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Organic Chemistry
Series Two

Volume 9
Alkaloids

Edited by K. Wiesner, F.R.S.

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University of New Brunswick

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Consultant Editor
D. H. Hey, F.R.S.

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The International Review of Science is an important venture in scientific publishing presented by Butterworths. The basic concept of the Review is to provide regular authoritative reviews of entire disciplines. Chemistry was taken first as the problems of literature survey are probably more acute in this subject than in any other. Biochemistry and Physiology followed naturally. As a matter of policy, the authorship of the Review of Science is international and distinguished, the subject coverage is extensive, systematic and critical.

The Review has been conceived within a carefully organised editorial framework. The overall plan was drawn up, and the volume editors appointed by seven consultant editors. In turn, each volume editor planned the coverage of his field and appointed authors to write on subjects which were within the area of their own research experience. No geographical restriction was imposed. Hence the 500 or so contributions to the Review of Science come from many countries of the world and provide an authoritative account of progress.

The publication of Organic Chemistry Series One was completed in 1973 with ten text volumes and one index volume; in accordance with the stated policy of issuing regular reviews to keep the series up to date, volumes of Series Two will be published between the middle of 1975 and early 1976; Series Two of Physical Chemistry will be published at the same time, while Inorganic Chemistry Series Two was published during the first half of 1975. Volume titles are the same as in Series One but the articles themselves either cover recent advances in the same subject or deal with a different aspect of the main theme of the volume. In Series Two an index is incorporated in each volume and there is no separate index volume.

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Consultant Editor's Note

The ten volumes in Organic Chemistry in the Second Series of the biennial reviews in the International Review of Science follow logically from those of the First Series. No major omissions have come to light in the overall coverage of the First Series. The titles of the ten volumes therefore remain unchanged but there are three new Volume Editors. The volume on Structure Determination in Organic Chemistry has been taken over by Professor Lloyd M. Jackman of Pennsylvania State University, that on Alicyclic Compounds by Professor D. Ginsburg of Technion-Israel Institute of Technology, and that on Amino Acids, Peptides and Related Compounds by Professor H. N. Rydon of the University of Exeter. The international character of the Series is thus strengthened with four Volume Editors from the United Kingdom, two each from Canada and the U.S.A., and one each from Israel and Switzerland. An even wider pattern is shown for the authors, who now come from some sixteen countries. The reviews in the Second Series are mainly intended to cover work published in the years 1972 and 1973, although relevant results published in 1974 and 1975 are included in some cases, and earlier work is also covered where applicable.

It is my pleasure once again to thank all the Volume Editors for their helpful cooperation in this venture.

London

D. H. Hey

Preface

We are now ready to present the second biennial volume on alkaloids. After the publication of the first volume the editor had the opportunity to discuss the articles it contained with many natural product chemists, most of whom have supported him in his original editorial policy.

Since it is impossible to review all alkaloid groups in approximately ten chapters which are self-contained, interesting to read and educational for the non-specialist, we are going to present topics selected according to the amount of relatively recent progress achieved and on a rotating basis. In this manner it is hoped that the second volume like the first one will not be in competition with but complementary to the *Specialist Periodical Reports* and that both publications each by its own peculiar approach will help natural product chemists to master the mushrooming alkaloid literature.

All chapters presented in the second volume are self-contained articles with major emphasis on recent developments but sufficient introduction to make them readable and interesting without looking up references.

Unfortunately, owing to difficulties of two of our prospective authors at a late date when they no longer could be replaced, only eight chapters are presented this time.

It is, however, the belief of the editor that all of the articles are of an exceptionally high standard and a pleasure to read.

Fredericton

K. Wiesner

Contents

1
Ormosia Alkaloids: Structure and Synthesis

Z. VALENTA
University of New Brunswick
and
H. J. LIU
University of Alberta

1.1 INTRODUCTION

A very intensive recent activity has led to a significant progress in the knowledge of the structure and stereochemistry of *Ormosia* alkaloids, as well as to their total synthesis. A brief review by Bohlmann[1] summarises work reported before 1966 and it is thus the purpose of this article to provide a full report on the solutions achieved during the past nine years.

