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THE CHEMISTRY OF PRETAZETTINE AND RELATED COMPOUNDS

by

David Tiffany Bailey

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1968

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INTRODUCTION

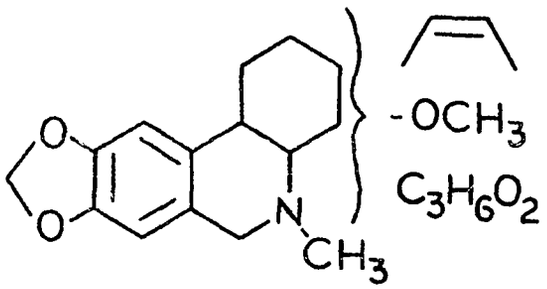
In the past the plant family Amaryllidaceae has provided a large number of alkaloids with interesting structures and reactivity. In recent years advances in isolation methods and spectroscopy have been employed widely in the search for bases which had escaped earlier detection and for the reexamination of previously known compounds. This thesis describes the isolation and characterization of a number of new alkaloids which possess the [2]benzopyrano[3,4c]indole nucleus. The reactivity of these and closely related compounds is outlined, thereby clarifying the true nature of the alkaloids tazettine and criwelline.

HISTORICAL

The structure of many [2]benzopyrano[3,4c]indole and 5,10b-ethanophenanthridine alkaloids are based ultimately on the structure of tazettine. A discussion of the chemical characteristics of this base will be followed by a summary of the chemistry of haemanthidine, criwelline, 6-hydroxycrinamine, and macronine as known before the research described in this thesis was begun. The biosynthetic and synthetic interconversions between these two nuclei are outlined.

Tazettine

Tazettine has been recognized as one of the most abundant alkaloids in the Amaryllidaceae.[1,2] The base crystallizes readily from crude alkaloid mixtures when it is a major component. It was isolated originally as a minor alkaloid from Narcissus tazetta L. in 1934 by Späth and Kahovec.[3] Preliminary studies by these workers led to the assignment of the partial structure 1. Wenkert[4] analyzed the existing data for the alkaloid and proposed the structure 2. This structure was found to be deficient when it failed to predict the proper structure of the tazettine Hofmann methine, N,N-dimethyl 6-phenylpiperonyl glycinate (3).[5] Ikeda et al.[6] concluded that although the original base does not have a carbonyl group, but an ester group appears in the methine, the alkaloid must contain a masked carbonyl group. It was proposed that the partial structure must be represented by 4 where the dashed lines indicate bonds broken in the formation of the Hofmann methine. On the basis of this and other data, the structure of tazettine was proposed



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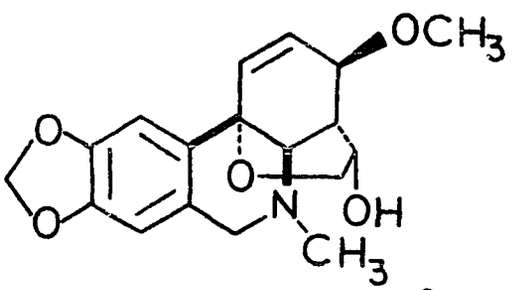

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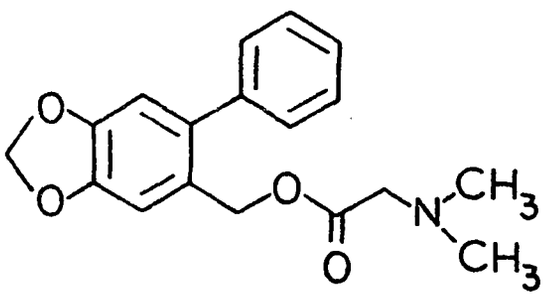

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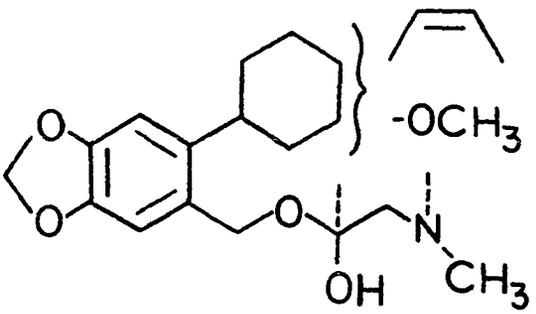
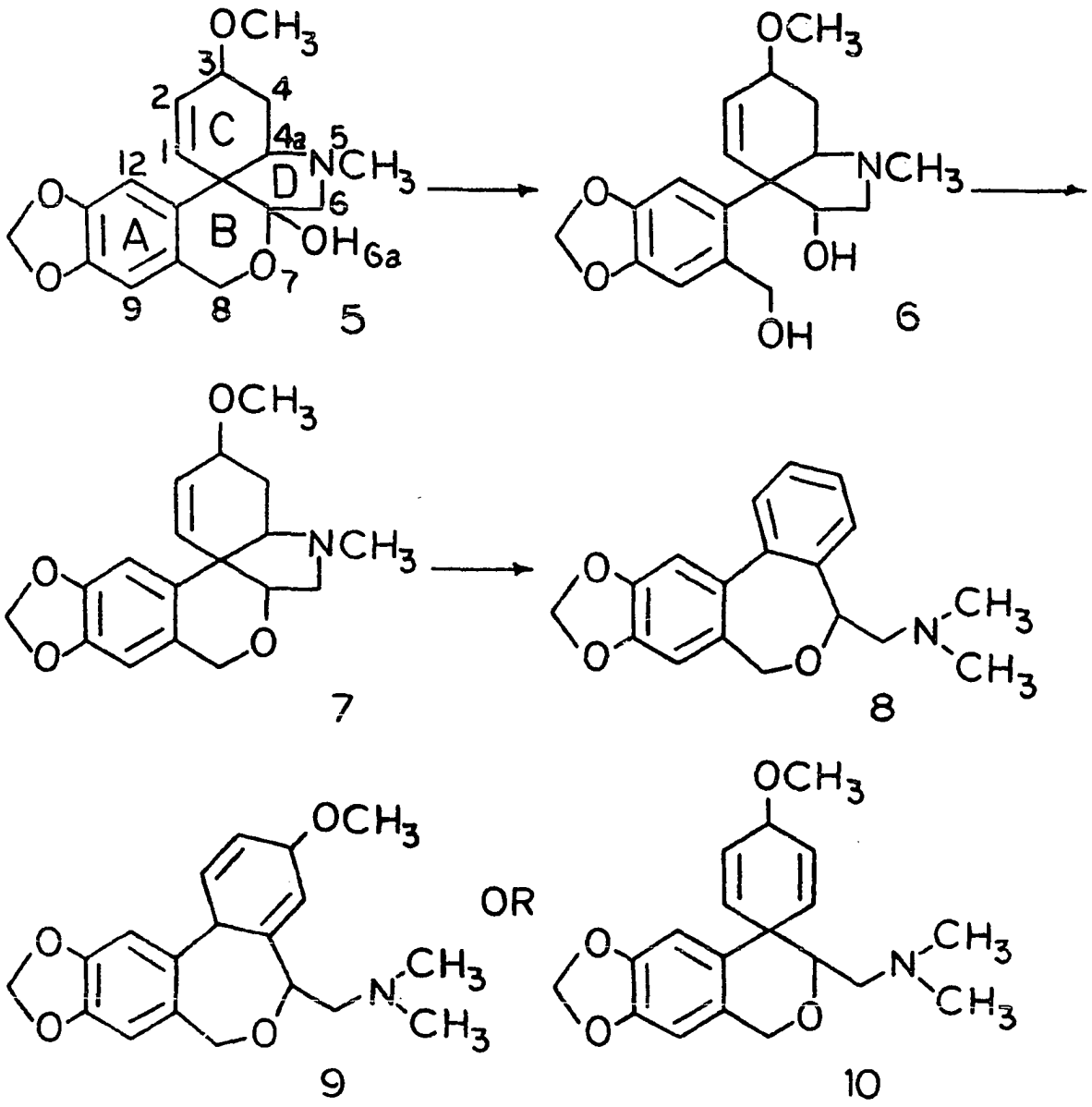


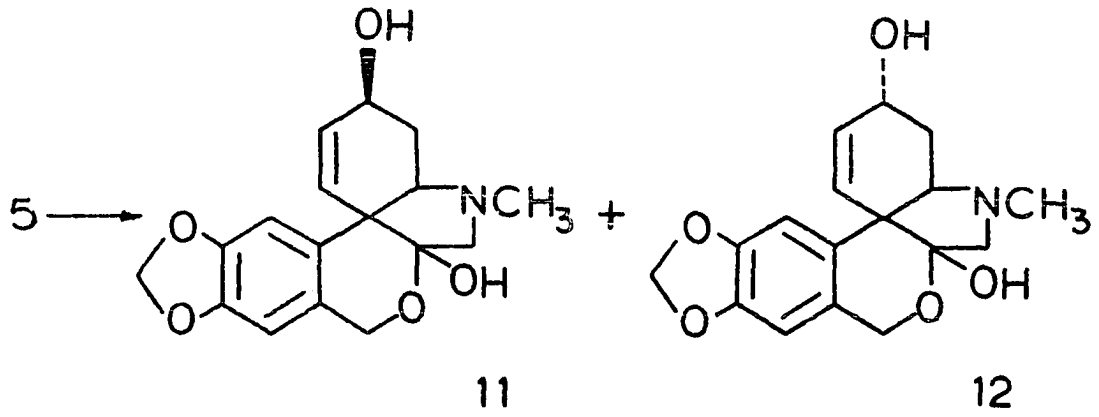
4

to be 5.

A hemiketal moiety was indicated when lithium aluminum hydride reduction of tazettine formed tazettadiol (6). This compound could be cyclized by acid to deoxytazettine (7). Hofmann degradation of 7 gave an unstable methine which, in the presence of acid, formed a neomethine (8) by the elimination of methanol. The structure of the neomethine was determined by further degradation of the base to a series of compounds which were identified and synthesized.[7] The structure of the neomethine required that the true methine must be either 9 or 10. The former structure was eliminated because it would not be expected to survive the Hofmann degradation by which it was formed. By elimination, the true methine was concluded to be 10. This information together with the partial structure 4 suggests that the structure of tazettine must be 5.[6]

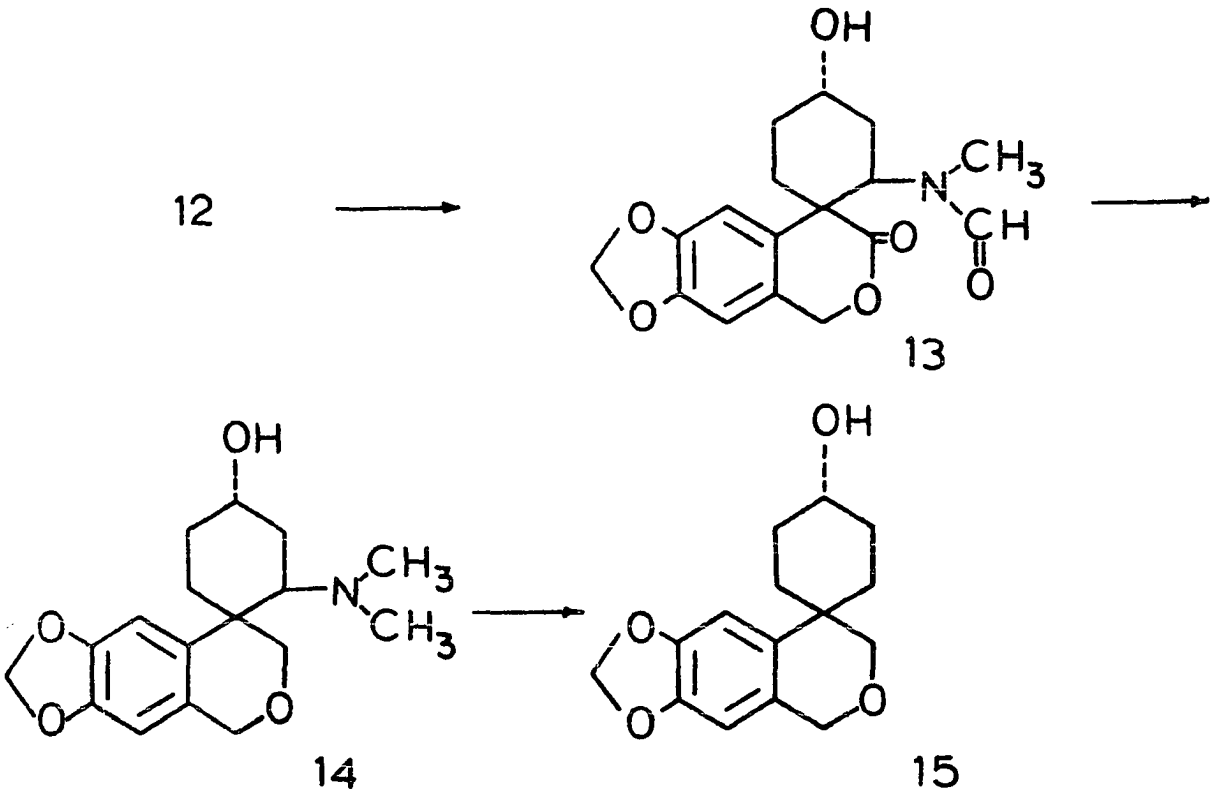


Tazettine contains asymmetric carbons at positions 3, 4a, 6a, and 12b. The stereochemistry of each of these centers was investigated by the study of a series of degradation products of the alkaloid. Acid hydrolysis of tazettine provides tazettinol (11) and isotazettinol (12) which differ only in the configuration of the C_3-hydroxyl group.[6] Isotazettinol (12) underwent catalytic reduction of the double bond and then treatment with manganese dioxide to form the lactone amide 13. Lithium

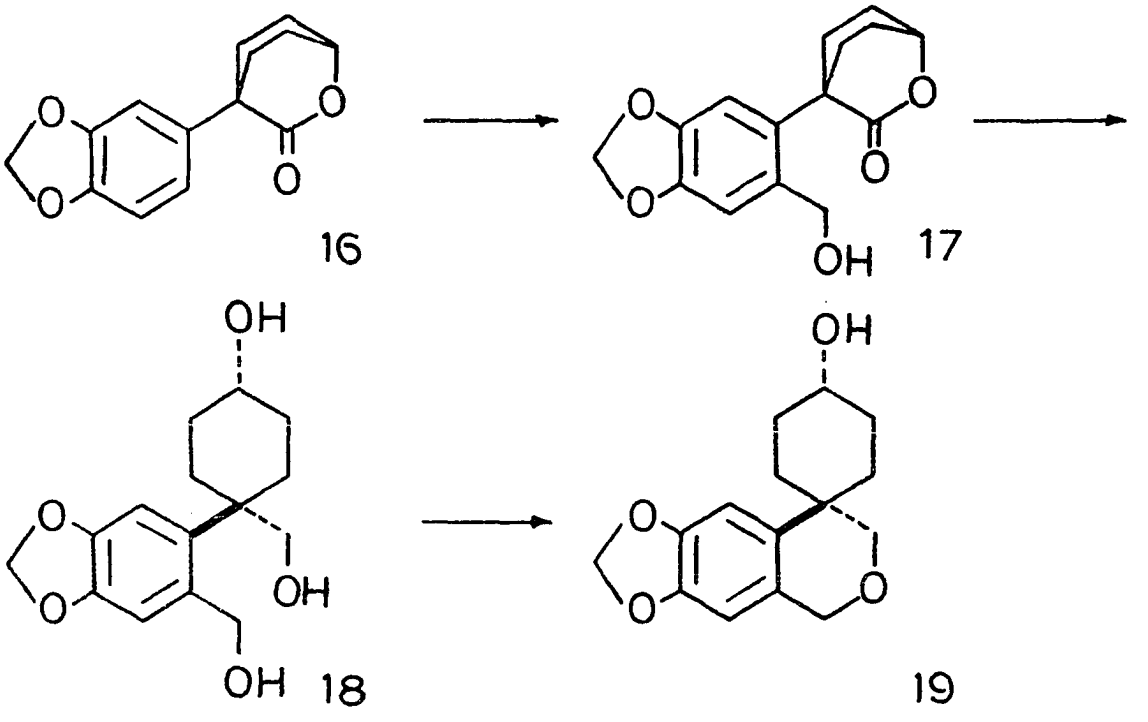


11 12

aluminum hydride reduction of the carbonyl groups and acid cyclization provided the amine 14. Emde degradation removed the dimethylamino group and provided compound 15. This product should reflect the same relationship between the hydroxyl group and the aromatic ring as in the parent compound isotazettinol (12).[8]



Synthesis of the ether alcohol 15 was undertaken to determine this stereochemical relationship.[8] Formation of the bicyclic lactone 16 was completed in several steps. Chloromethylation and hydrolysis formed 17.[9] Lithium aluminum hydride reduction followed by acid cyclization provided 19 which was identical in all respects with 15. Because the stereochemistry implicit with the bicyclic lactone was preserved in later compounds, the hydroxyl group of 19 and isotazettinol (12) must be <u>trans</u> to the aromatic ring. Therefore, tazettinol and tazettine must have a <u>cis</u> relationship between these groups.



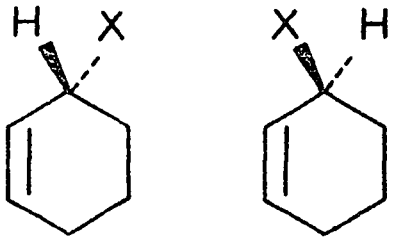
The configuration of the C_{4a}-amino group of tazettine (5) was assigned originally on the basis of pK_a measurements.[6] A comparison of deoxytazettinol and deoxyisotazettinol indicated that the latter compound

was more basic by 1.6 pK_a units. This difference was attributed to the ability of the oxygen of the C_3-hydroxyl group of deoxyisotazettinol to hydrogen bond with the hydrogen of the conjugate acid. This interaction could only occur if the groups are cis and diaxial. An axial amino group is consistent with the facile Hofmann degradation which occurs in these compounds. The methoxyl group of tazettine, cis to the aromatic ring and trans to the amino group, requires that the C-D ring fusion be cis. Additional evidence supporting these assignments has been provided by studies of the configuration of the 5,10b-ethanophenanthridine alkaloids[10] as well as the interconversion of haemanthidine to tazettine.[11,12]

The configuration of the C_{6a}-hydroxyl group in tazettine is defined by the nature of the B-D ring fusion. The more stable cis fusion, with the hydroxyl group in the α-configuration, was anticipated because of the inactivity of the hemiketal toward isomerization or carbonyl reagents. An extensive investigation of the products from the Hofmann degradation of O-methyltazettine methine methiodide led to the isolation of two compounds whose properties were interpreted in support of the more stable cis fusion.[13] These interpretations have been questioned,[14] and the configuration of the C_{6a}-hydroxyl group has not been proven conclusively by either chemical or spectral methods.

A nuclear magnetic resonance study of tazettine supports the foregoing structural details.[15] This investigation concluded that the C-ring is in a half-boat conformation which allows the C_3-methoxyl group to be pseudo-equatorial. This assignment can be achieved with either of the two possible conformers of the B-ring.

The absolute configuration of tazettine was assigned originally on the basis of Mills' rule. This rule applies to allylicly substituted cyclohexenes and cyclopentenes. It states that the molecular rotation of compounds with configuration 20 are more dextrorotatory than the corresponding epimer 21.[16] Since the isotazettine derivatives are more dextrorotatory than the tazettine derivatives, the former should be of type 20 and the latter of 21.[6] More recent degradative chemical evidence has supported this assignment,[17] and the structure of tazettine is assigned as 22.



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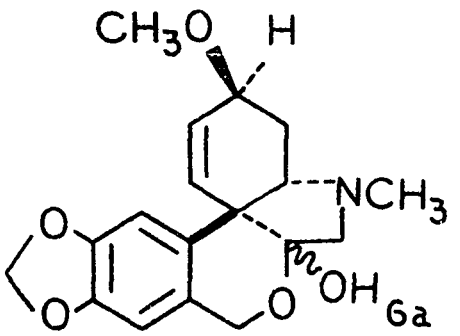
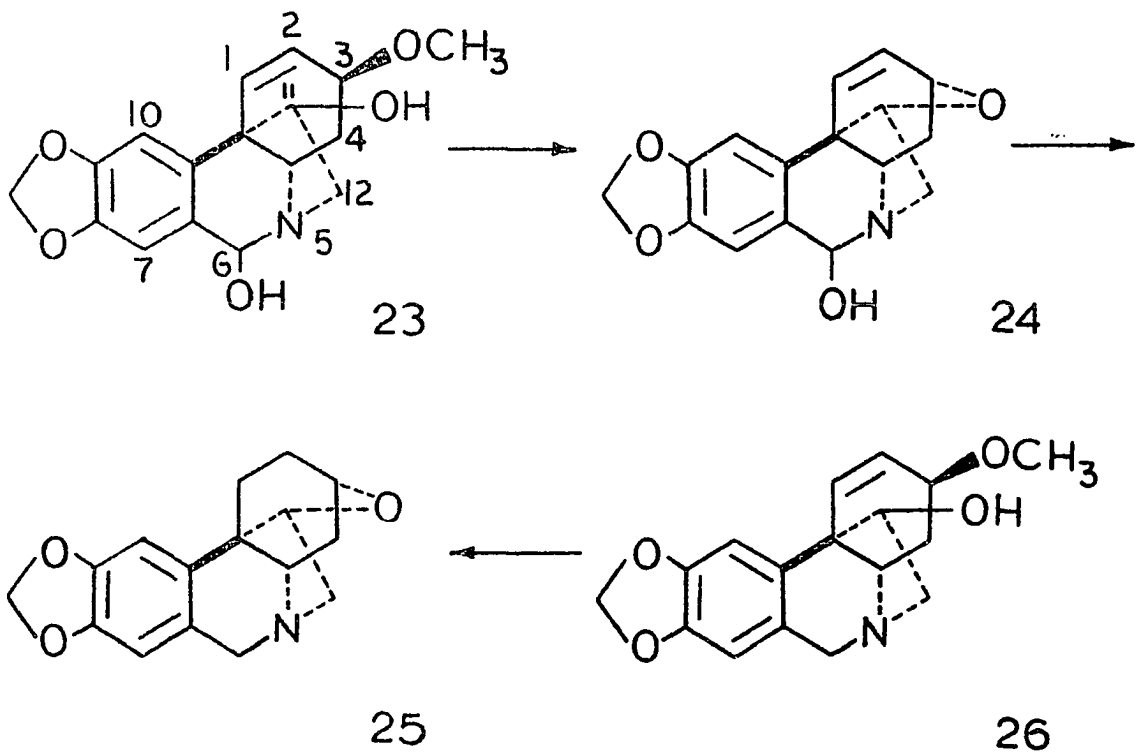


22

Haemanthidine

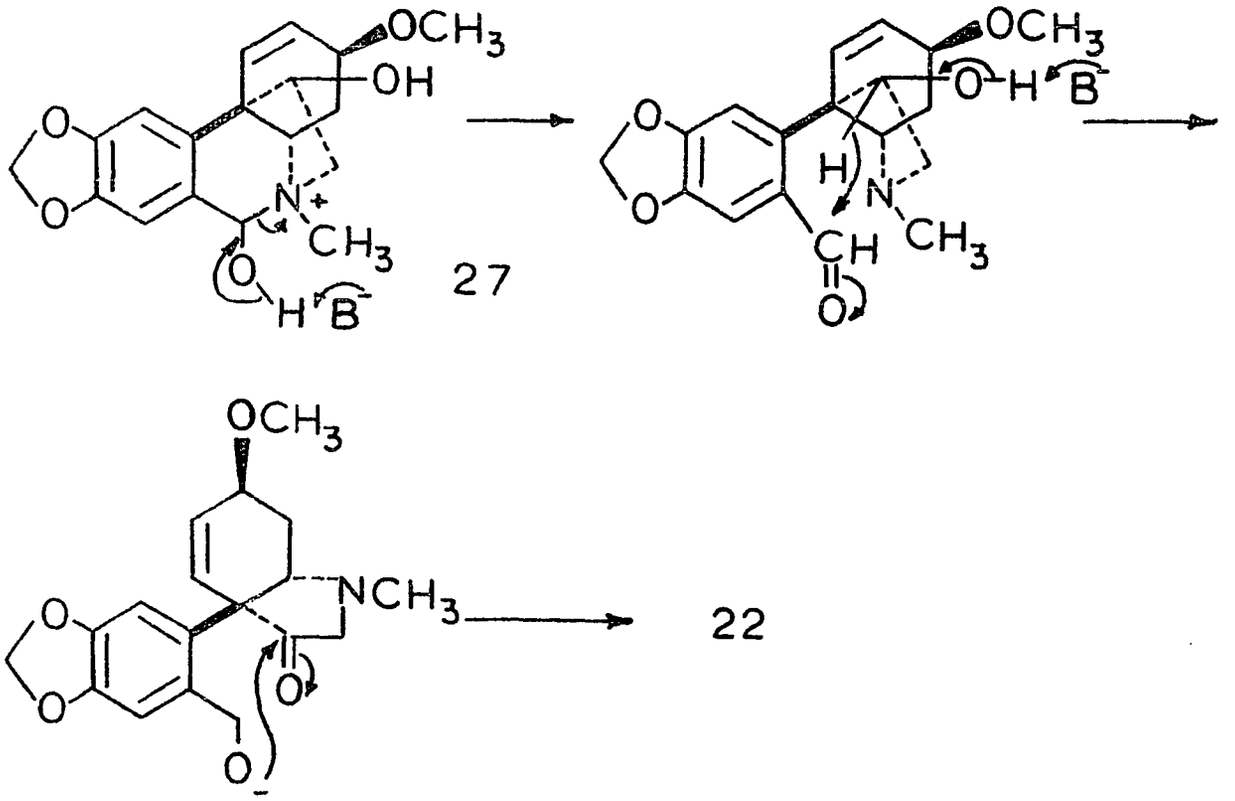
Haemanthidine, a moderately rare alkaloid in the Amaryllidaceae, was first isolated in 1954.[18] Although the base was originally thought to be N-demethyltazettine,[11,12] it was shown to form an O,O-diacetate[19] rather than the O,N-diacetate that would have been required for this structure. The actual ring system and many of the features of the compound were demonstrated by the interrelation with haemanthamine (26).[19] Haemanthidine (23), upon heating in strong acid, loses the elements of methanol to form the ether apohaemanthidine (24). Removal of both the double bond

by catalytic reduction and the remaining hydroxyl group of 24 by treatment with thionyl chloride followed by lithium aluminum hydride gave dihydroapohaemanthamine (25), which had previously been prepared from haemanthamine.

