-benzothiazoles are obtained from *ortho*-phenylenediamines and *S,S*-dimethyl-*N*-(2-bensothyazolyl)-carbonimido-dithioates in dimethylformamide (Scheme 2.56) [409].



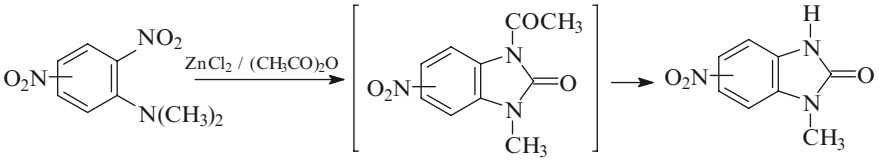
Scheme 2.56

The most widely spread synthetic route to benzimidazolone-2 nitroderivatives is provided by the reaction of *ortho*-phenylenediamine with phosgene or urea (Scheme 2.57) [105, 405, 407, 408, 410–412].



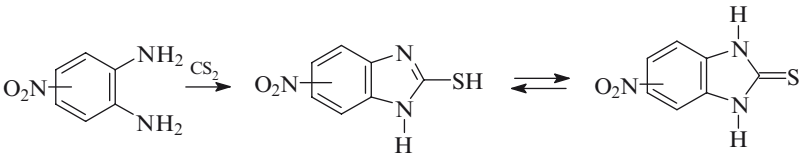
Scheme 2.57

1-Methyl-5- or 6-nitroderivatives were obtained as a result of intermolecular cyclization of *N,N*-dimethyl-2-nitro-5- or 5-nitroaniline with zinc chloride in acetic anhydride (Scheme 2.58) [411].



Scheme 2.58

Benzimidazolthione-2 nitroderivatives are obtained in a similar way under the influence of CS_2 (Scheme 2.59) [100, 407, 408, 413].

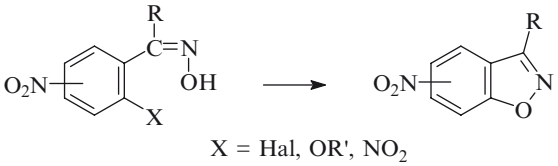


Scheme 2.59

A simple method for the preparation of 5-nitrobenzimidazolone-2, based on chemical [407, 408] or electrochemical reduction of 2,4-dinitrophenylurea [414], has been proposed. The electrochemical reaction occurs in a cell with an interelectrode space in aqueous solution of mineral acid at 85–95°C in the range of potentials from 0 to −200 mV relative to the silver electrode.

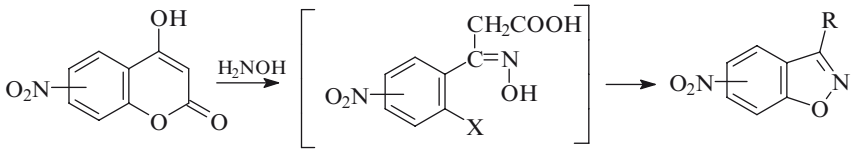
Nitrobenzisoxazoles, Nitrobenzoxazoles, and Nitrobenzoxadiazoles

The main method of producing 1,2-benzisoxazoles with the nitro group in the arylene fragment of the molecule is intermolecular condensation in an alkaline medium of the corresponding oxymes containing an easily eliminated group in the *ortho*-position (Scheme 2.60) [119, 298, 415–424].



Scheme 2.60

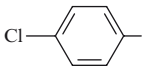
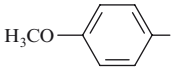
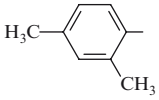
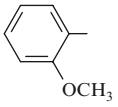
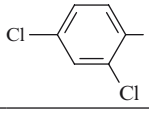
The same is true for halogens (bromine in most cases), hydroxy-, aryloxy-, or nitro group. The reaction of 4-hydroxycumarines with hydroxylamine proceeds in the same way (Scheme 2.61) [167, 419].



Scheme 2.61

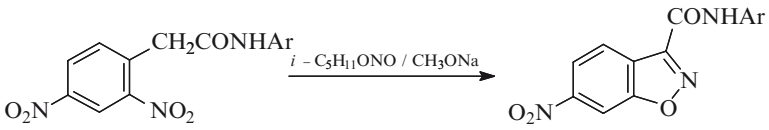
An attempt to substitute hydroxynitrocumarines by nitrocumarines failed: the yield of the final products fell to 5–17% [425].

Table 2 Characteristics of 3-substituted 6-nitro-1,2-benzisoxazoles

Ar	Yield (%)	mp (°C) (recryst.)	Ar	Yield (%)	mp (°C) (recryst.)
	60	214–216 (benzene)		50	236 (alcohol/ acetic acid)
	58	205–206 (CCl_4)		50	220–222 (alcohol/ acetic acid)
	40	211–214 (CCl_4)		65	228–230 (alcohol/ acetic acid)
	50	202 (CCl_4)		57	232 (alcohol/acetic acid)

In 1912, Borsche found out that the esters and amides of 6-nitro-1,2-benzisoxazole-3-carboxylic acid could be obtained in high yield in the reaction of isoamylnitrite with 2,4-dinitrophenylacetic acid derivatives in the presence of sodium methoxide [426].

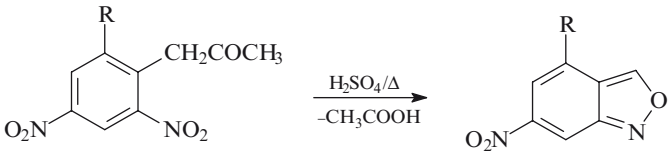
This reaction was successfully used for the preparation of arylamides of 6-nitro-1,2-benzisoxazole-3-carboxylic acid (Scheme 2.62 and Table 2.2) [427, 428].



Scheme 2.62

6-Nitro-1,2-benzisoxazolylketones can be obtained in an analogous manner [426]. 5-Nitrosalicilic aldehyde in an acid medium reacts with HN_3 to form a mixture of 5-nitro-1,2-benzisoxazole and 5-nitrobenzoxazole [429] – the latter being formed from 5-nitrosalicylic acid nitryl, a product of 5-nitro-1,2-benzisoxazole hydrolysis.

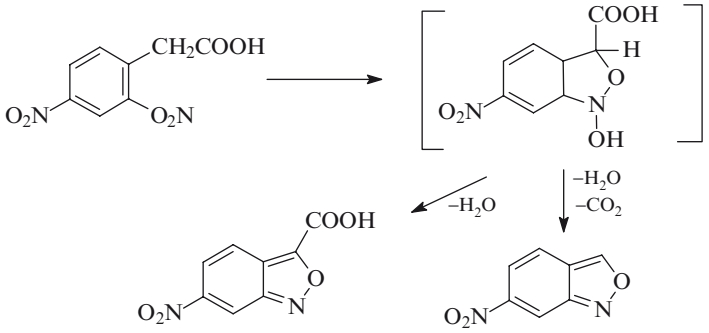
On heating with concentrated sulfuric acid 2,4-dinitrophenylacetone turns into 6-nitro-2,1-benzisoxazoles (Scheme 2.63) [430].



R = Cl (50 %), Br (49 %), I (46 %)

Scheme 2.63

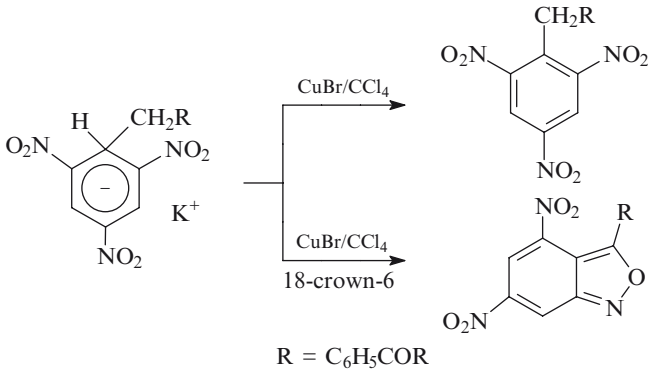
2,4-Dinitrophenylacetic acid reacts in a similar way and involves partial decarboxylation to form a mixture of 6-nitroanthranil-3-carboxylic acid and 6-nitroanthranil [431–433]. The reaction mechanism is a nucleophilic attack of the methylene carbon by the nitro group oxygen atom, as shown in Scheme 2.64. The formed cyclic product undergoes dehydration or dehydration with simultaneous decarboxylation.



Scheme 2.64

The methylene ester of 6-nitro-2,1-benzoxazole-3-carboxylic acid is obtained in a similar manner [434]. The reaction of oxidation of 1,3,5-trinitrobenzene σ-complexes, containing the C–C bond in the side chain, follows an interesting pathway [434].

Under the influence of oxidizing systems [copper(I) bromide – CCl_4] these systems are oxidized into the corresponding 1,3,5-trinitrobenzene derivatives, whereas in the presence of the same system and crown esters (e.g., 18-crown-6) 4,6-dinitroanthranils are formed (Scheme 2.65). So, the presence of the group in the geminal center of the σ-complex is a necessary condition for conversion of this type [435].

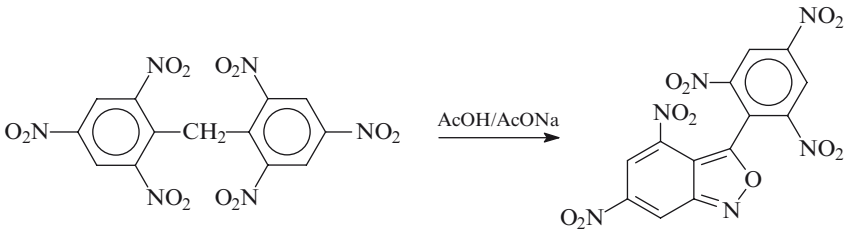


Scheme 2.65

3-Aryl-6-nitroanthranils are obtained on heating of 2,4-dinitrobenzaldehydes in sulfuric acid or polyphosphoric acids with aromatic carbohydrates [436–440]. Reductive heterocyclization of 2,6-dinitrobenzaldehyde in the presence of 2-bromo-2-nitropropane

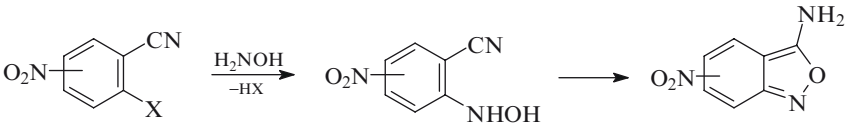
and indium (2:5) in an MeOH/H_2O solution leads to 4-nitro-2,1-benzisoxazole in good yield [425]. 3,6-Dichloro-2,5-dinitro-*p*-xylol on heating in oleum transforms to 4,7-dichloro-5-nitro-6-methyl-2,1-benzisoxazole [442, 443].

In the reaction with sodium acetate 2,2′,4,4′,6,6′-hexanitrodiphenylmethane undergoes an intermolecular cyclization, giving in a good yield 3-picryl-4,6-dinitroanthranil, a rather thermally stable explosive (Scheme 2.66) [444].



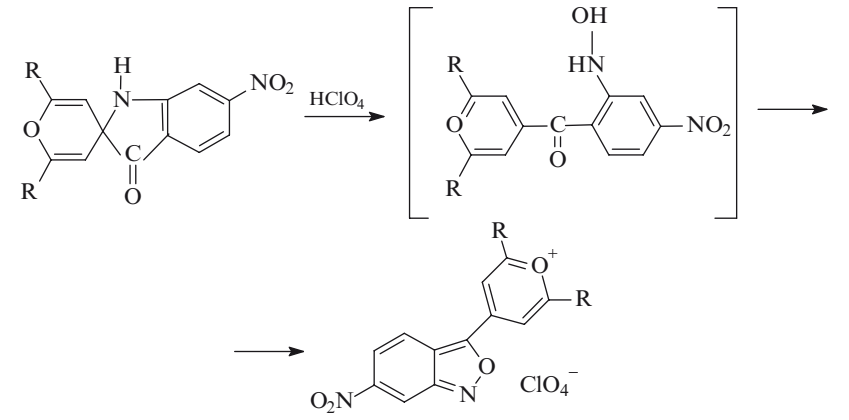
Scheme 2.66

2,1-Benzisoxazoles are obtained from *ortho*-nitroacetylbenzenes in the reaction with 3-phenylphosphate. 2-Amino-4-nitropropiophenone was obtained in the presence of a nitro group in the benzene ring along with nitroanthranil [445]. In hydrochloric acid the cyclization is accompanied by chlorination of the phenylene fragment [446]. The nitriles of *ortho*-halogenonitrobenzoic acids react with hydroxylamine to form nitrated 3-amino-2,1-benzisoxazoles (Scheme 2.67) [447].



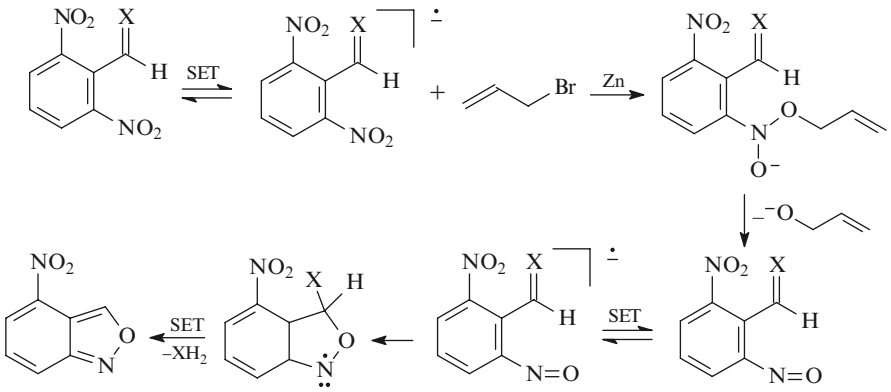
Scheme 2.67

(6-Nitro-2,1-benzisoxazolyl-3)pyrilium perchlorates have been obtained from the corresponding oxaspiroindolines (Scheme 2.68) [448].



Scheme 2.68

A mild and novel reaction route to 2,1-benzisoxazoles from 2-nitrobenzaldehydes in the presence of allyl bromide and zinc dust has been established [449]. The reductive cyclization of 2,6-dinitrobenzaldehyde was strongly retarded probably because of the inhibitory effect of the second nitro group [441, 449]. The authors assume a radical mechanism of the reaction, as demonstrated in Scheme 2.69 [449].



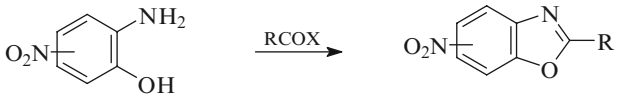
SET – single electron transfer, X = O, N-Ph

Scheme 2.69

This way would provide a useful synthetic technique along with reductive *N*,*O*-diallylation of nitrobenzene.

6-*tert*-Butyl-5-methoxy-4-nitro-2,1-benzisoxazole along with other products have been isolated on photolysis of 4-*tert*-butyl-3-methoxy-2,6-dinitrotoluene [450].

Nitrobenzoxazoles possessing nonlinear optical properties [451], like their nonnitrated analogs, are easily obtained in the reaction of the corresponding *ortho*-aminophenols with carboxylic acids [452–458], aldehydes [459, 460], or chloroanhydrides [134, 461–464] (Scheme 2.70).



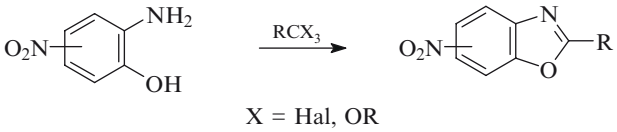
X = H, OH, Cl

Scheme 2.70

Mono- or diacyl derivatives that undergo cyclization to benzoxazoles on heating or under the influence of dehydrating agents are formed as intermediates in this reaction [134, 452, 453, 459, 461–473]. Phosphorus oxychloride [453, 457], boric anhydride [455, 461, 462], or polyphosphoric acid [134, 471] are used as condensing agents. In particular, 2-hydroxy-5-nitrobenzoxazole, used for the synthesis of antivirus medicines, has been obtained by the reaction of condensation of 4-nitro-2-aminophenol with $(NH_2)_2CO$ in pyridine [474].

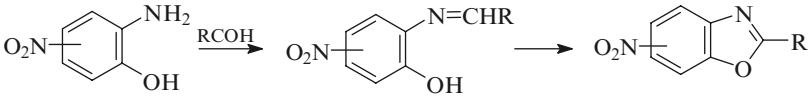
To prepare 2-trichloromethylbenzoxazole, nitrated *ortho*-aminophenoles are treated with iminoesters of trichloroacetic acid [52, 475, 476]. Some other 2-substituted nitrobenzoxazole derivatives were obtained in the same way [134, 360, 361].

For the formation of the benzoxazole cycle, compounds containing trichloromethyl [477, 478] or trialkoxymethyl groups can be made use of (Scheme 2.71) [478–480].



Scheme 2.71

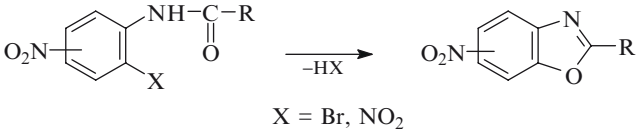
Nitrated *ortho*-aminophenols react with aldehydes to form Schiff's bases, which are easily oxidized into the corresponding benzoxazoles (Scheme 2.72) [481].



Scheme 2.72

Lead acetate [134, 482–484], nickel peroxide [445, 485, 486], and some other substances [487–489] are used as oxidants in most cases.

Sometimes, the corresponding *ortho*-bromo- or *ortho*-nitroacylanilides are used in place of aminophenols for the synthesis of nitrobenzoxazoles (Scheme 2.73) [490, 491].



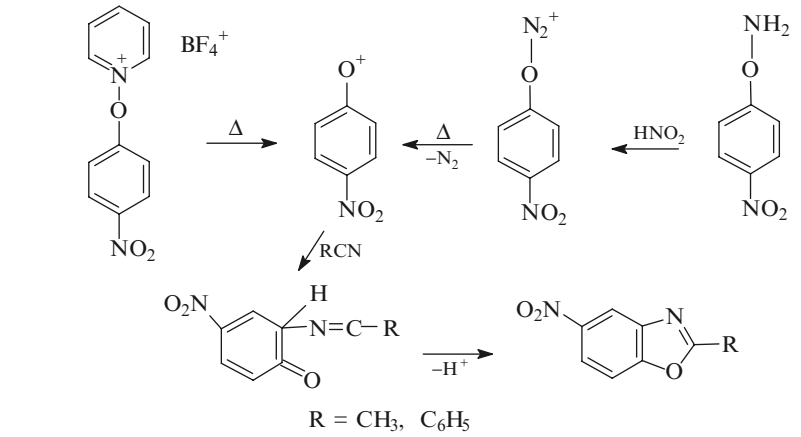
Scheme 2.73

N-aryloxypyridinium salts or diazotized aryloxyamines on heating generate aryloxene ions, which turn into benzoxazoles in the presence of acetonitrile or benzonitrile, as shown in Scheme 2.74 [492, 493].

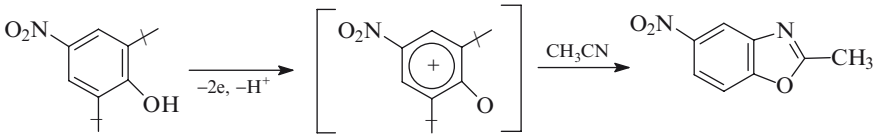
Suschitzky et al. have proposed an original synthesis of benzoxazole nitro derivatives in a mixture of carboxylic and polyphosphoric acids by heating aromatic aldehydes containing the nitro group in the *para*-position [471].

7-*tert*-Butyl-2-methyl-5-nitrobenzoxazole has been synthesized by electrochemical oxidation of 4-nitro-2,6-di-*tert*-butylphenol in acetonitrile (Scheme 2.75) [494].

7-*tert*-Butyl-4-methyl-5-nitrobenzoxazole and 6-*tert*-butyl-5-methoxy-4-nitro-2,1-benzisoxazole were found among the products of photolysis of 4-*tert*-butyl-3-methoxy-2,6-dinitrotoluene [450].

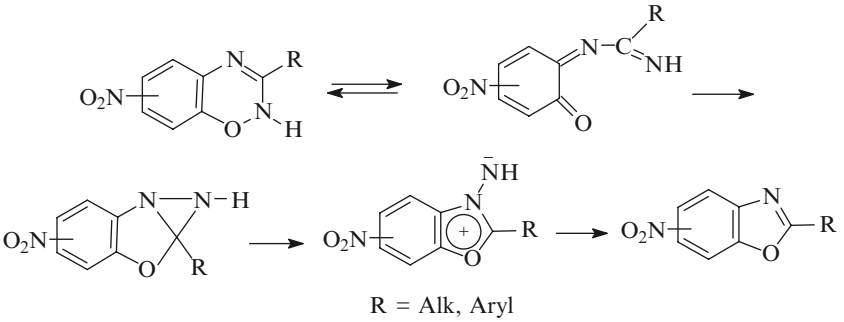


Scheme 2.74



Scheme 2.75

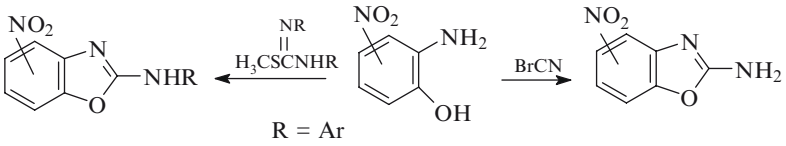
When heated, benzoxadiazines give benzoxazoles in good yield [495, 496]. The intermediate formation of *ortho*-quinonimine has been suggested on the basis of the proposed recyclization mechanism (Scheme 2.76).



Scheme 2.76

Heating of 7-nitro-1,2,4-benzoxadiazine-3-carboxylic acid or basic hydrolysis of its ethyl ester results in 2-amino-6-nitrobenzoxazole [495, 496]. Earlier this compound was wrongly ascribed the structure of 7-nitro-1,2,4-benzoxadiazine [497].

Nitrated 2-aminobenzoxazoles are obtained in good yield in the reaction of *ortho*-aminophenols with cyanogen bromide [498–500] or with *S*-methylisothiourea derivatives (Scheme 2.77) [501].

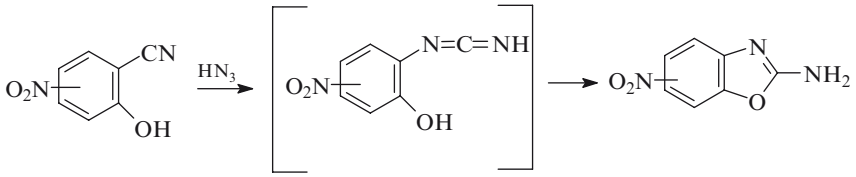


Scheme 2.77

5- or 6-Nitrobenzoxazoline-2-thiones react with morpholine and aromatic amines to form 2-aminobenzoxazoles [502]. When butylamines and some other amines are used the reaction stops at a stage of the formation of thiourea 2-oxyphenyl derivatives and for further cyclization to 2-aminobenzoxadiazoles the presence of silver salts is necessary (Scheme 2.78).

Scheme 2.78

The nitrile of salicylic acid and its nitroderivatives reacts with HN_3 to form 2-aminobenzoxazoles, as illustrated in Scheme 2.79 [503, 504].



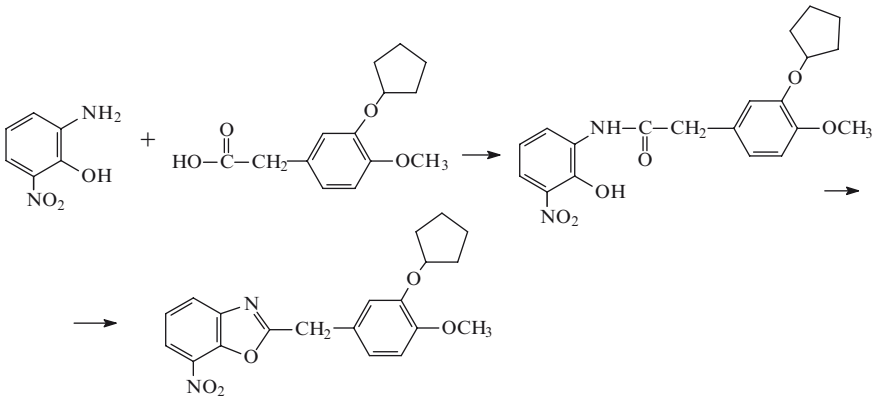
Scheme 2.79

2-(3-Cyclopentyloxy-4-methoxybenzyl)-7-nitrobenzoxazole used in the therapy of asthma has been obtained by condensation of *N*-(2-hydroxy-3-nitrophenyl)-3-cyclopentyloxy-4-methoxyphenylacetamide (Scheme 2.80) [505].

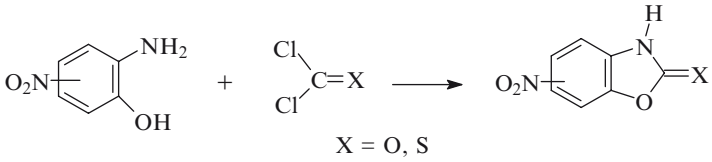
2-Thiol-5-nitrobenzoxazole, the structural material for the preparation of potential enantioselective inhibitors of leukotriene biosynthesis, has been synthesized by condensation of nitro-*ortho*-aminophenole with CS_2 [506].

Nitroderivatives of *ortho*-aminophenols react with phosgene and thiophosgene to form benzoxazolones-2 [507] and benzoxazolthiones-2, [508] respectively (Scheme 2.81).

Synthesis of nitrobenzoxazolones-2 by Beckman's rearrangement of 4-nitrosalicylhydroxamine acid has been reported [509]. The process is carried out on heating (4-nitro-2-oxyphenyl)-urea [510] or 4-(4-nitro-2-oxyphenyl)semicarbazide [511] with mineral acids and by oxidation of 6-nitro-2-hydroxymethylquinoline and its derivatives.



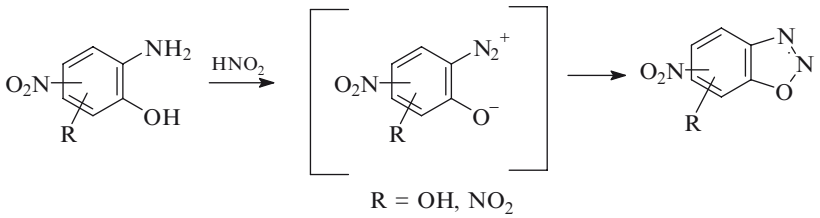
Scheme 2.80



Scheme 2.81

The most widespread preparative synthetic route to nitrobenzoxazolothione-2 is the reaction of nitroaminophenols with CS_2 [501, 512, 513].

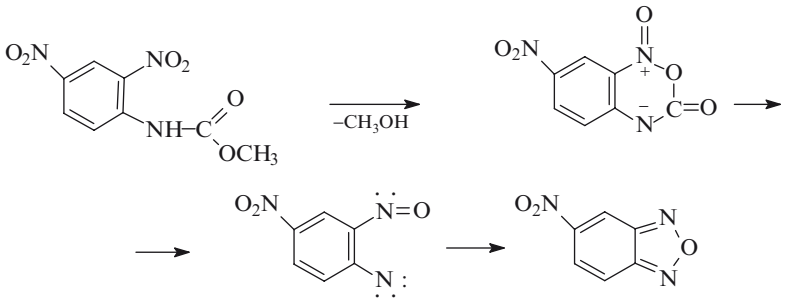
Nitroderivatives of *ortho*-aminophenole on diazotization form the corresponding *ortho*-diazophenols, which readily undergo cyclization into 1,2,3-benzoxadiazoles (Scheme 2.82) [513–518].



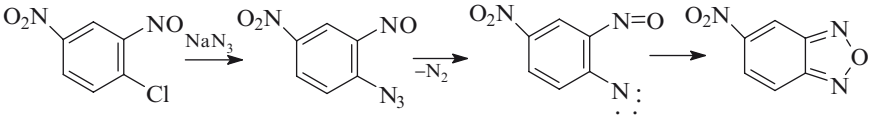
Scheme 2.82

On pyrolysis of methyl-*N*-(2,4-dinitrophenyl)carbamate 5-nitro-2,1,3-benzoxadiazole (5-nitrobenzofurazan) was isolated in a yield of 35% (Scheme 2.83) [519].

The key product in this process is *ortho*-nitrozophenylnitrene from which benzofurazan is formed later. The reaction of 2-chloro-5-nitronitrozobenzene with sodium azide in an aqueous acetone medium is likely to follow a similar pathway. In this case the yield of 5-nitrobenzofurazan reaches 73% (Scheme 2.84) [520].

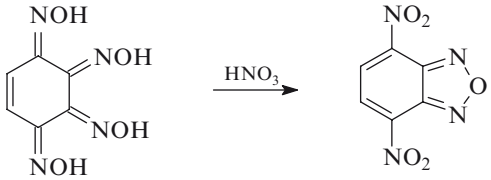


Scheme 2.83



Scheme 2.84

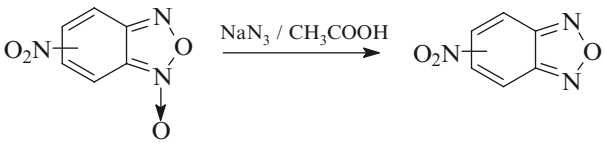
In the reaction of nitric acid with tetraoximecyclohex-5-ene-1,2,3,4-tetraone, the oxidation of two oxyme groups with simultaneous cyclization to 4,7-dinitro-2,1, 3-benzoxadiazole takes place (Scheme 2.85) [521].



Scheme 2.85

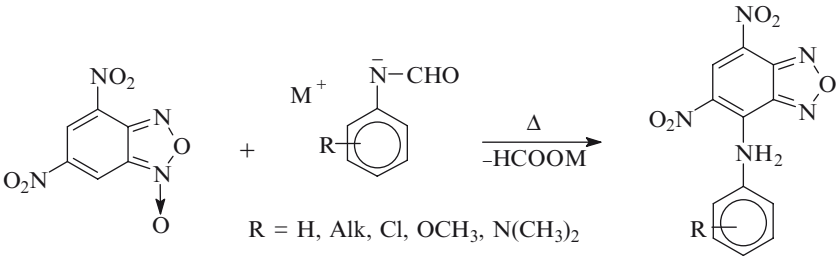
The most common method of the synthesis of nitrobenzofurazans is reduction of benzofuroxan nitroderivatives. A lot of examples of the synthesis of nitro-2,1, 3-benzoxadiazoles from the corresponding *N*-oxides have been described [149, 155, 156, 522–526]. Here, the results of electrochemical investigations of a more difficult reduction of exocyclic N→O bond, in comparison with the endocyclic one, look unexpected [527]. The following explanation for this apparent contradiction can be given. On the one hand, the process of chemical reduction can differ significantly from the mechanism of electrochemical reduction. On the other hand, the primary opening of the furoxan cycle with subsequent closing into furazan is possible; it is the endocyclic N→O bond that undergoes primary opening. Triphenylphosphine is used as a reducing agent in most cases [149, 155, 523, 524].

On heating of sodium azide with benzofuroxans in ethylenglycole or DMSO the corresponding benzofurazans are formed [523, 525]. If the reaction is carried out in a medium of acetic or *iso*-butyric acids, that is, actually using HN_3, the nitrobenzofurazans sought are formed in good yield (Scheme 2.86) [526].



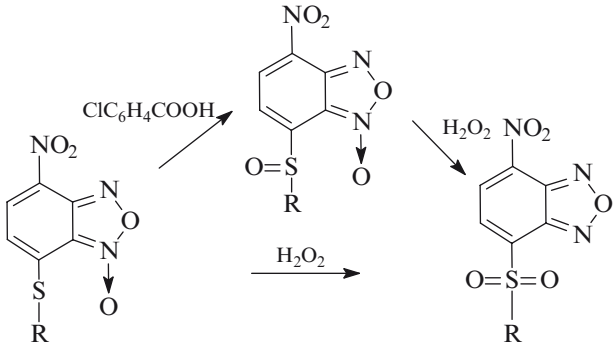
Scheme 2.86

4,6-Dinitrobenzofurazan 7-aminoderivatives have been obtained by the reaction of 4,6-dinitrobenzofuroxan with alkali metal salts of the corresponding formanylidines (Scheme 2.87) [527–529].



Scheme 2.87

On oxidation of 4-nitro-7-arylthiobenzofuroxanes with excess hydrogen peroxide the corresponding sulfonylbenzofurazans are obtained, whereas in mild conditions (*meta*-chloroperoxobenzoic acid, 0–20°C) intermediate nitro derivatives of sulfonylbenzofuroxan were isolated (Scheme 2.88) [530].



Scheme 2.88

On heating, the latter form 4-nitro-7-arylsulfonylbenzofurazans in high yield. In this case the observed migration of the furoxan cycle exocyclic oxygen to the neighboring

sulfoxide group follows an intermolecular mechanism. The rate of this rearrangement increases with introducing electron-donating substituents into the phenyl ring of the sulfoxide fragment. It should be noted that the oxygen atom migration from the furoxan ring moves only to the sulfoxide group and not to the sulfide one. In some cases the reaction goes without intermediate isolation of the furoxan cycle. For example, on heating 1,3-diamino-2,4,6-trinitrobenzene 4-amino-5,7-dinitrobenzofurazan is formed.

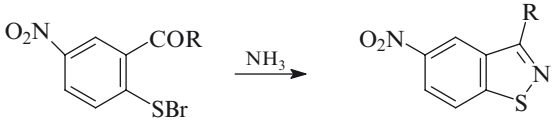
In recent years, particular attention focuses on reactivity of nitrobenzofuroxans and nitrobenzofurazans [531]. The latest are represented as a class of neutral 10-π-electron-deficient heteroaromatic substrates that exhibit an extremely high electrophilic character in many covalent nucleophilic addition and substitution processes.

Nitrobenzisothiazoles, Nitrobenzothiazoles, and Nitrobenzothiadiazoles

Nitroderivatives of aromatic aldehydes or ketones, containing sulfohalogen group in the *ortho*-position, undergo cyclization into the corresponding 1,2-benzisothiazoles under the influence of ammonia (Scheme 2.89) [173].

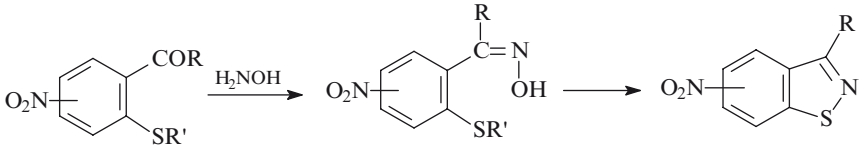
Later this process has been significantly simplified by using *ortho*-chloro substituted aldehydes or ketones as the initial products [532–536].

Another rather widely accepted synthesis of the aforementioned compounds is



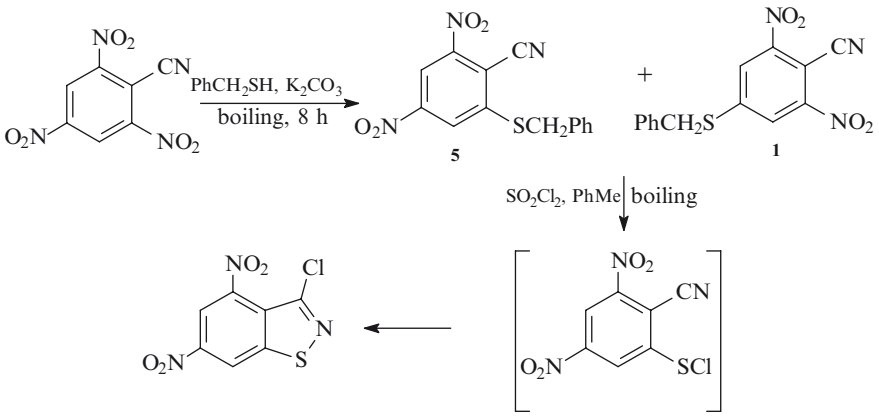
Scheme 2.89

the condensation of oximes of aldehyde or ketone nitro derivatives, containing sulfohydryl or sulfoalkyl groups in the *ortho*-position (Scheme 2.90) [166, 537, 538].



Scheme 2.90

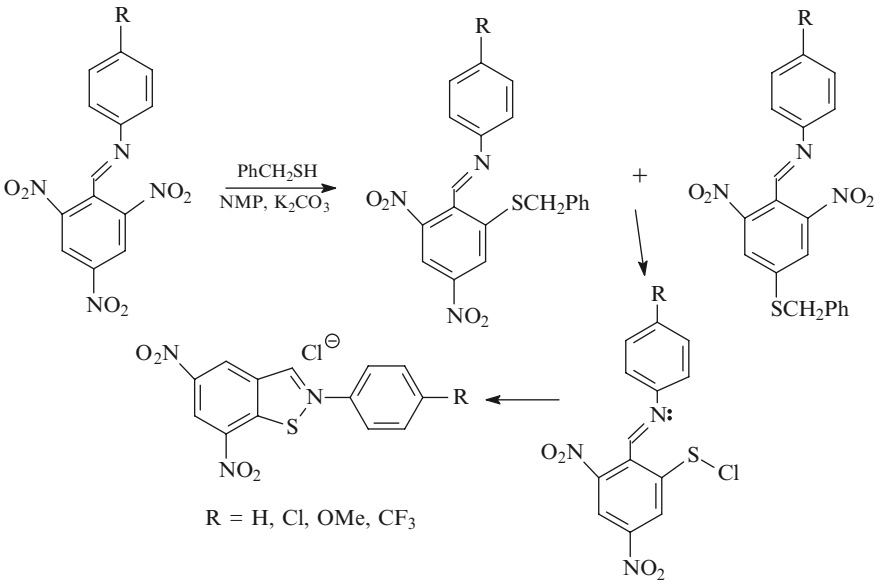
4,6-Dinitrobenzisothiazole derivatives and salts were prepared in the course of utilization of explosive 2,4,6-trinitrotoluene [539–541]. 3-Cloro-4,6-dinitrobenzisothiazole was prepared on using 2,4,6-trinitrotoluene, which can easily be transformed to 2,4,6-trinitrobenzonitrile (TNBN) by treatment with nitrosyl chloride [539]. The reaction of TNBN in the presence of K_2CO_3 led to both *ortho* and *meta* isomers, the products of substitution of NO_2 groups by a $PhCH_2S$ unit, with the ratio of isomers being dependent on the solvent polarity (Scheme 2.91).



Scheme 2.91

The fraction of *ortho* substitution considerably is increased with decreasing solvent polarity. The mixture (5:1) of *ortho* and *meta* isomers prepared in toluene was treated with SO_2Cl_2 to give 3-cloro-4,6-dinitrobenzisothiazole as a result of intramolecular cyclization [539].

2-Aryl-4,6-dinitrobenzisothiazolium chlorides can be obtained even at room temperature by treatment of the corresponding sulfuryl chlorides in dichloroethane without separation, as shown in Scheme 2.92 [540].

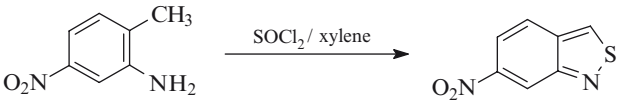


Scheme 2.92

Similarly to 1,2-benzisoxazoles, 1,2-benzisothiazoles with the nitro group in the arylene fragment can be obtained from 4-mercaptotocumarines and from hydroxylamine [167].

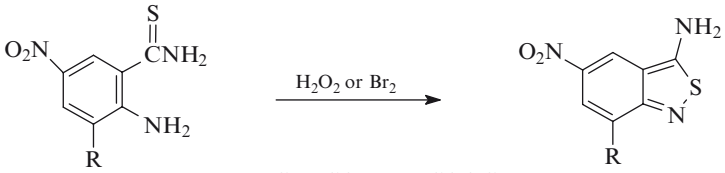
Synthesis of 5-nitro-1,2-benzisothiazolone-3 possessing thrombolytic and antibacterial activity has been described in reference [542].

The data on the synthesis of nitrated 2,1-benzisothiazoles are rather scarce in comparison with the corresponding benzisoxazoles. It has been reported that, like other 2-aminotoluenes, 2-amino-4-nitrotoluene reacts with thionyle chloride in xylene to form 6-nitro-2,1-benzisothiazole, whereas 2-amino-5-nitrotoluene does not enter into this reaction (Scheme 2.93) [543].



Scheme 2.93

3-Amino-5-nitro-2,1-benzisothiazole and its 7-substituted derivatives are obtained on oxidation of 5-nitro-2-amino-3-R-thiobenzamides with hydrogen peroxide or bromine (Scheme 2.94) [544–546].

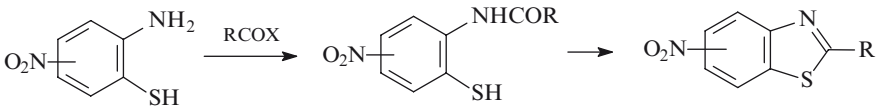


R = H, CN, $CONH_2$, $COOCH_3$

Scheme 2.94

In these conditions 5-nitrothioanthranilic acid is oxidized to 5-nitro-2,1-benzisoxazolone-3 [128, 547].

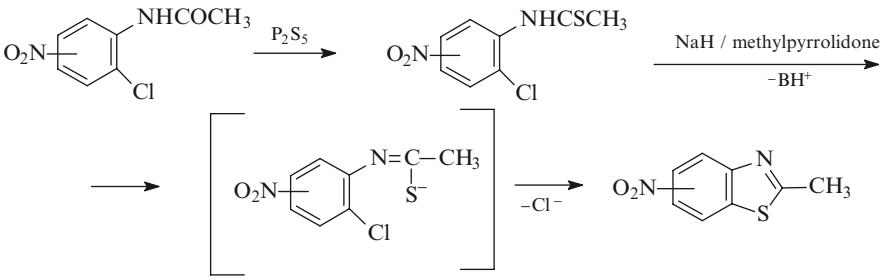
One of the most convenient and widespread syntheses of benzothiazole nitroderivatives is the reaction of the corresponding *ortho*-aminothiophenols with acids [134, 548–551], their anhydrides [195, 550, 552], chloroanhydrides [553] or benzaldehydes [554] according to Scheme 2.95.



X = OH, OCOR', Cl; R = H, Alk, Ar

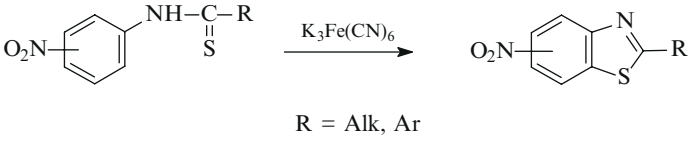
Scheme 2.95

ortho-Acetylaminothiophenols, which readily undergo cyclodehydratation, are intermediate products in these reactions [134, 555]. In this case *ortho*-acetylaminothiophenols are often not separated; instead, *ortho*-halogenoacylanilines are treated with alkali metal sulfides [183, 556–561]. In a modification of this process, *ortho*-halogenothioacylanilines are boiled with phosphorus pentasulfide in benzene, and the products, nitroaniline thioacylderivatives, undergo cyclization to nitrobenzothiazoles in amide solvents in the presence of bases (Scheme 2.96) [562, 563].



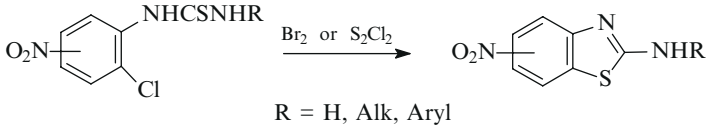
Scheme 2.96

Like other benzothiazoles, nitrobenzothiazoles can easily be obtained by Yakobson's method from thioacylanylides under the influence of potassium ferricyanide (Scheme 2.97) [564–567].



Scheme 2.97

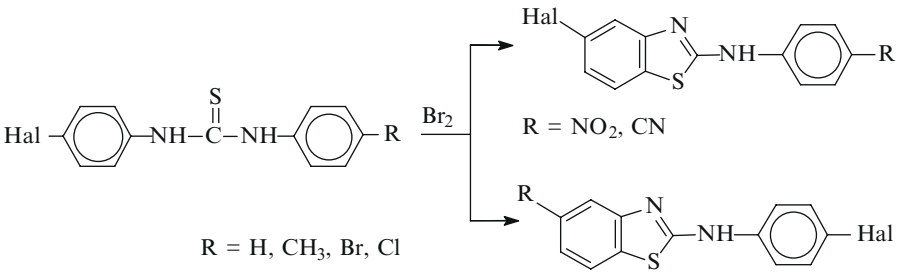
Later 2-methyl-6-nitrobenzothiazole was obtained by electrochemical oxidation of 4-nitrothioacetanylide [568]. Interestingly, there is no cyclization under the influence of potassium ferricyanide when arylthioureas are used. In this case other cyclizating agents have to be used as oxidizers. Bromine-induced oxidation of nitroarylthiourea with the formation of the corresponding 2-aminobenzothiazole nitroderivatives (Hugershoff's method) is used for preparative purposes [182, 569–574]. Sometimes sulfur monochloride is used as an oxidizer in place of bromine (Scheme 2.98) [575, 576].



Scheme 2.98

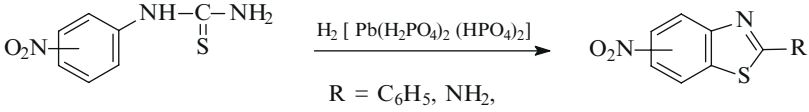
Introduction of the diazoarylamino groups into position 2 of 6-nitrobenzothiazoles leads to the thermal stability of nonlinear optical organic materials on the base nitrobenzazoles [577].

With *N*,*N*′-diarylthioureas the cyclization direction is determined by the character of substituents, and the introduction of a nitro group or other electron-withdrawing substituents decreases the reactivity of the aromatic ring [179]. This can be illustrated by the following Scheme 2.99.



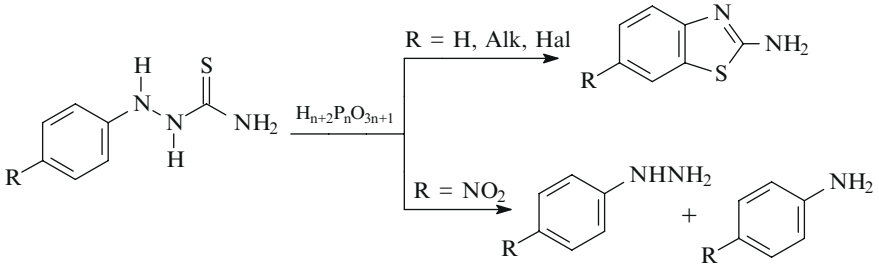
Scheme 2.99

The use of a mixture of Pb_3O_4 with *ortho*-phosphoric acid as an oxidizer allows the preparation of both 2-aryl- and 2-aminonitrobenzothiazoles (Scheme 2.100) [487].



Scheme 2.100

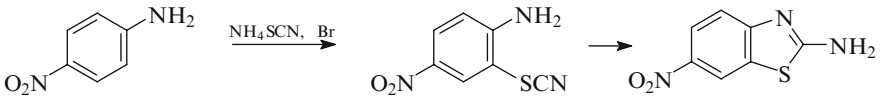
On heating in polyphosphoric acid 1-phenylthiosemicarbazides with alkyl or halogen substituent in the benzene ring turn into 2-aminobenzothiazoles in good yield (Scheme 2.101) [578].



Scheme 2.101

However, the presence of the nitro group in the *para*-position to the thiosemicarbazide group blocks the process of cyclization, and only the products of N–C and N–N bond splitting are obtained as a result.

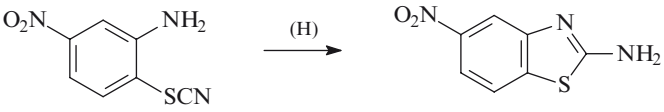
4-Nitroaniline reacts with ammonium rhodanide and bromine to form 2-rhodanyl-4-nitroaniline, which undergoes cyclization into 2-amino-6-nitrobenzothiazole under the reaction conditions on Scheme 2.102 [579–582].



Scheme 2.102

Other derivatives of 2-nitroaminobenzene were obtained in the same way [550, 580, 583], and in some cases the aforementioned rhodanylaniniles could be isolated [550, 583].

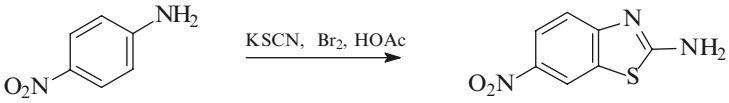
It should be taken into consideration that the rhodanation of substituted anilines goes mainly to the position 4. The reported synthesis of 2-amino-4-nitrobenzothiazole by rhodanation of *ortho*-nitroaniline [583] turned out to be incorrect. In fact, the authors obtained 2-nitro-4-rhodanylaniline of the same empirical formula [584, 585]. 2,4-Dinitrophenylthiocyanate is reduced to 2-amino-5-nitrobenzothiazole in acetic acid by iron (Scheme 2.103) [407, 408].



Scheme 2.103

The same compound can be obtained on heating 2,4-dinitrochlorobenzene with thiourea in sulfolane [586]. In the same manner 2-amino-7-trifluoromethyl-5-nitrobenzothiazole and 2-amino-7-nitrobenzothiazole were synthesized.

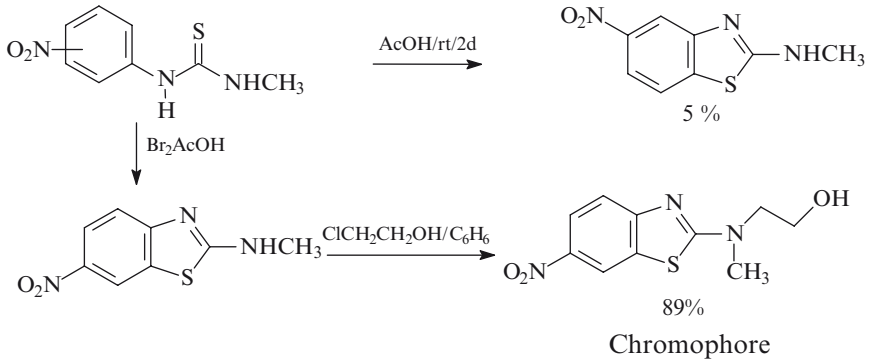
2-Amino-6-nitrobenzothiazole as a sodium flux inhibitor (anticonvulsant activity) has been synthesized from nitroaniline via a one-pot procedure (Scheme 2.104) [587].



Scheme 2.104

In this route, the thiourea is produced in situ and then oxidatively cyclized to the nitrobenzothiazole. This method failed for anilines containing an electron-withdrawing substituent in the *meta*-position.

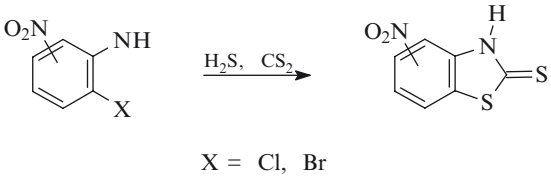
Nitrobenzothiazole chromophores [588, 589] and their precursors [590] are building blocks of nonlinear optical materials, which are extensively used in the field of optical information processing, optical sensing, data storage, and telecommunications [588, 591]. 5-Nitro- [590] and 6-nitro-2-(methyamino)benzothiazole [589] have been prepared from 3-nitro- and 4-nitrophenylthiourea correspondingly, as illustrated in Scheme 2.105.



Scheme 2.105

Preparation method of the chromophore involves the condensation of *para*-nitroaniline with thiocyanate in methanol and the bromine radical cyclization using bromine in acetic acid. In this case only one product – 2-(methylamino)-6-nitrobenzothiazole – was obtained, which is easily purified over column chromatography using neutral alumina [589].

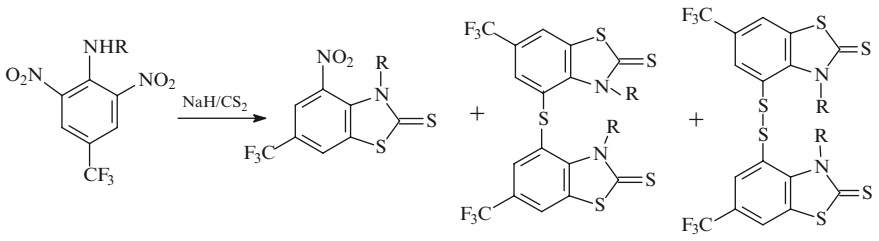
6-Methyl-5-nitrobenzothiazolone-2 has been obtained from (5-methyl-2,4-dinitrophenylthio)acetic acid and acetic anhydride [592]. Benzothiazolethione-2 nitroderivatives can readily be obtained by the following Scheme (Scheme 2.106) [184, 559].



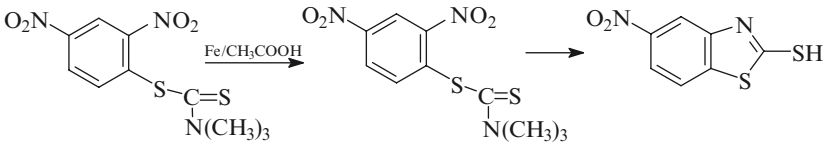
Scheme 2.106

An analogous reaction takes place with *ortho*-nitroanilines. For example, 4-amino-3,5-dinitrobenzotrifluoride and its *N*-alkylsubstituted derivatives react with CS_2 in dry dimethylformamide in the presence of sodium hydride to form the corresponding benzothiazolethiones (Scheme 2.107) [593].

2,4-Dinitrophenyl ester of *N*,*N*-dimethyldithiocarbamic acid is reduced with iron powder in glacial acetic acid with the formation of 5-nitrobenzothiazolethione-2 [407, 408] (Scheme 2.108), which is extensively used in coordinating chemistry [594–597].



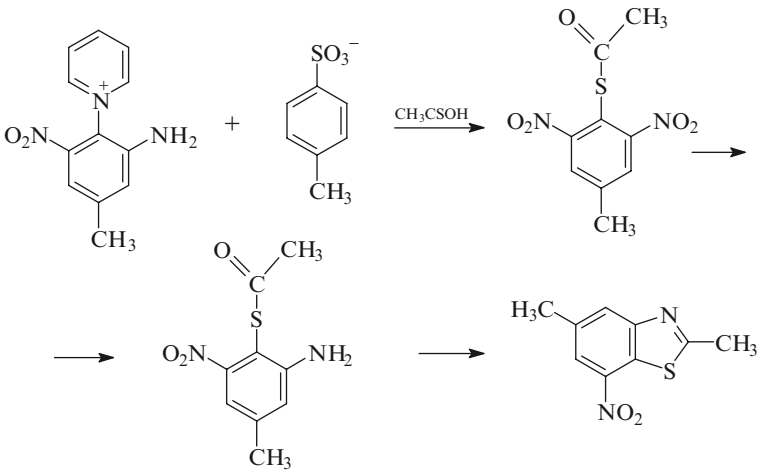
Scheme 2.107



Scheme 2.108

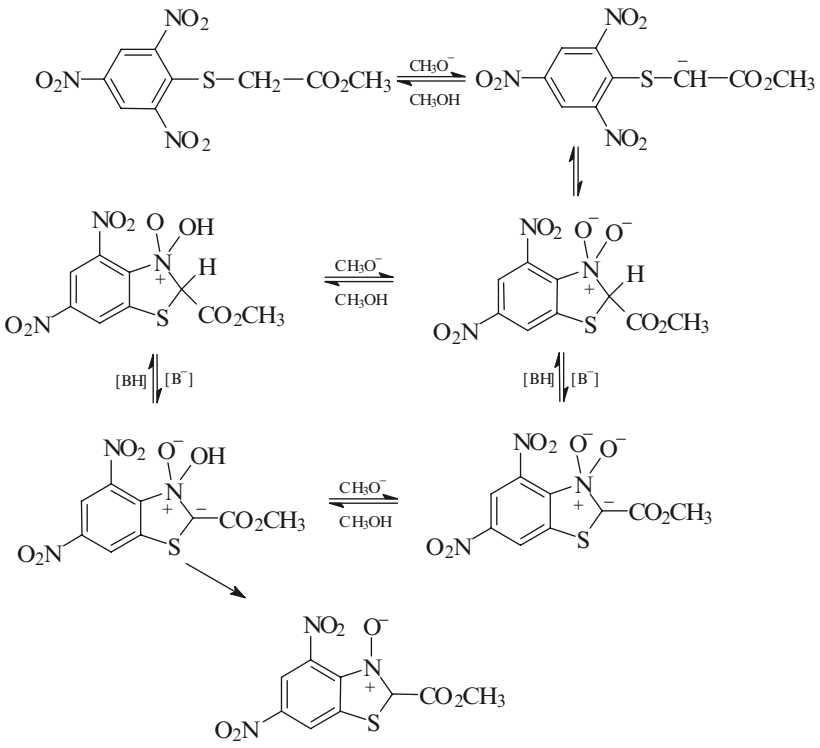
The heteroaromatic thioles, in particular 2-mercapto-6-nitrobenzothiazole, were studied in regard to their abilities to function as coinitiators in free-radical photopolymerizations induced by camphorquinone and isopropylthioxanthone [598].

Formation of 2-propyl-5-nitrobenzothiazole on reduction of 2,4-dinitro-butylthiobenzene with sodium polysulfite or trimethylphosphite has been observed [599]. *para*-Toluenesulfonate 2,5-dimethyl-7-nitrobenzothiazole was obtained under the action of excess thioacetic acid on *N*-(4-methyl-2,6-dinitrophenyl)pyridinium [600]. The reaction involves the formation of 4-methyl-2,6-dinitrothiophenol acetate in which, under experimental conditions, one of the nitro groups is reduced to an amino group with subsequent cyclization, as shown in Scheme 2.109.



Scheme 2.109

Kinetics of the formation of 2-methoxycarbonyl-5,7-dinitrobenzothiazole-3-oxide by cyclization of *S*-(2,4,6-trinitrophenyl)mercaptoacetate in acetate, methoxyacetate, or *N*-methylmorfoline buffers has been studied [601]. In the first two buffers the cyclization follows two reaction pathways, which differ in the order of reaction steps, with the proton splitting off from the C–H group being the rate-limiting step in either pathway (Scheme 2.110).



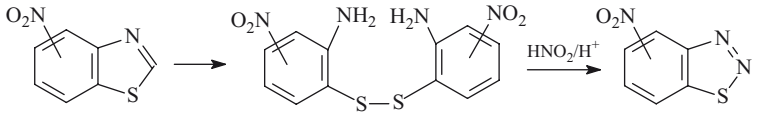
Scheme 2.110

In *N*-methylmorpholine buffer an increase in the concentration of the base results in a gradual decrease of the reaction order in the base and a change in the rate-limiting step of cyclization [601].

The synthesis, structure, and superoxide dismutase mimetic activity in vitro and the protection against reactive oxygen species in vivo of mononuclear copper complexes with 2-(4-methylphenylsulfamoyl)-6-nitrobenzothiazole have been reported [602].

Like 1,2,3-benzoxadiazoles, nitroderivatives of 1,2,3-benzothiadiazoles were obtained on diazotization of the corresponding *ortho*-aminothiophenoles [213, 218, 583]. The initial *ortho*-thiophenols for this reaction were synthesized by nucleophilic substitution of halogen in *ortho*-halogenoanilines. It turned out that 4-nitro- and

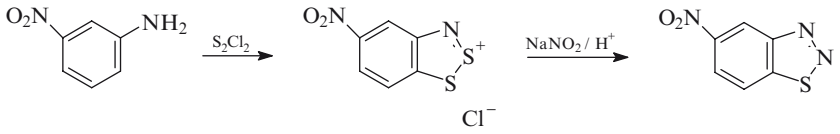
6-nitrobenzothiazoles on boiling with hydrazine in ethanol transformed to the corresponding disulfides, which form 4- or 6-nitro-1,2,3-benzothiadiazoles under the effect of nitrous acid (Scheme 2.111) [214].



Scheme 2.111

An attempt to synthesize 5- or 7-nitro-1,2,3-benzothiadiazoles in this way was unsuccessful. *meta*-Nitroaniline reacts with sulfur monochloride (Herz's reaction), while 1,2,3-benzothiazathiolium chloride reacts with nitrous acid to give a small amount of 5-nitro-1,2,3-benzothiadiazole, according to Scheme 2.112 [218, 603].

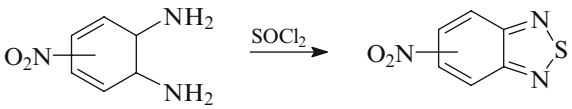
Different derivatives of 2,1,3-nitrobenzothiadiazole (earlier called nitropiazthiole)



Scheme 2.112

are obtained in the reaction between thionylchloride and the corresponding 1,2-diaminobenzenes [220, 223, 231, 246, 604–607]. Some of them, in particular, 4-nitro-2,1,3-benzothiadiazole (and also 4-nitro-2,1,3-benzoselenodiazole-nitropiazselenols) are effective against fungus diseases of cotton plants and grapes (Scheme 2.113) [607].

Sulfinylaniline [605, 608] or sulfur monochloride [609] can be used as cyclizat-

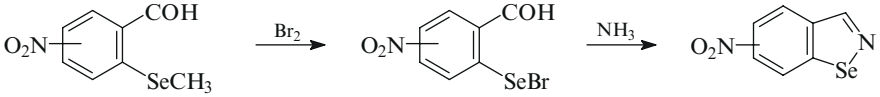


Scheme 2.113

ing agents. The formation of 5-nitro-2,1,3-benzothiadiazole in the reaction of 2,4-dinitroaniline with sulfur monochloride has been observed. Here, the reduction of substrate to 4-nitro-1,2-diaminobenzene followed by cyclization takes place [609].

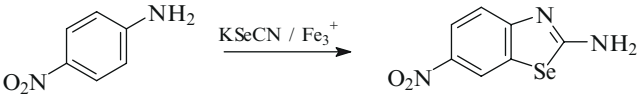
Nitrobenzisoselenazoles, Nitrobenzoselenazoles, and Nitrobenzoselenodiazoles

Analogously to the formation of 5-nitrobenzisothiazole [173], 5- and 7-nitrobenzisoselenazoles can be obtained in the reaction of 3- or 5-nitro-2-methylselenobenzaldehyde with bromine and ammonia (Scheme 2.114) [163].



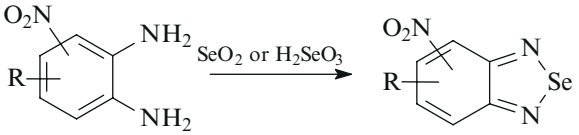
Scheme 2.114

para-Nitroaniline reacts with potassium selenocyanate in the presence of iron (III) salts to form 2-amino-6-nitrobenzoselenazole (Scheme 2.115) [610].



Scheme 2.115

The reaction of selenium dioxide or selenic acid with nitro-1,2-diaminobenzenes leads to the corresponding nitro-2,1,3-benzoselenodiazoles (Scheme 2.116) [223, 243, 244, 246, 366, 607, 611–620].



R = H, Alk, OAlk, Hal, Aryl

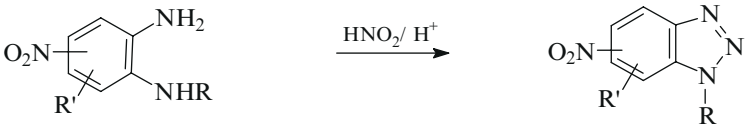
Scheme 2.116

In the literature [615–619] there are the results of quantitative investigations into the reaction of complex formation of H_2SeO_3 and aromatic *ortho*-diamines, –R–$C_6H_3(NH_2)_2$, which allow an accurate determination of the composition of the mixture at any pH, which is widely used in analytical chemistry of selenium.

Nitrobenzotriazoles

The most common and convenient way of obtaining nitro-1(*H*)-benzotriazoles is the condensation of nitro-1,2-phenylendiamines with nitrous acid [251, 252, 256,

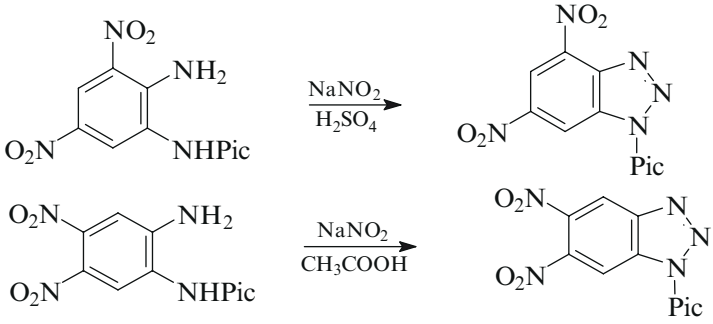
259–265, 342, 365, 366, 620–622]. In most cases this reaction is undertaken in the medium of hydrochloric acid or lower carboxylic acids – HCOOH, CH_3COOH (Scheme 2.117).



R = H, Alk, Ar, OH, OAlk, Het, SO_2Alk, SO_2Ar', R' = Alk, OCH_3

Scheme 2.117

High-energy materials such as 4,6-dinitro-1-(2′,4′,6′-trinitrophenyl)- and 5,6-dinitro-1-(2′,4′,6′-trinitrophenyl)benzotriazole have been obtained by treating the corresponding *ortho*-phenylenediamines with sodium nitrite in sulfuric and acetic acids, respectively (Scheme 2.118) [623].



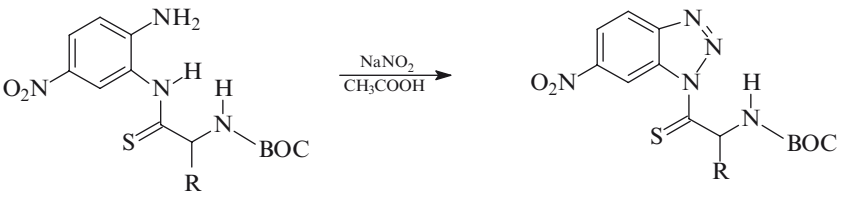
Scheme 2.118

The derivatives of nitrobenzotriazole α-aminothionic acids, used as thioacylating agents in the synthesis of thiopeptides and nitrobenzotriazole thioacylating reagents, have been obtained in a similar way (Scheme 2.119) [624, 625].

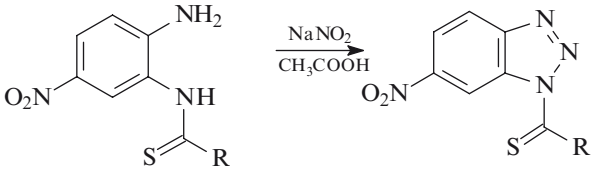
Thioanilides are treated with sodium nitrite either in the medium of glacial acetic acid or in 70% acetic acid to form the corresponding nitrobenzotriazoles in good yield (72–83%). In general terms, the stability of nonbenzenoid thiocarbonylbenzotriazoles is poor. Rapoport [624, 625] obtained aliphatic nitrated thiocarbonylbenzotriazoles. Probably, the electron-withdrawing nitro group in the benzotriazole ring improves the stability and allows isolating aliphatic thiocarbonylbenzotriazoles.

Following this method, the Katritzky team has prepared several novel aliphatic and aromatic thiocarbonyl-1*H*-6-nitrobenzotriazoles, as shown in Scheme 2.120 [5].

Interaction of 4-nitro-1,2-phenylendiamines with the respective acid chlorides gave regioselectively amides (83–99%). Resonance and inductive effect of the nitro group lowered the nucleophilicity of the amino group in the *para*-position, leaving

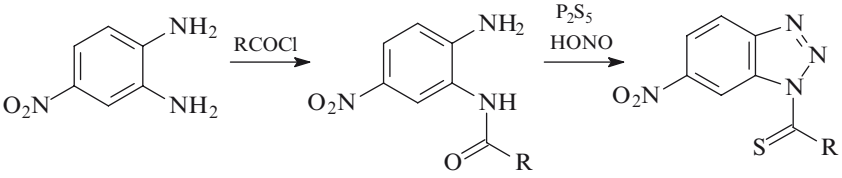


R = CH_3, CH_2Ph, $CH(CH_3)_2$, CH_2OBn, $CH_2CO_2CH_3$, $CH_2CO_2Bu^t$



R = $CH(OAc)CH_2CO_2CH_3$, $CH(OAc)Ph$, $CH{=}CHCO_2CH_3$—
$CH{=}CHCH_3$, $CH{=}CH_2$, $CH{=}CHPh$

Scheme 2.119



Yeilds of thiocarbonyl-1*H*-6-nitrobenzotriazoles (R, %)

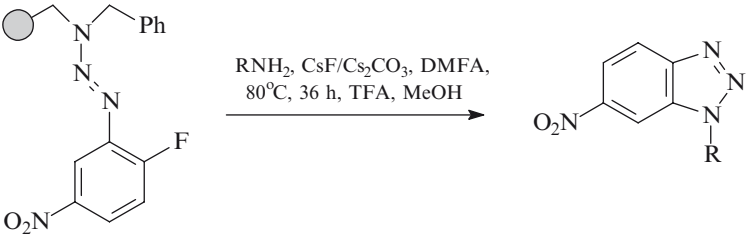
R	%	R	%
ethyl	84	4-methoxyphenyl	86
4-methylphenyl	98	4-bromophenyl	99
2-furanyl	95	pentyl	81
4-nitrophenyl	83	2-thienyl	91

Scheme 2.120

the *meta*-amino group to attack the carbonyl of acid chloride. Intermediated amides were converted to thiocarbonyl-1*H*-6-nitrobenzotriazoles crude yields by stirring at room temperature with phosphorus pentasulfide [5].

Benzotriazoles including nitrobenzotriazoles have been widely utilized by the research group of Katritzky as a synthetic auxiliary in a multitude of reactions [5, 626]. Benzotriazole is an inexpensive, stable, and biologically active compound, which can be easily introduced into organic molecules. The benzotriazole ring is extremely stable, and only rarely was ring cleavage encountered to give mostly products of nitrogen extrusion [626].

1-Alkyl-5-nitro-1*H*-benzotriazoles in excellent yield (90%) and purities (95%) were obtained, as illustrated in Scheme 2.121 [627].

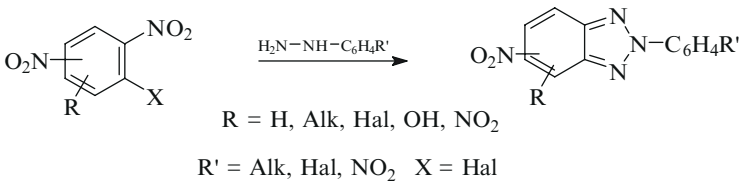


Scheme 2.121

Commercially available 2-fluoro-5-nitroaniline was diazotized and coupled to benzylaminomethylpolystyrene to give the immobilized triazene. After nucleophilic displacement with primary amines to furnish an aniline resin, the cleavage with trifluoroacetic acid in dichloromethane proceeded smoothly at room temperature within minutes, resulting in nitrobenzotriazoles [627].

4-Nitrobenzotriazole possessing an excellent herbicidal activity [628] has been prepared on oxidizing 2-acetylamino-6-nitrophenylhydrazine with chlorine [522]. *N*-Chloro derivative of 4-nitrobenzotriazole is used as an oxidizer of alkylamines [629]. 1-Acetyl-4-nitrobenzotriazole is the excellent selective *N*-acetylation agent for nucleosides [630].

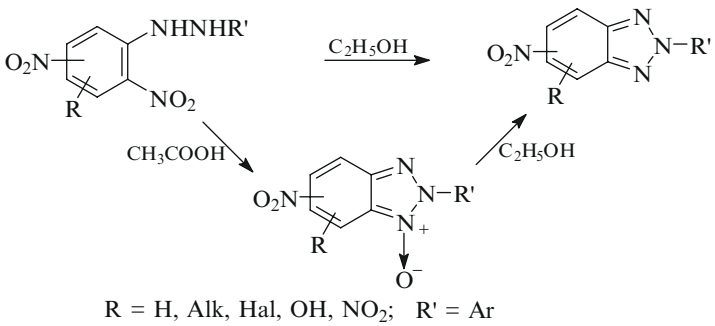
The most widely accepted way to the synthesis of 2*H*-benzotriazole nitroderivatives is the condensation of *ortho*-substituted halogenodinitro- or halogenopolynitrobenzenes with phenylhydrazine (Scheme 2.122) [260, 265, 271, 631–641].



Scheme 2.122

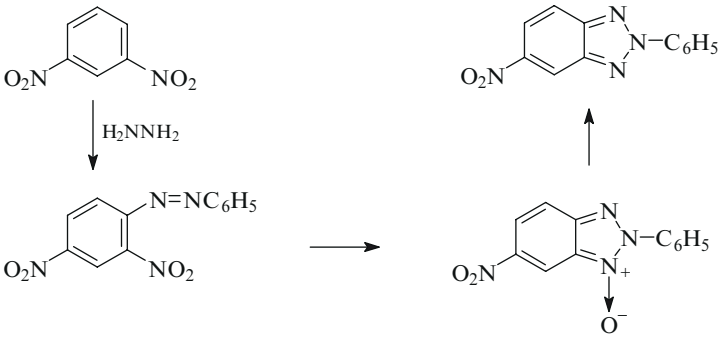
The initial stage of this reaction involves a nucleophilic halogen substitution followed by intermolecular redox cyclization of *ortho*-nitrohydrazobenzenes [642]. Instead of halogen the substrate can contain another group (NO_2, OAlk) [643–645]. It has been shown that in ethanol the aforementioned reaction proceeds with the formation of 2*H*-benzotriazole nitro derivatives, whereas in acetic acid their *N*-oxides are formed and, when boiled in ethanol, turn into the final products (Scheme 2.123) [637, 638, 646].

The reduction of 2,4-dinitroazobenzene by hydrazine in ethanol to 6-nitro-2-phenylbenzotriazole has been carefully studied [647]. The authors have proved that it goes via the formation of two intermediate products, that is, 2,4-dinitrohydrazobenzene



Scheme 2.123

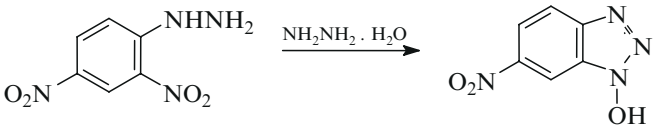
and 6-nitro-2-phenylbenzotriazol-1-oxide, which is obtained from the former as a result of cyclization (Scheme 2.124).



Scheme 2.124

The reaction of cyclization of 2,4-dinitrohydrazobenzene is described with a first order kinetic equation. The reaction rate depends on the pH value. In the pH range of 6.5–9.5 the rate constant is linearly dependent on the concentration of OH^- ions.

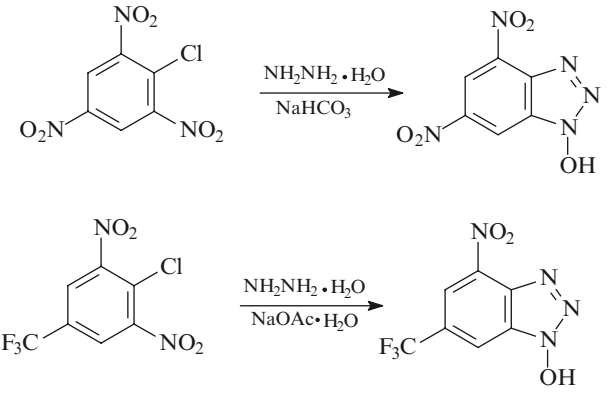
Synthesis of 1-hydroxy-6-nitrobenzotriazole from 2,4-dinitrophenylhydrazine has been described (Scheme 2.125) [647].



Scheme 2.125

1-Hydroxy-4,6-dinitrobenzotriazole [648, 649] and 1-hydroxy-4-nitro-6-trifluorome-thylbenzotriazole [649] have been synthesized in a similar manner. Later [650], an improved synthesis of these compounds from the corresponding

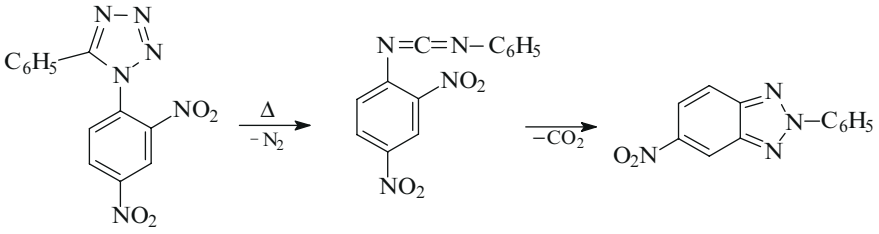
chlorinated nitrobenzenes with excess hydrazinium hydrate has been proposed (Scheme 2.126).



Scheme 2.126

The melting points of these compounds are significantly higher than those of compounds obtained by the method described in reference [649].

1-(2,4-Dinitrophenyl)-5-phenyltetrazole on heating turns to 2-phenyl-5-nitrobenzotriazole according to the Scheme 2.127 [392, 651].



Scheme 2.127

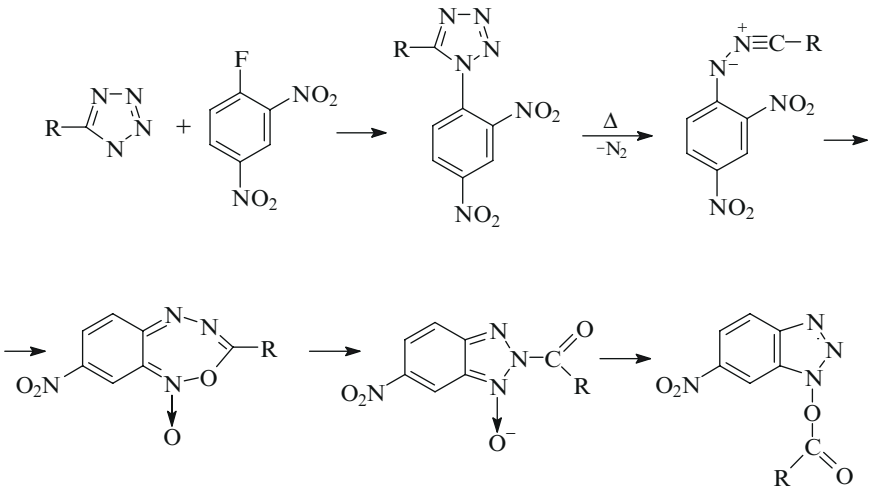
At the same time, the pyrolysis of its isomeric 2-substituted tetrazole results in 1-aroyloxy-6-nitrobenzotriazoles, as demonstrated in Scheme 2.128 [652].

4-Azobenzofuroxanes undergo intermolecular rearrangement to form 2-aryl-7-nitrobenzotriazoles (Scheme 2.129) [522].

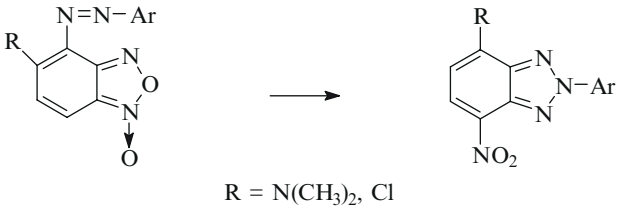
2-Aryl-4,7-dinitrobenzotriazoles are formed as a result of two rearrangements as shown in Scheme 2.130 [653].

The second transformation is a version of the aforementioned Boulton–Katrizky rearrangement [522]. Benzofuroxan was not isolated but appeared as an intermediate on heating 2,6-dinitro-3-azidoaryldiazenobenzene. The reaction starts with nucleophilic attack of the diazene fragment on the furoxan cycle nitrogen atom [653].

2,5-Diamino-4-nitroazobenzene turns into 2-phenyl-5-amino-6-nitrobenzotriazole in the presence of copper sulfite [654].

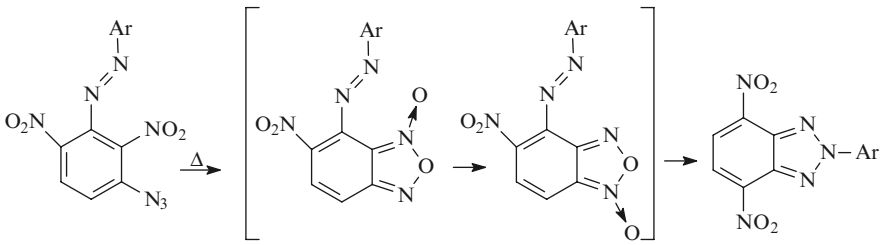


Scheme 2.128



R = $N(CH_3)_2$, Cl

Scheme 2.129

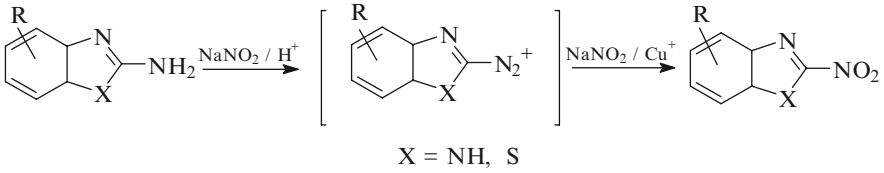


Scheme 2.130

Other Methods of Synthesis

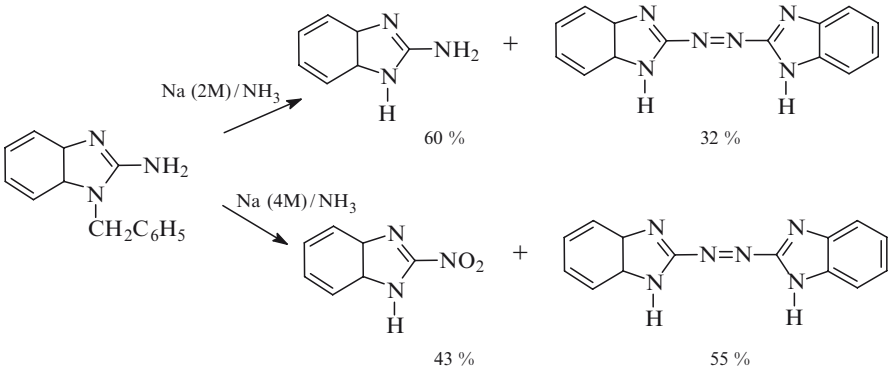
The Sandmeyer Reaction

The main method of introducing the nitro group into the benzazole cycle position 2 is Sandmeyer reaction (Scheme 2.131) [655–658].



Scheme 2.131

Pozharskii and his colleagues have established that 1-benzyl-2-aminobenzimidazole in liquid ammonia in the presence of metallic sodium turns into 2-nitrobenzimidazole and 2,2′-azobenzimidazole, as shown in Scheme 2.132 [659–661].



Scheme 2.132

The first stage of this unusual reaction involves debenzylation of the substrate to form 2-aminobenzimidazole polyaniones. The formation of 2,2′-azobenzimidazolone is the result of autooxidation of 2-aminobenzimidazole di- and trianiones, when 2-nitrobenzimidazole is formed on oxidizing of radical anions [660].

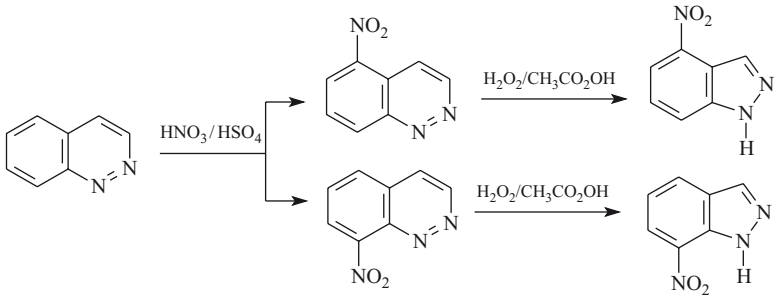
Recyclization

It is known that 5- and 8-nitrozinecolynes are oxidized to 4-nitro- and 7-nitroindazoles, respectively, by hydrogen peroxide in acetic acid (Scheme 2.133) [662].

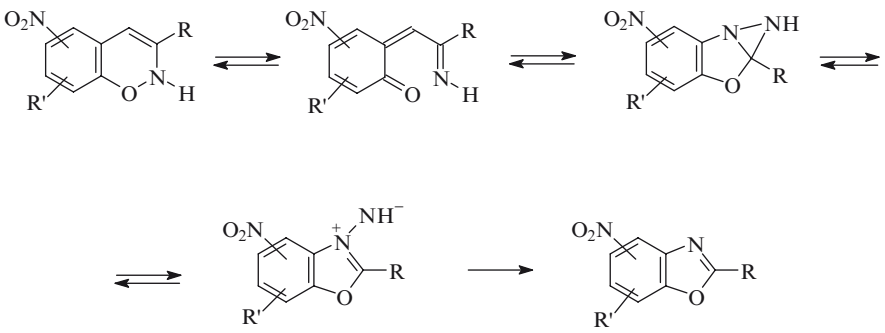
This is the way the synthesis of 4-nitro[3-^{14}C]- and 7-nitro[3-^{14}C]indazole has been performed [662].

A possible mechanism of the recyclization of 1,2,4-benzoxadiazones to form the corresponding benzoxazoles has been described, as illustrated in Scheme 2.134 [663].

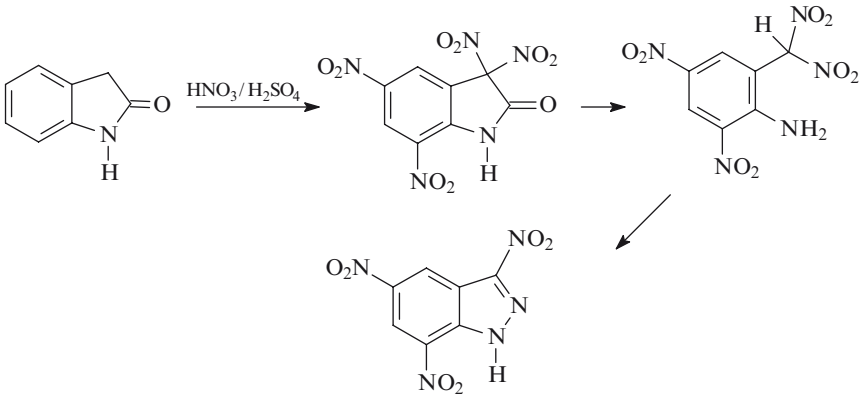
The nitration of oxyindole leads to 3,3,5,7-tetranitrooxindole, which transforms with ring-opening and undergoes decarboxylation to form 4,6-dinitro-2-(dinitromethyl)aniline. The latter is cyclized into 3,5,7-trinitroindazole [664]. The mechanism of ring transformation leading to nitroindazole is not clear yet and needs detailed examination (Scheme 2.135).



Scheme 2.133

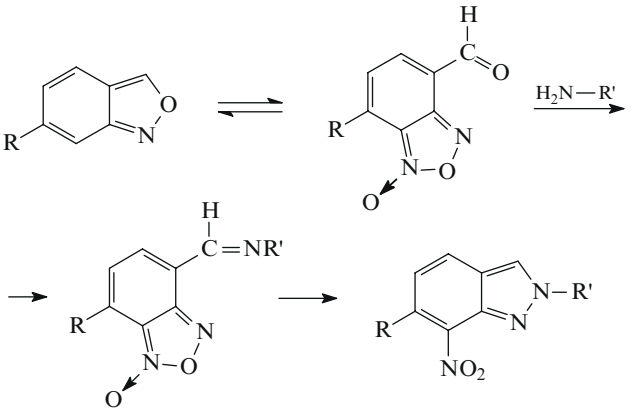


Scheme 2.134



Scheme 2.135

Interconversions of nitroanthranils equilibrated on heating with benzofurazan *N*-oxides lead to the formation of the corresponding nitroindazoles (Scheme 2.136) [665, 666].

