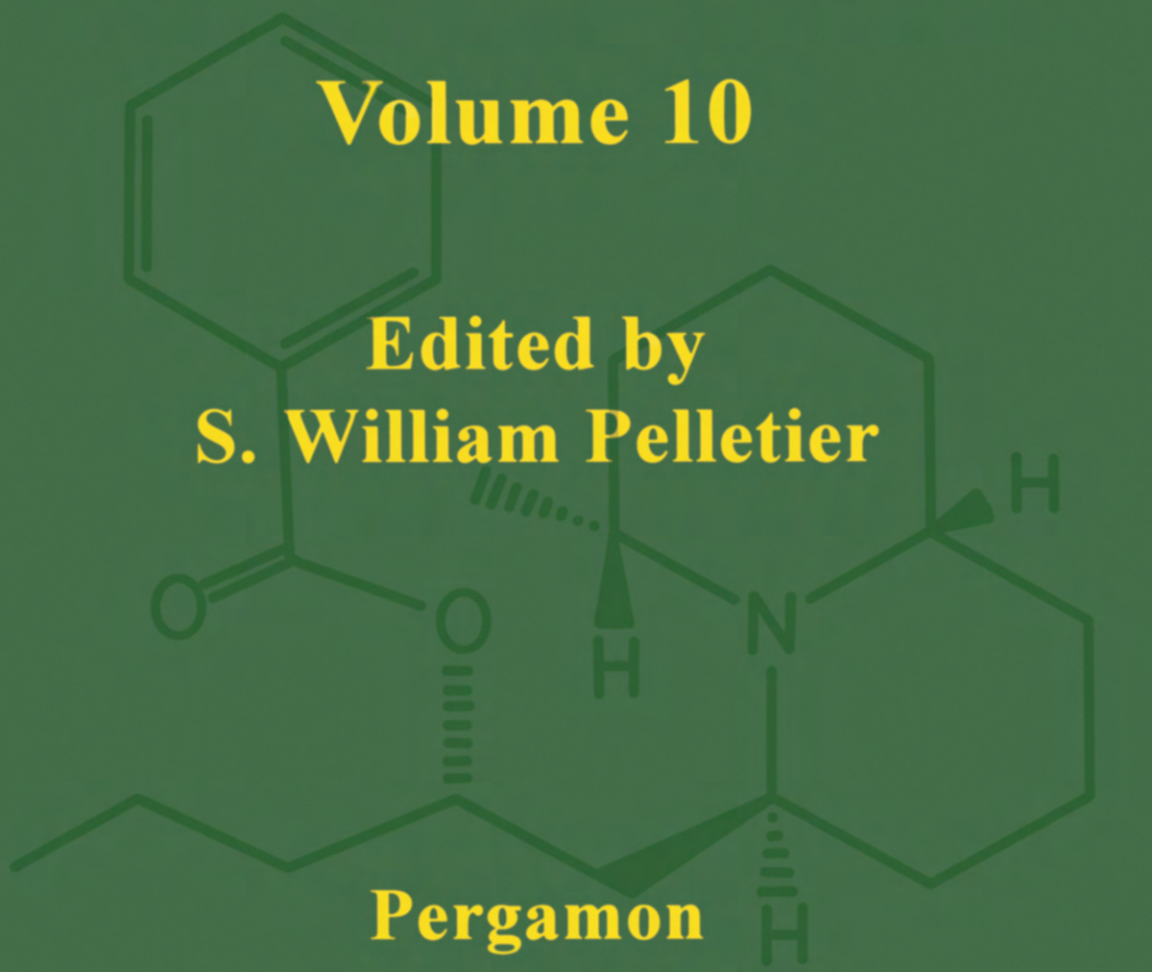
ALKALOIDS: CHEMICAL & BIOLOGICAL PERSPECTIVES

Volume 10

Edited by
S. William Pelletier



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ALKALOIDS: CHEMICAL AND BIOLOGICAL PERSPECTIVES

Volume Ten

Edited by

S. WILLIAM PELLETIER
Institute for Natural Products Research

and

The Department of Chemistry
University of Georgia, Athens

PERGAMON

U.K. Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, U.K.

U.S.A. Elsevier Science, Inc., 660 White Plains Road, Tarrytown, New York 10591-5153, U.S.A.

JAPAN Elsevier Science Japan, Tsunashima Building Annex, 3-20-12 Yushima, Bunkyo-ku, Tokyo 113, Japan

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First Edition 1996

Library of Congress Cataloging in Publication Data
A catalogue record for this serial is available from the Library of Congress

British Library Cataloging in Publication Data
A catalogue record for this book is available from the British Library

ISBN 0 08 042791 X

Printed and bound in Great Britain by Biddles Ltd, Guildford and King's Lynn

Dedicated to
the memory of

Hans Eduard Schmid
(1917–1976)

His scientific interest centered on the chemistry of organic natural products as well as on the mechanistic aspects of organic reactions. Important contributions in the field of alkaloids began in 1945 (together with Paul Karrer) when he investigated Calabash curare of the South American Indians. This muscle relaxant drug is a dark brownish mixture of more than 60 alkaloids. He separated this water-soluble mixture with newly developed methodology (cellulose column, two dimensional paper chromatography) and characterized the individual alkaloids mainly by their UV spectra and color reactions with Ce(IV) sulfate. Several observations facilitated structure elucidation of the hitherto unknown compounds. Alkaloids isolated from certain *Strychnos* species proved to be identical with some of the curare alkaloids. Other curare alkaloids could be prepared from *Strychnos* alkaloids by photochemical oxidation (e.g. curarine, calebassine). A sophisticated methylation experiment (1958) demonstrated that the most important (toxic) curare alkaloids are dimeric. In 1958 he discovered that the Weiland-Gumlich aldehyde, a well known degradation product of strychnine, can be dimerized to give the curare alkaloid dihyrotoxiferine. Subsequently, the structures of most of the curare alkaloids were elucidated.

When NMR and mass spectrometry became available, a large number of alkaloids from various apocynaceous plants were investigated (e.g. species of the genera *Alstonia*, *Aspidosperma*, *Conopharyngia*, *Gabunia*, *Hunteria*, *Iboga*, *Oncinotis*, *Rauwolfia*, *Vinca*). Villalstonine was the first bisindole alkaloid whose structure was elucidated by mass spectral analysis.

One of his special interests was the correlation of compounds by partial syntheses, including the determination of the absolute configuration of these natural products. During structural investigation of the spermidine alkaloid oncinotine, he observed a ring enlargement known as the Zip reaction.

Manfred Hesse

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Contributors

Raymond J. Andersen, Department of Chemistry and Oceanography, University of British Columbia, Vancouver, B.C., Canada V6T 1Z1

Bill J. Baker, Department of Chemistry, Florida Institute of Technology, Melbourne, Florida 32901, U.S.A.

I.R.C. Bick, Department of Chemistry, University of Tasmania, Hobart, Tasmania, Australia 7001

Fangming Kong, Department of Chemistry and Oceanography, University of British Columbia, Vancouver, B.C., Canada V6T 1Z1

Rob W. M. Van Soest, Department of Coelenterates and Porifera, Institute for Systematics and Population Biology (Zoologisch Museum), University of Amsterdam, P. O. Box 94766, 1090 AT Amsterdam, The Netherlands

Marilyn J. Schneider, Department of Chemistry, Lafayette College, Easton, Pennsylvania 18042-1782, U.S.A.

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Preface

Volume 10 of this series presents four timely reviews. Chapter 1 is a monumental survey of "Alkaloids from Australian Flora" by I. R. C. Bick of the University of Tasmania. This chapter provides a fascinating account of the history of alkaloid discovery in Australia beginning with the isolation of the first alkaloid from an Australian plant, the Tasmanian sassafras (*Atherosperma moschatum*), by Zeyer in 1861. Also included is a comprehensive survey of alkaloid-bearing plants, and a section dealing with detection, estimation, extraction, and work-up procedures for alkaloids.

Chapter 2 by Marilyn Schneider of Lafayette College provides a comprehensive up date to the chapter on "Pyridine and Piperidine Alkaloids" which appeared in volume 3 of this series. The focus of this chapter is on new alkaloids isolated, biosynthesis, and biological properties.

Chapter 3 by Raymond J. Andersen, Rob W. M. Van Soest and Fangming Kong of the University of British Columbia and the University of Amsterdam, treats "3-Alkylpiperidine Alkaloids Isolated from Marine Sponges in the Order Haplosclerida". Marine sponges occur in all the world's oceans and are frequently one of the dominant life forms on tropical coral reefs and under the Antarctic ice cap. Studies over the past thirty years have shown that sponges are a rich source of alkaloids. Many of these sponge alkaloids are related to each other by the presence of a 3-alkylpiperidine moiety in their structures. It happens that the sponges that have been reported to contain 3-alkylpiperidine alkaloids are all in the order Haplosclerida.

Chapter 4 by Bill J. Baker of the Florida Institute of Technology reviews "β-Carboline and Isoquinoline Alkaloids from Marine Organisms". β-Carboline and isoquinoline alkaloids are some of the pharmacologically most significant marine natural products. This chapter treats the isolation, structure elucidation, synthesis, biosynthesis, and pharmacological activity of these alkaloids.

Each chapter in this volume has been reviewed by at least one expert in the field. Indexes for both subjects and organisms are provided.

The editor invites prospective contributors to write him about topics for review in future volumes in this series.

S. William Pelletier
Athens, Georgia
October 1995

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Chapter One

Alkaloids from Australian Flora

I. R. C. Bick
Department of Chemistry
University of Tasmania
Hobart, Tasmania
Australia 7001

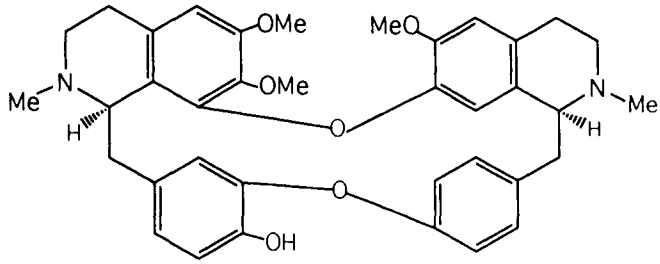
CONTENTS

1. INTRODUCTION

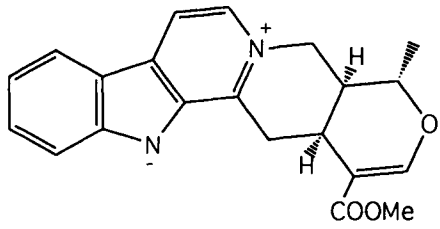
With the isolation of the first alkaloids in Europe in the early 19th century and a study of their properties, interest soon developed in examining the flora of countries throughout the world for plant bases that might be useful as drugs. The first alkaloid from an Australian plant, the Tasmanian sassafras (*Atherosperma moschatum*, family Monimiaceae), was isolated in a German laboratory about fifty years later by Zeyer [1] and named atherospermine; he described it thus:

> "Es stellt ein weisses, etwas ins Graue neigendes, zu kleineren Massen zusammengeballtes, leichtes, höchst elektrisches Pulver dar. Es ist geruchlos und schmeckt rein und ziemlich anhaltend bitter. Seine Form unter dem Mikroskope dürfte unbezweifelt eine krystallinische genannt werden, wenn gleich es mir nicht möglich war, derselben einen bestimmten Ausdruck zu geben. Auf Platinblech erhitzt schmilzt es, stösst einen Geruch nach faulem Fleisch aus und dann schwach nach Häringen, darauf entzündet es sich und verbrennt ohne Rückstand. Sein Schmelzpunkt liegt bei 128° C. In Wasser ist es fast ganz unlöslich; Aether löst bei +16° C ohngefähr 1/1000, im Kochen 1/100 des Alkaloïds auf. Alkohol löst bei +16° C 1/32, im Kochen schon die Hälfte seines Gewichts auf. Das Alkaloïd ist leicht löslich in Chloroform und Schwefelkohlenstoff, sowie in verdünnten Säuren. Die neutrale salzsaure Lösung giebt mit Ammoniak einen starken weissen Niederschlag, der durch einen Ueberschuss des Reagens nicht wieder verschwindet. Kalilauge und kohlensaure Alkalien verhalten sich ebenso".

Zeyer's alkaloid was almost certainly an impure sample of the bisbenzylisoquinoline berbamine (**1**), the principal alkaloid of the plant, but nearly a century went by before it was reisolated from sassafras and its structure fully elucidated [2]. Shortly after Zeyer's study, a second alkaloid, alstonine (**2**), was obtained in an impure form from another Australian plant, *Alstonia constricta* (Apocynaceae) [3]. This work was also done in Germany, and a similar period elapsed before the complete structure and stereochemistry of alstonine were established [4,443].



1. Berbamine

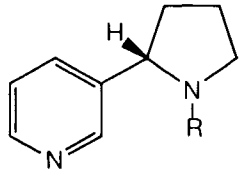


2. Alstonine

In the meantime the presence of alkaloids was observed in many other Australian plants, including a small tree whose leaves are known to the aborigines of central Australia as "pituri". In 1872 the effects of pituri, later identified as foliage of *Duboisia hopwoodii* (Solanaceae) [5], were studied by Joseph Bancroft [6], a Brisbane medico, who reported as follows:

> "The leaves are chewed by the natives as a stimulating narcotic. .... The old men, before any serious undertaking, chew the dried leaves, appearing to use about a tablespoonful. A few twigs are burnt and the ashes mixed therewith. After a slight mastication, the bolus is placed behind the ear -- to be again chewed from time to time -- the whole of which is at last swallowed. The native after this is in a sufficiently courageous state of mind to fight, or to undertake any serious business".

Further investigations, notably by Petrie [7], strongly suggested nicotine (**3**) as the principal alkaloid of the leaves; pituri was later shown to contain both **3** and nornicotine (**4**) as well as other minor alkaloids in varying amounts [8,9]. The alkaloids are present in the leaves as salts, and aboriginal experience had found that the maximum stimulating effect was obtained by adding wood ashes, which would result in release of the free bases.

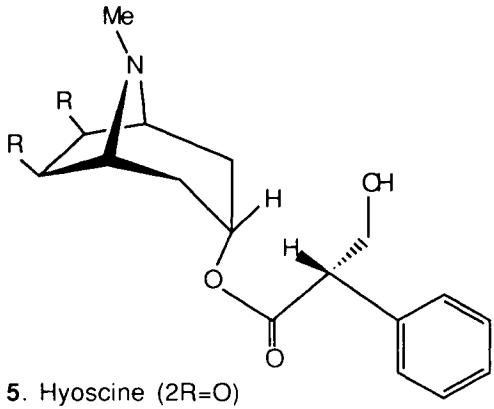


3. Nicotine (R=Me)

4. Nornicotine (R=H)

Among other plants studied by Bancroft was the related *D. myoporoides* [5], another species well-known to the aborigines from its intoxicating properties. However, Bancroft found its pharmacological effects were quite different from those of pituri; later studies by Petrie [7] and others indicated that the principal alkaloid of *D. myoporoides* was hyoscine (**5**),

and Petrie recognised that the plant produced varying amounts of hyoscyamine (**6**) and other alkaloids as well, thereby clearing up some previous confusion. This plant, together with a third species, *D. leichhardtii,* later became one of the most important international sources of hyoscine [10].



5. Hyoscine (2R=O)

6. Hyoscyamine (R=H)

The presence of alkaloids was discovered in many other Queensland plants by Dr. T.L. Bancroft, who continued the work of his father Joseph. Although the techniques and facilities available in Australia at that time were hardly adequate for the isolation, purification and structural determination of new alkaloids, or even for the identification of ones already known, the pioneering investigations by the Bancrofts, Petrie and others nevertheless formed a starting point for subsequent studies. T.L. Bancroft, for example, obtained impure samples of alkaloids from certain *Daphnandra* species (Monimiaceae) [11, 12], and studied their pharmacology. His work was later extended by Pyman in England [13], who isolated crystalline bases from *D. micrantha* that proved eventually [14] to belong to the same biscoclaurine series as berbamine (**1**).

Following the arrival of the first Europeans in Australia, observations gradually accumulated on plants used by the aborigines as medicines and narcotics, and for poisoning animals and fish. Captain James Cook had noted in 1770 that the natives "held leaves of some sort constantly in their mouths, as a European does tobacco and an East Indian betele". Some of the native remedies became known to the early squatters, bushmen and drovers, and a few were even recommended by pharmacists and physicians [26, 27]. Apart from medicinal plants, others were known to be exploited by the aborigines in food-gathering to stupefy fish and game; and a growing number of plants were recognised as being poisonous to stock.

Random observations made by state agricultural officers, pharmacists and amateur naturalists were coordinated and extended by the setting up of Poison Plants Committees in New South Wales, and later in Queensland, during the period between the world wars. The

former committee published a monograph in 1942 on N.S.W. plants toxic to stock, edited by Hurst [15]; it was followed six years later by a Council for Scientific and Industrial Research (C.S.I.R.) review compiled by Webb [16], of the medicinal and poisonous plants of Queensland. Many of the plants listed in these publications gave alkaloid tests, and their appearance evoked a good deal of interest in further studies.

A survey of Australian plants was initiated by the C.S.I.R. to find local sources of medicinal drugs in short supply during World War II. The survey developed into a major project of the Commonwealth Scientific and Industrial Research Organisation (CSIRO), as it became known after the war, to study alkaloids and other substances of medicinal interest in the Australian flora, and toxins present in plants that were known to be dangerous to stock. As far as the first part of the programme was concerned, efforts were concentrated initially on rain-forest species of Queensland and northern New South Wales. An intensive programme involving the collection and testing of native plants, carried out by Webb [17,18], was accompanied by the setting up of a supply service for selected specimens and the establishment of a well-staffed and equipped laboratory in Melbourne devoted to natural products research, with especial emphasis on alkaloids. Some of the facilities were made available to groups in various state universities whose interest in examining their local flora had been stimulated. The CSIRO subsequently extended its survey to Papua New Guinea [19], at that time under Australian control, and more recently has published details of extensive further alkaloid tests in a joint CSIRO-Monash University monograph [20]. Alkaloid surveys have also appeared covering the Western Australian [21] and the Tasmanian [22] flora, which were sponsored by the eponymous Universities with the collaboration of the W.A. Agricultural Department in the former case. These have been amplified by surveys of a more limited scope, including one under the joint auspices of the Waite Institute, Adelaide, and Monash University, Melbourne, which covered native *Solanum* species [23]. Two other surveys have been carried out by personnel of the University of Sydney with the aim of screening orchidaceous plants of Queensland and New South Wales [24], and of Papua-New Guinea [25] for alkaloids.

2. RESULTS OF PLANT SURVEYS

Plants that have given a positive test for alkaloids in one of the above-mentioned surveys are listed in Table 1 under family, genus and species. The list comprises mainly Australian plants but includes many from Papua New Guinea, and a few from other neighbouring Pacific islands that have been examined by Australian workers. Apart from endemic species, the list also includes some introduced plants that have become firmly established in certain areas. The following geographical abbreviations are used: NSW (New South Wales), NT (Northern Territory), PNG (Papua New Guinea), Q (Queensland), SA (South Australia), T (Tasmania) and WA (Western Australia). Positive tests are quoted as strong, medium or weak (s, m or w), and parts of plants examined have been abbreviated as follows: bark (B), flowers (Fl), fruit (F), leaves (L), roots (R), seeds (S), stem (St), tubers (T), wood (W), and whole plant (WP). Some explanatory notes on the compilation of the data are given in Section 4.1.