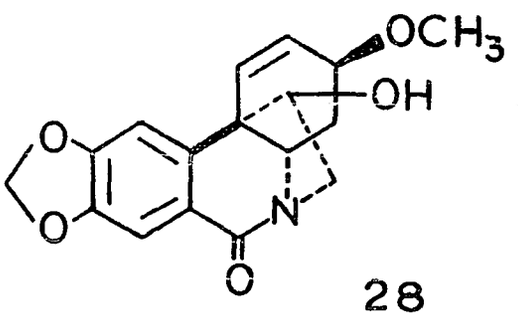


The treatment of haemanthidine methiodide (27) with strong base affords a quantitative conversion to tazettine.[11] This facile transformation has been reinvestigated recently and seems to involve an intramolecular hydride shift.[20]

The isolation of tazettine through this rearrangement demonstrated the position of the double bond, the placement and configuration of the C_3-methoxyl group, and the presence of hydroxyl groups at C_6 and C_{11} in haemanthidine. Hydrogen bonding studies indicated that the C_{11}-hydroxyl



group was in a conformation directed away from the aromatic ring.[21] Manganese dioxide oxidation of haemanthidine formed the bridgehead lactam 28.[19] This reaction confirmed the C_6-hydroxyl group in the base. The lability of an α-amino alcohol (such as 23) imparts unusual properties to the alkaloid. A spectral and chemical investigation has shown that



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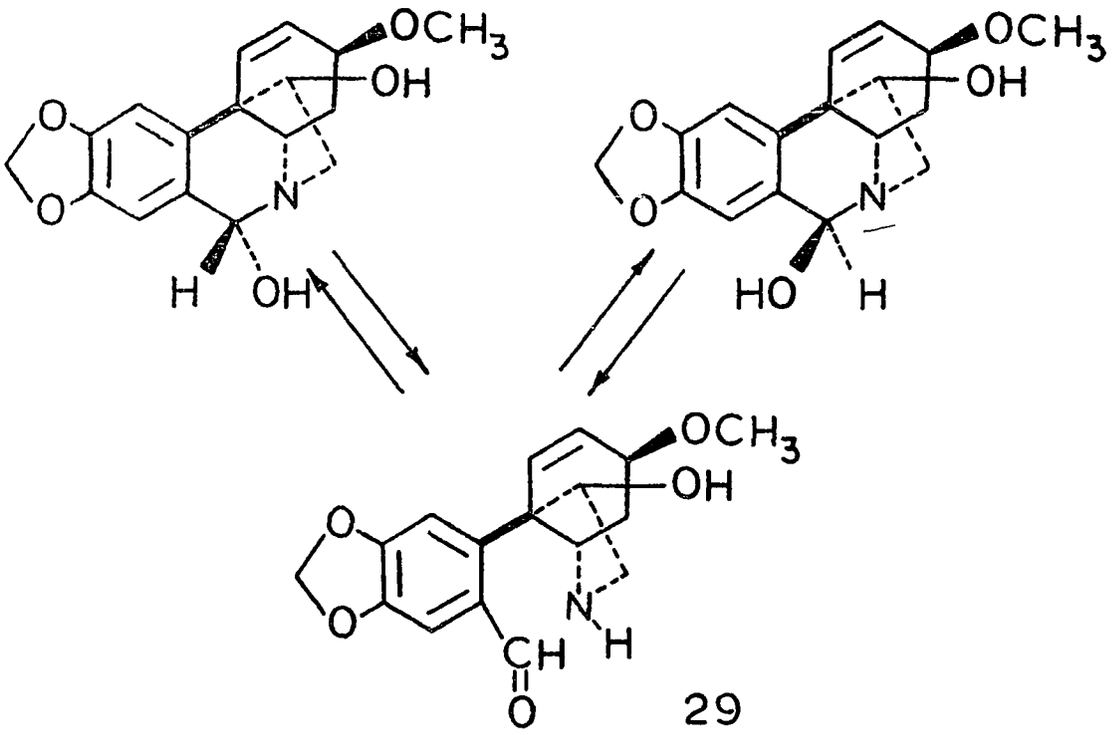
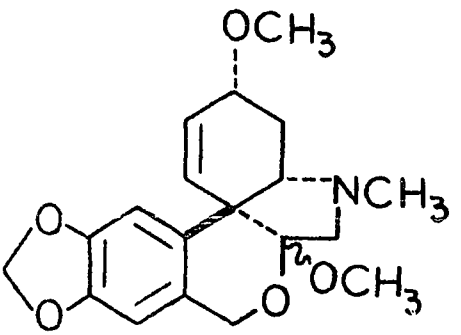
haemanthidine exists in solution as an equilibrating mixture of C_6-hydroxyl epimers. This epimerization was envisioned to proceed through the open chain aldehyde 29.[22]



29

Criwelline

O-Methylisotazettine (30) was found to be identical with the O-methylation product of a base isolated from several Crinum species.[23,24] The new base (31) was named criwelline and represents the C_3-epimer of tazettine. A nuclear magnetic resonance investigation of this compound provided spectral data consistent with the assigned structure.[15] This study indicated that the C-ring is in a half-chair conformation and the B-ring is so arranged as to place the double bond of the C-ring near the C_{12}-hydrogen.



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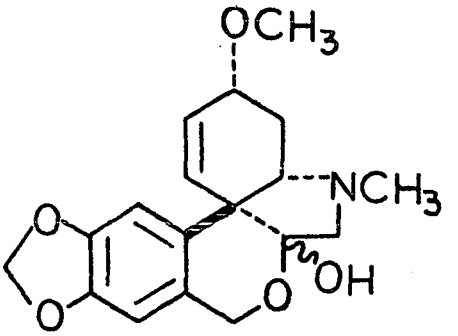
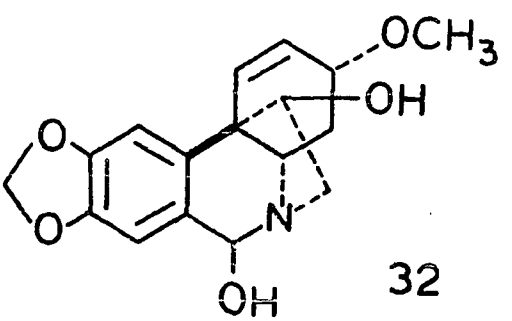


31

6-Hydroxycrinamine

6-Hydroxycrinamine (32) was first isolated from several Crinum "Milk and Wine" lillies in 1959.[24] Two reactions indicated the structure of this alkaloid. Treatment with strong acid causes a transformation to apohaemanthidine (24). Strong base converts 6-hydroxycrinamine methiodide to criwelline (31) by the same hydride shift mechanism which was discussed in the conversion of haemanthidine methiodide (27) to tazettine (22). These results are consistent only if 6-hydroxycrinamine is the C_3-epimer of haemanthidine. This structure has recently been confirmed by an x-ray crystallographic investigation.[25] 6-Hydroxycrinamine, like haemanthidine, exists in solution as an equilibrating mixture of 6-hydroxyl epimers.[22]



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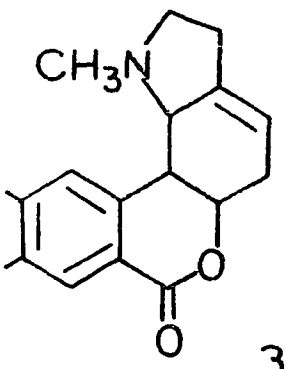
Macronine

Macronine was first isolated from Crinum macrantherum Engl. in 1964. Spectroscopic data identified many functional groups of the alkaloid and it was suggested that the base contained a [2]benzopyrano[3,4g]indole nucleus (33).[26] Further investigation, however, indicated that the ring system had been misassigned. The synthetic formation of macronine (34) from 6-hydroxycrinamine (32) demonstrated that the base was the third alkaloid to contain the [2]benzopyrano[3,4c]indole nucleus.[27] All aspects of the structure and stereochemistry of the base were described except for the configuration of the C_{6a}-hydrogen and hence the B-D ring fusion. Although evidence for a β-hydrogen seemed sound, this would be contradictory with the configuration found for the corresponding position in tazettine (22) and criwelline (31), the other members containing this ring system. Although unassigned in the communication, the configuration has been suggested to be beta.



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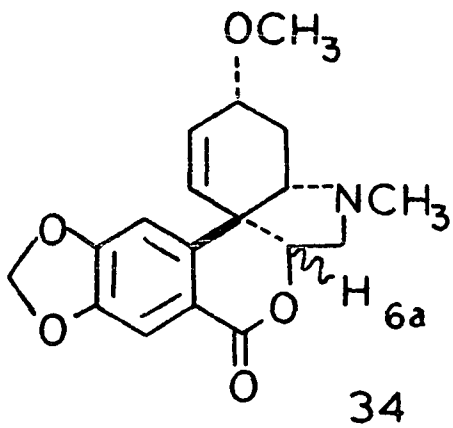
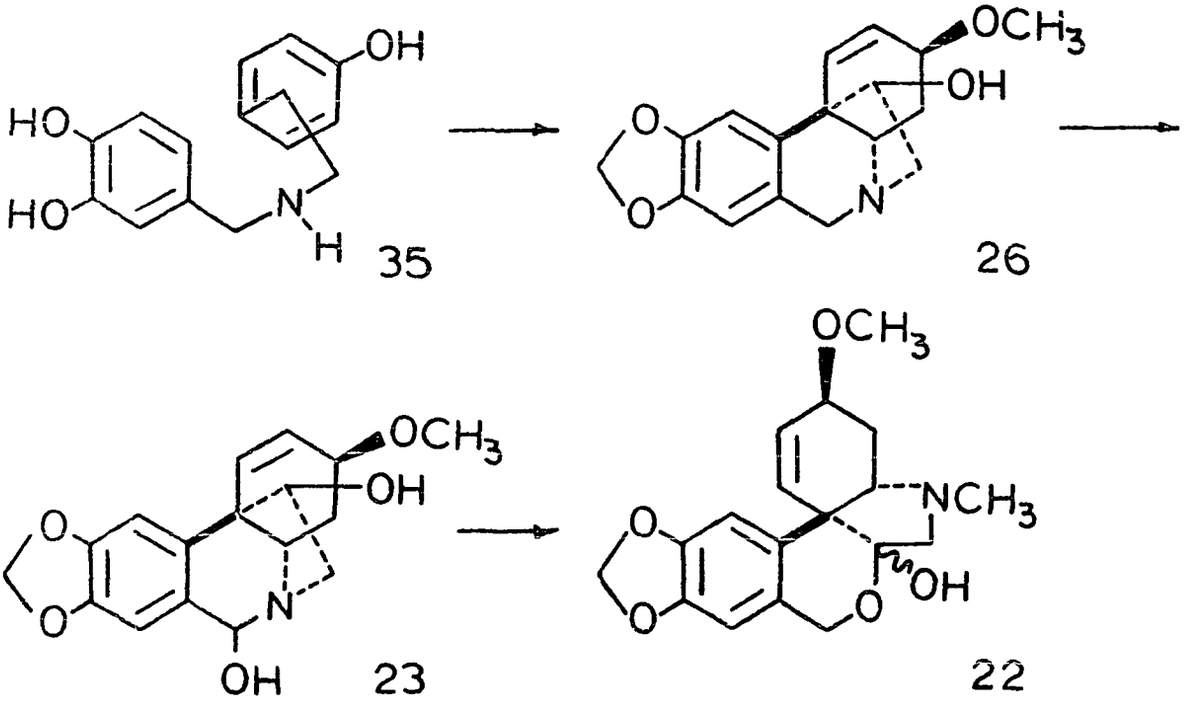


34

Biosynthesis

Early stage biosynthetic transformations have been investigated extensively in the Amaryllidaceae. These studies have demonstrated that

the alkaloids contain C_6-C_1 and C_6-C_2 units which are derived from phenylalanine and tyrosine respectively.[29-33] These two amino acids are modified and joined to form norbelladine (35).[34] The structure of the 5,10b-ethanophenanthridine alkaloids, which include haemanthamine and haemanthidine, can be accounted for biosynthetically by the phenyl-phenyl oxidative coupling of norbelladine.[35] However, the structure of the [2]benzopyrano[3,4c]indole alkaloids, such as tazettine, can not be explained so simply. The facile *in vitro* conversion of haemanthidine to tazettine by treatment with methyl iodide and base[11] might be indicative of a similar *in vivo* pathway. On the basis of the structures of these compounds and this rearrangement, a biological conversion of haemanthamine (26) to haemanthidine (23) and subsequently to tazettine (22) was suggested. This pathway was tested by several radioactive tracer

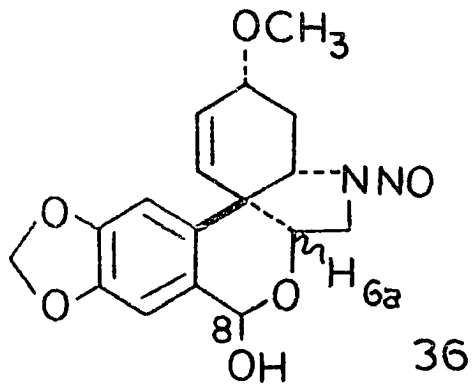


feeding experiments using Sprekelia formosissima. The results of this study fully confirmed this transformation sequence and indicated that it was essentially irreversible.[36] The corresponding biosynthetic sequence of crinamine, 6-hydroxycrinamine, criwelline is strongly suspected, but has not been experimentally tested. In the biosynthetic schemes presented to date no way has been found to account for macronine (34).

Synthetic Skeletal Interconversions

A number of examples are known for the conversion of the 6-hydroxy-5,10b-ethanophenanthridine alkaloids to the [2]benzopyrano[3,4c]indole ring system. The first examples of this rearrangement were the facile conversions of haemanthidine to tazettine (22).[11,12] Later, it was shown that N-demethyltazettine was produced when haemanthidine was treated with sodium ethoxide.[8] Identical reactions were reported in the conversions of 6-hydroxycrinamine (29) to criwelline (28)[24] and N-demethylcriwelline.[37] The tazettine-like compounds were assumed to be formed by an intramolecular hydride shift of the C_{11}-hydrogen of the reactant to the benzylic carbon atom of the product.[20]

Several additional rearrangements are known which produce compounds that differ from the tazettine-like molecules in possessing a non-etheral oxygen function in the C_8-position rather than the C_{6a}. 6-Hydroxycrinamine is converted to an N-nitroso derivative (36) on treatment with nitrous acid.[22] The corresponding C_3-epimeric N-nitroso compound has also been formed from haemanthidine.[21] Treatment of



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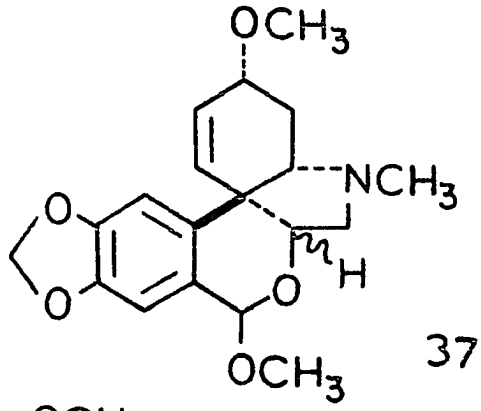

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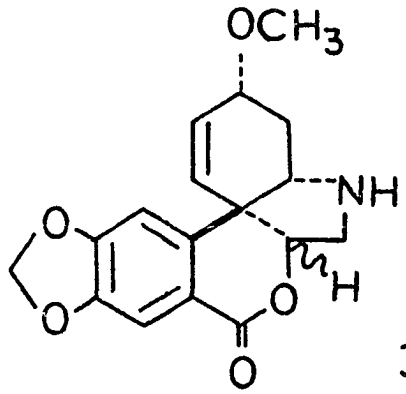

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6-hydroxycrinamine with methyl iodide in refluxing methanol produces 37.[27] Manganese dioxide oxidation of 6-hydroxycrinamine forms 6-oxocrinamine. Hydrolysis of this bridgehead lactam causes the formation of the lactone, N-demethylmacronine (38).[27]

RESULTS AND DISCUSSION

Isolation and Structures of Alkaloids from *Sprekelia formosissima* L. (Herb.) and *Ismene calithina* (Nichols)

Sprekelia formosissima has been reported to contain tazettine (the major alkaloid), haemanthamine and haemanthidine (both of intermediate concentration), and ismine (a minor base).[38,39] In a reexamination of the alkaloids of the plant, an isolation procedure was employed which was less drastic than that which had been in general use before.[40] Extremes in pH were avoided by acidification with aqueous tartaric acid and basification with dilute ammonium hydroxide. The entire isolation procedure was carried out as rapidly as possible to reduce the periods during which the compounds were in solution. Upon recovery of the alkaloid fractions, the contents of the basic mixture were examined by thin-layer chromatography. Haemanthamine and haemanthidine were present, but there was no indication of the presence of tazettine. Instead, thin-layer chromatography indicated a new alkaloid as the major component. *Ismene calithina* has been reported to contain galanthamine, haemanthamine, homolycorine, lycorine, nerinine, and tazettine.[41] When bulbs of this species were processed under similar rapid and mild conditions, thin-layer chromatography indicated the presence of all the expected bases except tazettine. A compound was present which corresponded to the new unknown alkaloid from *Sprekelia*.

An attempt was made to isolate this unknown alkaloid from the *Sprekelia* basic fractions by chromatography on alumina. Examination of the column eluates by thin-layer chromatography indicated that the new

compound was no longer present. Tazettine, now the major compound, was easily isolated by crystallization. The unknown alkaloid could be recovered in good yield from a silica gel column. Although thin-layer chromatography testified to the purity of the new alkaloid, it defied crystallization. Crystalline hydrochloride and hydrobromide salts were obtained.

Because the new alkaloid was converted readily to tazettine under a variety of basic conditions, it was named pretazettine. Chromatography on basic alumina or treatment with 0.1 N sodium hydroxide at room temperature for one hour afforded a quantitative conversion to tazettine. Pretazettine was unstable as the free base in solution and gradually rearranged to tazettine upon standing. An aqueous solution of pretazettine was converted to tazettine in less than one hour at 70°. Under dilute acidic conditions, however, pretazettine appeared to be stable. This facile rearrangement of pretazettine to tazettine under basic conditions suggested that the true major alkaloid in these plants is pretazettine. The tazettine isolated in all previous research could well be derived from this rearrangement which occurred during the basic conditions used in routine alkaloid isolations.[40]

The chemical and physical properties of pretazettine and its salts are in good agreement with those reported by Proskurnina for isotazettine.[42] A direct comparison has not been possible in this laboratory.*

*Subsequent to our initial publication[43] concerning the isolation and structure of pretazettine, similar results appeared.[44] These authors obtained an authentic sample of isotazettine and related their material with this sample. Our compound has identical characteristics with their material. Therefore, pretazettine has been indirectly related to authentic isotazettine.

The name isotazettine will not be used in this thesis because of the confusion that it introduces with the existing literature references to isotazettine (criwelline), tazettinol, and isotazettinol. All of these compounds are C_{6a}-hydroxyl derivatives of the [2]benzopyrano[3,4c]indole nucleus, but vary in the stereochemistry of the substituent at C_3.

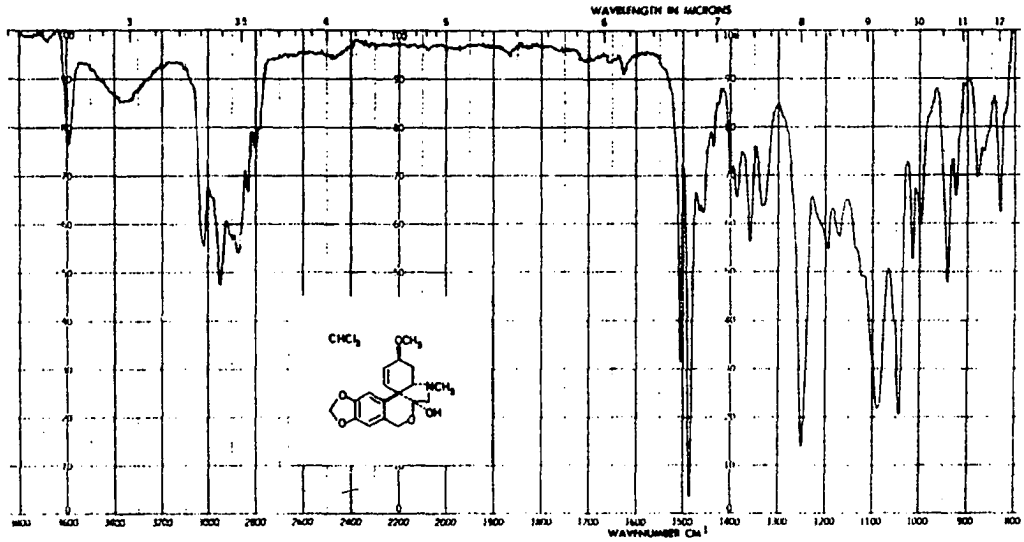
Comparison of the infrared spectra (ir) [Fig. 1] and nuclear magnetic resonance spectra (nmr) [Fig. 2] of tazettine (22) and pretazettine (39) indicates that the bases have many structural features in common. The ir spectra show that both contain a hydroxyl group, an aliphatic methoxyl group, and an aromatic methylenedioxy unit. The nmr confirms that both have a methylenedioxy group, an aliphatic methoxyl group, an N-methyl group, two aromatic protons, and two olefinic protons. A major difference between the two nmr spectra is found in the benzylic proton area. Tazettine contains a benzylic methylene AB pattern (4.91 and 4.65 ppm, J_{AB} = 15 Hz) which is not observed in the spectrum of pretazettine. In contrast, pretazettine has a one proton singlet (6.06 ppm). This would indicate that the benzylic position of pretazettine has been substituted. The presence of a benzylic hydroxyl group in pretazettine was confirmed by a manganese dioxide oxidation to a mixture of 40 and 41. Both compounds have infrared [Fig. 3] and ultraviolet spectra consistent with a conjugated carbonyl function.