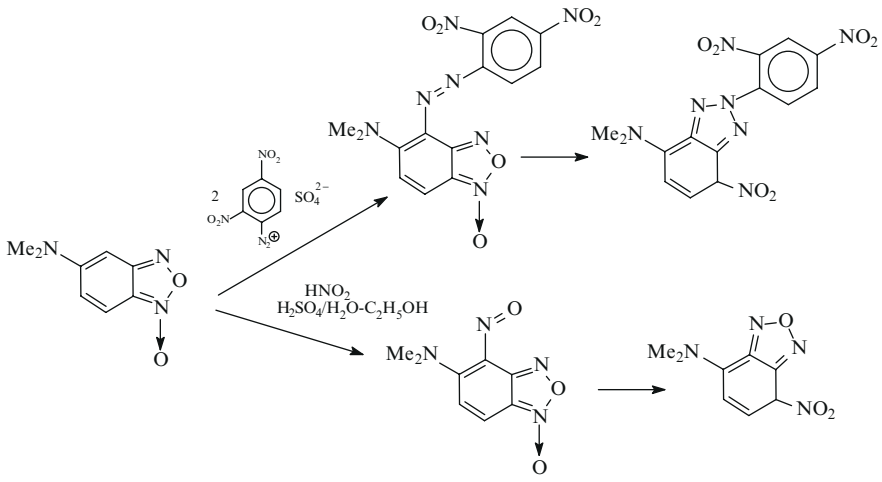


R = H, OMe, Cl; R' = Alk, Ph, CH_2Ph, OAlk, OPh, OCH_2Ph, NMe_2, NHPh

Scheme 2.136

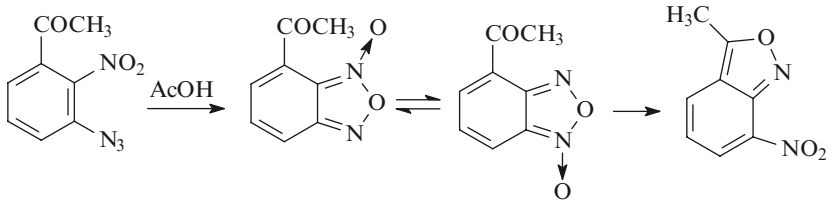
Selective reduction of nitrobenzothiazole *N*-oxides makes it possible to synthesize nitrobenzothiazoles, which so far were difficult or inaccessible to prepare [667–670].

Nitrated benzotriazole and benzofurazan were obtained as a result of an interesting rearrangement in the reaction of 5-dimethylaminobenzofuroxan with 2,4-dinitrobenzenediazonium sulfate or with HNO_2 in H_2SO_4/H_2O-C_2H_5OH (Scheme 2.137) [671].



Scheme 2.137

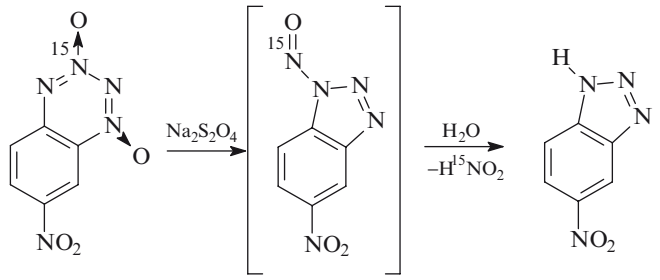
Similarly, heating of 2-NO_2-3-N_3-$C_6H_3COCH_3$ in AcOH to 120° gave nitroanthranyl and not the intermediate benzofuroxan system, as shown in Scheme 2.138 [671].



Scheme 2.138

4,6-Dichloro-5,7-dinitrobenzofuroxan was transformed to 4,6-dichloro-5,7-dinitrobenzofurazan by PPh_3 polymer support [672].

5(6)-Nitrobenzotriazole was obtained by reduction of benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs) with $Na_2S_2O_4$ or $SnCl_2$ via intermediate *N*-nitrosobenzotriazoles (Scheme 2.139) [162].



Scheme 2.139

The ^{15}N-labeling experiments have shown that the ^{15}N-3-labeling atom of N →O fragment of the tetrazine ring is incorporated into the nitroso group of benzotriazole. The authors [162] have suggested the biological activity of BTDOs to be due to their ability to release nitrosating species, that is, *N*-nitrosobenzotriazole, in the course of reduction.

It has already been shown that the nitration with nitric acid in acetic anhydride provides the general way of obtaining *N*-nitroheterocycles. As an alternative synthesis of the aforementioned compounds, and, in particular, 1-nitrobenzotriazole, the reaction of 1-chlorobenzotriazole with the silver nitrate–triphenylphosphite complex can be suggested [273].

Conclusions

The azoles occupy an important place in the chemistry of heterocyclic compounds. Their unique properties and specific biological activity attract much attention of scientists worldwide. A much used and convenient method for the preparation of

nitroazoles is the electrophilic nitration. Electrophilic substitution reaction of azoles and benzazoles is a complex process in which the experimental conditions can modify the product orientation. The ability of azoles to electrophilic substitution is determined by the activity of reagents, the basicity of substrates, and the acidity of medium. The existence of an annelated benzene ring in the benzazole molecule influences much of its ability for electrophilic substitution – all benzazoles are more easily nitrated than their five-membered analogs, and the nitro group is generally introduced into the arylene fragment of the molecule.

The nitration of benzazoles is usually effected using concentrated (65%) to fuming (100%) nitric acid generally at temperature between 0 and 5°C. Indazoles are usually nitrated into 5 position, benzimidazoles – as a rule – into 5- or 6-position of the phenylene fragment whereas benzotriazole into position 4 or 7. For the preparation of other nitrobenzazoles the reaction of heterocyclization is used.

The nitroazoles are widely used in the reaction of vicarious nucleophilic substitution of hydrogen. Vicarious nucleophilic *C*-amination is, practically, the single method of direct introduction of the amino group into nitro compounds. Using the vicarious nucleophilic substitution reaction we have successfully carried out the *C*-amination of some representatives of nitrobenzazoles, nitroazoles, and model compounds thereof and studied the structure of aminated products and the *C*-amination mechanism [673–678].

Recently, the investigations of nitrobenzisoxazoles mainly 6-nitrobenzisoxazole-3-carboxilate ions have received considerable interest due to their participation in reverse micellar systems [679–682]. Reverse micelles are of considerable interest as reaction media because they are powerful models for biological compartmentalization, enzymatic catalysis, and separation of biomolecules. Solutions of ionic surfactants in apolar media may contain reverse micelles, but they may also contain ion pairs or small clusters with water of hydration [679]. Molecular design of nonlinear optical organic materials based on 6-nitrobenzoxazole chromophores has been developed [451].

The polynitrobenzazoles are adequate precursors for the preparation of high-energy compounds. The investigations in the field of polynitro annelated azoles – dinitrobenzimidazoles [683], 4,6-dinitrobenzisoxazoles [684], 4,6-dinitrobenzisothiazoles [685], 4,6-dinitro-2,1,3-benzothiadiazole, 4,6-dinitrobenzo-2,1,3-selenadiazole, 4,6-dinitrobenzotriazoles [686], 4,6-dinitrobenzofurazans [686, 687], 4,6-dinitrobenzofuroxans [686, 688–692] – have great future prospect.

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Structure and Physical–Chemical Properties of Nitroazoles

Abstract The critical evaluation of a large body of the information on five-membered nitroazoles and nitrobenzazoles study by physical chemical methods – nuclear magnetic resonance (NMR), nuclear quadrupole resonance (NQR), electron spin resonance (ESR), ion-cyclotron resonance, UV and IR- spectroscopy, X-ray analysis, mass spectrometry, polarography, dipole moments, chromatography, luminescence, photolysis, etc. is presented. The extensive investigations of structure, tautomerism, and properties of nitroazoles by multinuclear ^{1}H, ^{13}C, ^{15}N, ^{19}F, ^{31}P, ^{29}Si and two-dimensional NMR spectroscopy are reviewed. A great emphasis is given to tautomerism studies of nitroazoles by multinuclear dynamic NMR because prototropic transformations of almost all azoles in solutions proceed so quickly. The mechanisms of electrochemical reactions and vicarious nucleophilic *C*-amination of nitroazoles are discussed. Quantum-chemical investigations of nitroazoles are covered in detail.

Molecular and Crystalline Structure

It is known that *C*-nitropyrazoles are more stable than *N*-nitropyrazoles. Nevertheless it is quite strange that 1-nitropyrazole was among the first of nitropyrazoles, which has been studied using X-ray technique. Bond lengths, valence (O–N–O), and torsion (N2–N1–N–O) angles for the 1-nitropyrazole molecule as well as the same parameters for some other *N*-nitroazoles are given in Table 3.1.

X-ray analysis data indicate that five-membered ring of 1-nitropyrazole remains planar in unsubstituted pyrazole, while nitro group is located in the plane of the ring [1]. The N1–NO_2 bond (1.399 Å) is longer than that of dinitramides O_2N–N–NO_2 (1.370 Å, n = 17), saturated five-membered cycles (1.385 Å, n = 52), and almost coincides with the bond length of the compounds containing 1,3-diazacyclopentan-2-one moiety (1.399 Å, n = 22). The N–NO_2 bond length is considerably longer than that in dimethyl

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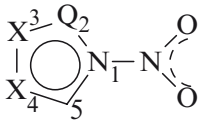


Table 3.1 Bond lengths (Å), valence, and torsion angles for the *N*-nitroazole molecules[a]

Compound	N1-NO_2	N1-Q	N1-C5	O-N-O	Q-N1-N-O	Refs
N-Nitropyrazole	1.399	1.357	1.364	128.536	1.64	[1]
1,4-Dinitroimidazole	1.420	1.374	1.371	129.255	9.84	[2]
1,4-Dinitro-2-isopropyl-imidazole	1.426	1.367	1.392	127.650	4.71 6.22[b]	[3]
1,1′-Dinitro-3,3′-azo-1,2,4-triazole orange polymorph	1.445	1.339	1.376	130.672	3.97	[4]
1,1′-Dinitro-3,3′-azo-1,2,4-triazole yellow polymorph	1.445	1.347	1.349	130.989	3.56	[4]
1,5-Dinitro-1*H*-indazole	1.393	1.366	1.380	127.695	0.23	[5]

[a]X-ray average data in this table; the following tables and text are derived from Cambridge Structural Database [8]
[b]Nitro group in position 4

amine (1.30 Å) and other nitramines (average of 1.372 Å) [6]. This tends to indicate a greater lability of the N–NO_2 bond in *N*-nitropyrazoles than in other aliphatic nitramines. *N*-Nitropyrazoles in the presence of Lewis or Bronsted acid catalysts were found to be effective transfer nitrating agent for aromatic substrates [7].

The N1–N2 (1.357 Å) and N1–C5 (1.364 Å) bonds in 1-nitropyrazole are slightly longer than the corresponding bonds in unsubstituted pyrazoles (1.349 Å and 1.330 Å), which were studied by different authors under various conditions. It is suggested [1] that this fact can be explained by electron-withdrawing character of the nitro group that decreases the double bond degree of these atoms. The absence of these bonds extension during the introduction of bulky substituent into position 1 favors this suggestion. For example, the bond lengths in 1-(adamantyl)-pyrazole are 1.349 and 1.343 [9]. The results of *ab initio* quantum chemical computations of the pyrazole nitro derivatives (6-31G*) [10] also support this hypothesis (Table 3.2).

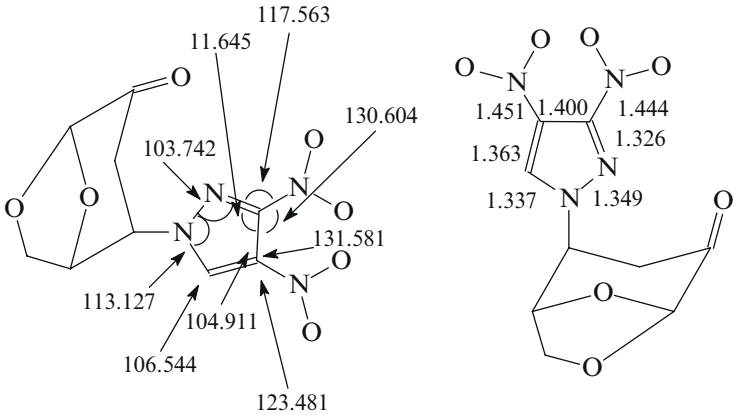


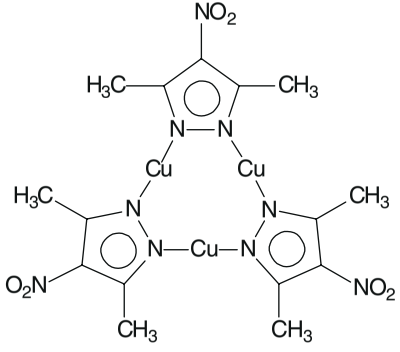
Table 3.2 Bond lengths (Å) and valence angles (°) in nitropyrazoles

Compound	N1-N2	N2-C3	C3-C4	C4-C5	C5-N1	C4-NO_2	C5N1N2	N1N2C3	N2C3C4	C3C4C5	C4C5N1	Refs
4-Nitropyrazole	1.344	1.318	1.371	1.373	1.314	1.416	109.130	108.808	107.800	106.519	107.743	[15]
3-Methyl-4-nitropyrazole	1.365	1.326	1.377	1.412	1.325	1.417	105.867	113.137	105.054	107.491	108.450	[16]
5-Methyl-4-nitropyrazole	1.366	1.319	1.393	1.387	1.338	1.430	113.575	104.950	109.958	107.535	103.958	[16]
3,5-Dimethyl-4-nitropyrazole	1.340	1.318	1.388	1.388	1.318	1.412	109.775	109.775	106.732	106.986	106.729	[17]
4-Nitro-5-(trimethylsilyl)pyrazole	1.363	1.308	1.391	1.386	1.336	1.423	115.288	103.975	110.278	108.243	102.215	[18]
1-(1-Adamantyl-3-ol)-4-nitropyrazole	1.369	1.326	1.376	1.361	1.337	1.428	112.074	104.138	111.038	106.704	106.029	[9]
3,5-Di-*tert*-butyl-4-nitropyrazole	1.360	1.330	1.415	1.389	1.337	1.438	113.703	106.477	107.586	108.471	103.739	[15]
3,5-Diphenyl-4-nitropyrazole	1.349	1.338	1.442	1.417	1.299	1.382	115.458	105.665	108.355	105.294	105.072	[15]
4-Nitropyrazole 3-methyl-5-amino-1,2,4-triazole	1.280	1.418	1.449	1.358	1.316	1.409	114.844	106.205	105.333	105.483	108.066	[19]
3,5-bis-(Dimethylaminomethylen)-amino-1-methyl-4-nitropyrazole	1.353	1.362	1.458	1.447	1.398	1.409	113.744	106.660	109.960	105.150	104.480	[20]
3-Methoxycarbonyl-1-methyl-4-nitropyrazole-5-carboxylic acid monohydrate	1.330	1.333	1.379	1.365	1.347	1.456	112.614	105.743	109.363	107.305	104.975	[21]
4-(3,4-Dinitropyrazolyl)-levoglucosenone	1.349	1.326	1.400	1.363	1.337	1.451	113.127	103.742	111.645	104.911	106.544	[22]
Bis(4-nitropyrazol-1-yl)methane	1.363	1.319	1.394	1.365	1.335	1.426	113.009	104.417	110.513	106.688	105.364	[23]
1,1′-Difluoroamino-3,3′,4,4′-tetranitro-5,5′-bipyrazole	1.346	1.301	1.403	1.367	1.373	1.441	114.692	102.857	113.127	105.779	103.540	[24, 25]
trans,trans-3-Ethoxycarbonyl-2-ethyl-5-methyl-4-nitro-1-phenylpyrazolidine	1.433	1.456	1.515	1.526	1.484	1.497	110.065	103.474	104.610	103.126	103.876	[11]
thiamine picrolonate dihydrate thiamine 3-methyl-4-nitro-1-(*para*-nitrophenyl)-2-pyrazolin-5-onate dehydrate	1.411	1.294	1.419	1.420	1.394	1.377	111.830	106.365	111.001	107.882	102.894	[26]

(continued)

Table 3.2 (continued)

Compound	N1-N2	N2-C3	C3-C4	C4-C5	C5-N1	C4-NO_2	C5N1N2	N1N2C3	N2C3C4	C3C4C5	C4C5N1	Refs
Ammonium 3-amino-4-nitro-1,2-dihydro-5-pyrazolone	1.402	1.328	1.422	1.438	1.352	1.368	112.677	106.961	108.685	107.879	103.637	[27]
4-Nitropyrazole-3,5-dicarboxylic acid bis(dioxane) clathrate	1.344	1.339	1.401	1.369	1.347	1.450	113.192	104.849	109.980	106.450	105.528	[28]
Catena-((4-nitropyrazole-3,5-dicarboxylic acid)-bis(dioxane)-sodium)	1.347	1.341	1.386	1.363	1.339	1.449	114.039	103.821	110.125	107.291	104.724	[29]
5-Methyl-4-nitropyrazole (R,R)-*trans*-4,5-bis(hydroxydiphenyl-methyl)-2,2-dimethyl-1,3-dioxolane toluene clathrate	1.358	1.316	1.390	1.378	1.338	1.429	111.840	106.762	109.079	107.725	104.567	[28]
Tris(μ_2-3,5-dimethyl-4-nitropyrazole)-tri-copper(I)	1.381	1.385	1.381	1.382	1.384	1.382	107.682	107.664	107.764	108.056	107.745	[29]



bis(Triethylammonium) hexakis(μ_2-3,5-dimethyl-4-nitropyrazole)-tetra-copper(I)	1.398	1.318	1.403	1.405	1.323	1.406	108.973	108.803	107.947	106.729	107.541	[29]
bis(μ_2-3,5-Dimethyl-4-nitropyrazole)-bis(cyclohexyliso-cyano)-di-copper(I)	1.388	1.337	1.388	1.374	1.343	1.433	107.690	108.870	107.512	107.527	108.397	[29]
bis(μ_2-3,5-Dimethyl-4-nitropyra-zole)-tetrakis(cyclohexylisocyano)-di-copper(I)	1.389	1.327	1.394	1.399	1.326	1.418	108.650	108.803	107.927	106.722	107.895	[29]
bis(μ_2-3,5-Dimethyl-4-nitropyrazo-le)-bis(triphenylphosphine)-di-copper(I)	1.393	1.327	1.397	1.399	1.328	1.417	108.783	108.882	107.565	107.216	107.538	[29]
(μ_2-oxo)-bis((μ_2-4-Nitropyrazolyl)-chloro-oxo-triphenylphosphine-rhenium(V)	1.394	1.298	1.396	1.368	1.326	1.440	108.018	107.288	110.433	104.774	109.464	[30]

(continued)

Table 3.2 (continued)

Compound	N1-N2	N2-C3	C3-C4	C4-C5	C5-N1	C4-NO_2	C5N1N2	N1N2C3	N2C3C4	C3C4C5	C4C5N1	Refs
bis(μ_2-3,5-Dimethyl-4-nitropyrazol-1,2-diyl)-bis(η_5-cyclopentadienyl)-di-nickel	1.386	1.335	1.390	1.394	1.343	1.427	108.325	109.441	106.969	108.050	107.135	[31]
(μ_2-Oxo)-bis((μ_2-4-nitropyrazolyl)-chloro-oxo-triphenylphosphine-rhenium(V))	1.394	1.298	1.368	1.396	1.326	1.440	108.018	107.288	110.433	104.774	109.464	[32]
bis(μ_2-3,5-Dimethyl-4-nitropyrazol-1,2-diyl)-bis(η_5-cyclopentadienyl)-di-nickel	1.386	1.335	1.394	1.390	1.343	1.427	108.325	109.441	106.969	108.050	107.135	[31]
3-Nitropyrazole	1.332	1.320	1.371	1.350	1.337	1.435[a]	112.631	102.675	113.776	103.494	107.421	[33]

[a]C3–NO_2 bond length

Nitro group of most compounds given in Table 3.2 is either located in the plane or slightly rotated with respect to the pyrazole cycle. When the substituents are introduced into neighbor positions of nitro group, the dihedral angle differs significantly from zero. So, for 3,5-di-*tert*-butyl-4-nitropyrazole [5] it equals to 47.7°, for 3-ethoxycarbonyl-2-ethyl-5-methyl-4-nitro-1-phenylpyrazolidine – 54.7° [11], 4-nitropyrazole-3,5-dicarboxylic acid bis(dioxane) clathrate – 75° [12], and in catena-(4-nitropyrazole-3,5-dicarboxylic acid)-bis(dioxane)-sodium) nitro group is perpendicular to the ring plane (89.6°) [12] (Table 3.2).

Despite the large amount of works dedicated to 4-nitropyrazole derivatives (and maybe owing to this) it was quite difficult to reveal unambiguous trends of geometrical parameter change. Meanwhile it is pertinent to note that geometry of the cycle is not substantially changed during the formation of coordinated compounds that may speak in favor of almost similar crystallographic and coordinated interaction effects.

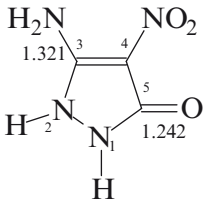
In 3-nitropyrazoles the C–NO_2 bond is longer than that of 4-nitroderivatives, while the N2–C3–C4 angle is significantly greater (Table 3.2).

Cationic complexes Ag with 3,5-dimethyl-4-nitropyrazole containing tetrafluoroborate, trifluoromethanesulfonate, or nitrate as counterions [13] and with 3,5-di(isopropyl)-4-nitropyrazole [14] have been studied by X-ray diffraction. The hydrogen bonding between the pyrazole moieties and the appropriate counterion and the orientation of the NH groups of the pyrazole ligands are determinant of one-dimensional polymeric arrays. 3,5-Dimethyl-4-nitropyrazole serves as *N*-monodentate ligand, which coordinates to the Ag center through its pyrazole nitrogen atom giving rise to an almost linear N-Ag-N geometry. The planar NO_3-counterion bridges two adjacent Ag centers to form a one-dimensional zigzag-shaped chain which is also supported by the presence of N–H...O bonds between the pyrazole NH group of adjacent cationic entities and the remaining O-atom of the bridging NO_3–. The chains are further extended to a two-dimensional layer-like structure through additional Ag...O interactions involving the NO_2 substituents at the pyrazole ligands [13].

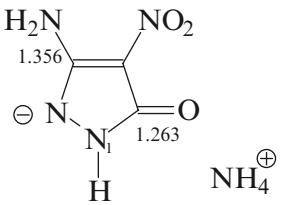
N-unsubstituted pyrazoles form hydrogen-bond networks of great complexity. It is known not less than four fundamental motifs – dimers, trimers, tetramers, and chains – and they are called catemers. One of the most fascinating properties of *N*-unsubstituted pyrazole crystals is the possibility that they present dynamic disorder involving the NH proton of the N–H…N hydrogen bond. This takes place only in cyclic structures (dimers, trimers, tetramers); moreover, the substituents in positions 3 and 5 should be identical. The triclinic unit cell of 3-nitropyrazole contains twelve molecules which form four hydrogen-bonded N–H…N trimers [33]. Each trimer comprises a pseudo ring in a flattened envelope distorted toward a chair conformation. The crystal packing consists of layers formed by centrosymmetric-related trimers joined through C–H…O interactions [33]. The dimer formed by 3,5-di-isopropyl-4-nitropyrazole was a good candidate for solid-state proton transfer [34] considering that 3,5-di-*tert*-butyl-4-nitropyrazole, a dimer [35], shows proton disorder [36]. However 3,5-di-isopropyl-4-nitropyrazole does not present solid-state proton transfer and the NH proton is clearly localized, may be due to the fact that the two isopropyl groups have different orientations [34].

Structural characteristics of nitropyrazolone A and its anion B are essentially differed [8].

A



B



	A	B
N1--N2	1.397	1.406
N2--C3	1.337	1.318
C3--C4	1.416	1.428
C4--C5	1.446	1.429
C5--N1	1.362	1.342
C4--NO2	1.367	1.368
C5--N1--N2	111.393	113.961
N1--N2--C3	108.670	105.252
N2--C3--C4	107.265	110.105
C3--C4--C5	108.697	107.061
C4--C5--N1	103.658	103.615

Desmotropy phenomenon (two tautomers crystallize in two different crystals) has been found for 3-methyl-4-nitropyrazole and its tautomer, 5-methyl-4-nitropyrazole by X-ray and ^{13}C CP/MAS NMR spectroscopy [16].

1-Methyl-3-nitropyrazole has crystallographic *m*-symmetry, while 1-methyl-4-nitropyrazole has no imposed symmetry [37]. The significant differences in bond distances and angles between the structures are ascribable to the electron-withdrawing effects of the nitro group attached to C-3 or C-4, respectively. In both structures, the molecules are organized into layers by an extensive network of C-H…O or C–H…N hydrogen interactions. Within a layer, the molecules are arranged in a similar way, although differences of up to 0.3 Å in the analogous H…O or H…N intermolecular distances are observed. The cohesion of the layers is due to Van der Waals and C–H…O contacts [37].

The structure of nitroimidazoles has been studied more thoroughly and can be explained by wide application of these compounds, especially in medicine. In Table 3.3 some structural characteristics (X-ray and neutron study) for the imidazole and 2-nitroimidazole derivatives are given.

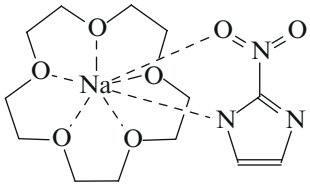
Molecules of 2-nitroimidazole (azomycin) are almost plane [41]. They are packed in layers due to the formation of either N1–H...N3 or C–H...O hydrogen bonds, caused by dipole-dipole interactions [41]. Intramolecular hydrogen bonds N1–H...N3 were also found in 2-methyl-4-nitroimidazole [54]. Availability of such bond provides for easy migration of proton from N1 to N3 during the dissolution in the corresponding solvents. The bond lengths in the imidazole ring are not practically changed when the nitro group is introduced into position 2. At the same time,

Table 3.3 Bond lengths (Å) and valence angles (°) in 2-nitroimidazoles

Compound	N1-C2	C2-N3	N3-C4	C4-C5	C5-N1	C2-NO_2	C5N1C2	N1C2N3	C2N3C4	N3C4C5	C4C5N1	Refs
Imidazole	1.340	1.320	1.368	1.355	1.364	–	106.436	112.350	104.747	109.924	106.540	[38–40]
2-Nitroimidazole	1.343	1.318	1.370	1.376	1.369	1.432	105.278	114.324	103.804	109.997	106.597	[41]
1-Methyl-2-nitro-5-vinyl-imidazole	1.339	1.316	1.321	1.397	1.380	1.524	102.706	117.903	101.102	113.016	104.978	[42]
2,4-Dinitroimidazole	1.363	1.287	1.337	1.371	1.360	1.468	106.059	114.931	101.435	115.153	102.402	[2]
1,8-Bis(dimethylamino)naphthalene 2,4-dinitroimidazolate	1.349	1.326	1.342	1.384	1.336	1.437	101.075	119.116	99.514	111.685	108.585	[43]
1-Methoxy-3-(2-nitro-1-imidazolyl)-2-propanol	1.359	1.307	1.366	1.356	1.361	1.434	104.451	113.801	104.233	109.946	107.569	[44]
1-(1-Aziridinyl)-3-(2-nitro-1-imidazolyl)-2-propanol	1.352	1.301	1.348	1.366	1.360	1.439	104.923	114.148	103.785	111.135	105.999	[45]
1-(2-Methyl-1-aziridinyl)-3-(2-nitro-1-imidazolyl)-2-propanol	1.354	1.310	1.360	1.362	1.362	1.437	104.735	114.108	103.695	110.651	106.809	[45]
N-(1-(2-Hydroxyethyl)-2-nitro-1*H*-imidazol-1-yl)acetamide	1.354	1.303	1.359	1.357	1.368	1.435	104.554	114.435	103.443	111.223	106.342	[46]
1-(2-(3-(4-(1,2-Dicarba-closo-dodecaboran-(12)-1-ylmethoxy)phenyl) isoxazol-5-yl)ethyl)-2-nitroimidazole	1.383	1.294	1.371	1.436	1.280	1.426	106.273	111.831	107.374	104.706	109.412	[47]
(15-Crown-5)-(2-nitroimidazolato)-sodium	1.331	1.338	1.327	1.386	1.355	1.400	101.882	117.822	101.032	111.279	107.971	[48]
Rac-(3,3,9,9-tetramethyl-1-(2-nitro-1*H*-imid-azolyl)-4,8-diazaundecane-2, 10-dionedioxi-mato-N,N′,N″,N‴)-oxo-technetium(V)	1.350	1.299	1.354	1.342	1.373	1.430	104.059	114.346	103.746	111.095	106.718	[49]
cis-Amine-dibromo-(1-((((2-hydroxyethyl)-amino)carbonyl)methyl)-2-nitroimidazole)-platinum(II)	1.337 1.330	1.323 1.290	1.375 1.371	1.343 1.340	1.344 1.339	1.430 1.477	107.604 105.985	111.112 114.462	104.807 102.392	109.551 111.175	106.890 105.969	[50] [51]
trans-Dichloro-bis(misonidazole)-platinum(II)	1.334	1.301	1.394	1.314	1.394	1.445	105.904	112.386	105.030	109.860	106.755	[52]
trans-Dichloro-bis(1-(2′-hydroxy-3′-metho-xypropyl)-2-nitroimidazole)-platinum(II)	1.338	1.299	1.383	1.338	1.353	1.464	104.939	112.261	106.513	106.554	109.734	[53]

the valence angles are altered significantly. The increase of angle of the imidazole ring at the atom attached to the nitro group as well as decrease of the adjacent angles is caused by electron-acceptor effect of the nitro group. Similar effect is observed for the most other nitroimidazoles (see tables). The exception is some compounds, such as, complexes with platinum, 1-(2-(3-(4-(1,2-dicarba-closo-dodecaboran(12)-1-ylmethoxy)phenyl)isoxazol-5-yl)ethyl)-2-nitroimidazole, where this angle is lower than in the imidazole.

Geometrical deformations in adduct of 2-nitroimidazole with sodium derivatives of crown ether (15-crown-5)-(2-nitroimidazolato)-sodium are observed [48].



The crystal structure of 4(5)-nitro-5(4)-methoxyimidazole contains a 1:1 mixture of two tautomers, 4-nitro-5-methoxy- and 5-nitro-4-methoxyimidazole [55]. This is one of the very few cases of 4,5-disubstituted imidazoles for which there are two annular tautomers in the crystal. The molecular structure is the superposition of these tautomer forms. The structure is centrosymmetric and the N-H hydrogen atoms are disordered over two ring N atoms. Owing to the hydrogen-bond pattern, the values of their site occupation factors have to be exactly equal to 1/2. The molecules are connected into a three-dimensional network by means of N–H…N and C–H…O hydrogen bonds [55].

The molecules of 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole are bound by hydrogen bonds O–N...N3 (2.816 Å) into crystalline structure [56]. In this compound the nitro group is rotated by 4.3° with respect to the imidazole ring plane, while the effect of NO_2 on valence angles of the imidazole cycle is similar to that of 2-nitroimidazole [41], *O*-methyl-[2-(2-methyl-5-nitroimidazole-1-yl)-ethyl]thiocarbamate (sulnidazole) [57], and *O*-methyl-[2-(2-methyl-5nitroimidazole-1-yl) ethyl]thiocarbamate monohydrate (carnidazole) [58]. In the latter case the role of water in the formation of three types of hydrogen bonds, i.e., with oxygen atoms of the nitro group (O–H...N, 3.062 Å), nitrogen atoms of the imidazole cycle (O–H...N; 2.818 Å), and thiocarbamate groups (N–H...O; 2.806 Å), was noted. Rather high deviation of the nitro group from the ring plane (8.2°) is observed for 5-methoxy-1-methyl-4-nitroimidazole [59] (Table 3.4), which results from steric interactions.

In this connection the results of the work [3] dedicated to the determination of 2-isopropyl-1,4-dinitroimidazole look quite unexpected. It is an open question why the angle between the nitro group plane at the N-1 atom and the imidazole ring plane (7.3°) is lesser than the analogous angle of the nitro group at the C-4 atom (10.0°). In addition, one should bear in mind that steric hindrances might appear between isopropyl substituent and the nitro group at the N-1 atom. From other side, in 1,4-dinitroimidazole, where such interactions are absent, rotation angle of the

Table 3.4 Bond lengths (Å) and valence angles (°) in nitroimidazole derivatives

Compound	N1-C2	C5-N1	C2-N3	N3-C4	C4-C5	C-NO2	C5-N1-C2	N3-C2-N1	N1-C5-C4	N3-C4-C5	C4-N3-C2	Refs
4-Nitroimidazole	1.348	1.350	1.319	1.363	1.361	1.420	108.006	112.039	104.369	112.176	103.408	[60]
	1.357	1.356	1.316	1.367	1.360	1.427	107.937	111.856	104.251	112.369	103.586	[61]
1-Trityl-4-nitroimidazole	1.367	1.361	1.307	1.361	1.359	1.434	106.302	113.366	104.480	113.116	102.733	[62]
1-Mesitylsulfonyl-4-nitroimidazole	1.378	1.370	1.301	1.362	1.348	1.444	107.232	111.871	103.502	113.802	103.592	[63]
2-Methyl-4-nitroimidazole	1.357	1.344	1.308	1.360	1.351	1.419	108.458	110.906	104.199	112.218	104.219	[54]
2,5-Dimethyl-4-nitroimidazole	1.363	1.360	1.311	1.376	1.362	1.416	109.073	111.250	103.013	113.037	103.621	[64]
2-Methyl-1-phenyl-4-nitroimidazole	1.377	1.352	1.307	1.351	1.349	1.416	107.442	110.997	104.311	112.996	104.248	[65]
2-Methyl-1-(*para*-methylphenyl)-4-nitroimidazole	1.378	1.354	1.316	1.358	1.352	1.417	107.567	110.419	105.054	111.980	104.978	[65]
1,4-Dinitroimidazole	1.374	1.371	1.300	1.378	1.354	1.440	109.934	110.257	101.635	114.060	104.113	[2]
1,4-Dinitro-2-isopropylimidazole	1.392	1.367	1.304	1.364	1.345	1.436	109.355	108.648	102.914	113.293	105.785	[3]
2,4-Dinitroimidazole	1.363	1.360	1.287	1.337	1.371	1.430	106.059	114.931	102.402	115.153	101.435	[66]
4-Nitro-5-chloroimidazole	1.360	1.347	1.311	1.356	1.364	1.441	106.789	112.286	105.427	111.448	104.043	[67]
6-((1-Methyl-4-nitroimidazol-5-yl)-mercapto)purine dehydrate	1.360	1.366	1.305	1.353	1.371	1.434	107.179	112.846	103.451	113.054	103.467	[68]
4-Nitro-L-histidine monohydrate	1.360	1.362	1.310	1.365	1.386	1.421	108.519	112.402	102.728	112.912	103.440	[69]
	1.361	1.355	1.318	1.365	1.380	1.418	109.309	110.987	103.034	112.418	104.196	
penta-Amine-(4-nitroimidazolato)-cobalt(III) dichloride monohydrate	1.364	1.356	1.328	1.360	1.379	1.421	104.939	114.457	106.408	111.636	102.560	[70]
3-(1-Methyl-4-nitro-5-imidazolyl)-thio-1*H*-1,2,4-triazole	1.353	1.361	1.320	1.349	1.379	1.430	107.481	112.209	104.145	112.012	104.131	[71]
6-((1-Methyl-4-nitroimidazol-5-yl)-thio) purine	1.320	1.359	1.308	1.290	1.353	1.462	101.871	118.354	105.007	115.071	99.508	[72]
5-(3′-Hydroxypyridyl-2′-thio)-4-nitro-1-methylimidazole	1.353	1.377	1.315	1.361	1.381	1.432	107.832	112.345	103.350	112.284	104.184	[73]
5-Methoxy-1-methyl-4-nitroimidazole	1.356	1.357	1.312	1.373	1.366	1.419	106.746	113.311	105.041	111.833	103.060	[59]
tert-Butyl 5-bromo-2-methyl-4-nitro-1H-imidazole-1-carboxylate	1.377	1.387	1.320	1.381	1.360	1.464	107.325	112.200	103.680	113.447	103.267	[74]

(continued)

Table 3.4 (continued)

Compound	N1-C2	C5-N1	C2-N3	N3-C4	C4-C5	C-NO2	C5-N1-C2	N3-C2-N1	N1-C5-C4	N3-C4-C5	C4-N3-C2	Refs
1-(4-Chlorophenacyl)-2-methyl-4-nitro-5-piperidinoimidazole	1.382	1.377	1.308	1.373	1.380	1.412	107.972	111.517	103.339	112.475	104.624	[75]
Ethylenediamine-(4-nitrohistidinato-N,N′,O)-chloro-cobalt(III) monohydrate	1.331	1.366	1.325	1.368	1.369	1.417	105.690	114.782	105.790	111.292	102.421	[76]
tetrakis(acetato-O,O′)-bis((6-(1-Methyl-4-nitroimidazol-5-yl)thio)purine)-dirhodium(II) (1-dimethylamino) acetone solvate	1.362	1.380	1.292	1.352	1.354	1.427	108.256	111.058	102.407	113.283	104.979	[77]
tetrakis(μ_2-3-(1-(4-Nitroimidazolyl) pro-pionato-O,O′))-diaqua-di-copper(II) dihydrate	1.353	1.358	1.308	1.348	1.365	1.434	106.677	113.037	104.325	112.546	103.395	[78]
bis(4-Nitroimidazole)-silver nitrate	1.341	1.343	1.310	1.365	1.364	1.423	107.719	112.004	105.455	110.360	104.460	[79]
bis(4-Nitroimidazole)-silver tetrafluoroborate	1.335	1.351	1.303	1.360	1.349	1.425	108.440	111.512	104.101	111.637	104.308	[79]
5-Benzylamino-1-methyl-4-nitroimidazole	1.395	1.368	1.288	1.374	1.400	1.382	105.900	114.512	103.848	112.647	103.087	[80]
(S)-(-)-1-(3-Chloro-2-acetoxypropyl)-2-methyl-4-nitroimidazole	1.384	1.362	1.311	1.361	1.358	1.428	107.237	111.286	104.379	112.826	104.262	[81]
bis((μ_2-6-(1-Methyl-4-nitro-5-imidazolylthio)-7*H*-purine-N3,N9)-dichloro-copper(II)) dimethyl-formamide solvate bis((μ_2-Azathioprine-N3,N9)-dichloro-copper(II)) dimethyl-formamide solvate	1.346	1.364	1.275	1.355	1.359	1.421	104.868	115.231	104.979	111.718	103.189	[81]
(1-Methyl-4-nitro-5-styryl)imidazole	1.362	1.385	1.295	1.356	1.387	1.425	107.553	113.040	102.202	113.211	103.979	[82]
1-(*N*-Morpholino)-4-nitroimidazole	1.378	1.371	1.304	1.412	1.334	1.429	106.360	113.528	105.290	112.864	101.958	[83]
bis(bis(μ_3-Azathioprine)-(μ_3-hydroxo)-(μ_2-2,2,6,6-tetramethylheptane-3,5-dionato)-tetrakis(2,2,6,6-tetramethylheptane-3,5-dionato)-tetra-copper(II)) acetonitrile solvate	1.366	1.360	1.312	1.357	1.375	1.463	106.863	114.104	102.922	114.618	101.337	[84]

Methyl-(4-nitroimidazolato-*N*)-mercury(II)	1.343	1.374	1.358	1.365	1.422	1.353	103.930	115.807	107.977	108.868	103.368	[85]
1-(4-Chlorophenacyl)-2-methyl-5-morpholino-4-nitroimidazole	1.399	1.384	1.298	1.369	1.378	1.431	108.668	110.137	102.381	112.971	105.830	[86]
1-(*para*-Acetylphenyl)-2-methyl-4-nitroimidazole	1.379	1.366	1.307	1.358	1.362	1.422	107.686	111.094	103.754	112.859	104.593	[84]
	1.386	1.369	1.313	1.354	1.352	1.430	107.298	110.893	103.961	113.492	104.347	
1-(4-Chlorophenacyl)-2-methyl-5-piperazino-4-nitroimidazole hydrochloricde methanol solvate	1.375	1.389	1.303	1.370	1.366	1.421	107.829	111.670	102.787	113.239	104.438	[87]
(S,S,S)-*cis*-4-Phenoxy-1-(1-oxo-2(S)-(4-nitro-1*H*-imidazol-1-yl)octyl)-L-proline methyl ester	1.376	1.378	1.297	1.340	1.341	1.434	105.407	112.697	104.248	113.846	103.747	[88]
1-Benzyl-5-methoxycarbonylmethylthio-4-nitroimidazole	1.353	1.376	1.304	1.356	1.377	1.427	107.155	113.324	103.098	112.974	103.442	[89]
1-(4-Chlorophenacyl)-2-methyl-4-nitro-5-pyrrolidino-imidazole	1.371	1.376	1.308	1.369	1.373	1.424	108.235	111.482	103.083	112.736	104.463	[90]
4,4′-Dinitro-2,2-bi-imidazole dimethylformamide solvate	1.357	1.357	1.312	1.358	1.359	1.435	106.786	112.782	104.676	112.511	103.237	[91]
Ammonium 1-(2-(ethylsulfonyl) ethyl)-4,5-dihydro-2-methyl-4-nitro-1H-imidazol-5-one	1.391	1.395	1.300	1.388	1.427	1.363	109.183	111.813	101.533	112.030	105.431	[92]
4,4′,5,5′-tetranitro-2,2′-bi-imidazole dehydrate	1.331	1.334	1.348	1.349	1.377	1.426	104.286	112.536	111.036	105.986	106.153	[93]
	1.348	1.349	1.331	1.334	1.377	1.449	106.153	112.536	105.986	111.036	104.286	
BIS(ethylenediamine)-(4-nitroimidazolato)-chloro-cobalt(III) chloride monohydrate	1.338	1.367	1.335	1.362	1.367	1.420	106.650	111.305	107.312	108.543	106.180	[94]
1,8-Bis(dimethylamino)naphthalene 2,4-dinitroimidazolate	1.349	1.336	1.326	1.342	1.384	1.427	101.075	119.116	108.585	111.685	99.514	[95]

(continued)

Table 3.4 (continued)

Compound	N1-C2	C5-N1	C2-N3	N3-C4	C4-C5	C-NO2	C5-N1-C2	N3-C2-N1	N1-C5-C4	N3-C4-C5	C4-N3-C2	Refs
(μ_2-trans-4,4′-Dinitro-2,2′-bi-imidazola-to-N,N′:N″,N‴)-tetrakis(triphenylphos-phine)-di-copper(I) N,N-dimethyl-formamide solvate	1.345	1.361	1.342	1.352	1.369	1.434	103.174	115.870	108.021	111.106	101.778	[96]
Dichloro-bis(2-methyl-4-nitroimidazolato-N,O)-copper(II)	1.365	1.354	1.330	1.370	1.366	1.429	110.138	109.013	103.675	111.781	105.377	[97]
Potassium 4,5-dinitroimidazole	1.340	1.346	1.339	1.346	1.394	1.437	102.947	116.014	109.032	109.024	102.980	[98]
Diammonium 4,4′,4,4′-tetranitro-2,2′-bi-imidazole	1.346	1.348	1.346	1.346	1.379	1.433	102.283	115.966	109.761	109.416	102.570	[99]
1,1′-Dimethyl-4,5′-dinitro-2,2′-bi-imidazolyl	1.333	1.357	1.352	1.377	1.362	1.433	105.568	112.983	108.708	108.709	104.030	[100]
	1.377	1.363	1.325	1.351	1.351	1.448	107.225	111.164	104.332	113.540	103.738	
1,2,3,4-Detrahydro-2,4,4-trimethyl-8-nitroimidazo(1,5-d)(1,2,4)triazine-1-one	1.354	1.367	1.316	1.363	1.368	1.438	107.103	112.842	104.287	112.364	103.395	[101]

nitro group at the N-1 atom is higher than at the C4 atom (9.4 and 1.9°, respectively) [2] (Table 3.4).

In 1-methyl-2,4,5-trinitroimidazole the bonds of C2-N2, C4-N4 and C5-N5 of nitro groups are not coplanar with the imidazole ring and displaced −0.0975 Å, −0.0676 Å and 0.1100 Å from the imidazole ring, respectively. The 2-, 4-, and 5-nitro groups are also twisted out of the imidazole plane by 24.2°, 9.8°, and 39.5°, respectively [102]. The bond lengths within the planar imidazole ring are similar to those of 2,4-dinitroimidazole [66]. The shortest C–N bond in 1-methyl-2,4,5-trinitroimidazole is C2–N3 – 1.2970(18) Å which means a double bond localization, and this is in good agreement with those reported in 2,4-dinitroimidazole [66] and 1,4-dinitroimidazole [2].

The determination of X-ray structure of 2-methyl-5-nitro-1-phenacyl-4-phenylaminoimidazole has been carried out [103]. The nitro and phenylamino groups on the one hand and the phenacyl residue on the other hand subtend very different interplanar angles to the imidazole ring. The dihedral angles between the planar phenylamino and nitro groups and the imidazole ring are 8.82(7) and 3.77(11)°, respectively, showing conjugation between these groups and the imidazole moiety. The resonance interaction is reflected in a significant shortening of the C–NO_2 bond length [1.3577(19) Å] [103], compared with the regular single bond Csp^2–NO_2 (1.468 Å [104]). Deformation of aromaticity in ammonium 1-(2-(ethylsulfonyl)ethyl)-4,5-dihydro-2-methyl-4-nitro-1-*H*-imidazol-5-one leads to the dramatic changes in the bond lengths.

The formation of 4-nitroimidazole complexes, such as pentamine-(4-nitroimidazolato)cobalt chloride, involves no deformation of coplanarity between the nitro group and the imidazole ring [70].

X-ray studies were also performed for bis(1,2,3,5-tetramethyl-4-nitropyrazolium salt [105], 1-methyl-4(5)-nitro-5(4)-styrylimidazole [82], 1-(*N*-morpholino)-4-nitroimidazole [83], 1-sodium salt of 4-[2-[(1-methyl-5-nitro-2-imidazolyl)thio] ethoxy]-benzoic acid [106], 1-methyl-4-nitro-5-chloroimidazole [107], ornidazole [81], megazole [108], 1-methyl-2-nitro-5-vinylimidazole [42], 1-[2-(ethylsulfonyl) ethyl]-2-methyl-5-nitroimidazole (tinidazole) and one of the basic tinidazole metabolites – ammonium salt of 1-[2-(ethylsulfonyl)ethyl]-4, 5-dihydro-2-methyl-4-nitroimidazole-5on [109], morpholino nitroimidazole derivatives [110, 111], 1-(2-bromoethyl)-2-methyl-5-nitroimidazole [112], 1-(4-chlorophenacyl)-2-methyl-4,5-dinitroimidazole [113], 4-methylacetophenone [(2-methyl-4-nitro-1*H*-imidazol-1-yl)acetyl] hydrazone [114], 2-(5-bromo-2-methyl-4-nitroimidazol-1-yl) 1-(2-chlorophenyl)ethanone [115], dimethyl (2E)-2-(4-nitroimidazol-1-yl)but-2-enedioate [116], 2-(1-methyl-5-nitroimidazol-4-ylmethylene)malonate [117], and other nitroimidazoles [118, 119]. Three polymorphic modifications of 1-methyl-2-nitro-5-vinylimidazole were found and investigated [42].

It is interesting to note that the bond lengths C-S in two structurally related compounds 1-(mesityl-2-sulfonyl)-3-nitro-1,2,4-triazole [120] and 1-(mesitylsulfonyl)-4-nitroimidazole [121] are similar (1.761 and 1.758 Å), while the S-N bond in imidazole analog is significantly shorter (1.736 and 1.708 Å).

In the crystals of 1-methoxy-3-(2-nitro-1-imidazolyl)-2-propanole (misonidazole) molecules are located as “head to tail,” while imidazole cycles are almost

parallel to each other, and nitro group is rotated by 7.9° with respect to the imidazole ring plane [44].

The dihedral angles between the imidazole ring and the attached nitro group in 1-(2-chloroethyl)-2-methyl-5-nitroimidazole (chlorometronidazole) [122] and 1-(2-iodoethyl)-2-methyl-5-nitroimidazole (iodometronidazole) [123] are 6.5 and 7.8°, correspondently.

1-(4-Nitrophenyl)-2-methyl-4-nitroimidazole and 1-phenyl-2-methyl-4-nitro-5-bromoimidazole have been studied by X-ray crystallography [124]. Crystals of 1-phenyl-2-methyl-4-nitro-5-bromoimidazole have undergone two reversible phase transitions between 295 and 100 K. Neither the molecular geometry nor the crystal packing shows any dramatic changes during these phase transitions. Halogen bonds C–Br…N and dihalogen interactions Br…Br play a crucial role in crystal packing determination and compete successfully with other kinds of weak intermolecular interactions [124]. The crystal structures of 1-allyl- and 1-(2-bromoethyl)-2-methyl-4-nitroimidazole have been determined by means of X-ray diffraction at 100 K [125]. In both cases the compounds crystallize with two different symmetry-independent molecules in the asymmetric part of the unit cell. The main motifs of crystal packing-molecular tapes are created by C-(HN)-N-... and strengthened by secondary C-(HO)-O-... hydrogen bonds. The tapes form bilayers via π,π-interaction. The creation of these bilayers, the primary building blocks of the crystal structures, is possible because two symmetry-independent molecules have different conformations or take part in different intermolecular interactions [125].

X-ray analysis data of platinum metronidazole complexes [126, 127] and other 5-nitroimidazole derivatives – pharmaceutical products [53, 73, 128–134] have been described. The molecules of ronidazole [(1-methyl-5-nitro-2-imidazolyl) methyl carbamate] are stacked in planes parallel to crystallographic *b* axis [135]. These molecular layers are built up by three hydrogen bonds. A fourth hydrogen bond connects these layers perpendicularly. The nitro group is turned by 11.1(1)° from the imidazole ring plane [128]. The molecules of 2-(5-nitro-2-styryl-1-imidazolyl)ethanol are linked in chains through hydrogen bonds O–H…N [1.99(3) Å] [133]. Nitro group is slightly rotated [4.7(1)°] with respect to the imidazole ring.

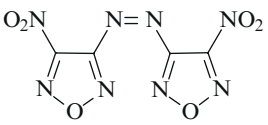
The structure of various nitrofurazans, high energetic compounds has been established in detail by an X-ray monocrystal investigation [135–142]. 3-Amino-4-nitrofurazan in the crystal cell has two independent molecules with some different conformations therewith the molecules are bound by hydrogen bonds N-H...N (2.68 Å) in chain dimers [135]. The crystal of bis(3-nitrofurazan-4-yl) ether (C4N6O7) has two independent molecules which consist of two approximately planar nitrofurazan moieties [140]. The intramolecular nonbonded contacts of nitrogen atoms N5–N5′ of both molecules are equal to 2.74 and 2.94 Å and are shorter than the two-fold Van der Waals radius (3.2 Å). The bond lengths and bond angles in the independent molecules are close to the standard values. The packing coefficient in the crystal is 0.653 [140]. In the sulfur analog of this compound the furazan rings are also planar and the nitro groups are almost coplanar with their heterocycles; the dihedral angles cycle/nitro group are 2.6 and 12.3° [142]. The dihedral angle between the nitrofurazan moieties is 107.8°. The S…O (NO_2)

intramolecular distance is shorter than the sum of the Van der Waals radius (2.922 Å). This distance corresponds to a S…O secondary bond which supplements the coordination of the S atom to a T-shape [142].

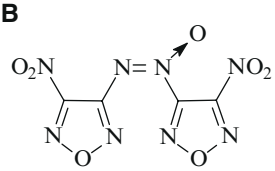
The structure of the nitroazofurazan derivatives has been studied in [137–139, 143].

Dinitroazofurazan **A** and dinitroazoxyfurazan **B** have two independent molecules in their crystal cells, but nitroaminoazoxyfurazan **C** – only one molecule [139, 143]. As expected the azo linkage possessed a *trans* geometry. The N=N double bond length (1.243 Å) in dinitroazofurazan **A** [139, 143] was comparable to the N=N double bond length of azobenzene and was slightly shorter than the azoxy N=N bond length of **B** (1.30 Å [143]) and **C** (1.31 Å [137, 143]).

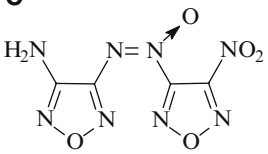
A



B



C



The C=C bond length in the furazan rings of **B** (1.402, 1.409, 1.409, 1.403 Å) was shorter than those observed on other furazan derivatives (1.413 to 1.446 Å) reported in the Cambridge Crystal Structure Database, including 3-amino-4-nitrofurazan [135]. Molecules of **A** are planar (±0.05 Å) throughout their azofurazan system [139]. The nitro groups on rings make dihedral angles of 4.8° and 85.4° with the azofurazan plane. In the other molecule, the dihedrals in rings are 8.1 and 81.9°. So, there is one nitro group which is perpendicular to the azofurazan π-system. This orientation is one way to minimize the electrostatic repulsion between the close electron-rich oxygen atoms of the two nitro groups [139].

The 1:1 cocrystal of 2-amino-5-nitrothiazole with 4-aminobenzoic acid comprises two constituent molecules associated by a hydrogen-bonded graph set dimer through the carboxylic group across the N/N site of the thiazole [O–H…N, 2.614(3) Å; N–H…O, 2.991(3) Å] [144]. 2-Bromo-5-nitrothiazole [145], tetrakis (*meta*-acetato)bis[2-(2-thionyl)-amino-5-nitrothiazole]-dirhodium-II-dihydrate [146], and *N*-(4-methoxybenzyl)-*N′*-(5-nitro-1,3-thiazol-2-yl) urea [147] have been studied by X-ray analysis.

Crystalline and molecular structure of 3-nitro-1,2,4-triazole [148, 149] and its derivatives have been investigated (Table 3.5). Intermolecular hydrogen bonds between the N-1 and the N-4 atoms were found. It was also shown that in crystalline form only 5-nitroisomer exists, while the nitro group is rotated by 2.94° with respect to the ring plane [149]. In 1-methyl-3,5-dinitro1,2,4-triazole the distance from the 1,2,4-triazole cycle to the nitro group in position 5 is shorter than the distance to the nitro group in position 3. At the same time the latter is deviated from the ring plane by the higher angle than the nitro group at the C-5 atom. Thus, the date obtained has revealed a spatial nonequivalence of the nitro group in positions 3 and 5, but the previous suggestions [150, 151] on noncoplanarity of the nitro group in position 5 of this compound were not proven.

Table 3.5 Bond lengths (Å) and valence angles (°) in nitrotriazoles

Compound	C5-N1	N1-N2	N4-C5	C3-N4	N2-C3	C3-NO_2	C5-N1-N2	N1-C5-N4	C3-N4-C5	N2-C3-N4	N1-N2-C3	Refs
3-Nitro-1,2,4-triazole	1.323	1.356	1.321	1.339	1.307	1.449	109.947	110.948	101.089	117.151	100.861	[149]
3-Amino-5-nitro-1,2,4-triazole	1.350	1.369	1.334	1.344	1.308	1.447	110.610	109.519	101.471	118.317	100.081	[152]
1-Methyl-3,5-dinitro-1,2,4-triazole	1.325	1.341	1.318	1.318	1.325	1.457	104.634	115.660	99.409	115.660	104.634	[153]
8-Quinolinesulfone-(3-nitro-1,2,4-triazolide)	1.366	1.373	1.303	1.347	1.304	1.459	110.153	110.100	101.369	119.278	99.098	[154]
1-(Mesityl-2-sulfonyl)-3-nitro-1,2,4-triazole benzene solvate	1.350	1.359	1.311	1.341	1.308	1.448	109.986	110.427	101.318	118.125	100.141	[119]
3,3′-Dinitro-5,5′-bi-(1,2,4-triazole) dehydrate	1.347	1.356	1.325	1.340	1.315	1.454	108.921	111.202	101.007	117.280	101.585	[155]
3-Nitro-3′-chloro-1H-5,1′-bi-1,2,4-triazoline	1.325	1.354	1.309	1.343	1.306	1.464	108.899	113.136	98.962	118.727	100.274	[156]
Ethylenediammonium bis(3-nitro-1,2,4-triazol-5-olate)	1.361	1.364	1.356	1.336	1.306	1.450	111.447	107.827	101.779	118.917	100.026	[157]
1,3-Diaminoguanidinium 3-nitro-5-oxo-1,2,4-triazolide	1.367	1.363	1.353	1.334	1.309	1.449	111.209	107.729	102.217	118.567	100.275	[158]
3-Amino-5-nitro-1,2,4-triazole monohydrate	1.357	1.367	1.342	1.337	1.305	1.445	110.394	109.147	101.437	118.689	100.326	[159]
Hydrazinium 3-amino-5-nitro-1,2,4-triazolide	1.344	1.386	1.341	1.341	1.309	1.438	105.468	113.864	99.964	116.992	103.710	[152]
hexa-aqua-Cobalt bis(3-nitro-1,2,4-triazol-5-one) dehydrate	1.358	1.364	1.358	1.343	1.303	1.444	111.653	107.810	101.685	118.728	100.121	[160]
hexa-aqua-bis(3-Nitro-1,2,4-triazol-5-onato)-dysprosium 3-nitro-1,2,4-triazol-5-one tetrahydrate	1.362	1.364	1.352	1.339	1.300	1.455	111.273	107.990	101.677	118.961	100.090	[161]
bis(3-Nitro-1,2,4-triazol-5-olato)-(nitrato)-penta-aqua-yttrium dehydrate	1.352	1.361	1.364	1.317	1.383	1.406	111.973	108.567	103.170	116.624	99.581	[162]

penta-aqua-tris(3-Nitro-1,2,4-triazol-5-onato)-europium pentahydrate	1.351	1.356	1.347	1.343	1.304	1.437	111.366	108.230	101.917	117.802	100.675	[163]
2-Azidoethylammonium 3-nitro-1,2,4-triazol-5-onate	1.357	1.363	1.348	1.339	1.305	1.454	111.386	108.676	100.871	119.635	99.415	[164]
N-(2-Hydroxyethyl)-2-(3-nitro-1,2,4-triazol-1-yl)acetamide	1.334	1.351	1.322	1.338	1.311	1.447	110.110	110.568	101.193	117.360	100.760	[165]
5-(1-Aziridinyl)-3-nitro-1-(3-oxo-butyl)-1,2,4-triazole	1.349	1.359	1.329	1.337	1.309	1.451	109.689	110.556	100.710	118.488	100.555	[165]
3-Amino-1,2,4-triazolium 3-nitro-1,2,4-triazol-5-one	1.370	1.366	1.360	1.336	1.309	1.448	110.867	107.661	102.404	118.140	100.925	[166]
diaqua-bis(3-Nitro-1,2,4-triazol-5-one-N)-copper(II) dehydrate	1.370	1.365	1.368	1.349	1.299	1.443	112.064	105.908	103.645	117.011	101.367	[167]

Structural analog of 3-nitro-1,2,4-triazole – bis-(3-nitro-1,2,4-triazole-5-yl) is crystallized as dihydrate, which is bound to the triazole cycle by strong hydrogen bond N–1–H...O (water) [155]. Bond lengths and valence angles of the triazole cycle are similar to these of 3-nitro-1,2,4-triazole, but the angle between plane triazole cycle and nitro group is slightly higher than 4.3°[155]. On the other hand a molecule of 3-nitro-1-nitromethyl-1,2,4-triazole consists of three planar fragments twisted in relation to each other, namely a triazole cycle, nitromethylene fragment, and nitro group [168]. Molecular conformation analysis shows that the first stage of thermal decomposition is a breakage of the $H_2C–NO_2$ bond.

The crystal cell of 5-acetylamino-3-nitro-1,2,4-triazole contains two molecules with identical planar form which have intramolecular hydrogen bond N–H…O [169].

The molecule of 3-nitro-3′-chloro-1*H*-bi-1,2,4triazole-5,1′-yl has transoid conformation, where the substituents (chlorine and nitro group) are most distant from each other and the rotation angle of two triazole rings is 5°, while the nitro group is rotated by 4° with respect to the triazole cycle [156]. Molecular and crystalline structures of 1-methyl-3,5-dinitro-1,2,4-triazole [153] and 1-(mesityl-2-sulfonyl)-3-nitro-1,2,4-triazole were determined [119].

X-ray crystal structure of the potassium dihydrobis(3-nitro-1,2,4-triazolyl) borate is reported [170]. The potassium salt is polymeric and shows several K...N and K...O interactions.

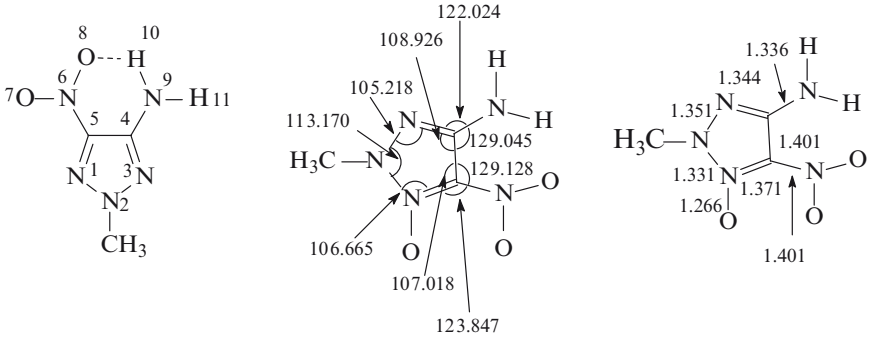
The crystal structures of coordinated compounds 1,2,4-triazolone-5 – Li(NTO) $2H_2O$ and Rb(NTO) H_2O have been studied [171]. The crystals belong to monoclinic system. The coordinate bonds in Li(NTO) $2H_2O$ possess a certain extent of covalent character, at that oxygen atom of NTO anion is bonded to Li atom. On the basis of calculations the nitro group will be lost when the NTO is decomposed. The trigondodecahedron configuration of Rb (NTO) H_2O is formed by nitrogen coming from NTO and oxygen from water molecule which is an eight-coordination compound around Rb+, i.e., a deformed sixgonal bi-pyramid. The radius of Rb+ is 0.147 nm, that of oxygen atom is 0.044 nm, and that of nitrogen is 0.070 nm. It is reasonable that the bond distances from Rb+ to O and N are about 0.3 nm [171].

For 1,1′-dinitro-3,3′-azo-1,2,4-triazole two modifications were obtained – yellow and orange. X-ray analysis has shown that in more dense orange modifications the bands formed by parallel molecules with intermolecular hydrogen bond were found [4].

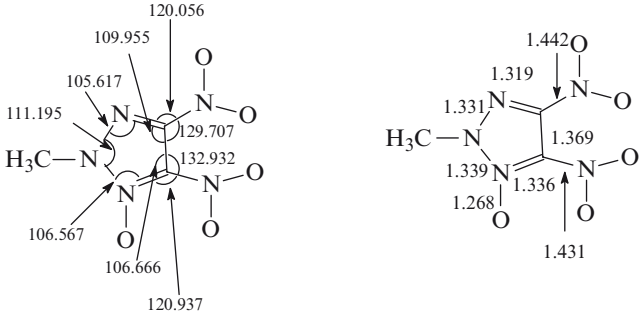
The structure of 3,5-disubstituted 1,2,4-triazole, including 5-amino-3-nitro-1,2,4-triazole [172], silver(I)-organophosphane complexes of the dihydridobis(3-nitro-1,2,4-triazolyl)borate ligand [173], 1,3-diaminoguanidinium salt of 3-nitro-1,2,4-triazolone-5 [158], and ethylene diammonium salt of 3-nitro-1,2,4-triazolone-5 [157], and other salts of 3-nitro-1,2,4-triazolone-5 [174] has been determined. The X-ray diffraction study of 3(5)-mono- and 3,5-disubstituted 1,2,4-triazoles having nonequivalent substituents in crystals exist as a tautomer in which the electron-acceptor substituent NO_2 occupies the 3 position, while the electron-donor substituent NH_2 resides in the 5 position. Symmetric 3,5-disubstituted 1,2,4-triazoles could give rise to tautomeric equilibrium between the 1*H*- and 2*H*-structures even in crystal [172]. The authors [157] have found that one of the

ammonium cations is located in the symmetry center. Around the cation are placed three independent triazole anions, whose geometrical parameters are almost identical (see table). Triazole rings are practically planar (with an accuracy of 0.01 A). The nitro groups are located in the planes bounded with the triazole cycle (deviation is lesser than 1°). All hydrogen atoms of the NH bond participate in hydrogen coupling.

The molecule of 4-amino-2-methyl-5-nitro-1,2,3-triazole 1-oxide is nearly planar, except that the hydrogen atoms of the methyl group deviate from the ring plane by 0.505, 0.918, and 0.324 Å [175]. Coplanarity of the nitro group with the ring plane (1.8°) is caused by intramolecular hydrogen bond O…H…N (the O…N distance is 2.851 Å). This fact also explains an elongation of N6–O8 bond (1.233 Å) relative to N6-O7 (1.225 Å).



The amine atom N9 has planar trigonal geometry, and deviation of the N9 from the H10, H11, and C4 plane is 0.05 Å [175]. The molecule of 2-methyl-4,5-dinitro-1,2,3-triazole 1-oxide has a similar structure [176]:



X-ray diffraction analysis of 2-(3-carboxamidofuroxan-4-yl)-4-nitro-5-carboxamido-2*H*-1,2,3-triazole shows that furoxan and 1,2,3-triazole rings are arranged at an angle of 70.2° [177]. The geometry parameters of this compounds are significantly different from those of the aforementioned 1,2,3-triazole 1-oxide derivatives [175]. This manifests itself in considerable differences between N–N and N–C bond lengths (0.03 and 0.04 Å, respectively) and in the pyramidalization of the N2 atom. The distance between the N2 atom and the planes N1, N3, and $C4_{fur}$ is 0.09 Å,

which is maximum for not only this heterocycle but also all 1,2,3-triazoles, in which maximum deviation of nitrogen atoms is 0.05 Å, as found by statistical data processing. The angle between the plane of 1,2,3-triazole and the N2-$C4_{fur}$ is 11.2° [177]. Amide groups participate in the intramolecular interactions and in the formation of intermolecular N–H…O bonds [2.820(2)–3.191(2) Å], which join molecules in hydrogen-bonded layers parallel to the crystallographic plane. The layers are joined in a three-dimensional framework through O…O contacts [2.839 Å], formed by NO_2 groups [177].

Nickel [178] and mercury salts of 5-nitrotetrazole [179] were studied using X-ray analysis technique.

Crystalline and molecular structure of benzazole nitro derivative has not been adequately explored.

5-Nitroindazole has a planar indazole ring, with the N1-bound nitro group almost coplanar with the ring [twist angle 3.9(2)°], while the C5-bound nitro group is twisted by 19.2(2)° out of the plane of the molecule. The molecules in the crystal structure are arranged in plane and connected to each other by weak C–H...O hydrogen bonds, with C...O distances of 3.276(3) Å [5]. X-ray analysis data of 1-tetrazolyl-4,6-dinitroindazole was reported [180], but no details except for the presence of three molecules of crystallization water in the compounds are given in the work.

X-ray crystallographic structures of nitric oxide synthases cocrystallized with nitroindazole – 5-nitro-, 6-nitro-, 7-nitro-, or 3-bromo-7-nitroindazole have been established [181].

The molecule of 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-nitroindazole in the crystal is almost planar: dihedral angles between the plane of the nitro group, phenyl substituent, and indazole system are 4.5(8) and 2.5(8)°. The C5–NO_2 bond length is 1.46(1) Å [182].

Wrzeciono et al. have investigated the structure of 4-nitro-7-phenylsulfonylindazole [183] and molecular complexes of 3,5-dinitroindazole with morpholine in the ratio of 2:1 [184], with thiomorpholine in the ratio of 1:1 [185], with pyrrolidine in the ratio of 1:1 [186], with piperidine and water 2:1:2 [187], with *N*-methylpiperazine and water 2:1:2 [188]. The indazole systems in the complexes are approximately planar.

Rapt attention has been focused on the structural studies of benzimidazoles exhibiting versatile pharmacological activities [189–204]. The crystal structure of 5,6-dinitrobenzimidazole monohydrate has been reported [189]. The crystal includes one water molecule and one 5,6-dinitrobenzimidazole molecule which form short intermolecular N-H…N hydrogen bond [N1…N1′ 2.883(4), H1…N1 2.03(5) Å, N1-H1…N1 172.8(4.5)°], and O_{water}-H…O hydrogen bond [O_{water}…O_{nitro} 2.954(6), H_{water}…O_{nitro} 1.98(5) Å, O–H_{water}…O_{nitro} 153(9)°] [189]. These hydrogen bonds are very effective in holding the molecule in a stable state as a whole, at the same time the dipole-dipole and Van der Waals interactions are also effective in molecular packing. The close contacts O_{nitro}…O_{nitro} 2.791(4), O_{nitro}…H4 2.551(3), O_{nitro}…H7

2.724(3) Å cause unavoidable crowding leading to steric hindrances between nitro groups, which prevents their rotations freely since there is no space. The phenylene fragment is close to planarity while the five-membered ring is planar [189].

5-Nitrobenzimidazole-2-carboxylate 3-oxides on X-ray diffraction data exist in *N*-hydroxy tautomers [190]. In the crystal a strong O-(HN)-N-...intermolecular bond gives rise to supramolecular polymeric chains in the lattice.

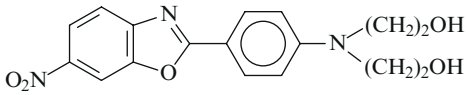
The phenyl and benzimidazole rings in 6-nitro-1-(2-phenylethyl)benzimidazole are each planar and have a dihedral angle of 43.9(1)° [195]. Its crystal structure is stabilized by weak intermolecular C–H…N hydrogen-bond interactions [195]. The piperidine ring in 5-nitro-1-(2-piperidinoethyl)benzimidazole has the usual chair conformation, and the benzimidazole cycle is almost planar [198]. The NO_2 group plane is almost coplanar with the benzimidazole plane. The nitrogen atom of NO_2 group deviates from this latter plane by 0.018(2) Å [198]. The bond lengths and angles in 1-methoxyethyl-5-nitrobenzimidazole are also unexceptional [197]. The dihedral angle between the phenylene and five-membered rings is 0.88(11)°. The crystal structure of 1-[2-(5-nitrobenzimidazol-1-yl)ethyl]morpholinium chloride exhibits an intramolecular N–H…Cl, and intermolecular C–H…Cl and C–H…O interactions [193].

Bond lengths and angles in bis[1-(but-2-enyl)-5-nitrobenzimidazole-κN^3]-dichlorocobalt(II) [200], diaqua-bis(3-hydroxybenzoato-κ*O*)bis(5-nitrobenzimidazole-κN^3)cobalt(II) bis(5-nitrobenzimidazole) dihydrate [199] and diaqua (5-nitrobenzimidazole-κN^3)(oxydiacetato-κ*O*,*O*′,*O*″)cobalt(II) monohydrate [194] have been reported. The nitro group in the last compound is coplanar with the benzimidazole ring, the maximum atomic deviation being 0.034(2) Å for one of oxygen atoms of NO_2 group [194]. The Co(II) atom in this compound is coordinated by one tridentate oxydiacetate dianion, one monodentate nitrobenzimidazoles molecule, and two water molecules in a distorted octahedral geometry. The face-to-face distance of 3.345(14) Å between parallel nitrobenzimidazole ligands of neighboring complexes indicates the existence of strong π-π stacking interactions. An extensive hydrogen-bonding network occurs in the compound, and atom H2 is involved in a bifurcated C–H O (NO_2) bond [194].

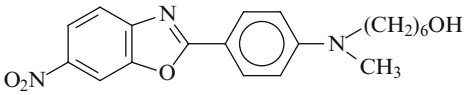
The structures of 5-nitro-1-(2-piperidinoethyl)-benzimidazole [205], 1-[2-(5-nitrobenzimidazol-1-yl)ethyl]morpholinium chloride [206], 1-(4-methylphenylsulfo-nyl)-5-nitrobenzimidazole [207], 1-(4-methylphenylsulfonyl)-5-nitro-2-propenyl-benzimidazole [208] and Co-II-containing complexes, accompanied by uncoordinated 5-nitrobenzimidazoles and water molecules [209], have been determined by X-ray analysis.

The crystal structures of 4-(6-nitro-2-benzoxazolyl)phenyl 4-(acryloyloxyhexyloxy) benzoate, 2-[4-*N,N*-bis(2-hydroxyethyl)] phenyl-6-nitrobenzoxazole monohydrate (**A**) and 2-[4-*N*-(6-hydroxyhexyl)-*N*-methyl] phenyl-6-nitrobenzoxazole (**B**) have been determined at room temperature by direct methods and refined by full-matrix least-squares method [210]. These compounds are monomer precursors of polymers with nonlinear optical properties of the second order.

A



B



The planar geometry is observed around the nitrogen atom of amino group in **A** and **B**. Some differences have been found in the molecular geometry of **A** and **B** as compared on similar benzoxazole derivatives. These differences are caused by the strong electron donor effect of the amino group and indicate enhanced conjugation in the molecules. The pattern of hydrogen bonding in the two compounds is also discussed [210].

The crystal and molecular structure of the potassium methoxide adduct of 4-methoxy-5,7-dinitrobenzofurazan, $K^+[(CH_3O)_2C_6H(NO_2)N_2O)]^-$ (Meisenheimer Complex), has been determined [211]. The two methoxy groups are covalently bonded to the same ring carbon atom with an average C–O bond length 1.415(6) Å. The sp_3-hybridized carbon atom (C4) in the ring produces distortions throughout the entire molecule. The electron-withdrawing influence of the coplanar furazan ring has a pronounced effect on the benzene ring system. The presence of the NO_2 group adjacent to the C1 atom makes a discussion of steric repulsions extremely difficult [211]. In 4,6-dinitrobenzofuroxan the 6-nitro group is very nearly coplanar with the benzofuroxan ring to give a short "nonbonded" N…O contact of 2.63 Å [212].

In [213] are given the X-ray analysis data related to 4-chloro-7-nitrobenzofurazan. The maximal differences in geometry of both independent molecules are observed for bond lengths C2–N3 (1.470 and 1.444 Å) and angles of the rotation of nitro groups with respect to plane condensed nucleus. The authors explain these differences by the effect of neighborhood in the crystal.

The structure of copper(II) complexes of *N*-substituted nitrobenzothiazole-sulfonamides has been reported [214].

The crystal structure of 2-amino-4-nitrobenzothiazole consists of centrosymmetric dimers, the principal intradimer interaction being two pairs of three-center hydrogen bonds involving the amino group, the ring N atom, and one O atom of the nitro group. The molecule exists as a resonance hybrid of two tautomers, one neutral and the other dipolar. Probably, π-density localized in the *N*-amino-C-N-ring portion of the molecule is in part transferred to the nitro group [215].

The structure of 5,7-dinitro-1-picrylbenzotriazole has been determined by single-crystal X-ray crystallography [216]. The nitro groups on C5, C7 and C_{para} are practically coplanar with their aromatic cycles, while those on two C_{ortho} atoms are rotated out of the plane of phenyl ring by approximately 50 and 27°. The phenyl and benzotriazole cycles of the molecule are twisted out of coplanarity by rotation about the N1–C_{ipso} bond. The four torsion angles about this bond deviate from planar

values (0 or 180°) on 78.7–87.4°, with an average deviation (twist) being 83.1°. Very similar geometry was also noted for the comparable structure 4,6-dinitro-2-(2′,4′,6′-trinitrophenyl)benzotriazole 1-oxide. The picryl group in the last compound is substituted onN2 rather N1, and there is an oxygen on N1. The plane of nitro groups is twisted by only 27 and 37°, and there is less twist between the phenyl and benzotriazole rings than in 5,7-dinitro-1-picrylbenzotriazole, with a range of torsions from 60.2 to 116.3° and an average deviation from planarity of 65.9°. This difference may be small enough to be due to dissimilarities in the packing of the two molecules, but probably indicates increased steric hindrance in 5,7-dinitro-1-picrylbenzotriazole [216].

Nuclear Magnetic Resonance

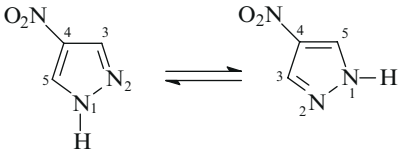
Nuclear magnetic resonance (NMR) spectroscopy provides one of the most powerful tools for the investigation of the electron structure, stereo dynamic and chemical behavior of organic (including heteroaromatic) compounds. NMR is the most convincing and fastest technique for structure determination in solution, since it can provide a wealth of data that can be related to chemical structure, conformation, and their relationship or interaction with the surroundings. During the past years due to the rapid progress in experimental engineering the performance of previously very difficult investigations on poorly abundant ^{13}C, ^{15}N, ^{17}O nuclei which are of key importance to the azoles (and heterocycles), has become quite possible and even routine procedure. This has greatly extended the capabilities and enhanced the information potential of NMR spectroscopy. The matter is that the range of variations (as well as the sensitivity toward electron density redistribution) of the chemical shifts of these nuclei is some scores as high as that of protons. As a rule, the shielding of these nuclei is more strongly dependent on the electron density, hybridization, and surrounding of a given atom, the relative influence of outside factors (magnetic anisotropy and electric field of neighboring fragments and bonds) being lower compared with that of protons. At the same time, in studying the electronic structure of aromatic heteroatom compounds by NMR spectroscopy it should be borne in mind that even minor changes in tautomer equilibrium constants and conformation of the molecule, temperature variations, or substitution of solvent can change markedly (and not always in line with the degree of electron redistribution) the nuclei shielding.

Multinuclear ^{1}H, ^{13}C, ^{14}N, ^{15}N, ^{17}O NMR spectroscopy is widely used for the structural determination of nitroazole derivatives. Some NMR data on the nitroazoles have been published in monographs [217–219], thesis [220], and reviews dedicated to five-membered heterocycles [221, 222], the derivatives of pyrazole [223–225], isoxazole [226], oxazole [227, 228], thiazole [229], 1,2,4-triazole [230], 1,2,3-triazole [231, 232], indazole [233], and our reports on trimethylsilylazoles [234], NMR of nitroazoles [235], etc. [236–240].

In the following we will dwell upon the most essential results achieved by the use of NMR spectroscopy in structural and analytical studies of azole nitro derivatives.

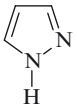
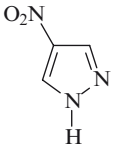
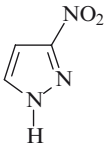
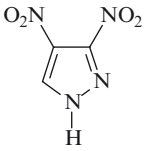
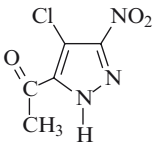
Pyrazoles

The chemical shift of equivalent H-3 and H-5 signals in unsubstituted pyrazole (Scheme 3.1) is 7.61 ppm, those of δ ^{13}C-3,5 and δ ^{13}C-4 signals being 133.8 and 104.9 ppm, respectively (acetone-d_6). The introduction of the nitro group into the pyrazole ring position 4 leads to an approximately 1 ppm shift of the H-3,5 signals, C-4 (or C-*ipso*) being shifted by 30 ppm downfield (Table 3.6–3.9) [20, 24, 220, 221, 225, 241–246]



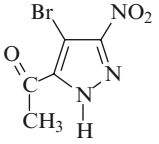
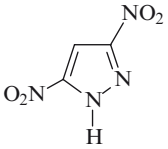
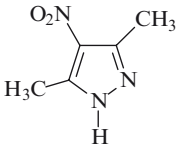
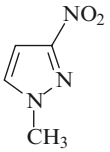
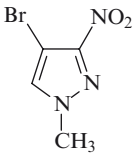
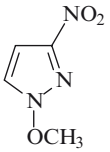
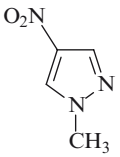
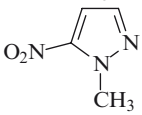
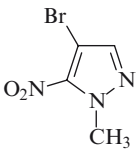
Scheme 3.1

Table 3.6 ^{13}C NMR Chemical shifts (ppm) and coupling constants (*J*, Hz) of nitropyrazoles

Compound	C-3	C-4	C-5	Solvent	Refs
	133.71	104.82	133.77	DMSO-d_6	[241]
	133.82	104.91	133.83	$(CD_3)_2CO$	[243]
	132.53	135.62	132.51	$(CD_3)_2CO$	[247]
	132.41	136.0	132.44	DMSO-d_6	[241]
	156.62	101.75	133.11	$(CD_3)_2CO$	[241]
	155.31	102.64	132.82	$(CD_3)_2CO$	[243]
	155.70	103.42	132.80	CD_3OD	[220]
	135.38	133.58	132.38	$CDCl_3$	[221][a]
	151.45	108.10	134.62	DMSO-d_6	[244]

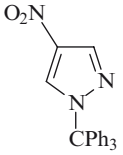
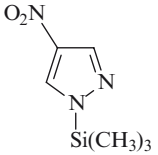
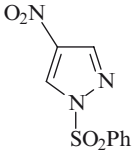
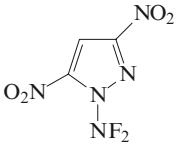
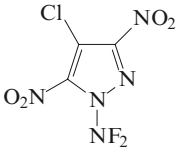
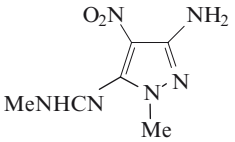
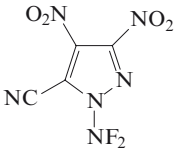
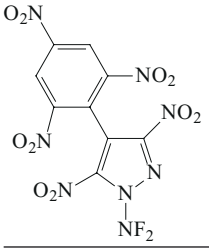
(continued)

Table 3.6 (continued)

Compound	C-3	C-4	C-5	Solvent	Refs
	153.27	92.18	136.09	DMSO-d_6	[244]
	151.5	100.1	151.5	DMSO-d_6	[225]
	130.04	143.46	130.04	$CDCl_3$	[221][a]
	154.9 155.37	102.7 103.14	134.5 132.64	DMSO-d_6 $CDCl_3$	[225] [221][a]
	151.5	89.5	136.5	DMSO-d_6	[248]
	148.9	101.6	124.4	$CDCl_3$	[225]
	135.0	134.9	130.6	DMSO-d_6	[225]
	137.6	106.3	145.8	DMSO-d_6	[225]
	139.5	93.6	142.5	DMSO-d_6	[248]

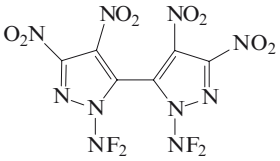
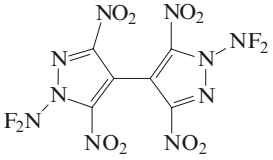
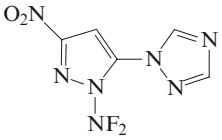
(continued)

Table 3.6 (continued)

Compound	C-3	C-4	C-5	Solvent	Refs
	135.8	134.7	131.4	$CDCl_3$	[225]
	138.78	133.96	137.61	Neat liquid	[220]
	139.85	137.00	131.75	DMSO-d_6	[225]
	153.28 t $^4J_{C–F}$ 1.7	103.80 d $^1J_{C–H}$ 199.8	144.24 td $^3J_{C–F}$ 1.8 $^2J_{C–H}$ 3.3	$(CD_3)_2CO$	[24]
	$\delta^{19}F = 109.87^b$, pK_a (H_2O) = 2.92			$(CD_3)_2CO$	[24]
	150.3	110.0	147.4	$CDCl_3$	[20]
	$\delta^{13}C$ = 107.01, 123.18 $\delta^{19}F$ 110.96; pK_a (H_2O) 4			$(CD_3)_2CO$	[24]
	150.34	121.00	142.40	$(CD_3)_2CO$	[24]
	$\delta^{13}C$ 108.47 (C-1′), 125.94 (dd C-3′, $^1J_{C–H}$ 181.5, $^3J_{C–H}$ 7.0), 150.42 (C-4′), 152.55 (C-2′) $\delta^{19}F$ 101.11; pK_a (H_2O) 3.5				

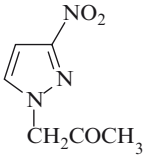
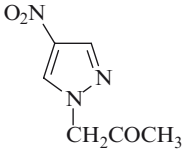
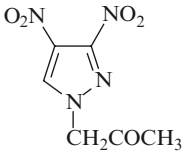
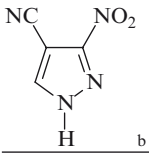
(continued)

Table 3.6 (continued)

Compound	C-3	C-4	C-5	Solvent	Refs
	148.10	128.03t $^4J_{C-F}$ 1.5	122.20	$(CD_3)_2CO$	[24]
	150.45	102.32t $^4J_{C-F}$ 2.1	141.43	$(CD_3)_2CO$	[24]
	$\delta^{19}F$ 111.69; pK_a (H_2O) 3			$(CD_3)_2CO$	[24]

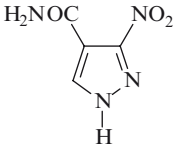
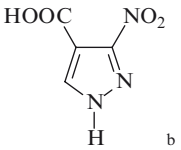
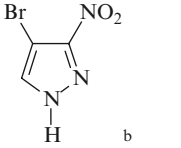
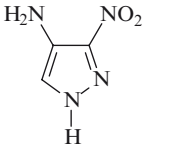
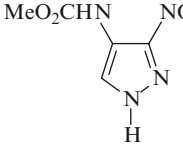
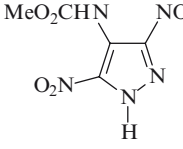
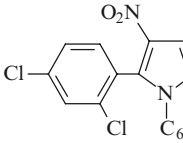
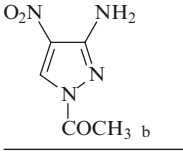
[a] We took the liberty to assign ^{13}C NMR signals of nitroazoles
[b] $\delta^{19}F$ are referred to as $\delta^{19}F$ ($CFCl_3$); all $pK_a(H_2O)$ values are given for the starting azoles

Table 3.7 ^{13}C and ^{15}N NMR chemical shifts (ppm) of nitropyrazoles in DMSO-d_6[a]

Compound	C-3	C-4	C-5	N-1	N-2	NO_2	Refs
	155.28	102.80	135.30	−174.0	−76.2	−20.4	[261]
	134.8	134.6	131.1	−174.0	−69.7	−18.8	[261]
	147.06	126.40	135.04	−181.0	−78.1	−26.8(3)- 26.7(4)(^{14}N)	[261]
 [b]	156.33	89.58	139.51	−177.0	–	−26.2	[262]

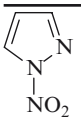
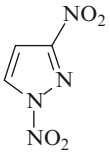
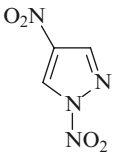
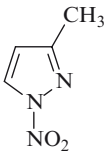
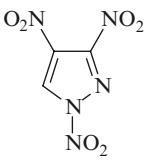
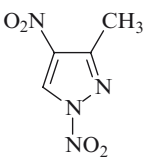
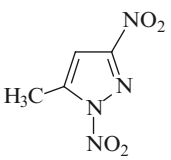
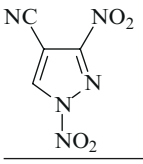
(continued)

Table 3.7 (continued)

Compound	C-3	C-4	C-5	N-1	N-2	NO_2	Refs
	153.44	112.93	132.80	–	–	−19.6	[262]
 [b]	156.34	108.44	135.71	−182.2	–	−20.1	[262]
 [b]	153.97	89.47	134.62	−178.2	–	−23.6	[262]
	141.61	130.90	119.30	–	–	−20.3	[262]
	144.35	129.3	131.99	–	–	−11.8	[262]
 [b]	144.38	113.29	144.38	–	–	−27.6	[262]
 [c]	137.0	137.95	137.12	−158.1[d]	–	–	[263]
 [b]	148.55	118.17	138.53	−302.62 NH_2		−18.6 (^{14}N)	[264]

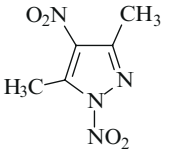
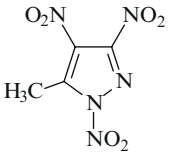
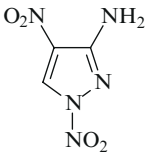
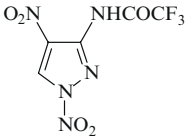
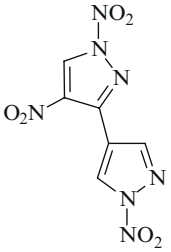
[a] ^{15}N and ^{14}N chemical shifts are referred to as CH_3NO_2
[b] In $(CD_3)_2CO$
[c] In $CDCl_3$
[d] In DMSO-d_6

Table 3.8 ^{13}C, ^{15}N, ^{17}O NMR chemical shifts of *N*-nitropyrazoles (ppm)[a]

Compound	C-3	C-4	C-5	N-1	N-2	NO_2	^{17}O	Refs
	141.90 142.0	110.10 110.3	126.71 128.9	−108.2 −107.8	−83.8 −82.9	−56.6	481.8	[249] [243]
	153.92	105.40	129.83	−113.1	−93.5	−63.2 −25.1 (3)	482.2 594.7	[249]
	135.51	137.09	125.61	−109.9	−84.2	−63.0 −23.2 (4)	–	[249]
	152.17	110.55	127.40	−112.5	−88.1	−55.7	478.1	[249]
	154.08	128.35	128.25	−117.0	−95.5	−68.6 −31.0 (3) −30.7 (4)	–	[249]
	146.40	126.48	135.24	−116.5	−88.6	−62.3 −21.1(4)	482.5 592.5	[249]
	151.96	105.30	143.75	−113.9	−92.3	−59.7 −24.2(3)	494.6 593.2	[249]
	151.52	92.70	135.38	−113.3	−91.6	−68.0 −30.2(3) −109.4(CN)	–	[249]

(continued)

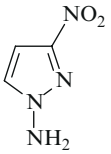
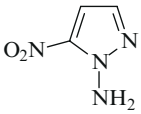
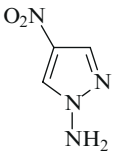
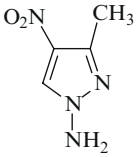
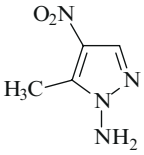
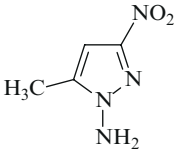
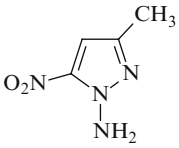
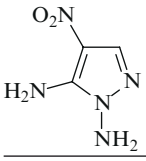
Table 3.8 (continued)

Compound	C-3	C-4	C-5	N-1	N-2	NO_2	^{17}O	Refs
	144.98	133.43	140.67	−114.8	−91.7	−58.8 −18.9(4)	497.8 595.5	[249]
	144.75	126.51	142.21	−118.8	−98.5	−65.7 −29.8(3) −28.8(4)	–	[249]
	150.28	130.83	128.24	–	–	−64.6 −26.6 (4)^{14}N	–	[264]
	137.64	130.57	127.49	–	–	−65.2 −25.2(4)	–	[264]
	137.07 (140.6)	134.18 (113.95)	128.10 (127.65)	−113.5 (−107.2)	(−83.3)	−64.5 −23.7(4) (−60.1)	–	[265]

[a] ^{17}O – in acetonitrile, ^{13}C, ^{14}N, ^{15}N – in acetone-d_6

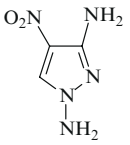
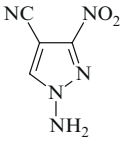
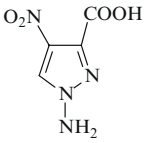
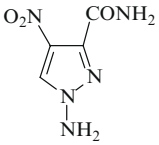
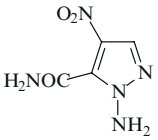
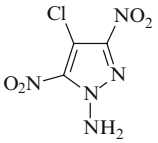
The C-3,5 carbon chemical shifts, on the contrary, change only slightly ($\Delta\delta \sim 1$ ppm) when the nitro group is introduced into position 4 [221, 241, 243, 247]. It should be noted that the change in the *ipso*-carbon chemical shift both in nitrobenzenes ($\Delta\delta \sim 20$ ppm) and nitropyrazoles ($\Delta\delta \sim 30$ ppm) is likely to be caused by some factors having nothing to do with the electron density on this carbon atom. The introduction of the nitro group into the pyrazole ring position 3 does not affect much C-4 and C-5 compared with unsubstituted pyrazole. At the same time, the substitution of the proton in position 1 by a nitro group considerably redistributes the chemical shifts of protons and carbons in the pyrazole ring (Tables 3.6–3.8) [225, 240, 243, 249].