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
ACANTHACEAE				
Calophanoides hygrophyloides (F. Muell.)	Imbil, Q	L, St	w	[18]
R. Baker [*Justicia hygrophyloides* L.]	Esk, Q	WP	w	[20]
Hypoestes floribunda R. Br.	Broadsound, Q	WP	w	[20]
	Chillagoe, Q	R	s	[17]
Pseuderanthemum variabile (R. Br.) Radlk.	Ipswich, Q	WP	m	[17]
ADIANTACEAE				
Pellaea falcata var. *nana* R. Br.	Unumgar, NSW	L, St	m	[20]
AGAVACEAE				
Cordyline terminalis (L.) Kunth.	Mt Glorious, Q	L	m	[18]
AIZOACEAE				
Gasoul crystallinum (L.) Rothm.	WA	WP	w	[21]
Glinus lotoides L. *(Mollugo glinus)*	Rockhampton, Q	L, St	w	[18]
Macarthuria australis Hueg.	WA	WP	s	[21]
Sesuvium portulacastrum L.	Cairns, Q	L, St	w	[18]
Tetragonia decumbens Mill.	WA	WP	m	[21]
T. eremaea Ostf.	WA	WP	m	[21]
T. expansa Murr.	Wandoan, Q	WP	s	[17]
	Bollon Stock Route, Q	F	m	[18]
Trianthema decandra L.	Maxwelton, Q	L, St	s	[18]
T. turgidifolia F. Muell.	WA	WP	m	[21]
AKANIACEAE				
Akania hillii J.D. Hook.	Burleigh, Q	L, B, W	s	[17]
A. lucens (F. Muell.) Airy Shaw	Binna Burra, Q	L	s	[18]
ALANGIACEAE				
Alangium villosum (Bl.) Wang	Malanda, Q	B	s	[17]
	Atherton, Q	L, B	s	[20]
A. villosum ssp. *polyosmoides* (F. Muell.)	Kirrama, Q	B, L	s	[18]
Bloemb.	Toonumbar, NSW	L, B, W	s	[20]
A. villosum ssp. *tomentosum* var. *australe* Bloemb.	Long I, Q	L	s	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
AMARANTHACEAE				
Achryanthes aspera var. *canescens* L.	Cloyna, Q	WP	w	[18]
Aerva tomentosa Lam.	WA	WP	w	[21]
Alternanthera denticulata R. Br.	Stanthorpe, Q	L, St	m	[18]
A. nodiflora R. Br.	WA	WP	m	[21]
Alternanthera sp.	Warwick, Q	L	w	[17]
Amaranthus pallidiflorus F. Muell.	WA	WP	m	[21]
A. spinosus L.	Brisbane, Q	R	w	[17]
A. viridis L.	Mackay, Q	L, St, F	s	[18]
Deeringia amaranthoides (Lam.) Merr.	Rockhampton, Q	L	s	[17]
	Blackall Range, Q	L, St, F	w	[18]
D. celosioides R. Br.	Croydon, Q	L, St	w	[20]
Gomphrenia celosioides Man.	Brisbane, Q	WP	w	[17]
	Mackay, Q	L, St, F	s	[18]
G. conica (R. Br.) Sprengel	Nonda, Q	St, Fl	s	[18]
Ptilotus aervoides (F. Muell.) F. Muell.	WA	WP	m	[21]
P. asterolasius F. Muell.	WA	WP	w	[21]
P. calostachyus F. Muell.	WA	WP	s	[21]
P. corymbosus R. Br.	WA	WP	m	[21]
P. divaricatus (Gaud.) F. Muell.	WA	WP	m	[21]
P. drummondii (Moq.) F. Muell.	WA	WP	s	[21]
P. exaltatus Nees	WA	WP	m	[21]
P. helipteroides (F. Muell.) F. Muell.	WA	WP	m	[21]
P. macrocephalus (R. Br.) Poir.	WA	WP	m	[21]
P. manglesii (Lindl.) F. Muell.	WA	WP	m	[21]
P. obovatus (Gaud.) F. Muell.	WA	WP	m	[21]
P. polystachyus (Gaud.) F. Muell.	WA	WP	s	[21]
P. rotundifolius (F. Muell.) F. Muell.	WA	WP	w	[21]
P. spathulatus (R. Br.) Poir.	WA	WP	w	[21]
P. stirlingii (Lindl.) F. Muell.	WA	WP	w	[21]
Trichinium alopecuroideum Lindley	Bollon Stock Route, Q	F	m	[18]
T. calostachyum (F. Muell.) Benth.	NT	L, St	w	[18]
T. exaltatum (Nees) Benth.	NT	L	w	[18]
T. obovatum Gaudich.	Maxwelton, Q	L, St	s	[18]
ANACARDIACEAE				
Buchanania arborescens (Bl.) Bl.	Rouna, PNG	L, B	w	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Dracontomelon dao (Blanco) Merr. & Rolfe [*D. puberulum* Miq.]	Trans-Busu, PNG	L	w	[19,20]
Euroschinus falcata (?) J. D. Hook.	Mt Glorious, Q	B	m	[17]
Rhodosphaera rhodanthema (F. Muell. ex Benth.) Engl.	Binna Burra, Q	L	w	[18]
ANNONACEAE				
Ancana stenopetala F. Muell.	Tamborine Mt, Q	L	w	[18]
Annona glabra L.	Cooktown, Q	L	s	[18]
	Daintree, Q	L	m	[20]
A. reticulata L.	Innisfail, Q	L	w	[18]
Annona sp.	Brisbane, Q	L	w	[18]
Annona sp.	Cairns, Q	L	s	[17]
Canangra odorata (Lam.) Hook. f. & Thoms.	Oomsis Ck, PNG	L	m	[19]
Cyathocalyx polycarpum White & Francis	Trans-Busu, PNG	L	w	[19]
Fitzalania heteropetala (F. Muell.) F. Muell.	Hayman I, Q	L	w	[18]
Friesodielsia sp.	Trans-Busu, PNG	L	w	[19]
Goniothalamus sp. aff. *G. coriaceus* Burck	Akuna, PNG	L, B	w	[19]
Haplostichanthus johnsonii F. Muell.	Malanda, Q	L	w	[18]
Mitrella kentii (Bl.) Miq.	Kauli Ck, PNG	B	w	[19]
Mitrephora sp.	Cairns, Q	L	w	[18]
Papualthia sp. aff. *P. rudolphi* Diels	Subitana, PNG	B	w	[19]
Petalolophus megalopus K. Schum.	Butibum R, PNG	L, B	w	[19]
Phaeanthus macropodus (Miq.) Diels	Butibum R, PNG	L, B	s	[19,20]
Polyalthia armitiana F. Muell.	Bamaga, Q	L, B	w	[20]
P. forbesii F. Muell.	Busu R, PNG	L, B	w	[19]
P. sp. aff. *P. forbesii* F. Muell.	Akuna, PNG	L, B	w	[19]
P. glauca (Hassk.) Boerl.	Butibum R, PNG	B	w	[19]
P. nitidissima (Dunal) Benth.	Imbil, Q	L	m	[18]
	Cannonvale, Q	B	s	[20]
P. oblongifolia Burck	Oomsis Ck, PNG	L, B, F	w	[19,20]
Polyalthia sp.	Omaura, PNG	L,B	w	[19, 20]
Popowia australis Benth.	Pt Essington, WA	L	w	[18]
Popowia cf. *cyanocarpa*Laut & K. Schum.	Busu R, PNG	B	s	[19]
Pseuduvaria cf. *dolichonema* (Diels) J. Sinclair	Busu R, PNG	L, B	m	[19]
	Busu R, PNG	L, B	s	[20]
Pseuduvaria cf. *grandifolia* (Warb.) J. Sinclair	Markham R, PNG	B	w	[19, 20]
P. sp. aff. *P. grandifolia* (Warb.) J. Sinclair	Busu R, PNG	L, B	w	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
P. silvestris (Diels) J. Sinclair	Oomsis Ck, PNG	B	w	[19]
cf. *Pseuduvaria*	Busu R, PNG	L, B	m	[19]
Rauwenhoffia leichhardtii (F. Muell.) Diels	Rockhampton, Q	L, St	m	[17,18]
Schefferomitra subaequalis (Scheff.) Diels	Butibum R, PNG	L, B, St	m	[19,20]
Uvaria membranacea Benth.	Buchan's Pt, Q	L	w	[18]
Xylopia papuana Diels	Trans-Busu, PNG	L, B, F	s	[19,20]
APIACEAE (UMBELLIFERAE)				
Ammi majus L.	Allora, Q	L, St	m	[17]
	Charleville, Q	L, F	m	[18]
Apium leptophyllum (Pers.) F. Muell.	Dalrymple Heights, Q	L, St	w	[18]
A. prostratum Labill.	WA	WP	w	[21]
Conium maculatum L.	Brisbane, Q	St, Fl	s	[17]
	Oakey, Q	L, Fl, St	s	[18]
Foeniculum vulgare Miller	Q	L, St, S	w	[17]
	WA	WP	w	[21]
Hydrocotyle pedicellosa Benth.	Mt Glorious, Q	L, St	w	[17]
Platysace compressa (Labill.) Norman	WA	WP	w	[21]
P. juncea (Bunge) Norman	WA	WP	w	[21]
Trachymene elachocarpa(F. Muell.) B.L. Burtt.	WA	WP	w	[21]
T. glaucifolia (F. Muell.) Benth.	WA	WP	w	[21]
	Cunnamulla, Q	St	w	[18]
T. ornata (Endl.) Druce	WA	WP	w	[21]
Xanthosia huegelii (Benth.) Steud.	WA	WP	w	[21]
X. rotundifolia DC.	WA	WP	w	[21]
APOCYNACEAE				
Allemanda cathartica L.	El Arish, Q	L, St	s	[20]
Alstonia actinophylla (A. Cunn.) K. Sch.	Chillagoe, Q	L, B	s	[17]
	Coen, Q	L, B	s	[20]
A. brassii Monachino	Yalu, PNG	L, B	s	[19]
	Coen, Q	B	s	[20]
Alstonia cf. *brassii* Monachino	Marafunga, PNG	L, B	m	[19]
A. constricta F. Muell.	McIntyre Brook, NSW	L	s	[18]
	Yarraman, Q	L, St	s	[20]
A. constricta var. *mollis* Bailey	Miles, Q	L	s	[17]
A. glabriflora Mgf.	Omaura, PNG	L, B	s	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
A. muelleriana Domin	Atherton, Q	B	s	[18]
A. scholaris (L.) R. Br.	Mulgrave R, Q	L	m	[18]
	Lae, PNG	L	s	[19]
A. spatulata Bl.	Red Hill, PNG	L, B	s	[19]
A. spectabilis R. Br.	Thursday I, Q	B	s	[18]
	Coopers Ck, C Tribulation, Q	L, B	m	[20]
A. villosa Blume	Cairns, Q	B	s	[17]
Alyxia buxifolia R. Br.	WA	WP	m	[21]
	Beachport, SA	L, St	s	[20]
A. ilicifolia F. Muell.	Atherton, Q	L	w	[18]
Alyxia cf. *lata* Mgf.	Oomsis Ck, PNG	L, St	m	[19]
A. markgrafii Tsiang	Red Hill, PNG	L	s	[19]
A. ruscifolia R. Br.	Rockhampton, Q	L, F	w	[17]
A. scabrida Mgf.	Akuna, PNG	L	m	[19]
A. spicata R. Br.	Machans Beach, Q	R	m	[20]
Alyxia sp.	Cairns, Q	L	w	[17]
Bleekeria coccinea (T. & B.)	Bulolo R, PNG	L	s	[19]
Carissa lanceolata R. Br.	Laura, Q	L	m	[20]
C. ovata R. Br.	Rockhampton, Q	B	m	[17]
	Maxwelton, Q	L, St	s	[18]
Catharanthus roseus (L.) G. Don	Markham Valley, PNG	L	w	[19]
[*Vinca rosea* L.]	Brisbane, Q	L, St	s	[17]
Chilocarpus australis F. Muell.	Mt Glorious, Q	L	w	[17]
Cryptostegia grandiflora R. Br.	Rockhampton, Q	L	w	[17]
C. madagascariensis Baj.	Q	L	m	[17]
Delphyodon oliganthus K. Schum.	Butibum R, PNG	L	s	[19]
Ervatamia angustisepala (Benth.) Domin	Brisbane, Q	L, B, St	s	[17,18]
	Whian Whian, NSW	L	s	[20]
E. coronaria Staph.	Brisbane, Q	L, St	s	[20]
E. orientalis (R. Br.) Domin	Mossman, Q	L, F	s	[17]
	Cairns, Q	L, St	s	[18]
	Tymne-Gurukor, PNG	L, B	s	[19]
	Babinda, Q	L	s	[20]
E. pubescens (R. Br.) Domin	Cairns, Q	L	m	[18]
	Bamaga, Q	L, St	s	[20]
E. pubescens var. *punctulala* (Warb.) Mgf.	Kakoda Road, PNG	L, B	s	[19]
Ervatamia sp.	Boonjie, Q	L	s	[18]
Ichnocarpus frutescens (L.) R. Br.	Lae, PNG	L	w	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Kopsia fruticosa (Ker) DC.	Lae, PNG	L	s	[19]
K. longiflora Merrill	Mossman Gorge, Q	L, B, St	s	[20]
Kopsia sp. nov.	Etty Bay, Q	L, St	s	[18]
Lepiniopsis ternatensis Val.	Markham R, PNG	L, B	m	[19]
Melodinus acutiflorus F. Muell.	Mt Glorious, Q	L, B	s	[17]
	Springbrook, Q	L, B	s	[18]
	Whian Whian, NSW	WP	s	[20]
M. australis (F. Muell.) Pierre	Atherton, Q	L, B	s	[18]
	Boonjie, Q	WP	s	[20]
M. bacellianus (F. Muell.) S.T. Blake	Babinda, Q	L	m	[18]
	Wongabel, Q	L, St	m	[20]
M. guilfoylei F. Muell.	MacPherson Range, Q	L, B	s	[18]
	Melbourne Botanic Gardens, V	L	m	[20]
M. landolphioides Laut. & K. Schum.	Crooked Ck, PNG	L	m	[19]
M. novoguineensis (Wernh.) Pichon	Akuna, PNG	L	m	[19]
Micrechetes rhombifolia Mgf.	Crooked Ck, PNG	L	w	[19]
Neisosperma kilneri (F. Muell.) Fosberg &	Mt Dryander, Q	WP	w	[20]
Sachet [*Ochrosia kilneri* F. Muell.]	Mackay, Q	L	m	[18]
N. poweri (Bailey) Fosberg & Sachet	Atherton, Q	L, B, St	s	[20]
[*Ochrosia poweri* Bailey]	Boonjie, Q	L, St	s	[17]
	Danbulla, Q	L	s	[18]
Nerium oleander L.	WA	WP	m	[21]
Ochrosia elliptica Labill.	Cardwell, Q	B, F	s	[17]
	Mission Beach, Q	L, B, St	s	[20]
O. cowleyi Bailey	Kamerunga, Q	L	s	[18]
O. moorei (F. Muell.) F. Muell. ex Benth.	Springbrook, Q	L, B	s	[18]
	Whian Whian, NSW	L, B, St	s	[20]
Parsonsia buruensis (?) (T. & B.) Boerl.	Rabaul, PNG	B, W	s	[18]
P. eucalyptophylla F. Muell.	Chinchilla, Q	L, St	s	[17]
P. latifolia (Benth.) S.T. Blake	Yarraman, Q	B	s	[17]
	Springbrook, Q	L, St	s	[18]
P. lilacina F. Muell.	Mt Glorious, Q	L, St	s	[18,20]
P. straminea (R. Br.) F. Muell.	Macpherson Range, Q	L	m	[18]
	Davies Ck, Q	L, St	w	[20]
P. velutina R. Br.	Brisbane, Q	L, St	m	[17]
	Atherton, Q	L, F	m	[18]
P. ventricosa F. Muell.	Mt Glorious, Q	WP	w	[20]
Rauvolfia canescens L.	Rockhampton, Q	L, F	s	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Rejoua aurantiaca (Gaud.) Gaud.	Markham R, PNG	L, B, F	s	[19]
R. novoguineensis (Scheff.) Mgf.	Lae, PNG	L	s	[19]
Thevetia neriifolia Juss.	WA	WP	w	[21]
Voacanga papuana (F. Muell.) K. Schum.	Kakoda Rd, PNG	L, B	s	[19]
Wrightia millgar (?) Bailey	Cairns, Q	B, S	s	[17,18]
W. *pubescens* (R. Br.) Domin	Massey Ck, Q	L, B, St	m	[20]
W. saligna (R. Br.) Benth.	Ayr, Q	B	w	[18]
Wrightia sp.	El Arish, Q	B	m	[18]
ARACEAE				
Aglaonema marantifolium Bl.	Oomsis Ck, PNG	WP	w	[19]
Alocasia macrorrhiza Bailey	Malanda, Q	R	w	[17]
Dieffenbachia aucta	Cairns, Q	L, R, St	w	[17]
Gymnostachys anceps R. Br.	Cairns, Q	L	w	[18]
ARALIACEAE				
Astrotricha asperifolia F. Muell. ex Klatt	Grampians, V	L	w	[20]
A. longifolia Benth.	Brisbane, Q	L	w	[17]
	Mt. Glorious, Q	L, F, St	m	[18]
Kissodendron australianum F. Muell.	Atherton, Q	L, B	w	[18]
Mackinlaya confusa Helmsley	Innisfail, Q	L	s	[17]
M. cf. *klossii* Philipson	Kratke Range, PNG	L	s	[19]
M. macrosciadia (F. Muell.) F. Muell.	Shute Bay, Q	WP	s	[20]
Polyscias elegans (C. Moore & F. Muell.) Harms	Imbil, Q	L	w	[18]
P. forbesii Bak. f.	Kaindi-Edie Ck, PNG	L	w	[19]
P. sambucifolia (Sieber ex DC.) Harms	Gibberagunyah Range, NSW	L, St	w	[20]
ARECACEAE (PALMAE)				
Calamus australis Mart.	Daintree, Q	L	m	[20]
ARISTOLOCHIACEAE				
Aristolochia deltantha F. Muell.	Brisbane, Q	L	s	[17]
A. elegans Mast.	Rockhampton, Q	L	s	[17,20]
	Brisbane, Q	L, St	s	[18]
A. praevenosa F. Muell.	Brisbane, Q	L	m	[17]
	Springbrook, Q	L, St	m	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
A. tagala Cham.	Babinda, Q	L	s	[18]
Aristolochia sp.	Innisfail, Q	L	s	[17]
ASCLEPIADACEAE				
Araujia hortorum Fourn.	Yarraman, Q	L, S	m	[20]
Asclepias curassavica L.	Cairns, Q	L	w	[18]
A. fruticosa L.	Tamborine, Q	L, S	w	[20]
	WA	WP	m	[21]
A. physocarpa (E. Mey.) Schlecht.	Rockhampton, Q	L, St	s	[18]
Calotropis procera (Aiton) W.T. Aiton	Chillagoe, Q	B, L	m	[17]
	Mareeba, Q	L	w	[20]
Cynanchum bowmanii S.T. Blake	Marburg Range, Q	L	s	[18]
	Pine R, Q	WP	w	[20]
C. floribundum R. Br.	?	L, F	w	[20]
Gymnema dunnii (Maiden & Betche) P. Forster	Unumgar, NSW	L, St	m	[20]
G. geminatum R. Br.	Chillagoe, Q	L, F	s	[18]
G. micradenia Benth.	Marmor, Q	L	w	[18]
Heterostemma sp.	Bulolo R, PNG	L	w	[19]
Hoya australis R. Br. ex Traill	Bamaga, Q	L	w	[20]
H. nicholsoniae F. Muell.	Mossman Gorge, Q	WP	w	[20]
Marsdenia australis (R. Br.) Druce	WA	WP	s	[21]
M. microlepis (?) Benth.	Rockhampton, Q	R	s	[18]
M. rostrata R. Br.	Mt Glorious, Q	L	m	[17]
M. rostrata var. *dunnii* Maiden & E. Betche	Brisbane, Q	L, B	w	[18]
Pentatropis linearis Dene.	WA	WP	s	[21]
Sarcostemma australe R. Br.	WA	WP	s	[21]
Tylophora crebriflora S.T. Blake	Conway, Q	WP	s	[20]
T. erecta Benth.	Sellheim, Q	L	s	[18]
T. floribunda Benth.	Tamborine Mt, Q	L	s	[18]
T. macrophylla S.T. Blake	Bamaga, Q	L, St	m	[20]
T. paniculata R. Br.	Mt Glorious, Q	L, St	m	[17,18]
Tylophora sp.	Milman, Q	R	m	[18]
Vincetoxicum ovatum Benth.	Rockhampton,Q	L	w	[17]
ASTERACEAE (COMPOSITAE)				
Acanthospermum hispidum DC.	Brisbane, Q	L, St	m	[17]
	Mackay, Q	WP	s	[18]
Achillea millefolium L.	Croydon, V	WP	m	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Ageratina adenophora (Spreng.) R.M. King & H. Robinson	Mullumbimby, NSW	WP	s	[20]
A. riparia (Regel) Robinson	Mullumbimby, NSW	L	s	[20]
Ageratum conyzoides L.	Mackay, Q	WP	s	[18]
Ambrosia artemisifolia L.	Beaudesert, Q	WP	m	[20]
Ammobium alatum R. Br.	Tenterfield, NSW	L, St	w	[20]
Artemisia verlotorum Lamotte	Kew, V	L	w	[20]
Arctotheca nivea (L.) Lewin	WA	WP	w	[21]
Aster subulatus Michaux	Miles, Q	L, St	w	[17]
Baccharis halimifolia L.	Brisbane, Q	L, St	m	[17]
Bedfordia linearis DC.	Tarraleah, T	L, F, B	m	[22]
B. salicina DC.	Hobart, T	L, B	s	[22]
Bidens pilosa L.	Brisbane, Q	L, St	s	[18]
Brachyscome ciliaris (Labill.) Less.	WA	WP	w	[21]
B. ciliocarpa W.V. Fitzg.	WA	WP	w	[21]
B. diversifolia (Graham ex Hook.) Fisch. & Meyer	Yetman, NSW	WP	w	[20]
B. microcarpa F. Muell.	Stanthorpe, Q	WP	m	[17]
Brachyscome sp.	Stanthorpe, Q	WP	w	[17]
Brachyscome sp.	Warwick, Q	WP	m	[17]
Calotis breviradiata (Ising) G.L. Davis	WA	WP	w	[21]
C. cuneifolia R. Br.	Dalby, Q	WP	m	[17]
C. hispidula (F. Muell.) F. Muell.	Coulston Lakes, Q	L, F, St	m	[18]
	WA	WP	w	[21]
C. lappulacea Benth.	Ma Ma Ck, Q	WP	w	[20]
	Miles, Q	WP	w	[17]
C. multicaulis (Turcz.) Druce	WA	WP	w	[21]
C. scabriuscula C. White	Stanthorpe, Q	WP	w	[17]
Carduus tenuiflorus Curtis	WA	WP	w	[21]
Cassinia compacta F. Muell.	Whian Whian, NSW	L, St	m	[20]
C. laevis R. Br.	Leyburn, Q	L	m	[17]
C. quinquefaria R. Br.	Stanthorpe, Q	L, St	w	[20]
Centaurea calcitrapa L.	Port Melbourne, V	WP	m	[20]
C. cyaneus L.	Mitcham, V	S	w	[20]
C. gymnocarpa Moris & De Not.	Nth Balwyn, V	WP	m	[20]
C. melitensis L.	Dalby, Q	WP	s	[17]
	Stanthorpe, Q	L	s	[18]
	V	L	m	[20]
	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
C. repens L.	Toowoomba, Q	L	m	[20]
C. solstitialis L.	Warwick, Q	L, St	m	[20]
Centipeda cunninghamii (DC.) R. Br. & Aschers	Melton, V	L, St	w	[20]
C. thespidioides F. Muell.	Cunnamulla, Q	L, Fl, St	s	[18]
Centratherum muticum (Kunth.) Less.	Brisbane, Q	WP	s	[17]
	Coolum, Q	L	m	[18]
	Tamborine, Q	L, St	m	[20]
Cephalipterum drummondii A. Gray	WA	WP	w	[21]
Chondrilla juncea L.	Invergordon, V	WP	m	[20]
Conyza bonariensis (L.) Cronq.	Kingaroy, Q	WP	m	[20]
C. primulifolia (Lam.) Cuatrec. & Lourt.	Stanthorpe, Q	L, St	m	[20]
C. sumatrensis (Retz.) E. Walker	Kingaroy, Q	WP	m	[20]
Cotula sp.	Mt Dickson, PNG	WP	w	[19]
Craspedia globosa (Bauer ex Benth.) Benth.	V	L	w	[20]
Cryptostemma calendulaceum R. Br.	Sandon, V	WP	m	[20]
Eclipta alba Hassk.	Mackay, Q	R	s	[18]
Emilia sonchifolia DC.	Mackay, Q	WP	s	[18]
	Mission Beach, Q	WP	s	[20]
Epaltes australis Less.	Pittsworth, Q	WP	w	[17]
Erechtites gunnii J.D. Hook.	Mt Wellington, T	St	w	[18]
E. quadridentata (Labill.) DC.	WA	WP	w	[21]
Erigeron canadensis L.	Q	L, St	w	[17]
E. liniifolius Willd.	Wandoan, Q	WP	m	[17]
Eupatorium riparium Regel	Mt Glorious, Q	L, F, St	m	[17]
Euryops abrotangifolius (L.) DC.	Mitcham, V	L	m	[20]
Gnaphalium luteo-album L.	Cairns, Q	WP	w	[18]
G. purpureum L.	Bundaberg, Q	WP	s	[18]
Gnaphalodes condensatum A. Gray	WA	WP	w	[21]
G. uliginosum A. Gray	WA	WP	w	[21]
Gnephosis cyathopappa Benth.	Bourke, NSW	L, Fl, St	w	[18]
G. skirrophora (Sond. et F. Muell.) Benth.	WA	WP	w	[21]
Gynura pseudochina (L.) DC.	Lamington National Park, Q	L	w	[18]
Helianthus annuus L.	WA	WP	w	[21]
Helichrysum apiculatum var. *minor* Benth.	Cecil Plains, Q	WP	w	[17]
H. blandowskianum Steetz	SA	L	m	[20]
H. bracteatum (Vent.) Willd.	Stanthorpe, Q	L, R, St	w	[17]
H. bracteatum var. *albidum* DC.	WA	WP	w	[21]
H. davenportii F. Muell.	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
H. diosmifolium (Vent.) Sweet	Warwick, Q	L, St	w	[17]
H. polyphyllum Conrath	Jandowae, Q	L, Fl, St	s	[18]
H. ramosissimum Hook.	Ipswich, Q	WP	w	[17]
H. rupicola DC.	Mission Beach, Q	L, St	w	[20]
Helipterum anthemoides (Sprengel) DC.	Pittsworth, Q	WP	m	[17]
H. battii F.Muell.	WA	WP	w	[21]
H. incanum (Hook.) DC.	Stanthorpe, Q	WP	m	[17]
H. polyphyllum F. Muell.	Gayndah, Q	WP	s	[20]
Ixiolaena brevicompta F. Muell	Q	L, Fl, St	m	[17]
	Gayndah, Q	L, St	w	[20]
I. leptolepis (DC.) Benth.	Darling Downs, Q	WP	w	[20]
I. tomentosa (?) Sonder	Miles, Q	WP	w	[17]
Ixodia achilleoides R. Br.	Mt Lofty, SA	WP	w	[20]
Lactuca scariola L.	Brisbane, Q	WP	s	[17]
Microseris scapigera (Sol. ex A. Cunn.) Schultz-Bip.	WA	WP	w	[21]
Millota greevesii F. Muell.	Bollon, Q	L, Fl, St	w	[18]
Minuria integerrima (DC.) Benth.	Roma, Q	WP	w	[20]
Montanoa grandiflora Hemsl.	Millaa Millaa, Q	WP	m	[20]
Nyassanthes diffusa R. Br.	Brisbane, Q	L, St	w	[17]
Olearia elliptica DC.	Karara, Q	L	w	[17]
O. heterocarpa S.T. Blake	Whian Whian, NSW	L, St	m	[20]
O. homolepis F. Muell.	WA	WP	w	[21]
O. rudis (Benth.) F. Muell.	WA	WP	w	[21]
O. aff. *stuartii* (F. Muell.) F. Muell. ex Benth.	WA	WP	w	[21]
O. subspicata (Hook.) Benth.	Tambo, Q	L, St	w	[20]
Olearia sp.	Rockhampton, Q	L	m	[17]
Olearia sp.	Miles, Q	L, St	m	[17]
Picris hieracioides L.	Dalby, Q	L, Fl, St	s	[18]
	Warwick, Q	L, St	m	[20]
Podolepsis arachnoidea (Hook.) Druce	Stanthorpe, Q	L, St	w	[20]
P. capillaris (Steetz) Diels	WA	WP	w	[21]
P. longipedata A. Cunn.	Bollon, Q	WP	w	[18]
	Broadbeach, Q	WP	s	[20]
P. rhytidochlamys F. Muell.	Cecil Plains, Q	WP	m	[17]
P. rugata Labill.	WA	WP	w	[21]
Pterigon odorus Benth.	Isisford, Q	WP	s	[18]
	Springsure, Q	L, St	m	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Pterocaulon cylindrostachyum C.B. Clarke	Brisbane, Q	L, St	s	[17]
P. serrulatus (Montr.) Guill.	Nonda, Q	L, Fl, St	s	[18]
	Rockhampton, Q	WP	w	[20]
P. sphacelatum (Labill.) F. Muell.	Atherton, Q	L, Fl, St	w	[18]
	Unumgar, NSW	WP	w	[20]
Schkuhria pinnata (Lam.) Kuntze	Mitchell, Q	L, St	w	[20]
Schoenia cassiniana (Gaud.) Steetz	WA	WP	w	[21]
Senecio amygdalifolius F. Muell.	Springbrook, Q	L, St	w	[18]
S. bipinnatisectus Belcher	Acacia Plateau, NSW	WP	w	[20]
S. cinerarea DC.	Mt Albert, V	WP	s	[20]
S. crassiflorus DC.	Kempsey, NSW	L, St	m	[20]
S. cruentus DC.	Mitcham, V	WP	m	[20]
S. cunninghamii DC.	Hay, NSW	WP	s	[20]
S. elegans L.	Rye, V	WP	m	[20]
S. gregorii F. Muell.	Inglewood, Q	L, St	s	[18]
	Mitchell, Q	L, St	s	[20]
S. hispidulis A. Rich.	Mt Dandenong, V	L	m	[20]
S. jacobaea L.	Foster, V	L	m	[20]
S. lautus Forst. f. ex Willd.	WA	WP	w	[21]
S. lautus forma Willd.	Stanthorpe, Q	WP	m	[17]
S. lautus sens. lat. (*S. spathulatus?*)	Southport, Q	WP	w	[17]
S. lautus var. *lanceolatus* Benth.	Macpherson Range, Q	Fl	m	[18]
S. lautus (var.) G. Forster ex Willd.	Rolleston, Q	WP	w	[20]
S. leptocarpus DC.	Hartz Mts, T	WP	w	[22]
S. linearifolius A. Rich.	Kalorama, V	WP	w	[20]
S. magnificus F. Muell.	Mt Cavanagh, NT	WP	s	[20]
	WA	WP	m	[21]
S. mikanioides Otto ex Walp.	Gosford, NSW	L, Fl	w	[18]
	Brighton, V	WP	s	[20]
S. minimus Poiret	Mt Evelyn, V	WP	w	[20]
S. odoratus Harnem.	Pyke's Ck, V	L, St	m	[20]
S. pectinatus DC.	Mt Kosiosko, NSW	WP	s	[20]
S. quadridentatus Labill.	Kalorama, V	WP	s	[20]
S. ramosissimus DC.	WA	WP	w	[21]
S. vagus F. Muell.	Mt Macedon, V	WP	s	[20]
S. velleioides Cunn. ex DC.	Toolangi, V	WP	s	[20]
S. vulgaris L.	Mitcham, V	WP	s	[20]
Sigesbeckia orientalis L.	Brisbane, Q	WP	s	[17]
	Augathella, Q	WP	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Silybum marianum (L.) Gaertn.	WA	WP	m	[21]
Sonchus oleraceus L.	Kangaroo Point, Q	WP	w	[20]
Soliva anthemifolia (A.L. Juss.) Loudon	Chinchilla, Q	WP	w	[17]
Spilanthes acmella (L.) Murray	Mareeba, Q	WP	w	[18]
S. grandiflora Turez.	Banana, Q	L, St	m	[20]
Tagetes minuta L.	Cairns, Q	S, B	w	[18]
Tithonia diversifolia A. Gray	Southport, Q	WP	s	[20]
Tridax procumbens L.	Mackay, Q	L, St	m	[18]
Verbesina encelioides (Cav.) A. Gray	Gatton, Q	L, Fl, St	s	[17]
	Toogoolawah, Q	WP	m	[20]
Vernonia cinerea Less.	Callide Valley, Q	L	m	[18]
	Mareeba, Q	WP	w	[20]
Vitadinia pterochaeta (Benth.) J. Black	Cunnamulla, Q	L, Fl, St	w	[18]
V. triloba (Gaudich.) DC.	Brisbane, Q	L, St	s	[17]
	Cunnamulla, Q	L, Fl, St	m	[18]
Waitzia acuminata Steetz	WA	WP	w	[21]
W. suaveolens (Benth.) Druce	WA	WP	w	[21]
Wedelia asperrima (Decne.) Benth.	Q	L, Fl	s	[17]
	Cloncurry, Q.	WP	m	[20]
Xanthium pungens Wallr.	Brisbane, Q	WP	s	[17]
	Nanango Sth, Q	WP	m	[20]
Zinnia elegans Jacq.	Yarraman, Q	WP	m	[20]
Z. pauciflora L.	Toowoomba, Q	WP	s	[17]
	Yarraman, Q	L	m	[20]
BALANOPACEAE				
Balanops australiana F. Muell.	Danbullah, Q	B	m	[18]
	Ravenshoe, Q	B	w	[20]
BERBERIDACEAE				
Nandina domestica Thunb.	Acacia Ridge, Q	WP	w	[20]
BIGNONIACEAE				
Pandorea pandorana (Andrews) Steenis	Mossman, Q	L	m	[17]
	Mt Glorious, Q	L, St	w	[18]
	Mt Olga, NT	L	m	[20]
P. jasminoides (Lindley) K. Schum.	Toonumbar, NSW	WP	m	[20]
Tecoma stans Juss.	WA	WP	m	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
BOMBACACEAE				
Bombax cetha L.	Bamaga, Q	B	w	[20]
BORAGINACEAE				
Amsinkia calycina (Moris) Chater	Beulah, V	L, S, St	s	[20]
A. intermedia Fisch. & C. Mey.	Bungaree,V	L, St	s	[20]
A. lycopsoides (Lehm.) Lehm.	Jung, V	L, St	s	[20]
Anchusa myostidiflora Lehm.	Mitcham, V	L	m	[20]
A. officinalis L.	Mitcham, V	L	w	[20]
A. sempervirens L.	Olinda, V	L	w	[20]
Argusia argentea (L. f.) Heine	Mission Beach, Q	L, St	w	[20]
Borago officinalis L.	Mitcham, V	L, S, St	m	[20]
Cordia dichotoma G. Forster	Eungella Range, Q	L	m	[20]
C. subcordata Lam.	Port Douglas, Q	L, St	m	[20]
Cynoglossum amabile Staph & Drummond	Mitcham, V	WP	s	[20]
C. australe R. Br.	Rye, V	L, St	s	[20]
C. latifolium R. Br.	Healesville, V	L	s	[20]
C. suaveolens R. Br.	Toonoombar, NSW	L	w	[18]
	Sandon, V	L, St	m	[20]
Echium candicans L. f.	Castlemaine, V	L	m	[20]
E. italicum L.	Mornington, V	L, St	s	[20]
E. plantagineum L.	Q	L	s	[17]
	Macpherson Range, Q	L, R	m	[18]
	Albury, NSW	L, St	s	[20]
Ehretia acuminata R. Br.	Wongabel, Q	L, B	s	[20]
E. membranifolia R. Br.	Maxwelton, Q	L, St	s	[18]
	Goodnight Scrub, Q	L	m	[20]
E. saligna R. Br.	Georgina R, Q	L, St	m	[20]
Ehretia sp.	Glengalla, Q	L, St	s	[18]
Halgania cyanea Lindley	Mildura, V	L	m	[20]
Heliotropium amplexicaule Vahl	Brisbane, Q	WP	s	[17, 20]
[*H. anchusifolium* Poiret]	Stanthorpe, Q	L, St	s	[18]
H. arborescens L.	Balwyn, V	L, St	m	[20]
H. curassavicum L.	Lake Albacutya, V	L, St	s	[20]
H. europaeum L.	Pinaroo, SA	L	s	[20]
H. indicum L.	Mackay, Q	WP	s	[18]
	Inkerman, Q	L, S	s	[20]
H. supinum L.	Warracknabeel, V	L, St	s	[20]
H. tenuifolium R. Br.	Alice Springs, NT	L, S	s	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
H. undulatum Vahl	WA	L, St	m	[20]
Lappula concava (F. Muell.) F. Muell.	Fisherman's Bend, V	L, St	s	[20]
Lithodora diffusa (Lag.) I.M. Johnston subsp. *diffusa*	Croydon, V	L, St	m	[20]
Lithospermum arvense L.	Dimboola, V	WP	m	[20]
Myosotis australis R. Br.	Rendlesham, SA	L	m	[20]
M. sylvatica Hoffm.	Mitcham, V	L, St	s	[20]
Nonea lutea (Desr.) Reichenb. ex A. DC.	Ballarat, V	L, St	m	[20]
Symphytum uplandicum Nym.	Burnley, V	L, St	m	[20]
Tournefortia sarmentosa Lam.	Tully, Q	L, St	s	[20]
Trachystemon orientalis (L.) G. Don f.	Mitcham, V	L, St	w	[20]
Trichodesma zeylanicum R. Br.	Gayndah, Q	WP	m	[20]
BRASSICACEAE (CRUCIFERAE)				
Arabidella trisecta (F. Muell.) Schultz	WA	WP	m	[21]
Brassica tournefortii Gouan.	WA	WP	m	[21]
Cakile maritima Scop.	WA	WP	m	[21]
Carrichtera annua (L.) Prantl.	WA	WP	m	[21]
Cheesemannia radicata (Hook. f.) O.E. Schultz	Rodway Range, T	L, S, St	w	[22]
Coronopus didymus (L.) Sm.	WA	WP	w	[21]
Diplotaxis tenuifolia (L.) DC.	WA	WP	s	[21]
Lepidium hyssopifolium Desv.	Thangool, Q	WP	w	[18]
L. oxystrichum Sprague	WA	WP	m	[21]
L. virginicum L.	Mackay, Q	L, Fl, St	s	[18]
Menkea australis Lehm.	WA	WP	m	[21]
M. sphaerocarpa F. Muell.	WA	WP	w	[21]
M. villosula (F. Muell. et Tate) Black	WA	WP	m	[21]
Phlegmatospermum cochlearinum (F. Muell.) O.E. Schultz	WA	WP	m	[21]
Raphanus raphanistrum L.	WA	WP	s	[21]
Rapistrum rugosum (L.) All.	Cunnamulla, Q	L, St	w	[18]
	WA	WP	s	[21]
Sisymbrium orientale L.	WA	WP	s	]21]
Stenopetalum filifolium Benth.	WA	WP	m	[21]
BRUNONIACEAE				
Brunonia australis Sm.	WA	WP	m	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
BURSERACACEAE				
Protium macgregorii (Bailey) Leenh.	Yalu, PNG	B	w	[19]
CAESALPINIACEAE (LEGUMINOSAE)				
Caesalpinia robusta (C. White) Pedley	Pine Mt, Q	L, R	w	[20]
C. sepiaria Roxb.	Brisbane, Q	L, St	m	[17, 18]
Cassia alata L.	Babinda, Q	L	w	[17]
C. bicapsularis L.	Innisfail, Q	L, F	w	[17]
C. brewsteri F. Muell.	Coppermine Ck, Q	B	m	[20]
C. chatelainiana Gaud.	WA	WP	m	[21]
C. circinata Benth.	Augathella, Q	L, St	w	[20]
C. floribunda Cav.	Akuna, PNG	L, B	w	[19]
C. javanica L.	Tymne-Gurukor, PNG	L, B	w	[19]
C. laevigata Willd.	Cunningham's Gap, Q	L	s	[17]
C. pleurocarpa F. Muell.	WA	WP	m	[21]
	Morven, Q	L, St	w	[20]
C. sophera L.	Nonda, Q	L, F, St	s	[18]
C. sophera var. *schinifolia* (A. DC.) Benth.	Rockhampton, Q	L	m	[17]
C. tomentella (Benth.) Domin	Rockhampton, Q	F	w	[17]
	Moura, Q	L, St	w	[20]
Cynometra tripa Kostel	Mossman, Q	L, St	w	[20]
Erythrophleum chlorostachys (F. Muell.) Baillon	Chillagoe, Q	L, S	s	[17]
	Mareeba, Q	L, B	s	[20]
Lysiphyllum hookeri (F. Muell.) Pedley	Coppermine Ck, Q	B	w	[20]
Mesonevron robustum C. White	Malanda, Q	L, R	s	[18]
Parkinsonia aculeata L.	Longreach, Q	L, Fl, St	s	[18]
Petalostylis cassioides (Benth.) D. Symon	Barrow Ck, NT	L, St	s	[20]
P. labicheoides R. Br.	Miles, Q	L, B	s	[17]
	Jericho, Q	L, St	s	[18]
	Tambo, Q	L, St	s	[20]
CAMPANULACEAE				
Isotoma anethifolia Summerh.	Stanthorpe, Q	WP	s	[17, 20]
I. axillaris Lindley	Melbourne, V	L, St	s	[20]
	Stanthorpe, Q	L, St	s	[18]
I. hypocrateriformis (R. Br.) Druce	WA	WP	s	[21]
I. longiflora (L.) C. Presl	Innisfail, Q	L, R	s	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
I. petraea F. Muell.	Springsure, Q	WP	s	[20]
	Broken Hill, NSW	L	m	[18]
Lobelia alata Labill.	Melbourne, V	WP	w	[20]
L. anceps Thunb.	WA	WP	s	[21]
L. gracilis (Forst.) Andrews	Stanthorpe, Q	WP	m	[20]
L. purpurascens R. Br.	Tamborine, Q	WP	s	[20]
	Stanthorpe, Q	WP	s	[17]
	Brisbane, Q	L, St	w	[18]
L. rhombifolia De Vriese	WA	WP	m	[21]
L. rhytidosperma Benth.	WA	WP	m	[21]
L. stenophylla Benth.	Musgrave, Q	L	m	[20]
L. tenuior	WA	WP	m	[21]
L. trigonocaulis F. Muell.	Mt Glorious, Q	WP	w	[20]
	Whian Whian, NSW	L, St	w	[18]
Pratia concolor (R. Br.) Druce	Beaudesert, Q	L, St	s	[18]
Wahlenbergia capensis A. DC.	WA	WP	m	[21]
W. gracilis (G. Forster) A. DC.	WA	WP	m	[21]
W. gracilis sens. lat.	Pittsworth, Q	WP	s	[17]
CAPPARACEAE				
Apophyllum anomalum F. Muell.	Chinchilla, Q	St	s	[17]
Capparis canescens DC.	Rockhampton, Q	L, B	s	[17]
C. lasiantha DC.	Rockhampton, Q	L, F	s	[17]
	Maxwelton, Q	L, B, St	s	[18]
C. lucida (DC.) Benth.	Mowbray R, Q	L	w	[18]
C. mitchellii Lindl.	Dalby, Q	B	s	[18]
	Augathella, Q	L, St	s	[20]
C. nobilis (Endl.) Benth.	Miles, Q	L	s	[17]
	Imbil, Q	L	s	[18]
C. sp. aff. *nobilis*	Wandoan, Q	L, B	s	[17]
C. nummularia DC.	Nonda, Q	L, St	s	[18]
C. sarmentosa Benth.	Brisbane, Q	L, St	s	[17]
	Ipswich, Q	L, Fl, St	s	[18]
C. sepiaria L.	Markham Valley, PNG	L	w	[19]
C. zippeliana Miq.	Oomsis Ck, PNG	B	w	[19]
Capparis sp.	Chillagoe, Q	L, B	s	[17]
Cleome tetrandra Banks	WA	WP	m	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Cleome sp.	Babinda, Q	WP	w	[17]
Gynandropsis pentaphylla (L.) DC.	Clermont, Q	L	w	[18]
Polanisia viscosa (L.) DC.	Rockhampton, Q	WP	m	[17]
	Stanthorpe, Q	WP	w	[18]
CAPRIFOLIACEAE				
Lonicera sp.	Brisbane, Q	L	s	[18]
Sambucus australasica (Lindley) Fritsch	Whian Whian, NSW	L, St	w	[20]
S. gaudichaudiana DC.	Q	L, St	w	[17]
S. xanthocarpa F. Muell.	Tamborine Mt, Q	L, St	m	[18]
CARYOPHYLLACEAE				
Kohlrauschia prolifer (L.) Kunth.	WA	WP	m	[21]
Polycarpon tetraphyllum Loef.	WA	WP	m	[21]
Silene gallica L.	WA	WP	w	[21]
Spergula arvensis L.	Brisbane, Q	WP	m	[20]
CASUARINACEAE				
Allocasuarina littoralis (Salisb.)	Whian Whian, NSW	L, St	w	[20]
CELASTRACEAE				
Bhesa archboldiana (Merr. & Perry) Ding Hou	Busu R, PNG	L, B	s	[19, 20]
Caryospermum arborescens F. Muell.	Atherton, Q	L	w	[18]
Cassine australis (Vent.) Kuntze	Melbourne, V	L	w	[20]
Celastrus cunninghamii (Hook.) F. Muell.	Chinchilla, Q	L	m	[17]
	Gosford, NSW	F	w	[18]
C. dispermus F. Muell.	Yarraman, Q	B, L	m	[17]
	Imbil, Q	L	w	[18]
Denhamia obscura (A. Rich.) Walp.	Rockhampton, Q	L	s	[17]
	Dalby, Q	L	w	[18]
D. pittosporoides F. Muell.	Coolangatta, Q	L, St	w	[17]
	Brisbane, Q	L, F, St	s	[18]
Elaeodendron australe Vent.	Q	F	w	[17]
	Tamborine Mt, Q	B	w	[18]
E. australe var. *angustifolia* Benth.	Wandoan, Q	B	s	[17]
E. melanocarpum F. Muell.	Rockhampton, Q	B	s	[17]
E. microcarpum C. White & Francis	Imbil, Q	L	s	[18]
Euonymus australiana F. Muell.	Portland Roads, Q	W	w	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Hexaspora pubescens C. White	Bartle Frere, Q	L	w	[18]
Maytenus emarginata (Willd.) Ding Hou	Jacky Jacky Ck, Q	L	w	[20]
M. disperma (F. Muell.) Loes.	Yarraman, Q	B	w	[20]
Psammomoya choretroides (F. Muell.) Diels et Loes.	WA	WP	w	[21]
Siphonodon australis Benth.	Rockhampton, Q	F	s	[17]
S. membranaceus Bailey	Malanda, Q	B	s	[17]
	Atherton, Q	B	m	[18]
	Gadgarra, Q	B	m	[20]
S. pendulus Bailey	Chillagoe, Q	B	s	[17]
CHENOPODIACEAE				
Arthrocnemum bidens Nees	WA	WP	w	[21]
Atriplex cf. *acutibractea* R.H. Anders.	WA	WP	w	[21]
A. bunburyana F. Muell.	WA	WP	w	[21]
A. campanulata Benth.	Bollon, Q	R	w	[18]
A. cinereum Poir.	WA	WP	m	[21]
A. cryptocarpa Aellen	WA	WP	m	[21]
A. hymenotheca Moq.	WA	WP	m	[21]
A. nummularia Lindl.	WA	WP	m	[21]
A. semibaccata R. Br.	Warwick, Q	L, St	m	[20]
A. spongiosa F. Muell.	WA	WP	w	[21]
A. vesicaria Heward ex Benth.	WA	WP	s	[21]
Bassia astrocarpa F. Muell.	WA	WP	w	[21]
B. bicornis (Lindley) F. Muell.	Bollon, Q	L, St	m	[18]
B. birchii (F. Muell.) F. Muell.	Bollon, Q	WP	w	[18]
B. carnosa (Miq.) R.H. Anders.	WA	WP	w	[21]
B. diacantha (Nees) F. Muell.	WA	WP	w	[21]
B. divaricata (R. Br.) F. Muell.	WA	WP	w	[21]
B. eremaea Ising	WA	WP	w	[21]
B. eriacantha (F. Muell.) R.H. Anders.	WA	WP	s	[21]
B. eurotioides F. Muell.	WA	WP	m	[21]
B. lanicuspis (F. Muell.) F. Muell.	WA	WP	m	[21]
B. obliquicuspis R.H. Anders.	WA	WP	w	[21]
B. paradoxa (R. Br.) F. Muell.	WA	WP	w	[21]
B. patenticuspis R.H. Anders.	WA	WP	w	[21]
B. quinquecuspis (F. Muell.) F. Muell.	Toowoomba, Q	L, St	w	[17]
B. quinquecuspis var. *villosa* (Benth.) Black	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
B. sclerolaenoides F. Muell.	WA	WP	m	[21]
B. uniflora (R. Br.) F. Muell.	WA	WP	w	[21]
Chenopodium album (?) L.	Brisbane, Q	L, St	s	[17]
C. blackianum Aellen	WA	WP	w	[21]
C. carinatum R. Br.	Miles, Q	WP	m	[17]
C. cristatum F. Muell.	WA	WP	m	[21]
	Warwick, Q	WP	m	[17]
C. desertorum Black	WA	WP	w	[21]
C. melanocarpum (Black) Black	WA	WP	w	[21]
C. murale L.	Thallon, Q	L, R, St	s	[18]
	WA	WP	s	[21]
C. myriocephalum (?) Benth.	Brisbane, Q	L, St	s	[17]
C. pumilio R. Br.	WA	WP	w	[21]
C. rhadinostachyum F. Muell.	WA	WP	m	[21]
Didymanthus roei Endl.	WA	WP	w	[21]
Enchylaena tomentosa R. Br.	Chinchilla, Q	L, St	w	[17]
	WA	WP	m	[21]
Kochia brevifolia R. Br.	WA	WP	m	[21]
K. carnosa (Moq.) R.H. Anders.	WA	WP	w	[21]
K. enchylaenoides (Black) Black	WA	WP	m	[21]
K. erioclada (Benth.) Gauba	WA	WP	m	[21]
K. excavata Black var. *trichoptera* Black	WA	WP	s	[21]
K. fimbriolata F. Muell.	WA	WP	w	[21]
K. georgei Diels	WA	WP	s	[21]
K. glomerifolia F. Muell. et Tate	WA	WP	w	[21]
K. ostenfeldii Paulsen	WA	WP	m	[21]
K. pyramidata Benth.	WA	WP	s	[21]
K. sedifolia F. Muell.	WA	WP	m	[21]
K. tomentosa F. Muell.	WA	WP	w	[21]
K. triptera Benth.	WA	WP	m	[21]
K. villosa Lindl.	WA	WP	s	[21]
K. aff. *villosa* Lindl.	WA	WP	s	[21]
Kochia sp.	Q	WP	s	[17]
Kochia sp. 1666	WA	WP	w	[21]
Rhagodia baccata (Labill.) Moq.	WA	WP	w	[21]
R. crassifolia R. Br.	WA	WP	w	[21]
R. gaudichaudiana Moq.	WA	WP	m	[21]
R. parabolica R. Br.	Chinchilla, Q	L, St	w	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Salsola kali L.	Rathdowney, Q	L, St	m	[17]
	Maxwelton, Q	WP	s	[18]
	Goondiwindi, Q	WP	w	[20]
	WA	WP	m	[21]
Threlkeldia proceriflora F. Muell.	Q	WP	s	[17]
	Longreach, Q	L, St	s	[18]
CHRYSOBALANACEAE				
Maranthes corymbosa Blume	Oomsis Ck, PNG	L, B	w	[20]
CLUSIACEAE (GUTTIFERAE)				
Garcinia warrenii F. Muell.	Bamaga, Q	L, B	w	[20]
COMBRETACEAE				
Terminalia oblongata F. Muell.	Bauhinia Downs, Q	L, B, St	m	[20]
COMMELINACEAE				
Aneilema acuminatum R. Br.	Brisbane, Q	WP	m	[17]
Commelina cyanea R. Br.	Brisbane, Q	L, St	w	[17]
C. undulata R. Br.	Q	L, St	w	[17]
CONVOLVULACEAE				
Convolvulus erubescens Sims.	WA	WP	m	[21]
Cuscuta sp.	Yarraman, Q	St	w	[17]
Evolvulus alsinoides L.	Cairns, Q	L, St	w	[18]
Ipomoea cairica (L.) Sweet.	WA	WP	w	[21]
I. calobra F. Muell.	St George, Q	L, R, St	w	[17]
I. grandiflora (?) Lam.	Rockhampton, Q	F	w	[18]
I. lonchophylla J. Black	Roma, Q	WP	w	[20]
I. longiflora (?) R. Br.	Rockhampton, Q	F	w	[17]
I. muelleri Benth.	WA	WP	w	[21]
I. plebeia R. Br.	Brisbane, Q	L, F, St	w	[17]
	Mackay, Q	WP	s	[18]
Porana sericea (Gaud.) F. Muell.	WA	WP	m	[21]
Wilsonia humilis R. Br.	WA	WP	w	[21]
CORYNOCARPACEAE				
Corynocarpus cribbianus (Bailey) L.S. Sm.	Marafunga, PNG	B	w	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
CRASSULACEAE				
Bryophyllum tubiflorum var. Harvey	Waterford, Q	WP	m	[20]
CUCURBITACEAE				
Bryonopsis laciniosa (L.) Naudin	Mossman, Q	F	w	[17]
Citrullus vulgaris Schrad.	WA	WP	s	[21]
Cucumis anguria L.	Brisbane, Q	L	m	[20]
C. myriocarpus Naudin	Chinchilla, Q	F	m	[17]
	Dirranbandi, Q	WP	s	[18]
	Hopetoun, V	WP	m	[20]
	WA	WP	w	[21]
Melothria cunninghamii (F.Muell.) Benth.	Cairns, Q	L, F	w	[18]
Mukia maderaspatana (L.) M.J. Roem.	WA	WP	m	[21]
Trichosanthes subvelutina F. Muell.	Whian Whian, NSW	L	m	[20]
CUNONIACEAE				
Akama paniculata Engl.	Mt Glorious, Q	B	s	[17]
Aphanopetalum resinosum Endl.	Brookfield, Q	L	s	[18]
Ceratopetalum succirubrum C. White	Danbullah, Q	B	w	[17]
Geissois benthamii F. Muell.	Atherton, Q	B	w	[17]
Pseudoweinmannia lachnocarpa (F.Muell.) Engl.	Mt Glorious, Q	B	w	[18]
CYCADACEAE				
Cycas circinalis L.	Mumeng, PNG	S	w	[19]
CYPERACEAE				
Cyperus rotundus L.	Brisbane, Q	R	w	[20]
Kyllinga cylindrica Wight	Brisbane, Q	WP	m	[18]
Scirpus nodosus Rottb.	WA	WP	w	[21]
DICHAPETALACEAE				
Dichapetalum timoriense (DC.) Boerl.	Crooked Ck, PNG	L	w	[19]
DILLENIACEAE				
Hibbertia linearis DC.	Mt Coot-tha, Q	L, R, St	s	[18]
DISCOREACEAE				
Discorea transversa R. Br.	Currumbin, Q	R	w	[17]
	Mt Glorious, Q	L, St	m	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
DIPSACACEAE				
Dipsacus fullonum L.	Belgrave, V	L, St	m	[20]
DROSERACEAE				
Drosera auriculata Backh. ex Planch.	Rokeby Hill, T	WP	w	[22]
EBENACEAE				
Diospyros australis (R. Br.) Hiern.	Rockhampton, Q	L	s	[17]
	Imbil, Q	L	s	[18]
D. hebecarpa Cunn. ex Benth.	Cairns, Q	L, B	w	[18]
Maba geminata R. Br.	Brisbane, Q	L, B	w	[17]
M. humilis R. Br.	Chillagoe, Q	L	w	[17]
ELAEAGNACEAE				
Elaeagnus latifolius L.	Innisfail, Q	L	s	[17]
	Mossman, Q	F	w	[18]
	Miriam Vale, Q	L	w	[20]
ELAEOCARPACEAE				
Aceratium megalospermum F. Muell.	Mission Beach, Q	L, St	m	[20]
Aristotelia australasica F. Muell.	Melbourne Botanic Gardens, V	L	s	[20]
A. peduncularis (Labill.) Hook. f.	Hartz Mts, T	L, R, St	s	[22]
Elaeocarpus altisectus Schltr.	Oomsis Track, PNG	L	m	[19,20]
E. cephalodactylus Schltr.	Okapa, PNG	L	w	[19]
E. densiflorus Knuth	Kaindi-Edie Ck, PNG	L	m	[19,20]
E. dolichostylus Schltr.	Butibum R, PNG	L	s	[19,20]
E. cf. *dolichostylus* Schltr.	Mt Shungol, PNG	L	w	[19]
E. filiformi-dentatus Knuth	Marafunga, PNG	L	w	[19]
E. grandis F. Muell.	Danbullah, Q	B	m	[17]
E. johnsonii C. White	Boonjie, Q	L, B	m	[17]
E. kaniensis Schltr.	Wanatabi, PNG	L	m	[19]
E. polydactylus Schltr.	Mt Sarawaket, PNG	L	s	[19,20]
E. sphaericus (Gaertn.) K. Schum.	Oomsis Ck, PNG	L, B	m	[19,20]
E. trichophyllus A.C. Sm.	Marafunga, PNG	L, B	m	[19]
Peripentadenia mearsii (C. White) L.S. Smith	Boonjie, Q	L, B, St	s	[20]
Sloanea woollsii F. Muell.	Mt Mistake, Q	L	w	[18]
	Toonumbar, NSW	L	w	[20]
Sloanea sp.	Okapa, PNG	B	W	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
EPACRIDACEAE				
Leucopogon juniperinus R. Br.	Mt Coot-tha, Q	L,St	s	[18]
Melichrus urceolatus R. Br.	Chinchilla, Q	L	w	[17]
ERYTHROXYLACEAE				
Erythroxylum australe F. Muell.	Wandoan, Q	L, B	s	[17]
	Cloyna, Q	L	s	[18]
	Springsure, Q	L, St	s	[20]
E. ecarinatum Hochr.	Danbullah, Q	L, B	s	[17]
	Kakoda Road, PNG	L	w	[19]
E. ellipticum R.Br.	Laura-Coen, Q	L, B	s	[20]
EUPHORBIACEAE				
Acalypha eremorum Muell. Arg.	Wandoan, Q	L, St	w	[17]
A. nemorum Muell. Arg.	Mt Coot-tha, Q	L, R, St	s	[18]
Actephila mearsii (?) C. White	Boonjie, Q	L, B	s	[18]
Alchornea aquifolium Domin	Melbourne, V	L	m	[20]
A. javanensis (Bl.) Muell. Arg. [*A. rugosa* (Lour.) Muell. Arg.]	Crooked Ck, PNG	L, B	m	[19,20]
Aleurites moluccana (L.) Willd.	Atherton, Q	S	s	[17]
Antidesma sp.	Butibum R, PNG	L, B	w	[19]
Baloghia lucida Endl.	Imbil, Q	L, B	s	[18]
Claoxylon australe Baillon ex Muell. Arg.	Brisbane, Q	L, F	m	[17]
	Red Scrub, NSW	L, B	m	[20]
Claoxylon sp.	Mt Glorious, Q	L, B	m	[17]
Cleistanthus apodus Benth.	Bamaga, Q	L	w	[20]
Codiaeum variegatum var. *moluccanum* (Decne.) Muell. Arg.	Atherton, Q	B	w	[18]
Coelebogyne ilicifolia J. Smith	Mt Mistake, Q	L	w	[18]
Croton acronychioides F. Muell.	Brisbane, Q	L, B	w	[17]
C. arnhemicus Muell. Arg.	Chillagoe, Q	B	s	[17]
	Bamaga, Q	L, B	w	[20]
C. insularis Baillon	Wandoan, Q	L	s	[17]
C. phebalioides Muell. Arg.	Ipswich, Q	L, St	m	[18]
C. verreauxii Baillon	Mt Lindesay, Q	L	m	[17]
Daphniphyllum gracile Gage	Bakaia, PNG	L, B	m	[19]
Euphorbia atoto Forster	Bamaga, Q	WP	s	[20]
E. boöphthona C.A. Gardn.	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
E. eremophyla Cunn.	Maxwelton, Q	WP	s	[18]
E. hirta L.	Mackay, Q	WP	m	[18]
E. macgillivrayi Boiss.	Inkerman, Q	WP	m	[20]
E. peplus L.	Mt Lindesay, Q	WP	w	[17]
	WA	WP	w	[21]
E. tannensis Sprengel ssp. *eremophila* (Cunn.) Hassall	Victory Downs, NT	L, St	m	[20]
E. terracina L.	WA	WP	w	[21]
Excoecaria agallocha L.	Beenleigh, Q	B, W	m	[20]
E. dallachyana (Baillon) Benth.	Rockhampton, Q	F	s	[17]
	Mt Lindesay, NSW	B, W	m	[20]
E. parviflora Muell. Arg.	Glengalla, Q	L, St	w	[18]
Fluggea leucopyrus Willd.	Chillagoe, Q	L	s	[17]
	Cannonvale, Q	L, B	m	[20]
F. virosa var. *melanthesoides* (F. Muell.) Webster	Cooktown, Q	B	w	[20]
Fontainea picrosperma C. White	Malanda, Q	L, B	s	[17]
Galearia celebica Kds.	Tymne-Gurukor, PNG	L	w	[19,20]
Glochidion philippicum (Cav.) Rob.	Huon Gulf, PNG	L, B	m	[20]
Glochidion sp. aff. *G. philippicum* (Cav.) Rob.	Huon Gulf, PNG	L, B	m	[19]
Gloriosa virescens Lindl.	Brisbane, Q	R, Fl, St	m	[18]
Hemecyclia australasica Muell. Arg.	Ipswich, Q	B	w	[17]
Leptopus decaisnei (Benth.) H. Pojark.	Elliott, NT	WP	s	[20]
Macaranga tanarius (L.) Muell. Arg.	Rockhampton, Q	F	w	[17]
Mallotus paniculatus Muell. Arg.	Cairns, Q	L	w	[18]
	Bailey's Ck, Q	B	m	[20]
M. philippinensis (Lam.) Muell. Arg.	Brisbane, Q	L	w	[17]
Monotaxis grandiflora Endl.	WA	WP	w	[21]
M. luteiflora F. Muell.	WA	WP	w	[21]
Monotaxis sp.	Miles, Q	R	w	[17]
Omalanthus novoguineensis (Warb.) Laut. & K. Schum.	Oomsis Ck, PNG	B	w	[19]
Petalostigma pubescens Domin	Mareeba, Q	L, St	m	[20]
P. quadriloculare F. Muell.	Kuranda, Q	B	m	[17]
Phyllanthus gasstroemi Muell. Arg.	Wandoan, Q	L, St	w	[17]
P. thesioides Benth.	Warwick, Q	WP	w	[17]
Phyllanthus sp.	Glengalla, Q	R, St	s	[18]
Pimeleodendron amboinicum Hassk.	Mumeng, PNG	L	w	[19]
Poranthera corymbosa Brongn.	Torrington, NSW	L, B, R	m	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
P. huegelii Klotzsch.	WA	WP	w	[21]
P. microphylla Brongn.	WA	WP	s	[21]
Ricinocarpus glaucus Endl.	WA	WP	s	[21]
Securinega leucopyrus (Willd.) Muell. Arg.	Chillagoe, Q	L	s	[18]
Spathiostemon javensis Bl.	Kokoda Road, PNG	L, B	m	[19, 20]
EUPOMATIACEAE				
Eupomatia laurina R. Br.	Toonumbar, NSW	L	w	[20]
	Busu R, PNG	L, B	m	[19, 20]
FABACEAE (LEGUMINOSAE)				
Abrus precatorius L.	Spring Ck, Q	WP	m	[20]
Aotus subglauca Blakely & McKie	Stanthorpe, Q	L, St	s	[20]
A. villosa sens. lat. Smith	Miles, Q	L, B	s	[17]
Bossiaea armitii F. Muell.	Laura-Coen, Q	WP	m	[20]
B. brownii Benth.	Blackdown Tableland, Q	L	w	[18]
B. rupicola Benth.	Mt Barney, Q	L	w	[18]
Callistachys lanceolata Vent.	Melbourne Botanic Gardens, V	L	w	[20]
Canavalia cathartica Thou.	Trans-Busu, PNG	L, St	m	[19]
C. maritima (Aubl.) Thou.	Huon Gulf, PNG	L	w	[19]
C. rosea (Sw.) DC.	Huon Gulf, PNG	L	w	[20]
	Pt Lookout, Q	S	s	[18]
Castanospermum australe Cunn. & Frazer ex Hook.	Brisbane, Q	L, B, S	s	[17]
	Moore Park, NSW	L, St	w	[20]
Chorizema aciculare (DC.) C.A. Gardn.	WA	WP	w	[21]
C. cordatum Lindl.	WA	WP	s	[21]
C. diversifolia DC.	WA	WP	m	[21]
Clianthus formosus (G. Don) Ford et Vickery	WA	WP	m	[21]
Clitorea ternatea L.	Inkerman, Q	L, St	w	[20]
	Home Hill, Q	L, S	s	[18]
Crotalaria agatiflora C. Schweinf.	Townsville, Q	L, St	s	[20]
C. alata Buch.-Ham. ex Benth.	Kimberleys, WA	L, St	s	[20]
C. aridicola Domin	Townsville, Q	WP	s	[20]
C. cunninghamii R. Br.	WA	WP	s	[21]
C. crassipes (?) Hook.	NT	L	w	[18]
C. crispata F. Muell. ex Benth.	Kimberleys, WA	L, St	s	[20]
C. dissitiflora Benth.	Cunnamulla, Q	L, St	s	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
C. eremaea F. Muell.	Thylurgie, Q	L, St	m	[20]
C. goreensis Guillaumin & Perottet	Ayr, Q	L, St	s	[20]
C. grahamiana Wight & Arn.	Kingscliff, NSW	L	s	[20]
C. grantiana Harv.	Gatton, Q	L	s	[20]
C. incana L.	Nanango, Q	L, St	m	[20]
	Dalby, Q	L, F	m	[17]
C. juncea L.	Gatton, Q	L, St	s	[20]
C. laburnifolia L.	C Palleranda, Q	L, St	s	[20]
C. lanceolata E. Meyer	Strathpine, Q	L, S, St	s	[20]
	Rockhampton, Q	L, F, St	s	[18]
C. linifolia L. f.	Nanango, Q	WP	m	[20]
	Brisbane, Q	WP	m	[17]
	Maxwelton, Q	WP	s	[18]
C. medicaginea Lam.	Gayndah, Q	WP	s	[20]
C. mitchellii Benth.	Gayndah, Q	L, St	s	[20]
	Miles, Q	WP	m	[17]
C. novae-hollandiae DC.	Mt Isa, Q	L, St	s	[20]
	Q	L, F, St	m	[17]
C. novae-hollandiae subsp. *lasiophylla* (Benth.) A. Lee	Mt Isa, Q	L, St	s	[20]
C. novae-hollandiae subsp. *novae-hollandiae*	Kimberleys, WA	S	s	[20]
C. ochroleuca G. Don	Strathpine, Q	L, St	m	[20]
C. pallida Alton	Babinda, Q	L, St	s	[20]
C. retusa L.	Alice Springs, NT	L, St	s	[20]
C. sericea Retz.	Mt Coot-tha, Q	L, R, S, St	s	[18]
C. sessiliflora L.	Butibum R, Q	F, St	w	[19]
C. smithiana A. Lee	Inglewood, Q	WP	m	[20]
C. spectabilis Roth	Ipswich, Q	L, St	s	[20]
C. striata DC.	Brisbane, Q	L,F,S,St	s	[17]
C. trifoliastrum Willd.	Rockhampton, Q	L, B	s	[17]
C. usaramoensis E.G. Baker	Rockhampton, Q	L, F, St	s	[18]
C. verrucosa L.	Mammoth Mine, Q	L, St	s	[20]
	Atherton, Q	L, F, St	s	[18]
C. zanzibarica Benth.	Babinda, Q	L, S, St	s	[20]
Crotalaria sp.	Brisbane, Q	L	m	[17]
Crotalaria sp.	Hughenden, Q	L, R, St	s	[18]
Cytisus prolifer L. f.	Kingaroy, Q	L	s	[18]
C. scoparius (L.) Link	Q	L, St	s	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Daviesia acanthoclona F. Muell.	WA	WP	w	[21]
D. alternifolia Endl.	WA	WP	w	[21]
D. arborea Hill	Whian Whian, NSW	B	w	[20]
	Currumbin, Q	L, B	m	[17]
D. brevifolia Lindley	Portland, V	L, St	w	[20]
D. cordata Sm.	WA	WP	m	[21]
D. corymbosa Smith	Stanthorpe, Q	L, B	s	[17]
D. corymbosa Sm. var. *mimosoides* (R. Br.) Benth.	Stanthorpe, Q	L	w	[20]
D. croniniana F. Muell.	WA	WP	s	[21]
D. divaricata Benth.	WA	WP	m	[21]
D. grahamii Ewart et White	WA	WP	m	[21]
D. latifolia R. Br.	Ebor-Guyra, NSW	L	w	[20]
D. mimosoides R. Br.	Glen Innes, NSW	L	m	[20]
D. nudiflora Meissn.	WA	WP	s	[21]
D. squarrosa Smith	Tamborine, Q	L, St	m	[20]
D. ulicina Smith	Tamborine, Q	L, St	m	[20]
	Cecil Plains, Q	L, St	w	[17]
D. wyattiana Bailey	Woolgoolga, NSW	L	w	[20]
Desmodium umbellatum (L.) DC.	Chillagoe, Q	L	w	[17]
Dillwynia floribunda Smith	Stanthorpe, Q	L, R, St	m	[17]
D. retorta (Wendl.) Druce	Pottsville, NSW	L, St	w	[20]
D. retorta ssp. B	Mt Mitchell, NSW	WP	w	[20]
D. sericea Cunn.	Stanthorpe, Q	L, St	w	[20]
Dioclea reflexa J.D. Hook.	Johnstone R, Q	L, S	m	[18]
Erythrina indica Lam.	Brisbane, Q	B	s	[17]
	Brisbane, Q	L, B	s	[18]
E. variegata L.	Huon Gulf, PNG	B	m	[19]
E. vespertilio Benth.	Moura, Q	L, St	s	[20]
	Mt Lindesay, Q	L, St	m	[17]
Euchilopsis linearis (Benth.) F. Muell.	WA	WP	w	[21]
Gastrolobium callistachys Meissn.	WA	WP	w	[21]
G. epacridioides Meissn.	WA	WP	w	[21]
G. grandiflorum F. Muell.	Davies Ck, Q	L, St	w	[20]
	Springsure, Q	L	s	[17]
Glycine clandestina Wendl.	Beaudesert Road, Q	L, St	w	[20]
G. sericea (F.Muell.) Benth.	WA	WP	s	[21]
G. tabacina (Labill.) Benth.	Pittsworth, Q	L, F, St	m	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Gompholobium polymorphum R. Br.	WA	WP	w	[21]
G. uncinatum Cunn. ex Benth.	Stanthorpe, Q	L, St	m	[20]
G. viscidulum Meissn.	WA	WP	m	[21]
Hardenbergia comptoniana (Andr.) Benth.	WA	WP	w	[21]
H. monophylla (Vent.) Benth.	Slack's Ck, Q	WP	w	[20]
	Dalby, Q	L, St	s	[17]
Hovea acanthoclada (Turcz.) F. Muell.	WA	WP	s	[21]
H. acutifolia Cunn.	Whian Whian, NSW	L	s	[20]
	Brisbane, Q	L, B	s	[17]
	Binna Burra, Q	L	s	[18]
H. chorizemifolia DC.	Lesmurdie, WA	L	m	[20]
	Woorooloo, WA	L	m	[18]
	WA	WP	s	[21]
H. elliptica (Smith) DC.	Albany, WA	L	s	[18]
	WA	WP	s	[21]
H. heterophylla J.D. Hook.	Mudgeeraba, Q	L, R, W	m	[18]
H. linearis R. Br.	Stanthorpe, Q	L, St	s	[20]
	Carnarvon Range, Q	L	s	[18]
H. longifolia R. Br.	Cardwell, Q	WP	s	[20]
	Dalby, Q	L, St	s	[17]
	Fraser I, Q	L	s	[18]
H. longifolia var. *pannosa* (A. Cunn. ex Hook.) Benth.	Ma Ma Ck, Q	L	s	[20]
H. longipes Benth.	Morven, Q	L, St	s	[20]
	Rockhampton, Q	L	s	[18]
H. pungens Benth.	Mundaring, WA	L	m	[18]
	WA	WP	s	[21]
H. trisperma Benth.	King's Park, WA	L	s	[20]
	Mundaring, WA	L	s	[18]
Indigofera australis Willd.	Ebor-Guyra, NSW	L	m	[20]
	Stanthorpe, Q	R	w	[17]
	WA	WP	w	[21]
I. australis var. *signata* Benth.	Stanthorpe, Q	R	w	[17]
I. brevidens Benth.	WA	WP	m	[21]
I. colutea (Burm. f.) Merr.	Mitchell, Q	L, St	s	[20]
I. enneaphylla L.	Springsure, Q	WP	w	[20]
I. georgei E. Pritzel	WA	WP	w	[21]
I. linifolia (L. f.) Retz.	Springsure, Q	L, St	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Isotropis cuneifolia (Sm.) Domin	WA	WP	m	[21]
I. juncea Turcz.	WA	WP	w	[21]
Jacksonia scoparia R. Br.	Miles, Q	B, St	m	[17]
J. thesioides Benth.	Kuranda, Q	R	m	[18]
Kennedia rubicunda (Schneev.) Vent.	Mt Lindesay, NSW	L, St	w	[20]
Lamprolobium fruticosum Benth.	Mt Carbine, Q	L, St	s	[20]
	Walsh R, Q	S	s	[18]
Lotus australis Andrews	Stanthorpe, Q	WP	w	[17]
L. cruentus Court	WA	WP	s	[21]
Lupinus angustifolius L.	WA	WP	s	[21]
L. cosentinii Guss.	WA	WP	s	[21]
Medicago minima (L.) Bartal.	WA	WP	m	[21]
M. polymorpha L.	WA	WP	m	[21]
M. savita L.	WA	WP	m	[21]
Melilotus indica (L.) All.	WA	WP	m	[21]
M. parviflora Desf.	Allora, Q	L, St	w	[17]
Millettia maideniana Bailey	Q	L	w	[18]
M. megasperma (F. Muell.) Benth.	Brisbane, Q	S	s	[17]
Mirbelia dilatata R. Br.	WA	WP	m	[21]
M. spinosa Benth.	WA	WP	w	[21]
Mucuna gigantea (Willd.) DC.	Rockhampton. Q	L, S	m	[17]
Oxylobium arborescens R. Br.	Shannon Road, T	L, S	s	[22]
O. ellipticum (Labill.) R. Br. var. *angustifolium* (Vent.) R. Br.	Fraser I, Q	L	s	[18]
O. ilicifolium (Andrews) Domin	Mt Lindesay, Q	L, St	m	[20]
Pachyrhizus erosus (L.) Urban	Redland Bay, Q	L, F, St	s	[18]
Phaseolus semierectus L.	Brisbane, Q	L, St	w	[17]
Phyllota phylicoides (Sieber ex DC.) Benth.	Wallum, NSW	L, St	w	[20]
Podopetalum ormondii F. Muell.	Bailey's Ck, Q	B	s	[20]
	Bloomfield R, Q	S	s	[18]
Pongamia pinnata (L.) Pierre	Cannonvale, Q	L, B	w	[20]
	Cairns, Q	B, F	m	[17]
	Brisbane, Q	S	m	[18]
Psoralea badocana (Blanco) Benth.	Port Moresby, PNG	L	w	[18]
P. cinerea Lindley	Nonda, Q	L, Fl, St	s	[18]
Psoralea sp.	Mt Coot-tha, Q	L, St	s	[18]
Pultanaea altissima F. Muell. ex Benth.	Buchan, V	L, St	s	[20]
P. euchila DC.	Ipswich, Q	L, St	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
P. hartmannii F. Muell.	Stanthorpe, Q	L	m	[20]
P. microphylla ex DC. var. *microphylla* Sieber	Ebor-Guyra, NSW	WP	w	[20]
P. polifolia Cunn.	Stanthorpe, Q	L	w	[20]
P. subternata H. Williamson	Carnarvon Range, Q	L, St	m	[20]
P. villosa Willd.	Pottsville, NSW	L, St	m	[20]
Sesbania aculeata Pers.	Bundaberg, Q	F, St	s	[18]
S. cannabina (Retz.) Poir. var. *cannabina* N.T. Burbage	WA	WP	w	[21]
Sophora fraseri Benth.	Enoggera Ck, Q	L, F, St	s	[18]
S. tomentosa L.	Bingle Bay, Q	S	s	[20]
	Mossman, Q	L, F	s	[18]
Sphaerolobium medium R. Br.	WA	WP	m	[21]
Swainsona campestris Black	WA	WP	m	[21]
S. canescens (Benth.) F. Muell.	WA	WP	m	[21]
S. canescens (Benth.) F. Muell. var. *canescens*	Victory Downs, NT	L	w	[20]
S. cyclocarpa F. Muell. var. *paradoxa* (W.V. Fitzg.) A. Lee	WA	WP	w	[21]
S. flavicarinata Black	WA	WP	w	[21]
S. galegifolia (Andrews) R. Br.	Brisbane, Q	L, F, St	s	[17]
S. greyana Lindley	Charleville, Q	L, F, St	s	[18]
S. incei Price	WA	WP	m	[21]
S. microphylla A. Gray ssp. *affinis* A. Lee	WA	WP	m	[21]
S. occidentalis F. Muell.	WA	WP	w	[21]
S. oroboides F. Muell. ex Benth.	WA	WP	m	[21]
S. procumbens (F.Muell.) F.Muell.	Bollon, Q	WP	s	[18]
S. luteola F. Muell.	Q	WP	s	[17]
S. rostellata A. Lee	WA	WP	s	[21]
S. stipularis F. Muell. var. *longialata* A. Lee	WA	WP	m	[21]
Templetonia egena (F. Muell.) Benth.	SA-NT border	L, St	s	[20]
T. retusa (Vent.) R. Br.	Perth, WA	L, St	s	[20]
	WA	WP	s	[21]
T. sulcata (Meissn.) Benth.	WA	WP	s	[21]
Tephrosia flammea F. Muell. ex Benth.	WA	WP	s	[21]
T. grandiflora (L'Herit. ex Prit.) Pers.	Pottsville, NSW	WP	w	[20]
T. macropoda Harv.	Brisbane, Q	L, F, St	w	[17]
T. purpurea (L.) Pers.	Clermont, Q	L, St	s	[17]
T. sp. aff. *coriacea*	Lawn Hill, Q	L	w	[18]
Tephrosia sp.	Chillagoe, Q	L, St	m	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Trifolium angustifolium L.	WA	WP	w	[21]
T. campestre Schreb.	WA	WP	w	[21]
T. subterraneum L.	WA	WP	w	[21]
Ulex europaeus L.	Toowoomba, Q	L, Fl, St	w	[18]
Vicia sativa L.	WA	WP	s	[21]
Vigna lanceolata Benth.	WA	WP	m	[21]
V. vexillata (L.) A. Rich.	Biloela, Q	L, St	m	[20]
FLACOURTIACEAE				
Casearia dallachyi F. Muell.	Atherton, Q	L, B	m	[18]
C. multinervosa C. White & Sleumer ex Sleumer	Kingaroy, Q	L, St	s	[18]
C. pachyphylla Gilg	Marafunga, PNG	B	w	[19]
Homalium alnifolium F. Muell.	Milman, Q	B	s	[18]
H. foetidum (Roxb.) Benth.	Trans-Busu, PNG	L	w	[19, 20]
FLAGELLARIACEAE				
Flagellaria indica L.	Atherton, Q	L, St	m	[18]
FUMARIACEAE				
Fumaria capreolata L.	WA	WP	s	[21]
GENTIANACEAE				
Erythraea centaurium (L.) Pers.	WA	WP	m	[21]
Villarsia calthifolia F. Muell.	WA	WP	w	[21]
V. lasiosperma F. Muell.	WA	WP	m	[21]
GERANIACEAE				
Erodium cygnorum Nees	Bollon, Q	L, Fl, St	s	[18]
GLEICHENIACEAE				
Dicranopteris linearis (Burn.) Und.	Tweed R, NSW	WP	w	[20]
GOODENIACEAE				
Dampiera coronata Lindl.	WA	WP	w	[21]
D. lavandulacea Lindl.	WA	WP	w	[21]
D. sacculata F. Muell. ex Benth.	WA	WP	m	[21]
D. stowardii S. Moore	WA	WP	w	[21]
D. stricta (Smith) R. Br.	Miles, Q	WP	w	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
D. tenuicaulis E. Pritzel	WA	WP	w	[21]
D. trigona DeVriese var. *latealata* E. Pritzel	WA	WP	w	[21]
D. wellsiana F. Muell.	WA	WP	w	[21]
Diaspasis filifolia R. Br.	WA	WP	w	[21]
Goodenia bellidifolia Smith	Stanthorpe, Q	WP	m	[17]
	Wallangarra, Q	WP	w	[20]
G. decursiva W.V. Fitzg.	WA	WP	w	[21]
G. discolor Krause	WA	WP	w	[21]
G. fasciculata (Benth.) Carolin	WA	WP	w	[21]
G. glabri R. Br.	WA	WP	s	[21]
G. grandiflora Sims	Tamborine Mt, Q	L	w	[18]
G. mueckeana F. Muell.	WA	WP	w	[21]
G. ovata Smith	Croydon, V	L	w	[20]
G. pinifolia DeVriese	WA	WP	w	[21]
G. pinnatifida Schlecht.	WA	WP	w	[21]
G. rotundifolia R. Br.	Brisbane, Q	WP	m	[17]
	Stanthorpe, Q	L, St	m	[20]
G. scapigera R. Br.	WA	WP	w	[21]
G. stelligera R. Br.	Pottsville, NSW	WP	w	[20]
G. subintegra F. Muell.	Dalby, Q	L, St	m	[20]
G. tenuiloba F. Muell.	WA	WP	w	[21]
Goodenia sp. aff. *hederacea* Smith	Warwick, Q	L	w	[17]
Goodenia sp.	Glengalla, Q	WP	s	[18]
Leschenaultia biloba Lindl.	WA	WP	m	[21]
L. formosa R. Br.	WA	WP	w	[21]
L. hirsuta F. Muell.	WA	WP	s	[21]
L. stenosepala E. Pritzel	WA	WP	w	[21]
L. tubiflora R. Br.	WA	WP	w	[21]
Scaevola aemula R. Br.	Stanthorpe, Q	L, St	w	[17]
	Augathella, Q	WP	m	[20]
S. densevestita Domin	Cloncurry, Q	L	m	[20]
S. frutescens K. Krause	Innisfail, Q	L, B	w	[17]
S. hispida Cav.	Stanthorpe, Q	L, St	w	[20]
S. nitida R. Br.	WA	WP	w	[21]
S. oppositifolia R. Br	Kauli Ck, PNG	L, St	w	[19]
S. oxyclona F. Muell.	WA	WP	w	[21]
S. platyphylla Lindl.	WA	WP	w	[21]
S. restiacea Benth.	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
S. spinescens R. Br.	WA	WP	w	[21]
Symphiobasis macroplecta (F. Muell.) Krause	WA	WP	m	[21]
Velleia arguta R. Br.	WA	WP	w	[21]
V. connata F. Muell.	WA	WP	w	[21]
V. hispida W.V. Fitzg.	WA	WP	m	[21]
V. paradoxa R. Br.	Ipswich, Q	WP	w	[20]
V. rosea S. Moore	WA	WP	m	[21]
Verreauxia reinwardtii (DeVriese) Benth.	WA	WP	w	[21]
GROSSULARIACEAE (ESCALLONIACEAE)				
Anopterus glandulosus Labill.	Maydena, T	L, B	m	[20]
	Savage R, T	L, Fl, B	s	[22]
A. macleayanus F. Muell.	Whian Whian, NSW	L, B, St	s	[20]
GYROSTEMONACEAE				
Codonocarpus attenuatus (Hook.) H. Walt.	Yarraman, Q	L, B, W	s	[20]
C. cotinifolius (Desf.) F. Muell.	WA	WP	m	[21]
	Victory Downs, NT	L, B, St	s	[20]
Gyrostemon ramulosus Desf.	WA	WP	s	[21]
	Ayer's Rock, NT	L, St	m	[20]
G. thesioides (Hook. f.) A.S. George	Beachport, SA	WP	m	[20]
Tersonia breviceps Moq.	WA	WP	m	[21]
HAEMODORACEAE				
Haemodorum paniculatum Lindl.	WA	WP	w	[21]
H. planifolium R. Br.	Cecil Plains, Q	WP	w	[17]
H. spicatum R. Br.	WA	WP	s	[21]
HALORAGACEAE				
*Halorrhagis tetragyna*var.	Stanthorpe, Q	R	m	[17]
Myriophyllum propinquum Cunn.	Waterford, Q	L, St	w	[20]
HERNANDIACEAE				
Gyrocarpus americanus Jacq.	Rockhampton, Q	B	s	[18]
	Palmer R, Q	L, B	s	[20]
Hernandia bivalvis Benth.	Ipswich, Q	L, B, W	s	[17]
	Pine Mt, Q	B	s	[20]
H. ovigera L.	Markham R, PNG	L, B	s	[19,20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
H. peltata Meissner	Tully, Q	L, B, F	s	[17]
	Mission Beach, Q	B	w	[20]
	Huon Gulf, PNG	L, B	s	[19]
Valvanthera albiflora C. White	Daintree R, Q	L	m	[18]
HIMANTANDRACEAE				
Galbulimima belgraveana (F. Muell.)	Tymne-Gurukor, PNG	L, B	s	[19]
Sprague (*G. baccata* Bailey)	Boonjie, Q	B	s	[17, 20]
	Danbullah, Q	L,	s	[18]
HYPERIACEAE				
Hypericum gramineum Forst. S.	Midlands, T	WP	w	[22]
ICACINACEAE				
Apodytes brachystylis F. Muell.	Malanda, Q	L, B	w	[18]
Gomphandra montana (Schellenb.) Sleum.	Tymne-Gurukor, PNG	L, F	w	[19]
G. papuana (Becc.) Sleum.	Butibum R, PNG	L	m	[19]
Hartleya inopinata Sleum.	Kaindi-Edie Ck, PNG	L, B	w	[19]
Medusanthera laxifolia (Miers) R.A. Howard	Markham R, PNG	L, B	w	[19]
Stemonurus ammui (Kan.) Sleum.	Huon Gulf, PNG	L	w	[19]
IRIDACEAE				
Gladiolus caryophyllaceus (Burm. f.) Poir.	WA	WP	w	[21]
G. cuspidatus Jacq.	WA	WP	w	[21]
Ixia meterlekampiae L. Bolus	WA	WP	w	[21]
Orthrosanthus laxus (Endl.) Benth.	WA	WP	w	[21]
Sisyrinchium micranthum Cav.	Stanthorpe, Q	WP	w	[17]
JUNCACEAE				
Juncus pallidus R. Br.	WA	WP	w	[21]
JUNCAGINACEAE				
Triglochin procera R. Br.	WA	WP	m	[21]
LAMIACEAE (LABIATAE)				
Ajuga australis R. Br.	Augathella, Q	WP	m	[20]
Hemiandra pungens R. Br.	WA	WP	s	[21]
Hemigenia divaricata C.A. Gardn.	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
H. macrantha F. Muell.	WA	WP	s	[21]
H. teretiuscula F. Muell.	WA	WP	s	[21]
Hyptis capitata Jacq.	Mission Beach, Q	L	w	[20]
Mentha satureioides R. Br.	Pittsworth, Q	WP	m	[17]
Microcorys exserta Benth.	WA	WP	m	[21]
Moschosma polystachyum (L.) Benth.	Nonda, Q	L, Fl, St	s	[18]
Ocimum sanctum L.	Rockhampton, Q	WP	m	[17]
Prostanthera baxteri A. Cunn. ex Benth.	WA	WP	s	[21]
P. baxteri var. *crassifolia* Benth.	WA	WP	s	[21]
P. euphrasioides Benth.	Miles, Q	L, St	m	[17]
P. leichhardtii Benth.	Dalby, Q	L	m	[20]
	Miles, Q	L	m	[17]
P. melissifolia F. Muell.	Toolangi, V	L, St	m	[20]
P. microphylla (R. Br.) A. Cunn.	WA	WP	w	[21]
P. nivea Cunn.	Stanthorpe, Q	L, St	m	[20]
	Stanthorpe, Q	WP	s	[17]
Prostanthera sp.	Dalby, Q	L, St	w	[17]
Salvia plebeia R. Br.	Mulgeldie, Q	L, St	s	[18]
S. reflexa Hornem.	Yarraman, Q	L, St	w	[20]
Teucrium argutum R. Br.	Mapleton, Q	L, Fl, St	w	[18]
T. fililobum F. Muell.	WA	WP	w	[21]
T. integrifolium Benth.	Maxwelton, Q	L, R, St	s	[18]
Westringia dampieri R. Br.	WA	WP	w	[21]
W. rigida R. Br.	WA	WP	w	[21]
LAURACEAE				
Actinodaphne nitida Teschn.	Yalu, PNG	L, B	m	[19,20]
Alseodaphne archboldiana (Allen) Kosterm.	Busu R, PNG	B	w	[19,20]
Beilschmiedia bancroftii (Bailey) C. White	Atherton, Q	F	s	[17]
	Cairns, Q	L	w	[18]
B. elliptica C. White & Francis	Toonumbar, NSW	B	s	20]
B. obtusifolia (?) (Meissner) F. Muell.	Brisbane, Q	B	m	[17]
B. podagrica Kosterm.	Omaura, PNG	L, B	s	[19,20]
Cassytha filiformis L.	Tambo, Q	WP	s	[20]
	Markham Valley, PNG	WP	m	[19]
C. glabella R. Br.	Frankston, V	L, St	w	[20]
C. melantha R. Br.	Dandenong-Frankston Road, V	WP	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
C. pubescens R. Br.	Clay Wells, SA	L, St	s	[20]
Cassytha sp.	Rockhampton, Q	St	m	[17]
Cassytha sp.	Ravenshoe, Q	St	m	[17]
Cinnamomum baileyanum (F. Muell. ex Bailey) Francis	Frazer I, Q	L, B	m	[20]
C. laubatii F. Muell.	Boonjie, Q	L, B	s	[20]
	Danbullah, Q	B	w	[17]
C. oliveri Bailey	Rockhampton, Q	L	w	[17]
	Macpherson Range, Q	L, B	w	[18]
C. virens R. Baker	Toonumbar, NSW	B	m	[20]
Cinnamomum sp.	Bakaia, PNG	L, B	m	[19]
Cryptocarya ainikini Kosterm.	Burep R, PNG	L, B	w	[20]
	Trans-Busu, PNG	L, B	m	[19]
C. alleniana C.T. White	Oomsis Ck, PNG	B	m	[19]
C. angulata C. White	Atherton, Q	L, B	s	[18]
C. archboldiana Allen	Wanatabi, PNG	B	w	[19]
C. australis (Hook.) Benth.	Brisbane, Q	L, B	s	[17]
Cryptocarya cf. *bernhardiensis* Allen	Oomsis Ck, PNG	L, B	m	[19]
C. bidwillii Meissner	Woodenbong, NSW	B	m	[20]
C. bowiei Druce	Bailey's Ck, Q	L	w	[20]
C. camptodroma Allen	Sogeri, PNG	L, B	w	[19]
C. cinnamomifolia Benth.	Rockhampton, Q	F	w	[17]
	Atherton, Q	B	s	[18]
	Kakoda Road, PNG	L, B	m	[19]
C. erythroxylon Maiden & Betche	Toonumbar, NSW	L	w	[20]
	Cunningham's Gap, Q	F	m	[17]
	Mt Mistake, Q	L, B	w	[18]
C. fluminensis Kosterm.	Port Moresby, PNG	B	w	[20]
	Laloki R, PNG	B	w	[19]
C. foveolata C. White & Francis	Mt Alford, Q	L, B	s	[20]
	Mt Mistake, Q	L, B	s	[18]
C. glaucescens R. Br.	Dorrigo, NSW	B	m	[20]
	Mt Glorious, Q	B	s	[17]
C. graebneriana Teschn.	Oomsis Ck, PNG	L, F	w	[19]
C. hypospodia F. Muell.	Atherton, Q	B	s	[18]
Cryptocarya sp. nov. aff. *hypsopodia* F. Muell.	Atherton, Q	B	s	[18]
C. iridescens Kosterm.	Busu R, PNG	L, B	w	[19]
C. laevigata Bl.	Butibum R, PNG	L, B	s	[19,20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
C. laevigata var. *bowiei* (Hoopk.) Kosterm.	Bailey's Ck, Q	L	s	[20]
C. mackinnoniana F. Muell.	Atherton, Q	B	m	[18]
Cryptocarya cf. *mackinnoniana* F. Muell.	Butibum R, PNG	B	w	[19]
C. meissneri F. Muell.	Whian Whian, NSW	L, B	s	[18]
C. microneura Meissner	Yarraman, Q	L, B	s	[17]
C. moretoniana Meissner	Brisbane, Q	L, B	s	[17]
C. multinervis Teschn.	Gurukor, PNG	L, B	m	[19,20]
C. multipaniculata Teschn.	Oomsis Ck, PNG	L, B	m	[19,20]
C. nothofagetorum Kosterm.	Kratke Range, PNG	L, B	m	[19]
C. novoguineensis Teschn.	Butibum R, PNG	L	w	[19]
C. obovata R. Br.	Mt Mistake, Q	L, B	s	[18]
C. pleurosperma C. White & Francis	Gadgarra, Q	L	w	[20]
	Boonjie, Q	L, B	s	[17]
C. rigida Meissner	Whian Whian, NSW	L, St	w	[20]
C. sulcata Allen	Wanatabi, PNG	L, B	w	[19]
C. triplinervis R. Br.	Upper Massey Ck, Q	B	s	[20]
	Imbil, Q	L, B	s	[17]
C. viridiflora Kosterm.	Oomsis Ck, PNG	B	w	[19]
C. xylophylla Kosterm.	Kaindi-Edie Ck, PNG	B	w	[19]
Cryptocarya sp. nov.	Mossman, Q	B	s	[18]
Cryptocarya sp.	Toonumbar, NSW	B	s	[18]
Cryptocarya sp.	Rockhampton, Q	L	w	[17]
Endiandra glauca R. Br.	Rockhampton, Q	L	w	[17]
E. introrsa C. White	Whian Whian, NSW	B	w	[20]
E. muelleri Meissner	Whian Whian, NSW	L	w	[20]
E. palmerstonii (Bailey) C. White & Francis	Boonjie, Q	B, S	w	[17]
E. pubens Meissner	Whian Whian, NSW	B	w	[20]
	Malanda, Q	L	w	[18]
E. sieberi Nees	Coolangatta, Q	B	w	[17]
E. tooram (?) Bailey	Mossman, Q	L	w	[18]
E. virens F. Muell.	Melbourne Botanic Gardens, V	L	w	[20]
	Brisbane, Q	L, B	s	[17]
Litsea bindoniana (F. Muell.) F. Muell.	Atherton, Q	B	s	[18]
L. dealbata (R. Br.) Steudel	Malanda, Q	B	s	[17]
L. dielsiana Teschn.	Oomsis Ck, PNG	L, B	w	[19]
L. domarensis O.C. Schmidt	Trans-Busu, PNG	B	m	[19]
L. engleriana Teschn.	Garaina, PNG	B	w	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
L. excudens Kosterm.	Marafunga, PNG	B	m	[19]
L. farruginea Bailey	Rockhampton, Q	B	m	[17]
L. fulvosericea Allen	Wanatabi, PNG	B	w	[19]
L. glutinosa (Lour.) C.E. Rob.	Garaina, PNG	L, B	m	[20]
	Cairns, Q	L, B	s	[18]
	Kauli Ck, PNG	L, B	s	[19]
Litsea sp. aff. *L. glutinosa* (Lour.) C.E. Rob.	Tymne-Gurukor, PNG	L, B	s	[19]
Litsea sp. aff. *L. habbemensis* Allen	Marafunga, PNG	B	s	[19]
L. ledermannii Teschn.	Garaina, PNG	L, B	w	[19]
L. leefeana (F. Muell.) Merr.	Boonjie, Q	L, B	m	[20]
	Atherton, Q	L, B	s	[18]
L. mafuluensis Allen	Bakaia, PNG	B	m	[19]
L. novoguineensis Teschn.	Tymne-Gurukor,PNG	B	m	[19]
L. reticulata (Meissn.) F. Muell.	Toonumbar, NSW	L	m	[20]
	Mt Glorious, Q	B	s	[17]
	Mt Mistake, Q	B	s	[18]
L. timoriana Span.	Butibum R, PNG	L, B	m	[19,20]
Litsea sp. aff. *glutinosa* (Lour.) C.E. Rob.	Morobe, PNG	L, B	s	[20]
Litsea sp.	Burleigh, Q	L, B, W	s	[17]
Litsea sp.	Akuna, PNG	B	s	[19]
Neolitsea australiensis Kosterm.	Toonumbar, NSW	L	s	[20]
N. dealbata (R. Br.) Merr.	Toonumbar, NSW	L	s	[20]
N. pubescens (Teschn.) Merr.	Marafunga, PNG	L, B	m	[19]
N. zeylanica (Nees & T. Nees) Merr.	Mt Mistake, Q	L, B, F	s	[18]
Phoebe forbesii Gamble	Oomsis Ck, PNG	L, B	s	[19,20]
LILIACEAE				
Agrostocrinum scabrum (R. Br.) Baill.	WA	WP	w	[21]
Anthericum divaricatum Jacq.	WA	WP	w	[21]
Arthropodium milleflorum (DC.) J.K. Macbr.	Epping Forest, T	L, Fl, St	s	[22]
Asparagus plumosus Baker	Rockhampton, Q	L, R	s	[18]
Borya septentrionalis F. Muell.	Walsh's Pyramid, Q	WP	w	[20]
Bulbine semibarbata (R. Br.) Haw.	Bollon, Q	R	s	[18]
Burchardia umbellata R. Br.	WA	WP	w	[21]
	Epping Forest, T	L, Fl, St	s	[22]
Corynotheca micrantha (Lindl.) Macbride	WA	WP	m	[21]
Crinum brisbanicum Bailey	Slack's Creek, Q	WP	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
C. macrantherum Engl.	Huon Gulf, PNG	L, St	w	[20]
Dianella caerulea Sims	Gordonvale, Q	R	s	[17]
	Rockhampton, Q	F	s	[18]
Iphigenia indica (L.) Kunth.	Brisbane, Q	WP	s	[17]
Johnsonia lupulina R. Br.	WA	WP	w	[21]
Kuntheria pedunculata (F. Muell.) Conran & Cliff.	Boonjie, Q	WP	s	[20]
Schelhammera multiflora R. Br.	Bamaga, Q	L, St	m	[20]
Sowerbaea laxiflora Lindl.	WA	WP	m	[21]
Stypandra glauca R. Br	Stanthorpe, Q	L, R, St	s	[17,20]
S. imbricata R. Br.	WA	WP	w	[21]
Thelionema grande (C. White) R. Henderson	Stanthorpe, Q	L, R, St	w	[20]
Thysanotus multiflorus R. Br.	WA	WP	w	[21]
T. patersonii R. Br.	WA	WP	w	[21]
T. tenellus Endl.	WA	WP	m	[21]
T. triandrus (Labill.) R. Br.	WA	WP	w	[21]
Thysanotus sp. 2221A	WA	WP	w	[21]
Tricoryne elatior R. Br.	WA	WP	m	[21]
Tripladenia cunninghamii D. Don	Whian Whian, NSW	WP	s	[20]
T. multiflora (R. Br.) Reichb.	Mt Lindesay, Q	WP	s	[17]
	Draper's Crossing, Q	L, R, St	s	[18]
Wurmbea dioica ssp. *dioica* (R. Br.) F. Muell.	Rosny Hills, T	L, Fl, St	s	[22]
W. uniflora (R. Br.) T. Macfarlane	Deloraine, T	L, Fl, St	s	[22]
LINACEAE				
Durandea jenkinsii Stapf.	Bamaga, Q	L	w	[20]
LOGANIACEAE				
Buddleja madagascariensis Lam.	Brisbane, Q	L	m	[18]
Fagraea cambagei Domin	Innisfail, Q	L	w	[17]
	Mossman, Q	L	w	[18]
F. muelleri Benth.	Mt Spurgeon, Q	F	m	[17]
	Danbulla, Q	L, B	s	[18]
	Gadgarra, Q	L, B, St	w	[20]
Geniostoma australianum F. Muell.	Cairns, Q	L	s	[18]
Logania albiflora (Andr.) Druce	Whian Whian, NSW	L, St	w	[20]
L. fasciculata R. Br.	WA	WP	w	[21]
L. floribunda R. Br.	Springbrook, Q	L, B, St	m	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
L. ovata R. Br.	WA	WP	w	[21]
Logania sp. aff. *pusilla* R. Br.	Redcliffe, Q	L, St	w	[18]
Mitrasacme alsinoides R. Br.	Waterford, Q	WP	m	[20]
Neuburgia corynocarpa (A. Gray) Leenh.	Kratke Range, PNG	L	m	[19]
	Burep R, PNG	L	w	[20]
Strychnos arborea A.W. Hill	Yarraman, Q	L, B, St	s	[17]
S. axillaris Colebr.	Trans-Busu, PNG	B	w	[19]
S. bancroftiana Bailey	Cairns, Q	L, S	s	[17]
	McIlwraith Range, Q	L	s	[20]
S. ledermannii Gilg & Bened.	Kauli Ck, PNG	L	m	[19]
S. lucida R. Br.	Chillagoe, Q	L, B, S	s	[17]
	Upper Massey Ck, Q	B	s	[20]
S. psilosperma F. Muell.	Biloela, Q	L, F, St	s	[20]
	Rockhampton, Q	L, B, S	s	[17]
LORANTHACEAE				
Loranthus quandang Lindley	Wandoan, Q	L	s	[17]
Loranthus sp.	Macpherson Range, Q	B	w	[18]
Loranthus sp.	Macpherson Range, Q	St	w	[18]
Loranthus sp.	Wandoan, Q	L	m	[18]
Notothixos subaureus Oliver	Brisbane, Q	L	s	[17]
Viscum angulatum DC.	Chillagoe, Q	L, St	w	[17]
LYCOPODIACEAE				
Phyloglossum drummondii Kunze	Melbourne, V	WP	w	[20]
Lycopodium cernuum L.	Kaindi-Edie Ck, PNG	WP	w	[19]
L. clavatum L.	Mt Sarawaket, PNG	WP	m	[19]
L. complanatum L.	Kaindi-Edie Ck, PNG	WP	w	[19]
L. deuterodensum Herter R.	Pirates Rd, T	L, St	m	[22]
L. ledermannii Hier.	Busu R, PNG	WP	m	[19]
L. nummularifolium Bl.	Garaina, PNG	WP	w	[19]
L. phlegmaria L.	Wanatabi, PNG	WP	w	[19]
L. phlegmarioides Gaud.	Bakaia, PNG	WP	w	[19]
L. pritzelii Hert.	Mt Dickson, PNG	WP	w	[19]
L. scariosum Forst.	Mt Sarawaket, PNG	WP	w	[19]
L. varium R. Br.	Norfolk Ck, T	L, St	s	[22]
L. volubile Forst.	Kaindi-Edie Ck, PNG	L, St	w	[19]
Lycopodium sp.	Marafunga, PNG	WP	m	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
LYTHRACEAE				
Ammannia auriculata Willd.	Townsville, Q	L, F, St	w	[18]
A. pentandra Roxb.	Charters Towers, Q	WP	w	[17]
Lythrum hyssopifolium L.	Kooweerup, V	L	s	[20]
L. salicaria L.	Woori Yalloch, V	St	w	[20]
Nesaea salicifolia Kunth.	North Pine R, Q	L	m	[18]
MAGNOLIACEAE				
Elmerrillia papuana (Schltr.) Dandy	Musgrave R, PNG	L, B	m	[19]
E. papuana (Schltr.) Dandy var. *glauberima* Dandy	Butibum R, PNG	L, B	m	[19,20]
MALPIGHIACEAE				
Banisteria chrysophylla Lam.	Brisbane, Q	L	s	[17]
MALVACEAE				
Abuliton cryptopetalum F. Muell. ex Benth.	WA	WP	w	[21]
A. malvifolium (Benth.) J. Black	Nonda, Q	L, St	s	[18]
A. otocarpum F. Muell.	WA	WP	w	[21]
Hibiscus diversifolius Jacq.	Mt Coot-tha, Q	L, St	s	[18]
H. farragei F. Muell.	WA	WP	w	[21]
H. radiatus Cav.	Kuranda, Q	R	s	[18]
H. sturtii Hook.	Miles, Q	St	s	[17]
Lavatera plebeia Sims.	WA	WP	w	[21]
Malva parviflora L.	WA	WP	w	[21]
Malvastrum coromandelianum (L.) Garcke	Beenleigh, Q	L, St	w	[20]
M. spicatum (L.) A. Gray	Chinchilla, Q	WP	m	[17]
	Springsure West, Q	L, St	w	[20]
M. tricuspidatum (W.T. Aiton) A. Gray	Q	L, S, St	w	[17]
Selenothamnus sp. 2531	WA	WP	w	[21]
Sida acuta Burman f.	Maxwelton, Q	L, R, St	s	[18]
S. atherophora Domin	Augathella, Q	L, St	s	[20]
S. cordifolia L.	Mackay, Q	WP	s	[18]
	Springsure, Q	L, St	s	[20]
S. corrugata Lindley	Dalby, Q	WP	w	[17]
S. fibulifera Lindley	Nonda, Q	L, Fl, St	s	[18]
S. rhombifolia L. var. *incana* Benth.	WA	WP	w	[21]
S. spinosa L.	Nonda, Q	WP	s	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
S. subspicata Benth.	Q	L, S, St	w	[17]
Thespesia populnea (L.) Sol. ex Corr.	Mission Beach, Q	L	w	[20]
Urena lobata L.	Mackay, Q	WP	s	[18]
MARSILEACEAE				
Marsilea brownii A. Br.	Waterford, Q	L, St	m	[20]
MELIACEAE				
Aglaia cf. *caroli* Harms	Kauli Ck, PNG	L	w	[19]
A. sapindina (F. Muell.) Harms	Malanda, Q	L	w	[18]
Aglaia sp. aff. *A. carrii* Harms	Busu R, PNG	L	w	[19]
Aglaia sp.	Yalu, PNG	L	w	[19,20]
Amoora nitidula Benth.	Mt Glorious, Q	L	w	[17]
[*Pseudocarapa nitidula* (Benth.) Merr. & Perry]	Imbil, Q	L	w	[18]
	Red Scrub, NSW	L	w	[20]
Dysoxylum decandrum (Blanco) Merr. [*D. gaudichaudianum* (Andr. Juss.) Miq.]	Mossman, Q	L, F, B	s	[17,20]
D. fraserianum (Adr. Juss.) Benth.	Cunningham's Gap, Q	L, F, B	w	[17,18]
D. muelleri Benth.	Mossman, Q	B	w	[18]
D. pettigrewianum Bailey	Atherton, Q	B	w	[17]
D. rufum (A. Rich.) Benth.	Toonumbar, NSW	L	w	[20]
Dysoxylum sp. aff. *klanderi* F. Muell.	Bloomfield, Q	L	w	[20]
Melia dubia Cav.	Brisbane, Q	L, F, St	s	[17]
	Whian Whian, NSW	S	w	[20]
Owenia venosa F. Muell.	Wandoan, Q	L	s	[17]
Pseudocarapa papuana Merr. & Perry	Garaina, PNG	L	w	[19]
Synoum muelleri C. DC.	Ravenshoe, Q	B	w	[17]
Xylocarpus granatum König	Mowbray R, Q	L	w	[18]
MENISPERMACEAE				
Arcangelisia cf. *tympanopoda* (Laut. & K. Schum.) Diels	Trans-Busu, PNG	L	w	[19]
Carronia multisepalea F. Muell.	Springbrook, Q	L, St	m	[18]
	Whian Whian, NSW	L	m	[20]
C. protensa (F. Muell.) Diels	Boonjie, Q	L, St	w	[20]
Cocculus triloba DC.	Brisbane, Q	L	w	[20]
Hypserpa decumbens (Benth.) Diels	Boonjie, Q	L	s	[18]
	Bamaga, Q	L, R	s	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
H. laurina (F. Muell.) Diels	Cairns, Q	L, B	s	[17,18]
Legnephora moorei (F. Muell.) Miers	Rockhampton, Q	B, L	s	[17]
	Whian Whian, NSW	WP	s	[20]
Pachygone pubescens Benth.	Bamaga, Q	WP	s	[20]
Pleogyne cunninghamii Miers	Brisbane, Q	L, F, B	s	[17,18]
	Beenleigh, Q	WP	s	[20]
Pycnarrhena australiana F. Muell.	Massey Ck, Q	L, F, B	s	[20]
P. ozantha Diels	Omaura, PNG	L, B	s	[19,20]
Sarcopetalum harveyanum F. Muell.	Brisbane, Q	L	s	[17]
	Gosford, NSW	L, R	s	[18]
	Whian Whian, NSW	WP	s	[20]
Stephania aculeata Bailey	Whian Whian, NSW	R	s	[18]
	Tweed R, Q	WP	m	[20]
S. hernandiifolia (Willd.) Walp. [*S. japonica* (Thb.) Miers var. *discolor* (Miq.) Forman]	Brisbane, Q	R	s	[17]
	Kauli Ck, PNG	WP	s	[19]
	Pottsville, NSW	WP	s	[20]
S. japonica Miers var. *timorensis* (DC.) Forman	McIlwraith Range, Q	R	s	[20]
Tinospora smilacina Benth.	Chillagoe, Q	L, B, St	s	[17]
T. tinosporoides (F. Muell.) Forman [*Fawsettia tinosporoides* F. Muell.]	Whian Whian, NSW	WP	s	[18,20]
MIMOSACEAE				
Acacia accola Maiden ex Betch	Montrose, V	L	s	[20]
A. acinacea Lindley	Castlemaine, V	L, St	w	[20]
A. acuminata Benth.	Geelong, V	L	s	[20]
	WA	WP	m	[21]
A. adunca Cunn. ex Don	Stanthorpe, Q	L, St	s	[20]
A. amblygona Cunn.	Springsure, Q	L, St	w	[20]
A. aneura F. Muell. ex Benth.	Charleville, Q	W	w	[18]
	Mt Eba, SA	L	w	[20]
A. angusta Maiden & Blakely	Springsure, Q	L, St	m	[20]
A. arabica (Lam.) Willd.	Rockhampton, Q	B, F	s	[17]
A. argentea Maiden	Marlborough, Q	L, St	s	[20]
A. aulacocarpa Benth.	Brisbane, Q	L	w	[17]
A. axillaris Benth.	Royal George, T	B	m	[22]
A. baileyana F. Muell.	Mitcham, V	L, St	w	[20]
A. bakeri Maiden	Whian Whian, NSW	L, St	s	[20]
A. beauverdiana A.J. Ewart ex Sharman	Montrose, V	L, St	m	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
A. burkittii F. Muell. ex Benth.	WA	WP	s	[21]
A. cedroides Benth. ex Schlecht.	WA	WP	w	[21]
A. complanata Cunn. ex Benth.	Pine Mt, Q	L, St	s	[20]
A. conferta Benth.	Miles, Q	L	w	[17]
A. cowleana Tate	Barrow Ck, NT	L	m	[20]
A. cunninghamii Hook.	Miles, Q	L	s	[17]
A. dealbata Cunn.	Miles, Q	L	w	[17]
	Royal George, T	L, St	w	[22]
A. deanei (R. Baker) Welch, Coombs A. McGlynn	Roma, Q	L, St	w	[20]
A. decora Reichb.	Miles, Q	L	m	[17]
A. decurrens Willd.	Warwick, Q	L	w	[17]
A. doratoxylon Cunn.	Coccaparra Range, NSW	L, St	m	[20]
A. estrophiolata F. Muell.	Montrose, V	L	w	[20]
A. excelsa Benth.	Tambo, Q	L, St	m	[20]
A. excelsa (?) Benth.	Chinchilla, Q	L	w	[17]
A. farnesiana Willd.	WA	WP	m	[21]
A. filifolia Benth. var. *pedunculata* C.A. Gardn.	WA	WP	w	[21]
A. fimbriata G. Don	Brisbane, Q	L, B	s	[17]
	Montrose, V	L	s	[20]
A. flexifolia Cunn. ex Benth.	Montrose, V	L	m	[20]
A. floribunda (Vent.) Willd.	Melbourne, V	L	w	[20]
A. fragilis Maiden et Blakely	WA	WP	w	[21]
A. gilbertii Meissner	Montrose, V	L	s	[20]
A. gonophylla Benth.	Montrose, V	L	w	[20]
A. harpophylla Benth.	Chinchilla, Q	L, B	s	[17]
	Coppermine Ck, Q	L, B	s	[20]
A. holosericea Cunn. ex Don	Lotus Ck, Q	L, B, St	s	[20]
A. implexa Benth.	Warwick, Q	L, F	s	[17]
	Legume, NSW	L	w	[20]
A. ixiophylla Jacques	Miles, Q	L	s	[17]
A. juncifolia Benth.	Carnarvon Range, Q	L	m	[20]
A. juniperina (Vent.) Willd.	Stanthorpe, Q	L, St	s	[17]
A. kettlewelliae Maiden	Creswick, V	L, St	s	[20]
A. kybeanensis Maiden ex Blakely	Montrose, V	L	w	[20]
A. latipes Benth.	Montrose, V	L	w	[20]
A. leichhardtii Benth.	Carnarvon, Q	L, St	m	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
A. leiocalyx (Domin) Pedley	Morven, Q	L, St	w	[20]
A. leiophylla Benth.	Rendlesham, SA	L	m	[20]
A. leptocarpa Cunn. ex Benth.	Bamaga, Q	L	m	[20]
A. aff. *leptoneura* Benth.	WA	WP	w	[21]
A. linearis Sims	Montrose, V	L	m	[20]
A. lineolata Benth.	WA	WP	w	[21]
A. longifolia (Andrews) Willd.	Mitcham, V	L, St	s	[20]
A. longissima H. Wendl.	Springbrook, Q	L, B	s	[20]
A. lunata Lodd.	Miles, Q	L	s	[17]
A. maidenii F. Muell.	Tamborine, Q	L, B	s	[17]
	Kyogle, NSW	B	s	[20]
A. maitlandii F. Muell.	Ayer's Rock, NT	L	w	[20]
A. mangium Willd.	Mission Beach, Q	L, B	w	[20]
A. melanoxylon R. Br.	Woodenbong, Q	L	s	[18]
	Healsville, V	L	s	[20]
A. mucronata Willd. ex H. Wendl.	Queenstown, T	L, B, R	s	[22]
A. mucronata Willd. var. *dependens*	Orford, T	L	w	[22]
A. mucronata Willd. var. *dissitiflora*	Healsville, V	L	m	[20]
	Orford, T	L, R	s	[22]
A. myrtifolia (Smith) Willd.	Whian Whian, NSW	L, St	m	[20]
A neriifolia Benth.	Dalby, Q	L	s	[17]
	Stanthorpe, Q	L, B	s	[20]
A. nervosa DC.	Montrose, V	L	s	[20]
A. obtusifolia Cunn.	Springbrook, Q	B	s	[20]
A. oxycedrus Sieber ex DC.	Powelltown, V	L, St	s	[20]
A. paradoxa DC.	Mitcham, V	L, St	m	[20]
A. pendula G. Don	Condamine, Q	L, B	s	[17]
	Rolleston, Q	L	s	[20]
A. penninervis DC.	Dalby, Q	L, B	s	[17]
A. podalyriifolia G. Don	Brisbane, Q	L, B	s	[17]
	Ipswich, Q	L, B, St	s	[20]
A. polystachya Cunn. ex Benth.	Massey Ck, Q	L, B	s	[20]
A. rhodoxylon Maiden	Sarina, Q	L, St	w	[20]
A. riceana Henslow	Swansea, T	R	w	[22]
A. salicina Lindley	Pittsworth, Q	L	w	[17]
A. salicina var. *varians* (Benth.) Benth.	Miles, Q	L	w	[17]
A. semilunata Maiden ex Blakely	Montrose, V	L	m	[20]
A. shirleyi Maiden	Springsure, Q	L	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
A. shirleyi (?) Maiden	Wandoan, Q	L	s	[17]
A. simsii Cunn. ex Benth.	Shute Bay, Q	L	m	[20]
A. sophorae (Labill.) R. Br.	Q	L	s	[20]
A. spectabilis Benth.	Miles, Q	L, B	s	[17]
	Roma, Q	L, St	w	[20]
A. stenoptera Benth.	Montrose, V	L	m	[20]
A. subcaerulea Lindl.	WA	WP	m	[21]
A. sutherlandii (F. Muell.) F. Muell.	Nonda, Q	L, St	s	[18]
A. torulosa Benth.	Coen, Q	L	m	[20]
A. triptera Benth.	Miles, Q	L, St	m	[17]
A. umbellata Cunn. ex Benth.	Shute Bay, Q	L	m	[20]
A. undulifolia G. Don	Warwick, Q	L	w	[17]
A. urophylla Benth. ex Lindley	Montrose, V	L	w	[20]
	WA	WP	s	[21]
A. verniciflua Cunn.	Montrose, V	L	w	[20]
A. verticillata (L'Hér.) Willd.	Portland, V	L, St	m	[20]
A. vestita Ker.	Montrose, V	L	s	[20]
A. viscidula Benth.	Stanthorpe, Q	L, St	s	[17]
	Ma Ma Ck Road, Q	L, St	w	[20]
A. xiphophylla E. Pritzel	WA	WP	m	[21]
Adenanthera pavonina L.	Solomon Is.	S	s	[18]
Albizia canescens Benth.	Charters Towers, Q	L, S, St	s	[18]
	Shute Bay, Q	L, St	w	[20]
Archidendron grandiflorum (Soland. ex Benth.) Nielsen	Whian Whian, NSW	L, St	w	[20]
A. lucyi (?) F. Muell.	Malanda, Q	B	s	[17]
A. vaillantii F. Muell.	Kirrama, Q	B	m	[18]
	Mission Beach, Q	B	w	[20]
Mimosa pudica L.	Mackay, Q	L, St, R	s	[18]
Pithecellobium grandiflorum Benth.	Tamborine, Q	L, B	s	[17]
	Imbil, Q	B	w	[18]
P. hendersonii (Benth.) Benth.	Coolangatta, Q	L	s	[17]
P. lucyi F. Muell.	Musgrave R, PNG	L	w	[19]
P. pruinosum (Benth.) Benth.	Rockhampton, Q	L, S	w	[17]
	Cedar Ck, Q	L	w	[18]
P. saman Benth.	Mossman, Q	B	s	[17]
Prosopis juliflora DC.	WA	WP	s	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Samanea saman Merr.	Sth Johnstone, Q	L, B	s	[20]
Schleinitzia novoguineensis (Warb.) Verdcourt [*Piptadenia novoguineensis* Warb.]	Markham R, PNG	L, B	w	[19,20]
MONIMIACEAE				
Atherosperma moschatum Labill.	Barrington Tops, NSW	L	s	[18]
	Melbourne, V	B	s	[20]
	Hartz Mts, T	L, St	s	[22]
Daphnandra dielsii Perkins	Malanda, Q	L, B, W	s	[17]
	Atherton, Q	B	s	[20]
D. micrantha (Tul.) Benth.	Brisbane, Q	B, W	s	[17]
	Brookfield, Q	W	s	[18]
	Boonjie, Q	B	s	[20]
D. repandula (F. Muell.) F. Muell.	Cairns, Q	L, B	s	[18]
	Boonjie, Q	B	w	[20]
D. tenuipes Perkins	Whian Whian, NSW	L, B	s	[18,20]
Doryphora aromatica (Bailey) L.S. Smith [*Daphnandra aromatica* Bailey]	Boonjie, Q	B	s	[17]
	Bailey's Ck, Q	L, B	s	[20]
D. sassafras Endl.	Macpherson Range, Q	L, B	s	[18]
	Acacia Plateau, NSW	B	s	[20]
Dryadodaphne pternadrica Schodde (ined.)	Kaindi-Edie Ck, PNG	L, B	s	[19]
D. novoguineensis (Perk.) A.C. Sm.	Wanatabi, PNG	L, B	s	[19]
Hedycarya angustifolia Cunn.	King I, T	L, St	w	[22]
H. loxocarya (Benth.) Francis	Atherton, Q	L	s	[18]
Kibara cf. *inamoena* Perk.	Bulolo R Gorge, PNG	B	w	[19]
K. macrophylla (R. Cunn.) Benth.	Mt Glorious, Q	L, St	m	[17]
Levieria acuminata (F. Muell.) Perkins	Mt Spec, Q	L	w	[18]
	Mareeba, Q	L, St	m	[20]
L. forbesii Perk.	Marafunga, PNG	L, B	m	[19]
L. montana Becc. [*L. schlecteri* Perk.]	Kauli Ck, PNG	B	w	[19,20]
L. cf. *schlecteri* Perk.	Kaindi-Edie Ck, PNG	B	w	[19]
Palmeria arfakiana Becc.	Kaindi-Edie Ck, PNG	L, B	m	[19]
	Wau, PNG	L, B	m	[20]
P. gracilis Perk.	Omaura, PNG	B	s	[19,20]
P. scandens F. Muell.	Macpherson Range, Q	L	m	[18]
Steganthera fengeriana Perk.	Butibum R, PNG	B	w	[19]
S. ilicifolia A.C. Sm.	Marafunga, PNG	B	w	[19]
Steganthera sp. aff. *insculpta* Perk.	Bakaia, PNG	L, B	w	[19]
S. riparia Kan. & Hat.	Akuna, PNG	L	w	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
S. schumanniana Perk.	Kratke Range, PNG	L	w	[19]
Steganthera sp.	Kauli Ck, PNG	WP	w	[19]
Tetrasynandra laxiflora (Benth.) Perkins	Atherton, Q	B	w	[18]
T. pubescens (Benth.) Perkins	Cairns, Q	B	s	[18]
Wilkiea hugeliana (Tul.) A. DC.	Macpherson Range, Q	L, B	s	[18]
W. macrophylla (R. Cunn.) A. DC.	Brisbane, Q	L, B	s	[18]
Wilkiea sp.	Danbulla, Q	L	s	[18]
Wilkiea sp. (?)	Big Tableland, Q	L	w	[18]
MORACEAE				
Cudrania cochinchinensis Lour.	Palen Ck, Q	B	w	[20]
[*C. javanensis* Trécul]	Atherton, Q	L, B	s	[18]
Ficus casearia (?) Benth.	El Arish, Q	B, L	s	[17]
F. congesta Roxb.	Daintree, Q	L, B	w	[20]
F. cf. *congesta* Roxb.	Busu R, PNG	L	w	[19]
F. insculpta Summerhayes	Zenag, PNG	B	w	[19,20]
F. pantoniana King	Crooked Ck, PNG	L	w	[19,20]
F. scandens var. *australis* Bailey	Dinner Ck, Q	L, St	s	[20]
F. septica Burm. f.	Laloki R, PNG	L, B	m	[19]
	El Arish, Q	L, B	s	[20]
F. sterrocarpa Diels	Omaura, PNG	B	m	[19,20]
F. subcongesta Corner	Umboi I, PNG	L	m	[19,20]
F. tinctoria Forst.	Musgrave R, PNG	L	w	[19]
F. virens Ait.	Garaina, PNG	L	m	[19]
Ficus sp.	Chillagoe, Q	B	w	[17]
Ficus sp.	Imbil, Q	B	s	[18]
Ficus sp.	Tully, Q	B	w	[18]
Pseudomorus brunoniana (Endl.) Bureau	Brisbane, Q	L, B	m	[17]
[*Streblus brunonianus* (Endl.) F. Muell.]	Palen Ck, Q	B	m	[20]
P. brunoniana (?)	Malanda, Q	L, B	s	[17]
MYOPORACEAE				
Eremophila alternifolia R. Br.	WA	WP	m	[21]
E. bignoniiflora (Benth.) F. Muell.	Glengalla, Q	L, St	s	[18]
E. clarkei F. Muell.	WA	WP	w	[21]
E. compacta S. Moore	WA	WP	w	[21]
E. cuneifolia F. Muell.	WA	WP	m	[21]
E. dempsteri F. Muell.	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
E. drummondii F. Muell.	WA	WP	m	[21]
E. duttonii F. Muell. var. *parvifolia* C.A. Gardn.	WA	WP	m	[21]
E. foliossima Kraenzl.	WA	WP	m	[21]
E. fraseri F. Muell.	WA	WP	s	[21]
E. gilesii F. Muell.	Coober Pedy, SA	L	w	[20]
E. glabra (R. Br.) Ostf.	WA	WP	w	[21]
E. granitica S. Moore	WA	WP	w	[21]
E. lachnocalyx C.A. Gardn.	WA	WP	w	[21]
E. latrobei F. Muell.	Coober Pedy, SA	L	w	[20]
	WA	WP	m	[21]
E. leucophylla Benth.	WA	WP	m	[21]
E. longifolia (R. Br.) F. Muell.	Jandowae, Q	L	w	[18]
	Springsure, Q	L, St	m	[20]
	WA	WP	m	[21]
E. mackinlayi F. Muell.	WA	WP	w	[21]
E. maculata (Kerr Gawler) F. Muell.	Nonda, Q	L, Fl, St	s	[18]
	WA	WP	m	[21]
E. margarethae S. Moore	WA	WP	m	[21]
E. mitchellii Benth	Miles, Q	L	m	[17]
	Moura, Q	L, St	w	[20]
E. oldfieldii F. Muell.	WA	WP	m	[21]
E. pachyphylla Diels	WA	WP	w	[21]
E. pantonii F. Muell.	WA	WP	w	[21]
E. saligna S. Moore	WA	WP	w	[21]
E. scoparia F. Muell.	WA	WP	w	[21]
E. spathulata W.V. Fitzg.	WA	WP	w	[21]
E. weldii F. Muell.	WA	WP	w	[21]
Eremophila sp. 2391	WA	WP	m	[21]
Eremophila sp. 2452	WA	WP	w	[21]
Myoporum acuminatum R. Br.	Chinchilla, Q	L	s	[17]
	WA	WP	m	[21]
M. desertii Benth.	Jandowae, Q	L, F, St	w	[18]
	WA	WP	m	[21]
M. diffusum R. Br. [*M. debole* R. Br.]	Rockhampton, Q	L, St	m	[18,20]
M. insulare R. Br.	Rendlesham, SA	L, St	m	[20]
	WA	WP	m	[21]
M . platycarpum R. Br.	WA	WP	w	[21]
M. serratum R. Br.	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
MYRISTICACEAE				
Gymnacranthera paniculata (A. DC.) Warb. var. *zippeliana* (Miq.) J. Sinclair	Oomsis Ck, PNG	L, B	s	[19,20]
MYRSINACEAE				
Embelia australiana (F. Muell.) Mez.	Whian Whian, NSW	L	m	[20]
Rapanea variabilis vel. aff.	Mt Edith, Q	L, St	w	[18]
MYRTACEAE				
Acmena cf. *dielsii* Merr. & Perry	Butibum R, PNG	B	w	[19]
Agonis abnormis C. White & Francis	Stanthorpe, Q	L, St	w	[17]
Angophora costata (Gaertner) J. Britten	Slack's Ck, Q	L	m	[20]
Backhousia angustifolia F. Muell.	Moura, Q	B	w	[20]
B. citriodora F. Muell.	Dayboro, Q	L	m	[18]
Calytrix tetragona Labill.	Stanthorpe, Q	L, St	w	[20]
Eugenia cormiflora F. Muell.	Atherton, Q	L	w	[18]
E. ventenatii Benth.	Brisbane, Q	L, St	w	[18]
Leptospermum flavescens Smith	Miles, Q	L	m	[17]
Melaleuca bracteata F. Muell.	Warwick, Q	L	s	[17]
M. nodosa (Gaertner) Smith	Warwick, Q	L, St	w	[17]
M. uncinata R. Br.	Dalby, Q	L	m	[17]
Myrtus dulcis C. White	Noosa Heads, Q	L	w	[18]
Rhodamnia sp.	Rouna, PNG	L, B	w	[19]
Rhodomyrtus psidiodes (G. Don) Benth.	Macpherson Range, Q	B	w	[18]
Syzygium crebrinerve (C. White) L. Johnson	Acacia Plateau, Q	B	w	[20]
Syzygium sp.	Kauli Ck, PNG	L	w	[19]
Thryptomene tuberculata E. Pritzel	WA	WP	w	[21]
Thryptomene sp.	Dalby, Q	L	m	[17]
Verticordia chrysantha Endl.	WA	WP	w	[21]
Xanthostemon chrysanthus (F. Muell.) F. Muell. ex Benth.	Babinda, Q	L	w	[20]
NYCTAGINACEAE				
Boerhaavia diffusa L.	WA	WP	m	[21]
B. repandra Willd.	WA	WP	m	[21]
Bougainvillea glabra Choisy	WA	WP	s	[21]
Nelumbo nucifera Gaertner	Cooktown, Q	L	s	[18]
Pisonia umbellifera (Forster & G. Forster) Seeman	Clump Point, Q	L	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
OCHNACEAE				
Schuurmansia henningsii K. Schum.	Kakoda Road, PNG	L	m	[19]
OLACACEAE				
Anacolosa papuana Schellenb.	Akuna, PNG	B	w	[19]
OLEACEAE				
Jasminum didymum Forst.	Bamaga, Q	L	s	[20]
J. didymum subsp. *lineare* (R. Br.) P.S. Green	Clark Ck, Q	L, St	m	[20]
J. domatiigerum Lingelsh.	Marafunga, PNG	L, St	m	[19]
J. papuasicum Lingelsh.	Markham Valley, PNG	L, F	w	[19]
J. racemosum F. Muell.	Wandoan, Q	L, B, R	s	[17]
J. schumannii Lingelsh.	Trans-Busu, PNG	L	m	[19]
J. simplicifolium G. Forster	Rockhampton, Q	L	s	[17,18]
J. simplicifolium subsp. *australiense* P.S. Green	Carnarvon Range, Q	L, St	w	[20]
J. singuliflorum Bailey & F. Muell.	Toonumbar, NSW	L, R	w	[20]
J. suavissimum Lindley	Toowoomba, Q	WP	m	[17]
	Stanthorpe, Q	WP	w	[20]
Jasminum sp.	Atherton, Q	B	m	[17]
Ligustrum novoguineense Lingelsh.	Crooked Ck, PNG	B	w	[19]
Ligustrum sp.	Brisbane, Q	L, B	m	[17]
Linociera axillaris (R. Br.) Knobl.	Atherton, Q	B	w	[18]
[*Chionanthus axillaris* R. Br.]	Davies Ck, Q	L, B	s	[20]
L. cf. *gigas* Lingelsh.	Trans-Busu, PNG	B	w	[19]
L. ramiflora (Roxb.) DC.	Innisfail, Q	L	w	[17]
	Cairns, Q	L, B	w	[18]
	Trans-Busu, PNG	L, B	w	[19]
L. cf. *sessiliflora* Hemsl.	Kauli Ck, PNG	L	w	[19]
Linociera sp.	Brisbane, Q	L	s	[17]
Notelaea ligustrina Vent.	Melbourne, V	L	m	[20]
	Kingston, T	B	w	[22]
N. longifolia Vent.	Brisbane, Q	L, St	s	[18]
	Unumgar, NSW	L	s	[20]
N. microcarpa R. Br.	Miles, Q	L	m	[17]
	Morven, Q	L, St	s	[20]
N. ovata R. Br.	Q	L, St	w	[18]
Olea europaea L. subsp. *europaea*	Eudunda, SA	L, F, St	s	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
O. paniculata R. Br.	Mt Glorious, Q	B	s	[17]
	Mt Mistake, Q	L, B	m	[18]
	Omaura, PNG	L	m	[19]
ONAGRACEAE				
Jussiaea repens L.	Chinchilla, Q	L, St	w	[17]
J. suffruticosa L.	Moura, Q	WP	w	[20]
OPILIACEAE				
Opilia amentacea Roxb.	Bamaga, Q	L, B	w	[20]
ORCHIDACEAE				
Acianthus caudatus R. Br.	NSW-Q	WP	w	[24]
A. fornicatus R. Br.	NSW-Q	WP	m	[24]
Acriopsis javanica var. *nelsoniana* (Bailey) J.J. Smith	NSW-Q	WP	w	[24]
Anoectochilus yatesae Bailey	NSW-Q	WP	w	[24]
Bulbophyllum bracteatum Bailey	NSW-Q	WP	s	[24]
B. elisae (F. Muell.) Benth.	NSW-Q	WP	w	[24]
B. largeniforme Bailey	NSW-Q	WP	m	[24]
Bulbophyllum sp.	Kratke Range, PNG	WP	w	[19]
Caladenia carnea R. Br.	NSW-Q	WP	w	[24]
C. flava R. Br.	WA	WP	w	[21]
Calanthe crysantha Schlechter	PNG	WP	w	[25]
C. triplicata (Willem.) Ames	NSW-Q	WP	w	[24]
Calochilus campestris R. Br.	NSW-Q	WP	m	[24]
C. paludosus R. Br.	NSW-Q	WP	s	[24]
C. robertsonii Benth.	NSW-Q	WP	m	[24]
Camarotis keffordii (Bailey) J.J. Smith	NSW-Q	WP	m	[24]
Chiloglottis gunnii Lindley	NSW-Q	WP	w	[24]
C. reflexa (Labill.) Druce	NSW-Q	WP	w	[24]
Chiloschista phyllorhiza (F. Muell.) Schltr.	NSW-Q	WP	w	[24]
Coelogyne asperata Lindley	PNG	WP	w	[25]
C. pustuloga Ridl.	PNG	WP	m	[25]
Corymborkis veratrifolia (Reinw.) Blume	Cairns, Q	L	w	[18]
	NSW-Q	WP	m	[24]
Cryptostylis fulva Schlechter	PNG	WP	s	[25]
Cymbidium canaliculatum var. R. Br.	Wandoan, Q	WP	m	[17]
Dendrobium adae Bailey	NSW-Q	WP	w	[24]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
D. antennatum Lindley	NSW-Q	WP	w	[24]
D. baileyi F. Muell.	NSW-Q	WP	w	[24]
D. cancroides Hunt	NSW-Q	WP	m	[24]
D. cucumerinum MacLeay	NSW-Q	WP	m	[24]
D. x *delicatum* (Bailey) Bailey	NSW-Q	WP	m	[24]
D. dicuphum F. Muell.	NSW-Q	WP	w	[24]
D. erectifolium J.J. Smith	PNG	WP	m	[25]
D. falcorostrum Fitzg.	NSW-Q	WP	w	[24]
D. fleckeri Rupp & C. White	NSW-Q	WP	w	[24]
D. gracilicaule F. Muell. var. *gracilicaule*	NSW-Q	WP	m	[24]
D. hollrungii Kränzlin	PNG	WP	w	[25]
D. x kestevenii Rupp	NSW-Q	WP	w	[24]
D. linguiforme Sw. var. *linguiforme*	NSW-Q	WP	w	[24]
D. linguiforme var. *nugentii* Bailey	NSW-Q	WP	w	[24]
D. luteochilum Rupp	NSW-Q	WP	w	[24]
D. monophyllum F. Muell.	NSW-Q	WP	w	[24]
D. moorei F. Muell.	NSW-Q	WP	w	[24]
D. mortii F. Muell.	NSW-Q	WP	w	[24]
D. pugioniforme Cunn.	NSW-Q	WP	m	[24]
D. schneiderae Bailey	NSW-Q	WP	w	[24]
D. striolatum H.G. Reichb.	NSW-Q	WP	w	[24]
D. x *superbiens* H.G. Reichb.	NSW-Q	WP	m	[24]
D. tenuissimum Rupp	NSW-Q	WP	w	[24]
D. teretifolium var. *fairfaxii* Bailey forma *aureum*	NSW-Q	WP	w	[24]
D. teretifolium var. *fairfaxii* Bailey forma *fairfaxii*	NSW-Q	WP	w	[24]
D. tetragonum Cunn. var. *tetragonum*	NSW-Q	WP	w	[24]
Dendrobium sp.	Bakaia, PNG	WP	w	[19]
Dendrochilum longifolium Reichb. var. *papuanum*	PNG	WP	m	[25]
Diplocaulobium glabrum (J.J. Smith) Kränzlin	NSW-Q	WP	w	[24]
Diuris pedunculata R. Br.	Great Lake, T	L, Fl, St	m	[22]
Ephemerantha comata (Blume) P. Hunt & Summerh.	PNG	WP	m	[25]
E. convexa (Blume) P. Hunt & Summerh.	NSW-Q	WP	w	[24]
Eria eriaeoides (Bailey) Rolfe	NSW-Q	WP	w	[24]
E. inornata Hunt	NSW-Q	WP	w	[24]
Galeola cassythoides H.G. Reichb.	NSW-Q	WP	m	[24]
G. foliata (F. Muell.) F. Muell.	NSW-Q	WP	m	[24]
Gastrodia sesamoides R. Br.	NSW-Q	WP	s	[24]
Goodyera papuana Ridl.	PNG	WP	m	[25]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Habenaria papuana Kränzlin	PNG	WP	s	[25]
Hetaeria polygonoides (F. Muell.) Doctr.	NSW-Q	WP	m	[24]
Liparis coelogynoides (F. Muell.) Benth.	NSW-Q	WP	s	[24]
L. fleckeri Nicholls	NSW-Q	WP	s	[24]
L. habenarina (F. Muell.) Benth.	NSW-Q	WP	s	[24]
L. nugentae Bailey	NSW-Q	WP	s	[24]
L. reflexa (R. Br.) Lindley	NSW-Q	WP	s	[24]
Liparis sp.	Garaina, PNG	L, St	w	[19]
Luisia teretifolia Gaudich.	NSW-Q	WP	w	[24]
Lyperanthus suaveolens R. Br.	NSW-Q	WP	s	[24]
Macodes sanderiana Rolfe	PNG	WP	w	[25]
Malaxis latifolia Smith	NSW-Q	WP	s	[24]
Malaxis sp.	Marafunga, PNG	WP	m	[19]
Microtis alba R. Br.	WA	WP	w	[21]
M. uniflora (G. Forster) H.G. Reichb.	NSW-Q	WP	w	[24]
Nervilia discolor (Blume) Schltr.	NSW-Q	WP	m	[24]
N. holochila (F. Muell.) Schultr.	NSW-Q	WP	s	[24]
Oberonia muelleriana Schultr.	NSW-Q	WP	m	[24]
O. palmicola F. Muell.	NSW-Q	WP	s	[24]
Paphiopedilum violascens Schlechter	PNG	WP	w	[25]
Peristeranthus hillii (F. Muell.) Hunt	NSW-Q	WP	w	[24]
Phaius australis F. Muell.	NSW-Q	WP	m	[24]
P. montanus Schlechter	PNG	WP	w	[25]
P. tankarvilleae (L'Hér.) Blume	NSW-Q	WP	w	[24]
Phalaenopsis amabilis var. *rosentromii* (Bailey) Nicholls	NSW-Q	WP	s	[24]
Pholidota pallida Lindley	NSW-Q	WP	m	[24]
Plocoglottis sp.	Bakaia, PNG	WP	w	[19]
Pomatocalpa marsupiale (Kränzlin) J.J. Smith	PNG	WP	m	[25]
Porphyrodesme papuana Schlechter	PNG	WP	w	[25]
Prasophyllum australe R. Br.	NSW-Q	WP	m	[24]
P. elatum R. Br.	NSW-Q	WP	w	[24]
Pterostylis curta R. Br.	NSW-Q	WP	w	[24]
P. cycnocephala Fitzg.	NSW-Q	WP	m	[24]
P. falcata R. Rogers	NSW-Q	WP	w	[24]
P. pusilla var. *prominens* Rupp	NSW-Q	WP	s	[24]
Renanthera edefeldtii F. Muell. & Kraenzl. ex Kraenzl.	PNG	WP	m	[25]
Rhinerrhiza divitiflora Benth.) Rupp	NSW-Q	WP	s	[24]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Robiquetia tierneyana (Rupp) Dockr.	NSW-Q	WP	w	[24]
Sarcochilus australis (Lindley) H.G. Reichb.	NSW-Q	WP	w	[24]
S. ceciliae F. Muell.	NSW-Q	WP	m	[24]
S. fitzgeraldii F. Muell.	NSW-Q	WP	m	[24]
S. hartmannii F. Muell.	NSW-Q	WP	w	[24]
S. hillii (F. Muell.) F. Muell.	NSW-Q	WP	m	[24]
S. moorei (H.G. Reichb.) Schlechter	NSW-Q	WP	w	[24]
Schistostylus purpuratus (Rupp) Dockr.	NSW-Q	WP	w	[24]
Schoenorchis densiflora Schltr. var. *densiflora*	NSW-Q	WP	w	[24]
Spiranthes sinensis (Pers.) Ames	NSW-Q	WP	w	[24]
Taeniophyllum wilkianum Hunt	NSW-Q	WP	s	[24]
Thelymitra crinata Lindl.	WA	WP	w	[21]
T. truncata R.S. Rogers	Cockle Bay, T	L, Fl, St	m	[22]
Thrixspermum arachnites Reichb.	PNG	WP	w	[25]
Vanda hindsii Lindley	PNG	WP	w	[25]
V. whiteana D. Herbert & S.T. Blake	NSW-Q	WP	w	[24]
Vandopsis longicaulis Schlechter	PNG	WP	w	[25]
V. warocqueana Schlechter	PNG	WP	w	[25]
PAPAVERACEAE				
Argemone mexicana L.	Brisbane, Q	L	w	[18]
	Rockhampton, Q	L, St	s	[17]
Eschscholzia californica Cham.	Stanthorpe, Q	WP	s	[17]
Glaucium corniculatum (L.) Curtis	Baralaba, Q	L	s	[18]
Papaver aculeatum Thunb.	Kyogle, NSW	L, St	m	[18]
Papaver hybridum L.	WA	WP	m	[21]
PASSIFLORACEAE				
Passiflora foetida L.	WA	WP	m	[21]
P. herbertiana Ker Gawler	Mt Glorious, Q	L, St	w	[17]
P. suberosa L.	Brisbane, Q	L	w	[17]
	Beenleigh, Q	WP	w	[20]
PHYTOLACCACEAE				
Codonocarpus australis Moq.	Miles, Q	L, B	s	[17]
Gyrostemon ramulosus Desf.	Q	B	s	[18]
Phytolacca octandra L.	Brisbane, Q	L, F	s	[17]
	WA	WP	s	[21]
Rivina humilis L.	Marburg, Q	L, St	s	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
PIPERACEAE				
Peperomia leptostachya Hook. & Arn.	Cairns, Q	L, St	w	[18]
	Conway, Q	WP	w	[20]
Piper banksii Miq.	Cairns, Q	L	s	[18]
P. novae-hollandiae Miq.	Rockhampton, Q	L	s	[17]
Piper sp.	South Johnstone, Q	L	m	[18]
Piper sp.	Cairns, Q	L	m	[18]
Piper sp.	Oomsis Ck, PNG	L, St	w	[19]
PITTOSPORACEAE				
Bursaria incana Lindley	Wandoan, Q	L	m	[17]
B. spinosa Cav.	Yarraman, Q	B	m	[17]
Cheiranthera filifolia Turcz.	WA	WP	w	[21]
Citriobatus pauciflorus	Wandoan, Q	B	w	[17]
Hymenosporum flavum (Hook.) F. Muell.	Rathdowney, Q	L, St	m	[17]
Marianthus coeruleo-punctatus Klotzsch.	WA	WP	w	[21]
M. pictus Lindl.	WA	WP	m	[21]
Pittosporum ferrugineum Dryander	Mossman, Q	L, F	m	[17]
	Cairns, Q	B	w	[18]
	Marafunga, PNG	B	w	[19]
P. phylliraeoides DC.	WA	WP	w	[21]
	Condamine, Q	F	w	[17]
P. ramiflorum (Z. & M.) Zoll.	Wanatabi, PNG	B	w	[19]
P. rhombifolium Hook.	Wandoan, Q	L, B	s	[17]
P. rubiginosum R. Cunn.	Atherton, Q	L	w	[18]
P. undulatum Vent.	Mapleton, Q	L, F, St	w	[18]
P. venulosum F. Muell.	Mossman, Q	L	w	[18]
Sollya heterophylla Lindl.	WA	WP	w	[21]
POACEAE (GRAMINEAE)				
Agrostis avenacea Gmel.	WA	WP	w	[21]
Aira cupaniana Guss.	WA	WP	w	[21]
Aristida contorta F. Muell.	WA	WP	w	[21]
Arundo donax L.	Brisbane, Q	L	s	[17]
Briza minor L.	WA	WP	w	[21]
Bromus gussonii Parl.	WA	WP	w	[21]
Catapodium rigidum (L.) C.E. Hubbard	WA	WP	m	[21]
Cenchrus ciliaris L.	WA	WP	m	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Chloris virgata Sw.	Boonah, Q	WP	s	[18]
Danthonia bipartita F. Muell.	WA	WP	w	[21]
D. setacea R. Br.	WA	WP	w	[21]
Deyeuxia quadriseta (Labill.) Benth.	WA	WP	w	[21]
Echinochloa crus-galli (L.) P. Beauv.	Mackay, Q	WP	s	[18]
Ehrharta brevifolia Schrad.	WA	WP	w	[21]
E. calycina Sm.	WA	WP	w	[21]
E. longiflora Sm.	WA	WP	w	[21]
Eleusine indica (L.) Gaertner	Slack's Ck, Q	WP	w	[20]
	Mackay, Q	WP	s	[18]
Eragrostis australasica (Steud.) C.E. Hubbard	WA	WP	w	[21]
E. curvula Nees	WA	WP	w	[21]
Eriachne aristidea F. Muell.	WA	WP	w	[21]
E. pulchella Domin	WA	WP	w	[21]
Hordeum leporinum Link	WA	WP	w	[21]
Leptochloa digitata (R. Br.) Domin	WA	WP	m	[21]
Lolium perenne L.	WA	WP	m	[21]
Microlaena stipoides (Labill.) R. Br.	WA	WP	m	[21]
Neurachne alopecuroides R. Br.	WA	WP	m	[21]
N. mitchelliana Nees	WA	WP	w	[21]
Paractenium novae-hollandiae Beauv.	WA	WP	s	[21]
Paspalum distichum L.	Castlemaine, V	WP	m	[20]
Pennisetum orientale Rich.	WA	WP	m	[21]
Phalaris aquatica L.	Glenroy, SA	WP	m	[20]
P. arundinacea L.	Canberra, ACT	WP	s	[20]
P. tuberosa L.	WA	WP	m	[21]
Setaria dielsii Herrm.	WA	WP	w	[21]
S. surgens Stapf	WA	WP	w	[21]
Spartochloa scirpoidea (Steud.) C.E. Hubbard	WA	WP	w	[21]
Spinifex hirsutus Labill.	WA	WP	w	[21]
S. longifolius R. Br.	WA	WP	s	[21]
Sporobolus capensis (Willd.) Kunth.	WA	WP	w	[21]
Stipa compressa R. Br.	WA	WP	w	[21]
S. elegantissima Labill.	WA	WP	w	[21]
S. nitida Summerh. & C.E. Hubbard	WA	WP	w	[21]
S. scabra Lindl.	WA	WP	w	[21]
S. semibarbata R. Br.	WA	WP	w	[21]
S. variabilis Hughes	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Tetrarrhena laevis R. Br.	WA	WP	m	[21]
Thelepogon elegans Roth. ex Roemer & Schult.	Samford, Q	L, St	s	[20]
Triodia scariosa N.T. Burbidge	WA	WP	w	[21]
Trisetum pumilum Kunth.	WA	WP	w	[21]
Triticum aestivum L.	WA	WP	m	[21]
POLEMONIACEAE				
Cobaea scandens Cav.	Mitcham, V	L, St	m	[20]
POLYGALACEAE				
Comesperma ericinum DC.	Stanthorpe, Q	L, St	w	[20]
	Mt Mee, Q	L, Fl, St	w	[18]
C. calymega Labill.	WA	WP	s	[21]
C. ciliatum Steetz	WA	WP	s	[21]
C. confertum Labill.	WA	WP	s	[21]
C. retusum Labill.	Whian Whian, NSW	L, St	m	[20]
C. scoparium Steetz	WA	WP	s	[21]
C. spinosum F. Muell.	WA	WP	s	[21]
C. virgatum Labill.	WA	WP	m	[21]
C. volubile Labill.	Epping Forest, T	WP	w	[22]
	WA	WP	s	[21]
Polygala japonica Houtt.	Kratke Range, PNG	WP	w	[19]
P. linariaefolia Willd.	Butibum R, PNG	WP	w	[19]
Xanthophyllum macintyrii F. Muell.	Boonjie, Q	L, B	s	[17]
POLYGONACEAE				
Emex australis Benth.	Dalby, Q	WP	s	[17]
Muehlenbeckia rhyticarya F. Muell.	Stanthorpe, Q	WP	m	[20]
Polygonum hydropiper L.	Mackay, Q	WP	s	[18]
	Copalabar, Q	L, St	w	[20]
P.orientale L.	Rockhampton, Q	L	s	[18]
	Beenleigh, Q	L, St	w	[20]
Rumex brownii Campderá	Brisbane, Q	R	s	[18]
POLYPODIACEAE				
Asplenium bipinnatifidum Bak.	Musgrave R, PNG	WP	w	[19]
A. praemorsum Swartz	WA	WP	w	[21]
Lindsaea linearis Swartz	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Polypodium phymatodes L.	Melbourne, V	L, St	w	[20]
P. subauriculatum Blume	Melbourne, V	L, St	w	[20]
Tectaria ferruginea (Mett.) Copel.	Butibum R, PNG	L	w	[19]
PORTULACACEAE				
Calandrinia liniflora Fenzl.	WA	WP	w	[21]
Portulaca oleracea L.	Mackay, Q	WP	s	[18]
	WA	WP	w	[21]
PRIMULACEAE				
Anagallis arvensis L.	WA	WP	w	[21]
PROTEACEAE				
Agastachys odorata R. Br.	Gordon R, T	L, R	m	[22]
Austromuellera trinervia C. White	Boonjie, Q	L, St	w	[20]
Bellendena montana R. Br.	Guilford, T	L, R, Fl	m	[22]
Conospermum mitchellii Meissner	Portland, V	L, St	w	[20]
Darlingia spectatissima F. Muell.	Innisfail, Q	L	w	[18]
Grevillia dielsiana C.A. Gardn.	WA	WP	m	[21]
G. incrassata Diels	WA	WP	w	[21]
G. robusta R. Br.	Brisbane, Q	B	w	[20]
Grevillia sp.	Chillagoe, Q	L	m	[17]
Hakea falcata R. Br.	WA	WP	w	[21]
Helicia cribbiana (?) (Bailey) Bailey	Malanda, Q	B	w	[18]
Lambertia multiflora Lindl.	WA	WP	w	[21]
Persoonia diadena F. Muell.	WA	WP	m	[21]
P. gunnii Hook. f.	West Central Plateau, T	F	m	[22]
P. tenuifolia R. Br.	Stanthorpe, Q	L, St	w	[17]
Triunia youngiana (C. Moore & F. Muell.) L. Johnson & B. Briggs	Whian Whian, NSW	L, St	w	[20]
PTERIDACEAE				
Pteris tremula R. Br.	Melbourne, V	L, St	w	[20]
RANUNCULACEAE				
Clematis glycinoides DC.	Brisbane, Q	L	s	[17]
C. pubescens Hueg.	WA	WP	m	[21]
Ranunculus colonorum Endl.	WA	WP	m	[21]
R. lappaceus Smith	Tenterfield, NSW	L, St	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
RESTIONACEAE				
Ecdeiocolea monostachya F. Muell.	WA	WP	s	[21]
RHAMNACEAE				
Alphitonia macrocarpa Mansf.	Rouna, PNG	L	w	[19,20]
A. whitei Braid	Gadgarra, Q	B	w	[20]
	Atherton, Q	B	w	[18]
Colubrina asiatica Brongn.	Shute Bay, Q	L, St	w	[20]
	Cairns, Q	B, R	s	[17]
Discaria pubescens (Brongn.) Druce	Shannon R, T	L, Fl, St	m	[22]
Emmenosperma alphitonioides F. Muell.	Mt Alford, Q	L, B	m	[20]
Spyridium vexilliferum (Hook.) Russ.	V	L	w	[20]
Ventilago ecorollata F. Muell.	Bailey's Ck, Q	WP	w	[20]
Zyziphus mauritiana Lam.	Chillagoe, Q	L, B	w	[17]
Z. oenoplia (L.) Miller	McIlwraith Range, Q	B, St	s	[20]
RHIZOPHORACEAE				
Bruguiera exaristata Ding Hou	Bamaga, Q	B	w	[20]
B. sexangula (Lour.) Poir.	Huon Gulf, PNG	B	w	[19,20]
Carallia brachiata (Lour.) Merr.	Upper Massey Ck, Q	F, B, R	s	[20]
	Cairns, Q	L	w	[18]
	Trans-Busu, PNG	L	m	[19]
C. integerrima DC.	Cairns, Q	L	w	[17]
Gynotroches axillaris Bl.	Mt Shungol, PNG	B	m	[19,20]
ROSACEAE				
Parinari corymbosa (Bl.) Miq.	Oomsis Ck, PNG	L, B	w	[19,20]
Sanguisorba minor ssp. *muricata* Briq.	Tenterfield, NSW	WP	w	[20]
Stylobasium spathulatum Desf.	WA	WP	w	[21]
RUBIACEAE				
Anthocephalus chinensis (Lam.) Rich. ex Walp.	Oomsis Ck, PNG	B	m	[19,20]
Antirhea myrtoides F. Muell.	Davies Ck, Q	B	w	[20]
A. putaminosa (F. Muell.) Bailey	Rockhampton, Q	L, F, B	s	[17]
	Markwell, Q	L	m	[20]
A. tenuiflora F. Muell. ex Juss.	Davies Ck, Q	L	s	[20]
Canthium attenuatum (R. Br.) Benth.	WA	WP	s	[21]
C. buxifolium Benth.	Maxwelton, Q	L, St	s	[18]
C. coprosmoides F. Muell.	Brisbane, Q	L, St	s	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
C. latifolium F. Muell.	WA	WP	m	[21]
C. longiflorum (Val.) Merr. & Perry	Crooked Ck, PNG	B	w	[19]
C. lucidum Hook. & Arn.	Rockhampton, Q	L	w	[17]
C. lucidum var.	Brisbane, Q	L	s	[17]
C. oleifolium Hook.	Wandoan, Q	L, B	m	[17]
C. odoratum Seem. vel. aff.	Atherton, Q	B	m	[18]
C. vacciniifolium F. Muell.	Chinchilla, Q	L	m	[17]
Canthium sp. ?	Malanda, Q	B	w	[18]
Caelospermum paniculatum F. Muell.	Pottsville, NSW	WP	w	[20]
	Coolangatta, Q	L, St	s	[17]
C. reticulatum (F. Muell.) Benth.	Stuart, Q	WP	w	[20]
	Rockhampton, Q	L, B	w	[17]
Cinchona ledgeriana (How.) Moens	Akuna, PNG	L, B	s	[19]
C. pubescens Vahl.	Omaura, PNG	L, B	s	[19]
Diplospora ixoroides F. Muell.	Coppermine Ck, Q	WP	w	[20]
	Wandoan, Q	B	w	[17]
Gardenia jardinei F. Muell.	Shute Bay, Q	L, St	w	[20]
G. macgillivraei Benth.	Bamaga, Q	L	w	[20]
G. ochreata F. Muell.	Cairns, Q	B, F	m	[17]
	Mt Surprise, Q	F	w	[18]
G. ovularis Bailey	Q	L, St	m	[17]
Hedyotis auricularia L.	Philippine Is	L	s	[18]
H. galioides F. Muell.	Ingham, Q	WP	m	[17,18]
Hodgkinsonia frutescens C. White	Wongabel, Q	WP	s	[20]
	Yungaburra, Q	L, B, F	s	[17]
	Atherton, Q	L, B	s	[18]
H. ovatiflora F. Muell.	Unumgar, NSW	WP	m	[20]
	Burleigh, Q	WP	s	[17]
Hydnophytum formicarum Jack	Bamaga, Q	L	w	[20]
Ixora amplexifolia Laut. & K. Schum.	Oomsis Ck, PNG	L	w	[19,20]
I. beckleri Benth.	Mt Lindsay, NSW	L, St	w	[20]
Ixora sp.	Atherton, Q	L, B, St	s	[18]
Mitragyna speciosa Korth.	Brown R, PNG	L, B	m	[19]
Morinda acutiflora F. Muell.	Bunya Mts, Q	L	w	[18]
M. citrifolia L.	Mission Beach, Q	L	s	[20]
	Cairns, Q	L	s	[17]
M. jasminoides Cunn.	Rockhampton, Q	L	m	[17]
Nauclea gordoniana Bailey	Cairns, Q	B	w	[18]
Neonauclea clemensiae Merr. & Perry	Crooked Ck, PNG	L	w	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Neonauclea sp. aff. *N. dahlii* (Val.) Merr. & Perry	Markham R, PNG	L	w	[19]
N. obersifolia (Val.) Merr. & Perry	Mt Shungol, PNG	L	w	[19]
N. schlechteri (Val.) Merr. & Perry	Oomsis Ck, PNG	L, B	m	[19]
Ophiorrhiza australiana Benth.	Thornton Peak, Q	R	w	[18]
Opercularia hispidula Endl.	WA	WP	m	[21]
O. turpis F. Muell. ex Miq.	Beachport, SA	L, St	w	[20]
Pavetta australiensis Bremek.	Cairns, Q	L, B	s	[17]
	Yarraman, Q	L	w	[18]
P. platyclada Laut.	Oomsis Ck, PNG	L	w	[19,20]
Pomax umbellata Sol. ex DC.	Moura, Q	WP	m	[20]
	Brisbane, Q	WP	m	[17]
Psychotria beccarioides Wernh.	Butibum R, PNG	L, B	s	[19,20]
P. coelospermum Bailey	Bailey's Ck, Q	WP	s	[20]
Psychotria sp.	Wanatabi, PNG	L, St	w	[19]
Randia benthamiana F. Muell.	Binna Burra, Q	L	s	[18]
R. chartacea (F. Muell.) F. Muell.	Brisbane, Q	L, B	s	[17]
	Imbil, Q	L	s	[18]
R. densiflora Benth.	Rockhampton, Q	L, B	s	[17]
	Bundaberg, Q	L, B	m	[18]
R. fitzalanii (F. Muell.) F. Benth.	Cairns, Q	F	w	[17]
R. hirta (F. Muell.) F. Muell.	Boonjie, Q	WP	m	[17]
R. tuberculosa Bailey	Atherton, Q	L	w	[18]
Richardsonia braziliensis Hayne	Brisbane, Q	L, St	w	[17]
Spermacoce brachystema Benth.	Brisbane, Q	WP	m	[17,18]
Tarenna dallachiana (Benth.) S. Moore	Atherton, Q	L	s	[18]
Timonius carstensensis Wernh.	Kaindi-Edie Ck, PNG	L	w	[19]
T. kaniensis Val.	Oomsis Ck, PNG	B	w	[19,20]
T. timon (Sprengel) Merr.	Cairns, Q	L, St	w	[18]
Timonius sp.	Mt Shungol, PNG	B	w	[19]
Uncaria bernaysii F. Muell.	Trans-Busu, PNG	L	s	[19,20]
U. ferrea DC.	Daintree, Q	WP	s	[20]
U. ferrea var. *appendiculata* (Benth.) Val.	Tymne-Gurukor, PNG	L	m	[19]
Urophyllum cf. *rostratum* Val.	Wanatabi, PNG	L, B	w	[19]
U. weichmannii Val.	Oomsis Ck, PNG	L	w	[19]
Urophyllum sp.	Mt Shungol, PNG	B	w	[19]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
RUTACEAE				
Acradenia frankliniae Milligan ex Kippist	Corinna, T	L	w	[22]
	Melbourne Botanic Gardens, V	L	w	[20]
	Launceston, T	L	w	[18]
Acronychia acidula F. Muell.	Atherton, Q	L, F, B	s	[17]
	East Barron, Q	L	w	[18]
A. baueri Schott	Brisbane, Q	L, B, F, W	s	[17]
	Yarraman, Q	L, St	s	[18]
A. haplophylla (F. Muell.) Engl.	Malanda, Q	L, B	s	[17]
	Cairns, Q	L, B	s	[18]
A. imperforata F. Muell.	Bamaga, Q	L, B	m	[20]
	Currumbin, Q	L	m	[17]
	Coff's Harbour, NSW	L	w	[18]
A. laevis Forster & G. Forster	Brisbane, Q	L, St	s	[17]
A. melicopoides F. Muell.	Gadgarra, Q	L, St	m	[20]
	Q	L	w	[18]
A. muelleri (Engl.) Francis	Cairns, Q	L, St	m	[18]
A. murina Ridl.	Bakaia, PNG	B	w	[19]
A. papuana Gibbs	Kaini-Edie Ck, PNG	B	w	[19]
A. parviflora C. White	Atherton, Q	L, B, St	m	[18]
A. pauciflora C. White	Croydon, Q	L	m	[20]
	Brisbane, Q	L, B	s	[17]
	Imbil, Q	L, B	s	[18]
A. pubescens (Bailey) C. White	Mebbin, NSW	L	w	[20]
	Mt Glorious, Q	L, B, St	m	[17]
	Macpherson Range, Q	L, B	w	[18]
A. pullii Laut.	Marafunga, PNG	B	w	[19]
A. suberosa C. White	Whian Whian, NSW	B	s	[20]
	Kyogle, NSW	L	w	[18]
A. vestita F. Muell.	Boonjie, Q	L	w	[18]
A. wilcoxiana (F. Muell.) T.G. Hartley	Pottsville, NSW	L, St	w	[20]
Acronychia sp.	Herberton, Q	W	s	[17]
Boronia algida F. Muell.	Braidwood, NSW	L, St	w	[18]
B. alulata Benth.	Cape Bedford, Q	L, St	s	[18]
B. bowmanii F. Muell.	Scrubby Ck, Q	L, St	s	[18]
B. caerulescens F. Muell.	WA	WP	s	[21]
B. citriodora Gunn ex Hook. f.	Mt Rufus, T	B	w	[22]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
B. glabra Maiden & Betche ex Cheel	Eidsvold, Q	L, St	w	[20]
	Goombungee, Q	L, St	s	[18]
B. granitica Maiden & E. Betche	Torrington, NSW	L, St	m	[18]
B. lanceolata F. Muell.	Westmoreland, Q	L, St	s	[18]
B. ledifolia (Vent.) DC.	Grafton, NSW	L, St	m	[18]
B. microphylla Sieber ex Sprengel	Stanthorpe, Q	WP	m	[20]
B. obovata C. White	Mt Moffatt, Q	L, St	s	[18]
B. pilosa Labill.	St Georges Bay, T	B	w	[22]
B. polygalifolia Smith	Glasshouse Mts, Q	L, St	s	[18]
B. rosmarinifolia Cunn.	Miami, Q	L	w	[20]
	Tin Can Bay, Q	L, B	m	[18]
B. ternata Endl.	WA	WP	m	[21]
B. thujona Penf. & Welch	Oxford Falls, NSW	L, St	w	[18]
B. whitei Cheel	Mt Norman, Q	L	m	[18]
Bosistoa euodiformis F. Muell.	Macpherson Range, Q	B	w	[18]
Bosistoa sapindiformis Benth.	Kin Kin, Q	L	w	[17]
Brombya platynema F. Muell.	Clump Point, Q	L	w	[18]
Chorilaena quercifolia Endl.	WA	WP	w	[21]
Citrus australis (Sweet) Planchon	Ipswich, Q	B, W	m	[17]
C. macroptera Montr.	Crooked Ck, PNG	B	w	[19,20]
Clausena brevistyla Oliver	Port Douglas, Q	L, St	m	[20]
	Imbil, Q	St	w	[18]
Correa reflexa (Labill.) Vent.	Casterton, V	L	w	[20]
C. speciosa W.T. Aiton	Mistake Plateau, Q	L	w	[18]
Diplolaena angustifolia Hook.	WA	WP	w	[21]
Eremocitrus glauca (Lindley) Swingle	Springsure, Q	L	w	[20]
	Chinchilla, Q	L	m	[17]
	Torrens Ck, Q	L	s	[18]
Eriostemon brucei F. Muell.	WA	WP	s	[21]
E. buxifolius Smith	Gosford, NSW	R	w	[18]
E. coccineus C.A. Gardn.	WA	WP	w	[21]
E. gracile R. Grah.	Melbourne, V	L	w	[20]
E. lanceolatus C.F. Gaertner	Gosford, NSW	L	w	[18]
E. myoporoides DC. forma	Mt Barney, Q	L	w	[18]
E. verrucosus A. Rich.	Swansea, T	B	m	[22]
Euodia alata F. Muell.	Busu R, PNG	L, B	m	[19,20]
	Lae, PNG	B	s	[18]
E. cf. *asteridula* Merr. & Perry	Lae, PNG	B	m	[19]
E. bonwickii F. Muell.	Gadgarra, Q	L	w	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
E. elleryana F. Muell.	Kauli Ck, PNG	L	m	[20]
	Mackay, Q	L	w	[18]
	L Wanum, PNG	L, B	w	[19]
E. cf. *elleryana* F. Muell.	Kauli Ck, PNG	L	m	[19]
E. micrococca F. Muell.	Whian Whian, NSW	L, B	m	[20]
	Yarraman, Q	L	s	[17]
	Toonumbar, NSW	L, B	m	[18]
E. vitiflora F. Muell.	Atherton, Q	B	w	[20]
	Tully, Q	L, B, St	s	[18]
(?)	Cairns, Q	B	s	[17]
E. xanthoxyloides F. Muell.	Malanda, Q	L, B	s	[17]
	Dunk I, Q	L	s	[18]
Euodia sp.	El Arish, Q	B	m	[17]
Euodia sp.	Malanda, Q	L, B	s	[17]
Euodia sp.	Kaindi-Edie Ck, PNG	B	w	[19]
Flindersia acuminata C. White	Boonjie, Q	B, W	s	[17]
	Johnstone R, Q	L	s	[18]
F. amboinensis Poir.	Oomsis Ck, PNG	L, B	s	[19]
F. australis R. Br.	Brisbane, Q	L, B	s	[17]
F. bennettiana Benth.	Imbil, Q	B	w	[17]
	Noosa Heads, Q	L, Fl, St	m	[18]
F. bourjotiana F. Muell.	Atherton, Q	B	m	[17]
	Atherton, Q	L	s	[18]
F. bourjotiana vel. aff.	Boonjie, Q	B	m	[17]
F. brayleyana F. Muell.	Atherton, Q	B	w	[17]
F. collina Bailey	Boonah, Q	L, B	s	[17]
	Binna Burra, Q	L	s	[18]
F. dissosperma (F. Muell.) Domin	Charters Towers, Q	L, St	s	[18]
F. laevicarpa C. White & Francis	Danbulla, Q	L, B, St	s	[18]
F. laevicarpa var. *heterophylla* (Merr. & Perry) Hartley	Rouna, PNG	L	w	[19]
F. maculosa F. Muell.	Goondiwindi, Q	B	s	[20]
	Blackall, Q	L	s	[18]
F. oxleyana F. Muell.	Ipswich, Q	L, B	s	[17]
F. pimenteliana F. Muell.	Atherton, Q	L, F, B	s	[17]
	Gadgarra, Q	L	s	[18]
	Kauli Ck, PNG	L, B	m	[19,20]
F. pubescens Bailey	East Barron, Q	L	s	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
F. schottiana F. Muell.	Whian Whian, NSW	B	s	[20]
	Imbil, Q	B	s	[17]
	Ithaca Ck, Q	L	s	[18]
F. xanthoxyla (Hook.) Domin	Whian Whian, NSW	L	s	[18]
Geijera paniculata (F. Muell.) Druce	Rockhampton, Q	L	w	[17]
	Gogano, Q	L	w	[18]
G. parviflora Lindley	Miles, Q	L, B	s	[17]
	Carbean, Q	L	w	[18]
G. salicifolia Schott	Unumgar, NSW	L, B	m	[20]
	Chillagoe, Q	L	s	[17]
	Magnetic I, Q	L	s	[18]
	Crooked Ck, PNG	L	w	[19]
Gelenznowia verrucosa Turcz.	WA	L	w	[18]
Glycosmis pentaphylla (Retz.) Corr.	Upper Massey Ck, Q	L, B	m	[20]
	Palm I, Q	L	s	[18]
Halfordia kendack (Montrouz) Guillaumin	Melbourne, V	L	w	[20]
	Macpherson Range, Q	L, B	w	[18]
H. papuana Laut.	Kratke Range, PNG	L, B	w	[19]
H. scleroxyla F. Muell.	Boonjie, Q	L, B, W	s	[17,20]
	Atherton, Q	L, B	s	[18]
Lunasia amara Blanco	Cape York, Q	B	m	[20]
	Iron Range, Q	L, B, St	s	[18]
	Busu R, PNG	L, B	m	[19]
Medicosma cunninghamii Hook. f.	Mt Dryander, Q	B	m	[20]
	Imbil, Q	L, B	m	[17]
	Samford Ck, Q	L	m	[18]
M. sessiliflora (C. White) T. Hartley	Bloomfield Rd, Q	L	w	[20]
Melicope broadbentiana Bailey	Atherton, Q	L, B	m	[18]
M. erythrococca (F. Muell.) Benth.	Yarraman, Q	B	s	[17]
	Atherton, Q	B	w	[18]
M. fareana (F. Muell.) Engl.	Boonjie, Q	L, B	s	[17]
	Etty Bay, Q	L	s	[18]
	Davies Ck, Q	B	s	[20]
M. melanophloia C. White	Kin Kin, Q	L, St	s	[18]
M. neurococca (F. Muell.) Benth.	Pine Mt, Q	L, B	w	[17]
	Upper Cedar Ck, Q	L	w	[18]
M. octandra (F. Muell.) Druce	Kyogle, NSW	L	m	[18]
M. perspicuinervia Merr. & Perry	Mt Sarawaket, PNG	L	w	[19]
M. sessiliflora C. White	Mossman, Q	L, B	w	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
M. stipitata C. White & Francis	Davies Ck, Q	L, St	m	[20]
Melicope sp.	Mt Spurgeon, Q	L	w	[18]
Melicope sp.	Mt Sarawaket, PNG	L	w	[19]
Microcitrus australis (Planch.) Swingle	Yarraman, Q	L, B	w	[20]
	Samford Ck, Q	L	w	[18]
M. inodora (Bailey) Swingle	Bellenden Ker, Q	L	s	[18]
Micromelum minutum (G. Forster) Wight & Arn.	Long I, Q	L	s	[18]
Murraya crenulata (Turcz.) Oliver	Vanuatu	L	m	[18]
M. ovatifoliolata (Engl.) Domin	Rockhampton, Q	L	s	[17,18]
Pagetia medicinalis F. Muell.	Yarrabah, Q	L	w	[18]
P. monostylis Bailey	Eumundi, Q	L	w	[18]
Pentaceras australis Hook.	Whian Whian, NSW	B	s	[20]
	Boonah, Q	L	m	[17]
	Cooper's Ck, NSW	L	s	[18]
Phebalium anceps DC.	WA	WP	w	[21]
P. drummondii Benth.	WA	WP	w	[21]
P. filifolium Turcz.	WA	WP	s	[21]
P. microphyllum Turcz.	WA	WP	m	[21]
P. rotundifolium Benth.	Stanthorpe, Q	L	w	[20]
	Ballandean, Q	L	m	[18]
P. squameum (Labill.) Engl.	Whian Whian, NSW	L	s	[20]
	Fern Tree, T	B	w	[22]
	Coolangatta, Q	L, St	s	[17]
	Yamba, NSW	L	w	[18]
Phebalium sp.	Miles, Q	L	w	[17]
Philotheca ciliata Hook.	Enniskillen, Q	L, St	w	[18]
P. hassellii F. Muell.	WA	WP	w	[21]
P. reichenbachii Sprengl.	Mt Park, NSW	L	w	[18]
Pleiococca wilcoxiana F. Muell.	Kin Kin, Q	L	s	[18]
Sarcomelicope simplicifolia (Endl.) Hartley ssp. *simplicifolia*	Whian Whian, NSW	B	s	[20]
Tetractomia lauterbachiana Merr. & Perry	Wanatabi, PNG	L	w	[19]
Zanthoxylum brachyacanthum F. Muell.	Killarney, Q	W	s	[20]
	Yarraman, Q	L, B	s	[17]
	Goodna, Q	L, St	m	[18]
Z consperispunctatum Merr. & Perry	Marafunga, PNG	L, B	m	[19]
Z. ovalifolium Wight	Rouna, PNG	L, B	s	[19]
Z. pluviatile Hartley	Busu R, PNG	L, B	w	[19]
Z suberosum C. White	Danbulla, Q	B	m	[18]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Z. torvum C. White	Cairns, Q	B	s	[17]
	Daintree R, Q	L	s	[18]
Z. veneficum Bailey	Malanda, Q	L, B	s	[17]
	Evelyn, Q	B	s	[18]
Zieria arborescens Sims	Taranna, T	L, Fl, St	m	[22]
Z. smithii Andrews	Brisbane, Q	L, R, St	s	[17]
Z. smithii ssp. *smithii* Jackson	Whian Whian, NSW	L, St	m	[20]
SANTALACEAE				
Anthobolus leptomerioides F. Muell.	WA	WP	s	[21]
Choretrum pauciflorum A. DC.	Cornucopia, V	WP	m	[20]
Exocarpos aphylla R. Br.	Ouyen, V	WP	m	[20]
E. cupressiformis Labill.	Healsville, V	WP	m	[20]
	Warwick, Q	St	m	[17]
E. latifolius R. Br.	Chillagoe, Q	L	s	[17]
	Hull R, Q	L	w	[18]
E. sparteus R. Br.	Ouyen, V	L, St	m	[20]
Henslowia sp. nov.	Atherton, Q	L, St	s	[18]
Leptomeria acida R. Br.	Cann R, V	L	w	[20]
Omphacomeria acerba (R. Br.) A. DC.	Gippsland, V	WP	w	[20]
Santalum acuminatum (R. Br.) A. DC.	Manangatang, V	B	s	[20]
S. lanceolatum R. Br.	Biloela, Q	L, B, St	m	[20]
	Miles, Q	L	s	[17]
S. murrayanum (Mitch.) C.A. Gardner	Manangatang, V	B	s	[20]
S. spicatum (R. Br.) DC.	WA	WP	s	[21]
SAPINDACEAE				
Alectryon connatus (F. Muell.) Radlk.	Wandoan, Q	L	w	[17]
A. oleifolius (Desf.) S. Reyn.	Bean Tree Ck, Q	L, B, St	w	[20]
Arytera distylis (Benth.) Radlk.	Imbil, Q	L	w	[18]
A. foveolata F. Muell.	Brisabane, Q	L, B	s	[17]
Atalaya hemiglauca (F. Muell.) F. Muell. ex Benth.	South Sarina, Q	L, St	m	[20]
A. virens C. White	Marburg, Q	B	s	[17]
Cupaniopsis anacardioides (A. Rich.) Radlk.	Imbil, Q	L	w	[18]
Diplopeltis huegelii Endl.	WA	WP	w	[21]
Dodonaea boroniifolia G. Don	Condamine, Q	L	m	[17]
	WA	WP	w	[21]
D. lanceolata F. Muell. var.	Stanthorpe, Q	L, St	w	[17]
D. microzyga F. Muell.	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
D. stenozyga F. Muell.	WA	WP	w	[21]
D. viscosa Jacq.	Warwick, Q	L	w	[17]
D. viscosa ssp. *cuneata* (Smith) J.G. West	Beachport, SA	L, St	w	[20]
Elattostachys nervosa (F. Muell.) Radlk.	Imbil, Q	L, B	s	[18]
Guioa semiglauca (F. Muell.) Radlk.	Brisbane, Q	L, St	s	[18]
Harpullia cupanioides Roxb.	Tymne-Gurukor, PNG	L	w	[19]
H. pendula Planch. ex F. Muell.	Palen Ck, Q	L	w	[20]
	Mt Lindesay, Q	L	m	[17]
H. rhyticarpa C. White & Francis	Cairns, Q	L, B	m	[17]
Mischocarpus sp. aff. *pyriformis* (F. Muell.) Radl.	Atherton, Q	L, B, St	w	[18]
Toechima tenax (Cunn. ex Benth.) Radlk.	Whian Whian, NSW	WP	w	[20]
SAPOTACEAE				
Amorphospermum antilogum F. Muell.	Imbil, Q	L	s	[18]
Hormogyne cotinifolia A. DC.	Yarraman, Q	B	w	[17]
Mimusops elengi L.	Airlie, Q	B	m	[20]
M. parvifolia R. Br.	Cairns, Q	L, B, F	m	[17]
Palaquium galactoxylum (F. Muell.) H.J. Lam var. *salomonensis* (C.T. White) v. Royen	Oomsis Ck, PNG	B	w	[19]
Planchonella anteridifera (White & Francis) H.J. Lam	Butibum R, PNG	L	m	[19]
P. cotinifolia (A. DC.) Dubard	Palen Ck, Q	L, B	w	[20]
	Imbil, Q	L, B, St	s	[18]
P. macropoda H.J. Lam	Marafunga, PNG	L, B	w	[19]
P. sp. aff. *obovata* (R. Br.) Pierre	Mossman, Q	L	w	[18]
P. pohlmaniana (F. Muell.) Pierre ex Dubard	Unumgar, NSW	L, B	s	[20]
	Mt Glorious, Q	L, B	s	[18]
Planchonella sp.	Imbil, Q	L, B	s	[18]
Pouteria sericea Dubard	Chillagoe, Q	L	w	]18]
Pouteria sp. aff. *malaccensis* (Clark) Baehni	Busu R, PNG	B	w	[19]
SAXIFRAGACEAE				
Abrophyllum ornans Hook. f.	Springbrook, Q	L, St	s	[20]
Carpodetus arboreus (Laut. & K. Schum.) Schltr.	Zenag, PNG	L, B	w	[19]
Cuttsia viburnea F. Muell.	Whian Whian, NSW	L, St	m	[20]
Dichroa febrifuga Lour.	Mt Shungol, PNG	B	w	[19]
Polyosma cunninghamii Bennett	Mt Glorious, Q	L, St	s	[17]
P. rhytophloia C. White & Francis	Boonjie, Q	L, B, St	m	[17,20]
Quintinia verdonii F. Muell.	Whian Whian, NSW	L, St	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
SCHIZAEACEAE				
Lygodium scandens Sw.	Tully, Q	WP	m	[20]
SCROFULARIACEAE				
Morgania glabra R. Br.	N Dulacca, Q	L, Fl, St	m	[18]
Peplidium muelleri Benth.	WA	WP	w	[21]
Scoparia dulcis Benth.	Waterford, Q	L, St	m	[20]
	Innisfail, Q	L, R, St	w	[17]
	Brisbane, Q	L, R, St	s	[18]
Verbascum virgatum Stokes	Ipswich, Q	L, St	w	[17]
	Q	L	w	[18]
	WA	WP	m	[21]
Veronica calycina R. Br.	WA	WP	w	[21]
SELAGINELLACEAE				
Selaginella caudata (Desv.) Spring	Umboi I, PNG	WP	w	[19]
S. longipinna Warb.	Mission Beach, Q	L, St	m	[20]
SIMAROUBACEAE				
Ailanthus glandulosa Desf.	Warwick, Q	L, R, St	s	[18]
A. imberbiflora F. Muell.	Innisfail, Q	L, B	m	[17]
A. triphysa (Denst.) Alston	Cannonvale, Q	B	w	[20]
Brucea sumatrana Roxb.	Cairns, Q	B	w	[18]
Guilfoylia monostylis (Benth.) F. Muell.	Acacia Plateau, Q	L, B	m	[20]
	Mt Mistake, Q	F	s	[18]
Harrisonia brownii Adr. Juss.	Pena Village, PNG	L	w	[18]
Hyptiandra bidwillii J.D. Hook.	Gundiah, Q	L	w	[18]
Picrasma javanica Bl.	Crooked Ck, PNG	B	s	[19,20]
Samandera baileyana Oliver	Bellenden Ker, Q	L	w	[18]
SMILACEAE				
Eustrephus latifolius R. Br.	Stanthorpe	F	m	[17]
E. latifolius var. *angustifolius* (R. Br.) Benth.	Pittsworth, Q	L, R, St	m	[17]
Geitonoplesium cymosum (Cunn.) R. Br.	Kakoda Road, PNG	L	w	[19]
Ripogonum discolor F. Muell.	Binna Burra, Q	L	w	[18]
SOLANACEAE				
Anthocersis eadesii F. Muell.	Nepean R, NSW	L, St	w	[18]
A. fasciculata F. Muell.	WA	WP	w	[21]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
A. genistoides Miers	WA	WP	s	[21]
A. littorea Labill.	WA	WP	s	[21]
A. microphylla F. Muell.	WA	WP	s	[21]
A. scabrella Benth.	Nepean R, NSW	R	m	[18]
A. tasmanica Hook. f.	Swansea, T	L, Fl, St	s	[22]
A. viscosa R. Br.	WA	WP	w	[21]
Anthotroche pannosa Endl.	WA	WP	m	[21]
Capsicum fastigiatum Blume	Rockhampton, Q	L, R	s	[17]
C. frutescens L.	Cairns, Q	L, F	w	[18]
Capsicum sp.	Yarraman, Q	L, F, St	s	[17]
Cestrum parqui L'Hér.	Brisbane, Q	L, St	s	[17]
Cyphomandra betacea (Cav.) Sendtner	Kenilworth, Q	F	w	[18]
Datura leichhardtii F. Muell.	WA	WP	s	[21]
	Ward R, Q	L	w	[20]
D. metel L.	Rathdowney, Q	L, St	s	[17]
D. stramonium L.	WA	WP	s	[21]
Duboisia hopwoodii F. Muell.	WA	WP	s	[21]
D. myoporoides R. Br.	Sydney, NSW	L	s	[18]
	Mt Glorious, Q	L	s	[17]
Lycium australe F. Muell.	WA	WP	s	[21]
L. ferocissimum Miers	WA	WP	s	[21]
Nicotiana cavicola N.T. Burbidge	WA	WP	w	[21]
N. exigua H. Wheeler	Dirranbandi, Q	WP	s	[18]
N. glauca Grah.	WA	WP	s	[21]
N. goodspeedii H. Wheeler	St George, Q	L, St	s	[18]
	WA	WP	m	[21]
N. gossei Domin	Dajarra, Q	L, R, St	s	[18]
N. megalosiphon Van Heurck & Muell. Arg.	Jandowae, Q	L, R, Fl, St	s	[18]
N. occidentalis Wheeler ssp. *obliqua* N.T. Burbidge	WA	WP	m	[21]
N. rosulata (S. Moore) Domin	WA	WP	s	[21]
N. rotundifolia Lindl. ssp. *aridicola* N.T. Burbidge	WA	WP	m	[21]
N. simulans N.T. Burbidge	WA	WP	m	[21]
N. velutina H. Wheeler	Bollon, Q	L, R, St	s	[18]
Nicotiana sp.	St George, Q	L	m	[18]
Physalis minima L.	Dirranbandi, Q	L, F, St	s	[18]
P. pendula Rydb.	Dalby, Q	L, F, St	s	[18]
Physalis sp.	Mt Glorious, Q	L, F, St	m	[17]
Physalis sp.	Atherton, Q	B	w	[17]
Solanum amblymerum Dunal	Stanthorpe, Q	L, R, St	s	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
S. americanum Mill.	Waite, SA	F	s	[23]
S. ashbyae Symon (MS)	Meekatharra, WA	L, St	w	[23]
S. asymmetriphyllum Specht	Arnhem Land, NT	F	s	[23]
S. auriculatum Aiton	Atherton, Q	L, B, F	s	[17]
S. aviculare Forst.	Healsville, V	L, F, St	s	[23]
S. beaugleholei Symon (MS)	Geikie Gorge, WA	L	w	[23]
S. brownii Dun.	Goulburn, NSW	F	s	[23]
S. callium C.T. White ex R.J.F. Henderson	Toonumbar, NSW	L, St	s	[23]
S. campanulatum R. Br.	Waite, SA	F	s	[23]
S. capsicastrum Schauer	Tamborine Mt, Q	L, St	s	[18]
S. capsiciforme Domin (Baylis)	Port Wakefield, SA	L, F	s	[23]
S. centrale Black	WA	WP	m	[21]
	Victory Downs, NT	L	m	[20]
S. chenopodinum F. Muell.	Waite, SA	F	s	[23]
S. chippendalei Symon (MS)	Kumarina, WA	F	s	[23]
S. cinereum R. Br.	Mt Brown, SA	F	s	[23]
S. clarkiae Symon (MS)	Arnhem Land, NT	F	w	[23]
S. cleistoganum Symon	Leonora, WA	F	w	[23]
S. coactiliferum J. Black	Dirranbandi, Q	WP	s	[18]
	Alice Springs, NT	R, F	w	[23]
S. cookii Symon (MS)	Evelyn, Q	F	s	[23]
S. cunninghamii Benth.	Broome, WA	F	s	[23]
S. dallachii Benth.	Innisfail, Q	F	w	[23]
S. densevestitum F. Muell.	Waite, SA	L	w	[23]
S. dianthophorum Dun.	Injune-Rolleston, Q	F	s	[23]
S. dimorphospinum C.T. White	Atherton, Q	L, F, St	s	[23]
S. dioicum W.V. Fitz.	Victory Downs, NT	F	s	[23]
S. discolor R. Br.	D'Aguilar Range, Q	L, St	s	[23]
S. diversiflorum F. Muell.	WA	WP	m	[21]
	Derby, WA	F	s	[23]
S. dunalianum Gaud.	Markham R, PNG	L, B, St	m	[19,20]
	Weipa, Q	L, F, St	s	[23]
S. eardleyae Symon (MS)	Mt Connor, NT	F	s	[23]
S. eburneum Symon	West Baines R, NT	F	s	[23]
S. elaeagnifolium Cav.	Hopetoun, V	F	s	[23]
S. elegans Dunal.	Gibraltar Range, NSW	L	s	[23]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
S. ellipticum R. Br.	Maxwelton, Q	L, R, St	s	[18]
	Dirranbandi, Q	L	m	[17]
	Sarina, Q	F	s	[23]
S. erianthum D. Don	Waite, SA	L, F, St	s	[23]
S. esuriale Lindley	Maxwelton, Q	WP	s	[18]
	Dirranbandi, Q	R	s	[17]
	Mt Isa, Q	F	s	[23]
S. ferocissimum Lindl.	Waite, SA	F	s	[23]
	WA	WP	s	[21]
S. ferox L.	Bamaga, Q	St	w	[23]
S. furfuraceum R. Br.	Waite, SA	L, F, St	w	[23]
S. gabrielae Domin	Wittenoom, WA	F	s	[23]
S. gilesii Symon	Halls Ck, WA	L	w	[23]
S. hoplopetalum Bitter et Summerh.	WA	WP	m	[21]
	Kalgoorlie, WA	L, F, St	s	[23]
S. horridum Dun	Mulga Downs, WA	F	m	[23]
S. inaequilaterum Domin	Levers Plateau, Q	F	w	[23]
S. karsensis Symon	Kars Station, SA	F	s	[23]
S. lachnophyllum Symon	Meekatharra, WA	F	s	[23]
S. laciniatum Aiton	Mt Glorious, Q	L, B	s	[17,18]
	Taroona, T	F	s	[23]
S. lacunarium F. Muell.	Waite, SA	F	s	[23]
S. lasiophyllum Dun.	WA	WP	s	[21]
	Payne's Find, WA	F	s	[23]
S. linearifolium Her.	Gibraltar Range, NSW	F	s	[23]
S. lucani F. Muell.	Hall's Ck, WA	F	w	[23]
S. macoorai F.M. Bailey	Evelyn, Q	L	w	[23]
S. marginatum L. f.	Waite, SA	F	s	[23]
S. mauritianum Scop.	Evelyn, Q	L, F, St	s	[23]
S. melanospermum F. Muell.	Waite, SA	F	s	[23]
S. multiglochidiatum Domin	Waite, SA	L	w	[23]
S. nemophilum F. Muell.	Dirranbandi, Q	L, St	s	[18]
S. nigrum L.	WA	WP	s	[21]
	Innisfail, Q	L, R	s	[17]
	Waite, SA	L, F, St	w	[23]
S. nummularium S. Moore	WA	WP	s	[21]
	Kalgoorlie, WA	F	s	[23]
S. oedipus Symon	Kalumburu, WA	F	s	[23]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
S. oldfieldii F. Muell.	WA	WP	s	[21]
	Waite, SA	F	s	[23]
S. oligocanthum F. Muell.	Coopers Ck, NT	L, St	s	[23]
S. opacum A. Br. & Bouché	Waite, SA	F	s	[23]
S. orbiculatum Dun.	WA	WP	m	[21]
	Kalgoorlie, WA	F	s	[23]
S. parvifolium R. Br.	Sarina, Q	L	w	[23]
S. petraeum Symon (MS)	Port Warrender, WA	F	w	[23]
S. petrophilum F. Muell.	WA	WP	m	[21]
	Waite, SA	F	s	[23]
S. phlomoides Benth.	Port Hedland, WA	F	s	[23]
S. plicatile (Moore) Symon (MS)	Scotia, WA	F	s	[23]
S. prinophyllum Dun.	Dungog, NSW	F	s	[23]
S. pseudo-capsicum L.	Obi Obi, Q	L, R, F	s	[18]
	Healsville, V	F	s	[23]
S. pugiunculiferum C.T. White	Waite, SA	L, S, St	s	[23]
S. pungetium R. Br.	Orbost, V	F	s	[23]
S. quadriloculatum F. Muell.	Waite, SA	L, St	w	[23]
S. seaforthianum Andrews	Rockhampton, Q	L, B	s	[17,18]
	?	L	s	[23]
S. seitheae Symon (MS)	Mt Isa, Q	F	w	[23]
S. simile F. Muell.	Cleve-Kimba, SA	L, F, St	s	[23]
S. sodomaeum L.	WA	WP	s	[21]
S. stelligerum Smith	Tamborine Mt, Q	L	s	[18]
	D'Aguilar Range, Q	F	w	[23]
S. sturtianum F. Muell.	WA	WP	s	[21]
	James Range, NT	L	s	[20]
	WA	F	w	[23]
(?)	Cunnamulla, Q	L, St	s	[18]
S. symonii Eichler	WA	WP	s	[21]
	Waite, SA	L, F, St	s	[23]
S. terraneum Symon (MS)	Leonora, WA	L, F, St	w	[23]
S. tetrandrum F. Muell.	Waite, SA	L	w	[23]
S. tetrathecum F. Muell.	Dirranbandi, Q	L, St	s	[18]
	Waite, SA	F	s	[23]
S. torvum Sw.	Innisfail, Q	L, R, F	s	[17]
	Gympie, Q	F	s	[23]
S. tudununggae Symon (MS)	Kalumburu, WA	F	s	[23]
S. tumulicola Symon	Dunmarra, NT	L	s	[23]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
S. verbascifolium L.	Rockhampton, Q	L, B	s	[17]
S. vescum F. Muell.	Tenterfield, NSW	F	s	[23]
S. viride R. Br.	Q	F	s	[23]
S. yirrkalensis Simon (MS)	Waite, SA	L, F, St	w	[23]
Solanum sp. 2457	WA	WP	m	[21]
Solanum sp.	Dirranbandi, Q	L, St	s	[18]
Solanum sp.	N Dulacca, Q	L, Fl, St	s	[18]
Solanum sp.	Warwick, Q	L, R, St	w	[17]
Solanum sp.	Boonjie, Q	F	m	[17]
Solanum sp.	Innisfail, Q	L	m	[17]
SONNERATIACEAE				
Sonneratia caseolaris (L.) Engl.	Huon Gulf, PNG	L	w	[19]
STACKHOUSIACEAE				
Stackhousia brunonsis Benth.	WA	WP	w	[21]
S. pubescens A. Rich.	WA	WP	m	[21]
S. viminea Sm.	WA	WP	w	[21]
STEMONACEAE				
Stemona australiana (Benth.) C.H. Wright	Red Island Point, Q	L, T	s	[20]
STERCULIACEAE				
Argyrodendron peralatum (Bailey) Edlin ex I.H. Boss	Ingham, Q	L, St	m	[20]
Brachychiton paradoxus Schott & Endl.	Chillagoe, Q	S	m	[17]
Commersonia bartramia (L.) Merr.	Cairns, Q	B	w	[18]
Heritiera littoralis Dryand. ex Ait.	Huon Gulf, PNG	L	w	[19]
	Cairns, Q	F	w	[18]
H. trifoliata (F. Muell.) Kosterm.	Toonumbar, NSW	L	m	[20]
Keraudrenia corollata (Steetz) Druce	Kingaroy, Q	L, R, Fl, St	s	[18]
Melochia umbellata (Houtt.) Stapf.	Oomsis Ck, PNG	L, B	m	[19,20]
Sterculia foetida L.	Port Douglas, Q	S	m	[17]
S. laurifolia F. Muell.	Atherton, Q	B	w	[18]
S. quadrifida R. Br.	Bailey's Ck, Q	B	m	[20]
S. cf. *schlechteri* Mildbr.	Mumeng, PNG	B	w	[19]
Tarrietia argyrodendron Benth.	Tamborine, Q	L, Fl	w	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
STYLIDIACEAE				
Stylidium amoenum R. Br.	WA	WP	w	[21]
S. falcatum R. Br.	WA	WP	w	[21]
S. laricifolium Rich.	Carnarvon, Q	WP	w	[20]
TAXODIACEAE				
Athrotaxis cupressoides D. Don	Mt Rufus, T	L	w	[22]
A. laxifolia Hook.	Austins Ferry, T	L	w	[22]
A. selaginoides D. Don	Zeehan, T	L, B	m	[22]
THYMELAEACEAE				
Pimelea colorans Meissner	Stanthorpe, Q	L, St	w	[18]
P. decora Domin	Glengalla, Q	L, St	s	[18]
P. glauca R. Br.	Beachport, SA	WP	m	[20]
P. haematostachya F. Muell.	Gunnawarra, Q	WP	m	[17]
P. latifolia R. Br.	Whian Whian, NSW	L	w	[20]
P. lindleyana Meisn.	Adamsfield Track, T	L, St	w	[22]
P. linifolia Smith	Stanthorpe, Q	WP	w	[17]
P. linifolia Smith ssp. *collina* (R. Br.) Threlfall	Tenterfield, NSW	L, St	s	[20]
Wikstroemia indica (L.) C. Meyer	Gympie, Q	R	s	[17]
TILIACEAE				
Corchorus sidoides F. Muell.	WA	WP	s	[21]
Grewia latifolia Benth.	Coppermine Ck, Q	WP	w	[20]
G. polygama Roxb.	Rockhampton, Q	L	w	[17]
TREMANDRACEAE				
Tetratheca thymifolia Smith	Stanthorpe, Q	WP	w	[20]
TROPAEOLACEAE				
Tropaeolum majus L.	WA	WP	m	[21]
TYPHACEAE				
Typha orientalis L.	Brisbane, Q	WP	w	[20]
ULMACEAE				
Aphananthe philippinensis Planch.	Unumgar, NSW	L, St	w	[20]
Celtis paniculata (Endl.) Planchon	Noosa Heads, Q	L, St	w	[18]
Trema aspera (Brongn.) Blume	Beenleigh, Q	L, St	m	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
URTICACEAE				
Aphananthe philippinensis Planchon	Brisbane, Q	L	w	[17]
Boehmeria platyphylla Don	Toonumbar, NSW	WP	m	[20]
Cypholophus decipiens H. Winkler	Trans-Busu, PNG	L	w	[19,20]
C. friesianus (K. Schum.) H. Winkler	Tymne-Gurukor, PNG	L, F	w	[19,20]
Cypholophus sp.	Wanatabi, PNG	B	w	[19]
Elatostema pachypoda Diels	Rouna, PNG	WP	w	[19]
Laportea photiniphylla (Kunth) Wedd.	Cairns, Q	L, B	m	[18]
Pipturus argenteus (Forst.) Wedd.	Oomsis Ck, PNG	L	w	[19]
VERBENACEAE				
Avicennia marina (Forsk) Vierh.	Tweed R, NSW	B	w	[20]
Callicarpa longifolia Lam.	Innisfail, Q	L	w	[17]
Clerodendrum brasssii Beer & Lam.	Tymne-Gurukor, PNG	B	w	[19]
C. floribundum R. Br.	Dunmara, NT	L	w	[20]
	Macpherson Range, Q	L	w	[18]
C. ingratum K. Schum. & Laut.	Markham Valley, PNG	L, F	w	[19]
C. sp. aff. *phyllomega* Steud.	Busu R, PNG	L	w	[19]
C. tomentosum (Vent.) R. Br.	Rockhampton, Q	L	m	[17]
Cyanostegia angustifolia Turcz.	WA	WP	w	[21]
Dicrastylis exsuccosa (F. Muell.) Druce	Barrow Ck, NT	L	w	[20]
Faradaya splendida F. Muell.	Cairns, Q	R	m	[17]
Glossocarya hermiderma (Benth.) B.D. Jackson	Rockhampton, Q	L	m	[17]
Gmelina fasciculiflora Benth.	Ravesnhoe, Q	B	w	[17]
G. smithii Moldenke	Akuna, PNG	B	w	[19]
Pityrodia axillaris (Endl.) Druce	WA	WP	w	[21]
P. bartlingii (Lehm.) Benth.	WA	WP	w	[21]
P. lepidota (F. Muell.) E. Pritzel	WA	WP	m	[21]
Premna corymbosa (Burm. f.) Rottb. & Willd.	Huon Gulf, PNG	L	w	[19]
	Port Douglas, Q	L, St	w	[20]
P. nauseosus Blanco	Chillagoe, Q	L, B	m	[18]
Spartothamnella juncea (Walp.) Briq.	?	L	w	[20]
	Wandoan, Q	L, St	s	[17]
S. puburula (F. Muell.) Maid. & Betche	Augathella, Q	L, St	w	[20]
S. teucriiflora (F. Muell.) Moldenke	WA	WP	s	[21]
Stachytarpheta mutabilis (Jacq.) Vahl	Q	L, St	m	[17]
Verbena bonariensis L.	Killarney, Q	L, Fl, R, St	s	[17]
V. tenera Sprengel	Q	L, St	m	[17]
V. venosa Gillies & Hook.	Brisbane, Q	L, Fl, St	m	[17]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
Vitex acuminata R. Br.	Rockhampton, Q	L, B	m	[17]
V. negundo L.	Clump Pt, Q	L, St	m	[20]
VIOLACEAE				
Hybanthus calycinus (Steud.) F. Muell.	WA	WP	s	[21]
H. enneaspermus (L.) F. Muell.	Brisbane, Q	WP	m	[17]
H. filiformis (DC. ex Ging.) F. Muell.	NSW-Q border	WP	w	[20]
	Stanthorpe, Q	WP	s	[17]
H. floribundus (Walp.) F. Muell.	WA	WP	s	[21]
Hymenanthera dentata DC.	Mt Wilson, NSW	L	w	[18]
VITACEAE				
Cayratia acris (F. Muell.) Domin	Q	L	w	[17]
Cissus opaca F. Muell.	Wandoan, Q	L	w	[17]
WINTERACEAE				
Bubbia argentea A.C. Sm.	Mt Dickson, PNG	B	w	[19]
B. sp. aff. *argentea* A.C. Sm.	Kaindi-Edie Ck, PNG	B	w	[19]
B. calothyrsa (Diels) A.C. Sm.	Marafunga, PNG	L, B	w	[19]
B. semicarpoides (F. Muell.) B.L. Burtt	Boonjie, Q	B, St	w	[20]
B. sylvestris A.C. Sm.	Omoretu, PNG	B	w	[19]
Drimys insipida (R. Br.) Pilger	Killarney, Q	L, St	w	[20]
	Macpherson Range, Q	L	w	[18]
D. membranea F. Muell.	Atherton, Q	L, B, St	s	[18]
Tasmannia buxifolia (Ridl.) A.C. Sm.	Bakaia, PNG	B	w	[19]
Tasmannia lanceolata (Poiret) A.C. Smith	Mt Macedon, V	B	w	[20]
	Cocle Ck, T	F	w	[22]
XANTHORRHOEACEAE				
Acanthocarpus preissii Lehm.	WA	WP	w	[21]
Chamaexeros fimbriata F. Muell.	WA	WP	m	[21]
C. serra (Endl.) Benth.	WA	WP	w	[21]
Dasypogon bromeliaefolius R. Br.	WA	WP	m	[21]
Kingia australis R. Br.	WA	WP	w	[21]
Lomandra hastilis R. Br.	WA	WP	w	[21]
L. pauciflora R. Br.	WA	WP	w	[21]
Xanthorrhoea gracilis Endl.	WA	WP	m	[21]
X. media R. Br.	Broadsound Range, Q	L, St	w	[20]

2.1. Table 1. Species giving Positive Tests for Alkaloids in Regional Surveys (cont.)
(for abbreviations, see Section 2)

Plant	Locality	Part tested	Test	Ref.
ZINGIBERACEAE				
Alpinia caerulea (R. Br.) Benth.	Whian Whian, NSW	R	w	[20]
Alpinia sp.	Butibum R, PNG	L, St	w	[19]
ZYGOPHYLLACEAE				
Kallstroemia platyptera (Benth.) Engl.	WA	WP	s	[21]
Nitraria schoberi L.	WA	WP	s	[21]
	Flinders Range, SA	L	s	[18]
Tribulus astrocarpus F. Muell.	Windorah, Q	L, B, St	s	[18]
T. hystrix R. Br.	WA	WP	m	[21]
T. terrestris L.	Namango, Q	L, St	w	[20]
	WA	WP	s	[21]
	Toowoomba, Q	WP	w	[17]
Zygophyllum apiculatum F. Muell.	Wandoan, Q	WP	m	[17]
	Roma, Q	L, St	w	[20]
Z. eremaeum Ostf.	WA	WP	w	[21]
Z. glaucescens F. Muell.	WA	WP	w	[21]
Z. idiocarpum F. Muell.	WA	WP	m	[21]

3. ALKALOID ISOLATION

Most of the isolation work had as its aim the discovery of new compounds of possible medical value, or the study of toxic substances responsible for stock losses. An overview of the results to date under each of these subheadings is given, with special reference to alkaloids of particular interest and importance from the point of view of structure, physiological or other properties, and possible mode of biogenesis.