The nmr spectrum of compound 41 [Fig. 4] was similar to that of pretazettine (39) except for the absence of the benzylic proton singlet at 6.06 ppm. In addition one aromatic proton (at 6.83 ppm in 39) had been shifted to 7.51 ppm. These data indicate that the benzylic hydroxyl group has been oxidized to a carbonyl group with the concomitant loss of

Fig. 1: Infrared spectra

a: Tazettine (71)

b: Pretazettine (39)


WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NCH₃
OH

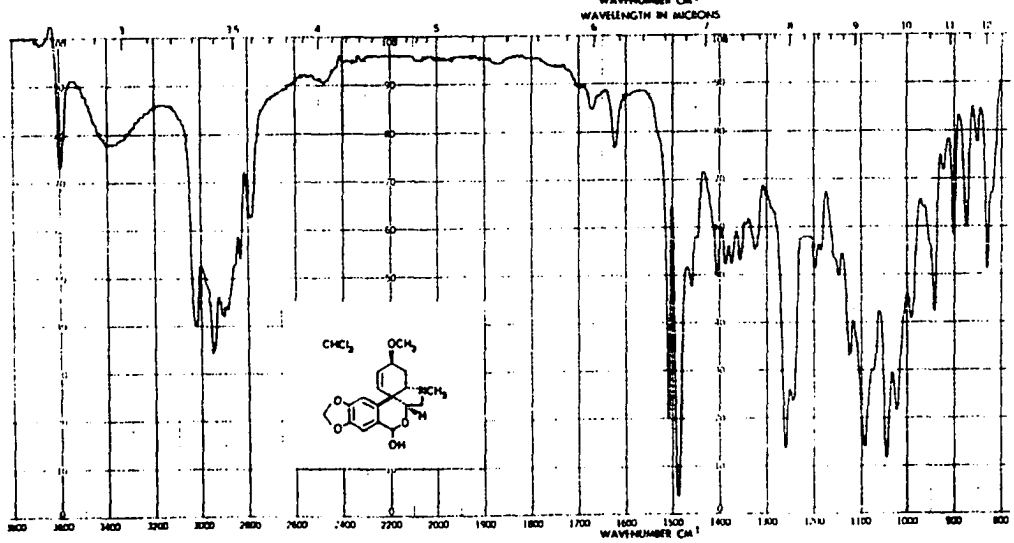
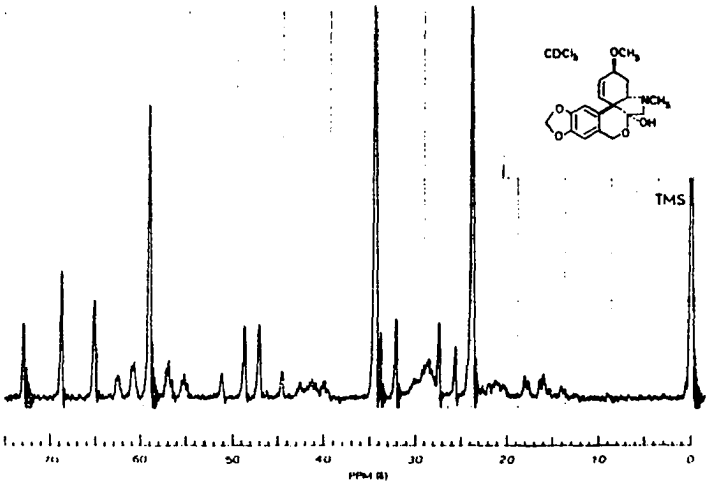
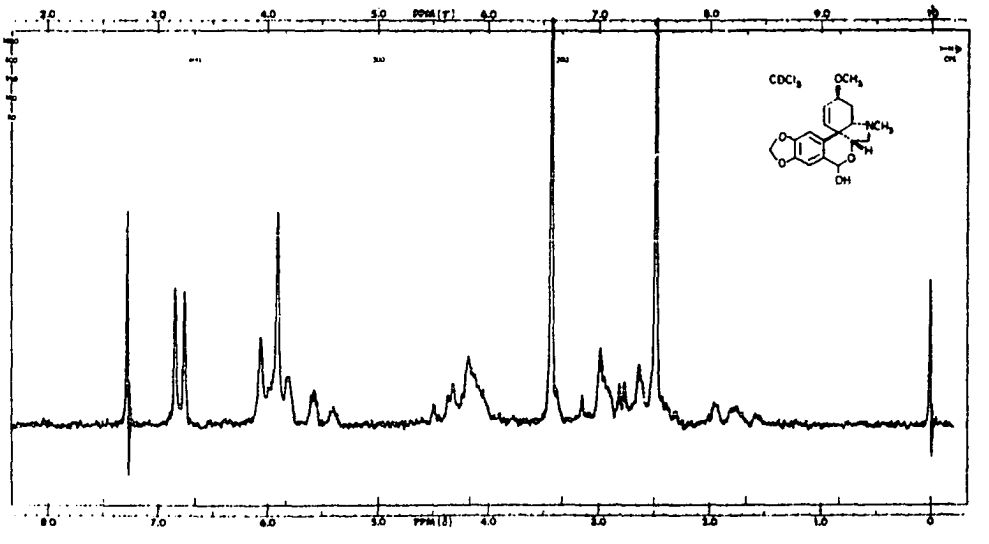

WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NCH₃
H
OH

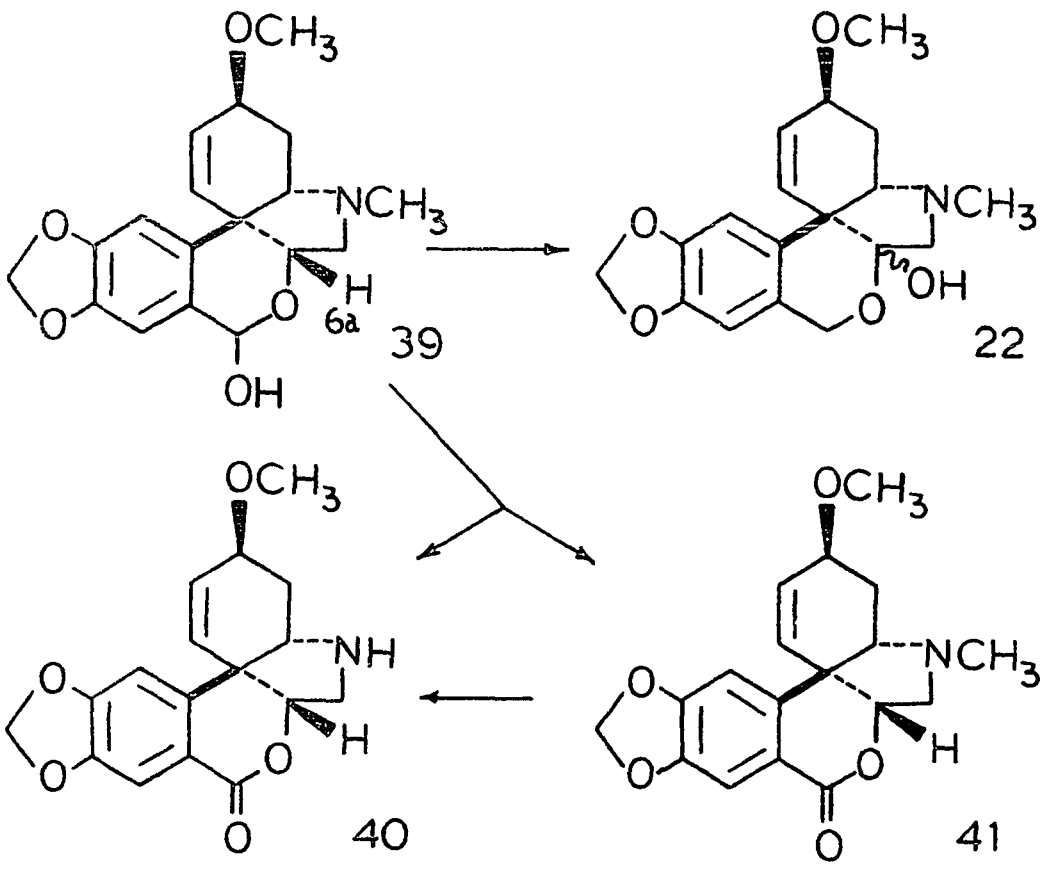
Fig. 2: Nuclear magnetic resonance spectra

a: Tazettine (71)

b: Pretazettine (39)


CDCl3
OCH3
NCH3
OH
TMS
70
60
50
40
30
20
10
0
PPM (δ)


CDCl3
OCH3
NCH3
OH
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
PPM (δ)



the benzylic proton. A carbonyl group at C_8 would explain the large shift of the adjacent aromatic proton. The nmr spectrum of 40 [Fig. 4] was similar to that of 41 except for the absence of the N-methyl singlet and presence of a proton at 1.89 ppm, which was exchangeable with D_2O. This indicated that the N-methyl group had undergone oxidative cleavage.[45] The infrared spectrum of the crude oxidation mixture showed a weak band at 1671 cm^{-1} suggesting traces of the N-formyl intermediate (41, N-CHO instead of $N-CH_3$). In subsequent experiments it was possible to convert 41 to 40 by manganese dioxide oxidation.

The structure and stereochemistry of 40 and 41 were proven by synthetic interconversions.[21] Haemanthidine (23) was oxidized to

Fig. 3: Infrared spectra

a: 6-Oxohaemanthamine (28)

b: N-Demethyl 3-epimacronine (40)

c: 3-Epimacronine (41)

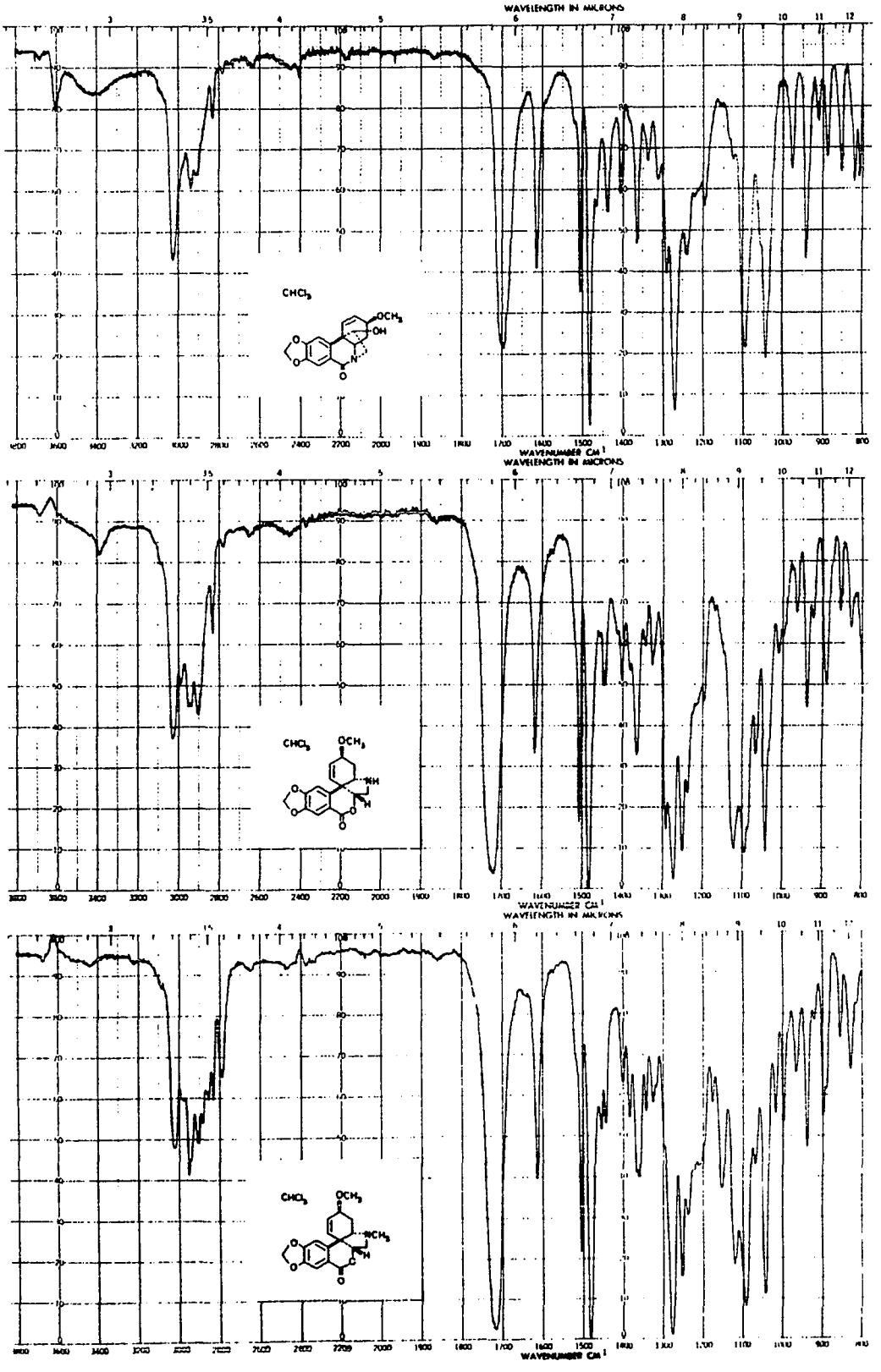
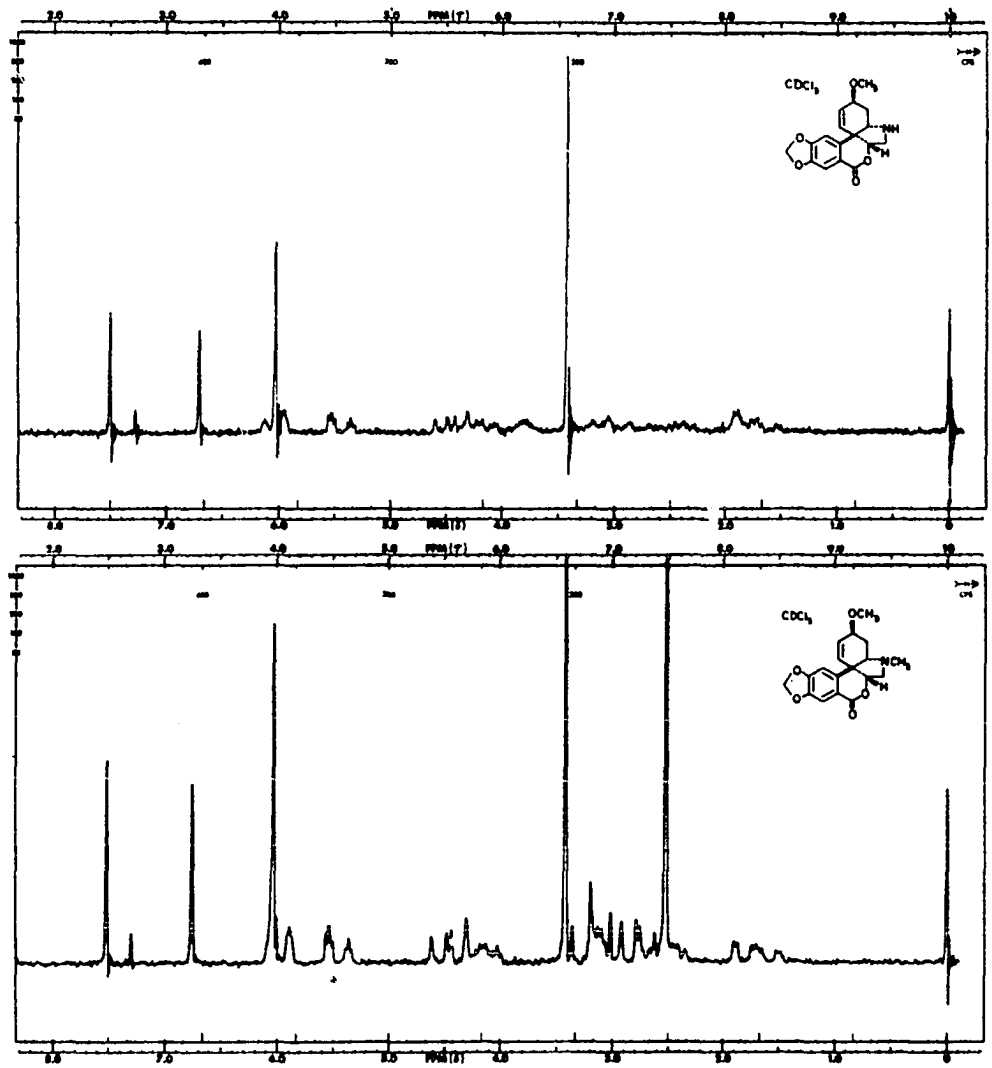
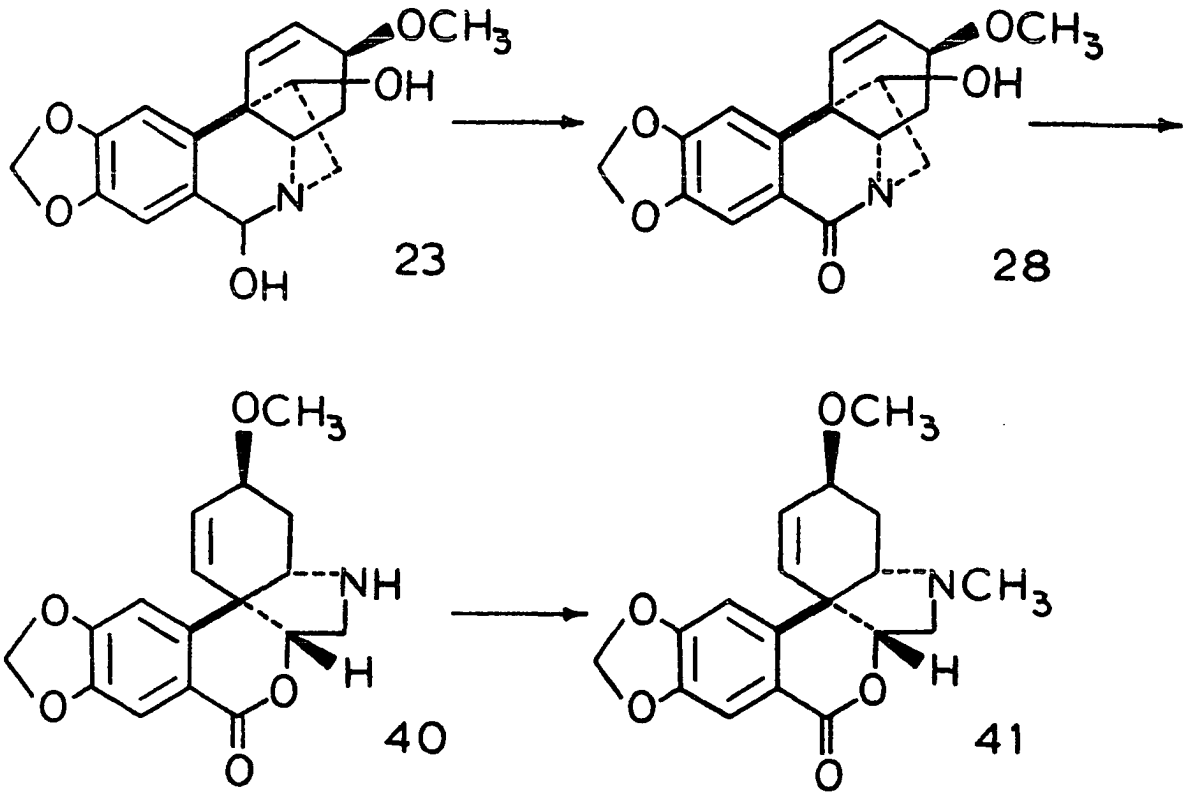

WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
OH
WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NH
H
WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NCH₃
H

Fig. 4: Nuclear magnetic resonance spectra

a: N-Demethyl 3-epimacronine (40)

b: 3-Epimacronine (41)


CDCl3
OCH3
NH
CDCl3
OCH3
NCH3



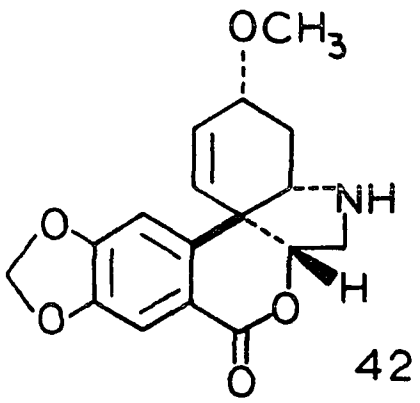
6-oxohaemanthamine (28) by manganese dioxide.[19] Upon refluxing 28 in a sodium acetate-acetic acid buffer, a compound was isolated the infrared and ultraviolet spectra of which showed the presence of a conjugated lactone group rather than the original lactam [Fig. 3]. The ir and nmr spectra of the reaction product indicated that the tertiary amide group of 28 had been converted to a secondary amine. This product was identical in all respects with 40 formed by the oxidation of pretazettine. This structure can be explained by the hydrolysis of the lactam to an amino acid which has subsequently undergone lactonization between the carboxylic acid and the C_{11}-hydroxyl group to provide 40. N-Methylation of 40 with formaldehyde and sodium borohydride gave 41.

By these conversions, the structure and stereochemistry of pretazettine (39) and haemanthidine (23) have been related. The C_{11}-hydroxyl group of haemanthidine has a configuration such that this group is directed toward the C_1-C_2 unsaturation.[21] There is no reason to suspect that, under the mild reaction conditions, the configuration of the C_{11}-hydroxyl group in 6-oxohaemanthamine (28) would be altered in the transformation to 40. Therefore, the configuration of the C_{6a}-hydrogen of 40 and 41 is beta (steroid convention), and the B-D ring fusion is trans. This is in contrast with the cis B-D ring fusion suspected for tazettine. If the structures assigned to 40 and 41 are correct, pretazettine must also have a trans B-D ring fusion and a beta C_{6a}-hydrogen as shown in 39. Further evidence of this configuration will be presented.

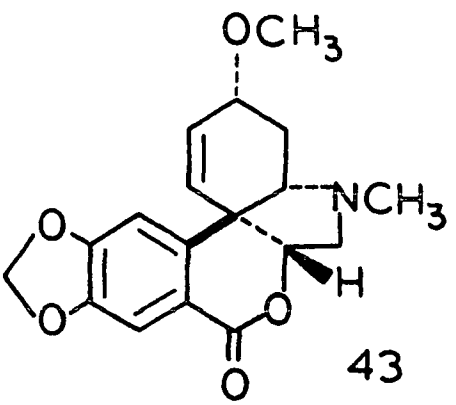
More detailed isolations of the minor alkaloids from S. formosissima gave a substance which was identical in all respects with 41. The new base was named 3-epimacronine because of the similarity of its assigned structure with that of the alkaloid macronine (34).

The proof of structure of macronine (34) involved a similar rearrangement utilizing 6-hydroxycrinamine (32) as starting material.[27] The configuration of the C_{11}-hydroxyl group of 32 is known to be anti to the aromatic ring.[25] By similar reasoning N-demethylmacronine and macronine must also have beta C_{6a}-hydrogens and have the complete structure as indicated in 42 and 43 respectively.

The configuration of the C_8-benzylic hydroxyl group is the only feature of pretazettine left to be described. Recently, it has been shown that alkaloids in the 5,10b-ethanophenanthridine nucleus which

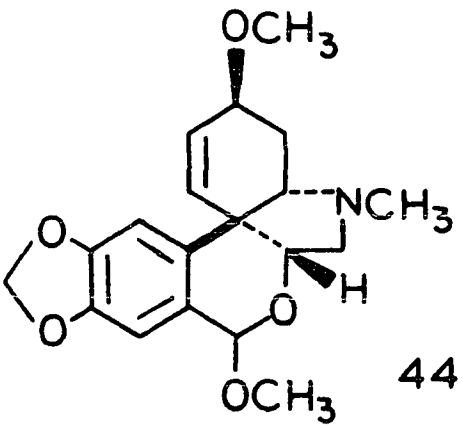


42



43

have a benzylic hydroxyl group (i.e. 23 and 32) exist in solution as a mixture of C_6-epimers. Although the benzylic hydroxyl group of pretazettine gives no spectral indication of epimeric character, there is chemical evidence for this mobility. Pretazettine, upon treatment with acidic methanol, gave a mixture of C_8-epimeric acetals corresponding to α-and β-O-methylpretazettine (44). The two acetals show slightly different R_f values by thin-layer chromatography, but all attempts to isolate the individual acetals were unsuccessful. Pretazettine was the only substance recovered after a mild hydrolysis of the

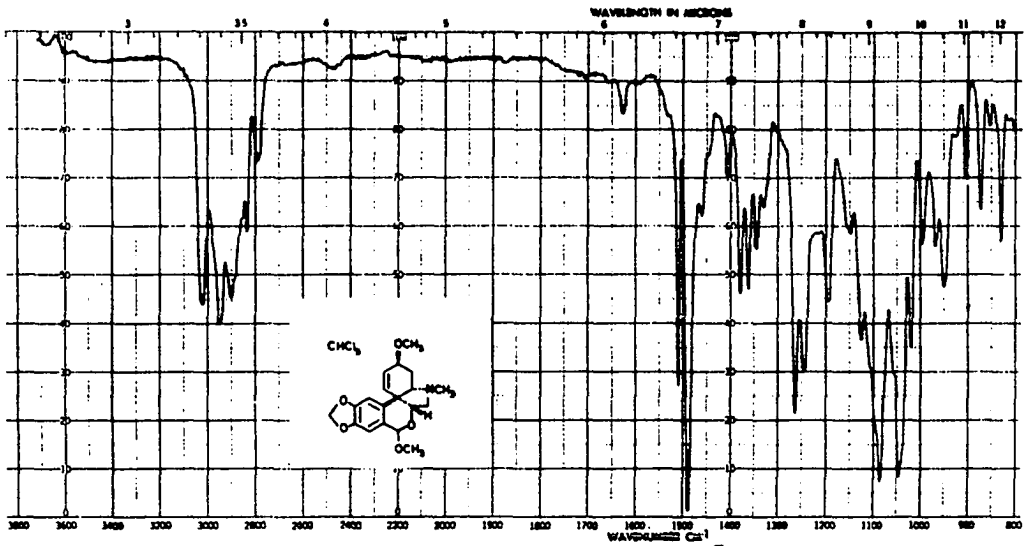


44

Fig. 5: Infrared spectra

a: O-Methylpretazettine (44)

b: O-Methylprecriwelline (46)


WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NCH₃
H
OCH₃

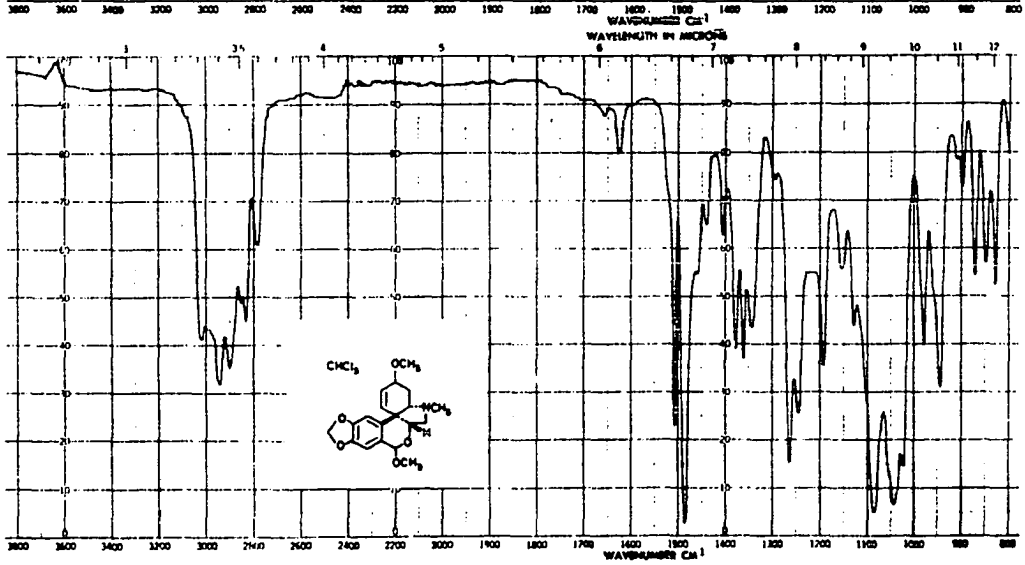
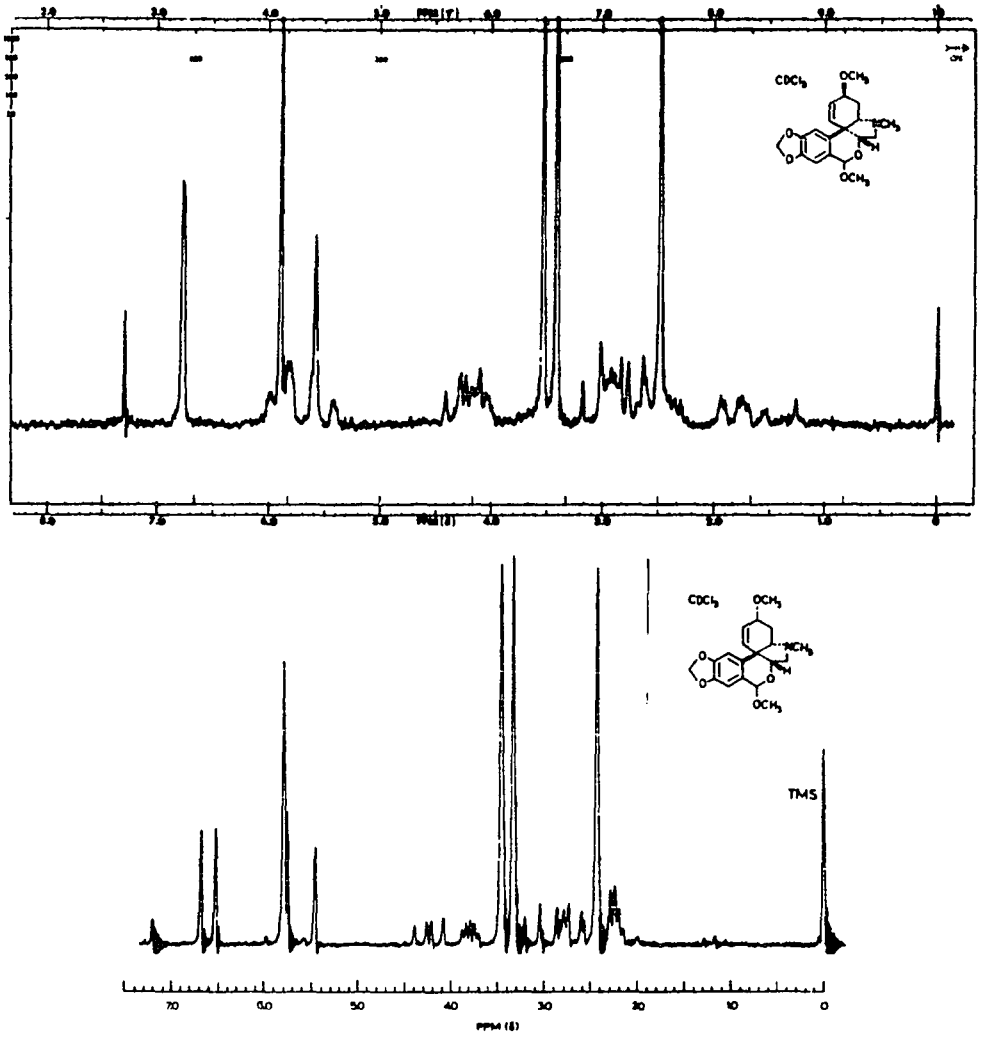

WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NCH₃
H
OCH₃

Fig. 6: Nuclear magnetic resonance spectra

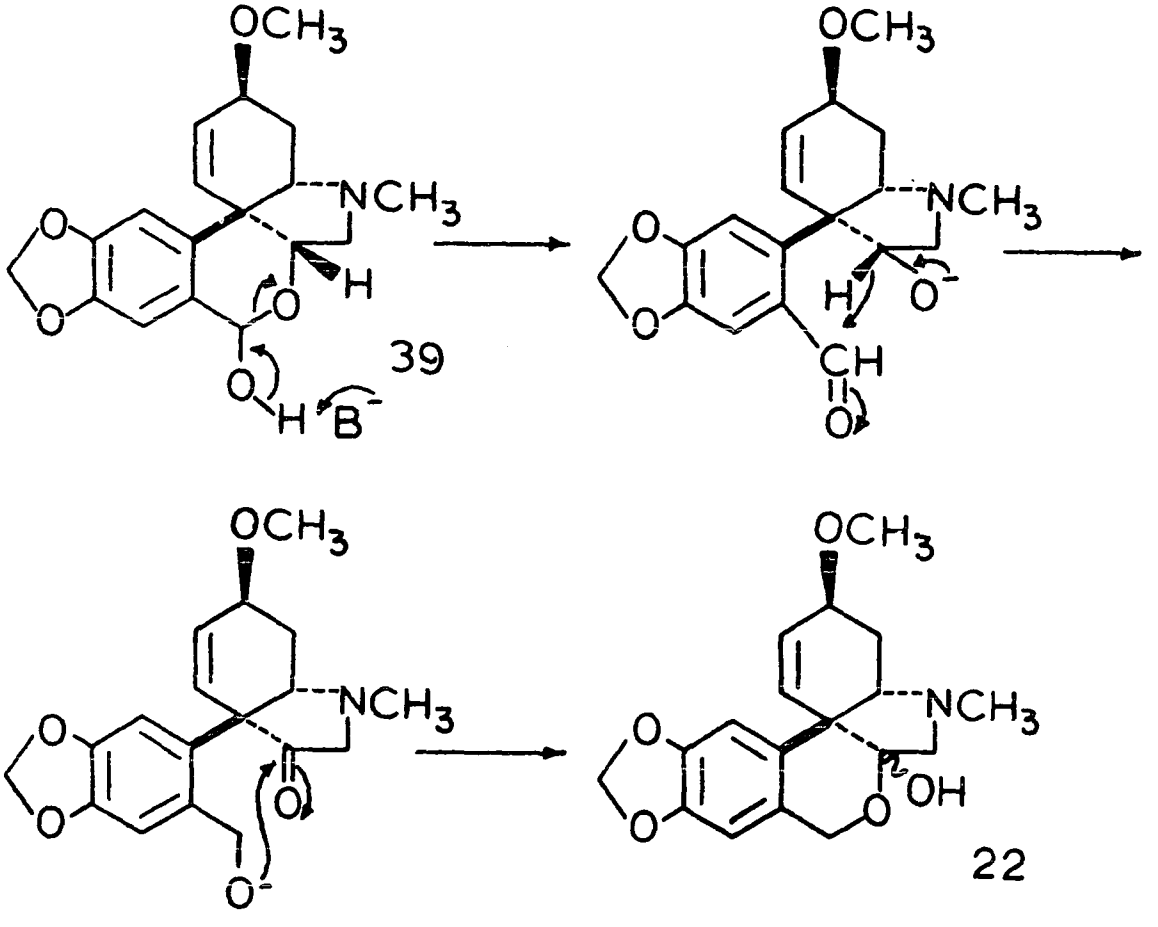
a: O-Methylpretazettine (44)

b: O-Methylprecriwelline (46)


CDCl3
OCH3
TMS
PPM (δ)

acetal mixture. The nmr spectrum of O-methylpretazettine [Fig. 6] is similar to that of pretazettine and shows only two aromatic protons and one benzylic proton. This indicates that the epimeric benzylic protons of pretazettine and O-methylpretazettine have equivalent chemical shifts.

The mechanism for the rearrangement of pretazettine to tazettine appears to be similar to that proposed earlier for the conversion of haemanthidine and 6-hydroxycrinamine methiodides to tazettine and criwelline, respectively.[20] Pretazettine has a <u>trans</u> B-D ring fusion and is a relatively strained molecule. Tazettine probably has a <u>cis</u> B-D fusion which allows more flexibility. The driving force for the



B-ring opening of 39 would appear to be the relief of this internal strain. The completion of the rearrangement may be considered an intramolecular crossed-Cannizzaro reaction with subsequent hemiketal formation. This final closure occurs in such a way as to give the B-D-fusion characteristic of tazettine.

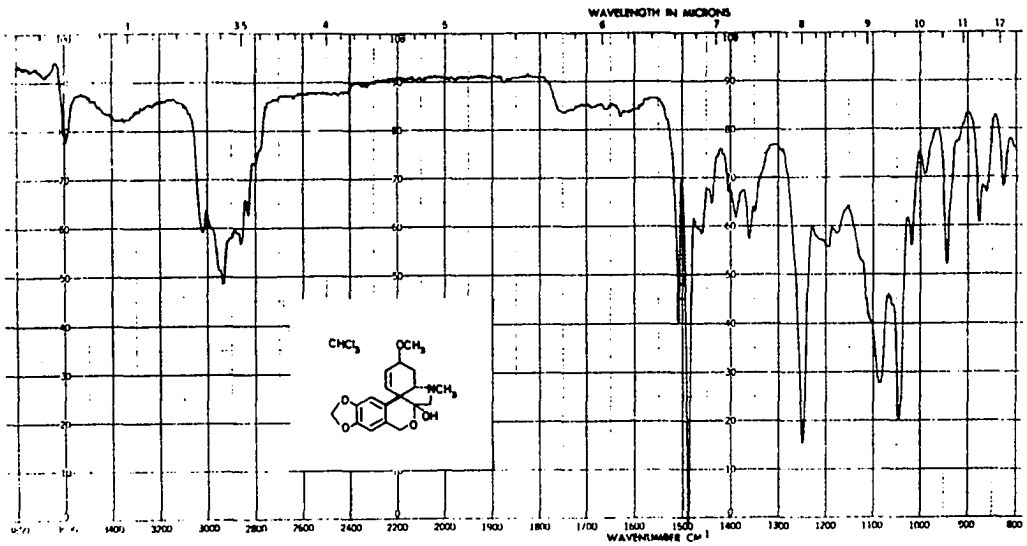
Isolation and Structures of Alkaloids from *Crinum powellii* Hort. var. *album*

Earlier workers have reported the isolation from *Crinum powellii* of criwelline, caranine, crinalbine, crinine, haemanthamine, ismine, lycorine, and powelline.[39,46] Our study of the facile rearrangement of pretazettine to tazettine led us to question the natural occurrence of criwelline (31). In our reinvestigation of this plant, bulbs were processed by the same isolation procedure which was used with *Sprekelia formosissima* to obtain pretazettine. Thin-layer chromatography of the total crude alkaloid fraction showed that criwelline was not present. Because the characteristic R_f values of precriwelline were not known, components of the mixture were separated by preparative thin-layer chromatography and identified by comparison of infrared spectra and physical properties with known alkaloids. One component (45) showed an ir spectrum [Fig. 7] similar to that of pretazettine [Fig. 1]. It resisted crystallization, but formed a crystalline hydrochloride salt. Treatment with dilute sodium hydroxide gave criwelline (31) in good yield. Oxidation with manganese dioxide gave two compounds which were identified as N-demethylmacronine (42) and macronine (43) by thin-layer chromatographic comparison. On the basis of this data and the similarity

Fig. 7: Infrared spectra

a: Criwelline (72)

b: Precriwelline (45)


WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl3
OCH3
NCH3
OH

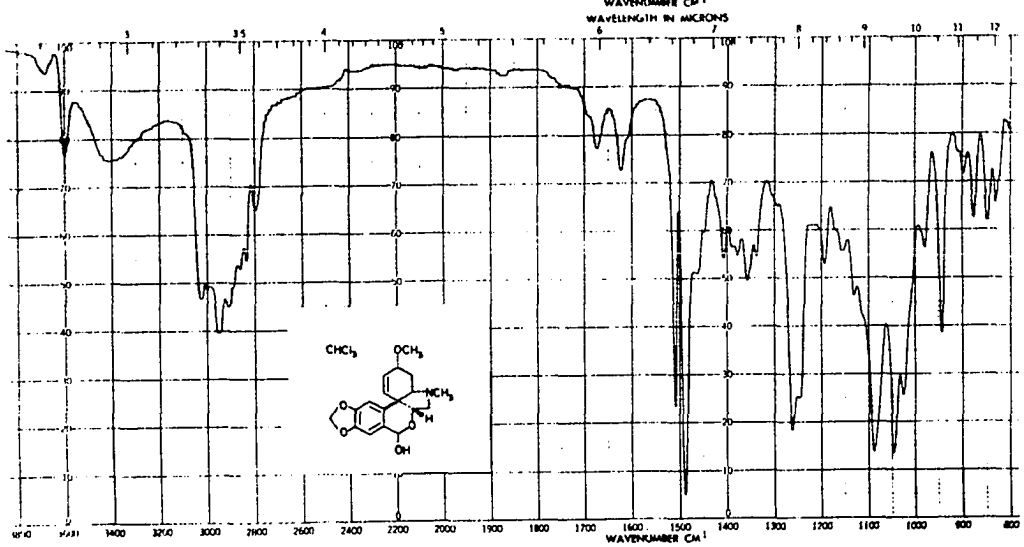
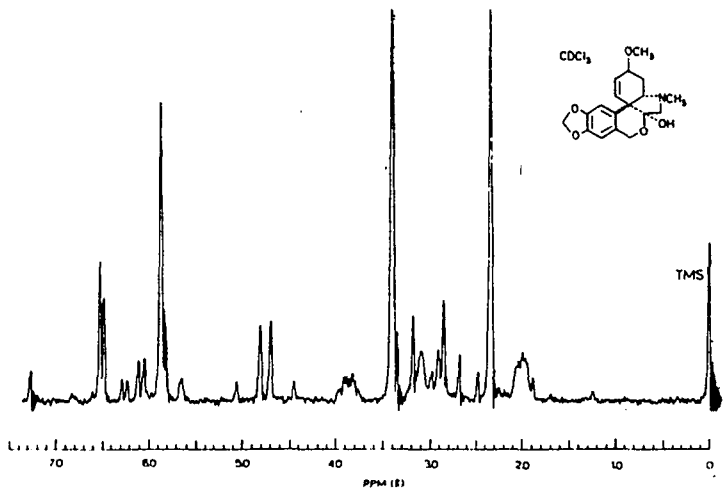
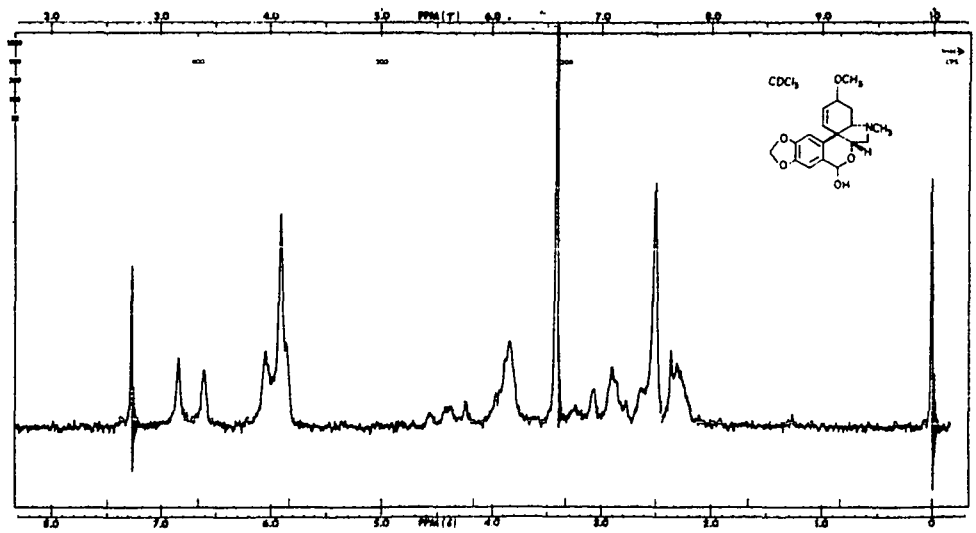

WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl3
OCH3
NCH3
H
OH

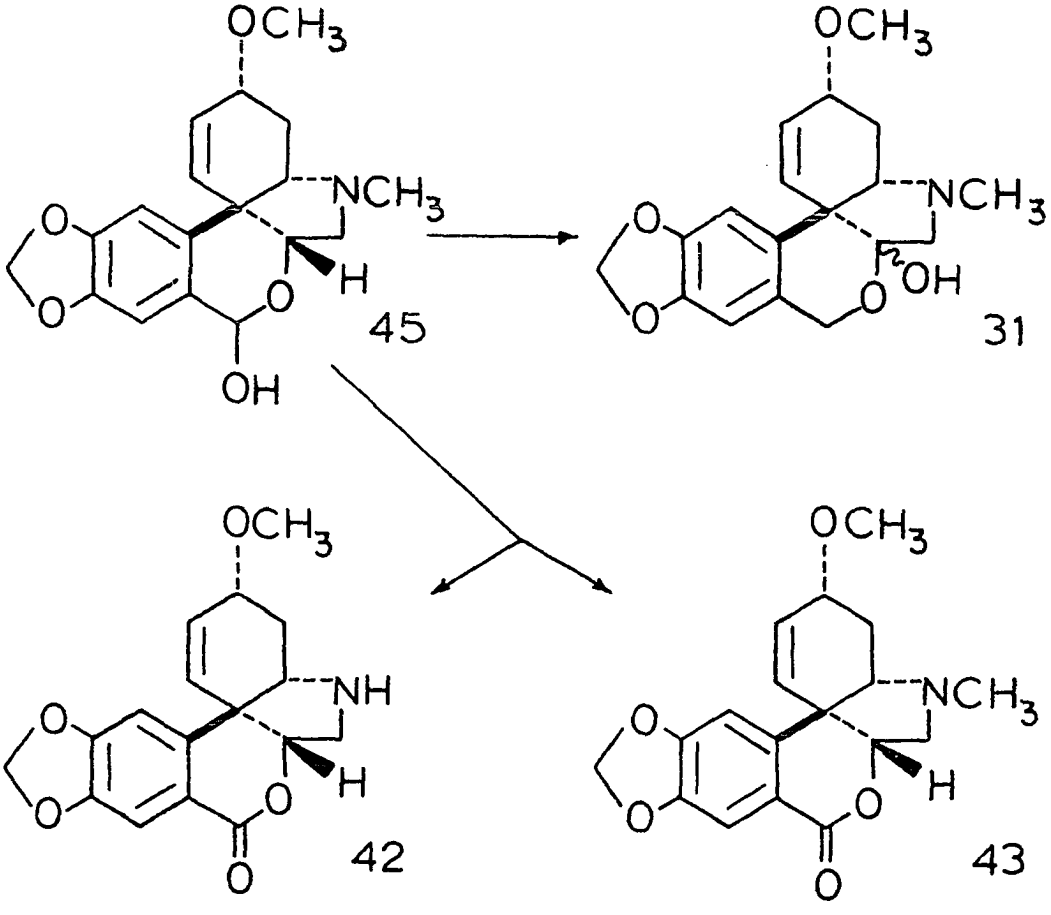
Fig. 8: Nuclear magnetic resonance spectra

a: Criwelline (72)

b: Precriwelline (45)


CDCl3
OCH3
NCH3
OH
TMS
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
PPM (δ)


CDCl3
OCH3
NCH3
H
OH
PPM (δ)



of this alkaloid with pretazettine, we consider this alkaloid to be precriwelline (45).

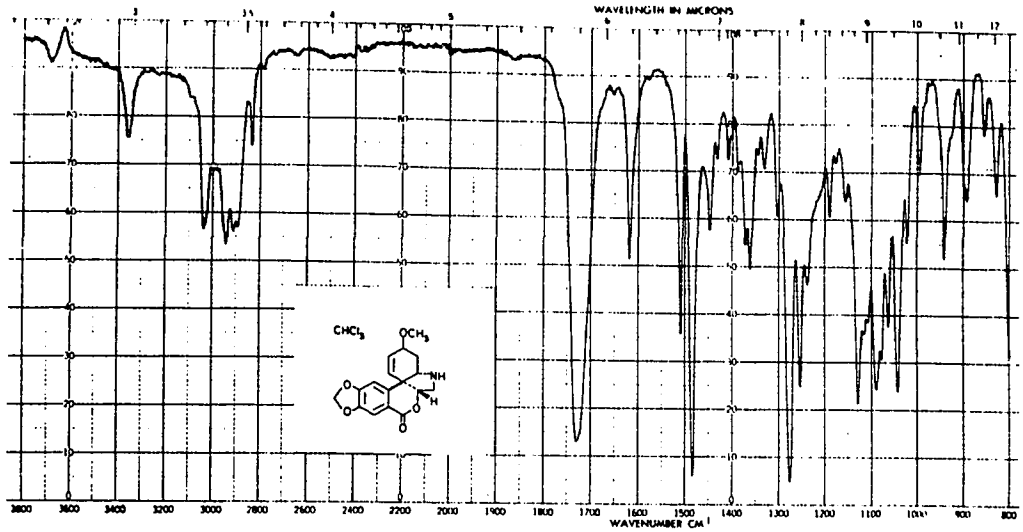
The nmr spectrum of precriwelline [Fig. 8] was never obtained in good quality although the sample was of sufficient concentration. All spectra were consistent with the assigned structure 45 for precriwelline. When precriwelline hydrochloride was refluxed in acidic methanol, O-methylprecriwelline (46) was formed. This compound is identical with compound 37 previously prepared by treatment of 6-hydroxycrinamine with methyl iodide in refluxing methanol.[27] The C_{6a}-hydrogen of 37 can now be assigned as having the beta configuration.

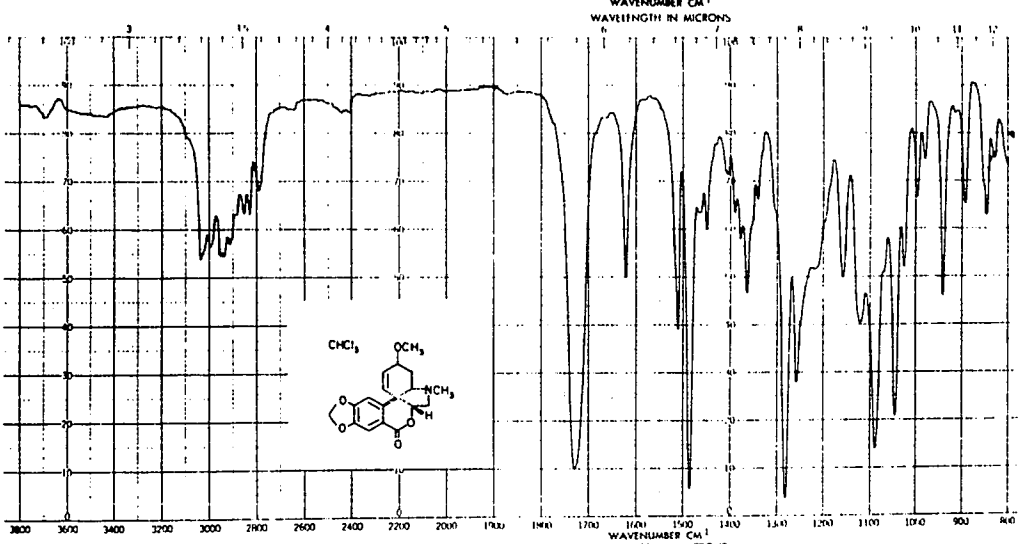
Fig. 9: Infrared spectra

a: N-Demethylmacronine (42)

b: Macronine (43)

c: N-Demethyl N-carboethoxymacronine (47)


WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NH
H
O
O
O
O


WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NCH₃
H
O
O
O
O

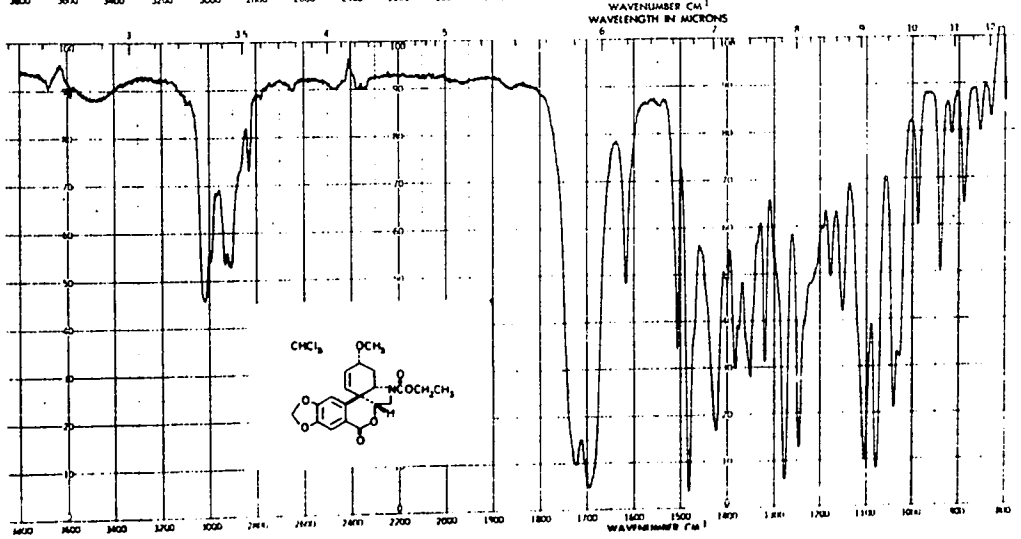
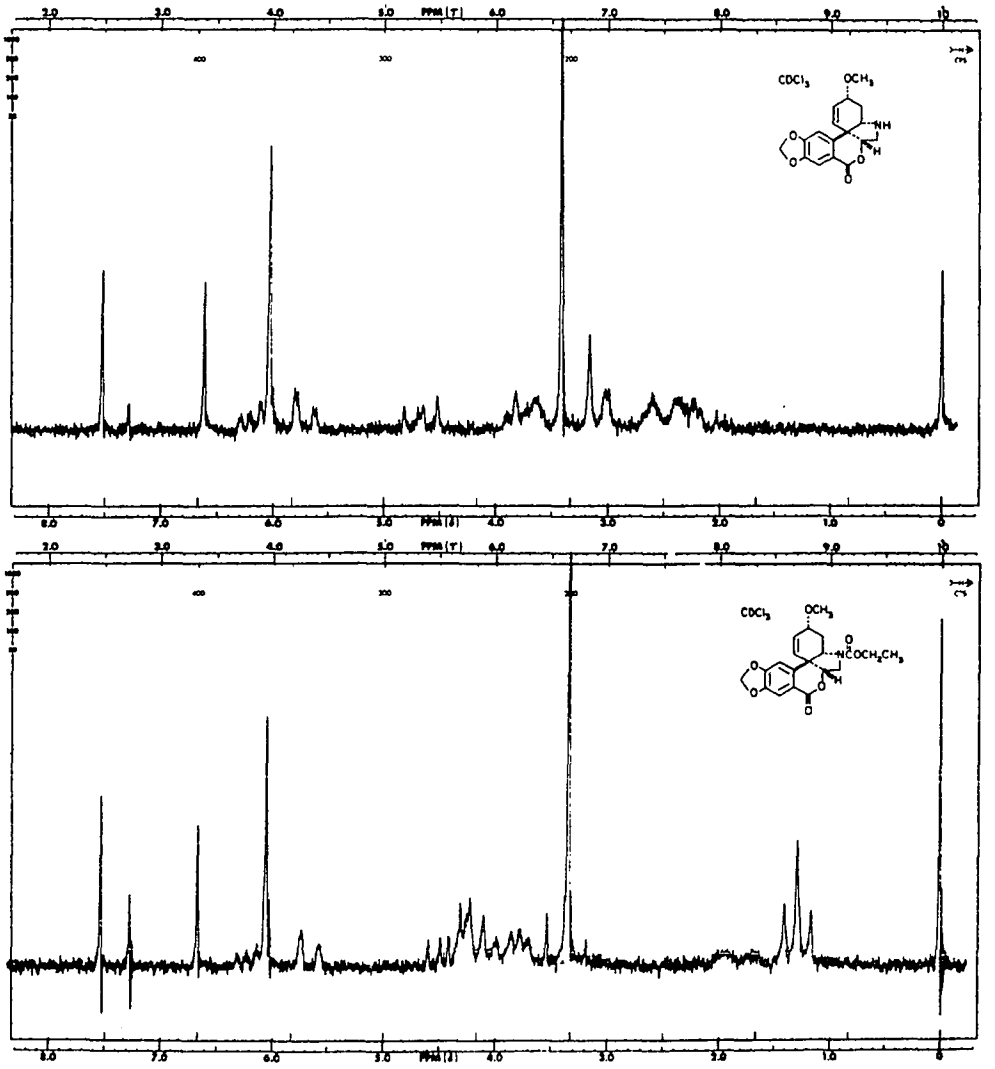
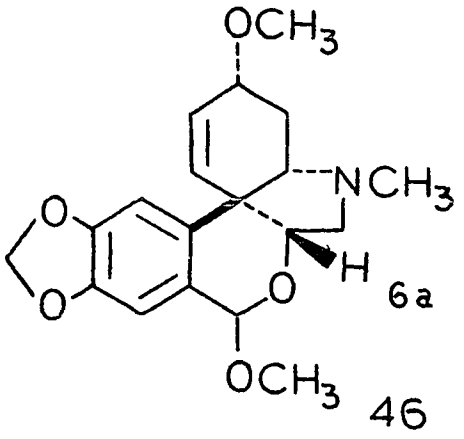

WAVELENGTH IN MICRONS
CHCl₃
OCH₃
NCOCH₂CH₃
H
O
O
O
O

Fig. 10: Nuclear magnetic resonance spectra

a: N-Demethylmacronine (42)

b: N-Demethyl N-carboethoxymacronine (47)


CDCl3
OCH3
NH
O
O
O
O
CDCl3
OCH3
O
NCOCH2CH3
O
O
O
O



46

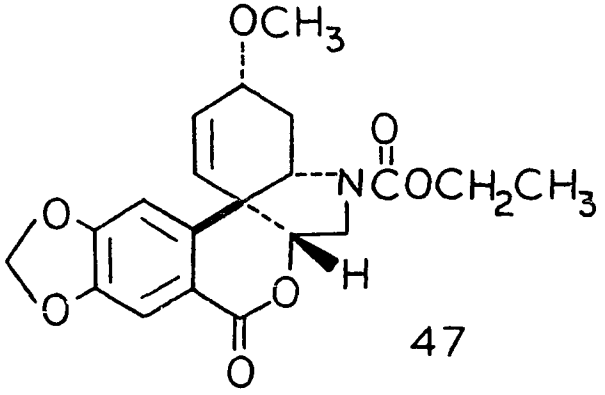
Isolation and Structures of Alkaloids from

Crinum erubescens Ait.

Earlier isolations from Crinum erubescens have shown the presence of crinamine, lycorine, 6-hydroxycrinamine, criwelline, and coranicine.[24,28] The use of a mild isolation procedure and thin-layer chromatographic techniques led to the isolation of a number of additional alkaloids which were known but had not been reported previously to occur in this plant: crinine, macronine, powelline, buphanidrine, flexinine, crinamidine, nerbowdine, and deacetylbowdensine. In addition, two new alkaloids containing the [2]benzopyrano[3,4c]indole nucleus were found. Purification by thin-layer chromatography led to the isolation of a new alkaloid of moderate concentration in the plant. By all spectroscopic [Fig. 9 and 10] and chromatographic criteria it was identical to N-demethylmacronine (42), known previously only by synthesis.[27]

The second alkaloid was present only in trace amounts. The ultraviolet and infrared spectra [Fig. 9] showed many similarities with N-demethylmacronine (42) and macronine (43). However, the compound

contained two carbonyl groups. The nmr spectrum [Fig. 10] was also similar to those of 42 and 43 except for an additional two proton quartet (4.16 ppm) and a three proton triplet (1.28 ppm) which suggested an ethoxyl group. The mass spectrum indicated that the compound had a molecular weight of 387. This data would be consistent with the carbamate structure 47. To verify this hypothesis, N-demethylmacronine



47

was treated with ethyl chloroformate. The reaction product was identical in all respects with the natural material. An ethyl carbamate such as 47 is most suspect as a natural product and may well be an artifact. This could be formed from phosgene, derived from the decomposition of chloroform, and from ethanol which are both present in the initial alkaloid isolation. These may react with the N-demethylmacronine that has been identified to occur in this plant.

Synthetic and Biosynthetic Skeletal Interconversions

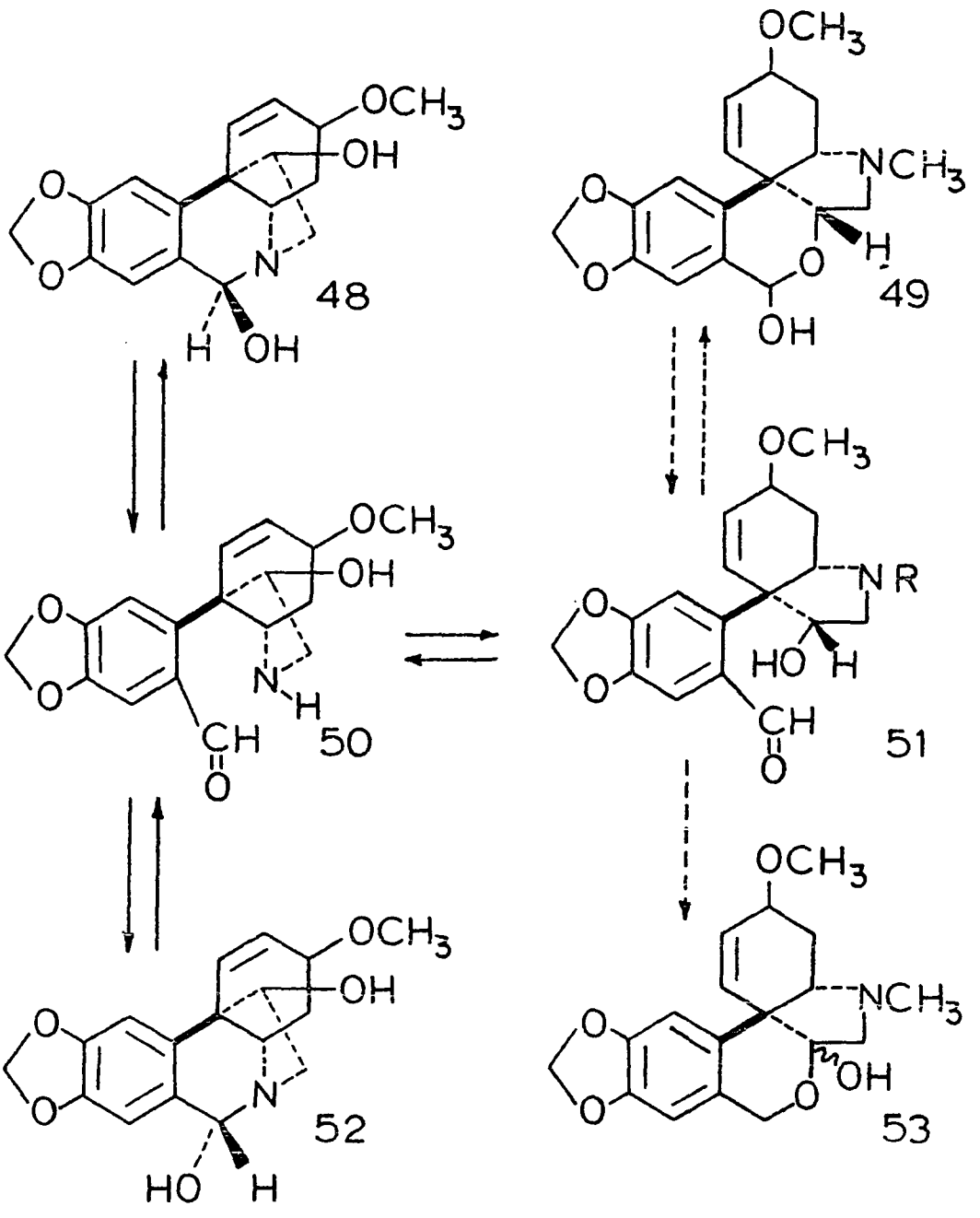
Although the intermediate 50 and its rotational equivalent 51 (R = H) have never been detected by spectral methods, these structures have considerable significance in the interrelationship of alkaloids related to structures 48, 49, and 53. In a chemical sence the alkaloids

haemanthidine (23) and 6-hydroxycrinamine (32) are amino alcohols formed by the ring closure of the intermediate amino aldehyde 50. The dynamic nature of this N-C_6 bond formation was realized when 23 and 32 were shown to exist in solution as equilibrating mixtures of 6-hydroxyl epimers.[22] The epimeric forms were proposed to be interconvertable through 50. The tendency of alkaloids of type 49 (pretazettine and precriwelline) to rearrange to the type 53 nucleus (tazettine and criwelline) has been demonstrated. This transformation was considered to proceed through 51 (R = CH_3) or the related alkoxide anion.

A number of examples for the conversion of the 6-hydroxy-5,10b-ethanophenanthridine alkaloids (48) to the [2]benzopyrano[3,4c]indole ring systems (49 and 53) were summarized in the historical section. While there is little doubt that these synthetic interconversions are basically correct, the lability of the amino alcohol, hemiacetal, and hemiketal moieties to even the mildest of isolation and identification procedures suggested that the fundamental reactions of these substances should be reexamined. Syntheses of pretazettine and precriwelline were primary objectives.

Syntheses of pretazettine (39) and precriwelline (45)

Reaction conditions necessary to convert the 6-hydroxy-5,10b-ethanophenanthridine alkaloids (48) to the [2]benzopyrano[3,4c]indole ring systems (49 and 53) indicated that treatment with all but the most dilute base (either in the course of the reaction itself or in the subsequent isolation procedure) often led to type 53 structures. These findings are consistent with the facile conversion of pretazettine (39)



to tazettine (22) by base. In contrast, syntheses of the type 49 compounds have, in all cases, proceeded in neutral or slightly acidic media. it appeared very possible that haemanthidine methiodide (27) might rearrange to pretazettine (39) under acidic conditions. To test this hypothesis, haemanthidine methiodide was dissolved in dilute

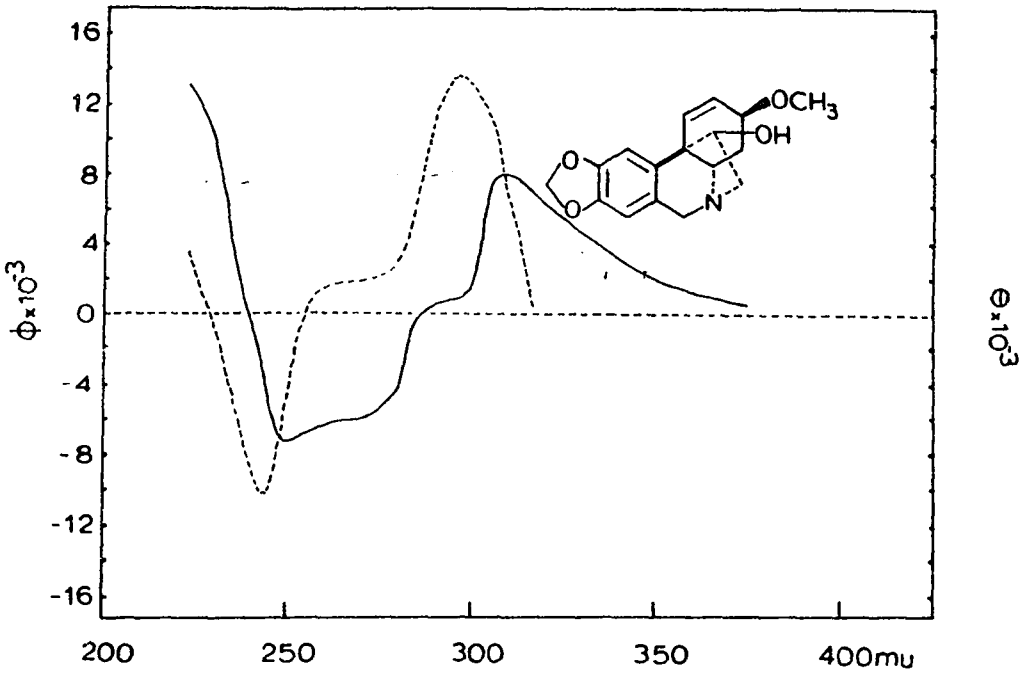
hydrochloric acid (pH 4) at room temperature. The solution was made basic (pH 10) with sodium carbonate and immediately extracted with chloroform. Evaporation of the chloroform to dryness under reduced pressure gave, in almost quantitative yield, pretazettine (39). By the same procedure, 6-hydroxycrinamine methiodide was converted to precriwelline (45).

These transformations can be attributed to either the effect of the acid on the methiodides or the basic conditions required for the isolation of the product. Spectroscopic studies were undertaken to elucidate the relationship between the methosalts of 23 and the hydrosalts of 39 in solution. Although the ir and nmr spectra of 27 and 39 are distinct, optical rotatory dispersion (ord) and circular dichroism (cd) measurements provided a more sensitive method for the differentiation of the two ring systems.[47,48] The ord and cd spectra of haemanthamine and haemanthamine methiodide in methanol [Fig. 11] are similar and distinctly different from those observed for tazettine [Fig. 12]. The spectra of pretazettine and O-methylpretazettine in methanol [Fig. 13] are similar and differ significantly from those observed for the other two ring systems. The ord and cd spectra of pretazettine hydrochloride in methanol [Fig. 12] were almost identical with those of haemanthamine in the same solvent. This suggests that pretazettine in methanol possesses the hemiacetal structure. However, the hydrochloride of pretazettine in this solvent exists in the 5,10b-ethanophenanthridine nucleus as the methosalt of haemanthidine (27). A recent communication[44] reported the cd spectrum of pretazettine. This curve was identical with that obtained from pretazettine hydrochloride rather than the

Fig. 11: Optical rotatory dispersion (——) and circular dichroism (----) spectra

a: Haemanthamine (26)

b: Haemanthamine methiodide


16
12
8
4
0
-4
-8
-12
-16
200
250
300
350
400mu
$\phi \times 10^{-3}$
$\Theta \times 10^{-3}$
OCH3
OH
O
O
N

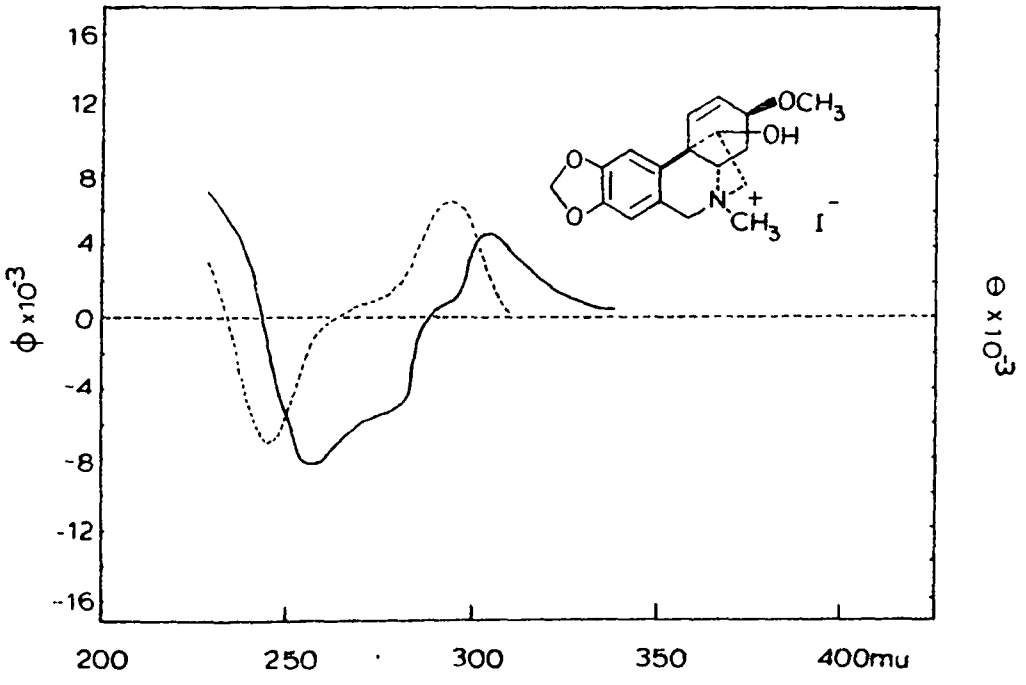
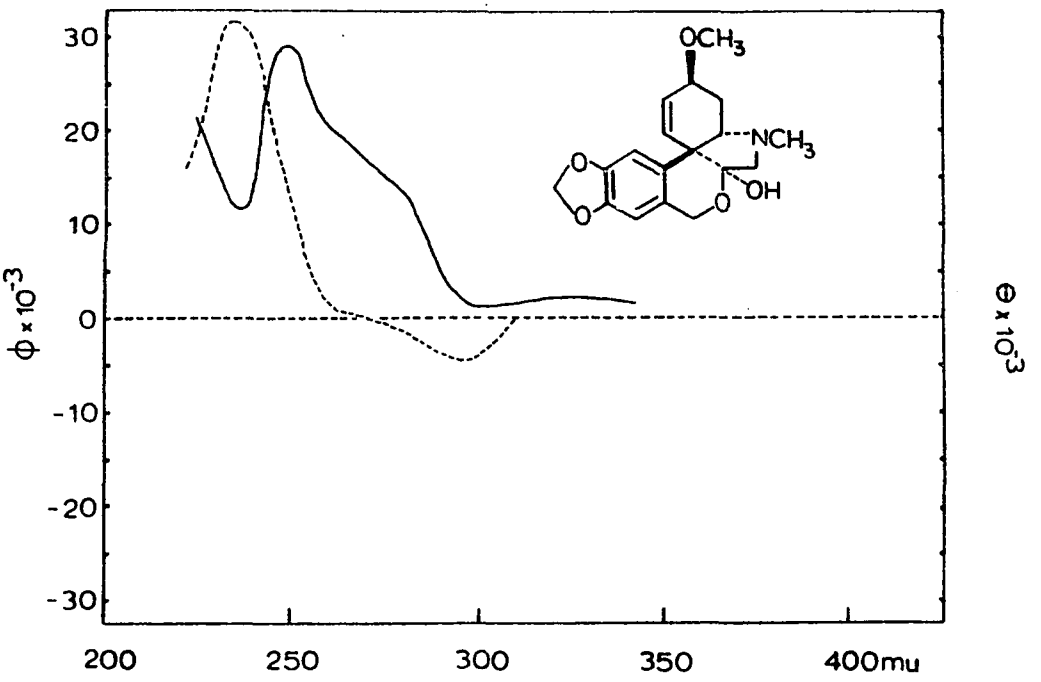

16
12
8
4
0
-4
-8
-12
-16
200
250
300
350
400mu
$\phi \times 10^{-3}$
$\Theta \times 10^{-3}$
OCH3
OH
O
O
N+
CH3
I-

Fig. 12: Optical rotatory dispersion (——) and circular dichroism (----) spectra

a: Tazettine (71)

b: Pretazettine hydrochloride (27)


30
20
10
0
-10
-20
-30
200
250
300
350
400mu
$\phi \times 10^{-3}$
$\Theta \times 10^{-3}$
OCH3
NCH3
OH
O
O
O

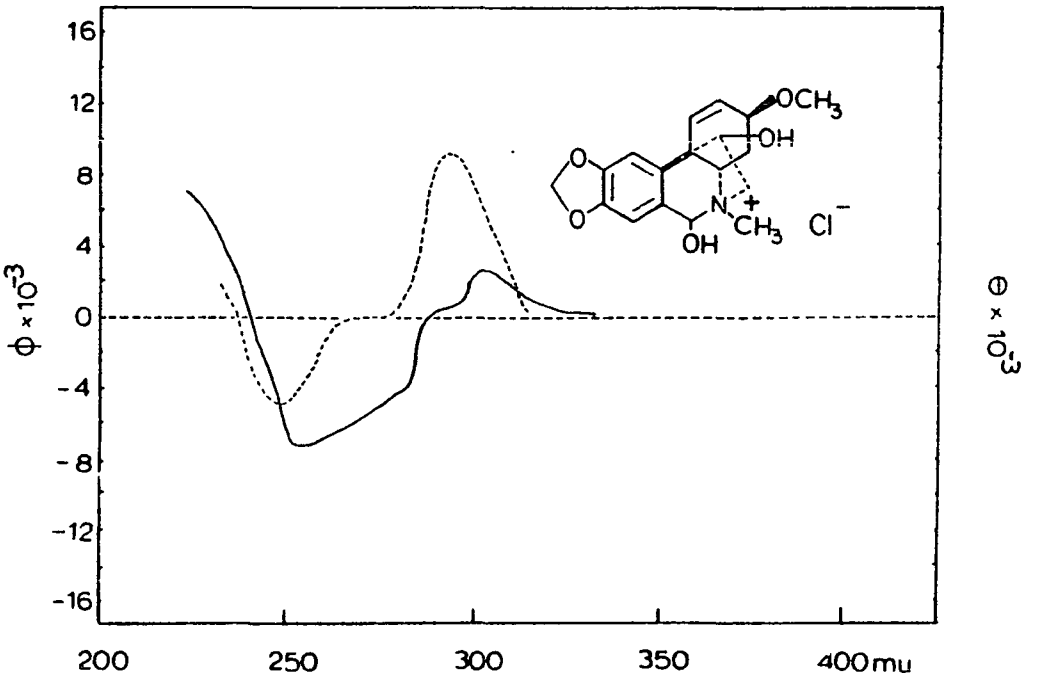
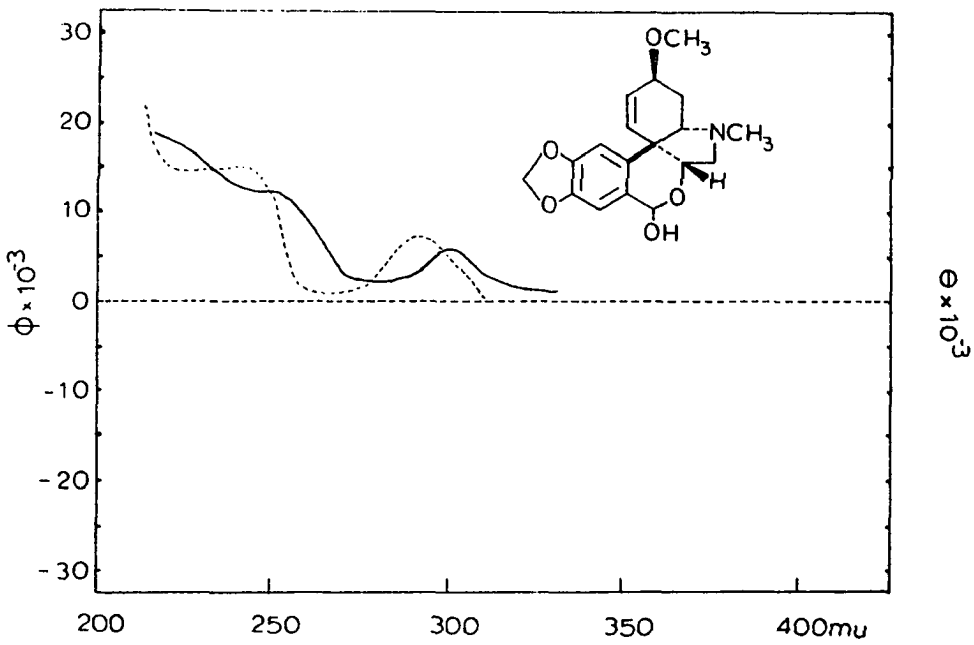
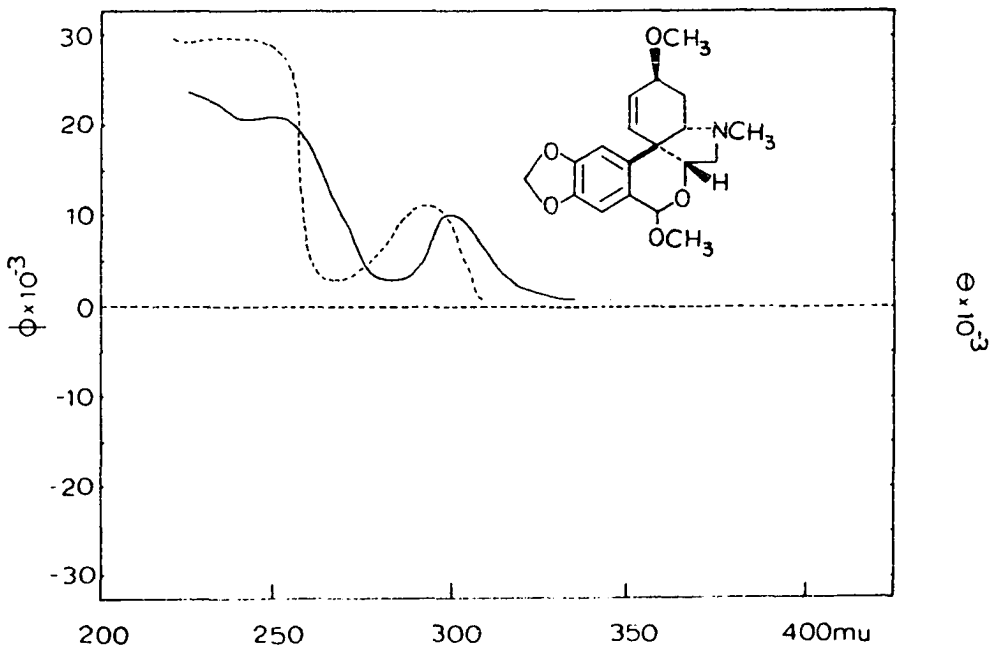

16
12
8
4
0
-4
-8
-12
-16
200
250
300
350
400mu
$\phi \times 10^{-3}$
$\Theta \times 10^{-3}$
OCH3
OH
OH
N
+
CH3
Cl−
O
O

Fig. 13: Optical rotatory dispersion (——) and circular dichroism (----) spectra

a: Pretazettine (39)

b: O-Methylpretazettine (44)


30
20
10
0
-10
-20
-30
$\phi \times 10^{-3}$
$\Theta \times 10^{-3}$
200
250
300
350
400mu
OCH_3
NCH_3
H
O
OH


30
20
10
0
-10
-20
-30
$\phi \times 10^{-3}$
$\Theta \times 10^{-3}$
200
250
300
350
400mu
OCH_3
NCH_3
H
O
OCH_3

free base as these authors indicated. The quaternary structure for pretazettine hydrochloride was supported also by nmr data. Pretazettine hydrochloride in D_2O and haemanthidine methiodide in D_2O were found to give identical nmr spectra [Fig. 14].