The genus *Ormosia*, native to tropical regions of the Americas and South East Asia and comprised of about 100 species of woody legumes[2,3], *Piptanthus nanus* M. Pop. in the Soviet Union[4] and, more recently, *Podopetalum ormondii* F. Muell. in Australia[5] and *Templetonia retusa* (Vent.) R. Br. in New Zealand[6,7] constitute the alkaloidal sources reported so far. It is not likely, however, that all the plants containing these alkaloids have been investigated and new isolations can thus be foreseen.

It has been known for a long time that the fruit of the Venezuelan legume *O. dasycarpa* Jacks. possesses hypnotic and analgesic properties[8] and other *Ormosia* species have apparently been used medicinally in the Orient[9]. An extensive report has been published more recently on the histamine-like effects in dogs of oxypanamine, an oxidation product of an alkaloid present in *O. panamensis* Benth.[10]. Although *Ormosia* alkaloids have, to our knowledge, not found commercial application in modern pharmacology, these reports on native use indicate that structural modifications including smaller molecules with specific features present in the alkaloids might well prove interesting physiologically in the future.

Two clearly distinguishable types of alkaloids are found in the plants listed above: C_{20} bases, which all possess the same skeleton and differ only in H-content (H_{31}–H_{35}) and stereochemistry, and bases identical to or derived from known lupin alkaloids. Examples of the second type are (−)-sparteine[11], angustifoline[12,13], 13-epihydroxylupanine[13,14], (−)-cytisine, (−)-anagyrine, (+)-lupanine[7], 11-oxotetrahydrorhombifoline[15], *N*-methylcytisine[3,16]

and α-methyltetrahydrocytisine[3]. Although the coexistence of these two structural types is of obvious interest botanically and biogenetically, only the C_{20} alkaloids, comprising a structurally uniform and novel class, are reviewed here.

The subject will not be treated historically, but credit is due to the pioneering isolation work by Hess and Merck on *O. dasycarpa* Jacks.[8], Konovalova, Diskina and Rabinovich on *Piptanthus nanus* M. Pop.[4,34,35], Lloyd and Horning on *O. panamensis* Benth. and other *O.* species[12,16,30], Clarke and Grundon on *O. dasycarpa* Jacks.[11,36] and Hassall and Wilson on *O. jamaicensis* Urb.[13,32], which clearly indicated the novel nature of the bases involved.

The somewhat unusual arrangement of the following sections — skeletal structure followed by total synthesis and finally by stereochemistry — has been chosen because the C_{20} *Ormosia* alkaloids show a truly impressive variation in stereochemical arrangement and this aspect is therefore the most interesting and complex. The structural and synthetic studies described first provide a body of information which makes the assignment of stereochemistry and structure to all known bases more logical and complete.

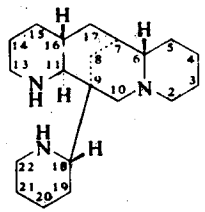
Several absolute configurations have been determined recently. In the interest of clarity, all formulae of bases for which the absolute configuration is known are provided with the appropriate rotation and reference in the formula schemes. All formulae not provided with such a notation represent racemic compounds (if indicated in the text) or compounds of unknown absolute configuration.

1.2 SKELETAL STRUCTURE

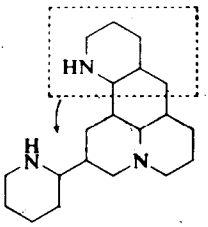
1.2.1 $C_{20}H_{35}N_3$ alkaloids

An x-ray crystallographic investigation of jamine (10), an adduct of formaldehyde and ormosanine, by Karle and Karle[17,18] made it possible to assign structure and relative configuration (1) to the racemic alkaloid ormosanine[19]. Skeletal structure (2), proposed at about the same time on the basis of chemical evidence[20], proved to be incorrect in the attachment of the 3-alkylpiperidine moiety. The misleading chemical information was a remarkably efficient conversion of ormosanine (1) into quinoline (3), containing all the C atoms of ormosanine, on dehydrogenation with palladium on charcoal at 275 °C. A possible mechanism for this deep-seated change has been described[21]. A diagnostic dehydrogenation with palladium on charcoal at 250 °C was performed on three alkaloids of *O. panamensis* Benth., ormosanine (1), panamine and ormosinine[22]. The resulting pyridine (4) contains the complete *Ormosia* skeleton and reveals the substitution pattern of two rings. Its stereochemistry is greatly simplified and it should be noted that an epimerisation has taken place at C-6 in the process[23,24].