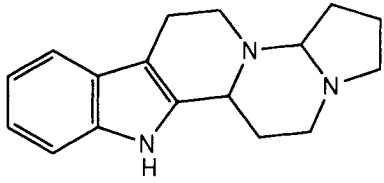
Table 2 comprises a list of plants, grouped under genus and species, from which alkaloids have been isolated, together with the bases obtained from them. Certain of these species do not appear in Table 1 for various reasons, in some cases because they grow in neighbouring Pacific countries but have been studied as a follow-up to work in Australian laboratories on closely related indigenous plants.

3.1. Alkaloids Potentially Useful as Drugs

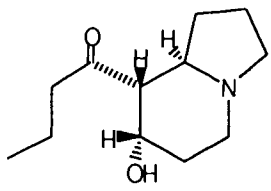
Some of the plants that gave strong tests in the surveys belong to families or genera not previously known to produce alkaloids. These plants were of special interest because of the

prospect of discovering bases of novel structural types, which at the same time might have new and potentially useful pharmacological properties. Apart from these, there was a range of other plants that tested positive but had not been studied previously, which belonged to families such as the Apocynaceae that have a high proportion of members known to produce interesting alkaloids.

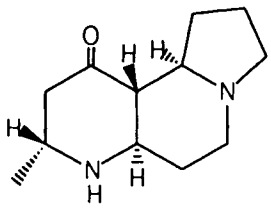
No alkaloids had been obtained from the family Elaeocarpaceae until a CSIRO group began a study of certain *Elaeocarpus* spp. from New Guinea. Amongst a score or so of alkaloids they isolated was a new indole base, elaeocarpidine (**7**), but most of the others had novel indolizidine structures exemplified by elaeokanine C (**8**), elaeokanidine A (**9**) and elaeocarpine (**10**) [28].



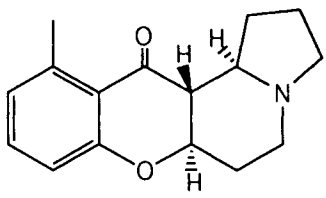
7. Elaeocarpidine



8. Elaeokanine C

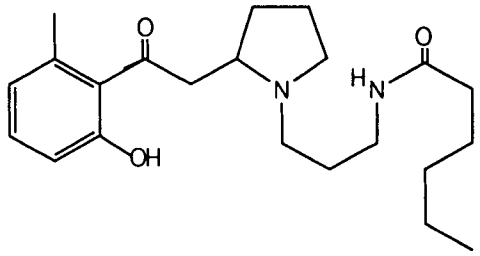


9. Elaeokanidine A

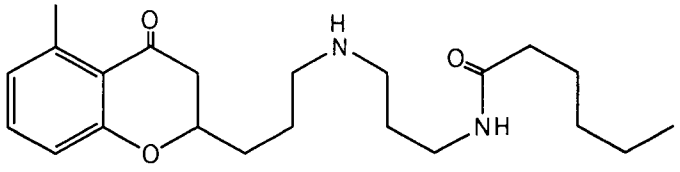


10. Elaeocarpine

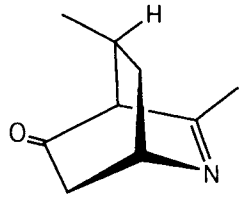
Another genus, *Peripentadenia* from north Queensland, produced a series of alkaloids with diverse structures which include peripentadenine (**11**) [29] and anhydroperipentamine (**12**) [30]. Most of them appear to be related biosynthetically to the *Elaeocarpus* alkaloids, with the possible exception of the unique isoquinuclidine base, mearsine (**13**) [31].



11. Peripentadenine

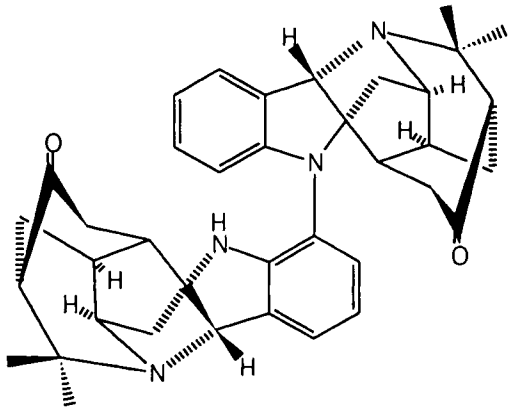


12. Anhydroperipentamine

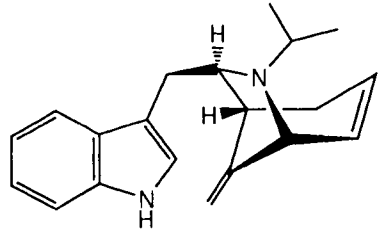


13. Mearsine

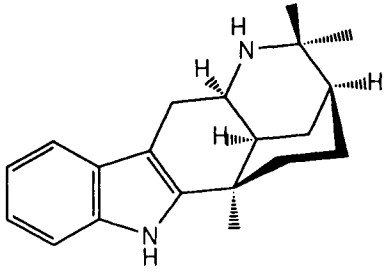
A third genus, *Aristotelia*, has two Australian species endemic in Tasmania and New South Wales, respectively. In contrast to the other genera, the *Aristotelias* furnished indole alkaloids exclusively, all with remarkable structures that are quite distinct even from that of elaeocarpidine (**7**). They appear to be formed biosynthetically from a tryptamine and an unrearranged terpenoid unit, but intricate rearrangements may take place subsequently [32]. One of the most complex *Aristotelia* alkaloids so far found is bisaristone A (**14**) from the N.S.W. species *A. australasica* [33]; others include peduncularine (**15**) [34] and aristoteline (**16**) (35) from *A. peduncularis*, and alloaristoteline (**17**), in which half the molecule is surprisingly inverted as compared with **16** [36].



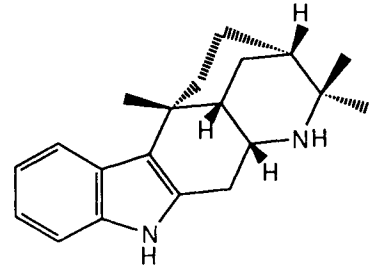
14. Bisaristone A



15. Peduncularine



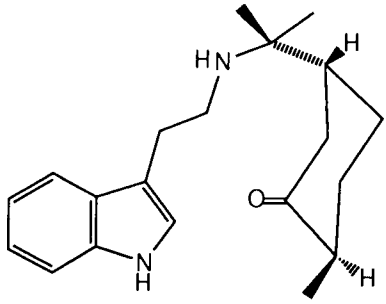
16. Aristoteline



17. Alloaristoteline

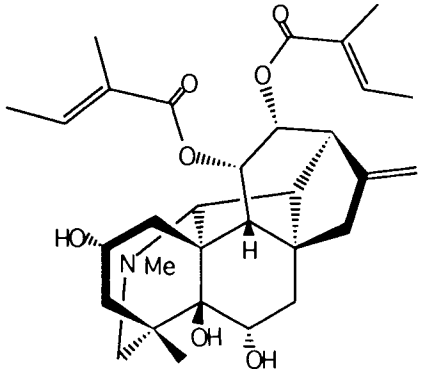
About forty *Aristotelia* alkaloids are now known, including examples from related species endemic in New Zealand and Chile [37]. Fruticosonine (**18**), the simplest *Aristotelia* alkaloid

isolated so far and the first to be synthesised, was obtained from the N.Z. species *A. fruticosa* [38].

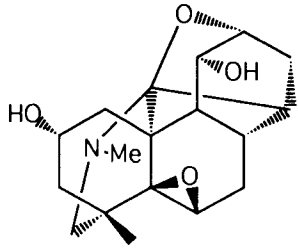


18. Fruticosonine

The genus *Anopterus*, which also has two species found in Tasmania and in New South Wales, respectively, belongs to the family Grossulariaceae and was likewise not known to elaborate alkaloids before a study by CSIRO workers. They found that both species produce a series of diterpenoid alkaloids with a new type of ring system, of which anopterine (**19**) [39] provides an example. The structure comprises several fused rings, and when the ester groups are hydrolysed and the resultant diol is oxidised, the nucleus becomes even more convoluted and forms the extraordinary cage structure **20** [40].



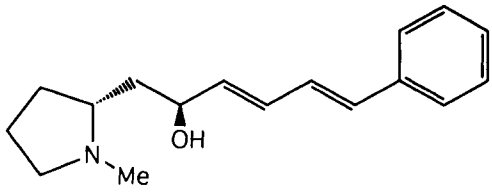
19. Anopterine



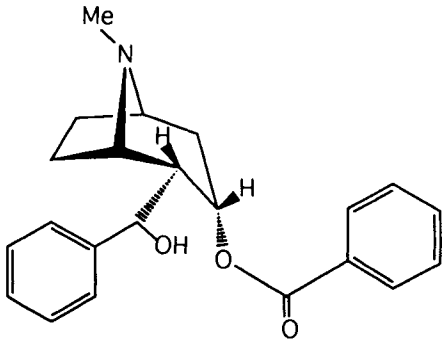
20.

The Proteaceae constitute one of the best-known and widely distributed families in Australia and southern Africa, but no alkaloids had ever been isolated from it until a study of

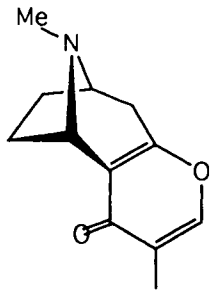
two Tasmanian species, *Bellendena montana* and *Agastachys odorata*, revealed the presence of a whole series of new bases. Others were later found in two *Darlingia* spp. from Queensland, and in a further genus from New Caledonia. There are now nearly fifty proteaceous alkaloids known, divided into several structural types ranging from comparatively simple pyrrolidines like darlingianine (**21**), tropines with unusual substitution patterns such as **22**, or a fused γ-pyrone ring like bellendine (**23**) [41, 42]. The list also includes the quite unrelated trimethylamine derivative **24** [43].



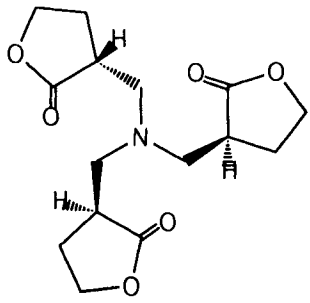
21. Darlingianine



22.

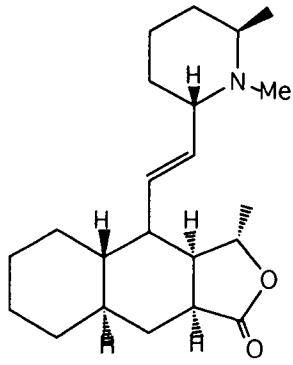


23. Bellendine

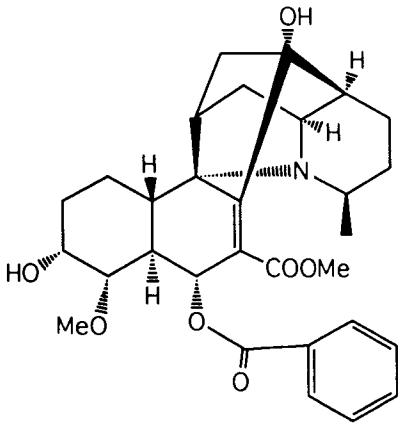


24.

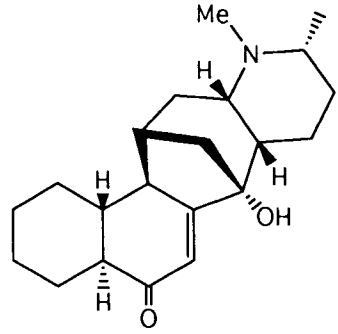
Only one species is attributed to the ancient relic family Himantrandaceae, but a large number of alkaloids have been isolated from it by a Sydney University group [44, 45]. The species, now known as *Galbulimima belgraveana,* occurrs in both New Guinea and north Queensland, and its content of alkaloids is very variable. They are, as might be expected, quite different in structure from any others, and some of the diverse types are represented by himbacine (**25**), himandridine (**26**) and himbadine (**27**).



25. Himbacine



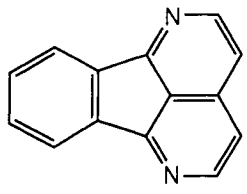
26. Himandridine



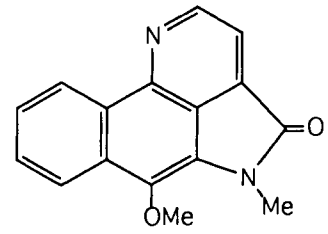
27. Himbadine

Another monogeneric family of great antiquity, the Eupomatiaceae, was also investigated in the University of Sydney, and the first species studied, *Eupomatia laurina,*

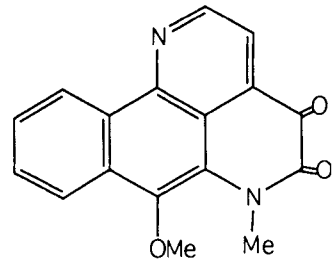
likewise grows in New Guinea as well as in Australia. In addition to known alkaloids of the aporphine type, it produced some novel and interesting structures such as those of eupolauridine (**28**) and eupolauramine (**29**) [46], which were confirmed by synthesis and by X-ray crystallography, respectively. Among the various bases isolated from a second species was imbiline I (**30**) with yet another type of skeleton [294].



28. Eupolauridine

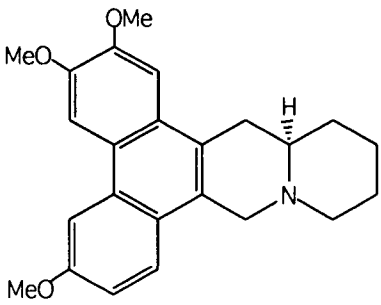


29. Eupolauramine

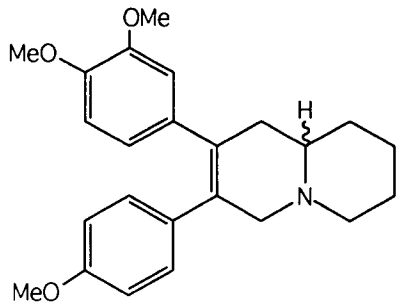


30. Imbiline I

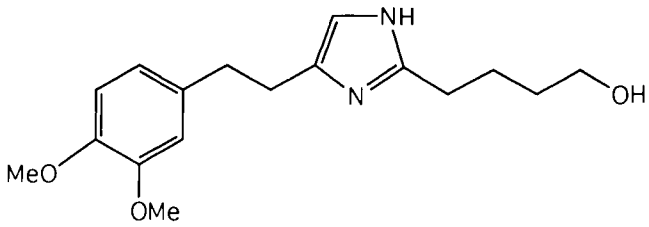
The pandemic nettle family, Urticaceae, was hardly known as a source of alkaloids until the isolation of the phenanthroquinolizidine base cryptopleurine (**31**) from two *Boehmeria* spp., together with certain others such as the seco-base, julandine (**32**), that appear to be biosynthetically related to it [47]. The latter had not been recorded previously, but cryptopleurine was already known, having been obtained from a lauraceous plant referred to later; apart from these examples, another genus of the Urticaceae, *Cypholophus*, produced cypholophine (**33**), a new type of imidazole alkaloid [48].



31. Cryptopleurine

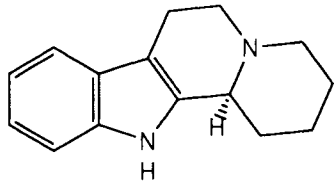


32. Julandine



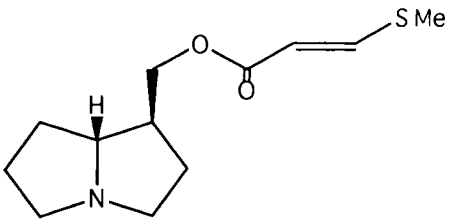
33. Cypholophine

Alkaloids were found for the first time in several other smaller families confined to north Queensland and to New Guinea. The alkaloids were mostly variants of known types, such as the indole base **34** isolated from *Dracontomelon mangiferum*, a member of the Anacardiaceae [49].

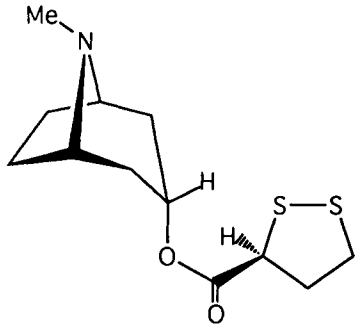


34.

Certain *Planchonella* spp. (Sapotaceae) furnished unusual pyrrolizidine alkaloids, including the methylthioacrylate ester of laburnine (**35**) [50]. Another uncommon sulphur-containing ester group was encountered in the structure of the tropane alkaloid brugine (**36**), furnished by the rhizophoraceous plant, *Bruguiera sexangula* [51].

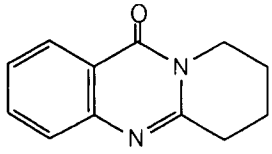


35.

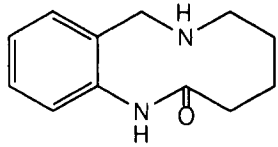


36. Brugine

The genus *Mackinlaya* (Araliaceae) on the other hand yielded quinazolines of a type not previously encountered, such as **37** [52], accompanied by a base (**38**) with a macro heterocyclic ring that appears to be biosynthetically related to the quinazoline types [53].

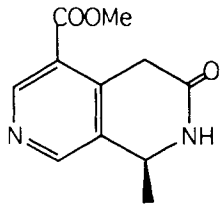


37.



38.

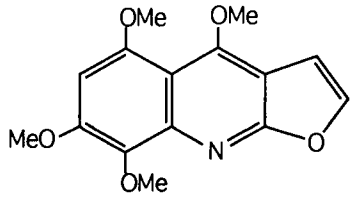
Some relatively simple but unusual pyridine derivatives, including jasminine (**39**), were isolated from *Jasminum* and *Olea* species belonging to the Oleaceae [54, 55].



39. Jasminine

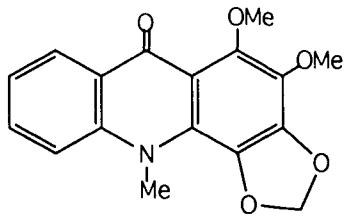
The family Rutaceae was one of the first to be examined as a result of the systematic alkaloid investigations launched by the CSIRO, and complemented by studies undertaken in several Australian universities. The family was already known to produce furoquinoline

alkaloids, and further examples of this type, such as acronycidine (**40**), were furnished by some of the genera found in Australia, including *Melicope, Flindersia, Euodia* and *Acronychia* [56].

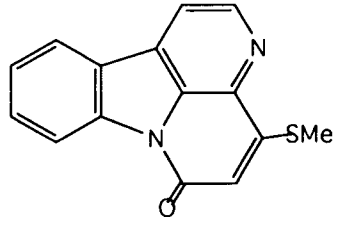


40. Acronycidine

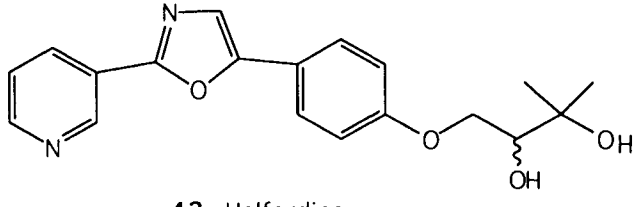
Other genera such as *Zanthoxylum* provided predominantly canidine- and chelidonine-type alkaloids [248]. In addition, these and other genera were found to produce several new structural types: feebly basic acridones like melicopine (**41**) [57], the first canthinone alkaloids including the 5-methoxy [58] and the 4-methylthio (**42**) [59] derivatives, and several oxazole alkaloids exemplified by halfordine (**43**) [60].



41. Melicopine

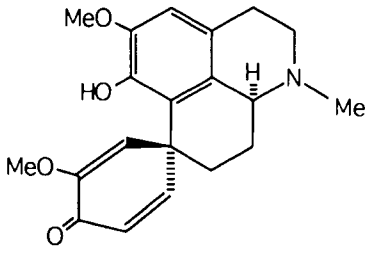


42. 4-Methylthiocanthinone

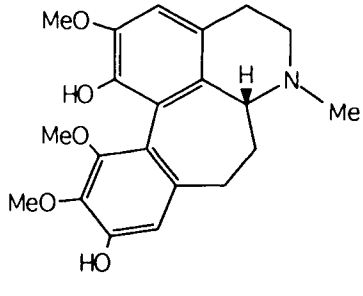


43. Halfordine

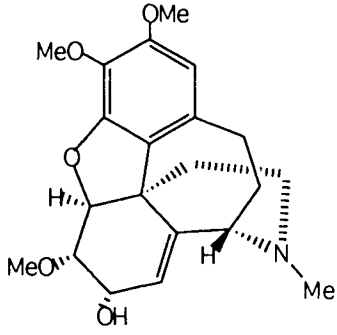
The Liliaceae were likewise already known as a family that produced alkaloids at the time when investigations were begun in the U.K. into a Queensland species now called *Tripladenia cunninghamii*. The bases isolated from this plant, however, turned out to have a range of interesting new structures, all related biosynthetically to phenethyltetrahydroisoquinoline. Some examples include kreysiginone (**44**) [61], floramultine (**45**) [62], and kreysiginine (**46**) [63, 64], which represent homo analogues of the well-known proaporphine, aporphine and morphine series, respectively. Even more interesting were the alkaloids isolated by a CSIRO group from another liliaceous Queensland plant, *Kuntheria pedunculata*. They proved to be the first homoerythrina alkaloids, of which schelhammerine (**47**) is an example [65]. There are now about fifty homoerythrina bases known [66], including ones that have been found in quite unrelated families like the Phellinaceae of New Caledonia, and the Taxodiaceae: the *Athrotaxis* species, which are the only members of the latter family in the southern hemisphere, are endemic in Tasmania, and the alkaloid selaginoidine (**48**) produced by one of them has a furan in place of the benzene ring of **47** [67].



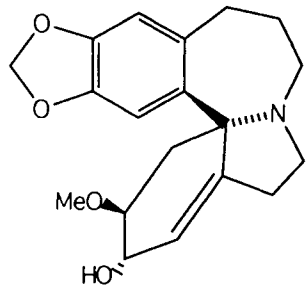
44. Kreysiginone



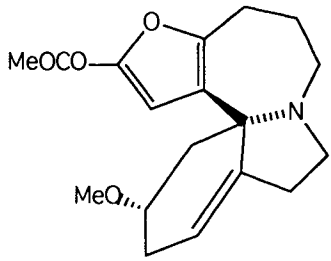
45. Floramultine



46. Kreysiginine

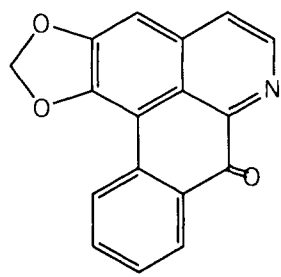


47. Schelhammerine

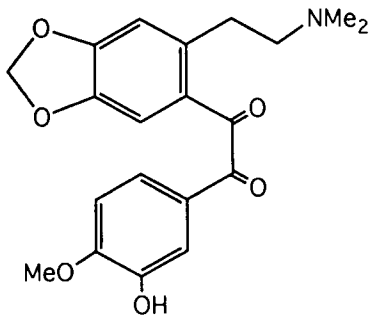


48. Selaginoidine

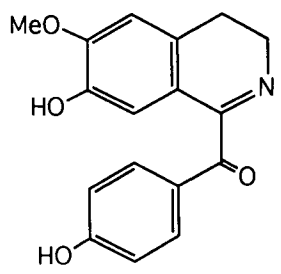
A large number of alkaloids related to benzylisoquinoline, especially aporphines and biscoclaurines, were obtained from plants belonging to the families Annonaceae, Hernandiaceae, Lauraceae, Magnoliaceae, Menispermaceae and Monimiaceae, all of which grow in rain-forest areas of Australia, New Guinea and other Pacific islands. Many of these bases were already known, or differed only in minor details from standard types. Some of the more unusual benzylisoquinoline-derived alkaloids produced by these families include spermatheridine (**49**) (later known as liriodenine), the first example of the now well-known oxoaporphine alkaloids, which was isolated originally from *Atherosperma moschatum* (Monimiaceae) [2, 68]; the interesting benzil derivative cryptopleurospermine (**50**) from *Cryptocarya pleurosperma* (Lauraceae) [69], and longifolonine (**51**) from the New Caledonian *C. longifolia* [70], which appears to be related biogenetically to **50**. As far as bisbenzylisoquinolines are concerned, the isolation of the first example, berbamine (**1**), from *A. moschatum*, has already been mentioned [1, 2]; apart from this, the first of the type with a benzodioxin group, micranthine (**52**), was obtained from another Australian monimiaceous plant, *Daphnandra micrantha*, early in the century in the U.K. [13], but its structure was not elucidated until much later [71].



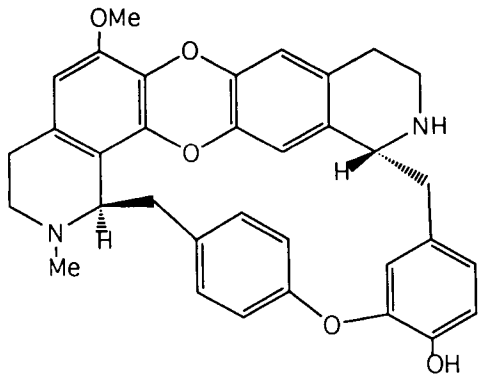
49. Spermatheridine (Liriodenine)



50. Cryptopleurospermine

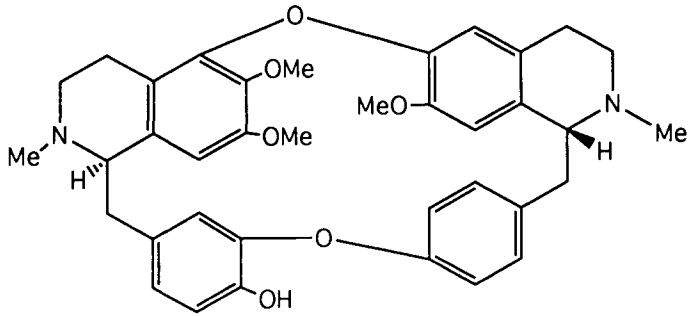


51. Longifolonine

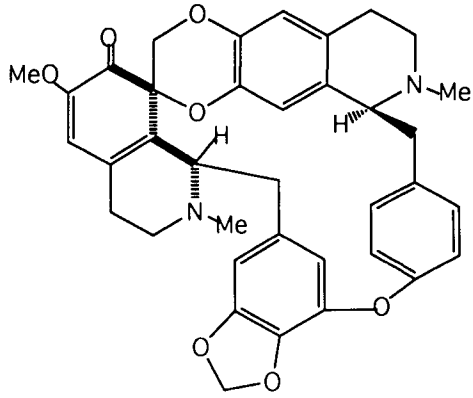


52. Micranthine

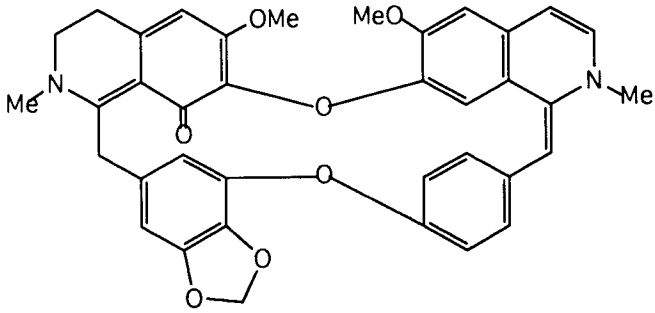
The related New Caledonian plant, *Nemuaron vieillardii*, produces nemuarine (**53**), the only bisisococlaurine alkaloid so far recorded [72], but the most remarkable bisbenzylisoquinolines are surely the two yellow alkaloids isolated from the north Queensland monimiaceous plant *D. repandula*: repanduline (**54**), with its spiro carbon and fused dioxin ring [73], and daphnine (**55**), which has amongst other features a unique 7-7' ether linkage between the isoquinoline units instead of the usual 8-7' one, suggesting that a Smiles-type rearrangement has occurred during its biosynthesis [74-76].



53. Nemuarine

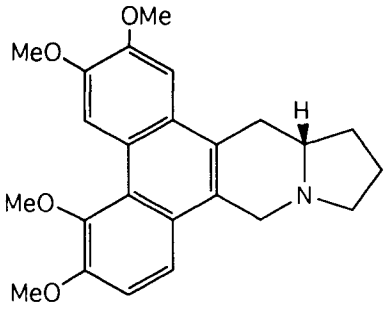


54. Repanduline

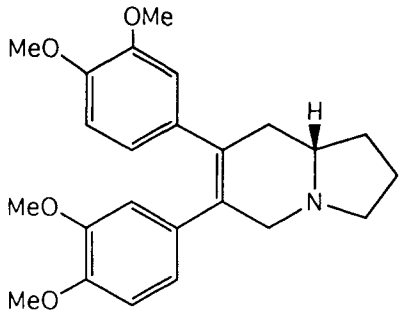


55. Daphnine

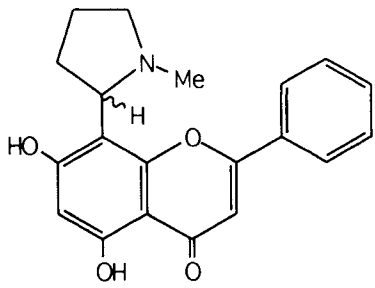
In addition to benzylisoquinolines, the family Lauraceae furnishes phenanthroquinolizidine alkaloids such as the previously mentioned cryptopleurine (**31**) [77], a highly cytotoxic and vesicant substance first isolated from *Cryptocarya pleurosperma* [78]. These alkaloids are closely related structurally to the phenanthroindolizidines, a group of bases found in the families Asclepidaceae and Moraceae that are likewise vesicant. An example is tylocrebrine (**56**), which is elaborated by a Queensland plant from each family, *Tylophora crebriflora* [79] and *Ficus septica* [80], respectively. In the latter it occurs along with the seco analogue septicine (**57**), its presumed biosynthetic precursor. Apart from phenanthroindolizidines, certain *Ficus* spp. produce some simple pyrrolidine bases such as ficine (**58**) that are noteworthy because of their flavonoid substituents [81].



56. Tylocrebrine



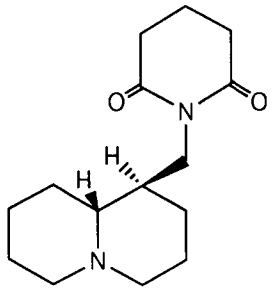
57. Septicine



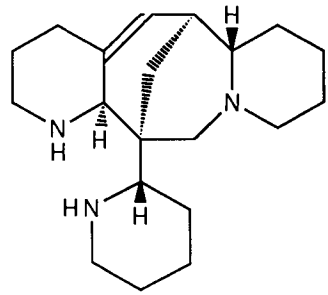
58. Ficine

A number of unusual quinolizidine alkaloids have been isolated from various leguminous plants now classified in the Fabaceae, such as lamprolobine (**59**) from *Lamprolobium fruticosum* [82], and podopetaline (**60**), a new member of the *Ormosia* group of alkaloids that was isolated from *Podopetalum ormondii* [83]. Other genera, including *Templetonia* and *Hovea*, have been found to produce well-known leguminous alkaloids such

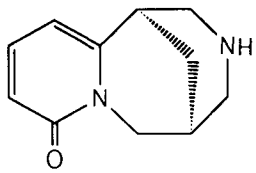
as cytisine (**61**) and sparteine (**62**), but in addition *Hovea longipes* furnishes the remarkable base hoveine (**63**) [84].



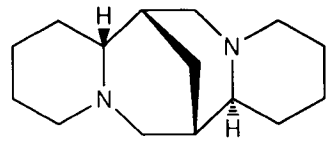
59. Lamprolobine



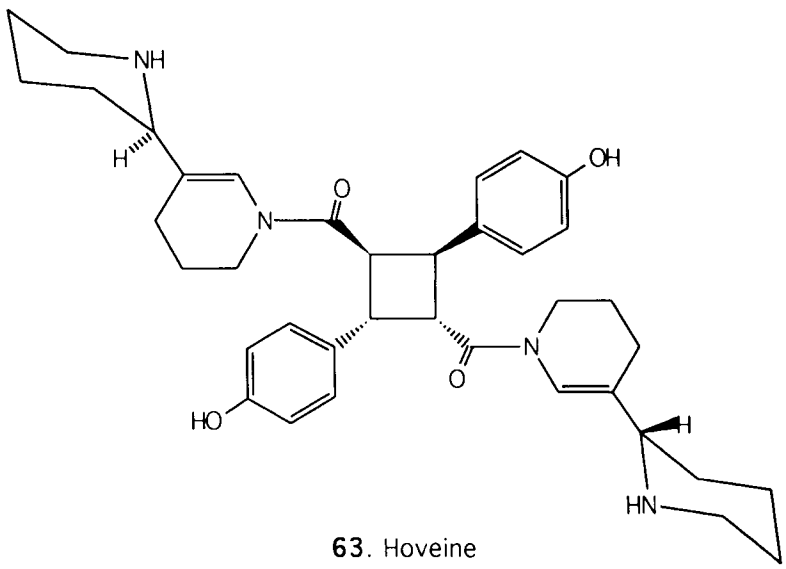
60. Podopetaline



61. Cytisine

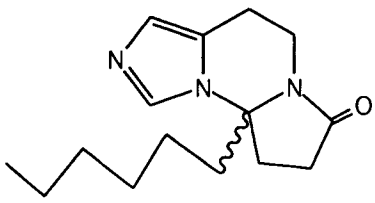


62. Sparteine

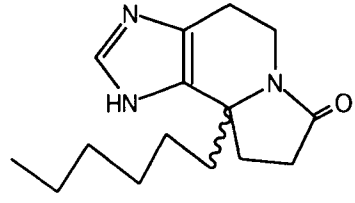


63. Hoveine

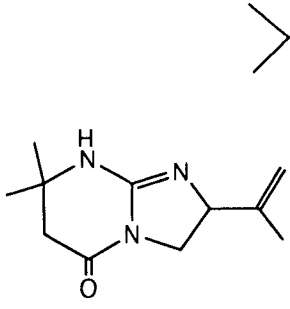
The family Euphorbiaceae has long been known to produce a series of interesting alkaloids of various structural types, and the representatives studied by the CSIRO have further extended the range. The New Guinea species, *Glochidion philippicum,* furnished the alkaloids glochidine (**64**) and glochidicine (**65**), each with ring systems not previously reported [85], while yet another type of nucleus was found in alchornine (**66**) from *Alchornea rugosa;* the latter base is perhaps related biosynthetically to the triisopentenylguanidine (**67**) which accompanies it [86].



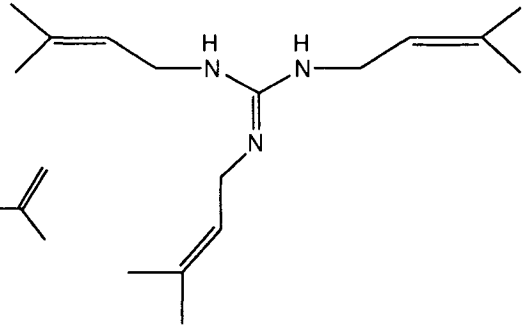
64. Glochidine



65. Glochidicine



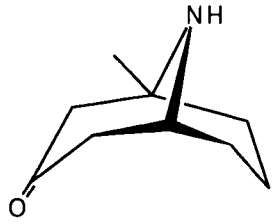
66. Alchornine



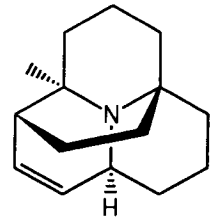
67.

Another species, *Euphorbia atoto,* contains the alkaloid euphococcinine (**68**) with a homotropane-type ring system [87]. It was found later that the same substance was elaborated by the Australian ladybird, *Cryptolaemis montrouzieri,* as a toxic defence substance against predators [88]. A further series of euphorbiaceous alkaloids with novel ring systems was provided by *Poranthera corymbosa,* from which porantherine (**69**), porantheridine (**70**) and poranthericine (**71**) were obtained. Some indication of their possible mode of biogenesis can be inferred from the quinolizidine alkaloid porantherilidine (**72**) which occurs in the same plant [89]. As a fascinating footnote to this group of euphorbiaceous alkaloids, it may be noted that the 9b-azaphenalene ring system, which is quite distinct from that in euphococcinine (**68**), was found for the first time in nature in poranthericine (**71**), but turned up shortly afterwards in

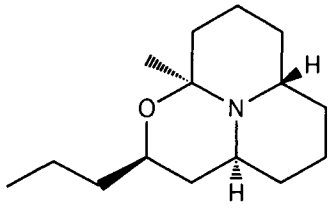
coccinelline (**73**), a defence substance of the European ladybird *Coccinella septempunctata* [90].



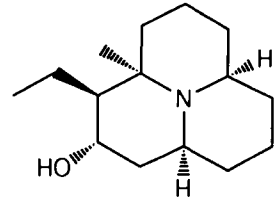
68. Euphococcinine



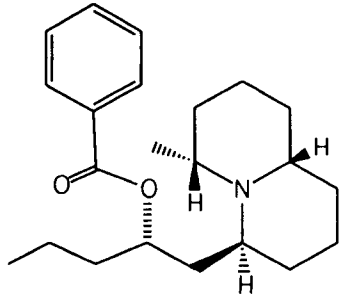
69. Porantherine



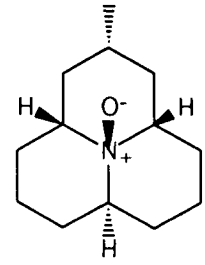
70. Porantheridine



71. Porantherícine



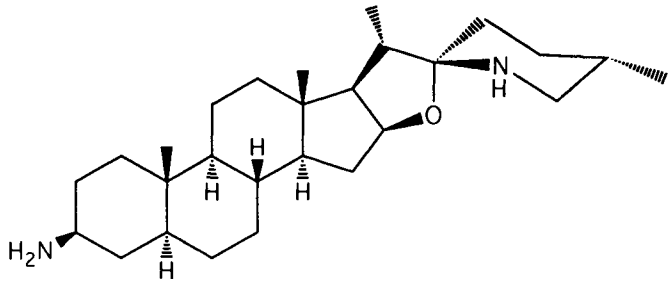
72. Porantherilidine



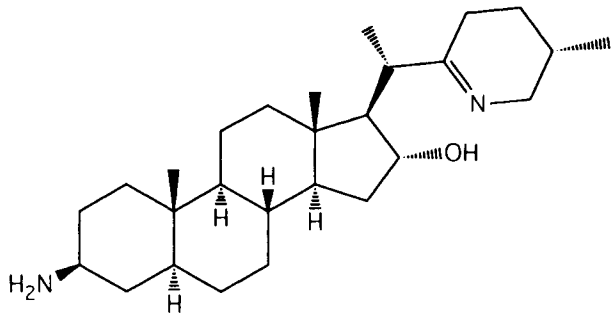
73. Coccinelline

Some new steroidal alkaloids, including the dibasic examples soladunalinidine (**74**) and solacallinidine (**75**), were isolated in the course of a systematic Australia-wide survey of

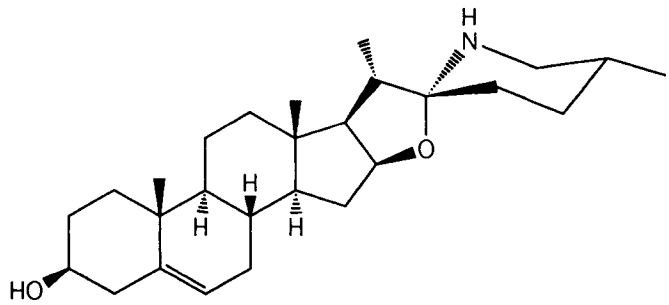
native *Solanum* spp. (Solanaceae) to find the most suitable species for use in the production of steroid hormones. None of the 85 species collected and examined as a result of this joint Monash-Waite Institute project proved superior to *S. aviculare*, which was already employed for the purpose because of its high solasodine (**76**) content [23].



74. Soladunalinidine

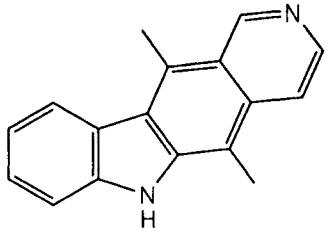


75. Solacallinidine

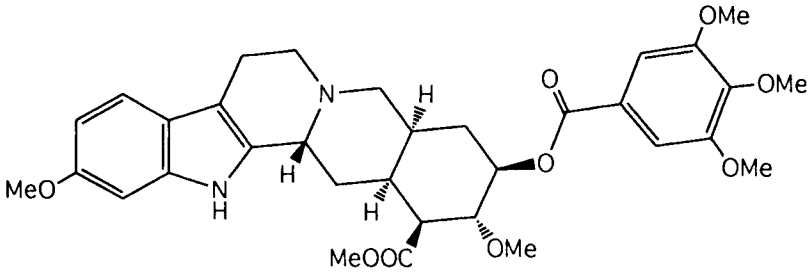


76. Solasodine

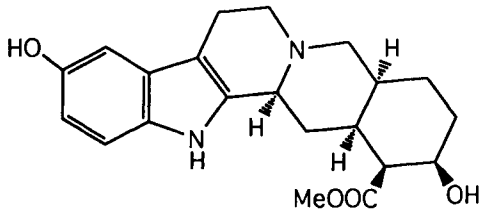
A wide range of indole alkaloids, some of which have been already mentioned, was obtained in the course of the CSIRO studies. They extend from simple tryptophan derivatives produced by leguminous plants of the genera *Acacia, Aotus* and *Pultanaea,* to quite complex ones furnished by the families Rubiaceae and Apocynaceae. The latter especially provided many indole bases from genera that occur elsewhere and were widely known as alkaloid producers, such as *Alstonia, Kopsia, Melodinus, Ochrosia* and *Voacanga.* Amongst the numerous known alkaloids obtained were ellipticine (**77**) and reserpine (**78**); they were accompanied by many unrecorded variations of the yohimbine, ajmaline, ajmalicine and other indolic types, whose structures were established as the result of much detailed chemical, spectroscopic and X-ray crystallographic work. An example is provided by powerine (**79**) [91], a yohimbine-type base from the north Queensland plant *Ochrosia poweri.* Syntheses were developed for ellipticine (**77**) [92] and other alkaloids of special interest by reason of their antitumor or other properties. Apart from alkaloids belonging to known structural types, the Apocynaceae also provided the first of a novel and intriguing series typified by ervatamine (**80**), a constituent of *Ervatamia orientalis* which was studied in the University of Western Australia [93]. This series differs from most types of indole alkaloid in having three carbons between the basic nitrogen and the indole nucleus, a structural feature it shares with ellipticine; both alkaloids pose intriguing biosynthetic puzzles.



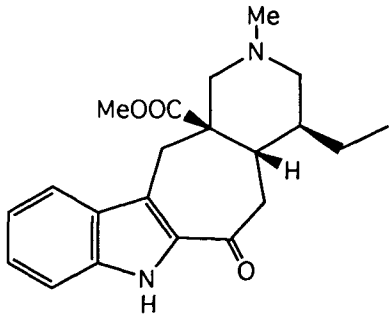
77. Ellipticine



78. Reserpine

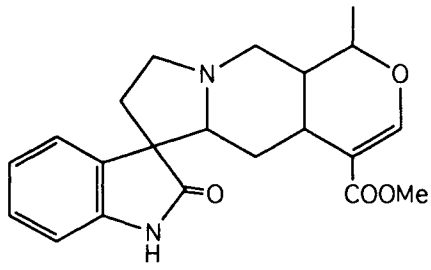


79. Powerine

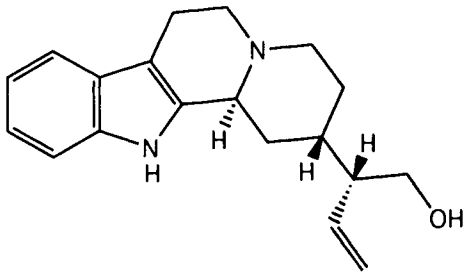


80. Ervatamine

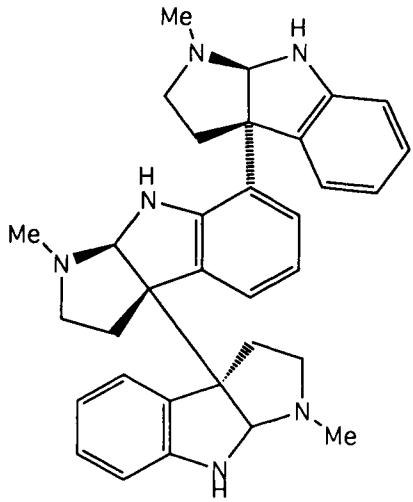
Many indole alkaloids were also obtained from the family Rubiaceae, including various examples belonging to the corynantheine and oxindole series; bases of the latter type were isolated from two *Uncaria* spp., and the configurations of the four isomeric uncarines so obtained, all with the general structure **81** [94], were elucidated together with those of two others already known; their stereochemistry was established through interconversions and careful spectroscopic studies by a CSIRO group [95]. Another example is furnished by antirhine (**82**), a new member of a rare type of indole base from *Antirhea putaminosa*, whose structure and absolute stereochemistry were also established by CSIRO workers [96]. Among the alkaloids with novel structures were some remarkable oligoindoles from *Hodgkinsonia frutescens*, e.g. hodgkinsine (**83**), which has three tryptamine units linked together [97, 98]; another with five linked units has been isolated from the New Guinea plant *Psychotria beccarioides* [99].



81. Uncarines A - F

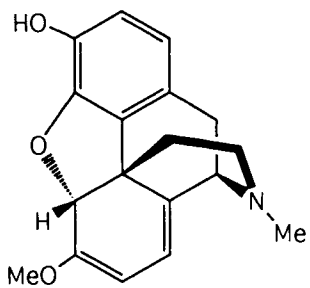


82. Antirhine

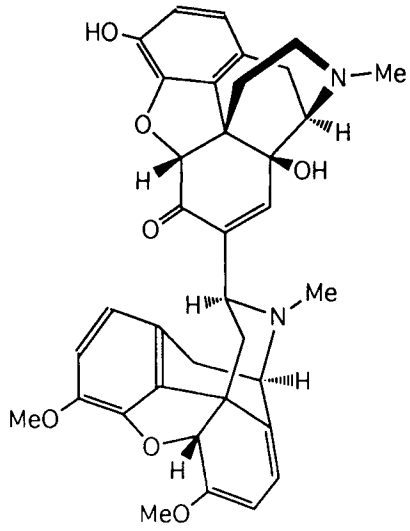


83. Hodgkinsine

The commercial cultivation of the opium poppy was commenced in Tasmania in the early 70s under Government supervision, and a special variety was developed for local conditions. In addition to high yields of the main alkaloids of economic interest, morphine and codeine, the variety produced considerable amounts of several other bases such as oripavine (**84**) [100] that had not been encountered previously in *Papaver somniferum;* others include the novel dimeric alkaloid somniferine (**85**) [101].

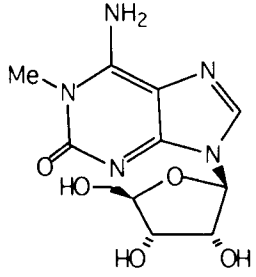


84. Oripavine

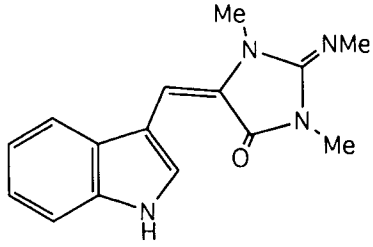


85. Somniferine

Alkaloids of Marine Origin. Interest in natural products from marine sources was stimulated throughout Australia in the mid 70s by the setting up of the Roche Research Institute of Marine Pharmacology (RRIMP) near Sydney by the Swiss pharmaceutical company. Its object was the isolation of new and useful drugs from organisms found in coastal waters, a special attraction being the wealth of marine life on the Great Barrier Reef. Among the many new substances isolated were a number of alkaloids with interesting pharmacological properties such as 1-methylisoguanosine (**86**) [102] and methyl aplysinopsin (**87**) [103].

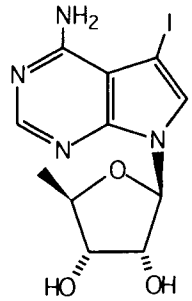


86. 1-Methylisoguanosine

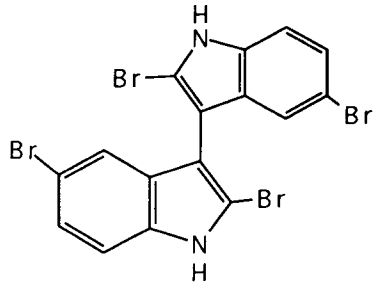


87. Methyl aplysinopsin

They were obtained for the most part from animal rather than plant sources, but some that do fall within the scope of this review include 5'-deoxy-5-iodotubercidin (**88**), obtained from the Western Australian red alga *Hypnea valendiae* [104], and the bisindole **89** from the blue-green alga *Rivularia firma* [105].



88. 5'-Deoxy-5-iodotubercidin



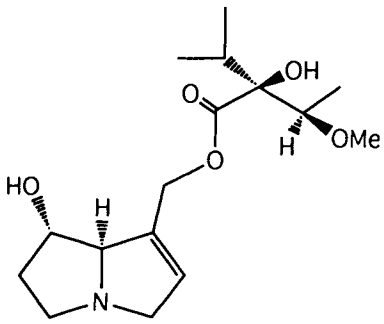
89.

3.2. Toxic Alkaloids from Poison Plants

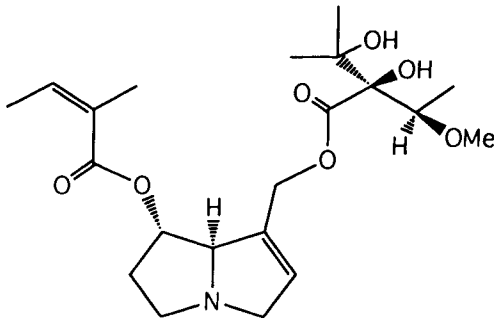
Whereas the search for plants that might yield useful drugs was concentrated mainly in the rain-forest areas of eastern Australia and New Guinea, another aim of the CSIRO's programme, to study plants poisonous to stock, was directed rather to the drier interior areas. A substantial proportion of the toxins proved to be alkaloids; a major part of the programme was centered around the pyrrolizidine bases found in various species of the Boraginaceae, and the genera *Crotalaria* and *Senecio* of the families Fabaceae and Asteraceae, respectively [106, 107]. In addition to well-known examples like heliotrine (**90**) and lasiocarpine (**91**), many new alkaloids, some with a standard type of pyrrolizidine nucleus but with a different combination of known necic acids, were isolated and their constitutions elucidated as a result of much painstaking work. One of the most unusual alkaloids found was the seco-base retusamine (**92**) [108,109] from *Crotolaria retusa*, a plant which was shown to be the main cause of Kimberley Horse Disease.

Apart from the chemistry of these pyrrolizidine alkaloids, their physiological effects, in particular their hepatotoxicity, have been investigated in depth by the CSIRO Division of Animal Health, as a result of which it has been possible to establish correlations between activity and structure: liver damage is caused by alkaloids such as **90** or **91** because unsaturated amino alcohols of this type, which are esterified on one or both hydroxyl groups, undergo metabolism in the liver to form the toxin **93**; this substance is immediately responsible for the mutagenic and carcinogenic effects observed [106, 107], which include

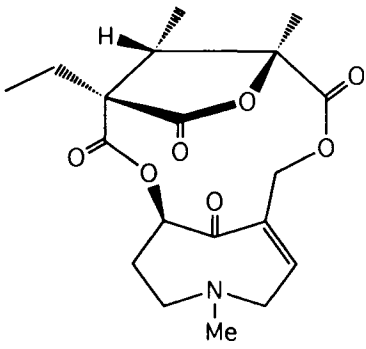
chromosome breakage [137]. As an interesting extension to the veterinary and toxicological work, the activities of certain Danaid butterflies that collect pyrrolizidine bases from various plants and store them for use as sex hormones were also studied [110].



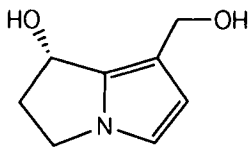
90. Heliotrine



91. Lasiocarpine

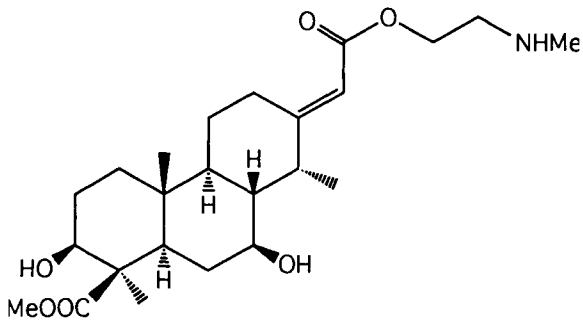


92. Retusamine



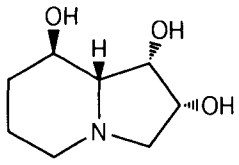
93.

From another leguminous plant now classified in the Caesalpiniaceae, *Erythrophleum chlorostachys*, several alkaloids typified by norerythrostachamine (**94**) were isolated and their structures elucidated: they occur as ethanolamine esters of diterpene acids, but readily rearrange to the corresponding amides [111]. These alkaloids are highly toxic and are responsible for cattle poisoning in the Darwin area.

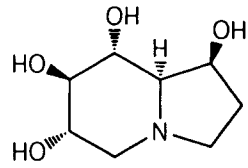


94. Norerythrostachamine

An investigation at Murdoch University into the toxic agent in the Western Australian fabaceous plant, *Swainsonia canescens*, which causes staggers in horses, led to the isolation of the indolizidine alkaloid swainsonine (**95**). The symptoms caused by ingestion of this plant were very similar to those observed in another veterinary disorder known to be occasioned by lack of α-mannosidase, and the Murdoch group was able to show that swainsonine did in fact cause inhibition of this enzyme [112].



95. Swainsonine



96. Castanospermine

Shortly afterwards, but quite unconnected with this work, a group in King's College, London, isolated castanospermine (**96**), the toxic agent in the seeds of another fabaceous plant, *Castanospermum australe* [113], and determined its structure. The noxious effects of these "Moreton Bay chestnuts" to man and animals had long been known: they cause severe intestinal irritation, even death, although the aborigines were reported to have made them edible by soaking them in water and roasting them [114].

A USDA group was struck by the similarity in structure between the two hydroxylated indolizidines **95** and **96**, and was led to examine the effect of castanospermine on hydrolytic enzymes. The American workers found it was a powerful inhibitor of both α- and β-glucosidases [115]; it was further shown to inhibit glycoprotein processing [116], which in

turn led to its recognition as a potential agent for inhibiting virus envelope glycoprotein processing of the Human Immunodeficiency Virus (HIV), and for the treatment of AIDS [117]. Castanospermine has also been shown to inhibit a range of other viral disorders such as cytomegalovirus [118], and its possible applications as an anti-inflammatory agent in cases of allergic encephalomyelitis [119], and in the treatment of rheumatoid arthritis [120] are at present under study.

3. 3. Table 2. Plants from which Alkaloids have been Isolated

Acacia adunca (Mimosaceae) *N*-Methylphenylethylamine	[138]
A. argentea N^{α}-Cinnamoylhistamine	[139]
A. complanata *N*b-Methyltetrahydroharman	[140]
A. harpophylla Hordenine	[138]
A. holosericea Hordenine	[138]
A. kettlewelliae *N*-Methylphenylethylamine	[138]
A. maidenii N^{b}-Methyltryptamine, $N^{b}N^{b}$-dimethyltryptamine	[141]
A. phlebophylla *N*b,*N*b-Dimethyltryptamine	[142]
A. polystachya N^{α}-Cinnamoylhistamine	[139]
Acronychia baueri (Rutaceae) Acronycine, melicopine, melicopidine, melicopicine, acronycidine, 1,2-dimethylquinol-4-one, xanthevodine, normelicopidine, supinine, rinderine, noracronycidine, isoacronycidine	[143 - 146]
A. haplophylla Acrophilline, acrophillidine, 4-hydroxy-2,3-dimethoxy-10-methylacridone	[147,148]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Actinodaphne nitida (Lauraceae) Boldine, laurolitsine	[149]
Agastachys odorata (Proteaceae) (-)-6β-Acetoxy-3α-tigloyloxytropane, 3α-(p. hydroxybenzoyloxy)trop- 6-ene	[128]
Alangium villosum ssp. *polyosmoides* (Alangiaceae) Tubulosine	[20]
Alchornea javanensis (Euphorbiaceae) Alchornine, alchornidine, N^1N^1-diisopentenylguanidine, $N^1N^2N^2$-triisopentenylguanidine, 2,2-dimethylacrylamide	[86,150]
Alphitonia macrocarpa (Thamnaceae) Adoetine X	[20]
Alseodaphne archboldiana (Lauraceae) (-)-Norarmepavine, (+)-reticuline, (+)- and (-)-coclaurine	[151]
Alstonia constricta (Apocynaceae) Reserpine, alstonidine, alstonilidine, vincamajine, *O*-(3,4,5-trimethoxycinnamoyl) vincamajine, *O*-(3,4,5-trimethoxybenzoyl) quebrachidine	[152,153]
A. glabriflora Pleiocarpamine, villalstonine, macralstonine, alstophylline	[154]
A. spectabilis Pleiocarpamine, vincamagine, quebrachidine, villalstonine, macralstonidine, *N*-methylsarpagine, alstonamine, echitenine, ditamine	[154]
Amsinckia calycina (A. hispida) (Boraginaceae) Intermedine, lycopsamine, echiumine	[133]
A. intermedia Intermedine, lycopsamine, sincamidine, echiumine	[133]
A. lycopsoides Intermedine, lycopsamine, echiumine	[133]
Anopterus glandulosus (Grossulariaceae) Anopterine, hydroxyanopterine, dihyroxyanopterine	[40]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

A. macleayanus [39,40,155,156]
Anopterine, anopterimine, anopterimine *N*-oxide, hydroxyanopterine, dihydroxyanopterine, 7β-hydroxyanopteryl-11α(E)-4-hydroxy-2-methylbut-2-enoate-12α-tiglate, 7β-hydroxyanopteryl-11α, 12α-ditiglate, anopteryl 12α-tiglate, anopteryl 11α-4-hydroxybenzoate 12α-tiglate, 7β-hydroxyanopteryl-11α-4-hydroxybenzoate 12α-tiglate

Anthocercis fasciculata (Solanaceae) [157]
(-)-Hyoscyamine

A. littorea [157]
(-)-Hyoscyamine, meteloidine, littorine

A. tasmanica [158]
Hyoscine, nicotine

A. viscosa [157]
(-)-Hyoscyamine

Anthotroche pannosa (Solanaceae) [159]
(-)-Hyoscyamine

Antirhea putaminosa (Rubiaceae) [96,160]
Antirhine

Aotus subglauca (Fabaceae) [161]
S-(+)-*N*b-Methyltryptophan methyl ester, *S*-(+)-*N*b,*N*b-dimethyltryptophan methyl ester

Argyrodendron peralatum (Sterculiaceae) [162]
N^{α}-Cinnamoylhistamine

Aristotelia australasica (Elaeocarpaceae) [33, 36, 163 - 165]
Bisaristones A and B, aristolasol, aristolasese, 17-hydroxyhobartine, hobartidiol, aristoteline, aristotelinone, aristolasicone, aristolasicol, aristocarbinol, aristolasicolone, epi-11-aristoteline, dehydro-9,10-aristoteline, aristoserratenine

A. fruticosa [38, 166]
Fruticosonine, aristofruticosine

A. peduncularis [34, 167 - 171]
Peduncularine, isopeduncularine, aristoserratine, hobartine, sorelline, tasmanine

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

A. serrata [35,169,172 - 176]
Aristoteline, aristoserratine, serratenone, serratoline, aristotelinone, aristomakine, makomakine, makonine, tasmanine

Atherosperma moschatum (Monimiaceae) [2,68,177 - 181]
Berbamine, isotetrandrine, isocorydine, atherosperminine, atherospermidine, spermatheridine, spermatherine, atherospermoline, atheroline, moschatoline, methoxyatherosperminine

Athrotaxis cupressoides (Taxodiaceae) [125]
Taxodine, 3-epischelhammericine, *O*-methylathrocupressine, 2-epihomoerythratine, homoerythratine, 2-hydroxytaxodine,athrocupressine, 2-acetoxytaxodine, 2-acetoxyisocupressine, 2-hydroxyisotaxodine, 2-epihydroxyisotaxodine

A. laxifolia [67]
Selaginoidine, taxodine, 3-epischelhammericine, homoerythratine, 2-hydroxytaxodine, 2-hydroxyisotaxodine, 2-epihydroxyisotaxodine

A. selaginoides [67]
Selaginoidine, taxodine, 3-epischelhammericine, homoerythratine, 2-hydroxytaxodine, 2-hydroxyisotaxodine, 2-epihydroxyisotaxodine, athrocupressine

Beilschmiedia elliptica (Lauraceae) [182]
Laurelliptine, isoboldine

B. podagrica [183]
(+)-2-Hydroxy-1,9,10-trimethoxyaporphine, (+)-2-hydroxy-1,9,10-trimethoxynoraporphine, glaucine, isocorydine, laurelliptine, isoboldine, (+)-2,11-dihydroxy-1,10-dimethoxyaporphine

Bellendena montana (Proteaceae) [43,134,184,185]
Bellendine, isobellendine, darlingine, 5,11-dihydroisobellendine, 2,3-dihydrobellendine, 2,3-epidihydrobellendine, 2,3-dihydrodarlingine, tri-(α-methylene-γ-butyrolactonyl)amine

Bhesa archboldiana (Celastraceae) [186]
9-Angelylretronecine *N*-oxide, 9-angelylretronecine, calycanthine

Bleekeria coccinea (Apocynaceae) [92,187]
9-Methoxyellipticine, ellipticine, reserpine, isoreserpiline, reserpiline

Boehmeria cylindrica (Urticaceae) [189]
Cryptopleurine, julandine

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

B. platyphylla 3,4-Dimethoxy-ω-(2'-piperidyl)acetophenone, cryptopleurine, julandine	[47,190]
Boronia lanceolata (Rutaceae) 1,8-Dihydroxy-9(10*H*)-acridone, 1,8-dihydroxy-10-methyl-9(10*H*)acridinone, 1,3,8-trihydroxy-10-methyl-9(10*H*)-acridinone, 1-acetoxymethyl-2,3-dimethyl-4-(1*H*)-quinolinone	[191]
B. ternata 2-Propyl-4-quinolone	[192]
Bruguiera exaristata (Rhizophoraceae) Brugine, tropine esters of acetic, propionic, butyric, isobutyric, α-methylbutyric or isovaleric and benzoic acids, tropine	[51]
B. sexangula Brugine, tropine esters of acetic, propionic, butyric, isobutyric, α-methylbutyric or isovaleric and benzoic acids	[51,193]
Carallia brachiata (Rhizophoraceae) (+)-Hygroline	[194]
Cassytha filiformis (C. americana)(Lauraceae) Cassythine, cassythidine, methoxycassythine, cassyfiline, actinodaphnine, *N*-methylactinodaphnine, launobine, bulbocapnine, *O*-methylcassifiline, dicentrine, neolitsine, (±)-nornuciferine, cassamedine, cassameridine	[195,196]
C. melantha Cassythicine, actinodaphnine	[197]
C. pubescens Nantenine, domesticine, isoboldine, laurelliptine, sinoacutine, nordomesticine	[198]
C. racemosa 1,2-Dimethoxy-9,10-methylenedioxy-7-oxodibenzo[de,g]quinoline, nornantenine, nantenine, isoboldine, laurotetanine, *N*-methyllaurotetanine, (+)-isococlaurine, laurelliptine	[199]
Castanospermum australe (Fabaceae) Castanospermine, (2*R*, 2*S*)-2-hydroxymethyl-3-hydroxypyrrolidine, 6-epicastanospermine	[113,188,200]
Choisya ternata (Rutaceae) Choisyine, skimmianine, evoxine	[201]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Chorilaena quercifolia (Rutaceae) Dictamnine	[202]
Cinnamomum laubatii (Lauraceae) Reticuline	[203]
Cinnamomum sp. TGH 13077 (-)-Cinnamolaurine, (+)-norcinnamolaurine, (+)-reticuline, (+)-corydine	[204,205]
Citrus macroptera (Rutaceae) (-)-Edulinine	[206]
Clausena brevistyla (Rutaceae) (±)-*N*-Benzoyl[2-hydroxy-2-(4'-methoxyphenyl)]ethylamine, *N*-benzoyltryptamine	[207]
Codonocarpus australis (Gyrostemonaceae) Codonocarpine, *N*-methylcodonocarpine, alkaloids IVa, IX, XII	[208,209]
Crinum macrantherum (Lilliaceae) Macranthine, *O*-acetylmacranthine, *O,O*-diacetylmacranthine, macronine, lycorine, crinamine, criwelline, acetylcaranine	[210]
Crotalaria agatiflora (Fabaceae) Madurensine	[211]
C. anagyroides Anacrotine, 1-methylenepyrrolizidine	[211,212,213]
C. aridicola 7β-Acetoxy-1-methoxymethyl-1,2-dehydro-8α-pyrrolizidine	[214]
C. brevifolia Integerrimine, usuramine	[215]
C. crispata Crispatine, fulvine, monocrotaline	[216]
C. damarensis (-)-1-Methylenepyrrolizidine	[213]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

C. goreensis 7β-Hydroxy-1-methylene-8β-pyrrolizidine, 7β-hydroxy-1-methylene-8α-pyrrolizidine, 1,2-epoxy-1-methylpyrrolizidine	[217]
C. laburnifolia Anacrotine	[215]
C. laburnifolia subsp. *australis* Anacrotine, madurensine	[218]
C. madurensis Madurensine	[211]
C. medicarginea 7α-Hydroxy-1-(methoxymethyl)1,2-dehydro-8α-pyrrolizidine	[214]
C. mucronata Usuramine	[215]
C. retusa Monocrotaline, retronecine *N*-oxide, retusine, retusamine	[108]
C. spectabilis Monocrotaline, spectabiline	[219]
C. trifoliastrum 1-Methoxymethyl-1,2-epoxypyrrolizidine, 1-methoxymethyl-$\Delta^{1,2}$ dehydro-8α-pyrrolizidine, 1-methoxymethyl-$\Delta^{1,2}$ dehydro-7β-hydroxy-8α-pyrrolizidine, 1β,2β-epoxy-1α-hydroxymethyl-8α-pyrrolizidine, 7α-hydroxy-1-(methoxymethyl)1,2-dehydro-8α-pyrrolizidine	[220,217]
C. usaramoensis Usaramine, integerrimine, serecionine, retrorsine	[221]
C. virgulata subsp. *grantiana* Grantianine, grantaline, 1-hydroxymethyl-1β,2β-epoxy-8α*H*-pyrrolizidine	[222]
Cryptocarya angulata (Lauraceae) Isocorydine, roemerine, 3,4-dimethoxy-1-(dimethylaminoethyl)phenanthrene	[223]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

C. archboldiana (-)-Armepavine	[224]
C. bowiei Cryptaustoline, cryptowoline	[225]
C. foveolata (+)-Reticuline	[226]
C. longifolia Thalifoline, longifoline, reticuline, coclaurine, longifolidine, longifolonine, *N*-methylcoclaurine, laurotetanine, *N*-methyllaurotetanine, laurolitsine, isoboldine, norisocorydine, norargemonine, bisnorargemonine, thalifoline, scoulerine	[70]
C. odorata (+)-Reticuline, laurotetanine, *N*-methyllaurotetanine, isocorydine, cryptodorine	[227]
C. phyllostemon (-)-Antofine, dehydroantofine, (-)-cryptowoline, (-)-cryptowolidine, (-)-cryptowolinol, (-)-phyllostemine, (-)-phyllosteminine, (-)-phyllostone, (+)-phyllocryptine, (+)-phyllocryptanine	[130]
C. pleurosperma Pleurospermine, cryptopleurine, cryptopleuridine, cryptopleurospermine	[69,78,228]
C. triplinervis Isocorydine, roemerine, 3,4-dimethoxy-1-(dimethylaminoethyl)phenanthrene	[223]
Cynoglossum amabile (Boraginaceae) Echinatine, amabiline	[229]
C. australe Cynaustraline, cynaustine	[229]
C. latifolium Latifoline, 7-angelylretronecine	[230]
Cypholophus friesianus (Urticaceae) Cypholophine, *O*-acetylcypholophine	[231,48]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Daphnandra apatela (Monimiaceae) Telobine, apateline, 1,2-dehydroapateline, 1,2-dehydrotelobine	[232]
D. aromatica Daphnine, aromoline	[233]
D. dielsii Repanduline, dielsine, (-)-nortenuipine-2β-*N*-oxide, pseudorepanduline, oxyacanthine, *N*-methylapateline, repandine, aromoline	[234 - 236]
D. johnsonii Johnsonine, *N*-methylapateline, *N*-methylnorapateline, repandinine, *O*-methylrepandine, nortenuipine, repandine	[237]
D. micrantha Micranthine, daphnoline, daphnandrine	[13,238]
D. repandula Repandinine, *O*-methylrepandine, repandine, repanduline, daphnine dihydrochloride	[74,238,239]
D. tenuipes Tenuipine, aromoline, repanduline	[238]
Daphnandra sp. Telobine, *O*-methylmicranthine, *N,O*-dimethylmicranthine, nortenuipine, fangchinoline	[71]
Daphnandra sp. Pseudorepanduline	[240]
Daphnandra sp. Isotenuipine	[241]
Darlingia darlingiana (Proteaceae) Darlingianine, darlingine, 5,11-dihydrodarlingine, ferruginine, darlinine, dehydrodarlingianine, isodarlingianine, 2-methylbellendine, epidarlinine, dihydrodarlingianine, tetrahydrodarlingianine, dehydrodarlinine	[242 - 244]
D. ferruginea (+) Ferrugine, 3α-benzyloxy-2α-hydroxybenzyltropane, darlingine, ferruginine, 2-methylbellendine	[244,246]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Datura candida sens lat. (Solanaceae) [246]
(-)-6β-,7β-Dihydroxytropan-3α-yl 3-phenyllactate, (±)-3α,7β-dihydroxytropan-6β-yl tiglate

Discaria pubescens (Rhamnaceae) [126,247]
R-(+)-Coclaurine, pubescine A

D. toumatou [249]
R-(+)-*N*-Methylcoclaurine

Doryphora aromatica (Monimiaceae) [250]
Aromoline, isotetrandrine, 1,2-dehydroapateline, isocorydine, daphnoline, homoaromoline, daphnandrine

D. sassafras [251]
Doryanine, liriodenine, isocorydine, anonaine, reticuline, corypalline, doryphorine, doryflavine, choline chloride

Dracontomelon mangiferum (Anacardiaceae) [49,252]
(-)-Octahydroindolo[2,3a]quinolizine, (-)-hexahydro-12*H*-indolo[2,3a]quinolizine

Dryadodaphne novoguineensis (Monimiaceae) [253]
Dryadodaphnine, laurotetanine, spermatheridine, atheroline

Duboisia hopwoodii (Solanaceae) [10,254,255]
Nicotine, nornicotine, metanicotine, anatabine, bipyridyl, cotinine, *N*-formylnornicotine

D. leichhardtii [10,256,257]
Hyoscine, hyoscyamine, norhyoscyamine, valeroidine, tigloidine, valtropine, butropine

D. myoporoides [10,256,258 - 260]
Hyoscine, hyoscyamine, norhyoscyamine, tigloidine, valtropine, scopolamine, valeroidine, tropine, noratropine, apohyoscine, tropyl butyrate, poroidine, isoporoidine, norhyoscine, acetyltropine, tetramethylputrescine, nicotine, anabasine, isopelletierine

Duboisia x [261]
6-Hydroxyhyoscyamine

Echium plantagineum (Boraginaceae) [262,263]
Echiumine, echimidine, 7-acetylcopsamine, acetintermedine, intermedine, acetylechimidine

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Elaeocarpus archboldianus (Elaeocarpaceae) Elaeocarpidine	[264]
E. densiflorus Elaeocarpidine	[265]
E. dolichostylus (+)-Elaeocarpine, (-)-isoelaeocarpine, (+)-elaeocarpiline, (-)-isoelaeocarpiline	[266,267]
E. kaniensis Elaeokanines A, B, C, D, E, elaeokanidines A, B, C	[268,269]
E. polydactylus (+)-Isoelaeocarpicine, (±)-elaeocarpine, (±)-isoelaeocarpine, elaeocarpidine	[266,270]
E. sphaericus (-)-Isoelaeocarpiline, (+)-elaeocarpiline, (±)-elaeocarpine, elaeocarpidine, (±)-isoelaeocarpine, (+)-epiisoelaeocarpiline, (-)-epielaeocarpiline, (+)-epialloelaeocarpiline, (-)-alloelaeocarpiline, (+)-pseudoepiisoelaeocarpiline	[271,272]
Elmerrillia papuana (Magnoliaceae) Elmerrillicine, liriodenine, norushinsunine, *N*-methylushinsunine iodide	[273]
Eriostemon australis subsp. *banksii* (Rutaceae) *Cis*-Eriaustralasine, *trans*-eriaustralasine, furoeriaustralasine	[274]
Ervatamia angustisepala (Apocynaceae) Ervatamine, epiervatamine	[93]
E. orientalis Ervatamine, 19,20-dehydroervatamine, 20-epiervatamine, ibogaine, iboxigaine, voacristine, vobasine, dregamine, tabernaemontanine, apparicine, voacamine, 16-demethoxycarbonylvoacamine, 19-dehydroervatamine, demethoxycarbonyldihydrovoacamine, 16-demethoxycarbonyl-20'-epidihydrovoacamine	[93,275 - 277]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Erythrophleum chlorostachys (Caesalpiniaceae) [111,278 - 281]
3β-Acetoxynorerythrostachamine, 3β-acetoxynorerythrophlamine, norerythrostachaldine, norerythrophlamine, *N*-2-hydroxyethyl-*N*-methylcinnamamide, β-dimethylaminoethylcinnamate, *N*-2-hydroxyethyl-*N*-methyl-trans-p. hydroxycinnamamide, *N*-2-hydroxyethylcinnamamide, norcassamidine, norcassamidide, norerythrostachamine, norerythrostachamide, norcassaidide, cassaidine, cassamidine, norerythrophlamide, 3β-acetoxynorerythrosuamine

E. ivorense [282]
Cassamide, erythrophalamide

Erythroxylum australe (Erythroxylaceae) [283,284]
(±)-6β-Hydroxytropan-3α-yl tiglate, (+)-3α-hydroxynortropan-6β-yl-2-hydroxy-3-phenyl propionate, (±)- 6β,7β-dihydroxytropan-3α-yl benzoate, meteloidine

E. ellipticum [285]
Tropine-3,4,5-trimethoxycinnamate

Euodia alata (Rutaceae) [286-288]
Evoxanthine, melicopidine, 1,2,3-trimethoxy-10-methylacridone, kokusaginine, evoprenine, evolatine, 1-hydroxy-2,3-dimethoxy-10-methylacridone, skimmianine, evoxine

E. elleryana [289]
Evellerine, 7-*O*-demethylevolitrine, skimmianine

E. littoralis [290]
Dictamnine, kokusaginine, evolitrine

E. xanthoxyloides [143,291 - 293]
Evoxanthine, melicopidine, kokusagine, xanthevodine, 1-hydroxy-2,3-dimethoxy-10-methyl-9 (10*H*)-acridone, evodine

Euphorbia atoto (Euphorbiaceae) [87]
(+)-9-Aza-1-methylbicyclo[3,1,1]nonan-3-one

Eupomatia bennettii (Eupomatiaceae) [294]
Liriodenine, imbilines 1, 2, 3, eupomatidine 1

E. laurina [46,294 - 296]
Eupolauramine, hydroxyeupolauramine, imbilines 1, 2, 3, eupomatidines 2, 3, liriodenine, norushinsunine, eupolauridine

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Exocarpos cupressiformis (Santalaceae) 1-Methoxycarbonylpyrrolizidine	[20]
Festuca arundinacea (Poaceae) Festucine	[297]
Ficus pantoniana (Moraceae) Ficine, isoficine	[81]
F. septica (-)-Tylophorine, (+)-tylocrebrine, septicine	[80]
Flindersia acuminata (Rutaceae) Dictamnine, maculine	[298]
F. bennettiana Skimmianine	[299]
F. bourjotiana Skimmianine, flindersiamine	[300]
F. collina Kokusaginine, flindersiamine	[301]
F. dissosperma Flindissol, flindersiamine, skimmianine, dictamnine, maculine	[302]
F. laevicarpa Skimmianine	[303]
F. maculosa Maculine, flindersiamine, skimmianine, kokusaginine, maculosine, maculosidine	[302,304,305]
F. pubescens Dictamnine, flindersiamine, skimmianine, maculosidine, kokusaginine	[306]
F. schottiana Maculine, kokusaginine	[306]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

F. xanthoxyla [307]
Maculine, flindersiamine

Galbulimima belgraveana (G. baccata)(Himantandraceae) [308-310]
Himbacine, himandridine, himbadine, himgaline, himbosine, himandrine, himgravine, himandreline, himbeline, himandravine, himgrine, alkaloid G.B. 13

Gastrolobium callistachys (Fabaceae) [311]
(*S*)-(+)-N_b-Methyltryptophan, (*S*)-(+)-N_b-methyltryptophan methyl ester, (*S*)-(+)-N_bN_b-dimethyltryptophan, (*S*)-(+)-N_bN_b- dimethyltryptophan methyl ester, methyl (*S*)-2-methyl-2,3-4,9-tetrahydro-1*H* -pyrido-[3,4b]indole-3-carboxylate

Geijera salicifolia (Rutaceae) [312]
Platydesmine, platydesmine acetate, fagarine, skimmianine

Glochidion philippicum (Euphorbiaceae) [85]
Glochidine, glochidicine, N^{α}(4'-oxodecanoyl)histamine, N^{α}(cinnamoyl)histamine

Glycosmis pentaphylla (Rutaceae) [313]
Skimmianine, kokusaginine

Gymnacranthera paniculata var. *zippeliana* (Myristaceae) [314]
1,5-Dimethoxy-3-(dimethylaminomethyl)indole, N_b-methyltetrahydro-β-carboline

Gynotroches axillaris (Rhizophoraceae) [315]
(+)-Hygroline

Gyrocarpus americanus (Hernandiaceae) [316]
Phaeanthine, (+)-magnocurarine

Halfordia kendack (Rutaceae) [317]
N-Methylhalfordinium chloride, halfordinone, kokusaginine, dictamnine

H. scleroxyla [60,317,318]
N-Methylhalfordinium chloride, halfordinone, halfordine, halfordinol, halfordinium chloride, halfordanine, dictamnine, kokusaginine, halfordinine

Hedycarya angustifolia (Monimiaceae) [135,319]
Isosevanine, *O*-methylcinnamolaurine, corydine, laurotetanine, boldine, glaucine, laureline, 6,6α-dehydronorlaureline, isouvariopsine

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Heliotropium curassavicum (Boraginaceae) [320,321]
Curassavine, coromandaline, heliovicine

H. europaeum [131,322 - 325]
Heliotrine, lasiocarpine, heliotrine *N*-oxide, lasiocarpine *N*-oxide, europine *N*-oxide, heleurine *N*-oxide, supinine, heliotridine, supinidine trachelanthate, supinidine heliotrate, acetyllasiocarpine, quaternary *N*-dihydropyrrolizinomethyl derivative of heliotrine

H. indicum [326,327]
Indicine *N*-oxide, indicine

H. supinum [328]
Supinine, heliosupine, echinaline, 7-angelylheliotridine trachelanthate, 7-angelylheliotridine viridiflorate

Hernandia ovigera (Hernandiaceae) [329 - 335]
Laurotetanine, hernandaline, nandigerine, ovigerine, hernovine, (-)-reticuline, hernandonine, actinodaphnine, *N*-methylnandigerine, hernagine, hernangerine, thalicarpine, *N*-methylhernangerine, xanthoplanine, dehydrothalicarpine, laudanidine, *N*-methylovigerine, *N*-methyl-6,7-dimethoxyisoquinolone, 1,2-methylenedioxy-7*H*-8,9-dimethoxydibenzo[de,g]quinolin-7-one

H. peltata [336 - 338]
(+)-6-Northalicarpine, (+)-thalicarpine-2-*N*-oxide, (+)-hebridamine, (+)-vilaportine, 6a,7-dehydrothalmelatine, (+)-norisocorydine, (+)-isocorydine, (+)-nornantenine, (+)-reticuline, (+)-laurotetanine, (+)-*N*-methyllaurotetanine, (+)-hernovine, (+)-hernagine, (+)-nandigerine, (+)-*N*-methylnandigerine, (+)-*N*-methylhernovine, (+)-ovigerine, efatine, ambrimine

Hodgkinsonia frutescens (Rubiaceae) [97]
Hodgkinsine

Hovea acutifolia (Fabaceae) [339]
(+)-Sparteine

H. elliptica [340]
(-)-Cytisine, (+)-sparteine, (-)-lupanine, (-)-anagyrine

H. linearis [341,342]
(±)-16-Epiormosanine, (±)-piptanthine, (+)-sparteine, (-)-*N*-methylcytisine, (-)-anagyrine, (-)-baptifoline

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

H. longifolia (+)-Sparteine	[339]
H. longipes (-)-Hoveine, baptifoline, cytisine	[84]
Istoma anethifolia (Campanulaceae) 1[6'-(2"-hydroxy-2"-phenylethyl)-1'-methyl-1',2',5',6-tetrahydropyridin-2'-yl]butan-2-one, lobeline, lobelanidine	[20]
Jasminum domatiigerum (Oleaceae) Jasminine	[54,55]
J. gracile Jasminine	[54]
J. lineare Jasminine	[54]
J. schumanii Jasminine	[54,55]
Jasminum sp. NGF 29929 4-Methoxycarbonyl-6,7-dihydro-6β-methyl-5*H*-2-pyrindine	[55]
Kopsia longiflora (Apocynaceae) Kopsamine, kopsinine, kopsilongine, kopsiflorine	[343,344]
Kuntheria pedunculata (Liliaceae) Schelhammerine, schelhammeridine, schelhammericine, alkaloids A, B, E, G, H, J, K, schelhammeridine *N*-oxide	[65,345,346]
Lamprolobium fruticosum (Fabaceae) Lamprolobine, base 2	[82,347]
Legnephora moorei (Menispermaceae) Isocorydine	[348]
Leucaena glauca (Mimosaceae) (-) Mimosine	[349]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Ligustrum novoguineense (Oleaceae) [54]
Jasminine

Litsea glutinosa (Lauraceae) [350]
Isoboldine, laurelliptine, liriodenine, laurotetanine, laurolitsine

L. leefeana [226]
Boldine, laurolitsine, (+)-reticuline

L. solomonensis [350]
Laurolitsine, (+)-reticuline

Litsea sp. aff. *L. brassii* et *L. glutinosa* [350]
Laurotetanine, laurolitsine, (+)-coclaurine, reticuline (?)

Litsea sp. TGH 12072 [350]
Laurolitsine

Lunasia amara (L. quercifolia)(Rutaceae) [351 - 353]
4-Methoxy-2-phenylquinoline, 5-hydroxy-1-methyl-2-phenyl-4-quinolone, (-)-*O*-methylluninium salts, lunasine, 4-methoxy-2-(3',4')-methylenedioxyphenyl)quinoline, eduline, lunamarine, lunine, hydroxylunine, lunacrine, hydroxylunacrine, hydroxylunidine, lunacridine, hydroxylunacridine, lunacrinol

Lupinus cosentinii (Fabaceae) [354]
Epilupinine, epilupinine *N*-oxide, multiflorine,
13-hydroxymultiflorine and mixed esters of these bases; alkaloid LC2

L. varius [355 - 357]
(-)-Δ^2 Dehydro-4-oxosparteine, (+)-epilupinine, (-)-sparteine, (+)-epilupinine *N*-oxide

Lycopodium volubile (Lycopodiaceae) [358]
Lycopodine, dihydrolycopodine

Mackinlaya macrosciadia (Araliaceae) [52,359]
6,7,8,9-Tetrahydro-11*H*-pyrido[2,1$_b$]-quinazoline, 6,7,8,9-tetrahydro-11*H*-pyrido[2,1$_b$]quinazolone, deoxyvasicinone, anabasine

M. subulata [52]
6,7,8,9-Tetrahydro-11*H*-pyrido[2,1$_b$]-quinazoline,
6,7,8,9-tetrahydro-11*H*-pyridol[2,1$_b$]quinazolone, anabasine

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Marsdenia rostrata (Asclepiadaceae) Rostratamine, rostratine, dihydrorostratine, anabasine	[360 - 362]
Medicosma cunninghamii (Rutaceae) Medicosmine, dictamnine, pteleine	[363]
Melicope fareana (Rutaceae) Melicopine, melicopidine, melicopicine, acronycidine, skimmianine	[143,364]
M. perspicuinervia Halfordinine, skimmianine, kokusaginine, (±)-platydesmine	[365]
Melodorum punctulatum (Annonaceae) Asimilobine, michelalbine, liriodenine	[366]
Mitrella kentii (Annonaceae) Liriodenine, anonaine, asimilobine, egeline	[367]
Myosotis sylvatica (Boraginaceae) Viridiflorine, heliosupine, 9-angelylretronecine, acetylheliosupine	[20]
Nemuaron vieillardii (Monimiaceae) Laurotetanine, *N*-methyllaurotetanine, norisocorydine, atheroline, *O*-methylflavinanthine, nemuarine	[368]
Neolitsea pubescens (Lauraceae) Roemerine, *N*-methyllaurotetanine, boldine, laurolitsine	[369]
Neonauclea schlechteri (Rubiaceae) Gambirine	[370]
Nicotiana excelsior (Solanaceae) Nicotine, nornicotine	[371]
Ochrosia elliptica (Apocynaceae) Ellipticine, 9-methoxyellipticine	[187,372]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

O. moorei	[92,373]
Ellipticine, 9-methoxyellipticine, ellipticine -N_2-oxide, 3,4-dihydroellipticine, tetrahydroalstonine, aricine, isoreserpiline pseudoindoxyl, 10,11-dimethoxypicraphylline, reserpinine, ochropposine, ochrolifuanine A, rauvoxine, isoreserpiline, reserpiline, ochropposinine, decarbomethoxydihydrogambirtannine, 10-methoxy-18,19-dihydrocorynantheol, isocarapanaubine, 10,11-dimethoxyajmalicinine, 10-hydroxy-18,19-dihydrocorynantheol, 11-methoxypicraphylline, 10,11-dimethoxy-18,19-dihydrositsirikine, ochropposinine oxindole, 10-methoxy-18,19-dihydrocorynantheol-(4*R*)-*N*-oxide, 10-methoxy-18,19-dihydrocorynantheol-(4*S*)-*N*-oxide, reserpiline-(4*R*)-*N*-oxide, reserpiline-(4*S*)-*N*-oxide, ajmalicinine	
O. poweri	[374 - 376]
Isoreserpiline, elliptamine, powerine, poweramine, poweridine, ochropamine, ochropine, powerchrine, reserpine	
Olea paniculata (Oleaceae)	[377]
Jasminine	
Pachygone pubescens (Menispermaceae)	[378]
Isotrilobine, acutumine, acutumidine	
Palmeria arfakiana (Monimiaceae)	[379]
Laurotetanine, *N*-methyllaurotetanine	
P. fengeriana	[380]
Laurotetanine, *N*-methyllaurotetanine	
P. gracilis	[379]
Laurotetanine, *N*-methyllaurotetanine	
Palmeria sp.	[379]
Laurolitsine (?), laurotetanine, *N*-methyllaurotetanine	
Papaver somniferum var. (Papaveraceae)	[101,102]
Somniferine, *O*-methylsomniferine, morphine, codeine, papaverine, thebaine, oripavine	
Parsonia eucalyptophylla (Apocynaceae)	[110]
Lycopsamine, indicine, acetylintermedine or acetylindicine	

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

P. straminea [110]
Lycopsamine, indicine, acetylintermedine or acetylindicine

Pentaceras australis (Rutaceae) [58,59,383]
Canthin-6-one, 5-methoxycanthin-6-one, 4-(methylthio)canthin-6-one, dihydrocanthine, 4-*N*,*N*-diethylaminoethylaminocanthin-6-one, 4-hydroxycanthin-6-one

Peripentadenia mearsii (Elaeocarpaceae) [29 - 31]
Peripentadenine, dinorperipentadine, peripentamine, mearsine, anhydroperipentamine

Petalostylis labicheoides (Caesalpiniaceae) [384]
Tetrahydroharman

P. labicheoides var. *casseoides* [385]
Tryptamine, *N*b-methyltryptamine, *N*b*N*1-dimethyltryptamine, tetrahydroharman

Phaeanthus macropodus (?) (Annonaceae) [386]
Phaeanthine, limacine

Phalaris aquatica (Poaceae) [387 - 389]
N,*N*-Dimethyltryptamine, 7-methoxygramine, 5,7-dimethoxygramine, 5-methoxygramine, *N*-methyltetrahydro-β-carboline, bufotenine, 6-methoxy-2-methyltetrahydro-β-carboline

P. arundinacea [390]
Gramine, *N*,*N*-dimethyltryptamine, 5-methoxy-*N*,*N*-dimethyltryptamine, bufotenine

P. tuberosa [390 - 392]
N,*N*-Dimethyltryptamine, 5-methoxy-*N*,*N*-dimethyltryptamine, bufotenine, 2-methyl-1,2,3,4-tetrahydro-β-carboline, 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline

Phoebe forbesii (P. clemensii) (Lauraceae) [393]
Isocorydine, 10-hydroxy-1,2-methylenedioxyaporphine, 2,11-dihydroxy-1,10-dimethoxyaporphine, laurolitsine

Picrasma javanica (Simaroubaceae) [394]
4-Methoxy-1-vinyl-β-carboline

Piper novae-hollandiae (Piperaceae) [448]
Piperine, *N*-isobutyl-2,4-decadienamide, *N*-isobutyl-2,4-octadienamide, chavicine, 3,4-methylenedioxycinnamoylpiperidine, piperlonguminine, $\Delta^{\alpha,\beta}$-dihydropiperine, fagaramide

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Planchonella anteridifera (Sapotaceae) Planchonelline, planchonelline tiglate, laburnine benzoate, laburnine tiglate	[395]
P. thyrsoidea Planchonelline, planchonelline tiglate, laburnine benzoate, laburnine tiglate, laburnine *trans*-β-methylthioacrylate	[395]
Planchonella sp. (-)-Isoretronecyl *trans*-β-methylthioacrylate, (-)-isoretronecyl tiglate	[50]
Pleogyne cunninghamii (Menispermaceae) (-)-Curine, (+)-isochondrodendrine	[396]
Podopetalum ormondii (Fabaceae) (-)-Podopetaline, (-)-ormosanine, 6-epipodopetaline	[83,397]
Polyalthia nitidissima (Annonaceae) Liriodenine, *N,N'*-dimethylindoldhamine, isodaurisoline, 7-methoxylindoldhamine, 7'-methoxylindoldhamine, reticuline, protosinomenine, ushinsunine, norushinsunine, stepholidine, lindoldhamine, daurisoline, dauricine	[398,399]
Popowia cyanocarpa (Annonaceae) 1-Hydroxy-2,9,10-trimethoxynoraporphine, *O*-methyldauricine, asimilobine, 1-hydroxy-2,10,11-trimethoxynoraporphine	[400]
Poranthera corymbosa (Euphorbiaceae) Poranthericine, porantheridine, porantherine, *O*-acetylporanthericine, porantherilidine	[89,401,402]
Pseuduvaria cf. *dolichonema* (Annonaceae) Glaucine, (+)-2-hydroxy-1,9,10-trimethoxynoraporphine, 1,2,9,10-tetramethoxynoraporphine	[398]
Pseuduvaria cf. *grandifolia* 1,2-Dimethoxynoraporphine, liriodenine, anonaine	[398]
Pseuduvaria sp. TGH 10530 Liriodenine, anonaine	[398]
Psychotria beccarioides (Rubiaceae) Psychotridine	[99]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Pultenaea altissima (Fabaceae) N_b,N_b-Dimethyl-(-)-tryptophan methyl ester	[403]
Pycnarrhena australiana (Menispermaceae) 2-*N*-Norberbamine, 2-*N*-norobamegine, liriodenine, berbamine, isotetrandrine	[404]
P. ozantha *N*,*N*-Bisnoraromoline, 2-*N*-norobamegine	[405]
Rejoua aurantiaca (Apocynaceae) Voacangine, voaluteine, vobtusine, iboluteine	[406]
Schefferomitra subaequalis (Annonaceae) Anolobine, aequaline, schefferine, anonaine, liriodenine, assimilobine, isoboldine, 10-amino-3,4-dimethoxyphenanthrene-1-carboxylic acid lactam	[398,407,408]
Schelhammera undulata (Lilliaceae) Alkaloids E and B	[409]
Senecio jacobaea (Asteraceae) Seneciphilline, jacobine, jacoline, jaconine, jacozine, senecioine	[410,411]
S. magnificus Senecionine, integerrimine	[412,413]
S. mikanioides Sarracine, sarracine *N*-oxide	[414]
S. quadridentatus Senecioine, seneciphylline, retrorsine	[415,416]
S. vulgaris Senecioine, senecioine *N*-oxide	[417]
Solanum americanum (Solanaceae) Solasodine	[418]
S. aviculare Solasonine	[419]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

S. callium 25-Isosolafloridine, solacallindine	[420]
S. dimorphospinum Tomatidine	[23]
S. dunalianum Soladunalinidine, tomatidine	[421]
S. erianthum Solasodine, tomatid-5-en-3β-ol, pimpinellidine	[422]
S. laciniatum Solasonine	[419]
S. liniarifolium Solamargine, solasonine	[423]
S. phlomoides Solasodine	[23]
S. simile Solasodine	[419]
S. sturtianum Methyl homohygrinate	[424]
S. vescum Solasonine	[418]
Spathiostemon javensis (Euphorbiaceae) *N*b-Methyltetrahydroharman	[425]
Strychnos ledermannii (Loganiaceae) Diaboline	[426]
S. lucida Strychnine, brucine, loganine, lucidine-S, lucidine-L	[427,428]
S. psilosperma Strychnospermine, spermostrychnine	[427.429]

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Symphytum x *uplandicum* (Boraginaceae) [430,431]
7-Acetyllycopsamine, 7-acetylintermedine, symlandine, uplandicine, echimidine, symphytine, lycopsamine, intermedine, echiumine

Templetonia egena (Fabaceae) [432]
Sparteine

T. retusa [433]
(-)-Templetine, (-)-cytisine, (-)-anagyrine, (+)-lupanine, (±)-piptanthine

Thelepogon elegans (Poaceae) [434]
Thelepogidine, thelepogine

Timonius kaniensis (Rubiaceae) [435]
Dihydrocupreine

Tournefortia sarmentosa (Boraginaceae) [436]
Supinine, supinine *N*-oxide

Tripladenia cunninghamii (Liliaceae) [62,63,437]
Kreysigine, diacetylcolchicine, kreysiginine, colchicine, *N*-formyl-*N*-deacetylcolchicine, multiforine, floramultine

Tylophora crebriflora (Asclepiadaceae) [79]
Tylocrebrine, tylophorine

Uncaria bernaysii (Rubiaceae) [438]
Uncarine C, D, E, F

U. ferrea [438]
Uncarine C, D, E, F

Verbesina encelioides (Asteraceae) [439]
Galegine, *N*-(2,3-dihyroxy-3-methylbutyl)-acetamide

Voacanga papuana (Apocynaceae) [406]
Voacamine, voacangine, vobtusine

Xylopia papuana (Annonaceae) [440]
(+)-Coclaurine, (+)-reticuline, (-)-xylopine, (+)-laurolitsine, (-)-roemerine, (-)-anonaine

3. 3. Table 2. Plants from which Alkaloids have been Isolated (cont.)

Zanthoxylum brachyacanthum (Rutaceae) (-)-α-Canadine methiodide, β-homochelidonine, chelerythrine, isocorydine methiodide	[441]
Z. conspersipunctatum α-Allocryptopine, (±) *N*-benzoyl-2-hydroxy-2-(4'-methoxyphenyl) ethylamine, chelerythrine, sanguinarine chloride, 13-acetonyldihydrochelerythrine, pseudoprotopine	[381,382,442]
Z. parviflorum Dictamnine, platydesmine, skimmianine, chelerythrine chloride, (-)-α-canadine methiodide, magnoflorine iodide	[248]
Z. suberosum Canthin-6-one	[441]
Z. veneficum (-)-α-Canadine methiodide, β-homochelidonine, chelerythrine, isocorydine methiodide	[441]

4. FIELD AND LABORATORY METHODS

4.1. Methods of Detection and Estimation

The field surveys referred to in Section 1 were carried out under a variety of test conditions. In the first extensive surveys by Webb [17, 18], the chopped plant material was extracted at field headquarters with dilute acid for a short period at moderate temperature, then the filtered extract was treated with a standard alkaloid reagent on a microscope slide. The presence of alkaloids was indicated by a precipitate, whose density was estimated visually and recorded on a scale of + to ++++. Freshly collected material was preferred, but where this was not available, herbarium material was used on occasion. Each sample was tested with at least three reagents, but most reliance was placed on solutions of iodine, and on Mayer's reagent. Similar methods were used in the survey of Western Australian plants [21], except that Mayer's reagent only was used, and the tests were modified for rough field conditions by carrying out the extraction of plant material at ambient temperature overnight; precipitates were ranked strong, medium or weak.

In cases where simple laboratory facilities were available, extraction with Prollius fluid [121], a mixture of ethanol, chloroform and concentrated ammonia, was used by Webb as a supplement to the acid extraction method, or in some instances as an alternative to it [17, 18]. The Prollius extract was decanted and allowed to evaporate on a watch-glass, then the residue was taken up in dilute acid and tested as before. Occasionally the straight acid treatment

produced a strong positive reaction, whereas Prollius extraction of the same material gave a negative result. It was recognised by Webb that while Prollius extraction alone would fail to reveal the presence of water-soluble bases, on the other hand the presence of proteins or other non-alkaloid material soluble in acid could lead to a false positive by the regular method.

In the CSIRO survey of Papua-New Guinea plants, a somewhat more elaborate testing method [19] was adopted: finely ground plant material was extracted with ammoniacal chloroform, then the filtered extract was shaken with sufficient dilute acid to neutralise the ammonia and to extract any alkaloid present. The clarified acid solution was tested with Mayer's reagent, and the result rated as - or + to ++++ as in the case of Webb's surveys. The necessary equipment was designed to fit into a portable kit that could be taken into the field. The same procedure was used in some later screens of mainland Australian plants by the CSIRO [20] and in the surveys of orchidaceous plants [24, 25]; also in the Tasmanian survey, with some modifications to make it more convenient under field conditions [22].

In general terms these methods served well enough for the rapid examination of large numbers of plants, either in the field or under simple laboratory conditions; however, different procedures could occasionally give widely varying results on the same plant material, and all the methods were subject to certain limitations [19, 122], some of which have already been mentioned. In cases where highly water-soluble alkaloids that would not be detected by the chloroform extraction method were suspected, the procedure was modified by reducing any *N*-oxides with zinc dust and acid beforehand, or if glycosides were involved, by first hydrolysing them with acid; strong quaternary bases, however, would still escape detection by this procedure. Very weak bases of the amide and acridone type such as commonly occur in rutaceous plants would give an exceedingly feeble or negative test, and on the other hand false positives were encountered occasionally, not only for the reason mentioned before, but also through the reaction of non-basic constituents with the ammonia used in the procedure [123].

For special cases such as these, and also in some of the earlier CSIRO survey work, laboratory extraction and titration was employed to estimate alkaloid content; results were expressed as percentage of dry plant material assuming a mean molecular weight of 300 [19, 20]. Quantitative determination was also used in the survey of *Solanum* species for alkaloids, a colorimetric procedure being applied which was based on solasodine as the standard [23]. In addition, a GLC method was developed by CSIRO workers for assaying pyrrolizidine alkaloids [124]: vicinal hydroxyls were first converted to the corresponding alkyl boronate derivatives and other hydroxyls protected by trifluoroacetylation, then the derivatised alkaloid mixture was separated on a chiral-phase column.

The diversity of procedures has occasioned some difficulties in collating the results of the various alkaloid surveys. For Table 1, it had been decided to list only plants that gave positive tests, and in most surveys these were expressed on a + to ++++ scale, but in one of the screens, positives were rated strong, medium or weak only; in some instances the results were given as a percentage, while in a few cases the tests were recorded simply as positive or

negative. In order to facilitate the work of compiling the table, a + test appears as weak (w), ++ as medium (m), and +++ or more as strong (s); in cases where a plant is simply recorded as having alkaloids present, the rating w is ascribed to it. Where results are quoted as percentage of dry plant weight, those plants with 0.1% or more crude alkaloid are ranked as s, those with a content between 0.01 and 0.1% as m, and cases where the assay is positive but below 0.01% are rated w. These assignments are rather arbitary, but appear to be reasonably consistent in most instances where the same plant has been tested by more than one procedure. A uniform and generally simplified system for citing parts of plants tested has also been adopted for the table.

4.2. Extraction and Work-up Procedures

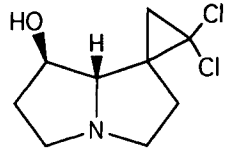
Methods for alkaloid isolation in Australian laboratories have in general followed classical lines, but the literature contains some useful modifications of standard procedures that were designed to facilitate the extraction of plant material and the recovery and purification of the alkaloids present, and to overcome various types of problems involved in the processes.

Alkaloid losses after collection. A number of instances have been recorded of plants that give a strong alkaloid test on fresh material, but by the time they are extracted in the laboratory, no alkaloid can be recovered [125-127]. In the interval during which the routine process of field drying in the shade, transporting to the laboratory, milling and percolation with solvents is carried out, enzymic action has presumably destroyed the alkaloids. To overcome this problem, freeze drying has been commonly used for marine material where shore or ship laboratory facilities are available close at hand, but this is hardly an option for terrestrial plants under primitive field conditions. In several such cases the losses were successfully countered by immersing the material straight after collection in a drum of methanol. The drum was transported to the laboratory, the material removed, dried rapidly and milled, then extracted with the same solvent [125].

Extraction and work-up. Of the standard methods of alkaloid extraction, percolation with methanol has been especially favoured by Australian workers, followed by removal of the solvent and dilute acid extraction. Besides alkaloids, methanol dissolves large amounts of other plant constituents which hamper the acid extraction. One strategy used to overcome this was to completely dissolve the residue left after removal of the methanol in a minimal quantity of warm glacial acetic acid, an excellent solvent for most plant constituents. The solution was then diluted with water until no more precipitate formed; if the evaporation of the methanol had been carried out in a pilot plant-scale rotary evaporator, the whole operation could be done in the same slowly rotating vessel. After separation of the precipitate, most of the dilute acid could be removed *in vacuo* in the same equipment to give an aqueous solution of crude alkaloid acetates largely free from non-basic materials [70].

Ammoniacal chloroform has been used occasionally for alkaloid extraction, and chloroform is frequently employed in work-up procedures. However, losses may be

occasioned from contaminants and decomposition products unless the chloroform is first purified. Common impurities include hydrogen chloride and brominated analogues of chloroform, which can cause problems owing to the separation of sparingly soluble hydrochlorides [444] and quaternary derivatives [445]. In one instance the dichlorocyclopropyl artefact **97** was formed from a pyrrolizidine alkaloid with a vinylidene group [446]. Dichloromethane appears to compare favourably with chloroform as an alkaloid solvent, with the advantages of lower boiling point, cost and toxicity; and in particular, it is less likely to cause problems arising from impurities.



97.

Removal of non-basic impurities. In the work-up of a crude mixture of water-insoluble alkaloids, isolation procedures are often impeded by the presence of persistent non-basic impurities that are difficult to remove by conventional means, including column chromatography; phenols and hydroxylated terpenoid constituents are particularly troublesome in this regard. In many instances, removal can be achieved by prolonged ether extraction of a dilute sulphuric acid solution of the crude bases in a continuous extraction apparatus [128]. In one case this also failed, but a counter-current method referred to later removed the impurity.

Water-soluble alkaloids. The isolation of water-soluble alkaloids has frequently posed problems. *N*-Oxides and glycosidic bases can be treated as described in Section 4.1, but for quaternary bases, no wholly satisfactory procedure that is generally applicable has been found. An early approach on an Australian plant consisted in extraction of an aqueous solution, from which tertiary bases had been removed, with phenol or *meta*-cresol, both effective, though disagreeable solvents for alkaloids. The extract was washed with a little water, diluted with a large volume of ether, then re-extracted with water, and the crude quaternary alkaloids were precipitated from the extract and crystallised as picrates [129]. A second method involved precipitation of the bases as reineckates, dissolution of the precipitate in aqueous acetone (1:2 v/v), addition of a slight excess of aqueous silver sulphate and removal of the precipitated silver reineckate, followed by addition of the calculated quantity of aqueous barium chloride to just precipitate all the sulphate and silver ions, leaving a solution of the quaternary alkaloid chloride [130]. A third procedure consisted in precipitating the quaternary alkaloids with Mayer's reagent, dissolving the precipitate in a methanol-acetone-water mixture (2:6:1 v/v), and passing the solution through an ion-exchange column to convert the Mayer's complex to the chloride [130].