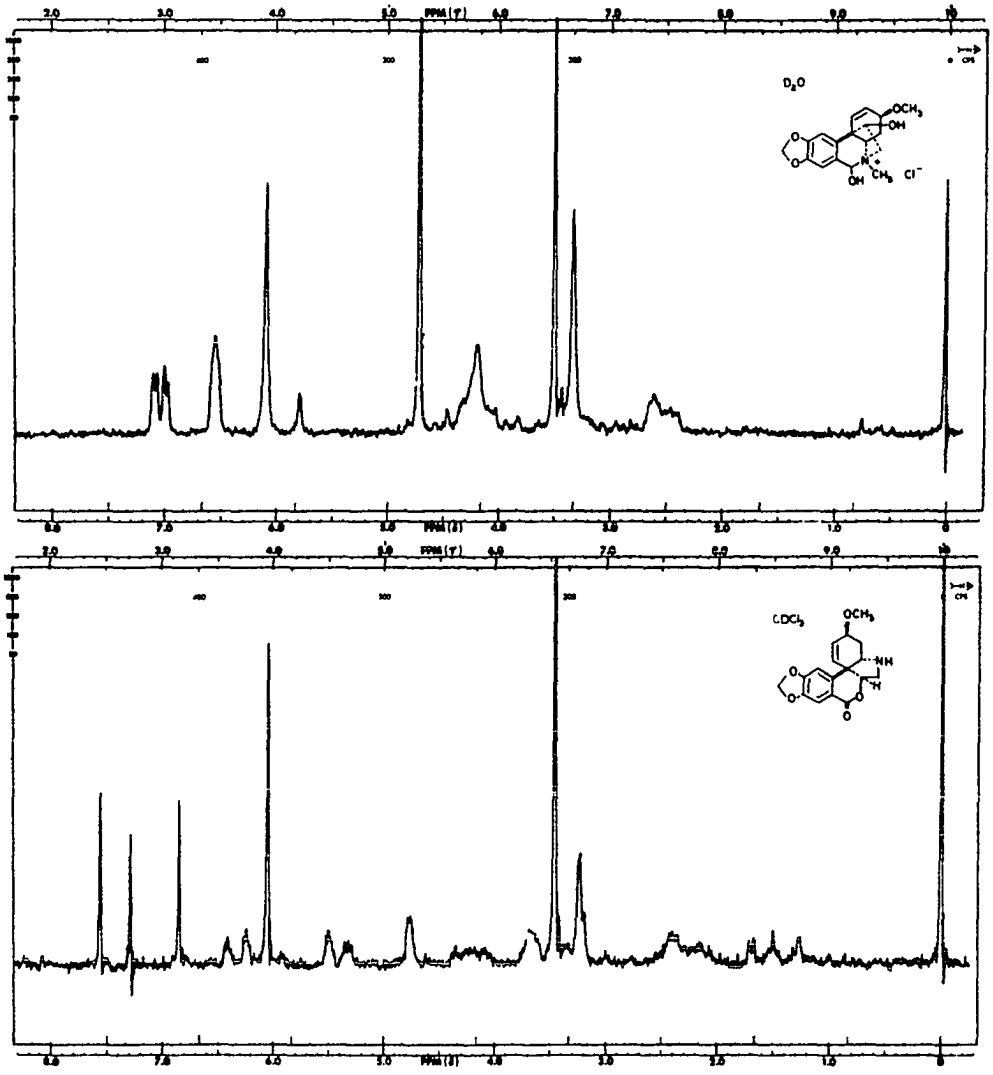
When a methanolic solution of pretazettine (39) was acidified (pH 4) with dilute hydrochloric acid, the alkaloid rearranged to the 5,10b-ethanophenanthridine ring system (27). The original tertiary base was completely reformed when the acidic solution was made basic (pH 10) with dilute ammonium hydroxide. The isomerization of pretazettine (39) to the methosalt of haemanthidine (27) is completely reversible. There is no apparent pathway by which the C_{6a}-hydrogen of pretazettine can be reversibly inverted in the isomerization process. This adds further proof for the beta configuration for this hydrogen in 39 and related compounds. In a recent communication,[44] pretazettine was assigned a structure which incorrectly implied an alpha hydrogen at the C_{6a}-position.

Pretazettine hydrochloride in aqueous solution exists in the quaternary amine form (27). An aqueous solution of the quaternary salt, made basic (pH 10) with ammonium hydroxide, rearranged completely to tazettine in one hour. There was no indication that 39 had been present. It appears that in aqueous solution, pretazettine preferred to remain as the more soluble quaternary amine 27. The recovery of pretazettine, as the tertiary amine, by chloroform extraction from a basic aqueous solution is due, not only to the basic conditions, but also to the solubility of the tertiary form of the amine in chloroform. The partial syntheses of pretazettine and precriwelline described earlier

Fig. 14: Nuclear magnetic resonance spectra

a: Pretazettine hydrochloride in D_2O (27)

b: 6a-Epi N-demethyl 3-epimacronine (73)

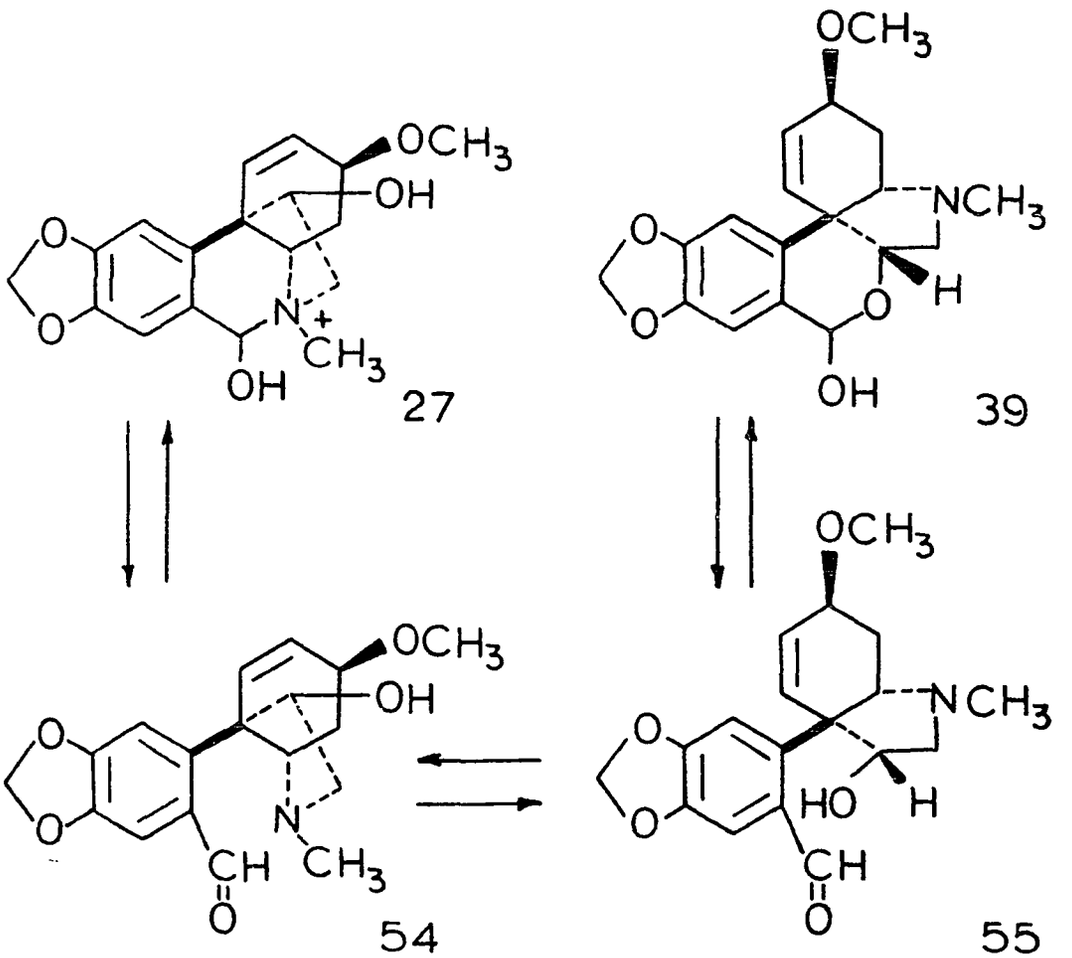

D2O
OCH3
OH
CH3
Cl⁻
CDCl3
NH
H
O

were not caused by the acidic hydrolysis, but rather by the chloroform and the dilute base used in the isolation procedure.

Independent evidence for this interconversion was found in the thin-layer chromatography of pretazettine on silica gel. When the alkaloid 39 was chromatographed on silica gel plates in chloroform-methanol-diethylamine (92:3:5:) the compound had an R_f value of approximately 0.5. Under these conditions, pretazettine has the mobility typical of other compounds having one hydroxyl group. When pretazettine was chromatographed on silica gel in the same solvent, but without the diethylamine, pretazettine remained essentially at the origin. This suggests that the silica gel is sufficiently acidic to cause the rearrangement of the base to the quaternary amine form 27.

Precriwelline (45) undergoes this same type of interconversion. On chromatography on silica gel in non-basic solvents, precriwelline did not migrate. Even in chloroform-methanol-diethylamine (92:3:5) the base still existed in the quaternary form. When the diethylamine content of the solvent system was increased to 10%, precriwelline migrated to R_f 0.2 indicating that the base under these conditions existed in the hemiacetal form. The reluctance of precriwelline to enter into the hemiacetal structure may be part of the reason that an nmr of this compound in $CDCl_3$ was never of good quality.

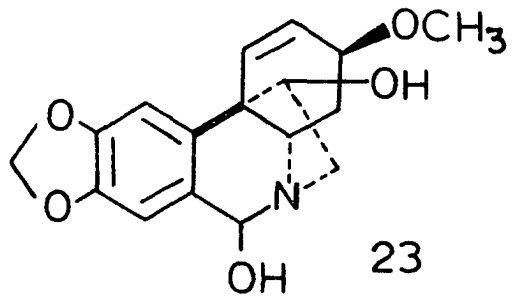
When haemanthidine methiodide is placed in a weakly basic methanolic solution, the amino aldehyde intermediate 54 is formed by hydrolysis of the amino alcohol. Rotation of 90° about the C_{10a}-C_{10b} bond and some deformation of the C and D rings brings the C_{11}-hydroxyl group into close proximity of the aldehyde 55. Base catalyzed formation of the



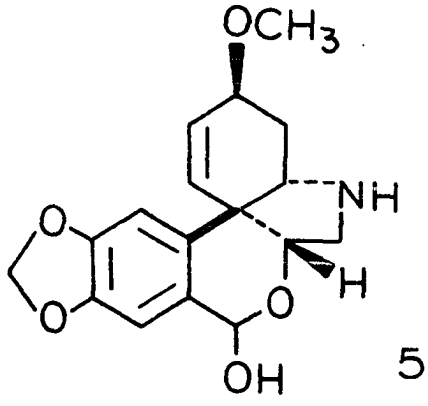
hemiacetal gives pretazettine (39). This process can also be visualized to occur in the reverse manner. The existence of two isomeric forms for pretazettine and precriwelline is due to the presence of an N-methyl group and a hydroxyl function, each capable of nucleophilic attack on the carbonyl of the intermediates 54 and 55. Because of the lability of both the hemiketal and the alpha amino alcohol moieties, neither product is so stable as to preclude ring opening and the reformation of the other isomer upon a change in the solvent conditions.

N-Demethylpretazettine (56)

Since haemanthidine methiodide (27) can be converted to pretazettine (39), it was expected that N-demethylpretazettine (56) might be formed by the rearrangement of haemanthidine (23). Several reactions are known which would indicate the existence of N-demethylpretazettine. The



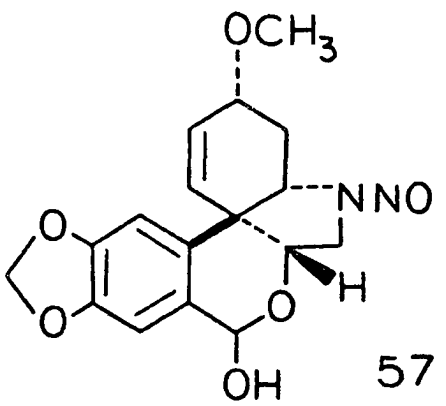
23



56

Eschweiler-Clarke methylation[49] is a well-known reaction for the alkylation of primary and secondary amines to form tertiary bases. The methylation of haemanthidine (23) under these conditions has been reported to give tazettine in good yield.[50] It seems most probable that pretazettine was the true reaction product, but the strong base used in the product isolation had caused a rearrangement to tazettine. To test this hypothesis, haemanthidine was resubmitted to the Eschweiler-Clarke conditions. When the reaction was completed, the product was recovered using a milder basic isolation procedure than had been used in the original work. Pretazettine was the only product present. Since tertiary amines are not susceptible to attack under Eschweiler-Clarke conditions, pretazettine can not, in this case, be derived from the formation and rearrangement of the methosalt of haemanthidine.

Therefore, a secondary amino group must have been present in sufficient concentration to allow the methylation to occur. Secondary amines react with nitrous acid to give N-nitroso derivatives, but tertiary amines provide only the corresponding hydronitrite salts. 6-Hydroxycrinamine reacts with nitrous acid to give 36.[22] On the basis of the beta C_{6a}-hydrogen in pretazettine and precriwelline, this N-nitroso compound 36 can now be assigned the complete structure 57.



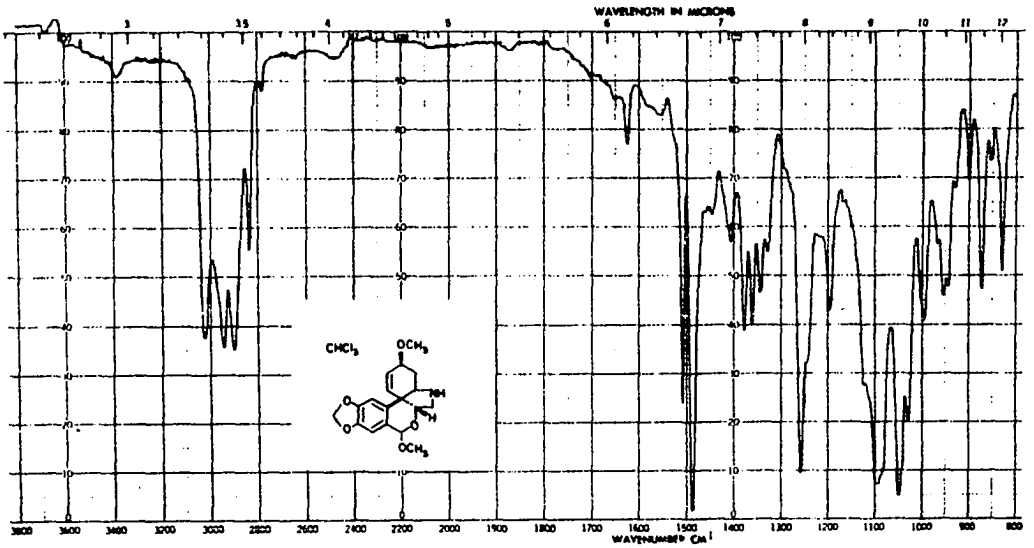
57

These two reactions indicate the presence of a secondary amine, but not its actual nature. The amine might be either the amino aldehyde 50 [where the amino group and the aldehyde remain closely associated], the hydroxy aldehyde 51 (R = H) [where the C-D ring portion of the intermediate may rotate freely], or the hemiacetal 56. Evidence has been found which indicates the hemiacetal form must be present in acidic media. When haemanthidine was refluxed in acidic methanol, the acetal, O-methyl N-demethylpretazettine (58), was obtained. The ir spectra [Fig. 15] of this product was very similar to that of O-methylpretazettine (44) [Fig. 5] except for the additional N-H stretching band (3385 cm^{-1}). The nmr spectrum [Fig. 16] and mass spectrum are consistent with

Fig. 15: Infrared spectra

a: N-Demethyl O-methylpretazettine (58)

b: N-Demethyl O-methylprecriwelline (59)


WAVELENGTH IN MICRONS
CHCl3
OCH3
NH
H
OCH3
WAVENUMBER Cm-1

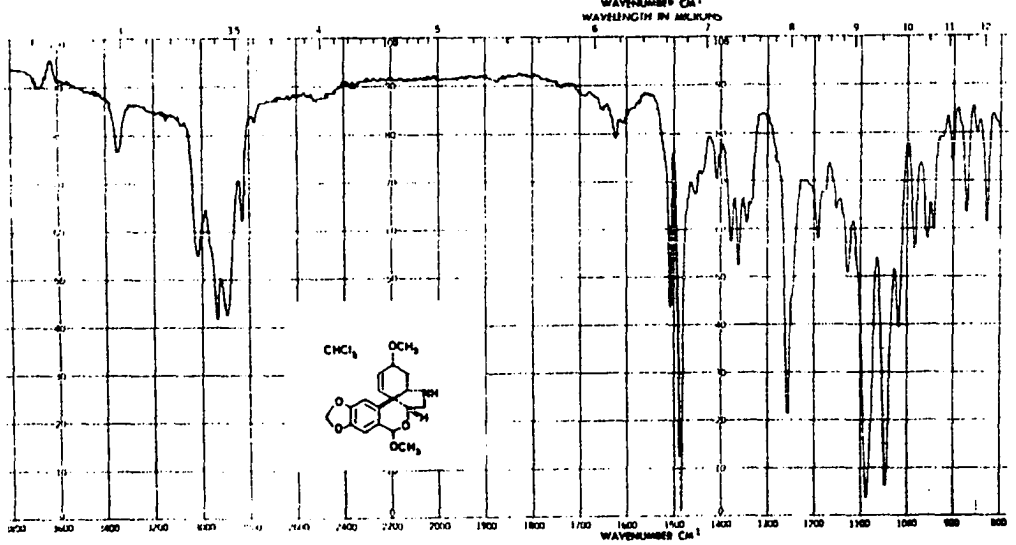
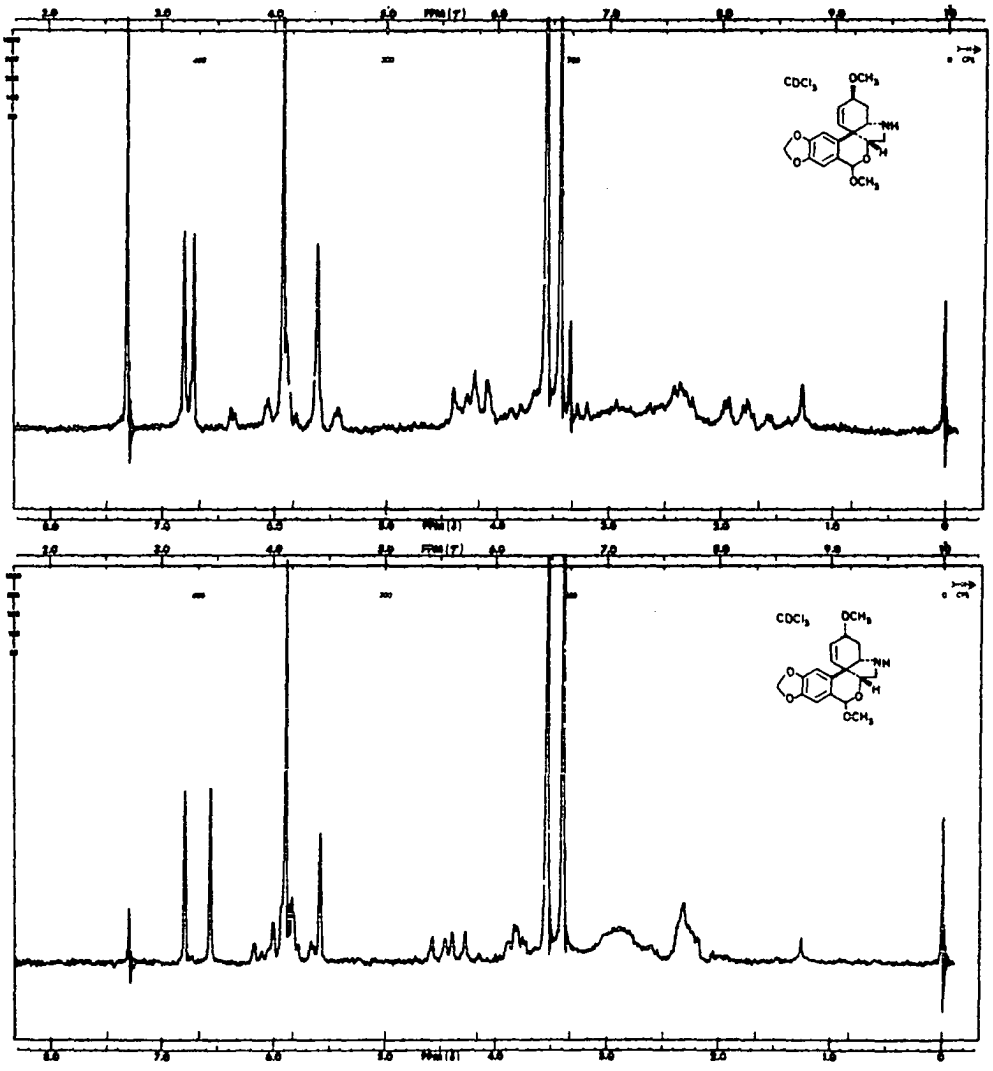
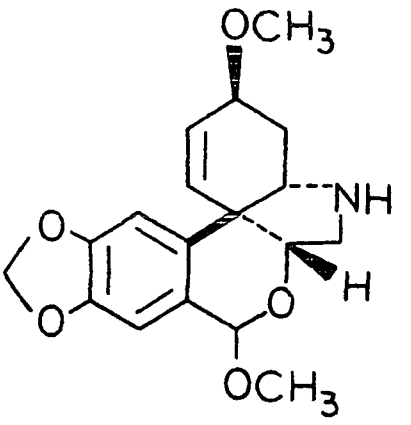

WAVELENGTH IN MICRONS
CHCl3
OCH3
NH
H
OCH3
WAVENUMBER Cm-1

Fig. 16: Nuclear magnetic resonance spectra

a: N-Demethyl O-methylpretazettine (58)

b: N-Demethyl O-methylprecriwelline (59)

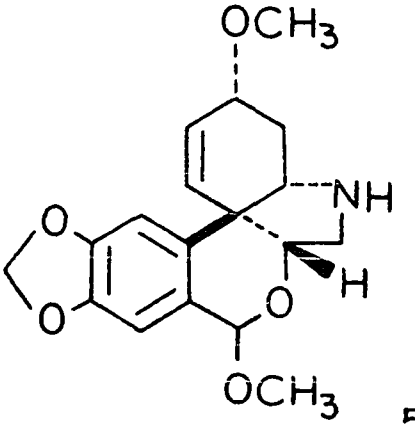

CDCl3
OCH3
NH
H
OCH3
PPM (T)
PPM (δ)



58

this assignment. The structure of O-methyl N-demethylpretazettine was proven by conversion to the previously known O-methylpretazettine (44) upon treatment with methyl iodide. In a conversion analogous to that of haemanthidine to O-methyl N-demethylpretazettine, 6-hydroxycrinamine (32) has been rearranged to O-methyl N-demethylprecriwelline (59).