Table 3.9 ^{13}C, ^{15}N NMR chemical shifts of *N*-aminonitropyrazoles (DMSO-d_6) [266]

Compound	C-3	C-4	C-5	N-1	N-2	N-$\underline{N}H_2$	NO_2 (NH_2)
	152.96	102.17	132.80	−158.3	−78.3	−290.3	−20.4
	133.60	104.72	142.26	–	–	–	–
	132.96	133.33	128.32	−156.7	−69.9	−29.3	−18.7
	142.89	130.84	129.34	−163.5	−73.6	−292.2	–
	132.86	130.84	129.34	−163.5	−73.6	−292.2	–
	150.24	100.36	140.75	−159.5	−65.3	−296.6	–
	142.11	103.03	142.05	–	−79.8	−311.6	–
	131.13	116.16	144.67	−190.3	−88.1	−306.8	(−326.9)

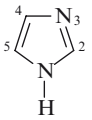
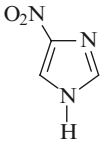
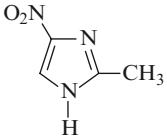
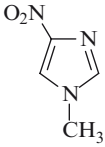
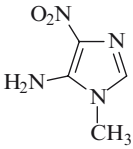
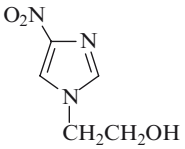
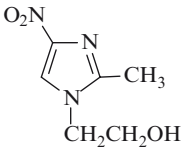
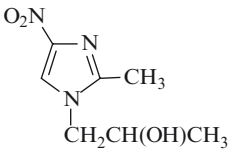
(continued)

Table 3.9 (continued)

Compound	C-3	C-4	C-5	N-1	N-2	N-$\underline{N}H_2$	NO_2 (NH_2)
	149.10	118.65	126.18	–	–	−291.1	(−320.1)
	150.62	87.30	137.91	−156.6	−74.5	−287.13	−26.2
	136.97	131.29	129.79	–	–	–	–
	140.11	130.09	129.10	−160.8	–	−291.0	(−268.8)
	132.46	130.12	134.71	−159.9	−73.6	−293.5	(−264.6)
	155.19	115.03	149.90	–	–	−236.2	−28.6

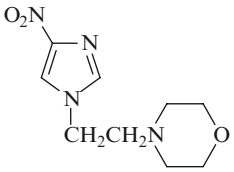
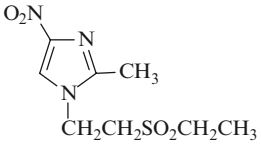
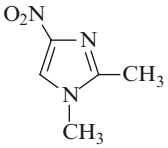
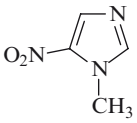
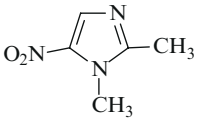
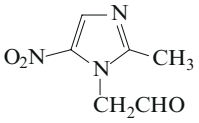
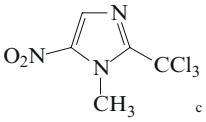
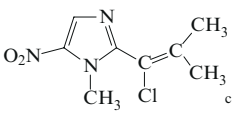
A new class of *N*-substituted azoles, the nitrated *N*-(difluoroamino)azoles (pyrazoles, imidazoles and 1,2,4-triazoles), were synthesized from NH-azoles, whose NH-acidity is $pK_a < 5$, and their structures were confirmed by ^{1}H, ^{13}C, ^{14}N, ^{15}N, and ^{19}F NMR spectroscopy (Tables 3.6, 3.10, 3.21) [24, 25]. The compounds are thermally unstable and highly sensitive to mechanical impact. The chemical shifts of the N–NF_2–group in the ^{19}F NMR spectra of nitrated *N*-(difluoroamino)azoles have a small sensitivity to changing the azole-cycle (+99 to +111 ppm) (Tables 3.6, 3.10, 3.21) [24]. The ^{19}F NMR spectrum of bis-dinitropyrazole (Table 3.6) shows two doublets with $^{2}J = 500$ Hz rather than a singlet as in the spectra of other compounds containing the *N*-(difluoroamino)-groups. Probably some magnetic nonequivalence

Table 3.10 ^{13}C, ^{14}N, and ^{15}N NMR chemical shifts (ppm) and coupling constants (*J*, Hz) of nitroimidazoles (DMSO-d_6)

Compound	C-2	C-4	C-5	^{14}N or ^{15}N	Refs
	135.8 135.4	122.2 121.9	122.2 121.9	−167(3)	[339] [321]
	136.0 136.7	−149.2	119.2 119.8	−202(5) −16(2) NO_2	[102] [339]
	145.8	148.0	119.5	−203(5) −16(2) NO_2	[322], [339]
	136.61 138.6	148.0 147.8	120.19 123.1	−208(5) −17(2) NO_2	[221][a] [322, 339]
	143.97	[b]	132.46	−218.8 N-1 −126.3 N-3 −26.1 NO_2	[220]
	137.80	147.03	121.99	−217.0 N-1 −120.2 N-3	[220]
	151.7	133.2	138.4	−217.0 N-1 −120.2 N-3	[329]
	151.9	132.9	138.5	−216.2 N-1 −120.4 N-3	[329]

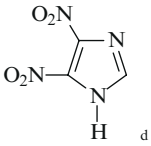
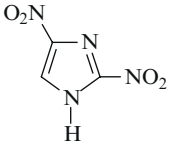
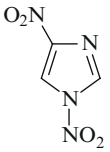
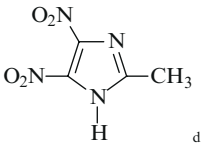
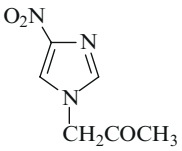
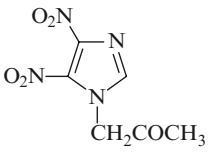
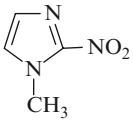
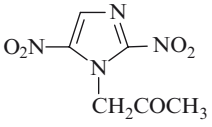
(continued)

Table 3.10 (continued)

Compound	C-2	C-4	C-5	^{14}N or ^{15}N	Refs
	143.4	133.1	138.4	−211.8 N-1 −120.3 N-3 −341.7 N_{mor} −25 NO_2	[329]
	151.4	133.0	138.3	−219.0 N-1 −119.7 N-3	[329]
	146.10 145.66	145.07 145.66	120.71 122.91	^{13}C others 12.85 CH_3 35.02 NCH_3	[221][a] [322]
	141.52 143.52	132.87 133.11	138.87 139.45	^{13}C others 35.02 NCH_3	[221][a] [322]
	149.98 151.14	131.89 132.23	Not observed	^{13}C others 13.70 CH_3 35.83 NCH_3	[221][a] [322]
	138.82	132.85	152.22	^{13}C others 196.14 CHO 54.99 CH_2 14.04 CH_3	[323]
	145.82	129.12	145.82	^{13}C others 35.83 NCH_3 87.31 CCl	[323]
	143.07	131.87	139.87	^{13}C others 21.23, 21.66 CH_3 34.02 NCH_3 111.71 CCl 147.65 CCH_3	[323]

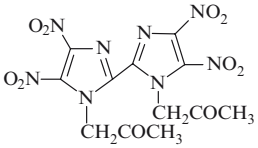
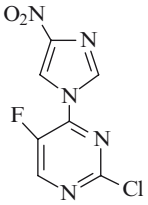
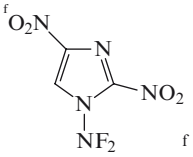
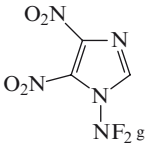
(continued)

Table 3.10 (continued)

Compound	C-2	C-4	C-5	^{14}N or ^{15}N	Refs
 [d]	133.4	134.9	134.9	−158(3) −28(1) NO_2	[339]
	144.0	–	123.1	–	[102]
	132.5	–	115.5	–	[102]
 [d]	144.0	133.9	133.9	−160(3) −27(1) NO_2	[339]
	138.20	146.80	122.6	−208.0 N-1 −126.7 N-3 −18.3 NO_2	[261]
	137.20	140.90	129.90	−213.5 N-1 −130.7 N-3 −32.6 5-NO_2 −24.0 4-NO_2	[261]
	136.63	128.63[e]	127.59[e]	–	[220]
	–	–	–	−213.10 N-1 −129.7 N-3 −31.10 2-NO_2 −22.7 4-NO_2	[261]

(continued)

Table 3.10 (continued)

Compound	C-2	C-4	C-5	^{14}N or ^{15}N	Refs
	132.38	139.89	133.81	−35.0 5-NO_2 −27.6 4-NO_2	[261]
	119.0	149.8	136.6	^{13}C other 144-1 C–N 147.8 C–Cl 149.8 C–F 151.4 C–H	[340]
 [f]	137.58 d $^3J_{C-H}$ 8.2	142.87 d $^2J_{C-H}$ 2.6	115.11 dt $^1J_{C-H}$ 213.2 J_{C-F} 4.9	−36.67 2-NO_2 −25.68 4-NO_2 −127.55 N-3 −62.50 t, NF_2 $^1J_{N-F}$ 168, in $CDCl_3$	[24]
 [g]	129.54 dt $^1J_{C-H}$ 233.9 $^3J_{C-F}$ 5.0	138.37 d $^3J_{C-H}$ 12.8	128.37	−32.41 4-NO_2 −42.95 5-NO_2 −127.92 d, N-3, $^2J_{N-F}$ 12.6 −69.07 t, NF_2 $^1J_{N-F}$ 166, in $CDCl_3$	[24]

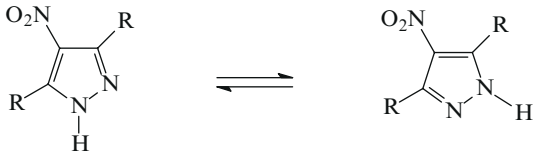
[a] $CDCl_3$ assignment of ^{13}C signals was made here
[b] Signal C-4 is not seen due to a broadening caused by the presence of neighboring nitro group
[c] In $CDCl_3$
[d] In $(CD_3)_2CO$
[e] Assignment of these signals may be reversed
[f] In $(CD_3)_2CO$, $\delta^{19}F = 99.51$, $\delta^1H = 8.79$, $pK_a(H_2O)$ 2.85
[g] In $(CD_3)_2CO$, $\delta^{19}F$ 100.46, $\delta^1H = 8.29$ (t, H-2, $^4J_{H-F}$ 1.1), $pK_a(H_2O)$ 3.39 – all $pK_a(H_2O)$ values are given for the starting azoles

of the fluorine atoms in the NF_2 group is observed. The presence and mutual arrangement of the difluoroamino and nitro groups in *N*-(difluoroamino)azoles was confirmed by $^{13}C–\{^1H, ^{14}N\}$ triple heteronuclear resonance.

NMR spectroscopy is known to be practically the only convenient method for the investigation of tautomerism, which allows evaluation of the thermodynamical

characteristics of exchange processes. This is also stated in the known monograph on tautomerism [219] and a series of works by Elguero and coauthors [for example, 250–253]. Therefore let us consider briefly some of these statements.

In normal conditions the 3,5-protons of 4-nitropyrazole (for example) are equivalent as a result of prototropic exchange (Scheme 3.2). A decrease in temperature splits the H-3,5 signal into two. The barrier of this tautomeric process in 4-nitropyrazole in acetone, free energy of activation ($\Delta G_c^{\neq}$) was evaluated to be 10 kcal/mol [247, 254]. This value does not change much with introducing the methyl groups into the 4-nitropyrazole positions 3 and 5 ($\Delta G_c^{\neq}$ = 9.5 kcal/mol, acetone) [247]. In methanol the barrier value is significantly higher both for 3,5-dimethyl-4-nitropyrazole (12.1 kcal/mol) [251] and 4-nitropyrazole (12 kcal/mol) [220]. A prototropic process depends upon a solvent nature.

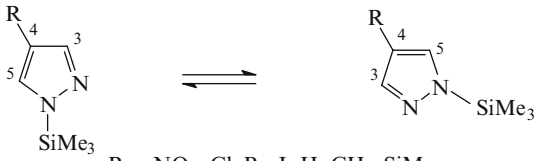


R = H, CH_3

$\Delta G_c^{\neq}$ = 9.5 – 12 kcal/mol

Scheme 3.2

The silylotropic exchange process in azoles is known to be rather slow in the NMR time scale. The migration dynamics can be observed only at high temperatures. With increasing temperature, the Me_3Si group in *N*-trimethylsilylazoles is prone to reversible 1,2-migration (Scheme 3.3) [220, 234, 255].



R = NO_2, Cl, Br, I, H, CH_3, $SiMe_3$

$\Delta G_c^{\neq}$ = 22-24 kcal/mol

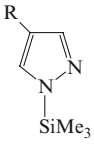
R = NO_2	δ^1H (ppm): 0.56 (CH_3), 8.15 (H-5), 8.41 (H-3) δ^{13}C (ppm): –1.37 (CH_3), 133.96 (C-5), .137.61 (C-4), 138.78 (C-3) δ^{29}Si (ppm): 22.1

Scheme 3.3

The free energy activation of silylotropy in 4-substituted *N*-trimethylsilylpyrazoles (4-R-1-TMC-pyrazoles) determined by dynamic NMR method is poorly dependent on the nature of substituent in position 4 [220, 255]. Whereas the δ^{29}Si in

N-trimethylsilylpyrazoles is sensitive to the influence of substituent in position 4, the increasing electron-withdrawing properties of those decrease the screening of silicone nucleus (12–22 ppm) [220].

The substituent effects in 4-substituted *N*-trimethylsilylpyrazoles are transmitted from position 4 to the silicon atom by the inductive mechanism in large measure (a>b) (~60%) by using substituent constants (XY) $\sigma_I\ \sigma_R$, $\sigma_I\ \sigma_R^{\circ}$, $\sigma_I\ \sigma_R^{-}$, and $\sigma_I\ \sigma_R^{+}$ according to equation (3.1) [220]:

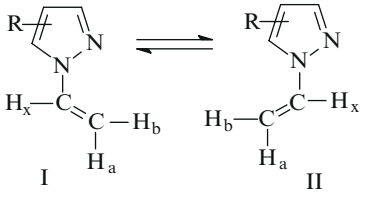


$$\delta\ ^{29}Si = aX + bY + d \quad (3.1)$$

$R = OCH_3, CH_3, H, Ph, Cl, Br, I, CN, NO_2$

By use of ^{13}C CP MAS NMR (crosspolarization/magic angle spinning) and X-ray diffraction the structure of 3(5)-methyl-4-nitropyrazole in the solid state was examined [252]. Desmotropy in azoles has been revealed for the first time. This means that the two tautomers, 3-methyl-4-nitro- and 5-methyl-4-nitropyrazole, are crystallized in two different crystals [252, 256]. The problem of proton transfer in solid-state heterocycles, including nitropyrazoles, was studied by CP MAS NMR and X-ray structural analysis [253, 257]. The kinetics of degenerate intermolecular triple proton and deuteron transfers in the cyclic trimer of polycrystalline 4-nitropyrazole (^{15}N-labeled) has been studied as a function of temperature and is compared to the kinetic of triple proton transfer in bulk solid 3,5-dimethylpyrazole. The results show that the transfer kinetics in the new trimer is much faster than that in 3,5-dimethylpyrazole. Nevertheless, the kinetics of HHH/HHD/HDD/DDD isotope effects of 4-nitropyrazole is similar to that of 3,5-dimethyl derivative [257].

It has been noted [258–260] that the introduction of the electron-withdrawing nitro group into the 1-vinylpyrazole ring shifts downfield the signals of all protons. To evaluate the portion of S-*cis* (N-2) (I) and S-*trans* (N-2) (II) isomers of 1-vinylpyrazoles the ΔJ parameter has been proposed ($\Delta J = {}^1J\ C_\beta H_a - {}^1J\ C_\beta H_b$) (Scheme 3.4).



R = Br, CH_3, NO_2

Scheme 3.4

On the basis of ΔJ analysis approximately equal proportions of forms I and II for the earlier-mentioned compounds have been suggested by the authors. The

introduction of the methyl group into the pyrazole ring position 5 leads to stabilization of the S-*cis* (N-2) conformer. The presence of the nitro group in the pyrazole ring position 4 considerably weakens the ring-vinyl group p-π conjugation both in 1-vinylpyrazoles and their 5-methyl derivatives, the conformer occupation remaining unchanged.

A large series of nitrated pyrazoles has been studied by ^{1}H, ^{13}C, ^{14}N, ^{15}N NMR spectroscopy at the Moscow Institute of Organic Chemistry (Tables 3.7–3.9) [249, 261, 262, 264, 265, 267–271]. Comparison of the ^{13}C chemical shifts of 1-nitropyrazole [249], 1-acetonyl- [261], 1-amino- [266], and 1-methylpyrazole [225] shows that δC-3 > δC-5 > δC-4. This seems to be due to different electronegativities of the "pyridine" and "pyrrole" nitrogen atoms [249]. The substitution of the methyl group in position 1 by NO_2 causes a 60–70 ppm increase in δ ^{15}N-1 and a 12–18 ppm decrease in δ ^{15}N-2.

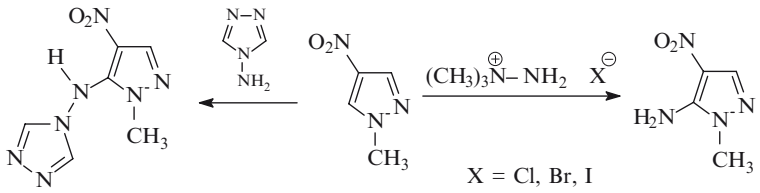
Comparing the ^{15}N chemical shifts of the nitro group in *N*-nitropyrazoles with those in *N*-nitramines of the aliphatic series and nitronium tetrafluoroborate, it has been suggested [229, 268] that the N–NO_2 bond ionicity increases on going from *N*-nitramines to *N*-nitropyrazoles.

The resonance signal of ^{15}N-1 in pyrazoles depends primarily on the nature of substituent attached to this atom (*ipso*-substituent). For example, if a nitro group is introduced into position 1, the $\delta^{15}N$ is in a range from −108.2 to −117 ppm depending on the pyrazole ring substituent, whereas with an analogous introduction of NH_2–, C_6H_5–, CH_2COCH_3– groups or H, δ ^{15}N-1 is observed in a range of −156.8 to −190.4, −158.13, −174 to −181, and −177 to −182 ppm, respectively. The ^{15}N-2 chemical shifts depend on the substitution in position 1 to a smaller extent and are mainly caused by the effect of substituent in position 3.

The nitro group N-15 chemical shift is chiefly dependent on the nature of atom attached to the NO_2 – group ($\delta^{15}N$ of the N–NO_2 fragments is in the −55 to −69 ppm range, while that of C–NO_2 can be seen in the −11.9 to −30.8 ppm range). As seen from Tables 3.7–3.10, $\delta^{15}NO_2$ of *C*-nitropyrazoles is fairly sensitive to the effect of substituents at neighboring atoms. Evidently, this can be explained by disturbance of the nitro group pyrazole ring plane coplanarity.

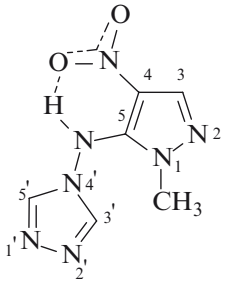
There has been some interest in the chemistry of aminonitroazoles when used as high energetic compounds. Data concerning direct introduction of the amino group into the nitroazole cycle have been absent in the literature till the present time. We have studied the vicarious nucleophilic substitution of 1-methyl-4-nitropyrazole and also 1-methyl-4-nitroimidazole (Table 3.10), 4-nitro-2-phenyl-1,2,3-triazole (Table 3.24), and nitrobenzimidazoles (Table 3.25) under the effect of 1,1,1-trimethylhydrazinium halides and 4-amino-1,2,4-triazole by NMR spectroscopy (DMSO-d_6) (Scheme 3.5) [220, 272–278]:

In the case of using 4-amino-1,2,4-triazole as an aminated agent an additional product was obtained – (1-methyl-4-nitropyrazol-5-yl)(1,2,4-triazol-4yl)amine. To our surprise the nitrogen chemical shift of the NO_2 group in these compounds is in higher field than the ones in the nitropyrazoles. Probably, the shielding of the nitrogen nuclear of nitro group is increased by sacrificing the formation of hydrogen-bond type N–H···O–N:



δ^{13}C, ppm	δ^{15}N, ppm	δ^{13}C, ppm	δ^{15}N, ppm
	–41.0 NO_2		
34.02 CH_3	–64.3 N-1',2'	35.04 CH_3	–40.5 NO_2
128.39 C-3	–117.0 N-2	117.84 C-4	–92.1 N-2
146.20 C-4	–180.8 N-4'	134.37 C-3	–207.2 N-1
155.04 C-5	–220.5 N-1	146.01 C-5	–316.9 NH_2
	–305.5 NH		

Scheme 3.5



In [267] some data on ^{17}O NMR study of nitropyrazoles are presented. The ^{17}O chemical shifts of N–NO_2 and C–NO_2 groups (478–498 and 592–596 ppm, respectively) are in lower field compared with NO_2BF_4 (420 ppm).

^{1}H and ^{13}C NMR spectroscopy provides a convenient tool for the identification of the nitration products of methylpyrazole [279, 280] and 1,3- and 1,5-diphenylpyrazoles [281]. C.L. Habraken et al. have investigated the reactions of "*cine*"-substitution of a large series of *N*-nitroazoles (including C-nitropyrazoles) [282–287] by ^{13}C NMR spectroscopy. It should be mentioned that in [285] the characteristics of the proton spectra of 4-nitro-3(5)-(4′-nitro-1′-pyrazolyl)pyrazole and 4-nitro-3(5)-(4′-nitro-1′-pyrazolyl)-5(3)-(1″-pyrazolyl)pyrazole are presented. Analysis of the ^{19}F NMR spectra of fluorinated nitropyrazoles has been carried out [288, 289].

The assignment of the H-3 and H-5 signals in several *N*-substituted nitropyrazoles was made by the use of NOE (Nuclear Overhauser Enhancement) difference spectroscopy [290]. NMR spectroscopy was employed for the investigation of metallotropic transitions in nitropyrazole organomercury derivatives [291]. By means of ^{1}H NMR spectroscopy the solvation effects of 4-substituted-1,3,5-trimethylpyrazoles in binary solvents (CCl_4/C_6H_6, benzene molar fractions) were studied [292]. The author of this

work also carried out a quantitative evaluation of the effect of substituents in position 4 on the CH_3 group protons in position 1 with respect to the σ_p- and σ_m-Hammett constants ($R=0.95$, $\rho=0.159$). The conclusions on correlation equations analysis [56] should be treated with care, since the Hammett constants in their initial form are shown to be of little use with heterocycles [293].

On the basis of NMR spectroscopy data the internal rotation barriers for $N(CH_3)_2$ groups in twenty 1-(*N,N*-dimethylthiocarbamoyl)pyrazole derivatives were determined [294].

The internuclear distance between the carbon atoms attached to the nitro group and the methyl group of 3-nitro- and 5-nitro-1-methyl-4-bromopyrazole (3.7 and 2.9 Å, respectively) was estimated by use of measured values of dipolar relaxation times T_1^{DD} [248].

The structure of 4-substituted 3,5-bis(2-pyridyl)pyrazoles [245], seventeen *C*-nitropyrazoles affected ocular blood flow and retinal function recovery after ischemic insult [244], and a large series of nitroazoloanhydrosacchares [295] has been determined by ^1H and ^{13}C NMR method.

The proton spectra of 1-substituted 3-nitropyrazoles [296], 5-substituted 3-methyl-1-aryl-4-nitropyrazoles [297, 298], 1,3- and 1,5-diphenyl-4-nitropyrazoles [281], 5-iodo-4-nitro-1,3-dimethylpyrazole [299], 1-methyl-3-nitro-4- and 1,3-methyl-4-nitro-5-phenylethynylpyrazoles [300], 1-methyl-3-nitro-5-methoxycarbonylpyrazole [301], 1-methyl-3-nitro- and 1-methyl-5-nitro-4-cyanopyrazoles [302], *N*-(2,4-dinitrophenyl)nitropyrazoles [303], α– and β–anomers of 3-nitro- and 4-nitropyrazolyl-1-ribonucleosides [304, 305], 3-substituted 1,5-dimethyl- [306] and 5-substituted 1,3-dimethyl-4-nitropyrazoles [279], 1-acetyl-3-anilino-4-nitro-5-dimethylaminopyrazoles [307], 3-substituted 4-nitro-5-carboxylic acid derivatives [308, 309], 4-nitropyrazolo[4,3-e][1, 4]diazepin-5,8-diones showing antimicrobial activity [310], 1-heteryl-4-nitropyrazole derivatives [311], 3-nitro- and 5-nitro-1-methylpyrazole [312], 4-nitro-5-(trimethylsilyl)pyrazole [313], 3-methyl-4-nitropyrazol-5-ones [298], and some other nitropyrazoles [248, 314–320] have been examined.

Imidazoles

As with pyrazoles, the introduction of the nitro group into the imidazole ring position 4(5) leads to an approximately 30 ppm lowfield shift of the *ipso*-carbon signal resonance (Tables 3.6 and 3.10) [24, 321–329]. Thus, the chemical shift of the carbon atom bonded to the NO_2 group (C-*ipso*) is 149.2 ppm, whereas that of neighboring carbon (C-5) is 119.8 ppm. In 1-substituted 4-nitroimidazoles (Table 3.11) the shifts of the same carbons are 146 ± 1 and 122 ± 2 ppm, while in 1-substituted 5-nitroimidazoles they are 138 ± 1 and 132 ± 1 ppm, respectively (Table 3.12). All this may be indicative of the possible existence of 4(5)-nitroimidazole as a 4-nitro tautomer. Moreover, another support for the structure may be provided by comparison of the proton spin-spin coupling constants – ^1J, ^2J and ^3J (^1H–^1H) [321, 322, 330].

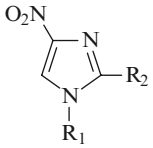


Table 3.11 ^{13}C NMR chemical shifts of 1,2-disubstituted 4-nitroimidazoles in DMSO-d_6 (ppm)

N	R_1	R_2	C-2	C-4	C-5	Ref.
1	CH_3	CH_3	145.66	145.66	122.91	[322]
2	CH_2CH_3	CH_3	144.94	145.80	121.57	[322]
3	CH_2CH_2Cl	CH_3	145.16	145.76	121.79	[322]
4	CH_2CH_2OH	CH_3	145.69	145.46	122.44	[322]
5	CH_2CO_2H	CH_3	145.75	145.16	122.75	[322]
6	$CH_2CO_2CH_3$	CH_3	145.56	145.56	121.34	[322]
7	$CH_2CO_2C_2H_5$	CH_3	1465.16	146.16	122.98	[322]
8	CH_2CH_2CN	CH_3	145.29	145.63	121.81	[322]
			146.1	146.5	122.0	[344]
9	$CH_2CH_2CO_2H$	CH_3	145.37	145.62	121.89	[322]
			145.76	146.0	122.43	[344]
10	$CH_2CH_2CO_2CH_3$	CH_3	145.23	145.66	121.59	[322]
11	$CH_2C_6H_5$	CH_3	145.14	145.14	122.48	[322]
12	$CO_2CH_2C_6H_5$	CH_3	147.29	145.80	119.31	[322]
13	$CO_2C_2H_5$	CH_3	145.69	145.46	122.44	[322]
14	$(C_6H_5)_3C$	CH_3	147.76	145.54	121.71	[322]
15	CH_3	$CH(CH_3)_2$	153.23	146.69	123.07	[322]
16	$CH_2C_6H_5$	CH_3	145.02	145.39	122.43	[345]
17	$CH_2CH_2SO_2C_2H_5$	CH_3	146.3	146.3	122.7	[344]
18	$CH_2CH_2CO_2C_2H_5$	CH_3	145.95	146.41	122.41	[344]
19	$CH_2CH_2COCH_3$	CH_3	146.23	146.51	122.57	[344]

The problem of structural identification of 1-substituted nitroimidazoles by NMR spectroscopy has been considered in many works [322, 328, 331–336]. In [333] an interesting approach to the structure determination of isomeric 4-nitro- and 5-nitro-1-organylimidazoles has been proposed (Tables 3.13 and 3.14). It is based on different directions of the shifts of ring proton and carbon signals in going from neutral molecule to the cation. The 5-nitro derivatives possess a much higher biological activity than the 4-nitro isomers; hence, it is important that an unambiguous method of structure assignment be available [79]. To our great surprise the ^{13}C NMR spectrum of 1-(2′,4′-dichlorophenyl)-2-(4-nitro-1*H*-1-imidazolyl)ethanone (acetone-d_6, 56.1, 123.0, 128.0, 130.9, 132.2, 132.7, 133.1, 138.1, 138.9, 147.1, 192.7 ppm) is presented without signal assignment [328].

^{13}C, ^{14}N, and ^{15}N NMR spectroscopy was used for the examination of nitroimidazole derivatives (Table 3.10) and their cations and anions (Table 3.15) [337, 338]. As seen from Table 3.10, the chemical shifts of the "pyridine" nitrogen atom of nitroimidazoles lie in the −130 ppm range, whereas those of the "pyrrole" nitrogen are located in the −208 to −219 ppm range. This is in higher field compared with the corresponding nitropyrazoles.

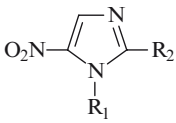


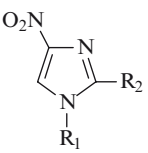
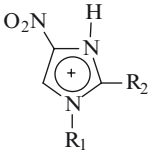
Table 3.12 ^{13}C NMR chemical shifts of 1,2-disubstituted-5-nitroimidazoles in DMSO-d_6 (ppm) .

N	R_1	R_2	C-2	C-4	C-5	Ref.
1	H	CH_3	145.0	147.0	119.2	[346]
2	CH_3[a]	CH_3	150.1	132.2	139.8	[346]
	CH_3	CH_3	151.14	132.23	–	[322]
3	CH_2CH_2OH	CH_3	151.8	132.8	138.3	[346]
			151.09	132.90	138.54	[322]
			152.46	131.26	139.47	[347][b]
4	CH_2CH_2Cl	CH_3	151.7	133.1	138.4	[346]
			151.90	133.20	138.48	[322]
5	$CH_2CH_2NH_2$	CH_3	151.1	129.1	138.5	[346]
6	$CH_2CH(OH)CH_2Cl$	CH_3	151.9	132.5	139.0	[346]
7	CH_2CH_2 $^+NC_5H_5$[a]	CH_3	151.7	133.5	138.4	[346]
8	CH_2CH_2 $^+NC_5H_5$[c]	CH_3	152.4	133.4	138.3	[346]
9	$CH_2CH_2{}^+NC_5H_2(CH_3)_3$	CH_3	151.1	133.5	138.5	[346]
10	$CH_2CH_2{}^+NC_5H_4(C(CH_3)_3)$	CH_3	151.7	133.6	138.5	[346]
11	CH_2CH_2 $^+NC_5H_2(C_6H_5)_3$	CH_3	151.0	131.1	138.2	[346]
12	$CH_2CH_2{}^+NC_5H_4(CONH_2)$[c]	CH_3	153.0	134.3	138.9	[346]
13	$CH_2CH_2{}^+NC_3H_3NCH_3$	CH_3	151.3	133.2	138.3	[346]
14	$CH_2CH_2NC_5H_8$	CH_3	151.6	133.0	138.6	[348]
15	$CH_2CH_2{}^+NC_5H_9$	CH_3	150.9	131.1	138.2	[348]
16	$CH_2CH_2NC_5H_7(C(CH_3)_3)$	CH_3	151.3	131.5	138.4	[348]
17	CH_3	$CH_2{}^+NC_5H_9$	145.41	120.52	146.27	[348]
18	$CH_2CH_2(OH)CH_3$[a]	CH_3	145.41	120.52	146.27	[349]
19	CH_2CH_2OH	CH_2OH	147.56	123.22	145.11	[349]
20	CH_2COOCH_3	CH_2OH	147.62	123.99	145.11	[349]
21	$CH_2COOC_2H_5$[a]	CH_2Br	142.87	122.50	146.28	[349]
22	CD_2COOCD_3[d]	CH_2OH	146.56	123.79	151.83	[349]
23	CH_2COOCH_3	CH_3	151.43	131.60	138.59	[322]
24	CH_2COOH	CH_3	151.56	132.21	138.61	[322]
25	$CH_2COOC_2H_5$	CH_3	151.53	132.10	138.70	[322]
26	CH_3	$CH(CH_3)_2$	157.84	132.04	138.60	[322]
27	CH_2CH_2CN	CH_3	152.48	134.1	139.20	[344]
28	CH_3	COH	141.2	132.1	143.1	[350]
			141.4	131.8	143.4	[350][b]
29	CH_3	$C(OH)_2H$	152. 3	130. 8	–	[350]

[a]In $CDCl_3$
[b]In CD_3COOD
[c]In D_2O
[d]In CD_3OD

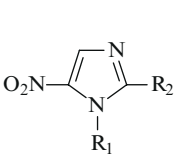
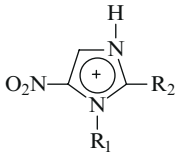
The N-NF_2–group in ^{15}N NMR spectra of nitrated *N*-(difluoroamino)imidazoles manifests itself as a triplet with chemical shifts from –60 to –70 ppm and $^1J_{N–F}$ coupling constants of 166–168 Hz (see Table 3.10) [24].

Table 3.13 ^{1}H NMR chemical shifts (ppm) of 4-nitroimidazoles (DMSO-d_6) and their cations (CF_3CO_2D) [333]

R_1	R_2	H-5	C-5	H-5	C-5	ΔδH	ΔδC
p-$C_6H_4NO_2$	CH_3	8.72	122.06	8.37	123.54	−0.34	1.48
p-$C_6H_4NO_2$	H	8.67	119.23	8.55	121.35	−0.11	2.12
p-C_6H_4COOH	CH_3	8.66	122.06	8.34	123.32	−0.36	1.26
p-$C_6H_4NH_2$	CH_3	8.38	122.36	8.36	123.39	−0.02	1.03
p-$C_6H_4NCOCH_3$	CH_3	8.52	122.20	8.27	123.19	−0.25	0.99

Table 3.14 ^{1}H NMR chemical shifts (ppm) of 5-nitroimidazoles (DMSO-d_6) and their cations (CF_3CO_2D) [336]

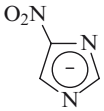
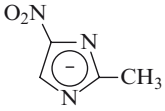
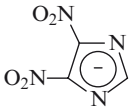
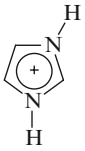
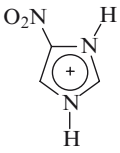



R_1	R_2	H-4	C-4	H-4	C-4	ΔδH	ΔδC
p-$C_6H_4NO_2$	CH_3	8.22	132.45	8.51	122.52	0.28	−9.93
CH_2CH_2OH	H	8.02	132.65	8.36	122.99	0.34	−9.41
$CH_2CH_2SO_2C_2H_5$	CH_3	8.04	122.80	8.40	123.39	0.35	−9.66
$CH_2CH_2N(CH_2CH_2)O$	H	8.06	132.88	8.52	124.46	0.45	−8.42

The chemical shifts of the carbon atom bonded to the nitro group qualitatively correlate with the carbon electron density. When several nitro groups are introduced a considerably worse additivity of ^{13}C chemical shifts compared with benzene derivatives is observed. The experimental ^{13}C shielding in dinitroimidazoles is smaller than that calculated by the additive scheme, and this points to a less clearly displayed conjugation between the nitro group and the imidazole ring compared with the benzene ring [339].

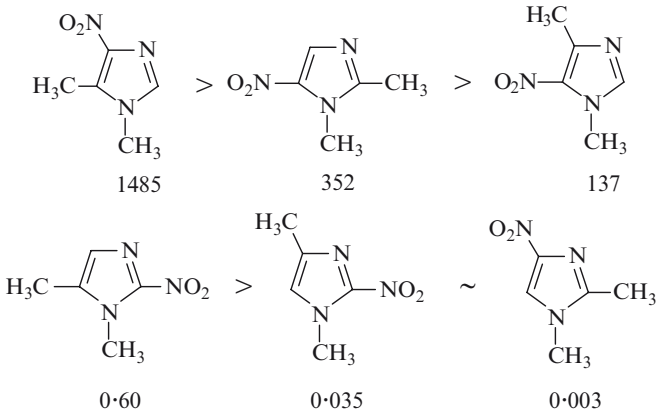
Compared with neutral molecules, the anions and cations of nitroimidazoles are characteristic of correspondingly low field and high field ^{14}N and ^{13}C nuclei resonance shift (Table 3.15) [337]. This trend in the NMR signal shifts of all nuclei can only be explained in terms of a change in average excitation energy, E, and this is supported by UV spectroscopy data. On the basis of qualitative evaluation it is stated that approximately one-third of the anion total negative charge is localized on the nitro group, thus giving rise to an anomalous change in the ^{13}C shift [337].

Table 3.15 ^{13}C and ^{14}N NMR chemical shifts of nitroimidazole anions and cations (H_2O, ppm) [337]

Compound	C-2	C-4	C-5	^{14}N
	143.8	125.9	125.9	−147(3)
	147.5	147.8	133.4	−129(5) −14.2 NO_2
	157.5	147.0	134.7	−129 −19 NO_2
	140.9	140.3	140.3	−17 NO_2
	134.1	119.7	119.7	−207(2)
	136.4	139.3	121.0	−201(5)

Thermal and solvent effects on the chemical shifts ^{13}C and ^{15}N of metronidazole [329] and transition-metal complexes with dimetridazole [341] were studied computationally with appropriate quantum-chemical methods. These effects can be notable, in particular for N-3 atom, which bears a lone pair amenable to hydrogen bonding with aprotic solvent. A DFT-based molecular dynamics simulation of the bulk aqueous solution offers a realistic description of the system, and good agreement is obtained between observed chemical shifts ^{13}C and ^{15}N and computed values averaged over the MD trajectory. A similar accord is obtained with a much less involved approach based on geometry optimization and chemical shift calculation in a polarizable continuum. This apparent inconsistency notwithstanding, theoretical computations of NMR parameters are emerging as useful complements to NMR spectroscopic studies of radiosensitizers [329].

A kinetic investigation of base-catalyzed exchange of *C*-methyl protons has been carried out for six possible *C,N*-dimethylnitroimidazole isomers [342]. In determining the exchange rate a change in the integral intensity of ^1H NMR signals relative to that of unexchangeable *N*-methyl groups was made. The proton exchange rates (K_{OD}, $M^{-1}\,min^{-1}$) decrease in the following order (Scheme 3.6) [342]:



Scheme 3.6

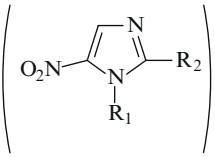
H-D exchange processes occurring in some imidazole nitro derivatives and their salts were studied by NMR spectroscopy [343]. A comparison of the chemical shifts and spin-spin coupling constants indicates that in going from neutral molecules to the salts the hydrogen exchange in the imidazole ring position 2 becomes easier. In the author's opinion this process simulates the carboxylation of 5-aminoimidazoleribo-nucleotide [343].

Complexes of type $[PtL_2X_2]$, where L are chemotherapeutic agents, 5-nitroimidazole derivatives, have been studied by ^{1}H, ^{195}Pt NMR spectroscopy, X-ray diffraction, electronic absorption spectroscopy, and polarography (Table 3.16) [351]. The ^{195}Pt chemical shifts of the dichloro-bis(5-nitroimidazole)-platinum(II) complexes are within the range from −2049 to −2075 ppm. The ^{195}Pt chemical shift of the metronidazole complex (X=Cl) *cis*- and *trans*- isomers differs by as small as 4 ppm, whereas ^{1}H by 0.22 ppm (H-4) and −0.09 ppm (2-CH_3) (Table 3.16). A considerably greater shift of ^{195}Pt NMR signals is observed with a change either in substituents attached to the platinum atom (X=Cl, Br, I, etc.) or in the nitro group position in the ring (from 5-nitro- to 4-nitro- or 2-nitro-). The latter is responsible for different donating ability of the "pyridine" nitrogen atom N-3 and the N-Pt bond "strength". The 4-nitro- and 2-nitroimidazole complexes show nearly the same ^{195}Pt chemical shifts (−1850 and −1856 ppm, respectively) reflecting a lower donor strength of these ligands [351].

A large series of 5-nitroimidazoles used for radiosensitization of hypoxic cells in cancer chemotherapy has been studied by ^{1}H and ^{13}C NMR spectroscopy (in Table 3.12 only ^{13}C data are presented) [346, 348].

The hyperfine-shifted proton resonance of metmyoglobin and methemoglobin complexes with imidazoles, in particular, 4-nitroimidazole, was studied in order to obtain an insight into the structural features of the iron-bound imidazole [352]. The structure of 1-(1,3-dihydroxy-2-propyl)-4-nitroimidazoles, so called acyclic nucleosides, has been established by ^{1}H and ^{13}C NMR [327].

Table 3.16 ^{1}H and ^{195}Pt NMR chemical shifts of5-nitroimidazole Pt^{II} complexes, *cis*-$[PtL_2X_2]$ (ppm)[a]



					$\delta^{1}H$		$\delta^{195}Pt$
N	L	R_1	R_2	X_2	H-4	R-2	
1		CH_3	H	Cl_2	8.24	8.58	–
2	Dimetridazole	CH_3	CH_3	Cl_2	8.30	3.01	–2060
3	Dimetridazole[b]	CH_3	CH_3	Cl_2	8.05	3.0	–
4		CH_3	CH_2OH	Cl_2	8.30	5.45	–
5		CH_3CO_2H	CH_3	Cl_2	8.45	2.99	–2074
6	Ronidazole	CH_3	$CH_2OC(O)NH_2$	Cl_2	8.40	5.86	–
7	Metronidazole	CH_2CH_2OH	CH_3	Cl_2	8.32	2.98	–2071
8	Metronidazole	CH_2CH_2OH	CH_3	Cl_2	8.10	3.07	–2067
9	Metronidazole	CH_2CH_2OH	CH_3	Br_2	8.43	3.04	–2401
10	Metronidazole	CH_2CH_2OH	CH_3	I_2	8.52	3.06	–3290
11		CH_2CH_2OH	CH_2OH	Cl_2	8.40	5.43	–
12	Bamnidazole	$CH_2CH_2OC(O)NH_2$	CH_3	Cl_2	8.34	3.05	–
13	Ornidazole	$CH_2CH(OH)CH_2Cl$	CH_3	Cl_2	8.32	3.0	–
14	Ipronidazole	CH_3	$CH(CH_3)_2$	Cl_2	8.41	4.98	–
15	Secnidazole	$CH_2CH(OH)CH_3$	CH_3	Cl_2	8.30	2.95	–
16	Tinidazole	$CH_2CH_2S(O_2)C_2H_5$	CH_3	Cl_2	8.34	2.96	–2075
17	Metronidazole	CH_2CH_2OH	CH_3	[c]	8.32	2.94	–1614
18	Metronidazole	CH_2CH_2OH	CH_3	[d]	8.30	3.88	–
19	Nimorazole	$CH_2CH_2N(CH_2CH_2)_2O$	H	Cl_2	8.03	8.76	–2049
20	Flunidazole	CH_2CH_2OH	*p*-C_6H_4F	Cl_2	7.4-8.0		-

[a]All $\delta^{1}H$ in acetone-d_6 except: **1** in DMF-d_6, **17** and **18** in D_2O, all $\delta^{195}Pt$ in DMF except: **5** and **17** in H_2O; $\delta^{195}Pt$ are referenced to $Na_2[PtCl_6]$
[b]*trans*-Complex
[c]Ethylmalonate
[d]Cyclobutane-1,1-dicarboxylate

A full assignment of the proton resonance of substituted 2-styryl-5-nitroimidazoles was carried out by the use of an addition increment method for chemical shift prediction [353]. Some 4-styryl-5-nitroimidazoles have been studied in [354].

The products of nitration of 1-hydroxyimidazol-3-oxides were identified by proton resonance along with other methods [355].

Aryl 1-methyl-4-nitro-5-imidazolyl sulfones, a new class of radiosensitizing pharmaceuticals [356–359], an extensive series of nitro derivatives of methylthio- [109] and ethylsulfonylimidazoles [360, 361], 1-alkyl [362]-, 1-trialkylsilylalkyl)-2-methyl-4-nitroimidazoles [363], allylated 4-nitroimidazoles [364], 5-amino derivatives of 4-nitroimidazoles [365], 5-azido-4-nitroimidazole [366], ^{15}N-labeled 4-nitroimidazoles [367], 1-methyl-5-nitro-2-(5-nitrofuryl-2)- [368] and 1-methyl-5-nitro-2-(5-nitrothienyl-2)-imidazole [369], 1-[2-(diarylmethoxy)ethyl]-2-methyl-5-nitroimidazoles targeted at HIV-1 reverse transcriptase [370], 2-heteryl-5-nitroimidazoles [371], triazolyl nitroimidazoles [372], 4-substituted

1,2-dimethyl-5-nitroimidazole [373], N-(2,4-dinitrophenyl)-nitroimidazole [303], the products of conversion of the 2-methyl group to nitrile in 1,2-dimethyl-5-nitroimidazoles [374], morpholino-substituted 5-nitroimidazoles [375], rhodium (III) complexes of 5-nitroimidazoles [376], ruthenium (II) complexes containing 4-nitroimidazoles [377, 378], halogen-substituted nitroimidazoles [379–383], carborane-containing 2-nitroimidazole compounds [384–386], 2-nitroimidazoles as radiosensitizers [387–389], nitroimidazole-substituted alkyl- and arylboronic acids [390], *N*-alkyl- [391] and other 4-nitroimidazoles [392–402], steroidal nitroimidazoles as potential site-selective radiosensitizers [403], 5-(nitroimidazolyl-1)-1,6-naphthyridin-2(1H)-ones [404], macromolecular products of metronidazole [405, 406], some antiprotozoal compounds – nitroimidazolylthiadiazoles, nitroimidazolyloxadiazoles [407], 5-guanidino-4-nitroimidazole [408–411], 1-(1-methyl-5-nitroimidazolyl-2)-2-oxotetrahydroimidazoles [412], 1-alkyl-5-nitroimidazoles (with a longer alkyl chain) exhibited antibacterial activity, especially against Gram-positive bacteria [413, 414], 2-nitroimidazoles [415, 416], 1-substituted- [417], vinyl-substituted- [418] and fluorinated 2-nitroimidazoles [419], bioreductive hypoxia markers – 2-nitroimidazoles with biotinylated 1-substituents [420], complexes of 99^{m} Technetium-(2-nitroimidazoles) [421], 1-amino- and 1-benzylidenamino-2-nitroimidazoles [422], 1-picryl-2- and -4-nitroimidazoles [423], nitroimidazolyl ribonucleosides [304, 305], 3′-(4-nitroimidazol-1-yl)-2′,3;-dideoxynucleosides of pyridine analogs [424], the products of hydroxymethylation and cyanoethylation of nitroimidazoles [425], dinitroimidazoles [2, 103, 426–428], nitroimidazolium perchlorates [248] have been synthesized and studied by NMR spectroscopy.

Some Indian researchers made use of NMR spectroscopy for the identification of compounds during the synthesis of a large series of nitroimidazole derivatives possessing many valuable properties [321, 380, 429–441]. Suwinski and coworkers have investigated a large amount of different nitroimidazoles used in tumor radiotherapy or as tuberculosis inhibitors [442–451].

NMR spectroscopy is widely accepted to prove the structure of diverse bioactive nitroimidazoles [282, 316, 332, 346, 373, 452–479].

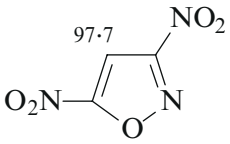
Isoxazoles, Oxazoles, and Oxadiazoles

Insertion of the nitro group into the isoxazole ring position 4 significantly shifts low-fields the signals of protons in positions 3 and 5, the largest shift being observed for the proton in position 5 [480, 481]. The hydrogen isotope exchange in the CH_3 groups of 3,5-dimethyl-4-nitroisoxazole with diethylamine-D_N has been studied by Sokolov et al. [482]. A decrease in the integral intensity of signals of the methyl group protons in position 5 indicates a selective character of deutero-exchange in nitroisoxazole [482].

In [483] the structure of the products of condensation of 3,5-dimethyl-4-nitroisoxazole and aromatic aldehydes was investigated by NMR, IR, and electron spectroscopy.

The introduction of NO_2 into the isoxazole position 3 also shifts to down-fields the ring proton signals (H-4 by 0.7 and H-5 by 0.4 ppm) [484]. The same shift value is observed for isostructural pyrazoles.

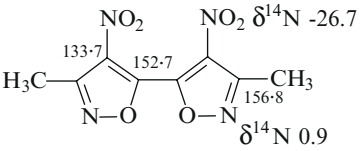
The proton spectra of 4-methyl- and 3,5-dinitroisoxazoles are presented in [485], those of nitroisoxazolines in [486] and nitroisoxazolidines in [487]. The ^{13}C and ^{14}N NMR spectra of 3,5-dinitroisoxazole have been considered in [488].



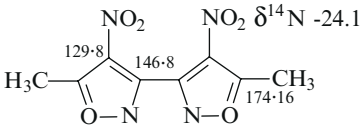
The $^{13}C–NO_2$ chemical shifts are equal to 165.6 and 167.0 ppm, the ^{14}N values of the nitro group being −30.9 and −35.4 ppm. Carbon-13 and nitrogen-15 chemical shifts, close to the earlier values, are also observed for *C*-nitrotetrazoles (see Table 3.23).

The authors [489] managed to prove the structure of previously unknown bi(3-methyl-4-nitroisoxazolyl-5) (**A**) and its isomer bi(5-methyl-4-nitroisoxazolyl-3) (**B**) by use of multinuclear NMR spectroscopy.

A

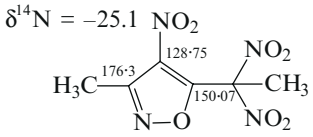


B



The values of C-3 and C-5 chemical shifts are dependent on both the methyl group position and isoxazole ring joint. With 5-5′-joint (**A**) the difference between C-3 and C-6 chemical shifts is 4 ppm, whereas with joint **B** this value is 27 ppm.

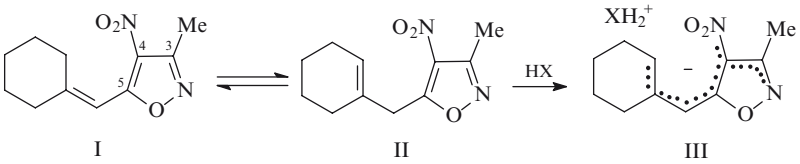
A large difference between $\delta^{13}C$-3 and $\delta^{13}C$-5 is also the case in unsymmetrical substituted isoxazole:



The C-4 chemical shifts in the compounds studied are poorly sensitive to structural changes [489].

The data of proton spectroscopy (chemical shifts and coupling constants) were used for the structural assignment of 3-methyl-4-nitro-5-arylisoxazoles [490–492].

In the synthesis of 3,5-dimethyl-5,6,7,8-tetrahydroisoxazolo[4,5-b]quinoline from 3,5-dimethyl-4-nitroisoxazole R. Nesi et al. [493] established the structure of the intermediates I-III by ^{1}H and ^{13}C NMR spectroscopy (Scheme 3.7).



Scheme 3.7

The C-3 chemical shifts show low sensitivity to changes in structure and charge of the molecule. The amplitude of changes of C-4 and C-5 chemical shifts caused by the earlier transformation of I-III is practically the same (Table 3.17).

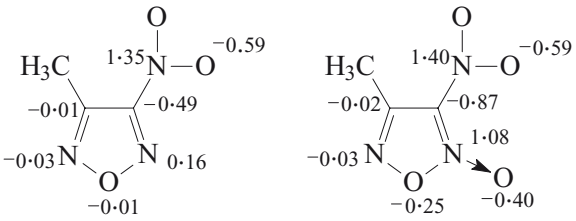
^{13}C NMR spectroscopy was used in the investigation of 5-substituted 3-phenyl-4-nitroisoxazoles (Table 3.17) [494–497].

The ^{1}H and ^{13}C NMR spectra of 3-methyl-4-nitro-5-styrylisoxazole photodimers [498] and other nitroisoxazole derivatives [499, 500] have been examined.

The structure of 5-substituted 4-nitro-2-phenyloxazoles obtained by recyclization of the corresponding isoxazoles was determined by ^{1}H and ^{13}C NMR [501, 502] (Table 3.18).

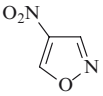
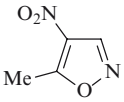
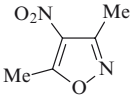
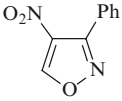
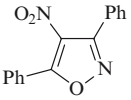
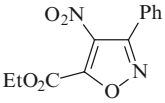
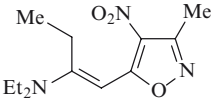
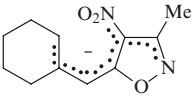
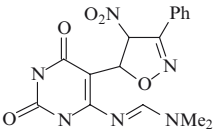
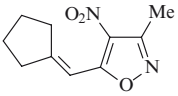
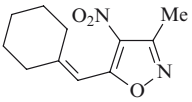
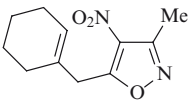
The chemical shift of the CH_3 group protons of 3-methyl-4-nitro-1,2,5-oxadiazole (3-methyl-4-nitrofurazan) is 2.72 ppm (acetone-d_6) [503]. The ^{13}C and ^{14}N NMR spectral characteristics of some nitrofurazans and –furoxans are presented in Table 3.19 [136, 488, 504–516].

The ^{13}C and ^{14}N chemical shifts of C–NO_2 are in the 153 to 160 and −28 to −45 ppm range, respectively, and have very small changes in both carbon and nitrogen NMR scales depending on the substituents in neighboring position of the furazan cycle (Table 3.19). The δ^{13}C (C–NO_2) value in nitrofuroxans is shifted upfield by ~30 ppm in comparison to nitrofurazans. The presence of electron-withdrawing N→O group in furoxan decreases the order of C=N(→O) double bond and increases the screening of the C–NO_2-group carbon. Indeed, our quantum-chemical PM3 calculations* on 3-nitro-4-methylfurazan and –furoxan show a significant increase of the negative charge on the carbon attached to the nitro group in nitrofuroxan:



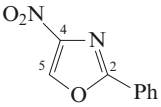
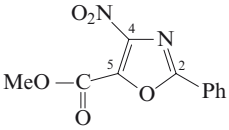
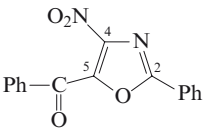
*PM3 calculations with geometry optimization (SPARTAN 5.0) have been carried out at Universite L. Pasteur, Chemistry Department, Strasbourg, France (with kind help of Dr. A. Varnek).

Table 3.17 ^{13}C NMR chemical shifts of nitroisoxazoles in $CDCl_3$ (ppm)

Compound	C-3	C-4	C-5	Refs
	157.84	144.44	157.84	[221][a]
	145.88	131.08	170.66	[221][a]
	155.50	130.14	171.89	[221][a]
	156.4	133.9	160.7	[494]
	158.02	126.16	168.05	[495]
	154.7	133.5	157.05	[496]
	155.47	121.86	168.65	[493]
	153.06	111.39	154.22	[493]
	151.8	83.9	94.0	[497]
	155.49	126.60	168.05	[493]
	155.52	128.20	168.14	[493]
	155.65	129.50	173.36	[493]

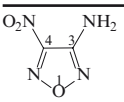
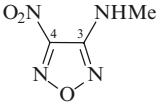
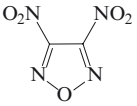
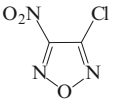
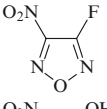
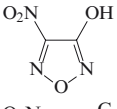
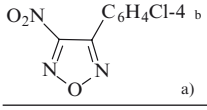
[a] We took the liberty to assign ^{13}C signals

Table 3.18 ^{13}C NMR chemical shifts of 4-nitrooxazoles in $CDCl_3$ (ppm)[a]

Compound	C-2	C-4	C-5	Other
	161.5	137.7	149.4	125.15, 127.0, 129.0, 132.25 (Ph)
	155.5	134.9	148.5	53.4 (OCH_3), 124.3, 127.6, 129.1, 133.05 (Ph), 160.9 (CO)
	160.6	134.9	142.5	127.5, 129.1, 129.2, 129.5, 132.9, 135.0, 147.3, (Ph), 181.2 (CO)

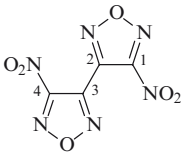
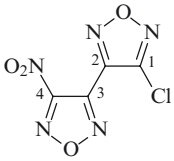
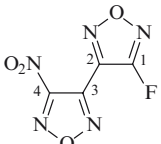
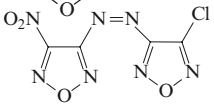
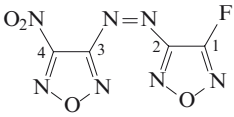
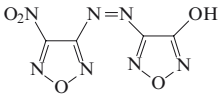
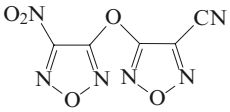
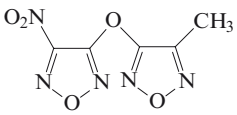
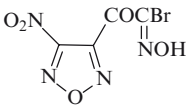
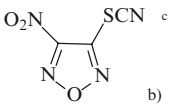
[a] We took the liberty to assign ^{13}C NMR signals of nitrooxazoles

Table 3.19 ^{13}C and ^{14}N NMR chemical shifts (ppm) and coupling constants (J, Hz) of nitrofurazans and nitrofuroxans

Compound	C-3	C-4	^{14}N-NO_2 ($\Delta\nu_{0.5}$, Hz)	Solvent	Refs
	152.3	153.9 $^1J_{CN}$ 17	−28.6 (16)	$(CD_3)_2CO$	[488]
	151.6	151.5	–	$CDCl_3$	[136]
	153.5 152.9	153.5 152.9	−44.0[a] −44.0	CD_2Cl_2	[506] [513]
	141.9	157.2	−45.5 (10)	$CDCl_3$	[511]
	159.0 d $^1J_{CF}$ 291.2 $\delta^{19}F$ −138.1	150.5	−35.4 (9)	$CDCl_3$	[504]
	158.3	153.2	–	$CDCl_3$	[508] [509]
 a)	148.3	158.6 t $^1J_{CN}$ 17	−30.5 (14)	$CDCl_3$	[488]

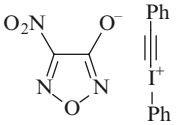
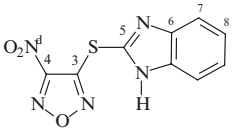
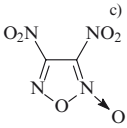
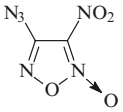
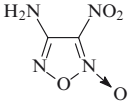
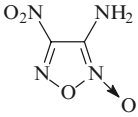
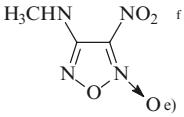
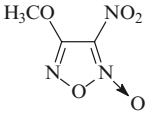
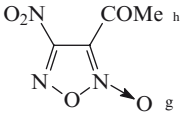
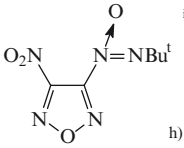
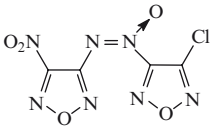
(continued)

Table 3.19 (continued)

Compound	C-3	C-4	^{14}N-NO$_2$ ($\Delta\nu_{0.5}$, Hz)	Solvent	Refs
	137.0	158.8 t $^1J_{CN}$ 19	−35.8 (7)	$CDCl_3$	[488]
	137.2	158.7	−40.0 (7)	$CDCl_3$	[511]
	146.2 C-2 136.7 (132.5 d C-2 $^2J_{CF}$ 21.6) δ^{19}F −140.0	140.5 C-1 158.4 (160.1 d C-1 $^1J_{CF}$ 276.1)	−40.3 (15)	$CDCl_3$	[504]
	153.17	155.91	−39.0 (9.5)	$(CD_3)_2CO$	[511]
	153.0 (153.3 d C-2 $^2J_{CF}$ 13.8) δ^{19}F −141.3	153.4 (159.1 d C-1 $^1J_{CF}$ 280.5)	−39.7 (22)	$CDCl_3$	[504]
	150.3 (158.2 C-2)	157.1 (156.2 C-1)	–	$(CD_3)_2CO$	[508] [509]
	156.1 (128.9 C-2) (106.4 C≡N)	153.8 (162.2 C-1)	−38.6 (10.2)	$(CD_3)_2CO$	[514]
	157.1 (146.6 C-2) (7.5 CH_3)	153.9 (162.1 C-1)	−37.8 (20)	$(CD_3)_2CO$	[514]
	153.17	155.91	–	$(CD_3)_2CO$	[515]
	145.9	160.8	−35.6	$(CD_3)_2CO$	[516]

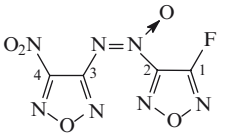
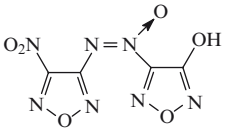
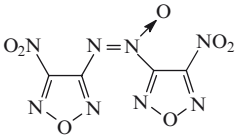
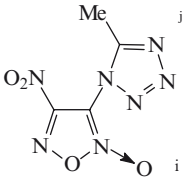
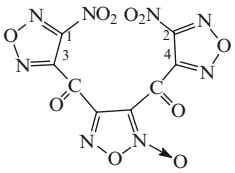
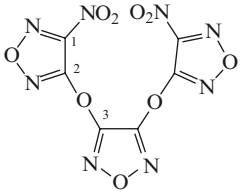
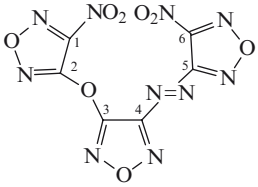
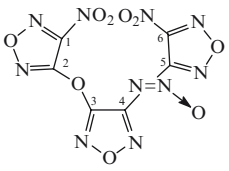
(continued)

Table 3.19 (continued)

Compound	C-3	C-4	^{14}N-NO_2 ($\Delta\nu_{0.5}$, Hz)	Solvent	Refs
	157.6	153.7	–	$(CD_3)_2CO$	[512]
	149.6	160.3	–35.1	$(CD_3)_2CO$	[516]
 c)	122.7	153.6	–47.7 (3-NO_2) –42.5 (4-NO_2)	$CDCl_3$	[516]
	128.3	148.1	–	$(CD_3)_2CO$	[516]
	128.0	152.3	–34.30[e]	$CDCl_3$	[516]
	158.0	126.7	–31.38[e]	$CDCl_3$	[516]
 f) e)	125.59	159.16	–	$CDCl_3$	[516]
 g) f)	123.10	158.87	–	$CDCl_3$	[516]
 h) g)	108.8	158.0	–	DMSO-d_6	[510]
 i h)	151.8 $^2J_{CN}$ 3.3	154.2 $^1J_{CN}$ 20.2	–42 (5) (–79 N→O)	$CDCl_3$	[507]
	148.0 (156.1 C-2)	155.0 (142.1 C-l)	–38.4 (13) (–65 N→O)	$CDCl_3$	[511]

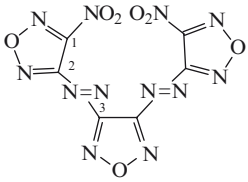
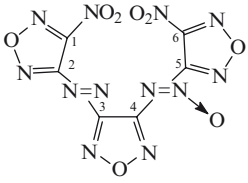
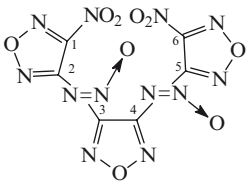
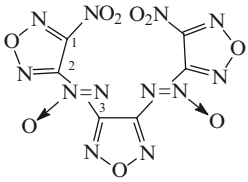
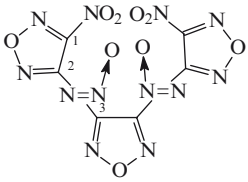
(continued)

Table 3.19 (continued)

Compound	C-3	C-4	^{14}N-NO$_2$ ($\Delta\nu_{0.5}$, Hz)	Solvent	Refs
	128.3 (148.0 d C-2 $^2J_{CF}$ 22.1) δ^{19}F −136.6)	155.0 (159.1 d C-1 $^1J_{CF}$ 279.2)	−38.7 (13) (−66 N→O)	$CDCl_3$	[504]
	149.8 (152.4 C-2)	157.0 (158.4 C-1)	−36.3 (10) (−61 N→O)	$CDCl_3$	[508]
	149.8 (153.6 C-2)	157.4 (155.2 C-1)	−37.2,-41.6 NO_2 (−69 N→O)	$(CD_3)_2CO$	[513]
	108.17	156.00	–	$CDCl_3$	[510]
	146.06 (C-1) 146.41 (C-2) 143.71 (C-3) 144.21 (C-4)		−38.63 −38.31	$(CD_3)_2CO$	[515]
	153.6 (C-1) 156.3 (C-2) 154.2 (C-3)		−38.4 (10)	$(CD_3)_2CO$	[505]
	153.0 (C-1), 154.9 (C-2) 154.2 (C-3), 158.6 (C-4) 157.4 (C-5), 156.2 (C-6)		−39.9 (15) −41.4 (15)	$(CD_3)_2CO$	[505]
	153.6 (C-1), 156.7 (C-2) 155.9 (C-3), 153.1 (C-4) 149.7 (C-5), 157.2 (C-6)		−39.0 (30) −37.2 (30) (−68.1N→O)	$(CD_3)_2CO$	[505]

(continued)

Table 3.19 (continued)

Compound	C-3	C-4	^{14}N-NO_2 ($\Delta\nu_{0.5}$, Hz)	Solvent	Refs
	156.1 (C-1) 157.6 (C-2) 158.9 (C-3)		−38.1 (40)	$(CD_3)_2CO$	[505]
	157.0 (C-1), 149.5 (C-2) 154.8 (C-3), 158.0 (C-4) 157.5 (C-5), 156.1 (C-6)		−38.1 (40) (−66.1N→O)	$(CD_3)_2CO$	[505]
	157.3 (C-1), 149.8 (C-2) 156.3 (C-3), 149.8 (C-4) 153.6 (C-5), 154.9 (C-6)		−38.7 (1-NO_2) −44.2 (6-NO_2) (−65.1 3-N→O) (−70.2 5-N→O)	$(CD_3)_2CO$	[505]
	155.2 (C-1) 153.4 (C-2) 150.7 (C-3)		−43.2 (30) (−69.7N→O)	$(CD_3)_2CO$	[505]
	156.9 (C-1) 149.5 (C-2) 153.8 (C-3)		−37.6 (15) (−69.9N→O)	$(CD_3)_2CO$	[505]

[a] Private communication of Dr. A. Sheremetev (N.D. Zelinsky Institute of Organic Chemistry, RAS, Moscow)
[b] δ^{13}C (Ph) 120.2, 129.7, 130.4, 138.6
[c] δ^{13}C (CN) 104.9
[d] δ^{13}C (BIM-cycle) 139.3 (C-5), 140.7 (C-6), 116.5 (C-7), 124.5 (C-8)
[e] In $(CD_3)_2CO$
[f] δ^{13}C (Me) 30.25
[g] δ^{13}C (OMe) 59.42
[h] δ^{13}C (Me) 28.50, 186.8 (CO)
[i] δ^{15}N (NO_2) −41.21
[j] δ^{13}C (Me) 8.98, δ^{13}C (C-tetraz) 184. 65

To the contrary, the $\delta^{14}N$ (NO_2) is not practically changed in going from nitrofurazans to nitrofuroxans (Table 3.19) as the calculated charges on the nitro group. As a rule, the carbon signal of the C-NO_2 in nitroazoles shows quadrupole broadening owing to spin-spin coupling ^{13}C–^{14}N (NO_2) [235, 261, 272, 510]. This broadening disappears in a triplet resonance experiment ^{13}C–{^{1}H,^{14}N} [510]. Nevertheless, there are rare examples of coupling between the ^{13}C of the nitro carbon and the ^{14}N of the nitro groups in nitrofurazans [488, 517]. The ^{13}C NMR spectra of 3-amino-, 3-(4-chlorophenyl)-4-nitrofurazan and 4,4′-dinitro-3,3′-bifurazan show well-resolved carbon triplets (17–19 Hz) (Table 3.19) and, what is more important, the ^{14}N signal in the latter was split into a doublet with the same coupling constant as the ^{13}C triplet (19 Hz) [517]. The N(O) atom of the azoxy group in bi- and trifurazans has narrow signals in the ^{14}N NMR spectra, and their chemical shifts are within the range from −60 to −70 ppm (Table 3.19) [505]. In these compounds due to ^{13}C–^{14}N coupling, the carbon spectra show broadened signals of the carbon atoms bonded to the azoxy group (as and with nitro).

The structure of high energetic materials – nitroazo(azoxy)furazans showing high crystal density and excellent energetic properties of detonation velocity and detonation pressure – has been studied by NMR spectroscopy [137, 139, 505, 508, 509, 511, 518, 519].

The nitro group position in the phenyl ring of 3-aryl-4-nitrofurazans during nitration was determined by proton resonance [520]. The structure of a large series of 3-(R-amino)-4-nitrofurazans formed by nucleophilic substitution of nitro group in dinitrofurazan with secondary and tertiary amines has been established by ^{1}H and ^{13}C NMR method [136].

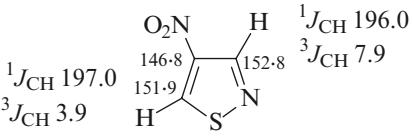
^{13}C and ^{14}N NMR spectroscopy was successfully used for the investigations of some 4-nitro- and 3-nitrofuroxan isomers [521, 522].

The internal rotation barriers of the dimethylamino groups in substituted azoles including 5-nitro-2-dimethylamino-1,3,4-oxadiazole ($\Delta G^{\neq}$ = 9 kcal/mol, 133°C) were also defined by NMR spectroscopy [523].

Isothiazoles, Thiazoles, and Thiadiazoles

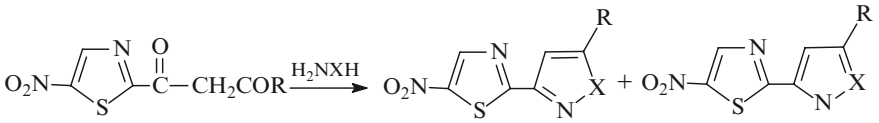
The introduction of the nitro group into the isothiazole ring position 4 gives, as with the earlier isoxazoles, an analogous picture with even a stronger downfield shift of signals [524–528]. A comparison of the ^{1}H NMR spectra of some nitroisothiazoles and their cations has been carried out [526]. The protonation of isothiazole and nitroisothiazole gives rise to a downfield (like with other heterocycles) shift of the resonance protons.

^{1}H and ^{13}C NMR shifts (DMSO, ppm) and spin-spin coupling constants (Hz) of isothiazole 4-derivatives, including 4-nitroisothiazole, have been examined [527, 529]:



The NMR data have been compared with the calculated total charge densities for isothiazoles.

NMR study of nitrothiazoles has been the subject of few number of works [525, 530–540]. The proton chemical shifts of about 30 thiazole derivatives including 5-nitrothiazole and 2-nitrothiazole are presented in [536]. The authors have found the coupling constants between H-2 and H-4 in most 5-substituted thiazoles to be negligible with the exception of 5-nitrothiazole and 5-thiazolecarboxylic acids [536]. The change in the H-4 chemical shifts of the 2-substituted 5-nitrothiazole fragment enables the ratio of isomeric products of the reaction of 5-nitrothiazole 2-(1′,3′-dicarbonyl) derivatives with hydrazine and hydroxylamine to be established (Scheme 3.8) [537].

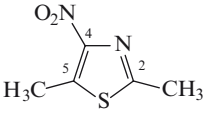
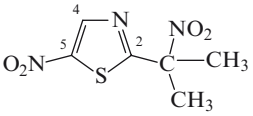
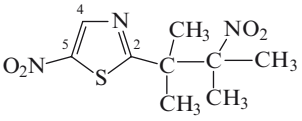


R = CH_3, C_6H_5; X = NH, NR, O

Scheme 3.8

The structure of a new alkylating agent, 2-(1-methyl-1-nitroethyl)-5-nitrothiazole and its *C*-alkylation product of the reaction with 2-nitropropane anion by $S_{RN}1$ mechanism has been assigned by proton and carbon NMR spectroscopy (Table 3.20) [541, 542].

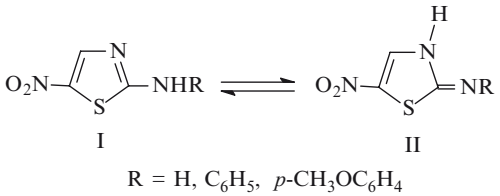
Table 3.20 ^{13}C NMR chemical shifts of nitrothiazoles ($CDCl_3$, ppm)

Compound	C-2	C-4	C-5	other	Refs
	161.29	150.84	138.36	13.10 5-CH_3 19.08 2-CH_3	[221][a]
	172.17	142.15	144.69	26.88 (CH_3) 88.78 (–CNO_2)	[541]
	187.11	143.29	144.94	29.63 (CH_3) 31.95 (CH_3) 53.48, 74.05	[541]

[a] We took a liberty to assign ^{13}C signals

The ^{13}C (C-5) chemical shifts in these nitrothiazoles are significantly displaced toward lower frequency field in comparison with other azoles.

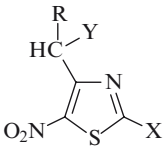
The tautomerism in 5-nitrothiazole 2-amino derivatives has been examined by ^{1}H NMR spectroscopy in DMSO-d_6 [538]. The amino form **I** in the tautomeric equilibrium is found to be prevalent (Scheme 3.9).



Scheme 3.9

The structure of 2-substituted 4-(2-furyl)-5-nitrothiazoles [543], 5-nitrothiazolyl-2-semicarbazides (homolog of strong antitrichomonade agent) [539] was proved by ^{1}H NMR spectroscopy. The NMR spectra were used for the identification of 5-nitrothiazole 2-amino derivatives [532, 544, 545]. The polymorphic azodyes containing 2-amino-5-nitrothiazole have been investigated by multinuclear NMR spectroscopy in solution and in solid-state (^{13}C CP/MAS) [544, 545].

Products of vicarious nucleophilic substitution of hydrogen in nitrothiazoles have been studied by NMR [546]:



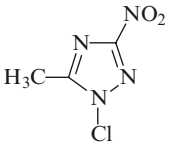
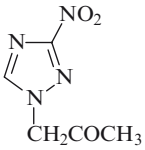
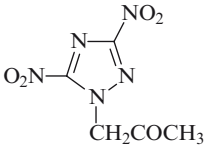
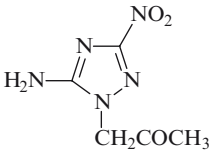
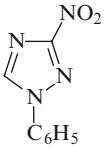
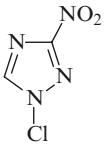
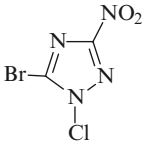
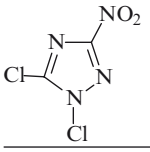
The VNS reaction on the author's opinion [546] proceeds via fast and reversible formation of the σ^{H} adducts followed by usually slower base-induced β-elimination.

The data of the NMR spectra of 1-{[(5-nitro-1,3,4-thiadiazol-2-yl)methylen]-amino}-2-imidazolidinone [540], 2-[(2-methyl-5-nitrothiazol-4-yl)methylene]-malonate and its imidazole analogs [547, 548] have been reported.

Triazoles and Tetrazoles

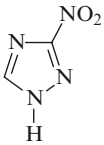
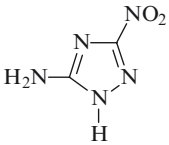
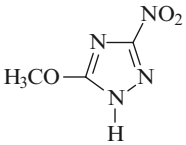
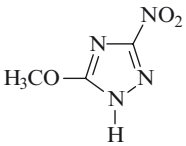
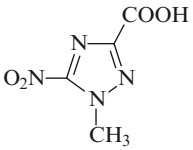
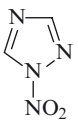
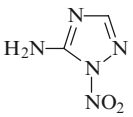
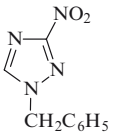
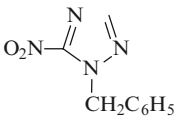
^{1}H, ^{13}C, ^{14}N, ^{15}N NMR spectroscopy is extensively used for the structural determination of nitrotriazoles [232, 261, 549–556]. Thus, for example, in the case of *N*-acetonylnitrotriazoles and -tetrazoles (see Tables 3.21–3.23) the proton spectra are poorly informative, whereas the presence of one or two nitro groups in the azole molecules leads to broadening of $^{13}C–NO_2$ signals [261]. Therefore the authors [261] worked out a heteronuclear triple resonance regimen, which means that ^{13}C

Table 3.21 ^{13}C and ^{15}N NMR chemical shifts (ppm) and coupling constants (*J*, Hz) of 1,2,4-nitrotriazoles[a]

Compound	C-3	C-5	^{15}N	Solvent	Refs
	160.85	159.25	−197.6 N-1 −82.2 N-2 −133.2 N-4 −28.4 NO_2	$(CD_3)_2CO$	[550]
	161.90	147.90	−166.3 N-1 −84.1 N-2 −135.9 N-4 −26.6 NO_2	DMSO-d_6	[261]
	158.50	152.10	172.9 N-1 75.4 N-2 −141.4 N-4 −31.2, −35.9 NO_2	DMSO-d_6	[261]
	159.59	157.27	−204.3 N-1 −99.5 N-2 −177.8 N-4 −23.9 NO_2 −324.2 NH_2	DMSO-d_6	[261]
	162.5	144.5	−151.6 N-1 −92.5 N-2 −133.9 N-4 −26.7 NO_2	DMSO-d_6	[551]
	C-3	C-5			
	163.72	146. 60		$(CD_3)_2CO$	[550]
	161.53	135.40		$(CD_3)_2CO$	[550]
	160.26	146.90		$(CD_3)_2CO$	[550]

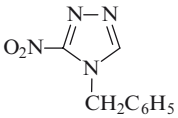
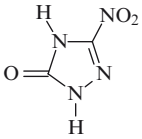
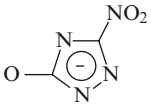
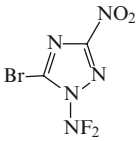
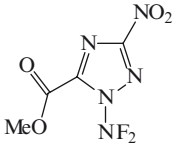
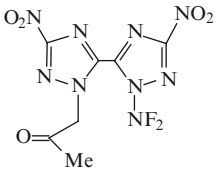
(continued)

Table 3.21 (continued)

Compound	C-3	C-5	Solvent	Refs
	164.23	147.0	DMSO-d_6	[557]
	161.08	157.63	DMSO-d_6	[220]
	160.95	159.26	DMSO-d_6	[220]
	156.66	147.68	DMSO-d_6	[220]
	151.00	152.69	DMSO-d_6	[220]
	149.7	138.5	DMSO-d_6	[240]
	143.1	163.1	DMSO-d_6	[558]
	162.55	144.71	$CDCl_3$	[559]
	149.61	151.5	$CDCl_3$	[559]

(continued)

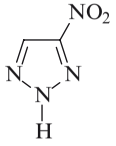
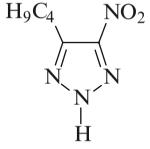
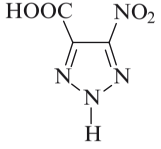
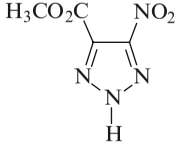
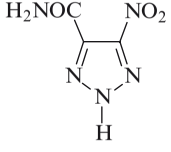
Table 3.21 (continued)

Compound	C-3	C-5	Solvent	Refs
	153	146.14	$CDCl_3$	[559]
	148.0	154.0	DMSO-d_6	[560]
	159–160	164.4–165	DMSO-d_6	[560]
	$\delta^{19}F = 110.59$, pK_a (H_2O) = 3		$(CD_3)_2CO$	[24]
	160.10 145.65	$\delta^{13}C$ 55.0 q, Me, $^1J_{CH}$ 150.3 153.86 q, CO, $^2J_{CH}$ 4.2 $\delta^{19}F$ 110.2, δ^1H 4.31 Me pK_a (H_2O) = 3.55	$(CD_3)_2CO$	[24]
		$\delta^{13}C$ 160.29 (C-3), 141.41 (t, C-5, $^3J_{C\text{-}CH2}$ 2.7) 162.05 (C-3), 143.14 (C-5), 27.19 (q, Me, $^1J_{CH}$ 129.0), 61.86 (t, CH_2, $^1J_{C\text{-}H}$ 145.3), 197.69 (qt, CO, $^2J_{C\text{-}Me}$ 5.0, $^2J_{C\text{-}CH2}$ 4.2), $\delta^{19}F$ 111.69, δ^1H 2.46 (Me), 5.74 (CH_2) pK_a (H_2O) = 2	$(CD_3)_2CO$	[24]

[a] pK_a (H_2O) values are given for the starting azoles

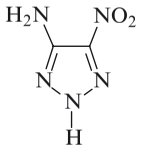
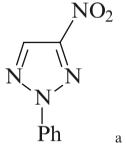
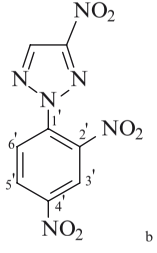
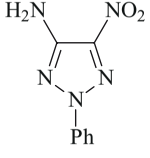
nuclei detection was undertaken at a wide band proton decoupling and selective nitro group ^{14}N nuclei decoupling. This made it possible to detect a narrow ^{13}C NMR signal of the carbon atom bonded to the NO_2 group. Interestingly, the ^{15}N chemical shifts of the nitroazole nitro group are changed in a fairly narrow range from −18 to −35 ppm (Tables 3.21–3.23) [261, 550, 551], i.e., structural factors do not affect much the nitro group ^{15}N resonance. For 1,2,4-nitrotriazoles the ^{15}N chemical shifts of "pyridine" N-2 and N-4 atoms change in the −68 to −99 and −121 to −177 ppm regions, respectively, and in the −150 to −204 ppm range in the case of a more shielded "pyrrole" nitrogen atom [261, 550, 551]. In contrast to 1,2,4-triazole nitro derivatives, the "pyrrole" ^{15}N chemical shifts for 1,2,3-nitrotriazoles, less sensitive to structural changes, are observed in the −130 to −140 ppm

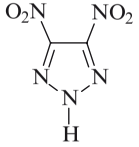
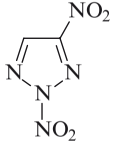
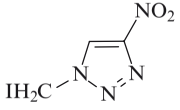
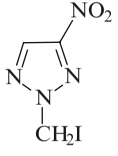
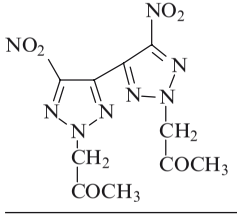
Table 3.22 ^{13}C and ^{15}N NMR chemical shifts (ppm) and coupling constants (J, Hz) of 1,2,3-nitrotriazoles

Compound	C-4	C-5	N-1	N-2	N-3	NO_2 (^{14}N)	Solvent	Refs
	153.7	125.5	−44.1	−105.0	−52.4	−23.9	DMSO-d_6	[549]
	151.20	140.99	–	–	–	(−23.2)	DMSO-d_6	[549]
	151.93	131.17	–	–	–	–	CD_3CN	[549]
	152.20	131.34	−50.3	−77.3	−19.2	−22.4	CD_3CN	[549]
	149.61	134.29	–	–	–	−332.0 NH_2	DMSO-d_6	[549]

(continued)

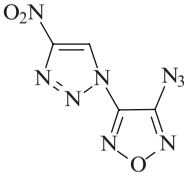
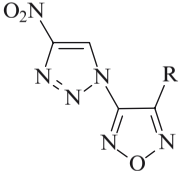
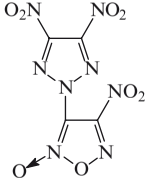
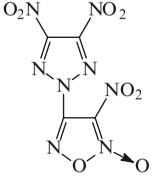
Table 3.22 (continued)

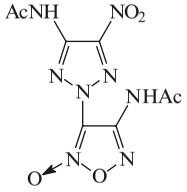
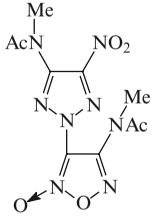
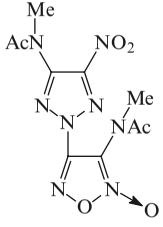
Compound	C-4	C-5	N-1	N-2	N-3	NO_2 (^{14}N)	Solvent	Refs
	142.80	136.50	–	–	–	–	DMSO-d_6	[549]
 a	154.22	132.99	−50.8	−122.8	−65.3	−27.0	DMSO-d_6	[220]
 b	155.49	134.66	−41.2	−136.1	−56.3	−27.4 −16.6 (2′) −17.2 (4′)	DMSO-d_6	[220]
	151.25 146.21	142.12 141.20	$^{13}C_{Ph}$: 120.77 C_{ortho}, 130.63 C_{para}, 131.35 C_{meta}, 140.68 C_{ipso} $^{13}C_{Ph}$: 117.77 C_{ortho}, 126.47 C_{para}, 129.64 C_{meta}, 143.48 C_{ipso}				Dioxane DMSO-d_6	[596] [277]

	144.91	144.91	–	–	–	(–33.9)	CD_2Cl_2	[549]
	150.60	131.10	–53.81	–69.7	–70.7	–30.0 4-NO_2 –54.4 2-NO_2	$CDCl_3$	[549]
	154.43	124.86	–	–	–	–	$(CD_3)_2CO$	[597]
	154.67	133.13	–	–	–	–	$(CD_3)_2CO$	[597]
	150.90	130.20	–35.8	–131.5	–50.3	–27.5	DMSO-d_6	[261]

(continued)

Table 3.22 (continued)

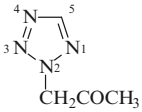
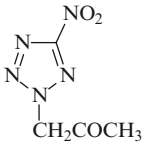
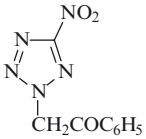
Compound	C-4	C-5	N-1	N-2	N-3	NO_2 (^{14}N)	Solvent	Refs
	125.74 149.76 C-3 fur	154.78 144.75 C-4 fur	−27.2, −28.7, −147.5				DMSO-d_6	[598]
 R = morpholino	128.04	153.69	^{13}C others 47.46 CH_2N 65.05 CH_2O 142.67 C-3 fur 154.56 C-4 fur				DMSO-d_6	[599]
	146.3, 113.6 C-3 fur	146.3, 154.8 C-4 fur	−36.4, −6.7 N-1 fur	−162.7	−36.4; −21.1 N-5 fur	−38.7 (37.0) −40.0,fur (−39.0) fur	$CDCl_3$	[552]
	147.96 124.48C-3 fur $^1J_{CN}$ 21.3	147.96 145.41 C-4 fur		–		(37.0); (43.0) fur	$CDCl_3$ –	[552]

	144.74 117.68 C-3 fur	146.02 150.14 C-4 fur	^{13}C others 29.19, 29.94 Me	(−26.6)	CF_3CO_2D	[552]
	148.34 115.15 C-3fur	145.20 150.42 C-4fur	^{13}C others 21.23 *Me*CO fur ^{1}J 141.6 21.90 *Me*CO triaz 31.10 NMe fur 35.44 NMe triaz ^{1}J 142.3 171.16 CO triaz 172.73 CO fur	(−28.0)	$(CD_3)_2CO$	[552]
	148.56 115.94 C-3 fur ^{3}J 3.0	145.20 150.07 C-4 fur	^{13}C others 21.53 (*Me*CO fur ^{1}J 129.3) 22.03 (*Me*CO triaz ^{1}J 142.3) 30.34 (NMe fur ^{1}J 137.2) 35.34 (NMe triaz ^{1}J 143.3) 170.26 (CO fur) 171.16 (CO triaz)	–	$(CD_3)_2CO$	[552]

[a] $^{3}C_{Ph}$: 119.37 C_{ortho}, 129.81 C_{para}, 130.05 C_{meta}, 138.22 C_{ipso}

[b] $^{13}C_{Ph}$: 121.57 C-3′, 127.33 C-6′, 128.86 C-5′, 133.64 C-1′, 142.65 C-2′, 147.91 C-4′

Table 3.23 ^{13}C and ^{15}N NMR chemical shifts of nitrotetrazoles (DMSO-d_6 ppm) [261]

Compound	N-1	N-2	N-3	N-4	N-5	Other
	−72.76	−103.61	0.77	−46.60	154.20	8.62 (H-5)
	−75.10	−99.20	8.70	−53.70	166.00	−33.8 NO_2
	−73.81	−99.05	10.34	−52.40	166.15	−33.4 NO_2

range, whereas the "pyridine" nitrogen shifts changed in a wider range, thus indicating a smaller shielding (−16 to −53 ppm) [261].