A different case of water-solubility is presented by castanospermine (**96**), which has five polar groups incorporated into a comparatively small molecule. The alkaloid was removed

from an aqueous extract of plant material onto a strongly acidic cation exchange column, from which it was recovered by elution with ammonia. Separation from accompanying amino acids was achieved on another ion-exchange column by a preliminary elution with pyridine [113].

Chromatographic separation. The wide range of chromatographic methods used for the separation and purification of individual alkaloids requires little comment. In the case of pyrrolizidine alkaloids, partition chromatography was found especially effective, the mixed bases being applied to the top of a column packed with powdered glass or kieselguhr that had been moistened with phosphate buffer. The column was then eluted with solvent mixtures of increasing polarity [131]. A more subtle approach was required to separate the diastereomeric pyrrolizidine alkaloids, intermedine and lycopsamine, which have vicinal glycol groups of different configurations. They complex to different extents with borate, and a column of glass powder moistened with aqueous borax, to which the mixed bases were applied in chloroform solution, achieved a complete separation [132].

Counter-current and DCCC separation. Counter-current separation in a Craig machine was extensively used in earlier isolation work, the alkaloid mixture being equilibrated between aqueous buffer solutions and an organic solvent such as chloroform [133]. An effective variation of the procedure was to use very dilute acid (e.g. N/1000 H_2SO_4) in place of the buffer solutions as moving phase. The alkaloids competed for the limited amount of acid and were collected separately as they emerged from the Craig machine in order of their basic strengths [134]. In droplet counter-current chromatography (DCCC), a more recent development of the same general method, a similar solvent system was successful in not only separating the mixed alkaloids from one another, but also from a persistent terpene diol impurity that resisted removal by other means [135]. DCCC proved effective also in separating a mixture of water-soluble alkaloids, using a two-phase solvent system made by equilibrating methanol, chloroform and water (5:5:3 v/v) [130].

Crystallisation. Apart from being generally accepted as a criterion of purity and an aid in characterisation, the crystallisation of an alkaloid or one of its salts is an essential preliminary to structural determination by X-ray crystallography. No certain way of inducing an amorphous substance to crystallise has been found, but the apparatus devised by Hope [136] has often proved successful, provided the material has first been purified by every other available means.

5. CONCLUSION

Since the period that commenced about the end of World War II, several thousand plants growing in Australia and New Guinea have been screened for alkaloids, and many hundreds of new bases, as well as large numbers of known ones, have been isolated. The greater part of this work was accomplished by the CSIRO in collaboration with the American pharmaceutical firm SKF, which carried out a wide range of pharmacological testing, and the US Cancer Chemotherapy National Service Center, which examined materials for anti-tumor activity. A

number of promising substances were discovered, but after extensive screening trials they were all found to have undesirable side-effects or to be otherwise unsuitable for use as medicinal drugs [20], and further work on them was discontinued.

In view of these discouraging results, the programme directed towards the discovery of alkaloids with useful medicinal properties was terminated by the CSIRO around 1970; however, studies on alkaloids in plants poisonous to stock were continued, and interest in alkaloid research was maintained in the Universities, although their work was no longer supported by the plant collection and other facilities formerly provided by the CSIRO.

A few years after the CSIRO had ended its main alkaloid programme, the Swiss pharmaceutical company, Hofmann La Roche, set up a well-staffed and equipped laboratory (RRIMP) at Dee Why, NSW, with the object of obtaining new and useful drugs from marine sources. Despite the isolation, over a seven-year period of intense activity, of many substances with interesting pharmacological properties, including a number of alkaloids, the project was terminated and the laboratory closed following a change in company policy in 1981. The programme had neverless run long enough to stimulate great interest in marine products amongst Australian chemists, and to produce a highly trained and enthusiastic staff, many of whom continued their work in various other institutes and universities throughout the country.

During the last half century, the number of alkaloids known to occur in the Australian flora has increased dramatically, and this has been accompanied by a corresponding expansion in knowledge and understanding of their chemistry, pharmacology and toxicology. However, much still remains to be done: there is still a large number of plants that have never been tested, and many others that are known to contain alkaloids but have not been further examined. There are also some plants that gave a strong alkaloid test in the field, but to date attempts to isolate alkaloids from them have been for one reason or another unsuccessful.

Apart from these factors, there have been very substantial advances made during the same period in the techniques of isolation and purification of alkaloids, and there is little doubt that the great majority of plants previously studied would yield many more interesting alkaloids by the application of modern methods. At the same time, the radical improvements in spectroscopy and X-ray crystallography which have taken place would permit the determination of structure of many alkaloids that were isolated in earlier studies, but in insufficient amount or unsuitable form for further work. Corresponding advances in pharmacological testing would also allow their assessment as potential drugs to be carried out on a much smaller scale.

These considerations point to the conclusion that, while a very promising start has been made to the study of Australian alkaloids, a major endeavour is required at this stage to extend and develop the knowledge gained to date; moreover, the case of castanospermine suggests that further advances are likely to come about as a result of a much closer collaboration between chemists, toxicologists and pharmacologists than in the past.

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Chapter Two

Pyridine and Piperidine Alkaloids: An Update

Marilyn J. Schneider
Department of Chemistry
Lafayette College
Easton, Pennsylvania 18042-1782
U. S. A.

CONTENTS

1. INTRODUCTION

The intent of this chapter is to provide an update of pyridine and piperidine alkaloid literature since this topic was last covered in Volume 3 of this series [1]. The approximate time period covered by this review is 1984-1994. Due to the wealth of information available, this review had to be somewhat selective. For example, with the exception of a few selected pyridine monoterpenes, alkaloids containing a pyridine or piperidine ring fused to another ring system were excluded. The focus of this review is placed on describing new compounds isolated, biosynthesis, and biological properties. Synthesis has not been emphasized; in most cases reference is made to only the most recent syntheses.

2. PYRIDINE ALKALOIDS (TABLE 1)

2.1. Nicotine and Related Alkaloids

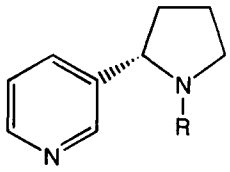
A series of reviews describing nicotine metabolism has recently appeared [2]. Specific topics covered include the biosynthesis and metabolism of nicotine and related alkaloids [3], an overview of mammalian nicotine metabolism [4], the role of cytochrome P450 in nicotine metabolism [5], nicotine metabolism beyond cotinine [6], *N*-oxidation, *N*-methylation, and *N*-conjugation reactions of nicotine [7], extrahepatic metabolism of nicotine and related compounds [8], metabolism of the minor tobacco alkaloids [9], analysis and levels of nicotine and metabolites in body fluids [10], kinetics of nicotine and its metabolites in animals [11], pharmacokinetics of (*S*)-nicotine and metabolites in humans [12], and sources of inter-individual variation in nicotine pharmacokinetics [13]. Another recent review described variables which affect nicotine metabolism [14]. Several compilations of studies or reviews on the tobacco-specific *N*-nitrosamines are available [15-18]

2.1.1. Nicotine and Cotinine

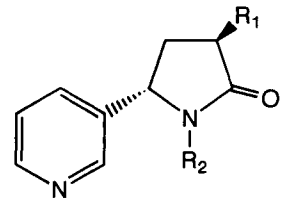
A compilation of studies describing the effects of nicotine (**1**) in biological systems is available [15]. Specific examples of the effects of nicotine and its primary metabolite, cotinine (**5**), are described below.

The effects of **1** and **5** on steroid metabolism continue to be investigated. Nicotine increased blood aldosterone and serum prolactin levels in rats, while cotinine caused a decrease in these levels [19]. Both **1** and **5** inhibited in vitro aldosterone synthesis in rat adrenal cells [20], and inhibited luteinizing hormone-stimulated or cAMP-stimulated testosterone production in mouse Leydig cells [21]. Nicotine (and **237**) inhibited hCG-stimulated androgen biosynthesis in rat testicular cell cultures [22]. In rat Leydig cells, **1** increased progesterone levels and decreased androstenedione and testosterone levels, while **5** increased levels of progesterone and androstenedione, and decreased testosterone levels [23]. Nicotine was a competitive inhibitor of 17α-hydroxylase (app Ki = 30 μM) and 17,20-lyase (app Ki = 18 μM) from rat testis, while cotinine was a competitive inhibitor of 17-ketosteroid reductase (app Ki = 46 μM)[23]. Both nicotine and cotinine were competitive inhibitors of rat adrenal 11β-hydroxylase (Ki = 96 μM and 32 μM, respectively)[24] and the human fetal adrenal enzyme (Ki = 9.9 μM and 9.0 μM, respectively)[25]. Nicotine, but not cotinine, was a competitive inhibitor of rat adrenal 21-hydroxylase [24] and the human fetal adrenal enzyme [25]. Both **1** and **5** were competitive inhibitors of 3α-hydroxysteroid dehydrogenase from dog prostate (Ki = 61 μM and 89 μM,

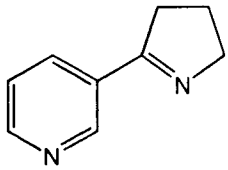
Table 1. Pyridine Alkaloids



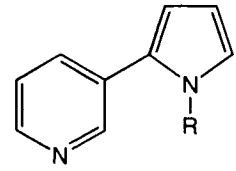
1 NICOTINE, R = CH_3
2 NORNICOTINE, R = H
3 *N'*-ETHYLNORNICOTINE, R = CH_2CH_3
4 *N'*-ACYLNORNICOTINE, R= Acyl



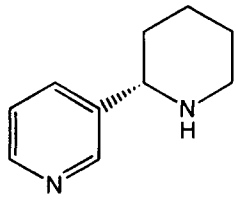
5 COTININE, R_1 = H, R_2 = CH_3
6 3'-HYDROXYCOTININE, R_1 = OH, R_2 = CH_3
7 *N*-HYDROXYMETHYLNORCOTININE R_1 =H, R_2 = CH_2OH



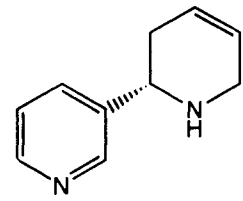
8 MYOSMINE



9 NICOTYRINE, R = CH_3
10 NORNICOTYRINE, R = H

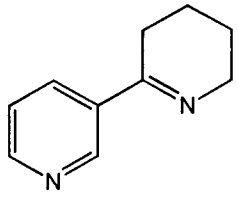


11 ANABASINE, R = H

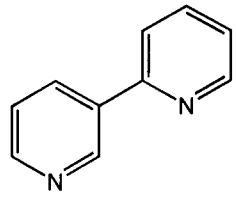


12 ANATABINE

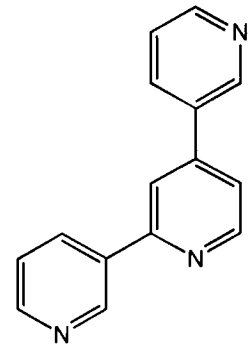
Table 1. (*cont.*)



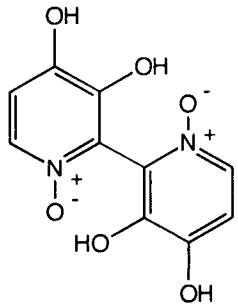
13 ANABASEINE



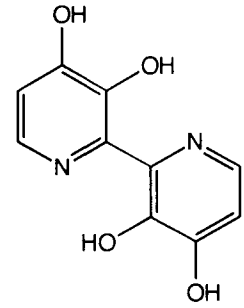
14 2,3'-DIPYRIDYL



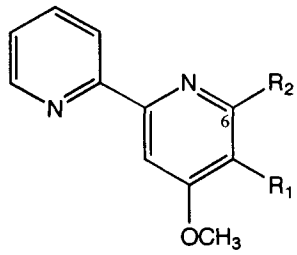
15 NICOTELLINE



16 ORELLANINE



17 ORELLINE



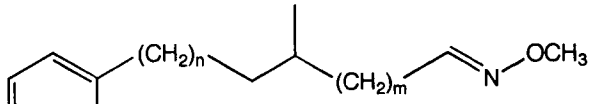
18a CAERULOMYCIN A,
R_1 = H, R_2 = anti-C=N-OH

18b CAERULOMYCIN E
R_1 = H, R_2 = CHO

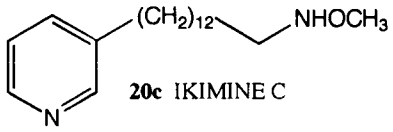
19a COLLISMYCIN A
R_1 = SCH_3, R_2 = anti-C=N-OH

19b COLLISMYCIN B
R_1 = SCH_3, R_2 = syn-C=N-OH

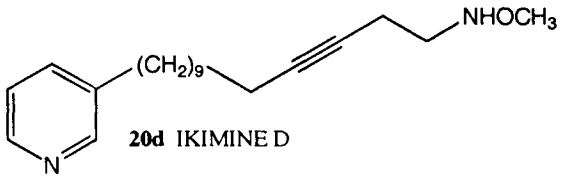
Table 1. (*cont.*)



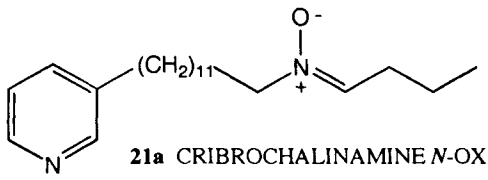
20a IKIMINE A n = 9, m = 0
20b IKIMINE B n = 11, m = 1



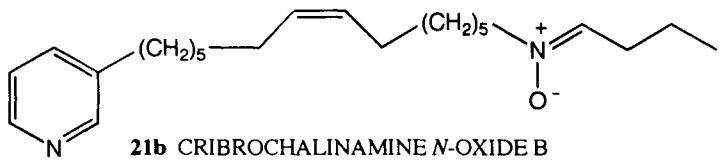
20c IKIMINE C



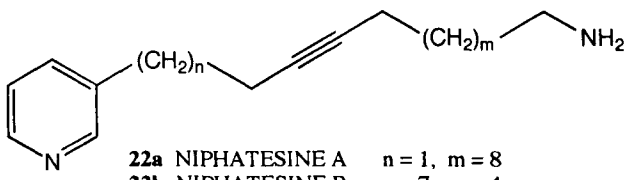
20d IKIMINE D



21a CRIBROCHALINAMINE *N*-OXIDE A

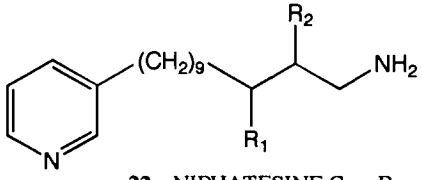


21b CRIBROCHALINAMINE *N*-OXIDE B

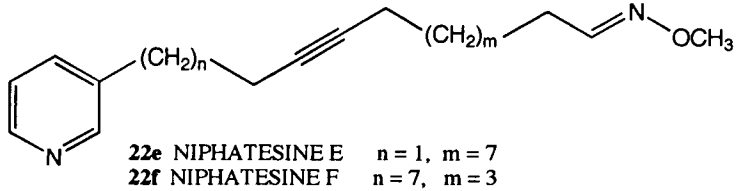


22a NIPHATESINE A n = 1, m = 8
22b NIPHATESINE B n = 7, m = 4

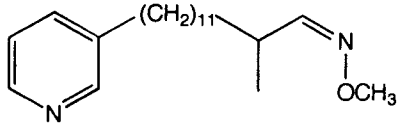
Table 1. (*cont.*)



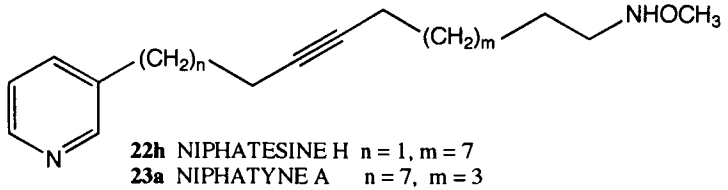
22c NIPHATESINE C $R_1 = H$, $R_2 = CH_3$
22d NIPHATESINE D $R_1 = CH_3$, $R_2 = H$



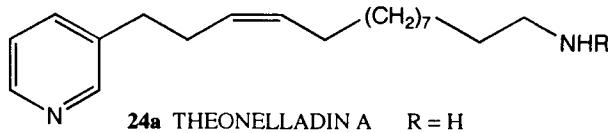
22e NIPHATESINE E n = 1, m = 7
22f NIPHATESINE F n = 7, m = 3



22g NIPHATESINE G

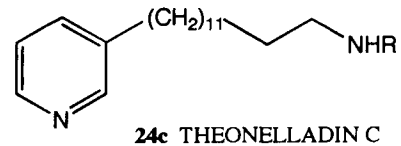


22h NIPHATESINE H n = 1, m = 7
23a NIPHATYNE A n = 7, m = 3
23b NIPHATYNE B n = 9, m = 1

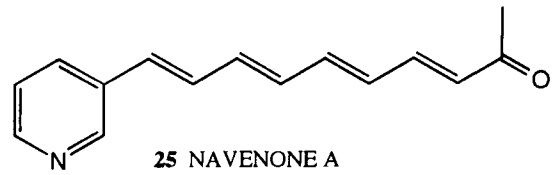


24a THEONELLADIN A R = H
24b THEONELLADIN B $R = CH_3$

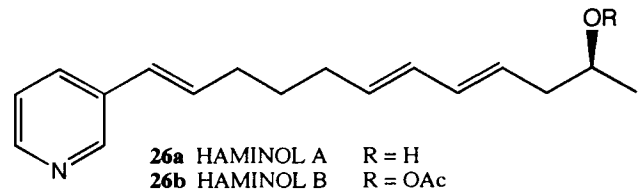
Table 1. (*cont.*)



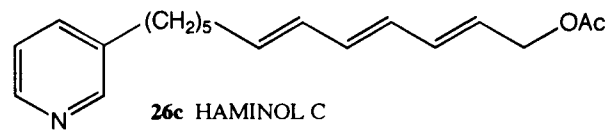
24c THEONELLADIN C R = H
24d THEONELLADIN D R = CH_3



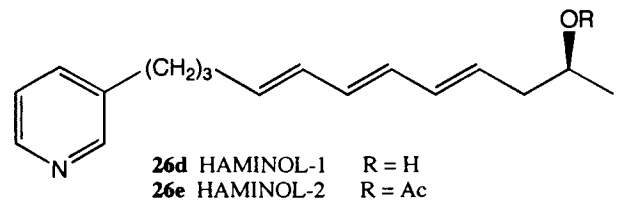
25 NAVENONE A



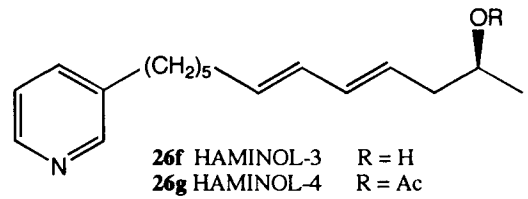
26a HAMINOL A R = H
26b HAMINOL B R = OAc



26c HAMINOL C

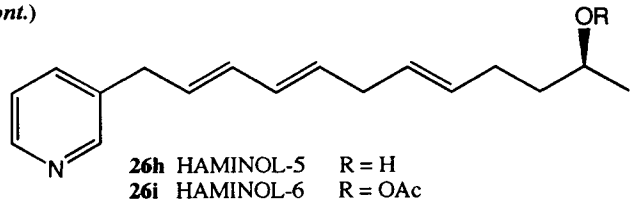


26d HAMINOL-1 R = H
26e HAMINOL-2 R = Ac

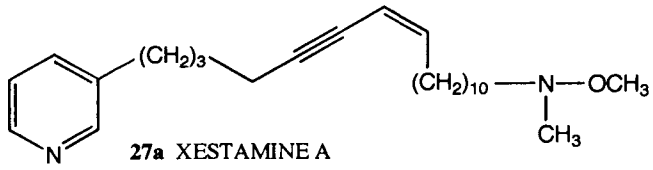


26f HAMINOL-3 R = H
26g HAMINOL-4 R = Ac

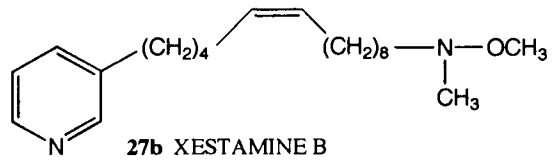
Table 1. (*cont.*)



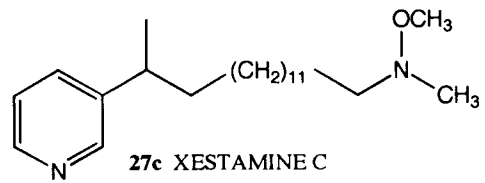
26h HAMINOL-5 R = H
26i HAMINOL-6 R = OAc



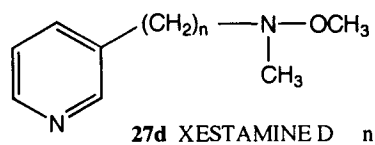
27a XESTAMINE A



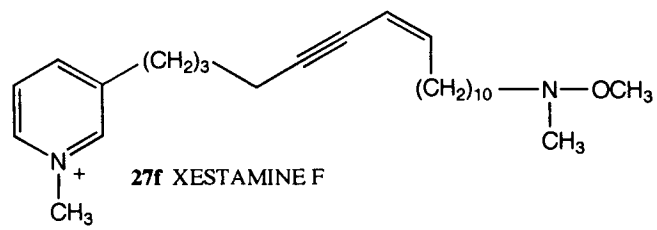
27b XESTAMINE B



27c XESTAMINE C

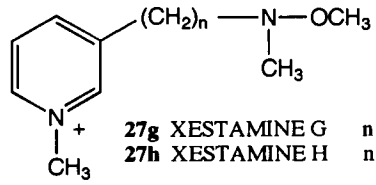


27d XESTAMINE D n = 14
27e XESTAMINE E n = 15

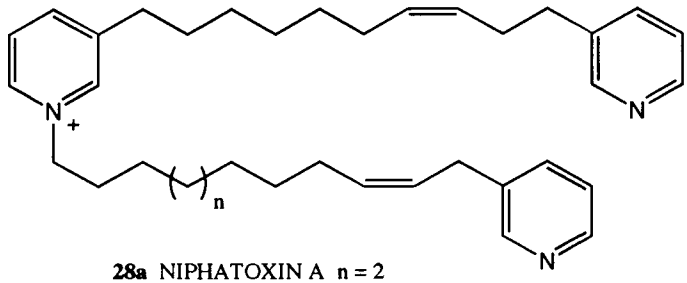


27f XESTAMINE F

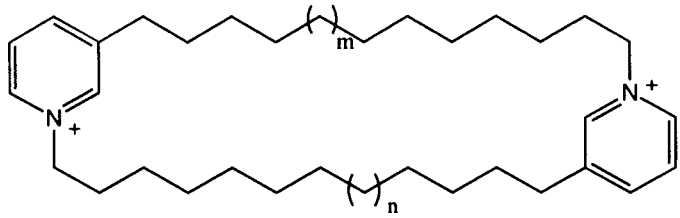
Table 1. (*cont.*)



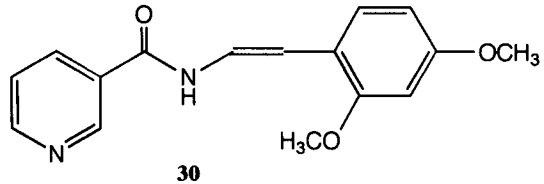
27g XESTAMINE G n = 14
27h XESTAMINE H n = 15



28a NIPHATOXIN A n = 2
28b NIPHATOXIN B n = 3



29a	CYCLOSTELLETTAMINE A	m = 1	n = 1
29b	CYCLOSTELLETTAMINE B	m = 1	n = 2
29c	CYCLOSTELLETTAMINE C	m = 2	n = 2
29d	CYCLOSTELLETTAMINE D	m = 1	n = 3
29e	CYCLOSTELLETTAMINE E	m = 2	n = 3
29f	CYCLOSTELLETTAMINE F	m = 3	n = 3



30

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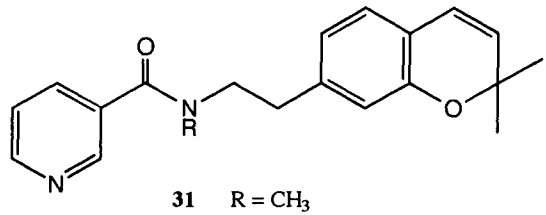
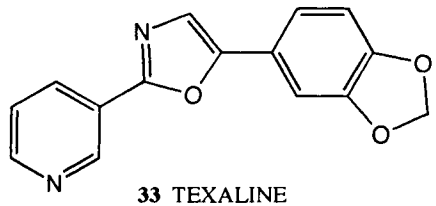
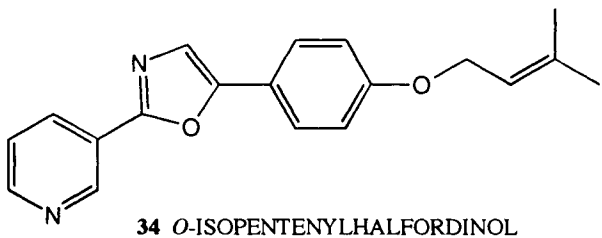


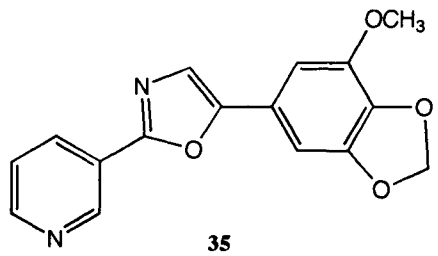
31 R = CH_3
32 R = H



33 TEXALINE

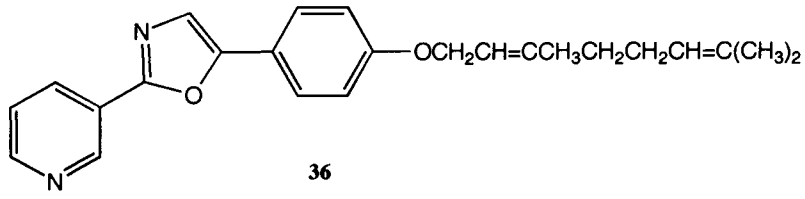


34 *O*-ISOPENTENYLHALFORDINOL

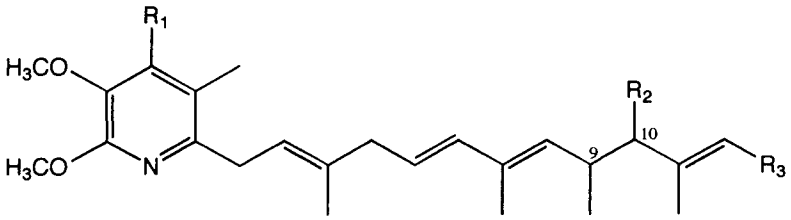


35

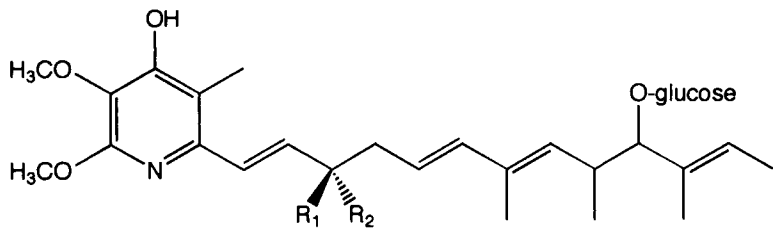
Table 1. (*cont.*)



36

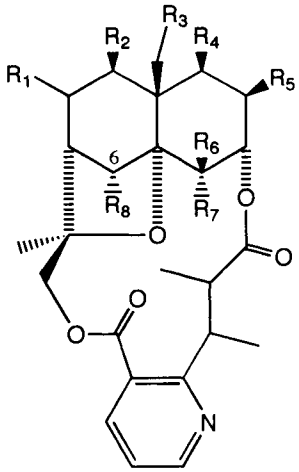


		R_1	R_2	R_3
37	PIERICIDIN A_1	OH	OH	CH_3
38	PIERICIDIN B_1	OH	OCH_3	CH_3
38a	PIERICIDIN B_1 *N*-oxide			
39	PIERICIDIN B_5	OH	OCH_3	CH_2CH_3
39a	PIERICIDIN B_5 *N*-oxide			
40a	GLUCOPIERICIDIN A	OH	O-glucose	CH_3
40b	GLUCOPIERICIDIN B	O-glucose	OH	CH_3
41	3'-RHAMNOPIERICIDIN A_1	O-rhamnose	OH	CH_3
42	3'-DEOXYTALOPIERICIDIN	O-deoxytalose	OH	CH_3
43	13-HYDROXYGLUCOPIERICIDIN A	OH	O-glucose	CH_2OH

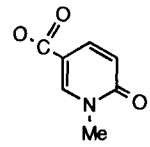


44a&b GLUCOPIERICIDINOL A_1 & A_2 $R_1, R_2 = CH_3, OH$

Table 1. (*cont.*)

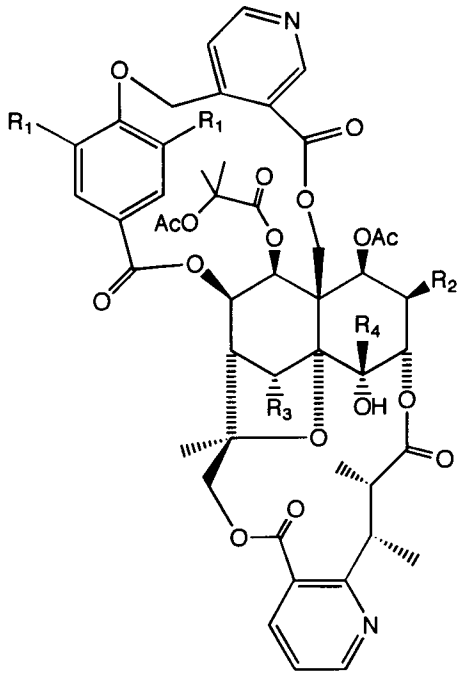


OTmb = *O*-3,4,5-trimethoxybenzoyl
OiBu = *O*-isobutyroyl
OAmp = *O*-2-acetoxy-2-methylpropanoyl
OBz = *O*-benzoyl
ONic = *O*-nicotinoyl
OMb = *O*-2-methybutyroyl
OMbu = *O*-2-methylbut-2-enyroyl
OPy =



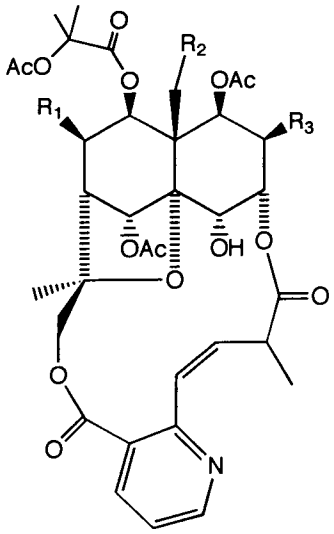
		R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
45	ACANTHOTHAMINE	α-OH	OAc	OAc	OAc	OAc	CH_3	OH	OH
46	ANGULATAMINE	β-OiBu	OAc	OAc	OAc	ONic	CH_3	OH	OAc
47	CATHEDULINE-E5	β-OTmb	OAmp	OPy	OBz	OAc	H	OH	OAc
48a	EBENIFOLINE E-I	β-OAc	OAc	OAc	OBz	OH	CH_3	OH	OAc
48b	EBENIFOLINE E-II	β-OAc	OAc	OAc	OBz	OAc	CH_3	OH	OBz
48c	EBENIFOLINE E-III	β-OAc	OBz	OAc	OBz	OAc	CH_3	OH	OAc
48d	EBENIFOLINE E-IV	β-OAc	OAc	OAc	OBz	OAc	CH_3	H	OAc
48e	EBENIFOLINE E-V	β-OAc	OBz	OAc	OBz	OAc	CH_3	OH	OH
49a	EMARGINATINE A	β-OAc	OAc	OAc	OAc	OPy	CH_3	OH	OAc
49b	EMARGINATINE B	α-OAc	OBz	OAc	OAc	OPy	CH_3	OH	OAc
49c	EMARGINATINE C	β-OAc	OH	OAc	OAc	OPy	CH_3	OH	OAc
49d	EMARGINATINE D	β-OAc	OAc	OAc	OH	OPy	CH_3	OH	OAc
49e	EMARGINATINE E	α-OAc	OH	OAc	OH	OPy	CH_3	OH	OAc
49f	EMARGINATINE F	α-OH	OAc	OAc	OBz	OPy	CH_3	OH	OAc
49g	EMARGINATINE G	β-OAc	OAc	OAc	OMbu	OPy	CH_3	OH	OAc
50a	EUOJAPONINE A	β-OAc	OAc	OAc	OBz	OAc	CH_3	OH	OH
50b	EUOJAPONINE C	β-OAc	OAc	OAc	OBz	OH	CH_3	OH	OBz
50c	EUOJAPONINE I	β-OAc	OAc	OAc	ONic	OAc	CH_3	OH	OAc
50d	EUOJAPONINE L	β-OAc	OAc	OAc	ONic	OH	CH_3	OH	OBz
50e	EUOJAPONINE M	β-OAc	OAc	OAc	ONic	OH	CH_3	OH	OAc
51	FORRESTINE	β-OAc	OAc	OAc	OAc	OBz	CH_3	OH	OAc
52a	HIPPOCRATEINE I	β-OAc	OAc	OAc	OBz	OPy	CH_3	OH	OAc
52b	HIPPOCRATEINE II	β-OAc	OAc	OMb	OBz	OPy	CH_3	OH	OAc
52	MAYTEINE	β-OAc	OAc	OAc	OBz	OAc	CH_3	OH	OAc
54	EVONINE	Oxo	OAc	OAc	OAc	OAc	CH_3	OH	OAc
55	6-DEACETYL-EVONOLIN	Oxo	OAc	OAc	OAc	OAc	CH_3	H	OH

Table 1. (*cont.*)

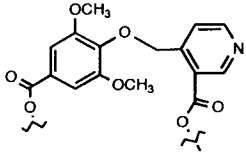


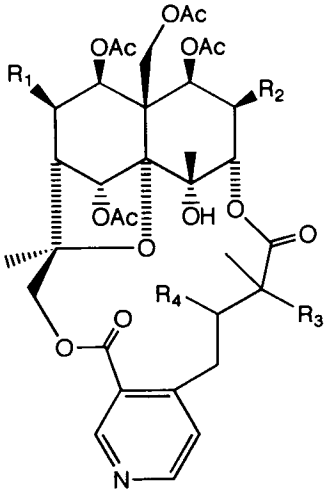
		R_1	R_2	R_3	R_4
56a	CATHEDULIN E3	H	OAc	OAc	H
56b	CATHEDULIN E4	H	OAc	OH	H
56c	CATHEDULIN K20	OMe	OBenzoyl	OAc	CH_3

Table 1. (*cont.*)



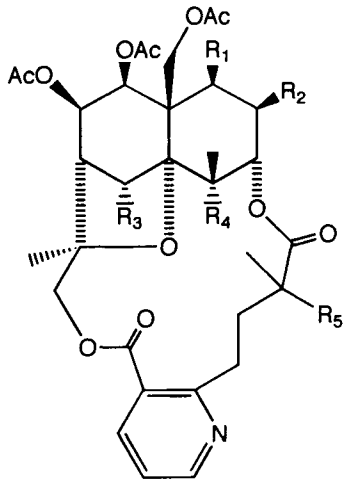
		R_1	R_2	R_3
57a	CATHEDULIN K17	OTmb	ONic	OBz
57b	CATHEDULIN K19			OAc



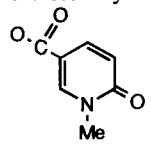


		R_1	R_2	R_3	R_4
58	ISOWILFORDINE	OAc	OBz	OH	H
59a	PERITASSINE A	OAc	OAc	H	CH_3
59b	PERITASSINE B	OBz	OAc	H	CH_3

Table 1. (*cont.*)

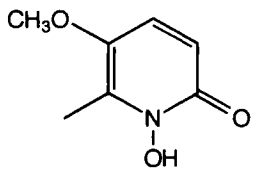


OBz = *O*-benzoyl
ONic = *O*-nicotinoyl
OFur = *O*-3-furanoyl
OPy =

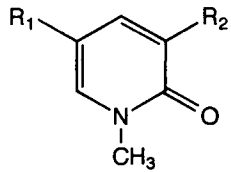


		R_1	R_2	R_3	R_4	R_5
60a	EBENIFOLINE W-1	OBz	OBz	OAc	OH	H
60b	EBENIFOLINE W-2	OBz	OBz	OH	OH	H
61	EMARGINATININE	OAc	OPy	OAc	OH	OH
62a	EUOJAPONINE D	OBz	OAc	OH	OH	H
62b	EUOJAPONINE F	OBz	OAc	OAc	OH	H
62c	EUOJAPONINE G	OBz	OAc	ONic	H	H
62d	EUOJAPONINE J	OBz	OH	OAc	H	H
62e	EUOJAPONINE K	OBz	OH	OAc	OH	H
63	EUONINE	OAc	OAc	OAc	OH	H
64	WILFORINE	OAc	OBz	OAc	OH	H
65	WILFORNINE	OAc	ONic	OAc	OH	H
66	DESACETYLWILFORTRINE	OH	OFur	OAc	OH	OH
67	DESACETYLWILFORDINE	OH	OBz	OAc	OH	OH
68	WILFORGINE	OAc	OFur	OAc	OH	H
69	WILFORTRINE	OAc	OFur	OAc	OH	OH
70	WILFORIDINE	OAc	OH	OAc	OH	OH
71	NEOWILFORINE	OAc	OBz	OAc	H	H
72	WILFORZINE	OAc	OBz	OH	OH	H

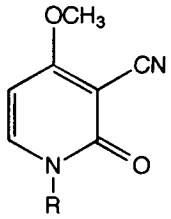
Table 1. (*cont.*)



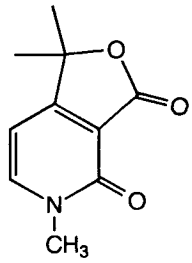
73 CEPABACTIN



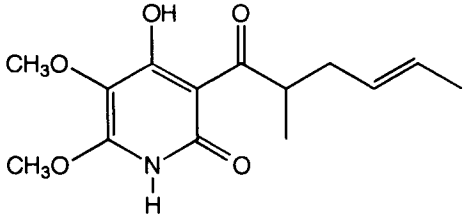
74 RICINIDINE $R_1 = H$, $R_2 = CN$
75 NUDIFLORINE $R_1 = CN$, $R_2 = H$



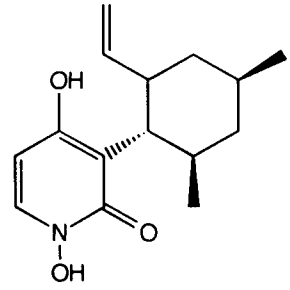
76 RICININE, R = CH_3
77 *N*-DEMETHYLRICININE, R = H



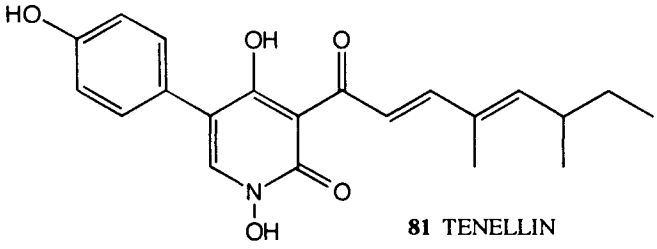
78 CERPEGIN



79 HARZIANOPYRIDONE

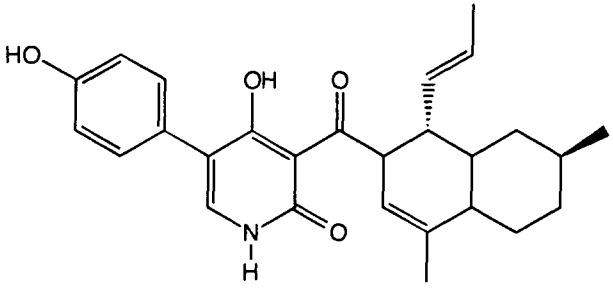


80 PYRIDOXATIN

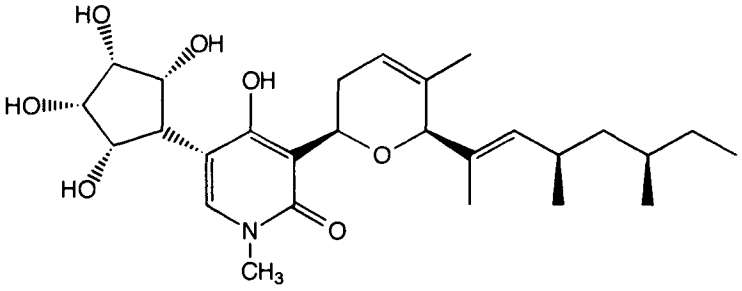


81 TENELLIN

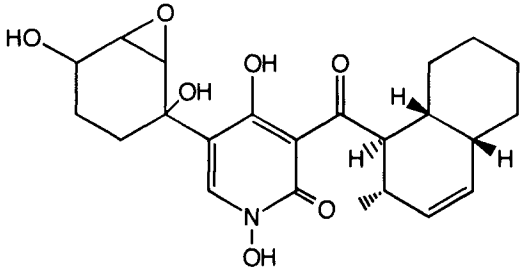
Table 1. (*cont.*)



82 ILICICOLIN H

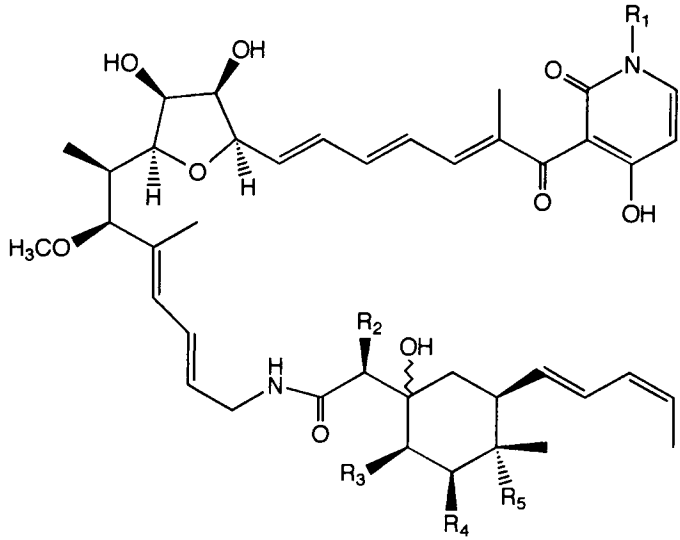


83 FUNICULOSIN



84 FISCHERIN

Table 1. (*cont.*)



		R_1	R_2	R_3	R_4	R_5
85	KIRROMYCIN	H	CH_2CH_3	OH	OH	CH_3
86	AURODOX	CH_3	CH_2CH_3	OH	OH	CH_3
87	EFROTOMYCIN	CH_3	CH_2CH_3	OH	sug	CH_3
88	HENEICOMYCIN	CH_3	CH_2CH_3	H	OH	CH_3
89a,c	SB22484 Factors 1, 3	H	CH_3	H	OH	H
89b,d	SB22484 Factors 2, 4	H	CH_2CH_3	H	OH	H

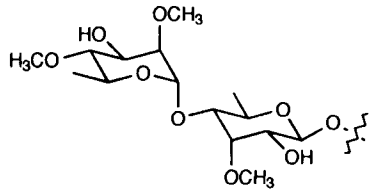


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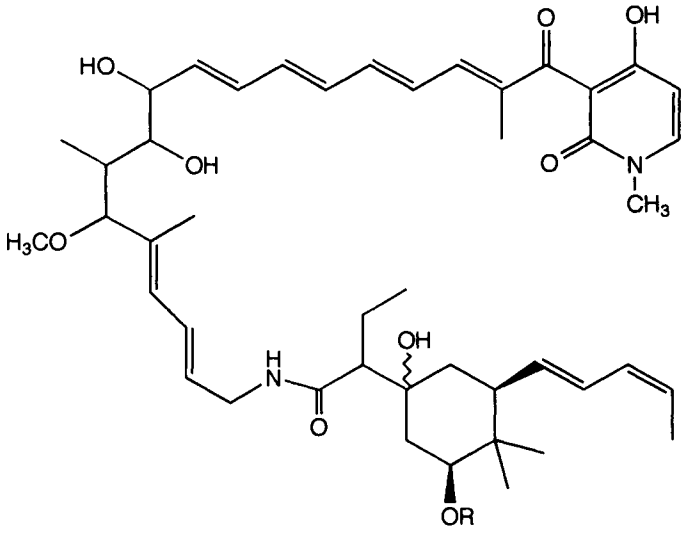
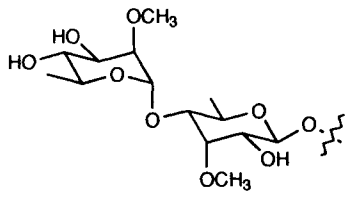
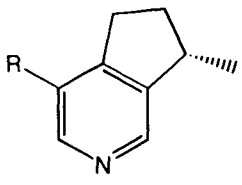
Table 1. (*cont.*)

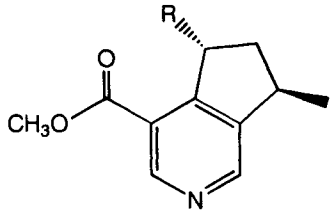


90 UK-69753, R =



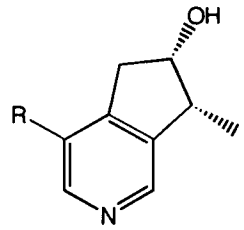


91 ACTINIDINE R = CH_3
92 TECOSTIDINE R = CH_2OH

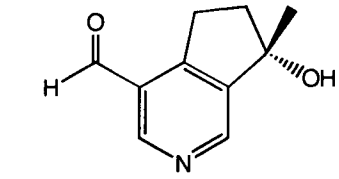


93 RHEXIFOLINE R = OH
94 DEOXYRHEXIFOLINE R = H

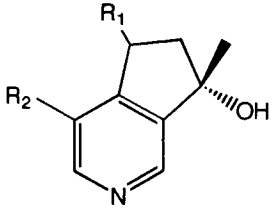
Table 1. (*cont.*)



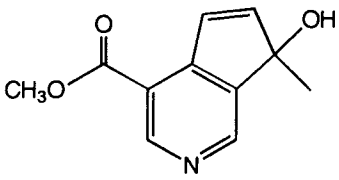
95 CANTLEYINE R = CO_2CH_3
96 VENOTERPINE R =H



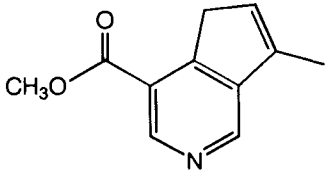
97 EUPHROSINE



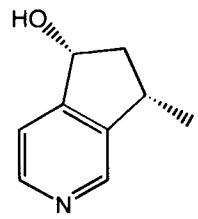
98 OXERINE, R_1 = α-OH, R_2 = H
99 PLECTRODORINE, R_1 = α-OH, R_2 = CO_2CH_3
100 ISOPLECTRODORINE, R_1 = β-OH, R_2 = CO_2CH_3



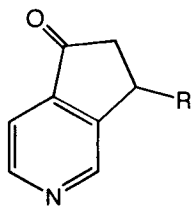
101 SCAEVOLINE



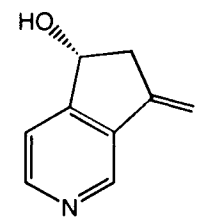
102 RACEMIGERINE



103 COELOBILLARDIERINE

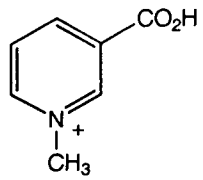


104 COELOSPERMINONE (AUCUBININE B) R = CH_3
105 AUCUBININE A R = CH_2OH

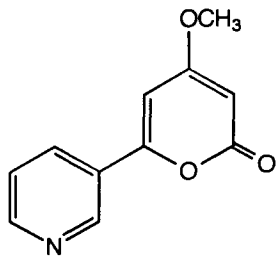


106 7,8-DEHYDROCOELOBILLARDIERINE

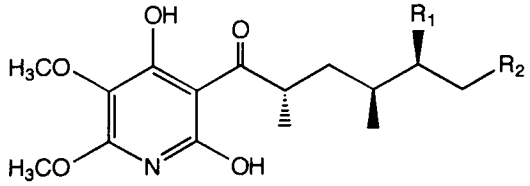
Table 1. (*cont.*)



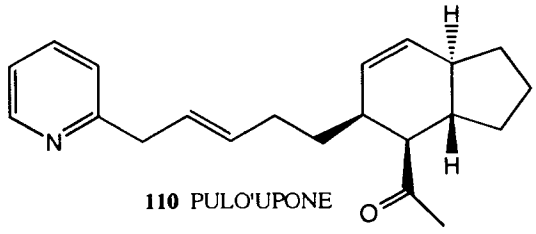
107 TRIGONELLINE



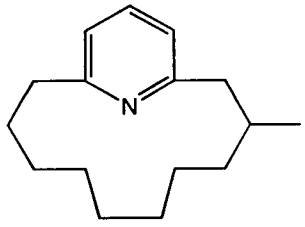
108 ANIBINE



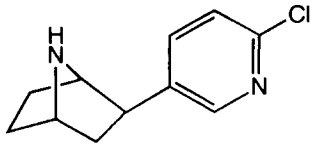
109a ATPENIN A_4 $R_1 = Cl$, $R_2 = H$
109b ATPENIN A_5 $R_1 = Cl$, $R_2 = Cl$
109c ATPENIN B $R_1 = H$, $R_2 = H$



110 PULO'UPONE

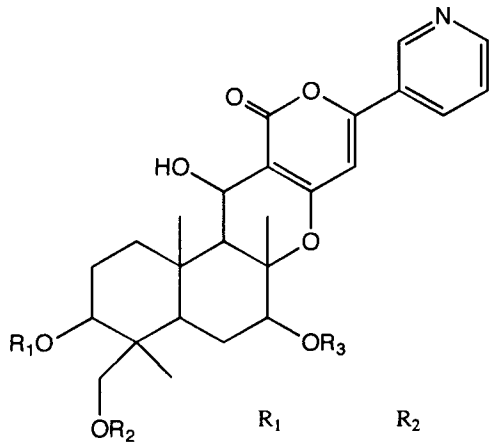


111 MUSCOPYRIDINE

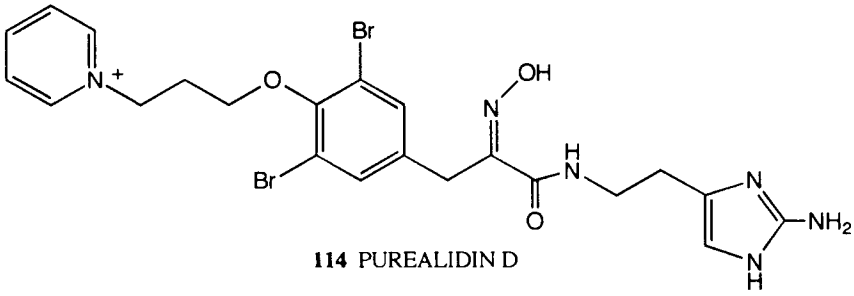


112 EPIBATIDINE

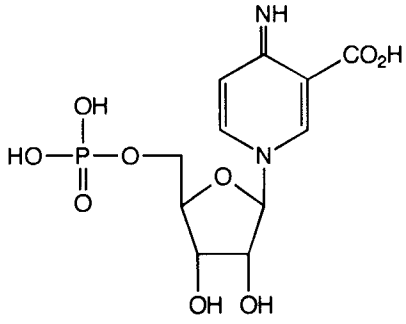
Table 1. (*cont.*)



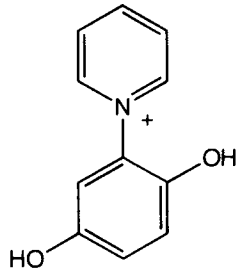
		R_1	R_2	R_3
113a	PYRIPYROPENE A	CH_3CO	CH_3CO	CH_3CO
113b	PYRIPYROPENE B	CH_3CO	CH_3CH_2CO	CH_3CO
113c	PYRIPYROPENE C	CH_3CO	CH_3CO	CH_3CH_2CO
113d	PYRIPYROPENE D	CH_3CH_2CO	CH_3CO	CH_3CO



114 PUREALIDIN D



115 CLITIDINE 5'-MONONUCLEOTIDE



116

respectively) [26]. Finally, nicotine, cotinine and anabasine (**11**) all inhibited aromatase in choriocarcinoma cell cultures and in term placental microsomes [27].

Cardiovascular effects of nicotine and cotinine have been studied. One study reported an increase in blood pressure in rats when either nicotine, cotinine, or nornicotine (**2**) was administered [28]. A long term study of the effects of cotinine indicated no significant changes in blood pressure, but a decreased heart rate was observed [29]. Nicotine inhibited prostacyclin synthetase in horse aorta microsomes, while cotinine stimulated this enzyme [30]. Both **1** and **5** increased prostaglandin E_2 synthesis, while decreasing leukotriene B_4 production in polymorphonuclear leukocytes, and decreased thromboxane B_2 production in platelet rich plasma [31]. Nicotine and cotinine activated platelet activating factor hydrolase, suggesting a possible role in cardiovascular disease [32]. Both **1** and **5** increased secretion of plasminogen activator in bovine aortic endothelial cell cultures, suggesting a possible fibrinolytic role in vivo [33].

A number of additional biological effects of **1** and **5** have been studied. Nicotine increased [^{3}H]-noradrenaline release from rabbit heart, while cotinine did not [34]. Nicotine inhibited (65%) the binding of [^{3}H]-dihydroalprenolol to the β_2-adrenergic receptor from catfish red blood cells [35]. Both **1** and **5** attenuated motor incoordination in mice produced by ethanol [36]. Nicotine inhibited ovulation and estradiol production in both in vivo and in vitro rat models, while cotinine had no effect [37]. Nicotine was a moderate inhibitor of acetylcholinesterase (IC_{50} = 823 μM), while cotinine was considerably less active [38]. Nicotine and cotinine were found to be potential carcinogens using the *Xenopus* teratogenesis assay [39]. Nicotine bound strongly to the [^{3}H]-α-bungarotoxin binding site on the nicotinic acetylcholine receptor for housefly and honeybee heads, while cotinine did not [40]. Both nicotine and cotinine were toxic to *Lucillia caesar* flies, and combination of these alkaloids produced a synergistic effect [41]. Nicotine was toxic to larvae of *Spodoptera littoralis*, while cotinine had no effect [42], and **1** was a feeding deterrent to larvae of the moth *Syntomis mogadorensis* [43].

Additional studies investigating nicotine and its biological effects are numerous; a few examples will be listed here. The damage induced increase in alkaloid production in *Nicotiana*, and its mechanism have been investigated [44,45]. Nicotine biosynthesis continues to be studied [46,47] and has included the use of ^{15}N NMR [48]. A synthesis of **1** from 3,3'-dipyridyl was reported [49]. Nicotine showed potential as a molluscicide [50], it was a potent inhibitor of TAK-induced activation of polymorphonuclear leukocytes [51], and it caused reduction of herpes simplex virus type 1 production, as well as reduction of viral attachment to cell membranes [52]. Mechanisms involved in the behavioral and cognitive effects of nicotine have been investigated [53].

2.1.2. Nornicotine

A number of studies regarding the biological activity of nornicotine (**2**) have been reported. Nornicotine increased blood pressure in rats [28], and inhibited by 55.7% the binding of [^{3}H]-dihydroalprenolol to the β_2-adrenergic receptor from catfish red blood cells [35]. Cultured striatal neurons were protected by **2** or **1** against *N*-methyl-*D*-aspartate-induced toxicity [54]. Nornicotine bound strongly to the [^{3}H]-α-bungarotoxin binding site on the nicotinic acetylcholine receptor for housefly and honeybee heads [40]. Nornicotine induced the release of [^{3}H]-dopamine from rat striatal slices [55], and from mouse striatal synaptosomes [56]. The displacement of nicotine from binding sites in rat brain by **2** was investigated [57,58].

The use of suicide inhibitors of ornithine decarboxylase and arginine decarboxylase, coupled with the efficiency of incorporation of labelled precursors, led to the conclusion that arginine decarboxylase was the source of putrescine for tobacco alkaloids including **1** and **2** [46]. Labelled spermidine was incorporated into **1** and **2**, apparently via degradation to putrescine [47]. In vitro properties of the nicotine demethylase activity from *Nicotiana otophora* were characterized [59].

Nornicotine was synthesized from myosmine via a chiral reduction [60].

2.1.3. *N'*-Ethylnornicotine

N'-Ethylnornicotine (**3**) was isolated from *Nicotiana tabacum*, and its structure determined by UV, IR, HRMS, ^{1}H and ^{13}C NMR, and by synthesis from nornicotine [61]. It was subsequently isolated from *N. rustica*, after the root cultures had been fed *N*-ethylputrescine dihydrochloride [62].

2.1.4. *N'*-Acylnornicotines and Related Alkaloids

A mixture of *N'*-hydroxyacylnornicotines (**4**), including *N'*-(3-hydroxy-12-methyltridecanoyl)nornicotine as the major component, was extracted from leaves of *Nicotiana repanda*, *N. stocktonii* and *N. nesophila* [63]. The mixture was toxic to larvae of the tobacco hornworm, *Manduca sexta* [63]. Feeding experiments with [2-^{14}C]-nicotine and [2'-^{14}C]-nornicotine suggested that the hydroxyacylnornicotines were biosynthesized in trichomes and then rapidly secreted from the plant [64]. The hydroxyacylnornicotines inhibited the growth of wheat coleoptiles and displayed antibiotic activity [65].

Hydroxyacylnornicotines [major component = *N'*-(3-hydroxyisotetradecanoyl)nornicotine] and a hydroxyacylanatabine [*N'*-(3-hydroxyisotetradecanoyl)anatabine] were isolated from

surface lipids of species in the Repandae section of *Nicotiana* [66]. The isolated hydroxyacylnornicotine mixture and individual synthetic compounds inhibited germination and growth of tobacco [66].

N-n-Octanoylnornicotine, isolated from cigarette smoke, and related acylated nornicotines and anabasines were found to inhibit human placental and breast cancer aromatase [67-69]. N-n-Octanoylnornicotine delayed the onset of *N*-nitroso-*N*-methylurea-induced breast cancer in rats, and had low toxicity (LD_{50} = 367 mg/kg) [67].

2.1.5. *trans*-3'-Hydroxycotinine and *N*-Hydroxymethylnorcotinine

trans-3'-Hydroxycotinine (**6**), a major metabolite of nicotine, was synthesized in two steps from cotinine via a carbonate intermediate [70].

Incubation of cotinine with hamster hepatic microsomes led to isolation of *N*-hydroxymethylnorcotinine (**7**) as a new metabolite. The structure of **7** was determined using GC-MS, UV and ^{1}H NMR, and by comparison with a synthetic sample [71].

2.1.6. Myosmine

Myosmine (**8**) was found, along with **1** and **11**, to moderately inhibit acetylcholinesterase [38]. The reduction potentials for **8** (as well as for **13** & **14**) were determined by cyclic voltammetry, since it was proposed that the biological activity of these compounds could be related to their electrochemical properties [72]. Myosmine (and **13**) was synthesized by the α-alkylation of a pyridyl-substituted imine with a protected ω-bromoamine, followed by deprotection and cyclization [73].

2.1.7. Nicotyrine and Nornicotyrine

α-Nicotyrine (**9**), α-nornicotyrine (**10**), and their β-isomers were synthesized. Addition of 2-pyridyllithium to 5-ethoxy-2-pyrrolidinone gave an open chain ketoaldehyde, which was cyclized with either methylamine or ammonium hydroxide to give **9** or **10** [74].

2.1.8. Anabasine

New sources of anabasine (**11**) continue to be reported. Anabasine was isolated from *Saurauia excelsa*, representing the first report of **11** in this genus [75]. Out of nineteen hoplonemertine species surveyed, **11** was found only in *Zygonemertes virescens* and *Amphiporus lactifloreus* [76]. It was found to be the major component in the poison gland of the ants *Messor ebeninus* [77] and *M. bouvieri* [78], and a minor component in *M. capensis* [79].

Investigation of the range of biological effects displayed by anabasine has continued. Anabasine acted as a feeding deterrent to moth larvae *Syntomis mogadorensis* [43]. It was found to be teratogenic in swine [80]. *Rana temporaria* sciatic nerve action potentials were decreased in amplitude by **11** [81]. It was a moderate inhibitor of acetylcholinesterase [38]. Anabasine reduced production of herpes simplex virus type 1, but did not affect viral protein synthesis at non toxic levels [52]. It stimulated RNA synthesis in germinating wheat embryos [82] and increased protein synthesis in rabbit neuronal nuclei [83]. Anabasine inhibited steroidogenesis via inhibition of aldosterone synthesis in rat adrenal cells [20], inhibition of rat adrenal 11β-hydroxylase and 21-hydroxylase [24], and inhibition of aromatase in human choriocarcinoma cells and term placental microsomes [27]. It inhibited by 51.7% the binding of [^{3}H]-dihydroalprenolol to the β_2-adrenergic receptor from catfish red blood cells [35]. Anabasine bound strongly to the [^{3}H]-α-bungarotoxin binding site on the nicotinic acetylcholine receptor for housefly and honeybee heads [40]. Anabasine, as well as **1** and **13**, displaced high affinity [^{3}H]-cytisine binding in rat brain membrane, and improved passive avoidance behavior [84]. Chronic infusion of either **1** or **11** led to an increase in [^{3}H]-nicotine binding in mouse brain [85]. While **11** acted in many ways similar to nicotine, it produced a different pharmacologic profile (including heart rate, blood pressure, respiratory rate, minute and tidal volume) [86].

Study of the biosynthesis of **11** has continued. In *Nicotiana rustica* and *N. tabacum* transformed root cultures, [2,2,4,4-^{2}H$_4$]-cadaverine was incorporated into **11**, providing label at the 3' and 5' positions. No label was incorporated into the pyridine ring, confirming that only the piperidine ring arises from cadaverine [87]. In *N. rustica*, only the pro-*S* hydrogen was lost after oxidation of a primary amino group of cadaverine, and nicotinic acid condensation with Δ_1-piperideine proceeded without stereoselectivity, providing both (*R*)- and (*S*)-**11** [87]. In *Anabasis aphylla*, [2-^{14}C]-lysine was incorporated only into the piperidine ring of **11** [88]. [2'-^{14}C]-nicotine was also incorporated, giving **11** labelled specifically at C(2') [89].

Anabasine was recently synthesized using a chiral boron complex to mediate an asymmetric aza-Diels Alder reaction as a key step [90].

2.1.9. Anatabine

High concentrations of nicotinic acid depressed alkaloid formation, but stimulated the production of anatabine (**12**) in *Nicotiana alata* root cultures [91]. A similar effect enhancing production of **12** in *N. tabacum* cultures had been observed earlier [91].

2.1.10. Anabaseine

Anabaseine (**13**) was found to be a component of the poison gland of the ant *Messor bouvieri* [78] and was the major component of the poison gland of *M. capensis* [79]. It was a potent agonist, as was **14**, at the pyridine receptor in single pyridine-senstive cells from crayfish walking legs [92]. Anabaseine and several analogs (including **1** and **11**) displaced high affinity [^{3}H]-cytisine binding in rat brain membrane, and improved passive avoidance behavior [84]. The reduction potentials of **13** in acid were determined by cyclic volammetry [72]. It was synthesized, as described for **8**, by α-alkylation of a pyridyl-substituted imine with a protected ω-bromoamine, followed by deprotection and cyclization [73].

2.1.11. 2,3'-Dipyridyl

Nineteen species of hoplonemertines were surveyed for the presence of pyridine alkloids. 2,3'-Dipyridyl (**14**) and a tetrapyridyl, nemertelline, were found in only one species, *Amphiporus angulatus*. Differing pyridine alkaloid contents were suggested to be of possible use in taxonomy [76].

2,3'-Dipyridyl was found to be mutagenic in a *Salmonella typhimurium* assay [93]. It was a potent agonist, as was **13**, at the pyridine receptor in single pyridine-senstive cells from crayfish walking legs [92]. The reduction potentials of **14** in acid were determined by cyclic voltammetry [72].

2.1.12. Nicotelline

Nicotelline (**15**) was synthesized using a palladium catalyzed coupling reaction of 3-bromopyridine (2 equivalents) with 2,4-bis(trimethylstannyl)pyridine [94].

2.2. 2,2'-Bipyridyl Alkaloids

2.2.1. Orellanine

Orellanine (**16**) is a toxin produced by a number of *Cortinarius* species [95]. A crystal structure for the hydrate of **16** has been reported [96], as well as a HPLC method for its determination [97]. Mass spectrometry [98] and ^{13}C NMR [99] of **16** has been described. Two recent syntheses of **16** have been published [100].

The nephrotoxicity of **16** continues to generate considerable interest. Orellanine was highly toxic to mice (LD_{50} = 12.5 mg/kg i.p.)[101] and caused interstitial nephritis and tubular necrosis in mouse kidney [102]. A summary of **16**-induced changes in renal function and morphology has been reported [103]. In LLC-PK_1 renal epithelial cell cultures, **16** decreased the activity of alkaline phosphatase and lactate dehydrogenase, and decreased the incorporation of ^{3}H-leucine and ^{3}H-thymidine [104]. Orellanine was a noncompetitive inhibitor of renal alkaline phosphatase, but a competitive inhibitor of the intestinal and placental enzymes [105]. In canine kidney MDCK cell cultures, **16**, or a metabolite of **16**, inhibited protein, RNA and DNA synthesis [106].

Orellanine (0.4 mM) inhibited photosynthesis in *Lemna minor*,without affecting the chloroplast electron transport chain [107]. It inhibited growth of *Escherichia coli* and the slime mold *Dictyostelium discoideum* [108]. Orellanine (and orelline **17**) suppressed the toxicity of aluminum ions on the fungus *Mycena septentrionalis*, via formation of a **16**(or **17**)-Al^{+3} complex [109]. The phototransformation of **16** to **17** has been described [110].

2.2.2. Orelline

A new five step synthesis of orelline (**17**) utilizes the metallation of methoxypyridines [111]. 2-Iodo-3,4-dimethoxypyridine, prepared from 4-methoxypyridine, was used in a homocoupling reaction and the product, on demethylation, gave **17**.

2.2.3. Caerulomycins

Caerulomycin E (**18b**) was isolated from cultures of *Streptomyces caeruleus*. Its structure was determined by MS and by comparison of its ^{1}H and ^{13}C NMR spectra with those of the previously isolated caerulomycin A (**18a**) and similar compounds [112]. Caerulomycin A (and its Z-isomer) have been synthesized from methyl picolinate and 3,5-dimethyloxazole [113].

The biosynthesis of **18a** was examined [112]. [U-^{14}C]-Lysine and [^{3}H]-picolinic acid were each incorporated into **18a**, with specific incorporations suggesting that lysine is converted into picolinic acid in the biosynthesis of the unsubstituted pyridine ring. [2-^{13}C, 1,3-^{14}C]-Glycerol labelled the substituted pyridine ring with the ^{13}C located at C(6) of **18a**. It was suggested that glycerol was incorporated as a unit, and that dihydroxyacetone phosphate could be a later intermediate. Remaining carbons in the substituted pyridine ring would be provided by acetate, and the nitrogen, from ammonia. The isolation of **18b** suggested that it might be a relatively late intermediate in the biosynthesis of **18a** [112].

2.2.4. Collismycins

Collismycins A and B (**19a,b**) were isolated from cultures of *Streptomyces* sp. MQ22 and their structures were determined by HRFABMS, UV, IR, and one- and two-dimensional ^{1}H and ^{13}C NMR [114]. These compounds did not interconvert at room temperature.

Both **19a,b** inhibited dexamethasone-glucocorticoid receptor binding in a dose dependent manner (IC_{50}=1.5 x 10^{-5} M and 1.0 x 10^{-5} M, respectively). [114]. Collismycins A and B were found to be cytotoxic against L1210 murine leukemia cells (IC_{50}= 0.08 μg/ml and 0.12 μg/ml, respectively), and to display antimicrobial activity [114].

2.3. 3-Alkylpyridines

A variety of pyridines substituted with long carbon chains at the 3 position have been discovered in recent years. Most of these compounds (**20-24,27-29**) were isolated from marine sponges, although two sets of alarm pheromones (**25,26**) were produced by marine molluscs.

2.3.1. Ikimines

Isolation of ikimines A-D (**20a-d**) from an unidentified Micronesian sponge was reported in 1990; their structures were identified using HREIMS, EIMS, ^{1}H NMR with homonuclear decoupling and ^{13}C NMR[115]. Ikimine A was later isolated from *Niphates* sp.[116]. Ikimines A-D were cytotoxic against KB cells with IC_{50} values ranging from 5 μg/ml (**1a**) to 10 μg/ml (**1c**)[115]. Ikimine A was also cytotoxic against murine lymphoma L1210 cells with an IC_{50} of 5.4 μg/ml, and displayed antimicrobial activity against some fungi and gram positive bacteria[116]. A synthesis of ikimine A has been reported[117].

2.3.2. Cribrochalinamine *N*-Oxides

Extracts of *Cribrochalina* sp, a marine sponge, displayed antifungal activity. Bioassay guided fractionation led to the isolation of cribrochalinamine *N*-oxides A and B (**21a,b**). Structures of these compounds were determined using HRFABMS, and one- and two-dimensional ^{1}H and ^{13}C NMR[118].

2.3.3. Niphatesines

Niphatesines A-H (**22a-h**) were isolated from *Niphates* sp, an Okinawan sponge[116,119]. Structures of **22a-h** were determined with HRFABMS, EIMS, one- and two-dimensional ^{1}H and ^{13}C NMR, UV, IR, and chemical conversion to known compounds[116,119]. Niphatesines A-H were all found to be cytotoxic against murine leukemia L1210 cells in vitro. The most active compounds in this assay (**22a-d,g,h**) displayed IC_{50} values ranging from 0.72 μg/ml (**22b**) to 7.9 μg/ml (**22g**) [116,119]. Compounds **22e-h** inhibited human carcinoma KB cells at 10 μg/ml from 16.8% (**22g**) to > 50% (**22h**), and displayed antimicrobial activity against some fungi and gram positive bacteria [116]. A synthesis of niphatesines A-D was reported, in which the absolute configurations of **22c,d** were established [120].

2.3.4. Niphatynes

Niphatyne A and B (**23a,b**) were also reported from a *Niphates* sp, and their structures were determined with HREIMS, CIMS, and ^{1}H and ^{13}C NMR. This study found niphatyne A was cytotoxic against P388 cells (IC_{50} = 0.5 μg/ml)[121].

2.3.5. Theonelladins

Theonelladins A-D (**24a-d**) were isolated from the Okinawan marine sponge *Theonella swinhoei*, and their structures were determined using HRFABMS, EIMS, UV, and ^{1}H and ^{13}C NMR[122]. These compounds displayed potent cytotoxic activity in vitro against murine lymphoma L1210 cells, with IC_{50} values ranging from 1.0 μg/ml (**24b**) to 4.7 μg/ml (**24a**) and against human carcinoma KB cells, with IC_{50} values from 3.6μg/ml (**24b**) to 10 μg/ml (**24a,c**)[122]. Theonelladins A-D were twenty times more potent than caffeine in Ca^{+2}-releasing activity from sarcoplasmic reticulum[122]. A recent synthesis of **24a-d** has been reported[123].

2.3.6. Navenone A

Navenone A (**25**) is an alarm pheromone which was reported isolated from the sea slug *Navanax inermis* in 1977[124]. Recent work has focused on its synthesis, including the report of a recent one-pot synthesis [125].

2.3.7. Haminols

Alarm pheromones haminols A and B (**26a,b**) were isolated from the cephalospidean mollusc *Haminoea navicula*, and their structures were determined using IR, UV, EIMS, ^{1}H and ^{13}C NMR, and by the conversion of **26b** to **26a** by acetylation [126]. The *S* absolute configuration of **26a** was established by reaction with a chiral isocyanate followed by degradation[126]. Investigation of additional *Haminoea* species found several new alarm pheromones: *H. orteai* contained haminols A-C (**26a-c**), *H. orbignyana* contained haminols 1 and 2 (**26d,e**), and *H. fusari* contained haminols 1-6 (**26d-i**)[127]. Structures of **26c-i** were determined using one- and two-dimensional ^{1}H and ^{13}C NMR, EIMS, and conversion of alcohols **26d,f,h** to the corresponding acetates **26e,g,i**[127]. The *S* absolute stereochemistry was determined for **26d,f,h** and confirmed for **26a** by their reaction with *S* and *R* Mosher's reagent [2-methoxy-2-(trifluoromethyl)-phenylacetyl chloride] followed by observation of the characteristic ^{1}H NMR shifts for the products[127].

2.3.8. Xestamines

Xestamines A-C (**27a-c**) were reported isolated from the marine sponge *Xestospongia wiedenmayeri* in 1990 [128]. Their structures were established using HRFABMS, UV, one- and two-dimensional NMR, and catalytic hydrogenation of the side chain of **27a** to the hexahydro derivative. Presence of the *N*-methyl-*N*-methoxylamine moiety in **27a** was confirmed by removal of the methoxy group from the above hexahydro derivative, and ^{1}H NMR analysis of the product [128].

In 1991, another group reported isolation of xestamines A,B, and D-H (**27a,b,d-h**) from a Caribbean sponge, *Calyx podatypa* [129]. Spectroscopic data for **27a** and **27b** agreed with the literature values [128]. Structures of **27d-h** were determined with GC-HREIMS, HRFABMS, ^{1}H and ^{13}C NMR, and synthesis of **27f** from reaction of **27a** with MeI [129].

Xestamines A-C were found to be inactive against P-388 cells in vitro [128]. Xestamines D-H displayed antimicrobial activity, although the pyridinium salts **27f,g,h** were ~100 times more

active than the pyridines **27d,e** [129]. The pyridines **27d,e** were, however, ~100 times more active than the pyridinium salts **27f,g,h** in the brine shrimp cytotoxicity assay [129].

2.3.9. Niphatoxins

Niphatoxin A and B (**28a,b**) were isolated from the Red Sea sponge *Niphates* sp. and their structures established using FABMS, HRCIMS, and one- and two-dimensional ^{1}H and ^{13}C NMR [130]. This study found niphatoxins A and B were ichthyotoxic, and cytotoxic against P388 cells (IC_{50} = 0.1 μg/ml).

2.3.10. Cyclostellettamines

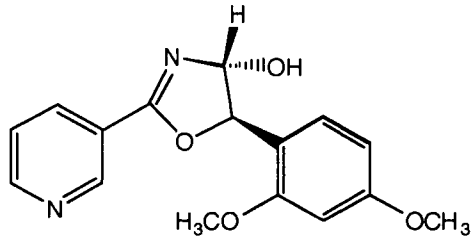
Muscarinic receptor antagonists cyclostellettamines A-F (**29a-f**) were isolated from the marine sponge *Stelletta maxima* , and their structures were determined using FABMS, and one- and two-dimensional ^{1}H and ^{13}C NMR [131]. Synthetic **29c** was found identical to the isolated material [131]. Cyclostellettamines A-F inhibited binding of [^{3}H]-methyl quinuclidinyl benzylate to three muscarinic receptor subtypes: M_1 (rat brain) [IC_{50} = 68-364 μg/ml], M_2 (rat heart) [IC_{50} = 26-150 μg/ml] and M_3 (rat salivary gland) [IC_{50} = 71-474 μg/ml]. In each case, activities decreased from **29a** (most active) to **29f** (least active) [131].

It is interesting to note that a large oligomeric or polymeric 1,3-dialkylsubstituted pyridinium compound, which is an inhibitor of epidermal growth factor, has been isolated from the Micronesian sponge *Callyspongia fibrosa* [132].

2.4. *Amyris* Alkaloids

The genus *Amyris* is known to produce alkaloids including nicotinamides and 2,5-diaryloxazoles. New nicotinamides isolated from this genus include (*Z*)-**30**, from *A. plumieri* [133], and **31**, from *A. texana* [134]. The structures of (*Z*)-**30** and **31** were determined using spectroscopic methods [133,134], and the structure of **31** was confirmed by its synthesis from tyramine [134]. The previously known (*E*)-**30** was reported from *A. sylvatica* [135], and was synthesized from 2,4-dimethoxybenzaldehyde [136]. The previously known **32** was isolated from *A. texana* [134].

Oxidative cyclization of (*Z*)-**30** with mercury (II) acetate produced an oxazoline (**A**). Although attempts to dehydrate oxazoline **A** to the corresponding oxazole were unsuccessful, its formation from (*Z*)-**30** suggests that the nicotinamides may be biosynthetic precursors of the diaryloxazoles found in *Amyris* [133].



A

A. texana was found to produce the new 2,5-diaryloxazole, texaline (**33**), along with the known *O*-isopentenylhalfordinol (**34**). The structure of **33** was established using MS, IR, UV and ^{1}H NMR [137].

Diaryloxazoles **35** and **36** were isolated from *A. plumieri* [138]. New constituents reported for *A. brenesii* include **34** and **35** [139]. *O*-Isopentenylhalfordinol has also been reported from *A. sylvatica* [135].

2.5. Piericidins

After the initial isolation of piericidins A and B [140,141], early workers found *Streptomyces* species which produce a variety of very similar compounds [142, 143]. This large group of piericidins was classified into groups A-D, and each compound in a group was given a numerical subscript for clarification. Thus, piericidins A and B were found to correspond to piericidin A_1 and B_1, respectively [142,143]. Numerical subscripts have not always been used by subsequent authors, thus reports of piericidin A have been described here along with those of piericidin A_1. In some reports, there has been no indication of classification group. For example, piericidin was reported to preferentially inhibit phagocytosis over pinocytosis by macrophages [144]. Piericidin was also reported as a weak growth inhibitor of *Plasmodium falciparum* (IC_{50} = 843 μM)[145].

2.5.1. Piericidin A_1

Piericidin A_1 (**37**) has been isolated from *Streptomyces* sp., including *S. mobaraensis* and *S. pactum* [140,142]. A potent insecticide [140], piericidin A inhibits mitochondrial electron transport through its action on NADH-ubiquinone reductase [146].

Recent studies with piericidin A_1 have included further investigation of its biological activity. Pieridicidin A_1 was reported to weakly suppress antibody formation to sheep red blood cells in

mouse spleen cultures without affecting cytotoxicity, and to cause 100% mortality in mice at a dose of 1.0 mg/kg (i.v.) [147]. Piericidin A was found to have relatively strong nematocidal activity against *Bursaphelenchus lignicolus* (IC_{50}=5.0 μg/ml) [148]

Synthetic analogs of piericidin A_1 were used in a structure activity study of the inhibition of NADH-ubiquinone reductase. Substitution of the lipophilic side chain with a saturated chain led to a decrease in activity. Substitution of the side chain with phenyl alkyl groups showed that the chain length was an important factor for activity. Replacement of the methyl group on the pyridine ring with longer chains led to decreased activity. Finally, substitution of a 4-hydroxyquinoline for the pyridine ring gave a series of compounds which displayed inhibition, with a similar activity trend as for the pyridine series [149].

1-Methyl-4-phenylpyridine (MPP^+)[150] and dihydrorotenone [151] appear to act at the same site as piericidin A on NADH-ubiquinone reductase. This site may, however, be different from the binding site for ubiquinone [151].

2.5.2. Piericidin B_1 *N*-Oxide

Piericidin B_1 *N*-oxide (**38a**) was isolated from *Streptomyces* strain MJ288-OF3 and its structure was determined using UV, IR, HRFABMS, ^1H and ^{13}C NMR. The structure of **38a** was confirmed by its reduction with zinc/acetic acid to give piericidin B_1 (**38**). The absolute configurations at C(9) and C(10) of **38a** were assigned as *S,S*, as its rotation was similar to that of **38** [152].

Piericidin B_1 *N*-oxide inhibited phosphatidylinositol turnover more strongly than piericidin B_1 (IC_{50} = 1.2 μg/ml, 5.0 μg/ml, respectively). It also displayed activity against gram positive and gram negative bacteria, and fungi, while **38** did not [152].

The mechanism of action and antitumor activity of **38a** was studied [153]. Piericidin B_1 *N*-oxide decreased EGF-stimulated phosphatidylinositol synthesis in a concentration dependent manner. It did not inhibit phosphatidic acid synthesis, phosphatidylinositol-4-kinase, phospholipase C, protein kinase C, EGF receptor tyrosine kinase, EGF-induced inositol phosphate formation, DNA synthesis, RNA synthesis, or protein synthesis at concentrations which caused inhibition of phosphatidylinositol synthesis [153].

ATP synthesis was inhibited ~30-40% in A431 cells at 1μg/ml **38a**. This inhibition was stronger than than observed for **37** or **38**. Growth of A431 cells was strongly inhibited at 1 μg/ml **38a**; this effect was reversible. Ehrlich carcinoma cells grown in mice were ~50% inhibited by **38a** (0.5 mg/kg, i.p., daily for 9 days). No antitumor effect was observed for **38a** (0.5 mg/kg) with P388 cells, or L-1210 leukemia cells in mice. Piericidin B_1 *N*-oxide was found to be toxic to mice at 1mg/kg [153].

CDP-DG:inositol transferase was proposed as the target for **38a** inhibition. The inhibition was not expected to involve blocking of electron transport [153].

2.5.3. Piericidin B5 and Piericidin B5 *N*-Oxide

Piericidin B5 (**39**) and piericidin B5 *N*-oxide (**39a**) were isolated from *Streptomyces* strain MJ288-0F3, and their structures were determined using UV, FABMS, and ^{1}H and ^{13}C NMR [154]. Reduction of **39a** with zinc/acetic acid, as expected, gave **39**. The absolute configuration at C(9) and C(10) in **39** and **39a** was established as *S,S*, as the optical rotations of **39** and **39a** were similar to those of **38** and **38a**, respectively [154].

Both **39** and **39a** inhibited phosphatidylinositol turnover in the A431 cell assay system, with IC_{50} = 10.0 μg/ml and 1.1 μg/ml, respectively[154]. Piericidin B5 *N*-oxide was active against gram positive and some gram negative bacteria and fungi; piericidin B5 was inactive [154].

2.5.4. Glucopiericidins A and B

Glucopiericidins A and B (**40a,b**) were isolated from the culture broth of *Streptomyces pactum*. Their structures were determined by elemental analysis, MS, ^{1}H and ^{13}C NMR, and acid hydrolysis to produce D-glucose [147].

Inhibition of antibody formation to sheep red blood cells in mouse spleen cultures was tested using **40a** and **40b** [147]. Glucopieircidin A totally inhibited antibody formation at 10^{-4} μg/ml without affecting cytotoxicity. Glucopiericidin B was more active, totally inhibiting antibody formation at 10^{-5} μg/ml, although concentration dependent cytotoxicity was observed. Both **40a** and **40b** were more active than **37** in this assay [147].

Glucopiericidin A inhibited growth of gram positive bacteria and *Piricularia oryzae* [147]. Glucopiericidin B was more active than **40a**, inhibiting fungal growth as well. Both **40a,b** were generally more active than **37** as antimicrobial agents. Glucopiericidins A and B were less acutely toxic to mice than **37**; an i.v. dose of 30 mg/kg resulted in 100% mortality while all survived at a dose of 10 mg/kg [147].

Glucopiericidin A was recently isolated from an actinomycete strain and described as an inhibitor of bleb formation by K562 cells induced by phorbol ester [155].

2.5.5. 3'-Rhamnopiericidin A_1

3'-Rhamnopiericidin A_1 (**41**) was isolated from *Streptomyces* sp SN-198 and its structure was determined by UV, IR, FABMS, one- and two-dimensional ^1H and ^{13}C NMR, and acid hydrolysis to give rhamnose [156]. 3'-Rhamnopiericidin A_1 was cytotoxic to HeLa and KB cells in vitro, with IC_{50} = 2.8 μg/ml and 0.74 μg/ml, respectively. Unlike the glucopiericidins, **41** was generally less active as an antimicrobial agent than **37** [156].

2.5.6. 3'-Deoxytalopiericidin A_1

3'-Deoxytalopiericidin A_1 (**42**) was isolated from a facultative oligotroph, a probable *Streptomyces* sp[157]. Its structure was determined using UV, FABMS, and ^1H and ^{13}C NMR. 3'-Deoxytalopiericidin A_1 displayed antitumor activity, by growth inhibition of murine Colon 26 cells and murine leukemia L1210 cells (IC_{50} = 0.81 μg/ml and 7.91 μg/ml, respectively) and by growth suppression of Colon 26 tumor implanted in mice [157].

2.5.7. 13-Hydroxyglucopiericidin A

13-Hydroxyglucopiericidin A (**43**) was isolated from *Streptomyces* sp. OM-5689 [158]. Its structure was determined using UV, ^1H and ^{13}C NMR. 13-Hydroxyglucopiericidin A appeared largely inactive as an antimicrobial agent, displaying only weak activity against *Piricularia oryzae* (MIC = 500 μg/ml). It was strongly cytotoxic against a variety of tumor cells in vitro with IC_{50} ranging from 0.066 μg/ml (H-69 human lung carcinoma) to 2.5 μg/ml (P388 murine leukemia) [158].

2.5.8. Glucopiericidinols A_1 and A_2

Glucopiericidinols A_1 and A_2 (**44a,b**) were isolated, guided by a cytotoxicity assay, from culture broth of *Streptomyces* sp. OM-5689 [159]. The structures of these compounds were determined using FABMS, HREIMS, IR, UV, ^1H and ^{13}C NMR. These two compounds were determined to be epimeric at C(3) due to their very similar spectra and comparison of their optical rotations [159].

Glucopiericidinols A_1 and A_2 displayed no antimicrobial activity against a range of organisms, except for *Piricularia oryzae* (MIC 125 μg/ml and 31 μg/ml, respectively)[83]. Both **44a,b** were cytotoxic to HeLa S_3 cells in vitro, with MIC = 0.39 μg/ml and 0.10 μg/ml,

respectively [159]. Significant cytotoxicity against additional tumor cell lines has been reported [158].

2.6. Celastraceae Alkaloids

Members of the Celastraceae family produce a wide variety of macrocyclic sesquiterpene pyridine alkaloids, which will be discussed below. In addition, various nicotinoyl esters of the base sesquiterpene structure β-dihydroagarofuran are produced, such as in the cangorins [160], wilforcidine [161], triptofordinines [162], and related compounds [163].

2.6.1. Acanthothamine

Acanthothamine (**45**) was isolated from *Acanthothamnus aphyllus*, and its structure was determined using ^{1}H NMR, ^{13}C NMR, and chemical transformations [164]. The position of the secondary hydroxyl groups was established after oxidation of **45** with pyridinium dichromate followed by ^{1}H NMR analysis. Methanolysis of **45** followed by ^{1}H NMR analysis demonstrated that an iso-evoninic acid residue was present [164]. X-ray crystallography confirmed the proposed structure and established the absolute stereochemistry for the evoninic acid residue as 17*R*, 18*S* [165].

2.6.2. Angulatamine

Angulatamine (**46**) was isolated from the root bark of *Celastris angulatus* and its structure was established by IR, UV, MS, and ^{1}H NMR [166].

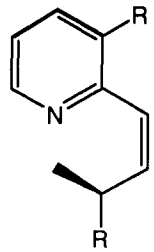
2.6.3. Cathedulins

Khat, a drug produced from leaves and shoots of *Catha edulis*, is used as a stimulant, primarily in East Africa and Southern Arabia [167]. Interest in this drug led to investigation of the components of *C. edulis*, which included a number of macrocyclic sesquiterpene pyridine alkaloids, the cathedulins.

Recent studies with the cathedulins have involved previously isolated cathedulins -E3 (**56a**), -E4 (**56b**), and -E5 (**47**), as well as the new cathedulins -K17 (**57a**), -K19 (**57b**), and -K20

(**56c**). An efficient isolation of cathedulins -E3, -E4, and -E5 from *C. edulis* using recycle high performance gel permeation chromatography has been reported [168]. All three compounds (**56a,b,47**) were found to exhibit potent growth inhibitory activity against the pink bollworm (*Pectinophora gossypiella*) at ~ 1 ppm [168].

Cathedulins -K17, -K19, and -K20 have been isolated from *C. edulis*, and their structures determined using FABMS, and one- and two-dimensional ^{1}H and ^{13}C NMR [169]. Cathedulins -K17 and -K19 each contain edulinic acid (**B**) as the acid component of the macrocyclic dilactone. The absolute configuration of **B** derived from cathedulin -K19 was established by synthesis of the (*S*)-dialcohol **C** from methyl (*R*)-3-hydroxy-2-methylpropionate. The product (**C**) was identical to the compound produced by $LiAlH_4$ reduction of cathedulin -K19, in sign of optical rotation, IR, ^{1}H and ^{13}C NMR spectra [170].



B, R = CO_2H

C, R = CH_2OH

2.6.4. Ebenifolines

Ebenifolines W-I (**60a**), E-I (**48a**), and E-II (**48b**) have been isolated from the stem bark of *Maytenus ebenifolia*. The structures of these compounds were determined using HRMS, IR, ^{1}H and ^{13}C NMR, and the absolute configuration of W-I was established using the exciton chirality method [171]. Additional alkaloids were subsequently reported from *M. ebenifolia*, ebenifoline W-II (**60b**), E-III (**48c**), E-IV (**48d**) and E-V(**48e**). Structures of these alkaloids were determined using MS, IR, and one- and two-dimensional ^{1}H and ^{13}C NMR [172].

Ebenifoline W-I was further studied to determine the configuration at C-9'. Two dimensional ^{1}H NMR studies established this configuration as *S*; the result was confirmed by X-ray crystallography [172]. Ebenifoline W-I has recently been isolated from *Peritassa compta* [173].

2.6.5. Emarginatines

Emarginatine A (**49a**) was originally isolated from *Maytenus emarginata*, guided by an in vitro KB cell assay. Its structure was determined with MS, UV, IR, and one- and two-dimensional ^{1}H and ^{13}C NMR, and confirmed by X-ray analysis [174]. This alkaloid (**49a**) was found to be cytotoxic against KB cells, with an ED_{50} = 4.0 μg/ml [174]. Emarginatine A has subsequently been reported from *Hippocratea excelsa* [175].

Emarginatine B (**49b**) has been isolated from *M. emarginata* and its structure determined by EIMS, UV, IR, and ^{1}H and ^{13}C NMR comparison with **49a** [176]. Emarginatine B was found to be significantly more cytotoxic than **49a** against KB cells, with an ED_{50} = 0.4 μg/ml [176].

Recently, additional alkaloids, emarginatines C-G (**49c-g**) have been isolated from *M. emarginata* [177,178]. Structures of these compounds were determined with MS, IR, UV, one- and two-dimensional NMR [177,178], and by the acetylation of **49c** and **49d** to give **49a** [177]. Emarginatine E and F were found to be cytotoxic against KB cells with ED_{50} = 2.5 μg/ml [177] and 0.5 μg/ml[178], respectively. Emarginatine F was found to be strongly cytotoxic to four additional tumor cell lines and weakly cytotoxic to one [178]. Emarginatines C, D, and G were found to be inactive in the cytotoxicity assay [177,178].

2.6.6. Forrestine

Forrestine (**51**) has been isolated as a new alkaloid from the root bark of *Tripterygium forrestii*. Its structure was established as a benzoylated euonymine by UV, IR, and comparison of its ^{1}H NMR spectra with those of known compounds [179].

2.6.7. Hippocrateines

Hippocrateine I and II (**52a,b**) were first isolated from root and stem barks of *Hippocratea excelsa*[180]. Structures of these compounds were established using FABMS, CIMS, and one- and two-dimensional ^{1}H and ^{13}C NMR. The structure of **52a** was confirmed by X-ray crystallography, and its absolute configuration determined by comparison with the known absolute stereochemistry of acanthothamine. Hippocrateine I (**52a**) was found to be slightly active in the brine shrimp lethality assay (LC_{50} = 212 μg/ml) and in the 9PS cytotoxicity assay (ED_{50} = 1.85 x 10^{-1} μg/ml), but it was inactive in the A-549, HT-29 and MCF-7 cell culture assays [180].

This work represents the first report of alkaloids in the Hippocrataceae family and supports a relationship between this family and the family Celastraceae. Recently, hippocrateine was reported from *Maytenus emarginata* (family Celastraceae) [178].

2.6.8. Mayteine

Mayteine (**53**) was isolated from the roots of *Maytenus guianensis* and its structure was established by IR, UV, MS and ^{1}H NMR [181]. Mayteine has subsequently been isolated from *Euonymus japonica* [182] and *Maytenus ebenifolia* [172].

2.6.9. Evonine

Structural modification of evonine (**54**)was sought to provide compounds which might possess enhanced insecticidal activity. Thus, treatment of evonine with *Arthrobacter citreus* selectively removed acetyl groups to yield pentadeacetylevonine as the sole product [183].

2.6.10. 6-Deacetylevonolin

6-Deacetylevonolin (**55**) was isolated from *Euonymus sachalinensis,* along with the known compound evonolin. [184]. The structure of **55** was determined using UV, ^{1}H NMR, FABMS, and treatment with acetic anhydride/pyridine to give evonolin [184].

2.6.11. Emarginatinine

Emarginatinine (**61**) was isolated from *Maytenus emarginata* and its structure established using MS and one- and two-dimensional ^{1}H NMR [177]. Emarginatinine was cytotoxic against KB cells with ED_{50} = 2.1 μg/ml [177].

2.6.12. Euojaponines

Euojaponines A,C,I,L and M (**50a-e**) were isolated from the root bark of *Euonymus japonica* and their structures were determined using IR, MS and one- and two-dimensional ^{1}H and ^{13}C NMR [182]. Euojaponines D,F,G,J, and K (**62a-e**) were shortly thereafter also

isolated from *E. japonica*, and their structures were established using the above spectroscopic methods [185,186]. Recently, **62b** has been isolated from *Maytenus ebenifolia* [172] and *Peritassa compta* [173].

2.6.13. Euonine

Recent reports concerning euonine (**63**) include its structure determination by X-ray crystallography [187], and study of its immunosuppressive effects [188]. Euonine has been reported from *Tripterygium wilfordii* [189], *Maytenus ebenifolia* [172], *Peritassa compta* [173], and *Euonymus japonica* [186]. Wilformine, an alkaloid isolated from *Tripterygium wilfordii* was found to be identical with euonine [190].

2.6.14. Wilforine

Investigation of the antifeedant activity of wilforine (**64**) has continued. After studying a variety of insect species, the cruciferivorous *Pieris rapae* and graminivorous *Locusta migratoria* were found most sensitive to **64**, while polyphagous feeders were less affected [191]. Wilforine was found to be effective in treatment of rheumatoid arthritis [192]. Wilforine has been isolated from *Tripterygium regelii* [193], *T. forrestii* [194], *Maytenus rigida* [191], and *Peritassa compta* [173].

2.6.15. Wilfornine

Wilfornine (**65**) was isolated from *Tripterygium wilfordii* roots. The alkaloid was found to have immunosuppressive activity in mice [189].

2.6.16. Desacetylwilfordine and Desacetylwilfortrine

Desacetylwilfortrine (**66**) and desacetylwilfordine (**67**) were isolated from *Tripterygium wilfordii* roots. Structures of these alkaloids were determined with FABMS, one- and two-dimensional ^{1}H and ^{13}C NMR, and by reaction with acetic anhydride/pyridine to form wilfortrine (**69**) and wilfordine[195].

2.6.17. Wilforgine

Wilforgine (**68**) was isolated from *Tripterygium wilfordii* and its structure identified by IR, NMR and MS [190]. The structure of **68** was confirmed and its absolute configuration established by X-ray crystallography [196,197]. The LD_{50} (i.p.) for **68** in mice has been determined as 474 mg/kg [192]. Wilforgine has also been isolated from *T. hypoglaucum* [198].

2.6.18. Wilfortrine

Several reports concerning the bioactivity of wilfortrine (**69**) have appeared. The immunosuppressive activity of **69** has been studied [188], and it has been found to inhibit leukemia cell growth in mice at 4 mg/kg [199]. Wilfortrine has been isolated from *Tripterygium wilfordii* [199] and *T. hypoglaucum* [198].

2.6.19. Wilforidine, Neowilforine, Wilforzine and Isowilfordine

Several additional alkaloids were isolated from *Tripterygium wilfordii*.. The structures of wilforidine (**70**)[200], neowilforine (**71**) [201], and wilforzine (**72**) [190] were established by chemical and spectroscopic studies. The structure of isowilfordine (**58**) was determined using ^{1}H and ^{13}C NMR, and by treatment with NaOMe/MeOH to provide an ester isomeric with dimethyl hydroxywilfordate [202].

2.6.20. Peritassines

Peritassines A and B (**59a,b**) were isolated from *Peritassa compta.* Their structures were assigned using IR, and one- and two-dimensional ^{1}H and ^{13}C NMR [173].

2.7. 2-Pyridones

2.7.1. Cepabactin

Cepabactin (**73**, BN227, G1549) was isolated from *Pseudomonas cepacia* and confirmed to act as a siderophore [203]. This siderophore was able to complex Al^{+3} as well as Fe^{+3}[204].

A six step synthesis of **73** and its analogues from 2-hydroxy-3-methoxypyridine has been reported [205]. The synthetic analogues displayed less antimicrobial activity than **73** [205].

2.7.2. Ricinidine

Ricinidine (**74**) has been synthesized in three steps from 3-formyl-1-methyl-2(1H)-pyridinethione [206].

2.7.3. Ricinine and *N*-Demethylricinine

Ricinine (**76**) and *N*-demethylricinine (**77**) are produced by *Ricinus communis* [207]. A pharmacological study of ricinine (**76**) has been reported [208]. The cyanide group of **76** was found to be essential for toxicity. Ricinine did not inhibit cytochrome oxidase; it presumably inhibited other respiratory enzymes. Administration of **76** to dogs (30 mg/kg, i.v.) caused a hypotensive effect and 30% decrease in renal blood flow. Administration of **76** to rabbits (>2.0 mg/ml cannula) led to dose dependent cardiac inhibition and reduced coronary blood flow. Ricinine stimulated the motility of rat uterus and rabbit intestine, and was highly toxic to mice (LD_{50} = 10.0 mg/kg) [208].

Adult grass grubs (*Costelytra zealandica*)[209] and phloem feeding green peach aphids (*Myzus persicae*)[210] were observed to die after feeding on *Ricinus communis*; **76** was identified as the responsible toxin. The presence of **76** in the phloem of *R. communis* indicated a possible role for the toxin in defense of the plant against aphids [210].

A short synthesis of **76** from commercially available 3-deazauracil has recently been reported [211].

Ricinis communis was shown to be effective in treatment of experimental liver injury [212]. Ricinine was not found to have hepatoprotective activity [213]. *N*-Demethylricinine, however, displayed dose-dependent choleretic activity, and anticholestatic and hepatoprotective activity against hepatic damage induced with paracetamol [213].

2.7.4. Nudiflorine

Nudiflorine (**75**) has been synthesized by a route involving an oxo-demethylation reaction of 1,6-dimethylnicotinamide [214].

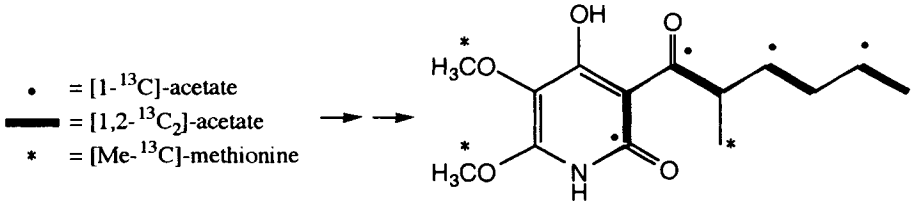
2.7.5. Cerpegin

Cerpegin (**78**) was isolated from *Ceropegia juncea* and its structure was determined using IR, UV, ^{1}H and ^{13}C NMR [215] and X-ray crystallography [216]. In a recent synthesis, **78** was obtained in five steps, beginning with a Michael reaction of phenylthioacetonitrile and 2-methoxycarbonyl-4,4-dimethyl-2-buten-4-olide [217].

2.7.6. Harzianopyridone

Harzianopyridone (**79**) was isolated as an antifungal metabolite of *Trichoderma harzianum*. Its structure was determined using MS, IR, UV, ^{1}H and ^{13}C NMR, and X-ray crystallography [218].

Biosynthetic studies feeding [1-^{13}C]- and [1,2-$^{13}C_2$]-acetate determined that **79** contained a tetraketide unit (Scheme 1). [Me-^{13}C]-methionine supplied the branched carbon on the side chain and the two methoxy carbons. The origin of the remainder of the pyridone ring has yet to be established [218].



Scheme 1. Biosynthesis of harzianopyridone

The biological activity of **79** has been investigated. Harzianopyridone was reported to display significant activity against the phytopathogenic fungi *Botrytis cinera* and *Rhizoctonia solani* [218]. Modest activity against a range of plant pathogenic fungi was observed [219]. (-)-Harzianopyridone was found active in the etiolated wheat coleoptile bioassay, with 100% inhibition at 10^{-4} M [220]. It displayed moderate activity against bacteria, and was relatively inactive against fungi [220].

2.7.7. Pyridoxatin

Pyridoxatin (**80**), a free radical scavenger, was isolated from *Acremonium* sp. BX86. Its structure was determined by HREIMS, elemental analysis, and one- and two-dimensional ^{1}H and ^{13}C NMR on **80** and a dimethyl ether derivative [221].

Pyridoxatin was ~20 times as active (IC_{50} = 0.55 μg/ml) as vitamin E as an inhibitor of free radical induced lipid peroxidation in rat liver microsomes [221]. It inhibited (IC_{50} = 1.95 μg/ml) hemolysis of rat erythrocytes catalyzed by a free radical initiator [221]. Pyridoxatin inhibited the growth of HeLa cells (IC_{50} = 1.0 μg/ml), but only displayed antimicrobial activity against *Candida albicans* (MIC = 1.64 μg/ml) [221].

The first total synthesis of **80** has been reported. Pyridoxatin was prepared in seven steps from cis-2,4-dimethylcyclohexanone [222].

2.7.8. Tenellin

A convergent total synthesis of tenellin (**81**) has been reported. A key step in the synthesis was a cyclocondensation reaction between two preformed segments to form the pyridone ring [223].

Isotopically labelled 3-amino-2-phenylpropionic acids were synthesized as possible biosynthetic precursors of the pyridone ring of **81**. Although *Beauveria bassiana* took up the compounds, no incorporation into **81** was observed [224].

2.7.9. Ilicicolin H

A convergent total synthesis of ilicicolin H (**82**) has been reported. This synthesis coupled a protected pyridone with a tetraene precursor, and later utilized an intramolecular cyclization to form the trans-decalin system [225].

2.7.10. Funiculosin

Funiculosin (**83**) inhibited growth of the malaria-causing organism *Plasmodium falciparum* [226]. The structure of a partial reduction product of **83**, tetrahydrofuniculosin, was investigated by X-ray crystallography [227]. The cyclopenanetetraol moiety of **83** has been synthesized [228].

Investigation of the binding of funiculosin to mitochondrial cytochrome b has continued. Use of mutants and other cytochrome b samples which are resistant to **83**, and analysis of funiculosin binding and shifts induced in optical spectra have allowed a better description of the funiculosin binding site. Sites on cytochrome b which were proposed to be involved in funiculosin binding include postions 126 and 194 (yeast) [229] and position 208 [230]. Funiculosin caused an increase in the midpoint potential of haem b_H (= b_{562}) and had a smaller effect on haem b_L (=b_{566}), suggesting that its binding site is close to haem b_H [231,232]. The binding site was also proposed to be close to the catalytic center *N*-site [230].

2.7.11. Fischerin

Fischerin (**84**) was isolated from *Neosartorya fischeri* var. *fischeri* as a metabolite which caused lethal peritonitis in mice. Its structure was established using one- and two-dimensional ^1H and ^{13}C NMR analysis of **84**, a dihydro derivative, a dimethyl ether derivative, and a triacetate derivative [233].

2.8. Elfamycins

The elfamycins are a group of antibiotics which are known to inhibit bacterial protein synthesis by binding to elongation factor Tu (EF-Tu). A review describing the mechanism of action of these antibiotics has been published [234]. FABMS and direct liquid introduction negative ion LC/MS have been utilized recently to determine molecular weights and obtain structural information for several of these compounds, including **85-89** [235]. Matrix-assisted laser desorption (MALD) MS has been used to study the EF-Tu-**85** complex, and desorption chemical ionization, FAB, and thermospray MS have been used to study the fragmentation pattern of **85-87** [236].

2.8.1. Kirromycin

Recent work with kirromycin (**85**, mocimycin) has included study of its interactions with EF-Tu. ^1H NMR has been used to examine the EF-Tu·kirromycin complex. Small changes in the pH titration curves for *E. coli* EF-Tu histidine residues were noted in the presence of **85**, and the acid stability of EF-Tu was increased slightly [237]. In another study, the 1:1 deuterated EF-Tu·**85** complex was examined by ^1H NMR. Differences in the spectrum of the complex were consistent with induction of a conformation similar to that of EF-Tu·GTP [238]. Results from

this study also suggested that the pyridone ring of **85** was not directly involved with binding to EF-Tu, but that the alkene regions [C(18)-C(24) and C(7)-C(13)] may be involved with binding [238]. A report of the full assignment of the ^{1}H and ^{13}C NMR spectra of **85** should facilitate further work in this area [239].

Examination of structure-activity relationships of kirromycin analogs (including **86** and **87**, among others) indicated that the pyridone region was not required for activity [240]. The EF-Tu.GDP/GTP·**85** complex was also studied using zone interference gel electrophoresis, GTPase stimulation, and fluorescence. All three methods indicated that **85** (as well as **86**) significantly decreased the stability of the EF-Tu·GTP·aa-tRNA complex, bringing it to essentially the same stability as that of **85** with EF-Tu·GDP·aa-tRNA [241]. An EPR study of EF-Tu containing Mn^{+2} rather than Mg^{+2} indicated that kirromycin binding appeared to cause a conformational change affecting the environment of the metal in the active site [242].

Recent work using kirromycin-resistant mutants of *Escherichia coli* [243], or *E. coli* and *Salmonella typhimurium* [244] identified mutation sites and concluded that **85** binds at the interface between domains I and III of EF-Tu·GTP. It was proposed that these mutations inhibit access of **85** to its binding site, and at high concentrations of **85**, EF-Tu·GDP·**85** complexes that did form would have an EF-Tu·GTP-like conformation, favoring release of **85** [243].

The action of **85** on EF-1α from calf brain was used to examine properties of this protein [245], and the addition of **85** to a mix of EF-Tu·GDP species having differing affinities for the antibiotic has been used for their separation [246]. Finally, **85** has been recently isolated from a novel source, an *Actinoplanes* strain [247].

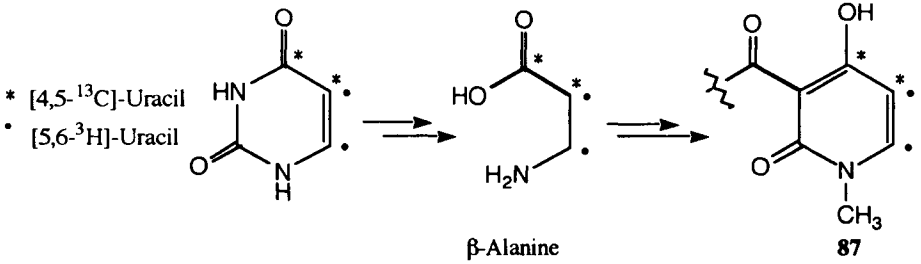
2.8.2. Aurodox

Recent work with aurodox (**86**) has included study of the interaction of **86** with EF-Tu and its total synthesis. The interaction of **86** with EF-Tu has been studied using fluorescence emission spectroscopy. The reaction of EF-Tu in the presence of **86** with 1-anilino-8-napthalenesulfonate [or 5,5'-dithiobis(2-nitrobenzoate)] was found similar to that of EF-Tu·GTP, supporting the formation of a GTP like conformation for the EF-Tu·GDP·**86** complex [248]. In addition, conformational changes to alter the environment around the sole tryptophan residue of EF-Tu were observed [248]. Incorporation of 3-fluorotyrosine into EF-Tu and subsequent ^{19}F NMR studies indicated that the conformation of EF-Tu·**86** was similar to that of EF-Tu·GDP·EF-Ts and EF-Tu·GTP, and quite different from EF-Tu·GDP [249]. In another study, **86** was found to increase the affinity of EF-Tu·GDP for aa-tRNA, and to decrease the affinity of EF-Tu·GTP [250]. The first total synthesis of **86** and **87** has been reported [252,253].

2.8.3. Efrotomycin

The structure of efrotomycin (**87**), isolated from *Nocardia lactamdurans*, was determined by MS, UV, ^{1}H and ^{13}C NMR on **87** and several degradation products [251]. The structure of **87** (and **86**) was confirmed by synthesis [252,253]. Efrotomycin was found highly active against *Clostridium difficile* [254]. It was effective in increasing the rate of weight gain and efficiency of feed utilization in swine [255] and was approved for such use by the U.S. Food and Drug Administration [256]. Efrotomycin also improved the rate of weight gain and feed utilization in chicks, and decreased cholyltaurine hydrolase activity [257]. It did not display cross-resistance with other antibacterial agents [258], and did not encourage growth of *Salmonella typhimurium* in swine [259].

The biosynthetic source of the pyridone ring of **87** was investigated [260]. Thymine was found to inhibit uracil catabolism and **87** biosynthesis by *Nocardia lactamdurans*; this inhibition was reversed by uracil catabolites. Both [5,6-^{3}H]-uracil and [4,5-^{13}C]-uracil were incorporated, with both labelled carbons of the latter being incorporated as a unit at C(4) and C(5) of **87**. The proposed biosynthetic pathway (Scheme 2) involved catabolism of uracil to β-alanine, which was then incorporated into the pyridone ring of **87** [260].