O-Methylprecriwelline (46) was formed when 6-hydroxycrinamine (32) was refluxed with methyl iodide in methanol. The mechanism that was originally proposed for this reaction[28] seemed most unlikely. From our work it can be seen that a trace of acid, presumably from the



59

decomposition of methyl iodide in methanol, would allow the formation of 59 from 6-hydroxycrinamine (32). The acetal in the presence of methyl iodide would then be N-methylated to form O-methylprecriwelline (46). If any dimethylation occurred, the resulting quaternary amine would not be recovered by the product isolation procedure.

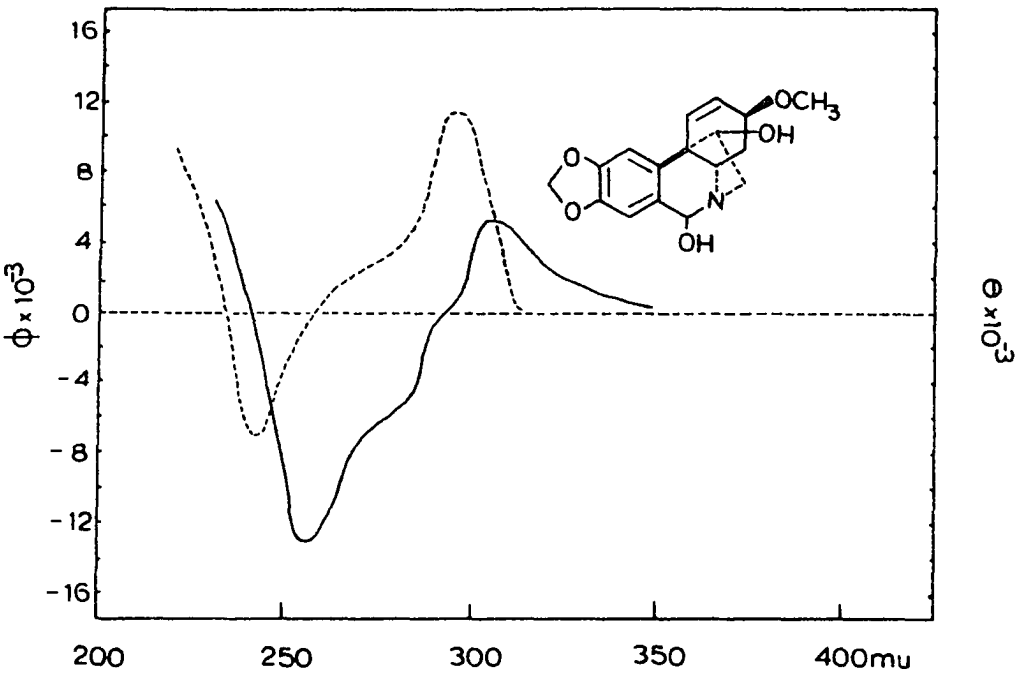
Because of our evidence that haemanthidine can be converted to 56, a study of the ord and cd spectra of 23 under various pH conditions was undertaken in an attempt to observe this transformation. Our results [Fig. 17] indicate that there is no difference between the spectra of haemanthidine and haemanthamine (which can not isomerize) between pH 2-12 in methanol. This demonstrates that haemanthidine must exist predominantly with the 5,10b-ethanophenanthridine nucleus under these conditions. Therefore, N-demethylpretazettine is formed from haemanthidine by a reversible process and probably only has a short lifetime.

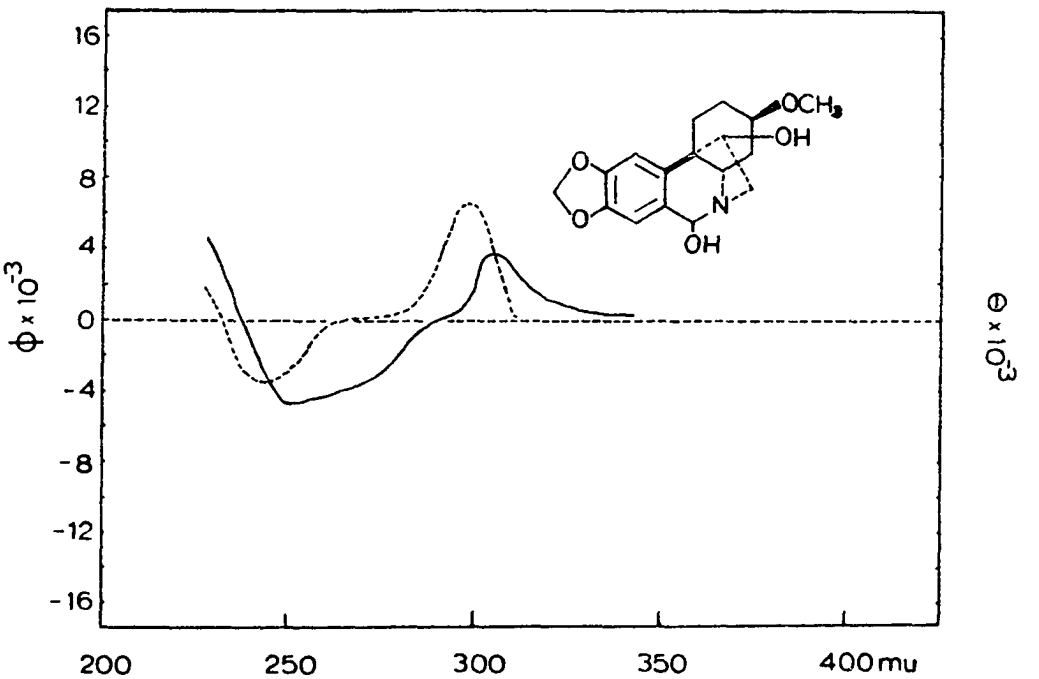
From these experimental results, it is possible to delineate some of the factors which influence the facile rearrangements of compounds of types 48, 49, and 53. The epimerization of the C_6-hydroxyl group of 48 and the evidence for the existence of N-demethylpretazettine indicates the ease with which the N-C_6 bond is broken to form the amino aldehyde intermediate 50. Hemiacetal (56) formation between the C_{11}-hydroxyl group and the aldehyde, must involve rotation about the C_{10a}-C_{10b} bond of 50 and subsequent deformation of the C and D rings. For these alterations to occur, the intermediate must have a considerable lifetime. However, the favorable attack of the secondary amine on the carbonyl of 50 to reform the B-ring tends to shorten the existence of this intermediate. The formation of the hemiacetal is not favored and can

Fig. 17: Optical rotatory dispersion (——) and circular dichroism (----) spectra

a: Haemanthidine (23)

b: Dihydrohaemanthidine


16
12
8
4
0
-4
-8
-12
-16
200
250
300
350
400mu
$\phi \times 10^{-3}$
$\Theta \times 10^{-3}$
OCH3
OH
O
O
N
OH


16
12
8
4
0
-4
-8
-12
-16
200
250
300
350
400mu
$\phi \times 10^{-3}$
$\Theta \times 10^{-3}$
OCH3
OH
O
O
N
OH

only be isolated when stabilized in some manner.

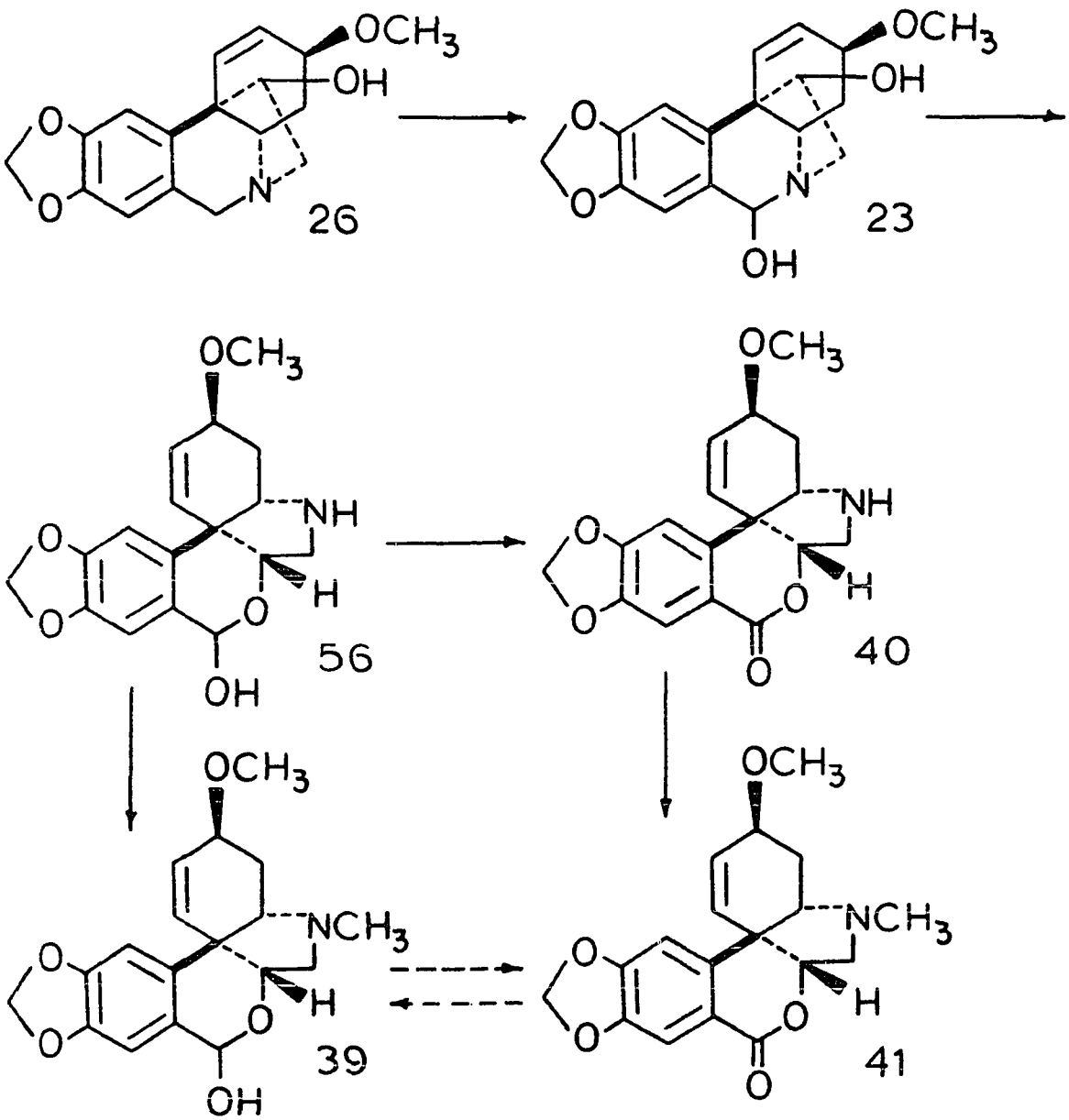
The reversible rearrangement of the methosalt of haemanthidine to pretazettine differs from the haemanthidine to N-demethylpretazettine case only by the additional N-methyl group. This additional group, for steric reasons, decreases the ability of the nitrogen to attack the carbonyl group and thus reform the 5,10b-ethanophenanthridine ring system. The N-methyl group, in effect, increases the lifetime of the intermediate. When the methosalt 27 is placed in weakly basic aqueous solution, the amino aldehyde intermediate 54 is formed by hydrolysis. There is time for rotation of 90° about the C_{10a}-C_{10b} bond (55) and for the necessary C and D ring bending to allow hemiacetal formation 39. Any group which interferes with the nucleophilic character of the nitrogen aids the formation of the 49 skeleton. It would appear in this case that the energetically unfavorable ring distortions necessary to form 39 are offset by the decreased nucleophilicity of the nitrogen.

Biosynthesis

Previous biosynthetic results have shown that Sprekelia formosissima converts haemanthamine (26) to haemanthidine (23) and ultimately to tazettine (22) in essentially an irreversable manner.[36] Our structural revisions do not alter the basic validity of this work, however certain changes are apparent. It seems certain that haemanthidine (23) arises from the hydroxylation of haemanthamine (26). Haemanthidine, in turn, undergoes a reversible rearrangement to N-demethylpretazettine (56). Although in vitro studies indicate only a fleeting existence for 56, its abundance in vivo may be much greater. This could be due to stabilizing

factors, such as glycoside formation, which might form a compound too sensitive to survive the alkaloid isolation procedures.

N-Demethylpretazettine (56) seems to be a key intermediate in the biosynthetic pathway. Methylation of 56 would form pretazettine (39), while oxidation of the C_8-hydroxyl group gives N-demethyl 3-epimacronine (40). Compound 40 has not been detected in natural sources, but the



C_3-epimer, N-demethylmacronine (42) has been isolated. N-Demethyl 3-epimacronine is presumably present in S. formosissima in trace ammounts. The secondary amine 40 may then be methylated to form 3-epimacronine (41). An interconversion between pretazettine (39) and 3-epimacronine (41) also appears possible. Pretazettine exists in aqueous solution and, therefore, probably in the tissue of the plant as the quaternary amine (27). Any biosynthetic conversion between 39 and 41 would require that at least one of these alkaloids must be able to rearrange to the other's ring system.

An alternative biosynthetic path might involve the N-methylation of haemanthidine to form the quaternary form of pretazettine (27). Since no quaternary amines have been isolated from the Amaryllidaceae, and because of the isomerization mechanism that is available to form the quaternary amine from the tertiary base, it seems unlikely to suspect an N-methylation of a tertiary amine to form pretazettine. However, if this did occur, the secondary amine, N-demethyl 3-epimacronine (40), would have to be derived from an unlikely demethylation process. In another alternate path, it is possible that haemanthidine (23) could be oxidized in the plant to 6-oxohaemanthamine (28). Although 28 has never been isolated from natural sources, it is neutral and might not be detected in the normal alkaloid isolation. In vitro basic hydrolysis of 6-oxohaemanthamine forms N-demethyl 3-epimacronine (40) and a similar process might be considered to occur in vivo. N-Methylation of 40 would yield 3-epimacronine (41). Pretazettine would then be formed by partial reduction of the lactone 41 to the hemiacetal 39. This pathway seems unlikely because it would necessitate

both an oxidation and then a reduction of the same C_8-oxygen to account for all the known compounds containing this ring system. It seems that the most acceptable pathway involves the existence *in vivo* of N-demethylpretazettine (56). These pathways are illustrated in the haemanthamine-pretazettine series. Identical processes can be visualized for the C_3-epimeric crinamine-precriwelline series as well.

Reduced strain compounds

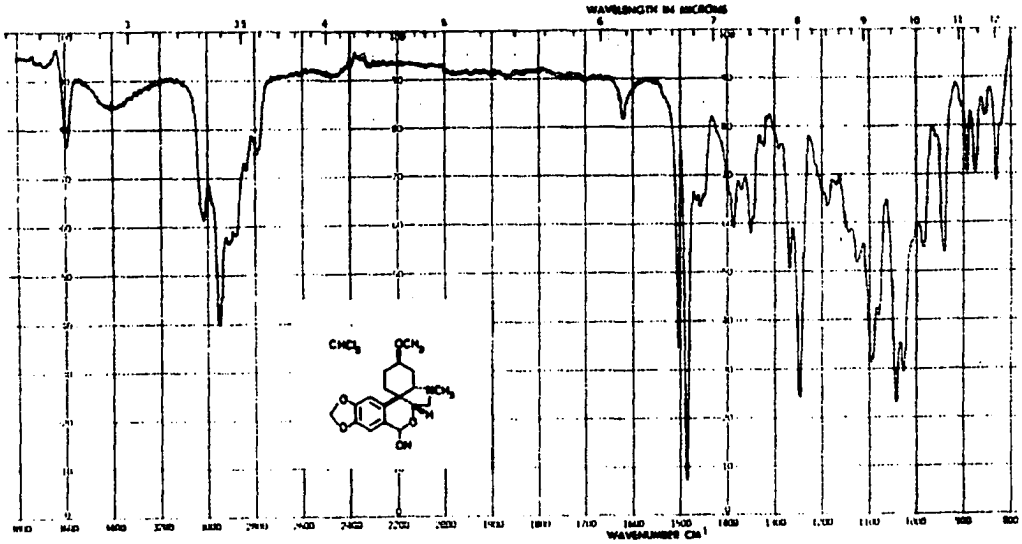
The trans B-D ring fusion introduces considerable strain into the [2]benzopyrano[3,4*c*]indole nucleus and it was of interest to study the rearrangements of less strained compounds having the same general structure. A more flexible skeleton can be achieved either by removal of the C_1-C_2 unsaturation or by conversion of the *trans* B-D ring fusion to the *cis* form.

Catalytic hydrogenation of pretazettine in glacial acetic acid afforded dihyropretazettine (62). The ir spectrum in chloroform [Fig. 18] was consistent with the expected structure. A substance with an identical ir spectrum was isolated when dihydrohaemanthidine methiodide (63) was dissolved with warming in dilute hydrochloric acid (pH 4), the solution made basic (pH 10) with ammonium hydroxide, extracted with chloroform and concentrated. The nmr spectrum of dihydropretazettine in $CDCl_3$ [Fig. 19] indicated that the base exists in solution as a mixture of benzylic hydroxyl epimers. The spectrum showed two minor peaks which corresponded to part of the C_9-aromatic hydrogen and the C_8-benzylic hydrogen of 63. A more complete discussion of this phenomenon has been discussed for the 5,10*b*-ethanophenanthridine ring system.[22,28]

Fig. 18: Infrared spectra

a: Dihydropretazettine (62)

b: 6a-Epi N-demethyl 3-epimacronine (73)


WAVELENGTH IN MICRONS
WAVENUMBER Cm⁻¹
CHCl₃
OCH₃
NCH₃
H
ON

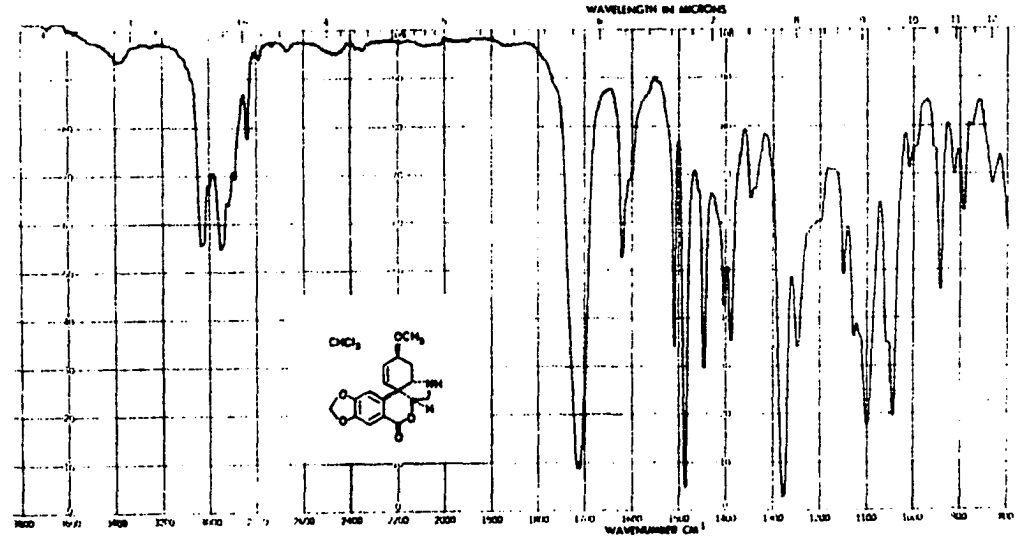
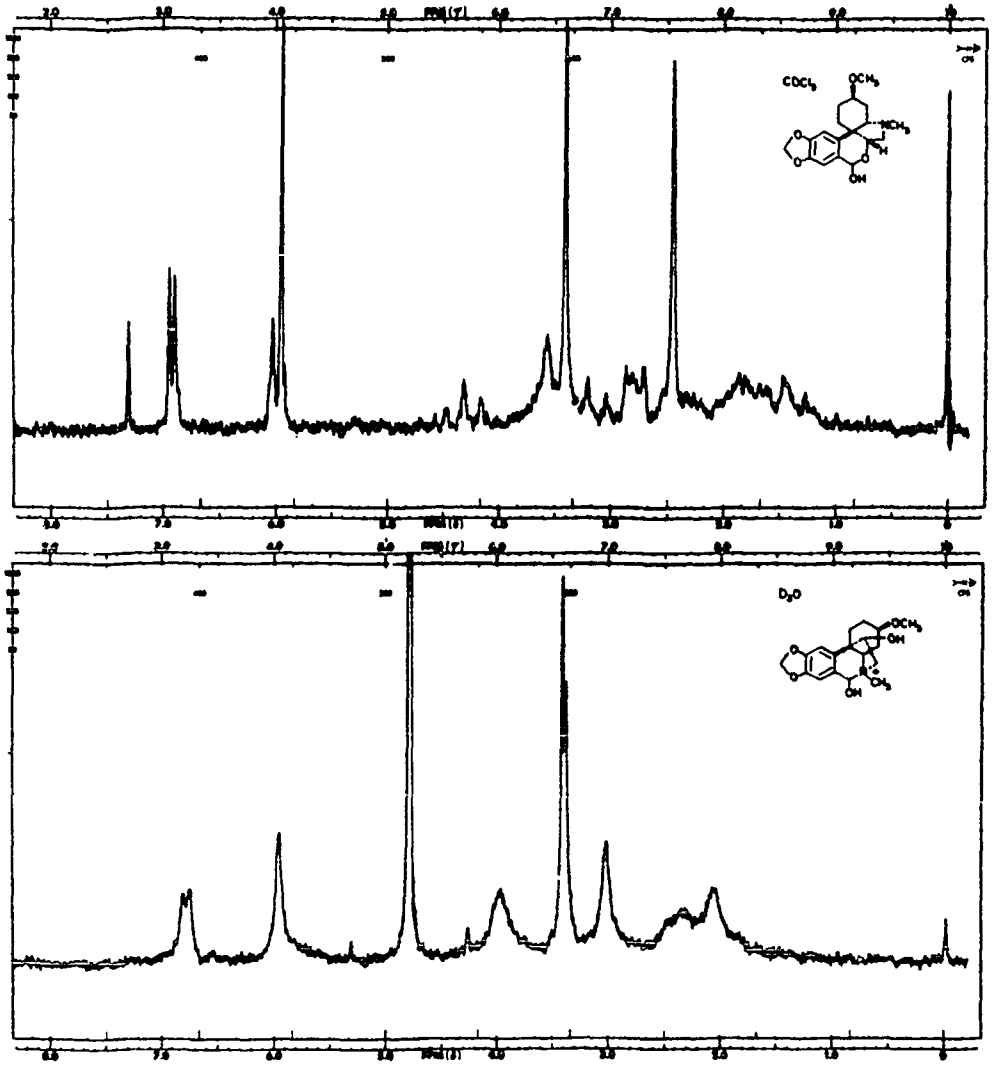
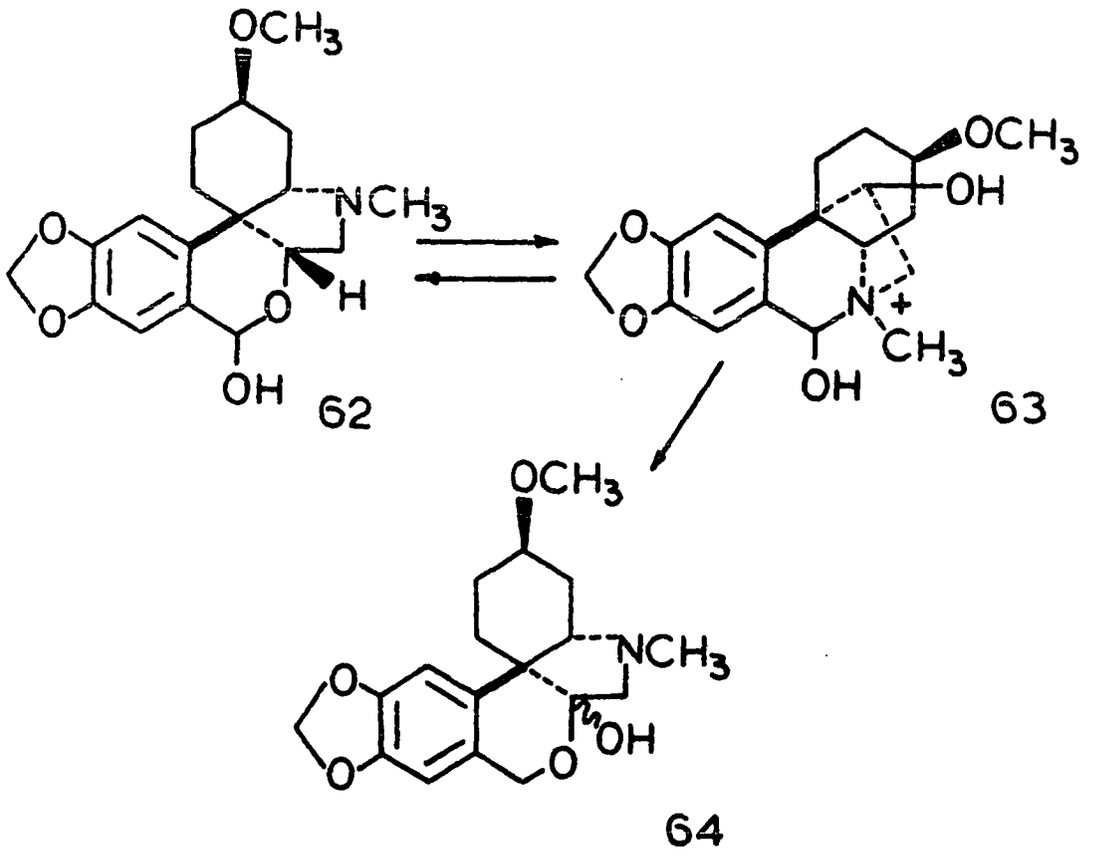

WAVELENGTH IN MICRONS
WAVENUMBER Cm⁻¹
CHCl₃
OCH₃
NH
H
O

Fig. 19: Nuclear magnetic resonance spectra

a: Dihydropretazettine in $CDCl_3$ (62)

b: Dihydropretazettine in D_2O (63)


COCH3
OCH3
NCH3
H
OH
D2O
OCH3
OH
N+
CH3
OH



Dihydropretazettine (62) was soluble in chloroform, carbon tetrachloride, methyl and ethyl alcohols. However, when the compound was dissolved in methanol and the solvent removed by evaporation, the residue was no longer soluble in carbon tetrachloride or chloroform. It now gave nmr spectra in CD_3OD and D_2O [Fig. 19] that indicated the compound existed in the 5,10b-ethanophenanthridine nucleus (63) as the methosalt of dihydrohaemanthidine. Consistent with this structural assignment, the compound dissolved easily in water at room temperature. Upon warming this aqueous solution to approximately 40°, the compound 63 reverted to 62 which is insoluble in water. This rearrangement could be reversed by cooling the solution to room temperature. The

tertiary amine 62 could be regenerated by dissolving the quaternary form 63 in water and making the solution basic (pH 10) with ammonium hydroxide. Chloroform extraction afforded 62. To further study the dihydro series, dihydrohaemanthidine was prepared.[18] As was observed in the case of haemanthidine, the ord and cd spectra [Fig. 17] indicated that dihydrohaemanthidine was stable in the 5,10b-ethanophenanthridine nucleus in methanol in the pH range 2-12.