The known [561, 562] difference in the ^{15}N chemical shifts of "pyrrole" and "pyridine" nitrogen atoms in azoles (~100 ppm) is widely used in signal assignment. However, this difference decreases for nitrotetrazoles as well as for 1,2,3-nitrotriazoles (see Tables 3.21–3.23). An unexpected presence of a low-field signal corresponding to nitrogen-15N-3 in tetrazoles should also be mentioned. The ^{15}N–^{1}H coupling constant values between the nuclei of exocyclic nitrogen and hydrogen atoms in each two or three bonds in *N*-acetonylazoles provide some information concerning the CH_2COCH_3 group position in the cycle. Geminal coupling constant values of the hydrogen atom having a "pyrrole" nitrogen atom are 10.8 Hz, whereas those with "pyridine" atom range from 11.9 to 14.5 Hz. Vicinal coupling constants of the hydrogen atom with "pyrrole" nitrogen are of 6.7–10.2 Hz, while those with "pyridine" nitrogen are less than 1 Hz [261].

The main problem of azole chemistry is a selectivity of the reaction. In series 1,2,4-triazole nitro derivatives the reaction selectivity has been sufficiently investigated [554–556]. 3(5)-Nitro-5(3)-R-1,2,4-triazoles have at least three nitrogen atoms able to alkylate. It has been reported [563, 564] that the alkylation of 3(5)-nitro-5(3)-R-1,2,4-triazole salts by alkyl halides or dimethylsulfate is a regioselective process, and the author's opinions about an attack place in heterocycle differ. Some authors [554] with the help of ^{1}H NMR method have been shown where alkylation leads to a mixture of 1-methyl-3-nitro- and 1-methyl-5-nitro-1,2,4-triazole isomers. All H-5 signals in spectra of 1-alkyl-3-nitro-1,2,4-triazoles are in more down field and proton signals of CH_3 group in position 1 – in more high field than the same signals in spectra of isomeric 1-methyl-5-nitro-1,2,4-triazole [554].

A complete structural assignment of some nitrotriazoles has been carried out [565]. The tautomerism and the isomerism of triazoles make the structure analysis of

such compounds a difficult problem. A definite structure determination of nitro-1,2,4- and -1,2,3-triazoles was achieved by combined application of nitrogen-15 NMR spectroscopy and increment calculations: an evaluation of the shift data and coupling modes gave systematic references to structure and substituent effects. The method is also needed in cases when the equilibrium of tautomers is presented [565].

Pevzner et al. widely used NMR spectroscopy in their structural investigations of diverse 1,2,4-triazole nitro derivatives [566–581]. In the series of 5-substituted 1-methyl-3-nitro-1,2,4-triazoles the correlation between the *N*-methyl group proton chemical shifts induced by 5-substituents (Δδ) and the substituent Hammett constants has been found to divide into two branches [577]. This nonordinal event is explained by impossibility of any additional contribution to the shielding of substituents having two and more lone electron pairs [577].

In the reaction of 3-nitro-1*H*-1,2,4-triazole with benzyl chloride it was possible to obtain 1-benzyl-3-nitro-1*H*-1,2,4-triazole (60%), 1-benzyl-5-nitro-1*H*-1,2,4-triazole (10%), and 4-benzyl-3-nitro-1*H*-1,2,4-triazole (4%), whose structures were determined by ^{1}H and ^{13}C NMR with homonuclear NOE difference spectroscopy (Table 3.21) [559].

The tautomerism of *C*-nitro-substituted 1,2,4-triazoles was studied by NMR and IR spectroscopy [582]. ^{31}P NMR spectroscopy was employed for the identification of nitrated triazolyl-1 phosphates [583, 584].

In the reaction of 3-nitro-5-R-1,2,4-triazolate-anion with 3,5-dinitro-1-(2-oxopropyl)-1,2,4-triazole both the products of nucleophilic substitution in position 5 and condensed compounds [5-methyl-5-(3-nitro-5-R-1,2,4-triazol-1-yl)-5,6-dihydroxazolo[3,2-b]-1,2,4-triazoles] are formed. Their structures were established by ^{1}H NMR and IR spectroscopy [585].

1,3-Dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate – a powerful condensing reagent for phosphate and phosphonate esters – has been studied by ^{1}H and ^{31}P NMR technique [586].

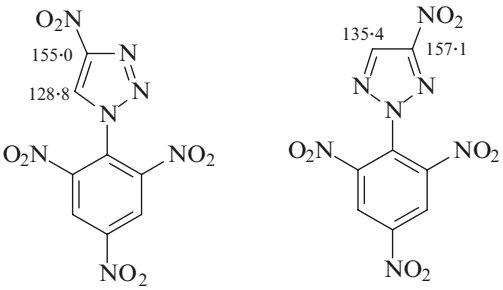
Proton spectra were used for establishing the structure of thermal decomposition product of ^{15}N-labeled 3-nitro-1,2,4-triazol-5-one [587], 1,4-dimethoxy-2-(3-nitro-1,2,4-triazol-1-yl)benzene and 1,1,4-trimethoxy-4-(3-nitro-1,2,4-triazol-1-yl)cyclohexane-2,5-diene [588], 4-(3-nitro-1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-O-acetylarabinofuranosyl)-pyrimidin-2-(1*H*)-ones [589], 1-glucosyl-nitro-1,2,4-triazoles [590], 3-nitro-5-amino-1-(3-oxobutyl)-1,2,4-triazole [591], 3-nitro-1,2,4- triazol-5-yl carboxylic acids [592], 3-nitro-5-(N-methyl-N-nitroso)amino-1,2,4-triazole [593], bis(3,5-dinitro-1,2,4-triazol-1-yl)methyl ether [594], 1-organyl-3-nitro-5-amino-1,2,4-triazoles [595].

The ^{13}C NMR spectra of 1-nitro-1,2,4-triazole [240] and 1-nitro-5-amino-1,2,4-triazole [558] are presented (see Table 3.21).

4-Nitro-1,2,3-triazole was synthesized from gem-dinitro compounds and studied by ^{1}HÇ^{13}CÇ^{14}N, and ^{15}N NMR spectroscopy [549] (Table 3.22).

^{1}H NMR spectroscopy was used for the investigation of 2-(2,4-dinitrophenyl)-4-nitro-1,2,3-triazole [600], 4-amino-3-(4-nitro-1,2,3-triazol-1-yl)furazan [601], 2-aryl(heteryl)-4-acetylamino-5-nitro-1,2,3-triazoles [141, 177, 602–604], nucleophilic substitution in the series of 4,5-dinitro-2-alkyl-1,2,3-triazoles [605] and 4,5-dinitro-2-aryl-1,2,3-triazole-1-oxides [606].

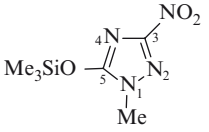
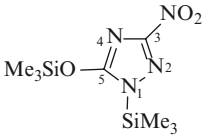
The structural, theoretical, and NMR spectroscopic assessments of differences in the properties of and the likely origin of the differences in the impact sensitivity of isomeric 4-nitro-1-picryl- and 4-nitro-2-picryl-1,2,3-triazoles have been discussed [607]:



^{1}H NMR spectra of 4- and 5-nitro-2-methyl-1,2,3-triazoles [608], 1,2-disubstituted 4-nitro-1,2,3-triazoles [609, 610] have been run.

^{13}C NMR spectra of 3-nitro-1,2,4-triazol-5-one and seven of its salts with different amines have been studied. The chemical shifts of C-3 and C-5 are independent of the nature of the cation (Table 3.21) [560]. NMR spectra of 1-nitro-1,4-dihydro-1-*H*-1,2,4-triazol-5-one, 5-(3-azido-1,2,4-triazol-3-yl)-3-nitro-1,2,4-triazoles [611], 1-alkyl-3-nitro-1,2,4-triazol-5-one [612], some 3-nitro-2-methyl-1,2,4-triazolone derivatives [613–615], and their mono- and dinitro energetic salts [616] have been discussed.

The products of the trimethylsilylation of 3-nitro-1,2,4-triazol-5-one and its methylated analog by hexamethyldisilazane have been supported by ^{1}H, ^{13}C, ^{15}N and ^{29}Si, NMR spectroscopy [220, 617].

Products of silylation	^{1}H, ppm	^{13}C, ppm	^{15}N, ppm	^{29}Si, ppm
	0.47 $OSiMe_3$	–0.48 $OSiMe_3$	–23.20 NO_2	25.6 $OSiMe_3$
	2.48 NMe	32.20 NMe	–94.82 N-2	
		155.53 C-3	–167.44 N-4	
		157.87 C-5	–194.85 N-1	
	0.46 $OSiMe_3$	–0.32 $OSiMe_3$	–23.20 NO_2	22.2 $NSiMe_3$
	0.56 $NSiMe_3$	–1.04 $NSiMe_3$	–94.82 N-2	
		161.73 C-3	–167.44 N-4	32.2 $OSiMe_3$
		162.06 C-5	–194.85 N-1	

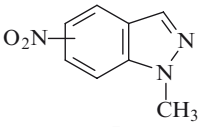
NMR spectroscopy is a powerful instrument in the identification of various 1,2,4-nitrotriazoles [574–576, 582, 618–631] and 1,2,3-triazole nitro derivatives [620, 632–634].

The literature NMR data on nitrotetrazoles are scarce [261, 635]. This is caused by their extreme instability and difficulty in handling. The ^{1}H, ^{13}C, and ^{15}N NMR spectra of *N*-acetonylnitrotetrazoles (Table 3.23) [261] and the proton spectrum of 2-allyl-5-nitrotetrazole [636], levoglucosenone derivative of *C*-nitrotetrazole [635], have been studied.

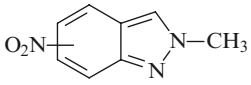
Indazoles

The introduction of the nitro group into the phenylene fragment of indazole system gives rise to a downfield shift of the *ipso*-carbon in the NMR spectra (~20 ppm), whereas the resonance of other carbons shows low sensitivity to the introduction of substituents (1–6 ppm) (Table 3.24) [233, 637–650]. The NO_2 group in the indazole ring position 1 shifts the C-3 signal to low fields and the C-8 signal to high fields. However, the nitro group introduction into position 2 leads to an upfield shift of the C-3 atom and to downfield shift of the C-8 atom (Table 3.24) [637, 638]. This regularity has been used for establishing the structure of the products of 3-chloroindazole nitration [638].

An attempt at identifying the products of nitroindazole methylation was unsuccessful [314]. The authors failed to distinguish the "kekule"-like (1-methyl) (**I**) and "quinoid"-like (2-methyl) (**II**) structures [651]:

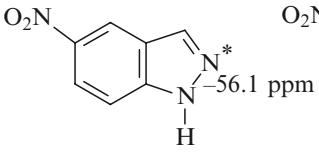


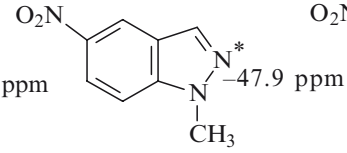
I

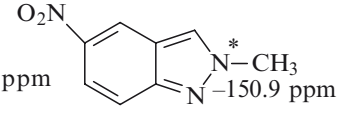


II

^{15}N marking of the N-2 nitrogen atom, use of ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy, and coupling constants measurements $^{2,3}J_{N-H}$ allowed establishing the fact that the alkylation of 5-nitroindazole occurs mainly at the N-1 atom [641].

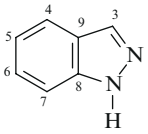
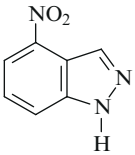
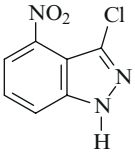
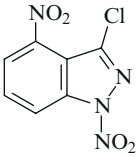
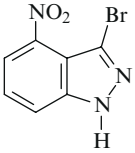
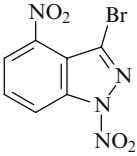
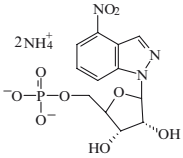
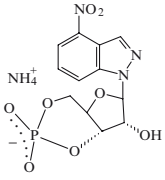






A detailed study of PMR spectra in various solvents made it possible to assign the product of dinitroindazole nitration the structure of 2,3,5,6-tetranitroindazole [653]. The ^{1}H and ^{13}C spectra of isomeric N-1 and N-2 propanamides of 5-nitroindazole have been presented (Table 3.24) [645]. By means of ^{13}C NMR spectroscopy the structure of the products of 1,5- and 1,6-dinitro-3-bromoindazole thermolysis in benzene was established [644]. The effect of the phenyl group on the chemical shifts of the nitrazole ring atoms has been discussed [644].

Table 3.24 ^{13}C NMR chemical shifts of nitroindazoles (DMSO-*d6*, ppm)

Compound	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Ref.
	133.4	120.4	120.1	125.8	110.0	139.9	122.8	[639]
	132.2	141.7	118.3	125.2	117.9	139.5	115.2	[639]
	130.5	141.1	118.9[a]	126.7	117.7[a]	143.1	110.4	[638]
	134.9	141.6	122.4[a]	132.7	119.7[a]	137.6	113.4	[638]
	117.1	141.1	118.5	126.4	117.1	142.7	112.2	[637]
	123.2	141.8	121.9[a]	132.4	119.2[a]	137.0	115.1	[637]
	123.33	151.00	127.69	127.28	126.6	141.28	114.98	[640][b]
	123.28	151.19	127.74	127.30	126.6	141.10	114.68	[640][b]

(continued)

Table 3.24 (continued)

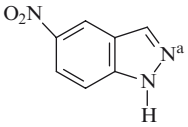
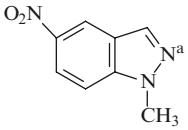
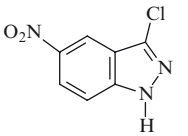
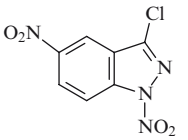
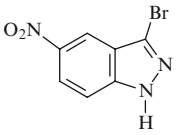
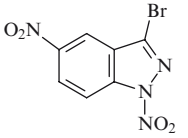
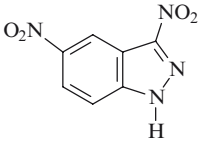
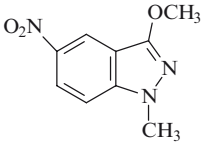
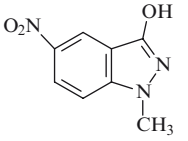
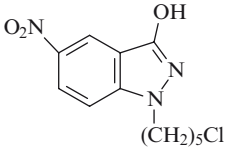
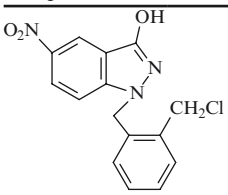
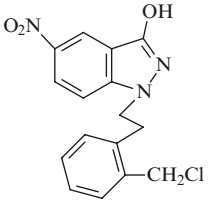
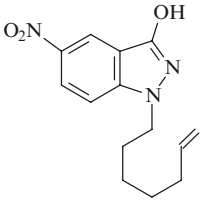
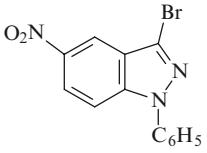
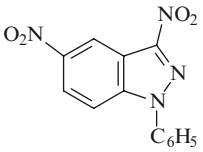
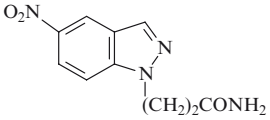
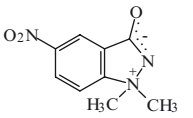
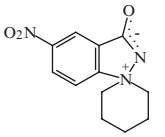
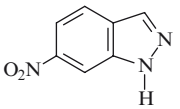
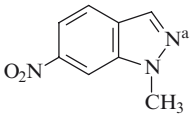
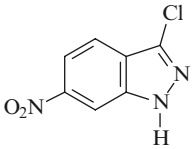
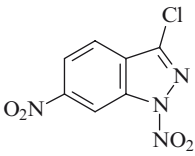
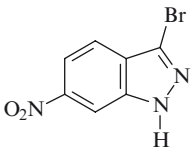
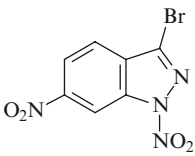
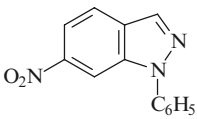
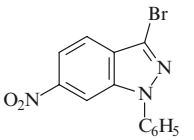
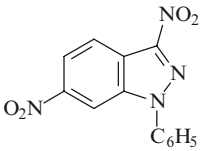
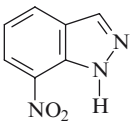
Compound	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Ref.
	136.7 136.62	118.7 118.69	141.5 141.95	120.8 120.77	110.9 110.01	141.8 141.68	122.1 121.10	[639] [641] [642]
	135.7	118.7	141.7[a]	120.6	110.3	141.3[a]	122.6	[639] [641]
	135.4 135.4	116.2 116.46	142.8 143.00	121.9 122.12	112.0 112.19	142.0 142.34	118.7 118.46	[638] [642]
	139.8	117.0	145.5	127.0	115.8	138.3	122.3	[638]
	123.4	116.7	142.7	121.9	111.3	142.0	121.3	[637]
	129.7	117.4	145.3	126.8	115.5	137.8	124.7	[637]
	149.76	117.17	144.71	122.57	113.54	143.00	114.44	[233]
	158.14	118.54	140.69	122.47	108.43	142.94	111.71	[643][a]
	156.25	118.51	139.63	121.43	109.77	142.11	111.25	[643]
	156.39	118.63	139.78	121.55	109.84	141.96	111.23	[643]

Table 3.24 (continued)

Compound	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Ref.
	156.77	118.67	140.15	122.05	109.97	142.40	111.85	[643]
	156.64	118.51	139.69	121.41	109.56	142.06	111.27	[643]
	158.38	118.60	139.69	121.49	109.72	141.91	111.20	[643]
	150.1	117.8	145.4	123.8	113.9	142.0	116.2	[644]
	126.2	118.4	143.2	123.2	111.2	141.5	124.5	[644]
		118.7	141.0	120.7	110.8	141.6	122.5	[645]
	173.88	129.09	151.28	120.59	119.53	158.77	130.67	[646][b]
	143.91	128.72	151.20	120.42	119.94	159.41	131.01	[646][c]
	134.0 134.11	121.6 121.80	114.6 114.70	145.6 145.91	106.8 106.94	138.4 138.64	125.9 126.00	[639] [642]

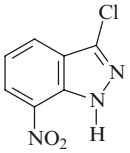
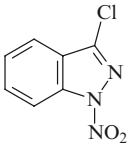
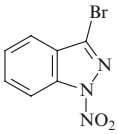
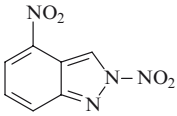
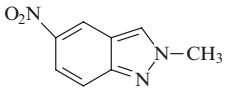
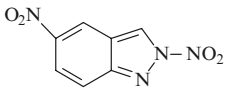
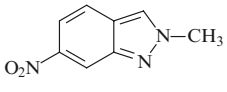
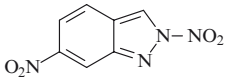
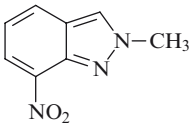
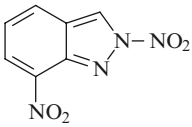
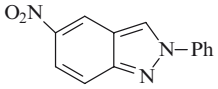
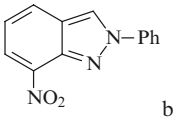
(continued)

Table 3.24 (continued)

Compound	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Ref.
	132.7	121.6	114.3	145.4	106.4	137.9	126.2	[639] [641] [647] [652]
	133.0 132.99	120.0 120.13	115.6 115.70	146.7 146.93	107.8 107.83	139.6 139.70	122.4 122.47	[638] [642] [647]
	138.9	122.3	121.3	149.7	110.2	135.6	125.6	[638]
	120.9	120.4	115.5	146.6	107.5	139.4	125.0	[637]
	128.5	122.8	121.1	149.5	109.9	134.9	127.9	[637]
	136.1	122.8	116.1	146.6	106.9	136.8	128.9	[644]
	123.5	121.8	117.2	147.8	107.8	138.1	127.2	[644][b]
	148.5	122.5	120.5	147.7	109.0	137.2	119.8	[644][b]
	135.6	129.8	123.4	120.1	132.0[a]	131.9[a]	127.1	[639]

(continued)

Table 3.24 (continued)

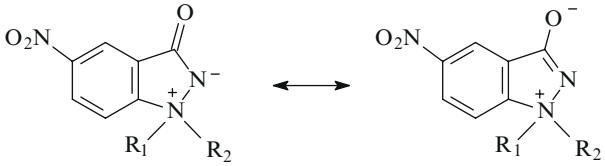
Compound	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Ref.
	134.8	127.6	124.8	121.1	132.4[a]	133.2[a]	123.5	[638]
	139.5	122.0	126.8	132.6	114.3	136.1	120.3	[638]
	129.3	121.0	126.6	132.4	114.1	135.5	124.4	[637]
	124.9	140.7	119.7	129.4	127.5	145.7	113.0	[637]
	128.7	119.3	141.8	120.1	117.6	149.1	120.0	[639]
	124.3	121.5	144.5	123.7	120.2	145.8	118.4	[637]
	126.1	122.2	114.5	146.0	114.5	147.8	124.0	[639] [647] [652]
	124.6	120.9	118.3	148.9	116.5	143.4	121.9	[637]
	127.7	129.8	124.5	119.5	136.3	139.6	125.3	[639]
	123.8	131.3	129.9	122.2	142.3	137.2	122.9	[637]
 b	124.44	118.98	143.54	120.99	119.69	150.42	–	[648]
 b	120.72	128.95	125.77	122.74	137.89	141.43	126.11	[648]

[a] Assignment of these signals may be reversed
[b] In $CDCl_3$
[c] In D_2O

Analytical ^{13}C NMR data for 4-nitro-1-β-D-ribofuranosylbenzazole 5′-monophosphate diammonium salts and 4-nitro-1-β-D-ribofuranosylbenzazole 3′,5′-cyclic monophosphate ammonium salts have been reported [640].

A series of ^{17}O-enriched heteroaromatic nitro compounds (5- and 6-nitroindazoles among them) was investigated by ^{17}O NMR spectroscopy [654]. The oxygen-17 chemical shifts of 5- and 6-nitroindazoles are 571 and 575 ppm, respectively.

Studies of the reactivity of 1,1-disubstituted indazol-3-yl oxides allowed the preparation of previously unknown betaines, 5-nitroindazole derivatives (Scheme 3.10) identified by ^{13}C NMR (Table 3.24) [643, 646, 655].



Scheme 3.10

Ammonium 3,5-dinitroindazolates have been studied in the solid state by ^{13}C and ^{15}N CP/MAS NMR spectroscopy [656].

The proton spectra obtained by Wrzeciono et al. in a large series of studies proved to be of help in establishing the structures of new nitroindazole derivatives [638, 657–667].

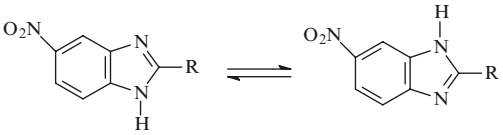
Shevelev and colleagues [649, 668, 669] have studied a large number of 3-substituted 1-aryl-6-nitro- and 1-aryl-4,6-dinitroindazoles by ^{1}H and ^{13}C NMR spectroscopy (DMSO-d_6/CCl_4).

1-*N*–CH_3- and 2-*N*–CH_3-nitroindazoles (5-, 6-, and 7-nitro isomers) and some other nitrobenzazoles possessing mutagenic activity have been synthesized and identified by spectroscopic methods including PMR spectroscopy [670]. All 1-*N*-methyl-7-nitrobenzazoles show an upfield shift of the phenylene protons in their NMR spectra as compared to the nonmethylated analogs. This shift arises from the steric crowding of the methyl group of the *peri* nitro group, twisting the nitro group out the plane of the azole ring and thus decreasing the deshielding effect of the nitro group [670]. This out-of-the plane conformation of the nitro group has been shown to affect the mutagenic activity of nitroarenes [671].

NMR spectra of vicarious *N*-alkylation products of 7-nitroinduzoles [672], 1-benzylamino-3-nitroindazole [673], 1- and 6-nitroglucosylindazoles [674], 1-acetyl-3-chloro-6-nitroindazole [675], the products of methylation and acetylation of 5- and 6-nitroindazoles in various solvents ($CDCl_3$, DMSO, acetone) [676], 5-nitro-7-methylindazole [677], 2-substituted 4,6-dinitroindazole [678], several dinitro indazoles [679], 6-nitroindazole derivatives [680], 44 nitrated 1- and 2-methylindazoles having H, Cl, and Br substituents in position 3 [681] have been obtained. ^{1}H NMR data of some nitroindazoles are presented in a few studies [682–684].

Benzimidazoles

The nitro group in the phenylene fragment of benzimidazole system produces downfield shift of the *ipso*-carbon resonance with respect to unsubstituted benzimidazole, the signals of neighboring carbon atoms being shifted upfield (Table 3.25) [685–690]. The introduction of the nitro group into the benzimidazole position 2 gives rise to only a slight downfield shift of the NMR signals of the phenylene fragment carbons (with the exception of C-8) [691, 692]. In the series of 2-substituted 5(6)-nitrobenzimidazoles (Scheme 3.11) an enhancement of the electron-withdrawing properties of 2-substituents shifts the nitro group N-15 resonance upfield [220, 687–689].

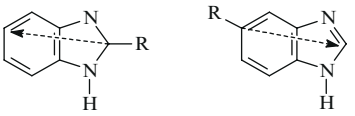


R	$N(CH_3)_2$	NH_2	OCH_3	C_2H_5	CH_3	H	$COCH_3$	Cl	CF_3	CN
$\delta^{15}NO_2$	–8.7	–8.2	–9.3	–9.4	–9.6	–9.8	–10.5	–10.7	–11.3	–11.7

Scheme 3.11

The results of two-parameter correlations of the ^{13}C and ^{15}N NMR chemical shifts of 2-substituted 5(6)-nitrobenzimidazoles with the induction and resonance constants (σ_I, σ_R) are given in Table 3.26 [688, 689]. The electronic influence of substituents on the chemical shifts of carbons (and protons) in positions 4 and 7 are mainly transmitted by a resonance mechanism, C-4 being more sensitive than C-7 to the substituent effect. For positions 5 and 6 a slightly smaller contribution from the resonance component to the total transmission of substituent effects is observed. However, analysis of correlation between δ ^{15}N and substituent parameters indicates an approximately equal influence of the induction and resonance substituent effects on the nitro group shielding (see Table 3.26) [688, 689]. When other sets of substituent constants (F and R, σ_I and σ_R^o, etc.) are used in the correlation the percentage ratios of resonance and inductive contributions remain unchanged.

The information concerning the character and degree of the substituent electronic effect transmission from C-2 to C-5(6) and in the opposite direction can readily be obtained from the correlation equation (3.2) of C-5(6) chemical shifts of 2-substituted benzimidazoles and C-2 chemical shifts of the 5(6)- isomers (Scheme 3.12) [220, 689, 691].

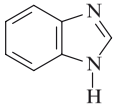
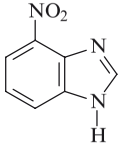
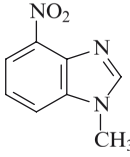
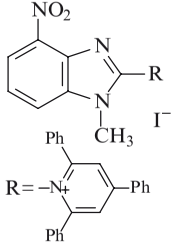
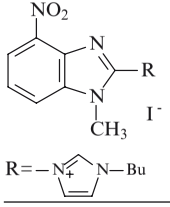


R = NH_2, OCH_3, CH_3, H, Cl, $COCH_3$, NO_2

$$\delta_{C\text{-}5} = (0.80\pm0.06)\delta_{C\text{-}2}+8.19,\ r = 0.981,\ s = 0.37,\ n = 7 \qquad (3.2)$$

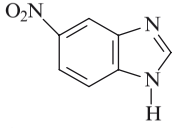
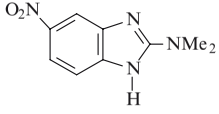
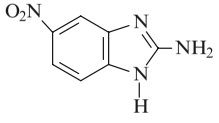
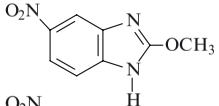
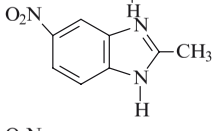
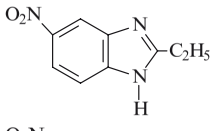
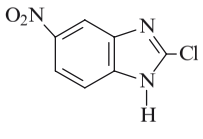
Scheme 3.12

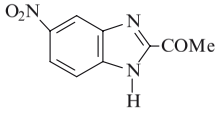
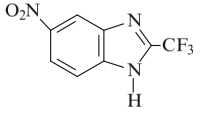
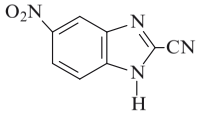
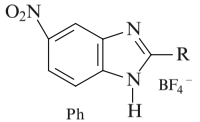
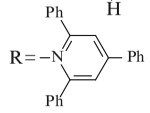
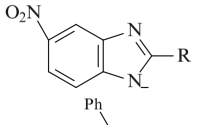
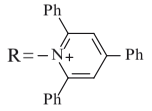
Table 3.25 ^{13}C NMR chemical shifts of nitrobenzimidazoles in deutero solvents (ppm).

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	Solv.	Ref.
	147.59	115.24	122.81	122.81	115.24	137.90	137.9	CD_3OD	[691]
	145.2	133.8	118.9	121.2	126.6	128.0	145.4	DMSO	[690]
	148.2	138.5	117.4	121.7	118.3	136.4	137.4	DMSO	[690]
	144.3	138.4	118.7	120.6	124.5	135.7	131.9	DMSO	[693]
	143.5	137.7	118.6	123.5	119.9	138.4	132.6	DMSO	[693]

(continued)

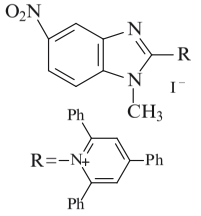
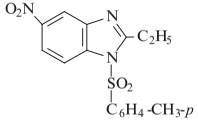
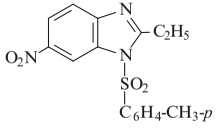
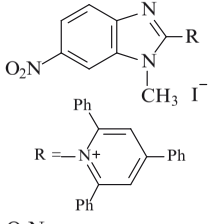
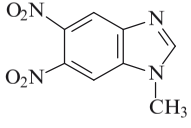
Table 3.25 (continued)

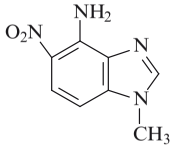
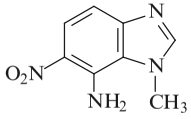
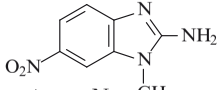
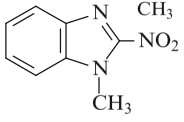
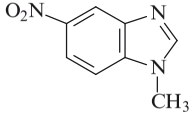
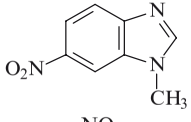
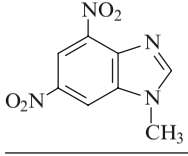
Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	Solv.	Ref.
	146.7 147.48 146.34	112.7 114.14 112.87	142.8 146.39 144.52	117.6 121.08 118.59	114.9 117.07 115.70	138.6 137.14 138.61	141.7 140.8 141.6	DMSO[a] CD_3OD	[685, 686, 688, 690]
	160.00	106.00	141.80	117.49	111.58	137.57	146.0	CD_3OD	[688, 689]
	159.28	107.22	141.99	117.49	111.58	137.31	145.3	CD_3OD	[688, 689]
	162.60	109.95	142.40	117.79	113.01	137.22	143.3	CD_3OD	[688, 689]
	157.20	111.27	143.72	118.00	113.82	138.81	142.5	CD_3OD	[688, 689]
	161.99	111.39	143.52	117.89	113.83	138.75	142.4	CD_3OD	[688, 689]
	–	111.91	144.31	118.83	114.33	138.84	142.3	CD_3OD	[688, 689]

	152.33	115.36	145.21	120.11	116.40	138.90	140.5	CD_3OD	[688, 689]
	145.50	114.50	145.57	120.16	116.26	138.87	141.3	CD_3OD	[688, 689]
	129.16	114.49	145.80	120.61	116.03	138.97	140.7	CD_3OD	[688, 689]
 	146.2	113.7	143.2	118.8	116.6	140.9	137.0	DMSO	[694, 695]
 	150.4	113.6	143.1	114.4	116.7	143.6	140.0	DMSO	[694, 695]

(continued)

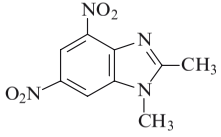
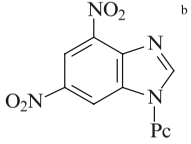
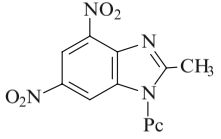
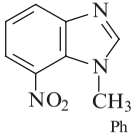
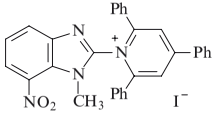
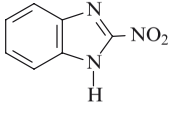
Table 3.25 (continued)

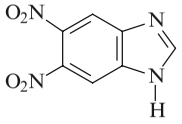
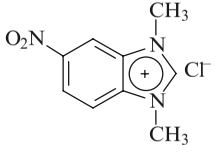
Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	Solv.	Ref.
	144.6	116.3	144.2	120.0	112.6	137.4	137.9	DMSO	[694, 695]
	134.71	113.59	159.43	120.07	115.92	141.76	137.3	$CDCl_3$	[696]
	134.46	119.90	119.90	160.88	109.90	146.14	132.6	$CDCl_3$	[696]
	145.5	120.9	118.9	144.3	108.7	133.2	142.8	DMSO	[694, 695]
	151.7	117.0	138.5	138.5	109.2	135.9	144.3	DMSO	[690]

	143.77	140.46	124.90	120.38	99.92	137.44	131.6	DMSO	[275]
	148.44	109.37	119.98	126.57	137.10	122.56	148.7	DMSO	[275]
	159.71	113.48	117.91	138.89	149.74	134.67	144.3	DMSO	[275]
	–	121.71	125.61	127.76	112.16	136.47	138.7	CD_3OD	[692]
	148.7	115.5	142.8	117.8	110.9	139.4	142.5	DMSO	[690]
	149.8	119.6	117.0	142.8	107.6	134.4	147.8	DMSO	[690]
	152.82	137.00	113.82	141.17	113.39	136.98	140.0	DMSO	[697, 698]

(continued)

Table 3.25 (continued)

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	Solv.	Ref.
	162.28	138.35	113.67	140.48	112.26	136.03	139.6	DMSO	[697, 698]
 [b]	151.52	138.06	115.65	143.14	113.83	137.17	139.6	DMSO	[697, 698]
	161.45	137.67	115.58	142.40	112.75	136.88	139.8	DMSO	[697, 698]
	149.0	126.4	121.3	120.0	–	126.5	147.4	DMSO	[690]
	144.4	127.0	123.3	122.5	126.2	125.4	141.7	DMSO	[693]
		117.37	126.40	126.40	117.37	138.32	138.3	CD_3OD	[691]

	149.5	113.9	138.3	113.9	–	–	–	DMSO	[690]
	147.4	110.7	145.4	121.3	114.7	135.2	131.4	DMSO	[690]

[a]In CD_3CO_2D
[b]Pc = 2,4,6-$(NO_2)_3C_6H_2$

Table 3.26 Parameters of the correlation equation $Y = a\sigma I + b\sigma_R + d$ for 2-substituted 5(6)-nitrobenzimidazoles [691]

Y	a	b	d	R	S	n[a]	% b[b]
$\Delta\delta$C-4[c]	2.96±0.86	6.80±0.51	0.34±0.12	0.984	0.495	10	79±5
$\Delta\delta$ C-5	2.03±0.38	3.23±0.22	−0.32±0.09	0.988	0.216	10	72±4
$\Delta\delta$ C-6	3.00±0.59	1.95±0.35	−0.07±0.04	0.956	0.336	10	51±7
$\Delta\delta$ C-7	2.09±0.59	4.05±0.35	−0.39±0.08	0.980	0.335	10	76±5
$\Delta\delta$ ^{15}N	−2.78±0.42	−1.84±0.25	−1.76±0.96	0.974	0.238	10	52±5

[a] $N(CH_3)_2$, NH_2, OCH_3, CH_3, C_2H_5, H, Cl, $COCH_3$, CF_3, CN
[b] Contribution of resonance component
[c] $\Delta\delta C = \delta C_x - \delta C_H$

As seen from equation (3.2), in these benzimidazole systems the substituent effects are transmitted by the same mechanism but with different intensities. The degree of this transmission in the 2→5(6) direction is approximately 20% lower than that in the opposite direction. The reason for this nonequivalence is likely to be due to the benzyl fragment polarization by electronegative nitrogen atoms of the five-membered heterocycle [689, 691].

^{1}H NMR spectroscopy has found use in establishing the position of *N*-substitution upon alkylation [319, 699–703], benzylation [699, 704], acylation [700], and ribosylation [705–707] of nitrobenzimidazoles. On the basis of proton spectra the ratio of the N-1 and N-2 products of alkylation of 5(6)- and 4(7)-nitrobenzimidazoles was determined [701, 702]. The alkylation of 2-nitrobenzimidazole has been studied in [708]. The structure of nitroaminobenzimidazoles prepared by preferential reduction of corresponding dinitro compounds has been confirmed [709].

By methods of ^{1}H, ^{13}C 2D NMR and NOE difference spectroscopy dinitropicrylbenzimidazoles possessing explosive properties were studied (δ ^{13}C in Table 3.25) [697, 698]. It has been found that both solvent and temperature significantly influence the proton chemical shifts of the benzimidazole ring [697].

N-(nitrobenzimidazol-2-yl)pyridinium derivatives have been synthesized in order to study their antiprotozoal activity [693–695]. A ^{1}H and ^{13}C NMR study has been carried out for structural determination of these compounds (δ^{13}C in Table 3.25). Quantitative structure-activity relationships (QSAR) between the in vitro antileishmanial activity of *N*-benzazolylpyridinium salts and their ^{13}C NMR chemical shifts have been studied in order to determine the influence of benzimidazole substituents upon antileishmanial activity [695].

Isomeric 5- and 6-nitro-1-*para*-toluene-sulfonyl-2-alkylbenzimidazoles have been studied by ^{1}H and ^{13}C NMR spectroscopy (δ^{13}Cin Table 3.25) [696, 710]. Signal assignment has been made by means of NOE difference NMR spectroscopy [345]. The proton spectra of 4-, 5- and 6-nitro-1-β-D-ribofuranosylbenzimidazole-3′,5′-phosphates are presented in [711].

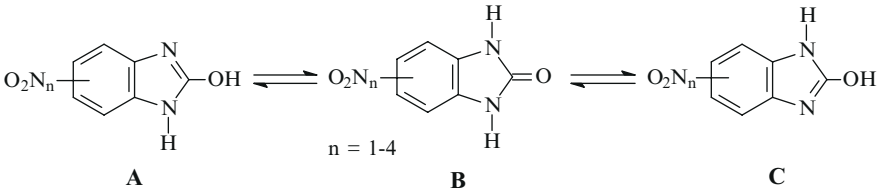
The proton chemical shifts of 2-organyl-5(6)-nitrobenzimidazoles [712, 713], mono- and polysubstituted nitrobenzimidazoles [714], 2-benzyl derivatives of 5(6)-nitrobenzimidazoles as potential antifilarial agents [715], 1-substituted-2-methyl-5-nitrobenzimidazoles [716], mono- and dinitro-substituted 2-alkylbenzimidazoles

[717], 2-arylthio- and 2-arylsulfono-5(6)-nitrobenzimidazoles as potential antihelmintics [718], 1-[bis-(β-chloroethyl)-carbamoyl-5- and -6-nitrobenzimidazoles and their 2-methyl derivatives [719], 2-aminoaryl-5(6)-nitrobenzimidazoles [720], 1-methyl-4-nitrobenzimidazole [721], mono-, di- and three nitro derivatives 2-organyl-5-hydroxybenzimidazoles [722], 2,5,6-trisubstituted 7(4)-nitrobenzimidazoles [723], 3-alkyl-1-[2-(4-nitro-1*H*-benzimidazol-2-yl)ethyl]imidazolium salts [724] have been reported.

Characteristics of the proton spectra of some nitrobenzimidazole derivatives are reported in [725–732].

The salts of benzimidazolium and nitrobenzimidazolium were examined by NMR spectroscopy in [690, 733, 734].

Analysis of the ^{13}C and ^{15}N NMR spectra of benzimidazolone and its nitro derivatives in comparison with those of model 1,3-dimethyl derivatives has shown nitrobenzimidazolone to exist in the benzimidazolone form **A** rather than in the 2-hydroxy-form **B** or **C** (Scheme 3.13, Table 3.27) [562]:



Scheme 3.13

The introduction of the nitro group does not affect much the tautomeric equilibrium in the series of benzimidazolones studied. However, the position and number of nitro groups in the compounds influence markedly the values of chemical shifts and coupling constants of ^{13}C and ^{15}N nuclei [562].

Benzoxazoles, Benzisoxazoles, and Benzofurazans

A relatively small number of nitrobenzoxazoles have been studied by ^{13}C NMR spectroscopy (Table 3.28) [735, 736]. Going from 5(6)-nitrobenzimidazoles to 6-nitrobenzoxazole the C-7 signal is shifted to high fields, those of other carbon atoms being shifted to low fields. Interestingly, for 6-nitrobenzothiazole (see Table 3.30), an upfield shift relative to 5(6)-nitrobenzimidazole, is observed only for C-8. The inversion of signs for C-7 and C-8 going from nitrobenzoxazoles to nitrobenzothiazoles may be explained by the significant difference in the electronegativity of heteroatoms, decreasing in the order: O (3.5) > N (3.0) > S (2.5).

The proton spectra of a number of other benzoxazole nitro derivatives are presented in [737, 738]. The proton chemical shifts and coupling constants are reported for 2-methyl-5-nitro-, 2-methyl-6-nitrobenzoxazole, and 2-methyl-5-nitrobenzothiazole

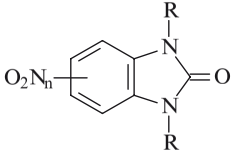
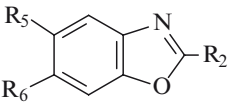


Table 3.27 ^{13}C and ^{15}N NMR chemical shifts of nitrobenzimidazolones in DMSO-d_6 (ppm) [247]

NO_2	R	C-2	C-4	C-5	C-6	C-7	C-8	C-9	N-1	N-2	NO_2
H	H	155.2	108.5	120.3	120.3	108.5	129.7	129.7	−259.9	−259.9	
5-NO_2	H	155.6	103.7	141.3	117.7	108.8	129.7	135.7	−258.7	−254.5	−10.2
5,6-$(NO_2)_2$	H	155.5	104.9	137.1	137.1	104.9	132.6	132.6	−253.4	−253.4	−14.3
4,5,6-$(NO_2)_3$	H	155.3	118.8	135.6	136.8	110.1	125.9	124.7	–	–	–
4,5,6,7-$(NO_2)_4$	H	155.2	122.1	133.3	133.3	122.1	130.8	130.8	−246.9	−246.9	−25.1 −25.4
H	CH_3	154.0	107.6	120.9	120.9	107.6	129.8	129.8	−269.7	−269.7	
5-(NO_2)	CH_3	154.1	103.1	141.5	117.7	107.1	129.6	135.0	−267.2	−263.0	−10.2
5,6-$(NO_2)_2$	CH_3	154.3	104.5	137.2	137.2	104.5	132.3	132.3	−261.4	−261.4	−14.0
4,5,6-$(NO_2)_3$	CH_3	154.3	125.3	134.5	134.8	106.2	131.7	126.4	−260.5	−257.8	−19.7

Table 3.28 ^{13}C NMR chemical shifts of nitrobenzoxazoles in DMSO-d_6 (ppm)

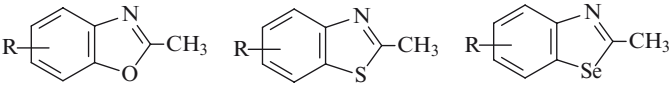


R_2	R_5	R_6	C-2	C-4	C-5	C-6	C-7	C-8	C-9	Refs
H	H	NO_2	158.8	120.5	120.5	145.2	107.9	148.7	144.9	[735]
CH_3	H	NO_2	169.3	119.3	120.3	144.4	107.1	149.3	146.6	[735]
NH_2	H	NO_2	166.4	114.1	121.0	140.4	104.5	147.2	151.0	[735]
N_3	H	NO_2	161.7	118.5	121.5	144.0	107.2	148.7	146.8	[735]
H	NO_2	H	157.4	116.4	–	121.7	112.1	–	–	[735]
CH_3	NO_2	7-*t*-Bu	166.2	113.6	144.9	117.4	135.4	152.9	142.2	[736][a]

[a]In $CDCl_3$

[738]. The ^{1}H NMR chemical shifts of 5- and 6-substituted benzoxazoles, benzothiazoles, and benzoselenazoles were measured [737].

The chemical shifts of their 2-methyl protons satisfactorily correlate with the Hammett substituent constants [737].



R = NO_2, Cl (or Br), H, CH_3, OCH_3, NH_2

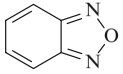
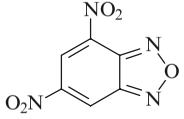
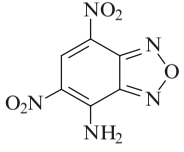
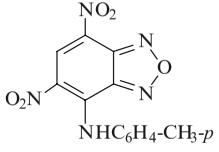
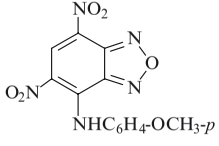
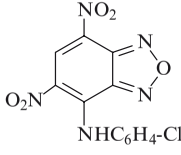
The chemical shifts and coupling constants of the products of nitration of 3-alkyl- and 3,6-disubstituted 1,2-benzisoxazoles point to the formation of 5-nitro- and 5,7-dinitro derivatives, respectively [739]. With 3,5-disubstituted 1,2-benzisoxazoles only 4-nitro compound is formed, the 3,7-disubstituted derivatives being nitrated to the corresponding 5-nitrobenzisoxazoles [739]. In studying the kinetics of 3-methyl-1,2-benzisoxazole nitration the proton spectra of both nitrated benzisoxazole and its salt, 2,3-dimethyl-5-nitro-1,2-benzisoxazolium tetrafluoroborate, have been recorded [740].

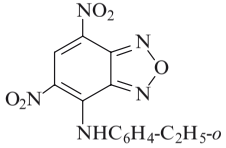
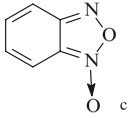
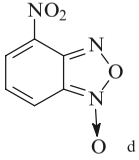
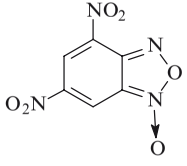
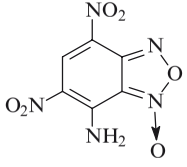
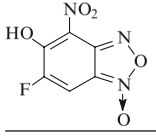
The structures of 5-nitro- [741] and 6-nitro-1,2-benzisoxazole-3-acetic acid, 6-nitro-1,2-benzisoxazole-3-yl acetonitrile [742], 6-nitro-1,2-benzisoxazole-3-carboxylates [742, 743] and 6-nitro-4-(R-sulfonyl)benzisoxazoles [744], 3-dinitromethyl-5-nitro-1,2-benzisoxazole and bis(5-nitro-1,2-benzisoxazol-3-yl)furoxan [741] were established with the use of proton spectra.

The oxidation of anionic σ-complexes of 1,3,5-trinitrobenzene with an oxidative $CuBr/CCl_4$ system led to the formation of 3-organyl-4,6-dinitroanthranyls (2,1-benzisoxazoles) the structure of which was proved by PMR, IR spectroscopy, and mass spectrometry [745].

Nitro derivatives of 2,1,3-benzoxadiazole (benzofurazan) and 2,1,3-benzoxadiazole-1-oxide (benzofuroxan) were studied by ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy (Table 3.29) [746–759].

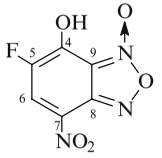
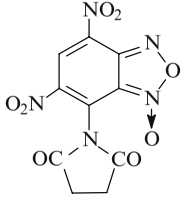
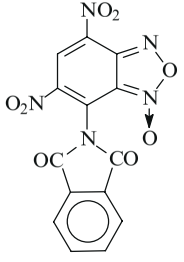
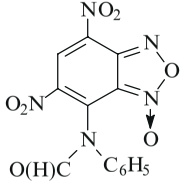
Table 3.29 ^{13}C and ^{15}N NMR chemical shifts (ppm) and coupling constants (Hz) of nitrobenzoxadiazoles.

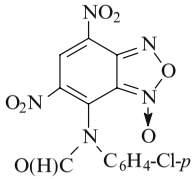
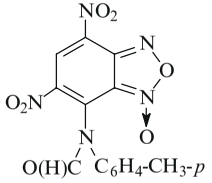
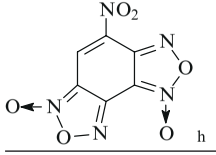
Compound	C-4	C-5	C-6	C-7	C-8	C-9	Solvent	Ref
	115.8	131.2	131.2	115.8	148.6	148.6	$CDCl_3$	[760]
	136.8 137.8	125.1 124.5	148.7 148.8	122.5 122.2	150.0 150.2	143.3 143.6	DMSO-d_6 CD_2Cl_2	[748]
	122.12	131.94	122.41	143.46	147.21	144.19	DMSO-d_6	[749]
	124.66	131.62	121.64	141.74	146.59	144.72	DMSO-d_6	[747],[749]
	124.32	131.51	122.51	142.32	146.54	144.72	DMSO-d_6	[749]
	124.58	131.36	122.86	141.66	146.59	144.58	DMSO-d_6	[747],[749]

	124.17	131.46	122.36	142.66	146.34	144.73	DMSO-d_6	[747],[749]
	115.0[a] 117.3[b]	130.4 132.3	130.4 128	115.0 112.1	113.7	152.2	$CDCl_3$	[760],[750]
	125.2	128.3	133.4	122.2	117.5	146.5	$(CD_3)_2CO$	[750]
	136.7 137.9	126.5 125.8	144.8 144.8	120.8 119.5	116.6 116.1	145.0 144.6	DMSO-d_6 CD_2Cl_2	[748]
	121.76	132.47	120.46	142.70	110.81	146.18	DMSO-d_6	[749]
	119.81 116.16	156.59 163.17	152.18 158.36	105.48 98.11	109.22 108.00	142.70 148.99	$CDCl_3$ [e] DMSO-d_6 [f]	[758]

(continued)

Table 3.29 (continued)

Compound	C-4	C-5	C-6	C-7	C-8	C-9	Solvent	Ref
	121.12	159.92	144.61	107.78	147.74	110.62	DMSO-d_6[g]	[758]
	136.41	128.01	141.13	121.65	113.22	145.00	DMSO-d_6	[749],[753]
	136.27	128.23	141.13	121.28	113.90	145.07	DMSO-d_6	[749],[753]
	135.4 (137.8)	128.8	141.3	122.6	113.8	145.5	DMSO-d_6	[753]

	136.7	128.7	141.5	124.6	113.9	145.5	DMSO-d_6	[752]
	135.3 (137.4)	128.7 (128.0)	141.6	122.9	114.0	145.5	DMSO-d_6	[752]
	135.1	128.8 (127.2)	140.9	125.2	114.1 (114.8)	145.5	DMSO-d_6	[752]
 [h]	125.2	122.4	110.9	141.4	105.0	146.7	$(CD_3)_2CO$	[750]

[a] +65°C
[b] −15°C, coalescence temperature at +35°C, $\Delta G^{\neq} = 14.0$ kcal/mol
[c] δ^{15}N −18.0 N→O, −4.5 N–O
[d] δ^{15}N −19.4 NO_2, −19.4 N→O, −4.7 N–O
[e] ^2J(C-5, F-6) 20.5, ^1J(C-6, F-6) 269.9, ^2J(C-7, F-6) 25.4, ^3J(C-8, F-6) 10.1
[f] ^2J(C-5, F-6) 22.4, ^1J(C-6, F-6) 264.4, ^2J(C-7, F-6) 29.1, ^3J(C-8, F-6) 14.1
[g] ^2J(C-6, F-5) 22.4, ^1J(C-5, F-5) 264.4, ^2J(C-4, F-5) 29.1, ^3J(C-7, F-5) 12.3
[h] δ^{15}N −22.4 NO_2, 18.8, 22.4 N→O, 6.5,−2.4 N–O

The pioneering work of Katritzky is presented as a complete interpretation for the proton spectra of benzofuroxan and four nitro-derivatives [757]. The temperature dependence of the spectra enables to calculate ΔG^* for the tautomeric change of the benzofuroxan heterocyclic ring [757].

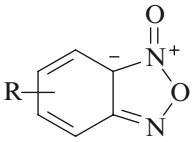
The tautomerism of nitrated 5(6)-fruorobenzofuroxans has been studied by Charushin and colleagues using dynamic ^{1}H, ^{13}C, ^{19}F NMR spectroscopy [758]. It has been discovered that 4-nitro-5-hydroxy-6-fluorobenzofuroxan, on dissolving in DMSO, transforms to 4-hydroxy-5-fluoro-7-nitrobenzofuroxan in a result of the Boulton-Katritzky rearrangement [758].

Nitrobenzofurazans have been observed as powerful inhibitors of nucleic acid biosynthesis, with an especially toxic effect on leukocyte metabolism in vitro. These compounds exhibit an extremely high electrophilic reactivity as reflected judging by their ability to form Meisenheimer σ-complexes, investigated in detail in [761–773].

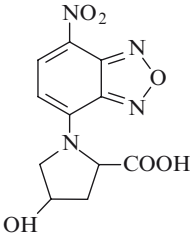
As evident from Table 3.29, the addition of oxygen to the nitrogen atom of the dinitrobenzofurazan causes a large upfield shift (34 ppm) of the resonance of C-8 close to the N-O function, while that of the remote carbon (C-9) is only slightly affected [748]. This agrees with the result reported in [760]. This strong substituent effect is due to the presence of a partial negative charge on C-8 resulting from a significant contribution of the second resonance canonical form (N=O):

Indeed, the X-ray crystallography data show that the C8–N1 bond (1.40 Å) is appreciably longer than the C9–N3 bond (1.37 Å) [748].

The introduction of the amino group into position 7 considerably changes the chemical shifts of the atoms C-4, C-6, and C-7 as revealed by comparison with 4,6-dinitrobenzofurazan (−26.3 ppm upfield shift for C-6). The effect of the aryl substituent on the chemical shifts of dinitrobenzofurazan is negligible [749].



Proton spectra of 4-methoxy-7-nitrobenzofurazan and 7-nitro-4-benzofurazanol and ^{1}H and ^{13}C spectra of 1-(7-nitro-4-benzofurazanyl)-4-hydroxy-L-proline (CD_3OD, 60°C; ^{13}C 173.2, 145.3, 144.7, 144.6, 136.1, 122.5, 102.7, 68.7, 63.2, 59.3, 39.0 ppm) have been examined [755]:

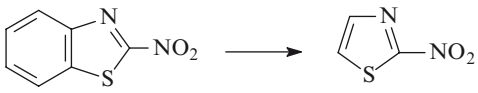


The nitrobenzofurazans used as fluorescent probe molecules in cell membranes were studied by NMR spectroscopy [774–777].

Benzothiazoles, Benzothiadiazoles, and Benzoselenazoles

Some differences in the change of ^{13}C NMR chemical shifts of nitrobenzothiazoles compared with nitrobenzimidazoles and nitrobenzoxazoles have been discussed. In Table 3.30 the ^{13}C NMR chemical shifts of nitrobenzothiazoles are presented. The nitro group introduction into position 2 leads to a 10 ppm down field shift of the *ipso*-carbon resonance, whereas a similar effect of the *ipso*-substitution in the phenylene fragment of benzothiazoles is ~20 ppm [778–781]. The results of regression analysis of the ^{13}C NMR chemical shifts of benzothiazoles in terms of the inductive and resonance constants of substituents (*F* and *R*, σ_I and σ_R, σ_I and σ_R^0) provide evidence for the fact that the substituent effect transmission from positions 2–6 is approximately 30% weaker than in the opposite direction [779]. As stated previously, an analogous picture is observed for benzimidazoles.

The transition from 2-nitrobenzothiazole to 2-nitrothiazole is reported [780] to involve a 6 ppm upfield shift of the carbon atoms resonance (Scheme 3.14).



Scheme 3.14

The proton chemical shifts of the CH_3-group in 2-methylbenzothiazoles (including nitro derivatives) were compared with charges (q) on the C-2 calculated by the PPP method [782].

The ^{13}C NMR spectra of 2-chloro-7-nitro-6-fluoromethoxybenzothiazole (DMSO-d_6; 120, 123, 130, 134, 135, 140, 150, 158 ppm) and 6-amino-2-chloro-7-nitrobenzothiazole ($CDCl_3$/CH_3OD; 114, 129, 132, 142, 147, 153 ppm) are presented without signal assignment [783].

Only a few examples of NMR investigation of nitrated 1,2-benzisothiazoles are known. 3-Substituted 4,6-dinitro-1,2-benzisothiazoles, 2-substituted 4,6-dinitro-1,2-benzisothiazol-3-ones and their oxides obtained using highly efficient technology for conversion of 2,4,6-trinitrotoluene have been identified by ^1H NMR spectra [784].

We venture to make an assignment of aromatic proton signals in phenylene fragment and have found that the changeover from 1,2-benzisothiazoles to their oxides and dioxides involves an increase of the chemical shift values H-7.

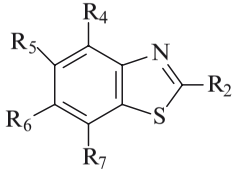
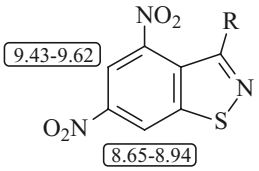


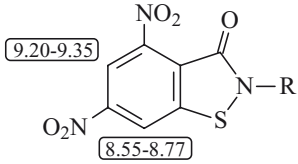
Table 3.30 ^{13}C NMR chemical shifts of nitrobenzothiazoles in DMSO-d_6 (ppm)

R_2	R_4	R_5	R_6	R_7	C-2	C-4	C-5	C-6	C-7	C-8	C-9	Refs
H	H	H	H	H	155.2	123.1	125.9	125.2	122.1	133.7	153.2	[778, 780]
H	NO_2	H	H	H	161.1	142.8	125.4	125.6	128.8	137.2	149.4	[778, 780]
H	H	NO_2	H	H	160.9	118.2	146.6	119.8	124.0	140.9	152.8	[778, 780]
H	H	H	NO_2	H	163.0	123.6	121.4	144.8	119.6	134.6	156.6	[778, 780]
H	H	H	H	NO_2	160.7	130.5	127.2	122.4	142.7	130.5	155.4	[778, 780]
NO_2	H	H	H	H	165.9	123.3	128.1	129.0	125.4	136.3	148.2	[778, 780]
CH_3	H	NO_2	H	H	171.1	116.3	145.7	118.6	122.7	141.9	152.1	[779]
CH_3	H	H	NO_2	H	173.6	121.7	120.7	143.6	118.3	135.4	156.2	[779]
					173.2	122.7	121.5	144.9	118.0	136.1	157.2	[781][a]
NH_2	H	H	NO_2	H	171.3	117.3	121.7	140.4	116.6	131.3	158.1	[779]
C_2H_5	H	H	NO_2	H	180.3	122.4	121.2	144.0	119.0	135.3	156.6	[779]
Cl	H	H	NO_2	H	159.4	123.1	122.3	144.9	119.6	136.5	154.3	[779]
OCH_3	H	H	NO_2	H	–	120.7	122.0	–	119.1	133.2	–	[779]
SC_6H_5	H	H	NO_2	H	177.4	121.8	121.6	144.0	117.1	135.7	157.7	[781][a]
SH	H	H	NO_2	H	192.9	112.3	123.2	143.7	116.1	130.4	146.1	[780]

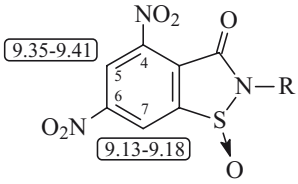
[a]In $CDCl_3$



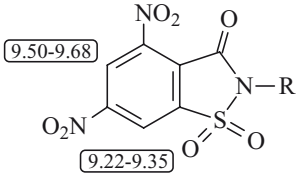
R = Cl, OCH_3, OCH_2Ph, $OCH_2CO_2C_2H_5$



R = CH_3, Ph, CH_2Ph, *p*-BrPh, *p*-OCF_3Ph, *p*-$OCClF_2Ph$



R = H, CH_3

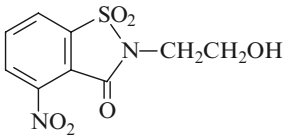


R = H, CH_3, Ph

NMR spectra of nonlinear optical materials containing nitrobenzothiazole chromophores [785–787], 2-methylamino-5-nitrobenzothiazole [788], 7-alkyl-4-nitrobenzothiazoles [789], 2-chloromethyl-6-nitrobenzothiazole and its sulfonylalkylation products [790], 2,7-disubstituted 4-nitrobenzothiazole used as antibacterial agents [791], 2-alkyl-5- and 2-alkyl-6-nitrobenzothiazole [792, 793], 2-methylmercapto-5- and 2-methylmercapto-6-nitrobenzothiazole [794], 1-(β-hydroxyethyl)-6-nitrobenzothiazolones-2 [795], 3-methyl- and 4-nitro-6-trifluoromethylbenzothiazolinethiones [796], 2-ethyl-3-methyl-6-nitrobenzothiazolium iodide and tosylate [797], copper(II) complex of N-2-(4-methylphenylsulfamoyl)-6-nitrobenzothiazole [214], and other nitrobenzothiazoles [798–802] have been measured.

In the context of chemical utilization of 2,4,6,-trinitrotoluene the different heterocyclic compounds including 3-chloro-4,6-dinitrobenzisothiazole [803], 2-aryl-4,6-dinitrobenzisothiazolium chlorides [804], etc. [805, 806] have been prepared and determined by NMR spectroscopy.

The structure of nitrosaccharine, 2-(2-hydroxyethyl)-4-nitro-2H-1,2-benzisothiazolone-3-1,1-dioxide was proved by ^{1}H NMR spectroscopy [807].



The proton spectra of 4-amino-5-nitro- and 6-chloro-7-nitroanthranile have been discussed in [808] and those of 6-methyl-7-nitroanthranile in [809].

The NMR spectra of nitro-1,2,3-benzothiadiazoles have been considered in [810–813] and those of nitro-2,1,3-benzothiadiazoles in [352, 813–816]. For the identification of

the structure of compounds a full analysis of ^{1}H and ^{1}H-^{1}H coupling constants of 4-nitro-, 5-nitro-, 6-nitro-, and 7-nitro-1,2,3-benzothiadiazoles has been carried out [812]. The calculated and measured ^{1}H chemical shifts of the nitration products of 5-chloro-6-methyl-2,1,3-benzothiadiazolone, i.e., 5-chloro-6-methyl-4-nitro- and 5-chloro-6-methyl-7-nitro-2,1,3-benzothiadiazolones, have been compared [352].

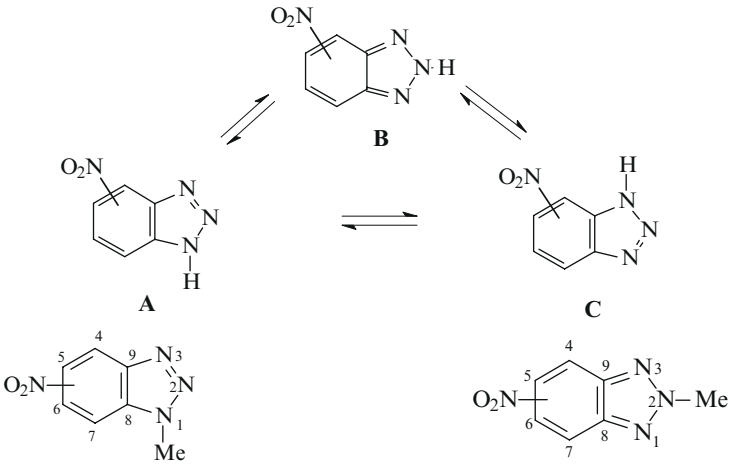
Characteristics of the proton spectra of 5-nitro- and 7-nitrobenzisoselenazoles, 2-methyl-6-nitrobenzoselenazole [737] and 4-nitro- and 5-nitro-2,1,3-benzoselenodiazoles are presented in [817] and [818], respectively.

Benzotriazoles

Benzotriazoles hold a special position in the chemistry of heterocycles. During the last few years, interest in the chemistry of benzazoles and, in particular, nitrobenzotriazoles has been increasing. Their unique properties and specific biological activity has attracted much attention of research chemists all over the world. Prototropic transformations of almost all benzazoles in solutions proceed so quickly on the NMR time scale that varying solution temperatures does not cause changes in the spectra. In all cases time-averaged signals are observed in the spectra. Speculation about the existence of tautomeric forms of benzotriazole in solution and in gas phase has persisted over a long period of time.

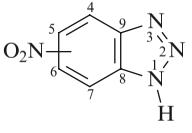
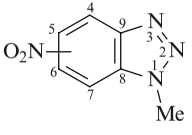
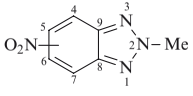
The investigation of nitrobenzotriazoles by NMR spectroscopy has been considered in works comparatively few in number [640, 819–826].

The electronic structure of tautomeric nitrobenzotriazoles and their 1-methyl- and 2-methylbenzotriazoles (Scheme 3.15) have been studied by means of multinuclear one- and two-dimensional ^{1}H, ^{13}C and ^{15}N NMR spectroscopy (Tables 3.31–3.33) and quantum chemistry (Table 3.34) [826]:



Scheme 3.15

Table 3.31 ^{1}NMR chemical shifts and coupling constants (J) of nitrobenzotriazoles and their 1-methyl- and 2-methyl derivatives (DMSO-d_6)

Compound	Position NO_2	No	δ^{1}H (ppm) and J (Hz) NH N–CH_3	H-4	H-5	H-6	H-7
	4(7)	1a	16.3[a]15.2[b] 12.0[c]	–	8.32 dd ^{3}J=8.1 ^{4}J=0.8	7.39 dd ^{3}J=8.1 ^{3}J=8.1	8.16 dd ^{3}J=8.1 ^{4}J=0.8
	5(6)	1b	16.0	8.97 dd ^{4}J=1.7 ^{5}J=0.6	–	8.32 dd ^{3}J=9.1 ^{4}J=1.7	8.11 d ^{3}J=9.1 ^{5}J=0.6
	4	2a	4.41 s	–	8.29 d ^{3}J=7.7	7.77 dd ^{3}J=8.3 ^{3}J=7.7	8.35 d ^{3}J=8.3
	5	2b	4.39 s	9.00 dd ^{4}J=2.0 ^{5}J=0.6	–	8.39 dd ^{3}J=9.2 ^{4}J=2.0	8.09 dd ^{3}J=9.2 ^{5}J=0.6
	6	2c	4.44 s	8.25 d ^{3}J=9.1	8.19 dd ^{3}J=9.1 ^{4}J=1.8	–	8.89 d ^{4}J=1.8
	7	2d	4.44 s	8.30 dd ^{3}J=7.8 ^{4}J=0.9	7.54 dd ^{3}J=8.2 ^{3}J=7.8	8.44 dd ^{3}J=8.2 ^{4}J=0.9	–
	4	3a	4.61 s	–	8.39 dd ^{3}J=8.2 ^{4}J=1.8	7.63 dd ^{3}J=8.2 ^{3}J=7.5	8.38 dd ^{3}J=7.5 ^{4}J=1.8
	5	3b	4.64 s	8.88 dd ^{4}J=2.0 ^{5}J=0.8	–	8.26 dd ^{3}J=9.3 ^{4}J=2.0	8.21 dd ^{3}J=9.3 ^{5}J=0.8

[a]+27°C
[b]+50°C
[c]+80°C

Table 3.32 ^{13}C NMR (ppm) chemical shifts and coupling constants $J(^{13}C\text{-}^{1}H)$ (Hz) of nitrobenzotriazoles and their 1-methyl- and 2-methyl derivatives (DMSO-d_6)

No	Position NO_2	δ ^{13}C (ppm) and J (Hz)						
		C-4	C-5	C-6	C-7	C-8	C-9	N-Me
1a	4(7)	146.59 $^{3}J=7.0$	126.88 $^{1}J=168.2$ $^{3}J=7.0$	123.67 $^{1}J=168.0$	123.74 $^{1}J=168.1$ $^{3}J=8.0$ $^{2}J=2.7$	126.92 br s	133.03 $^{3}J=7.4$	–
1b	5(6)	114.11 $^{1}J=175.3$ $^{3}J=8.1$	144.55 $^{3}J=4.4$	120.90 $^{1}J=171.3$ $^{3}J=4.4$	113.70 $^{1}J=171.3$	138.93 br s	140.15 br s	–
2a	4	137.86 $^{3}J=8.4$	118.83 $^{1}J=171.7$ $^{3}J=8.4$	126.78 $^{1}J=168.2$	121.52 $^{1}J=168.7$ $^{3}J=8.4$ $^{2}J=2.4$	135.86 $^{3}J=6.4$	137.41 $^{3}J=10.0$	34.98
2b	5	115.67 $^{1}J=172.9$ $^{3}J=4.7$	143.89	121.34 $^{1}J=169.5$ $^{3}J=4.4$	111.26 $^{1}J=172.9$	135.69 $^{3}J=5.4$	143.66	34.26
2c	6	120.21 $^{1}J=171.2$	118.60 $^{1}J=170.7$ $^{3}J=4.4$	147.20 $^{3}J=9.6$ $^{2}J=4.8$	108.64 $^{1}J=175.8$ $^{3}J=4.4$	132.79	146.17	35.02
2d	7	126.96 $^{1}J=169.0$ $^{3}J=8.0$	123.62 $^{1}J=169.0$	125.25 $^{1}J=169.0$ $^{3}J=8.4$ $^{2}J=2.4$	148.55 $^{3}J=10.0$	125.54 $^{3}J=7.6$	134.87 $^{3}J=7.6$	39.19
3a	4	145.77 $^{3}J=10.5$	125.84 $^{1}J=167.8$ $^{3}J=7.6$	125.01 $^{1}J=167.8$	124.11 $^{1}J=167.8$ $^{3}J=7.6$ $^{2}J=2.1$	137.01 $^{3}J=9.4$	136.92 $^{3}J=7.8$	44.40
3b	5	115.37 $^{1}J=173.4$ $^{3}J=4.2$	145.83 $^{3}J=9.5$	120.12 $^{1}J=170.2$ $^{3}J=4.8$	119.01 $^{1}J=171.5$	142.24 $^{3}J=5.7$	136.51 $^{3}J=9.1$	43.80

Table 3.33 ^{15}N NMR (ppm) chemical shifts of nitrobenzotriazoles and their 1-methyl- and 2-methyl derivatives (DMSO-d_6)

No	Position NO_2	δ ^{15}N (ppm)			
		N-1	N-2	N-3	NO_2
BT[a]		−96.7	7.5	−96.7	–
1a	4(7)	−171.0 (or −169.0)[b]	8.4[c]	−169.0 (or −171.0)[b]	−11.4
1b	5(6)	–	5.4[c]	–	−8.4
1-MeBT[a]		−161.8	−0.9	−40.8	–
2a	4	−153.7	8.3	−42.3	−10.8
2b	5	−155.8	12.9	−32.3	−8.2
2c	6	−152.4	14.7	−38.2	−8.2
2d	7	−156.6	10.7	−38.2	−11.0
2-MeBT[a]		−62.5	−117.0	−62.5	–
3a	4	−56.5	−106.0	−59.8	−11.3
3b	5	−52.3	−102.7	−58.3	−9.5

[a]Benzotriazole, $\delta^{\alpha 5}N$ from [220, 561]
[b]Broad signals and may be reversed
[c]Broad signal

Unlike methylated analogs nitrobenzotriazoles exist in tautomeric equilibria. The introduction of the nitro group into the benzotriazole ring leads to significant changes of chemical shifts. The ^{13}C and ^{15}N NMR spectra of 4(7)- and 5(6)-nitrobenzotriazole show signal broadening caused by prototropic exchange. The prototropic exchange in 5(6)-nitrobenzotriazole did not allow detection of the N-1 and N-3 signals in the ^{15}N NMR spectrum (Table 3.33). In the ^{15}N NMR spectra of 1-methyl-substituted benzotriazoles (no tautomerism) it was possible to identify all three ^{15}N signals of the benzotriazole skeleton [826].

An interesting regularity is observed in the proton spectra of 5-nitro- or 6-nitrobenzotriazole derivatives: the H-7 chemical shifts of isomers **A** are lower than the H-6 and H-4, whereas for the **C** isomers the H-7 are, on the contrary, higher than H-5 and H-4. The δ H-7 and δ H-6 of its **B** isomer have practically equal values [826]. An analogous phenomenon is also observed for other nitrobenzotriazole derivatives [820–822, 824].

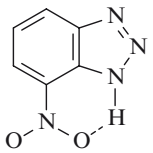
The ^{15}N chemical shift values of the N-1, N-2 atoms in *N*-unsubstituted benzotriazoles and their 1-methylated analogs are nearly coincident (Table 3.33). This provides good basis to assume that nitrobenzotriazoles exist as an equilibrium mixture:

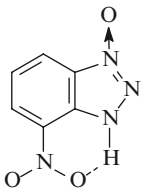
$$1\text{-NH} \rightleftarrows 3\text{-NH} \quad \text{i.e.,} \quad \mathbf{A} \rightleftarrows \mathbf{C}$$

but not

$$1\text{-NH} \rightleftarrows 2\text{-NH} \quad \text{i.e.,} \quad \mathbf{A} \rightleftarrows \mathbf{B}$$

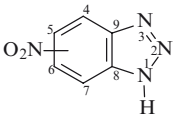
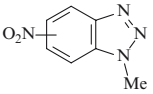
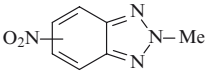
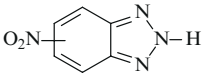
Moreover, the calculated ^{15}N chemical shift values of nitrobenzotriazoles are practically coincident with calculated and some experimental (N-2, N-3, NO_2) values of 1-methylated nitrobenzotriazoles (Tables 3.33 and 3.34). Thus, the experimental and calculated screening constant values indicate that *N*-unsubstituted benzotriazoles undergo a prototropic exchange **1** ⇌ **3**, but not **1** ⇌ **2**. The position of a nitro group at the phenylene fragment of benzimidazole cycle does not influence the tautomeric equilibrium significantly and has some impact only on screening constants of magnetic active nuclei of heterocycle. So, ^{15}N NMR spectroscopy along with quantum-chemical calculations is the convenient approach in the examination of tautomeric processes. In addition, the broad NH-signal (16 ppm) in the ^{1}H NMR spectrum of 4(7)-nitrobenzotriazole undergoes a 4 ppm low-frequency shift (12 ppm) when the sample temperature rises to +80℃ (Table 3.31). This may indicate the presence of N-O···H-N hydrogen bond and the existence of the 7-nitro tautomer [826].





The realization of an analogous structure *N*-oxy-7-nitrobenzotriazole has been reported in the literature [827]. According to ^{15}N NMR spectroscopy data the content of

Table 3.34 Calculated (B3LYP/6-311G+) ^{15}N NMR chemical shifts of nitrobenzotriazoles[a]

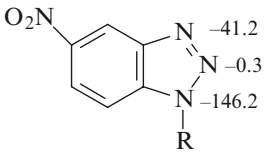
Compound	Position NO_2	δ ^{15}N, ppm			
		NO_2	N-1	N-2	N-3
	4	–14.9	–233.2	–11.0	–63.3
	5	–13.2	–234.6	–14.7	–54.1
	4	–14.5	–228.6	–2.6	–68.6
	5	–12.7	–230.0	–6.0	–58.5
	6	–12.8	–226.2	5.6	–71.1
	7	–11.8	–225.0	–3.5	–67.4
	4	–14.3	–93.4	–156.1	–98.8
	5	–12.4	–99.5	–153.7	–89.0
	4	–15.1	–99.0	–171.9	–98.7
	5	–13.0	–105.1	–169.7	–89.1

[a]Chemical shifts were referenced to nitromethane

the *N*-hydroxy tautomer in both equilibrium mixtures *N*-oxide ⇌ 1-hydroxybenzotriazole and in the *N*-oxide ⇌ 1-hydroxybenzimidazole mixture is significantly higher than that of *N*-oxide form and is proportional to the pK_a value of the solvent employed. The latter is a good accordance with electron spectroscopy data [827].

Characteristics of the carbon spectra of 2-nitro-4,5,6,7-tetrachlorobenzotriazole [823] and the nitrobenzotriazole adducts with aldehydes and ketones [824] are presented in Table 3.35.

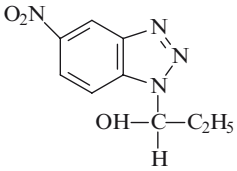
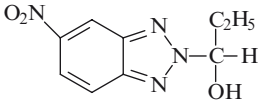
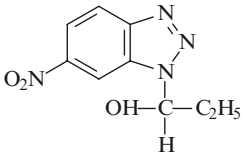
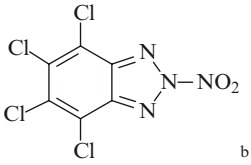
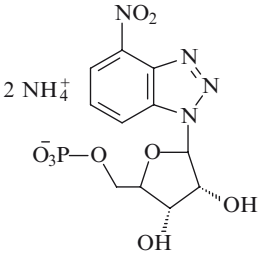
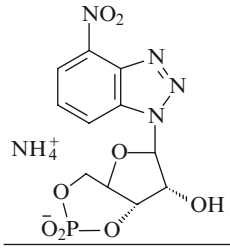
The ^{15}N chemical shifts of benzotriazoles [828], including those containing the nitro group, are in full agreement with regularities of the change in the ^{15}N value of 1,2,3-triazoles.



R = 5'-phosphoribosyl

NMR data were used to prove the structure of peptide-coupling reagents –[(6-nitrobenzotriazol-1yl)oxy]tris(dimethylamino)-, –(pyrrolidino)phosphonium hexafluorophosphates [829–831], 1-(2-nitrobenzenesulfonyloxy)-6-nitrobenzotriazole [832], and 1-(2-naphthylsulfonyloxy)-6-nitrobenzotriazole [833], complexes of 5-nitrobenzotriazole with palladium(II) and platinum(II) [834], some explosive substances such as 1-picrylbenzotriazole mono- and polynitro derivatives [835] as well as that of the Mesenheimer σ-complexes and 4,6-dinitrobenzotriazole-1-oxide [836, 847].

Table 3.35 ^{13}C NMR chemical shifts of nitrobenzotriazoles in DMSO-d_6 (ppm).

Compound	C-4	C-5	C-6	C-7	C-8	C-9	Refs
	116.3	144.3	121.9	112.8	134.4	147.7	[824]
	–	–	120.5	119.8	150.2	142.0	[824]
	120.4	118.8	146.1	109.0	131.0	144.7	[824]
 b	122.6	135.2	135.2	122.6	139.4	139.4	[823]
 c	147.79	129.26	129.26	128.58	138.27	138.71	[640]
	147.47	128.77	128.48	128.34	137.88	138.27	[640]

[a] In $CDCl_3$
[b] In D_2O

The structure of 1-acetyl-substituted [838] and 1-thiono-substituted 6-nitrobenzotriazoles [824, 839, 840] used as acylation and thioacylation agents, respectively, in the peptide synthesis has been confirmed by ^{1}H and ^{13}C NMR spectra.

Conclusions

The tautomerism and the isomerism of azoles make the structure analysis of such compounds a difficult problem. Structural investigation by ^{15}N NMR spectroscopy is a convenient and unique approach in the examination of tautomerism problems in azoles. Furthermore, the shielding of ^{15}N nuclei in benzazoles on going from the benzoic to the quinoid-like structure can be a test for the determination of the structure of nitrogen-containing heterocycles. However, in studying the electronic structure of aromatic heteroatom compounds by NMR spectroscopy it should be kept in mind that even minor variations in tautomeric equilibrium constants, molecular conformations, temperature, or solvents can change the nuclei shielding markedly, and this is not always in line with the electron redistribution. So, ^{15}N NMR spectroscopy provides the most convenient and foolproof method for the identification of structures and tautomeric forms of nitrogen-containing heterocycles.

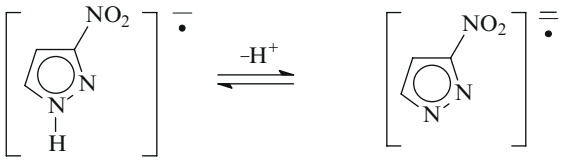
NMR spectroscopy is a very powerful analytical method for intermolecular interaction investigations and is unique in its ability to provide information on the structural, thermodynamic, kinetics, etc. aspects of the binding reaction. The application of NMR screening in drug discovery has recently attained heightened importance throughout the pharmaceutical industry [841–844]. NMR spectroscopy has long been a favorite tool of chemists interested in host-guest systems because it permits access to a wealth of information about the molecular recognition reaction. NMR has evolved dramatically in the last 15 years and, in parallel with the development of NMR methods for the determination of protein structure, a variety of tools aimed at detecting protein ligand interactions have been proposed and are being now used both in industrial and academic laboratories as valuable tools for drug discovery. Very recent developments have considerably increased the fraction of therapeutic targets that can be tackled by NMR and significantly reduced the amount of sample required for analysis. The new methodological and technical advances of recombinant DNA technology and NMR spectroscopy, together with the awareness that structure-based strategies will be key in the search of new drugs, have placed NMR in the center of a silent revolution in the field of drug discovery [841].