Scheme 2. Proposed biosynthesis of the pyridone ring of efrotomycin

2.8.4. Heneicomycin

Heneicomycin (**88**) had previously been isolated from *Streptomyces filipinensis*[261]. Its structure has now been reported, having been determined using UV, MS, HRMS, and one- and two-dimensional ^{1}H and ^{13}C NMR [262].

2.8.5. SB22484

SB22484 (**89**) was isolated from submerged cultures of *Streptomyces* sp NRRL 15496 as a complex composed of two isomeric pairs (**89a,c** and **89b,d**) [263]. The structures of **89a-d** were established using UV, IR, titrametric pK determination, MS, and one- and two-dimensional ^{1}H NMR [264]. The SB22484 complex (or individual elements) displayed antimicrobial activity, and was further tested against a variety of *Neisseria gonorrhoeae* strains (median MIC = 2 μg/ml) and *N. meningitidis* (MIC = 1-4 μg/ml) [263]. It was somewhat effective against *Streptococcus pyogenes* septicemia in mice (ED_{50} = 174 mg/kg), but ineffective against *S. pneumoniae* septicemia. SB22484 displayed a low half life in mouse serum, and low toxicity in the mouse (LD_{50} >1g/kg, i.p.) [263].

2.8.6. UK-69,753

UK-69,753 (**90**) was isolated from cultures of *Amycolatopsis orientalis* [265]. Its structure was determined using UV, FABMS, elemental analysis, ^{1}H and ^{13}C NMR, acid hydrolysis to give the disaccharide, and X-ray crystallography of the disaccharide unit [266]. In vitro assay showed **90** posessed antibacterial activity, being particularly effective against *Clostridium difficile* and *Treponema hyodysenteriae* (MIC = 0.39 μg/ml and 0.78 μg/ml, respectively [266]. In vivo, **90** (3.6 or 7.1 mg/kg/day) provided effective treatment of mice colonized with *T. hyodysenteriae* [266].

2.9. Pyridine Monoterpene Alkaloids

2.9.1. Actinidine

Actinidine (**91**) is produced by several insects. It was found to be a component of the ants *Iridomyrmex discors* [267], and *I. purpureus* [268]. Pygidial gland secretions of the ant *Tapinoma melanocephalum* contained **91**, and the alkaloid was repellent to worker ants of this species [269]. Actinidine was identified in a defensive secretion of the stick insect *Megacrania alpheus* [270], and it was present in trace amounts in the defensive secretion of rove beetles [271] and leaf beetles [272]. Ventral glands of *Nematus* sawfly larvae also contained low levels of **91** [273].

In one recent synthesis, **91** was prepared using a photoreductive cyclization of a *N,N*-unsaturated dialkyl-2-oxocyclopentanecarboxamide [274]. In another synthesis of **91**, a mixed copper, zinc organometallic reagent was added to a 2,5-disubstituted *N*-acylpyridinium salt to

introduce the required substituent at the 4-position. Subsequent cyclization of the five membered ring led to **91** [275].

2.9.2. Rhexifoline, Deoxyrhexifoline and Tecostidine

Rhexifoline (**93**) was isolated from blossoms and seeds of *Castilleja rhexifolia*, while deoxyrhexifoline (**94**) was isolated from seeds of *C. rhexifolia* aff *miniata* [276]. The structures of these alkaloids were determined using HRMS, UV and ^{1}H NMR [276], and by preparation of **93** from penstemonoside using β-glucosidase and ammonia [277]. Rhexifoline was judged to not be an artifact, as comparable amounts were obtained using either ammonia or NaOH in the isolation [276]. It was subsequently found in additional *Castilleja* species [278]. *Castilleja* is a host for the plume moth *Platyptilia pica*, and **93** was found in these adult moths [276,278].

Deoxyrhexifoline (**94**), tecostidine (**92**) and actinidine (**91**) have been synthesized from the iridoid glycoside loganin [279].

2.9.3. Venoterpine

The configuration of venoterpine (**96**) was established by correlation with cantleyine (**95**). Hydrolysis of the ester group of **95**, followed by decarboxylation, gave **96** [280].

2.9.4. Euphrosine

Euphrosine (**97**) was isolated from *Orthocarpus luteus*. It was not an artifact, as it could be obtained using either ammonia or NaOH/Na_2CO_3 in the isolation. The structure of **97** was determined using one- and two-dimensional ^{1}H and ^{13}C NMR, and by synthesis from the iridoid glucoside euphroside [281].

2.9.5. Oxerine

Oxerine (**98**) was isolated from *Oxera morieri*[282]. It was not an artifact, as no ammonia was used in the isolation. The structure of **98** was determined using MS, UV, IR, ^{1}H NMR, and formation of a monoacetyl derivative. The absolute configuration of **98** was established by its synthesis from the iridoid glycoside harpigide, using β-glucosidase and ammonium acetate [282].

2.9.6. Plectrodorine and Isoplectrodorine

Plectrodorine (**99**) and isoplectrodorine (**100**) were isolated from *Plectronia odorata*. Their structures were determined using MS, UV, IR, ^{1}H NMR, transformation of **99** to **94**, and by chemical correlation of **99** with 6-*O*-benzoyl shanzhiside methyl ester [283].

2.9.7. Scaevoline and Racemigerine

Scaevoline (**101**) and racemigerine (**102**) were isolated from *Scaevola racemigera*, along with cantleyine, tetrahydrocantleyine, the new tetrahydropyridine monoterpene strychnovoline, and derivatives of the above alkaloids. Structures of **101** and **102** were established with MS, IR, ^{1}H NMR, and synthesis of **102** from **95** [284].

2.9.8. Coelobillardierine, Coelosperminone and 7,8-Dehydrocoelobillardierine

Coelobillardierine (**103**), coelosperminone (**104**), and 7,8-dehydrocoelobillardierine (**106**) were isolated from *Coelospermum billardieri*, along with **95** and *cis*- and *trans*-coumarates of 9-hydroxycantleyine. Structures of **103,104 &106** were determined with MS, IR, ^{1}H and ^{13}C NMR, and by conversion of **104** to **103**, and conversion of **106** to **103** [285].

2.9.9. Aucubinines

Anaerobic incubation of the iridoid glucoside aucubin with strains of human intestinal or fecal bacteria produced the new alkaloid aucubinine A (**105**), as well as aucubinine B (**104**) [286], which had been isolated previously as coelosperminone [285]. The structures of **105** and **104** were assigned on the basis of MS, IR, ^{1}H and ^{13}C NMR, and synthesis of **104** and **105** from aucubin with β-glucosidase and ammonium chloride [286].

2.10. Miscellaneous Pyridine Alkaloids

2.10.1. Trigonelline

Trigonelline (**107**) has continued to be identified in a variety of plants, as exemplified by surveys of the Acanthaceae [287], Labiatae [288], Moraceae [289], assorted monocots and dicots [290], and red algae [291].

A number of reports have appeared on the biological activities of trigonelline. Continued investigation of **107** as an intercellular signal in legumes for induction of cell arrest in G2 has shown the carboxyl and *N*-methyl groups of **107** are required for activity [292]. Trigonelline was found to accumulate in plants such as poplar and salt marsh grass in response to salt stress, although the increased concentrations appeared too low to be osmotically significant [293,294]. It increased the thermal stability of pyruvate kinase from *Zea mays* and rabbit muscle, and protected pyruvate kinase from *Zea mays* against salt inhibition [295]. Trigonelline, a major component of alfalfa seed rinse, was found to induce nodulation gene transcription in *Rhizobium meliloti* via its activation of NodD2 protein [296]. It appeared to induce resistance in plants against fungal pathogens when applied at least two days prior to application of the pathogen [297]. Growth of *Lemna paucicostata* was promoted by **107** over a range of concentrations, with the greatest effect at 20 μM [298]. Trigonelline was isolated from the marine hydroid *Hydractinia echinata* as a morphogenetically active component which affected pattern formation [299]. It was identified as one of the components of *Achillea millefolium* which posessed mosquito repellant activity [300], and was isolated from an octocoral (*Dendronephthya* sp) as an antifouling agent which prevented settling of the barnacle *Balanus amphitrite* [301].

A redox drug delivery system using an attached 1,4-dihydrotrigonelline unit has been developed. The attachment confers increased lipophilicity , improving penetration of the blood brain barrier and skin. Rapid oxidation to the polar trigonelline form then keeps the delivery system in place and allows for slow release of the drug [302,303].

2.10.2. Alkaloids from Orange, Peppermint, Spearmint and Jonquil Oils

GC-MS has been utilized to analyze the composition of orange, spearmint, and peppermint oil. In each case, low levels of a large variety of substituted pyridines were detected. From Valencia orange oil, nineteen substituted pyridines were detected, the major component of these being 3-hexylpyridine (~20 ppb) [304]. From scotch spearmint oil, thirty-three substituted pyridines were detected (eleven newly identified), including 2-acetyl-4-isopropenylpyridine (3.34 ppm) [305]. The major component in a mix of substituted pyridines from peppermint oil was 4-isopropyl-2-methylpyridine (1.90 ppm) [305].

Jonquil oil was also found to contain substituted pyridines, specifically (*Z*)- and (*E*)-3-(but-1-enyl)pyridine (~10 ppm and ~1ppm, respectively) and (*Z*)- and (*E*)-3-(but-1-enyl)-4-propylpyridine (~20 ppm and ~10 ppm, respectively) [306]. The structures of these compounds were determined using GC-MS and ^{1}H NMR, and confirmed by synthesis. One or more of these alkaloids was also found in other sources, including patchouli oil [306].

2.10.3. Anibine

Anibine (**108**) was synthesized in three steps from a masked acyl anion equivalent, α-(3-pyridyl)-α-(4-morpholino)acetonitrile, and ethyl (*E*)-4-bromo-3-methoxy-2-butenoate. Acid hydrolysis of the product from this reaction, followed by a thermal, base promoted cyclization gave **108** [307].

2.10.4. Atpenins

Atpenins A4, A5, and B (**109a-c**) were isolated from *Penicillium* sp. FO-125 [308]. Their structures were determined using the MS, UV, IR, and one- and two-dimensional ^{1}H and ^{13}C NMR of **109a-c** and the catalytic hydrogenation product of **109c** [309]. The structure of **109a** was confirmed and its absolute configuration established by X-ray crystallography [309].

Atpenins A4, A5, and B were active against filamentous fungi, but inactive against gram positive and gram negative bacteria [308]. The LD_{50} (i.p.) values for **109a-c** in mice were determined as >50 mg/kg, 10 mg/kg, and >50 mg/kg, respectively. Atpenin B inhibited the growth of Raji cells (IC_{50} = 30μM) and inhibited the incorporation of [^{14}C]-palmitate into phospholipids and triacylglycerol in the cells [310]. Incorporation of [^{14}C]-leucine and [^{3}H]-thymidine into Raji cells was inhibited by **109c** (IC_{50} = 0.10 μM and 0.12 μM, respectively), and the cellular ATP level was decreased (IC_{50} = 0.020 μM) [310]. These results suggested that **109c** inhibited the ATP generating system of Raji cells [310].

The first total synthesis of **109c** was recently reported. Atpenin B was prepared in thirteen steps from 2-chloropyridine [311].

2.10.5. Pulo'upone

Pulo'upone (**110**) was isolated from the Hawaiin mollusk *Philinopsis speciosa*, and its structure was determined using HRMS, UV, and one- and two-dimensional ^{1}H NMR [312]. Several syntheses of **110** have been reported which utilize a Diels-Alder reaction for formation

of the trans-hydrindene moiety. A synthesis of (-)-**110** gave the absolute configuration for the molecule, by X-ray crystallographic analysis of the cycloaddition product [313]. A later asymmetric synthesis provided both enantiomers of **110** [314]. A recent synthesis provided racemic **110** under non-epimerizing conditions [315].

2.10.6. Pyripyropenes

Pyripyropenes A-D (**113a-d**) were isolated from *Aspergillus fumigatus* [316]. Their structures were established using EIMS, FABMS, UV, IR, and one- and two-dimensional ^{1}H and ^{13}C NMR on **113a** and trideacetyl-**113a** [317]. The relative stereochemistry of **113a** was determined using NMR and X-ray crystallography on **113a** and trideacetyl-**113a**, and the absolute configuration was obtained using a modified Mosher NMR method [318].

Pyripyropenes were potent inhibitors of *A. fumigatus* acyl CoA:cholesterol acyltransferase, with IC_{50} values ranging from 53 nM (**113c**) to 268 nM (**113d**) [316]. Cholesterol absorption in hamsters was inhibited by **113a** [316]. Pyripyropenes displayed no cytotoxicity to Vero cells at 177 μM, no antimicrobial activity at 1.77 mM, and no acute toxicity to ddY mice at 200 mg/kg [319].

2.10.7. Muscopyridine

A new synthesis of muscopyridine (**111**) was reported, beginning with 4-(1-nitro-2-oxocyclododec-1-yl)butanal [320].

2.10.8. Purealidin D

Purealidin D (**114**) was isolated from the Okinawan sponge *Psammaplysilla purea* as an inhibitor of Na^{+}, K^{+}-ATPase. Its structure was determined using FABMS, HRFABMS, IR, UV, and one- and two-dimensional ^{1}H and ^{13}C NMR [321].

2.10.9. Epibatidine

Epibatidine (**112**) was isolated from skin extracts of the Ecuadoran poison frog *Epipedobates tricolor*. Its structure was determined using MS, IR, UV, and ^{1}H NMR on **112** and the *N*-acetyl derivative of **112** [322].

The first total synthesis of **112**, from 6-chloronicotinaldehyde, confirmed the structure of the alkaloid [323]. There have been many subsequent syntheses of **112** and analogs. In one recent synthesis [324], (+)- and (-)-**112** were prepared after resolution of an intermediate via formation of a Mosher's ester. X-ray crystallography established the absolute configuration of the ester formed from (*R*)-(-)-Mosher's acid as 1*S*, 2*S*. This ester ultimately produced (-)-**112**, the unnatural enantiomer. Thus, the absolute configuration of the natural product was determined to be 1*R*, 2*R*, 4*S* [324].

The initial report of the potent biological activity of **112** generated a great deal of interest. Epibatidine was found to be 200 times and 500 times more potent than morphine in causing hot plate analgesia and in eliciting a Straub-tail reaction, respectively. It had a very low affinity for opioid receptor sites, which suggested an alternate mechansim of action was involved [322].

Although one molecular modeling study suggested that **112** could bind to an as yet unidentified opioid receptor [325], most subsequent efforts have focused on the ability of **112** to bind to nicotinic receptors. Both (-) and (+) enantiomers of **112** were found to bind to nicotinic receptors in rat brain (K_i = 0.058 nM and 0.045 nM, respectively) with an affinity ~twenty times that of (-)-nicotine [326]. Replacement of the chloro group of **112** with hydrogen gave an analog with comparable affinity for nicotinic sites, unlike replacement with an iodo or methyl group, which lowered the affinity [326].

In the tail flick assay, both (+) and (-) enantiomers of **112** displayed antinociceptive activity in mice (ED_{50} = 6.6 μg/kg and 6.1 μg/kg, respectively) and were ~200 times more potent than (-) nicotine [327]. Racemic **112** and a 7-N-methyl derivative of **112** were equally potent in this assay at 10 μg/kg, however the endo-**112** isomer was inactive [328]. In the hot plate assay, (+)- and (-)-**112** displayed potent analgesic activity. In this test, the natural (+)-**112** enantiomer (ED_{50} = 1.5 μg/kg, i.p.) was found to be ~two times more active than the (-)-enantiomer in mice [326]. The analgesic effect displayed by **112** in several studies was blocked by mecamyamine, but not by naloxone. Both enantiomers of **112** decreased locomoter activity and body temperature in mice, with no significant enantioselectivity [327]. Epibatidine demonstrated differential activity at subtypes of nicotinic acetylcholine receptors [329]. It was found to be a potent agonist of ganglionic nicotinic receptors [326,330] and it demonstrated cardiorespiratory effects similar to those of nicotine [330].

A recent review on epibatidine has been published [331].

2.10.10. Clitidine 5'-Mononucleotide

Clitidine 5'-mononucleotide (**115**) was isolated from the Japanese toadstool *Clitocybe acromelalga*. Its structure was determined by UV, FABMS, elemental analysis, and ^{1}H and ^{31}P

NMR. The absolute configuration was established by phosphorylation of clitidine to give **115**. Clitidine 5'-mononucleotide, like clitidine, was toxic to mice [332].

2.10.11. *N*-(2',5'-Dihydroxyphenyl)pyridinium chloride

N-(2',5'-Dihydroxyphenyl)pyridinium chloride (**116**) was isolated from leaf extract of *Punica granatum*[333]. Its structure was established with UV, FABMS, one- and two-dimensional ^{1}H and ^{13}C NMR, formation of a precipitate with aqueous $AgNO_3$, and alkaline fusion to give hydroquinone [333].

3. PIPERIDINE ALKALOIDS (TABLE 2)

3.1. *Areca* Alkaloids

The chewing of "betel quid" is a popular habit in India and Southeast Asia. *Areca catechu* nut (betel nut) is often a major component of the quid. The alkaloids of *Areca*, which have a variety of biological activities, have continued to generate considerable interest.

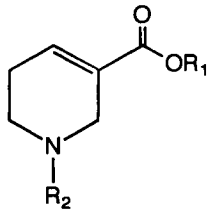
3.1.1. Arecoline

Arecoline (**117**) has been investigated as a possible memory enhancer for patients with Alzheimer's disease. The administration of arecoline and tacrine improved retention in mice more effectively than either compound alone [334]. A recent study showed improved memory in subjects with mild to moderate Alzheimer's disease on treatment with low doses of arecoline [335].

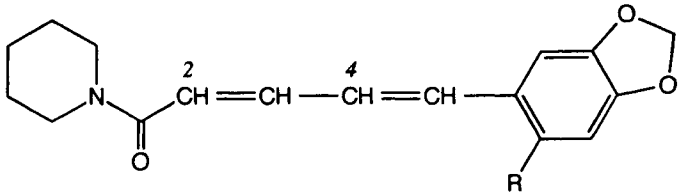
An investigation of the cardiovascular effects of **117** in dogs found that use of a low dose continual infusion, rather than a bolus administration, may reduce undesirable cardiovascular effects [336]. Arecoline increased mean arterial blood pressure [337] and selectively increased local cerebral glucose utilization in the hippocampus and median raphe [338]. In general, the effect of **117** on local cerebral blood flow and glucose utilization correlated well, but uncoupled effects were observed in some regions, such as the hippocampus [339].

The metabolism of **117** in the mouse was examined. Carboxylesterase was suggested as the agent primarily responsible for the rapid metabolism of **117** [340]. Treatment with tetra-isopropylpyrophosphoramide before administration of arecoline prolonged the lifetime of **117** in mouse brain [341].

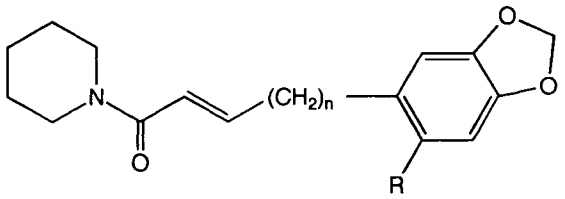
Table 2. Piperidine Alkaloids



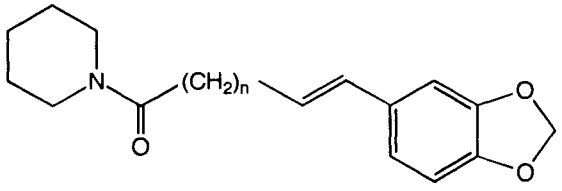
117 ARECOLINE, $R_1 = CH_3$, $R_2 = CH_3$
118 ARECAIDINE, $R_1 = H$, $R_2 = CH_3$
119 GUVACOLINE, $R_1 = CH_3$, $R_2 = H$
120 GUVACINE, $R_1 = H$, $R_2 = H$



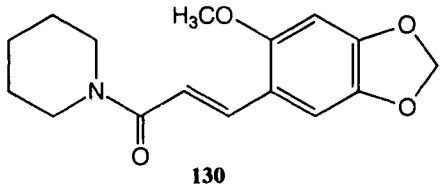
121 PIPERINE, *2E, 4E*, R = H
122 ISOCHAVICINE, *2E, 4Z*, R = H
123 PIPERX, *2E, 4Z*, R = OCH_3
124 WISANINE, *2E, 4E*, R = OCH_3



125 DIHYDROPIPERINE, n = 2, R = H
126 DIHYDROWISANINE, n = 2, R = OCH_3
127 PIPERINE S, n = 4, R = H

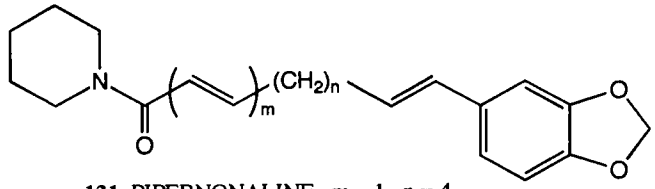


128 PIPEROLEIN A, n= 4
129 PIPEROLEIN B, n = 6

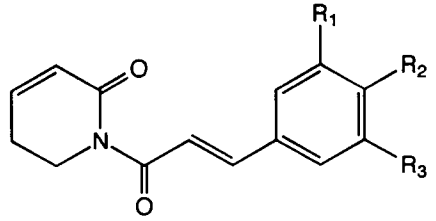


130

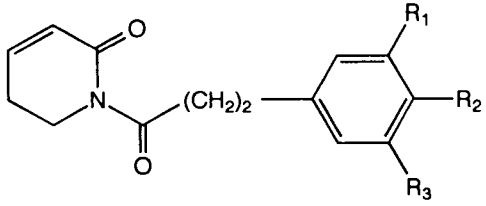
Table 2. (*cont.*)



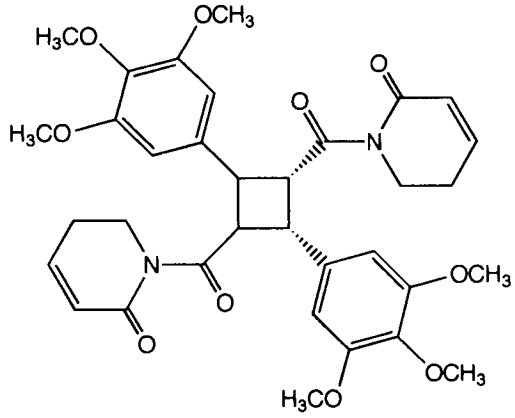
131 PIPERNONALINE, m = 1, n = 4
132 DEHYDROPIPERNONALINE, m = 2, n = 2



133 PIPLARTINE = PIPERLONGUMINE, $R_1 = R_2 = R_3 = OCH_3$
134 $R_1 = R_2 = OCH_3$, $R_3 = H$
135 $R_1 = OCH_3$, $R_2,R_3 = -OCH_2O-$

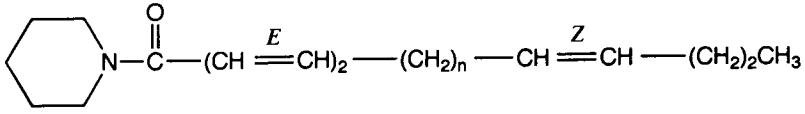


136 DIHYDROPIPLARTINE,
$R_1 = R_2 = R_3 = OCH_3$
137 $R_1 = OCH_3$, $R_2, R_3 = -OCH_2O-$

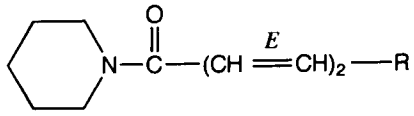


138

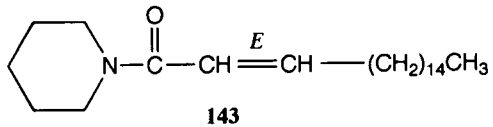
Table 2. (*cont.*)



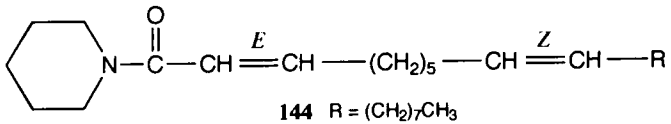
139 PIPEROCTADECALIDINE, n = 8
140 PIPEREICOSALIDINE, n = 10



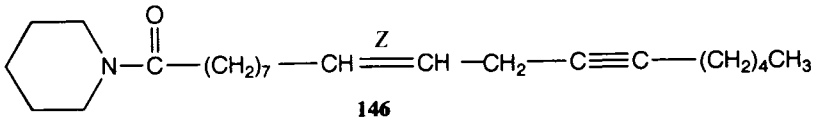
141 R = $(CH_2)_4CH_3$
142 R = $(CH_2)_8CH_3$



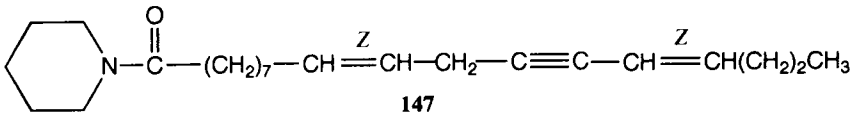
143



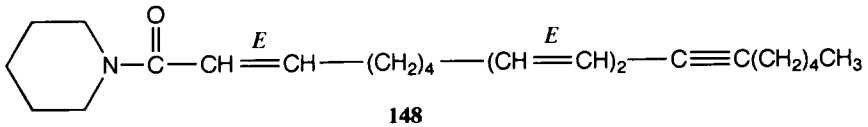
144 R = $(CH_2)_7CH_3$
145 R = $CH_2C{\equiv}C(CH_2)_4CH_3$



146

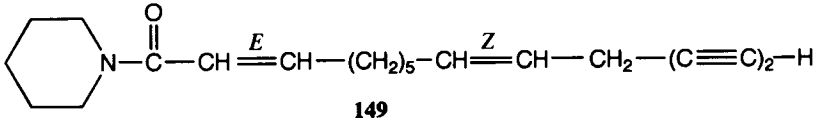


147

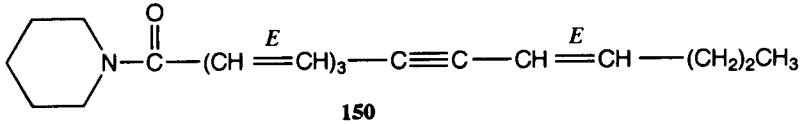


148

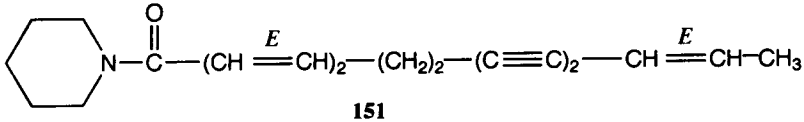
Table 2. (*cont.*)



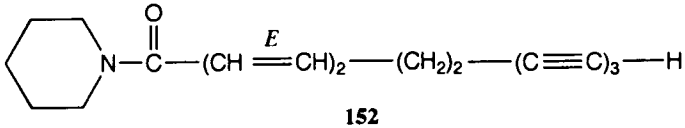
149



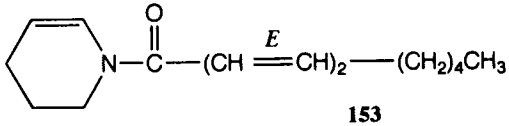
150



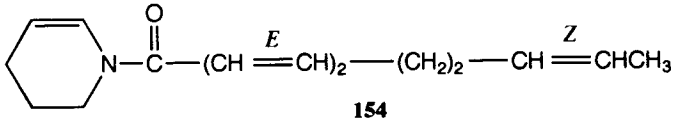
151



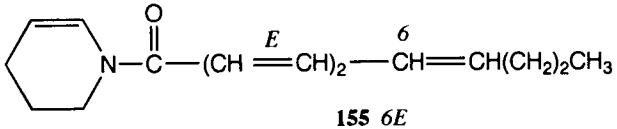
152



153

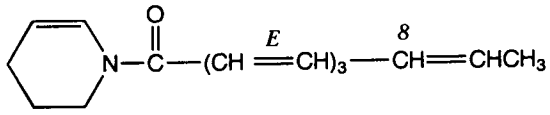


154

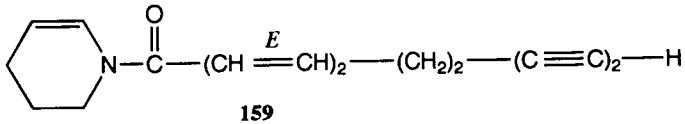


155 *6E*
156 *6Z*

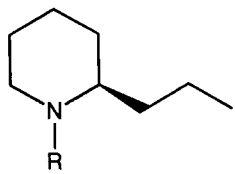
Table 2. (*cont.*)



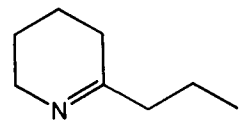
157 *8E*
158 *8Z*



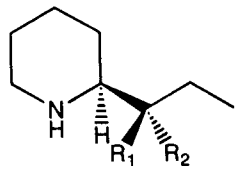
159



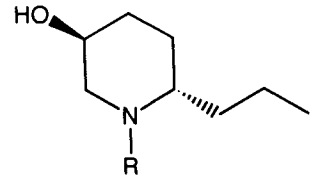
160 CONIINE, R = H
161 *N*-METHYLCONIINE, R = CH_3



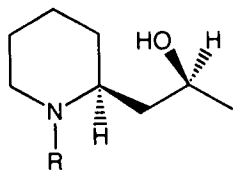
162 γ-CONICEINE



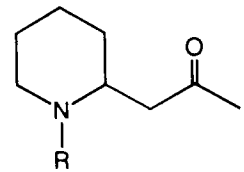
163 CONHYDRINE, R_1 = OH, R_2 = H
164 CONHYDRINONE, R_1, R_2 = O



165 PSEUDOCONHYDRINE, R = H
166 *N*-METHYLPSEUDOCONHYDRINE
R = CH_3

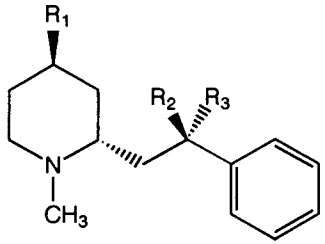


167 SEDRIDINE, R = H
168 *N*-METHYLSEDRIDINE, R = CH_3

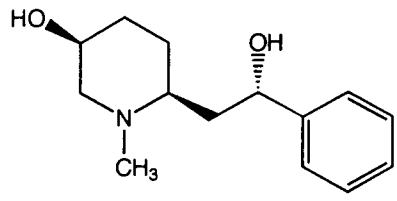


169 PELLETIERINE, R = H
170 *N*-METHYLPELLETIERINE, R =CH_3

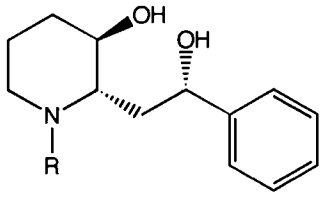
Table 2. (*cont.*)



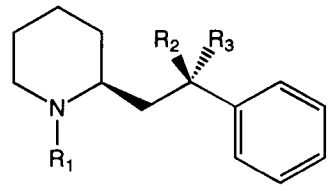
171 SEDAMINE, R_1 =H, R_2 = OH, R_3 = H
172 4-HYDROXYSEDAMINE,
R_1 = OH, R_2 = OH, R_3 = H
173 4-HYDROXYALLOSEDAMINE,
R_1 = OH, R_2 = H, R_3 = OH



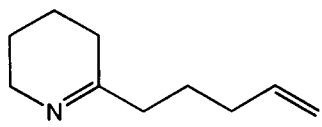
174 5-HYDROXYSEDAMINE



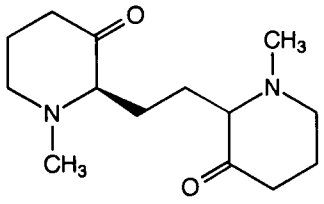
175 3-HYDROXYALLOSEDAMINE, R = CH_3
176 3-HYDROXYNORALLOSEDAMINE, R = H



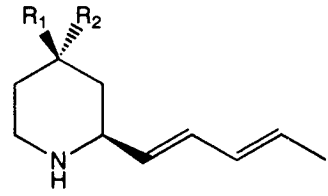
177 NORSEDAMINE,
R_1 = H, R_2 = H, R_3 = OH
178 ALLOSEDAMINE,
R_1 = CH_3, R_2 = OH, R_3 = H
179 NORALLOSEDAMINE,
R_1 = H, R_2 = OH, R_3 = H
180 SEDAMINONE,
R_1 = CH_3, R_2,R_3 = O



181

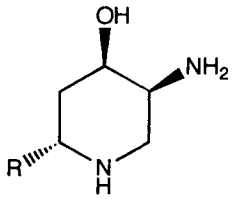


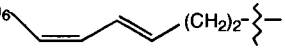
182 HYALBIDONE

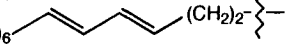


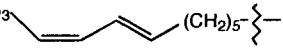
183 SS20846A, R_1 = H, R_2 = OH
184 R_1 = OH, R_2 = H
185 R_1 = R_2 = H

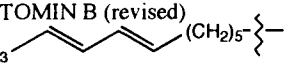
Table 2. (*cont.*)

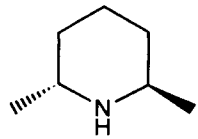


186a PSEUDODISTOMIN A
R = $CH_3(CH_2)_6$  $(CH_2)_2$-

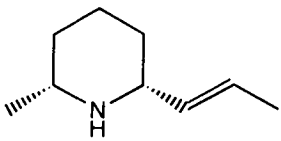
186b PSEUDODISTOMIN B
R = $CH_3(CH_2)_6$  $(CH_2)_2$-

186c PSEUDODISTOMIN A (revised)
R = $CH_3(CH_2)_3$  $(CH_2)_5$-

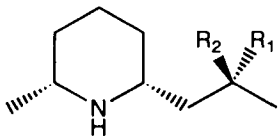
186d PSEUDODISTOMIN B (revised)
R = $CH_3(CH_2)_3$  $(CH_2)_5$-



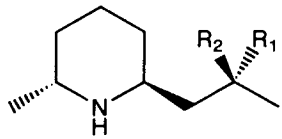
187 LUPETIDINE



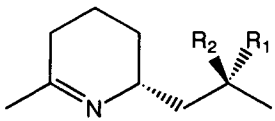
188 PINIDINE



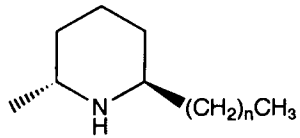
189 DIHYDROPINIDINE, $R_1 = R_2 = H$
190 PINIDINOL, $R_1 = OH$, $R_2 = H$
191 PINIDINONE, $R_1, R_2 = O$



192 EPIDIHYDROPINIDINE, $R_1 = R_2 = H$
193 $R_1 = H$, $R_2 = OH$
194 EPIPINIDINONE, $R_1, R_2 = O$

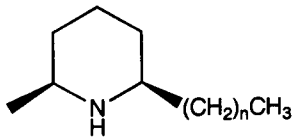


195 $R_1 = OH$, $R_2 = H$
196 $R_1, R_2 = O$

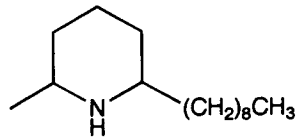


197 n = 8
198a SOLENOPSIN A n = 10
198b SOLENOPSIN B n = 12
198c SOLENOPSIN C n = 14
199 n = 16

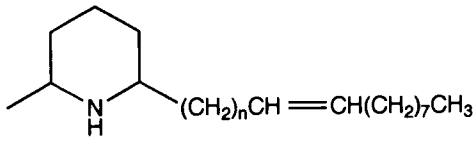
Table 2. (*cont.*)



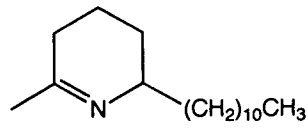
200 ISOSOLENOPSIN A, n = 10
201 n=12



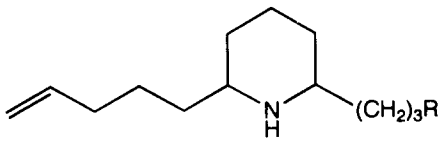
202



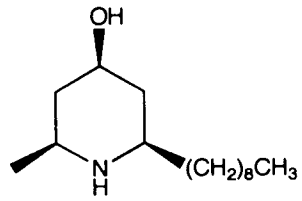
203 n = 3
204 n = 5
205 n = 7



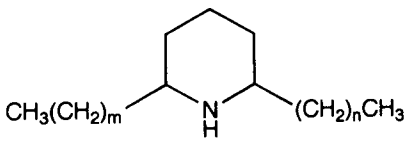
206



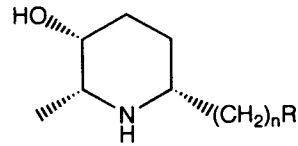
207 R = $CH{=}CH_2$
208 R = $(CH_2)_2CH{=}CH_2$
209 R = CH_2CH_3
210 R = $(CH_2)_3CH_3$



211 241D

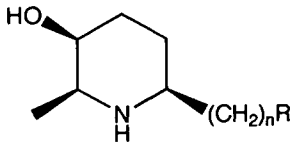


212 m = 4, n = 4
213 m = 3, n = 6

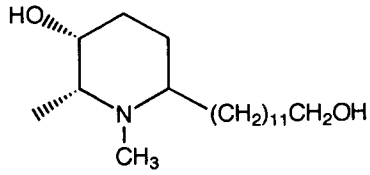


214 CASSINE, n = 10, R = $COCH_3$
215 PROSAFRININE,
n = 9, R = $COCH_2CH_3$
216 SPICIGERINE, n = 11, R = CO_2H

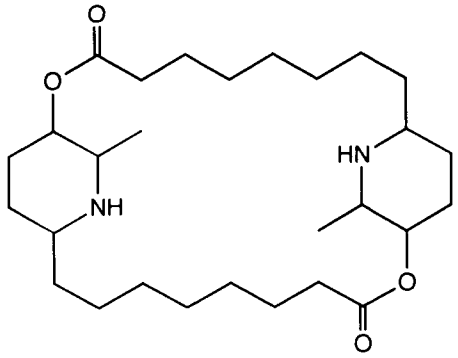
Table 2, (*cont.*)



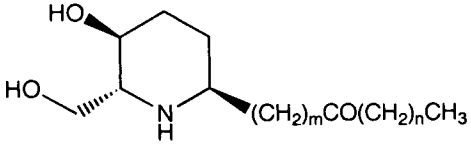
217 SPECTALINE, n = 12, R = $COCH_3$
218 AZIMIC ACID, n = 5, R = CO_2H
219 CARPAMIC ACID, n = 7, R = CO_2H



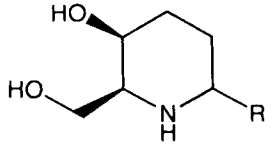
220 *N*-METHYLJULIFLORIDINE



221 CARPAINE



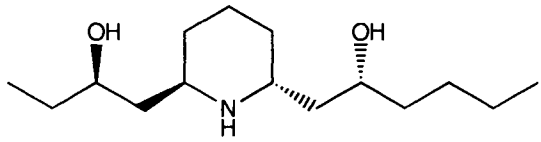
222 PROSOPININE, m = 9, n = 1
223a ISOPROSOPININE A, m = 6, n = 4
223b ISOPROSOPININE B, m = 7, n = 3



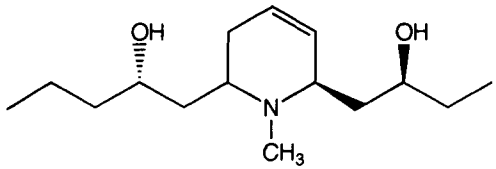
224 DESOXOPROSOPHYLLINE
R = β-$(CH_2)_{11}CH_3$
225 DESOXOPROSOPININE
R = α-$(CH_2)_{11}CH_3$

226 MICROPINE

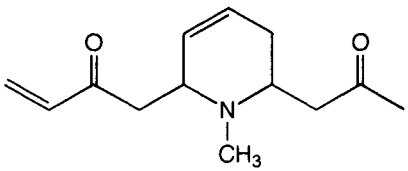
Table 2. (*cont.*)



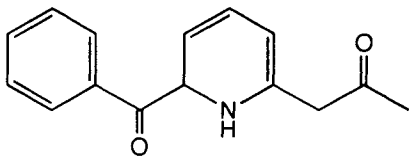
227 ANDRACHAMINE



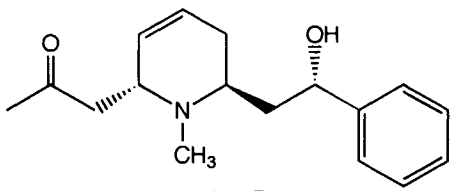
228 ANDRACHCINE



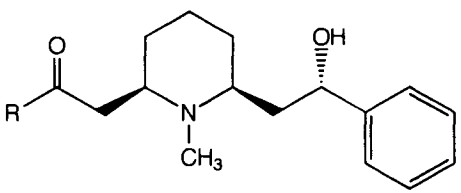
229 SEDIENE



230 SEDIENDIONE

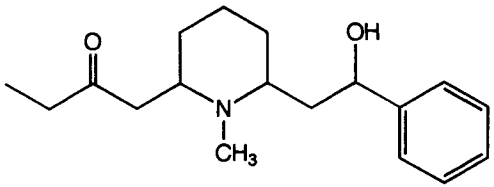


231 SEDACRINE

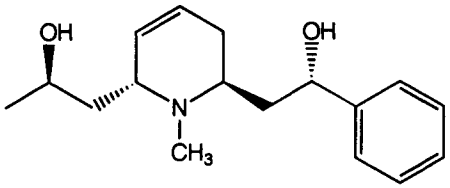


232 SEDINONE R = CH_3
233 HOMOSEDINONE R = CH_2CH_3
234 DIHOMOSEDINONE R = $CH_2CH_2CH_3$

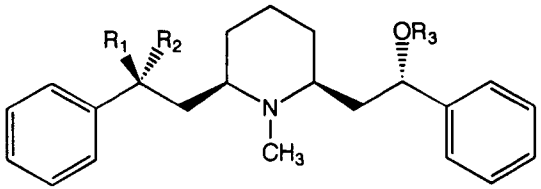
Table 2. (*cont.*)



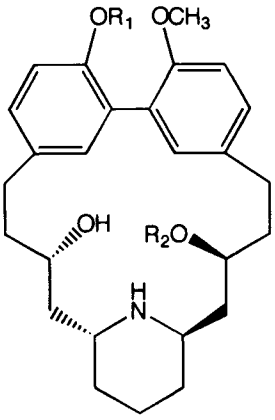
235 LELOBANONOLINE



236 SEDININE

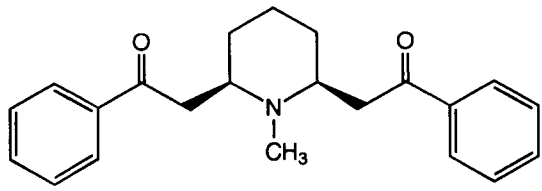


237 LOBELINE, R_1,R_2 = O, R_3 = H
238 LOBELANIDINE, R_1 = H, R_2 = OH, R_3 = H
239 LOBELANIDINE GLYCOSIDE, R_1 = H, R_2 = OH, R_3 = glucose

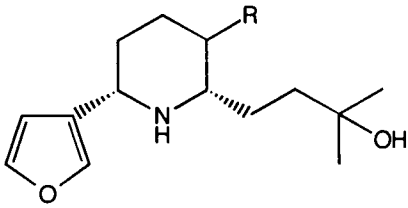


240 LYTHRANINE, R_1 = H, R_2 = Ac
241 LYTHRANIDINE, R_1 = R_2 = H

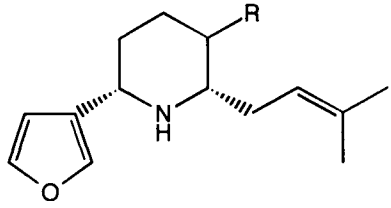
Table 2. (*cont.*)



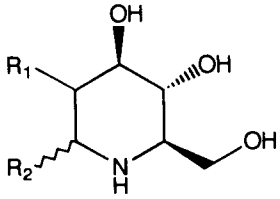
242 LOBELANINE



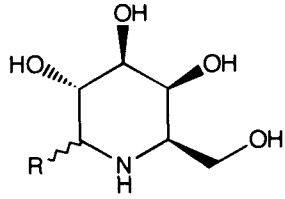
243 NUPHARAMINE, R = β-CH_3
244 3-EPINUPHARAMINE, R = α-CH_3



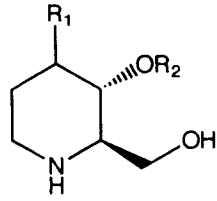
245 ANHYDRONUPHARAMINE, R = β-CH_3
246 NUPHENINE, R = α-CH_3



247 NOJIRIMYCIN, R_1 = α-OH, R_2 = OH
248 NOJIRIMYCIN B, MANNOJIRIMYCIN R_1 = β-OH, R_2 = OH
249 α-HOMONOJIRIMYCIN, R_1 = α-OH, R_2 = α-CH_2OH
250 DEOXYNOJIRIMYCIN, R_1 = α-OH, R_2 = H
251 DEOXYMANNOJIRIMYCIN, R_1 = β-OH, R_2 = H

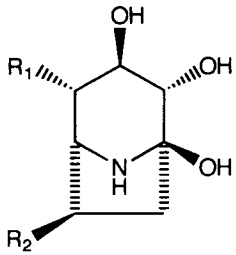


252 GALACTOSTATIN R = OH
253 DEOXYGALACTOSTATIN R = H

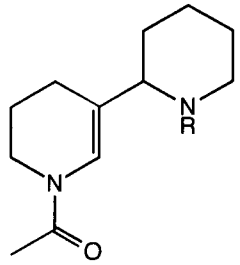


254 FAGOMINE, R_1 = β-OH, R_2 = H
255 FAGOMINE GLUCOSIDE, R_1 = β-OH, R_2 = Glucose
256 3-EPI-FAGOMINE, R_1 = α-OH, R_2 = H

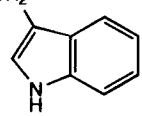
Table 2. (*cont.*)

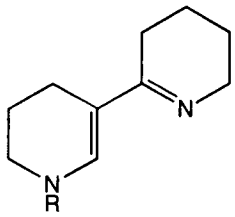


257a CALYSTEGIN A_3, $R_1 = R_2 = H$
257b CALYSTEGIN B_1, $R_1 = H$, $R_2 = OH$
257c CALYSTEGIN B_2, $R_1 = OH$, $R_2 = H$
257d CALYSTEGIN C_1, $R_1 = R_2 = OH$

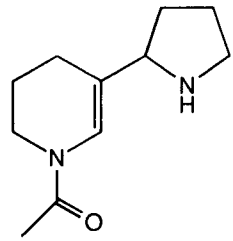


258 AMMODENDRINE R = H
259 *N*-METHYLAMMODENDRINE R = CH_3
260 GRAMODENDRINE R = CH_2

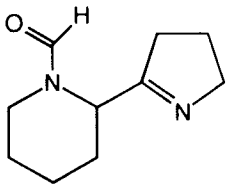




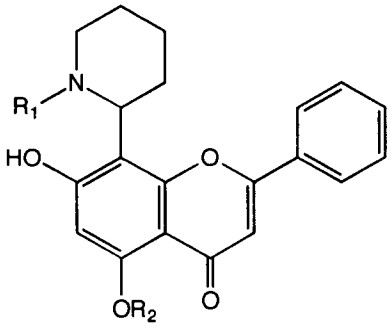
261 HYSTRINE R = H
262 *N*-ACETYLHYSTRINE R = $COCH_3$



263 MAACKIAMINE = NORAMMODENDRINE

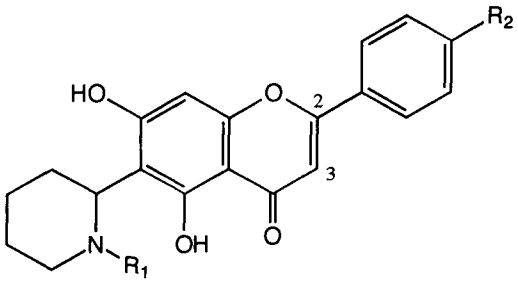


264 SMIPINE

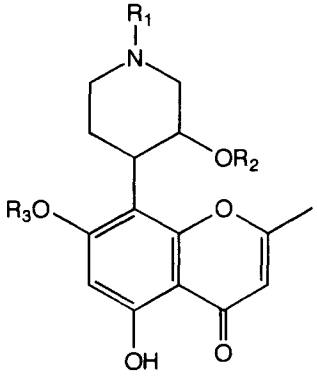


265 BUCHENAVIANINE, $R_1 = R_2 = CH_3$
266 *O*-DEMETHYLBUCHENAVIANINE, $R_1 = CH_3$, $R_2 = H$
267 *N*-DEMETHYLBUCHENAVIANINE, $R_1 = H$, $R_2 = CH_3$
268 *N,O*-DIDEMETHYLBUCHENAVIANINE, $R_1 = R_2 = H$

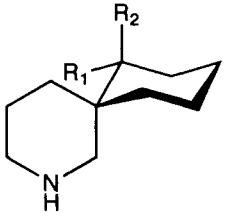
Table 2. (*cont.*)



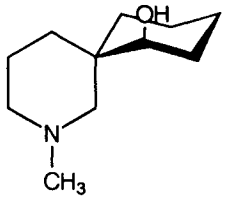
269 CAPITAVINE, $R_1 = CH_3$, $R_2 = H$
270 *N*-DEMETHYLCAPITAVINE, $R_1 = R_2 = H$
271 4'-HYDROXYCAPITAVINE, $R_1 = CH_3$, $R_2 = OH$



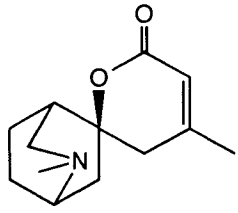
272 ROHITUKINE, $R_1 = CH_3$, $R_2 = R_3 = H$
273 *N*-DEMETHYLROHITUKINE-3'-ACETATE, $R_1 = H$, $R_2 = CH_3CO$, $R_3 = H$
274 TUBASTRAINE, $R_1 = CH_3$, $R_2 = R_3$ =4-Bromobenzoyl



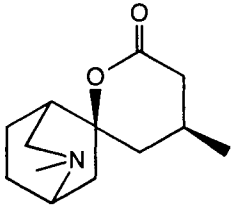
275 NITRAMINE, R_1 =OH, R_2 =H
276 ISONITRAMINE, R_1 =H, R_2 =OH



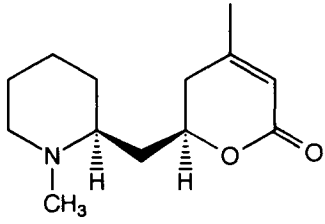
277 SIBIRINE



278 DIOSCORINE

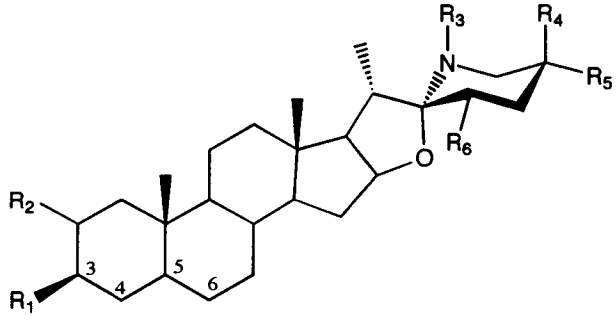


279 DIHYDRODIOSCORINE



280 DUMETORINE

Table 2. (*cont.*)



		R_1	R_2	R_3	R_4	R_5	R_6	Unsat
281	SOLASODINE	OH	H	H	H	CH_3	H	$\Delta^{5,6}$
282	*N*-METHYLSOLASODINE	OH	H	CH_3	H	CH_3	H	$\Delta^{5,6}$
283	*N*-HYDROXYSOLASODINE	OH	H	OH	H	CH_3	H	$\Delta^{5,6}$
284	SOLADULCIDINE	OH	H	H	H	CH_3	H	-
285	2α-HYDROXYSOLADULCIDINE	OH	α-OH	H	H	CH_3	H	-
286	23-HYDROXYSOLADULCIDINE	OH	H	H	H	CH_3	β-OH	-
287	INCANUMINE	S_A	H	H	H	CH_3	H	$\Delta^{5,6}$
288	KHASIANINE	S_B	H	H	H	CH_3	H	$\Delta^{5,6}$
289	RAVIFOLINE	S_C	H	H	H	CH_3	H	$\Delta^{5,6}$
290	SOLAMARGINE	S_D	H	H	H	CH_3	H	$\Delta^{5,6}$
291	SOLASONINE	S_E	H	H	H	CH_3	H	$\Delta^{5,6}$
292	ROBUSTINE	S_F	H	H	H	CH_3	H	$\Delta^{5,6}$
293	*N*-HYDROXYROBUSTINE	S_F	H	OH	H	CH_3	H	$\Delta^{5,6}$
294	25-ACETOXYROBUSTINE	S_F	H	H	AcO	CH_3	H	$\Delta^{5,6}$
295	SOLAPARNAINE	OH	H	H	H	CH_2OH	H	$\Delta^{5,6}$
296a	SOLAVEROL A	OH	H	H	H	CH_3	α-OH	$\Delta^{5,6}$
296b	SOLAVEROL B	OH	H	H	H	CH_2OH	α-OH	$\Delta^{5,6}$
297a	SOLAVERINE I	S_D	H	H	H	CH_3	α-OH	$\Delta^{5,6}$
297b	SOLAVERINE II	S_E	H	H	H	CH_3	α-OH	$\Delta^{5,6}$
297c	SOLAVERINE III	S_D	H	H	H	CH_2OH	α-OH	$\Delta^{5,6}$

S_A = Xyl(1-->4)Rha(1-->4)Glc-O-)
Xyl(1--3)/

S_B = Rha(1-->4)Glc-O-)

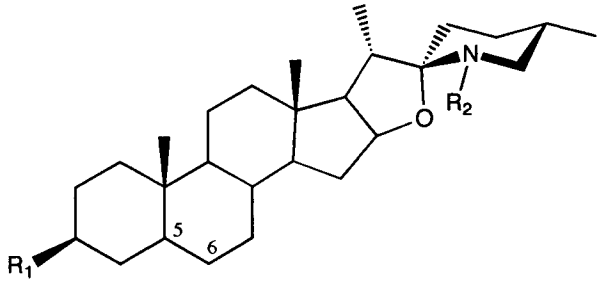
S_C = Rha(1-->4)Xyl-O-)
Rha(1-->2)/

S_D= Rha (1-->4)Glc-O-)
Rha(1-->2)/

S_E = Glc(1-->3)Gal-O-)
Rha(1-->2)/

S_F = Rha(1-->4)Glc-O-)
Ara(1-->3)/
Rha(1-->2)/

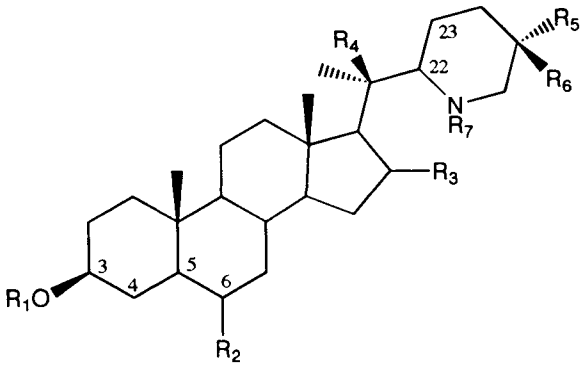
Table 2. (*cont.*)



	R_1	R_2	Unsat
298 TOMATIDINE	OH	H	-
299 *N*-HYDROXYTOMATIDINE	OH	OH	-
300 TOMATINE	S_G	H	-
301 TOMATIDENOL	OH	H	$\Delta^{5,6}$
302 SISUNINE	S_H	H	-
303 SOLADUNALIDINE	NH_2	H	-

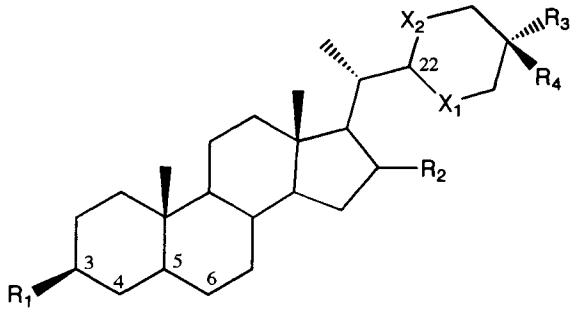
S_G = Xyl(1-->3)Glc(1-->4)Gal-O-)
Glc(1--2)/

S_H = Glc(1-->3)Glc(1-->4)Gal-O-)
Glc(1--2)/



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Unsat.
304a CORDATINE A	Glc	β-OH	H	H	H	CH_3	-	$\Delta^{22,N}$
304b CORDATINE B	Glc	β-OH	H	H	CH_3	H	-	$\Delta^{22,N}$
305 PETILINE	H	6-oxo	H	H	CH_3	H	-	$\Delta^{22,N}$
306 PETISINE	H	6-oxo	H	H	CH_3	H	-	$\Delta^{22,N}$,23-oxo
307 PINGBEININE	H	H	β-OH	H	OH	CH_3	CH_3	$\Delta^{5,6}$
308 PINGBEININOSIDE	Glc	H	β-OH	H	OH	CH_3	CH_3	$\Delta^{5,6}$
309 VERAZINE	H	H	H	H	CH_3	H	-	$\Delta^{5,6}$, $\Delta^{22,N}$
310 VERAZININE	Glc	H	H	H	CH_3	H	-	$\Delta^{5,6}$, $\Delta^{22,N}$
311 VERTALINE B	H	H	β-OH	OH	CH_3	H	H	$\Delta^{5,6}$

Table 2. (*cont.*)

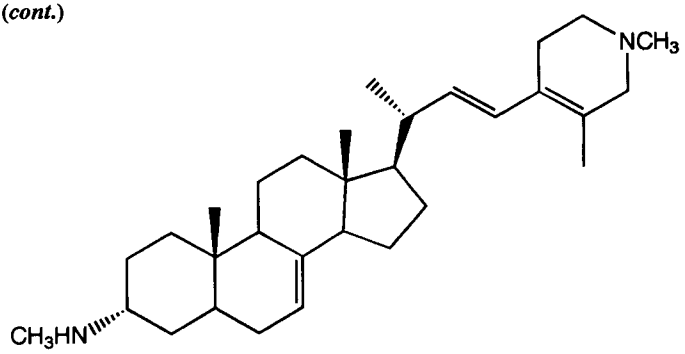


	R_1	R_2	X_1	X_2	R_3	R_4	Unsat.
312 CAPSICASTRINE	O-Gal	α-OH	NH	CH_2	CH_3	H	$\Delta^{5,6}$
313 ISOCAPSICASTRINE	O-Glc	α-OH	NH	CH_2	CH_3	H	$\Delta^{5,6}$
314 CAPSIMINE	OH	α-OH	CH_2	NH	CH_3	H	$\Delta^{5,6}$
315 CAPSIMINE-3-*O*-β-*D*-GLUCOSIDE	O-Glc	α-OH	CH_2	NH	CH_3	H	$\Delta^{5,6}$
316 ETIOLINE	OH	α-OH	N	CH_2	CH_3	H	$\Delta^{5,6}$, $\Delta^{22,N}$
317 25-ISOETIOLINE	OH	α-OH	N	CH_2	H	CH_3	$\Delta^{5,6}$, $\Delta^{22,N}$
318 ETIOLININE	S_1	α-OH	N	CH_2	CH_3	H	$\Delta^{5,6}$, $\Delta^{22,N}$
319 SOLACAPINE	NH_2	α-OH	CH, α-OH	NH	CH_3	H	-
320 EPISOLACAPINE	NH_2	α-OH	CH, β-OH	NH	CH_3	H	-
321 ISOSOLACAPINE	NH_2	α-OH	NH	CH, β-OH	H	CH_3	-
322 SOLACONGESTIDINE	OH	H	N	CH_2	H	CH_3	$\Delta^{22,N}$
323 SOLAFLORIDINE	OH	α-OH	N	CH_2	H	CH_3	$\Delta^{22,N}$
324 25-ISOSOLAFLORIDINE	OH	α-OH	N	CH_2	CH_3	H	$\Delta^{22,N}$
325 SOLAPHYLLIDINE	OH	α-AcO	CH, α-OH	NH	CH_3	H	4-oxo
326 DESACETYL-SOLAPHYLLIDINE	OH	α-OH	CH, α-OH	NH	CH_3	H	4-oxo
327 SOLAQUIDINE	3-oxo*	H	CH_2	NH	CH_3	H	-
328 TEINEMINE	OH	α-OH	CH_2	NH	H	CH_3	$\Delta^{5,6}$
329 22-ISOTEINEMINE	OH	α-OH	NH	CH_2	CH_3	H	$\Delta^{5,6}$

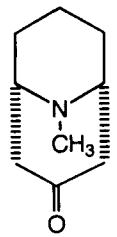
* Dimethyl Ketal

S_1 = Glc(1-->4)Glc-O-)

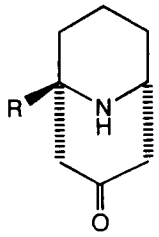
Table 2. (*cont.*)



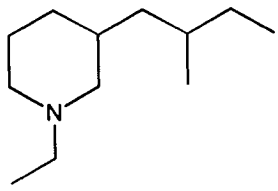
330 PLAKINAMINE B



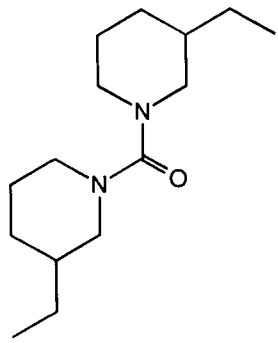
331 PSEUDOPELLETIERINE



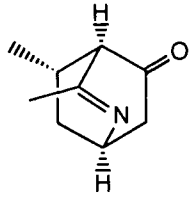
332 EUPHOCOCCININE R = CH_3
333 ADALINE R = n-C_5H_{11}



334 STENUSINE

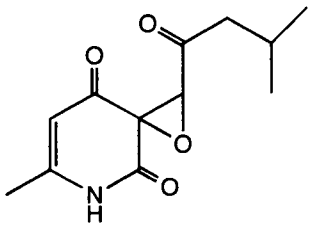


335 STRICTIMINE

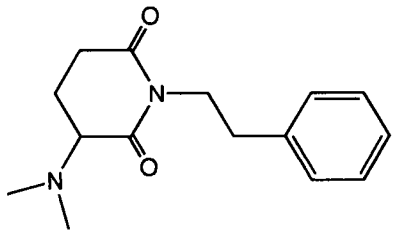


336 MEARSINE

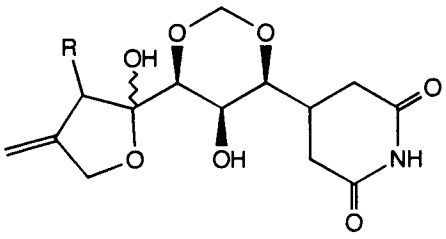
Table 2. (*cont.*)



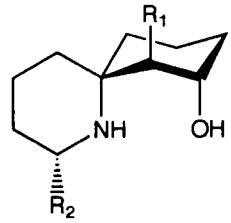
337 FLAVIPUCINE



338 PHYLLANTHIMIDE



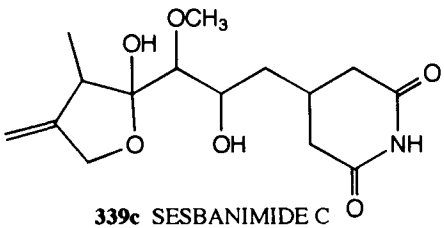
339a SESBANIMIDE A R = β-CH_3
339b SESBANIMIDE B R = α-CH_3



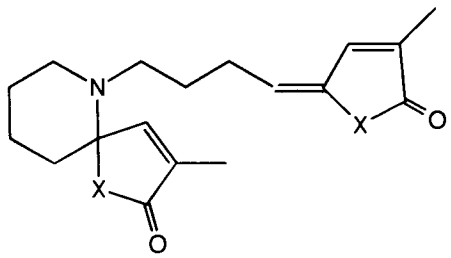
340 HISTRIONICOTOXIN
R_1 = -CH=CH—C≡CH (Z)
R_2 = $-CH_2CH$=CH—C≡CH (Z)

341 HISTRIONICOTOXIN 235A
R_1 = $-CH=CH_2$
R_2 = $-CH_2CH=CH_2$

342 PERHYDROHISTRIONICOTOXIN
R_1 = $(CH_2)_3CH_3$
R_2 = $(CH_2)_4CH_3$

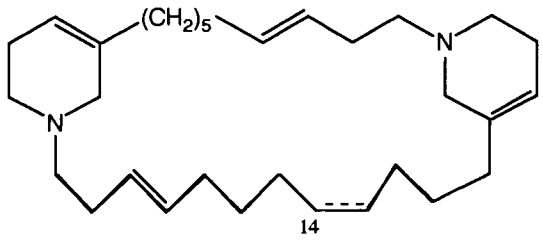


339c SESBANIMIDE C



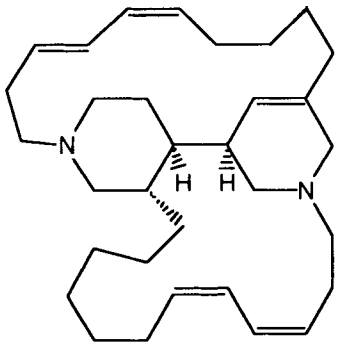
343 PANDAMARINE, X = NH
344 PANDAMARILACTONE-1, X = O

Table 2. (*cont.*)

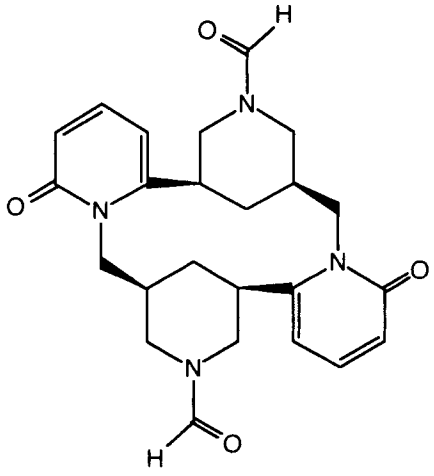


345a HALICLAMINE A

345b HALICLAMINE B, Δ^{14}



346 HALICYCLAMINE



347 GRIFFITHINE

Arecoline has demonstrated numerous additional biological activities. For example, it decreased permeability of the blood-brain barrier in the rat [342], produced hypoglycaemia in rabbits [343], and inhibited the TAK-induced activation of polymorphonuclear leukocytes [344]. In the mouse, **117** suppressed delayed type hypersensitivity reactions [345] and antibody titers [346] to sheep red blood cells. Arecoline increased levels of glutathione S-transferase, cytochrome b5, cytochrome P-450 and malondialdehyde in mouse liver, while decreasing levels of thiols [347]. Arecoline was an antifeedant for the blowfly *Phormia regina* [348] and the moth larvae *Syntomis mogadorensis* [43]. It displayed moderate molluscicidal activity against *Biomphalaria glabrata* [50] and was active against the protozoan parasite *Trypanosoma cruzi* [349].

The cytotoxic and genotoxic effects of arecoline continue to be investigated. Arecoline was cytotoxic to Hep 2 cells in an acidic medium, and decreased DNA and protein synthesis [350]. The observed cytotoxicity increased on addition of sodium nitrite [350]. Arecoline was found to be clastogenic and genotoxic by observation of chromosome aberrations and sister-chromatid exchanges in Chinese hamster ovary cells [351]. It induced unscheduled DNA synthesis in Hep 2 cells [352]. Arecoline decreased the survival and proliferation of cultured oral mucosal fibroblasts [353]. Glutathione and cysteine prevented this cytotoxicity, suggesting that thiol depletion could play a role in the toxicity of **117** [353].

3.1.2. Arecaidine, Guvacoline and Guvacine

Arecaidine (**118**), **117** and methyl substituted derivatives were tested to determine structural requirements for binding to muscarinic acetylcholine receptors [354]. Arecaidine and **117** stimulated collagen synthesis and increased proliferation of human mucosal fibroblasts [355]. Arecaidine increased micronuclei in mouse polychromatic erythrocytes, was mutagenic in V79 Chinese hamster cells [356], and induced sister-chromatid exchange in mouse bone marrow cells [357].

N-nitrosoguvacoline was formed on nitrosation of arecoline; this product was also found in the saliva of betel quid chewers [358]. Arecoline, guvacoline (**119**) and *N*-nitrosoguvacoline were cytotoxic and decreased levels of cellular thiols in human buccal epithelial cells, while arecaidine, guvacine (**120**) and *N*-nitrosoguvacine had only minor effects [359].

3.2. *N*-Acylpiperidines

3.2.1. Piperine

Piperine (**121**), a biologically active component of black pepper (*Piper nigrum*), long pepper (*P. longum*) and other *Piper* species, has been isolated from additional sources, including *Anethum sowa* [360], *Vicoa indica* [361], and an *Unocladium* sp [362].

The biological properties of piperine have continued to be of great interest. A review of the Ayurvedic preparation "Trikatu" has also reviewed the effects of piperine as a bioavailability enhancer for several drugs, its pharmacology and metabolism [363]. Several examples of the bioactivity of piperine will be described below.

The effect of **121** on inflammation in rats was studied using several experimental models. Piperine was not active against PGE_1-induced inflammation, which suggested its mode of action is involved in the early stages of the inflammation process [364]. Chronic treatment studies

suggested that **121** acts in part by stimulation of the pituitary adrenal axis [364]. Reactive oxygen species produced by macrophages can play a role in initiation of inflammation, and **121** was found to inhibit generation of these reactive species [365]. Piperine produced only marginal effects, however, in protection of polyunsaturated fatty acids from peroxidation [366].

Piperine stimulated the action of γ-glutamyl transpeptidases, enhanced amino acid uptake, and increased lipid peroxidation in isolated epithelial cells from rat jejunum, suggesting that **121** could enhance drug bioavailability by increasing the permeability of intestinal epithelial cells [367]. Piperine enhanced the bioavailability of aflatoxin B_1 in rat tissues, possibly by suppression of glucuronidation of its metabolites [368].

The interaction of piperine with cytochrome P-450 was investigated. In one study, pretreatment of mice with **121** caused an increase in cytochrome P-450 activity [369]. In contrast, another study found **121** pretreatment in rats caused no induction of activity [370]. Piperine caused differential inhibition of two forms of pulmonary cytochrome P-450 [371]. It protected against aflatoxin B_1 cytotoxicity and formation of micronuclei in H4IIE rat hepatoma cells [372]. This protective effect was suggested to occur via suppression of cytochrome P-450 activation of the aflatoxin B_1 [372].

Several studies reported the effect of piperine on other key enzymes. For example, **121** noncompetitively inhibited malate dehydrogenase (Ki=10 μM), inhibited NADH dehydrogenase, and activated Mg^{+2}-ATPase in isolated rat liver mitochondria and hepatocytes [373]. It noncompetitively inhibited guinea pig hepatic microsomal UDP-glucuronyltransferase and decreased UDP-glucuronic acid content [374]. Piperine noncompetitively inhibited UDP-glucose dehydrogenase in rat and guinea pig liver and intestine; analog studies indicated that conjugated double bonds in the side chain were important for the inhibition effect [375].

Piperine suppressed convulsions in E1 mice (ED_{50} = 21.1 mg/kg); levels of brain 5-hydroxytryptamine, dopamine and norepinephrine suggested **121** acts by inhibition of dopamine β-hydroxylase [376]. Catecholamine secretion from rat adrenal medulla was increased by infusion of **121** [377]. Study of piperine-induced positive chronotropic and inotropic effects in isolated rat atria suggested these responses occurred via release of endogenous calcitonin gene-related peptide from non-adrenergic non-cholinergic nerves [378]. Piperine was cytotoxic to cultured rat neurons [379], and suppressed neurite extension in these developing cells [380]. Piperine inhibited the fertilizing ability of hamster sperm by inhibiting both the uptake of Ca^{+2} and the acrosome reaction [381]. An infusion of **121** stimulated uptake of oxygen in the perfused rat hindlimb, although it was less active than capsaicin [382]. The effect of piperine on arterial blood pressure, heart rate, and respiration in dogs was investigated [383]. Dietary piperine in rats caused an increase in bile flow, a decrease in bile solids, and increased secretion of uronic acids into bile [384]. It provided significant protection against *t*-butylhydroperoxide- and carbon tetrachloride-induced hepatotoxicity [385]. Piperine promotion of benzo[a]pyrene cytotoxicity in V-79 lung fibroblast cells was suggested to occur via inhibition of glutathione S-

transferase and UDP-glucuronyl transferase, and by increased formation of a benzo[a]pyrene-DNA adduct [386].

Piperine displayed antifeedant activity against the moth larvae *Syntomis mogadensis* [43], the fifth instar larvae of the sorghum stem borer *Chilo partellus* [387], and larvae of the lepidopteran pest *Euproctis fraterna* [388]. It displayed moderate molluscicidal activity against *Biomphalaria glabrata* [50], inhibited in vitro growth of *Leishmania donovani* [389], and inhibited growth and aflatoxin production in *Aspergillus parasiticus* [390]. Piperine was also active against *Pseudomonas aeruginosa* and *Alcaligenes* [391].

Piperine was not found to have carcinogenic [392] or genotoxic [393] effects in mice. Instead, it showed significant activity in a 2-aminoanthracene antimutagenesis assay [394]. Piperine exhibited a protective effect on seedlings of *Hordeum vulgare* against chromosome aberrations produced by γ ray irradiation [395].

An acyltransferase which catalyzed the synthesis of piperine in the presence of piperine and piperoyl-coenzyme A was isolated from shoots of *Piper nigrum* and characterized [396]. The prior synthesis of piperoyl-coenzyme A assisted in this study [397].

Piperine was recently synthesized using a palladium catalyzed coupling of an (*E*)-β-bromoacrylamide with an alkynyl boronate [398]. A peroxidase catalyzed regioselective epoxidation of the C(2)-C(3) double bond in **121** has been described [399].

3.2.2. Isochavicine and Piperx

Isochavicine (**122**) was synthesized using a stereoselective, alumina-promoted rearrangement of a 3,4-dienamide to give the required 2*E*,4*Z* stereochemistry [400]. The structure of piperx (**123**) was confirmed by X-ray crystallography [401].

3.2.3. Wisanine, Dihydropiperine and Dihydrowisanine

Wisanine (**124**), dihydropiperine (**125**) and dihydrowisanine (**126**) were tested for antifeedant activity against fifth instar larvae of the sorghum stem borer, *Chilo partellus*. Relative antifeedant activity was **125>126>124**, with **125** being quite potent, comparable to **121** in its activity [387].

Wisanine was synthesized using either a Reformatsky or Wittig reaction to produce the acid required for formation of the amide [402].

3.2.4. Piperine S

Piperine S (**127**) was isolated from *Piper puberulum*. Its structure was established with HRMS, EIMS, UV, IR, and one- and two-dimensional ^{1}H and ^{13}C NMR [403].

3.2.5. Piperolein A and B

A recent synthesis of piperolein A (**128**) utilized an aldol-Grob type fragmentation with piperonal, cyclohexanone, and 1,3-propanediol to give an ester which was readily transformed into the amide [404]. Piperolein B (**129**) was found to display larvacidal activity against second stage larvae of the dog roundworm *Toxocara canis* [405].

3.2.6. Pipernonaline and Dehydropipernonaline

Dehydropipernonaline (**132**) was isolated from *Piper longum* and its structure was determined using HRMS, EIMS, UV, and ^{1}H and ^{13}C NMR [406]. This study also described its coronary vasodilating effect, as displayed by a concentration dependent inhibition of KCl-induced contraction of the coronary artery [406]. In a recent synthesis, both **132** and pipernonaline (**131**) were prepared using a palladium catalyzed coupling of a (*E*)-β-bromoacrylamide with an alkynyl- or alkenyl-boronate, respectively [398].

3.2.7. (*E*)-2- Methoxy -4,5-methylenedioxycinnamoylpiperidide

Amide **130** was isolated from *Piper amalgo* and its structure was determined using MS, IR, ^{1}H NMR, and hydrolysis to give piperidine [407].

3.2.8. Piplartine = Piperlongumine and Related Amides

Early confusion over the structure of piplartine (**133**) was resolved when X-ray crystallographic analysis of piplartine [408] and piperlongumine [409] showed that the two compounds were the same. Piplartine/piperlongumine was also synthesized to confirm its structure [408]. A more recent synthesis of **133** (and **121**) converted piperidine chloroacetamide to the pyrazinylsulfinyl substituted compound [410]. Subsequent deprotonation,

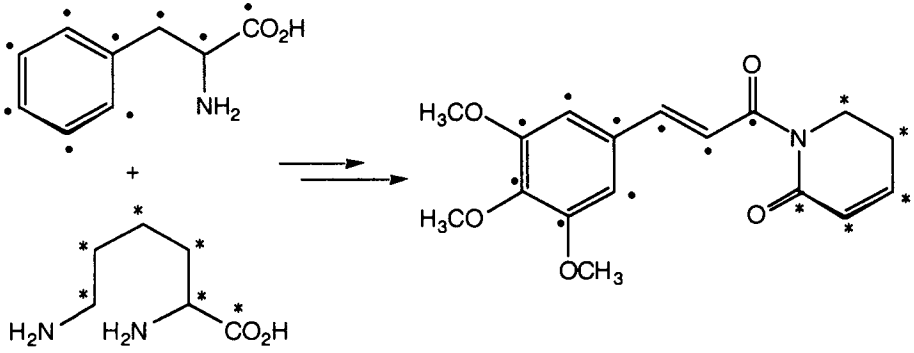
alkylation with an alkyl bromide, and elimination of the pyrazinylsulfinyl group gave the desired products.

The biosynthesis of **133** in *Piper longum* has been investigated [411]. Feeding studies with L-[U-^{14}C]-lysine and L-[U-^{14}C]-phenylalanine demonstrated that the piperidine ring was derived from lysine and the phenylpropanoate moiety from phenylalanine (Scheme 3). DL-[2-^{14}C]-tyrosine and [2-^{14}C]-sodium acetate were not significantly incorporated into **133** [411].

Bioassay guided fractionation of stems of *Piper aborescens* provided new compounds **134** and **135**, as well as the known **133** [412]. The structures of **134** and **135** were determined with HRMS, UV, IR, and one- and two-dimensional ^{1}H and ^{13}C NMR. The three compounds **134**, **135**, and **133** were all cytotoxic against KB cells (ED_{50} = 3.23 μg/ml, 2.62 μg/ml, and 1.80 μg/ml, respectively) as well as against P-388 leukemia cells (ED_{50} = 0.82 μg/ml, 0.43 μg/ml, and 0.90 μg/ml, respectively) [412].

Bioassay guided fractionation of leaves of *Piper aborescens* gave another new compound, **137**, along with the known **135**, **133**, and piplartine dimer **138** [413]. The structure of **137** was determined using HRMS, IR, UV, and one- and two-dimensional ^{1}H and ^{13}C NMR. Known compounds **133**, **135**, and **138** were significantly cytotoxic against A-549, HT-29, KB, and P-388 cells. Compound **137** was significantly cytotoxic against HT-29 and P-388 cells, and marginally active against KB and A-549 cells [413].

A new dihydropiplartine (**136**), along with **138**, was isolated from *Piper rugosum*. Its structure was determined using EIMS, UV, IR, and ^{1}H NMR [414].



Scheme 3. Biosynthesis of piplartine/piperlongumine

3.2.9. Piperoctadecalidine and Pipereicosalidine

Piperoctadecalidine (**139**) and pipereicosalidine (**140**) were isolated from the fruits of *Piper retrofractum*, along with **121** and **131**. The structures of **139** and **140** were determined using

HRMS, IR, UV, and one- and two-dimensional ^{1}H and ^{13}C NMR, and were then confirmed by synthesis [415].

3.2.10. Muntok Pepper Amides

Supercritical fluid extracts of Muntok pepper were analyzed by GC-MS (primarily) and GC-FTIR. Twenty one piperidides were identified [416].

3.2.11. *Achillea* Amides

A new piperidine amide (**150**) was isolated from *Achillea lingustica*. Its structure was determined using UV, MS and ^{1}H NMR [417].

Seven new piperidine amides were isolated from *Achillea* species [418]. Amides **143-147,** and **149** were obtained from *A. lycaonica*, and **148**, from *A. chamaemelifolia*. The structures of these compounds were determined using UV, IR, FDMS, EIMS, and ^{1}H NMR [418].

New piperidine amide **154** was isolated from *Achillea falcata*, along with several known amides. Its structure was established using MS, UV, IR and ^{1}H and ^{13}C NMR [419].^{13}C NMR spectra were obtained, and ^{1}H NMR-lanthanide induced shifts were determined for the amides [419].

A new piperideide (**155**) was isolated from *Achillea millefolium*, and its structure was determined using MS, UV, and ^{1}H NMR [420]. Several previously known piperidine amides were also isolated from this plant, including the dominant **156**. The stereochemistry of amides **157** and **158** was determined using the lanthanide induced shift method [420].

Five piperidine amides produced by *Achillea* (**151-153,156,159**) were tested as inhibitors of cyclooxygenase and 5-lipoxygenase, key enzymes in arachidonic acid metabolism. Each of the amides inhibited cyclooxygenase. Amides **152** and **153** inhibited 5-lipoxygenase, **156** and **159** were weak inhibitors of this enzyme, and **151** showed no inhibition. [421].

The *Achillea* amide **141** and related *Othantus maritimus* amide **142** were recently synthesized as illustration of a general approach to dienamides. Beginning with (1*E*,3*E*)-4-tri-*n*-butylstannyl-1-trimethylsilyl-1,3-butadiene, each terminal group was selectively substituted with the appropriate electrophilic reagent [422].

HPLC was used to separate and analyze amides in the *Achillea millefolium* group [423], and a number of known piperidine amides were isolated from *Achillea ptarmica* [424,425].

3.3. 2-Alkyl- and 2-Acylpiperidines

Many 2-substituted piperidine alkaloids are produced by *Sedum*. In one study, for example, TLC and GC/MS were used, to survey alkaloids in sixteen *Sedum* species. The alkaloids reported were sedridine (**167**), *N*-methylsedridine (**168**), pelletierine (**169**), *N*-methylpelletierine (**170**), 4-hydroxysedamine (**172**), norsedamine (**177**), allosedamine (**178**), 3-hydroxyallosedamine (**175**), as well as the 2,6-disubstituted piperidines sedacrine (**231**), sedinine (**236**), and sedinone (**232**) [426].

3.3.1. Coniine

Coniine (**160**) continues to be a popular synthetic target and numerous syntheses have been reported. In one recent synthesis, the reaction of a chiral cyclic 2-carbonylsultam-substituted *N*-hydroxy-2-propylpiperidine with NaH gave an amine which, after reduction, produced (-)-**160** [427]. Another synthesis began with a trans-oxazolopiperidone and obtained (-)-**160** after a separation of isomers in the penultimate step [428]. Yet another example of a (-)-**160** synthesis employed a lipase-catalyzed resolution of a racemic alcohol, followed by a Pd(II)-catalyzed cyclization to form the piperidine ring [429].

Coniine is the major alkaloid of hemlock (*Conium maculatum*). It has also now been found, along with γ-coniceine (**162**) and conhydrine (**163**) in a number of *Aloe* species [430]. Coniine is teratogenic to livestock, leading to arthrogyrposis [431]. Chick embryos were recently found to provide a reliable experimental animal model for coniine-induced arthrogyrposis and it appeared that this process was most likely a result of a nicotinic receptor blockade [432]. In other studies, **160** inhibited (40.2%) the binding of [^{3}H]-dihydroalprenolol to the β_2-adrenergic receptor from catfish red blood cells [35], and it was a feeding deterrent for the black blowfly *Phormia regina* [433].

3.3.2. *N*-Methylconiine

A recent synthesis of *N*-methylconiine (**161**) has been reported, based on the addition of *n*-PrMgCl to a chiral 1-acylpyridinium salt [434].

3.3.3. γ-Coniceine

Feeding *Conium maculatum* to pregnant gilts led to newborn pigs with a high incidence of cleft palate. Analysis of the alkaloid content of plant samples determined that γ-coniceine (**162**) was the responsible alkaloid. Thus, **162**, like **160**, is teratogenic in livestock [435].

3.3.4. Conhydrine

A recent synthesis of racemic conhydrine (**163**) was reported in which lithiation of *N*-BOC piperidine, reaction with DMF, and then reaction with ethyl magnesium chloride gave the protected diastereomeric conhydrines. Chromatographic separation followed by hydrolysis of the BOC group gave **163** [436].

3.3.5. Conhydrinone

The hemlock alkaloid conhydrinone (**164**), along with γ-coniceine (**162**), was identified in *Aloe ballyi* [437].

3.3.6. Pseudoconhydrine and *N*-Methylpseudoconhydrine

A recent synthesis of pseudoconhydrine (**165**) and *N*-methylpseudoconhydrine (**166**) utilized an osmium catalyzed asymmetric dihydroxylation of an *N*-alkenylurethane derived from L-norvaline [438].

3.3.7. Sedridine and *N*-Methylsedridine

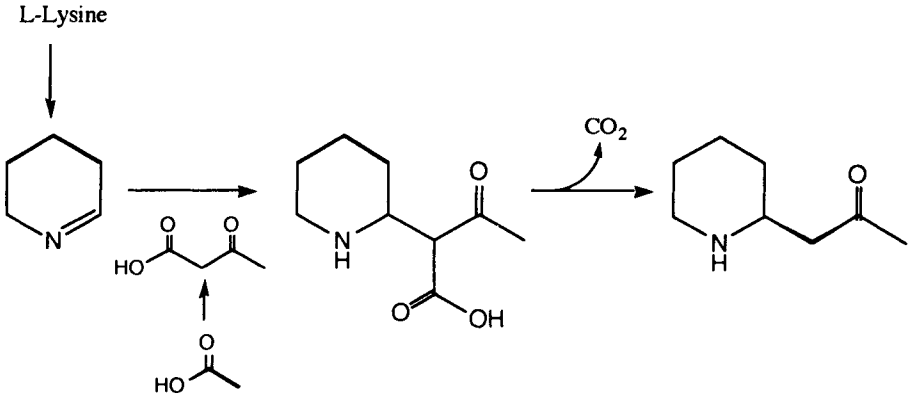
A recent synthesis of (+)-sedridine (**167**) was reported in which a key step was the asymmetric cycloaddition of the nitrone 2,3,4,5-tetrahydropyridine *N*-oxide with an asymmetric crotonic acid derivative containing a chiral auxilliary [439]. Sedridine has recently been isolated from the bark of *Punica granatum* [440].

N-Methylsedridine (**168**) was recently isolated, along with *N*-methylpelletierine (**170**) and euphococcinine (**332**), from a spruce, *Picea breweriana* [441].

3.3.8. Pelletierine and *N*-Methylpelletierine

A synthesis of pelletierine (**169**) was reported, based on the reaction of 2-hydroxypiperidine carbamate with a carbonyl-stabilized Wittig reagent [442].

The biosynthetic derivation of the side chain of *N*-methylpelletierine (**170**) was established [443]. Feeding [1,2,3,4-$^{13}C_4$]-acetoacetate to *Sedum sarmentosum* and isolation of **170** showed that the side chain of **170** was derived from the labelled precursor as an intact unit. Feeding [1,2-$^{13}C_2$]-acetate showed that the -$COCH_3$, but not the -CH_2CO portion of the side chain was derived from the intact labelled acetate. A pathway for biosynthesis of the pelletierine skeleton consistent with these results is outlined in Scheme 4.



Scheme 4. Biosynthesis of the pelletierine skeleton

N-Methylpelletierine was recently isolated from the spruce *Picea breweriana* [441] and both **169** and **170** were isolated from the bark of *Punica granatum* [440]. In a synthesis of **170**, the side chain was introduced by alkynylation of an *S*-methylthioamidium salt generated from *N*-methylpiperidine-2-thione [444].

3.3.9. Sedamine

Sedamine (**171**) was reported to competitively inhibit pea diamine oxidase (Ki = 0.9 mM) [445]. The preferred solution conformations of sedamine (**171**), allosedamine (**178**), norallosedamine (**179**), and norsedamine (**177**) were determined using ^1H and ^{13}C NMR [446]. A recent synthesis of sedamine was based on the addition of the enolate of acetophenone to a chiral 1-acylpyridinium salt [447].

3.3.10. 4-Hydroxysedamine and 4-Hydroxyallosedamine

(+)-4-Hydroxysedamine (**172**) and (+)-4-hydroxyallosedamine (**173**) were isolated from *Sedum acre* using countercurrent distribution and preparative chromatography [448]. Their structures were determined using MS, ^{1}H and ^{13}C NMR of **172**, **173**, and their diacetyl derivatives, and by synthesis via tetrahydro 1,3-oxazines of known absolute configuration. Conversion of these oxazines to **172** and **173** via a $LiAlH_4$ reduction established the absolute configuration of the new alkaloids [448].

3.3.11. 5-Hydroxysedamine, 3-Hydroxyallosedamine and 3-Hydroxynorallosedamine

5-Hydroxysedamine (**174**), 3-hydroxyallosedamine (**175**) and 3-hydroxynorallosedamine (**176**) were isolated from *Sedum acre* and their structures were determined by MS, IR, ^{1}H and ^{13}C NMR and chemical transformations [449]. Treatment of **176** with aqueous HCHO/KOH gave a tetrahydro 1,3-oxazine. Spectroscopic analysis of the oxazine and application of Horeau's method provided the relative and absolute configurations of **176**, respectively [449].

$LiAlH_4$ reduction of the above oxazine provided **175** with known absolute configuration, given the above application of Horeau's method. 3-Hydroxyallosedamine was readily converted with $TsCl/CHCl_3$, followed by strong base, into a tetrahydrofuran derivative, confirming the position of the 3-hydroxyl group in **176** and **175** [449].

Spectroscopic analysis of the diacetyl derivative of **174** was used to determine its structure. The structure was confirmed by a synthesis of **174** [and **175** and **176**] involving the cycloaddition reaction of styrene and a nitrone. Resolution of an intermediate and application of Horeau's method before completion of the synthesis provided the absolute configuration of **174** [449]. In a recent synthesis of (-)-**174**, a key step utilized the hydroboration of an appropriately substituted enecarbamate to introduce the 5-hydroxyl group [450].

3.3.12. Norsedamine

(-)-Norsedamine (**177**) was reported to competitively inhibit pea diamine oxidase (Ki=0.03 mM) [445]. Racemic **177**, as well as **171**, was synthesized using the trimethylsilyl trifluoromethanesulfonate-catalyzed addition of 1-trimethylsilyloxy-1-phenylene to *N-t*-butoxycarbonyl-2-ethoxypyridine as a key step [451].

3.3.13. Allosedamine

In a recent report, an asymmetric electrophilic hydroxyamination of a chiral *N*-acylsultam was used to give a nitrone which then underwent a cycloaddition reaction with styrene to ultimately produce, after several additional steps, (-)-allosedamine (**178**) [452].

3.3.14. Norallosedamine

Racemic norallosedamine (**179**) was reported to be a competitive inhibitor of pea diamine oxidase (Ki = 0.03 mM) [453].

3.3.15. Sedaminone

Racemic sedaminone (**180**) was synthesized in the same manner as reported for *N*-methylpelletierine (**170**), via alkylation of an *S*-methylthioamidium salt generated from *N*-methylpiperidine-2-thione [444].

3.3.16. 6-(4-Pentenyl)-2,3,4,5-tetrahydropyridine

A synthesis of **181**, a venom alkaloid of *Solenopsis* [454], was reported in which the tetrahydropyridine ring was formed in an intramolecular amine addition to an alkyne, catalyzed by a gold (III) salt [455].

3.3.17. SS20846A and Related Alkaloids

SS20846A (**183**) as well as **184** and **185** were isolated from *Streptomyces luteogriseus* and their structures determined by EIMS, and two-dimensional NMR [456]. SS20846A had been isolated previously from *Streptomyces* sp. S20846, and was found to inhibit intestinal motility in mice [457]. A recent synthesis of **183** has been reported in which a $LiClO_4$ catalyzed stereoselective cycloaddition of a 1-azatriene iron tricarbonyl complex with Danishefsky's diene was used to form the piperidine ring [458].

3.3.18. Pseudodistomins

Pseudodistomins A and B were isolated from the Okinawan tunicate *Pseudodistoma kanoko* and their structures determined (**186a** and **186b**, respectively) by HREIMS, IR, UV and one- and two-dimensional ^{1}H and ^{13}C NMR on the acetate derivatives [459]. Catalytic hydrogenation of the acetates gave the identical tetrahydroacetate derivatives, thus the absolute configurations of the two compounds were the same. The absolute configuration was determined by preparation of the 1-acetyl-4,5-bis(p-bromobenzoyl) derivative of tetrahydropseudodistomin and application of the dibenzoate chirality method [459]. The absolute configuration of pseudodistomins A and B has been confirmed by a recent synthesis of tetrahydropseudodistomin from D-serine [460].

The structure of pseudodistomin B has recently been revised as **186d**, based on its degradation reaction. The new structure was confirmed by synthesis of racemic **186d** [461]. Revision of the structure of pseudodistomin B led to reinvestigation of pseudodistomin A. Ozonolysis of pseudodistomin A led to a revision of its structure as **186c** [462].

Pseudodistomins A and B were cytotoxic against L1210 (IC_{50} = 2.5 μg/ml and 0.4 μg/ml, respectively) and L5178Y (IC_{50} = 2.4 μg/ml and 0.7 μg/ml, respectively) murine leukemia cells [459]. This study found that both **186c,d** were also potent inhibitors of calmodulin-activated brain phosphodiesterase ($IC_{50} = 3 \times 10^{-5}$ M).

3.3.19. Hyalbidone

Hyalbidone (**182**) was isolated from hairy root cultures of *Hyoscyamus albus* which were transformed with *Agrobacterium rhizogenes*. Its structure was established using MS and one- and two-dimensional ^{1}H and ^{13}C NMR [463]. Feeding [1-^{13}C, 2-^{2}H]-acetate to the above cultures of *Hyoscyamus albus* gave little incorporation of label into **182**, suggesting that **182** was either not derived from tropine, or was located near the end of the biosynthetic pathway [464].

3.4. 2,6-Disubstituted Piperidine Alkaloids

3.4.1. 2,6-Lupetidine

(-)-2,6-Lupetidine (**187**) has been synthesized from (*S*)-1,2-epoxypropane [465].

3.4.2. Pinidine

(-)Pinidine (**188**) was recently synthesized from methyl 6-ketoheptanoate. An asymmetric electrophilic hydroxyamination of a chiral *N*-acylsultam was used to form the piperidine ring, and hydrogenation of the nitrone gave the required cis-2,6 substitution [466].

Racemic **188**·HCl was found to be highly toxic and teratogenic in a frog embryo teratogenesis assay. The potency was increased with a cytochrome P-450 metabolic activation system [467].

3.4.3. Dihydropinidine

Dihydropinidine (**189**), along with **191**, **196**, and an alcohol from reduction of **191**, has been isolated from the Mexican Bean Beetle *Epilachna varivestis* and was identified using GCMS [468]. In a recent synthesis, racemic **189** was prepared from 4-methoxypyridine [469].

3.4.4. Pinidinol

The hemiparasite *Pedicularis bracteosa* was found to contain pinidinol (**190**), which had been taken up from a host spruce, *Picea engelmannii*. The structure of **190** was determined using MS and one- and two-dimensional ^{1}H and ^{13}C NMR [470]. The structure was confirmed, and absolute stereochemistry determined using X-ray crystallography [471]. Pinidinol, along with epidihydropinidine (**192**), was found to be present in a variety of *Picea* species [472]. It was also found in the pine *Pinus jeffreyi* [467]. Pinidinol was not active against several gram positive- or gram negative bacteria, or yeast [467].

3.4.5. Epidihydropinidine

Epidihydropinidine (**192**) was isolated from *Picea engelmannii* and its structure established using GC-MS and one- and two-dimensional ^{1}H and ^{13}C NMR. It was found to be present, along with **190**, in a variety of *Picea* species [472]. Its structure was confirmed and absolute configuration established by X-ray crystallography [467]. A preliminary study of an alklaloid mixture from *P. engelmannii* needles containing **192** and **190** indicated a moderate to high antifeedant activity with eastern spruce budworm [473].

In one recent synthesis, **192** (and **189**) were prepared using a $TiCl_4$ induced stereoselective intramolecular cyclization of an α-cyanoamine moiety with a vinyl group to form the piperidine

ring [474]. Another synthesis of (+)-**192** [and (+)-**198a**] began with a Sharpless aymmetric dihydroxylation of an *N*-alkenylurethane, followed by cyclization [475].

3.4.6. Additional *Picea* and *Pinus* Alkaloids

Additional 2,6-disubstituted piperidine alkaloids detected in *Picea* and *Pinus* include pinidinone and epipinidinone (**191** and **194**, from *Picea pungens*), **193** (from *Picea abies*, *P. pungens*), **195** (from *Pinus nigra*, *P. sylvestris*, *P. ponderosa*) and **196** (from *Picea pungens*, *Pinus ponderosa*, *P. sylvestris*, *P. nigra*)[467]. Pinidinone, an alcohol from reduction of pinidinone, and **196** have also been detected in the Mexican Bean Beetle, *Epilachna varivestis* [468].

3.4.7. *Solenopsis* Alkaloids

Ant venoms from the genus *Solenopsis* have provided an array of 2,6-disubstituted piperidines, including **197-206**. A review of the fungicidal, insecticidal and repellent activity of these alkaloids has appeared [476]. Both solenopsin A (**198a**) and isosolenopsin A (**200**) were potent inhibitors (Ki = 0.16 μM and 0.24 μM, respectively) of [^{3}H]-perhydrohistrionicotoxin binding to sites associated with the nicotinic receptor-gated ion channel in the *Torpedo californica* electric organ [477].

Synthetic cis- and trans-*Solenopsis* alkaloids were tested as inhibitors of the response to acetylcholine by receptors on the cell body membrane of the fast coxal depressor neurone of the cockroach *Periplanata americana* [478]. The order of activity was **200** ~ **198a/200** mix > **201/198b** mix > **201**. The blocking action of **198a/200** mix was independent of membrane potential, and the mixture did not inhibit binding of propionylated α-bungarotoxin to meta-thoracic ganglion homogenates, suggesting that the alkaloids do not act on the open receptor/ion channel complex [478].

The activity of a mixture of the principal alkaloids (**198b,198c,203,204**) from *Solenopsis invicta* venom on platelets and neutrophils was reported. The alkaloid mixture caused an increase in intracellular Ca^{+2} levels and an increase in aggregation with platelets and, to a lesser extent, with neutrophils. In platelets, a synergism was found between the alkaloid mixture and platelet activating factor for the increase in intracellular Ca^{+2} concentrations [479].

A rapid GC-FTIR method for determination of the cis or trans configuration of 2,6-disubstituted piperidines was developed using, among others, the *Solenopsis* alkaloids **198a**, **198b**, **202** and the *Monomorium* alkaloids **207-209** [480]. A method for determination of the absolute configuration of *Solenopsis* alkaloids was developed, in which the amines are

converted to diastereomeric amides using (*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid chloride and the chromatographic behavior of the products is analyzed [481]. This procedure was applied to alkaloids including both cis and trans isomers of **197**, **198a-c**, **203**, and **204**. The absolute configuration of the trans alkaloids was (2*R*,6*R*) and that of the cis alkaloids was (2*R*,6*S*) [481].

Two new alkaloids (**199**, **205**) were recently isolated from the venom of *Solenopsis invicta*. Their structures were established using MS and by synthesis [482].

There have been a number of recent syntheses of *Solenopsis* alkaloids. (-)Solenopsin A was synthesized from 4-methoxy-3-(triisopropylsilyl)pyridine via α-lithiation/alkylation of *N*-Boc-2-undecylpiperidine [483]. An asymmetric synthesis of both solenopsin A (**198a**) and isosolenopsin A (**200**) beginning from L-alanine was reported [481]. (+)-Solenopsin A was synthesized as described for (+)-**192**, using a Sharpless asymmetric dihydroxylation of an *N*-alkenylurethane, followed by cyclization [475]. Yet another recent synthesis of **198a** followed the method used for (-)-**160**, by the reaction of a chiral cyclic 2-carbonylsultam-substituted *N*-hydroxy-2-undecylpiperidine with NaH, followed by reduction of the product [427]. Solenopsin B (**198b**) was synthesized from L-glutamic acid, using a stereoselective DIBALH reduction of a bicyclic *N*,*O*-ketal as a key step [484]. A synthesis of **206** (and **198a**) was based on the Pd (II) catalyzed intramolecular reaction of alkynylamines [485]. Another synthesis of **206** used the same approach as reported for **181**, in which a gold (III) catalyzed intramolecular reaction of alkynylamines formed the tetrahydropyridine ring [455]. Finally, **197**, and **198a-c** were synthesized using a sodium cyanoborohydride reductive amino-cyclization of alkane-2,6-diones [486].

3.4.8. *Monomorium* Alkaloids

New 2,6-dialkylated piperidines (**207-210**) have been isolated as cis/trans mixtures from the ant venom of *Monomorium delagoense* [487]. Their structures were determined using MS, catalytic hydrogenation to the hydrocarbons, and methoxymercuration-demercuration followed by MS analysis. The structures of **207-209** were confirmed by synthesis of the cis/trans mixtures from the corresponding dialkyl pyridines. The major venom component, cis/trans **207**, displayed potent insecticial activity against *Reticulitermes* worker termites (LD_{50} = 150 μg/g termite). In addition, **207** was a potent repellent for the ants *Pheidole* and *Iridomyrmex* [487].

3.4.9. Dendrobatid Frog Alkaloids

The 2,6-dialkyl piperidines **212** and **213** have been detected in *Dendrobates histrionicus* and *Dendrobates trivittatus*, respectively [488]. Alkaloid 241D (**211**) was isolated from *Dendrobates speciosus* and its structure determined by HRMS, CIMS, and one- and two-dimensional ^{1}H NMR [489]. The structure of **211** was confirmed in a two-step synthesis via condensation of 3-penten-2-one, decanal, and ammonia, followed by sodium borohydride reduction [490].

3.4.10. Cassine, Spectaline, Prosafrinine and Spicigerine

(-)Cassine (**214**) and (+)-spectaline (**217**) were synthesized, beginning with both enantiomers of an appropriately trisubstituted piperidine. The starting materials were prepared via a lipase catalyzed transesterification or hydrolysis of a glycol or diacetate [491,192].

A synthesis of racemic prosafrinine (**215**) and epiprosafrinine was reported in which the piperidine ring was formed through catalytic hydrogenation of a nitro ketone and accompanying intramolecular cyclization [493]. The same general methodology was used to prepare racemic spicigerine (**216**), spicigerine methyl ester, and spectaline (**217**) [494]. In a recent synthesis of spicigerine methyl ester, **214**, and **217**, the side chain was added to a bromopyridine in a Ni (II) catalyzed reaction [495].

3.4.11. *N*-Methyljulifloridine

N-Methyljulifloridine (**220**) was isolated from the shrub *Prosopsis juliflora*. Its structure was determined using MS, IR, and one- and two-dimensional ^{1}H and ^{13}C NMR [496].

3.4.12. Azimic acid and Carpamic acid

(+)-Azimic acid (**218**) was synthesized in eleven steps from (2*S*,6*S*)-6-hydroxy-2-methyl-*N*-tosyl-Δ^{4}-piperidone-3 [497]. (+)-Carpamic acid (**219**), along with **218**, was synthesized using the same approach as for spicigerine methyl ester, **214** and **217**, in which a Ni (II) catalyzed reaction is used to attach the side chain to a bromopyridine [495].

3.4.13. Carpaine

Carpaine (**221**) in low doses (1-5 mg/kg) caused dilation of blood vessels, hypotension and cardiostimulation in rabbits, rats, and mice[498]. Larger doses (>10 mg/kg) caused the reverse effects. Injection of **221** (1-5 mg/kg) led to myocardial ischemia [498].

3.4.14. Prosopinine

Racemic prosopinine (**222**) was synthesized using an aza-annulation to form the piperidine ring, and homologation of the lactam to prepare the alkyl side chain [499].

3.4.15. Isoprosopinines

Isoprosopinine A and B (**223a,b**) were synthesized via a coupling reaction of a bromoalkyl piperidine with sulphone anions to extend the side chain. Removal of the sulphone groups with sodium amalgam, and further deprotection gave **223a,b** [500].

3.4.16. Desoxoprosophylline and Desoxoprosopinine

(-)-Desoxoprosophylline (**224**) and (-)-desoxoprosopinine (**225**) were synthesized from a *D*-glucose-derived percursor via a palladium (0)-catalyzed intramolecular *N*-alkylation to form the piperidine ring in a key step [501].

3.4.17. Micropine

Micropine (**226**) was isolated from the leaves of *Microcos philippinensis*. Its structure was determined using MS, IR, UV, and one- and two-dimensional ^{1}H and ^{13}C NMR on **226** and a perhydro-derivative [502].

3.4.18. Andrachamine and Andrachcine

A crude alkaloid extract of the shrub *Andrachne aspera* had been found to show antibacterial and other biological activity [503]. A new alkaloid, andrachamine (**227**) was isolated from this

plant, and its structure established using HRMS, IR, UV, and one- and two-dimensional ^{1}H and ^{13}C NMR [504]. Application of the Horeau method led to the assignment of the absolute configurations of the hydroxylated carbons as *S,S* [504]. A synthesis of **227** was reported which utilized the cycloaddition of alkenes to tetrahydropyridine oxides for introduction of the side chains [505].

A second new alkaloid, andrachcine (**228**) was isolated from *Andrachne aspera*. Its structure was determined using HRMS, IR, UV and ^{1}H NMR. Once again, application of the Horeau method led to assignment of the absolute configuration at the hydroxylated carbons as *S,S* [506].

3.4.19. Sediene and Sediendione

Structures were proposed for the new *Sedum acre* alkloids sediene (**229**) and sediendione (**230**) based on GC-MS analysis [507]. The structure of **230** was further investigated using UV, IR and GC-MS [508]. An extract of *S. acre* containing **229**, **171**, and hydroxysedamine at 0.02% (w/v) displayed antimicrobial activity [508].

3.4.20. Sedacrine and Sedinone

Sedacrine (**231**) and sedinone (**232**), along with **236** and a number of other *Sedum* alkaloids, were investigated by ^{1}H and ^{13}C NMR to determine their preferred solution conformations [509]. Both **231** and **232** were synthesized using anodic oxidation to functionalize and allow for the addition of the side chains as a key step [510].

3.4.21. Homosedinone, Dihomosedinone and Lelobanonoline

Homosedinone (**233**) and dihomosedinone (**234**), along with their C(6) epimers, were isolated in small amounts from *Sedum acre*. Support for the proposed structures and the absolute configurations was supplied by the synthesis of **233** and **234** from a derivative of (-)-norsedamine using anodic oxidation to allow addition of the side chains [511].

An alkaloid, termed lelobanonoline (**235**) was isolated from *Lobelia davidii*, and its structure identified by MS, IR, ^{1}H and ^{13}C NMR [512]. The basic structure proposed for **235** (no stereochemistry was indicated) matched that for homosedinone (**233**).

3.4.22. Sedinine

Sedinine (**236**) was synthesized from an *N*-carbomethoxy, alkynyl substituted dihydropyridine [513].

3.4.23. Lobeline

The action of lobeline (**237**) as a nicotinic receptor agonist has continued to generate considerable interest. (-)-Lobeline demonstrated a potent hyperalgesic effect, similar to that of nicotine, when tested in the low intensity thermally evoked tail avoidance response assay [514]. It improved cognition and retention in rats comparably to nicotine [515]. Both **237** and nicotine exhibited anxiolytic effects in mice [516] and partially inhibited *N*-methyl-*D*-aspartate-induced responses in rat cortical neurons in vitro [517]. It was a potent inhibitor of nicotine-induced prostration in rats (ED_{50} = 10 nM) and antagonized additional actions of nicotine including systolic blood pressure increases, seizure, and death [518].

In a number of cases, actions of lobeline differed significantly from those of nicotine. For example, chronic treatment of mice with nicotine led to an increase in the number of brain nicotinic receptors, which was not seen with lobeline treatment [85]. Unlike nicotine, lobeline pretreatment did not reduce hypothermia and locomotor suppression in mice, produced by a nicotine challenge [519]. Lobeline failed to elicit the "nicotine cue", a discriminative effect in rats [520], and produced a pharmacologic profile (including heart rate, blood pressure, respiratory rate, minute and tidal volume) which differed from nicotine [86]. Such studies have led to the proposal that lobeline, in at least some of its effects, acts via a different mechanism than nicotine [86,519].

Lobeline had been marketed as a smoking deterrent [521], however the US Food and Drug Administration did not recognize such products as safe and effective [522].

Lobeline has exhibited a number of additional biological activities. It inhibited hCG-stimulated androgen synthesis and cAMP accumulation, as well as FSH-induced progesterone synthesis and cAMP production in rat testicular cell cultures [22] and rat granulosa cells [523], respectively. It suppressed the slow action potential and force of contraction of papillary muscle in guinea pig [524], and increased levels of 3,4-dihydroxyphenylacetic acid and homovanillic acid in rat striatum [525]. Lobeline increased the activity of the phrenic, recurrent laryngeal and particularly, the hypoglossal nerves in cats [526]. It inhibited the human red cell Ca^{+2}-dependent K^+ channel (IC_{50} = 60 μM) [527], and caused stomatocytosis of red cells [528]. Lobeline was found to be a competitive inhibitor of pea diamine oxidase (Ki = 0.17 mM) [453]. Inhibition of the enzyme by **237** became noncompetitive with changing pH when putrescine was

used as the substrate [529]. Finally, lobeline acted as a feeding deterrent for *Syntomis mogadorensis* [43].