In comparison with other alkaloidal classes, the unique feature of the C_{20} *Ormosia* alkaloids is the complete constancy of their skeleton. No alkaloid has been found so far which does not contain the skeleton of (1), the only minor variations being a double bond at C-16—C-17 and an N—C-22 bond (Sections 1.2.2 and 1.2.3). As if to compensate for this lack of skeletal varia-



(1) (+)-ormosanine[7]



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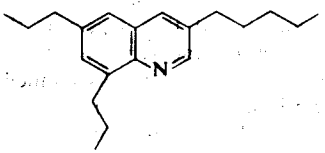

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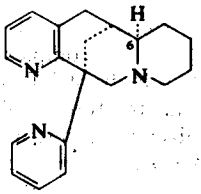


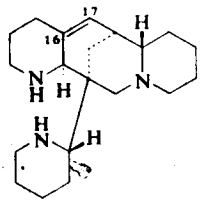
(4) (−)-pyridine[7]

tion, however, Nature has taken full advantage of the stereochemical possibilities, creating many of the possible diastereoisomers and using both antipodal series. Section 1.4 analyses this aspect fully; here, it is only necessary to stress that the establishment of structure (1) thus solved the basic structural problem for all *Ormosia* alkaloids.

1.2.2 Pentacyclic $C_{20}H_{33}N_3$ alkaloids

An x-ray study by Hart *et al.*[5] has shown that (−)-podopetaline, one of the alkaloids of *Podopetalum ormondii* F. Muell., possesses the structure and absolute configuration (5). Previously, McLean *et al.* had proposed structure and relative stereochemistry (5) for ormocastrine, an alkaloid of *O. semicastrata*, on the basis of correlative evidence[25]. The concern that one of the assignments must be incorrect, since the two alkaloids were reported to have markedly different physical properties, was finally dispelled when it was shown that ormocastrine is in fact podopetaline hydrochloride[26,48]. These two independent structural solutions are important because they confirm the normal position of the double bond to be at C-16—C-17 of the *Ormosia* skeleton and because, very significantly, the correctness of the chemical solution[25] is a prerequisite for any confidence in the rather complex arguments leading to stereochemical assignments in this class which are described in Section 1.4.

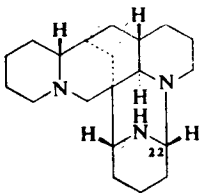
Three additional alkaloids of this type were isolated in our laboratory[27]. In addition to other C_{20} *Ormosia* alkaloids, the beans of *O. amazonica*[28] were found to contain dihydro-ormojanine, amazonine and 18-epiamazonine, all diastereoisomers of (5).



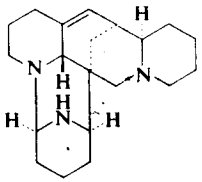
(5) (−)-podopetaline[5]

1.2.3 Hexacyclic $C_{20}H_{31-33}N_3$ alkaloids

Three naturally occurring alkaloids possess a different structural feature: a sixth ring created in the basic skeleton by an N-C-22 bond formation. Structure and relative configuration (6) was proposed[29] on the basis of correlative evidence for panamine, an alkaloid of *O. panamensis* Benth.[30], and confirmed by x-ray analysis[31]. Recently, a correlation of the naturally occurring (−)-panamine with (−)-templetine led to an assignment of absolute configuration indicated in (6)[7,50]. It should be noted that the relative configuration of all chiral centres in ormosanine (1) and panamine (6) is identical.



(6) (−)-panamine[7]



(7)

Ormosajine, one of the alkaloids of *O. jamaicensis* Urb.[13,32], is a diastereoisomer of panamine. Its conversion into dasycarpine, $C_{20}H_{35}N_3$, on catalytic hydrogenation[32] led to the elucidation of its structure and stereochemistry[24]. Ormojanine, present in the same plant[13], was assigned structure and relative configuration (7)[21,24]; it can be seen that it combines both unsaturation features found in this class of alkaloids.