Modern inverse detection techniques have pushed the detection limits even to the submilligram level, especially in the case of small organic molecules. With the introduction of new technologies (cryogenic probes, solid-state accessories), high-field magnets, and developments in methodology, ^{15}N NMR spectroscopy at natural abundance has developed and become an approach complementary to ^{13}C NMR [220, 845–848]. Its strength lies in the investigation of the intermolecular interactions of nitrogen-containing compounds, including hydrogen bonding, tautomerism, and complexation with transition metals. The sensitivity of nitrogen NMR parameters to topological changes is primarily encoded in the direct involvement of the nitrogen unit in the earlier-mentioned processes. However, nitrogen NMR is also employed advantageously in characterizing such subtle structural changes as C-N rotations, ring conformation, and many other phenomena. Solid-state NMR techniques have opened a totally new scope in the study of the structure, dynamics, and interactions in solids – both amorphous and crystalline.

Electron Spin Resonance Spectroscopy

An electron spin resonance (ESR)[1] spectroscopy is an excellent method for studying problems of electron transfer in such fields as radiation chemistry, photochemical synthesis, biochemistry in vivo and etc. Nitroazoles are "fertile field" for the investigation by ESR method. The presence of the nitro group gives the possibility to obtain free radicals by electrochemical, photochemical, and chemical methods and use ESR spectroscopy for studying the electron structure peculiarities and reactivity of nitroazoles.

Nitro derivatives of azoles owing to electron deficiency are capable of being reduced with the formation of radical ions. 3-Nitropyrazole in the conditions of pulse radiolysis, depending on pH medium, forms radical anions (RA) or radical dianions (RDA), which were registered by ESR method [849] (Scheme 3.16). A hyperfine structure (HFS) constant (a, mT) is a main parameter in the ESR spectrum indicating the interaction of the unpaired electron with all magnetic active nuclei of radical.



Scheme 3.16

pH 8; a(NO_2) = 1.516 mT	pH 14; a(NO_2) = 1.605 mT
a(N-1), a(N-2) = 0.218, 0.115	a(N-1), a(N-2) = 0.169, 0.127
a(H-1), a(H-4), a(H-5), = 0.179, 0.221, 0.063	a(H-4), a(H-5), = 0.249, 0.034,

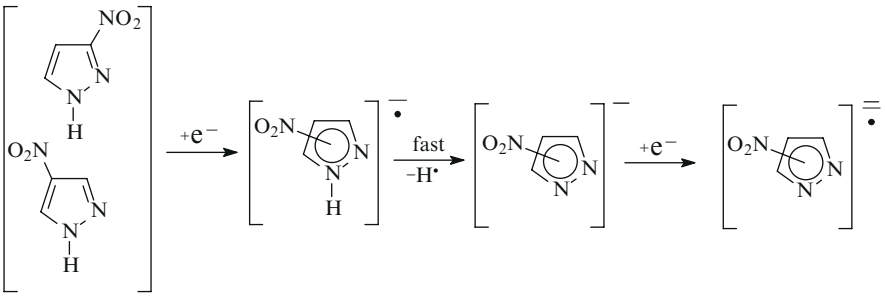
HFS constant of hydrogen nuclear of NO_2 group – a(NO_2) of 3-nitropyrazole RDA is more than the constant of corresponding RA.

The mechanism of electrochemical reduction (ECR) of *C*- and *N*-nitroazoles in the aprotic solvents (the acetonitrile, DMSO) was investigated by ESR method [850–854]. Nitroazoles, with unsubstituted nitrogen atom, on transfer of the first electron to the molecule, form radical anions, which quickly break up with the elimination of atomic hydrogen [850–853], as illustrated in Scheme 3.17:

The formed anions at second half-wave potential are reduced up to RDA, the ESR signals of which could be fixed (Table 3.36).

N-Alkylnitroazoles at first half-wave potentials form stable RA and their ESR spectra parameters as given in Table 3.36 [850–853] (Scheme 3.18).

[2]For electron paramagnetic resonance (EPR) spectroscopy, we prefer to use the title ESR in organic chemistry

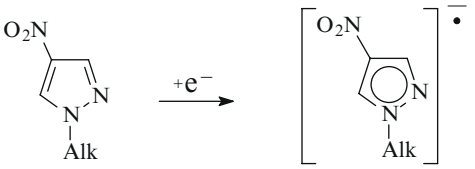


Scheme 3.17

Table 3.36 Electrochemical reduction parameters of nitroazoles.

Compound	$E'_{1/2,}$ $E''_{1/2}$ V	radical ion	ESR coupling constants, mT				
3-Nitropyrazole	1.55	RDA	3(NO_2)	2(H-4)	3(N-2)	3(N-1)	2(H-5)
	2.17		1.510	0.230	0.164	0.084	0.015
4-Nitropyrazole	1.46	RDA	3(NO_2)	3(H-3,5)	5(N-1,2)	–	–
	2.18		1.620	0.251	0.026		
1-Methyl-4-nitropyrazole	1.72	RA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.54		1.400	0.398	0.208	0.038	0.032
1-Ethyl-4-nitropyrazole	1.73	RA	3(NO_2)	2(H-5)	3(N-2)	2(H-3)	3(N-1)
	3.10		1.507	0.525	0.080	0.047	0.010
1,4-Dinitropyrazole	0.55	RA[a]	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	1.25		1.430	0.470	0.170	0.046	0.032
	1.70						
	2.20						
	2.75						
4(5)-Nitroimidazole	0.82	RDA	3(NO_2)	2(H-5)	3(N-3)	3(N-1)	2(H-2)
	2.23		1.552	0.400	0.070	0.054	0.01
1-Methyl-4-nitroimidazole	1.75	RA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.98		1.323	0.470	0.170	0.046	0.032
1-Ethyl-4-nitroimidazole	1.74	RA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	3.02		1.300	0.470	0.170	0.046	0.032
2-Methyl-4(5)-nitroimidazole	0.93	RDA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.39		1.559	0.470	0.170	0.046	0.032
1,2-Dimethyl-4-nitroimidazole	1.75	RA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.95		1.478	0.470	0.170	0.046	0.032
1-Methyl-5-nitroimidazole	1.53	RA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.75		1.270	0.470	0.170	0.046	0.032
1-Ethyl-5-nitroimidazole	1.67	RA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.97		1.488	0.470	0.170	0.046	0.032
1,2-Dimethyl-5-nitroimidazole	1.51	RA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.85		1.353	0.470	0.170	0.046	0.032
2-Nitroimidazole	0.71	RDA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.37		1.405	0.470	0.170	0.046	0.032
1-Methyl-2-nitroimidazole	1.49	RA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.54		1.160	0.470	0.170	0.046	0.032
1-Ethyl-2-nitroimidazole	1.45	RA	3(NO_2)	2(H-5)	2(H-3)	3(N-2)	3(N-1)
	2.54		1.175	0.470	0.170	0.046	0.032

[a] RA of dimer (see below)

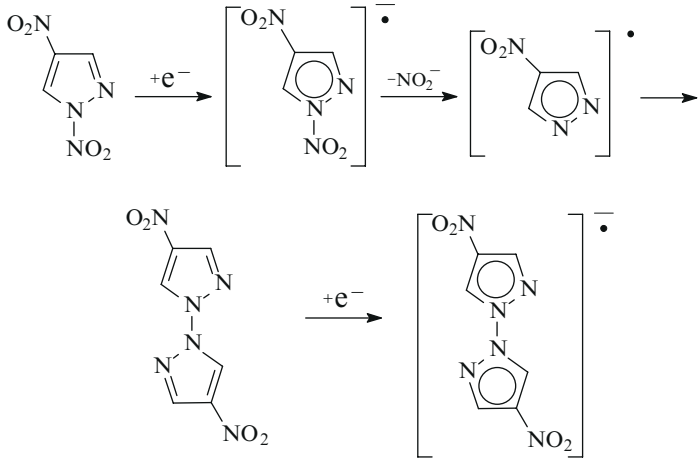


Scheme 3.18

The character and the hyperfine structure of ESR signals correspond to the interaction of the unpaired electron with all magnetic active nuclei of radical ion. In radical dianions of nitroazoles 60% of the spin density is concentrated at the nitro group, and in RA – 45–50% (Table 3.36). So higher value of the HFS $a_N(NO_2)$ of nitroazole RDA in comparison with its RA is connected with greater electronegativity of the first.

The character of spin density distribution in an RA of 1-ethyl-4-nitropyrazole differs from that in 1-methyl-isomer. 1-Nitropyrazole does not show an ESR signal in the conditions of both pulse radiolysis [849] and electrochemical reduction [851].

While the electrochemical reduction of 1,4-dinitropyrazole allows to observe the well-resolved ESR spectrum, the HFS character proves to be a dimeric radical product [851] (Scheme 3.19):



Scheme 3.19

The spin density in the dimer radical anion is concentrated mainly at one azolyl cycle because of uncoplanarity of the cycles [851].

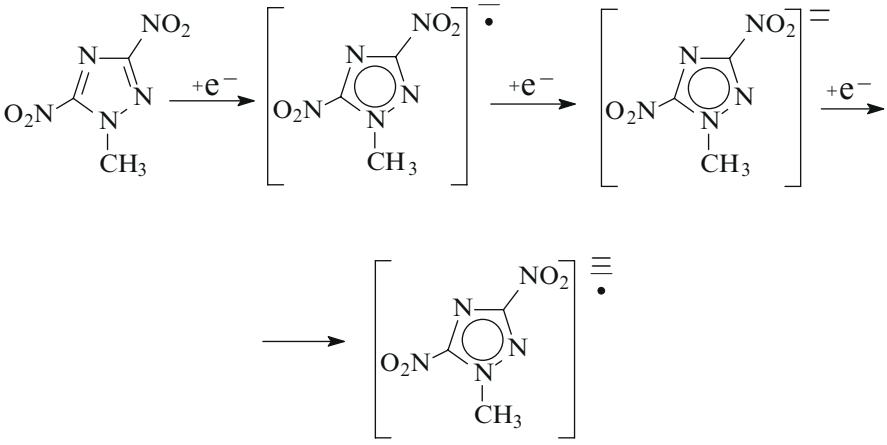
The comparison of nitro group nitrogen constants in 1-methyl-substituted nitroimidazole RAs shows that the spin density transmission degree to the heterocycle is decreased in the following order of the nitro group position in the imidazole ring (Table 3.36):

2- > 5- > 4-NO_2

1.16 > 1.27 > 1.32 mT

The unexpectedly large constant $a_N(NO_2)$ of the radical anion of 1-ethyl-5-nitroimidazole can be explained by the contribution of steric effects [852].

The electrochemical reduction process of 1-methyl-3,5-dinitro-1,2,4-triazole is unusually proceeded: ESR spectrum of its radical trianion in acetonitrile is identified [853] (Scheme 3.20).



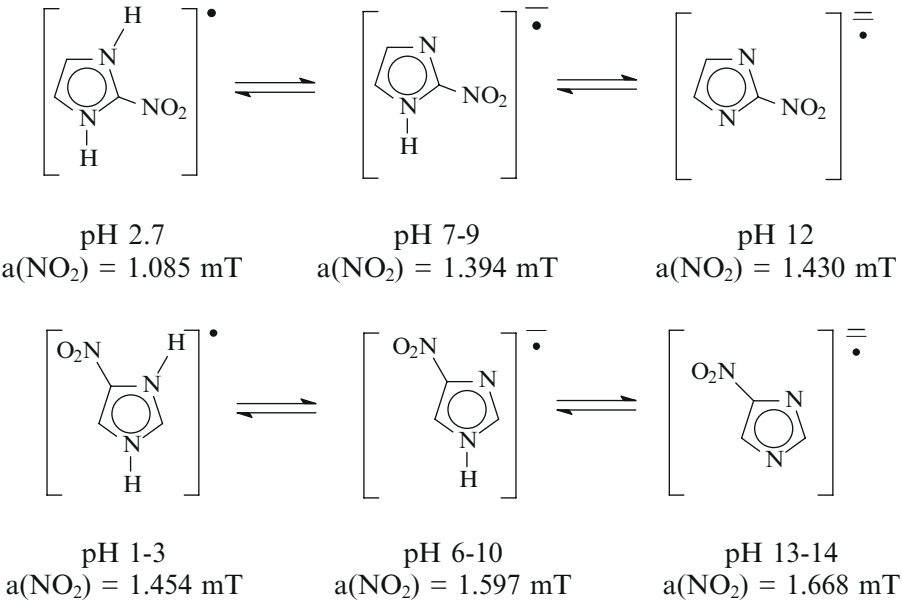
Scheme 3.20

Atom	3($\underline{N}O_2$)	3($N\underline{O}_2$)	3(N)	3(N)	4($C\underline{H}_3$)	3(N)
a, mT	1.302	0.250	0.176	0.154	0.136	0.046

Its HFS character is caused by interaction of the unpaired electron with five nitrogen atoms and three equivalent protons. It is impossible to fix an ESR signal of its radical anion in the experimental conditions. Actually, the polarography data prove the fast passing reactions of primary RA dimerization [853]. The assignment of the HFS constants in radical ions of the nitroazoles was made with the help of quantum chemistry calculation [855].

The ESR spectra of radical ions of known radiosensitizers metronidazole, misonidazole, ornidazole, and other nitroimidazoles have been investigated in the conditions of photolysis [856, 857], pulse radiolysis [849, 856, 858–865], and in the presence of other donors of free electrons [866–872]. Radical anions of 2-nitroimidazole [849] and 4(5)-nitroimidazole [860] depending on medium pH can exist in three forms (Scheme 3.21):

pH 2.7 $a(NO_2) = 1.085$ mT	pH 7–9 $a(NO_2) = 1.394$ mT	pH 12 $a(NO_2) = 1.430$ mT



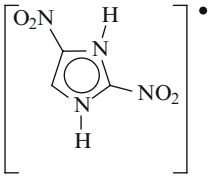
Scheme 3.21

On going from a radical to RA and RDA the HFS constant of nitro group nitrogen atom grows [849, 852, 860]. In connection with this the characteristics of ESR spectra of 2,4(5)-dinitro- and 1-(2-hydroxyethyl)-2,4(5)-dinitroimidazoles (used as radiosensitizers selectively sensitizing hypoxic mammalian cells to the lethal effect of ionizing radiation) cause surprise [862] (Scheme 3.22).

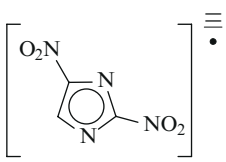
A nitro group in position 2 being more electron deficient than the 4(5)-NO_2 group because of the presence of the two electronegative nitrogen atoms is reduced first and has a large HFS constant. Probably, the 4(5)-NO_2 is uncoplanar with benzimidazole ring. Therefore the nitrogen HFS constant of nitro group in position 4(5) has small value.

The HFS $a_N(NO_2)$ in 2-nitroimidazole RA is much less than the one in the RA of 4(5)-nitroimidazole because the nitro group arranges between two electronegative nitrogen atoms. A similar regularity for these nitroimidazoles has been observed [852]. The ESR spectra of radicals formed by electrochemical reduction of 2-nitroimidazole and 4(5)-nitroimidazole in mixed solvents have been studied [873]. The behavior of HFS $a_N(NO_2)$ with the solvent composition is discussed in terms of equilibrium between radicals in different solvents.

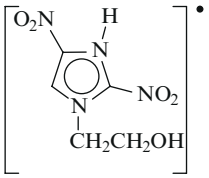
The kinetics of misonidazole degradation in a model system (a solution hemoglobin and vitamin C) has been investigated [874]. The formed RAs react with molecular oxygen, its superoxide radical anions, having been formed here, and can be the additional reason of the compound toxicity in the presence of oxygen.



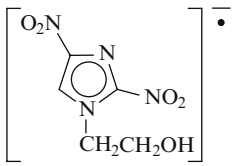
pH 3.3
$a(NO_2)$ = 1.231 mT, $a(NO_2)$ = 0.236,
a_N = 0.131 mT, a_N = 0.088 mT



pH 12.6
$a(NO_2)$ = 0.829 mT, $a(NO_2)$ = 0.348,
a_N = 0.279 mT, a_N = 0.019 mT



pH 3.4
$a_N(NO_2)$ = 1.233, a_N = 0.225,
a_N = 0.150 mT, a_N = 0.076 mT



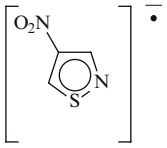
pH 7.6
$a_N(NO_2)$ = 1.229, a_N = 0.243,
a_N = 0.279 mT, a_N = 0.019 mT

Scheme 3.22

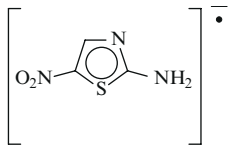
The radical anions of 2-, 4-, and 5-nitroimidazole derivatives – the most frequently used drug in the cases of anaerobic infections – were registered by ESR method after anaerobic incubation with hydrogenosomes from *Trichomonas vaginalis* supplemented with pyruvate, succinate, and ADP [872]. The metronidazole – 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (METRO) radical anions have been recorded also in vivo in the sexually transmitted human parasite (*Trichomonas vaginalis*) [875]. The intensive signal of metronidazole radical anions has been detected in ESR spectrum of irradiated tumor tissue after injection METRO to animals. The radicals are on the trapping of electrons obtained at irradiation by METRO electron-withdrawing nitro group [876].

The effect of gamma irradiation on physical and chemical properties of metronidazole, ornidazole, and tinidazole in solid state has been studied by ESR [877, 878].

ESR spectrum characteristics of 4-nitrothiazole and 2-amino-5-nitrothiazole RAs, as seen in the conditions of pulse radiolysis, are obtained [849] (Scheme 3.23):



pH 8; $a(NO_2)$ = 1.479 mT



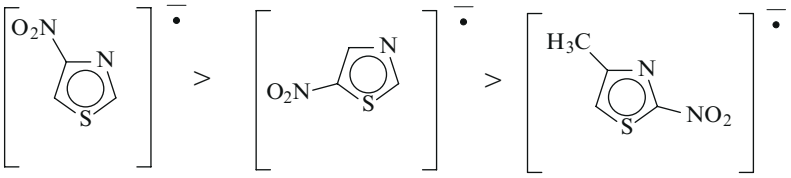
pH 9; $a(NO_2)$ = 1.349 mT

Scheme 3.23

The last compound does not give ESR signals in alkaline medium.

The ESR and the ENDOR investigations of radicals formed by X-ray irradiation of a single crystal 2-bromo-5-nitrothiazole have been carried out [145]. The experimental tensor HFS constants are compared with the theoretical constants, and calculated for azaallyl and allyl radicals.

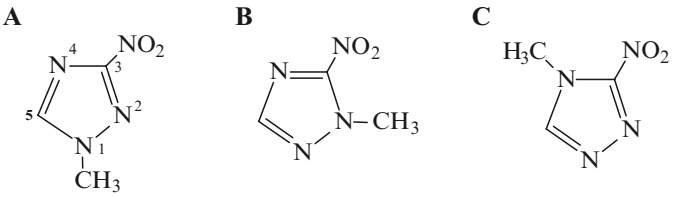
The spin density on nitro group in nitrothiazole RA, obtained by reduction with the help of glucose and strong basis, decreases in the following sequence [879] (Scheme 3.24):



Scheme 3.24

The authors [879] tried to estimate the energy of conformational transfers in 4-nitro-5-alkyl- and 5-nitro-4-alkylthiazolyl RAs. With the help of nonlinear regression method it was possible to construct theoretical ESR spectra of radical anions of some derivatives of thiazoles, including 2-nitro-4-methylthiazole [880].

The position of *N*-methyl group in *C*-nitro-1,2,4-triazoles influences the spin density redistribution at the nitrogen atoms of triazole cycle and is particularly displayed in the changing of proton-coupling constant [881]. Nitro group passes approximately half of all spin density (Table 3.37).



The pyridine nitrogen atoms in radical anion **A** are practically equivalent; therefore, in radical anions **B** and **C** HFS nitrogen constants of pyrrole and pyridine nitrogen atoms are the same (Table 3.37). ESR spectra of radical anions of 3-nitro-1,2,4-triazole *N*-methyl-isomers (**A**, **B,** and **C**) are presented in Fig. 3.1. Analogical

Table 3.37 HFS constants of radical anions of *N*-methyl-*C*-nitro-1,2,4-triazoles (mT)

1,2,4-Triazole isomers	$a(NO)_2$	a(N-1)	a(N-2)	a(N-4)	a(H-5)	$a(C\underline{H}_3)$
1-methyl-3-nitro- (**A**)	1.150	0.050	0.150	0.120	0.460	0.050
2-methyl-3-nitro- (**B**)	1.180	0.140	0.110	0.400	0.280	0.025
4-methyl-3-nitro- (**C**)	1.105	0.130	0.240	0.130	0.120	0.020

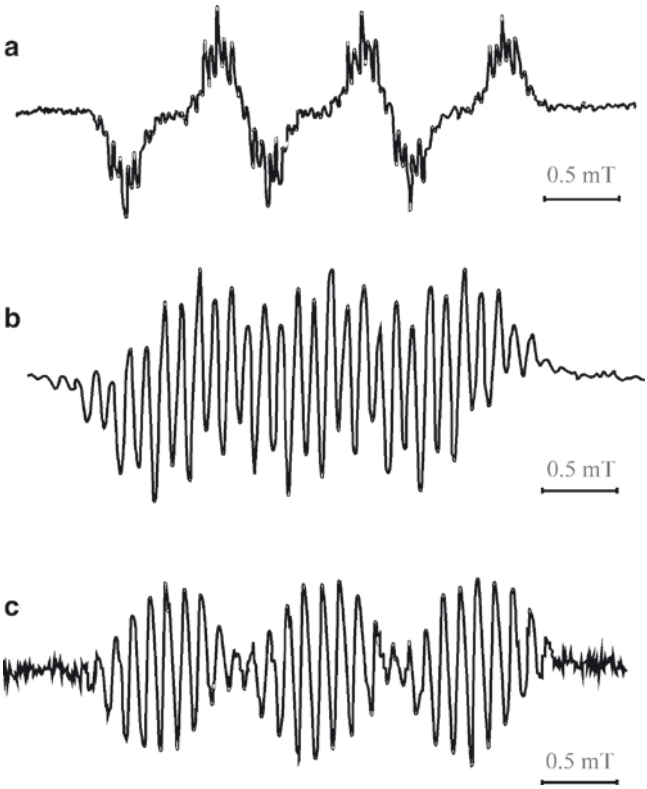


Fig. 3.1 ESR spectra of radical anions of *N*-methyl-3-nitro-1,2,4-triazole isomers.

character of spin redistribution on magnetic nuclei connected with intramolecular position of nitro group is reflected in LUMO structures obtained for more stable stationary states of isolated neutral molecules **A–C** [881].

Firstly, the nondegenerated tautomers of 3-nitro-1,2,4-triazole-5-one (NTO) radical anions were investigated by ESR method during electrochemical reduction of NTO in aprotic medium at different temperatures. It was shown that observed reversible temperature variations in the ESR spectra of radical anions were caused by tautomerism. Quantum chemical calculations evidence that 1,4-*H*-tautomer of radical anion is most preferable [881].

The limited number of works is devoted to the research of benzazoles by ESR method [689, 850, 882–887]. The ESR spectra analysis of 2-substituted 5(6)-nitrobenzimidazoles RDA obtained by electrochemical generation method in acetonitrile has been carried out (Table 3.38) [689, 883, 884].

Electrochemical reduction mechanism of nitrobenzimidazoles is similar to the aforementioned one for the five-membered nitroazoles (Scheme 3.25):

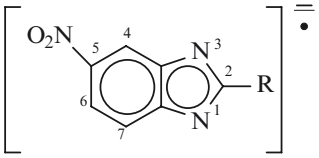
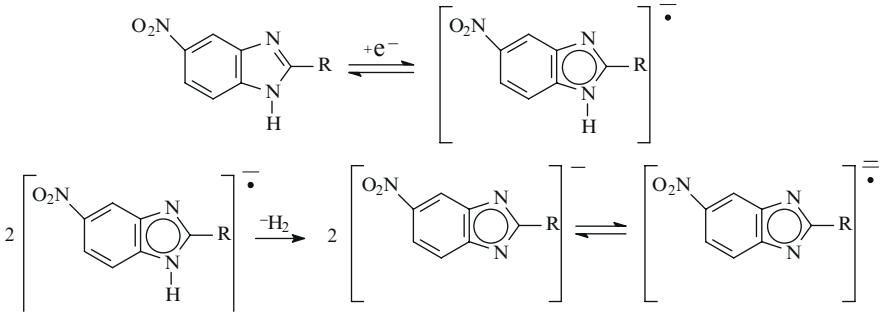


Table 3.38 HFS constants of 2-substituted 5(6)-nitrobenzimidazoles radical dianions (mT)

R	a(NO_2)	a(H-4)	a(H-6)	a(H-7)	a(N-1)	a(N-3)	H
$N(CH_3)_2$	1.458	0.356	0.267	0.089	0.020	0.015	0.015
NH_2	1.471	0.365	0.280	0.090	0.018	0.015	0.015
OCH_3	1.445	0.400	0.300	0.095	0.015	0.010	0.015
OC_2H_5	1.419	0.400	0.297	0.105	0.015	0.010	0.015
CH_3	1.393	0.416	0.240	0.110	0.023	0.010	0.015
C_2H_5	1.393	0.420	–	–	–	–	–
C_6H_5	1.367	0.438	0.240	0.110	0.025	0.015	0.030
H	1.359	0.460	0.243	0.113	0.027	0.015	0.015
Cl	1.326	0.464	0.260	0.100	0.025	0.015	0.015
$COOCH_3$	1.290	0.546	0.215	0.100	0.058	0.046	0.020
$COOC_2H_5$	1.303	0.546	0.215	0.120	0.060	0.042	0.017
$COCH_3$	1.316	0.550	0.210	0.100	0.060	0.042	0.030
CF_3	1.251	0.380	0.207	0.130	0.202	0.202	0.010
CN	1.225	0.562	0.190	0.089	0.063	0.046	0.030



Scheme 3.25

With the help of a rotating platinum disk electrode with a ring allowing to fix fast processes, it has been shown that as a result of reduction of 5(6)-nitrobenzimidazoles the molecular hydrogen is formed because of bimolecular reaction of two primary radical anions [689, 888]. The assignment of HFS constants in ESR spectra of the corresponding RDA is made on the basis of quantum chemical calculation of spin density of their radical dianions [689, 884]. The HFS constants of nitro group nitrogen atom and H-4 are most sensitive to the substituent effects in position 2 (Table 3.38). The $a_N(NO_2)$ of nitro group decreases with the increase of electron-withdrawing properties of the substituents in position 2 of nitrobenzimidazoles while a(H-4) – is increased (Table 3.38). The results of $a_N(NO_2)$ correlations with substituent constants σ_I and σ_R show that the contribution of an inductive and resonance components to the general transmission of substituent effects is approximately identical (3.3):

$$a(NO)_2 = (-1.865 \pm 0.253)\,\sigma_I + (-1.887 \pm 0.167)\,\sigma_R + (13.593 \pm 2.128) \quad (3.3)$$

$$r = 0.989,\ s = 0.125,\ n = 7,\ \%\sigma_R = 59.4$$

$$R = NH_2,\ OCH_3,\ CH_3,\ H,\ Cl,\ CF_3,\ CN$$

Therefore the electron substituent effects in radical dianions of 2-substituted 5(6)-nitrobenzimidazoles are transmitted with approximately equal contributions of inductive and resonance components. A similar picture is observed for *para*-substituted nitrobenzene radical anions also [689, 883]. Actually, the $a_N(NO_2)$ correlation of 2-substituted 5(6)-nitrobenzimidazoles RDA (RDA BI) with the $a_N(NO_2)$ of *para*-substituted nitrobenzene RA (RA Bz) indicates the same mechanism of substituent effects transmission but with different intensity, as shown in equation (3.4):

$$a(NO_2)_{RDA\ BI} = (0.502 \pm 0.025)\,a(NO_2)_{AR\ Bz} + 8.520 \quad (3.4)$$

$$r = 0.991,\ s = 0.114,\ n = 7$$

$$R = NH_2,\ OCH_3,\ CH_3,\ H,\ Cl,\ CF_3,\ CN$$

The substituent effects in RA Bz are transmitted twice more intensively than in RDA BI, which is apparently connected to the inhibiting effect of electronegative nitrogen atoms of benzimidazole [689, 883].

Also the $a_N(NO_2)$ correlation of RDA BI (ESR data) with $\delta^{15}N$ (NO_2) BI neutral molecule (NMR data) is observed (equation 3.5):

$$a(NO_2) = (0.735 \pm 0.037)\delta^{15}N + 20.919 \quad (3.5)$$

$$R = 0.987,\ s = 0.123,\ n = 10$$

$$R = N(CH_3)_2,\ NH_2,\ OCH_3,\ CH_3,\ H,\ Cl,\ COCH_3,\ COOCH_3,\ CF_3\ ,CN$$

So, in a neutral molecule of benzimidazole the electronic substituent effects from position 2 to the nitro group are transmitted with greater intensity than in its radical ion. The unpaired electron density in ion radicals of nitro compounds (including nitroazoles) is concentrated approximately on 60% on nitro group, owing to that $a_N(NO_2)$ RDA BI becomes less sensitive to electronic substituent effects.

Character of ESR spectra of 2-phenyl-5(6)-nitrobenzimidazoles RDA registered in DMF (Table 3.39) [885] differs from that in acetonitrile [883] and has higher value

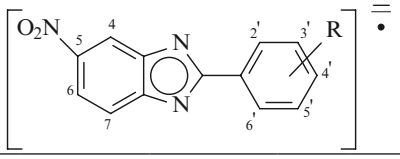


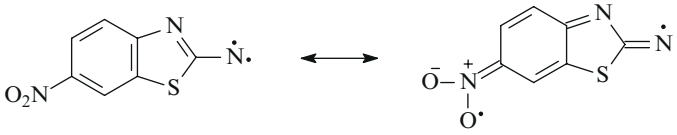
Table 3.39 HFS constants (mT) of 2-aryl-5(6)-nitrobenzimidazoles RDA (DMF)

R	H-4	$a_N(NO_2)$	H-6	H-7	H-2′	H-3′ or NO_2	H-4′ or NO_2	H-5′	H-6′
H	0.23	1.44	0.52	0.13	[a]	–	–	–	–
4′-NH_2	0.27	1.47	0.49	0.13	–	–	–	–	–
4′-NO_2	–	–	–	–	0.07	0.35	1.00[b]	0.35	0.07
3′-NO_2	–	–	–	–	0.40	1.23[b]	0.40	0.13	0.47

[a] The constant less 0.03 mT
[b] $a_N(NO_2)$

of nitrogen HFS constant of the NO_2 group (1.44 mT). The introduction of the donor substituent such as NH_2 to the phenyl ring results only in insignificant increase of a constant on nitrogen atom of nitro group (1.47 mT). At the same time the splitting from hydrogen atoms of a phenyl ring in ESR spectra is not observed (see Table 3.39). It proves the absence of direct conjugation of the earlier-mentioned molecules. The mononitration in a phenyl ring results in essential redistribution of unpaired spin density in RDA. Moreover as is visible from Table 3.39, spin density is located mainly in a phenyl part of a molecule [885].

The ESR spectrum 2-azido-6-nitrobenzothiazole (77K), obtained by a UV irradiation consists of two signals 1.62 ($g=4.0$) and 3.200 ($g=2$) mT [882]. The first signal the authors [882] assign to nitren in triplet state, and the second – to a free radical (Scheme 3.26).



Scheme 3.26

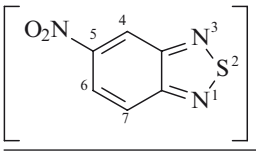
Thus, the equilibrium between nitren with unpaired electron and biradical with a conjugated system bond is supposed.

The radical anions of five isomers of nitrobenzothiazole (4-NO_2-, 5-NO_2-, 6-NO_2-, 7-NO_2- and 2-NO_2-) have been obtained by electrochemical reduction in DMSO and easily characterized by ESR spectroscopy [889]. To the contrary, the chemical reduction in alkaline solution (*t*-BuOK in DMSO or glucose and MeOK in MeOH) presented some problems with 6-NO_2- and 4-NO_2-benzothiazoles, and 2-NO_2-benzothiazole did not provide any detectable paramagnetic species [889].

Copper(II) complexes of 6-nitrobenzothiazole-*N*-sulfonamides as protective agents against superoxide anion have been investigated by ESR spectroscopy [890].

The ESR spectrum of 5-nitro-2,1,3-benzothiadiazole RA obtained by electrochemical generation in DMF was reported [886]. Unfortunately, the HFS constants of this radical anion are absent and we estimated the HFS constants from simulated spectrum (Table 3.40).

Table 3.40 Simulated splitting constants (mT) in ESR spectra of 5-nitro-2,1,3-benzothiadiazole RA (DMF)[a]

	$a_N(NO_2)=0.77$ a_H(H-4)$=0.59$ a_H(H-6)$=0.39$ a_N(N-1 or N-3)$=0.03$ or 0.02 a_H(H-7)$=0.02$

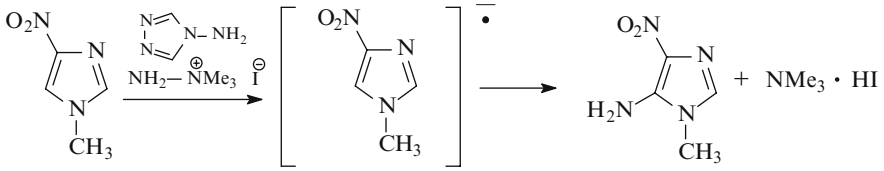
[a] The simulation of the spectrum was carried out by Dr. T. Vakulskaya with the use of Bruker program WINEPR SimPhonia 1.26, 1996

To our surprise, nitrogen HFS constant of nitro groups has a little value in comparison with other nitrobenzazole radical ions, whereas proton constants are sometimes increased. Perhaps the nitro group exists in a significant conjugation with anthranil cycle and because of that the delocalization of spin electron density is observed.

One-electron reduction of misonidazole – 2-nitroimidazole radiosensitizer [891], (nitroimidazolyl)succinic esters [892] and nitroindazoles [893, 894] has been studied by ESR and polarography. Misonidazole is participated in the determination of potentiation degree of the anticancer agent cytotoxicity [891].

Vicarious nucleophilic substitution (VNS) of hydrogen is a convenient method for the introduction of different functional groups into aromatic or heterocyclic systems [894–898]. The introduction of amino group into nitroazoles and their model compounds via reaction of vicarious nucleophilic *C*-amination [272–278, 899, 900] is the only method of direct introduction of amino group into nitroazoles. Aminonitroazoles containing simultaneously nitro and amino groups have essentially enriched the arsenal of previously hard-hitting high energy azoles. Vicarious *C*-amination proceeding in the condition of super base medium is attended by processes of one-electron transfer with formation of radical anions of initial nitroazoles [273–277].

The interaction of 1-methyl-4-nitroimidazole [273], 1-methyl-4-nitropyrazole [272, 276], 2-pheny-4-nitro-1,2,3-triazole [274, 277] with 1,1,1-trimethylhydrozinium iodide or 4-amino-1,2,4-triazole in *t*-BuOK/DMSO or MeONa/DMSO leads exceptionally to 5-amino derivatives corresponding to nitroazoles, as shown in Scheme 3.27 for nitroimidazole.



Scheme 3.27

C-amination of 1-methyl-5-nitro- and 1-methyl-6-nitrobenzimidazoles in the analogous conditions gives 1-methyl-4-amino-5-nitro-, 1-methyl-7-amino-6-nitro-, and 1-methyl-2-amino-6-nitrobenzimidazoles [275].

The observation of ESR signals of nitroazoles radical anions during ESR monitoring and the appearance of blue color in the reactions of substrates with 1,1,1-trimethylhydrozinium iodide or 4-amino-1,2,4-triazole in *t*-BuOK/DMSO or MeONa/DMSO suggests that the reaction includes a one-electron transfer stage. ESR spectra of radical anions of 1-methyl-4-nitropyrazole, 1-methyl-4-nitroimidazole and 2-phenyl-4-nitro-1,2,3-triazole are presented in Figs. 3.2–3.4, correspondingly.

Except for the substrate RA, the radical cation of reagent $(CH_3)_3N^+–N^{\bullet}H$ has been registered and identified in the reaction mixture of 2-phenyl-4-nitro-1,2,3-triazole with 1,1,1-trimethylhydrazinium iodide (Fig. 3.4) [274, 277].

It should be noted that ESR spectra of radical anions of 1-methyl-4-nitroimidazole [850, 852], 1-methyl-4-nitropyrazole [850, 851], and 1-methyl-5-nitrobenzimidazole

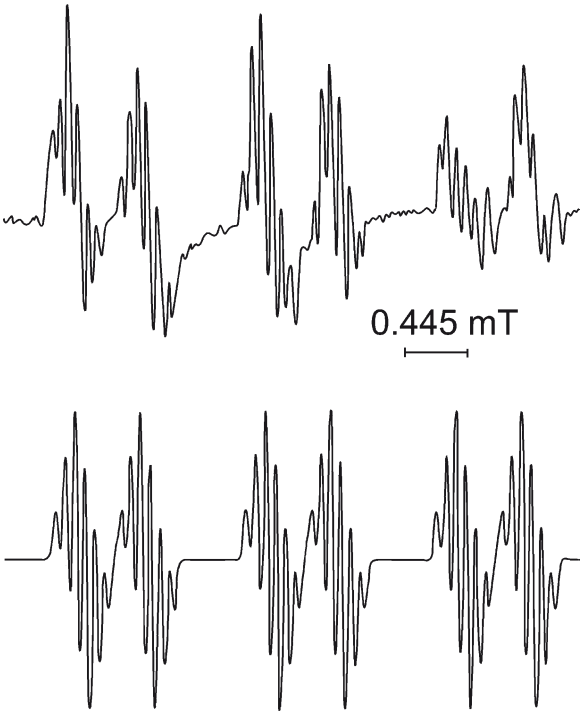


Fig. 3.2 ESR spectrum of 1-methyl-4-nitroimidazole radical anion recorded in the reaction obtained in vicarious C-amination condition (top); simulated ESR spectrum of 1-methyl-4-nitroimidazole RA (bottom) for HFS-coupling constants (a, mT): 1.388 (1N, NO_2), 0.477 (1H, H-5), 0.070 (2N, N-1,3), 0.056 (1H, H-2), 0.020 (3H, N–CH_3)

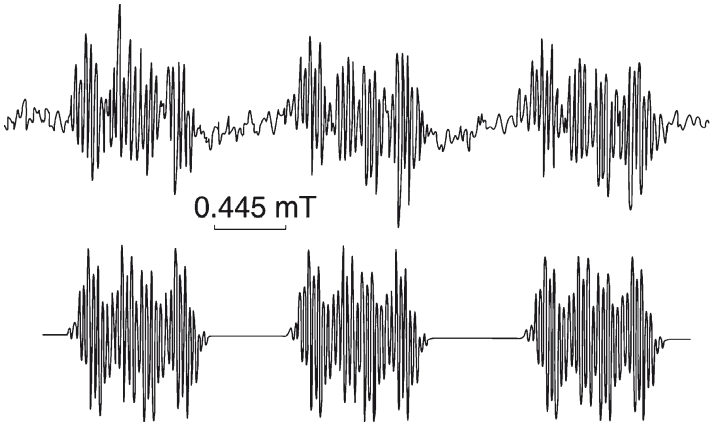


Fig. 3.3 ESR spectrum of 1-methyl-4-nitropyrazole radical anions recorded in the reaction obtained in vicarious C-amination condition (top); simulated ESR spectrum of 1-methyl-4-nitropyrazole RA (bottom) for HFS-coupling constants (a, mT): 1.430 (1N, NO_2), 0.352 (1H, H-5), 0.220 (1H, H-3), 0.033 (1N, N-2), 0.0275 (1N, N-1), 0.060 (3H, N-CH_3)

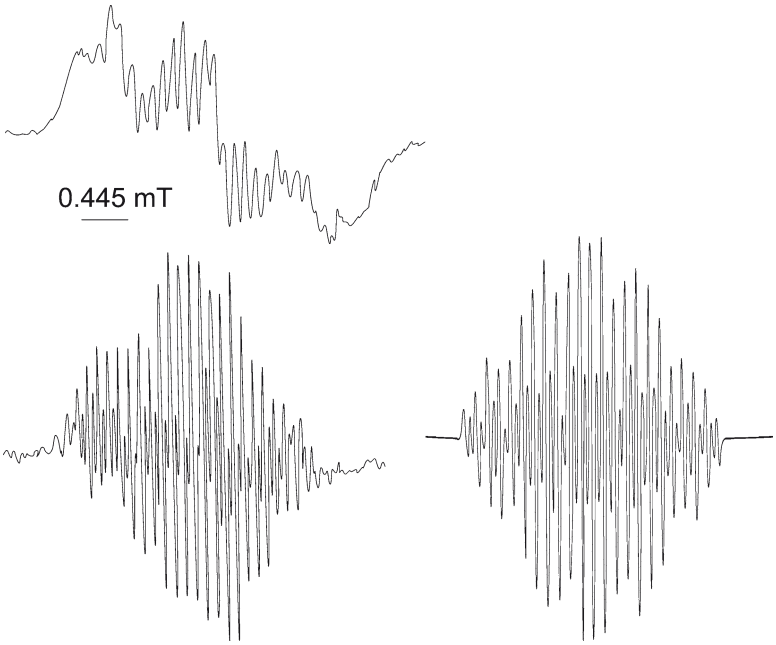
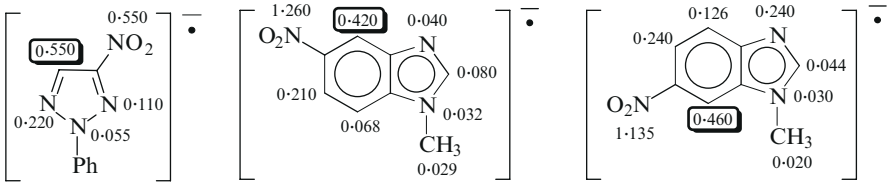


Fig. 3.4 The ESR spectrum recorded in the reaction of 2-phenyl-4-nitro-1,2,3-triazole with 1,1,1-trimethylhydrazinium iodide in *t*-BuOK-DMSO: after 25 minutes (top) and after 45 minutes (bottom left) from the beginning of reaction, computer simulation of ESR signal of radical anion (bottom right)

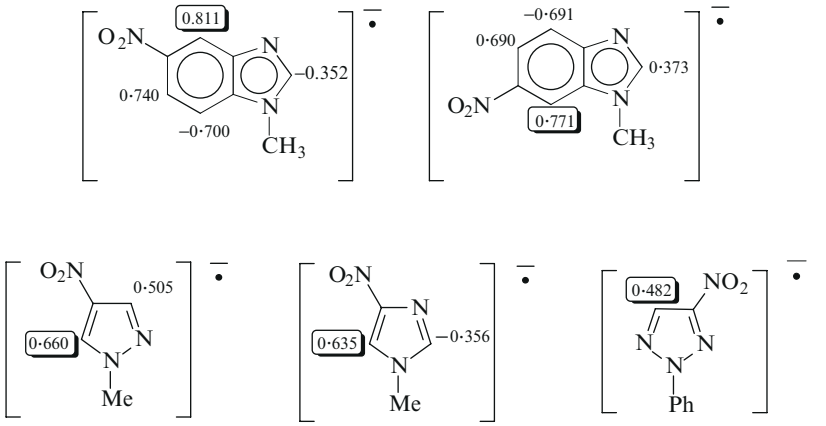
[689, 883] independently obtained by electrochemical reduction (Table 3.36) are practically identical with the spectra recorded in vicarious *C*-amination conditions. ESR signals are not observed when any reagent is absent in the reaction mixture.

ESR spectral parameters of radical anions of 2-phenyl-4-nitro-1,2,3-triazole, 1-methyl-5-nitrobenzimidazole, and 1-methyl-6-nitrobenzimidazole are illustrated in Scheme 3.28.



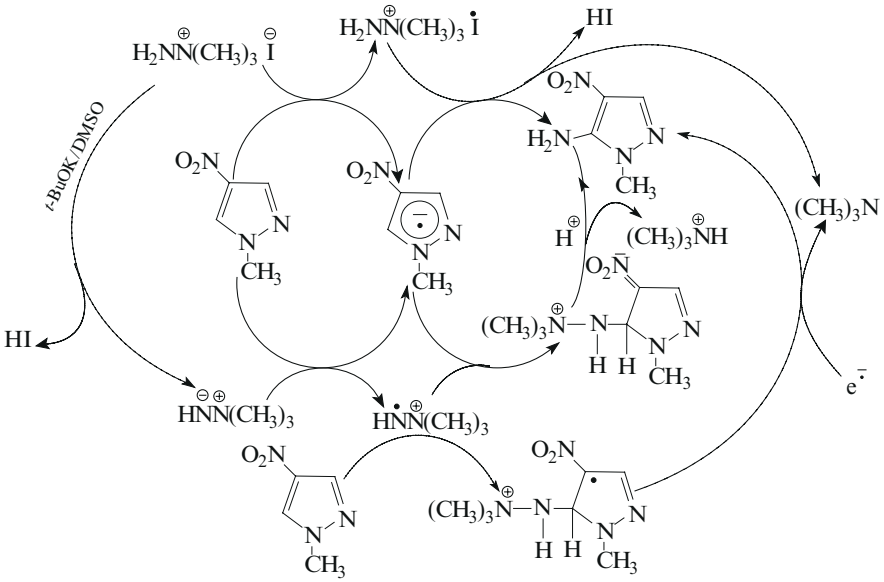
Scheme 3.28

Ab initio (B3LYP/6-31G* or UHF/6-31G*) quantum-chemical calculations of spin density distribution in nitroazole radical anions (Scheme 3.29) are in a good agreement with experimental data (Scheme 3.28, Figs. 3.2 and 3.3) and show that the largest positive spin density is located at the carbon atom of azole ring, where the vicarious *C*-amination is realized [277].



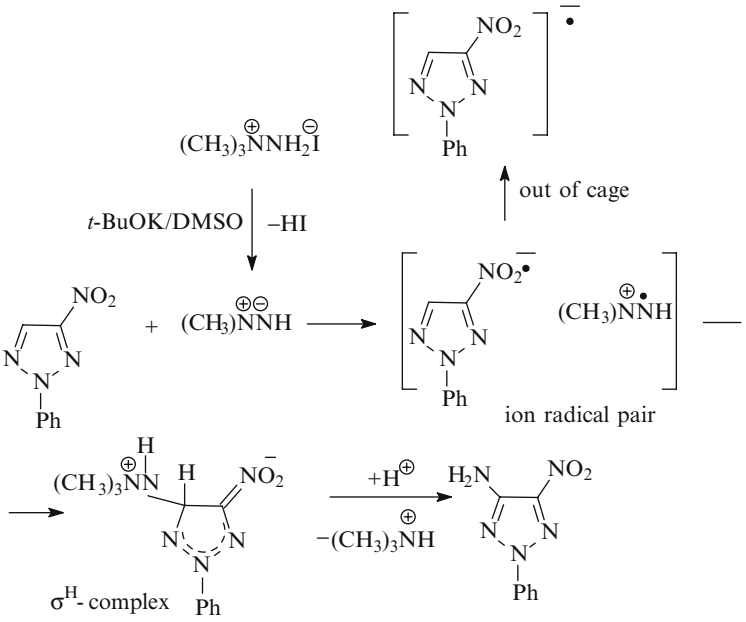
Scheme 3.29

The mechanism of vicarious *C*-amination of nitroazoles is presented in Schemes 3.30 (1-methyl-4-nitropyrazole), 3.31 (2-phenyl-4-nitro-1,2,3-triazole), 3.32 (1-methyl-5-nitrobenzimidazole), and 3.33 (1-methyl-6-nitrobenzimidazole) [273, 275–278].

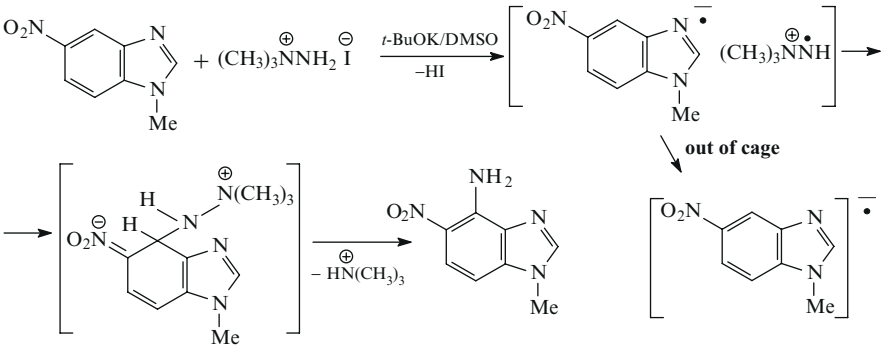


Scheme 3.30

First the mechanism of vicarious nucleophilic substitution of hydrogen in nitroazoles and nitrobenzene has been discussed in terms of an electron transfer [273–277]. Community of the observed effects in vicarious *C*-amination of nitroazoles allows



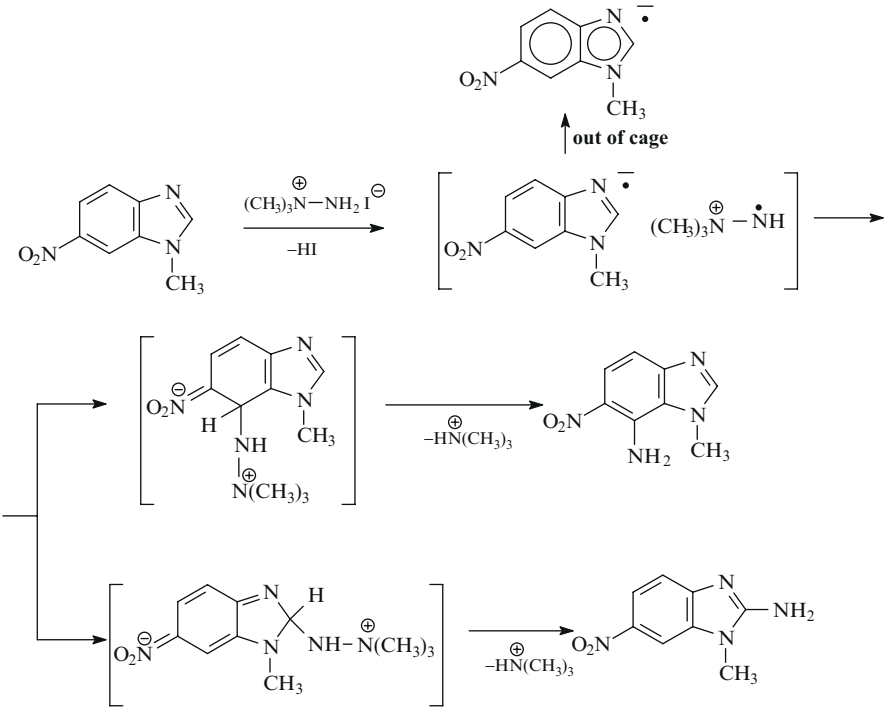
Scheme 3.31



Scheme 3.32

considering that the channel of a one-electron transfer in VNS processes was disclosed by ESR spectroscopy. This point of view gives a chance to explain the orientation of nucleophile anion to the largest spin density place (position) of substrate RA.

Free radicals may be reaction intermediates in biological systems in more situations than are presently recognized. However, progress in detecting such species by ESR has been relatively slow. ESR is a very sensitive technique for free radical detection and characterization. It can be used to investigate very low concentrations of radicals provided that they are stable enough for their presence to be detected. For unstable radicals special techniques have to be employed [901]. One of these methods is



Scheme 3.33

called Spin Trapping. The special review [902] summarizes some of the more relevant achievements of ESR and Spin Trapping applications in parasitic diseases studies. The use of ESR spectroscopy to obtain relevant information about free radical characterization and the analysis of the mechanisms of action of drugs involved in several parasitic diseases is also presented.

So, nitroazoles are beneficial materials to be investigated by ESR method. The presence of the nitro group causes the possibility of obtaining free radicals (radical anions, radical cations, and neutral radicals) by chemical, electro-, and photochemical methods and of use of ESR spectroscopy for studying the structure peculiarities and chemical behavior of nitroazoles. Unfortunately, until now, the ESR method, because of its specific character, does not find comprehensive application as an express method as, for example, does NMR spectroscopy. Therefore it has wide perspectives, justifying carrying out a labor-intensive, long, and fine experiment. ESR monitoring can shed light on the mechanism of the action of different drugs on the basis of nitroazoles.

Free radicals may be reaction intermediates in biological systems in more situations than are presently recognized. However, progress in detecting such species by Electron Spin Resonance has been relatively slow. ESR is a very sensitive technique for free radical detection and characterization. It can be used to investigate very low concentrations of radicals provided they are stable enough for their presence to be detected.

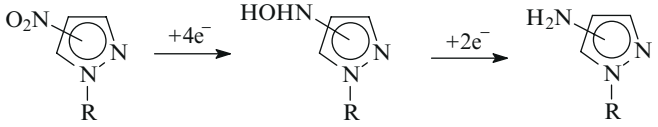
For unstable radicals special techniques have to be employed. One of these methods is called Spin Trapping.

Parasitic diseases in tropical and subtropical areas constitute a major health and economic problem. The range of antiparasitic drugs varies widely in structural complexity and action at the subcellular and molecular levels. However, a number of these drugs are thought to exert their action by generating free radicals. Most of the free radicals producing drugs used against parasites are nitroheterocyclic compounds.

Polarography

The electron transfer is a main stage in the chemical reaction mechanism, photosynthesis, catalysis, transfer energy, etc.

Dumanovic with colleagues carried out polarographic investigation of various derivatives 3-, 5-nitropyrazoles and 2-, 4-, 5-nitroimidazoles in aqueous buffer solutions (pH 1.8–9.3) and 0.1 M solution NaOH [903–912]. On polarograms all the investigated nitroazoles have one or two waves of reduction both in acid and neutral medium. The first four-electron wave corresponds to reduction of nitro group to hydroxylamine one. The second two-electron wave corresponds to further reduction of hydroxylamine derivative to aminoazole (Scheme 3.34).

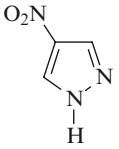
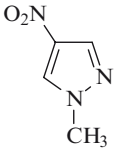
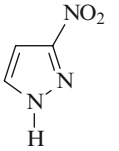
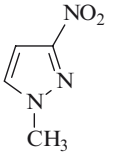
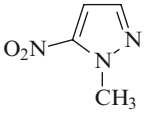
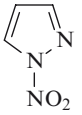


Scheme 3.34

By increasing the medium pH the first half-wave potential ($E'_{1/2}$) value of all investigated compounds is displaced in the negative region (Table 3.41). Besides, for *N*-substituted nitroazoles a considerably greater displacement is observed, as in alkaline media these compounds form anions. This allows the determination in alkaline media the presence of both *N*-substituted and *N*-unsubstituted forms of nitroazoles. The authors also utilized the $E_{1/2}$/pH dependence for identification of the earlier-stated nitroazole forms (Table 3.41) [903, 904, 909, 910].

As seen from Table 3.41, the half-wave potentials of 3(5)-nitropyrazole and 1-methyl-3-nitropyrazole are practically identical at all pH values. In the authors' opinion, this may be due to the fact that 3(5)-nitropyrazole contains, mainly, 3-nitro tautomer [904]. A similar regularity is observed for 4(5)-nitroimidazole and 1-methyl-4-nitroimidazole [903]. The $E_{1/2}$ values of 1-methyl-3-nitropyrazole lie in more a negative region than those of 1-methyl-5-nitropyrazole. Probably it is related to the fact that nitro group in 1-methyl-3-nitropyrazole is located near electron-donative "pyridine" nitrogen atom (N-2). This is also the case for imidazoles: 1-methyl-4-nitro- and 1-methyl-5-nitroimidazole.

Table 3.41 The dependence of nitropyrazoles $E_{1/2}$ (V) values on media pH

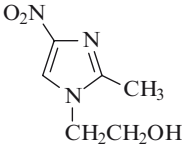
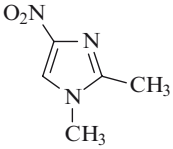
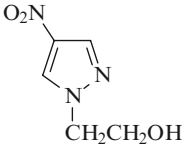
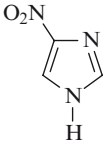
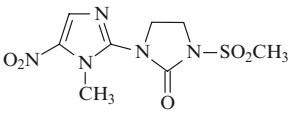
Compound	pH					0.1M NaOH
	1.83	3.20	6.06	7.04	9.30	
	–0.24	–0.33	–0.56	–0.63	–0.73	–0.92
	–0.21	–0.29	–0.53	–0.57	–0.69	–0.72
	–0.18	–0.25	–0.44	–0.56	–0.62	–0.83
	–0.17	–0.23	–0.42	–0.49	–0.61	–0.65
	–0.09	–0.15	–0.31	–0.39	–0.49	–0.51
	–0.21	–0.22	–0.25	–0.25	–0.25	–0.24

1-Alkyl-4-amino-5-nitroimidazoles and 1-alkyl-4-nitro-5-aminoimidazoles are reduced in a single six-electron wave [910]. The dehydration of the hydroxylamino derivative is favored, apparently due to an internal base catalysis. The shifts of half-wave potentials with pH differ principally from those of all other nitroimidazoles and indicate the predominant role of the amino group in the proton transfer [910]. The reduction of 1-nitropyrazole in acidic media leads to cleavage of the N-N bond and formation of nitrous acid, which is further reduced at more negative potentials [908].

Correlation dependences between half-wave potentials of nitroimidazoles and their pH values are found out (Table 3.42) [913, 914].

Satranidazole (1-methylsulfonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone) is reduced more easily at pH 7 and is more sensitive to pH than other nitroazoles (Table 3.42). Based on the comparison of the reduction potentials of satranidazole (at pH 7) with the potentials of 5-nitro- and 2-nitroimidazole derivatives and on the

Table 3.42 Half-wave electrochemical potentials of some nitroazoles and their dependence on pH (Ag/AgCl)

Compound	$E_{1/2}$ (pH 7.0) (V)	Equation
	−0.385	$E_{1/2} = -0.065\text{pH} + 0.07$
	−0.475	$E_{1/2} = -0.065\text{pH} + 0.02$
	−0.500	$E_{1/2} = -0.060\text{pH} + 0.08$
	−0.540	$E_{1/2} = -0.070\text{pH} + 0.05$
	−0.230	$E_{1/2} = -0.047\text{pH} + 0.100$

analysis of electronic stoichiometry of complete reduction of these compounds, the authors [914] have concluded this compound to be closer to 2-nitro derivative than to its 5-nitroisomere. However, it should be noted that there are no compounds with the electron-withdrawing substituents among the analyzed 5-nitroimidazole derivatives. This should decrease the E_{LUMO} energy and, consequently, move $E_{1/2}$ to the region of positive values.

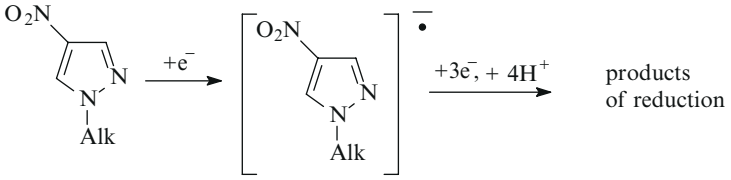
In polymerization reactions by methyl methacrylate [915] a relationship between the reduction potentials of 1-methyl-3-nitropyrazole, 1-methyl-5-nitropyrazole, and 1,2-dimethyl-5-nitropyrazole and their inhibited properties has been established.

The electrochemical reduction of 2-nitroimidazole in an aqueous mixed [916] and aprotic [917] medium has been carried out using cyclic voltammetry at a mercury electrode. The voltammetric behavior of 2-nitroimidazole in the aqueous mixed medium is substantially different from that in nonaqueous medium; in fact, only in the aqueous medium is it possible to study in isolation the nitro radical anion.

The electrochemical reduction of *C*- and *N*-nitroazoles has been investigated in detail in an aprotic media [850–853]. The reduction potentials of nitropyrazoles in acetonitrile are presented in Section 3.3 (Table 3.36). *N*-substituted 3(5)-nitro- and -4-nitropyrazoles in acetonitrile are reduced in two one-electron stages [850, 851].

The first and the second waves on the polarogram correspond to irreversible and reversible electron transfer, respectively. The addition of the first electron results in the generation of radical anions, which break up on the N-H-bond with elimination of atomic hydrogen and the formation of anions. At the second half-wave potential the nitroazole anions are reduced to the corresponding radical dianions registered by the ESR method [852–854].

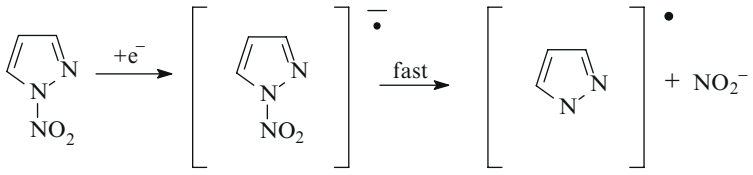
N-Alkylnitropyrazoles are also reduced in two stages: the first stage corresponds to reversible one-electron transfer (Scheme 3.35). In comparison with nitropyrazoles not substituted on nitrogen atom, the first half-wave potentials of *N*-alkylnitropyrazoles are essentially moved in cathodic region. Using the ESR method the signals of primary radical anions are recorded.



Scheme 3.35

The second wave corresponds to the irreversible process. It is identical to the second polarographic wave of nitrobenzene obtained in the same conditions [851].

The presence of N-NO_2 fragment in 1-nitropyrazole significantly facilitates the process of electrochemical reduction $E'_{1/2} = -0.95$, $E''_{1/2} = -1.73$ V (acetonitrile). The first wave corresponds to a one-electron irreversible transfer; the second wave is approximately 3.5 times higher and shows sharp drop prior to background discharge (Scheme 3.36). Analysis of the dependence of 1-nitropyrazole reduction potentials on pH shows that the second wave corresponds to the reduction of the NO_2 anion (nitrite ion) formed [851].



Scheme 3.36

ESR Signal of the intermediate radical anion was not observed [851].

The polarogram of 1,4-dinitropyrazole is considerably more complex and has five waves (Table 3.36, Section 3.3). This compound is reduced more easily than all the investigated nitroazoles. The first wave corresponds to an irreversible one-electron transfer (Scheme 3.19). As with 1-nitropyrazole, at this stage an unstable anion radical is formed and then breaks up at bond N–NO_2. The NO_2 anion is reduced at potential −1.7 V. 4-Nitropyrazolyl radical further is dimerized with subsequent reduction [851].

N-nitropyrazoles (1-nitro-, 1-nitro-3-methyl-, 1-nitro-5-methyl- and 1-nitro-3,5-dimethylpyrazoles), a new class of NO-generating activators of soluble guanylate cyclase, have been studied [918]. NO (nitrogen oxide) forms from nitrite ion as a result of chemical or electrochemical reduction. Correlation between spasmolytic activity of *N*-nitropyrazoles and their ability to activate guanylate cyclase indicates biological effect of the compounds is based on nitrogen oxide released during their biotransformation and subsequent guanylate cyclase activation [918].

Comparison of the reduction potentials of some nitroazoles including nitropyrazoles with their radiosensitizing properties has been carried out (Table 3.43) [919].

The sensitization threshold is at half-wave potential −0.50 V of a sensitizer; with displacement $E_{1/2}$ to more positive region the sensitizing properties of nitroazoles are nonlinearly growing (see Table 3.43) [919]. The best sensitizing properties are marked on nitroazoles, reduced in the potentials $E_{1/2}$ range from −0.2 to −0.35 V. A linear dependence has been found out between one-electron redox potentials of nitroimidazoles and – log 1/R37 values ($r = 0.96$, $n = 6$). Parameter R37 characterizes an activity of a drug (37% of DNA X174 population survival) [919].

Electrochemical (EC) oxidation of nitroazole anions in acetonitrile by a rotating platinum electrode has been investigated (Table 3.44) [920].

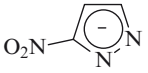
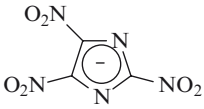
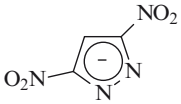
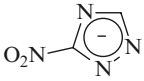
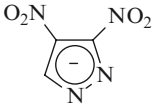
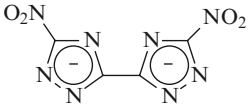
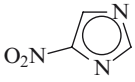
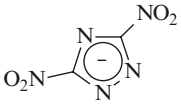
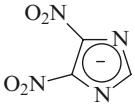
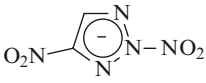
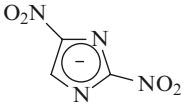
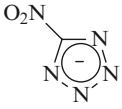
The EC oxidation first wave is diffusive and corresponds to one-electron transfer. An increase in the number of ring nitrogen atoms (the number of nitro group being the same) in a series of imidazole, pyrazole, triazole, tetrazole, as well as an increase in the number of nitro groups in the series nitroazole, di-, and trinitroazole essentially complicates the ability of nitroazole anions to electrochemical oxidation. [920]. In case of bicyclic C–C bound nitroazole dianions there is a dramatic decrease in $E_{1/2}$ that

Table 3.43 Reduction half-wave potentials of nitroazoles and their radiosensitizing abilities

Radiosensitizer	$E_{1/2}$ (V)	P[a]
1-(5-Nitro-2-thiazolyl)-2-imidazolidenon	−0.26	1.64
2-Brom-5-nitrothiazole	−0.30	1.60
2-Nitro-5-pyridinylthiadiazole	−0.20	1.52
5-Cyano-1,3-dimethyl-4-nitropyrazole	−0.45	1.47
5-Nitrothiazolyl-2-1-methylimidazolyl-2-sulfide	−0.40	1.37
1-(2-Nitro-1-imidazolyl)-3-methoxy-2-propanol	−0.30	1.18
4-Nitroisothiazole	−0.45	1.10
3-Nitrotriazole	−0.55	1.05
1-Nitropyrazole	−0.33	1.03
2-Nitroimidazole	−0.40	1.00
2-Amino-5-nitrothiazole	−0.50	1.00
2-Nitropyrazole	−0.53	1.00
2-Nitro-5-aminothiadiazole	−1.16	1.00
2-Methyl-5-nitroimidazole	−0.56	1.00
4-Nitroimidazole	−0.60	1.00
2-Piperidino-5-nitrothiazole	−0.50	0.94
2-Amino-4-methyl-5-nitrothiazole	−0.49	0.90

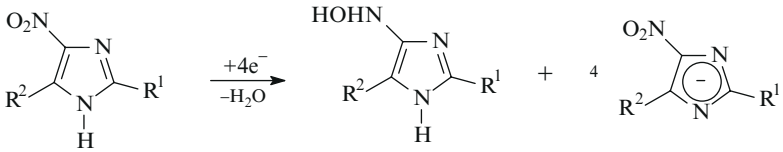
[a] Coefficient of radiosensitizing ability

Table 3.44 $E_{1/2}$ Values of electrooxidation of nitroazole anions (V)

Anion	$E_{1/2}$	Anion	$E_{1/2}$
	−1.17		1.94
	1.60		1.77
	1.85		0.90
	1.05		2.22
	1.26		1.86
	1.36		2.30

seems to be caused by an increase in stability of anion radical formed due to unpaired electron delocalization on two azolyl rings [920].

The mechanism of nitroimidazole EC reduction has been fairly well considered in the literature [921–926]. The way of *N*-substituted nitroimidazoles EC reduction at the first half-wave potentials is presented in Scheme 3.37:



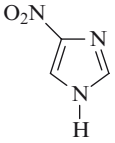
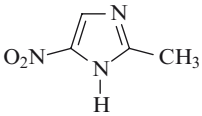
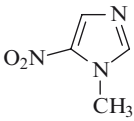
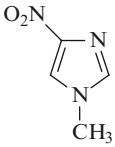
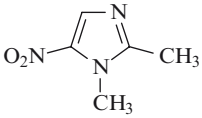
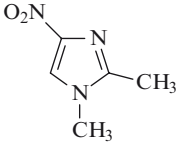
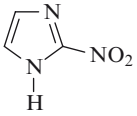
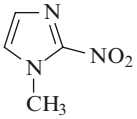
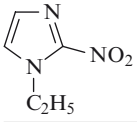
R^1, R^2 = Alk, Hal

Scheme 3.37

Irreversibility of the first wave is caused by decomposition of nitroimidazole primary radical anions owing to fast protonation of initial nitroimidazole (reactions such as "the father with the son") with the formation of anion and neutral radical. The last radical at same potential is quickly reduced to a hydroxylamine derivative. The process includes 4 electrons on 5 nitroimidazole molecules, i.e., only one-fifth of the

initial molecules are exposed to electrochemical reaction [921, 923]. Deprotonated molecules are reduced at potential of the second half-wave potential to form radical dianions detected by ESR spectroscopy (Table 3.45) [850, 852, 923].

Table 3.45 The reduction potentials of some nitroazoles

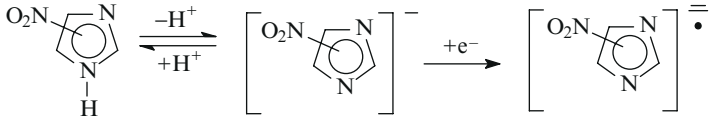
Compound	$E'_{1/2}$ (V)	$EC_{1/2}$ (V)	Refs
	1.14	1.97	[921][a]
	0.82	2.23	[852][b]
	1.18	2.00	[921]
	0.93	2.39	[852]
	1.14	2.05	[921]
	1.53	2.75	[852]
	1.36	2.23	[921]
	1.75	2.98	[852]
	1.18	2.13	[921]
	1.51	2.85	[852]
	1.39	2.23	[921]
	1.75	2.95	[852]
	0.71	2.37	[852]
	1.49	2.54	[852]
	1.45	2.54	[852]

[a]DMF, TEAP refer to calomel electrode
[b]Acetonitrile, TBAP refer to mercury bottom

Thus, *N*-substituted nitroimidazoles are reduced to form radical anions [852, 921, 924], the ESR signals of which are fixed [852].

On EC reduction, ionization of the N-H bond of nitroimidazole derivatives in buffer solutions (pH 7.0–7.4) occurs (Table 3.46) (Scheme 3.38) [919, 927–929].

The anions formed are reduced to radical dianions. As should be expected, N-H nitroimidazoles are more difficult to reduce than *N*-substituted ones (not exposed to ionization) (Table 3.46) [928].

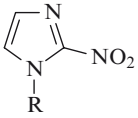
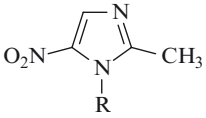


Scheme 3.38

2-Nitroimidazoles are reduced more easily than 4(5)-nitroimidazoles. The nitro group is located between two electronegative nitrogen atoms in ring (see ESR Section). At the same time, 1-substituted 2-nitroimidazoles are reduced with more difficulty than the corresponding 2-nitrobenzimidazoles. The presence of phenylene fragment in the latter increases the delocalization degree of electron density in the cycle and facilitates, thereby, the reduction processes [928].

Polarographic reduction of pH dependence of metronidazole [931], 2-nitroimidazoles, 4(5)-nitroimidazoles, 4-nitro- and 5-nitro-1-methylimidazoles [932–936] *N*-nitroimidazoles [937], and 1-aryl-4-nitroazoles [938] has been investigated. A smaller diffusive current for 2-nitroimidazoles in comparison with other isomers noted by the authors is thought to be possibly due to its increased acidity [932]. Electrochemical reduction of the nitro group in 1-aryl-4-nitroazoles occurs in

Table 3.46 The reduction potentials of some nitroimidazoles

Compound	R	$E'_{1/2}$ (V)	pH	Refs
	H	0.481	7.4	[928]
	$CH_2CONHCH_2OH$	0.413	–	[928]
	$CH_2CONHCH_2CH(OH)CH_2OH$	0.386	7.0	[928]
	$CH_2CH_2CH(OH)CH_2OH$	0.370	–	[928]
	$CH_2CH_2SOCH_3$	0.360	7.0	[928]
	$CH_2CON(CH_2CH_2OH)_2$	0.353	–	[928]
	$CH_2CH(OH)CH_2NHCH_2CH_3 \cdot HCl$	0.348	7.0	[928]
	$CH_2CH(OH)CH_2OCH_3$	0.337	7.0	[919]
		0.300	7.0	[929]
		0.395	7.2	
	H	0.550	7.4	[927]
	CH_2CH_2OH	0.465	7.0	[928]
		0.486	7.0	[930]

slightly acidic medium as an untypical four-electron process leading to hydroxylamine group formation [938].

The increased interest to study of one-electron reduction process of nitroimidazoles is caused, in particular, by their use as radiosensitizers [53, 395, 913, 919, 930, 939–947].

Analyses of the electrochemical data for 2-, 5-, and 4-nitroimidazoles show them to be the weakest oxidants with one-electron redox potentials (E_7^1) of only −0.517 V [940]. The potentials E_7^1 for 2-nitroimidazoles and 5-nitroimidazoles vary within a range from −0.243 to 0.423 and −0.457 to −0.486 V, respectively (Table 3.47) [940, 941]. A linear dependence of one-electron reduction potentials of substituted 2- and 5-nitroimidazoles on the sizes [S] is observed (Table 3.47) [940, 941].

This dependence may be useful in search of potential radiosensitizers.

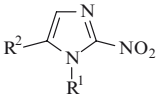
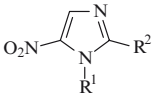
Determined with the help of pulse radiolysis, the thermodynamic potentials of one-electron reduction of 2-, 4-, and 5-nitroimidazoles (pH 7) have a higher negative values than those obtained by classical polarography (pH 7.4) [946]. Probably, it is generated by the fact that the process of electrochemical reduction involves irreversible stages of the decomposition of nitroimidazole anion radicals. The correlation of E_7^1 (and $E_{1/2}$) of nitroimidazoles and their radiosensitizing properties is discussed. With E_7^1 values the correlation is found to be better [946].

The electrocatalytic mechanism of the reduction of 2-nitro- and 4-nitroimidazole [948, 949] and 3-nitro-1,2,4-triazole [950] on gold (Au) potential deposition electrode proceeds through chemisorption of the nitro group and reductive cleavage of one of the two N–O bonds and gives diffusion-controlled limiting currents.

The electron affinity of 2- and 5-nitroimidazoles calculated by a semiempirical quantum-mechanical method satisfactorily correlates with experimental values of one-electron reduction potentials measured by pulse radiolysis [942].

Pulse radiolysis has been used to measure the bimolecular rate constants of the electron transfer reaction for substituted 2- and 5-nitroimidazoles of interest as antiprotozoal drugs and radiosensitizers [951]. The mechanism of inhibition of

Table 3.47 One-electron redox potentials and radiosensitizing properties of nitroimidazoles [941]

Compound	R^1	R^2	$-E^1{}_7{}^a$ (V)	$[S]_{1.6}{}^b$, mmol.dm^{-3}
	CH_3	CHO	0.243	0.02
	$CH_2CO_2CH_2CH_3$	CH_2CH_3	0.388	0.35
	$CH_2CH(OH)CH_2OH$	H	0.389	0.90
	$CH_2CH(OH)CH_2OCH_3$	H	0.389	0.30
	CH_2CH_2OH	H	0.398	0.30
	$CH_2CH_2OCOCH_3$	CH_3	0.420	1.0
	CH_2CH_2OH	CH_3	0.423	1.0
	CH_2CH_2OH	CH_3	0.479	1.0
	$CH_2CH(OH)CH_2OCH_3$	CH_3	0.486	1.0

[a] One-electron redox potentials at pH 7

[b] Sensitizer concentration at which the radiosensitization factor is 1.6

many nitroreductases by oxygen can be explained in terms of electron transfer to oxygen from the nitroazole radical anions identified as the first intermediate in some reductase systems.

One-electron redox potentials of 2-substituted 1-methyl-4-nitroimidazoles correlate with their antiparasitic activity (*Entamoeba histolytica*): the activity is increased with decreasing redox potentials [952].

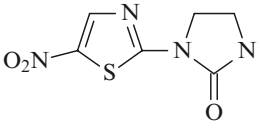
Misonidazole and its azo- and azoxy derivatives have been investigated in detail by polarography, cyclic voltammetry, and pulse radiolysis methods [947].

It is offered a polarographic method for the determination of the nitro group position in 4- and 5-nitroimidazole derivatives [953].

The microquantitative determination of some medicinal drugs such as metronidazole [927, 954–957], misonidazole [958], dimetridazole [959], and other nitroazoles [912] is carried out with the help of classical and differential pulse polarography.

The application of polarographic methods for the measurement of dissolution rate of medicinal drugs (ornidazole, isonidazole) in 0.1 N HCl is described [960]. Electrode kinetic parameters for metronidazole and azathioprine (immunosuppressor) – 6-(1-methyl-4-nitroimidazolyl-5)-mercaptopurine have been determined [961]. A comparison of reduction potentials of nitroimidazoles with their cytotoxicity, [962–965], mutagenity [966], and antimicrobial activity properties [967, 968] has been carried out. The polarographic behavior of metronidazole at mercury [969, 970], Pt [971], glassy carbon [970] electrodes and also in the presence of DNA bases [970, 972–976] has been studied. All electrodes showed a similar trend in the reduction mechanism for metronidazole, dependent on pH in the acid and neutral media and independent in alkaline media [970]. Electrochemical parameters of 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole (tinidazole) [977] and rhodium-nitroimidazoles complexes [978] have been determined. The processes of polarographic and cyclic voltammetric behavior [979–981] and enzymatic reduction [982] of megazole [1-methyl-2-(5-amino-1,3,4,-thiadiazole)-5-nitroimidazole] and related nitroimidazoles have been studied.

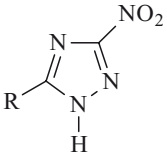
Polarography investigations of nitrothiazoles are carried out in some works [535, 929, 931, 983, 984]. The investigation of fourteen 2-R-5-nitrothiazoles it is shown that the compounds of greater toxicity have higher negative reduction potential values [535]. The polarographic characteristics of 2-acetamido-5-nitrothiazole [931, 983] and niridazole (ambilhar) [929] have been obtained.



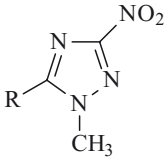
ambilhar

The dependence of the $E_{1/2}$ values of 4-nitroisoxazole of media pH has been described [985, 986].

The mechanism of electrochemical reduction of 3(5)-nitro-1,2,4-triazoles in acetonitrile has been investigated [850, 853]:



R = $N(CH_3)_2$, NH_2, C_2H_5, CH_3, H, C_6H_5, Br, $COCH_3$, $COOCH_3$, NO_2



R = NH_2, H, NO_2

Principally, two waves are observed on polarograms of these compounds. The reduction mechanism of nitrotriazoles is similar to that of the described earlier for nitropyrazoles and nitroimidazoles. The bimolecular process of interaction of nitroazole primary anion radicals not substituted in nitrogen atoms accompanying molecular hydrogen elimination, apparently, is most probable and for nitrobenzimidazoles and is proved by a method of a rotating disk electrode with a ring [888]. The presence of electron-withdrawing substituents in the investigated series of compounds essentially facilitates ECHR process [853].

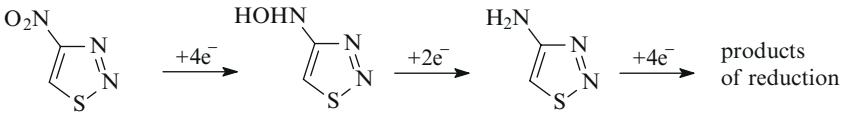
EC reduction of complexes of 3-nitro-1,2,4-triazoles with Ni (II), Zn (II), and Cd (II) is investigated in the buffer Britton-Robinson (pH 1.7–9.5) and in DMF [987]:

pH	1.7	2.5	3.5	4.5	5.5	6.5	7.5	8.5	9.5
$-E_{1/2}$	0.45	0.48	0.51	0.53	0.55	0.62	0.70	0.75	0.77

The results allowed a conclusion on the possibility of separate determination of metals and nitrotriazoles from the solution [987]. The influence of nitrated 1,2,4-triazoles on corrosion and electrochemical behavior of low-carbon steels in aqueous solution of sodium sulfate has been investigated [988]. The strong passivating action of nitrotriazoles on steel is caused by the formation of stable chemosorbed metal-azole films.

One-electron reduction potentials have been measured for regioisomer derivatives of 3-nitro-1,2,4-triazoles for the development of new radiosensitizers of hypoxic cancer cells for radiotherapy [989].

The route of polarographic reduction of 4-nitro-1,2,3-thiadiazole is presented in Scheme 3.39 [990].

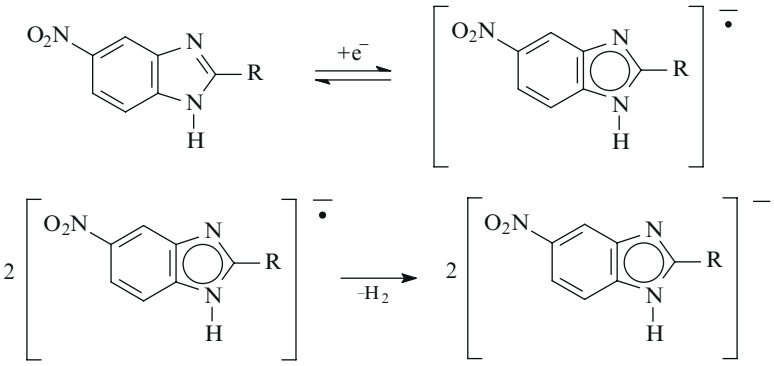


Scheme 3.39

The electron affinity of 3-(*N*-methylpiperazino)-5-nitroindazole, 3,5-dinitroindazole, and molecular complex of the last with water is discussed on the basis of their half-wave potentials and in connection with their eventual radiosensitizing properties [667].

The mechanism of EC behavior of 2-substituted 5(6)-nitrobenzimidazoles in acetonitrile has been investigated by classical polarography, cyclic voltammetry, and platinum rotating disk electrode with a ring (RDER) [888, 991]. It is shown that

at the first stage of reduction the formed radical anions break up on the bimolecular mechanism with excretion of molecular hydrogen (Scheme 3.40) [888]:



Scheme 3.40

The half-wave potentials ($-E'_{1/2}$ and $-E''_{1/2}$) are given in Table 3.48. The $E'_{1/2}$ values are changed in the region –0.75 to –1.24 V, whereas the $E''_{1/2}$ values – in the region –1.30 to –1.64 V [991].

The results of two parameter correlations $\Delta E'_{1/2}$ and $\Delta E''_{1/2}$ ($\Delta E_{1/2} = E_{1/2}^{X} - E_{1/2}^{H}$) with constants of the substituents $\sigma_I\sigma_R$, $\sigma_I\sigma_R^{o}$, *FR* and $\sigma_I\sigma_R^{+}$ (Table 3.49) show that the substituent influence on the first half-wave potential follows both induction and resonance mechanisms, the ratio of contributions of these effects being approximately equal and, practically, independent of a choice of the substituent parameters. The correlation results between $\Delta E''_{1/2}$ and substituent parameters indicate that the substituent influence is mainly achieved by the resonance mechanism (approximately 80%) (Table 3.49) [991].

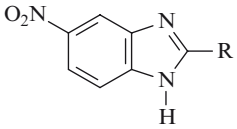


Table 3.48 Electrochemical reduction data of 2-substituted 5(6)-nitrobenzimidazoles in acetonitrile

R	$-E'_{1/2}$ (V)	$-E''_{1/2}$ (V)
$N(CH_3)_2$	1.24	1.64
NH_2	1.24	1.62
OCH_3	1.16	1.62
OC_2H_5	1.17	1.65
CH_3	1.14	1.47
H	1.13	1.47
Cl	0.95	1.43
$COOCH_3$	0.91	1.34
$COCH_3$	0.92	1.32
CF_3	0.88	1.33
CN	0.75	1.30

Table 3.49 Parameters of correlation equation $\Delta E_{1/2} = ax + by = d$.

$\Delta E_{1/2}$	xy	a	b	d	r	s	n	b, %[a]
$\Delta E'_{1/2}$	$\sigma_I\sigma_R$	0.49±0.06	0.26±0.03	0.03±0.01	0.984	0.03	11	54±4
	$\sigma_I\sigma_R^o$	0.49±0.05	0.38±0.03	0.02±0.01	0.990	0.02	11	55±3
	FR	0.29±0.06	0.25±0.05	0.03±0.01	0.964	0.04	11	54±7
	$\sigma_I\sigma_R^+$	0.48±0.09	0.14±0.02	0.03±0.00	0.966	0.04	11	53±6
$\Delta E''_{1/2}$	$\sigma_I\sigma_R$	0.15±0.07	0.31±0.03	0.04±0.00	0.968	0.03	11	82±7
	$\sigma_I\sigma_R^o$	0.16±0.05	0.45±0.04	0.03±0.00	0.981	0.03	11	82±5
	FR	0.16±0.07	0.31±0.05	0.04±0.00	0.941	0.05	11	87±13
	$\sigma_I\sigma_R^+$	0.15±0.10	0.16±0.03	0.04±0.01	0.931	0.05	11	81±11

[a]b is the contribution of resonance effect

Indeed the substituent effects in anions of 2-substituted benzimidazoles transmit mainly by resonance mechanism [691]. Probably, this is connected with the fact that the polarization of π-electrons in benzimidazole anion is higher than in the neutral molecule.

Correlations in view of the third parameter $\sigma^\bullet$ (the radical stabilizing factor), describing stabilization of the radical state, do not allow reliably to discuss about the contributions to common substituent effect as the dependence between resonance and $\sigma^\bullet$ parameters is found out ($r_{23} = 0.7$) [991].

The excellent correlation between $E'_{1/2}$ of 2-substitued 5(6)-nitrobenzimidazoles and their E_{LUMO} (INDO approximation) [884] points out to a linear dependence between these sizes (3.6) [991]:

$$-E'_{1/2} = (-0.62 \pm 0.04)E_{HBMO} + 0.06 \quad (3.6)$$

$$r = 0.987,\ s = 0.02,\ n = 7$$

$$R = NH_2,\ OCH_3,\ CH_3,\ H,\ Cl,\ COCH_3,\ CN$$

The electrochemical behavior itself 5(6)-nitrobenzimidazole is investigated depending on media pH by classical polarography [992–994], constantly current, and variable current [995, 996]. The reduction 5(6)-nitro-2-arylbenzimidazoles is carried out in DMF and H_2O/DMF media [997]. The polarography was utilized in a study of the influence of 5(6)-nitrobenzimidazole on corrosion-electrochemical behavior of chromos steel [998].

The oxidation potentials of 2-mercapto-6-nitrobenzothiazoles were measured in regard to their abilities to function as coinitiators in free-radical photopolymerizations induced by camphorquinone and isopropylthioxanthone [999].

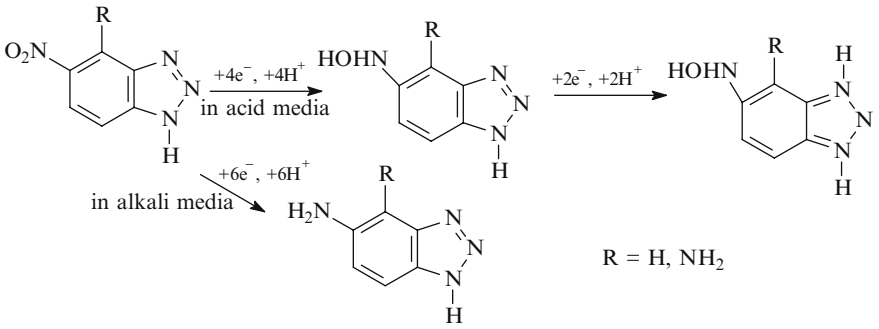
The oscillographic polarography data of 4-nitro- and 6-nitro-2-aminobenzothiazole (in aqueous-alcoholic solutions) are reported [1000]. The electrochemical behavior of dyes is investigated into which 5-nitrobenzothiazole or 5-nitrobenzoselenadiazole is added [1001]. The authors of this work have utilized a RDER, glass-graphite, and mercury-dropping electrode. The oxidation potentials of 2-alkylsubstituted 6-nitrobenzimidazoles are determined using Pt electrode [1002].