The effects of **237** in combination with other compounds have been examined. In one study, neither lobeline nor ethyl alcohol were found to be clastogenic in human lymphoblastoid cell cultures. The combination of lobeline with ethyl alcohol, however, produced a marked increase in genetic damage [530]. In another study, the toxicity of **237** in mice was modified by pretreatment with SKF 525-A, phenobarbital, or 3-methylcholanthrene [531]. Pretreatment of mice with SKF 525-A caused a dose-dependent enhancement of lobeline toxicity. Pretreatment with phenobarbital or 3-methylcholanthrene served to decrease the toxicity of **237**, suggesting that hepatic microsomal monooxygenases are involved in the detoxification process.

An X-ray crystallographic analysis of (-)-**237**·HCl was reported and its pKa was determined as ~8.6 [532]. Subsequently, the solid state structure of (-)-**237**·HBr was determined by X-ray crystallography [533]. The β-hydroxyphenethyl residue was found to exist in a different conformation in the hydrobromide salt than found earlier with the hydrochloride salt. The solution conformations for (-)-**237** and its hydrochloride salt were determined using ^{1}H and ^{13}C NMR, and the proposed bioactive conformation of (-)-**237** was found to have a different acetophenonyl group arrangement than that found for the hydrochloride or hydrobromide salts in the solid state [533].

Hairy root cultures of *Lobelia inflata*, induced by *Agrobacterium rhizogenes*, were found to produce lobeline in levels comparable to those found in the cultivated plant [534]. Different clones responded quite differently to illumination with regard to the levels of lobeline produced in their hairy root cultures [535].

3.4.24. Lobelanine, Lobelanidine and Lobelanidine Glycoside

Lobelanine (**242**) and lobelanidine (**238**) blocked nicotine-induced seizures in rats (ED_{50} = 25 nmole each) [518]. Lobelanidine was found to be a competitive inhibitor of pea diamine oxidase (Ki = 0.36 mM); **242** was inactive [453]. Both **242** and **238** were recently synthesized and **238** was found to be a respiratory stimulant [536].

Lobelanidine glycoside (**239**) was isolated from *Sedum acre*. Its structure was determined using MS and by X-ray crystallography of the pentaacetate derivative [537].

3.4.25. Lythranine and Lythranidine

The conformational chiralities of lythranine (**240**), lythranidine (**241**) and the related oxoquinolizidine alkaloid lythramine were determined from the Cotton effects observed in the

circular dichroism spectra of these compounds [538]. These solution chiralities were in agreement with those determined by X-ray crystallography on derivatives of these compounds [539]. A synthesis of racemic **241** has been reported in which the trans 2,6-disubstituted piperidine ring was formed with a nitrone cycloaddition, and the macrocyclic ring was cyclized via coupling of aryl iodides using bis(triphenylphosphine)nickel dichloride [540].

3.5. *Nuphar* Alkaloids

A recent enantiospecific synthesis of (-)-nupharamine (**243**), (+)-3-epinupharamine (**244**), (-)-anhydronupharamine (**245**) and (-)-nuphenine (**246**) has been reported, starting with either (+)- or (-)-carvone [541]. In this synthesis, a key acyclic precursor with the required stereochemistry was produced via regioselective fragmentation of a γ-halo-ester, and the piperidine ring was formed using an aza-Wittig reaction.

3.6. Polyhydroxylated Piperidine Alkaloids

Polyhydroxylated alkaloids have been of great interest due to their activity as glycosidase inhibitors. These alkaloids, including **247**, **250**, and **251**, were described in Volume five of this series [542]. A molecular modeling study has attempted to explain the inhibitory properties of these compounds [543]. Several reviews of these alkaloids are available [544-546].

3.6.1. Nojirimycin and Nojirimycin B

Nojirimycin (**247**) inhibited protein synthesis and decreased the specific activity of γ-glutamyltransferase in rat hepatoma cells [547]. It stimulated β-glucosidase synthesis in *Sporotrichum thermophile* [548], and inhibited pulmonary colonization by B16-F10 murine melanoma cells [549].

Nojirimycin B (**248**, mannojirimycin) was isolated from the culture broth of *Streptomyces lavendulae*, along with nojirimycin [550]. The structure of **248** was established by ^{1}H NMR and by its oxidation to mannonic-δ-lactam. Nojirimycin B was a potent inhibitor of apricot emulsin and rat epididymal α-mannosidase, but was less active against *Trichoderma viride* β-glucosidase. It was weakly active against *Xanthomonas oryzae*, but inactive against other bacteria [550].

(-)-Nojirimycin and (-)-nojirimycin B were recently synthesized from serine using a 2-thiazolyl ketone as a masked aldehyde intermediate [551]. In another recent synthesis,

nojirimycin B was prepared from chlorobenzene, relying on fermentative production of 1-chloro-2,3-dihydroxycyclohexa-4,6-diene by *Pseudomonas putida* 39D, and subsequent controlled ozonolysis [552].

3.6.2. α-Homonojirimycin

α-Homonojirimycin (**249**) was isolated from *Omphalea diandra* and its structure was determined with MS, ^{1}H and ^{13}C NMR and by comparison with a synthetic sample [553]. α-Homo-nojirimycin was a potent inhibitor of α-glucosidase in mouse gut [553], and it moderately inhibited hydrolysis of sinigrin by mustard myrosinase [554]. *Omphalea diandra* is a larval food plant for the moth *Urania fulgens*, and **249** was found in eggs, pupae, and adults of these moths [555]. A synthesis of β-homonojirimycin has been reported which utilized the rabbit muscle fructose 1,6-bisphosphate aldolase-catalyzed reaction of a four carbon azido lactol with dihydroxyacetone phosphate [556].

3.6.3. Deoxynojirimycin

A recent review of the sources, biosynthesis, synthesis, and biological activity of deoxynojirimycin (**250**) is available [557]. Additional reports published since this review will be described below.

The biosynthesis of **250** in *Bacillus subtilis* was found to proceed similarly to that reported earlier in *Streptomyces subrutilis* [558], although cleavage of glucose to three carbon units was suggested to occur as a minor pathway [559]. When maintained at 55°C, cyclodextrin glycosyltransferase and β-amylase were stabilized by 4-*O*-glucopyranosyl-1-deoxynojirimycin and its *N*-substituted derivatives, while glucoamylase under these conditions was stabilized by **250** and its *N*-substituted derivatives [560]. Deoxynojirimycin displayed antifeedant activity against *Spodoptera frugiperda* [561]. Nine glycosides of **250** isolated from *Morus alba* were identified as 2-*O*-, 3-*O*-, and 4-*O*-α-*D*-glucopyranosyl-1-deoxynojirimycin, 2-*O*-, 4-*O*-, 3-*O*-, and 6-*O*-β-*D*-glucopyranosyl-1-deoxynojirimycin, and 2-*O*- and 6-*O*-α-*D*-galactopyranosyl-1-deoxynojirimycin; inhibitory activities of the latter four glycosides against several glycosidases were reported [562]. *N*-Methyldeoxynojirimycin was isolated from *Morus bombycis* and its structure determined using ^{1}H and ^{13}C NMR and comparison with a synthetic sample [563].

A double nucleophilic attack by benzylamine on a symmetric bis-epoxide, prepared from *D*-mannitol, was used in a recent synthesis of **250** [564]. In another recent report, 5-keto-*D*-glucose was reacted with diphenylmethylamine and sodium cyanoborohydride in a key step in the formation of **250** [565].

3.6.4. Deoxymannojirimycin

Deoxymannojirimycin (**251**) was found to be a potent phagostimulant for the larvae of *Heliothis virescens* [561]. Its action as an α-mannosidase inhibitor has led to its investigation in a number of experimental systems. For example, **251** inhibited *D*-[2-^{3}H]-mannose uptake by differentiated intestinal HT-29 cells [566], and it inhibited capillary tube formation in endothelial cells [567]. With MDCK cells grown in PBS medium, **251** strongly inhibited mannose incorporation into secreted glycoproteins and into lipid-linked oligosaccharides, but did not alter incorporation of [^{3}H]-leucine into the secreted glycoproteins [568]. Deoxymannojirimycin inhibited the invasion of malignant and invasive cell lines in reconstituted basement membranes, and decreased adhesion of these cells to a reconstituted basement membrane or to an endothelial cell monolayer [569]. In sciatic nerve endoneural slices, **251** reduced degradation of the major myelin protein, P_O [570].

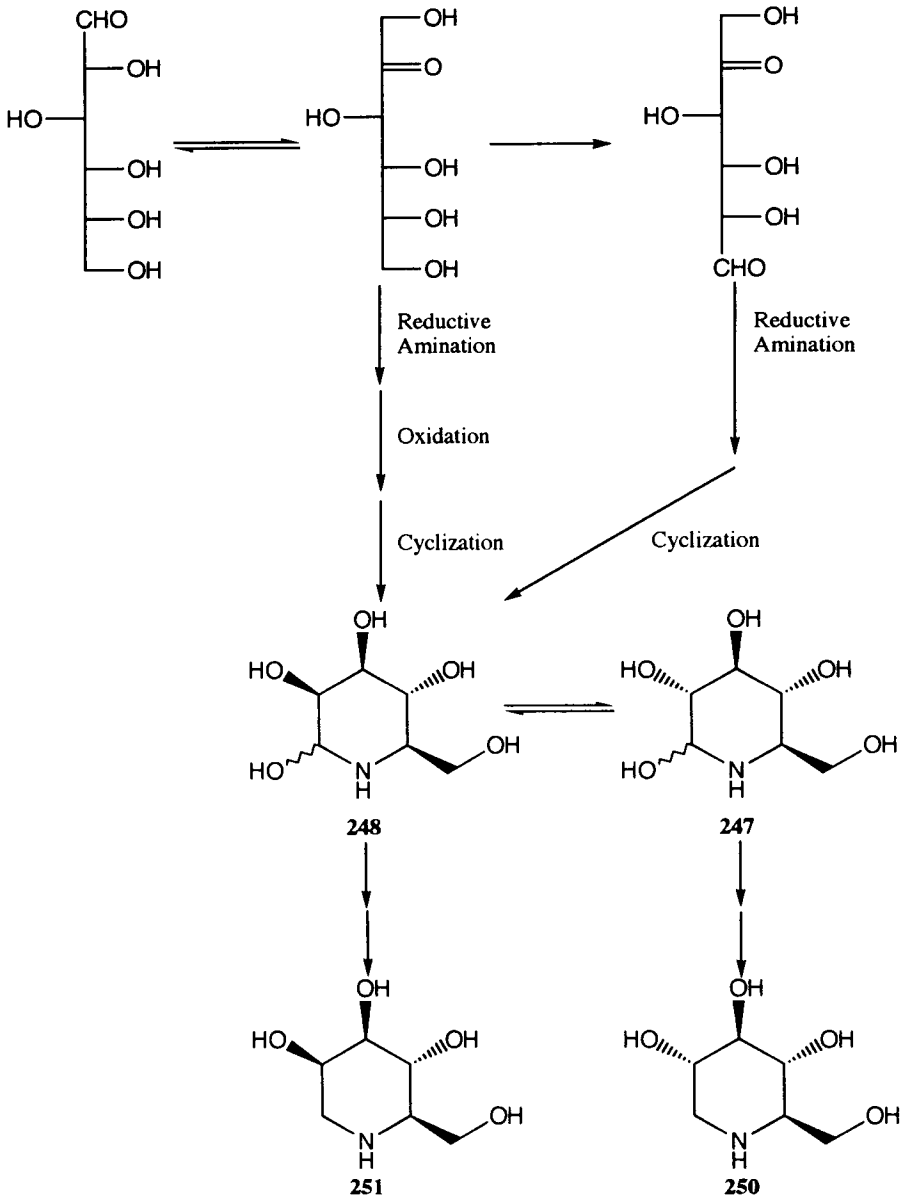
The biosynthesis of **251** (and **250**) in *Streptomyces subrutilis* was investigated using [1-^{2}H]-, [2-^{2}H]-, [5-^{2}H]-, and [6,6-$^2H_2$]-*D*-glucose as biosynthetic precursors. The biosynthetic pathway proposed, in which nojirimycin B (mannojirimycin, **248**) serves as an intermediate for both **251** and **250**, is outlined in Scheme 5 [558].

Several recent syntheses of **251** have been reported. Deoxymannonojirimycin was synthesized using the reaction of 5-keto-*D*-mannose with diphenylmethylamine and sodium cyanoborohydride as a key step [565]. Another synthesis of **251** used *D*-mannitol as a starting material [571], while yet another began with *D*-glucono-δ-lactone [572]. Finally, racemic **251** was synthesized using an aza-annulation to form the piperidine ring [573].

3.6.5. Galactostatin and Deoxygalactostatin

Galactostatin (**252**) was isolated from *Streptomyces lydicus* [574,575] and its structure determined using EIMS, IR, ^{1}H and ^{13}C NMR, and dehydration to a pyridine derivative followed by UV analysis [576]. It was a strong inhibitor of β-galactosidases from several sources [574,575,577]. Galactostatin and its synthetic derivatives deoxygalactostatin (**253**) and galactostatin lactam, were competitive inhibitors of β-galactosidase from *Penicillium multicolor* (Ki=4.0 x 10^{-9} M, 3.3 x 10^{-8} M and 1.3 x 10^{-5} M, respectively) [577] and inhibited Coxsackie virus A9 (ID_{50} = 200 μg/ml, 250 μg/ml, and 125 μg/ml, respectively) [576].

(+)-Galactostatin and (+)-deoxygalactostatin were recently synthesized from L-quebrachitol using the regioselective opening of an epoxide by sodium azide, and a regioselective Baeyer-Villiger cleavage of the cyclohexane ring [578]. The key step in another synthesis of **253** was the fuculose-1-phosphate aldolase catalyzed condensation of 3-azido-2-hydroxypropanal and dihydroxyacetone phosphate [579].



Scheme 5. Biosynthesis of deoxymannojirimycin and deoxynojirimycin in *Streptomyces subrutilis*.

3.6.6. Fagomine, 4-*O*-(β-*D*-Glucopyranosyl)fagomine and 3-*epi*-Fagomine

The 4-*O*-β-*D*-glucopyranose derivative of fagomine (**255**) was isolated from *Xanthocercis zambesiaca* [580]. Its structure was determined using IR, MS, one- and two-dimensional ^{1}H NMR and acid hydrolysis to produce fagomine [580]. Neither fagomine (**254**) nor its glucoside (**255**) showed inhibition with a variety of glycosidases [580]. Both compounds acted as phagostimulants for *Spodoptera frugiperda* [561].

New sources of **254** include *Angylocalyx pynaertii* [581], *Morus bombycis* [563], and *M. alba* [582]. A recent synthesis of fagomine was based on the yeast transketolase-catalyzed reaction of 3-hydroxy-4-oxobutyronitrile with lithium hydroxypyruvate [583].

3-*epi*-Fagomine (**256**) was isolated from *Morus alba* [582]. Its structure was established using EIMS, one- and two-dimensional ^{1}H and ^{13}C NMR, and synthesis of **256** from fagomine. IC_{50} values for **256** inhibition of a variety of glycosidases are reported [582].

3.6.7. Calystegins

Calystegins A_3, B_1 and B_2 (**257a-c**) were isolated from *Calystegia sepium*. These alkaloids were also present in *Convolvus arvenis* and *Atropa belladonna*, and they were found to be catabolized by *Rhizobium meliloti* strain 41 [584]. The structures of **257a-c** were determined with HRMS, and ^{1}H and ^{13}C NMR, and were confirmed by the synthesis and NMR analysis of model compounds [585]. ^{14}C-Putrescine served as a biosynthetic precursor for the calystegins [586].

Although calystegins are *nor*tropane alkaloids, they are included in this review due to their activity as glycosidase inhibitors, as is the case with other polyhydroxylated piperidine alkaloids. Calystegin A_3 and a 27:73 mix of calystegins B_1 and B_2 inhibited almond β-glucosidase (Ki = 4.3 x 10^{-5} M and 3 x 10^{-6} M, respectively) and *Aspergillus niger* α-galactosidase (Ki = 1.9 x 10^{-4} M and 7 x 10^{-6} M, respectively) [587].

Recent efforts have identified **257a,c** in *Solanum tuberosum*, and **257c** in *S. dulcamara*, *S. melongena*, *S. dimidiatum*, *S. kwebense* and *Datura wrightii* [588]. Calystegins were also found in the death's head hawk moth (*Acherontia atropus*) and in a dried sample of the butterfly *Mechanitis polymnia*, where they may serve a protective function [588]. Calystegin B_2 (nortropanoline) was also isolated from *Morus bombycis* [563].

In 1994, a new calystegin, calystegin C_1 (**257d**) was reported from *Morus alba*, along with **257c** [582]. The structure of **257d** was established with FABMS and one- and two-dimensional ^{1}H and ^{13}C NMR. This report included IC_{50} values for **257c,d** inhibition of a variety of glycosidases.

Calystegin A3 has been synthesized from 4-aminocyclohexanol, using the intramolecular cyclization of a 4-aminocycloheptanone [589]. Both enantiomers of calystegin B_2 were synthesized from glucose, again relying on ring expansion followed by an intramolecular cyclization of a substituted 4-aminocycloheptanone [590,591].

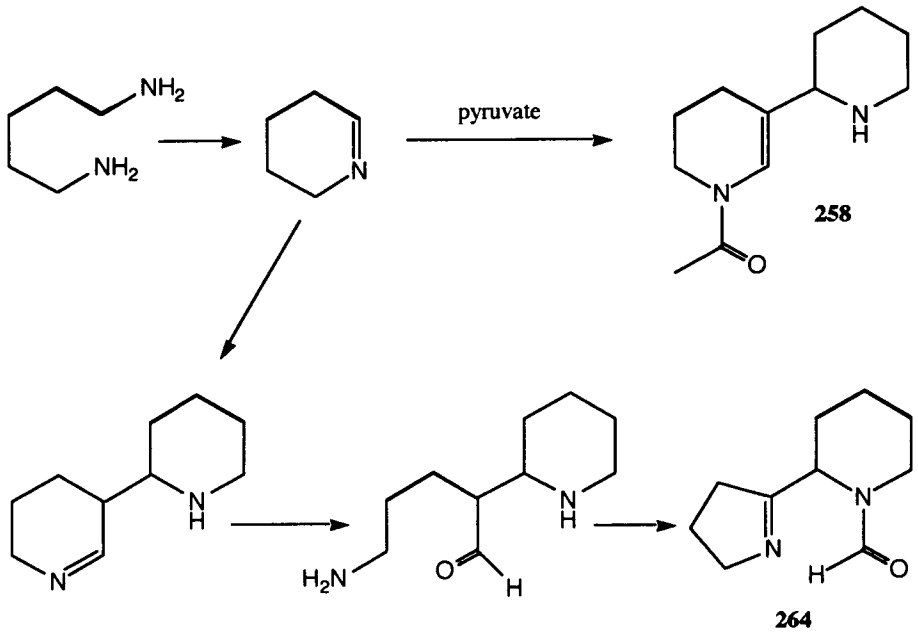
3.7. Ammodendrine and Related Alkaloids

Ammodendrine (**258**) has been isolated from a number of plant genera, usually in the presence of quinolizidine alkaloids [592]. Its presence, sometimes accompanied by related alkaloids such as *N*-methylammodendrine (**259**), *N*-acetylhystrine (**262**) and smipine (**264**) can be useful in chemotaxonomy [593]. The root parasite *Viscum cruciatum* was found to take up **258**, along with quinolizidine alkloids from its host *Retama sphaerocarpa* [594].

Ingestion of *Lupinus formosus* and other *Lupin* species by livestock can lead to the congenital deformity, crooked calf disease [595]. Analysis of *L. formosus* for piperidine alkaloids found ammodendrine, *N*-methylammodendrine, hystrine (**261**), *N*-acetylhystrine and smipine were present; ammodendrine was believed to have been responsible for the congenital deformities [595]. Measurement of **258**, **259**, and **262** levels in blood of cattle, sheep and goats after feeding *L. formosus* [596], and comparison of the toxicity of lupine species with different alkaloid contents [597] implicated **262** as a possible teratogen. Ammodendrine and gramodendrine (**260**) caused a reduction in spontaneous motor activity and depressed the central nervous system in mice [598].

Maackiamine (norammodendrine, **263**) was isolated from flowers of *Maackia amurensis* var. *buergeri*. Its structure was determined using IR, EIMS, and ^1H and ^{13}C NMR [599].

The biosynthesis of these alkaloids has been investigated [592]. Feeding deuterium labelled cadaverine to leaves of *L. polyphyllus* established it as a precursor of both rings of ammodendrine. Cell free extracts of *L. arboreus* and *Pisum sativum* produced smipine in the presence of cadaverine. If cadaverine and pyruvate were added to the cell free extracts, then ammodendrine was produced. A proposed biosynthetic scheme is outlined in Scheme 6 [592].



Scheme 6. Proposed biosynthesis of **258** and **264** in cell free extracts

3.8. Chromone-Substituted Piperidines

A review describing chromone alkaloids is available [600]. Four piperidine substituted chromones and their derivatives are described below.

3.8.1. Buchenavianines and Captivines

Six new alkaloids, buchenavianine (**265**), *O*-demethylbuchenavianine (**266**), *N*-demethylbuchenavianine (**267**), *N,O*-didemethylbuchenavianine (**268**), *N*-demethylcapitavine (**270**), and the 2,3-dihydroderivative of **269**, were isolated from the fruit of *Buchenavia macrophylla*, while an additional three new alkaloids, capitavine (**269**), 4'-hydroxycapitavine (**271**) and its 2,3-dihydroderivative were obtained from the seeds of *B. capitata* [601]. The structure of these alkaloids were determined with UV, MS, IR, and ^{1}H and ^{13}C NMR [601].

O-Demethylbuchenavianine (**266**) was found active against human immunodeficiency virus (EC_{50} = 0.26 μM), but its cytotoxicity to CEM-SS host cells (IC_{50} = 0.66 μM) led to a lower

therapeutic index. Alkaloids **265** and **268** were less cytotoxic, but also demonstrated less antiviral activity [602].

3.8.2. Rohitukine

Rohitukine (**272**), originally isolated from *Amoora rohituka* [603], was isolated from stem bark of *Dysoxylum binectariferum* as an antiinflammatory and immunomodulating agent [604]. Rohitukine and *N*-demethylrohitukine-3'-acetate (**273**) were also isolated from *Schumanniophyton magnificum* [605,606]. Rohitukine acted as an antiinflammatory in the carrageenin-induced rat paw oedema assay (ED_{50} = 9 mg/kg, p.o.) and inhibited immune complex mediated inflammation in rats [604,607]. Study of a rat model of adjuvant arthritis suggested **272** had promising anti-rheumatic activity [607]. It did not inhibit cyclooxygenase or lipoxygenase, and it showed excellent gastric tolerance in rats [607]. Rohitukine displayed activity against human immunodeficiency virus and herpes simplex virus; **273** was less active [608].

Both enantiomers of **272** were synthesized from *N*-methyl-4-piperidinone and 1,3,5-trimethoxybenzene [604]. The 3'-hydroxyl was introduced with hydroboration of an alkene and then inversion via oxidation to the ketone and $NaBH_4$ reduction. Introduction of the chromone moiety via acylation of the phenyl ring, followed by *O*-demethylation, provided **272** [604]. Subsequently, additional analogs of **272** were synthesized and tested for biological activity [609].

3.8.3. Tubastraine

Tubastraine (**274**) was isolated from the stony coral *Tubastraea micrantha*. Its structure was established with IR, MS, one- and two-dimensional ^1H and ^{13}C NMR, and by its synthesis from **272** [610].

3.9. *Nitraria* Alkaloids

A recent synthesis of (+)-nitramine (**275**) and (-)-isonitramine (**276**) has been reported [611]. Resolution of an α-substituted β-ketoester with pig liver esterase was the key improvement to provide the required chiral quaternary carbon. Subsequent cyclization of the piperidine ring gave **275** and **276**. In a recent synthesis of sibirine (**277**), α-deprotonation/alkylation of an imine gave an intermediate having the required quaternary carbon,

which was later cyclized to form the piperidine ring [612]. In the final step, a highly diastereoselective cerium (III) chloride catalyzed sodium borohydride reduction of a ketone gave **277**.

3.10. *Dioscorea* Alkaloids

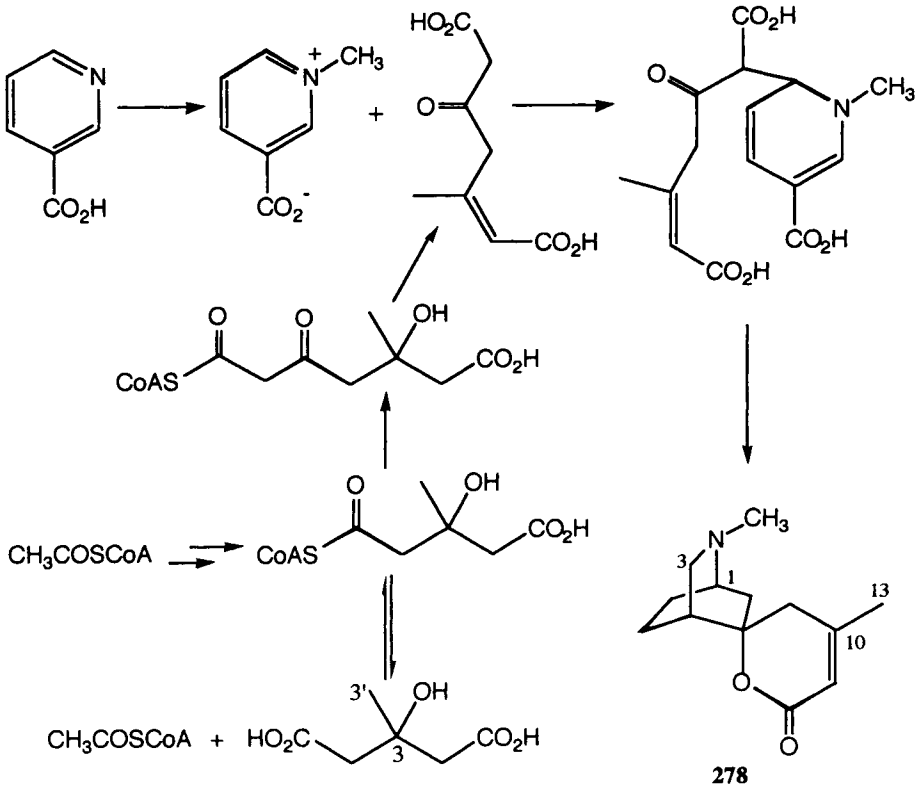
3.10.1. Dioscorine

Investigation of the biosynthesis of dioscorine (**278**) has continued. Feeding [6-^{14}C,2-^{3}H]-nicotinic acid, [6-^{14}C,6-^{3}H]-nicotinic acid, [Me-^{14}C,2-^{2}H,^{3}H]-trigonelline or [Me-^{14}C,6-^{2}H,^{3}H]-trigonelline to cultures of *Dioscorea hispida* led to isolation of **278** with complete retention of ^{3}H relative to ^{14}C. Thus, trigonelline (**107**), in addition to nicotinic acid, is a biosynthetic precursor of the isoquinuclidine portion of **278** [613]. All incorporated ^{14}C was located on the *N*-methyl group of **278** and deuterium NMR established the location of label for the [2-^{2}H]- and [6-^{2}H]-trigonelline on C(3) (pro-*R*) and C(1) of **278**, respectively [613]. Feeding [3-^{14}C]- or [3,3'-^{13}C$_2$,3-^{14}C]-3-hydroxyglutaric acid also led to labelled **278**. Incorporation of ^{14}C was at C(10) and the ^{13}C$_2$ unit was incorporated at C(10) and C(13) of **278** [614]. Thus 3-hydroxyglutarate, or more likely, its CoA ester, is a biosynthetic intermediate in the acetate-derived portion of **278**. Ethyl [6-^{14}C]-orellinate was not incorporated into **278**. The proposed biosynthetic pathway for **278** is outlined in Scheme 7 [614].

A brief reduction in physical activity of mice after dosing with an extract of the tropical yam, *Dioscorea hispida*, was attributed to the alkaloid **278** [615].

3.10.2. Dihydrodioscorine and Dumetorine

Dihydrodioscorine (**279**) and dumetorine (**280**) were isolated from the yam *Dioscorea dumetorum* and their structures established using IR, and one- and two-dimensional ^{1}H and ^{13}C NMR [616]. The absolute configurations of **279** (10*S*) and **280** (1*S*,5*R*) were determined in the same report using the method of molecular rotation additivity and model compounds. The structure of **280** was confirmed by synthesis, in which a stereospecific cycoaddition of a terminal alkene with a nitrone was a key step [617]. At a concentration of 0.1%, dihydrodioscorine (**279**) was found to inhibit the growth of five plant pathogenic fungi [618].



Scheme 7. Biosynthesis of dioscorine

3.11. Steroidal Piperidine Alkaloids

A large number of steroidal alkaloids have been described in the literature. Recent reviews covering *Solanum* alkaloids [619] and the anticancer activity of solasodine glycosides [620] are available.

3.11.1. Solasodine

Solasodine (**281**) was found to be more teratogenic in hamsters than soladulcidine (**284**) [621] and caused malformations in the *Xenopus* embryo teratogenesis assay [622]. It was

cytotoxic against PLC/PRF/5 and KB cell cultures [623]. Solasodine was toxic to rainbow trout embryos (*Oncorhynchus mykiss*), but did not affect the Japanese rice fish (*Oryzius latipes*) [624]. It inhibited morphogenetic and gonadotropic processes in the insect *Dysdercus similis* [625] and caused morphogenetic aberrations in the stem borer *Chilo partellus* [626]. The motility of buffalo bull [627], human and bovine [628] spermatozoa was decreased by **281** and enzymes of carbohydrate metabolism in spermatozoal homogenates were inhibited. Solasodine interfered with spermiogenesis in rhesus monkey and decreased production of Leydig cells [629]. The biosynthesis of cholesterol from dihydrolanosterol was inhibited by **281** [630]. Finally, solasodine reduced serum cholesterol and LDL cholesterol and prevented atherogenesis in hyperlipidaemic rabbits [631].

A review of the occurrence in nature and production of solasodine is available [632]. The completely assigned ^{1}H and ^{13}C NMR spectra of **281** have been reported [633].

3.11.2. *N*-Methylsolasodine and *N*-Hydroxysolasodine

N-Methylsolasodine (**282**) was isolated from *Solanum nigrum* [634]. *N*-Hydroxysolasodine (**283**) was isolated from roots of *Solanum robustum*, and its structure determined using HRMS, one- and two-dimensional ^{1}H and ^{13}C NMR, and catalytic hydrogenation to the saturated derivative [635]. *N*-hydroxysolasodine was synthesized from solasodine by hydrogen peroxide oxidation in the presence of selenium dioxide [636].

3.11.3. Soladulcidine

Soladulcidine (5,6-dihydrosolasodine, **284**) exhibited potent activity against liver damage induced by carbon tetrachloride [637]. Soladulcidine was markedly less teratogenic in hamsters than solasodine (**281**), consistent with the proposal that C(5)-C(6) unsaturation is an important factor in teratogenicity for this class of compounds [621].

3.11.4. Hydroxysoladulcidines

2α-Hydroxysoladulcidine (**285**) was isolated from roots of *Lycianthes biflora* [638], and 23-hydroxysoladulcidine (**286**), from roots of *Solanum panduraeforme* [639]. In both cases, the structure was established using MS and one- and two-dimensional ^{1}H and ^{13}C NMR. The 23-*O*-acetyl derivative of **286**, along with the C(25) epimer of this derivative, were isolated from roots of a hybrid of *Lycopersicon esculentum x L hirsutum* [640].

3.11.5. Incanumine

Incanumine (**287**) was isolated, along with khasianine (**288**) from *Solanum incanum* [623]. The structure of **287** was established using IR, EIMS, FABMS, ^{1}H and ^{13}C NMR, and acidic hydrolysis to give glucose, rhamnose, xylose and solasodine [623].

3.11.6. Khasianine

Khasianine (**288**) was produced via metabolism of solamargine (**290**) by *Aspergilllus niger* [641]. In another study, **288** displayed strong activity against carbon tetrachloride-induced liver damage [637]. The complete assigned ^{1}H and ^{13}C NMR spectra for **288** have been reported [642].

3.11.7. Ravifoline

Ravifoline (**289**) was isolated from berries of *Solanum platanifolium*, and its structure determined using one- and two-dimensional ^{1}H and ^{13}C NMR, and comparison of these spectra with the completely assigned spectra for **288**, **290**, and **291** [642].

3.11.8. Solamargine

Solamargine (**290**) was cytotoxic against KB cells (ED_{50} = 1.53 μg/ml) [623]. It preferentially inhibited uptake of [^{3}H]-thymidine by cancer cells (ovarian, HeLa, lymphoblastoid and fibroblasts) and had little effect on lymphocytes (unstimulated, and stimulated with Con A, PHA or PWM) [643].

Solamargine inhibited larval development and pupation of *Earias insulana* [644] and was toxic to adults and microfilaria of the filarial parasite *Setaria cervi* [645]. It inhibited elongation of lettuce seed radicles [646]. Mycelium development in the fungi *Phoma medicaginis* and *Rhizoctonia solani*, and spore germination in *Alternaria brassicola* were inhibited by **290**; a synergistic effect was observed when **290** and **291** were combined [647].

The membrane-disrupting effects of **290** have been investigated. Solamargine disrupted phosphatidylcholine/cholesterol liposomes and lysed *Penicillium notatum*-derived protoplasts and bovine erythrocytes; combinations of **290** and **291**, **290** and solanine, or **290** and chaconine produced a synergistic effect [648]. In another report, solamargine was highly active

at lysing several types of sterol-containing liposomes at pH> 7; greater leakage was observed with increasing sterol concentrations [649].

The completely assigned ^{1}H and ^{13}C NMR spectra of **290** in pyridine-d_5 [650] and in dioxane-d_8 [642] have been reported.

3.11.9. Solasonine

The relative embryotoxicity of several steroidal alkaloids was determined using the *Xenopus* embryo teratogenesis assay [651]. Solasonine (**291**) and α-tomatine (**300**) were both teratogenic. Glycoalkaloids were more toxic than aglycones, the nature of the carbohydrate moiety strongly affected potency, and the steroid nitrogen was required for teratogenicity [651].

Solasonine inhibited larval development and pupation in *Earias insulana* [644], inhibited elongation of letuce seed radicles [646], inhibited the infectivity of herpes simplex virus type 1 and was cytotoxic to Vero cell cultures [652]. Solasonine weakly inhibited mycelium development in the fungus *Phoma medicaginis*; synergism was observed in combination with **290** [647]. Solasonine lysed *Penicillium notatum*-derived protoplasts and bovine erythrocytes [648] and weakly disrupted stigmasterol and ergosterol liposomes [649]; in each case, **290** was considerably more active. The completely assigned ^{1}H and ^{13}C NMR spectra for **291** have been reported [642].

3.11.10. Robustine, *N*-Hydroxyrobustine and 25-Acetoxyrobustine

Robustine (**292**), *N*-hydroxyrobustine (**293**) and 25-acetoxyrobustine (**294**) were isolated from roots of *Solanum robustum*, and their structures were established using MS, and one- and two-dimensional ^{1}H and ^{13}C NMR [653].

3.11.11. Solaparnaine

Solaparnaine (**295**) was isolated from green berries of *Solanum asperum* [654]. Its structure was established using IR, MS and ^{13}C NMR [654].

3.11.12. Solaverols and Solaverines

Solaverines I and II (**297a,b**) were isolated from *Solanum toxicarium*, and solaverine III (**297c**), from *S. verbascifolium* [655].Their structures were established by FABMS, EIMS, ^{1}H and ^{13}C NMR of **297a-c** and of solaverol A (**296a**), the acid hydrolysis product of **297a,b**. Solaverine III was determined to be a glycoside of solaverol B (**296b**) [655]. The following year, a report appeared of the isolation of 23-hydroxysolasodine (solaverol A, **296a**) from *Solanum canense* and *S. fraxinifolium* [656]. Solaverol A has been synthesized from solasodine (**281**) [657].

3.11.13. Tomatidine

Tomatidine (**298**) was found to be a feeding deterrent to sixth instar larvae of the spruce budworm *Choristoneura fumiferana* [658] and it strongly inhibited growth in the *Xenopus* embryo teratogenesis assay [651]. The 3-oxo derivative of **298**, and the 23-acetoxy derivative have been isolated from roots of a hybrid of *Lycopersicon esculentum x L hirsutum* [640].

3.11.14. *N*-Hydroxytomatidine

N-Hydroxytomatidine (**299**) was synthesized from tomatidine by hydrogen peroxide oxidation in the presence of selenium dioxide [636].

3.11.15. Tomatine

Tomato fruits were found to synthesize tomatine (**300**) [659]. Fruits also metabolized [^{14}C]-tomatine; label appeared primarily in chlorophyll and carotenoids [659].

Many studies have investigated the action of tomatine on plant pests. Tomatine was found to be a feeding deterrent to sixth instar larvae of the spruce budworm *Choristoneura fumiferana* [658], and to *Phormia regina* [660], and was toxic to the larvae of the Mediterranean fruit fly *Ceratitis capitata* [661]. It inhibited larval development and pupation in the spiny bollworm *Earias insulana* [644], influenced feeding preference behavior in the tobacco hornworm *Manduca sexta* [662], inhibited growth of the fungus *Beauveria bassiana* [663], and was toxic to larvae of the soybean looper *Pseudoplusia includens* [664]. Tomatine was toxic to both *Heliothis zea* and *Spodoptera exigua*, but addition of equimolar cholesterol to the diet removed the toxicity to *H. zea* and decreased the toxicity to *S. exigua* [665]. The presence of **300** in the diet of *Heliothis*

zea protected it against the pathogenic fungus *Nomuraea rileyi* [666]. Tomatine inhibited normal chemosensory responses in the Colorado potato beetle *Leptinotarsa decemlineata* [667]. Despite the antifeedant activity of **300** towards *L. decemlineata*, studies found no correlation between tomatine content and consumption of plant material by this plant pest [668,669].

A number of additional biological activities have been reported for **300**. It inhibited elongation of lettuce seed radicles [646], and additional histological changes on ground meristem tissue of lettuce were reported [670]. Tomatine was a potent inducer of stomatal closure in epidermal peels of *Commelina communis* [671]. Tomatine disrupted 3-β-hydroxy sterol-containing liposomes and was proposed to act by binding to sterols located in the membrane [672]. An influx of Ca^{+2}, presumably due to destabilization of the membrane, was observed in several types of cultured cells after treatment with **300** [673]. Tomatine inhibited the infectivity of herpes simplex virus type 1 and was cytotoxic to cultured Vero cells [652]. It inhibited acetylcholinesterase [674] and was teratogenic and embryotoxic in the *Xenopus* frog embryo assay [651].

3.11.16. Sisunine

Sisunine (**302**) was isolated from a clone of a hybrid *Solanum acaule* and *S. x ajanhuiri* [675]. The structure of **302** was determined by FABMS, GC-MS, and acid hydrolysis to give galactose, glucose, and tomatidine (**298**). Sisunine formation was the result of independent inheritance of the aglycone and saccharide moieties [675].

3.11.17. Soladunalidine

Soladunalidine (**303**) has been synthesized from tomatidine (**298**) [676].

3.11.18. Capsicastrine, Isocapsicastrine, Capsimine and Capsimine-3-*O*-β-*D*-glucoside

Several alkaloids were isolated from root bark of *Solanum capsicastrum*. The structure of capsicastrine (**312**) was determined with IR, EIMS, ^{13}C NMR, acid hydrolysis to give isoteinemine (**329**) and galactose, and preparation of a hexaacetate derivative [677]. Capsicastrine and its acetate strongly inhibited carbon tetrachloride-induced liver damage [678]. Capsicastrine was cytotoxic against PLC/PRF/5 cells in vitro (ED_{50}=1.78 μg/ml) [637].

The structures of isocapsicastrine (**313**) and capsimine (**314**) were established with IR, EIMS, ^{1}H and ^{13}C NMR, and acid hydrolysis of **313** to give teinemine (**328**) and glucose [678]. Capsimine was cytotoxic against PLC/PRF/5 cells (ED_{50} = 1.97 μg/ml) and KB cells (ED_{50} = 1.35 μg/ml) in vitro [637].

Finally, the structure of capsimine-3-*O*-β-*D*-glucoside (**315**) was determined with IR, EIMS, FABMS, one- and two-dimensional ^{1}H and ^{13}C NMR, and acid hydrolysis to give glucose and capsimine [637].

3.11.19. Etioline, 25-Isoetioline and Etiolinine

Etioline (**316**) was cytotoxic against human PLC/PRF/5 cells in vitro [637] and displayed strong activity against carbon tetrachloride-induced liver damage [678]. 25-Isoetioline (**317**) was isolated from the leaves and stems of *Solanum canense* and *S. fraxinifolium* [679]. Its structure was determined with IR, MS, and ^{1}H NMR [679]. Etioline and 25-isoetioline were synthesized from tomatidenol (**301**) and solasodine (**281**), respectively [680].

Etiolinine (**318**) was isolated from *Solanum havanense*, and its structure determined by IR, GC and ^{1}H NMR [681].

3.11.20. Solacapine, Episolacapine and Isosolacapine

Solacapine (**319**), episolacapine (**320**) and isosolacapine (**321**) were isolated from *Solanum pseudocapsicum* [682]. The structures of these compounds were determined by MS, IR, CD of 3-*N*-salicylidene derivatives, ^{1}H and ^{13}C NMR, preparation of *N*-di- or trimethyl derivatives and their acetates, and synthesis of **319** and **320** from solanocapsine [682]. The structure of isosolacapine was confirmed by its conversion to solanogantamine [683].

3.11.21. Solacongestidine, Solafloridine and 25-Isosolafloridine

Solacongestidine (**322**) and solafloridine (**323**) each inhibited cholesterol biosynthesis from dihydrolanosterol in rat liver homogenate [630]. Solacongestidine was strongly active against *Candida albicans*, *Trichophyton rubrum*, and *Cryptococcus albidus*, and prolonged the life of mice infected with *Candida albicans* [684]. In the same study, solafloridine demonstrated activity against *C. albicans* and *T. rubrum*. 25-Isosolafloridine (**324**) caused tremors and convulsions in rats [685].

3.11.22. Solaphyllidine and Desacetylsolaphyllidine

Solaphyllidine (**325**) and desacetylsolaphyllidine (**326**) were examined for their biological effects in mice [686]. The two alkaloids exhibited comparable toxicity (LD_{50} = 14.5, 12 mg/kg). Both **325** and **326** decreased pentobarbital-induced sleeping time, while **325** increased locomotor activity [686].

3.11.23. Solaquidine

The configuration of solaquidine (**327**) was determined to be 5α, 22*S*, 25*R* by its synthesis from solasodine (**281**) [687].

3.11.24. Teinemine and 22-Isoteinemine

Teinemine (**328**) and 22-isoteinemine (**329**) were synthesized from tomatidenol (**301**) [680].

3.11.25. Cordatines

Cordatines A and B (**304a,b**) were isolated from petals of *Lilium cordatum* [688]. Their structures were established using IR, EIMS, FABMS, ^{1}H and ^{13}C NMR, CD, and acid hydrolysis to give glucose and the aglycones [688].

3.11.26. Petiline and Petisine

The 25*S* configurations of petiline (**305**) and petisine (**306**) were confirmed using circular dichroism [689].

3.11.27. Pingbeinine and Pingbeininoside

Pingbeinine (**307**) and pingbeininoside (**308**) were isolated from leaves of *Fritillaria ussuriensis* [690]. The structures of these alkaloids were determined with UV, IR, HRMS, ^{1}H and ^{13}C NMR, and acid hydrolysis of **308** to give **307** and glucose [690].

3.11.28. Verazine and Verazinine

Verazine (**309**) was active against *Candida albicans* and *Trichophyton rubrum* [684], and inhibited DNA formation by hepatoma and S180 cells [691]. Verazine isolated from *Veratrum maackii* was found by ^{1}H and ^{13}C NMR studies to be a 20*R*/20*S* epimeric mixture [692].

Verazinine (**310**) was isolated from *Zygadenus sibiricus* as a new alkaloid [693].

3.11.29. Vertaline B

Vertaline B (**311**) was isolated from *Veratrum taliense*, and its structure was determined with MS, and ^{1}H and ^{13}C NMR [694].

3.11.30. Plakinamine B

Plakinamine B (**330**) was isolated from a marine sponge *Plakina* sp., using bioassay-guided fractionation [695]. Its structure was determined using ^{1}H and ^{13} C NMR and UV. The hydrochloride salt of **330** inhibited the growth of *Staphylococcus aureus* and *Candida albicans* [695].

3.12. Bicyclic Piperidine Alkaloids

3.12.1. Pseudopelletierine

Pseudopelletierine (**331**) was isolated from *Punica granatum* bark [440], and was synthesized by mercuric acetate oxidation of *N*-methylpelletierine (**170**) [696]. Pseudopelletierine oxime was found to be asymmetric, and the (+)-oxime was resolved [697].

3.12.2 Euphococcinine

Euphococcinine (**332**) was isolated from several new sources, including the blood of the Mexican bean beetle *Epilachna varivestis* [698], the pines *Pinus edulis*, *P. ponderosa*, *P. nigra* and *P. sylvestris* [467] and the spruces *Picea pungens* [467] and *P. breweriana* [441]. Euphococcinine was active as a feeding deterrent to the spider *Phidippus regius* and the ant

Monomorium pharaonis [698]. It was weakly active against *Bacillus subtilis* (MIC = 1 mg/ml) and *Micrococcus luteus* (MIC = 10 mg/ml) [467].

Euphococcinine and adaline (**333**) were synthesized from a 2-cyano-6-oxazolopiperidine [699]. An anion at C(2) was condensed with 3-bromo-2-methoxy-1-propene, and after elimination of cyanide, the resultant iminium ion was alkylated with either a methyl- or pentyl-Grignard reagent to form the quaternary carbon. The second ring was closed with an intramolecular Mannich reaction.

3.12.3. Adaline

Adaline (**333**) was synthesized as described above for euphococcinine [699]. The two-spot ladybird beetle *Adalia bipunctata* was found to have a considerable investment in defense via its secretion of adaline-rich reflex blood [700].

3.13. Miscellaneous Piperidine Alkaloids

3.13.1. Stenusine

(+)-Stenusine (**334**) was recently synthesized from an *N*-alkylated 2-piperidone using a stereoselective α-alkylation of a lactam as a key step [701].

3.13.2. Strictimine

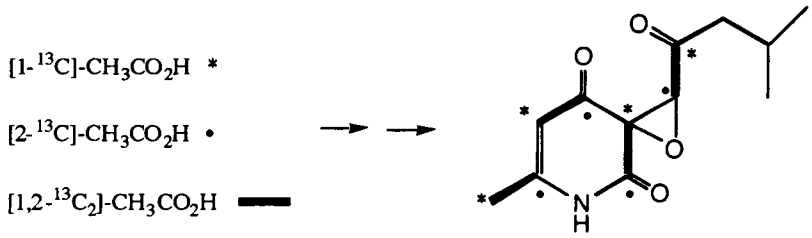
Strictimine (**335**) was isolated from roots of *Rhazya stricta*. Its structure was determined using HRMS, UV, IR, and ^{1}H and ^{13}C NMR [702].

3.13.3. Mearsine

Mearsine (**336**) was isolated as a minor alkaloid of *Peripentadenia mearsii* [703]. Its structure was determined with elemental analysis of the crystalline picrate, MS, IR, UV, ^{1}H and ^{13}C NMR, diacetylation of the $NaBH_4$ reduction product, and X-ray crystallography [703,704]. The structure was confirmed by synthesis of (+)-**336** from (-)-5-methyl-2-cyclohexenone via a Mannich reaction [705]. The structure of **336** suggested its biosynthesis was from acetate via a polyketide pathway [703].

3.13.4. Flavipucine

The biosynthesis of flavipucine (**337**) was investigated by feeding [1-^{13}C]-, [2-^{13}C], and [1,2-$^{13}C_2$]-acetate to cultures of *Aspergillus flavipes* [706]. Analysis of the ^{13}C NMR spectrum of the isolated **337** showed all carbons were enriched except for the isobutyl side chain. The observed labelling pattern is outlined in Scheme 8 [706].



Scheme 8. Biosynthesis of flavipucine

3.13.5. Phyllanthimide

Phyllanthimide (**338**) was isolated from *Phyllanthus sellowianus* and its structure determined using UV, IR, MS, and one- and two-dimensional ^{1}H and ^{13}C NMR [707]. Preliminary biological testing on rat uterus showed **338** had no antispasmodic activity [707], however it did display antimicrobial activity [708].

3.13.6. Sesbanimides

Sesbanimides A-C (**339a-c**) were isolated from seeds of *Sesbania drummondii* using cytotoxicity and antitumor assay guided fractionation [709]. The structures of these compounds were determined using HRMS, X-ray crystallography (**339a**), and one- and two-dimensional ^{1}H and ^{13}C NMR on **339a-c** and their acetate derivatives [709,710]. In addition to *S. drummondii*, *S. punicea* [710] and *S. vesicaria* [711] have been reported sources of the sesbanimides. Sesbanimides A-C were cytotoxic to KB cells and inhibited PS leukemia [709]. Sesbanimide A was toxic to mice [712] and inhibited murine L1210 cells [711].

Sesbanimides have been an attractive synthetic target. Two recent formal syntheses focused on stereoselective formation of the 1,3-dioxane ring [713] and the imide ring [714].

3.13.7. Histrionicotoxins

The structures, synthesis, and biological activity of the histrionicotoxins were reviewed in Volume 4 of this series [715]. Work described below was published subsequent to this review.

Alkaloid profiles of three different populations of *Dendrobates auratus* were found to be considerably different [716]. Descendents of these frogs did not produce alkaloids unless they were raised on wild-caught insects [716]. Thus, environmental factors have a significant role in either initiating or otherwise promoting alkaloid production in dendrobatid frogs.

(-)-Histrionicotoxin (**340**) and (-)-histrionicotoxin 235A (**341**) were synthesized from (*S*)-6-hydroxy-8-nonenoate, using an allylic epoxide cyclization to generate three of the required chiral centers [717]. A recent synthesis of the histrionicotoxin ring system employed a tandem Michael addition-nitrone cyclization [718]. GC-MS, GC-FTIR, and revised ^{13}C NMR spectral data have been reported for a number of histrionicotoxins [719].

Perhydrohistrionicotoxin (**342**) has been a simpler synthetic target. A recent formal synthesis of (+)-**342** used a palladium-catalyzed carbonyl allylation to form the spiro ring system [720].

Histrionicotoxin, **342**, and synthetic analog inhibition of ligand binding at sites associated with the sodium, potassium, and calcium channels in brain membrane preparations has been investigated [721]. The effects of **342** on the ion channel of central nervous system nicotinic acetylcholine receptors [722], and on post-tetanic potentiation of mouse and rat phrenic nerve diaphram preparations have been described [723].

3.13.8. Pandamarine and Pandamarilactone-1

Pandamarine (**343**) was isolated as the major alkaloid in *Pandanus amaryllifolius* and its structure was determined by ^{1}H and ^{13}C-NMR, and X-ray crystallography [724]. Pandamarilactone-1 (**344**) was subsequently reported from *P. amaryllifolius*, its structure having been established by HRMS, IR, UV, and one- and two-dimensional ^{1}H and ^{13}C NMR [725].

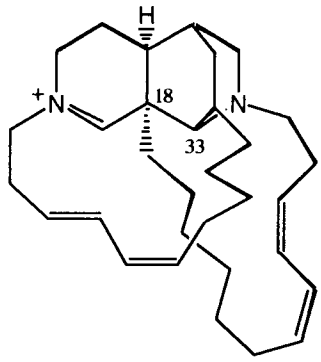
3.13.9. Haliclamines

Haliclamines A and B (**345a,b**) were isolated from a sponge *Haliclona* sp as antifungal agents using bioassay guided fractionation [726]. The structures of these compounds were determined using HREIMS, EIMS, UV, IR, ^{1}H and ^{13}C NMR, and by dehydrogenation of **345a** to a 3-substituted pyridine. Haliclamines A and B inhibited cell division of fertilized sea

urchin *Hemicentrus pulcherrimus* eggs, and inhibited growth of murine leukemia L1210 cells (IC_{50} = 1.5 μg/ml and 0.9 μg/ml, respectively) and P388 cells (IC_{50} = 0.75 μg/ml and 0.39 μg/ml, respectively). The haliclamines were suggested to act as biosynthetic precursors for more complex marine alkaloids, such as the xestospongins and halitoxin [726].

3.13.10. Halicyclamine A

Halicyclamine A (**346**) was isolated from a marine sponge *Halicona* sp [727]. Its structure was determined using HREIMS, EIMS, IR, and one- and two-dimensional ^{1}H and ^{13}C NMR. While **346** appears similar to the haliclamines (**345**), it was suggested that **346** may arise biosynthetically from cleavage of the C(18)-C(33) bond in the xestocyclamine/ingenamine type structure **D** [727].



D

3.13.11. Griffithine

Griffithine (**347**) was isolated from the shoots of *Sophora griffithii*. The structure of this dimeric alkaloid was established with HRMS, UV, IR, and extensive one- and two-dimensional ^{1}H and ^{13}C NMR [728].

ACKNOWLEDGEMENT

John C. Schmidhauser is acknowledged for his assistance in structure preparation.

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Chapter Three

3-Alkylpiperidine Alkaloids Isolated from Marine Sponges in the Order Haplosclerida

Raymond J. Andersen,[a] Rob W. M. Van Soest[b] and Fangming Kong[a]

[a]*Departments of Chemistry and Oceanography*
University of British Columbia
Vancouver, B.C.
Canada V6T 1Z1

[b]*Department of Coelenterates and Porifera*
Institute for Systematics and Population Biology (Zoologisch Museum)
University of Amsterdam, P.O. Box 94766, 1090 AT Amsterdam
The Netherlands

CONTENTS

1. INTRODUCTION

Marine sponges (Phylum Porifera) are primitive metazoans that are found in all of the world's oceans at depths ranging from the shallow intertidal zone to the deep abyssal plain [1,2]. These sessile filter feeding invertebrates are frequently one of the dominant life forms on tropical coral reefs and under the Antarctic ice cap [3,4,5]. Hooper and Wiedenmeyer have estimated that there are 15,000 sponge species in the contemporary oceans [6]. Less than half of the total number of extant species have been taxonomically described. Chemical studies carried out over the last three decades [7] have shown that sponges are an extremely rich source of novel steroids [8], terpenoids [9], peptides [10], macrolides [11] and alkaloids [12]. Many sponge secondary metabolites exhibit potent biological activities making them useful tools for cell biology research [13] or promising leads for drug development [14,15]. Sponge secondary metabolites have also served as useful markers to clarify taxonomic uncertainties [16].

Our knowledge of sponge secondary metabolism has matured in the last two decades to the point where it is now possible to recognize major categories of compounds that are related by their putative biogenetic origins. One such group of compounds is a structurally diverse

collection of alkaloids that are nevertheless all related to each other by the presence of a 3-alkylpiperidine motif in their structures and the presumption of a common biogenesis. The alkyl component of the common structural motif is most often a linear chain, either saturated or unsaturated, ranging in length from eight to sixteen carbons. Several examples of a single methyl branch near the distal end of the alkyl chain are also known. The six-membered nitrogen heterocycle in the common structural element of these alkaloids is encountered in the pyridine, tetrahydropyridine or piperidine oxidation states. Roughly one third of the known members of this group of compounds, that are either simple monomers or high molecular weight oligomers or polymers, all contain only pyridine rings. Almost all of the remaining two thirds of the alkaloids in this group, that have more complex cyclic structures and appear to be biogenetically derived from macrocyclic dimers, contain piperidine or tetrahydropyridine heterocycles.

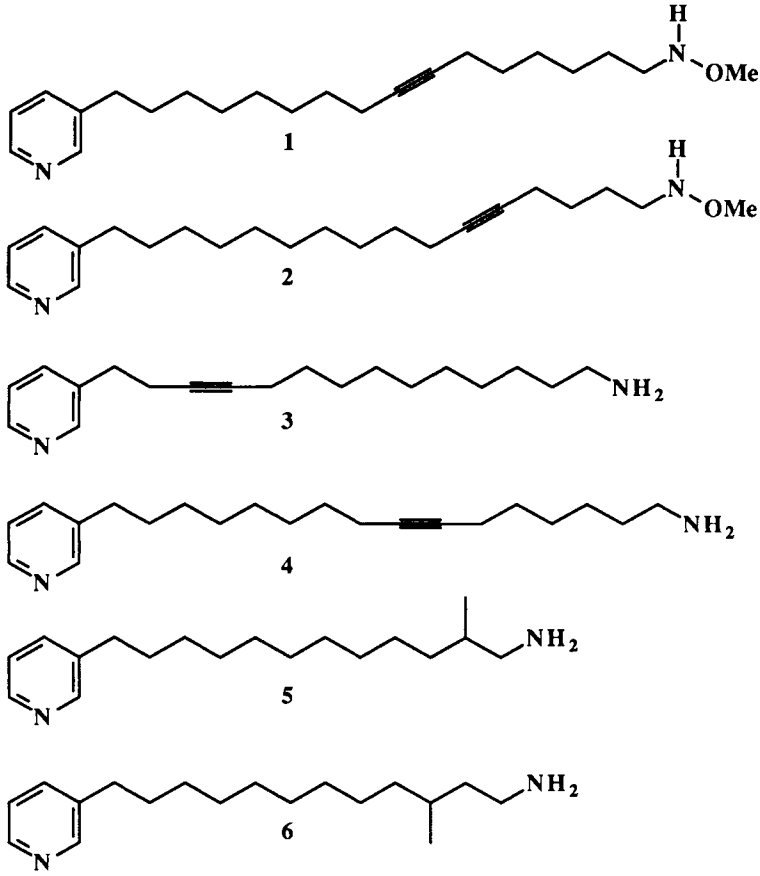
Since no biosynthetic experiments have been carried out on this group of alkaloids to date, it is not known if pyridine rings are the precursors to the piperidine and tetrahydropyridine rings found in the more complex structures or if piperidine rings are the precursors to the pyridine rings found in the simpler structures. This biosynthetic uncertainty complicates the choice of a trivial name that would encompass the whole group of alkaloids. Various authors have referred to individual members of the group as '3-alkylpyridine alkaloids' or as '3-alkylpiperidine alkaloids', but there appears to have been no previous attempt to devise a suitable label for the entire group. For the purposes of this review, we have somewhat arbitrarily chosen to use the label '3-alkylpiperidine alkaloids' because the majority of compounds, including those with the most complex structures, contain six-membered nitrogen heterocycles at the piperidine or terahydropyridine oxidation states. Our use of the 3-alkylpiperidine label implies that the piperidine ring can exist in any oxidation state up to and including the pyridine oxidation state.

The presumption of a common biogenetic origin for the 3-alkylpiperidine sponge alkaloids is based on several pieces of evidence. Perhaps the most compelling evidence is the incorporation of a clearly recognizable 3-alkylpiperidine substructure in all of the alkaloids in the group. 3-Alkylpiperidine biogenetic building blocks are not widespread in nature so their occurrence in a group of metabolites isolated from members of a particular phylum, such as the Porifera, is a significant indication of biogenetic relatedness. This argument is analogous to the recognition that the presence of isoprene units provides compelling evidence for terpenoid biosynthesis. The observation that the sponges which have been reported to contain 3-alkylpiperidine alkaloids are all in the Order Haplosclerida, as outlined in section 4 below, provides taxonomic support for a common biogenetic origin and argues for their biosynthesis by sponge cells rather than by symbiont cells. In addition, as outlined in section 3, there have been convincing proposals put forth by several authors that provide elegant rationalizations for the formation of all of the known 3-alkylpiperidine alkaloids via a common biogenetic pathway.

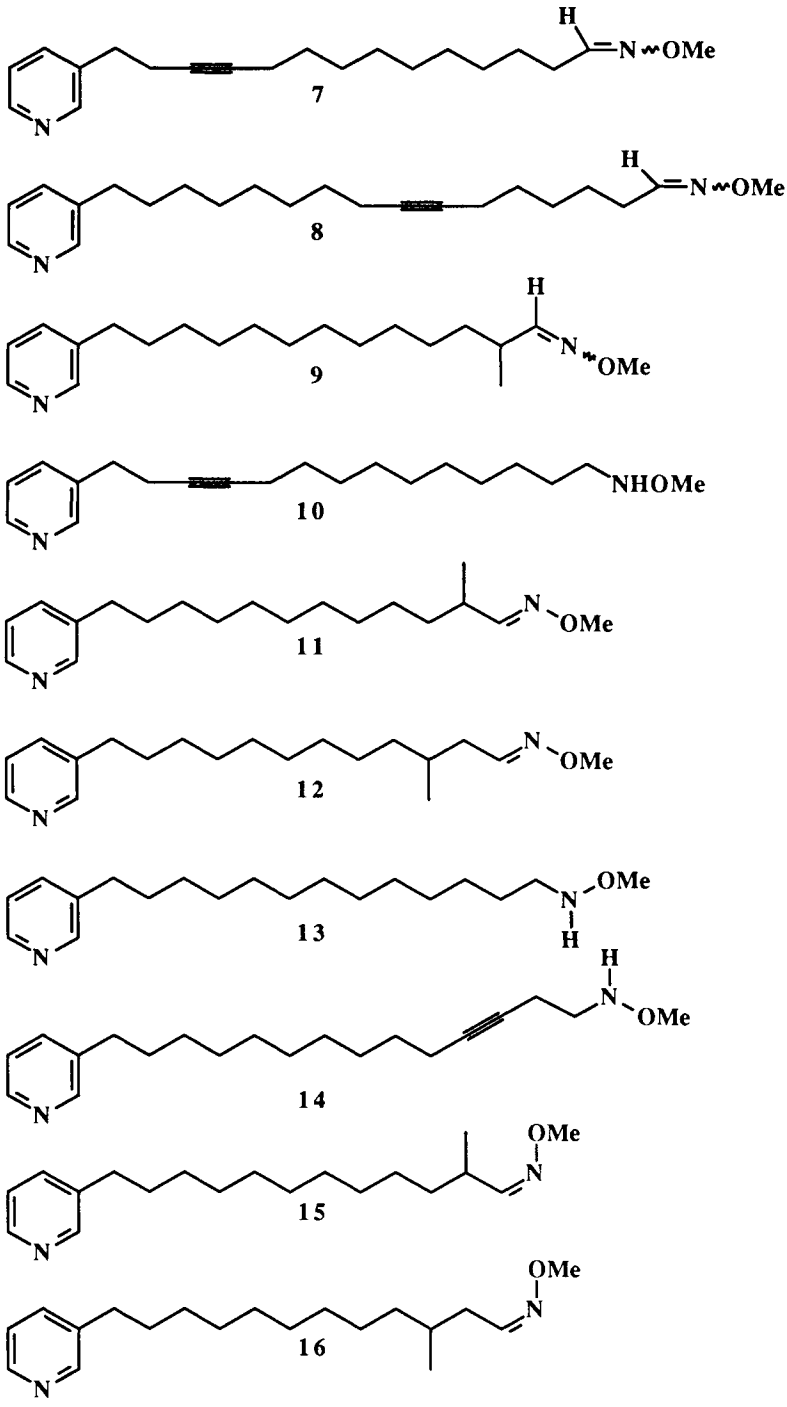
2. STRUCTURAL TYPES

2.1) Monomers

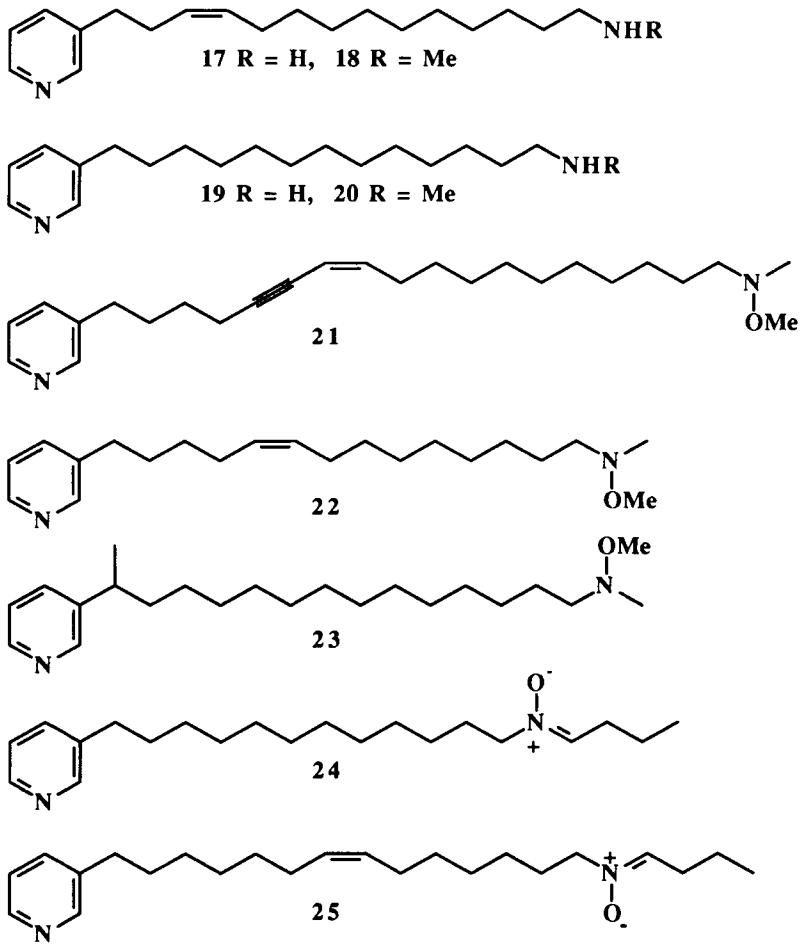
The monomeric structural unit of the 3-alkylpiperidine alkaloids is readily apparent in a number of simple 3-alkylpyridines isolated from marine sponges. In all known examples, the 3-alkyl component of the monomeric unit is attached to a primary amine, methyl amine, methoxy amine, methoxy methyl amine, imine oxide or oxime methyl ether functionality at the distal terminus.



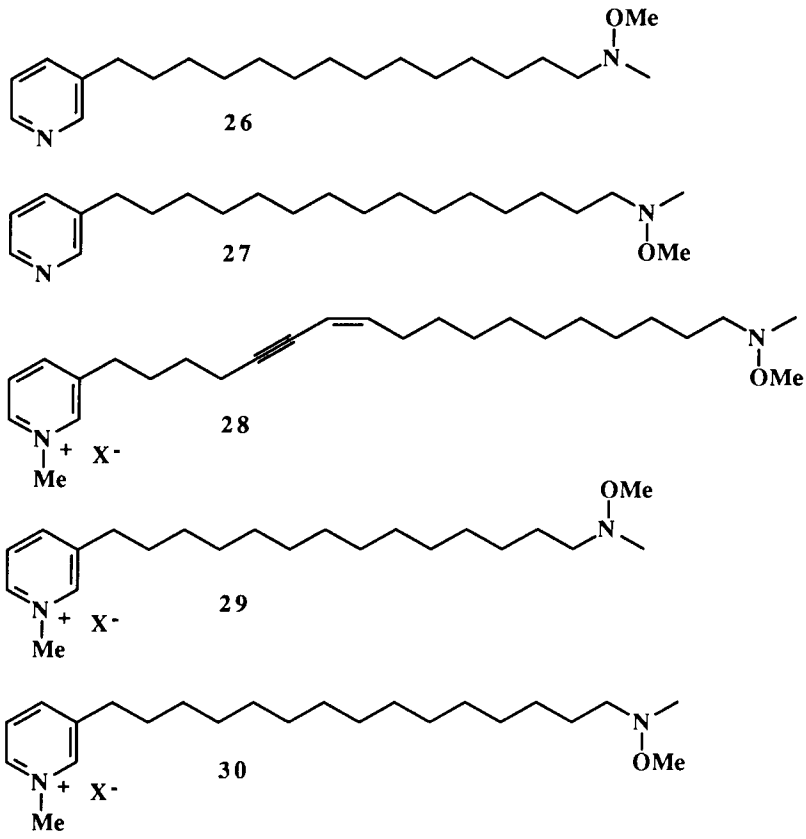
Niphatynes A (**1**) and B (**2**) isolated from a *Niphates* sp. collected off Vitu Levu in the Fijian Islands were the first reported examples of monomeric 3-alkylpyridines from sponges [17]. These two metabolites, which contain the alkyne and methoxy amine functionalities encountered in many of the monomeric 3-alkylpyridines, were reported to be cytotoxic to murine leukemia P388 *in vitro* (niphatyne A (**1**): ED_{50} 0.5 μg/ml). Niphatesines A (**3**), B (**4**), C


H
N
OMe
7
8
9
NHOMe
10
11
12
13
14
15
16

(**5**), and D (**6**), which all have primary amine functionalities at the remote terminus of the 3-alkyl chain, were isolated from the Okinawan sponge *Niphates* sp. [18]. The same *Niphates* sp. yielded niphatesines E (**7**), F (**8**), G (**9**) and H (**10**) and ikimine A (**11**) [19]. Niphatesines E (**7**), F (**8**) and ikimine A (**11**) are the oxime methyl ether analogs of niphatesines A (**3**), B (**4**) and C (**5**), respectively, and niphatesine H (**10**) is the methoxy amine analog of niphatesine A (**3**). The niphatesines were found to be mildly antimicrobial against some fungi and gram positive bacteria and to exhibit *in vitro* cytotoxicity against murine leukemia L1210 and human epidermal carcinoma KB cells.



An unidentified sponge collected at Ant Atoll in Micronesia yielded ikimines A (**11**), B (**12**), C (**13**) and D (**14**) [20]. In chloroform solution, ikimines A (**11**) and B (**12**) isomerized to

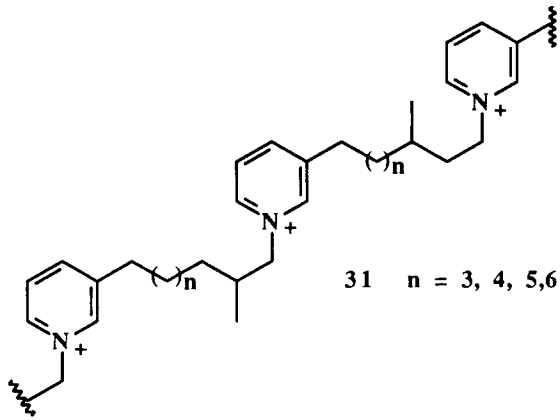


produce 3:1 mixtures of the natural products and their *syn*-isomers **15** and **16**. The ikimines were reported to be cytotoxic to KB cells with IC_{50} values ranging from 5 to 10 μg/ml. Theonelladins A (**17**), B (**18**), C (**19**) and D (**20**) were isolated from an Okinawan sponge identified as *Theonella swinhoei* [21]. They were reported to be cytotoxic to murine leukemia L1210 and human epidermal carcinoma KB cells *in vitro* (IC_{50} 1 - 5 μg/ml) and they also showed powerful Ca^{+2} -releasing activity from sarcoplasmic reticulum, being twenty times more potent than caffeine, a well known Ca^{+2} inducer. The sponge *Xestospongia wiedenmayeri* collected at Acklin Island in the Bahamas yielded xestamines A (**21**), B (**22**) and C (**23**) [22]. The 3-alkyl chains in the xestamines all terminate in a *N*-methyl-*N*-methoxyamine functionality. Xestamine C (**23**) is unique in having a methyl branch at the carbon attached to the pyridine ring rather than near the remote terminus as in the niphatesines C (**5**), D (**6**) and G (**9**) and the ikamines A (**11**) and B (**12**). Cribrochalinamine oxides A (**24**) and B (**25**) were isolated from the sponge *Cribrochalina* sp. collected off Hachijo-jima Island in Japan [23]. The azomethine *N*-oxide functionality present in the cribrochalinamine oxides is

rare in nature. *Calyx podatypa* collected at Jamaica Bay off Acklins Island in the Bahamas yielded the previously described xestamines A (**21**) and B (**22**) along with the novel analogs xestamines D (**26**), E (**27**), F (**28**), G (**29**) and H (**30**) [24]. Xestamines F (**28**), G (**29**) and H (**30**) represented the first examples of *N*-methylpyridinium salts amongst the 3-alkylpyridine monomers reported to date. It was found that xestamines F (**28**), G (**29**) and H (**30**), containing the ionic *N*-methyl pyridinium end group, were 100 times more active as *in vitro* antimicrobial agents versus *Staphylococcus aureus*, *Bacillus subtilus* and *Candida albicans* than were the unsubstituted pyridine analogs xestamines A (**21**), D (**26**) and E (**27**). Interestingly, the *N*-methyl pyridinium containing metabolites xestamines G (**29**) and H (**30**) were roughly 100 times less cytotoxic than the unmethylated analogs xestamines D (**26**) and E (**27**) (LD_{50} < 1 X 10^{-6} M) in a brine shrimp assay.

2.2) Oligomers

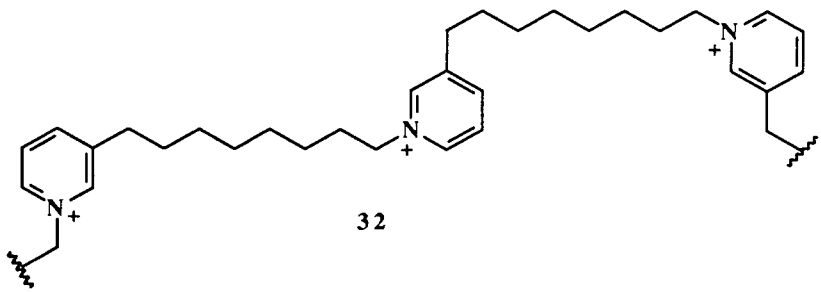
The halitoxins isolated from several species in the genus *Amphimedon* (originally identified as *Haliclona*) were the first examples of 3-alkylpiperidine alkaloids reported from sponges [25]. Prior to the chemical characterization of the halitoxins, biologists had known for some time that many sponges in the genus "*Haliclona*" gave extracts that were toxic to fish and mice [26,27]. Fractionation of the cytotoxic methanol extracts obtained from "*Haliclona rubens*" (= *Amphimedon compressa*) via membrane ultrafiltration gave molecular weight range fractions of 500 - 1,000, 1,000 - 25,000 and greater than 25,000 [25]. The ^{1}H NMR spectra of all three molecular weight range fractions were identical and all three fractions exhibited the same *in vitro* cytotoxicity against human epidermal KB cancer cells (IC_{50} 5-7 μg/ml).



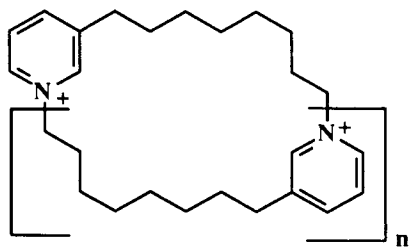
31 n = 3, 4, 5,6

Detailed analysis of the ^{1}H NMR spectra of the halitoxins revealed the presence of 3-substituted pyridinium rings. Pyrolysis at 140-160°C decomposed the halitoxins giving a mixture of low molecular weight products that could be purified by preparative GC and analyzed by ^{1}H NMR and mass spectrometry. The pyrolysis products were found to be 3-

alkenylpyridines in which the alkyl groups consisted of linear carbon chains of between six and ten carbons in length having a single methyl branch at the iso or anteiso carbons. Since there were no olefinic proton or vinyl methyl signals in the ^1H NMR spectra of the halitoxins, the unsaturation sites in the 3-alkenylpyridine pyrolysis products had to mark the sites of nitrogen-alkyl links in the toxins. Thus this analysis indicated that all of the 3-alkyl chains must be joined through a terminal methylene group to nitrogen. The ^1H NMR spectra of the halitoxins contained a resonance at δ 4.5 ppm. Comparison with the ^1H NMR data for synthetic model compounds indicated that this resonance could be assigned to methylene protons on a carbon bonded to the quaternary nitrogen of the pyridinium rings in agreement with the pyrolysis evidence. The absence of ^1H NMR resonances that could be assigned to terminal methyl groups or to pyridine rings without quaternary nitrogens led to the conclusion that the halitoxins were oligomeric or polymeric structures as shown in **31**. The lack of evidence for terminal alkyl chains or nonquaternized pyridine rings suggested that the oligomers in the molecular weight range of 500 - 1000 were macrocyclic.



32



33 n = 1

34 n = 2

35 n = 3

A halitoxin has more recently been isolated from the sponge *Callyspongia fibrosa* as part of a screening program designed to discover epidermal growth factor (EGF) antagonists [28]. NMR analysis showed that the monomeric unit in the *C. fibrosa* halitoxin **32** consisted of a pyridine ring substituted in the 3 position with a linear saturated eight carbon alkyl chain. Once again there were no ^1H NMR signals that could be assigned to terminal methyl or

pyridine rings which suggested "a cyclic structure or a linear head-to tail polymer that is so large that ^{1}H NMR signals due to the terminal units are not observed". The electrospray MS of the *C. fibrosa* halitoxin gave an intense peak at m/z 379 which was originally interpreted to be arising from a dimer **33** that underwent the fragmentation shown in Figure 2.1. Synthesis of the

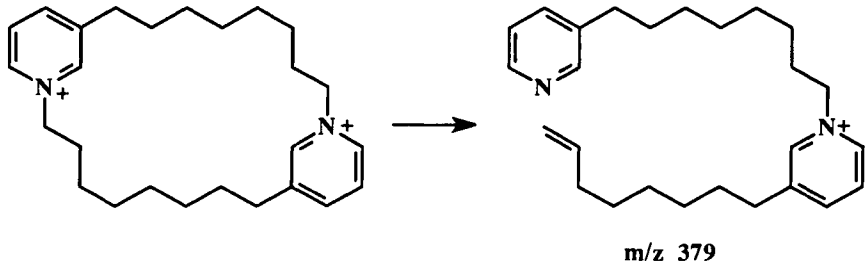
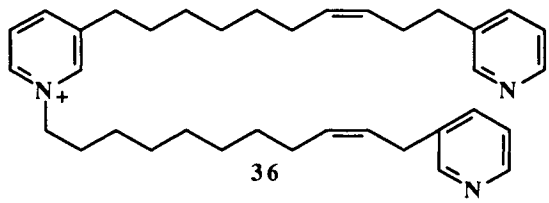


Figure 2.1

Suggested fragmention of a candidate dimeric structure **33** to give the intense ion observed at m/z 379 in the electrospray MS of the *C. fibrosa* halitoxin [28].

dimer **33**, trimer **34** and tetramer **35** gave authentic materials for comparison with the natural halitoxin **32**. MS and TLC comparison showed that the *C. fibrosa* halitoxin was larger than a tetramer and that it was most likely an oligomer or polymer containing at least eight subunits.



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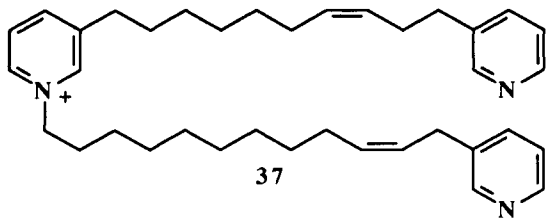
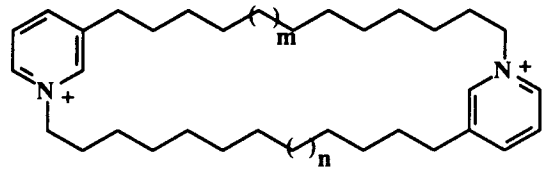


37

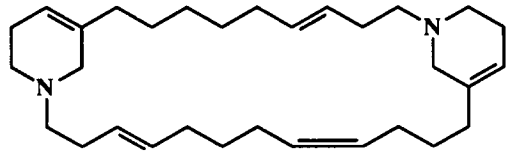
A *Niphates* sp. collected at Eilat in the Red Sea yielded the cytotoxic (*in vitro* P388: IC_{50} 0.1 μg/ml) and icthyotoxic alkaloids niphatoxin A (**36**) and B (**37**) [29]. Although the

niphatoxins have structural elements in common with the simple 3-alkylpyridine monomers (Section 2.1) and the high molecular weight oligomeric halitoxins (e.g. **31** and **32**), they contain one structural feature not found in any other 3-alkylpiperidine sponge alkaloid. This is the substructure containing a pyridinium ring and a pyridine ring both attached at the 3 position to the same linear alkyl chain. In all other dimeric or higher oligomeric 3-alkylpiperidine alkaloids reported to date, or in their proposed biogenetic precursors, the alkyl group attached at the 3 position of a piperidine or pyridine ring always terminates at a nitrogen atom that is part of another piperidine or pyridine ring. A substructure in which two pyridine rings are linked through the 3 position to the same alkyl chain can easily be accommodated by the same biogenetic pathways that have been proposed for all the other 3-alkylpiperidine sponge alkaloids (See Section 3 - Figure 3.2).

2.3) *Bis*- 3-Alkylpiperidine Macrocycles



38 m=1, n=1
39 m=1, n=2
40 m=2, n=2
41 m=1, n=3
42 m=2, n=3
43 m=3 n=3



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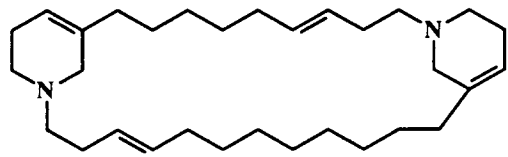
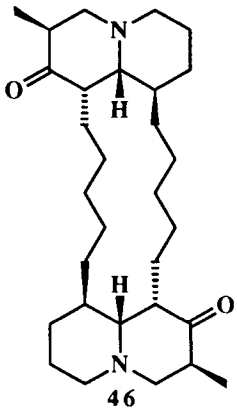


45

The proposed biogenetic pathways (See Section 3) to 3-alkylpiperidine sponge alkaloids that have complex structures and nitrogen heterocycles at the piperidine or tetrahydropyridine oxidation states all proceed through a partially reduced *bis*-3-alkylpyridine

macrocyclic intermediate. Two sponges have yielded natural products corresponding with these *bis*-macrocyclic intermediates, providing support for the biogenetic proposals. Cyclostellettamines A (**38**) to F (**43**) were isolated from *Stelletta maxima* collected off the Sata Peninsula, Shikoku, Japan [30]. The structures of the cyclostellettamines were confirmed by synthesis. Cyclostellettamines blocked the binding of [^{3}H]-methyl quinuclidinyl benzilate (QNB) to muscarinic acetylcholine receptors. The cytotoxic haliclamines A (**44**) and B (**45**) were isolated from a *Haliclona* sp. collected off Hiburi-jima Island in the Uwa Sea, Japan [31]. Haliclamines A (**44**) and B (**45**) inhibited cell division of fertilized sea urchin eggs (*Hemicentrotus pulcherrimus*) at concentrations of 5 and 10 μg/ml, respectively, and they showed *in vitro* cytotoxicity against murine leukemia P388 (**44**: IC_{50} 0.75 μg/ml; **45**: IC_{50} 0.9 μg/ml).

2.4) *Bis*-Quinolizadine and *Bis*-1-Oxaquinolizadine Macrocycles



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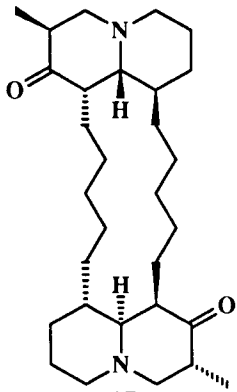

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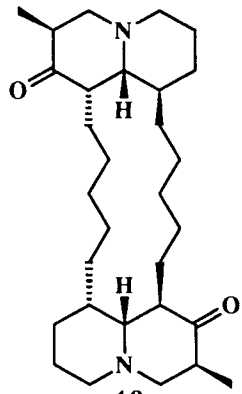
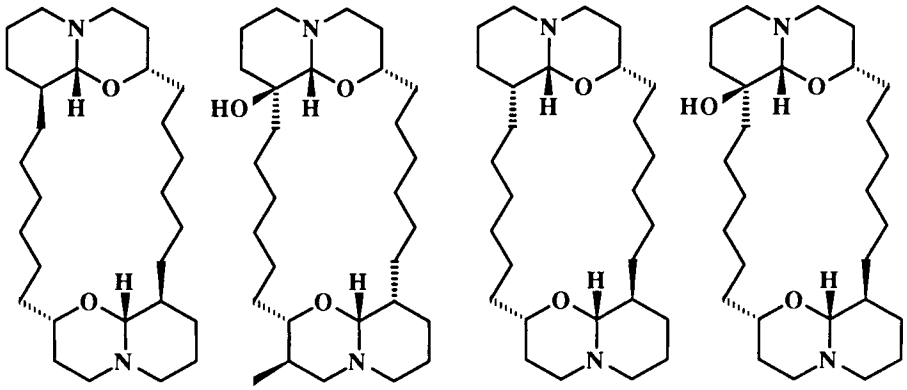


48

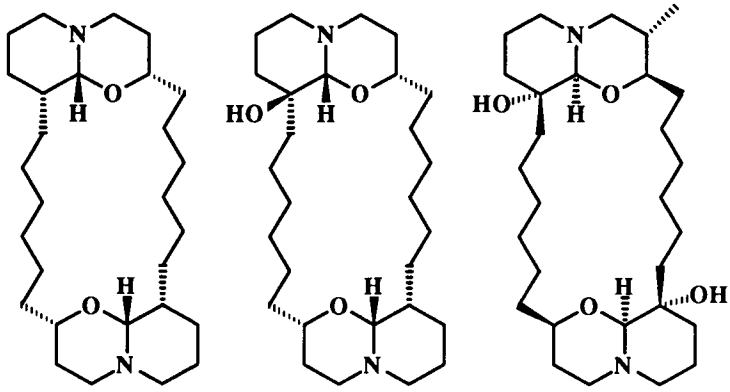
Extracts of the sponge *Petrosia seriata* collected around Laing Island, Papua New Guinea are toxic to the tropical fish *Lebistes reticulatus* [32,33,34]. The toxicity is associated with petrosin (**46**) (LD_{100} = 10 mg/l), petrosin A (**47**) and petrosin B (**48**), three *bis*-quinolizadine alkaloids that are present in the extracts. Petrosin (**46**), the major component, was isolated as optically inactive crystals that showed a two-fold element of symmetry in the NMR data. X-ray diffraction analysis established the structure **46** for petrosin, which is present in the sponge *P. seriata* as a naturally occurring racemate [32]. The structures of petrosins A (**47**) [33,34] and B (**48**) [33] were assigned on the basis of spectroscopic analysis. Interestingly, in petrosin (**46**) the two quinolizadine moieties have the same absolute configurations, in petrosin A (**47**), a meso compound, the two quinolizadine moieties have the opposite absolute configurations and in petrosin B (**48**) the two quinolizadine moieties have different relative

configurations. The petrosins were the first examples of naturally occurring compounds having a *bis*-quinolizadine macrocyclic skeleton.



Xestospongins A (**49**), B (**50**), C (**51**) and D (**52**), four macrocyclic *bis*-1-oxaquinolizadine alkaloids, were isolated from the Australian sponge *Xestospongia exigua* [35]. The structure of xestospongin C (**51**) was established by single crystal X-ray diffraction analysis. A *Xestospongia* sp. collected in Okinawa, Japan yielded a series of closely related *bis*-1-oxaquinolizadines that were named araguspongines A (**53**), B (**54**), C (**55**), D (**49**), E (**56**), F (**57**), G (**58**), H (**59**) and J (**60**) and assigned the structures shown [36,37]. Aragupetrosine A (**61**), a hybrid of petrosin (**46**) and araguspongine F (**57**), and the previously reported metabolites petrosin (**46**) and petrosin A (**47**) were isolated from the same extract [38]. Araguspongines B, D and E were shown to be present in the sponge extract as mixtures of enantiomers that could be separated by chiral HPLC. Araguspongines F, G, H and J were demonstrated to be optically pure by chiral HPLC analysis and their absolute configurations were determined to be those shown in **57** to **60**. (+)-Araguspongine D (**49**), whose absolute configuration was also determined by physical methods and chemical degradation, was shown to be identical with xestospongin A. It is interesting to note that the structures assigned to (+)-araguspongine B ((+) **54**), (-)-araguspongine D ((-) **49**) and (+)-araguspongine E ((+) **56**) differ only in the orientations of the bridgehead nitrogen lone pairs of electrons relative to the chiral centers at C2, C9a and C9 on the 1-oxaquinolizadine rings. Both (+)-araguspongine B (**54**) and (+)-araguspongine E (**56**) were found to be convertible to (-)-araguspongine D (**49**) when heated to 80°C in the presence of alumina. The interconversion was attributed to bridgehead nitrogen lone pair inversion. The araguspongines C, D, E and J were found to be more potent vasodilators than papaverine in a perfusion model experiment using an isolated mesenteric rat artery.

A detailed analysis of the conformational and configurational equilibria in model 1-oxaquinolizadines related to the xestospongin/araguspongine alkaloids led to a reassignment of the structures of araguspongines B and E [39]. The correct structure for (-)-araguspongine B was proposed to be **62** and the correct structure for (-)-araguspongine E to be **51**, identical with the structure of (-)-xestospongin C. In the new proposal, the structures of araguspongines B (**62**), D (**49**) and E (**51**) all have different relative configurations at the C2, C2', C9 and C9' positions of the 1-oxaquinolizadine rings, rather than just different relative orientations of the bridgehead nitrogen lone pairs of electrons. The conversion of (-)-araguspongine B (**62**) and (-)- araguspongine E (**51**) to (+)-araguspongine D (**49**) when heated in the presence of alumina was proposed to occur via the iminium ion/enamine epimerization mechanism shown in Figure 2.2, rather than by nitrogen lone pair inversion as originally suggested.



62 63 64

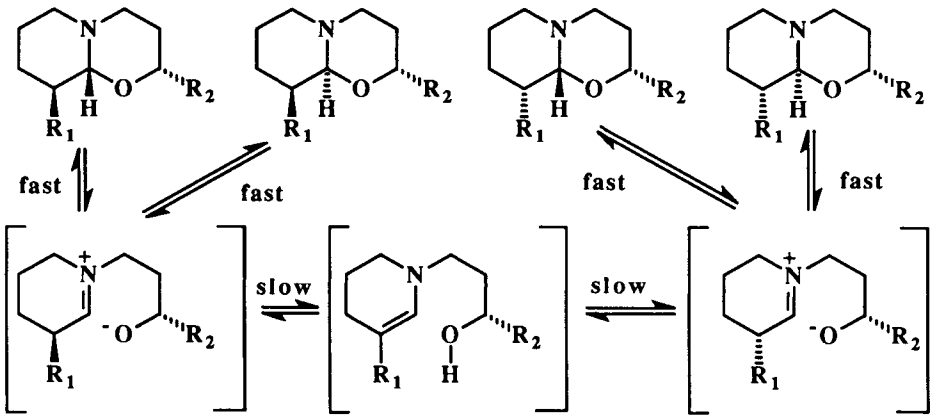
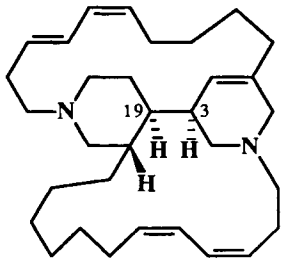


Figure 2.2

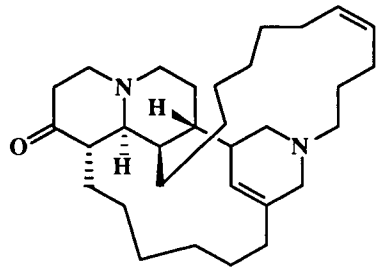
Proposed mechanism for the interconversion of (-)-araguspongine B (**62**), (+)-araguspongine D (**49**) and (-)-araguspongine E (**51**) [39].

A *Xestospongia* sp. collected in New Caledonia yielded the known compounds xestospongin B (**50**), xestospongin D (**52**) and araguspongine F (**57**) along with the new analog demethylxestospongin B (**63**) [40] and *Haliclona exigua* collected at Chidiatapu, Andaman Islands, India yielded the known compounds araguspongines C (**55**), D (**49**), E (**51**) and xestospongin D (**52**) along with the new analog 3α-methylaraguspongine C (**64**) [41].

2.5) Macrocycles with Conjoint Piperidine Rings

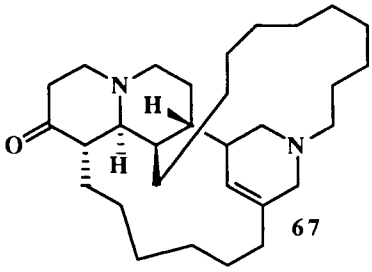


65

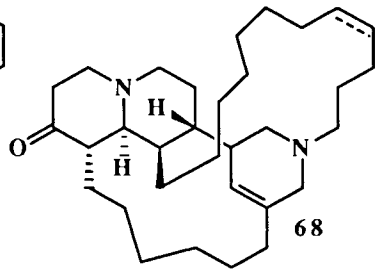


66

A small number of 3-alkylpiperidine alkaloids containing macrocylic structures with a transannular conjoint linkage between two piperidine rings have been reported. The simplest of these is halicyclamine A (**65**) isolated from a *Haliclona* sp. collected in Biak, Indonsesia [42]. Interest in the *Haliclona* sp. had been stimulated by the observation that its crude extracts inhibited the enzyme target inosine monophosphate dehydrogenase (IMPDH) at a concentration of 1 μg/ml. The relative configurations at C3 and C19 in halicyclamine A (**65**) were based on a proposed biogenesis from an ingenamine-type precursor (See Section 3).



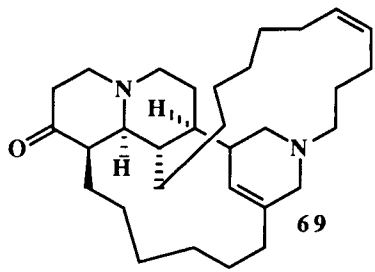
67



68

The sponge *Reniera sarai* collected in the Bay of Naples, Italy yielded saraines-1 (**66**), -2 (**67**) and -3 (**68**) along with the stereoisomers isosaraines-1 (**69**), -2 (**70**) and -3 (**71**) [43, 44, 45,46,47]. Work on the *R. sarai* alkaloids was first initiated in the 1970's; however, the complexity of their ^{1}H NMR spectra coupled with the unavailability of crystals suitable for X-ray diffraction analysis stalled their structure elucidations until the mid to late 1980's. By that time, 2D NMR experiments conducted on high field NMR spectrometers were finally equal to the extreme challenge of solving the saraine structures. The saraines and isosaraines, which can be viewed as hybrids of the petrosins and halicyclamine A, all contain a quinolizadine system

linked via a single transannular bond to a piperidine ring. Saraines-1 (**66**) to -3 (**68**) were shown to be moderately cytotoxic in brine shrimp and fertilized sea urchin egg bioassays [47].



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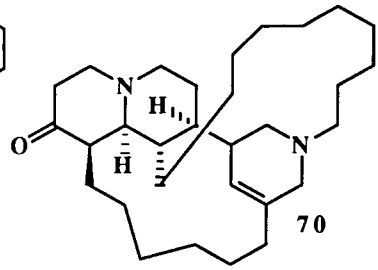

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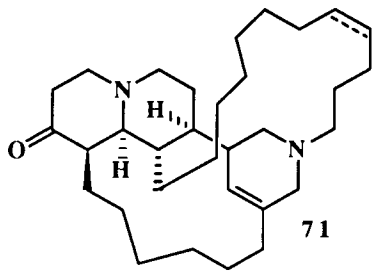
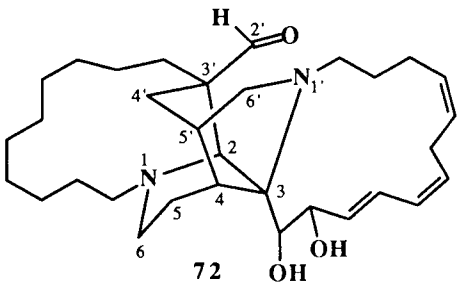


71

2.6) Condensed *Bis*-3-Alkylpiperidines with Unrearranged Skeletons



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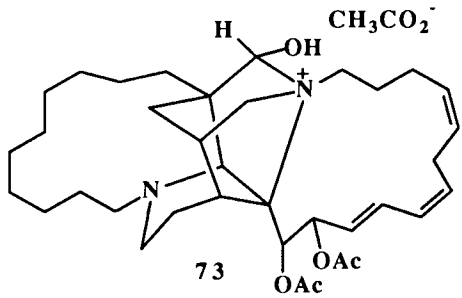
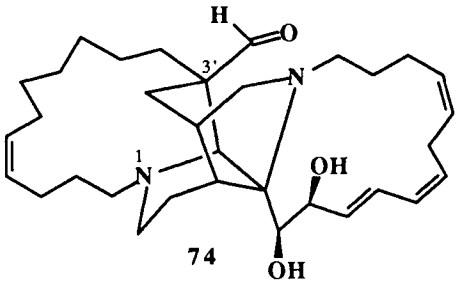


73

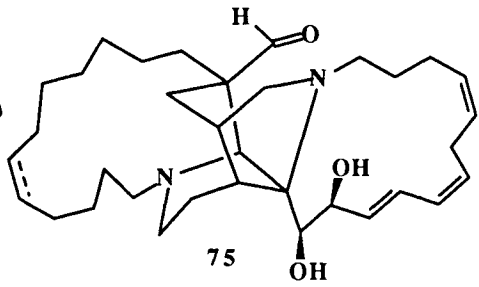
Two groups of complex polycyclic 3-alkylpiperidine alkaloids have tricyclic or tetracyclic core structures resulting from the formation of two or three transannular bonds between the two piperidine rings of a *bis*-3-alkylpiperidine macrocycle. Saraine A (**72**), the

first compound of this type to be characterized, was isolated from the same Bay of Naples *Reniera sarai* sample that was the source of the saraines-1 (**66**) to -3 (**68**) and isosaraines-1 (**69**) to -3 (**71**) [48,49]. The spectroscopic data obtained for saraine A (**72**) was very complex and it contained a number of pieces of conflicting information that prevented a structure elucidation based on spectroscopic evidence alone. For example, the IR spectrum of saraine A contained a strong band at 1660 cm^{-1}, apparently attributable to a carbonyl functionality, but the ^{13}C NMR spectrum was completely devoid of signals in the region of δ 150 to 220 ppm. Fortunately, a diacetylated derivative **73** of saraine A gave crystals that were suitable for X-ray diffraction analysis.

The X-ray analysis provided a structure for the diacetate **73** of saraine A but it did not completely resolve the difficulties in interpreting the spectroscopic data originally obtained for both the natural product **72** and the diacetate **73**. A detailed NMR study of saraine A (**72**), undertaken after the X-ray structure of its diacetate **73** was in hand, ultimately led to an adequate rationalization for its unusual spectroscopic behavior. As a result of the NMR study, a strong "proximity" effect between the tertiary amine at N1' and an aldehyde functionality at C2' in saraine A (**72**) was postulated. Similar "proximity" effects had been previously observed in studies of cyclic amino ketones and they had been found to lead to strong modifications of the spectroscopic features of both the carbonyl and amino functionalities [50]. In general, a strong "proximity" effect results in a significant decrease in the carbonyl IR stretching frequency and treatment with acid favors the formation of a C-N transannular bond and a hydroxyl group, leading to a complete loss of the carbonyl stretching band in the infrared spectrum. The carbonyl stretching frequency observed at 1660 cm^{-1} in the IR spectrum of saraine A (**72**) was significantly lower than the value expected for an aliphatic aldehyde and the band disappeared completely when **72** was treated with HCl. NMR spectra recorded on an equimolar mixture of saraine A (**72**) and CD_3CO_2D showed a new proton signal at δ 5.23 ppm that was correlated in a HETCOR experiment with a new carbon resonance at δ 98.0 ppm. These signals were assigned to a methine carbon (C2') attached to a quaternary nitrogen and a hydroxyl group as shown in structure **73**.

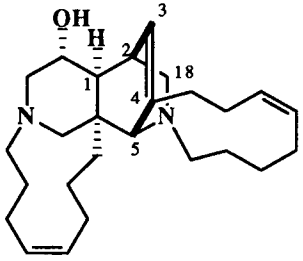


74

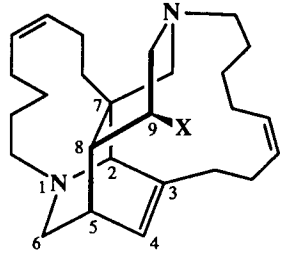


75

Saraines B (**74**) and C (**75**) differed from saraine A (**72**) in the length and degree of unsaturation of the N1 to C3' alkyl bridge [47]. Saraine A (**72**) had a ten carbon fully saturated bridge, saraine B (**74**) had an eleven carbon monoolefinic bridge and saraine C (**75**) had a twelve carbon monoolefinic bridge. Saraines A (**72**) to C (**75**) were found to be cytotoxic in brine shrimp and fertilized sea urchin egg bioassays.



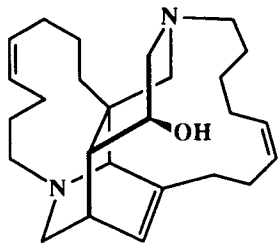
76



77 X = OH

78 X = H

Xestocyclamine A isolated from a *Xestospongia* sp. collected in the Milne Bay region of Papua New Guinea was the first member of the second group of condensed *bis*-3-alkylpiperidines with unrearranged skeletons to be reported [51]. The proposed structure **76** assigned to xestocyclamine A was based on extensive analysis of 2D NMR data. The authors suggested that the biogenesis of the unprecedented pentacyclic skeleton of xestocylamine A involved an intermolecular [4 + 2] cycloadditon reaction between two monomeric 3-alkyldehydropiperidine macrocycles. Xestocyclamine A was found to be a moderately active inhibitor of PKC ε (IC_{50} 4 μg/ml).



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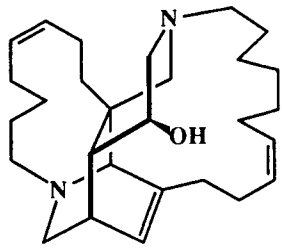

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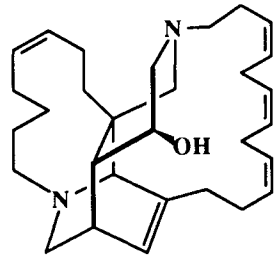
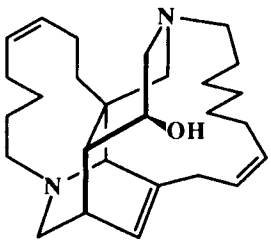


81 X = OH

82 X = H

Shortly after the structure of xesocyclamine A appeared, Kong *et al.* reported that ingenamine (**77**) had been isolated from the Papua New Guinea sponge *Xestospongia ingens* [52]. The pentacyclic skeleton of ingenamine (**77**) was isomeric with the proposed skeleton for xestocyclamine A (**76**). The authors suggested that the biogenesis of ingenamine involved an intramolecular [4 + 2] cycloaddition reaction between two dehydropiperidine rings in a *bis*-3-alkylpiperidine macrocyclic precursor (See Section 3). Ingenamine (**77**) showed *in vitro* cytotoxicity against murine leukemia P388 (IC_{50} 1 μg/ml). The structure of keramaphidin B (**78**), isolated from an *Amphimedon* sp. collected off the Kerma Islands, Okinawa, Japan, was solved by single crystal X-ray diffraction analysis [53]. Keramaphidin B (**78**), which differs from ingenamine (**77**) only by the absence of the hydroxyl group, was reported to exhibit *in vitro* cytotoxicity against murine leukemia P388 (IC_{50} 0.28 μg/ml) and human epidermal KB cancer cells (IC_{50} 0.3 μg/ml). The structure **76** originally proposed for xestocyclamine A was subsequently shown to be incorrect and the structure was revised to **79** [54], which has the same pentacyclic skeleton as ingenamine (**77**) and keramaphidin B (**78**).



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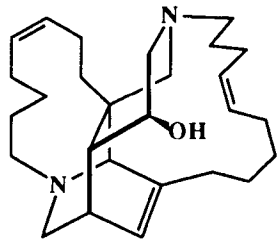

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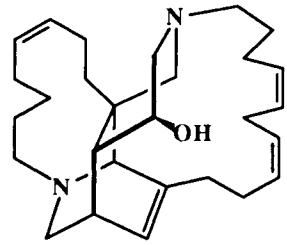
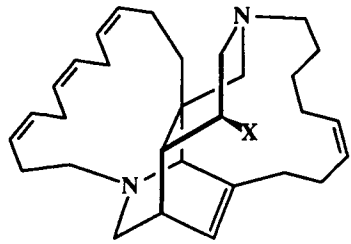


85

86 X = OH

87 X = H

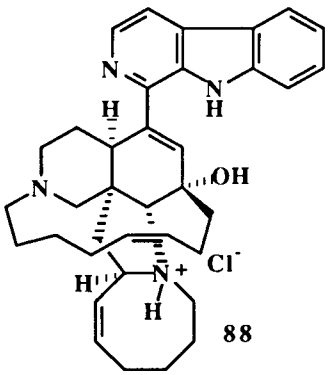


A number of additional ingenamine-type alkaloids have been reported. Xestocyclamine B (**80**) was isolated from the same *Xestospongia* sp. that was the source of xestocyclamine A (**74**) [54]. *Xestospongia ingens* yielded ingamines A (**81**) and B (**82**), ingenamines B (**83**), C

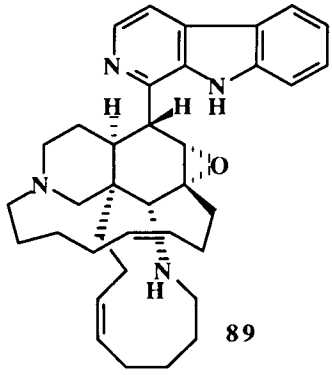
(**84**), D (**85**), E (**86**) and F (**87**), xestocyclamine B (**83**) and keramaphidin B (**78**) [55,56]. Mosher ester methodology was used to determine the absolute configurations of the samples of ingenamine (**77**), ingamine A (**81**) and ingenamine E (**86**) isolated from *Xestospongia ingens* [56]. All three were found to have the 2R, 5S, 7S, 8R, 9S configurations shown. The keramaphidin B (**78**) isolated from *Xestospongia ingens* was found to be optically active in contrast to the keramaphidin B (**78**) isolated from *Amphimedon* sp. that was reported to be a naturally occurring racemate [53].

2.7) Condensed *Bis*-3-Alkylpiperidines with Seco or Rearranged Skeletons

The biogenetic origins of three groups of 3-alkylpiperidine alkaloids from *bis*-3-alkylpiperidine macrocyclic precursors is obscured by rearrangements in the carbon skeletons and hydrolytic cleavages of C-N bonds that are required to convert the macrocyclic precursors to the natural products. As a consequence, it is only possible to find one clearly defined 3-alkylpiperidine residue in the skeletons of these compounds.

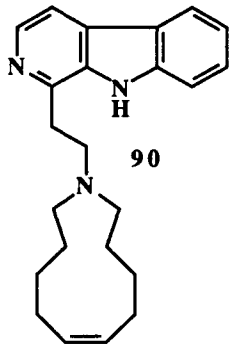


88



89

Manzamine A (**88**), isolated from a *Haliclona* sp. collected off Okinawa, Japan, was the first member of this group of 3-alkylpiperidine alkaloids to be reported [57]. The complexity of manzamine A (**88**) made structure elucidation by spectroscopic and chemical means impractical. Fortunately, manzamine A gave good quality crystals that were subjected to X-ray diffraction analysis to give the structure **88** including the absolute configuration shown. At the time of discovery, the biogenetic origin of manzamine A remained obscure. Subsequently, the appearance of an elegant biogenetic proposal provided a convincing argument that the non-aromatic portion and C10 of the β-carboline fragment of the manzamine skeleton came from a *bis*-3-alkylpiperidine macrocycle via an ingenamine-type intermediate (see Section 3) [58]. Manzamine A (**88**) showed potent *in vitro* cytotoxicity against murine leukemia P388 (IC_{50} 0.07 μg/ml). Further examination of the extracts of the *Haliclona* sp. led to the isolation of



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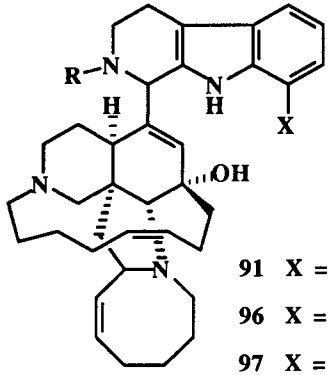
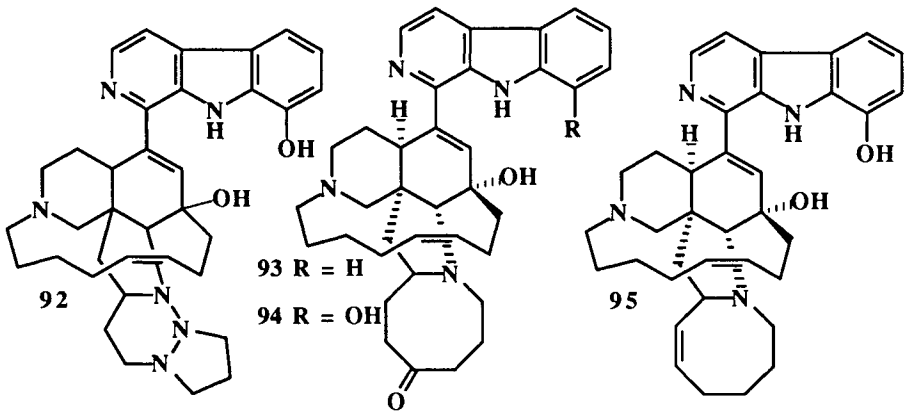


91 X = H, R = H

96 X = OH, R = Me

97 X = OH, R = H

manzamines B (**89**), C (**90**) and D (**91**) [59,60]. The structures of manzamines B (**89**) and C (**90**) were also solved by single crystal X-ray diffraction analysis. Manzamines B (**89**) and C (**90**) both showed *in vitro* cytotoxicity against murine leukemia P388 with IC_{50} values of 6 and 3 μg/ml, respectively.