1.2.4 Dimeric alkaloids

Ormosinine, an alkaloid of *O. panamensis* Benth.[30], has been shown to be a dimer of panamine (6)[24]. The two alkaloids show identical mass spectra[19], sublimation of ormosinine gives pure panamine and an osmometric molecular weight determination gave a value of 640 for ormosinine. Mainly on the basis of this evidence, three possibilities for the structure of ormosinine were

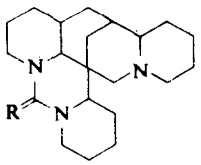
suggested, formed via two N—C-22 bonds between two molecules of panamine in its imine form[24].

Analogously, alkaloid ormojine of *O. jamaicensis* Urb.[13,32] was found to be a dimer of ormosajine[33] (see above). In contrast to ormosinine, however, ormojine shows a parent ion $C_{40}H_{66}N_6^+$ in a high-resolution mass spectrum. Furthermore, two related alkaloids, ormojine and ormosajine, form an equilibrium mixture on treatment with dilute hydrochloric acid. A dimeric structure was proposed in which the two monomers are joined by a C—C bond formed by an enamine–imine reaction[33].

The exact nature of the linking bonds in the two dimers is not rigorously established, nor is it known with certainty that the dimers (or the corresponding monomers) are not isolation artefacts.

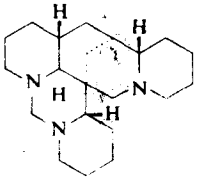
1.2.5 N—C—N bridging reactions

All *Ormosia* alkaloids containing two secondary N atoms have been shown to form homo derivatives of type (8) on treatment with formaldehyde and homoxy derivatives of type (9) on treatment with phosgene (or ethyl chloroformate) in the presence of triethylamine. Eisner and Sorm[37] were the first to formulate these derivatives correctly in their study of the alkaloid piptanthine and to suggest that the carbonyl stretching frequency of the cyclic urea (9) (1643 cm^{-1}) indicates a 1,3-attachment of two secondary N atoms in the alkaloid.



(8) R = H_2
(9) R = O

A racemic alkaloid, jamine, was isolated from the seeds of *O. panamensis* and *jamaicensis*[19]; it was shown to have structure (10) by x-ray crystallography[17,18] and to be identical to homo-ormosanine, the adduct of formaldehyde and ormosanine (1)[19]. Jamine is the only reported naturally occurring homo derivative. Since it was found, however, that piptanthine forms homopiptanthine on paper chromatography[37] and since details of the jamine isolation have not been reported, the possibility that jamine is an isolation artefact cannot be completely excluded.

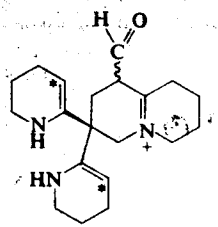


(10)

It is important to add that the formation of cyclic ureas of type (9) has been used to advantage in this field; these derivatives have often been found to be more stable, crystalline and easier to separate.

1.2.6 Biogenesis

No experimental work on the biosynthesis of the C_{20} *Ormosia* alkaloids has been reported to our knowledge. It is interesting to note, however, that lupin bases are found together with *Ormosia* alkaloids in various plants[29] (see Section 1.1) and share with them the general composition $(C_5N)_x + C_5$ as well as the absence of *C*-methyl and *N*-alkyl groups[21]. It thus appears very reasonable to postulate that the *Ormosia* alkaloids are formed from four lysine equivalents[20,29], particularly since the formation of skeleton (1) can then readily be formulated using normal aldol- and Mannich-type reactions[29].



(11)

The presence of both antipodal series in this class is unusual in view of the number of chiral centres present in the molecule. While other explanations are of course possible, it has been pointed out that an advanced biosynthetic intermediate of type (11) can be postulated to form from four lysine units[24]. It should be noted that the enol (or enolate) of aldehyde (11) is a symmetrical molecule and that the two corresponding enantiomeric aldehydes can condense with the appropriate C* atom to give the two antipodal pentacyclic derivatives. Racemate (11) could thus possibly give racemic products non-enzymatically, whereas one or the other pure enantiomer (11) could lead to optically active series in an enzymatic reaction.

1.3 SYNTHESIS

1.3.1 Synthetic approach

The total synthesis of ormosanine (1), panamine (6) and several other C_{20} bases has recently been completed[38,39]. This review summarises published as well as completed unpublished work[40] and, specifically, corrects stereochemical assignments given for C-6[38] and C-11[39] in certain synthetic intermediates. All bases reported in this section are racemic.

The 11-step synthetic sequence to ormosanine starts with ethyl pyridine-