Polarographic behavior 4(7)-nitrobenzotriazole [1003], 5(6)-nitrobenzotriazole [1003, 1004], and 5(6)-nitro-4(7)-aminobenzotriazole [1004] has been studied at

various media pH. The last two compounds in acid media have one irreversible reduction wave [1004]. With increase in media pH (5.0–9.2) on polarogram there are two waves, which are shifted to a more negative potential range. This fact indicates dependence $E_{1/2}$ of the compounds from media pH:

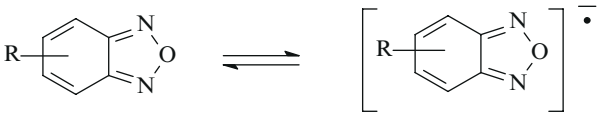
$E_{1/2}$=0.41 - 0.07 pH $E_{1/2}$=0.29 - 0.10 pH
$E_{1/2}$=0.21 - 0.14 pH $E_{1/2}$=0.47 - 0.10 pH

The reduction mechanism of these benzotriazoles can be submitted as follows (Scheme 3.41) [1004]:



Scheme 3.41

Benzofurazans, except for nitrated ones, at reduction on a dropping mercury electrode (in acetonitrile or DMF) on polarogram, have the one-electron wave, which corresponds to reduction of furazan cycle (Scheme 3.42) [1005]:

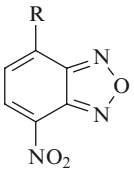
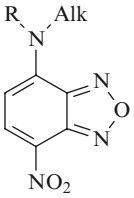
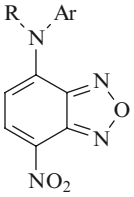


R = H, 4-CH_3, 4-Cl, 4-OCH_3, 5-CH_3, 5-Cl, 5-OCH_3, 5,6-$(CH_3)_2$

Scheme 3.42

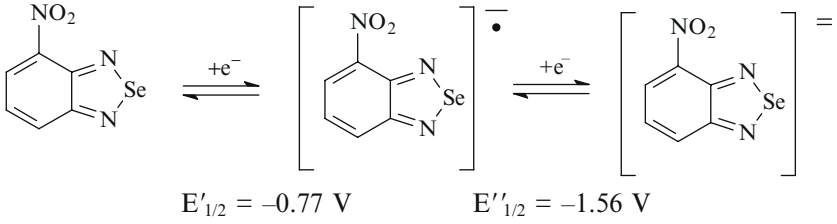
4-Nitro- and 5-nitrobenzofurazan have two resolute peaks registered by a cyclic voltammetry [1005], apparently, concerning reduction: of two competitive centers, nitro group and furazan fragment. What is amazing is that the authors managed to record ESR spectra of radical anions of all investigated compounds, except for those nitrated [1005]. The electrochemical behavior of 4-substituted 7-nitrobenzofurazans depending on media pH has been investigated [1006, 1007]. The half-wave potentials of these compounds well correlate with substituent constants (Table 3.50):

Table 3.50 Correlation of the half-wave potentials of nitrobenzofurazans with substituent constants (σ_p and σ^*)

	$\sigma_p = -0.00417\ (-E_{1/2}) + 0.64056$ R = 0.98, s = 0.32, n = 7	1006
	$\Sigma\sigma^* = -0.0242\ (-E_{1/2}) + 8.348$ R = 0.98, s = 0.30, n = 14	1007
	$\Sigma\sigma^* = -0.00417\ (-E_{1/2}) + 0.64056$ R = 0.97, s = 0.28, n = 10	1007

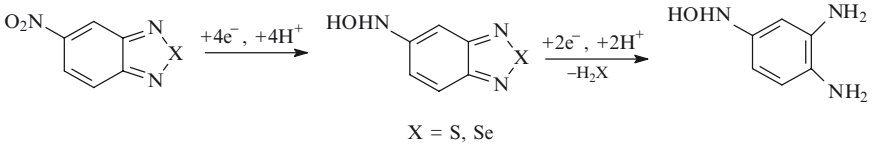
Relationship $E_{1/2}$ and transfer band of a charge in UV spectra of these compounds in detail will be reported in Section on UV Spectroscopy [1007].

5-Nitro-2,1,3-benzothiadiazole and 4-nitro-2,1,3-benzoselenadiazole in DMF are reduced into half by the one-electron and reversible waves (Scheme 3.43) [1008, 1009].



Scheme 3.43

The same compounds in aqueous solutions (pH 0.6–11.8) are reduced in the following way (Scheme 3.44) [1010]:



Scheme 3.44

Previously the electron transfer reactions attracted more attention of researchers [1011, 1012]. Electrochemical data mainly in common with ESR spectroscopy data are the important source of the information about the reaction mechanism and also about structure, reactivity, properties of intermediate free radicals of different classes of organic, organometallic, and inorganic reactions. Elucidation of the mechanism and problems of reactivity in the chemistry of one-electron transfer can be of main significance in such fields as synthesis and catalysis, radical chemistry, photochemical synthesis, biochemistry of in vivo organism.

Infrared Spectroscopy

In the infrared spectra (IR) of nitroazoles characteristic bands correspond to asymmetric (ν_{as}) and symmetric (ν_s) stretching vibrations of the nitro group. It is known that the position of ν_{as} band is more subject to the substituent influence in comparison with the position of ν_s band of the complicated form. This appears to be related to some vibrations of the cycle. Thus, variation of the substituents is reflected in vibrations of the heterocycle, which, in turn, results in shifting the nitro group ν_s frequency, even in cases when there are no changes of force constants or electron distribution in the NO_2 group. Therefore, the frequencies vary rather randomly.

Nitropyrazoles

Asymmetric vibrations of the *C*-nitro group in nitropyrazoles are observed in the 1490–1560 cm^{-1} region and symmetric ones – in the 1315–1355 cm^{-1} region [245, 295, 301, 302, 686, 1013–1021]. Similar vibrations of the *N*-nitro group are in a narrower range of frequencies, ν_{as} – 1610–1650 cm^{-1}, ν_s – 1270–1294 cm^{-1} [686, 1013, 1019]. The results of analysis of the experimental and calculated vibration spectra of pyrazole, 3-nitropyrazole, and 1-nitropyrazole show that a change of the nitro group position in the cycle renders influence on both the electron structure of the pyrazole ring and the character of interaction of the electron-withdrawing substituent with the heterocycle [1019]. The potential energy constants rather correlate well with the appropriate bond order values (Table 3.51).

Table 3.51 Force constants of pyrazole ring bonds

Coordinate of molecule	Bond order of pyrazole	$K_i \cdot 10^6$, cm^{-2}		
		Pyrazole	1-Nitropyrazole	3-Nitropyrazole
Q1	0.441	11.0	12.5	11.6
Q2	0.770	12.5	11.0	12.0
Q2	0.581	11.5	10.5	11.4
Q3	0.765	12.3	11.5	12.5
Q4	0.396	10.5	10.0	11.3

Introduction of the nitro group into the ring changes all bond force constants of the cycle. Some alignment of bond force constants of the cycle in 3-nitropyrazole in comparison with pyrazole testifies to leveling of their bond orders that results in an increase of the pyrazole ring aromaticity. In 1-nitropyrazole the nitro group promotes division of the ring chemical bonds in double and single ones to a greater degree than in pyrazole. The aromaticity of 1-nitropyrazole is likely to be reduced. The presence of electron-withdrawing NO_2-group in the pyrazole ring displaces fundamental stretching bands of the cycle (Table 3.52) [1019].

The microwave spectra and *ab initio* calculations (MP2/6-31G**) of 1-nitropyrazole indicate the planar structure of the molecule [1022]. The initial assignment of the spectrum was carried out using a radio frequency-microwave double resonance technique.

The NH-bond stretching vibrations in the spectra of pyrazole and 3-nitropyrazole have absorption maxima at 2980 and 2970 cm^{-1} [1021].

Two-centered H-complexes, 3,5-dimethyl-4-nitropyrazole, *N*-methyltrifluoromethanesulfonamide, etc. with protophilic solvents have been studied using NH-bond stretching vibrations in IR spectra (Table 3.53) [1023]:

In protophilic media, amides exist as monomeric H-complexes with a two-centered H-bond and 1:2 H-complexes of the open-chair dimer with a bifurcated (three-centered) hydrogen bond. The formation of a strong bifurcated H-bond weakens the bridging N–H…O=S bond.

As already mentioned, the frequency of NO_2 asymmetric absorption band depends on the nature of substituent, the electron-withdrawing substituents moving it, as a rule, to a higher frequency region, as in both *N*-nitro- [686, 1013], and *C*-nitropyrazoles [279, 301, 302, 1024–1027].

The IR spectra of 4-nitropyrazoles used as ligands are presented in [1016]. Kinetics of the heterocyclization of nitroazidopyrazoles into nitropyrazolo[1,5-d]-tetrazoles has been studied using ν_{as} of azido group (2120 cm^{-1}) [1028]. The vibration spectra of aminonitropyrazoles [1014], the nitration and halogenation products of pyrazoles [1029], 1-alkyl-3-methyl-4-nitro-5-pyrazolecarbonylclorides [310], 1,3-dialkyl-4-nitroisomeric arylazo-1-methylnitropyrazoles [318], *N*-phenyl-substituted

Table 3.52 Stretching vibration bands of the pyrazole cycle.

Compound	Frequencies, cm^{-1}				
Pyrazole	1550	1530	1460	1390	1355
1-Nitropyrazole	1525	1402	1320	1290	1262
3-Nitropyrazole	1508	1480	1430	1420	1375

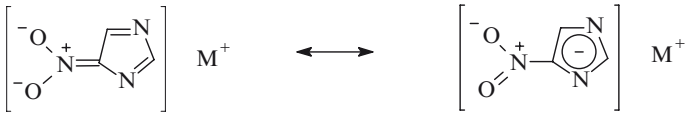
Table 3.53 NH-stretching vibration bands of 3,5-dimethyl-4-nitropyrazole H-complexes with protophilic solvents.

Protophilic solvent (H-acceptor)	ν_{NH}, cm^{-1}
Phenetole ($C_6H_5OC_2H_5$)	3305
Anisole	3300
Dioxane	3240
1,2-Dimethoxyethane	3233
Tetrahydrofuran	3180

3-methyl-4-nitropyrazole-5-carboxyhydrazides [1030], nitroazoloanhydrosaccharides [295], and some other nitropyrazole derivatives are reported [308].

Nitroimidazoles

Similarly, in nitropyrazoles the *C*-nitro group ν_{as} and ν_{s} stretching frequencies are found in a range of 1510–1586 and 1320–1408 cm^{-1} [73, 297, 328, 362–364, 428, 465, 1031–1041], whereas the absorption maxima of nitroimidazole anions are displaced to the low-frequency region – 1120–1200 and 1108–950 cm^{-1}, respectively [1033]. The authors [1033] have established that the nitroimidazole sodium and potassium salts have a structure, with the negative charge mainly located on the nitro group (Scheme 3.45):



Scheme 3.45

Another evidence for the benefit of this structure is provided by the displacement of NO_2-group absorption maxima of ν_{as} and ν_{s} stretching frequencies to a lower frequency region compared to the neutral molecule (Table 3.54) [1033].

As seen from Table 3.54, the spectra of polynitroimidazole salts show bands of two types that can indicate the negative charge localization on only one of the groups [1033].

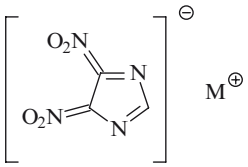


Table 3.54 Stretching vibration bands of the nitro group of nitroimidazoles

	Neutral molecule		Anion	
Compound	ν_{as}, cm^{-1}	ν_{s}, cm^{-1}	ν_{as}, cm^{-1}	ν_{s}, cm^{-1}
4(5)-Nitroimidazole	1561	1344	–	–
4(5)-Nitroimidazole, Na-salt	–	–	1173, 1160	950
2-Nitroimidazole	1540, 1518	1362	–	–
2-Nitroimidazole, Na-salt	–	–	1197	1062
4,5-Dinitroimidazole	1548, 1532	1358, 1326	–	–
4,5-Dinitroimidazole K-salt	–	–	1187, 1528	960, 1366
2-Methyl-4,5-dinitroimidazole	1554, 1523	1334	–	–
2-Methyl-4,5-dinitroimidazole K-salt	–	–	1197	1108

In the vibration spectra of *N*-nitroimidazoles and *N*-nitropyrazoles the maxima of nitro group absorption are observed in higher frequency region in comparison with those of *C*-nitroisomers, i.e., ν_{as} – 1635–1647 and ν_s – 1286–1332 cm^{-1} [2, 1033].

The complex formation process of metronidazole with polyvinylpyrrolidone (PVP) or poly(acrylic acid) (PAA) has been studied by IR spectroscopy [1038–1041]. These complexes possess antibacterial properties. The absorption bands at 3100 and 3210 cm^{-1}, typical of the initial compound, disappeared from the IR spectra of the complexes, as well as from the spectrum of a solution of metronidazole in dioxane (film); in the latter case, the band 3430 cm^{-1} corresponding to vibrations of free OH groups retained in the spectrum. The complex metronidazole-PAA showed a broad absorption band 3405 cm^{-1} due to stretching vibrations of the acid OH groups involved in hydrogen bonding. The IR data suggest that metronidazole molecules exist as open-chain structures like -N…$HO(CH_2)_2N$ – (an absorption band at 3430 cm^{-1} was present together with on bands at 3100 and 3220 cm^{-1}). However, the formation of dimers cannot be ruled out. Unsubstituted imidazoles are known to undergo association to give linear polymeric structures, but no such associates are formed when the hydrogen atom on the "pyrrole" nitrogen atom is replaced by an alkyl or aryl group. It turned out that introduction of a hydroxyethyl group into the 1 position favors hydrogen bonding [1038, 1041].

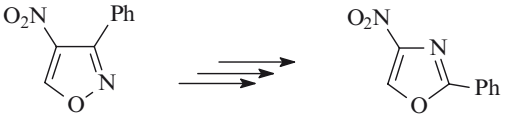
IR spectra, total energy, Gibbs free energy, and the highest π and σ electronic states calculated for tautomers of 5-substituted imidazoles by *ab initio* (MP2, RHT/6-311++G**) show that such substituents as NO_2, NH_2, CN, etc. stabilize the N3-H tautomer more [1042]. Therefore the conclusions derived from these data are related to molecules in the gas state and cannot be extended to the imidazoles in the solvated state.

Infrared spectroscopy is widely used for the structural determination of tautomers, isomers conformers of various nitroimidazoles [42, 1043]. Vibration spectra of different 1-alkyl [362]-, 1-(trialkylsilylalkyl)-2-methyl-4-nitroimidazoles [363], allylated 4-nitroimidazoles [364], dinitroimidazoles [428] have been studied. The vibration frequencies of some medicinal compounds on the base nitroimidazoles, for example, diasteriomeric *nido*-carboranyl misonidazole congeners [389], antiviral agents [452], and adrenergic-receptor agonists [454] are analyzed. In the literature the number of publications devoted to vibration spectra is rather limited and, as a rule, the absorption band frequencies of nitroimidazoles are considered in synthetic works concerned with structure identification such as, for example, [354, 429, 461–464, 468–471, 1044–1047].

Nitroisoxazoles, Nitrooxazoles, and Nitrooxadiazoles

Stretching bands corresponding to the nitro group in nitroisoxazole and nitrooxazole derivatives are observed in the 1520–1570 (ν_{as}) and 1360–1380 cm^{-1} (ν_s) regions [501, 502, 1048–1050].

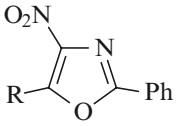
4-Nitro-2-phenyloxazole was isolated (29%) as a result of temperature transformation (155°C) of corresponding nitroisoxazole in xylene with a trace amount of same acid and confirmed by IR spectroscopy (Scheme 3.46) [501, 502]:



Scheme 3.46

IR (KBr): 3163 (Ph), 1608 (C=C), 1561 (C=N), 1530, 1377 (NO_2) cm^{-1}

IR NO_2 stretching vibrations of 5-substituted 4-nitro-2-phenyloxazoles are in the region [502]:



R = H, CO_2Me, COPh

1530–1570 ν_{as}, 1360–1380 ν_a cm^{-1}

The nature of substituents in aryl fragments of 3,5-diaryl-4-nitroisoxazole practically does not influence either the nitro group ν_{as} or the band frequencies of the isoxazole ring itself (Table 3.55) [486, 1048, 1049].

The characteristic frequency of asymmetric stretching vibrations of methyl groups (2900–3000 cm^{-1}) is widely applied in the studies of organic compounds, for

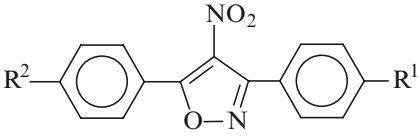


Table 3.55 Absorption bands in the IR spectra of 4-nitroisoxazoles (cm^{-1}) .

R^1	R^2	$\nu_{as}(NO_2)$	$\nu_s(NO_2)$	$\nu(C\equiv N)$	$\nu(C=C)$	Other bands
H	H	1517 1520	1362	1612	1574–1583	1182, 1153, 1020, 940, 876
OCH_3	H	1515	1360	1612	1572–1585	1174, 1156, 1028, 942, 882
CH_3	H	1515	1365	1600	1565–1574	1182, 1146, 1018, 938, 898
Cl	H	1535 1540	1365	1615	1585–1590	1184, 1156, 1020, 943, 876
OC_2H_5	H	1512	1360	1610	1570–1580	1172, 1155, 1034, 940, 895
H	CH_3	1520	1360	1615	1565–1575	1185, 1150, 1020, 940, 885
H	OCH_3	1518	1358	1608	1575–1590	1174, 1150, 1024, 940, 880
H	Cl	1530	1366	1615	1565–1574	1184, 1168, 1012, 942, 875

example, for the determination of the number of CH_3-groups. The examination of methyl group reactivity in 4-nitro-3,5-dimethylisoxazole indicates that the methyl group in position 5 is highly reactive in condensation reactions compared to analogous compounds. The introduction of nitro group into position 4 results in increasing the ν_{as} (CH_3) frequency up to 20 cm^{-1}. A shift of this kind as well as chemical behavior of the aforementioned compound can be explained by C-H bond polarization in the methyl group in position 5, arising under action of the adjacent electron-withdrawing substituents. The analysis of integrated intensity $(A_{CH}{}^s)^{1/2}$ of the ν_{as} (CH_3) band in the IR spectra of some investigated azoles, including nitrated ones (Table 3.56), shows that the influence of several substituents and heteroatoms is subject to the principle of additivity (3.7) [1051]:

$$\left(A_{CH}^{S}\right)^{1/2} = 4.8 + 0.8\sum\left(A_{CH}^{S}\right)^{1/2} \qquad R = 0.946, \quad n = 18 \tag{3.7}$$

The dependence between the $(A_{CH}{}^s)^{1/2}$ band and calculated charges on the ethyl group atoms shows that the dominant role in the intensity change of C–H stretching bands belongs to electronic effects [1051].

Vibration spectra characteristics of 3-nitroisoxazoline *N*-oxides and other nitroisoxazole derivatives are reported [499, 1052, 1053].

When going to nitrofurazans and nitrofuroxans, the $\nu_{as}(NO_2)$ frequency is reduced by approximately 20 cm^{-1} (Table 3.57) [136, 137, 506, 508, 511, 518].

Nitroisothiazoles and Nitrothiazoles

Vibration spectra of several isothiazoles have been reported [1054]. IR NO_2 absorption bands of nitrothiazole derivatives have been analyzed (Table 3.58) [534, 535,

Table 3.56 The intensities of symmetric vibration bands of C–H–methyl group in some nitroazoles ($\nu_{CH} = 2935 \pm 10$ cm^{-1})

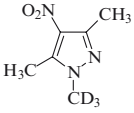
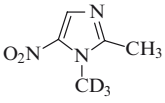
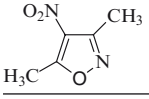
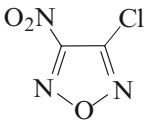
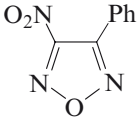
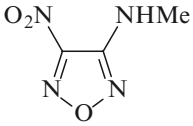
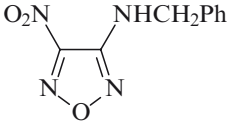
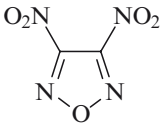
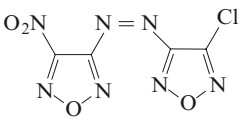
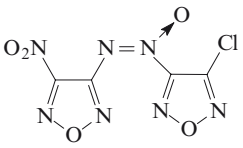
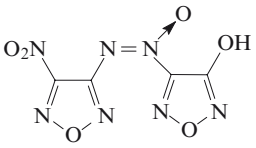
Compound	$A_{CH}{}^s$		$\Delta q(CH_3)$, a.u.
	Experimental	Calculated	
	18.9	18.4	0.0616
	17.0	17.1	0.0236
	11.6	7.9	0.0580

Table 3.57 IR Absorption bands of nitrofurazans and nitrofuroxans (cm^{-1})

Compound	$\nu_{as}(NO_2)$	$\nu_s(NO_2)$	Ring bands and others	Refs
	1570	1330	1610, 1180, 860	[511]
	1580	1355	1465, 1230, 1020	[520]
	1530	1355	1615, 1530, 1480, 1375, 1315, 1242, 1210, 1035, 1004	[136]
	1520	1360	3384, 2904, 2872, 1616, 1456, 1440, 1400, 1304, 1200, 1064, 1048	[136]
	1557	1360	1591, 1460, 1145, 1040, 849, 812	[506]
	1540	1360	-	[511]
	1550	1350	1580, 1170, 1105, 915, 870	[511]
	1580	1345	1495, 1425, 1245, 1180, 1120, 1090, 1020	[508]

1055, 1056]. The range of changing ν_{as} and ν_s NO_2 in nitrothiazoles is the same as for other nitroazoles.

The structure of some medicines containing nitrated 1,3,4-thiazole fragments was confirmed by IR spectroscopy [1057, 1058].

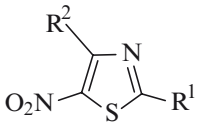


Table 3.58 Stretching vibration bands of 5-nitrothiazole derivatives (cm^{-1}) .

		Nitro group		
R^1	R^2	ν_{as}	ν_s	N(C=O)
CH_3CONH	CHO	1500	1310	1675, 1698
CH_3CONH	$CH{=}NNHC_6H_5$	1510	1290	1632
CH_3CONH	$CH{=}NC_6H_5$	1540	1330	1700
Br	$CH_2COPh/CH{=}C(OH)Ph$[a]	1612	1323	1681
		1518	1277	(3443 OH)
$NHNO_2$	CH_2Cl	1540	1350	–
$NHCOCH_3$	CH_2Cl	1540	1330	–
$NHCOCH_3$	CHO	1540	1310	1698
				1710
$NHCOCH_3$	$CH{=}NO{-}C_6H_4{-}C(CH_3)_2$	1540	1320	–

[a]Keto-enol mixture

Nitrotriazoles

Structure and ratio of *N*-1- and *N*-2-alkyl isomers of 4-nitro-1,2,3-triazole obtained by alkylation reaction in various solvents have been investigated by IR spectroscopy [620]. The structure of 4-aryl-5-nitro-1,2,3-triazoles [1610–1615 (double bonds), 1510–1530 and 1374–1380 (NO_2), 990–1022 (triazole ring) cm^{-1}] [553], 1-aryl(heteryl)- and 2-aryl(heteryl)-4-nitro-1,2,3-triazoles [141, 177, 602–604] have been confirmed by infrared spectra.

The vibration spectra of nitrated 1,2,4-triazoles were investigated most widely and completely [554–556, 566–573, 580, 581, 585, 1057, 1059–1070]. The nitro group vibrations are in a range of about 1550–1580 cm^{-1} (ν_{as}) and 1300–1360 cm^{-1} (ν_s) (Table 3.59 and 3.60). For more reliable interpretation of the IR and Raman spectra of 1-methyl- and 3-nitro-1,2,4-triazole calculations of frequencies and normal vibration forms have been carried out [1060, 1061]. On introduction of the nitro group into position 3 a change of the potential energy constants of valence and angular coordinates of the cycle is observed. In this case the force constants of N–N and C–N bonds are increased, and this should lead to an enhancement of their double-bonding degree [1061]. The NO_2-group vibrations with the most characteristic frequency are located in rather narrow spectral intervals: asymmetric – ~1555, symmetric – 1302–1315, nonplanar – 680–700, and deformational – ~645 cm^{-1}. Deformational stretching vibrations of the ring C–N bond are displayed in a range of 1385 and 1420 cm^{-1}, whereas the exocyclic ones of C–N bond are in the 1400–1480 cm^{-1} region [1060, 1061]. The band at ~1275 cm^{-1} is assigned by the authors to the triazole ring N–N bond vibrations and considered to be characteristic to some extent [1061].

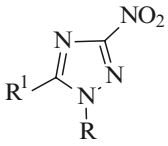


Table 3.59 Vibration frequencies of the nitro group of 3-nitro-1,2,4-triazole derivatives (cm^{-1})

R	R^1	ν_{as}	ν_s	Refs
H	H	1570	1320	[1057]
H	CH_3	1545	1310	[554, 1057]
H	C_6H_5	1560	1310	[1057]
H	NO_2	1560	1310	[1057]
CH_3	H	1545	1310	[554, 1057]
C_2H_5	H	1550	1305	[554]
C_2H_5[a]	H	*1562*	*1325*	[555]
C_3H_7	H	1550	1305	[554]
i-C_2H_5	H	1555	1305	[554]
CH_3	CH_3	1540	1312	[554]
CH_3[b]	CH_3	*1560*	*1330*	[580]
CH_3[c]	I	*1575*	*1320*	[580]
CH_3	N_3	1560–1530	1315	[1063]
CH_3	NH_2	1510	1320	[1067]
CH_3	NHCH=CH_2	1533	1313	[1067]
CH_3	4-$NO_2C_6H_4$	1560, 1525	1360, 1315	[1067]
CH_2COCH_3	H	1580	1315	[568]

[a]1,4-diethyl-3-nitro-1,2,4-triazolium perchlorate, 1080 cm^{-1} (ClO_4)
[b]1,4,5-trimethyl-3-nitro-1,2,4-triazolium iodide
[c]1,4-dimethyl-5-iodo-3-nitro-1,2,4-triazolium iodide

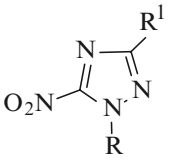


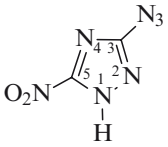
Table 3.60 Vibration frequencies of the nitro group of 5-nitro-1,2,4-triazole derivatives (cm^{-1})

R	R^1	ν_{as}	ν_s	Refs
CH_3	H	1556	1338	[554]
		1555	1320	[1057]
C_2H_5	H	1558	1336	[554, 555]
C_3H_7	H	1560	1335	[554]
i-C_2H_5	H	1558	1330	[554]
CH_3	CH_3	1562	1346	[554]

Both absorption bands (ν_{as}) and (ν_s) in 3-nitro-1,2,4-triazole isomers are shifted to the lower frequency region on 25–34 cm^{-1} in comparison with 5-nitro isomers [554].

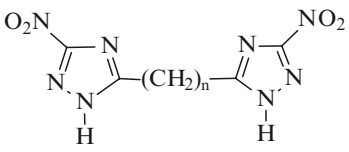
Splitting of the NO_2 absorption bands in the IR spectra of 3,5-dinitro-1,2,4-triazole derivatives reported in [1060] may testify to dimensional and electronic

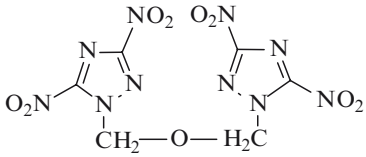
nonequivalence of the nitro groups. Really, a better agreement of the calculated and experimental frequencies is observed for models with a turned out nitro group in position 5 of 3,5-dinitro-1,2,4-triazole and its 1-methyl isomer. Infrared spectra of nitrated azidotriazoles detected the azido group band at ~2160 cm^{-1} [1062, 1063]. The calculated data show a low sensitivity of frequencies to the nitro group turn in 3-azido-5-nitro-1,2,4-triazole in contrast to 3,5-dinitrotriazoles. The presence of a strong electron-withdrawing group in position 5 results in polarization of the triazole cycle π-bonds and electron density shift from C-3 atom to C-5 along C-3>N-4>C-5 bond system of the cycle [1062].



The IR spectra of nitroazole anions have some features [1064, 1065]. The ν_s (NO_2) of nitrotriazole anions are in a narrow spectral region of 1300–1315 cm^{-1} that may be indicative of a coplanar arrangement of the nitro group and the triazole ring, the NO_2 ν_{as} frequencies are displaced by 15–20 cm^{-1} to the lower frequency region in comparison with those of neutral molecule [1060]. The decrease of vibration frequency can point out to an increase of the nitro group participation in both delocalization of the negative charge and reduction of the NO bond multiplicity [1065]. The nitro groups in 3,5-dinitrotriazole anions are also coplanar with the triazole ring plane, since no splitting of the nitro group ν_{as} and ν_s frequencies could be found in IR and Raman spectra [1064]. This means that in the 3,5-dinitro-1,2,4-triazole anion these two nitro groups are equally involved in the negative charge delocalization and that should lead to an increase of the anion symmetry up to C_{2v}.

The nitro group vibration frequencies do not depend much on the number of CH_2- units in *C*-bicyclic nitrotriazoles [1057] and are comparable with those of *N*-bicyclic nitrotriazoles [594].

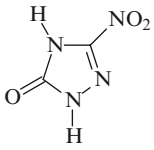


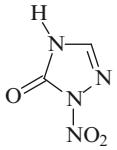


ν_{as}, cm^{-1}	1560–1555	1580
ν_s, cm^{-1}	1320–1310	1320

The vibration spectra of nitrated 1,2,4-triazol-5-ones [611, 614, 615] and their energetic salts [616] are discussed. The thermal decomposition mechanism under rapid heating of thin films of 3-nitro-1,2,4-triazol-5-one was studied by pulsed infrared laser and Fourier-transform infrared spectroscopy [1071].

All characteristic absorption bands in 1-nitro-1,2,4-triazol-5-one are shifted on 30–50 cm^{-1} in comparison with 3-nitro-1,2,4-triazol-5-one [611].





IR (KBr), cm^{-1}	1358, 1548 (NO_2), 1719 (C=O)	1326, 1579 (NO_2), 1767 (C=O)

The IR spectroscopy data for 1-(1-adamantyl)-3-nitro-1,2,4-triazole [1072] and other substituted nitrotriazoles [574–576, 582, 583, 621–625, 1066, 1073–1077] are mainly reported to confirm the structure.

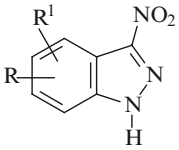
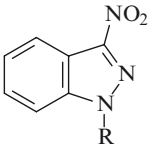
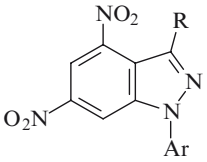
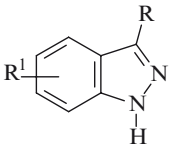
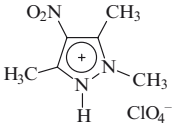
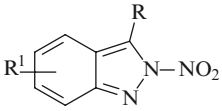
Nitrotetrazoles

The structure of 5-nitrotetrazole and its *N*-substituted analogs has been determined by infrared spectra [1076–1079]. Nitro group stretching vibrations in *N*-substituted 5-nitrotetrazole are observed in the 1500–1580 (ν_{as}) and 1315–1350 cm^{-1} (ν_s) regions [1078, 1079]. Deformational stretching vibrations of the cycle are displayed in a range of 1020 and 1045 cm^{-1}. As shown by calculations, the vibration spectrum of 1-methyl-5-nitrotetrazole has appeared to be not sensitive to a change of turning angle of the nitro group in position 5 [1077]. So, the vibration spectroscopy methods do not yield opportunities to make a choice in favor of one or other molecular conformation. The NO_2-group stretching vibration frequencies in 1-methyl-5-nitrotetrazole are in the 1550 (ν_{as}) and 1330 cm^{-1} (ν_s) region [1077], whereas those in *N*-acetonyl-5-nitrotetrazole are observed in the ranges 1573 and 1316, 1340 cm^{-1}, respectively [1076].

Nitroindazoles

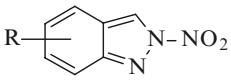
The substituent electron effects in indazole and other azoles essentially influence the nitro group ν_{as} (Table 3.60). The valence vibration bands of the *C*-nitro group in nitrated indazoles are in a frequency range of 1560–1510 (ν_{as}) and 1380–1310 cm^{-1} (ν_s) [644, 657–664, 668, 669, 673, 679, 680]. The introduction of the nitro group into position 1 in indazole displaces the asymmetric band to higher frequencies (~1620–1610 cm^{-1}), and symmetric frequency, on the contrary, to lower frequencies (~1280–1240 cm^{-1}) in comparison with *C*-nitroindazoles (Table 3.61) [657, 659, 663, 664]. Similar changes are observed in 5-membered nitroazoles.

Table 3.61 Stretching vibration bands of nitro groups in nitroindazoles (cm^{-1})

Compound	R	R^1	ν_{as}	ν_s	Refs
	H	H	1535	1385	[679]
	4-NO_2	H	1525	1348	[679]
	5-NO_2	H	1540	1348	[679]
	6-NO_2	H	1520	1364	[679]
	7-NO_2	H	1530, 1500	1335	[679]
	$NHCH_2Ph$		1520	1389	[673]
	CN, CHO, CO_2H, $CH(NH_2)CH_2CO_2H$, $CH{=}CH(CO_2H)_2$, $CH{=}C(CN)CO_2Et$ $CH{=}C(CO_2H)_2$,$CH(OH)$ CH_2–2,4,6,$(NO_2)_3$–C_6H_2		1540–1560	1340–1360	[668, 669, 805]
	H	4-NO_2	1510	1325	[658]
	$N(CH_3)_2$	4-NO_2	1525	1355, 1330	[658]
	H	7-NO_2	1550	1342, 1320	[679]
	$N(CH_3)_2$	7-NO_2	1510	1310	[661]
	Cl	5-NO_2	1535	1335	[657]
	NO_2	5-NO_2	1510	1335	[660]
	H	5-Cl	1600[a]	1265[a]	[662]
	H	5-NO_2	1610[a]	1245[a]	[659]
			1515	1340	
	Cl	5-NO_2	1624[a]	1280[a]	[657]
			1530	1340	
	H	5-Cl	1630[a]	1256[a]	[662]
	H	5-NO_2	1650[a], 1506	1266[a], 1337	[679]
	H	4-NO_2	1640[a]	1275[a]–1270[a]	[658, 679]
			1510–1506	1340	
	H	7-NO_2	1650[a], 1520	1265[a], 1340	[679]
	H	6-NO_2	1650[a], 1530	1285[a]–1280[a]	[659, 679]
				1345–1340	

[a] $\nu(N–NO_2)$

In the 2-nitroindazoles the ν_{as} and ν_s values are even more shifted to higher and lower frequencies, respectively (Table 3.60) [657–664, 679]. This is likely to be caused by the presence of quinoid structure of the following type:



Tautomeric processes in some nitroindazoles, 6-nitroindazole-based complexes, and other nitrated indazoles have been investigated by vibration spectroscopy [583, 645, 655, 1080–1084].

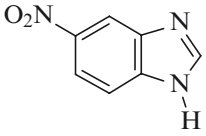
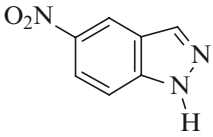
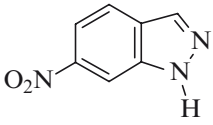
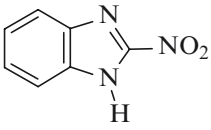
Nitrobenzimidazoles

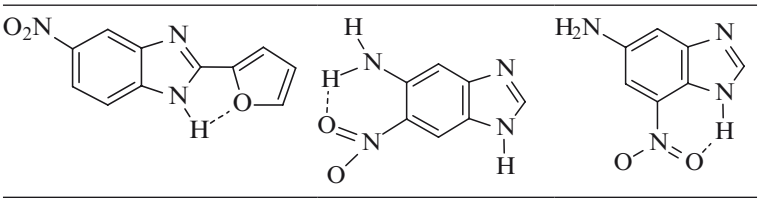
Characteristic stretching vibrations of the nitro group of 5(6)-nitrobenzimidazoles lie in frequency ranges of 1540–1510 (ν_{as}) and 1350–1330 cm^{-1} (ν_s) [709, 715, 1085–1090]. The NO_2 stretching vibration frequencies of 5(6)-nitrobenzimidazoles and 5- and 6-nitroindazole have been measured (Table 3.62).

As seen from Table 3.62, the asymmetric vibration frequency is sensitive to the position of the benzazole ring heteroatom. In 2-nitrobenzimidazole the NO_2 asymmetric vibration frequency is more sensitive to the nitro group position in the ring ($\Delta\nu_{as} = 36$ cm^{-1}) than symmetric one is ($\Delta\nu_s = -10$ cm^{-1}) [1091, 1092].

The existence of an intramolecular hydrogen bond in 2-furyl-5(6)-nitrobenzimidazole (ν 3400–3150 cm^{-1}) [1093], 5(6)-amino-6(5)-nitrobenzimidazole (ν 3590, 3320–3300 cm^{-1}), 4(7)-amino-6(5)-nitrobenzimidazole (ν 3370–3309 cm^{-1}) [709] is proven by IR spectroscopy:

Table 3.62 The nitro group vibration frequencies of nitrobenzazoles (cm^{-1})

Compound	ν_{as}	ν_s	Refs
	1514	1345	[1088]
	1539	1345	[1088]
	1529	1325	[1088]
	1551	1335	[1091, 1092]

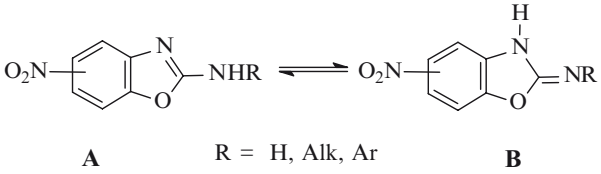


The tautomerism of nitrated benzimidazolones and benzimidazolethiones is studied [1094, 1095]. The vibration frequencies of complexes of 5(6)-nitro- [1096], 4(7)-nitrobenzimidazole [1097] and 5-nitrobenzotriazole [1098] with transition metal ions (Co, Cu, Ni, Zn, Cd, Hg) are reported. The characteristics of infrared spectra of other nitrobenzimidazoles are given in [1099–1101].

Nitrobenzisoxazoles, Nitrobenzoxazoles, Nitrobenzoxadiazoles

As far as nitrobenzisoxazoles are concerned, the valence vibration frequencies of the carbonyl group of 3-aldehydo-5-nitro-1,2-benzisoxazole and 5-nitro-1, 2-benzisoxazolyl-3 acetic acid (1700, 1720 cm^{-1}, correspondently) [739] and ν(C≡N) of 6-nitrobenzisoxazolyl-3 acetonitrile [742] are reported.

Only few publications are devoted to the vibration spectra of nitrated benzoxazoles [1102, 1103]. The authors [1102] have investigated the tautomerism in 5- and 6-nitrobenzoxazoles (Scheme 3.47):

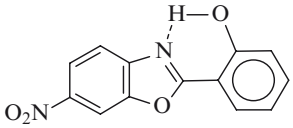


Scheme 3.47

5-Nitrobenzoxazoles in Vaseline oil bring about only vibration bands of exocyclic (**B**) azomethine group (1675–1680 cm^{-1}), whereas 6-nitrobenzoxazoles cause two bands: in the 1645–1650 (endocyclic azomethine group) (**A**) and 1690–1695 cm^{-1} region (exocyclic azomethine group) (**B**). This suggests that 6-nitroisomeres in the solid state exist simultaneously in two forms [1102]. In the chloroform solution they are present as aminobenzoxazoles (ν 1640–1657 cm^{-1}) (**A**) [1102].

Intra- and intermolecular hydrogen interactions in 2-(2-oxyaryl)benzazoles including 6-nitrobenzoxazole derivative are investigated [1103]. Two intense bands

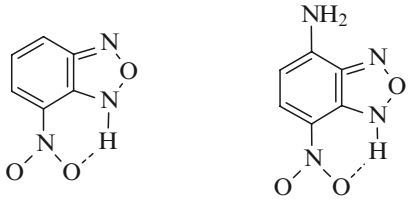
in the 3495 and the 3320 cm^{-1} regions in the IR spectra of this compound are related to the intermolecular hydrogen bond O–H…O_2N, and a wide absorption band in the 3200–2400 cm^{-1} region corresponds to the OH band which participates in the intramolecular hydrogen bridge O–H…N of type below [1103]:



At the same time in the IR spectra of 2-(2-oxyaryl)benzazoles there is a wide smearing band in the 3400–2400 cm^{-1} region, which is characteristic of intramolecular hydrogen bond O–H…N. This distinction results from the introduction of the nitro group and is caused, in the author's opinion, by a decrease in the π_N-orbital population owing to conjugation with the nitro group.

The structure of nitrobenzoxazolone alkylammonium salts was confirmed by IR spectroscopy and electroconductivity measurements [1104]. The vibration spectra of *N*-(6-nitrobenzoxazolonyl)-β-propionitrile are presented in [1105].

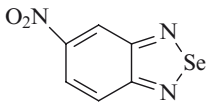
The nitro group valence vibration bands of nitrobenzofurazans are in the frequency ranges 1475–1540 (ν_{as}) and 1270–1350 cm^{-1} (ν_s) [762, 763, 769, 773, 1106–1109]. Splitting of the NO_2 symmetric vibration band of 7-nitrobenzofurazan and 4-amino-7-nitrobenzofurazan found by the authors [1104] may be connected with nonequivalence of the N–O bonds in the nitro group which forms a weak intramolecular hydrogen bond with the proton NH and by that is located in the benzofurazan ring plane in the two molecules.

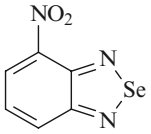


The rapid thermal decomposition of the energetic materials – mono- and dinitrobenzofuroxans – has been examined by rapid-scan FTIR spectroscopy as a function of heating rate and pressure [1110]. The IR spectral assignments for these molecules are severely complicated by overlapping characteristic frequencies and coupling among the motions. The 1400–1600 cm^{-1} range contains modes expected of ν(C=N→O), ν_{as} (NO_2), ν(O-N→O), δ (CH), ν(C=C), and δ (NH_2) [1110]. Tentative assignments were made through correlations with known infrared spectra of nitrofuroxes. Kinetic measurements on pyrolysis of nitrobenzofuroxans have been carried out with help of IR spectroscopy [1111].

Nitrobenzoselenodiazoles

Probably for the same reason 4-nitrobenzoselenadiazole shows two ν_{as} bands in the IR spectrum in comparison with 5-nitro derivatives [1112].

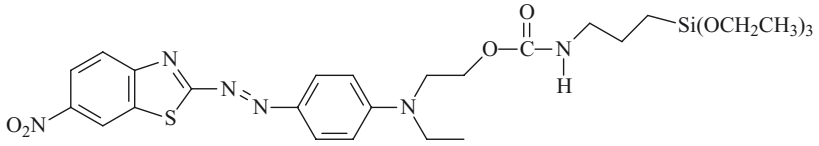




ν_{as}, cm^{-1}	1515	1498 and 1546
ν_{s}, cm^{-1}	1330	1315

Nitrobenzothiazoles

Only some publications are devoted to the vibration spectra of nitrobenzothiazoles [214, 785, 786, 795, 1113, 1114]. The infrared and Raman frequencies of 2-amino-6-nitrobenzothiazole have been assigned to different modes of vibrations on the basis of normal coordinate calculations assuming C_s point group symmetry [1114]. The structure of Alkoxysilane Dye on the base of nitrobenzothiazole has been confirmed by IR spectra [786]:



3389 (NH), 1699 (C=O), 1600 (C_6H_4), 1527, 1335 (NO_2), 1105, 1079 ($SiOCH_2CH_3$) cm^{-1}

Vibration spectrum of copper(II) complexes of *N*-2-(4-methylphenylsulfamoyl)-6-nitrobenzothiazole 1550, 1314 (NO_2), 1151 (SO_2), 955 (S–N) cm^{-1} has been reported [214]. Imidomethylation of nitrobenzothiazoles with *N*-hydroxymethylphthalimide in sulfuric acid has been studied with the help of infrared spectra [1113].

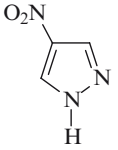
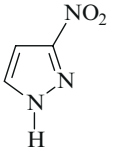
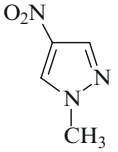
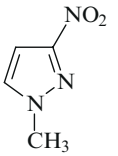
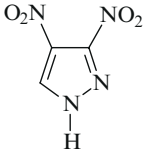
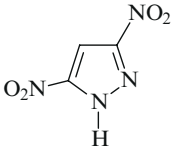
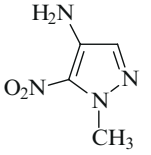
UV Spectroscopy

Nitropyrazoles

Introduction of the nitro group into the azole cycle leads to a significant bathochromic shift of the absorption band maximum in the electron spectra. The absorption band of pyrazole is near λ_{max} 210 nm, whereas that of 4-nitropyrazole lies in the λ_{max}

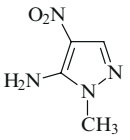
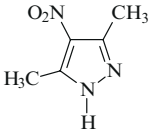
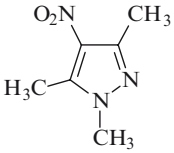
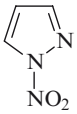
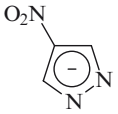
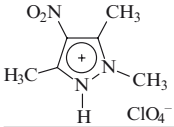
269–280 nm region and the band of 3(5)-nitropyrazole is observed in the λ_{max} 254–266 nm region [272, 1115–1124] (Table 3.63). It results from π→π* electron transition in the pyrazole ring with contribution of the charge transfer from π-system to the nitro group. The position of this absorption band strongly depends on the effects of medium and substituents, and on the ionization processes of the molecule.

Table 3.63 The characteristics of electron absorption spectra of nitropyrazoles (ethanol).

Compound	λ_{max}, nm	lg ε	References
	268, 274–275 320[a] (0.1 *N* NaOH) 238[b] (71% H_2SO_4)	3.91 3.07 3.89	[1115, 1116, 1119, 1120]
	254–255 261 (0.05 *N* HCl) 316* (0.05 *N* NaOH)	3.79 3.86	[1115, 1119, [1122]
	273	3.99	[1117]
	267	3.93	[1117]
	267 (0.05 *N* HCl) 312* (0.05 *N* NaOH)	3.73 3.79	[1115]
	270 (0.05 *N* HCl) 305* (0.05 *N* NaOH)	–	[1115]
	287 408	3.63 3.59	[1117]

(continued)

Table 3.63 (continued)

Compound	λ_{max}, nm	lg ε	References
	269 339	3.55 3.77	[1119]
	287 321[a] (0.05 *N* NaOH) 256[b]	3.93 3.93 3.86	[1115, 1125]
	282 303*	–	[1115, 1119]
	266	–	[1119]
	318[a]	–	[1119]
	259[b]	3.89	[1125]

[a]Anion
[b]Cation

In neutral media the band of pyrazole nitro derivatives is in the 250–290 nm region; in acid media it is shifted by ~30 nm to the short-wave region; and in alkaline media a ~40 nm shift to the long-wave region occurs [246, 1115, 1116, 1119–1126]. These shifts are caused by protonation and deprotonation of nitropyrazoles that is widely used in studying the acid-base properties of nitroazoles since the existence of these shifts allows spectrophotometrical determination of the pK_a and pK_{BH+} values of these compounds.

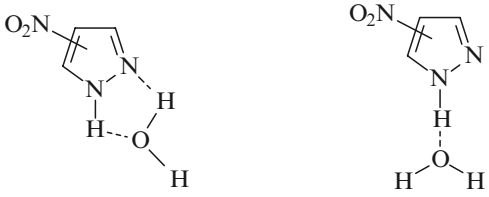
The presence of electron-donating substituents (NR^1R^2) in the adjacent position to the nitro group in nitropyrazoles results in the appearance of an additional padding band in the area λ_{max} 322–408 nm in their spectra [279, 307, 1117]. This band corresponds, apparently, to the electron transfer with a charge transition from electron-donating to the nitro group. The position and the intensity of this maximum strongly depend on the mutual disposition of the amino and the nitro group in

the nitropyrazole ring [1117]. The authors have investigated the influence of solvent on the position of the long-wave band in these compounds as the replacement of nonpolar solvent (benzene) by a polar one (ethanol) leads to a significant (20 nm) bathochromic displacement.

Quantum-chemical calculations satisfactorily predict the long-wave band position in the electron absorption spectra of aminonitropyrazoles [1118]. The dominating contribution to the electron transfer corresponding to this band is brought in by a single-excited configuration Φ_{6-7} (C_1 0.98–0.99). This means that, according to the accepted numeration of molecular orbitals (MO) of aminonitropyrazoles, MO_6 is the highest occupied molecular orbital (HOMO), and MO_7, accordingly, the lowest unoccupied one (LUMO). In this case, there is an increase in the π-charge on the amino group nitrogen atom that allows the assignment of the long-wave band to a charge-transfer band [1118].

Solvatochromism and specific features of interaction between nitropyrazoles and amphiprotic solvents have been studied in detail by Prof. Turchaninov's team [1119–1123, 1127]. The dependence on acid-base properties of solvents of the electron transition in 4-nitropyrazole connected with intramolecular charge transfer has been analyzed [1121]. Amphiprotic solvents with a pronounced acidic function form with 4-nitropyrazole cyclic solvates. The results of *ab initio* calculations 6-31G* show that a cyclic complex of both 4-nitropyrazole and 3-nitropyrazole with one water molecule is thermodynamically more stable than a linear complex of the same composition by 0.38 and 1.0 kcal/mol, accordingly [1120–1123]:

The solvatochromism of H-complexes of 5-amino-1-methyl-4-nitropyrazole in aprotic protophilic media has been described by Kamlet-Taft empirical parameters. Specific solvation affects only one of the two long-wave bands, namely that corresponding to an electronic transition involving orbital electron density transfer from the H-bound nitrogen atom [1123].

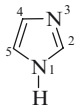
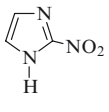
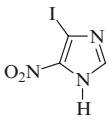
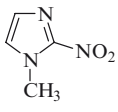
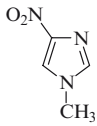
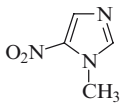


A structural study of some derivatives of 3- and 5-nitropyrazoles [1128], 4-nitropyrazole [315], and 4-nitropyrazole-5-ones [1129] with the help of UV spectroscopy has been reported.

Nitroimidazoles

Mononitration into the imidazole ring causes more significant changes in UV spectra ($\Delta\lambda_{max}$ 100 nm) than the nitro group introduction into the nitropyrazole cycle ($\Delta\lambda_{max}$ 30 nm). In the spectra of nitroimidazoles there are usually two maxima, one

of which, a poorly expressed one, is situated in the area of λ_{max} 220–260 nm, and the other, rather intense and characteristic one, lies in the area of λ_{max} 300–360 nm and corresponds, apparently, to $\pi \rightarrow \pi^*$ electron transfer of the imidazole ring [2, 364, 1123, 1124, 1130]. The position and the intensity of the latter depend both on the nature and the position of substituents in nitroimidazoles, and on the pCof the medium [321, 1131, 1132]. Thus, the λ_{max} values of some nitroimidazoles are given in the following scheme [321, 381, 1130].

						
λ_{max} nm	207–208	325	336	325	300–303	303–305

4(5)-Nitroimidazole in solution (amphiprotic medium) is stabilized as the 5-nitro isomer due to formation of hydrogen bond with an aprotic protophilic solvent [1124]. The medium favors displacement of the tautomeric equilibrium toward the 4-nitro isomer via formation of a solvate complex at the same time 4-nitroimidazole acts as hydrogen-bond acceptor. The specific solvatochromic effect in the UV spectrum of 4-nitroimidazole is caused by the electronic configuration of the excited π,π^*-state [1124].

N-methylation of 2-nitroimidazole does not influence the absorption band. Methylation of 4(5)-nitroimidazole results in the formation of two isomers: 1-methyl-4-nitroimidazole and 1-methyl-5-nitroimidazole, whose absorption spectra are poorly distinct [321].

It is noted [321] that alkylated 5-nitroimidazoles show more distinct maxima in a field of 220–260 nm than the corresponding 4-nitroisomers. This band is also slightly displaced to the long-wave area (7–13 nm) for 5-nitrosubstituted compounds in comparison with 4-nitroimidazoles. Thus, statistical analysis of the absorption spectra of 1-alkylnitroimidazoles allows establishing the nitro group position in the ring that is extremely valuable in the nitration chemistry of imidazoles. The absorption bands of 1-allyl-4-nitroimidazoles are observed in the λ_{max} 284–302 nm region [364].

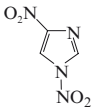
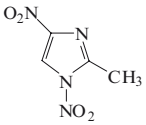
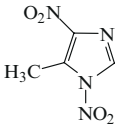
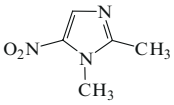
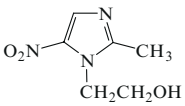
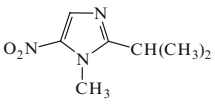
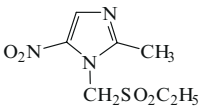
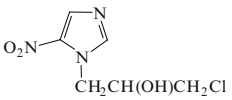
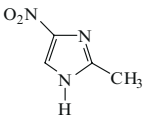
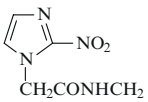
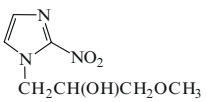
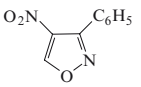
The kinetics of hydrolysis [445] and reactivity of 1,4-dinitroimidazole [444, 447] has been investigated by UV spectroscopy.

With the help of UV spectroscopy the acid-base properties of nitroimidazole in various environments have rather widely been investigated with the help of UV method [321, 331, 1131–1134].

Differential UV spectrophotometry is also used for quantitative determination of compounds that increases the accuracy of the analysis of nitroimidazole-based pharmaceuticals [1131].

The electron absorption spectra of well-known drugs such as 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) (Table 3.64) [351, 1131, 1132, 1135], 1-methyl-2-isopropyl-5-nitroimidazole (ipronidazole) [1135], 1-substituted 2-methyl-5-nitroimidazoles [325, 387, 413, 414] have been described. UV absorption spectra

Table 3.64 Electron absorption spectrum characteristics of nitroimidazoles and some medicines (ethanol).

Compound	λ_{max}, nm	lg ε	Refs
[2] 	208	3.89	[2]
	226 275	4.02 3.64	
	227 288	4.04 3.68	[2]
	208 225 275	3.90 3.98 3.52	[2]
	320–321 (pH 6) 277[b] (3M H_2SO_4)	–	[1135, 1156]
	320 (pH 6) 277[b] (3M H_2SO_4)	–	[1135,1156]
	323 (pH 6) 277[b] (3M H_2SO_4)	–	[1135, 1156]
	318	-	[1156]
	320	-	[1156]
	313 (pH 6) 366[a] (0.1M NaOH) 277[b] (3M H_2SO_4)	-	[1135]
	323	-	[1156]
	324	-	[1156]

[a]Anion
[b]Cation

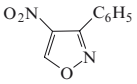
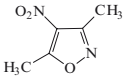
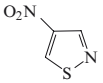
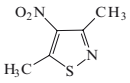
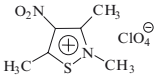
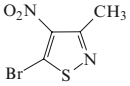
of (2-methyl-4-nitro-1-imidazolyl)acetic acid [443], 1-alkyl- [400] and 1-aryl-4-nitroimidazoles [395], halonitroimidazoles [381, 1136], bis-nitroimidazoles [1137], vinylsubstituted 2-nitroimidazoles [418], and other derivatives [248, 332, 342, 354, 381, 412, 429, 430, 463–465, 1032, 1138–1158] have been investigated.

Nitroisoxazoles, Nitrooxazoles, and Nitrooxadiazoles

The data on UV-spectroscopy of nitroisoxazoles are rather scarce. It is known that λ_{max} for 3,5-dimethylisoxazole is 215–220 nm, whereas that for its 4-nitroderivative lies in a field of 250–270 nm depending on the medium (see Table 3.65) [483, 499, 1125, 1159]. It is shown [483] that for 5-(p-methoxystyryl)- and 5-cinnamylidene derivatives of 3-methyl-4-nitroisoxazole, the absorption band is moved to the long-wave area (290 nm, lg ε 4.15). The absorption band maxima of 3-methyl-4-nitro-5--styrylisoxazole photodimers lie in field of 268–272 nm. In works of the Italian authors the electron absorption spectra of some derivatives of nitroisoxazole are described [1160].

By means of UV-spectroscopy monoprotonated, diprotonated, and nonprotonated forms of 3-nitro-4-aminofurazan have also been investigated [513, 1161].

Table 3.65 The characteristics of electron absorption spectra of nitroisoxazoles and nitroisothiazoles.

Compound	λ_{max}, nm	lg ε	Refs
	252 (CH_3COOH)	3.78	[1159]
	267	3.73	[1125]
	264 (CH_3COOH)	3.74	[1159]
	223[a]	3.89	[1125, 1159]
	209 (Heptane)	3.95	[524]
	265[a]	3.92	
	216.5	4.04	[1125]
	278.5	3.82	
	210[a]	4.17	
	264[a]	3.90	
	265[a]	3.89	[1125]
	220 (Heptane)	4.01	[524]

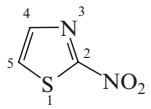
[a]Cation

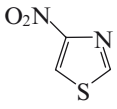
Nitroisothiazoles and Nitrothiazoles

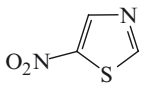
The list of literature describing the electron absorption spectra of nitroisothiazoles is also rather limited. Only few studies of the electron spectra of nitroisothiazoles are known [524, 1125, 1162–1164]; some of them are presented in Table 3.65. In their spectra there are two maxima, one is fixed in the area of λ_{max} 209–220 nm and the other is in the long-wave area (λ_{max} = 263–278 nm) [524, 1125, 1163]. The calculated λ_{max} values for nitroisothiazole-based diazo dyes are in rather good agreement with the experimental data (536 and 558 nm, respectively) [1164].

There are some more data on the spectra of nitrothiazoles [530, 1165–1172]. Unlike the spectra of nitroisothiazoles, there are three maxima, λ_{max} = 202–222, 235–260, and 298–314 nm in their spectra [530, 1165, 1166].

The analysis of quantum-chemical calculations of electron density distribution in the molecules of 2-nitro-, 4-nitro-, and 5-nitrothiazole allows a conclusion that the nature of all three bands is related to π→π* electron transfers [1166].







The long-wave band in the field of 298–314 nm, corresponding to the interaction of the nitro-group with the ring, strongly depends on its position in the ring and decreases in the following order: 2>5>4 [1166]. The monomethylation of nitrothiazole does not influence the position of bands in the spectrum much [1166, 1167].

The influence of the medium on the optical characteristics of nitrothiazoles is discussed in [1166–1169, 1171] (Table 3.66). The authors [1167] note that 2-amino-5-nitrothiazole (nitragine) in ethanol has a short-wave band with λ_{max} 239 nm, which, when compared with a similar band for 2-aminothiazole, decreases in intensity and is hypsochromically displaced, which corresponds to energy of 33 kJ/mole.

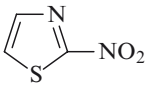
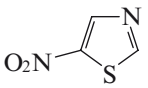
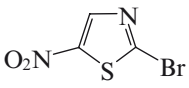
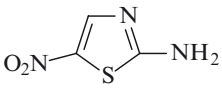
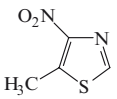
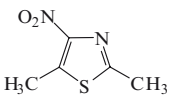
The calculated and experimental values of λ_{max} (452 and 529 nm, correspondingly) of 2-*N*-phenylpyrroly-dinylazo-5-nitrothiazole are reported [1164].

With the help of UV spectroscopy the formation of palladium II complexes with 5-nitrothiazolyl-2-azoderivatives has been investigated [1169]. For the identification of 2-organylamino-5-nitrothiazoles UV-spectra were used [1173].

The UV spectra of nitroazole radical anions have been studied (Table 3.67) [849].

Each of the spectra is due to a single species whose rates of formation and decay are independent of monitoring wavelength. In each case the rate of formation of nitroazole radical anions was concomitant with the rate of decay of hydrated electron (e_{aq}^-) from which the absolute rate constant for the reaction of e_{aq}^- with nitroazoles was obtained [849]. Hydrated electron attacks, in addition to forming a transient absorbing species radical anions, also destroy the UV-absorbing chromophore associated with the nitro group.

Table 3.66 The characteristics of electron absorption spectra of nitrothiazoles (ethanol).

Compound	λ_{max}, nm	lg ε	References
	202.5 235 308	3.59 3.61 3.68	[1166]
	222 240 298.5	3.57 – 3.68	[1166]
	220 298 229[a] (0.1 *N* NaOH) 420[a] (0.1 *N* NaOH) 220[b] (98% H_2SO_4) 283[b] (98% H_2SO_4)	3.57 3.95 4.10 3.70 3.80 4.05	[1167]
	239 380 231[a] (0.1 *N* NaOH) 410[a] (0.1 *N* NaOH) 235[b] (98% H_2SO_4) 324[b] (98% H_2SO_4)	3.69 4.25 3.96 3.51 3.95 4.08	[1167]
	215.5 235 281	4.00 3.60 3.70	[1166]
	219 290	4.07 3.69	[1166]

[a]Anion
[b]Cation

Table 3.67 The characteristics of electron absorption spectra of radical anions of nitroazoles (*tert*-butanol).

Nitroazole	λ_{max}, nm	lg ε
3-Nitropyrazole	340	2.1
1-Nitropyrazole	380	~1
4-Nitroimidazole	380	~1
2-Methyl-5-nitroimidazole	390	1.7
2-Nitroimidazole	410	1.1
4-Nitroisothiazole	510	2.0

Nitrotriazoles

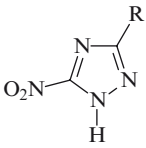
The replacement of –CH by –N in heterocyclic system does not influence, as a rule, the absorption spectra. Actually, λ_{max} for 4-nitro-2-(4-nitrophenyl)-1,2,3-triazole and 4-nitro-1-(4-nitrophenyl)pyrazole are 304 (lg ε 4.36) and 306 nm (lg ε 4.37).

This can be of help in structural assignments in the chemistry of heterocycles. The electron spectra of 1- and 2-alkylderivatives of 4-nitro-1,2,3-triazole, which show an identical band λ_{max} 257 nm also independent on the medium (pH 1 or 11 or ethanol), are described [634]. However for 1-alkyl-4-nitro-5-amino-1,2,3-triazoles the absorption maximum is shifted to the long-wave region (332–356 nm).

The ultraviolet spectra of nitrated 1,2,4-triazoles have been described in detail [554–556, 1174]. The absorption of unsubstituted 1,2,4-triazoles in the UV-spectrum is observed at 186 nm, and there are no absorption bands in the field of longer wave-lengths. The mononitration of 1,2,4-triazoles causes a bathochromic shift of the triazole ring absorption band to the 215–230 nm (lg ε 3.8–4.0) region and the appearance of a new band at 230–340 nm (1 g ε 3.6–3.9). The latter seems to be caused by the conjugation of the nitro group with the triazole cycle [1174]. In contrast to the long-wave maximum, the short-wave one is less sensitive to the substituent nature and triazole cycle ionization [554–556, 1174–1176]. The characteristics of long-wave bands of some nitrated 1,2,4-triazoles are given in Table 3.68 [554, 555, 618, 1174–1176].

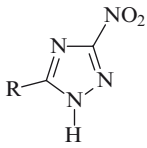
The introduction of both electron-donating and electron-withdrawing substituents into 3-nitro-1,2,4-triazole results in a bathochromic shift of the NO_2-group long-wave band in comparison with that of 3-nitro-1,2,4-triazole. The introduction of substituents which are capable of conjugation with the triazole ring (phenyl and acetyl) induces a bathochromic shift with a simultaneous increase in the absorption intensity [1174]. The position of the nitro-group in the cycle also has an effect on the λ_{max}, value, so in the spectra of 5-substituted 1-methyl-3-nitro-1,2,4-triazoles the absorption maximum is displaced by 9–16 nm to the short-wave area in comparison with the spectra of their 5-nitroisomers. In the aforementioned series the position of absorption maximum is considerably more sensitive to the influence of electron-donating and electron-withdrawing groups simultaneously present in the cycle and to the coincidence of polarization, caused by them, with the direction of the triazole cycle polarization.

An attempt to estimate the transmission of electronic influence of substituents R from positions 3–5 and from 5–3, using correlations between wave numbers and (σ_I, σ_c) constants of substituents R, was made in [1177]



$$\nu \cdot 10^{-4} = 10.153\sigma_I + 1.179\sigma_C + 3.886$$

$$\frac{\rho_C}{\rho_I} = 7.70;\ \mathrm{R} = 0.945;\ n = 13;\ S = 0.12$$

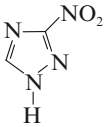
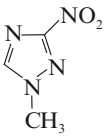
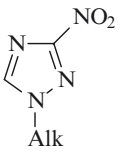
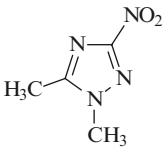
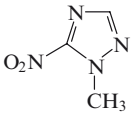
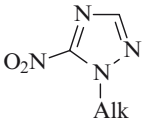
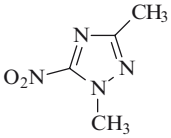
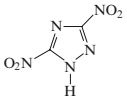
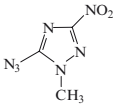
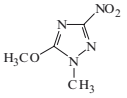


$$\nu \cdot 10^{-4} = 0.425\sigma_I + 0.936\sigma_C + 3.560$$

$$\frac{\rho_C}{\rho_I} = 2.21;\ \mathrm{R} = 0.733;\ n = 8;\ S = 0.20$$

In the author's opinion, in these compounds the main role is played by the effect of conjugation; however, this conclusion does not seem reasonable because of low correlation coefficient in the latter.

Table 3.68 The characteristics of long-wave absorption bands of 1,2,4-triazoles (ethanol)

Compound	λ_{max}, nm	lg ε	Refs
	230 (pH 1) 290[a] (pH 13) 220[b] (83.4% H_2SO_4) 282 (H_2O)	3.73 3.81 3.81	[618, 1175]
	255 (pH 7) 230[b] (83.4% H_2SO_4)	3.74 3.75	[554, 1174–1176]
	255–257[c]	-	[554]
	266 262.5	-	[554, 1174]
	265 270 (pH 7) 245[2] (83.4% H_2SO_4)	3.66 3.70	[554, 1175]
	266–267[c]	-	[554]
	280 279	3.79 3.90	[554, 1174]
	255 285[a] (H_2O)	3.79 3.90	[1174, 1175]
	290	3.63	[1174]
	288	3.64	[1174]

[a]Anion
[b]Cation
[c]Alk = Et, Pr, *i*-Pr

UV spectra of 3-nitro-5-carboxy-1,2,4-triazole and 1-methylsubstitutred nitrotriazoles have been investigated [1175]. Comparison of the absorption spectra of these compounds at different pHs has shown that the elimination of the proton bound to the nitrogen atom causes a strong bathochromic shift (50 nm), while the dissociation to carboxylic group results only in an insignificant bathochromic shift (5 nm). In *N*-methyl-substituted nitrotriazoles not containing imine hydrogen no changes are observed in the spectra in going to an alkaline medium. The addition of a proton to a neutral molecule of nitrotriazole gives rise to a 25–35 nm hypsochromic shift of the absorption maximum.

The *E,Z*-isomerization of 1,2,4-nitrotriazole diazaderivatives has been investigated with the help of ultra-violet spectroscopy in a series of works [593, 1178, 1179].

Influence of pH medium on the UV-absorption spectra of 5-nitro-1,2,4-triazole, 3-methyl-5-nitro-1,2,4-triazole, 4-nitro-2-(1,2,4-triazole-3-yl)-1,2,3-triazole and nitroderivatives of 1,2,4-triazolone-5 [611, 613, 1180] has been considered.

The absorption spectra of some other derivatives of nitrotriazole are presented in [589, 590, 619, 1176, 1181].

Nitrotetrazoles

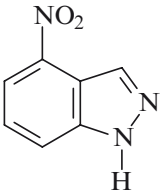
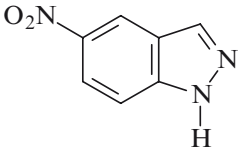
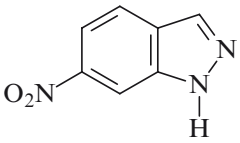
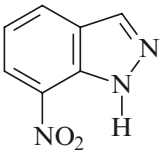
The low stability of nitrotetrazoles hinders a detailed study of their spectral characteristics [1078, 1182–1185]. It is known that 5-nitrotetrazole in an aqueous solution of sulfuric acid shows maximum absorption in the region of λ_{max} 235 [1183], whereas its anion absorbs in the region 257 nm [1182].

Nitroindazoles

The electron absorption spectra of 4-, 5-, 6-, and 7-nitroindazoles (Table 3.69) have been described [1186]. There are three absorption maxima in the 230–360 nm region (λ_{max} 230–250, 250–305 and 305–360 nm). Unfortunately, the data available by the present time do not allow establishing the relationship between the position of maxima in the electron spectra of nitroindazoles and the ring position of the nitro group. Apparently, for this purpose a systematic study of the absorption spectra of isomeric nitroindazoles should be carried out under unified conditions. The presence of methyl group in position 3 does not influence much the absorption spectra of nitroindazoles.

Comparison of the electron spectra of 3-arylazo-5-nitroindazoles and their 1- and 2-methylderivatives suggests arylazoindazoles to exist as 1*H*-tautomers [1187]. The ultraviolet spectra of 6-nitroindazoles and their 1- and 2-ethyl derivatives [1188], 1-acetonitrylnitroindazoles, and other derivatives of nitroindazole [683, 1189] have been investigated.

Table 3.69 The characteristics of electron absorption spectra of nitroindazoles (ethanol)

Compound	λ_{max}, nm	lg ε
	228	4.09
	339	3.83
	230	4.11
	244	4.20
	304	3.85
	390*	3.86
	250	4.14
	288	3.87
	337	3.44
	280[a]	3.76
	230	3.88
	310	3.48
	356	3.91
	435[a]	3.80

Nitrobenzimidazoles

Unsubstituted 5(6)-nitrobenzimidazole has two absorption bands in the field of 230–235 and 300–309 nm [1186, 1190–1192]. Its long-wave band, as compared with the initial benzimidazole, is bathochromically moved by approximately 25 nm and does not show vibrational structure. The short-wave band, on the contrary, undergoes a hypsochromic shift (~10 nm) upon mononitration [709, 1193]. Band displacement of this kind and the disappearance of vibrational observed for the long-wave band are responsible for essential differences in the localization and, hence, in the nature of, at least, one of the transitions. For example, from CNDO/S calculations it follows that the long-wave transition of benzimidazole is multiconfigurational (Table 3.70) and results in the total molecular excitement [1193].

The UV-spectra of 2-substituted 5(6)-nitrobenzimidazoles with R = CH_3, C_2H_5, CN, Cl, CF_3, CCl_3 look like the spectrum of unsubstituted 5(6)-nitrobenzimidazole and are interpreted analogously (Tables 3.70 and 3.71). The situation is more complicated with the spectra of nitrobenzimidazoles having a substituent such as C_6H_5, OCH_3, OC_2H_5, NO_2, etc. in position 2.

Table 3.70 Experimental and theoretical characteristics of the UV spectra of benzimidazole and 5(6)-nitrobenzimidazole

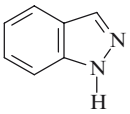
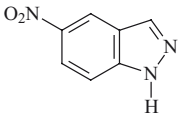
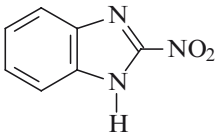
Compound	λ_{max}, nm (exp) (lg ε)	λ	*f*	Transition type	Main configurations
	279 (3.37)	276.3	0.023	π→π*	2→1* (0.34); 1→2* (0.35)
	244(3.74)	247.2	0.012	π→π*	3→1* (0.40); 3→3* (0.22)
		241.6	0.283	π→π*	1→1* (0.68); 1→2* (0.18)
		216.6	0.241	π→π*	2→1* (0.36); 1→3* (0.29)
	303 (4.13)	399.3	0.000	n_0→π*	6→1* (0.92)
		354.9	0.035	π→π*	1→1* (0.91)
		306.9	0.459	π→π*	2→1* (0.94)
	235(4.46)	253.2	0.048	π→π*	1→3* (0.38); 2→2* (0.33)
		236.2	0.538	π→π*	1→2* (0.70); 1→3* (0.19)

Table 3.71 The characteristics of electron absorption spectra of 2-substituted 5(6)-nitrobenzimidazoles (ethanol) [1192]

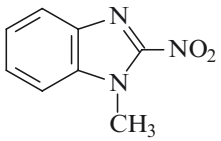
R	λ_{max}, nm	lg ε
CH_3	240	4.48
	304	4.08
Cl	235	4.43
	303	4.10
CF_3	235	4.53
	292	4.19
CN	251	4.55
	304	4.27
C_6H_5	268	4.50
	321	4.33
	333	4.32
OCH_3	230	4.40
	246	4.24
	322	3.98
OC_2H_5	230	4.28
	245	4.11
	322	3.98
NO_2	215	4.35
	277	4.32
	326	4.24

Electron absorption spectra of 4(7)-amino-, 6(5)-amino-5(6)-nitrobenzimidazoles and their naphthylazo derivatives have been measured [709].

In the UV-spectra of 2-nitrobenzimidazoles a stronger bathochromic shift of absorption bands is noticed in comparison with that of 5(6)-nitrobenzimidazole [1192].



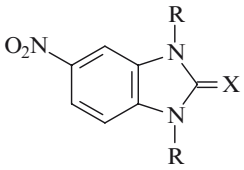
342 nm (methanol)
365 nm (0.1*N* NaOH)



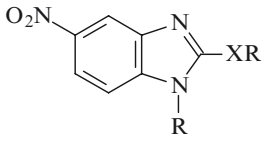
333 nm (ethanol)

The electron spectra of 4(7)-nitrobenzimidazoles are investigated in works [1087, 1186, 1194]. They are characterized by strong hypso- and bathochromic displacements of the absorption bands compared to 5(6)-nitrobenzimidazole, which can indicate a more effective interaction of vacant $\pi(NO_2)$-MOs of the nitro group and benzimidazole framework.

UV spectroscopy method was used to study the acid-base properties of nitroderivatives of benzimidazolones [1194] and benzimidazolthiones [1195]. Essential distinctions in the UV spectra of isomers **I** and **II** can be used for establishing the alkylation center of corresponding benzimidazolones [1195] and benzimidazolthiones [1196].



I



II

R = O, S

Electron spectra of 2-(2-tosylaminophenyl)- [1197, 1198], 2-benzylidenamino-5(6)-nitrobenzimidazole [1199] have been investigated.

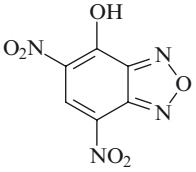
Nitrobenzoxazoles and Nitrobenzoxadiazoles

It is interesting to note that 5-nitrobenzoxazole has two absorption maxima λ_{max} 224 (4.39) and 270 nm (3.84), while 6-nitrobenzoxazole shows only one maximum in area λ_{max} 282 nm (4.01) [1200]. A similar pattern is observed for 5-nitro- and 6-nitro-2-alkyl(aryl)benzoxazole too. The available experimental data are not enough to explain spectral differences of this kind. Apparently, it would be well to carry out quantum-chemical calculations or to involve other physical-chemical methods. An investigation of chromophoric 2-(4′-diphenyl)-5-nitrobenzoxazole with the help of UV (λ_{max} 305 nm), fluorescence and laser spectroscopy has been reported by Chinese chemists [1201]. Chromophores 2-(2′-hydroxy-4′-aminophenyl)-6-nitrobenzoxazole [1202], 2-{4-[4-(*N*,*N*-dihydroxyethyl-amino)-phenylazol]-phenyl}-6-nitrobenzoxazole, 2-[4-(*N*-methyl,*N*-hydroxyethyl-amino)

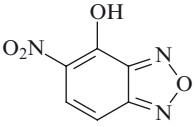
phenylazo]-phenyl-6-nitrobenzoxazole [1203, 1204] possessed a second-order nonlinear optics properties were characterized by UV-visible absorption.

In recent years nonlinear optical materials on the basis of nitroazoles, especially nitrobenzoxazoles and nitrobenzoxadiazoles, have investigated under intense scrutiny, at that and UV and fluorescence spectroscopy is widely used in studying of their structure and dynamics [1202–1225]. 4-Aminosubstituted 7-nitrobenzofurazans have a strong band in the visible region (λ_{max} = 457–483 nm) due to their chromophore properties [777]. 4-Substituted 7-nitrobenzofurazans possess a strong fluorescence that has led to their use as biochemical fluorescent probes in cell membranes [777, 1226–1228].

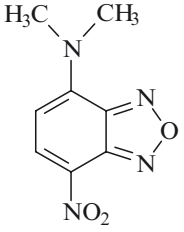
A comprehensive research of a large number of benzofurazan nitro derivatives using UV spectroscopy and other physical-chemical methods has been carried out [777, 1006, 1007, 1106, 1107, 1229–1241]. The frequencies of long-wave absorption bands of hydroxy- and aminosubstituted of nitrobenzofurazans greatly depend on the solvent nature [1106, 1107, 1230–1233, 1235, 1236]. They are assigned to the bands of intramolecular charge transfer [1007, 1232]. Correlation relationships between the wave number ($\tilde{\nu}$) and the Kamlet-Taft solvatochromic parameter (π^*) are presented in the works cited:

I 

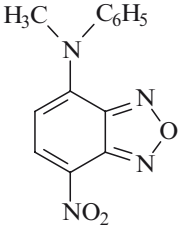
$\tilde{\nu}$ = –4534π^*+27038
r = 0.989; n = 6 — 1232

II 

$\tilde{\nu}$ = –4543π^*+30351
r = 0.978; n = 6 — 1232

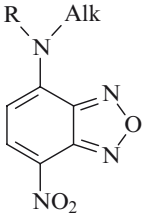
III 

$\tilde{\nu}$ = –1910π^*+22436
r = 0.9907; n = 13 — 1107

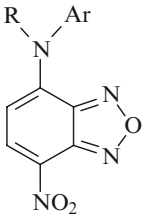
IV 

$\tilde{\nu}$ = –2140π^*+22553
r = 0.9866; n = 13 — 1107

Analysis of the correlation dependences of $\tilde{\nu}$ on π* shows that the introduction of one nitro group into position 7 of 4-hydroxy-5-nitrobenzofurazane displaces the charge transfer band approximately by 3500 cm^{-1} to the short-wave region independent of the solvent. It should be noted that compound **IV** is more sensitive to the solvent effect than compound **III** [1107]. In going from 4-hydroxy-7-nitrobenzofurazans to aminonitrofurazans the sensitivity of $\tilde{\nu}$ to the solvent effect decreases twice, which provides evidence for an increase in the charge transfer degree in the latter. It is worth noting fairly rather good correlations of the reduction potentials ($E_{1/2}$) of nitrobenzofurazan nitro group and charge transfer bands ($\tilde{\nu}$).



$-E_{1/2} = -0.0177\ \tilde{\nu} + 722.83$
r = 0.965; n = 12



$-E_{1/2} = -0.0891\ \tilde{\nu} + 2182.95$
r = 0.961; n = 10

R = H, Alk

The UV spectra of 4-hydroxy-7-nitrobenzofurazan and its conjugate anion have been recorded in 23 solvents and analyzed according to the Kamlet-Taft treatment and compared with that of some parent compounds: 4-methoxy-, 4-propylamino- and 4-diethylamino-7-nitrobenzofurazan [1236]. The phenolate anion of 4-hydroxy-7-nitrobenzofurazan has been shown to exhibit the solvatochromic behavior characteristic for nitrobenzofurazan series in aprotic media, although in protic media hydrogen bonding had a drastic effect on the absorption spectra. MNDO calculations are given of strong negative charges located on the C-5 and C-7 atoms of the anion, indicating that strong hydrogen bonding may take place with solvent molecules. Nevertheless, the stabilization of the anion by hydrogen bonding does not seem to influence the dissociation equilibrium, the acidity of 4-hydroxy-7-nitrobenzofurazan being perfectly in line with that of other nitro phenols whatever the solvent [1236].

The absorption spectra of 4-hydroxy-5,7-dinitrobenzofurazan in solvents with low dielectric permeability (1,2-ethylene dichloride, chloroform) consist of two absorption bands with maxima at 325–328 and 370 nm, dissociation being absent according to conductometry data for the solvents of this type [1230]. In solvents with higher dielectric constant (water, methanol, etc.) in the spectra there are already four individual bands corresponding to different ionic forms of this compound, since according to electroconductivity data 4-hydroxy-5,7-dinitrobenzofurazan in methanol is mainly present as ions ($\lg k_{as} = 1.33$) [1230].

The acid-base equilibrium constants of 3-oxy-7-nitrobenzofurazans were determined with the help of UV spectroscopy [1106, 1234]. Kinetics of the reaction of methoxydegalogenization and hydrolysis of 4-chloro-7-nitro-2,1,3-benzoxadiazole has been investigated [1106]. UV-spectra of some nitrobenzofurazan derivatives are described [1242–1244].

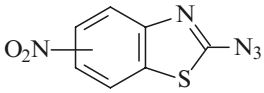
UV-visible spectra of porphyrin systems obtained on the base 4-nitro-, 4-chloro-7-nitro-2,1,3-benzoxadiazoles or 4-nitro-2,1,3-benzoselenadiazole have been studied in detail [1241].

Nitrobenzothiazoles, Nitrobenzothiadiazoles

The UV-spectra of 6-nitrobenzothiazole are characterized by two absorption bands in area λ_{max} 219–220 and 281–285 nm [1245]. The large distance between the long-wave and the short-wave parts of the spectrum can be caused by the presence of the nitro group in the molecule, as well as in the case of nitrobenzimidazoles. Similar but less expressed pattern is also observed and for other nitroisomers of benzothiazole [1245].

The intense investigations in the field of nitrobenzothiazoles have received significant interest due to their application in nonlinear optical materials [785–787, 1246–1248].

The reactions of photochemical decomposition of azides of nitrobenzthiazoles of the following general formula have been investigated in [882, 1249].



The quantum yields of photochemical reactions of azides in polymeric matrixes and their spectral sensitivity have been determined. In the UV-spectra of the aforementioned azides there are two absorption bands distinguished in position and intensity. Highly intense bands (because of the $\pi \rightarrow \pi^*$ transitions of aromatic system) lie in the short-wave part of the spectrum and have the absorption maximum in area λ_{max} 225–230 nm. Bands with smaller intensity in the field of 258–342 nm are assigned [1249] to intramolecular charge transition from the azido group to the nitro group of aromatic system. It is possible to relate a band appearing in the long-wave spectral region 320–330 nm to local transfer of the excited azido group. The maximal quantum yield (at 313 nm) is likely to correspond to the excited state of a molecule with electron transfer from the azido group to the aromatic system [1249].

Mononuclear and dinuclear Cu(II) complexes of *N*-substituted nitrobenzothiazole-sulfonamides [214], alkylation products of 2-amino-6-nitro-benzothiazole [795] have been studied by UV visible spectroscopy.

Questions concerning the application of UV- and IR-spectroscopy for solving the problem of thione-thiol dynamic tautomerism of benzothiazolinthione derivatives including nitrated ones have been considered in detail in [1250].

Some characteristics of the absorption spectra of dyes based on nitrobenzothiazoles are presented in [1001, 1164, 1251–1254]. UV-spectra of other nitroderivatives of benzothiazole can be found in [1199, 1255–1258].

The authors [1259] managed to determine the position of the absorption maximum of 4-nitro-2,1,3-benzothiadiazole; however, because of poor solubility of the substance (*n*-hexane) its concentration and extinction factor remained unknown.

Nitrobenzotriazoles

There are only few examples of the use of UV-spectroscopy for the investigations of nitrobenzotriazoles, while benzotriazoles have an excellent effect of absorbing ultraviolet rays [1260–1263]. Benzotriazoles have been widely developed at present time as a very important industrial ingredient for absorbing UV, mainly as a UV absorber for plastics [1260]. A bathochromic shift in the UV-spectra of 5(6)-nitro- and 4(7)-nitrobenzotriazoles in the alkaline medium indicates the dissociation of compound and, hence, the presence of anions in the solution. The nature of alkoxy group (methoxy, ethoxy, *n*-propoxy, etc.) in 1-alkoxy-4-nitrobenzotriazoles does not influence the position of the absorption bands (λ_{max} 215 and 278 nm) [1261]. The coordination compounds of nitrogen-donor ligand 5-nitrobenzotriazole with palladium(II) and platinum(II) were characterized by physicochemical and spectroscopic methods. The benzotriazole acts as monodentate ligands binding through N-3 [1262].

Dipole Moments

The introduction of highly polar nitro group into molecule usually increases the dipole moment value. Dipole moments (μ) of some nitroazoles are presented in Table 3.72. For example, the dipole moment of 1-methyl- and 3,5-dimethylpyrazole is 2.28 and 2.31 D [1264–1266], and those of their nitro derivatives are 6.26 and 4.18 [1267]; and that of 1,2,4-triazole varies in the 3.16–3.29 D [1265], whereas the dipole moment of 3(5)-nitro-1,2,4-triazole is 6.74 D [1268], etc. (Table 3.72). But there are exceptions. So, the dipole moment of 3,5-dimethylisoxazole is equal to 3.18 D, and dipole moment of its 4-nitroisomer comes out to 1.39 D [1269].