92

93 R = H

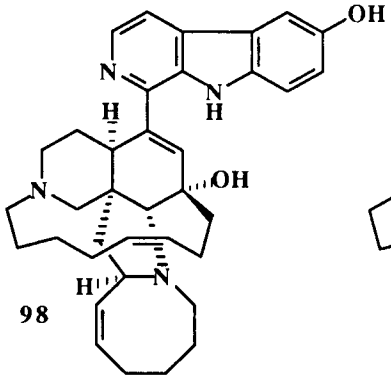
94 R = OH

95

Extracts of an Okinawan sponge identified as a *Pellina* sp. yielded two related β-carboline alkaloids named keramamines A and B [61]. Keramamines A and B were reported to show antimicrobial activity against *Staphylococcus aureus* with MIC values of 6.3 and 25 μg/ml, respectively. The structure of keramamine A, which was solved by single crystal X-ray

diffraction analysis, turned out to be identical with that of manzamine A (**88**). Keramamine B was assigned the structure **92** on the basis of spectroscopic analysis. A *Xestospongia* sp. collected off of Miyako Island, Okinawa was found to contain manzamines E (**93**) and F (**94**) [62]. Spectroscopic comparison of manzamine F (**94**) with the previously reported keramamine B showed that the two compounds were identical, leading to a revision of the structure of keramamine B from **92** to **94**. Manzamines E (**93**) and F (**94**) both exhibited *in vitro* cytotoxicity against murine leukemia P388 with identical IC_{50} values of 5 μg/ml.

The sponge *Pachypellina* sp. collected at Manado Bay, Sulawesi, Indonesia yielded 8-hydroxymanzamine A (**95**) [63]. Compound **95** exhibited *in vitro* antiviral activity against HSV-II (MIC 0.1 μg/ml) and *in vitro* cytotoxicity against human KB (IC_{50} 0.30 μg/ml) and LoVo cells (IC_{50} 0.26 μg/ml), but was inactive *in vitro* against murine leukemia P388. A collection of *Petrosia contignata* obtained at Milne Bay in Papua New Guinea was found to contain 1,2,3,4-tetrahydro-2-*N*-methyl-8-hydroxymanzamine A (**96**) and 1,2,3,4-tetrahydro-8-hydroxymanzamine A (**97**) [64]. The desmethyl compound **97** was also obtained from a specimen of *Cribochalina* sp. collected near Madang, Papua New Guinea [64]. 1,2,3,4-Tetrahydro-2-*N*-methyl-8-hydroxymanzamine A (**96**) was reported to be cytotoxic to murine leukemia P388 *in vitro* with an IC_{50} of 0.8 μg/ml. Kobayashi *et al.* reported the isolation of 6-hydroxymanzamine A (**98**) and 3,4-dihydromanzamine A (**99**) from an *Amphimedon* sp. collected in Okinawa [65]. Both compounds showed antimicrobial activity against the Gram positive bacterium *Sarcina lutea* (MIC: **93** 1.25 μg/ml, **94** 4 μg/ml) and *in vitro* cytotoxicity against murine leukemia L1210 (IC_{50}: **93** 1.5 μg/ml, **94** 0.48 μg/ml) and human epidermal KB cells (IC_{50}: **93** 2.5 μg/ml, **94** 0.61 μg/ml). The same group has reported the isolation of keramaphidin C (**100**) and keramamine C (**101**) from an Okinawan *Amphimedon* sp. [66] and they have suggested that **100** and **101** are plausible biogenetic precursors to manzamine C (**90**).



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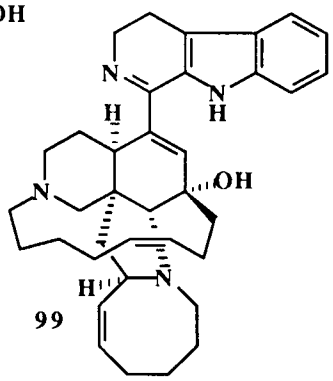

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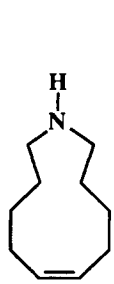

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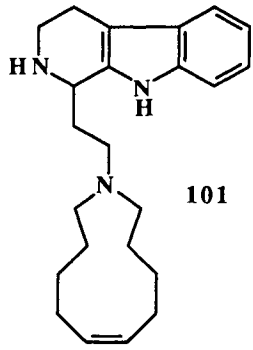
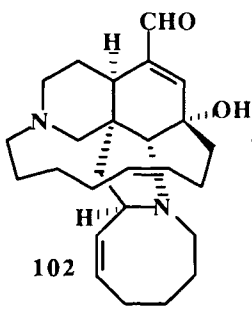


101

An *Ircinia* sp. collected off Kise, Okinawa, Japan yielded ircinals A (**102**) and B (**103**) as well as manzamines A (**88**), B (**89**), D (**91**), H (**104**) and J (**105**) [67]. The structures of ircinal A, ircinal B, manzamine H and manzamine J were proposed on the basis of spectroscopic analysis and confirmed by chemical interconversion with manzamines A (**88**) and B (**89**). Pictet- Spengler cyclization of ircinal A (**102**) with tryptamine in the presence of trifluoroacetic acid gave manzamine D (**91**), which was converted into manzamine A (**88**) by DDQ oxidation. The spectroscopic data and $[\alpha]_D$ of manzamine A (**88**) prepared from ircinal A (**102**) were identical with those of authentic material. Similarly, Pictet-Spengler condensation of tryptamine and ircinal B (**103**) gave manzamine H (**104**) that was converted by DDQ oxidation to manzamine J (**105**). Treatment of manzamine B (**89**) with NaH gave manzamine J (**105**) that was identical in all respects to the material prepared from ircinal B (**103**). The ircinals are probable biosynthetic precursors to the manzamines. Ircinals A (**102**) and B (**103**) exhibited *in vitro* cytoxicity against murine leukemia L1210 with IC_{50} values of 1.4 and 1.9 μg/ml and against human epidermal KB cells with IC_{50} values of 4.8 and 3.5 μg/ml, respectively.



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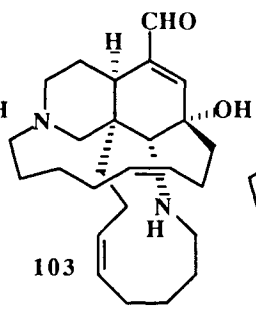

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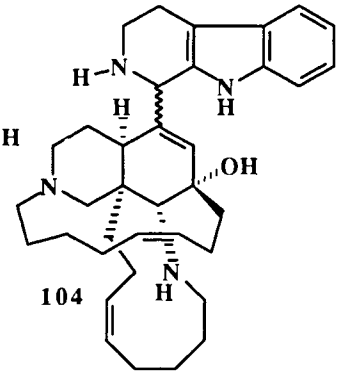

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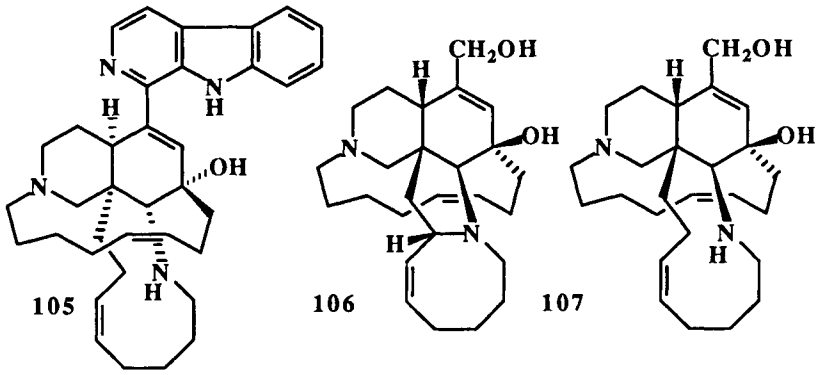
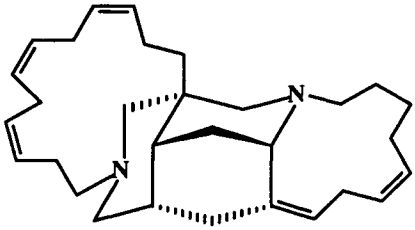


The Okinawan sponge *Amphimedon* sp., collected off the Kerama Islands, yielded manzamines A (**88**), B (**89**) and C (**90**), ircinals A (**102**) and B (**103**) and ircinols A (**106**) and B (**107**) [68]. Spectroscopic analysis showed that the constitution of the ircinols A (**106**) and B (**107**) corresponded with the C1 primary alcohol analogs of the aldehydes ircinal A (**102**) and B (**103**), respectively. Reduction of the co-occurring ircinals A and B with DIBALH gave products that were identical with ircinols A and B by NMR, MS and chromatographic comparisons. However, the optical rotations of ircinols A and B generated by reduction of ircinals A and B had the opposite signs from the optical rotations of the naturally occurring ircinols A and B. Therefore, ircinols A (**106**) and B (**107**) have absolute configurations that are antipodal to those of the manzamines and ircinals that occur in the same sponge, but identical with the configurations to the ingenamine alkaloids (i.e. **77**, **81** and **86**) isolated from *Xestospongia ingens*. Ircinols A (**106**) and B (**107**) exhibited *in vitro* cytotoxicity against murine leukemia L1210 with IC_{50} values of 2.4 and 7.7 μg/ml and against human epidermal KB cells with IC_{50} values of 6.1 and 9.4 μg/ml, respectively; ircinol A (**106**) inhibited endothelin converting enzyme with an IC_{50} of 55 μg/ml.

Madangamines A (**108**), B (**109**), C (**110**), D (**111**) and E (**112**) have been isolated from the same *Xestospongia ingens* specimens collected at Madang in Papua New Guinea that yielded the ingenamines [69,70]. The madangamines are the only 3-alkylpiperidine sponge alkaloids reported to date with rearranged carbon skeletons. The biogenesis of the madangamine skeleton has been suggested to involve rearrangement of an ingenamine-type precursor (See Section 3). Madangamine A (**108**) exhibited *in vitro* cytotoxicity against murine leukemia P388 with an IC_{50} value of 1 μg/ml.



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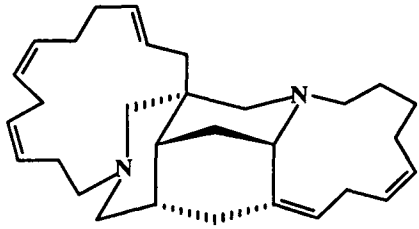

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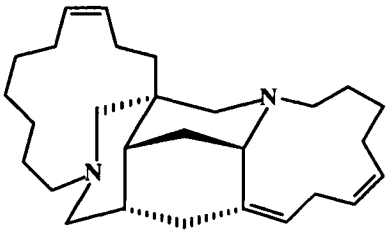

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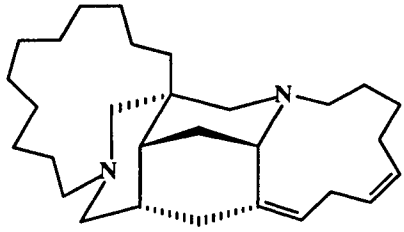

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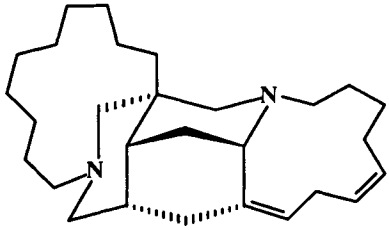

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3. BIOGENETIC PROPOSALS

Cimino and co-workers put forth the first biogenetic proposal for 3-alkylpiperidine alkaloids obtained from marine sponges [46,49]. They suggested that the xestospongins, petrosins and saraines shared a common origin from *bis*-3-alkylpiperidine macrocycles and they indicated that there was likely a biogenetic relationship between the oligomeric halitoxins and the aforementioned macrocyclic alkaloids. The key elements of Cimino's biogenetic hypothesis are shown in Figure 3.1. Subsequently, Kitigawa and co-workers expanded on Cimino's proposal to generate a detailed hypothetical pathway for the formation of the araguspongines, petrosins and aragupetrosine A in the sponge *Xestospongia* sp. [37,38]. The biogenetic origin of manzamines A (**88**) and B (**89**) was not obvious when their structures were first elucidated [57]. An elegant proposal, published some years later by Baldwin and Whitehead, revealed the relationship between the manzamines and the xestospongins, petrosins and saraines [58]. Baldwin and Whitehead's proposal also provided the first suggestion about

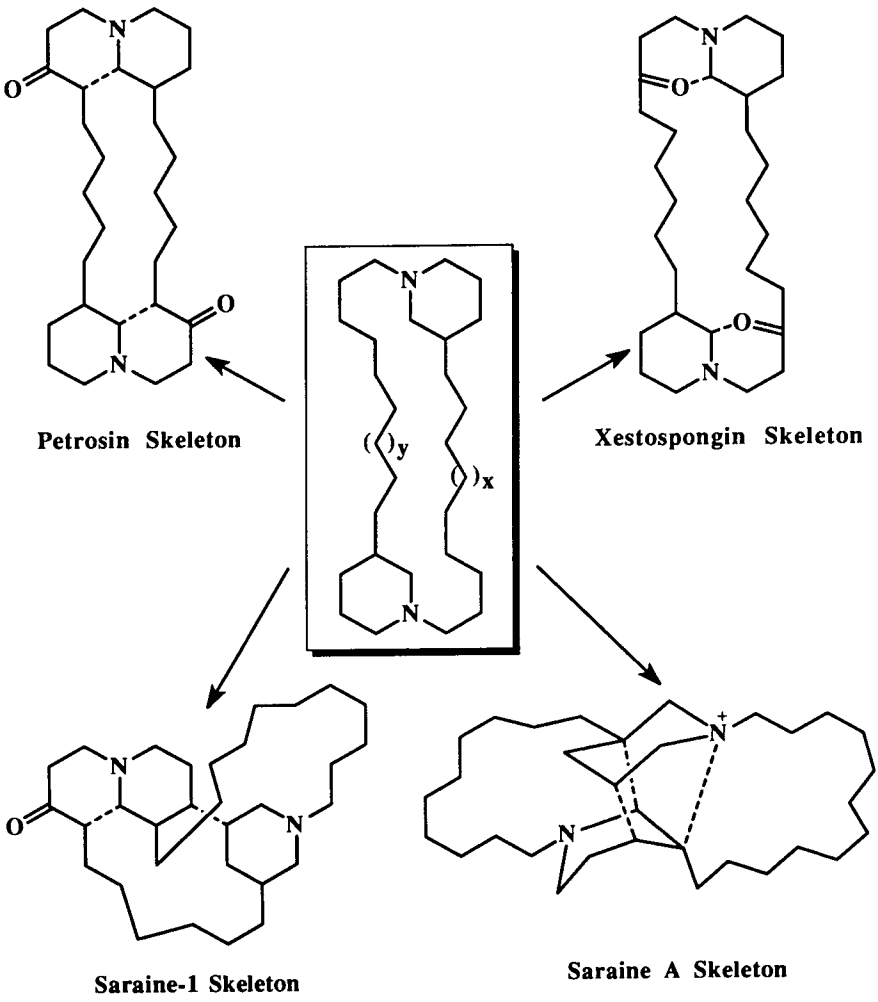


Figure 3.1

Cimino and co-worker's biogenetic proposal for the formation 3-alkylpiperidine alkaloids [46,49].

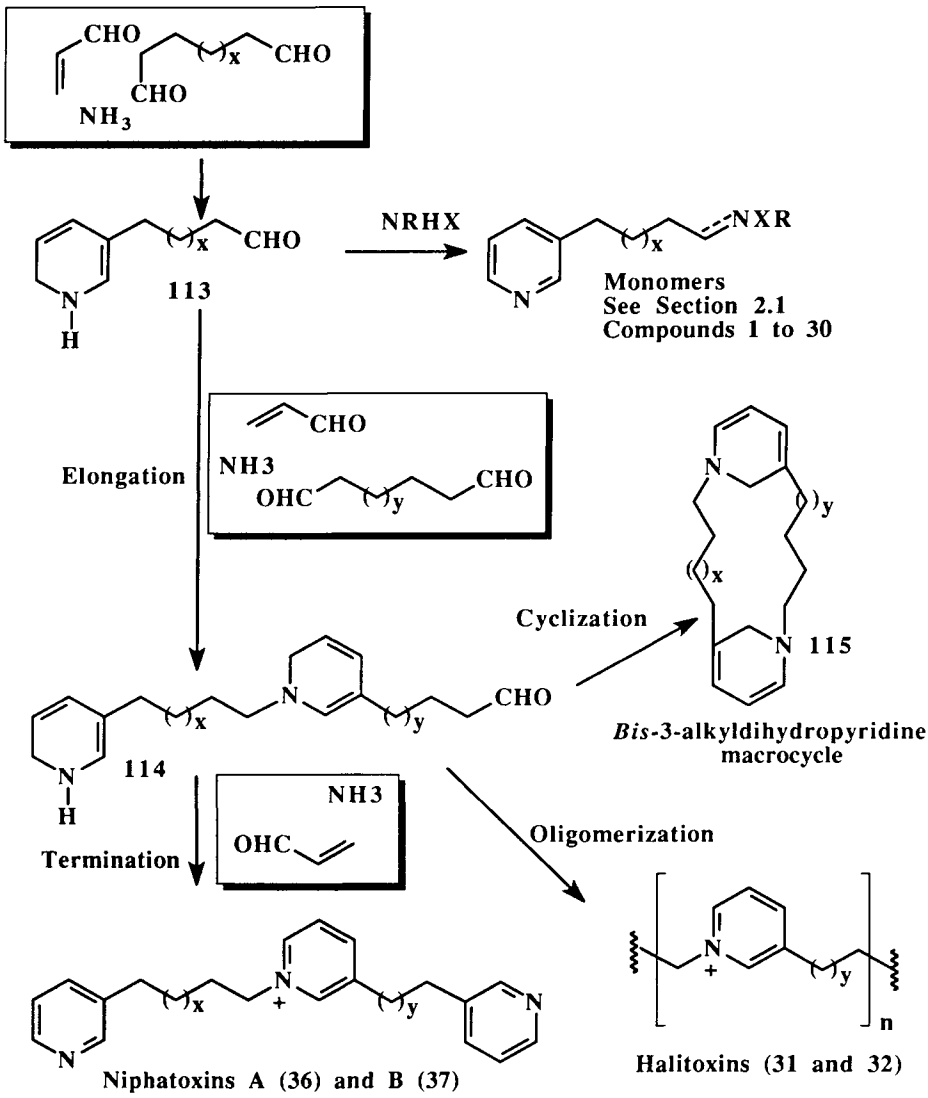


Figure 3.2

A proposed biogenesis for the formation of monomeric, dimeric and oligomeric 3-alkylpiperidine alkaloids. The proposal is based on Baldwin and Whitehead's proposed biogenesis for the manzamines [58].

the biogenetic origin of the piperidine ring atoms and foresaw the occurrence of the ircinal and ingenamine alkaloids. Subsequently, Crews et al., Kong et al., and Gil et al. have used elements of the Baldwin and Whitehead proposal to generate hypothetical pathways to the halicyclamine, saraine A to C, saraine 1-3 and madangamine skeletons [64,69,72].

The basic biogenetic building blocks in the Baldwin and Whitehead proposal [58], as shown in Figure 3.2, consist of ammonia, a three carbon unit represented by propenal and a variable length saturated or unsaturated linear dialdehyde. These three basic building blocks can account for the formation of all of the 3-alkypiperidine alkaloids reported to date and they can also account for the formation of the related alkaloids manzamine C (**90**), keramaphidin C (**100**) and keramamine C (**101**). Reductive coupling of one equivalent of ammonia with one propenal unit and one terminus of the linear dialdehyde gives the dihydropyridine **113** which has a linear alkyl aldehyde attached at the 3 position. Oxidation of the dihydropyridine ring and condensation of the free aldehyde functionality with ammonia, methoxy amine or simple alkyl amines followed by oxidative or reductive transformations of the resulting imine leads directly to the monomeric 3-alkylpiperidines (**1** to **30**) described in Section 2.1. Alternatively, elongation of a nicotinic acid starter unit also represents a reasonable hypothetical route to the monomeric units of the 3-alkylpiperidine alkaloids. Detailed biosynthetic investigations will be required to distinguish between the various hypothetical pathways.

Elongation can occur if the aldehyde functionality in **113** undergoes reductive condensation with ammonia, another equivalent of propenal and one terminus of another dialdehyde chain to give the dimer **114** that has a second dihydropyridine ring. Multiple repetitions of the elongation sequence are necessary to generate the halitoxins **31** and **32**. Ultimately the oligomerization has to be terminated.

Three types of termination reactions are illustrated by the pathways in Figure 3.2. Reaction of the terminal aldehyde functionality with an NHRX group as in the formation of the monomers described in section 2.1 represents one type of termination. Cyclization involving condensation of the terminal aldehyde functionality at one end of the oligomer and the amino nitrogen in the dihydropyridine ring on the other terminus of the oligomer as illustrated in the formation of the *bis*-3-alkylpiperidine macrocycle **115** in Figure 3.2 represents a second type of termination reaction. The niphatoxins A (**36**) and B (**37**) provide an example of a third type of termination reaction that involves condensation of the aldehyde and the α carbon in the dimer **114** in an alternate manner with ammonia and a propenal unit to generate a terminal pyridine ring as shown. Structural studies carried out to date on the halitoxins have failed to unambiguously demonstrate whether the large oligomers are macrocyclic or linear [25,28]. Comparison with synthetic macrocyclic oligomers has shown that the natural materials are octamers or larger [28]. Given that each monomeric unit has at least an eight carbon alkyl substituent and three ring atoms involved in the growing oligomeric skeleton, a macrocyclic octamer would have a 88 membered ring. While perhaps not impossible, the formation of such a large macrocycle seems unlikely. Therefore, it might be reasonable to assume that the higher

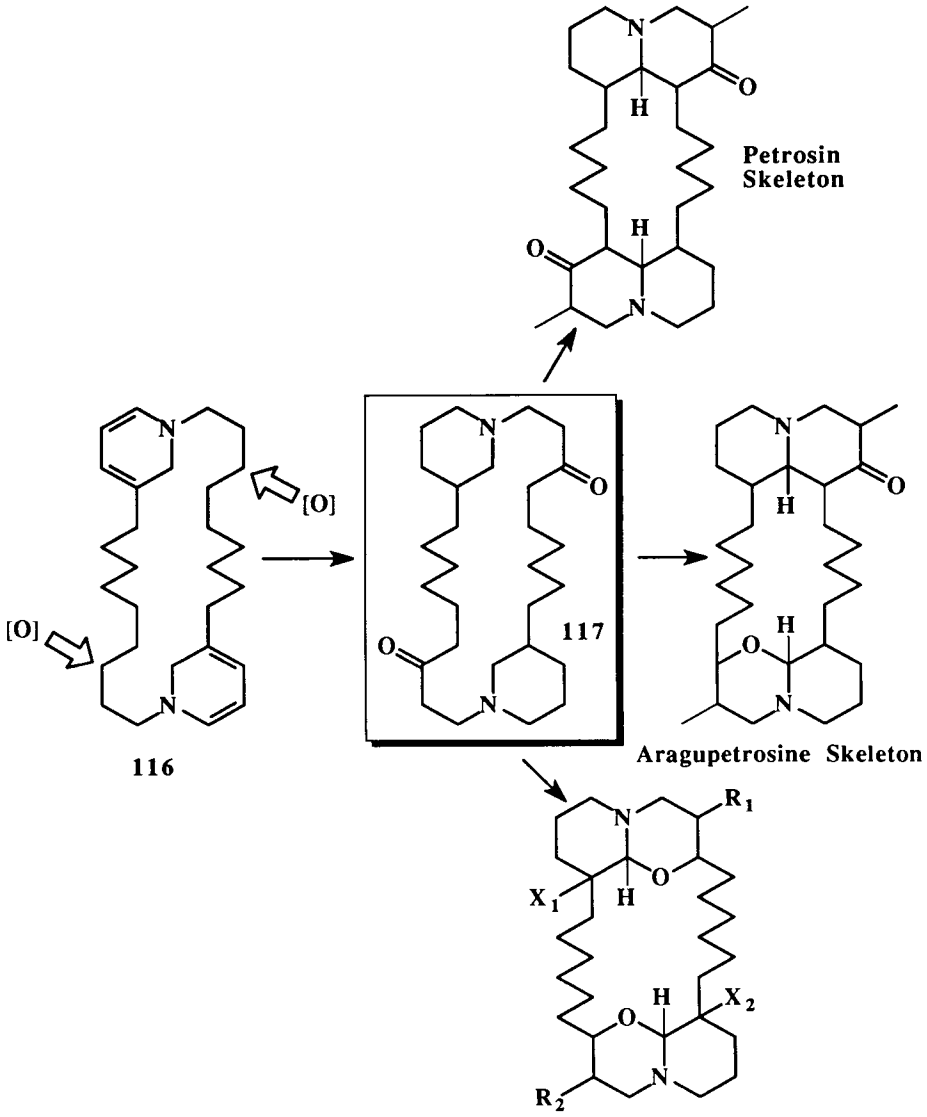


Figure 3.3

Cimino and Kitagawa's proposals for formation of the petrosin, aragupetrosine and xestospongin/araguspongine skeletons [37, 38, 46, 49].

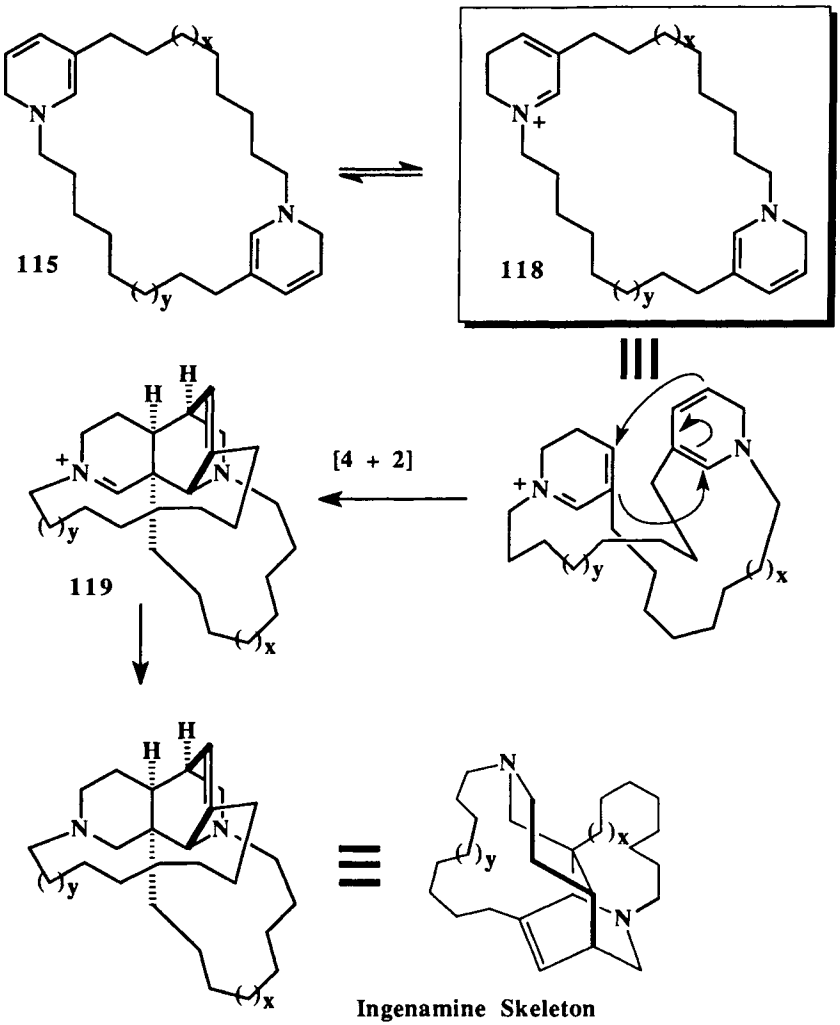


Figure 3.4

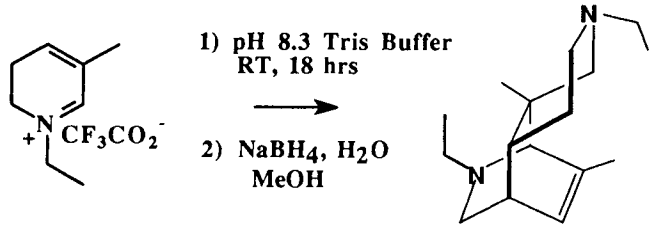
Proposed biogenesis for the ingenamine skeleton. Based on the Baldwin and Whitehead's proposed biogenesis for the manzamines [52, 58].

molecular weight halitoxins are linear and that they terminate in monoalkylated pyridine rings as found in the niphatoxins or in simple amino functionalities as found in the monomers described in section 2.1.

The generalized *bis*-3-alkyldihydropyridine macrocyclic structure **115** in Figure 3.2 represents a common element in the biogenesis of all the remaining 3-alkylpiperidine alkaloids. Oxidation of the dihydropyridine rings in a macrocycle containing the appropriate linear alkyl bridges leads to the cyclostellettamines (**38-43**) while reduction of the dihydropyridine rings in an appropriate macrocycle leads to the haliclamines (**44, 45**). Two C_{11} dialdehyde components are required for the biogenesis of a hypothetical macrocyclic precursor **116** to the xestospongins, petrosins, araguspongines and aragupetrosine A (Figure 3.3). Oxidation of the alkyl chains to give the diketo-macrocycle **117** followed by carbocyclic or heterocyclic ring formation can generate either the quinolizadine or the 1-oxaquinolizadine ring systems found in the petrosins, xestospongins, araguspongines and aragupetrosines as proposed by Cimino and Kitagawa (Figure 3.3) [46,49,38]. Secondary transformations involving methylation and hydroxylation are common in the biosynthesis of the petrosins, xestospongins and araguspongines.

The Baldwin and Whitehead proposed biogenesis for the manzamine alkaloids (Figure 3.4) [58] suggested that the pentacyclic skeleton **119** of the ingenamine alkaloids arises from a biological intramolecular [4 + 2] cycloaddition reaction between the tautomeric forms of the two dihydropyridine rings in a *bis*-3-alkyldihydropyridine macrocycle **118**. The full connectivity and relative stereochemistries observed in the ingenamine alkaloids follows from the expected *endo* and regiochemical preferences of the [4 + 2] cycloaddition reaction.

As part of a biomimetic approach to the synthesis of the manzamine alkaloids, Baldwin et al. found that treatment of model compound **120** in pH buffer 8.3 for 18 h followed by reduction with excess sodium borohydride gave the adduct **121** in low yield (Figure 3.5) [71].



120 121

Figure 3.5

A model reaction carried out by Baldwin and coworkers as part of a biomimetic synthesis of the manzamine alkaloids [71]. This reaction generates the tricyclic core of the ingenamine alkaloids.

The adduct **121** was presumed to arise from a cycloaddition reaction between the iminium ion **120** and its 1,6-dihyropyridine tautomer. Adduct **121** has the same regiochemistry and relative stereochemistry as the naturally occurring ingenamine alkaloids.

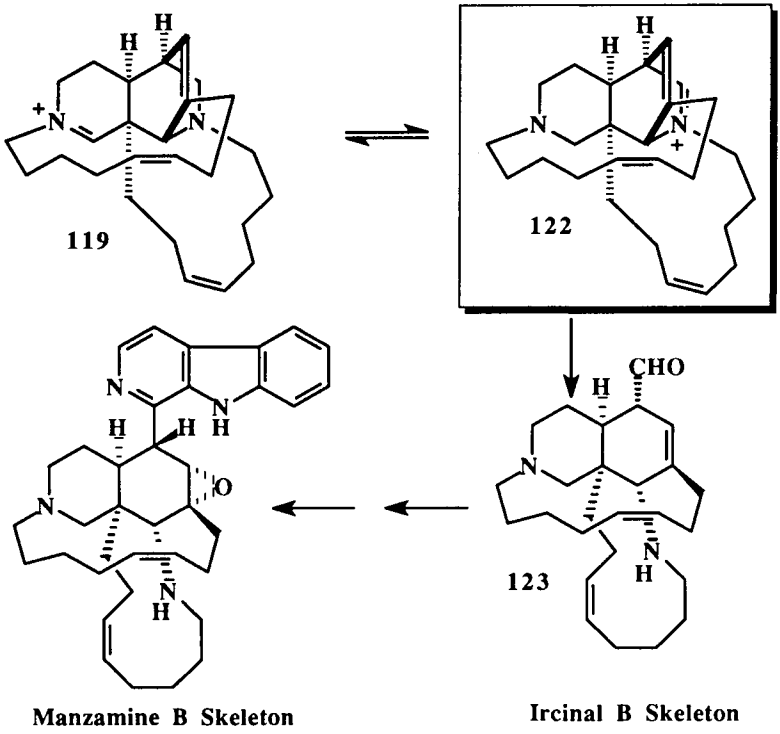


Figure 3.6

Baldwin and Whitehead's proposal for the conversion of their pentacyclic (ingenamine type) intermediate into the manzamine B skeleton [58].

The Baldwin and Whitehead proposal [58] went on to suggest that the initial [4 + 2] adduct **119** can undergo redox exchange to give the pentacyclic intermediate **122** shown in Figure 3.6. Hydrolysis of the iminium ion functionality in **122** leads to a tetracyclic seco-skeleton containing an aldehyde functionality. The skeleton and aldehyde functionality present in the Baldwin and Whitehead tetracyclic intermediate **123** correspond exactly with the skeleton and aldehyde functional group placement in ircinals A (**102**) and B (**103**). Finally,

they proposed that condensation of the ircinal-type intermediate **123** with tryptamine and oxidation of the resulting product would lead directly to the skeleton of manzamine B (**89**).

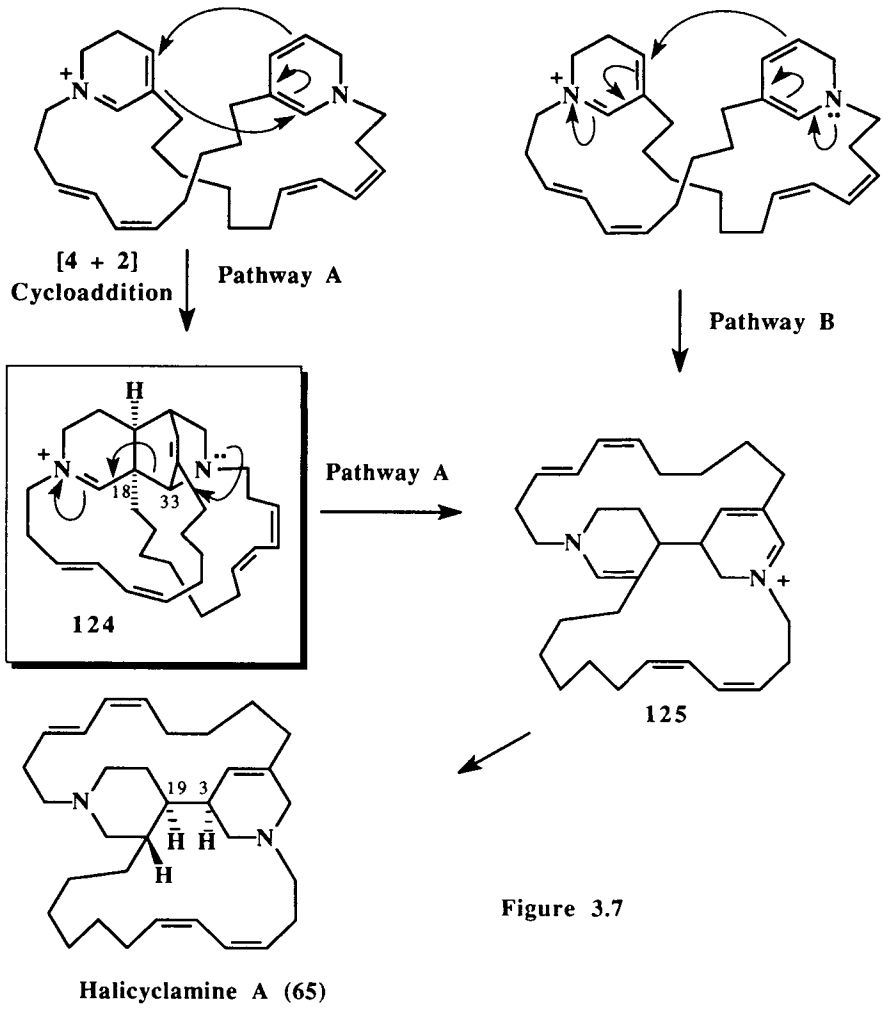


Figure 3.7

Proposed biogenesis for halicyclamine A (**65**) (Pathway A) [42]. Pathway B represents an alternative biogenetic pathway to **65**.

Ingenamine-type intermediates have been proposed as on the biogenetic pathways to both halicyclamine A and the madangamines. Jaspers et al. suggested that cleavage of the C18-C33 bond in the ingenamine-type intermediate **124** formed via pathway A in Figure 3.7 could

lead directly to the halicyclamine skeleton [42]. This biogenetic hypothesis was used to assign the relative stereochemistry at C3 and C19 in halicyclamine A (**65**). Alternatively, it would appear that formation of a single transannular bond between the two pipridine rings of a *bis*-3-alkyldihydropyridine macrocycle could perhaps occur directly via pathway B as shown in Figure 3.7 to give the halicyclamine skeleton [72].

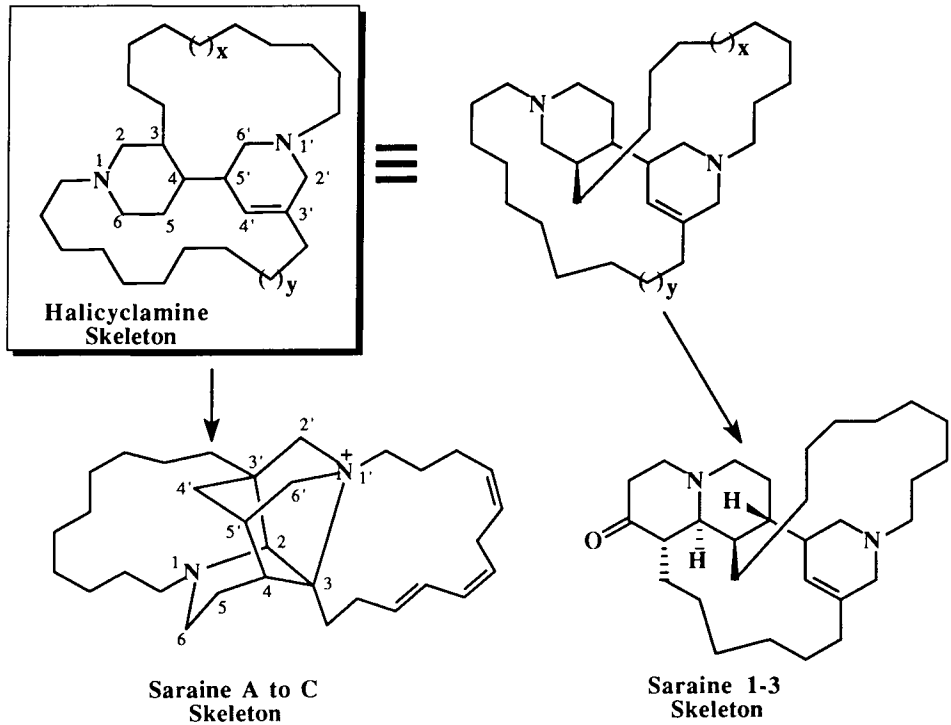


Figure 3.8

A proposed biogenetic relationship between the saraine A to C and saraine 1-3 skeletons and a putative halicyclamine precursor [64].

One additional cyclization to form a quinolizadine ring system transforms a halicyclamine-type intermediate into the saraine-1 (**66**) to -3 (**68**) skeleton as shown in Figure 3.8 [64]. Examination of the saraine A skeleton reveals that disconnection of the C2-C3' and C3-N1' bonds in saraine A generates a halicyclamine skeleton. Crews et al. have proposed that the biogenesis of saraines A to C proceeds through a halicyclamine-type intermediate [64]. Gil et al. have suggested that the sequence of steps outlined in Figure 3.9 might be involved in the

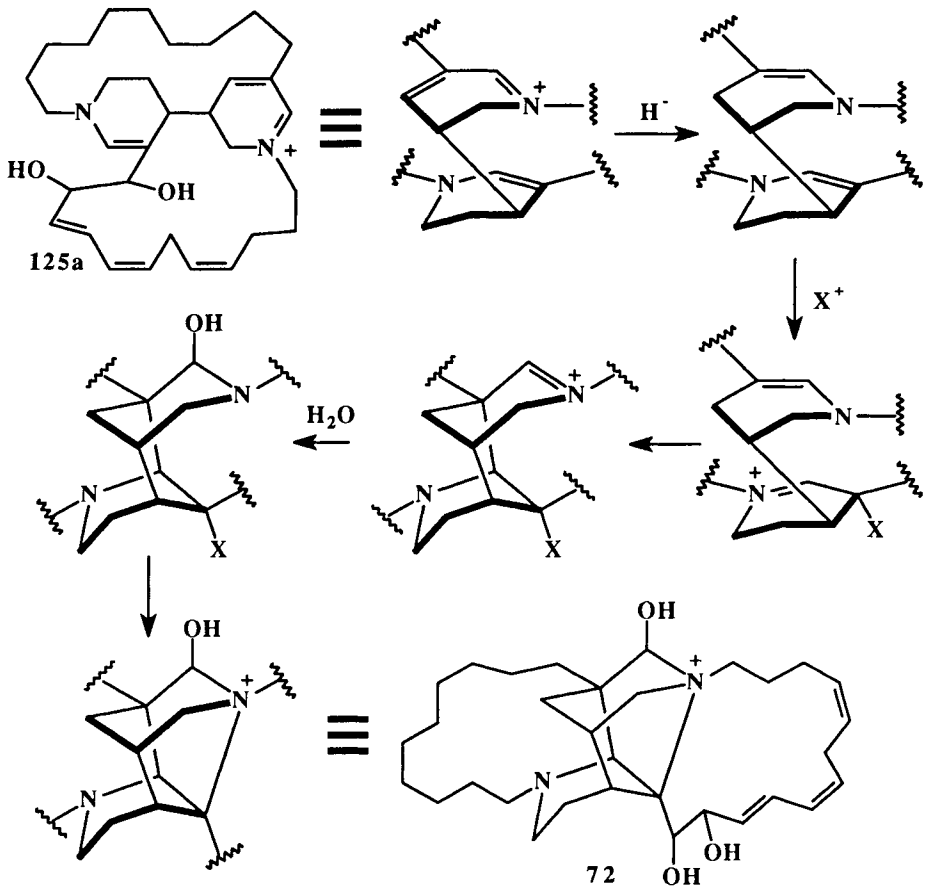


Figure 3.9

Proposed steps in the biogenetic conversion of a halicyclamine-type intermediate **125a** into saraine A (**72**) [72].

conversion of a halicyclamine precursor **125a** to saraine A (**72**) [72].

Rearrangement of the ingenamine-type intermediate **126**, as shown in Figure 3.10, can lead to the madangamine skeleton [69]. The madangamines are the only examples to date of 3-alkylpiperidine alkaloids with rearranged carbon skeletons.

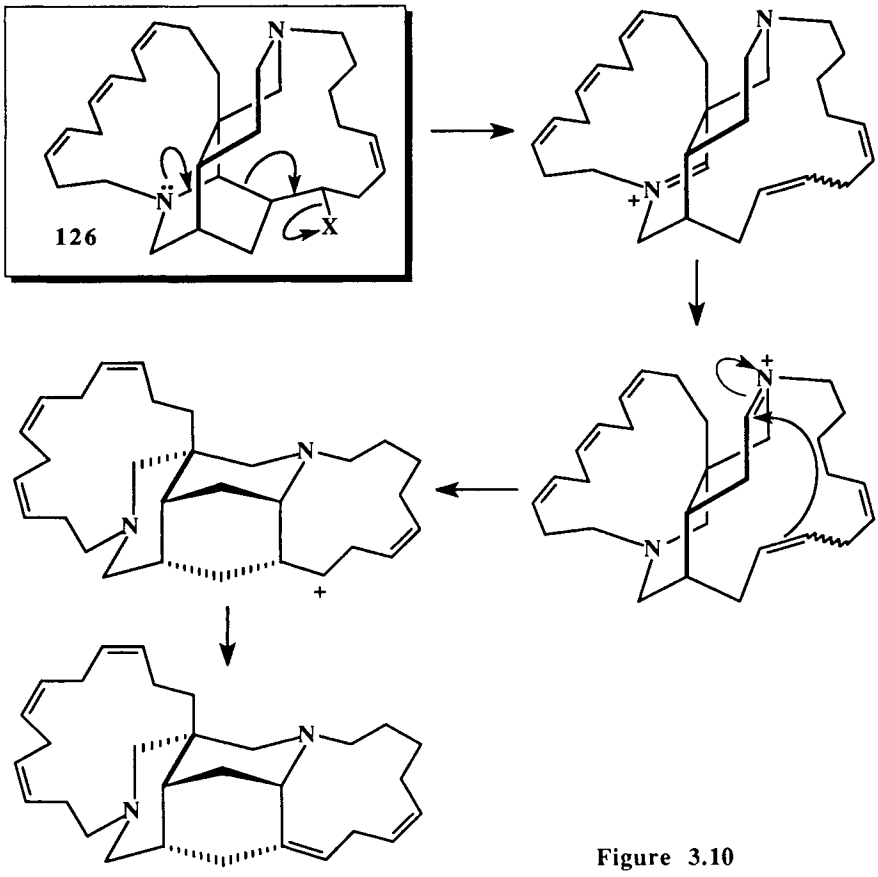


Figure 3.10

A proposed biogenesis for the madangamine skeleton [69].

As outlined above, the Baldwin and Whitehead proposal for the biogenesis of the manzamines has provided a mechanistic framework that can be used to formulate rather detailed step by step hypotheses for the formation of all known 3-alkylpiperidine alkaloids. Figure 3.11 shows an overall scheme for the biogenesis of the 3-alkylpiperidine alkaloids that incorporates elements of all of the individual proposals that have been put forth to date.

Manzamine C (**90**) contains a skeleton in which similar building blocks (C_3 and C_{10}) appear to have been assembled in a manner different from that which leads to the 3-

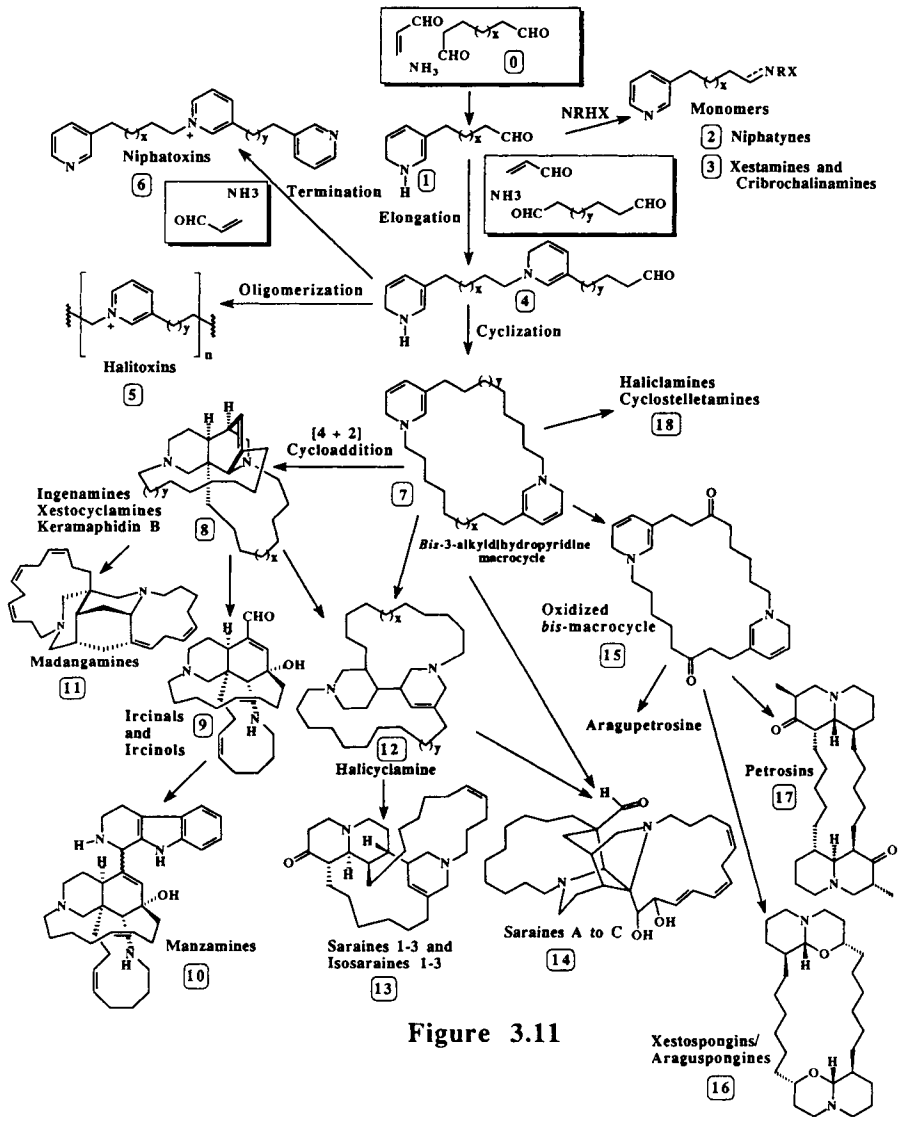


Figure 3.11

An overall biogenetic scheme for the 3-alkylpiperidine alkaloids isolated from sponges in the order Haplosclerida. The numbers indicate molecular structures used as 'character states' in the phylogenetic analysis based on molecule types presented in section 4.3.

alkylpiperidine alkaloids (Figure 3.12). Therefore, manzamine C (**90**) might be viewed as a prototype of a parallel group of alkaloids from sponges in the order Haplosclerida that are assembled from the same basic building blocks found in the alkaloids featured in this chapter but which lack the 3-alkylpiperidine motif.

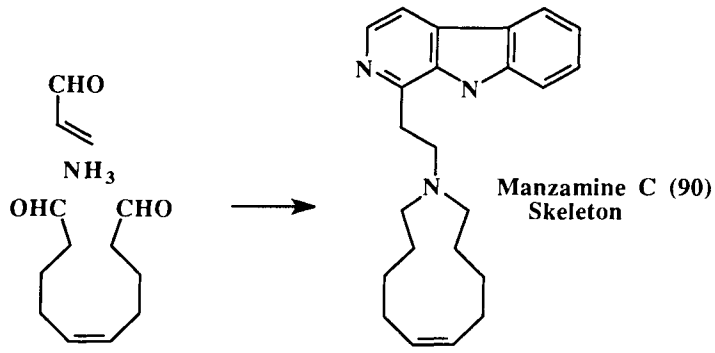


Figure 3.12

Proposed biogenesis for the manzamine C (**90**) skeleton [64].

One interesting feature of the 3-alkylpiperidine alkaloids reported to date is that many of them have been isolated as naturally occurring racemates or unequal mixtures of enantiomers and others that appear to be produced by the same biogenetic manifold have opposite absolute configurations. An Okinawan *Xestospongia* sp. yielded araguspongine B (**64**) and petrosin (**46**) as racemic mixtures, araguspongine D (**49**) as a 3:7 mixture of (+) and (-) enantiomers, araguspongine E (**51**) as a 3:2 mixture of (+) and (-) enantiomers and araguspongines F (**57**), G (**58**), H (**59**), J (**60**) and aragupetrosine A (**61**) as single enantiomers [37,38]. Kitigawa and Kobayashi have suggested that "the fact that araguspongines F, G, H, and J were obtained as single enantiomers while the related compounds were obtained as enantiomeric mixtures or meso compounds may be explained by presuming enantio-selective oxidation or methylation occurs at C9 or C3 prior to or after formation of intermediary 1-oxaquinolizadine moieties" [37].

A comparison of the absolute configurations reported for manzamines A (**88**) and B (**89**), ircinals A (**102**) and B (**103**), ircinols A (**106**) and B (**107**), ingenamine (**77**), ingamine A (**81**), ingenamine E (**86**) and keramaphidin B (**78**) shows that although all of these alkaloids appear to be formed by the same biogenetic pathway passing through an ingenamine-type intermediate (Figures 3.4 and 3.6), they do not all have the same absolute configurations. Manzamines A and B, ircinals A and B and one enantiomer of the racemic keramaphidin B

belong to one configurational series. Ingenamine, ingamine A, ingenamine E, ircinols A and B and the other enantiomer of keramaphidin B belong to the other configurational series. According to the Baldwin and Whitehead proposal [58], the chirality of these alkaloids is established by the biological equivalent of an intramolecular [4 + 2] cycloaddition reaction of an achiral *bis*-3-alkyldihydropyridine macrocycle (Figure 3.4). Therefore, it appears that there are enantiomeric enzymes capable of catalyzing this intramolecular condensation.

4. PHYLOGENETIC DISTRIBUTION

4.1) Limited Distribution of 3-Alkylpiperidine Derivatives

With the exception of four records, the above described compounds were all found in sponges belonging to the order Haplosclerida sensu lato (s.l.) (orders Haplosclerida sensu stricto (s.s.) and Nepheliospongida/Petrosida as used by various authors). The exceptions are:

- ikamines in an unidentified sponge
- theonelladins in *Theonella swinhoei*
- cyclostellettamines in *Stelletta maxima*
- ircinols and ircinals in *Ircinia* spec.

The first of these is assumed to have been a Haplosclerida s.l.; this remains somewhat uncertain since the existence of a voucher was not mentioned in the paper. The other three sponges are phylogenetically distant from Haplosclerida s.l. and moreover unrelated among themselves: *Theonella* belongs to the lithistid order Desmophorida, *Stelletta* to the tetractinellid order Astrophorida, and *Ircinia* to the keratose order Dictyoceratida. Of the four possible explanations for the distribution of related compounds in Haplosclerida s.l. and these three others, viz. independently developed, microsymbiont origin, wrong identification, or mixed samples, the latter possibility is the most likely. Independent development of these structurally complex and biogenetically related molecules in four independent evolutionary lines is an unlikely assumption. There is no evidence that the three sponges share a similar microsymbiont with the genera and species of Haplosclerida s.l. containing the 3-alkylpiperidine derivatives. The sponges were identified (see Table 4.1) by reliable sponge taxonomists.

In support of the fourth possibility is the fact that all three non-Haplosclerida s.l. sponges are big sponges with an irregular, often encrusted surface. They typically are covered by many epibiotic organisms (algae, hydroids, bryozoans, tunicates and other sponges), and it is quite likely that the specimens had a cover of some haplosclerid species. In fact, one of the specimens, the *Stelletta maxima*, identified by one of us (RvS) after reexamination of the voucher was indeed found to be encrusted by an orange *Haliclona* spec. We are satisfied that Haplosclerida s.l. species are exclusively responsible for the biosynthesis of the 3-alkypiperidine derivatives.

TABLE 4.1

Authorities for identification of the various sponges containing 3-alkypiperidine alkaloids. Unreliable or improbable identifications are indicated by a "?" in the family assignment column, and ignored in the phylogenetic analysis.

compound type	sponge species	authority	comment	family
MONOMERS				
niphatynes A(**1**) - B(**2**)	Niphates spec. [17]	Diaz	OK	Niphatidae
niphatesines A(**3**) - H(**10**), ikimine A(**11**)	Niphates spec. [18,19]	Nagahama	?	?
ikimines A(**11**) - D(**14**)	unidentified [20]	unknown	?	?
theonelladins A(**17**) - D(**20**)	Theonella swinhoei [21]	Bergquist	OK *	?
xestamines A(**21**) - C(**23**)	Xestospongia wiedenmayeri [22]	Pomponi	genus OK	Petrosiidae
cribrochalinamine oxides A(**24**) - B(**25**)	Cribrochalina spec. [23]	Bergquist	?Petrosia	?Petrosiidae
xestamines A(**21**), B(**22**), D(**26**) - H(**30**)	Calyx podatypa [24]	Van Soest	OK	Phloeodictyidae
OLIGOMERS				
halitoxins (**31**)	Haliclona rubens [25,26,27]	not given	= Amphimedon	Niphatidae
	Haliclona viridis	not given	= Amphimedon	Niphatidae
	Haliclona erina	not given	= Amphimedon	Niphatidae
	Haliclona spec.	not given	?	?
halitoxin (**32**)	Callyspongia fibrosa [28]	Van Soest	OK	Callyspongiidae
niphatoxins A (**36**) - B (**37**)	Niphates spec. [29]	Ilan	OK	Niphatidae
***BIS*-MACROCYCLES**				
cyclostellettamines A(**38**) - F(**43**)	Stelletta maxima [30]	Van Soest	= Haliclona sp.	Chalinidae
haliclamines A(**44**) - B(**45**)	Haliclona spec. [31]	Watanabe	OK	Chalinidae
***BIS*-QUINOLIZADINES etc.**				
petrosin (**46**), A(**47**) - B(**48**)	Petrosia seriata [32,33,34]	Thomas	genus OK	Petrosiidae

Table 4.1 (cont.)

xestospongins A(**49**) - D (**52**)	Xestospongia exigua [35]	not given	?	?
araguspongines A(**53**) - J(**60**)	Xestospongia spec. [36,37]	Lévi	OK	Petrosiidae
petrosin (**46**), petrosin A(**47**), aragupetrosine A(**61**), araguspongines A(**53**) - J(**60**)	Xestospongia spec. [38]	Bergquist	OK	Petrosiidae
xestospongins B(**50**) & D (**52**), araguspongine F(**57**), demethylxestospongin B(**63**)	Xestospongia spec. [40]	Lévi	OK	Petrosiidae
3-α-methylaraguspongine C(**64**), araguspongines C(**55**), D(**49**), E(**51**), xestospongin D(**52**)	Haliclona exigua [41]	Thomas	=Xestospongia	Petrosiidae
MACROCYCLES WITH CONJOINT PIPERIDINE RINGS				
halicyclamine A(**65**)	Haliclona spec. [42]	Diaz	OK	Chalinidae
saraines 1(**66**) - 3(**68**), iso-saraines-1(**69**) - 3(**71**)	Reniera sarai [43-47]	Sarà	=Haliclona	Chalinidae
CONDENSED *BIS* 3-ALKYLPIPERIDINES WITH UNREARRANGED SKELETONS				
saraines A(**72**) - C(**75**)	Reniera sarai [47-49]	Sarà	=Haliclona	Chalinidae
xestocyclamines A(**79**) - B(**80**)	Xestospongia spec. [51,54]	Diaz	OK	Petrosiidae
ingenamine (**77**), ingenamines B(**83**) - F(**87**), ingamines A(**81**) - B(**82**), keramaphidin B(**78**), xestocyclamine B(**80**)	Xestospongia ingens [52,55,56]	Van Soest	OK	Petrosidae
keramaphidin B(**78**)	Amphimedon spec. [53]	Fromont	OK?**	?Niphatidae
CONDENSED *BIS* 3-ALKYLPIPERIDINES WITH SECO OR REARRANGED SKELETONS				
manzamines A(**88**) - D(**91**)	Haliclona spec. [59,60]	not given	?	?
manzamines A(**88**) & F (**94**)	Pellina spec. [61,62]	Hoshino	?Oceanapia	Phloeodict.
manzamines E(**93**) - F(**94**)	Xestospongia spec. [62]	not given	?	?
8-hydroxymanzamine A(**95**), manzamine A(**88**)	Pachypellina spec. [63]	Kelly-Borges	?Calyx	Phloeodict.
tetrahydromanzamines **96** & **97**	Petrosia contignata [64]	Diaz	OK	Petrosiidae
tetrahydromanzamine **97**	Cribrochalina spec. [64]	Bergquist	?Petrosia	?Petrosiidae
manzamine A(**88**), 6-hydroxymanzamine A(**98**),				

Table 4.1 (cont.)

3,4-dihydromanzamine A(**99**)	Amphimedon spec. [65]	Fromont?	OK?**	?Niphatidae
ircinals A(**102**) - B (**103**), manzamines A(**88**), B(**89**), D(**91**), H(**104**), J(**105**)	Ircinia spec. [67]	Bergquist	OK *	?
ircinols A(**106**) - B(**107**), manzamines A (**88**) - C(**90**), ircinals A(**102**) - B (**103**)	Amphimedon spec. [68]	Fromont?	OK?**	?Niphatidae
madangamines A(**108**) - E(**112**)	Xestospongia ingens [69,70]	Van Soest	OK	Petrosiidae

*) These sponges are reliably identified but are big epibiont-carrying species. Since the greater majority of 3-alkylpiperidine alkaloids are produced by Haplosclerida, it is assumed that unknown Haplosclerida species were encrusting these sponges and "contaminated" the extracts with their 3-alkylpiperidine compounds.
**) Fromont's concept of Amphimedon does not correspond to the type species of Amphimedon, so the family allocation of these specimens is uncertain.

4.2) Significance of Distribution of 3-Alkylpiperidine Derivatives for the Ordinal Classification

The Haplosclerida s.l. as an integrated unit were first recognized by Topsent [73] and subsequently by all major authors until 1980, when Bergquist proposed to separate the group into two distinct orders, Haplosclerida s.s. and Nepheliospongida, newly erected by her [74]. Arguments for this action were the reproduction (viviparity in the Haplosclerida s.s. and oviparity in the Nepheliospongida), and the biochemistry (occurrence of unusual cyclosterols in Nepheliospongida). Basing her proposal on fossil evidence presented by Wiedenmayer [75] she argued that the two orders were unlikely to be closely related groups because the separation would have been effected back in paleozoic times. Morphological similarities would have been the result of parallel development. Bergquist's (l.c.) proposal received support from Hartman [76]. Boury-Esnault & van Beveren [77] supported it too, but proposed to name the new order Petrosida instead of Nepheliospongida, following Van Soest's [78] rejection of the fossil *Nepheliospongia* as a member of this group.

Resistance against the creation of two orders in an otherwise seemingly homogeneous group came up almost immediately and has never disappeared. Notably, De Weerdt [79,80] and Van Soest [81] advocated the integrity of the Haplosclerida s.l., conceding Bergquist the recognition of her groups at the subordinal level. The arguments against an independent status of Haplosclerida s.s. and Petrosida are based on the observation that both share a number of morphological similarities not found in other groups. The apomorphic (i.e. evolutionary derived) characters of Petrosida (oviparity and cyclosterols) could only serve to distinguish this group as a discrete unit, not determine its ordinal or subordinal status. The value of oviparity as a synapomorphy (i.e. a shared evolutionary derived character) is contested by Van Soest [82], who pointed out that oviparity / viviparity issues are linked to life history and thus easily switched on or off, depending on the ecological strategy of species.

Fromont [83] tried to find support for either classification by studying reproductive behaviour of a series of species belonging to both Haplosclerida s.s. and Petrosida, but decided that both points of view had merits. Fromont & Bergquist [84] emphasized again that all investigated species of Haplosclerida s.s. were viviparous, and all Petrosida were oviparous. Fromont et al. [85] also examined the biochemical evidence for the existence of a separate order Petrosida by investigating the sterol composition of a series of species of both groups. The conclusions from that study are that there is no support in the distribution of sterols for a two way classification. The earlier reported cyclosterols were never found again in any of the Petrosida [74]. It is likely that these are confined to *Calyx*. No other sterols were found to characterize either a separate Petrosida nor a separate Haplosclerida s.s.

Sequencing of 28-S ribosomal DNA [86] did not find support for an independent two-way separation of Haplosclerida s.l., but supported the hypothesis of an early separation of this group from other morphologically related groups such as the Poecilosclerida.

The position at the present time is a stalemate: Bergquist maintaining a two order

classification, Fromont in doubt, and De Weerdt/Van Soest advocating for integrity of a single order.

3-Alkylpiperidine derivatives have not been reported from any of the related orders (Poecilosclerida, Halichondrida/Axinellida). They are not confined to a single family, but occur in at least Niphatidae, Callyspongiidae, Chalinidae (viviparous, thus belonging to Bergquist's Haplosclerida s.s.) and Petrosiidae (oviparous, thus belonging to the Petrosida). If identifications are correctly interpreted (cf. Table 4.1), some Phloeodictyidae (oviparous, thus Petrosida) also contain these molecules. This distribution of 3-alkylpiperidine derivatives creates a strong argument for the integrity of the Haplosclerida s.l. and the abandonment of the order Nepheliospongida/Petrosida.

3-alkylpiperidine alkaloids are not the only secondary metabolites found in sponges of the order Haplosclerida. A literature survey revealed reports of a whole array of different compounds from haplosclerids: xestoquinones, halenaquinones, siphonodictyals, polyacetylenes, petrosamine, strongylophorines and amphimidine. Possibly, some of these are also are confined to this order or one or more of its families. Further chemosystematic studies are necessary to evaluate their value as taxonomic markers. In the following we will confine ourselves to 3-alkylpiperidine derivatives.

4.3) 3-Alkylpiperidine Derivatives as Phylogenetic Characters for a Family Classification

The diversity of various derivatives of 3-alkylpiperidine derivatives suggests that considerable chemical evolutionary developments must have taken place in the Haplosclerida. It appears to be a singularly unique opportunity to examine the distribution of the various molecule types over the families and genera of Haplosclerida in order to retrace the steps of this development. For this, there are various options to consider: if a phylogeny (i.e. a hypothesis of evolutionary diversification) has already been established reliably , e.g. based on morphological characters, tracing the distribution of the molecules over this phylogenetic tree would support a hypothesis on biogenetic pathways. Alternatively, if the phylogeny based on morphological characters is weakly supported or unsolved, the distribution of "related" compounds might help to refute or support rivaling hypotheses, or solve the relationships. Finally, a phylogeny may be built using exclusively chemical characters to see how it compares with a morphological tree. The latter approach has not been attempted previously in sponges and has potential to create a new alley for cooperative research between chemists and evolutionary biologists .

Phylogenetic trees were generated by analyzing matrices of taxa (families of Haplosclerida) and characters (morphological, chemical) with the computer program PAUP 3.1.1 [87] in a MacIntosh environment. Morphological characters are copied from De Weerdt [88], who is the only author who has formulated a detailed phylogeny of Haplosclerida families. Chemical characters are those discussed in the previous chapters, summarized in Table 4.1.

a. *Phylogeny of the Haplosclerida based on morphological characters*

The matrix of morphological characters is given in Table 4.2. To De Weerdt's [88] 10 morphological characters two others ("abruptly pointed oxeas/strongyles", and "viviparity") are added, and the outgroup taxon is changed from "Esperiopsidae" to Desmacellidae (for reasons see Hajdu et al. [89]), but the tree generated by PAUP is the same as hers. The well-supported tree is shown in figure 4.1, dark squares represent synapomorphic morphological characters.

TABLE 4.2

Matrix of Haplosclerid families and morphological characters derived from De Weerdt's study [88]. "1" means presence of a character state, "0" means absence. Compared to her analysis, two characters were added to her list (viz. 1 and 12), and the outgroup taxon is changed from Esperiopsidae into Desmacellidae. The matrix was used to generate the phylogenetic tree given in Fig. 4, using the program PAUP 3.1.1 [87].

character	1	2	3	4	5	6	7	8	9	10	11	12
Callyspongiidae	1	1	0	1	1	1	0	0	0	0	0	1
Niphatidae	1	1	0	1	1	0	1	0	0	0	0	1
Chalinidae	1	1	0	0	0	0	0	1	1	0	0	1
Petrosiidae	1	0	1	0	0	0	0	0	0	1	0	0
Phloeodictyidae	1	0	1	0	0	0	0	0	0	0	1	0
Desmacellidae	0	0	0	0	0	0	0	0	0	0	0	0

Character 1= main spicule type abruptly pointed, 2= ectosomal skeleton organized, 3= choanosomal skeleton isotropic, 4= ectosomal skeleton multispicular, 5= peripheral choanosomal skeleton condensed, 6= ectosomal double meshwork, 7= choanosomal primary multispicular tracts, 8= choanosomal unispicular secondary lines, 9= choanosomal paucispicular primary lines, 10= choanosomal skeleton alveolar, 11= reinforcing spicule tracts, 12= viviparity.

b. *Phylogeny based on molecule types*

A first attempt at phylogenetic reconstruction of the Haplosclerida using 3-alkylpiperidine alkaloids, consisted of analyzing a matrix (not shown) of the various molecule types of 3-alkylpiperidine derivatives over the families by PAUP. This yielded a partly unsolved tree (not shown) with an unlikely sistergroup relationship of Niphatidae and Petrosiidae. The next-related group would be either the Chalinidae or the Phloeodictyidae and these would be more closely related to the Niphatidae-Petrosiidae-Chalinidae than are the Callyspongiidae. This phylogeny appears rather artificial, with the group with the fewest characters (Callyspongiidae) ending at the base of the tree. Even if some morphologcial characters would be recoded or differently interpreted, it would seem impossible to reconcile the chemical and the morpholical tree. More importantly, however, these chemical characters

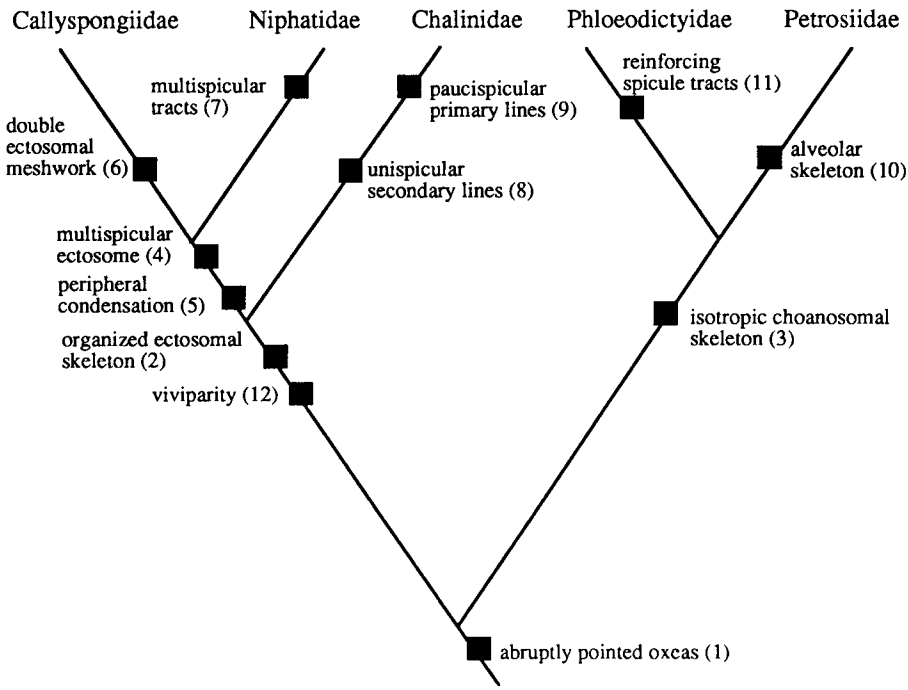


FIGURE 4.1: Phylogenetic tree based on De Weerdt's [88] morphological character analysis. Black squares represent (syn)apomorphic characters of clades and terminal taxa. The tree is the result of a reanalysis of De Weerdt's data using PAUP 3.1.1 [87] (single most parsimonious tree). The taxon-character matrix is given in Table 4.2.

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are all interrelated and very probably originate from a single parent molecule. This means that the characters do not meet the demand for a character analysis, viz. that they are independent of each other. The various molecule types need to be treated as states of a single character.

Thus, a more apropriate analysis was made by interrelating the various chemical characters in a single character in accordance with observations made in the previous chapter. A summary of hypothesized molecular evolution is given in Fig. 3.11. A hypothetical ancestral parent molecule supposedly gave rise to monomers as well as to a hypothetical intermediate molecule which in its turn gave rise to oligomers and -through intramolecular cyclization- to

TABLE 4.3

Stepmatrix representing hypothesized interrelationships of 3-alkylpiperidine alkaloids used for a single multiple state PAUP 3.1.1. [87] parsimony analysis of Haplosclerida family relationships. Column numbers are the various molecule types depicted in Figure 3.11 (see Section 3). Their biogenetic transformation is postulated as unidirectional from molecule 1 to the various types described. Hypothetical precursors are molecules 0, 1,4, 7 and 15. The data in the columns represent numbers of steps between molecule types. i = "infinite", an artificial coding in PAUP for indicating irreversible steps.

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
0	1	2	2	2	3	3	3	4	5	6	5	4	5	5	4	5	5	4
i	0	1	1	1	2	2	2	3	4	5	4	3	4	4	3	4	4	3
i	i	0	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i
i	i	i	0	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i
i	i	i	i	0	1	1	1	2	3	4	3	2	3	3	2	3	3	2
i	i	i	i	i	0	i	i	i	i	i	i	i	i	i	i	i	i	i
i	i	i	i	i	i	0	i	i	i	i	i	i	i	i	i	i	i	i
i	i	i	i	i	i	i	0	1	2	3	2	1	2	2	1	2	2	1
i	i	i	i	i	i	i	i	0	1	2	1	i	i	i	i	i	i	i
i	i	i	i	i	i	i	i	i	0	1	i	i	i	i	i	i	i	i
i	i	i	i	i	i	i	i	i	i	0	i	i	i	i	i	i	i	i
i	i	i	i	i	i	i	i	i	i	i	0	i	i	i	i	i	i	i
i	i	i	i	i	i	i	i	i	i	i	i	0	1	1	i	i	i	i
i	i	i	i	i	i	i	i	i	i	i	i	i	0	i	i	i	i	i
i	i	i	i	i	i	i	i	i	i	i	i	i	i	0	i	i	i	i
i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	0	1	1	i
i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	0	i	i
i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	0	i
i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i	0

various *bis*-macrocycles. Such a scheme may be translated into a "stepmatrix" of a single character (see Table 4.3). An added complication is that several molecule types (i.e. character states) are often found in the same family. PAUP's "multistate taxa" (states interpreted as "uncertain" rather than "polymorphic") has been utilized to represent this distribution of character states in the matrix of taxa and character (see Table 4.4). The data were analyzed using the "exhaustive" search option; this yielded a single most parsimonious tree (out of 945 possible trees) of 6 steps, given in Fig. 4.2. This "chemical" phylogeny supports the morphological tree in all aspects. Chemical synapomorphies (synapomorphy = shared character (e.g. baleines in a group of whales) - synapomorphies define groups of taxa) for the four clades are: hypothetical molecule 1 and manzamines 10 for all Haplosclerida, monomers 3 for the clade Petrosiidae-Phloeodictyidae, hypothetical molecule 4 for the clade Callyspongiidae-Niphatidae-Chalinidae, and halitoxins for the clade Niphatidae-Callyspongiidae. Chemical autapomorphies (autapomorphy = uniquely derived character (e.g. white hair of a polar bear) - autapomorphies define single taxa) for the five families are: for

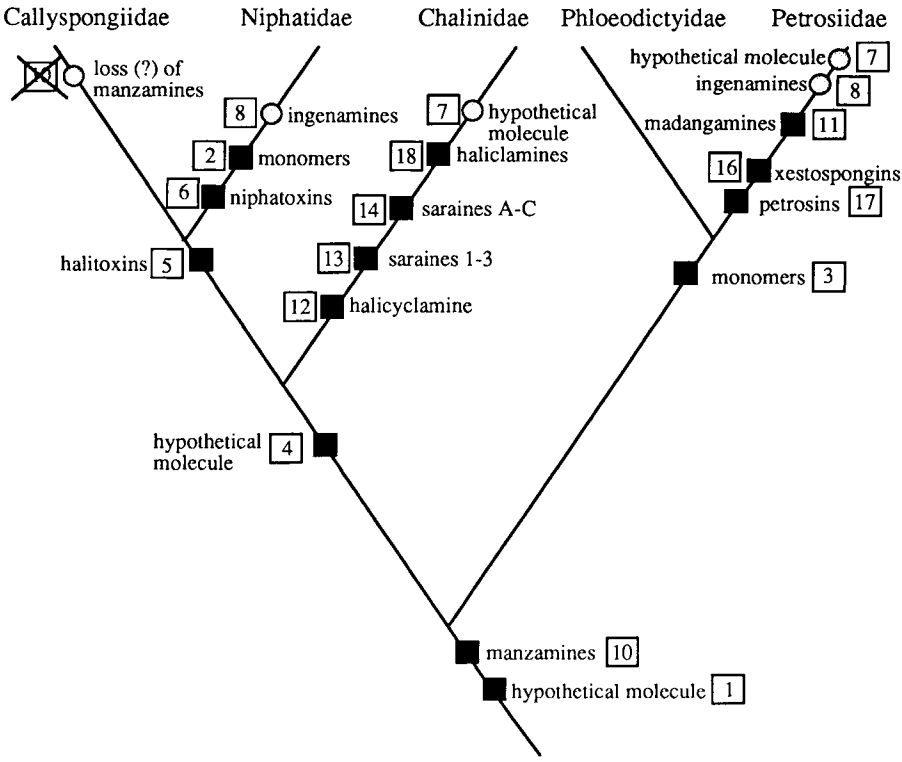

FIGURE 4.2: Phylogenetic tree generated by a PAUP 3.1.1 [87] analysis of the distribution of 3-alkylpiperidine alkaloids over the families of Haplosclerida. The alkaloids are treated as states of a single character, which were interrelated in the stepmatrix of Table 4.3 based on the hypothetical biogenetic scheme of Fig. 3.11. The multistate taxa ("uncertain") option was used, yielding a single most parsimonious tree of 6 steps. Black squares represent (syn)apomorphic alkaloids for the various clades and terminal taxa. Shaded circles are incongruently distributed (homoplastic) alkaloids.

Callyspongiidae: none, for Niphatidae: monomers 2 and niphatoxins, for Chalinidae: halicyclamine, saraines 1-3 and A-C, and haliclamines, for Phloeodictyidae: none, and for Petrosiidae: xestospongins and petrosins. There are several molecule types which have a distributions over two or more families incongruent with the phylogenetic tree: ingenamines found in Niphatidae and Petrosiidae, and hypothetical molecule 7 according to the biogenetic scheme of Fig. 3.11 and the phylogenetic tree would have to be found in families Chalinidae

and Petrosiidae. Callyspongiidae are the only group in which no manzamines have been found. Such incongruent distributions may reflect uncertain identities (e.g. Fromont's Amphimedons) and insufficient knowledge of secondary metabolite occurrence (e.g. Callyspongiidae).

TABLE 4.4

Matrix of Haplosclerid families and the states of a single "3-alkylpiperidine alkaloid biogenetic pathway" (represented in Fig. 3.11), used for a PAUP 3.1.1. [87] analysis. The interrelationships of the states are given in the stepmatrix of Table 4.3. State numbers are given in Fig. 3.11.

Families	Character 1 (states)
Callyspongiidae	5
Niphatidae	2, 5, 6, 8, 10
Chalinidae	10, 12, 13, 14, 18
Petrosiidae	3, 8, 10, 11, 16, 17
Phloeodictyidae	3, 10

5. SUMMARY

The first 3-alkylpiperidine sponge alkaloids, the halitoxins **31**, were discovered less than twenty years ago [25]. Since that time, more than one hundred biogenetically related alkaloids have been isolated from marine sponges in the order Haplosclerida. As a group, the 3-alkylpiperidines are characterized by the diversity and complexity of their chemical structures and by the range of biological activities that they exhibit. To date there are eleven macrocyclic skeletons known among the 3-alkylpiperidine alkaloids. These include the haliclamine/cyclostellettamine, ingenamine, madangamine, ircinal, manzamine, halicyclamine, saraine 1-3, saraine A to C, petrosin, xestospongin/araguspongine and aragupetrosine skeletons shown in Figure 3.11. Three of these skeletal types, belonging to the ingenamine [52], madangamine [69] and halicyclamine alkaloids [42], were first reported in the single year 1994. In addition, it has recently been recognized that the papuamine [64] and manzamine C [58] skeletons are biogenetically related to the 3-alkylpiperidines. Therefore, the evidence to date indicates that the ammonia, propenal and long chain dialdehyde units that are the putative biogenetic precursors to the 3-alkylpiperidine alkaloids can be combined in a wide variety of ways to generate complex structures and it is reasonable to expect that many more alkaloid skeletal types will be discovered in Haplosclerida sponges in the years to come.

The distribution of various 3-alkylpiperidine alkaloids over the five families of Haplosclerida forms a strong indication that this order of sponges is a monophyletic group, despite a recent attempt to subdivide it into two non-related units. The diversity of related 3-alkylpiperidine derivatives was utilized to explore phylogenetic relationships of the families.

The results support the previously published schemes based on morphological characters.

From the outset, 3-alkylpiperidine alkaloids have represented a substantial challenge to the extant methodology for chemical structure elucidation. For example, the monomeric units of the halitoxins are now well characterized but an effective molecular weight determination or description of the nature of oligomer/polymer termination has thus far proven elusive [25,28]. The difficulties associated with analyzing the NMR data for the long chain alkyl bridges spanning the nitrogen containing polycyclic cores has complicated the structure elucidation of most of the macrocyclic 3-alkylpiperdine alkaloids, occasionally leading to incorrect structural proposals. It is interesting to note that the saraines were first isolated in the early 1970's but their chemical structures were not elucidated until the 1980's when the availability of 2D experiments conducted on high field NMR spectrometers finally proved to be a powerful enough structural tool to meet the challenge of determining unambiguous connectivity in their long chain alkyl bridges [43,44,45,46]. Fortunately, several of the 3-alkylpiperidine alkaloids have given crystals suitable for X-ray diffraction analysis and this has provided solid evidence for the petrosin [32], xestospongin [35], saraine A to C [48], manzamine [57] and ingenamine skeletons [53].

Along with the characterization of the 3-alkylpiperidine structures have come biogenetic proposals for their formation [45,48,37,58,64,69,72]. Initally the origins of some types such as the manzamines was not clear [57]. Baldwin and Whitehead's proposal for the biogenesis of the manzamines proved to be a turning point in our understanding of the relationships between the various skeletal types [58]. With their insight in hand, it is now possible to test structures assigned to newly discovered 3-alkylpiperidines for biogenetic reasonableness.

3-Alkylpiperidine alkaloids have been found to exhibit many types of biological activity suggesting potential for development into drugs. The cytotoxicity of the manzamines [57] and the vasodilatory properties of the araguspongines [37] have attracted the most attention. The combination of potent biological activity and structural complexity found in the 3-alkylpiperidine alkaloids has also caught the attention of synthetic chemists. To date there have been synthetic efforts undertaken towards the synthesis of manzamines A [71,90,91,92,93,94,95,96,97], C [98,99] and D, saraine A [100], petrosin [101], the xestospongins/ araguspongines [40,102,103], and the ingenamines [71,72].

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Chapter Four

β-Carboline and Isoquinoline Alkaloids from Marine Organisms

Bill J. Baker
Department of Chemistry
Florida Institute of Technology
Melbourne, Florida 32901
U. S. A.

CONTENTS

1. INTRODUCTION

Nitrogenous marine natural products have steadily increased as a proportion of compounds reported from marine organisms over the last decade. Exact figures for marine plant and invertebrate derived substances are hard to come by; this is due in part to structural and taxonomic revisions, which makes tracking individual structures difficult, and in part to the sheer number of metabolites being reported each year. However, it can be educational to consider a compilation of data from periodic reviews that have appeared over the last three decades (1-12) which, while not entirely comprehensive, are certainly representative. These sources describe just over 5700 unique substances, nearly 1450 (25%) of which contain nitrogen. During the period 1977 to 1984, 21% of reported marine natural products were nitrogenous (3-5, 13), while nitrogen-bearing compounds reported in 1992 comprised 30% the total (12); the proportion varies considerably among algae and invertebrate phyla (Figure 1). Sponges dominate all other invertebrates in terms of the number of metabolites containing nitrogen (Figure 1) as well as in terms of total number of compounds characterized (Figure 2); while sponges have long held the former position, algae once represented the source of most marine natural products (13). Tunicates produce the highest proportion of nitrogenous metabolites (Figure 3).

Figure 1. Phyletic distribution of nitrogenous substances reported from marine organisms from 1977 to 1992 (1-12).

Figure 2. Phyletic distribution of marine natural products reported from 1977 to 1992 (1-12).

Several interesting observations come out of this compilation; 25% of marine nitrogenous substances are halogenated, 13% bear sulfur in one of several oxidation states, 8% are polypeptides, and 7% have an N-O bond. If fatty acid amides, polypeptides and other classes of natural products not generally considered alkaloids are removed from the total of nitrogenous substances, approximately 70% of marine derived nitrogenous substances would be considered alkaloidal. If tryptophan contributes all indole rings and arginine contributes the guanidino groups, then these are the two most common amino acids, contributing to 17% and 10% of the total of marine derived nitrogenous compounds, respectively; proline and valine are the most common amino acids in polypeptides, being present in roughly 56% of them.

A recent report of cytotoxic marine derived substances (14) described 434 of the most potent cytotoxins, 29% of which were alkaloidal and 48% of which contained nitrogen, while

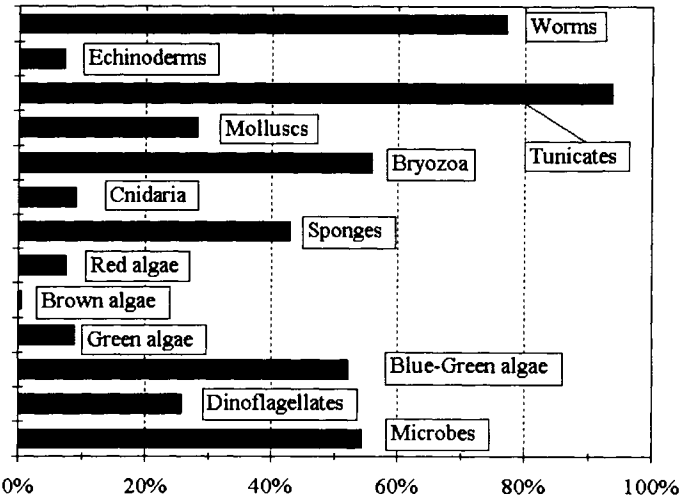


Figure 3. Phylogenetic comparison of proportion of marine-invertebrate derived substances which bear nitrogen reported during the period 1977 to 1992 (3-12).

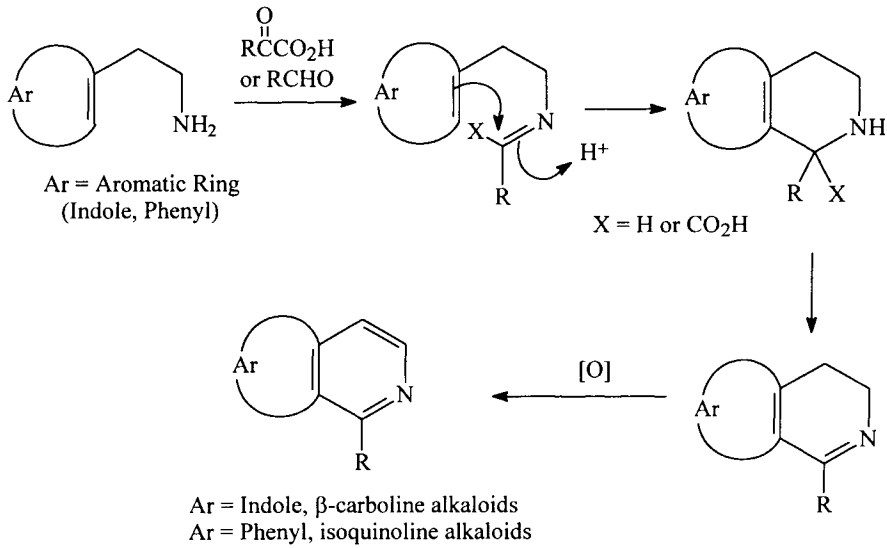
70% of antiviral (15) and antiparasitic (16) compounds reported were nitrogenous. Of compounds referred to as biomedically significant (17, 18), 60% were nitrogenous. In a recent report (19) of marine anticancer drug candidates, three of six were nitrogenous, two being polypeptides and the third an alkaloid. Bioassay guided isolations utilizing biomedical screens are clearly contributing to the aforementioned increase in the proportion of nitrogenous substances being reported.

Several reviews of marine derived alkaloids, most focusing on specific groups of compounds, have been published (20-24). β-Carboline and isoquinoline alkaloids, the subjects of this report, are some of the pharmacologically most significant marine natural products (see below). These two alkaloids share a common biosynthetic origin; condensation of tryptamine or tyramine with an aldehyde or α-keto acid (Scheme 1) leads, after ring closure and aromatization, to the respective β-carboline or isoquinoline ring system (25). This report covers the literature published up to and including 1994.

2. ISOLATION, STRUCTURE DETERMINATION AND DISTRIBUTION

2.1. β-Carboline Alkaloids

Alkaloids bearing the β-carboline ring system have been reported from sponges, tunicates, Cnidaria, Bryozoa and microalgae. The first reports of this ring system appeared in the early 1980's when β-carboline itself and harman (1-methyl-β-carboline) were reported from a bioluminescent marine dinoflagellate (see below), followed by the discovery by Rinehart, at the University of Illinois, Urbana-Champaign, (26-28) of the eudistomins from the tunicate *Eudistoma olivaceum*. The first group of sponge β-carboline alkaloids appeared only a short time later when Higa reported the first member of the manzamine family, manzamine A. Other



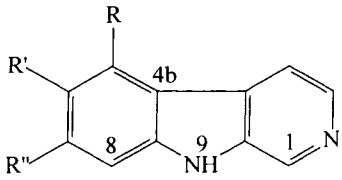
Scheme 1. Biosynthetic relationship between β-carboline and isoquinoline ring systems.

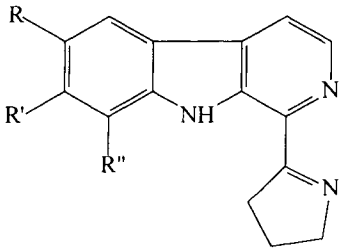
than a few simple β-carboline derivatives from hydroids, the recent report of the villagorgins, from the soft coral *Villagorgia rubra*, by the Riguera group in Italy is the first report of β-carbolines from the Cnidaria. The manzamines and eudistomins are the most studied of the marine derived β-carbolines, since they have been the subject of innumerable synthetic efforts as well as pharmacological evaluation.

2.1.1. The eudistomins and related β-carbolines from tunicates

The eudistomins (26-34, 38-40), eudistomidins (35-37), woodinine (41), and eudistalbins (42) are a series of amino acid derived (see Section 4) β-carboline antibiotics. They are produced by tunicates belonging to three different families: the Polycitoridae *Eudistoma olivaceum* (26-28, 30), *E. fragum* (41), *E. glaucus* (35-37), *E. album* (42), the Polyclinidae *Ritterella sigillinoides* (29, 31-33) and the Didemnidae *Lissoclinum fragile* (34). Because of the wide geographic and taxonomic distribution of these metabolites, and the diverse substitution patterns on the β-carboline ring system, it appears they may be produced by an associated microorganism (34). With respect to the different compound names, Rinehart's "eudistomin" is used herein to describe this family of compounds. Rinehart and the University of Montana group led by Cardellina have used this name extensively for β-carbolines isolated from *E. olivaceum*, Blunt and Munro have used it for *R. sigillinoides* congeners, and Francisco followed suit with eudistomin U from *L. fragile*. Kobayashi, at the Mitsubishi-Kasei Institute of Life Sciences, has used the term eudistomidin to describe the β-carbolines from *E. glaucus*. Pais and coworkers have adopted eudistalbin and woodinine for *E. album* and *E. fragum* derivatives.

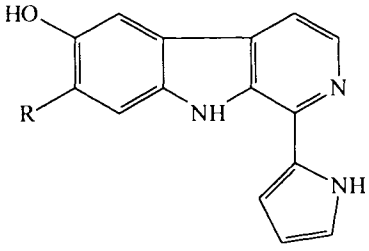
The eudistomins can be grouped into distinct classes according to their apparent biosynthetic origin from condensation of tryptophan with a second amino acid. Eudistomins D, J, N, O **(1-4)** and eudistomidin D **(5)** are bromo- and hydroxy-substituted β-carboline alkaloids. A proline-derived precursor is evident in eudistomins G, H, I, P, Q, A, and M **(6-10, 12, 13)**, eudistomidin A **(11)** and woodinine **(14)** while eudistomins R, S, and T **(15-17)** and eudistomidin B **(18)** display evidence of a phenylalanine precursor. Some of the structurally more intriguing members of this group of alkaloids are those bearing the oxathiazepine ring, apparently originating from condensation of tryptophan with cysteine. Eudistomins C, E, F, K, and L **(19-23)**, and their derivatives **24** and **25**, have in addition to unusual structures, significant antiviral activity (see Section 5). Further examples of cysteine adducts include eudistomidins C, E, and F **(26-28)**. Eudistalbins A and B **(30, 31)** likely derive from isoleucine.

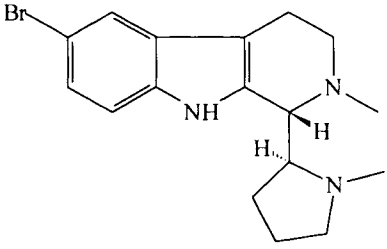




1 Eudistomin D: R = Br, R' = OH, R" = H
2 Eudistomin J: R = H, R' = OH, R" = Br
3 Eudistomin N: R = R" = H, R' = Br
4 Eudistomin O: R = R' = H, R" = Br
5 Eudistomidin D: *N*(9)-methyleudistomin D

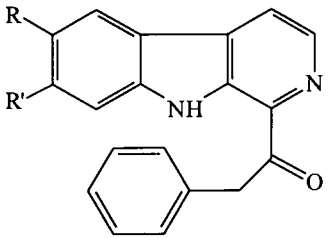
6 Eudistomin G: R = R" = H, R' = Br
7 Eudistomin H: R = Br, R' = R" = H
8 Eudistomin I: R = R' = R" = H
9 Eudistomin P: R = OH, R' = Br, R" = H
10 Eudistomin Q: R = OH, R' = R" = H
11 Eudistomidin A: R = Br, R' = H, R" = OH

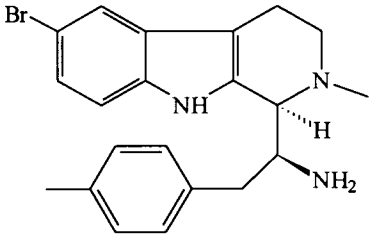




12 Eudistomin A: R = Br
13 Eudistomin M: R = H

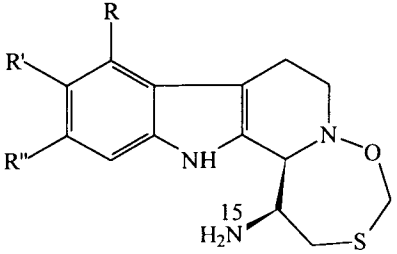
14 Woodinine

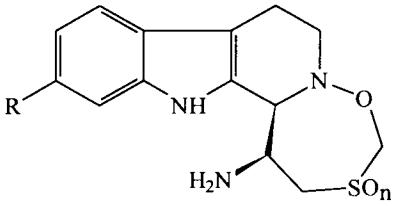




15 Eudistomin R: R = H, R' = Br
16 Eudistomin S: R = Br, R' = H
17 Eudistomin T: R = R' = H

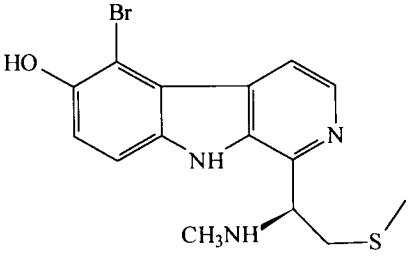
18 Eudistomidin B

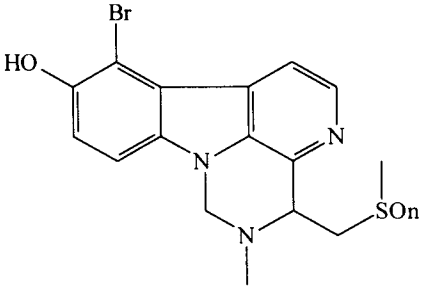




19 Eudistomin C: R = H, R' = OH, R" = Br
20 Eudistomin E: R = Br, R' = OH, R" = H
21 Eudistomin F: *N*(15)-acetamidoeudistomin C
22 Eudistomin K: R = R' = H, R" = Br
23 Eudistomin L: R = R" = H, R' = Br

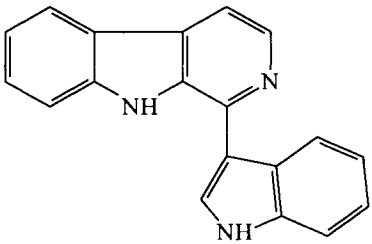
24 Eudistomin K sulfoxide: R = Br, n = 1
25 Debromoeudistomin K: R = H, n = 0



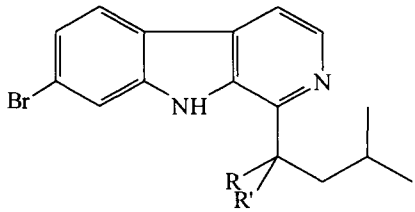


26 Eudistomidin C

27 Eudistomidin E: n = 1
28 Eudistomidin F: n = 0



29 Eudistomin U



30 Eudistalbin A: R = H, R' = NH_2
31 Eudistalbin B: R = R' = O

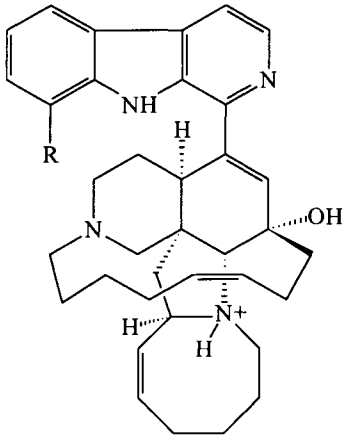
Eudistomin U **(29)**, recently reported by the Francisco group in France, bears an indole ring at C(1), suggesting two tryptophan biosynthetic units (34). However, it must arise from a different biosynthetic pathway since the attached indole ring is deficient by two carbons relative to the tryptophan precursor. That is to say, all other eudistomins have the full complement of carbons from their constituent amino acid precursors. Further evidence to suggest the biosynthetic pathway is different in this tunicate, *Lissoclinum fragile*, collected off Guadeloupe, France, is the accompanying α-carboline with an indole at C(4) (34).

The eudistomins from *E. olivaceum* extract readily into a non-polar phase, toluene (26-28) or dichloromethane (29), and require repeated chromatographic steps to separate one from another, especially within a related class. Separation in some cases is especially problematic (28, 29); for example, eudistomins N **(3)** and O **(4)** proved inseparable at the time they were reported. Structure elucidation relied heavily on interpretation of spectral data, especially 500 MHz NMR and mass spectra (26); several members of the series have now been synthesized (see Section 3). Eudistomin K has been crystallized and subjected to X-ray analysis (32) revealing the absolute configuration of the oxathiazepino-eudistomins.

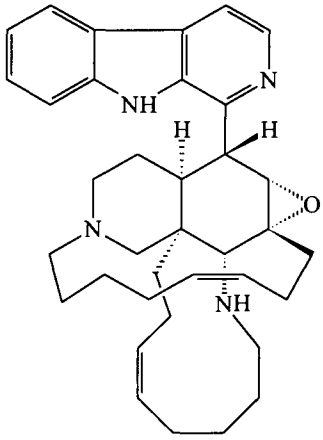
2.1.2. Manzamines

The manzamines are a group of complex sponge alkaloids bearing not only a β-carboline ring system but also isoquinoline and macro-heterocyclic ring systems. Manzamine A **(32)** was first reported by Higa and coworkers at the University of the Ryukyus (43) from a sponge of the genus *Haliclona* while the same compound (under the name keramamine-A) was reported from a *Petrosia* sp. by the Nakamura group (44). Manzamine A, isolated as the hydrochloride salt, drew considerable attention due to significant bioactivity and unprecedented structure. Subsequent reports from Higa (45, 46), Kobayashi (47, 49), Scheuer, at the University of Hawaii (48), and Crews, at the University of California at Santa Cruz (50), have described eleven derivatives **(33-43)**, four **(33, 38, 40, 41)** of which are hydroxylated at C(8) and four **(37, 38, 41, 42)** of which are 1,2,3,4-tetrahydro-β-carboline alkaloids. The manzamines are extracted from the wet sponge into acetone. Chromatography of the ethyl acetate soluble portion of the crude acetone extract on silica gel followed by recrystallization from methanol yielded a sample of manzamine A suitable for X-ray analysis. Manzamines B and C have also been analyzed by X-ray diffraction; structures of other members of the group have been elucidated by spectroscopic analysis and comparison of the spectral data with that of manzamines A-C. Various manzamines have now been reported from sponges of eight different genera belonging to five different families (50): *Haliclona* (43, 45) from the family Chalinidae, *Pellina* (44) and *Pachypellina* (48) from the Oceanapiidae family, *Ircinia* (47) from

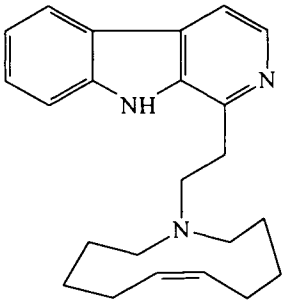
the Thorectidae family, *Petrosia* (50) from the family Petrosiidae, and, from the Niphatidae family, *Cribrochalina* (50), *Xestospongia* (46), and *Amphimedon* (49). This diversity of origin suggests a microbial source (46).



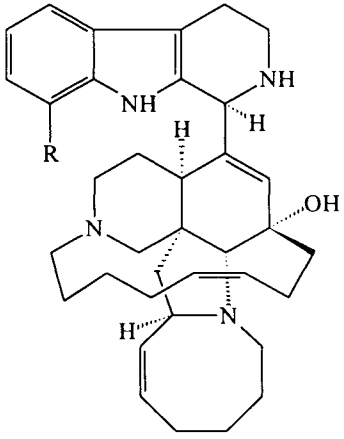
32 Manzamine A: R = H
33 8-Hydroxymanzamine A



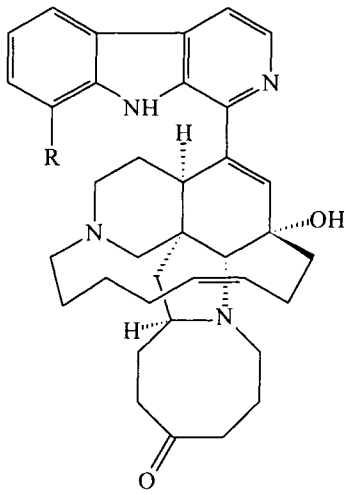
34 Manzamine B



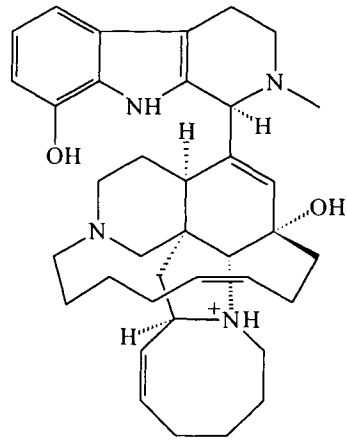
35 Manzamine C
36 Keramamine C: 1,2,3,4-tetrahydro



37 Manzamine D: R = H
38 R = OH



39 Manzamine E: R = H
40 Manzamine F: R = OH



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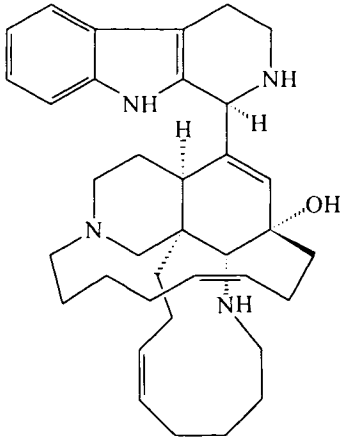
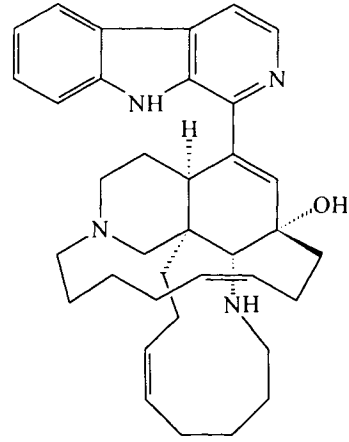


42 Manzamine H

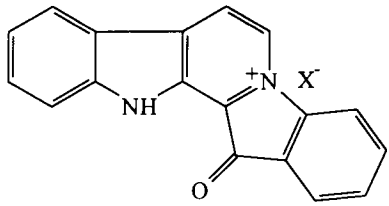


43 Manzamine J

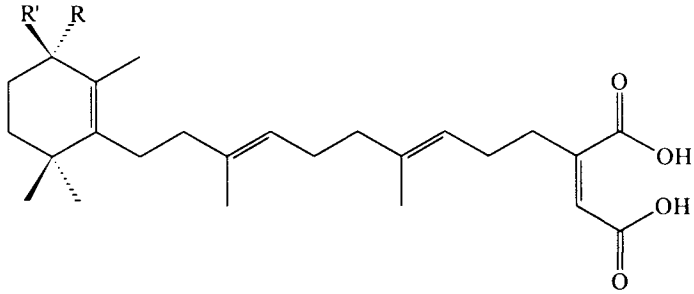
2.1.3. Fascaplysins and reticulatines

Indo-Pacific sponges of the genus *Fascaplysinopsis* produce a series of bis-indole alkaloids known as the fascaplysins (51) and reticulatines (52), some of which are β-carbolinium ion alkaloid salts of terpene carboxylates. Fascaplysin **(44)**, which was reported by Ireland and coworkers, at the University of Utah, from a Fijian collection of *Fascaplysinopsis* sp., is a fused pentacyclic pigment exhibiting antimicrobial and cytotoxic properties. Crews

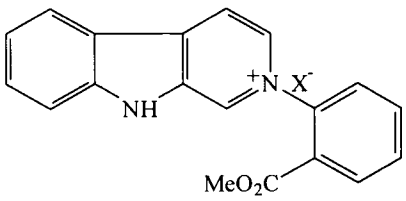
subsequently reported fascaplysin A and B **(45, 46)**, from the red-brown *Fascaplysinopsis reticulata*, also collected in Fiji (52). While **45** and **46** share the pentacyclic cation of **44**, they differ in bearing the luffariellolide diacid anions **47** and **48**, respectively, as counter ions. Further examples of salts containing luffariellolide diacid anions **47** and **48** were reported by Crews (52, 53) and include reticulatine A and B **(49, 50)** and homofascaplysin A **(51)**, all three of which are from *Fascaplysinopsis reticulata*. Homofascaplysin B and C **(52, 53)** as well as secofascaplysin A **(54)** are the only neutral alkaloids from this sponge. Fascaplysin was isolated from the chloroform partition fraction obtained from Kupchan partitioning of the lyophilized sponge. Purification on Sephadex LH-20 followed by reversed phase HPLC on ODS-3, or recrystallization from MeOH yielded blood red prisms (2% of dry weight) that were subjected to X-ray analysis. Other members of the group were isolated in 1 X 10^{-4} to 2 X 10^{-3}% yield of wet weight and were characterized based on spectral analysis.