The dipole moments of nitroazoles measured in chloroform are lower than the values obtained in dioxane (Table 3.72) [1268]. This effect is supposed to be caused by mutual orientation of the substrate and chloroform dipoles, which leads to partial compensation of charges and, hence, to the reduction of polarization. The substitution of hydrogen atom of the NH-fragment by a methyl group does not influence much the dipole moment value of nitroazole. Nevertheless, the dipole moment is, for example, sensitive to substitution in position 5 of the 1,2,4-triazole cycle [1268]. The introduction of electron-donating substituent (methyl group)

Table 3.72 Dipole moments (μ, D) of nitroazoles (dioxane, 25ºC)

Compound	$\mu_{exp.}$, D	References
1-Methyl-3-nitropyrazole	6.20, 6.26[a]	[1267]
3(5)-Nitropyrazole	6.19	[1124]
	7.1[b]	[1127]
4-Nitropyrazole	7.0[b]	[1127]
Dioxane complex of 3(5)-nitropyrazole	6.19, 7.12[a]	[1267]
1-Methyl-4-nitropyrazole	4.83	[1124]
3,5-Dimethyl-4-nitropyrazole	4.18, 3.88[a]	[1264, 1265, 1267]
1,3,5-Trimethyl-4-nitropyrazole	4.89, 4.63[a]	[1267]
1-Vinyl-3,5-dimethyl-4-nitropyrazole	4.19	[1124]
3(5)-Mehtyl-5(3)-chloro-4-nitropyrazole	5.92[a]	[1265, 1266]
1-(4-Nitro-Ph)-3-methyl-5-chloro-4-nitropyrazole	2.97[a]	[1265, 1266]
4(5)-Nitroimidazole	8.03[c]	[1124]
	7.38	[256]
1-Methyl-4-nitroimidazole	7.36	[256]
	7.30	[1124]
1-Methyl-5-nitroimidazole	4.07	[256]
5-Nitroimidazole	3.8[c]	[1124]
1,2-Dimethyl-4-nitroimidazole	7.64	[1124]
3,5-Dimethyl-4-nitroisoxazole	1.39[a]	[1269]
3-Phenyl-4-nitroisoxazole	1.10[a]	[1269]
3(5)-Nitro-1,2,4-triazole	6.74	[1268]
3(5)-Methyl-5(3)-nitro-1,2,4-triazole	7.19	[1268]
3(5)-Propyl-5(3)-nitro-1,2,4-triazole	7.26	[1124]
1-Methyl-3-nitro-1,2,4-triazole	6.78, 4.98[d]	[1268]
1-Methyl-5-nitro-1,2,4-triazole	3.30, 2.47[d]	[1268]
4-Methyl-3-nitro-1,2,4-triazole	5.96, 3.76[d]	[1268]
1-Methyl-3,5-dinitro-1,2,4-triazole	4.96, 3.32[d]	[1268]
1-Methyl-3-nitro-5-chloro-1,2,4-triazole	6.05, 4.40[d]	[1268]
1-Methyl-3-nitro-1,2,4-triazol-5-one	1.40	[1124]
4-Methyl-3-nitro-1,2,4-triazol-5-one	1.59	[1124]
1-Adamantane-3-nitro-1,2,4-triazole	7.56	[1072]
5-Nitrothazoline-2-thion	4.71	[1250]
5-Nitroindazole	4.51	[1270]
6-Nitroindazole	2.88	[1270]
5,6-Dinitroindazole	6.14	[1270]
5,7-Dinitroindazole	3.22	[1270]
1-Methyl-5,6-dinitroindazole	6.43	[1270]
2-Methyl-5,6-dinitroindazole	8.96	[1270]
3,5,7-Trinitroindazole	3.39	[1270]
3,4,6-Trinitroindazole	6.80	[1270]
3,5,6-Trinitroindazole	6.57	[1270]
2,3,5,6-Tetranitroindazole	2.19	[1270]
1-(3,4-Dinitrophenyl)-4,6-dinitroindazole	3.62	[1270]
5(6)-Nitrobenzimidazole	5.95	[1265]
2-Methyl-5(6)-nitrobenzimidazole	6.57	[1265]
2-Phenyl-6-nitrobenzoxazole	4.23	[1103, 1265]

(continued)

Table 3.72 (continued)

Compound	$\mu_{exp.}$, D	References
2-(2-Oxyphenyl)-5-nitrobenzoxazole	5.50	[1103, 1265]
4-Nitrobenzothiazole	5.20[a]	[1245]
2-Methylthio-6-nitrobenzothiazole	4.62	[1250]
6-Nitrobenzothiazoline-2-thion	3.40	[1250]
4-Nitro-2,1,3-nitrobenzothiadizole	4.08[a]	[1273]
5-Nitro-2,1,3-nitrobenzothiadizole	2.75[a]	[1273]
5-Nitro-2,1,3-benzoselenadiazole	3.59[a]	[1273]

[a] In benzene (25ºC)
[b] In 1,2-dichloroethane (25°C)
[c] Calculated
[d] In chloroform

causes, as expected, an increase of μ, while an electron-deficient substituent in the same position decreases the dipole moment.

The difference in the μ values of 5(6)-nitrobenzimidazole and its 2-methyl derivative is 0.62 D, which, obviously, can be explained by σ,π-conjugation of the methyl group with the benzimidazole ring [1265].

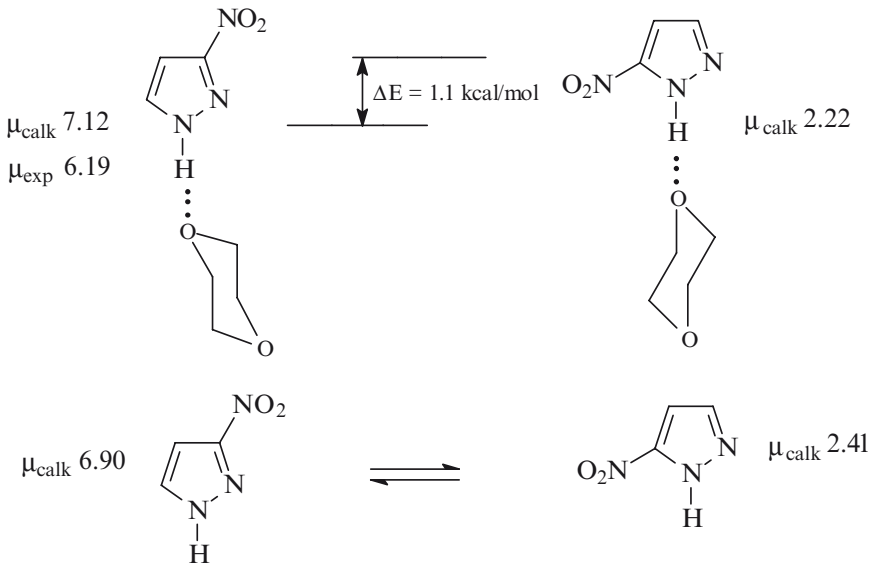
In many cases knowledge of dipole moments allows a conclusion concerning the tautomeric equilibrium state of nitroazoles in the solution [256, 1124, 1250, 1268, 1270, 1271]. The values of dipole moments are in agreement with the data on the acid-base properties of nitroazoles [1175], and also with Charton′s assumption [1272] that in nitrogen-containing aromatic heterocycles with several nitrogen heteroatoms (able to tautomeric transformations) the tautomer having the proton at a heteroatom most remote from the electron-withdrawing substituent is prevailing.

The results of the tautomeric equilibrium study of 4(5)-nitroimidazole show that in the gas phase both tautomers have similar energy, but in the solution the 4-tautomer is more stable than the 5-nitro one [256, 1124]. The dipole moment of 4(5)-nitroimidazole is practically the same as that of 1-methyl-4-nitroimidazole (Table 3.72).

3(5)-Nitropyrazole is insoluble in a low-polar medium at concentrations sufficient for measuring the dipole moment. In solving dioxane, 3(5)-nitropyrazole forms a hydrogen bond with dioxane (H-complex), it is the so-called dioxane effect (Scheme 3.48).

Ab initio calculated (6-31G*) dipole moments of 3- and 5-nitropyrazoles and their H-complexes and experimentally measured values of 1-methyl-3-nitropyrazole (6.20 D, see Table 3.72) show that the tautomeric equilibrium is shifted to 3-nitropyrazole in dioxane [1267]. Calculations show that the dipole moments of the molecule and the corresponding H-complexes slightly differ (~0.2 D) and the difference between the energies obtained for these complexes is 1.1 kcal/mol [1267].

Dipole moments, static averaged polarizabilities and hyperpolarizabilities of thiazole, benzothiazole, and their dipolar nitro and amino derivatives possessed



Scheme 3.48

nonlinear optical properties have been calculated by B3LYP and MP2 theories [1274]. The 6-nitrobenzothiazole-2-amine and 2-nitrobenzothiazole-6-amine show the largest electric properties from the investigated set of molecules. Benzothiazole (thiazole) as a bridging unit between NO_2 and NH_2 groups exhibits slightly enhanced nonlinear optical characteristic than *para*-nitroaniline. Thiazole behaves as a dipolar bridge rather than just an electron acceptor substituent in singly substituted derivatives.NO_2 group interacts better with thiazole than NH_2, which can result from the tendency to pyramidization of the NH_2 group. The effectiveness of thiazole and benzothiazole as a conjugative pathway between electron acceptor NO_2 and electron-donor NH_2 substituents has been compared with benzene [1274].

The calculated dipole moment values of 5-substituted (including nitrotetrazole) correlate well with σ_p constants of substituents [1271].

The *ab initio* calculations of dipole moments of ion pairs of 4-nitropyrazolide anion have been carried out [1275].

Semiempirical optimization of molecular structures and *ab initio* calculations of dipole moments of nitrobenzoxazole family of potential nonlinear optic materials have been carried out [1202]. Clear evidence was found that conditions such as conjugation efficiency and electron donor/acceptor strength cannot be evaluated separately, due to structural changes in molecular distribution.

Dipole moments of 1,3-dimethyl-2,2-tetramthylene-5-nitrobenzimidazoline, perspective for photorefractive polymeric materials [1276], and some nitrobenzofurazans [1206, 1277] have been measured.

The electrostatic parameters for generating partial charges in the calculation of dipole moments were modified to achieve better correlation with experimental

dipole moments for a training set of 160 compounds, which included aromatic, heteroaromatic molecules, etc. [1278]. The conjugate nitro group parameters have been included in the system calculation within the MM2 force field [1279]. New parameters have been estimated by a statistical process from X-ray molecular structures. Comparison of the corresponding results with those given by the MM2(91) force field parameters shows a clear improvement for dihedral and bond angles. For N–O and C–N bond lengths a slight global improvement is also observed. A closer examination of the results for the latter bond shows that the parameters proposed are more adapted to five-membered ring derivatives. The introduction of a correction factor to the calculated molecular dipole moment in conjunction with a necessary re-estimation of some *C*-bond dipole moments also leads to improved total molecular dipole moments [1279].

Mass Spectrometry

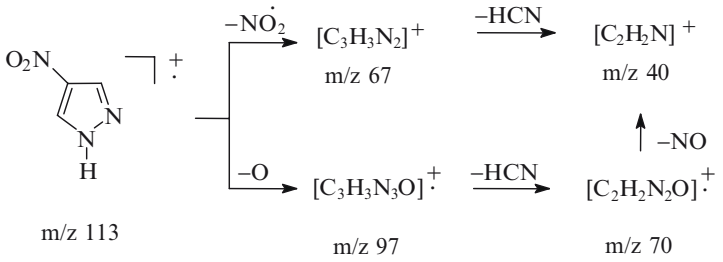
Mass spectrometry has been widely used for the elucidation and determination of the structure of heterocyclic compounds. There is no doubt that mass spectrometry due to its extraordinary sensitivity is one of the major tools to help solve structural problems of varying degrees of complexity. During the last years there has been an almost explosive growth in the use of mass spectrometry by organic chemists. The rapid growth of the technique has been accompanied by, and to a large extent engendered by, the development of relatively simple theories for the rationalization of the observed fragmentation. Nowadays, mass spectrometry together with other spectral methods represents an integral part of any scientific investigation in organic chemistry.

In a recently published book [1280] on mass spectrometry, the fragmentation of organic molecules under electron impact, electron capture, and other ionization methods is described not in the traditional way – *by classes* – but rather by isomerization and fragmentation *types* with simple bond cleavage, hydrogen- and skeletal rearrangements with systematic thermodynamic approach and separately for positive and negative ions. Our review on mass spectrometry of nitroazoles has been reported in 1998 [1281].

Nitropyrazoles

Electron-impact (EI) fragmentation of nitropyrazoles gives rise to the main ions $[M–O]^+$, $[M–NO]^+$, $[M–NO_2]^+$ which are typical for aromatic nitro compounds [1282–1286]. 4-Nitropyrazole fragmentation to $[C_2H_2N]^+$ follows two pathways (Scheme 3.49) [1285]:

The structure of 5-substituted 4-nitropyrazoles [246, 1287], 3,5-dinitropyrazole ammonium salt has been confirmed by mass spectrometry [1288]. Mass spectra

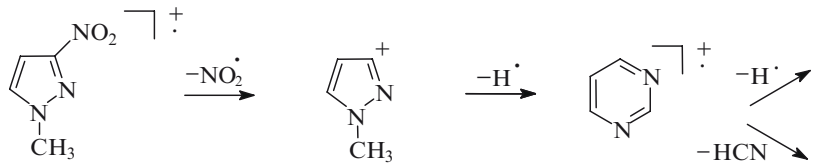


Scheme 3.49

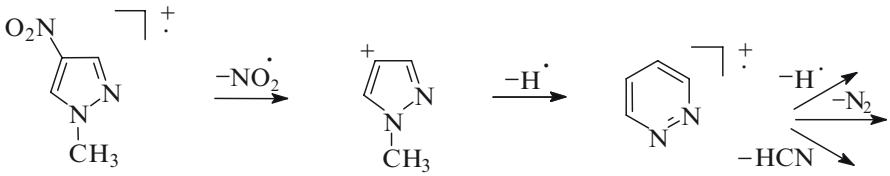
analysis of labeled 4(5)-nitro-5(4)-cyanoimidazoles (^{15}N and ^{13}C) shows that during fragmentation in mass spectrometer the labeled atoms are present in all the main fragmentation ions of *m/z* higher than 42 [1287].

Mass spectral analysis of methylated nitropyrazoles has been carried out [302, 1282–1284]. The primary steps of fragmentation involve, as a rule, elimination of nitro and nitroso groups. The mass spectra of 1-methyl-substituted nitropyrazoles are characterized by a stable molecular ion [1282]. After CO extrusion the $[C_4H_3N_2O]^+$ ion with *m/z* 97 is transformed to $[C_3H_5N_2]^+$ with *m/z* 69 which further breaks down in two ways. On the one hand, after elimination of C_2H_2 a $[CH_3N_2]^+$ ion with *m/z* 43 is formed. On the other hand, NCH loss leads to $[C_2H_4N]^+$ with *m/z* 42. Another very interesting process involves direct formation of $[CH_3N_2]^+$ ion when the $[C_3H_2NO_2]$ fragment is expelled from $[M]^+$ [1282].

Unlike 5-nitro-1-methylpyrazole the fragmentation of 3-nitro- and 4-nitro-1-methylpyrazole $[M–NO_2]^+$ ions results in the formation of pyrimidine and pyridazine radical cations, respectively (Schemes 3.50 and 3.51) [1282]:



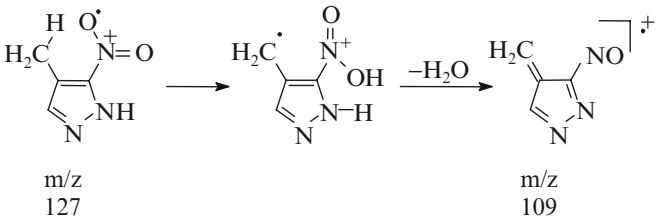
Scheme 3.50



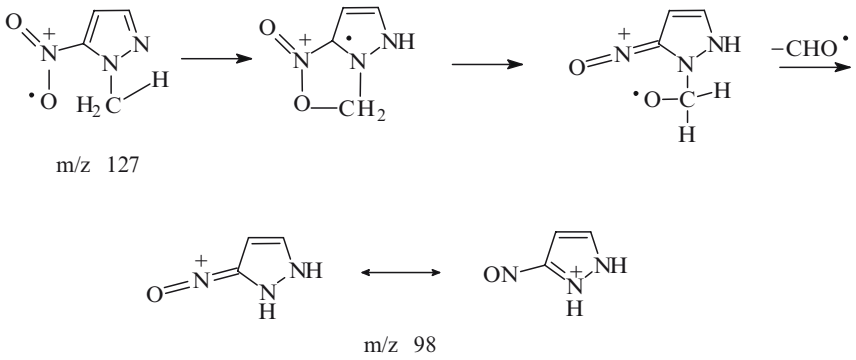
Scheme 3.51

Methyl-substituted nitrodiazoles (nitropyrazoles and nitroimidazoles) in which the substituents occupy adjacent positions in the cycle are subject to several *ortho* effects [1283, 1284]. The latest are useful in structure determination and isomer recognition of compounds. These effects are attributed to interaction of the substituents only. As a result, in some cases loss of $OH^{\bullet}$ and H_2O [1283], and $CHO^{\bullet}$ and $CH_2O^{\bullet}$ [1284] is observed. The way by which loss of H_2O in 3(5)-nitro-4-methylpyrazole occurs is shown in Scheme 3.52 [1283]:

At variance with 3(5)-nitro-4-methylpyrazole, for 1-methyl-5-nitropyrazole the loss of $CHO^{\bullet}$ is observed (Scheme 3.53) [1284]:

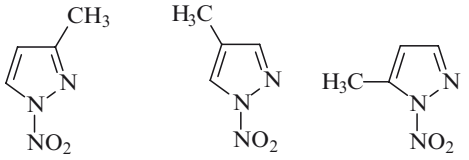


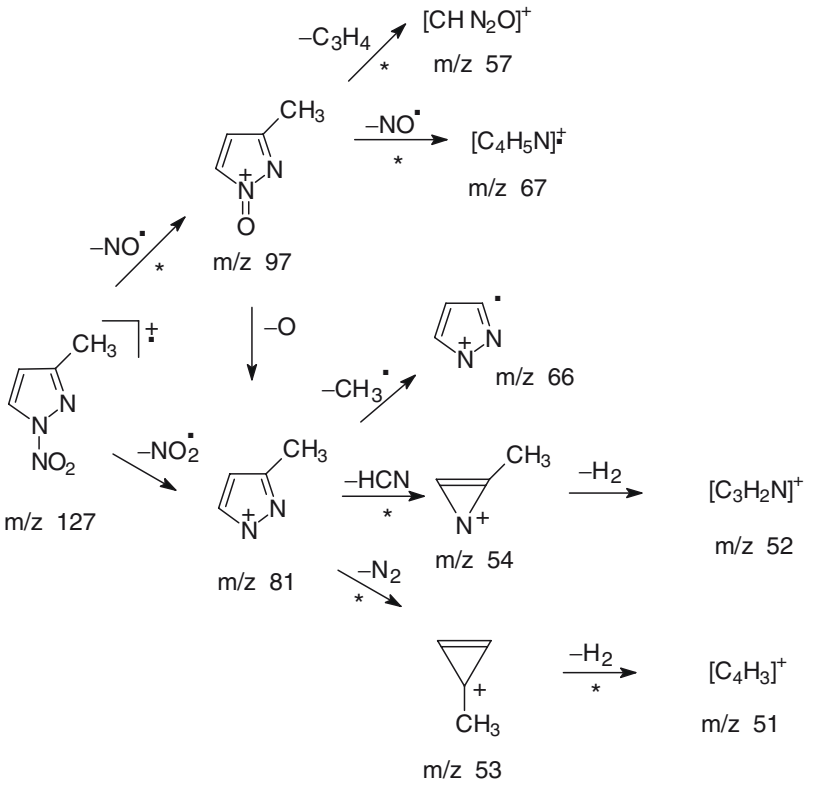
Scheme 3.52



Scheme 3.53

The mass spectra of three monomethylated isomers of *N*-nitropyrazole have been studied [1284]:





Scheme 3.54

Unlike C-NO_2-pyrazoles the main common features of N-NO_2-pyrazoles are the loss of an $NO^{\bullet}$ fragment and the absence of an $[M\text{-}O]^+$ fragment and of an $[M\text{-}NO]^+$ ion. The last ion (*m/z* 81) has a moderate intensity and is the main source of secondary fragmentation. As an example, the fragmentation of 1-nitro-3-methylpyrazole is shown (Scheme 3.54) [1284].

The structure of *N*-nitration products of 3(5)-substituted pyrazoles has been confirmed by mass spectra [1289].

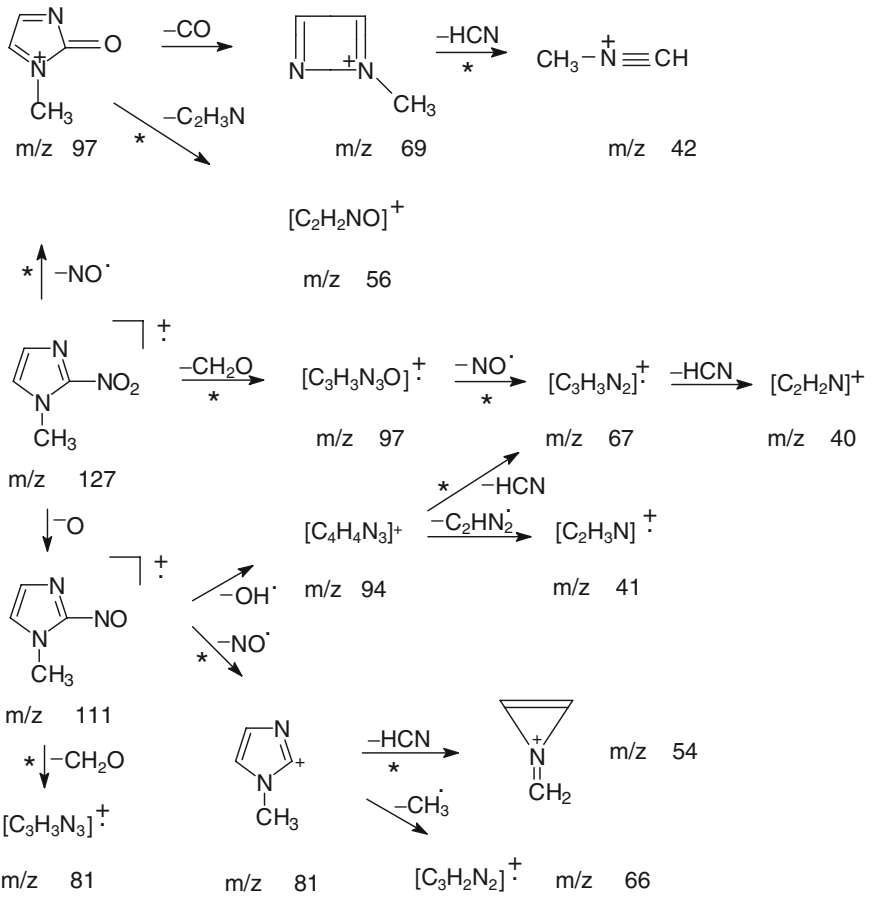
A mass spectrometric study of 3-amino- and 5-amino-1-methyl-4-nitropyrazole and 3-nitro-, 5-nitro-4-amino-1-methylpyrazoles has been performed [1286]. The highest relative intensity of the $[M\text{-}NO]^+$ peak is observed with 5-amino-1-methyl-4-nitropyrazole. The authors believe this to be related with the pyrazole ring π-excessive position 4 and the easy transmission of the electronic effect of the amino group through the (C-4)-(C-5) bond. The $[M\text{-}NO]^+$ peak relative intensity is minimal for 4-amino-1-methyl-3-nitropyrazole. This indicates a lower stabilization of the $[M\text{-}NO]^+$ ion by the N-1 atom compared with that produced by the N-2 atom seemingly due to the electron-withdrawing properties of the pyrazole ring N-2 atom [1286].

The mass spectrometric behavior of iridium(I) and iridium(II) 3,5-dimethyl-4-nitropyrazolates was studied in detail with the aid of linked scans and mass analyzed ion kinetic energy spectra [1290].

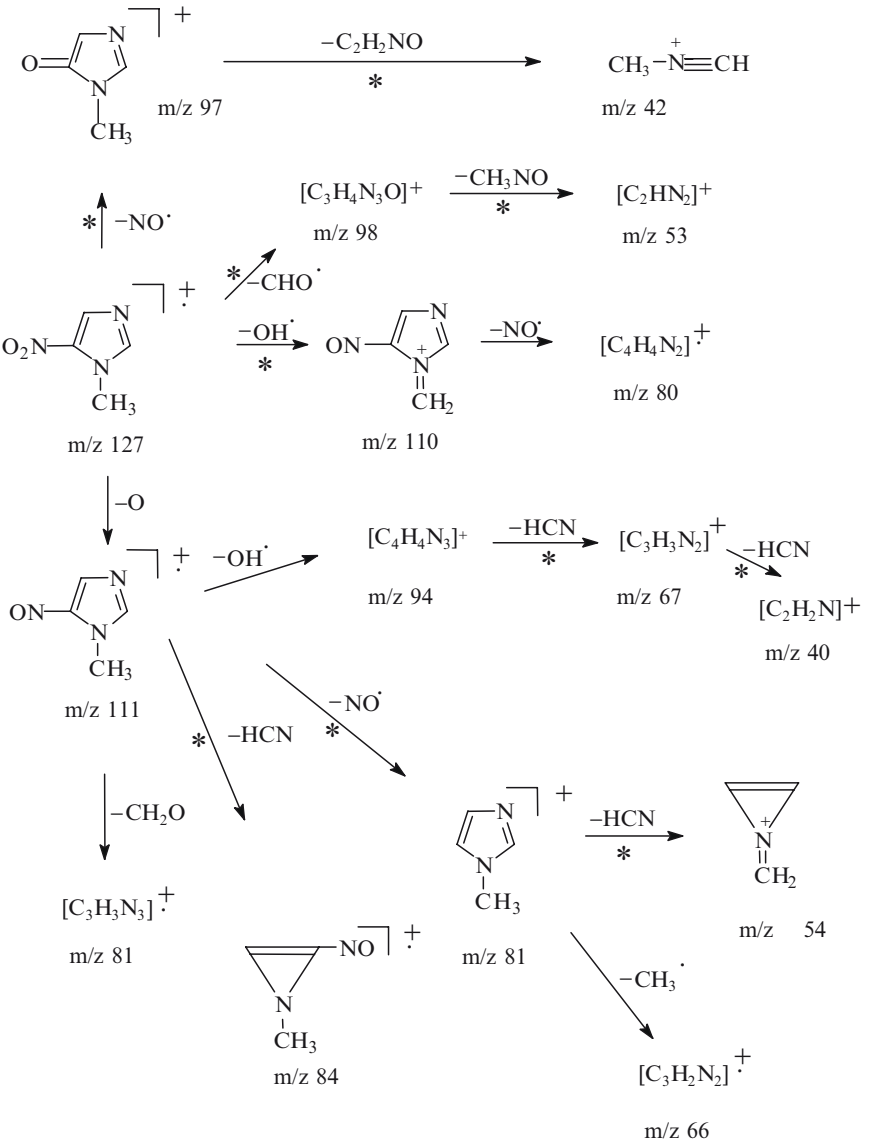
Mass spectrometry has been used for the structural determination of isomeric 1-methyl-3(5)-nitro-4-pyrazolcarbonitriles [302], 1,5-dimethyl-3,4-dinitropyrazole [279], 4,4-dinitro-1,1-methylenedipyrazole [1291], 3-amino-5-benzylamino-4-nitropyrazole [317], amino derivatives of 4-nitropyrazole [1292], antibacterial compounds 3-(3-methyl-4-nitro-1*H*-pyrazole-5-yl)- and 3-(3-methyl-4-nitro-1-alkylpyrazole-5-yl)-5-methyl-4-nitroisoxazoles [500], some 1-heteroaryl-4-nitropyrazoles [311].

Nitroimidazoles

A detailed analysis of the mass spectra of methylated nitroimidazoles has been carried out [321, 1283, 1284, 1293–1296]. These compounds are characterized by an intense molecular ion peak, the fragmentation pattern being the same as that of aromatic nitro compounds (Schemes 3.55 and 3.56) [1293].



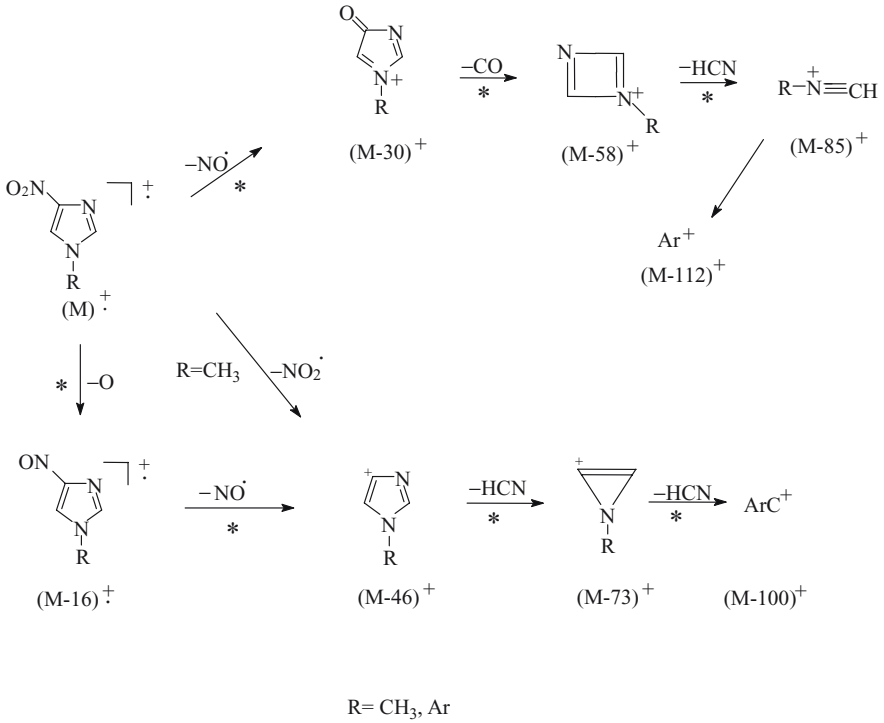
Scheme 3.55



Scheme 3.56

A distinctive fragmentation feature of these compounds is that the $[M\text{-}NO]^+$ peak intensity of 1-methyl-2-nitroimidazole is much higher than that of isomeric 4- and 5-nitroimidazoles [1293]. The first fragmentation stages of 1-methyl-4-nitroimidazole involve $[NO_2]^{\bullet}$ abstraction which does not occur in the case of 1-methyl-5-nitroimidazole (Scheme 3.56) [1293].

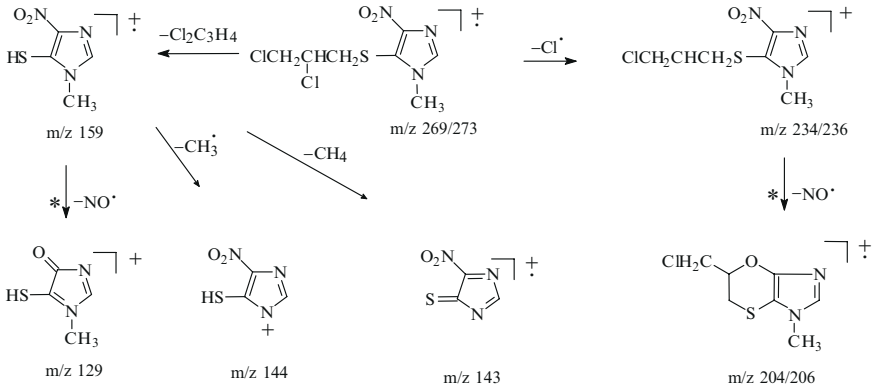
In the mass spectra of 1-aryl-4-nitroimidazole $[NO_2]^{\bullet}$ abstraction from the molecular ion is not observed [1297] at variance with 1-methyl-4-nitroimidazole [1293] (Scheme 3.57).



Scheme 3.57

The main fragmentation pathway of 1-aryl-4-nitroimidazoles does not differ significantly from that of 1-methyl-4-nitroimidazoles [1293] and 4(5)-nitroimidazoles [1298]. Nevertheless, unlike 4(5)-nitroimidazoles and 1-alkyl-4-nitroimidazoles in the mass spectra of all 1-aryl-4-nitroimidazoles and 1-aryl-2-methyl-4-nitroimidazoles the peaks due to ArC^+ ions appear [1297]. In this work the EI mass spectra of 2- and 5-methyl-1-aryl-4-nitroimidazoles are also analyzed in detail.

It is interesting to notice that also the fragmentation of halogen-containing 4-nitro- and 5-nitroimidazole isomers occurs in different ways. The fragmentation of the 4-nitro isomer leads to aziridine ions, whereas that of the 4-nitro isomer gives rise to cyclopropenone [1296]. One of the fragmentation pathways of 1-methyl-4-nitro-5-(2,3-dichloropropyl)-thioimidazole involving loss of $Cl^{\bullet}$ and $NO^{\bullet}$ gives rise to a 1,4-oxathian cycle annealated with an imidazole ring [1299] (Scheme 3.58).



Scheme 3.58

In the mass spectra of 1-hydroxy-2-aryl-4-nitroimidazole-3-oxides the molecular ions and the fragments [M – O], [Ar-CH=NH], [Ar-CNH], [ArCN] were observed [355, 1300]. A careful mass spectrometric investigation of these oxides showed an unusual fragmentation. Along with an O-shift (with subsequent formation of O_2) and the formation of the [Ar-C(O]$^+$ the cation and other processes an unexpected release of N_2O_3 (or $N_2O + O_2$) from the molecular ion with formation of the [HC(CN(O)CHAr]$^+$ fragment was noticed [1300].

The use of mass spectrometry in tautomerism studies of azoles, in particular of 4(5)-nitroimidazoles [1297, 1301], 2-methyl-4(5)-nitroimidazoles [367] and 3(5)-methyl-5(3)-nitropyrazole [1282], can afford only qualitative information.

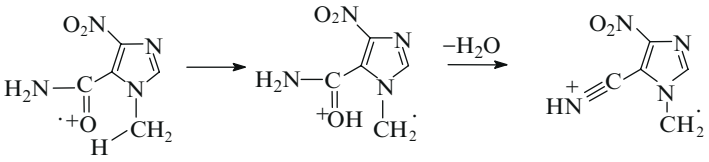
When N′-4-[*bis*(2-chloroehtylamino]benzylidenehydrazines of 4-nitroimidazol-1-acetic acid are melted, they undergo rearrangement to the azines of the corresponding benzaldehyde [1303].

Some fragmentation pathways of 4(5)-piperidino-, 4(5)-pyrrolidino- and 4(5)-morpholinosubstituted 5(4)-nitro-2-methylimidazoles [1303], and 1-organyl-2-methyl-4-nitroimidazoles and their 5-iodo derivatives have been studied [1304].

By the negative chemical ionization (NCI) mass spectral method the negative ions of 2-nitroimidazole are obtained [1305]. This method is much more sensitive than the positive chemical ionization one. The analytical potential of the NCI mass spectrometry for the analysis of different classes of nitro compounds has been discussed [1305].

Mass spectra of 1,4-dinitro-, 2,4-dinitro-, and 4,5-dinitroimidazoles have been studied [1306]. Comparisons of mass spectra (70 eV) of these compounds have shown that the fragment product ions have the same *m/z* values, but differ in their relative abundance and in the ion appearing the main peak. It seems that this difference is due to the nitramine functionality of 1,4-dinitroimidazole [1306].

The mechanism of electron-impact-induced loss of water from the molecular ion of nitroimidazoles has been studied [1295, 1307]. A possible mechanism of the elimination of water from 1-methyl-4-nitroimidazole-5-carboxamide [1307] is presented in Scheme 3.59:



Scheme 3.59

The *N*-methyl group is the source of one of the eliminated hydrogen. The subsequent loss of water by 1,2-elimination gives rise to the formation of the nitrile structure. Mass spectra of mono- , di-, and trideuterated nitroimidazoles were investigated in order to prove the fragmentation mechanism [1307].

The formation of labeled (2-methyl-4-nitro-1-[^{15}N-1]imidazolyl)acetic acid [443], 4-nitroimidazole nucleosides [1308], 1-(2′-deoxy-2′-D-glucopyranosyl)-4-nitroimidazoles [448] from 1,4-dinitroimidazole in result of ANRORC reaction (degenerated transformation of imidazole ring) was confirmed by mass spectral analysis.

Mass spectrometry is widely used to prove the structure of compounds. Mass spectra of misonidazole [1035, 1309], secnidazole, ronidazole, dimetridazole [1310, 1311], 1,4-dinitroimidazoles and their 2-, and 5-methyl derivatives [426], some dinitro- [380] and halonitroimidazole derivatives [373, 380, 381], 5-guanidino-4-nitroimidazole [1312], 4(5)-(4-alkoxyphenyl)- [459] and 4(5)-(4-acetylaminophenyl)-5(4)-nitroimidazoles [460], 1-(2′,4′-dichlorophenyl)-2-(4-nitro-1*H*-1-imidazolyl)ethanone [328], 5-nitroimidazole derivatives (antitrichomonal agents) [1313], nitroimidazole metabolites [1037, 1130], products of hydroxymethylation and cyanomethylation of 2-, 4-, and 5-nitroimidazoles (potential radiosensitizers) [425], cyano derivatives of nitroimidazoles [471], a large series of nitro derivatives of alkylthio- and alkylsulfonylimidazoles [360], *N*-substituted products of 2-methyl-5-nitroimidazoles (chemotherapeutic agents) [325, 326, 344, 413, 414], (1-methyl-5-nitro-2-imidazolyl)pyrazole derivatives [1314], 2-(2-oxazolyl)- and 2(2-oxazolinyl)-1-methyl-5-nitroimidazole [475], thiazolyl nitroimidazoles [372], 1-organyl-2-nitroimidazoles [387, 389, 421], an oligo *N*-methylimidazole carboxamide containing a terminal 2-nitroimidazole nucleus [1315], and other nitroimidazoles [310, 1145, 1146, 1262, 1316] have been studied.

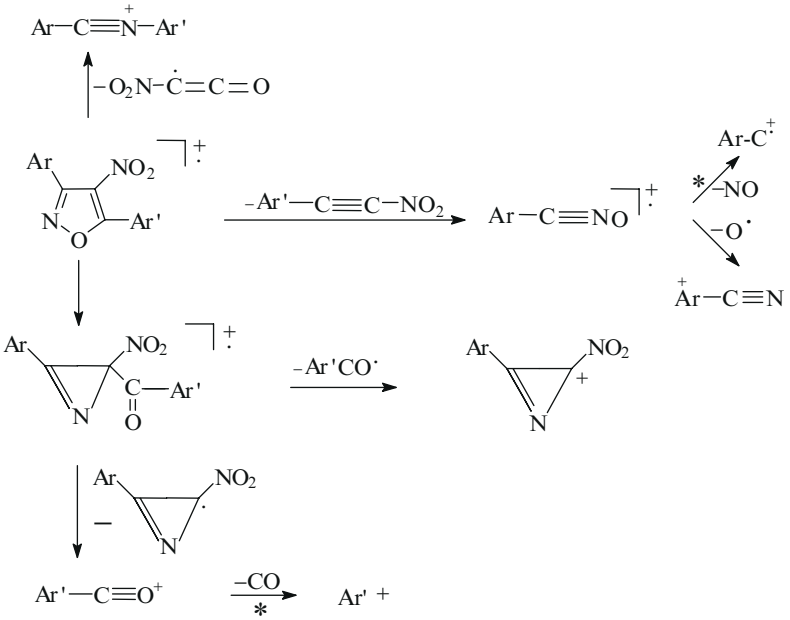
5-Guanidino-4-nitroimidazole formation in peroxynitrite-treated DNA was characterized by electrospray ionization mass spectrometry with selected reaction monitoring [409].

The base mass spectra peaks of 5-(2-aminoethylamino)-4-nitroimidazole [365], iodo and bromo derivatives of 4-nitro-, and 5-nitro-1-methylimidazoles [461], 4(5)-nitroimidazole-5(4)-carboxaldehyde and (5(4)-nitroimidazole-4(5)-yl)methyl nitrate [462], and some 1-aryl(organyl)-4-nitroimidazole [394, 400, 401, 449] have been discussed.

Nitroisoxazoles

Analysis of mass spectra of nitroisoxazoles has been carried out in a small number of works [1317–1321]. In general, the mass spectra of isoxazoles are significantly different from those of oxazoles because the initial fragmentation of isoxazoles involves N-O bond cleavage. Surprisingly, we were unable to find mass spectra of nitrooxazoles in the literature.

Electron-impact fragmentation of 3,5-diaryl-4-nitroisoxazoles occurs by the Scheme 3.60 [1317]:



Scheme 3.60

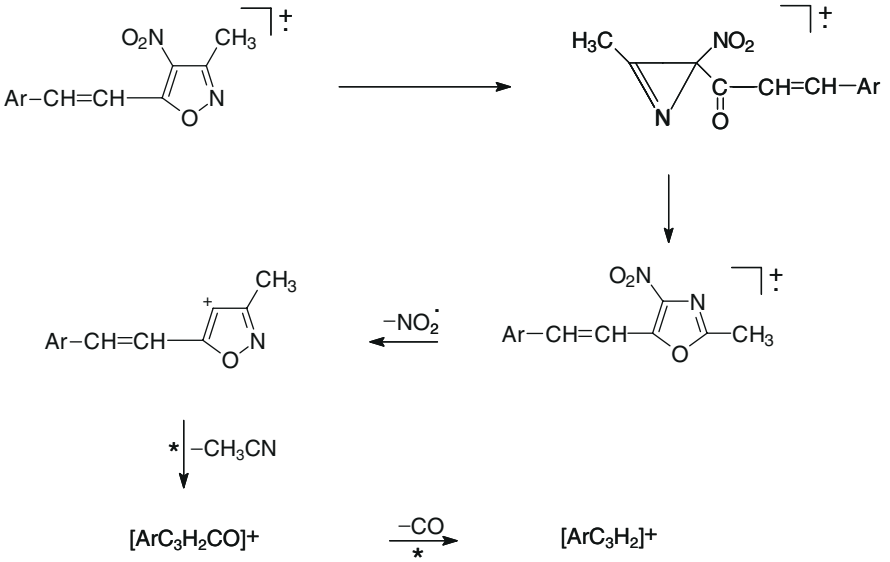
In the mass spectra of nitro compounds there are, as a rule, rather intense peaks due to the $[M\text{-}O]^+$, $[M\text{-}NO]^+$, $[M\text{-}NO_2]^+$ ions, whose intensity is however negligible in the case of 4-nitroisoxazoles [1317, 1319, 1320]. Molecular ion fragmentation proceeds with cleavage of the ring N–O bond and subsequent formation of an $[Ar´\text{-}C{\equiv}O]^+$ ion (aroyl ion). The aroyl ion displays the highest intensity in all the compounds examined [1317]. Generally, the formation of the aroyl cation is reduced when an electron-releasing substituent is placed on the Ar group. The arylnitriloxide ion $[Ar\text{-}C{\equiv}N\text{-}O]^+$ is stabilized and the retro-1,3-dipolar cycloaddition prevails over the formation of aroyl cation. The position of the Ar and Ar´ substituents in the isoxazole ring was established by mass spectrometry [1317].

The fragmentation of styryl-substituted 4-nitroisoxazoles has been studied [1319, 1320]. One of the possible fragmentation ways of 3-methyl-4-nitro-5-styrylisoxazole is presented in Scheme 3.61 [1319]:

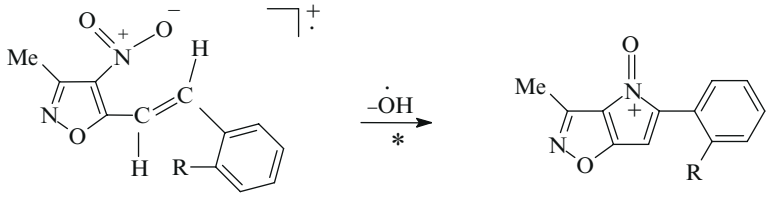
In this case the isoxazole ring is transformed to an oxazole ring.

For 3-methyl-4-nitro-5-(*ortho*-R-styryl)isoxazoles one can observe an $[M-17]^+$ peak formed upon abstraction of oxygen from the NO_2 group and an α-hydrogen of the styryl fragment(Scheme 3.62) [1320]:

This fragmentation is also observed in other nitro compounds [1322].



Scheme 3.61



M_i^+ m/z (229+R) m/z (M-17) $^+$

R = OH, Cl, NO_2, OMe, H, Me, COOMe, NH_2

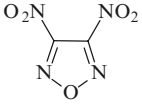
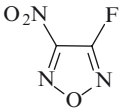
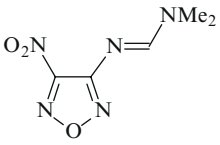
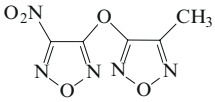
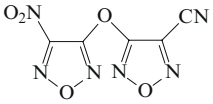
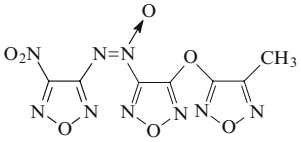
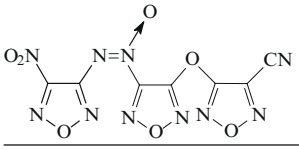
Scheme 3.62

The mass spectra of a large series of alkyl- and arylisoxazole derivatives including 3,5-dimethyl-4-nitroisoxazole are presented [1321].

Mass spectrometry was used for the structural identification of the *bis*(3-methyl-4-nitroisoxazol-5-yl) and ethyl ether of 3-methyl-4-nitroisoxazol-5-yl pyruvic acid [1319], the antibacterial compounds 3-(3-methyl-4-nitro-1*H*-pyrazole-5-yl)- and 3-(3-methyl-4-nitro-1-alkylpyrazole-5-yl)-5-methyl-4-nitroisoxazoles [489], 7-hydroxy-2-methyl-3-[2-(3-methyl-4-nitro-5-isoxazolyl)-ethyl]-3-hydroxyiminobutyrate and 7-hydroxy-2-methyl-3-[2-(3-methyl-4-nitro-5-isoxazolyl)-1-arylethyl]-chloromones [490], and 4-aryl-3-(3-methyl-4-nitroisoxazol-5-yl)-2-pyrazolines [1323].

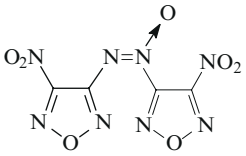
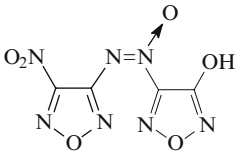
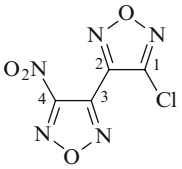
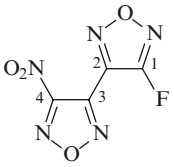
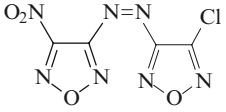
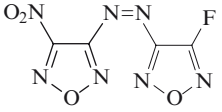
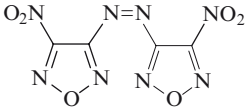
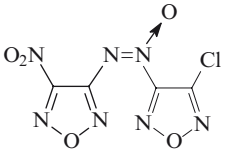
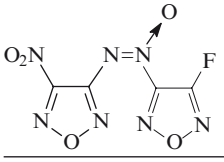
Recently a number of energetic nitrofurazans have been obtained and their structure was confirmed by mass spectrometry [136, 139, 408, 504, 506, 508, 511, 514, 519] (Table 3.73).

Table 3.73 Mass spectra of nitrofurazans

Compound	*m/z*	Refs
	160 (M^+), 68, 52, 46, 44, 30	[506]
	160 (M^+), 114 [M – NO_2]$^+$, 98 [M – O–NO_2]$^+$, 68 [M – 2NO_2]$^+$	[408]
	133 (M^+), 87 [M – NO_2]$^+$, 98 [M – NO_2–NO]$^+$	[504]
	185 (M^+), 139 [M – NO_2]$^+$	[511]
	213 (M^+), 167 [M – NO_2]$^+$, 137 [M – NO2–NO]$^+$	[514]
	224 (M^+), 178 [M – NO_2]$^+$	[514]
	325 (M+), 309 [M – O]$^+$, 295 [M – NO]$^+$, 264 [HM – NO_2] $^+$	[514]
	336 (M^+), 320 [M – O]$^+$, 290 [M – NO_2]$^+$, 244, 214, 178 (NCFOF)	[514]

(continued)

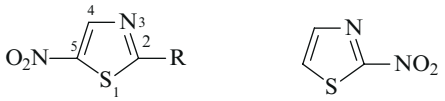
Table 3.73 (continued)

Compound	*m/z*	Refs
	272 (M^+), 256 $[M - O]^+$, 226 $[M - NO_2]^+$, 210 $[M - NO_2–NO]^+$	[408]
	185 $[M - N_2–NO]^+$	[508]
	218, 216 $[M]^+$	[511]
	216 $[M]^+$, 155 $[M - NO_2]^+$	[504]
	247, 245 $[M]^+$	[511]
	229 $[M]^+$	[504]
	257 $[MH]^+$	[139]
	263, 261 $[M]^+$	[511]
	245 $[M^+$, 229 $[M - O]^+$, 158 $[O_2NFuN_2O]^+$, 153 $[M - O–NO_2–NO]^+$, 142 $[O_2NFuN_2]^+$, 117 $[FFuNO]^+$, 115 $[FFuN_2]^+$, 96, 95, 70, 69, 68	[504]

Nitroisothiazoles, Nitrothiazoles, and Nitrothiadiazoles

The spectra of 16 isothiazole derivatives including 4-nitroisothiazoles have been examined [1324]. Electron impact induces cleavage of the S-N bond and abstraction of a fragment of type R_3CN or HCN occurs [1324].

An analysis of the mass spectra of 2-substituted 5-nitrothiazoles and 2-nitrothiazole has been carried out (Scheme 3.63) [1325]:

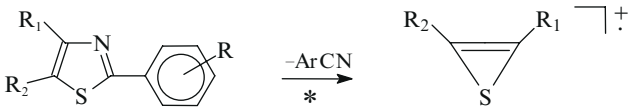


R = NMe_2, NHCOMe, NH_2, H, Br, Cl

Scheme 3.63

It is believed that the fragmentation of the compounds studied proceeds via 1–2 and 3–4 bond cleavage. The nitro group of the above compounds decreases the molecule stability, whereas the dimethylamino group stabilizes the cycle. The Cl and Br atoms influence the thiazole ring fragmentation in different ways [1325].

The derivatives of 2-arylthiazoles (including 2-aryl-5-nitrothiazoles) have been synthesized and studied by mass spectrometry [533]. The main fragmentation of 2-aryl-5-nitrothiazoles is presented in the general view of Scheme 3.64 [533]:



m/z 56 + R_1

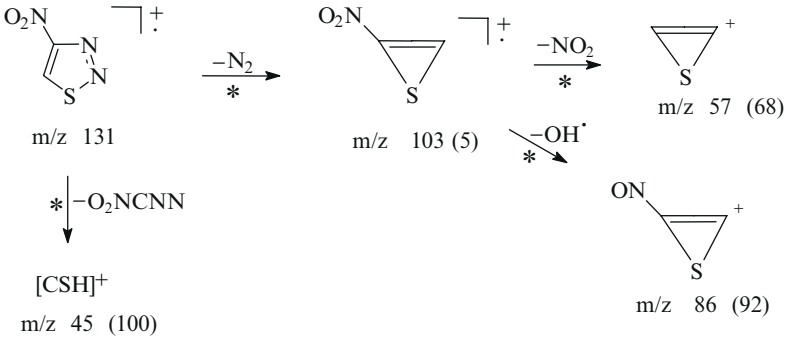
Scheme 3.64

The base fragmentation peaks of 4-methyl-5-nitrothiazol-2-yl derivatives of urea and thiourea [1165] and 4-substituted 2-halogen-5-nitrothiazoles [546] are discussed.

2-Amino-5-nitrothiazole is widely used as effective matrixes in matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) study of oligonucleotide and protein [1326].

The route of 4-nitro-1,2,3-thiadiazole fragmentation is given in Scheme 3.65 (peak intensities are indicated in brackets) [1327].

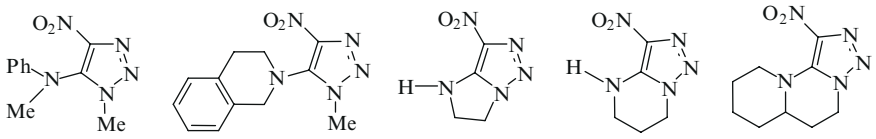
The fragmentation proceeds in a manner typical for unsaturated 1,2,3-thiadiazoles; however, an N_2 evolution takes place and the generated ion loses either the hydroxy radical or the NO_2 group [1327].



Scheme 3.65

Nitrotriazoles and Nitrotetrazoles

The mass spectral characteristics are considered as a proof of the structure of 1-aryl(heteryl)- and 2-aryl(heteryl)-4-nitro-1,2,3-triazoles 141,177,602–604, 1-organyl-4-nitro-1,2,3-triazoles [597], some 4-nitro-1,2,3-triazoles of potential interest as antiprotozoal agents [1328]. The molecular ion peaks of the following 4-nitro-1,2,3-triazole derivatives are reported (Scheme 3.66) [1328].



Scheme 3.66

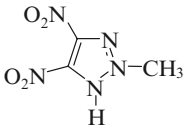
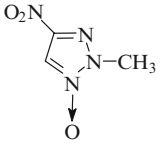
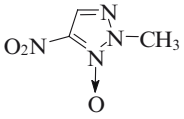
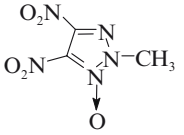
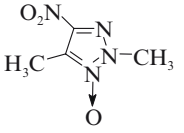
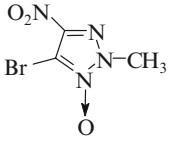
A large series of 1,2,3-triazole-1-oxide derivatives including nitro-substituted ones was synthesized and studied by mass spectrometry (Table 3.74.) [177, 608].

A more intensive peak in nitro derivatives of 1,2,4-triazole is *m/z* 30 (NO^+) that is caused by the presence of NO_2-group (Scheme 3.67, Table 3.75) [1329].

As seen from the schema the available radical center in ionized nitro group —N^+(=O)–$O^·$ gives the possibility of interaction of this center with the π-system of the azole cycle or migration to one the hydrogen atoms. The generation of the cation or cation-radical (CR) plays the great role in the formation of the final products. The positive charge of the CR is stabilized by lone-pair of nitrogen atom, and radical center – by N and O atoms and the π–system. Herewith it is observed the segregation of the neutral molecules N_2, H_2O, N_2O, HCN, HNC, HCNO, Cl_2, or radicals NO_2, HOO, etc. having relatively low enthalpy of formation [1329].

The analogical fragmentation way shows the isomeric 1-chloro- and 5-chloro-3-nitro-1,2,4-triazoles herewith that the isomers have some differences. 5-Chloro

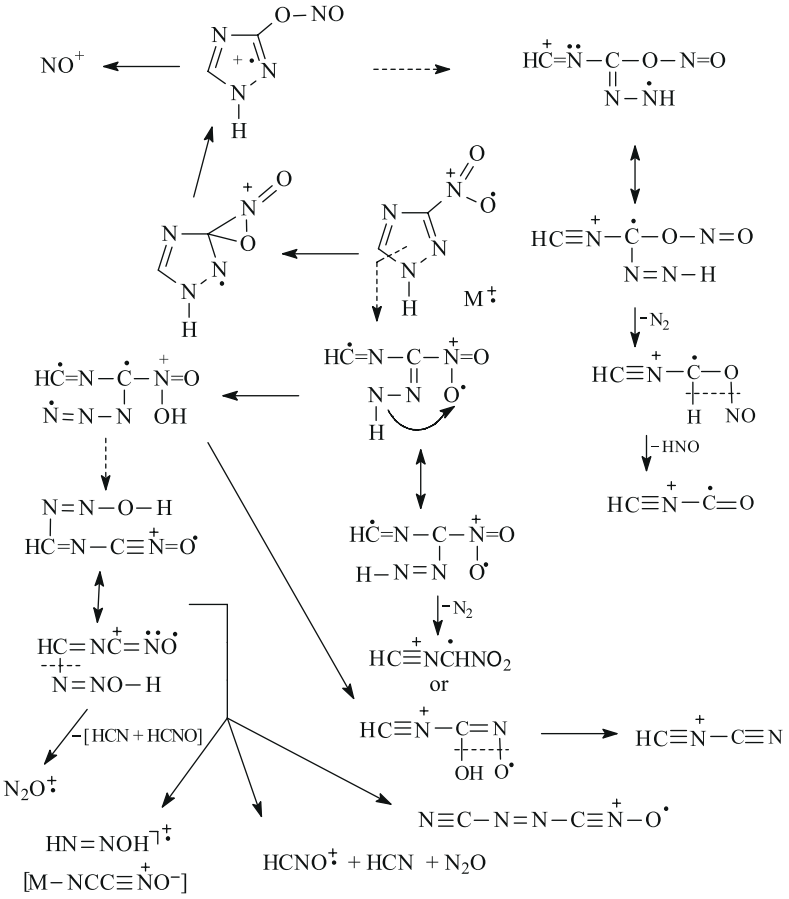
Table 3.74 Mass spectral data of nitro-1,2,3-triazole-1-oxides and 2-methyl-4,5-dinitro-1,2,3-triazole [608]

Compound	*m/z*	I, %	Fragment
	173	100	M^+
	157	34	$[M - O]^+$
	81	26	
	144	62	M^+
	128	5	$[M - O]^+$
	114	43	$[M - O_2]^+$
	98	27	$[M - NO_2]^+$
	68	92	
	53	100	
	144	38	M^+
	128	7	$[M - O]^+$
	112	9	$[M - O_2]^+$
	98	100	$[M - NO_2]^+$
	189	26	M^+
	173	2	$[M - O]^+$
	143	16	$[M - NO_2]^+$
	97	100	
	158	57	M^+
	128	3	$[M - NO]^+$
	112	3	$[M - NO_2]^+$
	82	45	
	67	100	
	222+224	60	M^+
	206+208	1	$[M - O]^+$
	176+178	7	$[M - NO_2]^+$
	146+148	82	
	131+133	70	

derivative has an intensive peak of ion *m/z* 76/78 (30 and 9.3%, respectively) (Scheme 3.68):

A more intensive ion peak in mass spectrum of 1-chloro-3-nitro-1,2,4-triazole is $[M\text{-}(Cl{+}N_2)\text{-}NO_2]^+$ with *m/z* 39 (C_2NH^+). The similarity of mass spectra of these isomers indicates active rearrangement processes with participation of nitro group and migration of Cl and H atoms (Table 3.75) [1329]. Fragmentation of bromo-containing nitrotriazoles in comparison with chloro derivative comes more profoundly: the intensity of molecular peaks and the peaks obtained by ejecting small fragments is essentially decreased. It is interesting that the mass spectrum of 1,5-dichloro-3-nitro-1,2,4-triazole has a very intensive ion peak $Cl–N^+{\equiv}N$, whereas the same peak in the spectrum of 1-chloro-5-bromo-derivative has a small intensity [1329].

Probably technical possibilities of method in those times have not allowed determining all peaks of these compounds (Tables 3.74 and 3.75).



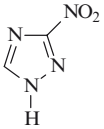
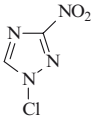
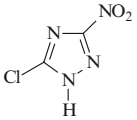
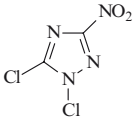
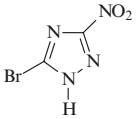
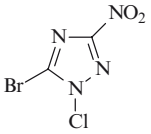
Scheme 3.67

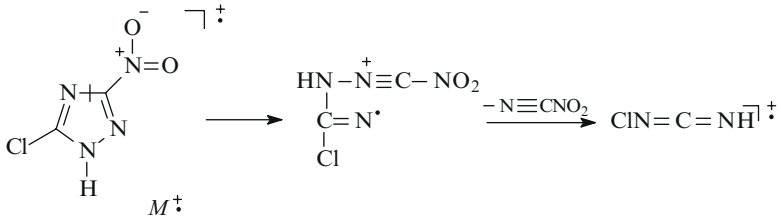
The thermal decomposition of 3-nitro-1-nitromethyl-1,2,4-triazole [1331] and 3-nitro-1,2,4-triazol-5-one [587, 1332] has been studied by electron impact and chemical ionization. Mass spectrum of 3-nitro-1,2,4-triazol-5-one consists of three characteristic parts: the molecular ion (*m/z* 130), the group at *m/z* 83, 84, and 85 (the azole ring), and the azole ring fragment group (*m/z* 41, 42, 43, and 44) (Scheme 3.69) [1332].

Mass spectrum of 1-nitro-1,2,4-triazol-5-one has only two intensive peaks with mass *m/z* 101 $[M-30+1]^+$ and *m/z* 85 $[M-46+1]^+$ corresponding NO and NO_2 [611].

The alkylation products of *N*-chloro-3-nitro-1,2,4-triazole [580], heterylation products of nitrotriazoles [612], glycosylation products of 3-bromo-5-nitro-1,2,4-triazole, 2,4-dinitroimidazole and 3-nitro-1,2,4-triazolon-5 [402] were identified by mass spectrometry.

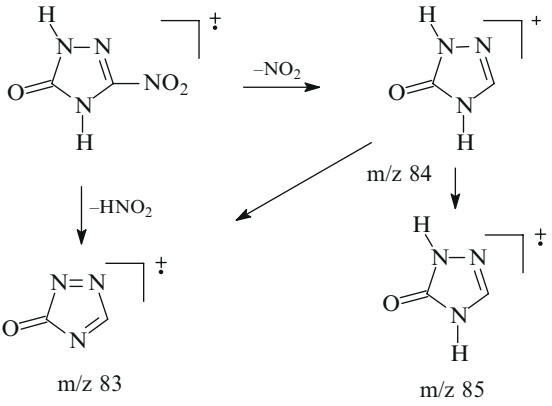
Table 3.75 Mass spectral data of 3-nitro-1,2,4-triazoles

Compound	*m/z* (I, %)
	114, (M^+) (30), 98 (2.3), 86 (2.0) 69 (20), 68 (2.8), 55 (2.0), 53 (3.6), 46 (15), 45 (3.1), 44 (5.5), 43 (4.9), 42 (6.5), 41 (16), 40 (11), 30 (100), 29 (16)
	150 (2.5), 148 (M^+) (6.7), 114 (3.1), 72 (9.5) 70 (17), 69 (4.2), 65 (3.1), 64 (24), 63 (11), 62 (6.4), 53 (8.1), 46 (21), 44 (5.7), 43 (2.5), 42 (2.6), 41 (3.2), 40 (3.6), 39 (21), 38 (6.7) 37 (3.6), 36 (7.6) 35 (11), 30 (100), 29 (7.6)
	150 (5.2), 148 (M^+) (17), 141 (2.0), 139 (15), 137 (23), 120 (2.2), 105 (5.2), 78 (9.3), 76 (30), 75 (2.6), 73 (7.6), 67 (4.5), 65 (2.5), 64 (5.2), 63 (10), 62 (17), 61 (4.1), 54 (5.2), 52 (6.2), 50 (2.1), 49 (7.6), 48 (6.5), 47 (21), 46 (13), 44 (16), 43 (8.6), 42 (2.5), 42 (7.6), 41 (7.9), 40 (3.4), 39 (4.8), 38 (14), 37 (2.5), 36 (25), 35 (8.6), 32 (2.5), 30 (100), 29 (31)
	184 (3.9), 182 (M^+) (6.0), 147 (4.7), 103 (3.9), 89 (2.0), 87 (3.1), 75 (3.4), 74 (3.2), 73 (8.2), 72 (19), 70 (31), 65 (12), 63 (41), 62 (3.9), 61 (6.9), 54 (4.6), 52 (4.9), 49 (3.6), 47 (7.1), 46 (15), 44 (7.7), 43 (3.5), 41 (3.1), 40 (2.2), 38 (11), 37 (4.9), 36 (30), 32 (3.5), 30 (100), 29 (6.5)
	194 (2.9), 192 (M^+) (2.9), 147 (3.0), 145 (3.8), 117 (2.6), 115 (2.6), 107 (2.5), 106 (4.2), 105 (4.1), 104 (4.2), 91 (3.2), 89 (3.2), 81 (5.5), 79 (5.6), 67 (8.5), 54 (5.9), 52 (4.9), 47 (2.2), 46 (11), 44 (6.0), 43 (4.6), 42 (2.2), 41 (5.7), 40 (3.6), 39 (6.1), 38 (13), 36 (10), 35 (3.1), 30 (100), 29 (25)
	226 (M^+) (no), 160 (1.4), 149 (1.3), 146 (1.4), 133 (1.1), 131 (1.0), 119 (6.3), 117 (5.4), 116 (2.4), 114 (2.0), 109 (12), 107 (16), 104 (2.6), 93 (2.6), 91 (2.7), 81 (10), 79 (10), 72 (4.5), 70 (8.6), 63 (3.1), 54 (5.4), 52 (3.2), 49 (2.2), 46 (15), 44 (4.2), 40 (2.9), 39 (2.8), 38 (21), 37 (3.4), 36 (4.6), 30 (100), 29 (4.4)



Scheme 3.68

The structure and the tautomerism of 5-nitrotetrazole and its substituted analogs have been investigated by mass spectrometry [1078, 1079, 1333]. According to the data of mass and photoelectronic spectra the 2*H*-tautomer prevails in the gas phase [1078, 1079, 1334, 1335].



Scheme 3.69

Table 3.76 The partial mass spectrum of 3-nitro-1,2,4-triazole [1330] (N_2^+ – 100%)

No	Fragment	*m/z* (I, %)
1.	$C_2H_2N_4O_2^+$	114 (7) M
2.	$C_2H_2N_4O^+$	98 (1)
3.	$C_2H_2N_2O_2^+$	86 (5)
4.	$C_2H_3N_3^+$	69 (8)
5.	NO_2^+	46 (11)
6.	CH_2NO^+	44 (13)
7.	$CHNO^+$	43 (22)
8.	$CH_2N_2^+$, CNO^+	42 (10)
9.	CHN_2^+	41 (10)
10.	CN_2^+, $C_2H_2N^+$	40 (6)
11.	C_2HN^+	39 (6)

Nitroindazoles

A mass spectrometric study of nitroindazoles has been carried out [683, 1336–1338]. In Table 3.77 the spectral characteristics of five nitroindazole isomers are presented [1337].

The molecular ion peaks of all the compounds studied are the most intense ones, while the *m/z* 147 and 148 peak intensities are negligible. It has been shown [1337] that metastable ion peaks (*m/z* 133, $[M\text{-}NO]^+$) can be of help in distinguishing the five nitroindazole isomers, but in general their spectra are much alike. The fragmentation route to $[M–NO]^+$ for the 4-nitro isomer is as follows (Scheme 3.70):

The mechanism of the formation of $[MH\text{-}30]^+$ ions upon chemical ionization (methane) of 6-nitroindazole has been studied [1338]. The absence of metastable peaks corresponding to this abstraction as well as comparison of the mass spectra of coimpact-activated ions $[MH\text{-}30]^+$ arisen from 6-nitroindazoles with MH^+ ions

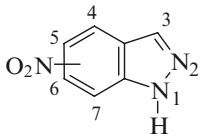
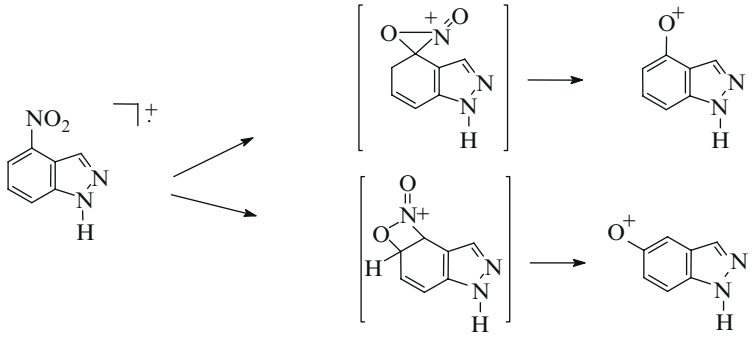


Table 3.77 The base peaks in mass spectra (EI) of nitroindazoles

m/z	Fragment	3-NO_2	4-NO_2	5-NO_2	6-NO_2	7-NO_2
163	$[M]^+$	100	98[a]	100	100	100
147	$[M–O]^+$	2	2	2	<2	<2
133	$[M–NO]^+$	22	25	29	15	11
117	$[M–NO_2]^+$	14	46	24	30	14
105	$[M–NO – CO]^+$	10	43	13	16	15
90	$[M–NO_2–HCN]^+$	76	100	67	73	83
78	$[M–NO – CO – HCN]^+$	3[b]	3	9	7	7
63	$[M–NO_2–2HCN]^+$	28	45	34	36	27

[a] $[M]^+$ *N*-hydroxy-4-nitroindazole *m/z* 193
[b] *m/z* 77 (41%)



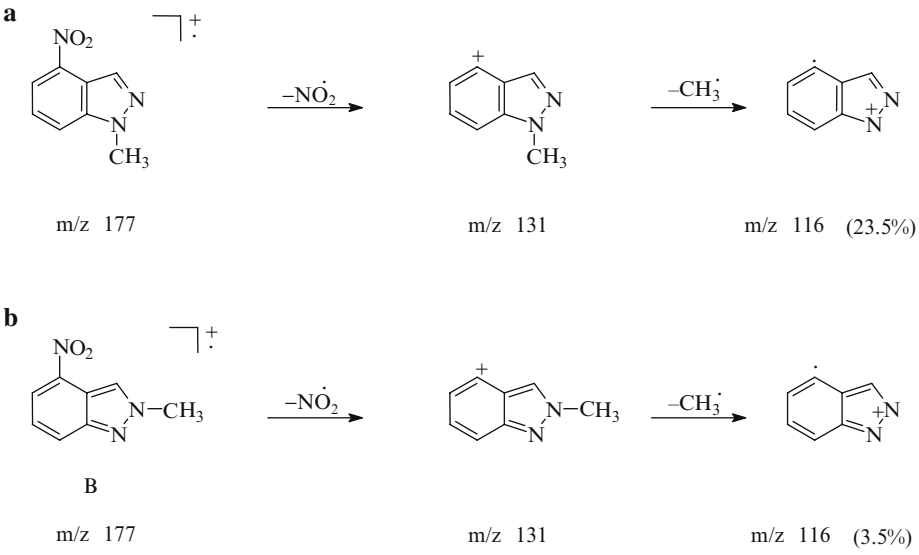
Scheme 3.70

from 6-aminoindazole provide evidence for the fact that the formation of $[MH-30]^+$ ions in the case of chemical ionization of nitro aromatic compounds is caused not by NO abstraction from the protonated molecular ion, but by a reduction reaction in the ion source with subsequent protonation [1338].

The mass spectra of 1-methyl- (**A**) and 2-methyl-4-nitroindazole (**B**) show similar fragmentation patterns and differ in the relative abundance of some fragments [384]. The peak *m/z* = 116 (23.5 and 3.5%) is the most important in this respect (Scheme 3.71):

It is believed [384] that this difference is caused by the greater lability of the N-methyl bond of compound **A**. The rupture of this bond gives rise to the formation of a more stable radical in the case of **A** (23.5 %) than in the case of **B**.

1-Methyl- and 2-methylnitroindazoles (also nitrobenzimidazoles) possessed mutagenic activity that have been synthesized and identified by electron-impact



Scheme 3.71

mass spectrometry (Table 3.78) [670]. A distinguishing feature in the mass spectra of the 5-, 6-, and 7-nitro-2-methylindazoles is a prominent peak at *m/z* 42. This fragment is characteristic of diazomethane and arises from the two indazole nitrogen atoms and the methyl group [670].

The structure of 5- and 6-nitroindazole derivatives – analogs of the biological active allopurinole – was established with the aid of spectral methods including mass spectrometry (Table 3.79) [680, 1339].

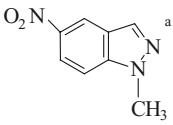
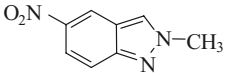
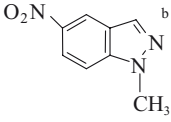
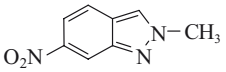
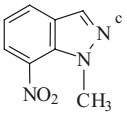
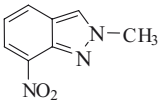
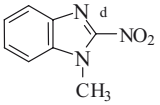
The mass spectra of 4-, 5-, 6-nitroindazoles and 7-methyl-, 7-chloro-5-nitroindazoles [683], and 1-tetrazolyl-4,6-dinitroindazole [1336] are reported.

Mass spectrometry has been also used for the structural determination of 1-acetyl-3-chloro-6-nitroindazole [675] and 5-nitro- and 6-nitro-1-aminoindazole [1083].

Nitrobenzimidazoles

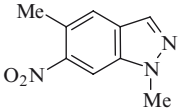
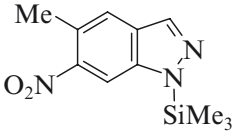
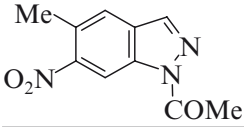
Nitrated benzimidazoles are less stable to electron impact than not nitrated ones [1340–1345]. An analogous behavior is observed with nitrobenzenes as well. We have studied a large series of 2-substituted 5(6)-nitrobenzimidazoles by mass spectrometry (Table 3.80) [1281, 1344]. In general, the molecular ion peaks (M^+) of nitrobenzimidazoles are the most intense ones except for 2-ethoxy-, 2-methoxycarbonyl- and 2-ethoxycarbonyl-5(6)nitrobenzimidazoles (Table 3.80). In the spectra of these compounds the most intense peaks are related to ions $[M\text{-}C_2H_4]^+$, $[M–COOCH_2]^+$, $[M–COOC_2H_4]^+$, respectively. One of main processes of electron-impact fragmentation

Table 3.78 *m/z* Values and relative ion intensities (I) nitroindazoles and nitrobenzimidazole

m/z/I, %	177	147	131	119	116	104	90	77	63	51	42	39	28	15
	100	35	43	13	45	38	–	41	56	30	–	15	24	21
	100	27	39	30	–	60	94	64	54	24	83	32	33	46
	100	10	62	21	52	45	45	34	79	23	–	16	27	23
	91	–	56	27	13	27	100	50	25	17	76	25	18	39
	52	–	35	–	42	46	43	49	86	48	–	27	52	54
	73	27	27	42	–	22	100	54	33	31	97	40	61	98
	49	20	–	30	–	19	–	100	–	40	–	30	96	31

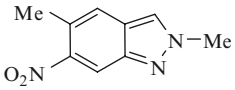
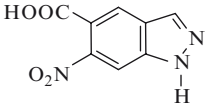
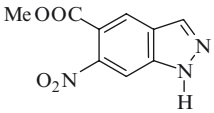
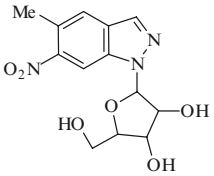
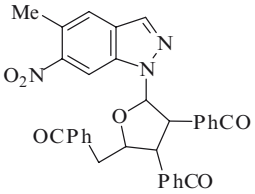
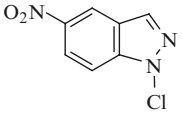
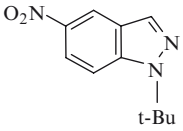
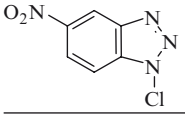
[a] *m/z* 89 (42)
[b] *m/z* 30 (22)
[c] *m/z* 160 (27), 148 (15), 132 (24), 130 (100)
[d] *m/z* 92 (13), 64 (19)

Table 3.79 Mass spectral data of 5- and 6-nitroindazoles and 1-chloro-5-nitrobenzotriazole

Compound	*m/z*	I, %	Fragment	Ref
	191	75	M^+	[680]
	174	100	$[M - OH]^+$	
	177	100	$[M - SiMe_3]^+$	[680]
	219	35	M^+	[680]
	177	61		
	160	100	$[M - CH_2CO]^{+\cdot}$	

(continued)

Table 3.79 (continued)

Compound	*m/z*	I, %	Fragment	Ref
	191 174	55 100	M^+	[680]
	207 190 177 163 44	8 5 3 6 100	M^+[M – OH]$^+$ [M – NO]$^+$ [M – CO_2] $^{+\cdot}$	[680]
	221 190	47 100	M^+ [M – CH_3O]$^+$	[680]
	309	21	M^+	[680]
	621 445	0.9 60	M^+ Tri-O-benzoyl-ribosyl$^+$	[680]
	197 163	62 100	M^+	[1339]
	219 163	34 100	M^+	[1339]
	198 164	3 100	M^+	[1339]

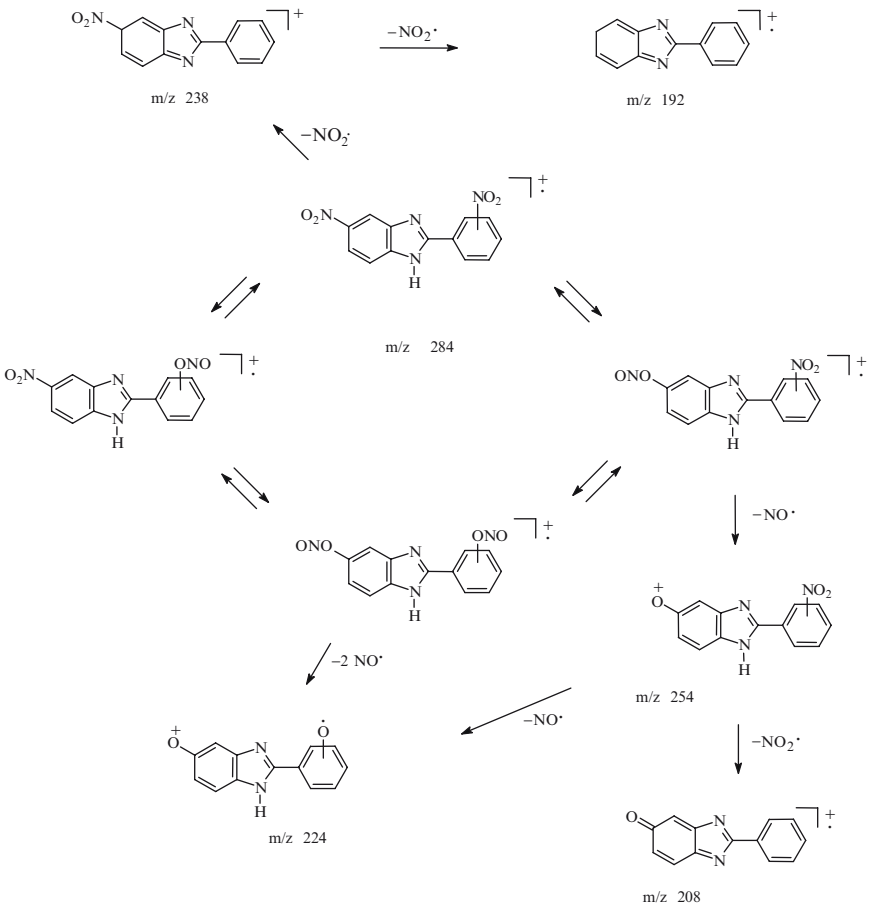
of nitrobenzimidazoles is elimination of the nitroso group caused by nitro-nitrite rearrangement [1342–1344]. In the mass spectra of 2-dimethylamino- and 2-acetyl-5(6)-nitrobenzimidazole a CH_3 radical migration toward the imidazole ring takes place, whereas in the spectra of 2-trifluoromethyl-5(6)-nitrobenzimidazole an analogous migration of the fluorine atom is observed (Table 3.80).

Table 3.80 Mass spectral characteristics of 2-substituted 5(6)-nitrobenzimidazole ions [a]

Fragment\R	$N(CH_3)_2$	NH_2	OC_2H_5	OCH_3	C_2H_5	CH_3	H	C_6H_5	Cl	$COCH_3$	CO_2CH_3	$CO_2C_2H_5$	CF_3	CN	NO_2
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
M^+	206(100)	178100)	207(68)	193(100)	191(100)	177(100)	163(100)	239(100)	197(100)	205(100)	221(33)	235(20)	231(100)	188(100)	208(100)
$(M–O)^+$	190(1)	162(1)	–	177(2)	175(1)	161(1)	147(2)	–	181(1)	189(1)	205(1)	219(1)	215(1)	172(1)	192(2)
$(M–NO)^+$	176(3)	148(22)	–	163(12)	168(3)	147(17)	133(23)	209(19)	167(30)	175(6)	191(5)	–	201(15)	158(30)	178(16)
$(M–NO_2)^+$	160(15)	132(25)	161(7)	147(30)	145(37)	131(33)	117(45)	193(28)	151(36)	159(5)	175(2)	189(5)	185(33)	142(50)	162(9)
$(M–NO–CNH_2)^+$	–	120(9)	149(31)	135(7)	133(4)	119(8)	105(11)	181(7)	139(13)	–	–	–	173(5)	130(17)	–
$(M–NO_2–R)^+$	–	–	–	–	116(3)	116(1)	116(4)	–	116(89)	–	116(7)	116(4)	116(29)	–	–
$(M–NO–OH)^+$	159(10)	131(7)	–	–	144(37)	–	116(4)	192(9)	–	–	–	–	–	–	–
$(M–NO_2–NCR)^+$	90(11)	90(6)	–	90(3)	90(15)	90(18)	90(68)	90(21)	90(4)	90(27)	90(12)	90(10)	90(14)	90(33)	–
$(M–NO_2–NCH)^+$	133(9)	105(66)	–	120(3)	118(8)	104(22)	90(68)	166(21)	124(18)	–	–	–	–	115(43)	–
$(M–H)^+$	205(3)	117(13)	–	192(13)	190(85)	–	–	–	–	–	–	–	–	–	–
$(M–R+H)^+$	163(1)	–	163(3)	163(12)	163(1)	–	163(100)	–	–	163(17)	163(100)	163(100)	–	163(1)	–
$(M–CH_3)^+$	191(31)	–	192(12)	–	176(3)	–	–	–	–	190(10)	–	–	–	–	–
$(M–NO_2–CH_3)^+$	145(46)	–	146(5)	132(14)	130(7)	–	–	–	–	144(6)	–	–	–	–	–
$(M–C_2H_4)^+$	–	–	179(100)	–	163(1)	–	–	–	–	177(42)	–	–	–	–	–
$(M–NO_2–C_2H_4)^+$	–	104(10)	133(53)	119(3)	117(5)	–	–	165(2)	–	131(15)	–	–	–	–	–
$(C_5H_3)^+$	63(7)	63(15)	63(2)	63(4)	63(9)	63(23)	63(5)	63(31)	63(29)	63(14)	63(11)	63(6)	63(17)	63(33)	63(18)
$(C_5H_2)^+$	62(2)	62(6)	62(5)	62(2)	62(5)	62(7)	62(4)	62(6)	62(14)	62(7)	62(7)	62(3)	62(5)	62(12)	62(12)
$(M–NO_2–CR)^+$	104(3)	–	104(6)	104(11)	–	–	–	104(13)	–	–	104(5)	–	–	–	104(5)
$(M–NO_2–CR+H)^+$	105(4)	–	105(27)	–	105(2)	–	–	105(3)	–	105(7)	–	105(2)	–	–	105(3)
$(M–NO_2–CR–H)^+$	103(3)	–	–	–	103(2)	–	–	–	103(3)	–	103(3)	–	–	103(6)	–
$(M–NO_2–R+H)^+$	117(7)	–	–	–	117(5)	–	–	–	–	117(45)	117(6)	117(9)	–	–	–
$(M–NO_2–NCRH)^+$	–	–	–	–	–	–	–	–	89(7)	89(5)	89(6)	89(3)	89(4)	–	89(13)
$(M–NO_2–NCRH_2)^+$	–	–	–	–	–	–	–	–	88(7)	–	88(5)	–	88(3)	–	88(9)

[a] *m/z* (I, %)

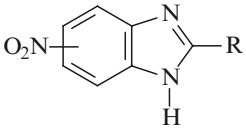
The mass spectra of nitro derivatives of 2-phenylbenzimidazoles show the dissociative ionization to be characterized by two trends involving the formation of $[M–NO]^+$ and $[M–NO_2]^+$ ions (Scheme 3.72) [1342]:



Scheme 3.72

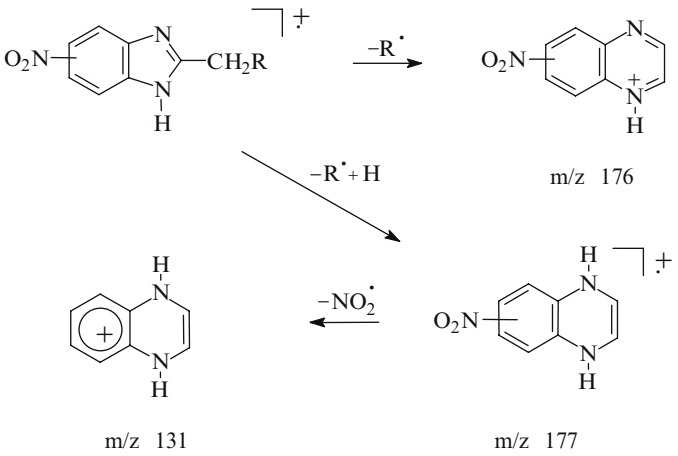
When the ionizing electrons are of lower energy, the probability of nitrite rearrangement is greater [1342].

Amjad et al. [1341] have examined the mass spectra of a series of nitrobenzimidazoles.



R = $(CH_2)OH$, $(CH_2)_2CH(OH)CH_2CH_2OC_2H_5$

The main fragmentation pathway of these compounds is as follows (Scheme 3.73):



Scheme 3.73

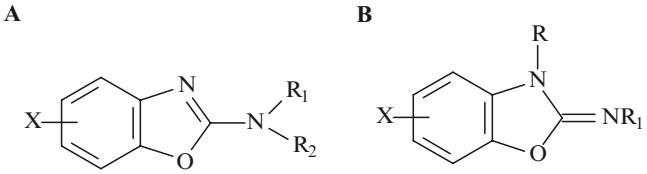
The most intense ion peak in the spectra of these compounds is that due to the ion with *m/z* 177 [1341].

The fragmentation of isomeric 5- and 6-nitro-1-*p*-toluenesulfonyl-2-alkylbenzimidazoles[695,710],S-{5(6)-nitrobenzimidazol-2-ylmethyl}*N*-morpholino-dithiocarbamate [1090], 4-, 5-, and 6-nitro-1-β-*D*-ribofuranosylbenzimidazole 3′,5′-phosphates [711], and the products of alkylation of 5(6)- and 4(7)-nitrobenzimidazole derivatives [702] has been studied. The molecular ion peaks of 2-alkylthio- and 2-ethylsulfono-5(6)-nitrobenzimidazole are reported [718].

Nitrobenzisoxazoles, Nitrobenzoxazoles, and Nitrobenzoxadiazoles

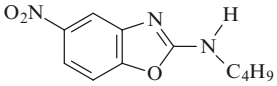
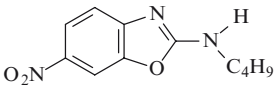
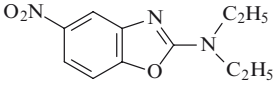
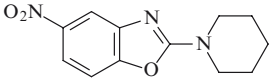
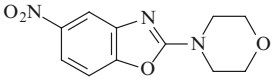
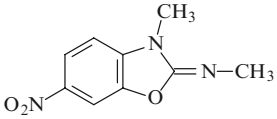
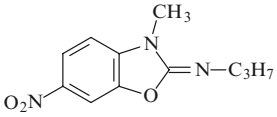
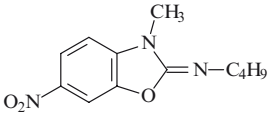
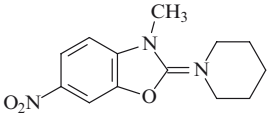
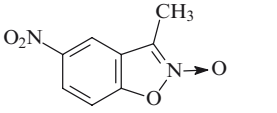
The structure of 3-cyano-4,6-dinitrobenzisoxazole and its reaction products with anionic nucleophiles have been confirmed [1346]

It has been found [1347] that mass spectrometry provides useful information in the study of tautomerism:



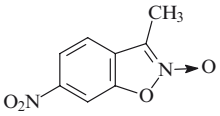
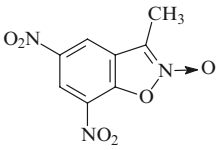
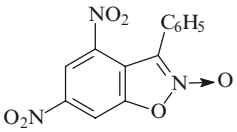
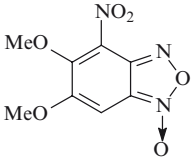
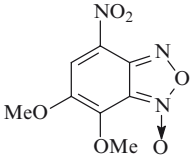
The molecular ions of aminobenzoxazoles (**A**) (including nitrated species) turned out to be more stable than those of iminobenzoxazolines (**B**). In Table 3.81 the mass spectral data of **A** and **B** are presented.