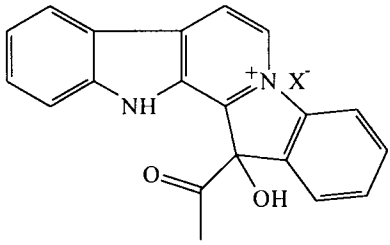
44 Fascaplysin: $X^- = Cl^-$
45 Fascaplysin A: X^- = anion of **47**
46 Fascaplysin B: X^- = anion of **48**



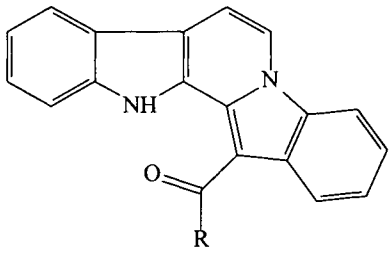
47 R = R' = H
48 R = R' = O



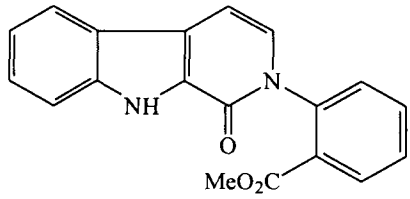
49 Reticulatine A: X^- = anion of **48**
50 Reticulatine B: X^- = anion of **47**



51 Homofascaplysin A: X^- = anion of **47**



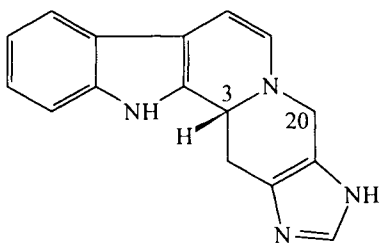
52 Homofascaplysin B: R = CO_2Me
53 Homofascaplysin C: R = H



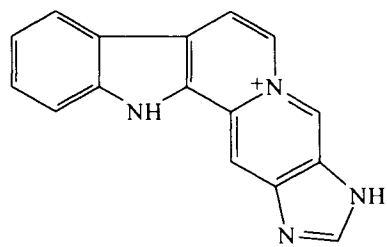
54 Secofascaplysin A

2.1.4. Villagorgin

The report by the Riguera group of alkaloids in the New Calidonian soft coral *Villagorgia rubra* (54) was surprising since gorgonians are generally characterized by the presence of terpenes (1-12). The alkaloids, villagorgin A and B **(55, 56)**, were extracted from the lyophilized sponge into MeOH, then partitioned into *n*-BuOH. After adsorption and size exclusion chromatography the alkaloids were separated by reversed phase HPLC. The structures were secured by extensive use of 2D NMR techniques, including HMBC and long-range relay COSY experiments, and high resolution electron-impact mass spectroscopy (HREIMS). The absolute configuration of **55** is based on a nuclear Overhauser enhancement (NOE) observed between H(3) and $H(20_{ax})$ in combination with circular dichroism (CD) data which showed a negative Cotton effect at 277 nm ($\Delta\varepsilon$ -0.19).



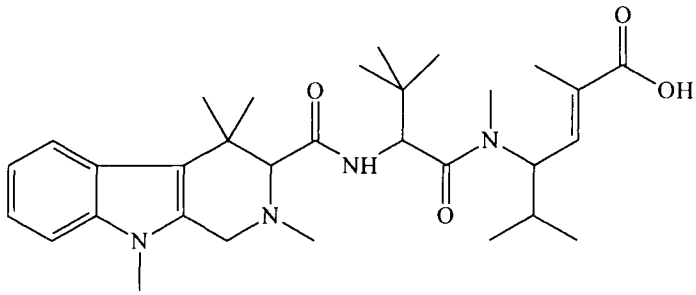
55 Villagorgin A



56 Villagorgin B

2.1.5. Milnamide

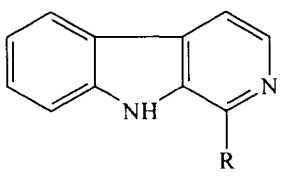
An intriguing cytotoxic and highly methylated tripeptide, milnamide A **(57)**, was recently isolated by Crews and coworkers from the orange sponge *Auletta* cf. *constricta*, collected in Papua New Guinea (55). Cytotoxicity observed in the crude extract was partitioned into a dichloromethane layer which was further purified to yield milnamide A and an unrelated cyclic peptide. The structure is based on spectroscopic data, especially 2D NMR techniques; the stereochemistry has not been established. A related tripeptide from the South African sponge *Hemiasterella minor* (also reported without stereochemistry) lacks only the C(1) methylene, and thus the β-carboline ring system (56).



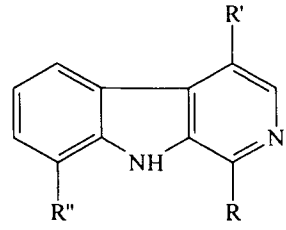
57 Milnamide A

2.1.6. Simple β-carboline alkaloids

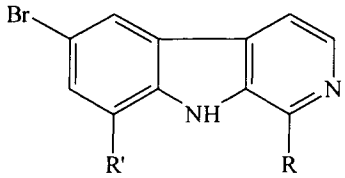
The simplest β-carboline alkaloids, those with short-chain alkyl substitution at C(1), have been reported from sponges, bryozoans, tunicates and a hydroid, as well as the aforementioned microalgae. β-Carboline (norharman) and/or harman **(58, 59)** were first reported by the Inoue group as the fluorescent substance from the dinoflagellate *Noctiluca miliaris* (57). Subsequently, Blackman reported harman from the bryozoan *Costaticella hastata* (58), then Blunt and Munro found it in the tunicate *Ritterella sigillinoides* (29) and in the bryozoan *Cribricellina cribraria* (59). The two bryozoans, in addition to a third bryozoan, *Catenicella cribraria* (60), were reported to elaborate C(1)-ethyl, -vinyl, and 1'-hydroxyethyl substituted β-carboline alkaloids **(60-62, 64-69)**, some with oxidation at C(8) **(64-68)**, and one with a sulfone at C(4) **(69)**. Cardellina and coworkers reported that the Bermudan sponge *Tedania ignis* contains 1-acetyl-β-carboline **(63)** (61). Brominated analogs of methyl- and ethyl-substituted β-carboline **(70-72)** have been found in the hydroid *Aglaophenia pluma* (62). From the New Caledonian sponge *Xestospongia* sp., xestoamine **(73)** was isolated (63), while 1,2,3,4-tetrahydro-β-carboline **(74)** was reported from the gorgonian *Villagorgia rubra* (54).



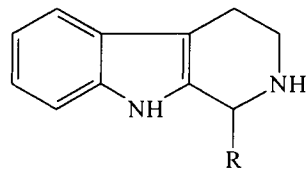
58 β-Carboline: R = H
59 Harman: R = CH_3
60 R = CH_2CH_3
61 R = $CH{=}CH_2$
62 R = $CH(OH)CH_3$
63 R = $C(O)CH_3$



64 R = CH_2CH_3, R' = H, R" = OH
65 R = $CH{=}CH_2$, R' = H, R" = OH
66 R = CH_2CH_3, R' = H, R" = OCH_3
67 R = $CH{=}CH_2$, R' = H, R" = OCH_3
68 R = $CH{=}CH_2$, R' = H, R" = $OCOCH_3$
69 R = CH_2CH_3, R' = SO_2CH_3, R" = H



70 R = CH_2CH_3, R' = H
71 R = CH_3, R' = H
72 R = CH_2CH_3, R' = Br

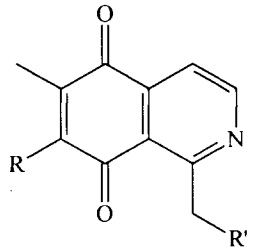


73 Xestoamine: R = $CH_2N(CH_3)_2$
74 R = H

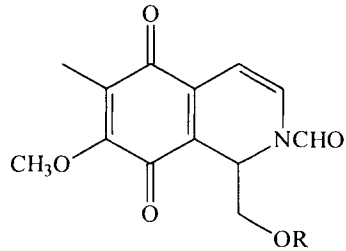
2.2. Isoquinoline Alkaloids

2.2.1. Renierone and related isoquinolinequinones

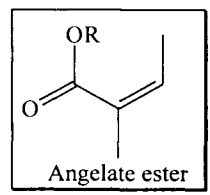
The first marine isoquinoline alkaloid, renierone **(75)**, was reported by McIntyre and Faulkner, at Scripps Institute of Oceanography, in 1979 (64) from the intensely blue sponge *Reniera* sp. collected in Mexico. Prior to Faulkner's report, isoquinolinequinones, such as mimosamycin **(87)**, were known as metabolites from *Streptomyces lavendulae* No. 314 (65-67). Mimosamycin itself was subsequently found in *Reniera* sp., along with renierone and its derivatives **(76, 77, 84)** (68). Further examples of this class of antibiotic have been reported from *Xestospongia* sp., including renierol **(78)**, reported by McKee and Ireland (69), and acetate derivatives **79** and **80**, from Scheuer's group (70). Kobayashi and coworkers, at Hokkaido University, reported aminomimosamycins **88-89** (71) from a blue Indian Ocean *Petrosia* sp., while another specimen yielded renierone derivative **80** (72). A Gujarat coast (India) *Haliclona* sp. was found to elaborate **83** (73). Pettit reported that the deep-blue sponge *Cribrochalina* sp. produces the cribrostatins 1 and 2 **(81, 90)**, which display potent cytotoxicity (74). Given the diversity of organisms from which these isoquinoline alkaloids have been reported, an associated streptomycete is likely to be the ultimate source (68).

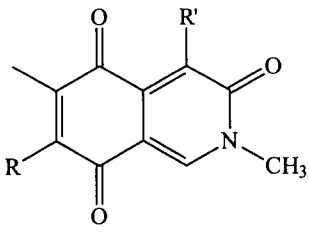


75 Renierone: R = CH_3, R' = O-angelate
76 R = H, R' = O-angelate
77 R = OCH_3, R' = H
78 Renierol: R = OCH_3, R' = OH
79 R = OCH_3, R' = $OCOCH_3$
80 R = OH, R' = $OCOCH_3$
81 Cribrostatin 1: R = NH_2, R' = H
82 R = OCH_3, R' = $OCOCH_2CH_3$
83 R = O-**75**, R' = O-angelate (dimeric ether)



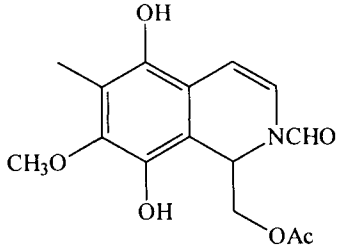
84 R = angelate
85 R = $OCOCH_3$
86 R = $OCOCH_2CH_3$



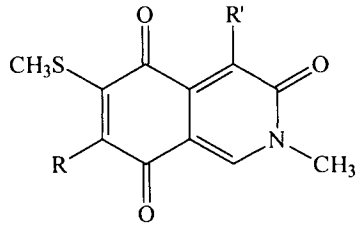


87 Mimosamycin: R = OCH_3, R' = H
88 R = OCH_3, R' = NH_2
89 R = NH_2, R' = H
90 Cribrostatin 2: R = OCH_2CH_3, R' = H

While sponges are clearly the dominant source of marine isoquinolinequinone antibiotics, the alkaloids have been reported from other marine invertebrates as well. Scheuer and coworkers found that the nudibranch predator, *Jorunna funebris*, of a Sri Lankan sponge *Xestospongia* sp. contained, in addition to *Xestospongia* metabolites **79** and **85**, two propionate derivatives **(82, 86)**, hydroquinone **91** and mimosamycin **(87)**; the relationship between *J. funebris* and *Xestospongia* is unusual in that sponges usually display greater diversity of secondary metabolites than their predators (70). Two bryozoans have been shown to elaborate sulfur-containing isoquinolinequinones distantly related to those described the above. The South Australian bryozoan *Membranipora perfragilis*, investigated by the Schmitz group at the University of Oklahoma, contains **92** and **93** (75) while Blackman's group reported that the Tasmanian *Biflustra perfragilis* contains **93** and **94** (76). Due to the uncertain nature of taxonomy of these bryozoans, *B. perfragilis* and *M. perfragilis* may well be identical (76).



91

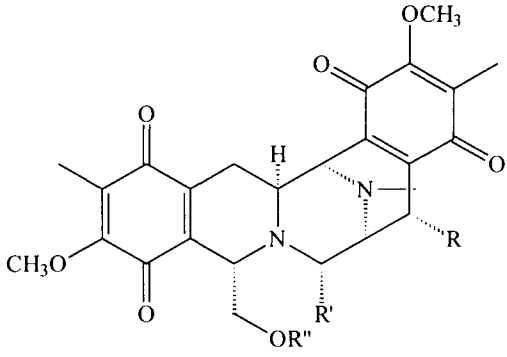


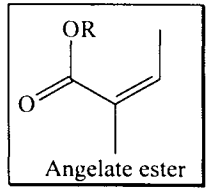
92 Perfragilin A: R = NH_2
93 Perfragilin B: R = SCH_3
94 R = H

The isoquinolinequinones can be purified from the ethyl acetate soluble fraction of the crude alcohol extracts, after repeated silica gel chromatography and/or recrystallization. Yields vary among sources, though renierone is generally found in the highest concentration, 0.3% of the dry weight; other *Reniera* compounds are found in 0.027 to 0.002% (dry weight), the cribrostatins are produced in 10^{-6}% yield, and perfragilin A and B in 0.07 and 0.03%, respectively. Renierone, mimosamycin, cribrostatin 1 and perfragilin B have been the subject of X-ray crystallographic studies; others structures were based on spectroscopic data.

2.2.2. Renieramycin, xestomycin and ecteinascidins

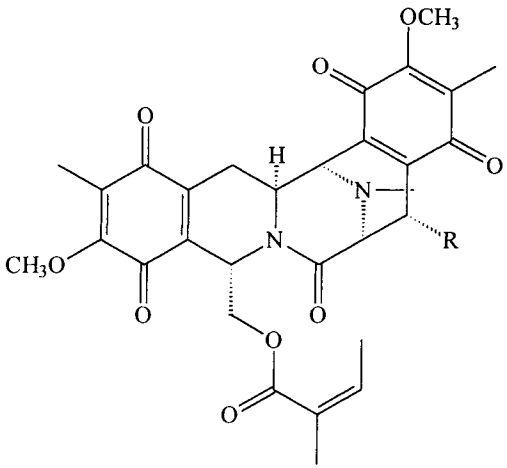
Faulkner and coworkers also reported bis(isoquinolinequinone) alkaloids from *Reniera* sp.; renieramycins A-G **(95-98, 100-102)** and xestomycin **(99)**, appear to incorporate two renierone-type moieties. Like the "monomer" isoquinolinequinones, the dimeric isoquinolinequinones were first reported from *Streptomyces lavendulae* No 314 (77), and subsequently have been reported in sponges and a tunicate. Renieramycins A-D **(95, 96, 100, 101)** (68), E and F **(97, 98)** (78) were isolated from *Reniera* sp. while renieramycin G **(102)**, reported by Davidson at the University of Hawaii (79), and Scheuer's xestomycin **(99)** (70) were obtained from *Xestospongia* spp. Dimeric isoquinolinequinones are isolated concurrently with the monomers; during the isolation of renieramycin E and F, concentrations of the monomers renierone **(75)** and mimosamycin **(87)** were found to increase with chromatography or on standing in chloroform, suggesting that at least some of the monomers may be degradation products. An optimized isolation technique to minimize degradation on silica gel utilized Sephadex LH-20 and reversed phase HPLC (78). Renieramycin A-F are found in 0.001 to 0.027% (dry weight), respectively, of *Reniera* sp.





95 Renieramycin A: R = OH, R' = H, R" = angelate
96 Renieramycin B: R = OCH_2CH_3, R' = H, R" = angelate
97 Renieramycin E: R = H, R' = OH, R" = angelate
98 Renieramycin F: R = OMe, R' = OH, R" = angelate
99 Xestomycin: R = OCH_3, R' = H, R" = $COCH_3$

The bright orange mangrove tunicate *Ecteinascidia turbinata* was first reported to produce cytotoxic extracts in 1969, producing impressive treatment versus control (T/C) ratios against P-388 with 66% cures in one case (80). Due to limited availability of tunicate and the trace quantities produced (81, 82), it was only recently that the structures of the cytotoxic agents were solved, simultaneously by Rinehart and the Harbor Branch group. Tunicates from the Florida Keys and the Caribbean produce six tris(tetrahydroisoquinoline) metabolites, ecteinascidins 729, 743, 745, 770, 759A and 759B **(103-108)**, and two tetrahydro-β-carboline bis(tetrahydroisoquinoline) analogs, ecteinascidins 722 and 736 **(109, 110)** (83). The ecteinascidin nomenclature is based on their observed molecular ions in the fast atom bombardment mass spectrum (FABMS), but differ from the true molecular weight by 18 mass

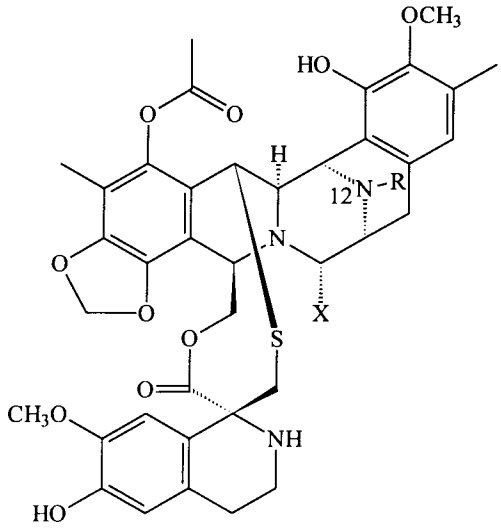


100 Renieramycin C: R = OH
101 Renieramycin D: R = OCH_2CH_3
102 Renieramycin G: R = H

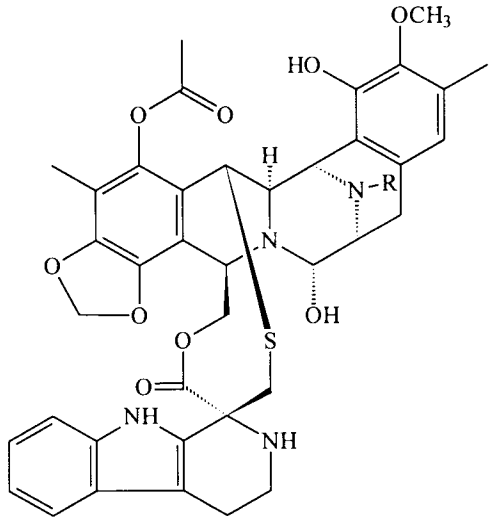
units (dehydration). Isolation of the ecteinascidins involved repeated reversed phase HPLC chromatography of the *n*-butanol partition fraction of a methanol/toluene extract, providing 10^{-4}-10^{-5}% yield. Extensive use of 2D NMR techniques in combination with FABMS/MS, defined the planar structures and the stereochemistry was secured by NOE studies. Ecteinascidins 759A and 759B are isomeric *N*(12)-oxides of ecteinascidin 743, one of which has been studied by X-ray crystallography (83, 84); since the report of the crystal structure does not use the 759A/759B nomenclature it is not obvious which of the two designations to use. The crystal structure clarified the stereocenters at C(1') and C(4) and the absolute stereochemistry of the ecteinascidins. The ecteinascidins are among the few marine natural products that have advanced to clinical trials as anticancer agents (19).

2.2.3. Theoneberine

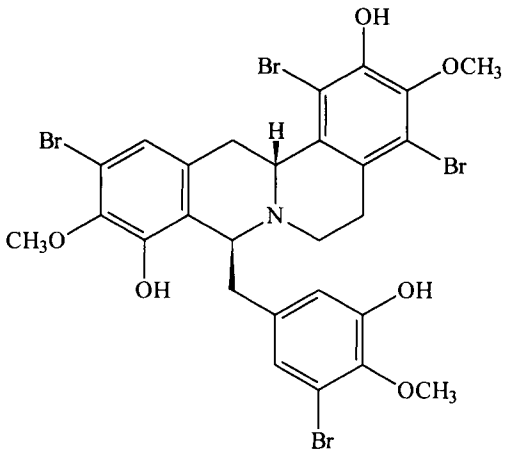
The unique marine alkaloid theoneberine **(111)** was isolated by Kobayashi and coworkers from the Japanese sponge *Theonella* sp., collected off the Island of Ie, Okinawa (85). Theoneberine is unusual in bearing a tetrahydroprotoberberine skeleton substituted with a tyrosine-derived group, and is the first brominated protoberberine. The structure is based on extensive one- and two-dimensional NMR analysis and conversion to a tridebromo-derivative, which facilitated assigning carbons bearing bromine. The two asymmetric carbons could be assigned relative stereochemistry based on observed NOESY (2D NOE) correlations between the ring-junction proton and the benzylic methylene group of the benzyl substituent. Theoneberine was extracted from the wet sponge into methanol then partitioned into ethyl acetate. Silica gel chromatography of the ethyl acetate soluble fraction followed by repeated reversed phase HPLC then Sephadex LH-20, yielded 0.0004% (wet weight) of theoneberine.



103 Ecteinascidin 729: R = H, X = OH
104 Ecteinascidin 743: R = CH_3, X = OH
105 Ecteinascidin 745: R = CH_3, X = H
106 Ecteinascidin 770: R = CH_3, X = CN
107 Ecteinascidin 759A: Ecteinascidin 743 *N*(12)-oxide
108 Ecteinascidin 759B: Ecteinascidin 743 *N*(12)-oxide



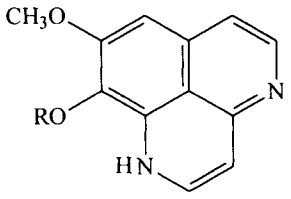
109 Ecteinascidin 722: R = H
110 Ecteinascidin 736: R = CH_3



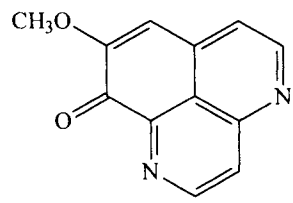
111 Theoneberine

2.2.4. Sponge heteroaromatics: aaptamine, amphimedine and petrosamine

The Okinawan sponge *Aaptos aaptos* was the source of the first marine fused heteroaromatic natural product, aaptamine **(112)**, which was shown by Nakamura's group to have α-adrenoceptor blocking activity (86). Two derivatives, **113** and **114**, were later reported from the same sponge as minor constituents (87). Aaptamine has also been isolated by Bergquist and Cambie, at the University of Auckland, from an Australian collection of *Suberites* sp. (88) and was the basis for reassigning the taxonomy of *Suberites* sponges. Aaptamine was characterized based on analysis of 270 MHz NMR data and chemical degradation; it was isolated in 0.17% yield by recrystallization of a fraction from silica gel chromatography of the ethanol-soluble portion of the crude methanol extract of the wet sponge.



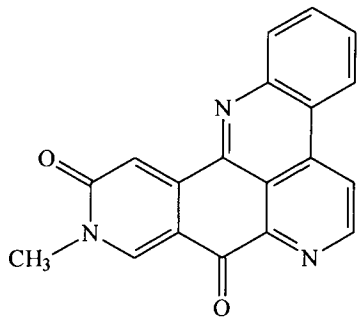
112 Aaptamine: R = CH_3
113 Demethylaaptamine: R = H



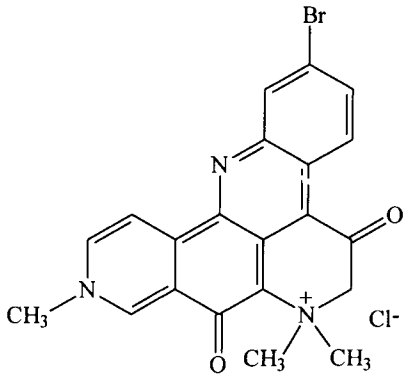
114 Demethyloxyaaptamine

The South Pacific and Caribbean sponges *Amphimedon* sp. and *Petrosia* sp. are the source of fused aromatic alkaloids sharing a common carbon skeleton, amphimedine **(115)**, isolated by Schmitz and coworkers (89), and petrosamine **(116)**, reported by Faulkner's group (90). The structure of amphimedine was secured by two-dimensional NMR techniques, in particular the natural abundance ^{13}C-^{13}C coupling correlation experiment, INADEQUATE. Amphimedine was isolated by Soxhlet extraction of the freeze-dried sponge with chloroform. Silica gel and

alumina chromatography yielded the sparingly soluble yellow solid. Petrosamine on the other hand, is a dark green crystalline material, 0.1% of the dry weight of the sponge, which was analyzed by X-ray crystallography.



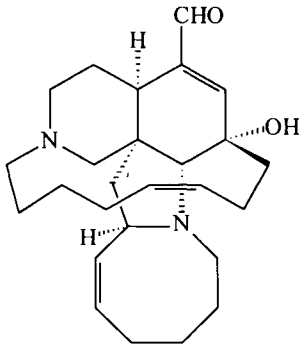
115 Amphimedine



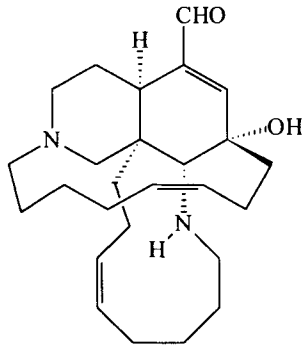
116 Petrosamine

2.2.5. Ircinals and ircinols

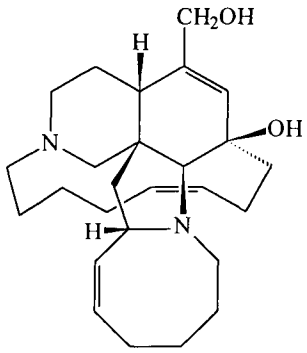
Kobayashi and coworkers have reported ircinals A and B **(117, 118)** (47) and their corresponding, though antipodal, alcohols **(119, 120)** (91), each of which bears the isoquinoline and macroheterocyclic ring systems of the manzamines **(32-43)** and thus appear to be biogenetic precursors; in fact, manzamines A and B **(32, 34)** have been prepared by Pictet-Spengler cyclization of ircinal A and B with tryptamine (47). The ircinals were reported from a Kise, Okinawa, specimen of *Ircinia* while the ircinols were found in *Amphimedon* sp. from the Kerama Islands of Okinawa. All four compounds were partitioned into ethyl acetate from the concentrated aqueous methanol extract, and were purified by repeated silica gel chromatography to yield 0.0002% to 0.0052% alkaloids based on wet weight.



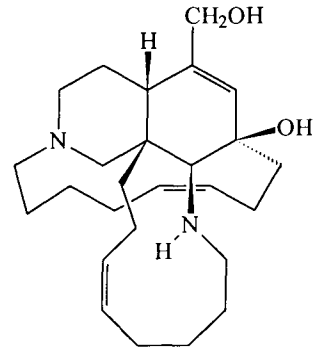
117 Ircinal A



118 Ircinal B



119 Ircinol A



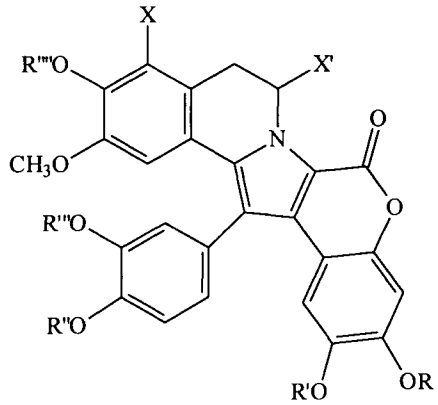
120 Ircinol B

2.2.6. Lamellarins

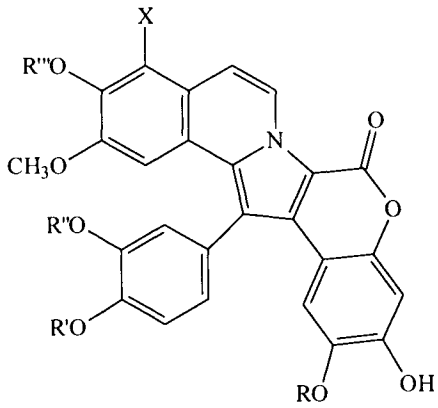
The lamellarin group of isoquinoline alkaloids **(121-134)** were first reported by Faulkner's group from the prosobranch mollusc *Lamellaria* collected in Palau (92). Prosobranchs, like opisthobranchs, lack an external shell for defense and thus are subject to the same predation pressure that may have been the factor forcing opisthobranchs to sequester secondary metabolites for their own defense (93). Discovery of lamellarins in a tunicate, first by Fenical's group at Scripps (94) and then by Bowden and coworkers at James Cook University (95), supported this hypothesis, since *Lamellaria* are known to feed on compound tunicates (92). The purple or brown ascidian *Didemnum chartaceum* (94), from the Seychelles, and *Didemnum* sp from Australia (95) have both been shown to elaborate lamellarins. More surprising is the isolation by Capon's group at the University of Melbourne of biosynthetically related metabolites, albeit non-isoquinoline alkaloids, from the Australian sponge *Dendrilla cactos* (96). The lamellarin alkaloids are extracted into dichloromethane or ethyl acetate from the crude methanol extract and can be further purified on preparative TLC or reversed phase HPLC to yield 3 to 13 mg/mollusc or 0.015% to 0.095% dry weight of the tunicate. Lamellarin A **(121)** and E **(123)** were subjected to X-ray crystallography, while the structures of the other lamellarins were based on spectroscopic comparisons to **121** and **123**.

2.2.7. Imbricatine and fuscusine

Elliott and coworkers (97) have demonstrated that the Northeastern Pacific anemone *Stomphia coccinea* responds to a substance, imbricatine **(135)**, released by the sea star predator *Dermasterias imbricata*, by detaching from the substratum and propelling itself away from danger with a series of "whip-like" motions. Imbricatine, an isoquinoline alkaloid with an unusual thiohistidinyl group, was isolated and characterized by Pathirana and Andersen at the University of British Columbia (98). A related, though structurally simpler, isoquinoline alkaloid, fuscusine **(136)** was isolated by Faulkner's group from the antarctic sea star *Perknaster fuscus* (99). Fuscusine differs by the presence of an arginine side chain in place of tyrosine and lack of the histidinyl thioether, the dimeric disulfide of which has been isolated from echinoderm eggs (100). Bioassay guided isolations were carried out in both cases;

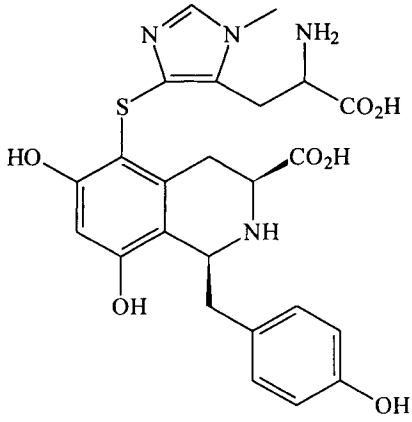


		R	R'	R''	R'''	R''''	X	X'
121	Lamellarin A:	H	Me	H	Me	Me	OMe	OH
122	Lamellarin C:	H	Me	H	Me	Me	OMe	H
123	Lamellarin E:	H	Me	Me	H	Me	OH	H
124	Lamellarin F:	H	Me	Me	Me	Me	OH	H
125	Lamellarin G:	Me	H	Me	H	H	H	H
126	Lamellarin I:	H	Me	Me	Me	Me	OMe	H
127	Lamellarin J:	H	Me	Me	Me	H	H	H
128	Lamellarin K:	H	Me	H	Me	Me	OH	H
129	Lamellarin L:	H	Me	Me	H	H	H	H

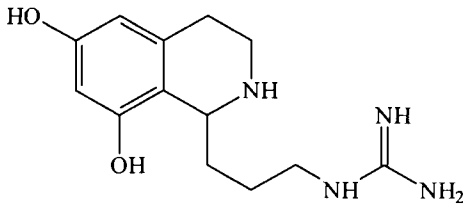


		R	R'	R''	R'''	X
130	Lamellarin B:	Me	H	Me	Me	OMe
131	Lamellarin D:	Me	H	Me	H	H
132	Lamellarin H:	H	H	H	H	H
133	Lamellarin M:	Me	H	Me	Me	OH
134	Lamellarin N:	Me	Me	H	H	H

imbricatine was obtained from the methanol extract of *D. imbricata* by adsorption and size-exclusion chromatography at a level of 6-7 mg per echinoderm. Both structures are based on analysis of one- and two-dimensional NMR data and imbricatine has been the subject of synthetic efforts (101, 102).



135 Imbricatine



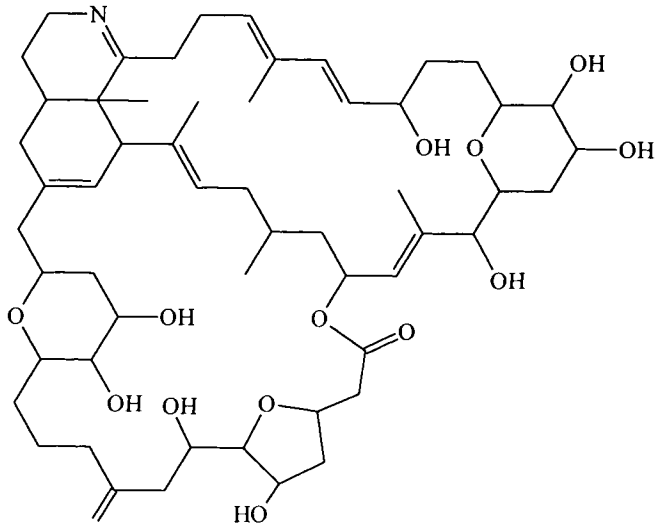
136 Fuscusine

2.2.8. Prorocentrolide

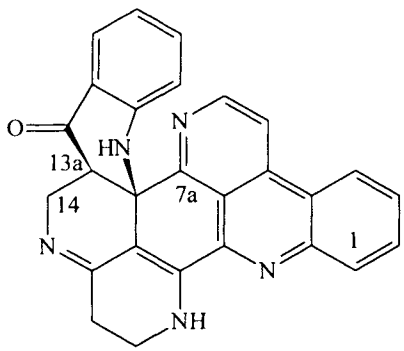
Marine dinoflagellates have been a rich source of structurally intriguing natural products, especially toxins (103). The first and so far only isoquinoline member of this group of toxins is the hexahydroisoquinoline prorocentrolide **(137)**, reported by Yasumoto and coworkers from Tohoku University, from the cultured benthic dinoflagellate *Prorocentrum lima* (104). Collected at Sesoko Island, Okinawa, algal cells from a 1000L culture were extracted with acetone and methanol and the combined crude extract concentrated and partitioned between ether and water, then *n*-butanol. Repeated normal and reversed phase chromatography yielded 70 mg of the toxin. The structure was elucidated primarily by evaluation of 2D NMR spectra with NOE experiments to assist the assignment of ether rings. Minor prorocentrolides have apparently been isolated (105) though their structures have not been published.

2.2.9. Eudistones

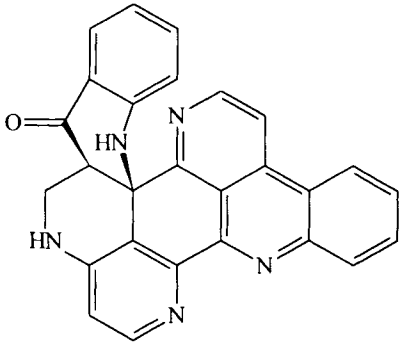
He and Faulkner (106) reported eudistones A and B **(138, 139)**, octacyclic fused heteroaromatic alkaloids bearing an isoquinoline group, from the dark green tunicate *Eudistoma* sp. collected in the Seychelles. Eudistone A, an amorphous yellow powder, and B, a white amorphous powder, are minor products relative to another alkaloid, ascididemnin. Butanol partition of the crude CH_2Cl_2/MeOH extract was subjected to Sephadex LH-20 then reversed phase HPLC to obtain 0.0023% eudistone A and 0.0018% eudistone B. Structure elucidation of the compounds relied exclusively on 2D NMR techniques to establish the planar structure. The *cis*-disposition of the appended quinoline ring was based largely on coupling constants; the coupling between H(13a) and C(7a) (1.5 Hz) was suited to a *cis* configuration (calculated for 2.6 Hz) rather than *trans* (calculated for 8.4 Hz), as were the coupling constants between $H(14_{ax})$-H(13a) and $H(14_{eq})$-H(13a).



137 Prorocentrolide



138 Eudistone A



139 Eudistone B

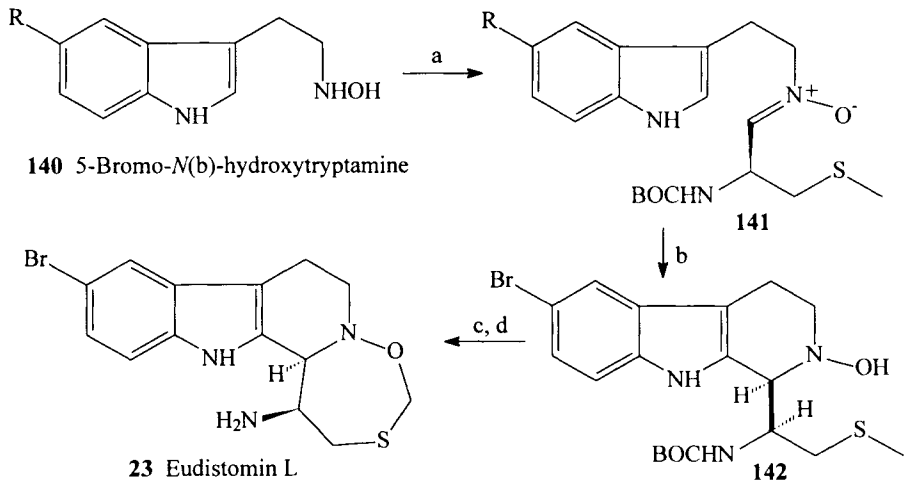
3. SYNTHESIS

3.1. β-Carboline Alkaloids

The tricyclic β-carboline system itself is most conveniently prepared by one of two methods, both of which are conducive to substitution at C(1). The Pictet-Spengler (PS) reaction has been used in many of these syntheses, especially those requiring tetrahydro-ring C

(107-119). The Bischler-Napieralski (BN) method has demonstrated great utility for fully aromatic β-carboline rings. Substitution on carbocyclic ring A of the β-carboline system requires suitably substituted tryptamine which can be prepared via the Fischer indole synthesis or one of several methods for synthesis of indole rings (28, 128).

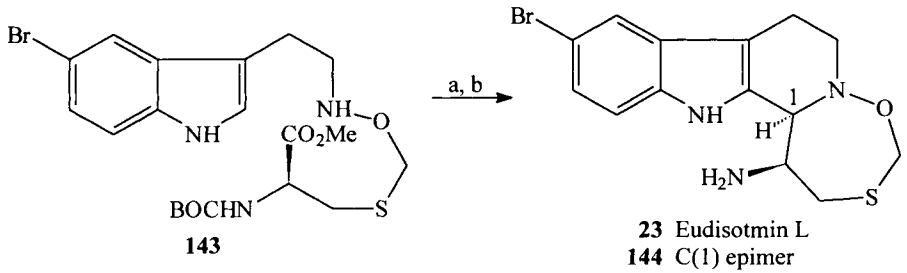
The synthetic challenge of the oxathiazepine ring of eudistomins **19-23**, combined with the potent antiviral activity, has lured several groups to devise methods leading to this unusual seven-membered ring (107-119). Eudistomin L **(23)**, for example, has been prepared (111) by the Nakagawa and Hino groups, at Chiba University, via the PS reaction of nitrone **141**, prepared by condensation of 5-bromo-*N*(b)-hydroxytryptamine **(140)** with *N*-*t*-butylcarbamate (BOC) protected D-*S*-methylcysteinal. Subsequent NCS chlorination effected the intramolecular Pummerer reaction (Scheme 2). Debromoeudistomin L (a.k.a. debromoeudistomin K **(25)**), eudistomins C, E, F, and K **(19-22)** were also prepared by this method by the Hino group (111, 113, 114). *N*(10)-Acetoxyeudistomin L was prepared by Still and coworkers using sila-Pummerer modification (110) which improves on the poor yields of the NCS-catalyzed Pummerer reaction. The highest yields of the oxathiazepine ring system have been achieved by Yoon's group in Seoul, via phase-transfer catalysis utilizing a thiol derivative of **142** and dihalomethanes (119).



140 5-Bromo-*N*(b)-hydroxytryptamine

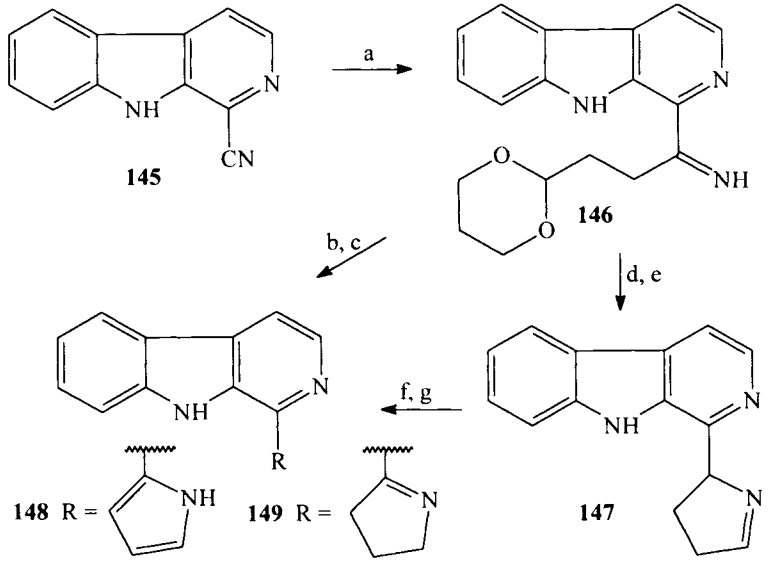
Scheme 2. Reagents and conditions: a) *N*-BOC-*S*-methyl-D-cysteinal, CH_2Cl_2, RT, 2 hr (93%). b) Trifluoroacetic acid (TFA), -78 °C, 90%. c) *N*-chlorosuccinimide, CH_2Cl_2, -78 °C, 8%. d) 1:1 TFA-CH_2Cl_2, RT, 94%.

An alternative approach, utilized extensively by Scheeren's group in the Netherlands (115-117), to circumvent the poor results with the intramolecular Pummerer reaction is to perform the Pummerer reaction first (intermolecular) followed by an intramolecular PS reaction. Thus the intermolecular Pummerer reaction was used to produce **143** (Scheme 3) which was treated under PS conditions to provide high yields of the oxathiazepine ring system (115-118); however, the intramolecular PS reaction appears to prefer the "unnatural" configuration at C(1) **(144)** (117).



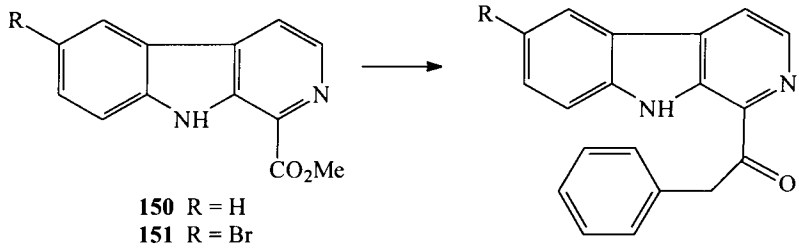
Scheme 3. Reagents and conditions: a) Di-*i*-butylaluminum hydride (DIBAH). b) TFA, -75 °C, 73% for 2 steps.

The pyrrolinyl- **(6-11)** and pyrrolyl-substituted **(12-13)** eudistomin skeletons were first prepared by Rinehart from 1-cyano-β-carboline **(145)**, which can be obtained from the corresponding acid (28). Grignard reaction with appropriately protected 3-bromopropanal (Scheme 4) provided the necessary carbons with appropriate oxidation level for cyclization to either of these ring systems. The pyrrolyl-substituted eudistomins then result upon hydrolysis of the imine and acetal functions with concomitant cyclization in the presence of ammonia. The pyrrolinyl-eudistomins require reduction of the imine to the amine followed by acetal hydrolysis and simultaneous ring closure to isomer **147**. Reduction of the imine **147** followed by allylic oxidation with sodium hypochlorite isomerizes **147** to the pyrrolinyl-eudistomin skeleton **(149)**.



Scheme 4. Reagents and conditions: a) 2-(1,3-dioxa-2-cyclohexyl)ethyl magnesium bromide, THF, 0 °C. b) H^+, 84% for 2 steps. c) NH_4OAc, HOAc, reflux, 88%. d) $NaBH_4$, MeOH, 78% for 2 steps. e) aq. $HClO_4$, THF, 74%. f) $BH_3{\cdot}NMe_3$, HOAc, THF, 0 °C, 75%. g) NaOCl. h) Na_2CO_3, 75% for 2 steps.

Eudistomins S and T **(16, 17)** have been prepared by a similar strategy. Still and McNulty (120) treated 1-carbomethoxy-β-carboline **(150)**, or its 5-bromo analog **(151)**, with a modified Grignard reagent, leading directly to eudistomins S and T (Scheme 5). A direct route to 1-cyano-β-carboline **(145)** was developed by Bracher and coworkers from 1-oxo-β-carboline, as was the elaboration of **145** into eudistomin T on treatment with benzylmagnesium chloride (121).



150 R = H
151 R = Br

16 Eusistomin S: R = Br
17 Eudistomin T: R = H

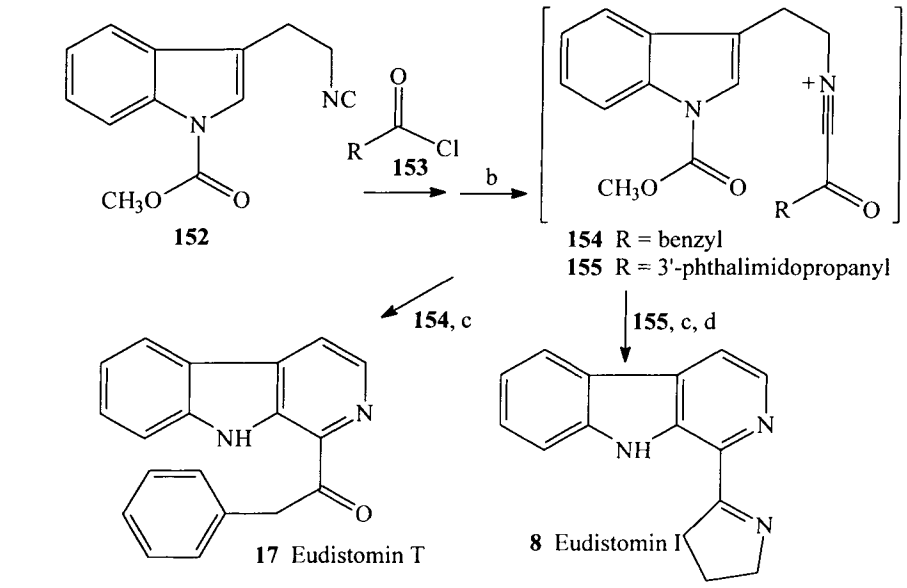
Scheme 5. Reagents and conditions: Benzylmagnesium chloride, LiCl, Et_2O, reflux.

Two alternate approaches to eudistomin T **(17)** have appeared, both of which also provided a route to eudistomin I **(8)**. VanWagenen and Cardellina treated isonitrile **152** (Scheme 6) with the appropriate acid chloride **(153)** to yield the α-ketoimidoyl chloride **154** (or **155**), which underwent silver ion mediated cyclization to the β-carboline ring system (122). Wasserman and Kelly (123), on the other hand, used acid chlorides **153** (Scheme 7) to acylate triphenylphosphine **156**. Subsequent condensation of tricarbonyl **158** (R = benzyl), from ozonolysis of **157**, with tryptamine, followed by oxidization yields eudistomin T. Eudistomins I **(8)** and M **(13)** were also obtained by the latter, tricarbonyl, method (123); eudistomins M and A **(12)** were obtained, by Molina's group in Spain, utilizing an aza-Wittig reaction (124).

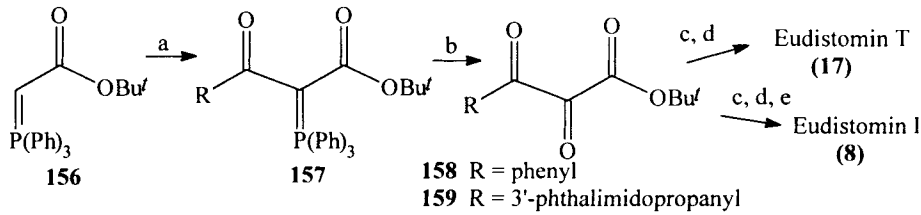
The PS reaction has been used by Still and coworkers to prepare woodinine **(14)**, eudistomin T **(17)** , and a eudistomidin B analog (Scheme 8) (125, 126). Woodinine was prepared from L-proline via intermediate **160**; the diastereoselectivity of the PS reaction provides roughly an 85/15 ratio of the desired "trans" isomer. Intermediate **161** has previously been elaborated into eudistomins I **(8)** (28) and eudistomin H **(7)** can be derived directly from eudistomin I (127). That woodinine derives from an L-amino acid while the oxathiazepino-eudistomins derive from a D-amino acid is curious from a biosynthetic point of view.

Eudistomidin A **(11)** and eudistomins H **(7)**, I **(8)** and P **(9)** have been made (127, 128) by the Bischler-Napieralski (BN) reaction, a method used extensively by the Hino group. Appropriately substituted tryptamine was condensed with BOC-prolinoyl chloride, then treated under BN conditions ($POCl_3$ or polyphosphoric ester (PPE)) to produce a 5,7-disubstituted eudistomin skeleton **(163)**. Eudistomin I thus results when starting from tryptamine (Scheme 9, R = R' = H), eudistomin H from 5-bromotryptamine (Scheme 9, R = Br, R' = H), eudistomidin A from 5-bromo-7-hydroxytryptamine (Scheme 9, R = Br, R' = tosylate); eudistomin P is obtained from the use of 6-bromo-5-methoxytryptamine.

The simplest eudistomins, substituted β-carboline alkaloids, have been prepared either by derivatization of β-carboline itself, or by placing the substituents on aniline and building the indole ring. Eudistomin D **(1)** and N **(3)**, for example, were prepared by treatment of

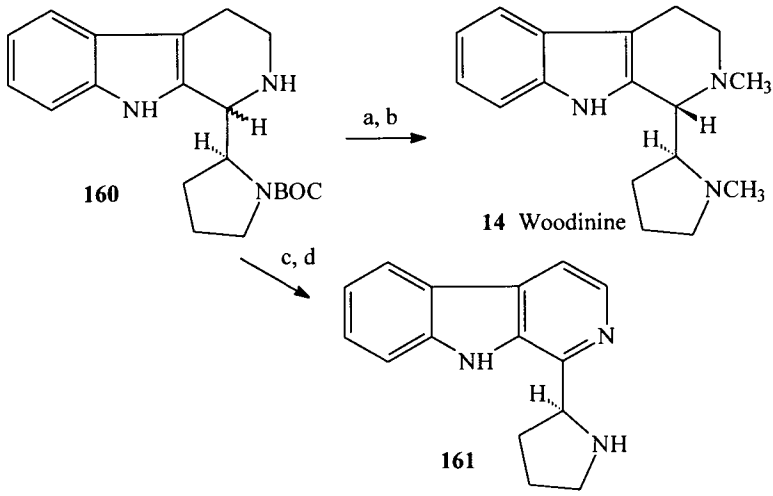


Scheme 6. Reagents and conditions: b) $AgBF_4$, -20 °C, 92% for 2 steps, **152** to **154**, or 52% for 2 steps, **152** to **155**). c) S_8, 200 °C, 73%. d) H_2NNH_2, MeOH, 23% for 2 steps.

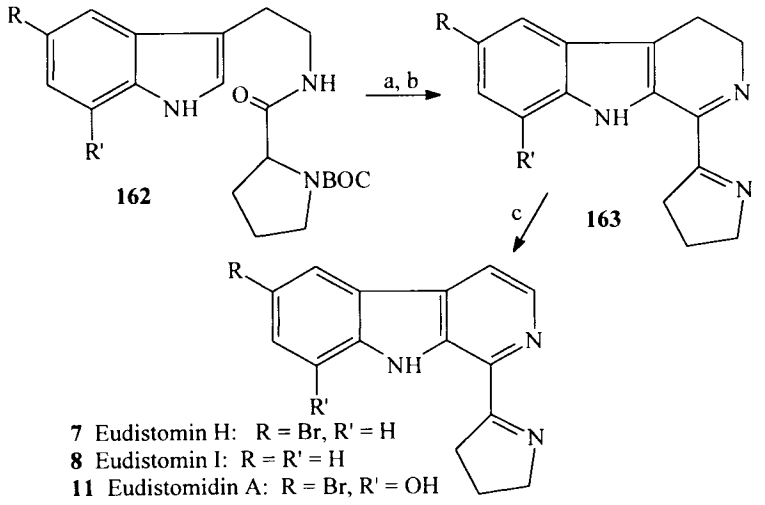


Scheme 7. Reagents and conditions: a) Acid chloride **153**, PhH, 94-96%. b) O_3, 64-78%. c) Tryptamine, TFA, PhH, 76-82%. d) Pd/C or S_8, 83-88%. e) NH_2NH_2, EtOH/PhH, 86%.

appropriately substituted β-carboline with bromine and eudistomin O **(4)** was prepared from 6-bromoindole (28). An approach to 1-substituted β-carbolines utilizing an aza Wittig reaction of an iminophosphorane has been described, leading to the carbon skeleton of the pyrrolyl-substituted eudistomins (124), though complete synthesis of the natural products has yet to be reported.

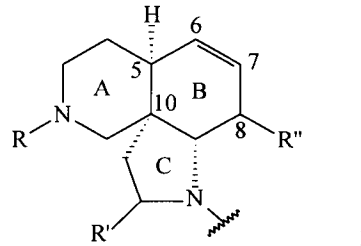


Scheme 8. Reagents and conditions: a) $ClCO_2CH_3$, Et_3N, CH_2Cl_2, 20 °C, 3 hr, 93%. b) $LiAlH_4$, THF, Δ, 7.5 hr, 65%. c) Pd/C, Δ, xylene, 6 hr, 80%. d) TFA, CH_2Cl_2, 30 min, 65%.



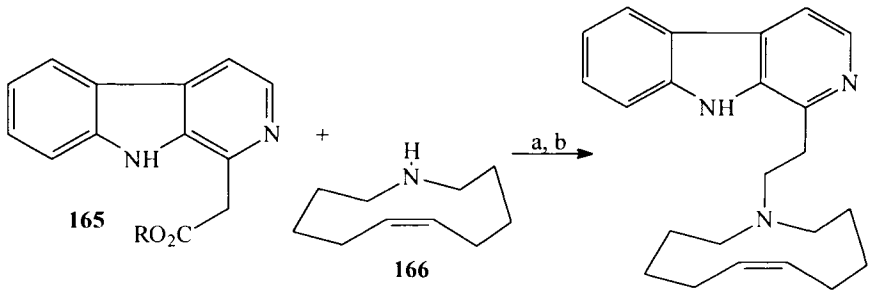
Scheme 9. Reagents and conditions: a) PPE or $POCl_3$, CH_2Cl_2, 70-75%. b) TMSI, 48%. c) DDQ, PhH, 64%.

Most synthetic effort directed toward the manzamines has focused on the complex isoquinoline core **(164)**, and none has succeeded in completing the preparation of one of the isoquinoline-bearing manzamines. However, two total syntheses of manzamine C **(35)**, which lacks the tricyclic core **(164)**, have been reported, one by Hino utilizing a Bischler-Napieralski (114, 129, 130), the second by Gerlach, at the University of Bayreuth, Germany, using the Pictet-Spengler (131) reaction; intermediate **165** (Scheme 10) was central to both the BN and PS methods.



164 Tricyclic core of the manzamines

In the preparation of β-carbolines such as **165**, aromatization of ring C has proved much more difficult from the PS tetrahydro-β-carboline intermediate than the BN dihydro-β-carboline intermediate (129, 123). Coupling **165** with macrocycle **166** yielded an amide which was reduced to the tertiary amine, manzamine C.

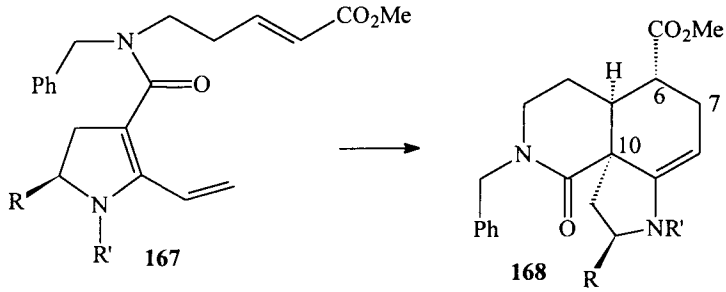


35 Manzamine C

Scheme 10. Reagents and conditions: a) R = K; DMF, diphenylphosphoryl azide (DPPA), Et_3N, 87%. b) $LiAlH_4$, THF, 46%.

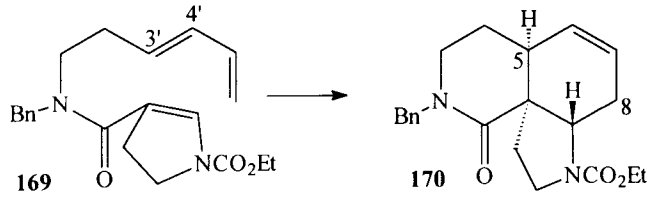
The tricyclic core **(164)** has been prepared by a number of different routes, most commonly by a Diels-Alder reaction. Three approaches to the Diels-Alder have been followed. Pandit, at the University of Amsterdam, first prepared the tricyclic core (132, 133) focusing on the concurrent construction of the C(6)-C(7) and C(5)-C(10) bonds via an intramoleculer Diels-Alder reaction (Scheme 11). The stereochemical preference for **168** results from an unfavorable interaction of the alkoxymethylene (R in **168**) with the dienophile, leading to a 3.5:1 mixture in favor of the desired diastereomer **168** (134).

Two other intramolecular Diels-Alder reactions focus on concurrent formation of the C(5)-C(10) and C(8)-C(9) bonds (135-138). Martin and coworkers at the University of Texas at Austin (135, 136) found that Lewis acid catalysis of **169** provided the desired diastereomeric product, **170** (Scheme 12); the stereochemical consequences of cyclization of **169** was investigated with respect to the $\Delta^{3'}$ stereochemistry, demonstrating maximum selectivity (8:1), over the C(5) epimer, when the $\Delta^{3'}$ olefin was *cis* (136). A subsequent extension of this method by Martin resulted in the introduction of an alkoxymethylene group to C(6) of **170**, thus setting up intermediate **170** for attachment of the β-carboline ring system (136). The



Scheme 11. Reagents and conditions: $PhCH_3$, Δ, 6 hr, 96% (R = H, R' = CO_2Et) or xylene, Δ, 2 hr, 90% (R = $CH_2OTBDMS$, R' = CBz).

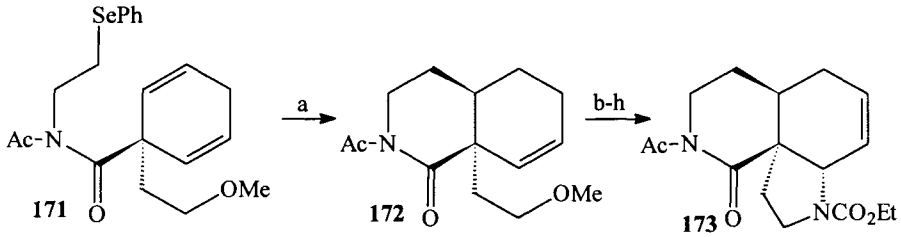
second of these Diels-Alder approaches was developed by Leonard, at the University of Salford; this method utilized a sulfolene to generate the diene, resulting in the desired stereochemistry about the octahydroisoquinoline ring junction in a model study (137); however, with the appended ring C, the undesired C(5β) epimer of **170** predominated (138).



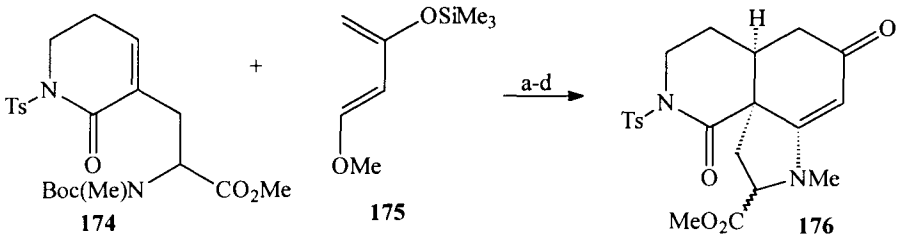
Scheme 12. Reagents and conditions: $EtAlCl_2$ (1.5 eq), $PhCH_3$, 110 °C, 72 hr, 71%.

A radical cyclization has been used by Hart, at The Ohio State University, to prepare the manzamine tricyclic core (139). Utilizing tri-*n*-butyltin hydride to mediate the cyclization of selenide **171**, the desired stereochemistry of the octahydroisoquinoline ring **(172)** was established (Scheme 13); electrophilic catalysis generated the tricyclic intermediate **174**. An anionic cyclization leading to a tricyclic intermediate is being developed by Markó, at the University of Sheffield, toward which he has recently reported a model study (140).

Intermolecular Diels-Alder approaches have concentrated on the C(5)-C(6) and C(9)-C(10) bond forming reaction (141-146). Representative of the intermolecular Diels-Alder is that developed by Nakagawa and Hino (Scheme 14) involving high pressure treatment of dieonphile **174** with the Danishefsky diene **(175)** (141, 142), to produce, after removal of the protecting group, the desired tricycle **176**. An alternative intermolecular Diels-Alder reaction, from the laboratory of Simpkins at the University of Nottingham, utilizing a similar dienophile and an 8-hydroxy-3-octen-substituted diene, set up to form the macrocyclic ring D of manzamine A, produced disappointing levels of macrocyclization product (145, 146).

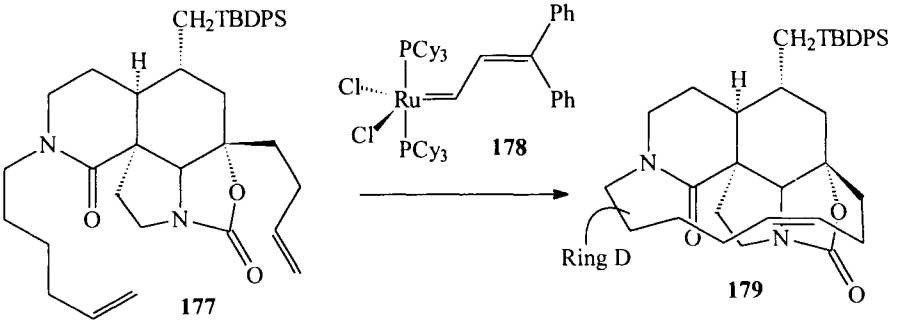


Scheme 13. Reagents and conditions: a) *n*-Bu_3SnH, AIBN, PhH, Δ 67% (4:1 mixture with epimer). b) BBr_3, CH_2Cl_2, -78 °C to RT, 74%. c) TsCl, pyridine, 0 °C. 64%. d) NaN_3, DMF, RT to 40 °C, 68%. e) Ph_3P, H_2O, THF. f) $ClCO_2Et$, Et_3N, 70%. g) I_2, K_2CO_3, 76%. h) DBU, $PhCH_3$, Δ, 62%.



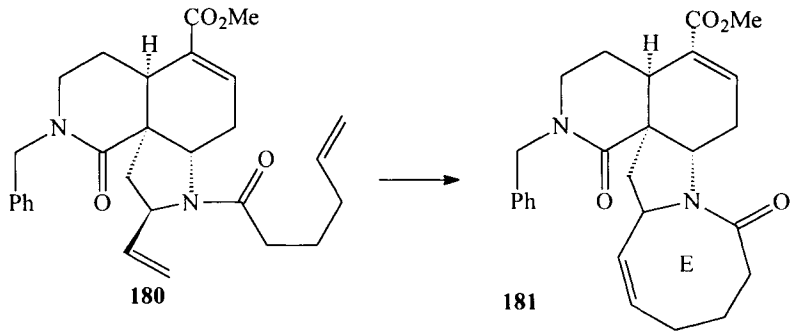
Scheme 14. Reagents and conditions: a) High pressure (11Kb), 90 hr, $PhCH_3$. b) Camphorsulfonic acid, THF. c) TFA, CH_2Cl_2. d) K_2CO_3.

Ring D (see Scheme 15) has been successfully appended to the tricyclic core by an olefin metathesis reaction (147). Treatment of **177**, prepared largely by the method described in Scheme 11, with the ruthenium complex **178** (Cy_3P = tricyclohexylphosphine) resulted in the ABCD ring system of the manzamines.

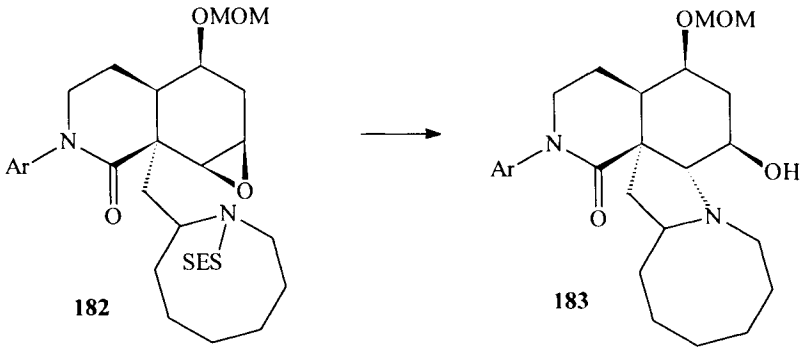


Scheme 15. Reagents and conditions: Benzene-d_6, 5 days, RT, 30%.

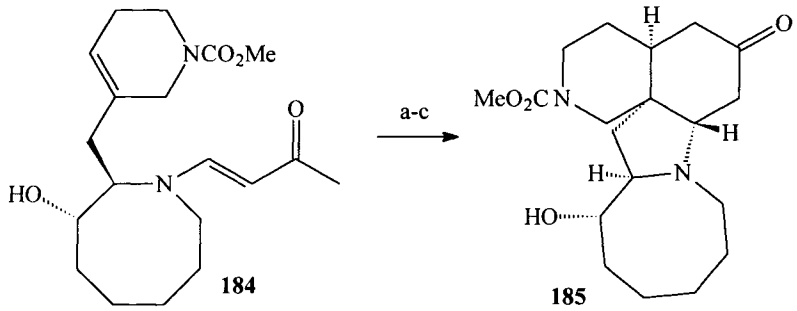
Ring E (see Scheme 16) has also been assembled onto the tricyclic core (147-152). Two of the procedures, reported by Hino (149) and Pandit (151) involve homologation of previously prepared tricyclic core with C_6 alkenyl chains terminated by a carboxylate group, leading to ring E lactams. The olefin metathesis reported by Pandit (147), illustrated in Scheme 16, also produces a ring E lactam while two other methods produce ring E as the desired macrocyclic tertiary amine (148, 152). In one such syntheses an epoxide ring opening reaction serves to complete the ABCE ring system (Scheme 17); the eight-membered azocine **182** was prepared by Campbell and Hart via intramolecular *N*-alkylation utilizing a new *N*-acyl sulfonamide protecting group (148). Winkler, at the University of Pennsylvania, has developed a nice method utilizing an intramolecular vinylogous amide photocycloaddition reaction (Scheme 18); using eight-membered ring precursor **184**, prepared in four steps from readily available starting material, the desired tetracycle **185** was produced with the appropriate stereochemistry in just three steps (152).



Scheme 16. Reagents and conditions: $Mo(CHCMe_2Ph)[N\text{-}2,6\text{-}(i\text{-}Pr)_2C_6H_3][OCMe(CF_3)_2]_2$, PhH, 50 °C, 4 hr, 63%.



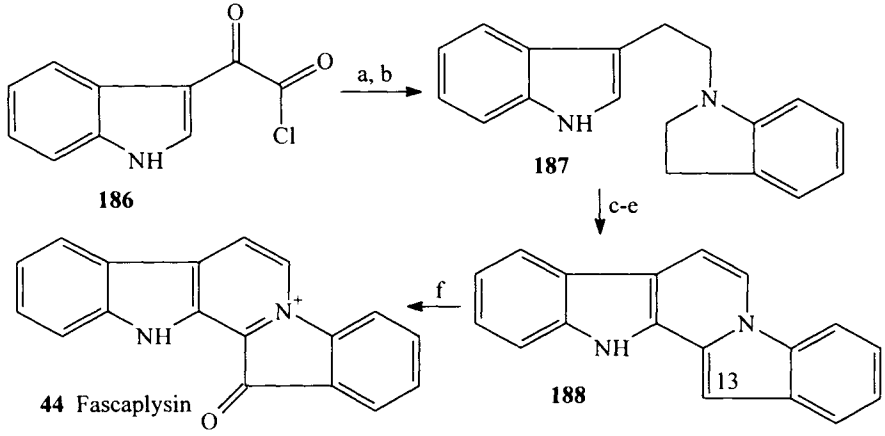
Scheme 17. Reagents and conditions: CsF, DMF, Δ, 72%.



Scheme 18. Reagents and conditions: a) hν,/Et_2O, -78 °C. b) Et_3N-HCl. c) *N,N*-dimethylaminopyridine (DMAP), 36% for 3 steps.

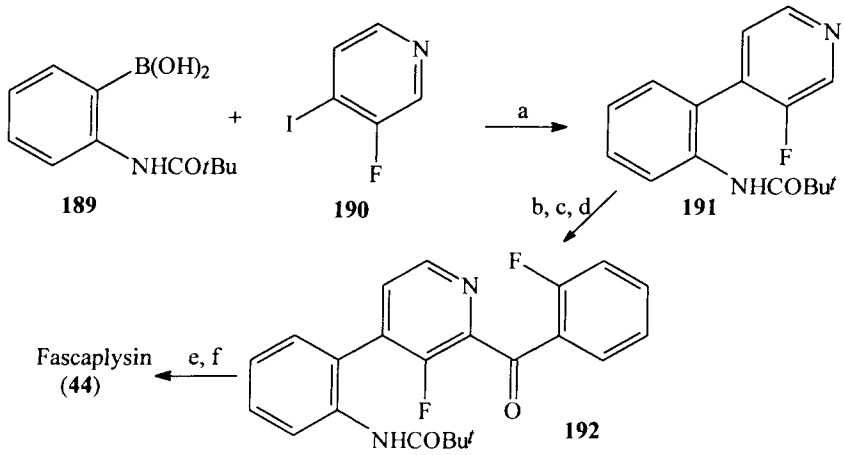
Two other methods toward the manzamines have been reported recently. A preliminary report by Baldwin's group at Oxford of a biomimetic approach described the preparation of a key tricycle, which bears a resemblance to likely natural product precursors to the manzamines (153). A multistep synthesis from Overman's group at the University of California at Irvine, featuring an intermolecular Mannich reaction, starts from D-(-)quinic acid, thus setting the absolute stereochemistry (154).

Three quite distinct and highly efficient methods have been reported for the preparation of fascaplysin **(44)**. The first such synthesis (155, 156), reported by Gribble and Pelcman at Dartmouth College, and involved coupling of two indoles (Scheme 19), leading to fascaplysin in a 65% overall yield and requiring only a single chromatographic step. The aromatic intermediate **188** undergoes facile electrophilic substitution at C(13), yielding, on treatment with oxalyl chloride or Vilsmeier reagent ($POCl_3$, DMF), homofascaplysins B **(52)** and C **(53)** in equally impressive 76% and 67% overall yields (from indole).



Scheme 19. Reagents and conditions: a) Indoline, K_2CO_3, THF, RT, 2 hr, 93%. b) AlH_3, THF, RT, 75 min, 97%. c) MnO_2, $CHCl_3$, Δ, 4 hr, 99%. d) TFA, RT, 30 min, 88%. e) Pd/C, $(EtOCH_2CH_2)_2O$, Δ, 6 hr, 93%. f) CH_3CO_3H, MeOH, HOAc, 0 °C, 45 min, then conc HCl, 85%.

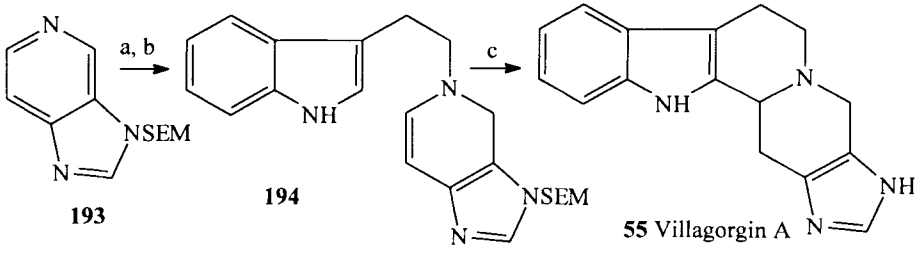
The second synthesis of fascaplysin **(44)**, from labs at the CNRS, is also very high in overall yield (157). Palladium-catalyzed cross-coupling of the boronic ester **189** with the halogenated pyridine **190** lead to intermediate **191** (Scheme 20). Metalation of **191** with *n*-BuLi was regioselective, due in part to the inductive effects of nearby electronegative groups. The double cyclization of **192** to fascaplysin provides the natural product in 76% overall yield.



Scheme 20. Reagents and conditions: a) $Pd(PPh_3)_4$, 2M K_2CO_3, toluene, reflux under Ar, 48 hr, 98%. b) BuLi, THF, -75 °C, 1 hr. c) 2-fluorobenzaldehyde, 1Hr, -75 °C, 95% for 2 steps. d) MnO_2, toluene, reflux, 2 hr, 99%. e) Pyridine, HCl, 170 °C, 10 min. f) NH_4OH/ice, 82% for 2 steps.

A more recent synthesis of fascaplysin **(44)**, from Molina and coworkers at the Universidad de Murcia, Spain, utilized a tandem aza-Wittig with electrocyclic ring-closure to generate the β-carboline ring (158).

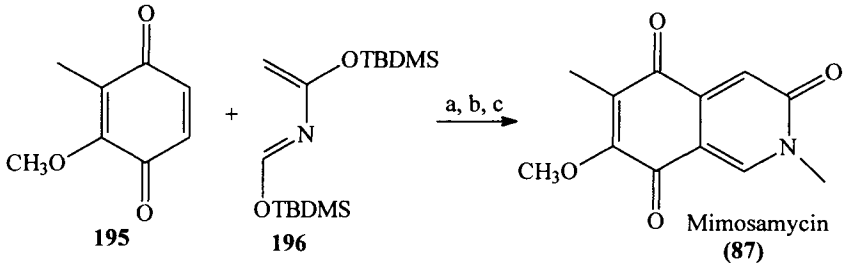
Villagorgin A **(55)** was recently prepared, by Grazul and Kuehne at the University of Vermont, by an expedient method (Scheme 21), confirming the unique structure (159). Villagorgin B **(56)** can be obtained from villagorgin A by oxidation.



Scheme 21. Reagents and conditions: a) Tryptophyl bromide, MeOH, $NaHCO_3$, 29%. b) NaBH4, NaCN, water/methanol, ether (10:1:25), 75%. c) MeOH, 25% Aq. HCl, Δ, 65%.

3.2. Isoquinoline Alkaloids

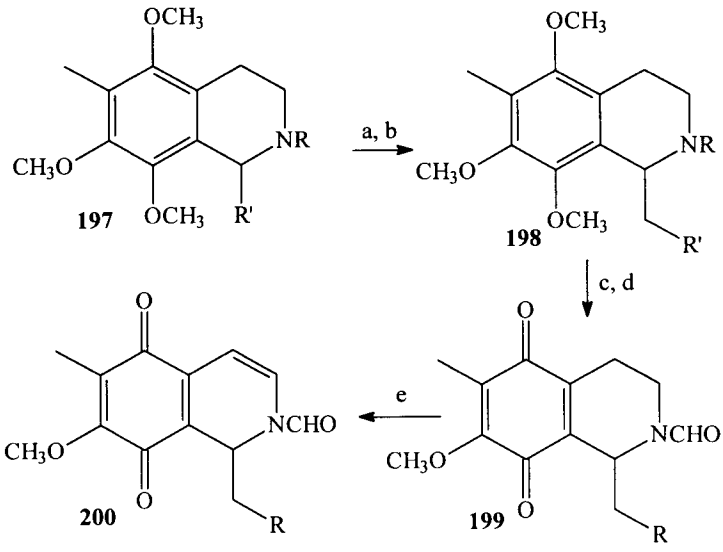
Mimosamycin **(87)** has been synthesized by several routes (160-164). The most expedient synthesis was reported by McKillop and Brown, at the University of East Anglia, and utilized a heterodiene approach to the Diels-Alder reaction (Scheme 22) to convert quinone **195** into mimosamycin (163). Phase-transfer catalysis was used to effect the notoriously difficult methylation (step c) in 90%. Similar methodology has been used by Park and Schmitz to prepare perfragilin B **(93)**, whereby a 2,3-di(methylthio)ether quinone was used in place of 2-methoxy-3-methylquinone **(195)** (165).



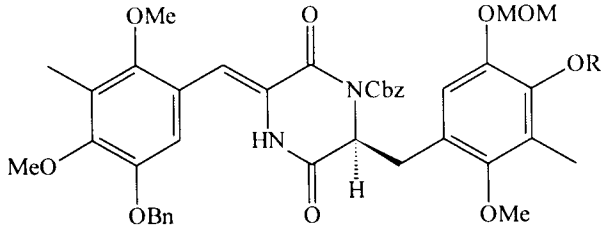
Scheme 22. Reagents and conditions: a) PhH, reflux. b) HCl, 60% for 2 steps. c) CH_3I, Na_2CO_3, DMF, phase-transfer catalyst, 90%.

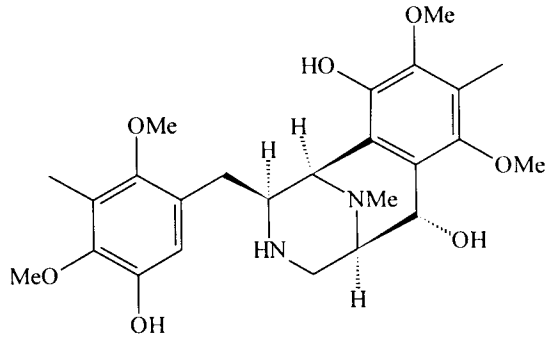
Renierone **(75)** and several of its naturally occurring derivatives have been the subject of several syntheses (166-171). An efficient method to these sponge and nudibranch compounds is illustrated in Scheme 23 (166-169); **197** (R = benzyl, R' = CO_2Bu), available in three steps from the corresponding trimethoxy-*N*-benzyl amine (165, 169), can be elaborated into **198** (R = H, R' = CH_2OH), which is set up to be converted into renierol by ceric ammonium nitrate (CAN) (168) or silver (166) catalyzed hydrolysis to the *p*-quinone, followed by palladium on carbon oxidation to the fully aromatic alkaloid (166, 168). Alternately, **197** (R = benzyl, R' = CN), available in four steps from a trimethoxybenzaldehyde, has been reduced to R' = methyl, then similarly aromatized to yield the natural product **77** (168). Reduction of **197** (R = benzyl, R' = CO_2Bu) to the primary alcohol **198** (R = H, R' = CH_2OH), followed by *N*-formylation, yields an intermediate **200** (R = OH) which has been elaborated into the various *N*-formyl derivatives, **84** (**200**, R = O-angelate) (169), **85** (**200**, R = OAc), and **86** (**200**, R = $OCOCH_2CH_3$) (170).

Renieramycin A **(95)** has been synthesized recently by the Fukuyama group at Rice University (172), utilizing methodology they had previously developed for the synthesis of saframycin. Requiring twenty-nine steps from 2,4-dimethoxy-3-methylbenzaldehyde, the general scheme involved constructing the diketopiperazine **201** followed by acyliminium ion-mediated cyclization to generate the new ring present in **202**. Intermediate **202** underwent a Pictet-Spengler reaction with glycolaldehyde which, after oxidation of the two hydroquinone rings to quinones, resulted in renieramycin A. X-ray crystallography of the Pictet-Spengler product secured the relative stereochemistry at that position.

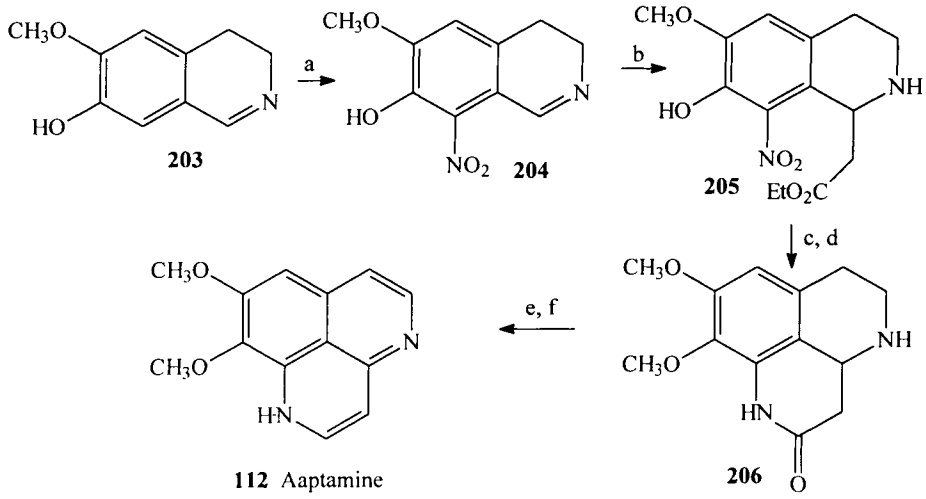


Scheme 23. Reagents and conditions: a) Aq. MeCN, pyridine-2,6-dicarboxylic acid *N*-oxide, 0-5 °C, 2 hr, 52-56%. b) Potassium nitrosodisulfonate, 64%. c) Acetyl or propionyl chloride, pyridine, 80%. d) CAN, 52%. e) Pd/C, PhH.

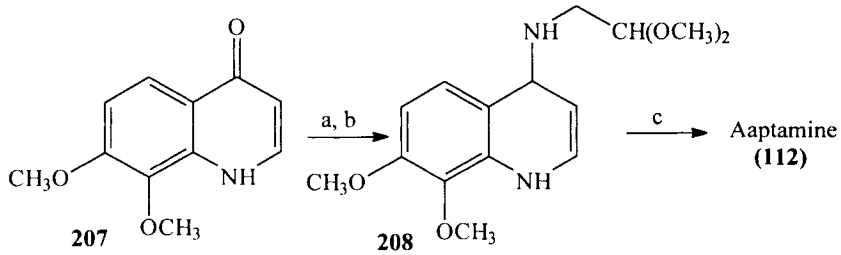




Seven syntheses of aaptamine **(112)** have appeared (173-181). The first synthesis, reported by Pelletier and Cava (173, 174), prepared the tricyclic system of aaptamine via lactam **206** (Scheme 24). This synthesis proved amenable to preparation of demethyloxyaaptamine **(114)** as well. Kelly and Maguire, at Boston College, developed an alternative method whereby quinolone **207** was elaborated into aaptamine by an intramolecular Pomeranz-Fritsch type reaction (Scheme 25), leading directly to the natural product (175).



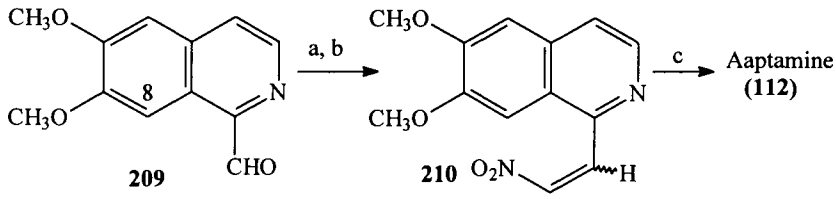
Scheme 24. Reagents and conditions: a) 40% HNO_3, $NaNO_2$ (cat), 5 °C, 60%. b) $HO_2CCH_2CO_2Et$ (1.3 eq), 120 °C, 70%. c) CH_2N_2, Et_2O, CH_2Cl_2, 100%. d) H_2, Pd-C, 10% HCl, 65%. e) BH_3, THF, 95%. f) 5% Pd-C, xylene, reflux, 60%.



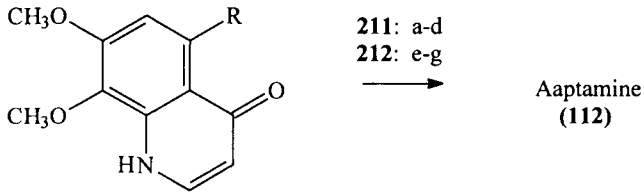
Scheme 25. Reagents and conditions: a) $POCl_3$, 86%. b) $H_2NCH_2CH(OCH_3)_2$, 52%. c) CF_3SO_3H, SbF_5, TFA, 34%.

Two highly efficient preparations of aaptamine have appeared; the first, from the Tollari lab in Milan, took advantage of a rare nitrene-insertion reaction (Scheme 26) yielding aaptamine in three steps (50% overall yield) from the known 6,7-dimethoxyisoquinoline-1-carboxaldehyde **(209)** (177). The second, from Kubo's group at the Meiji College of Pharmacy, utilized an aaptamine precursor very similar to **210** in having a second nitro group at C(8) (see **209**), which was efficiently cyclized, on reduction of the two nitro groups, to aaptamine in 83% yield

(171); the dinitroisoquinoline cyclization precursor was prepared in moderate yield in two steps from a known compound. A thermal cyclization of a 1-azahexatriene, prepared from **211** (Scheme 27), was utilized by Hibino and coworkers at Fukuyama University, providing the natural products **112** and **114** in eight and nine overall steps, respectively, of moderate yield (179); a series of similar synthetic steps led to **212** which was efficiently converted into aaptamine by Raphael's group at Cambridge (178). Yamanaka's group at Tohoku University used palladium-catalyzed couplings in a 12-step preparation of aaptamine (176).



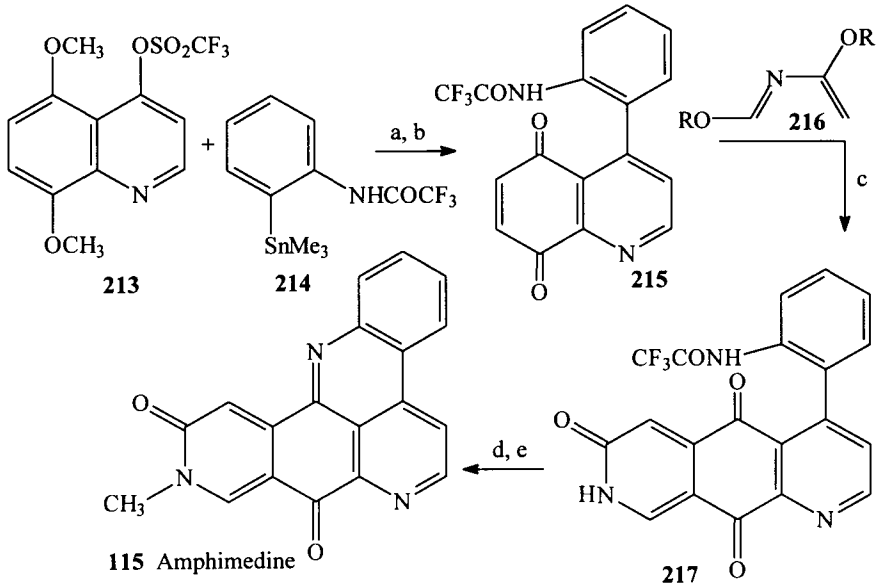
Scheme 26. Reagents and conditions: a) Nitromethane, Et_2NH, 0 °C, 1 hr. b) Pyridine, Ac_2O, 0 °C, 14 hr, 85% for 2 steps. c) Triethylphosphite, reflux, 150 min, 58%.



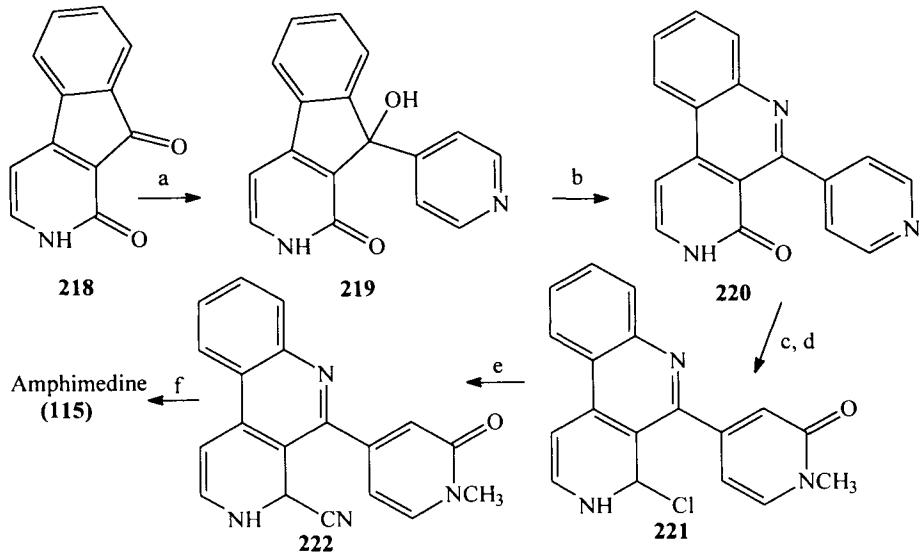
211 R = $CH{=}CH_2$
212 R = CH(OTBDMS)CN

Scheme 27. Reagents and conditions: a) Benzyl bromide (BnBr), NaH, NH_2OH, NaOAc, EtOH, reflux, 1hr, 33%. b) BnBr, NaH, DMF (13%). c) Δ, 67%. d) HCl (con), reflux, 90%. e) Ra-Ni, H_2, 91%. f) Hexamethyldisilazane, TsOH (cat). g) MeOH, HCl, 51% for 2 steps.

Three total syntheses of amphimedine **(115)** have appeared (182-188). Echavarren and Stille used the quinoline **213**, obtained in one step from readily available starting materials, to elaborate (Scheme 28) amphimedine in seven steps (21-23% overall yield), utilizing a palladium-catalyzed cross coupling reaction of stannane **214** and a hetero-Diels-Alder of quinone **215** (182). A similar strategy by Kubo and Nakahara, involving essentially the same key hetero-Diels-Alder reaction, resulted in much lower yields of cycloadduct (183); solvent apparently plays a crucial role in this step (182). A significantly different approach by Prager's group at the Flinders University of South Australia, yielded amphimedine in six steps of generally high yield starting from the known azafluoreone **218** (Scheme 29) (184, 185). Other approaches are being studied but have not yet been completed (186-188), two of which utilize hetero-Diels-Alder reactions, either for construction of the lactam ring (184) or for the terminal heterocyclic ring, the later being an intramolecular hetero-Diels-Alder utilizing an oxazole diene, a Kondrat'eva reaction (187). A vinyl nitrene was used to construct one of the heteroaromatic rings in one synthesis (186).



Scheme 28. Reagents and conditions: a) $Pd(PPh_3)_4$, LiCl, dioxane, 100 °C, 16 hr, 71%. b) $CeNH_4NO_3$, acetonitrile-water, 23 °C, 15 min, 85%. c) THF, 23 °C, 6 hr, 48%. d) HCl-THF, 70-80 °C, 3 hr, 86%. e) Me_2SO_4, K_2CO_3, DMF, 23 °C, 3 hr, 96%.

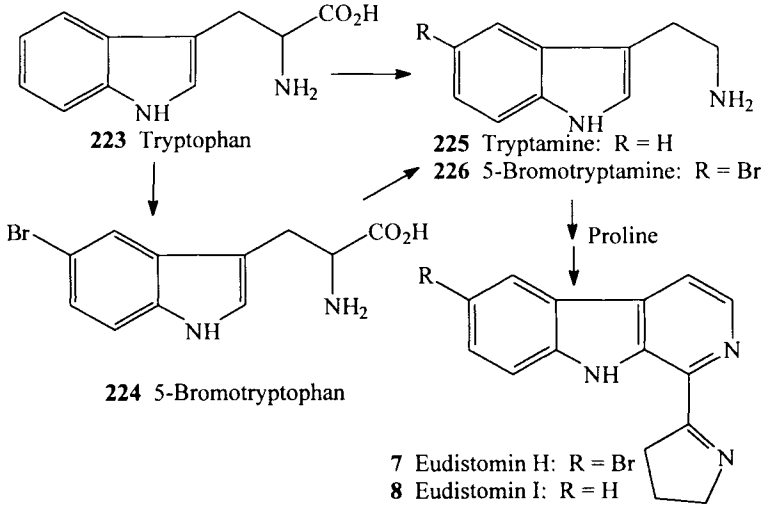


Scheme 29. Reagents and conditions: a) Me_3SiCl, Et_3N, THF, 60 °C, then 4-bromopyridine, BuLi, -40 °C, 2 hr, 87%. b) NaN_3, PPA, 45 °C, 20 hr, 69%. c) PCl_5, DMF (cat) in $POCl_3$, 180 °C, 20 hr, 90%. d) $MeOSO_2F$, 20 °C, 40 min, then KOH, $K_3Fe(CN)_6$, 20 °C, 10 hr, 61%. e) CuCN, DMSO, 150 °C, 4 hr, 70%. f) PPA, 90 °C, 5 hr, 35%.

4. BIOSYNTHESIS

Biosynthetic investigation of marine metabolites is a field in its infancy with methodology undergoing constant development (189, 190). Biosynthetic investigations of marine invertebrate metabolites have been carried out with organisms from most marine phyla, including macrofauna such as sponges, corals, ascidians, and nudibranchs (189, 190), as well as marine microorganisms (189).

Tunicates are the only marine invertebrates in which alkaloid biosynthesis has been extensively investigated (189). In addition to the eudistomins, described below, the tripeptide tunichromes have been investigated, by Nakanishi and coworkers at Columbia University, in the solitary tunicate *Ascidia nigra* (191) and shermilamine, a benzo-3,6-phenanthroline alkaloid, has been studied in *Cystodytes dellechiajei*, by Steffan and coworkers at the University of Munich (192). The origin of the β-carboline ring system of the eudistomins has been studied, by Baker's group at Florida Tech, in *Eudistoma olivaceum* (193, 194). Radiotracer experiments were used to elucidate the biosynthetic precursors to eudistomin H **(7)** and I **(8)** in Floridian collections of *Eudistoma olivaceum*. Both radiolabeled tryptophan and proline were incorporated by *E. olivaceum* into eudistomins H and I and tryptamine was incorporated into eudistomin I, to the exclusion of eudistomin H. Bromotryptamine and bromotryptophan are incorporated into eudistomin H (Scheme 30). These results suggest eudistomin biosynthesis proceeds from the amino acids via decarboxylation, halogenation, then condensation with proline.

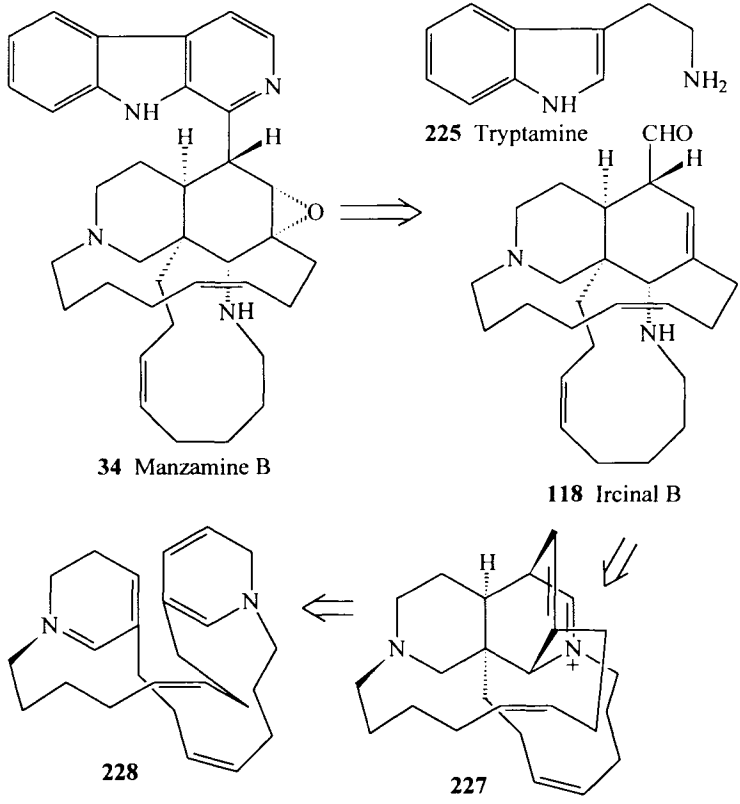


Scheme 30. Biosynthetic origin of Eudistomins H and I in *Eudistoma olivaceum*.

The specificity of tryptamine incorporation into eudistomin I **(8)** has been demonstrated using stable isotopes while tryptophan was demonstrated to be a specific precursor using double-label radiolabeled precursors. In the latter case, incorporation of L-[5-^{3}H]tryptophan/ L-[*side chain* 3-^{14}C]tryptophan into eudistomin I (193) was observed to occur without change in the ^{3}H/^{14}C ratio. In the former experiment, enhancement of the ^{13}C signal at C(2) of eudistomin I was observed when [2'-^{13}C]tryptamine was administered to the tunicate (195).

A brief report (105) of prorocentrolide (**137**) biosynthesis suggests acetate, polyketide, succinate and hydroxymethylglutarate units are present. The origin of the nitrogen is as yet unknown, though polyketide carbons contribute to the isoquinoline ring system.

While no biosynthetic work has been published on the manzamines, a significant accumulation of data, in the form of closely related natural products, has led to reasonable conjecture as to the origin of this complex alkaloid ring system (50, 196, 197). The "retro-biosynthetic" scheme illustrated in Scheme 31 was suggested in 1992 by Whitehead and Baldwin (196) and in the ensuing two years several of the proposed intermediates have actually been described as natural products from sponges. For example, the discovery by Kobayashi of the ircinals and ircinols (47, 91) adds significant credence to the proposed pathway since the β-carboline ring system could arise from condensation of the aldehyde with tryptamine (see Scheme 1). Further, pentacyclic alkaloids ingenamine, isolated by Andersen and coworkers from *Xestospongia ingens* (197), and keramphidin B, reported by Kobayashi's group from an Okinawan *Amphimedon* sp. (198), are essentially reduced-imine analogues of **227**. The Okinawan sponge also contained ircinals and manzamines. The absolute stereochemistry of the manzamines (43) and ircinals (47) differ from that of ircinols (91) and ingenamines (199), suggesting either that enantiomeric enzymes participate in this unique biosynthetic pathway, or that the enzymes involved in the early stages of the biosynthesis are indiscriminate.



Scheme 31. Retrobiosynthetic analysis of the manzamine skeleton (adapted from 196).

5. BIOACTIVITY

Many of the β-carboline and isoquinoline alkaloids described here display potent, and often selective, cytotoxicity (Table 1, 2) or exhibit antimicrobial activity (Table 3). Specific activity in enzyme-based assays and other activity is described below.

The eudistomins display a variety of pharmacological activities including potent antiviral activity (26, 28), broad spectrum antibiotic activity (Table 3) and cytotoxicity (Table 1, 2). The oxathiazepino-eudistomins **(19-25)** are the most potent antiviral agents; eudistomin K is significantly active against Herpes simplex Type I (HSV-1) (40-250 ng/disk) (26, 28, 29) and Polio virus (40-50 ng/disk) (29) while the sulfoxide **(24)** and debromo **(25)** derivatives are active against both viruses at 400 ng/disk (29) or 200 ng/mL (32). Most potent against HSV-1 are eudistomin C **(19)** and E **(20)** (25 ng/disk) (28), though eudistomin L **(23)** displays modest (100 ng/disk) (26, 28) activity. Eudistomin O **(4)** has been reported both inactive (28) and moderately (500 ng/disk) active (29) toward the test viruses. β-Carboline **(58)** itself is slightly active against HSV-1 and Polio (2 μg/disk) (29). Eudistomins D **(1)**, H **(7)**, and P **(9)** had minor antiviral activity (28). Enhancement of antiviral activity correlates to bromination at C(7) (29).

Eudistomidin A **(11)** and C **(26)** display calmodulin antagonist activity (IC_{50} 2 X 10^{-5} and 3 X 10^{-5} M, respectively) (35, 36). Eudistomidin B **(18)** activates rabbit heart muscle actomyosin ATPase by 93% at 3 X 10^{-5} M and eudistomidin D **(5)** induces Ca^{2+} release from sarcoplasmic reticulum at ten times the potency of caffeine (36) while eudistomin derivatives 7-bromoeudistomin D (38) and 9-methyl-7-bromoeudistomin D (39) were 400 and 1000 times more potent, respectively, than caffeine. Eudistomins D **(1)**, N **(3)**, and O **(4)** display phosphodiesterase inhibition, although several synthetic analogues are more potent than the natural products (200). Eudistomin U **(29)** is active in a DNA binding assay (34).

Three eudistomins display phototoxicity against several viruses, bacteria, yeast and mammalian cells (201, 202) when the natural products are exposed to ultraviolet (UVA) irradiation. The activity appears to diminish with increasing side chain complexity; eudistomin N **(3)** is most active, being similar in phototoxicity to β-carboline and harman. Eudistomins M **(13)** and O **(4)** were moderately active while eudistomins H **(7)** and I **(8)** were effectively inactive even in the presence of UVA.

Eudistomin G **(6)** and H **(7)** inhibited larval settlement of the potentially fouling *Bugula neritina* at concentrations as low as 0.5% of their natural concentration (203).

Villagorgin A **(55)** inhibits acetylcholine induced contraction of guinea-pig ileum and thrombin and calcium ionophore A23187 induced aggregation of human platelets, a calcium-calmodulin mediated event (54). Several of the simple β-carbolines are cytotoxic (Table 1). 1-Acetyl-β-carboline **(63)** is cytotoxic toward brine shrimp causing 100% mortality in 24 hr (61).

Manzamines exhibit potent cytotoxicity (Table 1). Manzamine A **(32)** and its 8-hydroxy **(33)** and 8-methoxy derivatives are active against this HSV-II (IC_{50} 0.05, 0.1 and 0.1 μg/mL, respectively) (48). Manzamine C **(35)** is an inducer of EL-4.IL-2, which is a measure of perturbation of signal transduction (204). Ircinol A **(119)** showed inhibition against endothelin converting enzyme (IC_{50} 55 μg/mL) (91).

Most of the isoquinoline quinones described above have antibacterial activity (Table 3) and moderate levels of cytotoxicity (Table 1) have been reported. Other bioactivity reported for mimosamycin and 7-amino-7-demethoxymimosamycin **(89)** are aldose reductase inhibition, 34.6% at 10 μmol dm^{-3}, and cAMP phosphodiesterase inhibition, 26.3% at 100 μmol dm^{-3}, respectively (71).

Table 1. *In vitro* cytotoxicity of marine β-carboline and isoquinoline alkaloids against P-388 and L-1210 murine leukemias, KB human nasopharyngeal carcinoma, A-459 non-small cell lung carcinoma and other cell lines, (IC_{50}, μg/mL).

Compound	P-388	L-1210	KB	A-549	Other	Ref
Eudistomidin D **(5)**		2.4			1.8[5]	36
Eudistomidin B **(18)**		3.4			3.1[5]	36
Eudistomin E **(20)**			5[1]			42
Eudistomin K **(22)**	0.01					29
Eudistomidin C **(26)**		0.36			0.42[5]	36
Eudistalbin A **(30)**			3.2[1]			42
Manzamine A **(32)**	0.07		0.05	1.3	0.8[6], 0.15[7]	48,204
Manzamine B **(34)**	6.6			4.5	1.6[6]	204
8-hydroxy-**32** **(33)**			0.30		0.26[7]	48
8-methoxy-**32**			0.33		0.10[7]	48
Manzamine C **(35)**	2.6			3.5	1.5[6]	204
Manzamine D **(37)**	0.5					205
Manzamine E **(39)**	5.0					46
Manzamine F **(40)**	5.0					46
Manzamine H **(42)**		1.3	4.6			47
41	0.8[1]					50
Manzamine J **(43)**		2.6	>10			47
Fascaplysin **(44)**		0.2				51
Milnamide A **(57)**	0.74			4.1	2.8[6], 3.3[8]	55
61	0.1					59
65	0.1					59
67	0.1					59
68	0.65					59
Renierone **(75)**	2.75[1]					74
76	8.36[1]					74
Renierol **(78)**		3.0				69
Cribrostatin 1 **(81)**	1.58[1]					74
Mimosamycin **(87)**	0.74[1]					74
Cribrostatin 2 **(90)**	2.73[1]					74
Perfragilin A **(92)**	0.8[1]					75
Perfragilin B **(93)**	0.07[1]					75
Renieramycin G **(102)**			80[4]		0.8[4,7]	79
Ecteinascidin 729 **(103)**	0.93[2]					81, 82
Ecteinascidin 743 **(104)**	1.3[2]	0.5[2]				81, 82
Ecteinascidin 745 **(105)**		88[2]				82
Ecteinascidin 722 **(109)**		2.5[3]				83
Ecteinascidin 736 **(110)**		5.0[3]				83
Theoneberine **(111)**		2.9	10			85
Demethylaaptamine **(113)**					0.5[1,9]	87
Demethyloxyaaptamine **(114)**					0.87[1,9]	87

Table 1. (cont.) *In vitro* cytotoxicity of marine β-carboline and isoquinoline alkaloids against P-388 and L-1210 murine leukemias, KB human nasopharyngeal carcinoma, A-459 non-small cell lung carcinoma and other cell lines, (IC_{50}, μg/mL).

Compound	P-388	L-1210	KB	A-549	Other	Ref
Ircinal A **(117)**		1.4	4.8			47
Ircinal B **(118)**		1.9	3.5			47
Ircinol A **(119)**		2.4	6.1			91
Ircinol B **(120)**		7.7	9.4			91
Lamellarin I **(126)**	0.25			0.25		95
Lamellarin K **(128)**	0.25			0.25		95
Lamellarin L **(129)**	0.25			0.25		95
Imbricatine **(135)**					23±9[1,10]	207
Prorocentrolide **(137)**		20				104

[1]ED_{50}. [2]ng/mL. [3]ID_{90} (ng/mL). [4]MIC (ng/mL). [5]L517y cell line. [6]HT-29 colon adenocarcinoma cell line. [7]LoVo cell line. [8]B16 melanoma cells. [9]HeLa cells. [10]T-47D drug-sensitive breast-cancer cell line.

Fascaplysin **(44)**, in addition to cytotoxicity (Table 1) and antimicrobial activity (Table 3), is active against reverse transcriptase (58%); the latter activity is also present (94%) in **51** (homofascaplysin A/dehydroluffariellolide) (53).

Aaptamine **(112)** was isolated as an α-adrenoceptor blocking agent (86), effective at 3×10^{-5} M, acting as a competitive antagonist of α-adrenoceptor in vascular smooth muscles (206). Demethyloxyaaptamine **(114)**, dihydroaaptamine and dihydrodemethylaaptamine had no effect on the dose-response curve for noradrenaline at 10^{-5} to 10^{-4} M and are thus inactive.

Lamellarin C and D **(122, 131)** caused 15% and 78% inhibition, respectively, of cell division in the fertilized sea urchin egg assay at 19 μg/mL (92). Lamellarin K and L demonstrated immunomodulatory activity (LcV:MLR 147 and 98, respectively) (95). Prorocentrolide **(137)**, in addition to the reported cytotoxicity (Table 1), displays mouse lethality at 0.4 mg/kg (ip) (104).

Table 2. *In vivo* cytotoxicity of Ecteinascidins and Eudistomin K against P-388 leukemia, B-16 melanoma, Lewis Lung carcinoma xenograft (LL), M5076 ovarian sarcoma and MX-1 human mammary carcinoma xenograft, doses in μg/kg/day.

	T/C (dose)					
Compound	P-388	B-16	LL	M5076	MX-1	Ref
Et* 722 **(109)**	>265 (25)	200 (50)	0.27 (50)			83
Et 729 **(103)**	190 (12.5)	253 (12.5)	0.00 (25)	204 (12.5)	0.05 (37.5)	83
Et 743 **(104)**	167 (15)					82
Et 745 **(105)**	111 (250)					82
Eudistomin K **(22)**	137 (100)					29

*Ecteinascidin

Table 3. Antimicrobial activity of β-Carboline and Isoquinoline Alkaloids. Reported as: zone of inhibition/μg of compound per disk, against *Staphylococcus aureus* (Sa), *Bacillus subtilis* (Bs), *Escherichia coli* (Ec), *Candida albicans* (Ca), *Saccharomyces cerevisiae* (Sc), *Vibrio anguilarium* (Va).

Compound	Sa	Bs	Ec	Ca	Sc	Other	Ref
Eudistomin D **(1)**		14/100					28
Eudistomin N **(3)**		14/100					28
Eudistomin H **(7)**					20/100		28
Eudistomin I **(8)**		14/100					28
Eudistomin P **(9)**		15/100			20/100		28
Eudistomin Q **(10)**		14/100					28
Woodinine **(14)**	16/100		8/100				41
Eudistomin C **(19)**		26/100	22/100			27/100[5]	28
Eudistomin E **(20)**		17/100					28
Eudistomin K **(22)**		23/100	15/100		24/100	27/100[5]	28
Eudistomin L **(23)**		27/100	20/100		28/100	32/100[5]	28
Manzamine A **(32)**	6.3[1]						44
Manzamine F **(40)**	25[1]						44
Fascaplysin **(44)**	15/0.1		8/5	11/1	20/0.1		51
Renierone **(75)**	8/10	10/10	8/10				68
77	9/50	10/10	9/10				68
76	12/100	8/100				9/100[7]	68
84	18/50	11/10		8/50		8/10[7] 10/50[2]	68
Renierol **(78)**	10/100						69
79	*/10	*/10					70
82	*/10	*/10					70
Mimosamycin **(87)**	14/50	11/50		9/50		11/10[7] 10/10[2]	68
85	*/10	*/10					70
86	*/10	*/10					70
91	*/10	*/10					70
Renieramycin A **(95)**	14/10	10/10				9/100[7]	68
Renieramycin B **(96)**	9/50	8/10					68
Renieramycin C **(100)**		8/10					68
Renieramycin D **(101)**	8/100	8/10					68
Xestomycin **(99)**	*/10	*/10					70
Theoneberine **(111)**	16[1]	66[1]				2[1,3], 4[1,4]	85
113	1.5[1]	3[1]				6[1,6]	87
114	3.13[1]	6.25[1]				12.5[1,6]	87

*No zone reported. [1]MIC (μg/mL). [2]Marine strain B-329. [3]*Sarcina lutea.* [4]*Mycobacterium* sp 607. [5]*Penicillium atrovenetum.* [6]*Proteus vulgaris.* [7]*Vibrio anguilarium*

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