Table 3.81 Mass spectra of some nitrobenzoxazoles, nitrobenzisoxazoles, and nitrobenzofuroxans

Compound	*m/z* (Relative intensity, %)	Refs
	235 (76) M^+, 193 (32), 192 (70), 179 (100), 146 (96), 133 (60), 105 (47), 91 (71), 78(48), 77(67)	[1347]
	235 (91) M^+, 193 (35), 192 (70), 179 (100), 105(66), 91 (91), 88 (44), 77 (76), 69 (68), 78 (74)	[1347]
	235 (51) M^+, 220 (26), 207 (6), 206 (34), 193 (5), 192 (100), 146 (25), 71 (20), 63 (12), 56 (14)	[1347]
	247 (100) M^+, 201 (15), 192 (19), 90 (28), 83 (15), 79 (15), 77 (16), 69 (75), 63 (31), 55 (69)	[1347]
	249 (100) M^+, 203 (6), 193 (6), 192 (86), 191 (36), 178 (2), 175 (2), 161 (5), 146 (11), 145 (17)	[1347]
	207 (100) M^+, 206 (6), 192 (6), 161 (9), 160 (11), 111 (4), 81 (11), 73 (19), 60 (26)	[1347]
	235 (8), 207 (11), 206 (100), 160 (29), 92 (4), 85 (4), 71 (8), 69 (7), 60 (5), 57 (14)	[1347]
	249 (11), 207 (18) 206 (100), 160 (31), 98 (11), 97 (10), 92 (11), 71 (15), 69 (11), 57 (29)	[1347]
	275 (55), 258 (6) 246 (7), 233 (15), 232 (100), 81 (11), 71 (13), 69 (21), 57 (17), 55 (11)	[1347]
	194 (64) M^+, 178 (5), 165 (33), 164 (57), 163 (46), 147 (12), 145 (12), 138.6 (194-164), 135 (8), 119 (12), 118 (100), 117 (36), 105 (7), 91 (28), 90 (93), 89 (77), 79 (12), 78 (15), 77 (17), 68.6 (118-90), 65 (19), 64 (37), 63 (72), 62 (31)	[1348]

(continued)

Table 3.81 (continued)

Compound	*m/z* (Relative intensity, %)	Refs
	194 (78) M^+, 178 (11), 165 (40), 164 (55), 163 (100), 150 (6), 147 (22), 135 (6), 121 (6), 120 (6), 119 (12), 118 (50), 105 (12), 91 (24), 90 (50), 89 (69), 77 (11), 76 (24), 63 (67), 51 (29), 50 (16)	[1348]
	239 (13) M^+, 223 (4), 211 (62), 209 (8), 184 (8), 181 (79), 167 (10), 166 (100), 165 (13), 155.2 (211-181), 149 (26), 120 (50), 119 (22), 105 (12), 92 (24), 91 (19), 79 (11), 78 (8), 77 (16), 63 (31)	[1348]
	301 (33) M^+, 285 (21), 271 (61), 270 (29), 225 (13), 224 (8), 212 (8), 198 (18), 197 (100), 196 (11), 67 (16), 165 (15), 151 (65), 150 (95), 126 (9), 125 (16), 105 (14), 77 (23), 76 (21), 75 (34), 74 (21), 63 (29), 51 (23), 50 (15)	[1348]
	242 (M+1, 7.7), 241 (76.5) M^+, 225 (M-16, 7.9), 207 (1.3), 196 (4.0), 181 (M-60, 31.5), 166 (11.7), 165 (8.0), 151 (M-90, 6.1), 136 (11.0), 123 (14.1), 108 (12.0), 93 (37.5), 77 (48.3), 75 (100), 69 (18.1), 63 (13.0), 53 (14.1) 51 (26.1)	[1349]
	242 (M+1, 8.5), 241 (50) M^+, 225 (M-16, 5.2), 196 (1.3), 181 (M-60, 26.4), 166 (5.2), 151 (M-90, 2.3), 136 (7.2), 123 (13.8), 108 (10.5), 93 (28.9), 75 (44.1), 77 (20.3), 69 (2.6), 63 (3.2), 51 (1.8)	[1349]

Mass spectra of 5,6-dimethoxy- and 6,7-dimethoxy-4-nitrobenzofuroxan show an intensive molecular ion peak, intensive $[M-60]^+$ peaks characteristic of the furoxan ring, and a weak $[M-90]^+$ peaks due to loss of N_2O_2 and NO groups, characteristic of nitrobenzofuroxans [1350]. Nitrobenzofuroxans with a nitro group *ortho* to the furoxan ring exhibit predominant loss of NO from position 1 of the furoxan ring [1350].

Mass spectral fragmentation of the products of electron-impact fragmentation of 6-nitro-2,1-benzisoxazole (6-nitroanthranil) [1351], 3-substituted 6-nitroanthranils [1352], 4-arylamino-5,7-dinitrobenzofurazan [747], 4-(2-aminoethylamino)-7-nitrobenzofurazan [1353], 12-O-tetradecanoyl phorbol-13-O-acetate containing 4-nitrobenzofurazan [1354], and fluorescent probes on the base nitrobenzofurazans [777] have been discussed.

Nitrobenzoisothiazoles, Nitrobenzothiazoles, and Nitrobenzothiadiazoles

2-Aryl-4,6-dinitrobenzisothiazoles, 3-substituted 4,6-dinitrobenzisothiazoles, and their salts and oxides prepared by the utilization of 2,4,6,-trinitrotoluene or the transformation of 4,6-dinitrobenzamides have been investigated with help of mass spectrometry [784, 803–806].

Fragmentation of 2,5-disubstituted benzothiazoles (including 2-ethyl-6-nitrobenzothiazole) has been studied in detail by mass spectrometry [1355].

An analysis of the behavior of positive and negative ions in mass spectra of 4-nitro-, 6-nitro-, and 4,6-dinitro-2-aminobenzothiazole has been carried out [1356]. These compounds give rise to intense peaks due to M^+ and M^- molecular ions and display abnormal fragmentations for both positive and negative ions. A fragmentation scheme of 4,6-dinitro-2-aminobenzothiazole is presented in Scheme 3.74 [1356].

The M^+ fragmentation proceeds via O, NO, NO_2, or HNCO elimination; the fragments formed further abstract CO, HCN, HNCO.

In the first stage of negative molecular ion fragmentation (M^-) abstraction of OH, NO_2, (HNO_2) from all the compounds studied occurs. H_2O and NO elimination is also typical of M^- ion of 6-nitro- and 4,6-nitro-2-aminobenzothiazole. As an example, we give here one of the ways of the fragmentation of the M^- – ion derived from 4-nitro-2-aminobenzothiazole (Scheme 3.75) [1356]:

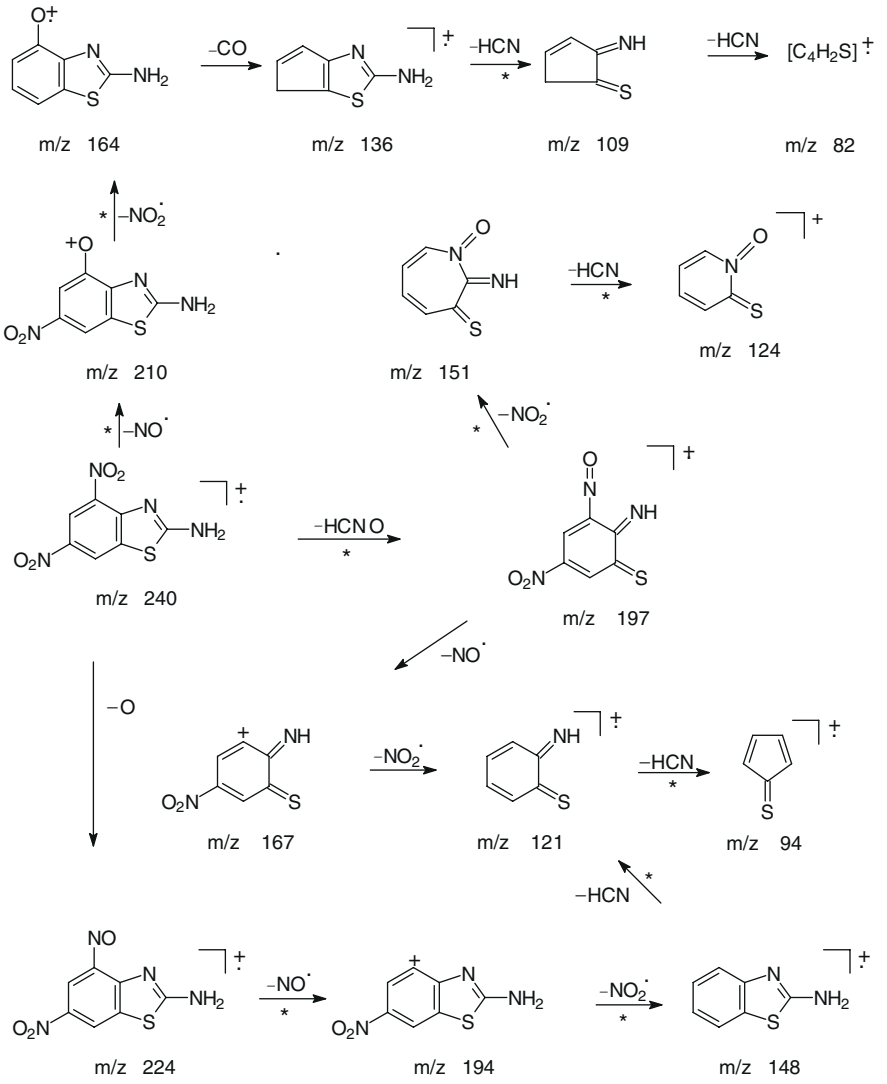
An HCN abstraction is characteristic of this compound and its 6-nitro isomer [1356].

Spectrometric data of 1-(6-nitrobenzothiazol-2-yl)-4-[(1*H*)imidazole-4-yl)] piperidine [1357] and 6-nitro-2-oxo-3(2*H*)-benzothiazolineacetonitrile [1358] are reported.

The mechanism of electron-impact-induced sulfur dioxide elimination from the molecular ions of 4-nitro-2,1-benzisothiazoline and 6-nitro-2,1-benzisothiazoline 2,2-dioxide derivatives has been examined [1359]. The light fastness of dyes based on 3-amino-5-nitro-2,1-benzisothiazole was studied in relation to mass spectral data [1251].

Nitrobenzoselenodiazoles

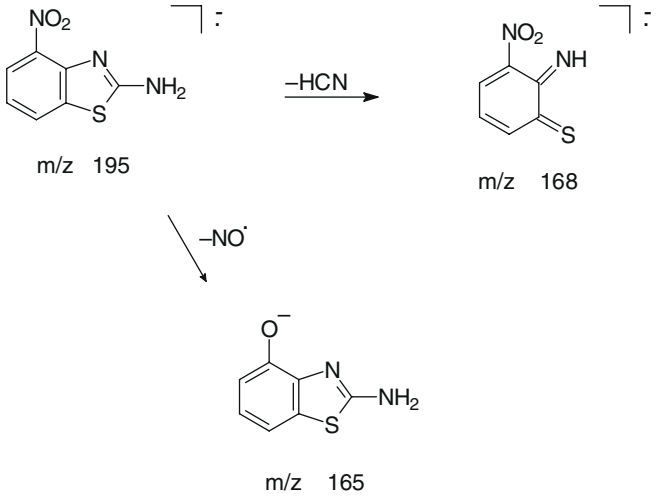
Mass spectra of the following series of nitro derivatives of 2,1,3-benzothiadiazole have been studied [1360] (Table 3.82). Their mass spectra are characterized by an intense peak of the molecular ion. The fragments NO_2, NO, H, HCN, and NS are the most important elimination fragments. The nitro group position does not affect much the fragmentation outcome; the spectra of 4-nitro- and 5-nitro-2,1,3-benzothiadiazoles are nearly the same [1360].



Scheme 3.74

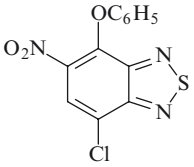
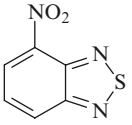
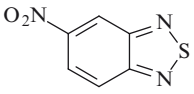
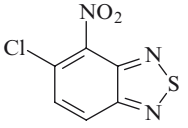
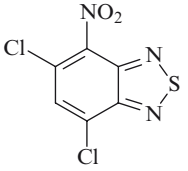
The mass spectral characteristics of 4,7-dibromo-5,6-dinitro-2,1,3-benzothiadiazoles and 4-bromo-5-nitro-6,7-(2′,1′,3′-oxadiazole)-2,1,3-benzothiadiazole have been considered [1361].

The mass spectra of 5-nitro-2,1,3-benzoselenodiazole have been mentioned [1362, 1363]. During the synthesis of potent mutagens, the intermediates 5-chloro- and 5-methylamino-4-nitro-2,1,3-benzoselenodiazole were studied by spectral methods including mass spectrometry (Table 3.83) [1364].



Scheme 3.75

Table 3.82 Mass spectra of nitrated 2,1,3-benzothiadiazoles

Compound	*m/z* (Relative intensity, %)
	309 (8), 307 (20) M^+, 292 (8), 290 (10), 262 (10), 260 (6), 216 (7), 214 (16), 206 (5), 204 (8), 186 (9), 170 (5), 119 (9), 118 (6), 94 (6), 93 (100), 86 (8), 77 (40), 70 (5), 65 (49), 51 (34)
	183 (7), 182 (9), 181 (100) M^+, 151 (30), 136 (5), 135 (50), 123 (24), 109 (7), 108 (23), 104 (14), 91 (7), 83 (5), 82 (5), 76 (13), 75 (5), 70 (5), 64 (20), 52 (6), 51 (6), 50 (5), 46 (5), 45 (29)
	183 (6), 182 (6), 181 (100) M^+,151 (11), 136 (4), 135 (42), 123 (22), 109 (5), 108 (22), 91 (5), 83 (5), 77 (5), 76 (8), 64 (16), 50 (6)
	220 (6), 218 (8), 217 (35), 216 (9), 215 (100) M^+, 204 (5), 187 (17), 185 (50), 183 (5), 181 (7), 172 (5), 171 (7), 170 (13), 169 (20), 159 (17), 142 (10), 135 (8), 134 (25), 133 (9), 125 (5), 108 (12), 107 (6), 98 (7), 89 (5), 83 (12), 76 (10), 75 (10), 70 (17), 69 (8), 64 (9), 52 (5), 51(7), 46 (7), 45 (7)
	253 (15), 252 (11), 251 (73), 250 (10), 249 (100) M^+, 233 (5), 223 (15), 222 (13), 221 (76), 220 (20), 219 (83), 206 (16), 205 (11), 204 (22), 203 (19), 195 (8), 193 (43), 192 (5), 171 (10), 170 (24), 169 (12), 168 (43), 161 (13), 159 (17), 158 (5), 142 (18), 133 (12), 117 (9), 101 (12), 100 (12), 98 (16), 83 (10), 75 (15), 74 (14), 70 (20), 59 (19), 46 (14), 45 (15), 44 (12)

(continued)

Table 3.82 (continued)

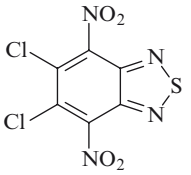
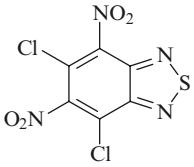
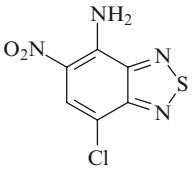
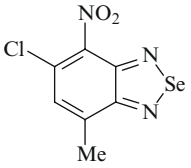
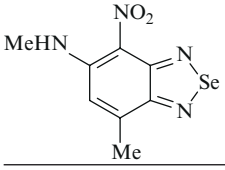
Compound	*m/z* (Relative intensity, %)
	298 (14), 297 (7), 296 (63), 295 (9), 294 (100) M^+, 248 (5), 222 (5), 220 (8), 219 (5), 206 (9), 204 (13), 202 (9), 200 (13), 186 (5), 184 (6), 172 (8), 170 (13), 169 (6), 155 (8), 136 (7), 135 (10), 134 (8), 132 (27), 123 (9), 117 (16), 109 (10), 100 (14), 99 (16), 85 (12), 83 (11), 70 (9), 46 (11), 44 (17)
	298 (12), 297 (5), 296 (19), 295 (7), 294 (80) M^+, 265 (12), 263 (17), 250 (9), 248 (13), 240 (7), 238 (7), 222 (41), 221 (7), 220 (69), 218 (11), 208 (12), 206 (40), 205 (7), 204 (51), 202 (11), 201 (28), 200 (9), 199 (78), 171 (25), 169 (21), 167 (16), 155 (13), 132 (31), 117 (11), 109 (13), 79 (20), 52 (13), 44 (39), 30 (100)
	232 (34), 231 (10), 230(100) M^+, 212 (13), 202 (14), 200 (41), 186 (27), 185 (10), 184 (70), 172 (43), 171 (9), 170 (80), 152 (14), 151 (24), 150 (40), 135 (21), 124 (16), 108 (10), 103 (10), 98 (13), 94 (11), 78 (9), 77 (19), 76 (9), 70 (11), 64 (13), 63 (11), 52 (20), 51 (14)

Table 3.83 Mass spectra data of 4-nitro-2,1,3-benzoselenodiazole derivatives

Compound	*m/z* (Relative intensity, %)
	277(54) M^+, 247 (74), 140 (100), 139 (50), 124 (62), 115 (74), 88 (57), 64 (73), 63 (54), 63 (44)
	272 (54) M^+, 144 (40), 118 (47), 107 (71), 105 (45), 93 (58), 80 (54), 78 (42), 66 (40), 52 (41)

Nitrobenzotriazoles

The mass spectra of 1-chloro-5-nitrobenzotriazole (EI, 70 eV; Table 3.79) [88], 1-hydroxy 4,6-dinitrobenzotriazole [1365] and other benzotriazoles are reported [1366]. The characteristic ions in the mass spectrum of 1-(2-hydroxyethyl)-5-methoxy-6-nitrobenzotriazole were observed at *m/z* 238 (42%), M^+ ; 208 (31), $[M - HCHO]^+$; 207 (8), $[M - OCH_3]^+$; 193 (100), $[M - CH_2CH_2OH]^+$; 192 (14), $[M - NO_2]^+$ [1367]. The mechanism of reduction of benzo-1,2,3,4-tetrazine 1,3-dioxides with

$Na_2S_2O_4$ or $SnCl_2$ via intermediate *N*-nitrosobenzotriazoles to nitrobenzotriazoles has been confirmed by mass spectrometry [1368].

Conclusions

The reported data show the increasing importance of mass spectrometry as a method of structure determination in organic chemistry. A large number of publications are devoted to the electron-impact fragmentation of *C*-nitroazoles, while mass spectra of *N*-nitroazoles are discussed only in some studies. Mass spectra of nitrotriazoles and nitrothiazoles are only little studied. We are sure that works filling up this gap will soon appear. The isotopic labeling – ^{13}C, ^{15}N, and ^{17}O is increasingly important in elucidating the complex mass spectral behavior of nitroazole compounds.

Other Physical–Chemical Properties

Flash photolysis of misonidazole, metronidazole, and nitrobenzothiazoles has been carried out in [1369–1371]. Laser flash-photolysis (355 nm) allows to determine relatively stable anion-radicals of misonidazole and metronidazole in aqueous solutions [1370]. Solvated electrons have been formed at harder irradiation, the result of which interaction with nitroimidazole molecules is generation of their radical anions [1372]. The authors [1372] have also found that fluorescence intensity of metronidazole is about 20 times more than that of misonidazole in same conditions. Photochromic properties of benzothiazole derivatives containing nitro and methyl groups in the ortho positions with respect to each other were studied by flash photolysis [1371]. The application of the thermodynamic approach to predict the kinetic stability of formed nitronic acids is limited owing to specific intramolecular interactions. The lifetime of photoinduced nitronic acid anions tends to increase with rise in the chemical shift of the methyl protons. The rate constants photoinduced nitronic acids and their anions increase as the $CH_3C\text{-}CNO_2$ bond becomes longer [1371].

Nanosecond laser flash-photolysis and spectrofluorimetry have been used on investigation of 2-mercapto-6-nitrobenzothiazoles in regard to their abilities to function as coinitiators in free-radical photopolymerizations induced by camphorquinone and isopropylthioxanthone [1373].

Nitro blue tetrazolium ion (NBT^{2+}) usually used for the detection of superoxide anion ($O_2^{\cdot-}$) produced biologically has been studied by laser photolysis [1374]. It turned out that the triplet riboflavin reduced NBT^{2+} into nitro blue tetrazolinyl radical, NBT^{+},·which disappeared according to pseudo first-order kinetics with bimolecular rate constant [1374]. Therefore NBT^{2+} is not always a good detecting reagent for the O_2^{-} when the formation of the anion is mediated by riboflavin.

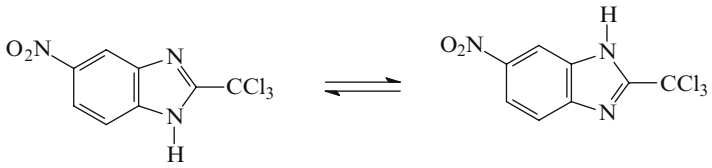
One approach to the identification of hypoic cells has been to take advantage of the inhibition by oxygen of the reductive metabolism *of fluorescent* nitroaromatic compounds in cells [1375]. The nitro group quenches the fluorescence of the aromatic ring system, but on bioreduction of the nitro group in hypoxic cells the ring system becomes fluorescent. Numerous nitroazole structures have been evaluated in model systems in vitro. Fluorescence of alkylated 4-nitropyrazoles under the influence of ultraviolet has been studied in detail [1372]. The reactivity and fluorescence and thermodynamic properties of nitrobenzofurazans [775, 777, 1376–1393] and nitrobenzofuroxans [1394–1396] have been studied. 4-Aminosubstituted 7-nitrobenzofurazans are widely used in bioanalytical chemistry due to their strong fluorescence properties [777, 1226–1228]. The fluorescence spectra of fluorescent probe, 6-amino-*N*-(7-nitrobenzofurazan-4-yl)hexanoyl were measured in methanol, aqueous solution, and aqueous solution containing phospholipid vesicles [775]. The fluorescence of the probes depends on the environment of the pheromones and can be used to monitor the association of the pheromones with the lipid bilayer [775]. Fluorescence data of 2,5-bis-(6-nitro-2-benzothiazolyle)furan [1258], 4-cloro-7-nitrobenzofurazan [1106, 1397, 1398], *N*-(4-nitrobenzofurazan)monoaza-18-crown-6 [1399], 4-(*N*-methylamino)-7-nitrobenzofurazan [1400, 1401] have been analyzed. The last is obtained by oxidation of nonfluorescent 4-(*N*-methylhydrazino)-7-nitrobenzofurazan (a novel fluorogenic peroxidase substrate) in the presence of H_2O_2 and peroxidase [1400]. The absorption and *fluorescence* characteristics of 4-(α-*N*-L-alanine)7-nitrobenzofurazan in different solvents reveal large changes which correlate with medium polarity [1229]. Fluorescence emission spectra and quantum yield of 4-nitrobenzofurazan-lysozyme have been measured [1402]. Fluorescence sensor reagents and labels on the base nitrobenzofurazans show fluorescence emission between 382–529 nm affording various utilization possibilities [1378].

Luminescence and photochemistry study of azoles is covered in the excellent Osipov's and colleagues' review [1403]. The questions concerning desactivation processes of electron-exited state of azole molecules, including 2-aryl-nitrobenzothiazoles, are critically considered in the review.

Photochromism of 4-nitro-, 6-nitro-, and 4,6-dinitro-5-methylbenzimidazole bases and their quaternary salts has been examined by pulse photolysis [1404]. Generated neutral medium anions of aci-nitroacids have, in case of compounds with 4-nitro groups, the lifetimes 3 orders more than those of 6-nitroisomers [1404].

Photoelectron spectra (PE) experimental of some 4-nitropyrazoles, nitroimidazoles, [1119, 1405] and nitrobenzimidazoles [1193, 1406] have been recorded and interpreted in terms of semiempirical AM-1 method. PE spectroscopy is not a widely used method to study tautomeric equilibria in the gas phase although it can give excellent results. PE spectra data and 6-31G/6-31G calculations show that in the gas phase tautomers 4-nitro- and 5-nitroimidazole have the similar energy [1301]. However in water, 4-nitroimidazole is much more stable ($\delta\Delta G^{o}$ = 3.5 kcal/mol >99% at 25°C.) than the 5-nitro tautomer. The authors [1301] show that this is conditioned by solvation effect. Probably it is connected with the large difference in dipole moments of the tautomers (see Table 3.72).

With the help of ^{35}Cl *Nuclear Quadrupole Resonance* (NQR) spectroscopy and AM1, MNDO и PM3 calculation data of tautomers of 2-trichloromethyl-5(6)-nitrobenzimidazole it is established that 5-nitro tautomer is more preferable than its 6-isomer (Scheme 3.76) [1407].



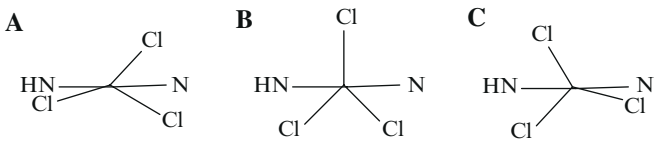
5-nitro tautomer 6-nitro tautomer

Scheme 3.76

The insertion of nitro group into 2-trichloromethylbenzimidazole raises the ^{35}Cl NQR average frequency due to electron-withdrawing effect of NO_2 despite its remoteness from the indicator atom [1407].

The formation heats of conformers **A** and **C** of 2-trichloromethyl-5(6)-nitrobenzimidazole (Scheme 3.77) calculated by AM1, MNDO, PM3 methods and ^{35}Cl NQR frequencies computed from the Townes-Dailey equation [1408] (TD) and modification Townes-Dailey equation (3.8) [1409, 1410] (MTD) have been analyzed (Table 3.84) [1407].

The modified Townes-Dailey theory takes out the influence of the different diffusivity of the p_i-orbital on the electric field gradient [1409, 1410].



Scheme 3.77

$$\upsilon_{M.T.D.} = k_2 \left(\left(\xi_z\right)^3 P_{zz} - \frac{\left(\xi_x\right)^3 P_{xx} + \left(\xi_y\right)^3 P_{yy}}{2} \right) \qquad 3.8$$

where ν – calculated NQR frequency; k – empirical constant, p_{xx} , p_{yy}; and p_{zz} – the population of the corresponding p-orbital of the indicator atom; ξ – exponent index of the corresponding p_i-orbital of the Slater type.

The analyses of these data and others [1409, 1410] show that application of the modified Townes-Dailey equation is more preferable than Townes-Dailey equation

Table 3.84 The formation heats (H, kcal/mole) of the conformers **A** and **C** of 2-trichloromethyl-5(6)-nitrobenzimidazole and ^{35}Cl NQR frequencies (ν, MHz), obtained from TD and MTD equations

		5-Nitro tautomer				6-Nitro tautomer			
	Angle	0		180		0		180	
Method	Aproximation	TD	MTD	TD	MTD	TD	MTD	TD	MTD
AM1	H	56.487		56.126		57.097		56.780	
	ν	50.452	45.650	51.557	46.481	50.496	45.724	51.535	46.524
		50.443	45.646	49.179	44.666	50.502	45.729	49.107	44.657
		48.425	43.957	48.719	44.304	48.558	44.098	49.098	44.657
MNDO	H	47.255		46.202		48.002		47.478	
	ν	46.868	42.621	48.144	43.727	47.031	42.785	48.032	43.661
		46.866	42.617	45.514	41.501	46.834	42.618	45.657	41.641
		45.126	41.147	45.503	41.490	45.216	41.258	45.653	41.638
PM3	H	20.300		20.437		20.786		21.066	
	ν	54.414	46.961	55.666	47.542	54.512	47.105	55.734	47.624
		54.370	46.977	52.419	45.642	54.460	47.109	52.541	45.865
		51.477	44.691	52.384	45.743	51.629	44.885	52.445	45.775

for the determination structure and assignment signals in ^{35}Cl NQR spectra of chloro-containing organic compounds [1407].

The asymmetry parameter in 1,2-disubstituted 5-nitroimidazoles decreases with increasing the substituent size. The π–electron density and N-1 bond population is calculated according to the Townes-Dailey theory and described in detail by Dr. Lucken [1408] and Dr. Dolgushin [1409, 1410] based on height with lengthening of the substituent on N-1 [1411].

Electron density distribution in substituted 5-nitroimidazoles studied by ^{14}N NMR-NQR double resonance spectroscopy changes insignificantly in comparing with one in itself imidazole [1411–1413]. The introduction of nitro group and others substituents into imidazole ring leads to increasing the quadrupole constants of N-1 and N-3 atoms (Table 3.85).

Thermodynamic stability of indazole has been studied by ^{14}N NMR-NQR spectroscopy and *ab initio* calculations [1414].

Ion cyclotron double resonance has been usefully applied by the authors [1415] for structural identification of isomeric ions with m/z 152 obtained under electron impact of both 1-methyl-4-nitro-5-caronitrylimidazole and 1-methyl-4-nitro-5-caroxamidimidazole. The ion cyclotron resonance and mass spectrometry data show that the protonation 3- and 4-nitropyrazole proceeds on the heterocyclic nitrogen rather than on the oxygen of the nitro group [1416].

The catalytic activity of Ag/Pd bimetallic nanoparticles immobilized on quartz surfaces was tested for 4-nitro-3-pyrazole carboxylic acid with help from surface *plasmon resonance*, *scanning electron microscopy*, and *surface-enhanced Raman scattering* (SERS) measurements [1417]. The SERS spectra showed that the nitro group reduces to amino group.

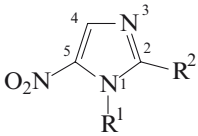


Table 3.85 Quadrupole-coupling constants ($X = e^2Qq_{zz}/h$) and asymmetry parameters (η) in 1,2-disubstituted 5-nitroimidazoles[a]

Substituent		N-1		N-3		NO_2	
R^1	R^2	X	η	X	η	X	η
H	CH_3	3.243	0.250	1.569	0.82	1.225	0.36
CH_2CH_2OH	CH_3	3.299	0.150	2.467	0.32	0.936	0.38
$CH_2CH_2OCOCH_3$	–CH=CHPhCH_3O	3.755	0	2.566	0.24	0.921	0.24
Imidazole		3.222	0.119	1.391	0.93	–	–

[a] The quadrupole constant due to a single 2p electron ($X_0 = e^2Qq_0/h$) was taken to be 9.4 MHz; the NQR frequencies were recorded on NMR-NQR double resonance spectrometer built at the Department of Physics, University of Ljubljana (Slovenia) (the accuracy ~1 kHz)

Kinetics of *thermodecay* of mononitroderivatives of five-membered nitrogen-containing heterocycles salts including 4-nitropyrazole and 4(5)-nitroimidazole in solid state and the activation energy of their thermal decomposition has been determined [1418]. The stability of the salts decreases with the increase of the nitroazole acidity. The decomposition of 5-nitro-1,2,4-triazole-3-one (NTO) induced by X-ray, UV, laser, photochemical irradiation has been described [1332, 1419]. High-speed photographic studies of the impact responses of the nitrotriazole and thermal decomposition of labeled NTO have been discussed [1419]. The laser ignition measurements showed that the sensitivity to ignition is slightly higher than that for trinitrotoluene [1332]. Molecular design of the probable mechanisms of the thermolysis of nitro and nitramino-1,2,4-triazoles has been carried out by methods of mathematical chemistry [1420]. It was established that the formation is possible of a more diverse spectrum of products in their destruction than was previously recorded by different experimental methods. Subsequent assessment of the thermochemical preference for pathways of decomposition of the compounds was carried out by the density functional method in the B3LYP/6-31G* approach. It was determined that the thermal destruction of *C*-and *N*-nitramino-substituted polynitrogen heterocycles, capable of tautomeric conversion, was most probably through the thermochemically least stable nitro- or nitramine form. Thermal decomposition of the considered tautomers is preferred at the NO_2 or NNO_2 fragment and not at the triazole ring [1420]. The thermal decay of 3-nitro-1-nitromethyl-1,2,4-triazole proceeds homolytically with initial rupture of the CH_2–NO_2 bond. Activation parameters of the process were $E_a = 172.6$ kJ/mol, log A = 14.25. The primary pathway of fragmentation of 3-nitro-1-nitromethyl-1, 2,4-triazole under electron impact agrees with the first step of thermal decomposition [1331].

Thermal stability and some other properties of very hydroscopic 5-nitrotetrazole have been reported [1079, 1271, 1421]. Tetrazole possess a high enthalpy of formation: its decomposition results in liberation of two nitrogen molecules and a significant amount of energy. The thermal stability of 5-nitrotetrazole is the intensive decomposition with the loss of 75% of weight, 115-120°C; impact sensitivity – 100%

of explosions; detonation velocity – 8.5 km/s ($\rho \sim 1.7$ kg/m^3 [1079, 1421]. Heats of formation in gas phase and detonation properties including heats of detonation, relative specific impulses, detonation velocities, and crystal densities of nitrofurazans and nitrofuroxans have been calculated by quantum chemistry, molecular mechanics, and Monte Carlo methods [1422]. 3,4-Dinitrofurazan and 3-nitro-4-nitroaminofurazan are recommended to be promising energetic compounds on a comprehensive account. The crystal densities, detonation properties, and sensitivities of most nitro furazans and furoxans are high, and it is not an efficient way to enhance detonation properties by increasing furazans or furoxans. Consequently, the smaller molecules are preferentially recommended, and therefore the kinds, orders, and quantities of the linking groups in poly-furazans and poly-furoxans can affect the detonation properties [1422]. The basic *thermal stability* of 5-nitro-1,2,4-triazole-3-one has been determined by differential scanning *calorimetry* (DSC) [1332]. The DSC spectra have only one peak, a very strong exothermic peak at 253°C. Nonisothermal differential scanning *calorimetry* has been used for the estimation of the kinetic parameters and the critical rate of temperature rise in the thermal explosion from the exothermic autocatalytic decomposition of 3,4-bis(4′-nitrofurazan-3′-yl)-2-oxofurazan [1423]. The influence of the substituents on both formation and thermal properties of the ionic liquids – the salts of 1,3-dimethyl-4-nitroimidazolium, 1-ethyl-3-methyl-4-nitroimidazolium, 1,2,3-trimethyl-4-nitroimidazolium, 1,3-dimethyl-2-nitroimidazolium, and 1-ethyl-3-methyl-2-nitroimidazolium has been determined by DSC, TGA, and single crystal X-ray diffraction [1424]. These data show that an electron-withdrawing nitro substituent can be successfully appended and has a similar influence on the melting behavior as that of corresponding methyl group substitution. In the solid state, the nitro group has a suggestive effect, beyond the steric contribution, on the crystal packing [1424]. Differential scanning *calorimetry* and *thermogravimetric analysis* have used in studying thermal stability of 2,4,5-trinitroimidazole derivatives [1425], fluorescent molecule 2(2′-hydroxy-4′-aminophenyl)-6-nitrobenzoxazole [1202], and chromophores on the base 6-nitrobenzothizole [787].

The neural network (NN) studies to predict impact sensitivities of various types of explosive molecules including nitropyrazoles, nitroimidazoles, nitrotriazoles, and nitrofurazans have been utilized [1426]. More than two hundred explosive molecules have been taken from a database archived by Storm, Stine, and Kramer (SSK) on the basis of experimental values of impact sensitivity for a variety of explosive molecules. The optimization of NN architecture has been carried out by examining seven different sets of molecular descriptors and varying the number of hidden neurons. For the optimized NN architecture, 17 molecular descriptors have been used. These results showed that the subsets composed of compositional and topological descriptors provide better results than those composed of electronic descriptors. Optimized NN architecture will be of great use in predicting the impact sensitivity of novel energetic molecules and may serve as a practical solution in guiding of new energetic materials in terms of safety [1426].

The stability, tautomerism, and ionization of 5-substituted 1,2,3-triazoles, including nitroderivatives [1427], and 5-nitro-1,2,4-triazole-3-one [1428] have

been studied by B3LYP (or B3PW91) calculations using the 6-31+G*, 6-311+G** or 6-311++G** basis sets. For all studied 1,2,3-triazoles, the most stable is the N2-H tautomer [1427].

The *electroconductivity* of alkylammonium salts of nitrobenzoxazoles [1104], 4-hydroxy-7-nitrobenzofurazan [1235], 2-amino-6-nitrobenzothiazoles, and their charge transfer complexes with acceptors [1429] has been studied. The positive temperature coefficients of the electrical conductivity of thiazoles suggested their semiconducting characteristics. The correlation between the activation energies of the charge transfer complexes and either the electron affinities of acceptors or the ionization potentials of donors was not found. This can be explained by assuming that the geometrical and not the electronic structure of the complexes is the determining factor [1429]. The conductometry measurements of 4-oxy-5,7-dinitrobenzofurazan and its potassium salt solutions show that it exists, mainly, in ion form, for example, lg K_{acc} value of the first compound is 1.33 [1230].

A comparison of *inelastic neutron scattering* spectrum of 3-amino-5-nitro-1,2,4-triazole (1200 cm^{-1}) with B3LYP/6-311G** calculations of isolated molecule shows generally good frequency and intensity agreement with two notable differences in intensity [1430]. Periodic density functional theory calculations are used to determine whether the intermolecular hydrogen bonding is the origin of these differences between the B3LYP/6-311G** and neutron spectrum.

The method of *atomic adsorption analysis* has been proposed for quantitative determination of mercury in the correspondent salt of 5-nitrotetrazole [1182].

Chromatography is widely used for analysis and separation of nitroazoles. For example, thin-layer chromatography was used for separation of nitropyrazoles [1431, 1432], nitroimidazoles [1133, 1309, 1431], nitrobenzoxazole derivatives [1433], and 5-nitro-2,1,3-benzoselenadiazole [1434].

High-performance liquid chromatography (HPLC) has been used to analyze metronidazole [1435–1437], misonidazole [1309, 1438], and other nitroimidazoles [1435, 1439] in body fluids or pharmaceutical dosage forms. HPLC analysis of effect of hypoxic-cell radiosensitizer misonidazole on the radiation-induced reduction of DNA bases (thymine, cytosine, and adenine) has been carried out [1440, 1441]. HPLC was employed to characterize different nitroimidazoles [327, 366, 388, 409, 450, 1442–1444], nitropyrazoles [246, 301], nitrothiazoles [366], 1-aryl(hetaryl)-4-nitro-1,2,3-triazoles [601], nitrobenzimidazoles [707], nitrobenzofurazans [774, 1445–1449], nitrobenzotriazoles [1450].

Flash chromatography has been applied to study the vicarious nucleophilic substitution products of nitroazoles (pyrazoles, imidazoles, indazoles, and benzimidazoles) [319], the thermal isomerization of the nitroisoxazoles into nitrooxazoles (with petroleum ether/ethyl acetate 10:1 v/v as eluent) [501, 502].

Gas chromatography was used to separate a large number of *N*-nitro- and *C*-nitroazoles [320, 328, 1260, 1268, 1451]. Chromatographic constants R and log P have been determined in series of 5-nitroimidazoles. Relationship of structure and activity has been analyzed [1452]. 2-Substituted 4,6-diniroanthranils on cleaning were isolated by chromatography using a SiO column [1453].

The *Raman spectra* of insensitive energetic material 5-nitro-2,4-dihydro-1,2,4-triazole-3-one have been measured in a high-pressure vessel diamond anvil cell [174]. Raman bands show a blue shift because of the nature of the molecule packing as a high-pressure effect, but some particular bands exhibited a red shift, disappearance, split, or slight shifting in spectra. Those red-shifting bands concerning hydrogen bonds, i.e., carbonyl and amino groups, are likely to work as a stabilizer against stimuli to the molecule or crystal. This stabilizing nature might characterize the insensitivity of NTO [174].

Optical methods have found a wide usage for quantitative determination of medical drugs, like tinidazole [1134, 1454], metronidazole [1455–1458]. In particular, a spectrophotometric method for the estimation of metronidazole and its benzoate in pure form and in pharmaceutical preparations has been used [1458]. The method is based on the development of a stable pink color with potassium hydroxide in methanol-isopropyl alcohol solution which can be quantitatively measured at 370 nm. The authors of the work [1457] have stated that the method proposed by them has less error (3–4%) and is less complicated than the used before. The optical properties of organic luminescent microcrystals on the basis of nitrobenzofurazans have been studied [1459].

The results of *mathematical analysis*, based on the methods of the theory of recognition types, theory of groups, and regression analysis of benzimidazole derivatives with antivirus activity constructing, have showed that nitro-containing benzimidazoles (2- and 5(6)-nitrobenzimidazole) cannot mainly have such activity [1460]. The N–N bond nature in 1,2,5-trinitroimidazole and 1,2,4,5-tetranitroimidazole has been examined with various levels of *ab initio* and density functional (DF) theories [1461]. According to calculations the N–N bonds of these compounds have a significant ionic nature, at that the 1-nitro group bears a considerable positive charge and has attractive electrostatic interactions with O atoms of adjacent nitro groups. Significantly long N–N bond lengths calculated with MP2 and DF theories imply a strong hyperconjugation effect, which may explain a tendency to form a salt in these compounds easily [1461].

Computational analysis of stacking interactions of 4-nitropyrazoles and 5-nitroimidazoles [1462], *theoretical studies* of oxidation products of guanine – 5-guanidino-4-nitroimidazoles[1463,1464],1-methyl-2-(5-amino-1,3,4-thiadiazole)-5-nitroimidazole (megazole) [1465, 1466], 4-amino-5-nitro-1,2,3-triazole dimers [1467], and 3-nitro-1,2,4-triazol-5-one [1468–1471] have been studied. The structure and the design of megazole and its azaheterocyclic analogs were described by semiempirical calculations to investigate the possible pharmacophoric contribution of the 1,2,4-triazole nucleus, the position of the heterocyclic nucleus, and presence of the nitro group, to the activity against the bloodstream trypomastigote forms of *Trypanosoma cruzi* [1466]. The correlation of some stereo electronic properties with biological activity in an attempt to understand the possible mechanism of action of the designed series of compounds has been discussed.

The acidity constants (pK_a) of the N-H sites in 2-substituted 5(6)-nitrobenzimidazoles (NBI) and 5,6-dinitrobenzimidazole (DNBI) were measured by potentiometric

method in aqueous solution [1472] and nonaqueous solvents (acetonitrile, dimethylsulfoxide) [991, 1473] (Table 3.86).

The results of correlation pK_a values of 2-substituted nitrobenzimidazoles with the σ_I σ_R substituent parameters show that the contribution of the inductive effect is significantly prevailed (3.9) [991]:

$$pK_a = (-9.95 \pm 0.98)\sigma_I + (-1.44 \pm 0.46)\sigma_R + (0.60 \pm 0.13); \quad (3.9)$$
$$r = 0.981, s = 0.48, n = 11$$

R = $N(CH_3)_2$, NH_2, OCH_3, OC_2H_5, CH_3, H, Cl, $COOCH_3$, $COCH_3$, CF_3, CN

The stability constants of the 1:1 complexes formed between Mg^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, and Cd^{2+} and the anionic 5(6)-nitrobenzimidazolate or 5,6-dinitrobenzimidazolate were obtained by the same method in aqueous solution (25°C; I=0.5 M, $NaNO_3$). The electron-withdrawing properties of (N-3)-bound metal ions facilitate the release of the proton from the (N-1)–H site in the M(NBI)(2+) and M(DNBI)(2+) complexes, if compared to the situation in the free ligands [1472].

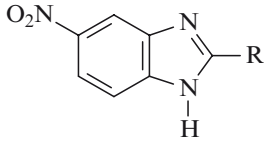
Acid-base titration method was employed for quantitative determination of metronidazole in pharmaceutical dosage forms and compared with the other methods [1474].

The *potentiostatic polarization method* has been used to study the inhibitive behavior of 5-nitrobenzothiazoles on the corrosion of pure aluminum in 0.1 M HCl [1475]. A possible mechanism for the corrosion and inhibition processes has been proposed based on the obtained activation parameters.

A new *capillary zone electrophoresis* method has been developed and used for the separation of enantiomers, for example, omeprazole [1476] and nitrobenzofurazans [1385, 1388, 1447].

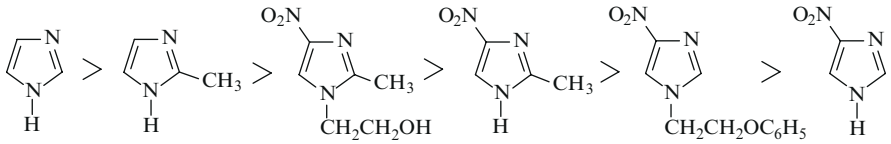
Solubility nitroazoles, a prospective medicine, plays a very important role in medical practice. A number of works are devoted to the problem of nitroimidazole

Table 3.86 The acidity constants (pK_a) values of 2-substituted 5(6)-nitrobenzimidazoles .



R	pK_a		
	Acetonitrile	DMSO	Water
$N(CH_3)_2$	23.16	–	–
NH_2	22.48	–	–
OCH_3	21.38	–	–
OC_2H_5	21.72	–	–
CH_2OH	–	12.86	2.21
CH_3	23.40	12.77	5.16
H	23.31	11.75	3.93
CH_2Cl	–	11.36	2.21
Cl	17.40	–	–
$COOCH_3$	20.24	–	–
$COCH_3$	20.78	–	–
CF_2Cl	–	8.97	–0.77
CF_3	17.90	8.17	–0.18
CN	16.63	–	–

solubility [1135, 1477–1484]. Solubility of imidazoles decreases in the following row (Scheme 3.78) [1478]:



Scheme 3.78

Limited solubility of nitroimidazole in water and other polar solvents can be explained not only by hydrophobic properties of nitroimidazole, but also with decreased basicity of the N-3 nitrogen atom. Hydrophobic properties of nitroimidazole are conditioned by the presence of the nitro group; unsubstituted imidazole is, as known, highly hydrophilic [1478]. Solubility of azaheterocycles in protic solvents is determined much by the azagroup (=N–) and less by the – NH-group, since the lone electron pair increases the strength of the hydrogen bond and hence the N-3 atom solvation.

The solubility of metronidazole, dimetridazole, ipronidazole, tinidazole, omindazole, and model compounds *N*-alkyl-2-methyl-4-nitroimidazoles has been examined [1135, 1483, 1485, 1486]. The results show that the aqueous solubility of ipronidazole increases exponentially following the addition of a cosolvent [1135, 1483, 1485]. The coefficients of distribution (log P) between water and octanole for the large number of nitroimidazole derivatives have been determined [1479, 1481–1483]. Analysis of correlations between distribution coefficients and Hansch constants has been carried out; the possibility of using log P for evaluating the constants of tautomeric equilibrium in nitroimidazoles [1479]. The solubilization of three commercial drugs – omindazole, metronidazole, tinidazole and model compounds *N*-alkyl-2-methyl-4-nitroitnidazoles on aggregates formed by anionic polyelectrolytes, carrying alkyl side chains of different length, has been investigated in aqueous solution at pH 3.0, 7.0, and 11.0. The results indicate that solubility of alkyl-nitroimidazoles on polymer micelles depends mainly on the length of the alkyl chain and therefore is determined by the heterocyclic group. On the other hand, the solubilization of 1-hexyl-2-methyl-4-nitroimidazole increases with decreasing length of the side alkyl chain [1486].

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Application of Nitroazoles

Abstract The application of *C*- and *N*-nitroazoles, many of which are well-known medicines, hypoxic cell radiosensitizers, explorer materials, and important building blocks in drug discovery is described. Main attention is paid to nitroimidazole derivatives among which are medicines with a vividly expressed therapeutical activity (azomycine, metronidazole, ipronidazole, carnidazole, dimetridazole, secnidazole and many others) and also to nitrotriazoles, nitrotetrazoles, nitrobenzazoles, and polynitroazoles used as high-energy compounds. Nitrobenzazoles are often used in drug design and also in nonlinear optical materials, food additives, and energetic compounds. They also show versatile pharmacological activities, such as antifungal, antibacterial, antitumor, antihelmintic, antiallergic, antineoplactic, local analgesic, and spazmolytic.

Introduction

The nitro derivatives of azoles have found wide applications in different fields of medicine, technology, chemistry, and agriculture. Various therapeutic products (metronidazole, tinidazole, nitazole, azomycin, ronidazole, etc.), herbicides, pesticides, and plant growth regulators have been created from them. The interest in nitro derivatives of azoles is rising continuously because such compounds are utilized as radiosensitizers, energetic materials, powerful veterinary medicines, and antifog additives in film and photoindustry, and organic synthesis intermediates in nanochemistry.

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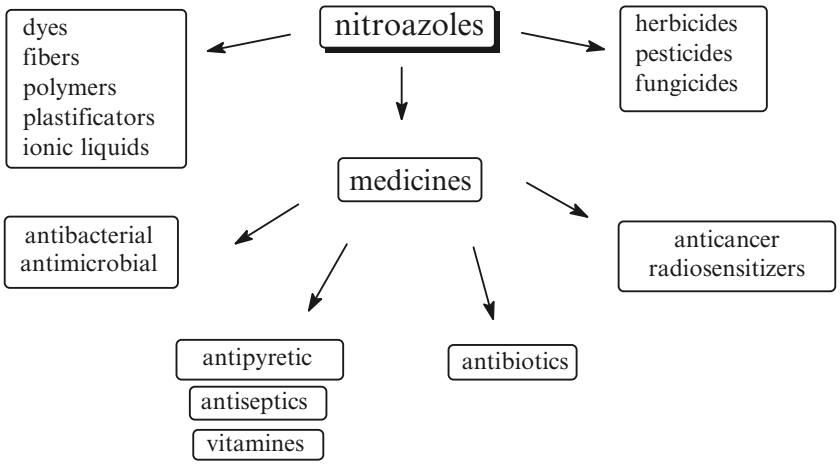


Some data on the application of nitroazole derivatives have been mentioned in reviews and monographs on the chemistry of nitroazoles [1], pyrazoles [2], furoxans [3], benzimidazole [4], and benzotriazole [5, 6], etc. Special monographs and reviews have been devoted to biological and clinical application of different nitroimidazoles [7–23] and chemotherapy of metronidazole [24]. Therefore, it is not given much attention to metronidazole here.

Five-Membered Nitroazoles

Nitroimidazole derivatives possess a very broad spectrum of practical application in medicine [25–30]. The nitroimidazole group of drugs is remarkable in two respects [19]:

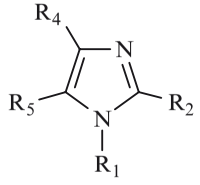
1. For its spectrum of activity against Gram-positive and Gram-negative bacteria, protozoa, the occasional helminth, and even hypoxic tumors.
2. That despite its use for 40 years, the incidence of resistance in anaerobes is still very low.

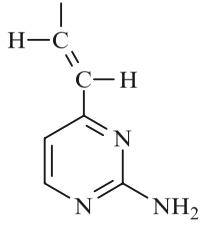
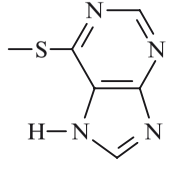
No other group of drugs displays this range of action both in human and veterinary medicine or the relative lack of resistance. These characteristics explain why numerous researches are devoted to such interesting molecules.

More popular drugs on the base of nitroimidazoles are presented in Table 1.

The 5-nitro derivatives of imidazole, in particular metronidazole – 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole, the usually used, are accepted as drugs of choice for the radiosensitization of hypoxic tumors and also for anti-infectious chemotherapy against protozoa and anaerobic bacteria. Resistance to these compounds has been shown in Trichomonas vaginalis and Bacteroides fragilis, in both natural and in vitro under drug pressure-induced populations. Other nitroimidazoles have been found to be mutagenic and carcinogenic [7, 8, 24].

Table 1 Nitroimidazole drugs



Commercial name	Substituents			
	R_1	R_2	R_4	R_5
Azanidazol	CH_3		H	NO_2
Azathioprine	CH_3	H	NO_2	
Azomicin	H	NO_2	H	H
Benznidazole	$CH_2CONHCH_2C_6H_5$	NO_2	H	H
Carnidazole	$CH_2CH_2NHC(S)OCH_3$	CH_3	H	NO_2
Chlonidazole	CH_3	H	Cl	NO_2
Dimetridazole	CH_3	CH_3	H	NO_2
Etanidazole	$CH_2CONHCH_2CH_2OH$	NO_2	H	H

(continued)

Table 1 (continued)

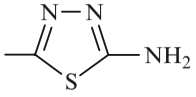
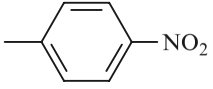
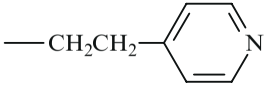
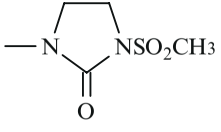
	Substituents			
Commercial name	R_1	R_2	R_4	R_5
Fexinidazole	CH_3	$CH_2OC_6H_4SCH_3$	H	NO_2
Flunidazole	CH_2CH_2OH	C_6H_4F	H	NO_2
Ipronidazole	CH_3	$CH(CH_3)_2$	H	NO_2
Megazol	CH_3		H	NO_2
Metronidazole	CH_2CH_2OH	CH_3	H	NO_2
Misonidazole	$CH_2CHOHCH_2OCH_3$	NO_2	H	H
Nimorazole	$CH_2CH_2NC_4H_8O$	H	H	NO_2
Nitrefazole		CH_3	NO_2	H
Nitazole	$CH_2CH(OH)CH_2Cl$	CH_3	H	NO_2
Ornidazole	$CH_2CH(OH)CH_2Cl$	CH_3	H	NO_2
Paniazole		CH_3	H	NO_2
Ronidazole	CH_3	CH_2OCONH_2	H	NO_2
Satranidazole	CH_3		H	NO_2
Secnidazole	$CH_2CH(OH)CH_3$	CH_3	H	NO_2
Sulnidazole	$CH_2CH_2NHSCOCH_3$	CH_2CH_3	H	NO_2
Ternidazole	$CH_2CH_2CH_2OH$	CH_3	H	NO_2
Tinidazole	$CH_2CH_2SO_2CH_2CH_3$	CH_3	H	NO_2

Table 2 Utilization of misonidazole in medicine and biology

Application	References
Radiosensitizing effect	[31]
In the presence of chemical radioprotectors	[32–43]
Hypoxic cells	[32–34, 36, 37–43, 44–95]
Normal tissue	[44, 52, 62, 63, 93, 95, 96–99]
Toxicity to hypoxic cells	[34, 44, 47, 49–51, 53, 55, 57, 60, 66, 67, 69, 70–76, 85, 97, 99–116]
Toxicity in vivo	[48, 59, 61, 64, 71, 72, 76, 99, 101, 104, 114, 117][a]
Postirradiation synthesis DNA[b]	[32, 41, 42, 50, 51, 57, 69, 75, 90, 99, 103, 109, 112, 118]
Antimicrobial drug	[35, 40, 51, 53, 67, 88, 101, 103, 112, 119, 120]
Others: rat brain capillary permeability	[121]
Somatosensory deficits	[73]
Enhancement DNA cross-linking	[122]
Activity mutagenicity	[114]
Structure – activity	[90, 115, 116]
Veterinary	[58]

[a]Neurotoxicity in vitro and in vivo
[b]Effect on single- or double-stranded

The more popular and widespread drug after metronidazole and dimetridazole is misonidazole – 1-(α-methoxymethyl ethanol)-2-nitroimidazole (code name Ro-7-0582) – trichomonicide and experimental mutagen, antineoplastic, and radiosensitizer, probably due to its ability to form DNA-attacking free radical under hypoxic conditions. Exhibiting high electron affinity, misonidazole induces the formation of free radicals and depletes radioprotective thiols, thereby sensitizing hypoxic cells to the cytotoxic effects of ionizing radiation. These single-strand breaks in DNA induced by this agent result in the inhibition of DNA synthesis. The various uses (and references) of misonidazole are given in Table 2.

The utilization and activity (antimicrobial, antiprotozoan, antibacterial, antitrichomonal, etc.) of other 2-nitroimidazole derivatives and also 4- and 5-nitroimidazoles are summarized in Table 3. The various activities of nitropyrazoles, nitrotriazoles, nitrotetrazoles, and nitrothiazoles are presented in Table 4.

Nitroimidazoles possess enormous arsenal of activities, for example, against anaerobic bacteria, whereas aerobic and facultative bacteria are generally resistant to it. The 5-nitroimidazoles usually have significantly greater biological activity than the 4-nitro isomers. 1-Substituted 4- and 5-nitroimidazoles have been prepared in a variety of ways, the most common of which is by alkylation of 4(5)-nitroimidazoles or nitration of alkylated imidazoles. The ultimate orientation of the nitro group, however, depends on a number of factors, the most important of which appears to be the nature of the alkylating or nitrating agent used and the reaction conditions employed. So, it is significant that an unambiguous method of structure assignment be available.

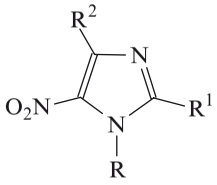
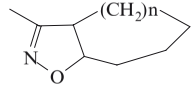
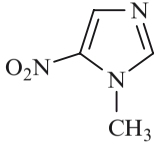
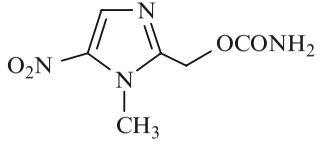
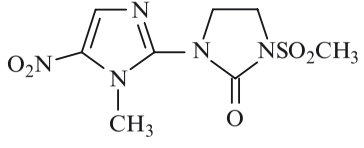
Table 3 Application of nitroimidazole derivatives

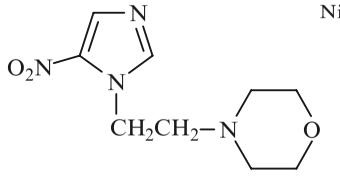
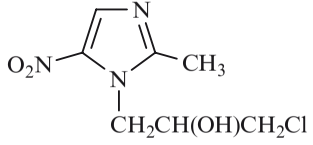
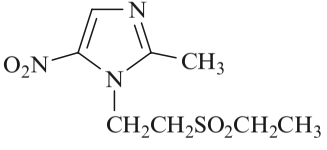
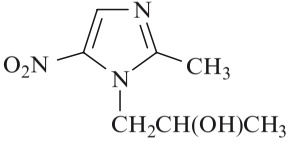
Compound	Activity and application
2-Nitroimidazole – azomicine, Ro-5-9129	Radiosensitizing effect in hypoxic cells [84, 91, 123–126], in normal tissue [123]; toxicity to hypoxic cells [112, 113, 115, 116, 124, 125, 127], toxicity in vivo [128]; antimicrobial drugs (effect on single- or double-stranded DNA *Escherichia coli*) [112]; antiprotozoan, antibacterial (*Salmonella typhimurium cells* [123] and antitrichomonal activity [128, 129]); inhibition of ribonucleotide-reductase [130]; structure–activity [115, 116, 127]
(3-(2-Nitro-1-imidazolyl)-propionic acid), Ro 31-0258	Radiosensitizing effect in hypoxic cells [84, 91]
2-Nitroimidazole hydrofluoride	Dental therapy [131]
(1-(2-Nitro-1-imidazolyl)-3-*N*-piperidino-2-propanol), Ro 03-8799	Radiosensitizing effect in hypoxic cells [82, 84, 86, 91]
1-(2-Nitro-1-imidazolyl)-3′-hydroxy-3-*N*-piperidino-2-propanol, Ro 31-0052	Radiosensitizing effect in hypoxic cells [84]
1-[3-Aziridinyl-2-hydroxypropyl]-2-nitroimidazole, RSU 1069	Radiosensitizing effect in hypoxic cells, toxicity to hypoxic cells [132]
N-benzyl-2-nitro-1-imidazole-acetamide – benznidazole, Ro 07-1051	Radiosensitizing effect in hypoxic cells [89]; toxicity to hypoxic cells [102, 112, 115, 116]; DNA damage [112], antitrichomonal activity [137], structure–activity [115, 116]; inhibition of *T. cruzi* growth at concentrations that do not stimulate $O_2^{\bullet-}$ and H_2O_2 production (reduced metabolites of benznidazole are involved through covalent binding to macromolecules in its trypanocidal and toxic effects) [133]
1-(2-Nitro-1-imidazolyl)-3-methoxy-, -3-allyloxy-2-propanol; *N*-butyl-, *N,N*-dimethyl-2-nitro-1-imidazoleacetamide; 1-(*p*-nitrobenzyl)-2-nitroimidazole	Antiprotozoan and antibacterial activity against *Trichomonas (T.) vaginalis, T. foetus, Endamoeba histolytica, Triponasoma cruzi, Streptococcus pyogens, Escherichia (E.) coli* [134]
3-(2-Nitro-1-imidazolyl)-1,2-propandiol), Ro-5-9963	Against *T. vaginalis, T. foetus* [134], toxicity to hypoxic cells [102], mutagenic action on *Klebsiella pneumoniae* [135]
N-(2-Hydroxyethyl)-2-nitro-1-imidazoleacetamide – etanidazol	Radiosensitizing effect in hypoxic cells [136, 137], against *Streptococcus pyogens*, *E. coli* [134]
Other 1-substituted 2-nitroimidazoles	Radiosensitizing effect in hypoxic cells [88, 89, 93, 138–142], in normal tissue [93], toxicity to hypoxic cells [113, 128, 139, 140, 143], toxicity in vivo [144], DNA damage *E-coli* [88], HeLa cells [143], against *Streptococcus lactis* [88], *T. vaginalis, T. foetus, Endamoeba histolytica* [128, 145], herpes [141])
1-R-2-nitroimidazoles, R = $CH_2CH(OH)CH_2.NC_4H_8$ (Ro 03-9310), $CH_2CH(OH)CH_2.NC_4H_8O$ (Ro 03-8800)	Radiosensitizing effect in hypoxic cells [91]
1,5-Disubstituted 2-nitroimidazoles L-6802; L-7138, L-8711, L-6678	Radiosensitizing effect in hypoxic cells [45, 85], toxicity to hypoxic cells [85, 102, 104, 105], toxicity in vivo [104, 128], against *T. vaginalis* [119, 128], *Staphylococcus aureus*, *Psevdomonas aeruginosa* [146])

1,5-Disubstituted 2-nitroimidazoles L-8580, RGW-613, RGW-801, RGW-806, L-10333	Antitrichomonal activity [119]
2,5-dinitroimidazole	DNA damage [118]
1-Methyl-2,5-dinitro-imidazole	Radiosensitizing effect in hypoxic cells [147]
1-Morpholine or piperidine substituted 2-nitroimidazoles	Radiosensitizing effect in hypoxic cells, toxicity to hypoxic cells, toxicity in vivo [148]
2-Nitroimidazole fluorine derivatives	Radiosensitizing effect in hypoxic cells [149, 150]
4(5)-Nitroimidazole	Radiosensitizing effect in hypoxic cells [151], toxicity to hypoxic cells [103, 115, 116, 151], toxicity in vivo [103], DNA damage [103, 118, 151], antitrichomonal activity [103], prevention of histomoniasis in turkeys [152, 153] and ocular hypertension, ischemia [154], structure–activity [115, 116]
4(5)-Nitroimidazole-5(4)-carboxyhydrazide	Antimicrobial effect, inhibition of purine biosynthesis [155]
1-Methyl-4-nitroimidazole	Effect on neuromuscular transmission [156]
1-Methyl-5-sulfonamide-4-nitroimidazole	Radiosensitizing effect in hypoxic cells [157]
1-Methyl-5-bromide-4-nitroimidazole	
1-(2-Hydroxyethyl)-2-methyl-4-nitroimidazole (SC-16427)	Radiosensitizing effect in the presence of chemical radioprotectors [158], trichomonicide [119]
6-[(1-Methyl-4-nitroimidazole-5-yl)thio]purine, azathioprine	Toxicity in vivo [159], efficiency in preventing rejection of transplants [160], immunosuppressant [159, 161]
6-[(1,2-Dimethyl-4-nitroimidazole-5-yl)thio]purine	Antineoplastic, immunosuppressant [162]
2-Alkyl-4(5)-nitroimidazoles	Analgesic activity [163], control of histomoniasis (blackhead) in turkeys [153]
2-Methyl-4-nitro-1-(4-nitrophenyl)imidazole (nitrefazole, altimol)	Antialcohol drug [164, 165]
4-Nitro-1-carboxymethylimidazole	Against ocular hypertension, ischemia [154]
Methyl-4-nitromidazole-5-carboxylate	Staphylocoagulase [166]
1,2-Dimethyl-4-nitroimidazole, 8609 RP	Radiosensitizing effect in hypoxic cells [151], toxicity to hypoxic cells [103, 151], toxicity in vivo [103], DNA damage [103, 118, 151], antitrichomonal activity [103]
1,2-Dimethyl-4-nitro-5-(3-hydroxystyryl)imidazole	Against *T. vaginalis* [167]
4-Nitro-5-thioimidazoles	Toxicity in vivo [167]
2-Methyl-4-nitroimidazole derivatives	Radiosensitizing effect and toxicity in hypoxic cells [124]
N-aryl derivatives of 4-nitroimidazole and 2-methyl-4-nitroimidazole	Antituberculosis activity [168]
2-(Fluorophenyl)-4(5)-nitroimidazole	Against turkey histomoniasis [169]
5-Chloro-4-nitroimidazole HCl salt	Herbicide [170]
Halogenated 4- and 5-nitroimidazoles	Radiosensitizing effect in hypoxic cells [171]

(continued)

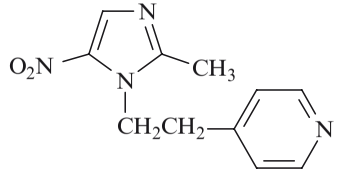
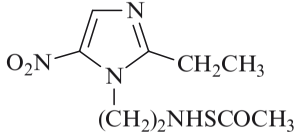
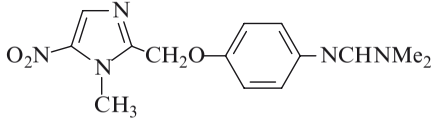
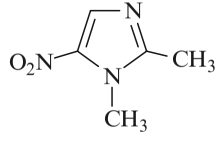
Table 3 (continued)

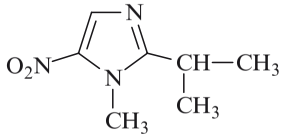
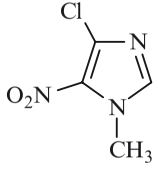
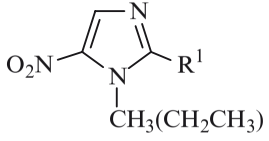
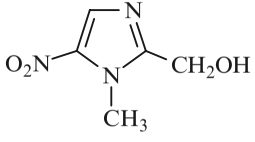
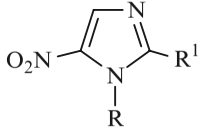
Compound	Activity and application
	Trichomonicide, against amebiasis [172], antiprotozoa [173]
$R=CH_3$, $R^1=PhOCH_3$, $R^2=H$ $R=CH_3$, $R^2=H$, $R^1=$ 	*Trypanosoma brucei* [174] *Endamoeba hystolytica* [175]
$R=CH_3$, $R^2=H$, $R^1=$2-oxo-tetrahydroimidazole-2-thiazolyl $R=CH_3$, $R^1=H$, $R^2=PhO$	*T. vaginalis* [176]
	Against histomoniasis [177], effect on neuron-muscular transmission of *Rana temporaria* [156], mutagenic activity [178]
Ronidazole 	Against *T. vaginalis* [119], *T. foetus* [179], *Giardia intestinales* [180], *Treponema hyodysenteriae* [181], coccidiostatic agent [182], antibacterial in mice (*E. coli, Klebsiella pneumniae, Salmonella pullorum*) [183], veterinary [184–190], increase of gain of turkey and pigs [191]
MF nitroimidazole	Against *T. foetus* [179]
Satranidazole CG-10213-Go 	Against anaerobic (*Bacteroides spp.*) and Aerobic bacteria (*Salmonella typhimurium*), microaerophilic campylobacters (*Campylobacter jejuni* and *Campylobacter coli*) [192], C*aecal amoebiasis* [193], *Giardia intestinales* [180], structure-activity [194]

Nimorazole		Radiosensitizing effect in hypoxic cells [91, 195], toxicity in hypoxic cells [102, 115, 116], trichomonicide [119, 196–199], against *Bacteroides fragilis* [199], eye drops, liniments for treatment of blepharitis [200], structure-activity [115, 116]
Ornidazole		Toxicity in hypoxic cells [103, 112, 115, 116], toxicity in vivo [103], DNA damage [103, 112, 118], antimicrobial [103, 112, 119, 197–199, 201, 202] and antitrichomonal activity [203, 204], against *Bacteroides fragilis* [199, 205], *Giardia intestinales* anaerobic microorganisms [180, 206], *Salmonella typhimurium* [207], *Bacteroides endodontalis* [208], *E. hystolitica* [203], eye drops, liniments for treatment of blepharitis [200], structure–activity [115, 116], sterilization under γ-irradiation [209], effect on microtubule formation [210], as internal standard for the estimation of ursodiol in human plasma [211]
Tinidazole		Radiosensitizing effect in hypoxic cells [195, 212, 213], toxicity in hypoxic cells [103, 115, 116, 213], toxicity in vivo [103, 213], DNA damage [103], antimicrobial [103, 119, 196–199, 201, 202, 214, 215], antibacterial [216, 217], antiprotozoal [217, 218], and antitrichomonal activity [203], against *Bacteroides fragilis* [199], anaerobic microorganisms [206], *E. hystolitica* [203], *E. invadens* [219], *Helicobacter pylori* [220], *T. vaginalis, Entamoeba histolytica, Giardia lamblia* [221], eye drops, liniments for treatment of blepharitis [200], pharmaceutical compositions [222], antihelmintic drug [223], against rheumatoid artritis [224], structure-activity [115, 116]
MY-40/20		*Salmonella typhimurium* [207]
Ternidazole		Antiprotozoa activity [205]
Secnidazole		Radiosensitizer [195], trichomonicide, *Bacteroides fragilis* [199], pharmaceutical tablets [225], toxicity in hypoxic cells, toxicity in vivo, DNA damage [103, 151, 226]

(continued)

Table 3 (continued)

Compound	Activity and application
Fexinidazole	Antiprotozoa activity (trichomonicide, *Entamoeba hystolitica*, *Troponasoma cruzi*) [227]
 Paniazole	Amebicide [228]
 Sulnidazole	Toxicity in hypoxic cells, toxicity in vivo, DNA damage, antitrichomonal activity [103]
 S 750400A	Antiprotozoal drug against *Giardia intestinales* [180]
Megazol 1-methyl-2-(5-amino-1,3,4-thiadiazole)-5-nitroimidazole	Antibacterial and antiparasitic activity particularly against trypanosomes [133, 229]
 Dimetridazole	Antibiotic [230], trichomonicide [119, 196], antimicrobial [214], coccidiostatic agent [182], prevention of histomoniasis in turkeys [152, 153, 184–187, 231–239], pigs [240], swine dysentery [241–243], stimulant for growing pigs [244], in food for prevention of diseases [191, 245–248], against *Salmonella typhimurium* [249], *Campylobacter spp.* [250], *Treponema hyodysenteriae* [181], *Trifolium pratense L.* [251], carcinogenicity [252]; structure–activity [115, 116], additive to oil products for prevention of anaerobic sulfate-reducing bacterium growth [253]
Dimetridazole phosphates	Antidepressants, antibacterial [254], in veterenary against histomoniasis [255]
Dimetridazole potassium sulfate	In veterenary against histomoniasis [255]

2-R-1-methyl-5-nitroimidazoles R = SMe; SOMe; SO_2Me	Antifungal, genotoxic [256]
SC-28538	Trichomonicide [119]
Azanidazole	Antiprotozoal (genetically active on *S. cerevisiae* D_7 in the intrasanguineous host-mediated assay) [257]
 Ipronidazole	Promoting of swine growth [258, 259], against swine dysentery [184, 260], infection in turkeys [190, 261]
 Chlomizole	Antiprotozoal activity [262, 263]
 R^1 = phenoxyalkyl derivatives, 16 compounds	Antitrichomonal activity [264]
	Against dysentery (veterenary) [265]
 Carnidazole	Trichomonicide [199], antiprotozoal (*Salmonella typhimurium*) [207], eye drops, liniments for treatment of blepharitis [200]

(continued)

Table 3 (continued)

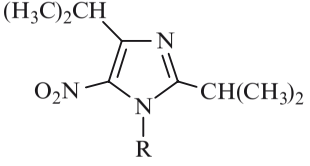
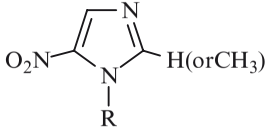
Compound	Activity and application
MK-0436	Toxicity in vivo, tripanocidal activity, mutagenic [266]
R = $CH_2CH(OH)CH_2Cl$, $R^1 = CH_3$ Ro 07-0207 R = CH_3, $R^1 = CH(CH_3)_2$ Ro 07-1554	Radiosensitizing effect in hypoxic cells [92]
	
R = CH_3, C_2H_3, C_2H_5OH, $CH_2CH(OH)CH_3$, $CH_2CH(OH)CH_2Cl$, CH_2CH_2Cl	Herbicides [267]
 R = Haloethyl	Against *Histomonas meleagridis* in vivo [268]
Nitroimidazoloyl ureas, carbamates	Antiprotozoal activity [269]
1-R-2-methyl- and 1-methyl-2-R-5-nitroimidazoles	Antiprotozoal activity [203]
Pt-complexes of mononitro-substituted imidazoles	Radiosensitizing effect in hypoxic cells [94]
Bis(nitroimidazoles)	Radiosensitizing effect in hypoxic cells, toxicity in hypoxic cells, toxicity in vivo [270]

Table 4 Application of nitropyrazoles, nitrotriazoles, nitrothiazoles, and nitrotetrazoles

Compound	Activity and application
4-Nitropyrazole	Mutagenic activity [178], ocular hypertension, ischemia [154]
3- and 5-substituted 4-nitropyrazole	Ocular hypertension, ischemia [154]
4-Nitropyrazole 1,3,5-derivatives (Ro 08-9141, Ro 10-2730, Ro 10-4876)	Radiosensitizing effect in hypoxic cells [92]
1-Methyl-4-nitropyrazole	Mutagenic activity [178]
N-aryl 4-nitropyrazoles	Antituberculosis activity [168]
1-Hydroxyethyl-4-nitropyrazole (M & B 4998)	Radiosensitizing effect [151], toxicity in hypoxic cells [103, 151], toxicity in vivo, trichomonicide [103], DNA damage [103, 118, 151]
3,5-Dimethyl-4-nitropyrazole	Mutagenicity [178], ocular hypertension, ischemia [154]
1-Carboxymethyl-3,5-dimethyl--4-nitropyrazole, -5-methyl-3,4-dinitropyrazole	Ocular hypertension, ischemia [154]
1-Substituted 3,5-diamino-4-nitropyrazole	Precursors of energetic materials [271]
4,4′-Dinitro-1,1′-methylenedipyrazole	Mutagenicity [178]
3-Nitropyrazole and its 1-, 4-, and 5-derivatives	Ocular hypertension, ischemia [154]
N-nitropyrazoles	Generator of NO [272], ocular pharmacology and therapeutics (ocular blood flow, recovery of retinal function after ischemic insult) [273]
Pt-complexes of mononitro-substituted pyrazoles	Radiosensitizing effect in hypoxic cells [94]
3-Nitro-1,2,4-triazole	Ocular hypertension, ischemia [154]
N-aryl 3-nitro-1,2,4-triazoles	Antituberculosis activity [168]
3-Nitro-1,2,4-triazole derivatives	Radiosensitizing effect in hypoxic cells [124, 141, 274, 275], toxicity in hypoxic cells [124, 274], against herpes [141]
3-Nitro-1,2,4-triazole fluorine containing	Radiosensitizing effect in hypoxic cells [149, 150, 276]
Sanazole or senazole (AK-2123) 3-nitrotriazole derivative	Radiosensitizing effect in hypoxic cells [277–287], anticancer therapy [285–289]
1-Glucosyl-3-nitro-1,2,4-triazole	Trichomonicide [290]
5-Nitro-4,6-bis-(3-nitro-1H-1,2,4-triazol-1-yl)pyrimidine	Secondary explosive [291]
3-Nitro-1,2,4-triazole-5-one (NTO)	In gas-generation compositions [292], explosive [293–298]; *Bacillus lichenifomis* strain was isolated from industrial waste containing high concentrations of the explosive [295]

(continued)

Table 4 (continued)

Compound	Activity and application
3-Nitro-1,2,4-triazole-5-one picryl derivatives, amine salts	Explosive [299, 300]
Nitrotriazoles	Nucleotide activating groups [301]
2-Methyl-5-nitrotetrazole	Deflagration-detonation [302]
5-Nitrothiazole	Carcinogenicity [178]
2-Amino-5-nitrothiazole	Against *Schistosoma mansoni* and *Schistosoma haematobitan* [303], trichomonicide [304]
2-Acetylamino-5-nitrothiazole (Enheptin A^2)	Trichomonicide [304], against histomoniasis in turkeys [236]
3-(5-Nitro-2-thiazolyl)-2-imidazolidinone, niridazole	Antihelmintic [305], antibacterial [306], aerobic, microaerobic, anaerobic activity [307, 308], against *Salmonella typimurium, Campylobacter spp. Bacteroides spp.* [192], *T. vaginalis* [309, 310], *Schistosoma haematobium, Schistosoma mansoni*, [310, 311], *Salmonella* [312], *Campylobacter fetus subsp. jejuni* [313], toxicity in hypoxic cells, structure–activity [127]
1-Hydroxymethyl-3-(5-nitro-2-thiazolyl)-2-imidazolidinone, Ba 35597	Aerobic, vicroaerobic, anaerobic activity [307]
Ba 35969, Ba 37215, Ba 40922, Ba 36208, Ba 42517, Ba 30515, Ba 36435, Ba 34358, Ba 36204, Ba 32641, Ba 32476	Trichomonicides [201]
2-Acetylamino-5-nitrothiazole hydrofluoride	Dental therapy [131]
2-Methyl-4-nitrothiazole, 2-acetamido-5-nitrothiazole	Against *T. vaginalis* [314]
2-Amino-5-nitrothiazole	Carcinogenicity [252]
Pt-complexes of mononitro substituted thiazoles	Radiosensitizing effect in hypoxic cells [94]

Table 5 Application of nitroindazoles, nitrobenzimidazoles, nitrobenzoxazoles, nitrobenzothiazoles, and nitrobenzotriazoles

Compound	Activity and application
5-Nitroindazole	Mutagenicity [316]
5-Nitroindazole, 6-nitroindazole, 7-nitroindazole and 3-bromo-7-nitroindazole	Nitric oxide synthesis inhibitors [317]
7-Nitroindazole	Minor neuroprotector at ischemia [318–320], anxiolytic activity [321], inhibitor of monoamine oxidase [322], inhibitor of neuronal nitric oxide synthesis 323, 324]
4-Nitrobenzimidazoles	Trichomonicide [325], insecticides [326]
5-Nitrobenzimidazoles	Antibacterial, antihelmintic, antiviral activity, anaesthetic, inflammatory [327], analgetic [328], inhibitors of phenylethanolamine *N*-methyltransferase in pharmaceutical composition [329], high electroconductivity [330], in manufacture of epoxy polymers [331], in photography [332–335], metal corrosion inhibition [336–338]
5(6)-Nitro-2-cyanomethylbenzimidazole	Precursor of cyanine dyes [339]
6-Nitrobenzimidazoles	Analgetic [328], carcinogenicity [252], in photography [340], high electroconductivity [330]
6-Nitrobenzimidazol-1-acetyl amino acids	Antihelmintic agents [341]
2-Chloro-5(6)-nitrobenzimidazole	Activity against human cytomegalovirus (HCMV) and herpes simplex [342]
5,6-Dinitrobenzimidazole	Herbicide [343]
7-Nitrobenzimidazole	Analgetic [328]
Copper(II) complexes of 2-methyl-5-nitrobenzimidazole	Anticonvulsant drug [344]
2-Mercapto-5-nitrobenzimidazole	For treatment of Au electrode in thin film transistors [345]
2-Substituted 5-nitrobenzimidazoles	Angiotensin II receptor antagonists [346]
2-Aryl-6-nitrobenzoxazoles	Precursors of nonlinear optical materials [347]
2-Hydroxy-5-nitrobenzoxazole	Antivirus agent [348]
2-Thiol-5-nitrobenzoxazole	Potential enantioselective inhibitors of leukotriene biosynthesis [349]
2-(3-Cyclopentyloxy-4-methoxybenzyl)-7-nitrobenzoxazole	Therapy of asthma [350]
7-Nitrobenzofurazans	Optical properties, fluorescent microcrystals [351–357]
4-(*N*-methylamino)-7-nitrobenzofurazan	Strong fluorescent as model system [358]
5(7)-Nitro-3-R-1,2-benzisothiazoles	Antibacterial, antifungal activity [359]
5-Nitro-1,2-benzisothiazolone-3	Thrombolytic and antibacterial activity [360]
2-Amino-6-nitrobenzothiazole	Anticonvulsant activity as a sodium flux inhibitor [361]

(continued)

Table 5 (continued)

Compound	Activity and application
6-Nitro-2-R-benzothiazoles	DNA damage, against *Staphylococcus aureus, Bacillus subtilis* [362], *Euglena gracilis* [363], azo disperse dyes in textile [364]
5-Nitrobenzothiazole coumarines	fluorescent dyes [365, 366]
2-(4-Carboxyphenyl)-6-nitrobenzothiazole	*E. coli* strain, expressing nitroreductase and mutase enzymes, converts title compound to 4-(6-anilino-5-hydroxybenzothiazol-2-yl)benzoic acid [367]
6-Nitrobenzothiazoles	Chromophores for nonlinear optical materials [368–371]
5-Nitrobenzotriazoles, 4,6-dinitrobenzotriazoles	Inhibitor of corrosion [372, 373]
1-R-6-nitrobenzotriazole	Coupling reagent in peptide synthesis [374], anti-inflammatory agents [375]
2-Aryl-4,6-dinitrobenzotriazole 1-oxides	Superelectrophiles [376]

Nitrobenzazoles

Fused nitroazoles have attracted considerable attention due to their presence in a number of therapeutically and biologically active compounds. Nitrobenzazoles are often used in drug design and also in nonlinear optical materials, food additives, and energetic compounds. They also show versatile pharmacological activities, such as antifungal, antibacterial, antitumor, antihelmintic, antiallergic, antineoplastic, local analgesic, spazmolytic, etc. (Table 5). Some nitrobenzimidazoles are relatively efficient substrates for DT-diaphorase, and this enzyme is partly responsible for their cytotoxicity to bovine leukemia virus-transformed fibroblast culture [315].

Conclusions

Nitroazoles are compounds of very considerable commercial and chemotherapeutic importance. The introduction of metronidazole, dimetridazole, and their condensed analogs has stimulated much synthetic chemistry of nitroazoles resulting in the discovery of a number of compounds that are important for the treatment of different human and/or animal diseases.

Earlier the process of new drug development involved mainly either synthesis of new compounds based upon the existing drugs of synthetic and natural origin or simple biochemical concepts. It was supported by desultory screening of novel chemical structures and intuition (as it is even now and will always be). The compounds were basically screened directly in animal models rather than against biological targets. In vitro tests helping the chemists to find out the biological activity were relatively scarce. For example, in the cases of amebic and helmintic infections microbiology used more in vitro tests than in vivo studies. The compounds chosen for further development underwent full biological characterization, ADME (absorption, drug metabolism, excretion), and toxicological studies of various durations and kinds. According to the results of these studies the candidate drug would undergo clinical trials and the successful one would eventually get marketing permission [23].

Since the 1980s global changes have taken place in the search for new drugs. Revolution in molecular biology, the revelation of several genomes, and the arrival of microarray technology have made possible the isolation of some proteins, enzymes, and receptors that are relevant to therapy of various diseases. Binding/inhibition by test compounds offers a rational approach as a first step toward finding the drugs for these diseases. The development of high-throughput screening (HTS) has made this process very rapid. Unlike the earlier days, since HTS is performed in vitro, only milligram quantities of the test compounds are needed [23].

Recently a large number of papers have been devoted to the preparation of nitropyrazoles [377–380], nitroimidazoles [381–388], nitroisoxazoles [389–391], nitrothiazoles [392], nitrotriazoles [393–396], and nitrobenzazoles [397–399] due

to the fact that they are important intermediate products in the synthesis of highly effective medical products (metronidazole, dimetridazole, sanazole, etc.). Really, as compared to imidazole, natural pyrazoles and other azoles are rare compounds. At the same time a new class of azoles – *N*-nitropyrazoles – possess the spazmolitic and antihypertension activity compared with mono- and dinitrate isosorbite, which is caused by the ability of *N*-nitropyrazoles to generate nitrogen monooxide at biotransformation in organisms [272, 400].

It is known that 3-nitro-1,2,4-triazolon-5 is one of the most popular and widely used explosive compounds. Currently, wide possibilities of the preparation of new high-density energetic compounds on the base nitrofurazans and nitrofuroxans obtained by oxidation of the corresponding aminooxadiazoles in the presence of mainly H_2O_2/H_2SO_4 are opened up.

The substantial progress of the pharmaceutical chemistry is due in no small way to the creation of new drugs containing a tetrazole ring as structural fragment. Tetrazoles have not been found in nature. With rare exceptions these compounds do not exhibit appreciable biological activity, but they are at the same time resistant to biological degradation. It is this property that makes it possible to use tetrazoles as isosteric substituents of various functional groups in the development of biologically active substances [401, 402]. At the present phase in the development of medicine the creation of novel drugs is based on study of the pathogenic aspects of diseases. The attention of investigators is largely attracted to the processes involved in the transfer of information between cells, the destruction of which in many cases gives rise to the development of a pathological process. A similar process can be observed in many fields of medical science: cardiology, immunology, endocrinology, etc. The methodology of the search for new methods of medical intervention is predetermined by the fact that intercellular communication necessarily includes the transfer of a signal by means of chemical compounds, for which purpose there are special receiving elements (receptors) on the recipient cells. Today most of all pharmaceutical drugs prescribed by doctors act by a specific “receptor” mechanism. In the search for such drugs investigators are turning more and more to tetrazoles, since these compounds are hardly affected at all as a result of the metabolic processes in the organism. This makes it possible to create more effective and safer products capable of reaching the necessary receptor without undergoing any undesirable side transformations. Finally, analysis of the dynamics of the development of investigations into the medical application of tetrazoles gives grounds to suppose that considerably greater attention will be paid to their study in the coming decade than in previous years.

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Abbreviations

B3LYP	Becke-3 parameter density functional theory with Lee–Yang–Parr correlation functional
BP	Becke and Perdew–Wang functionals
CIDNP	Chemically induced dynamic nuclear polarization
CP/MAS	Cross polarization/magic angle spinning
DF	Density functional
DFT	Density functional theory
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EC	Electrochemical (oxidation, reduction)
ENDOR	Electron-nuclear double resonance
EPR	Electron paramagnetic resonance
ESR	Electron spin resonance
FTIR	Fourier transformation infrared (spectroscopy)
HEDM	High energy density materials
HFS	Hyperfine structure
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HTS	High-throughput screening
IR	Infrared
LUMO	Lowest unoccupied molecular orbital
METRO	Metronidazole
MP2	Moller–Plesset second-order perturbation method
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NQR	Nuclear quadruple resonance
NTO	3-Nitro-1,2,4-triazole-5-one
PE	Photoelectron spectra
pK_a	Acidity constant
pK_{BH+}	Basicity constant
PM3	Parametrized model 3
PWC	Perdew–Wang functional

QSAR	Quantitative structure-activity relationship
RA	Radical anion
RDA	Radical dianion
RDER	Rotating disk electrode with a ring
SOPPA	Secondary order polarization propagator approximation
TNBN	2,4,6-Trinitrobenzonitrile
TNT	2,4,6-Trinitrotoluene
UHF	Unrestricted Hartree Fock
UV	Ultraviolet
VNS	Vicarious nucleophilic substitution

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