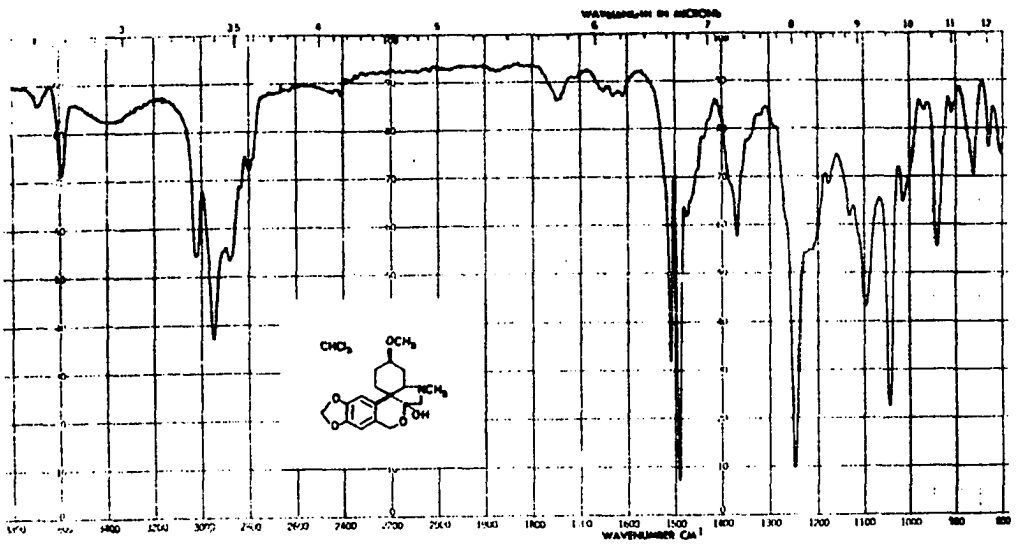
The double bond does not seem to play a significant role in the conversion of either haemanthidine methiodide or pretazettine to tazettine.[20] A similar hydride shift mechanism was expected to convert dihydropretazettine to dihydrotazettine (64). This rearrangement does occur, but it requires much more forceful conditions in terms of base strength, temperature, and time. The product 64 was identical to that obtained by the catalytic reduction of tazettine.

Dihydropretazettine, when refluxed in wet chloroform for 24 hours, was converted to 6a-epidihydrotazettine (65). This rearrangement had not involved the loss of any functional groups because 65 could be converted to dihydrotazettine (64) upon treatment with aqueous base. 6a-Epidihydrotazettine gave ir [Fig. 20] and nmr [Fig. 21] spectra very similar to those of dihydrotazettine. The nmr spectrum of 65 contained a two proton singlet (4.69 ppm) assigned to the benzylic methylene group. The presence of two hydrogens at the C_8-position indicated that 65 was formed after the molecule had undergone the same intramolecular hydride shift observed in the conversion of pretazettine (39) to tazettine (22). The final hemiketal closure can occur to form either of two possible B-D ring fusions. This is the first instance

Fig. 20: Infrared spectra

a: Dihydrotazettine (64)

b: 6a-Epidihydrotazettine (65)


WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NCH₃
OH

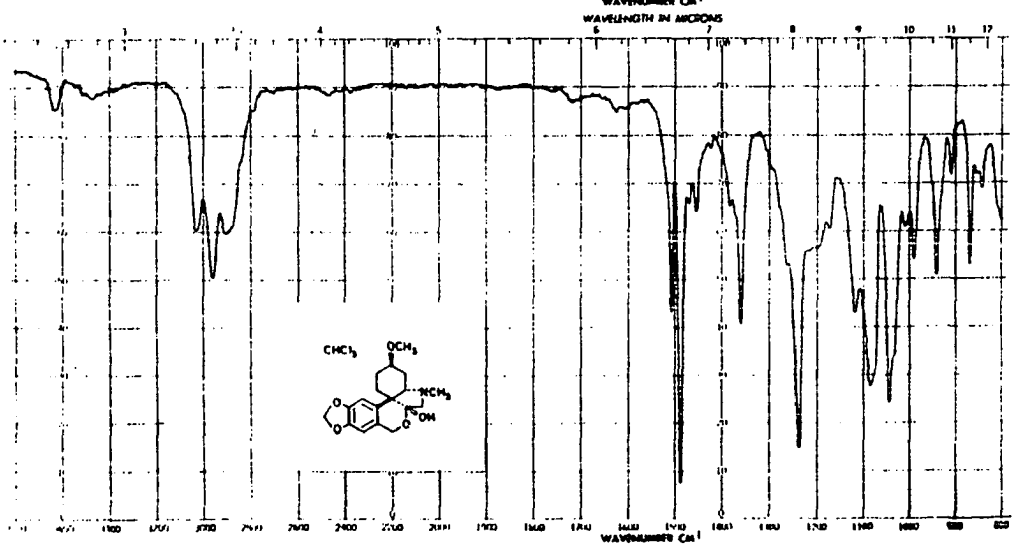
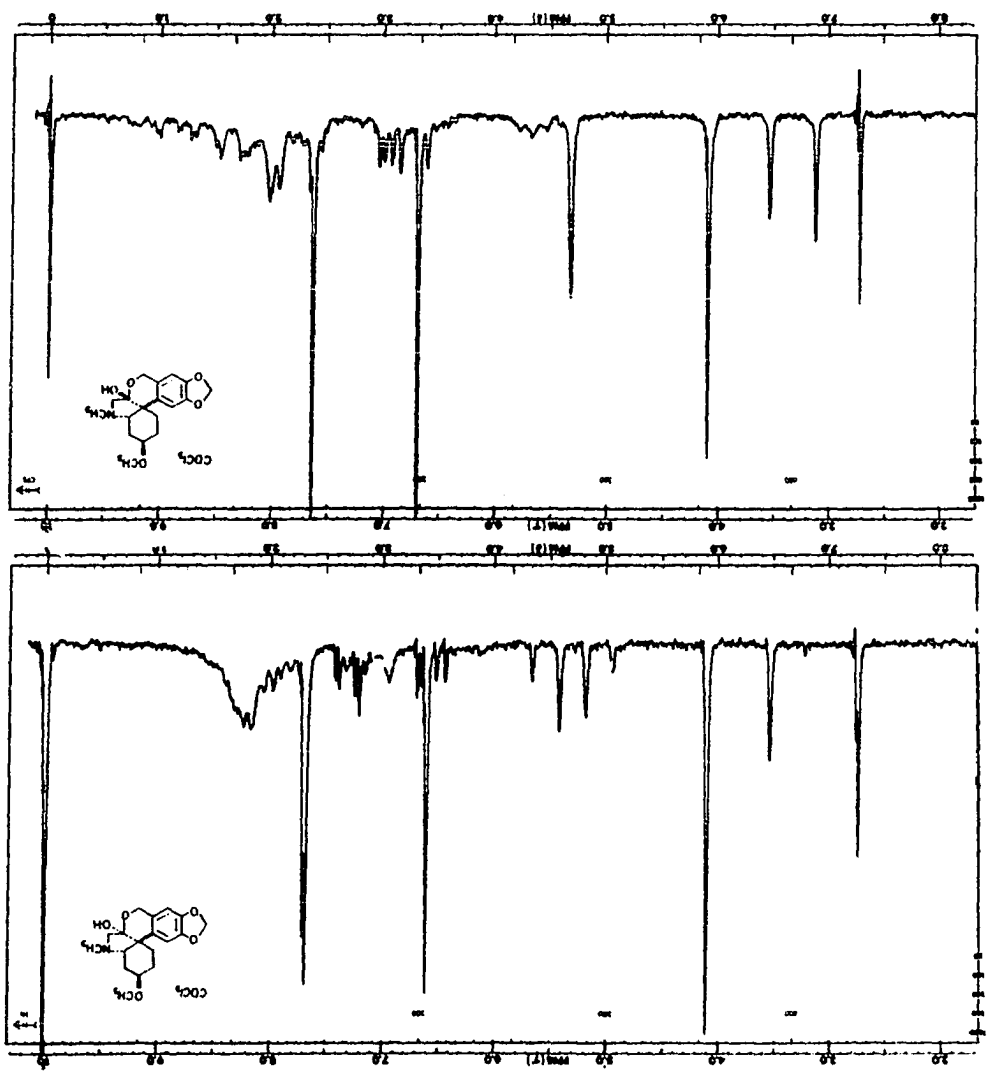
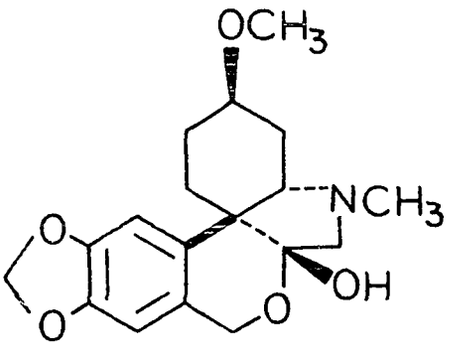

WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NCH₃
OH

Fig. 21: Nuclear magnetic resonance spectra

a: Dihydrotazettine (64)

b: 6a-Epidihydrotazettine (65)





65

where compounds which possess both possible hemiketal closures have been obtained. The rearrangement of 65 to 64 lends support to the supposition that tazettine (22) contains the more stable cis B-D ring fusion. Therefore, 6a-epidihydrotazettine must contain the trans B-D fusion and be represented by structure 65.

Synthesis of the pretazettine nucleus with the inverted cis B-D ring fusion (70) requires molecular modification of 23. The configuration of the C_{11}-hydroxyl group of 23 determines the configuration of the B-D ring fusion in the rearranged product. 11-Epihaemanthidine (68) would serve for entry into the cis B-D [2]benzopyrano[3,4c]indole series. In order to prepare 68, haemanthidine was oxidized by acetic anhydride and dimethyl sulfoxide. 6-Acetyl 11-oxohaemanthidine (66) was the sole product. The ir spectrum [Fig. 22] of this compound showed a broad carbonyl absorption (1751 cm^{-1}). The nmr spectrum [Fig. 23] indicated an acetate group had been introduced and that no free hydroxyl groups were present. Hydrolysis of 66 afforded 11-oxohaemanthidine (67). The ir spectrum [Fig. 22] of 67 indicated one ketone carbonyl group (1765 cm^{-1}) and one hydroxyl group (3600 cm^{-1}).

Fig. 22: Infrared spectra

a: 6-Acetyl 11-oxohaemanthidine (66)

b: 11-Oxohaemanthidine (67)

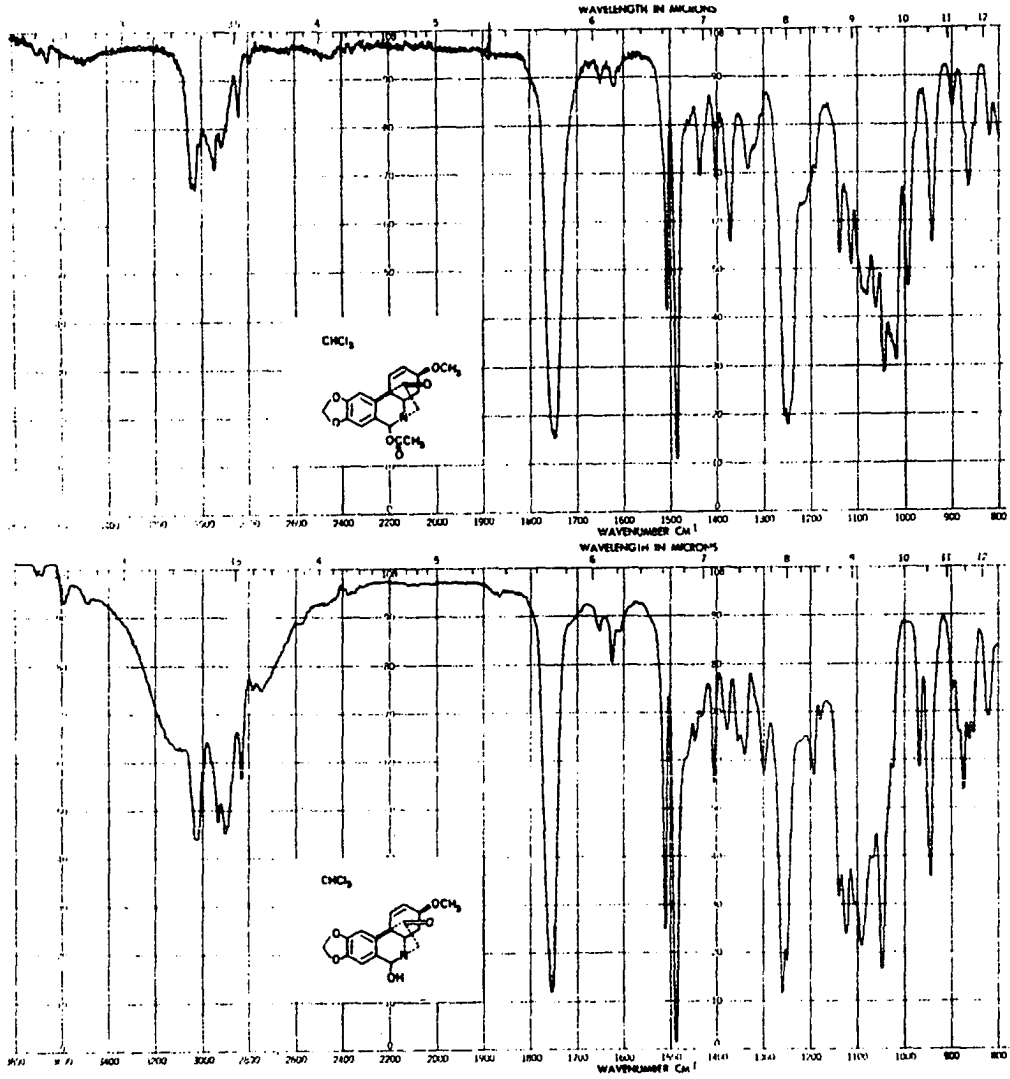
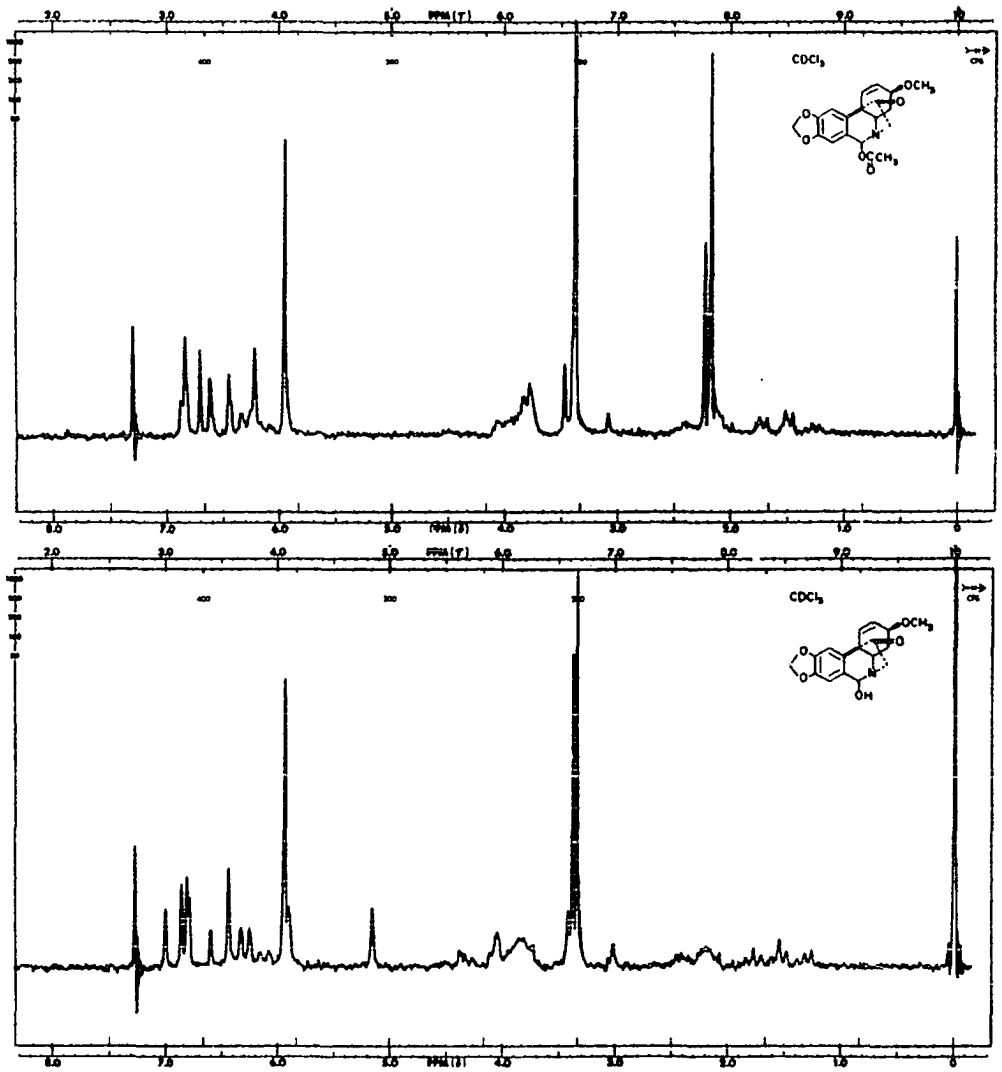
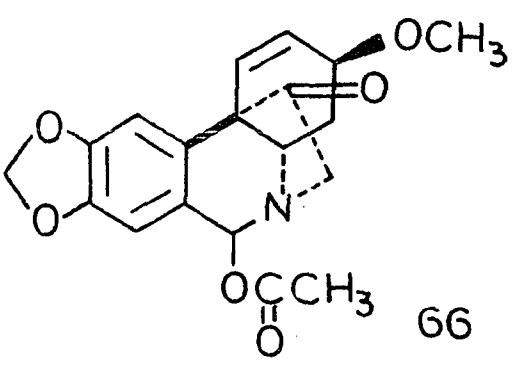

WAVELENGTH IN MICRONS
CHCl3
OCH3
OCCH3
WAVENUMBER CM-1
WAVELENGTH IN MICRONS
CHCl3
OCH3
OH
WAVENUMBER CM-1

Fig. 23: Nuclear magnetic resonance spectra

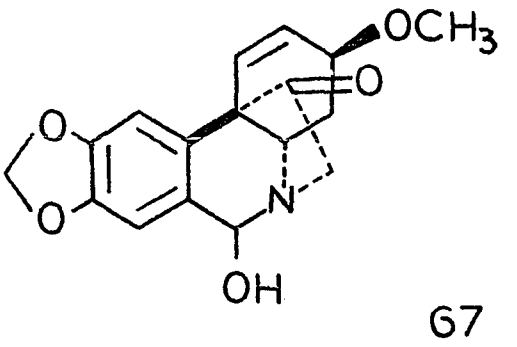
a: 6-Acetyl 11-oxohaemanthidine (66)

b: 11-Oxohaemanthidine (67)


CDCl3
OCH3
OCCH3
CDCl3
OCH3
OH



66



67

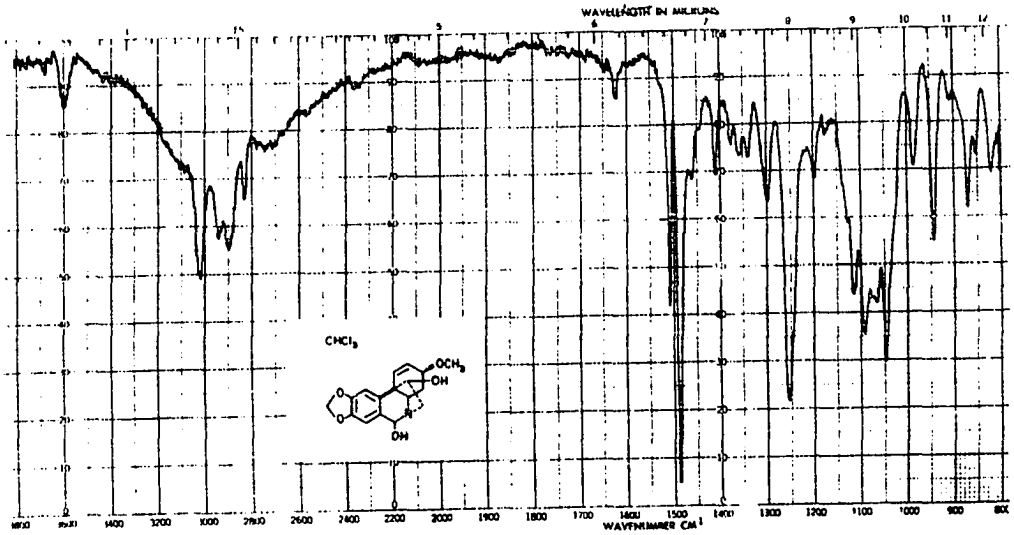
From earlier experience with 11-oxohaemanthamine,[51] we expected the formation of haemanthidine (23) and 11-epihaemanthidine (68) upon reduction of 66 with lithium aluminum hydride. Haemanthidine was isolated from the reduction in approximately 10% yield. The major product defied crystallization, but was pure by thin-layer chromatographic criteria in several solvent systems. The ir spectrum [Fig. 24] of the compound was considerably different from that of haemanthidine [Fig. 24], but indicated the presence of the anticipated methylenedioxy, hydroxyl, and aliphatic methoxyl groups. The nmr spectrum [Fig. 25] showed two large (6.69 and 6.79 ppm) and two small (6.75 and 6.90 ppm) aromatic proton singlets, and one large (5.87 ppm) and one small (5.57 ppm) singlet corresponding to the benzylic proton. Our original interpretation of this spectrum was in terms of the desired 11-epihaemanthidine (68). The observed complex signals could be attributed to the compound's existence in solution as a mixture of 6-hydroxyl epimers. This compound was treated with methyl iodide, followed by evaporation to dryness, and solution in dilute (pH 4)

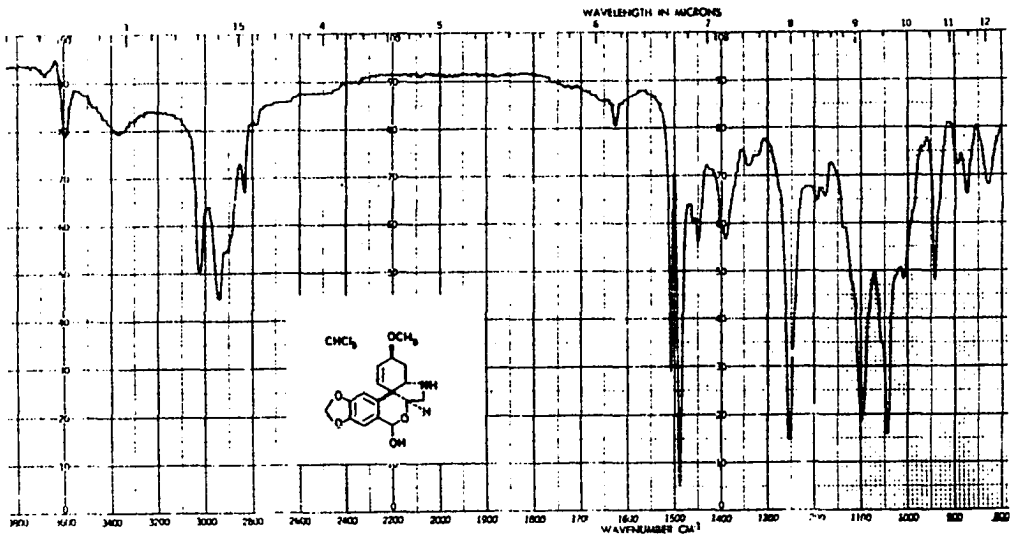
Fig. 24: Infrared spectra

a: Haemanthidine (23)

b: N-Demethyl 6a-epipretazettine (69)

c: 6a-Epipretazettine (70)


WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
OH
OH


WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NH
H
OH

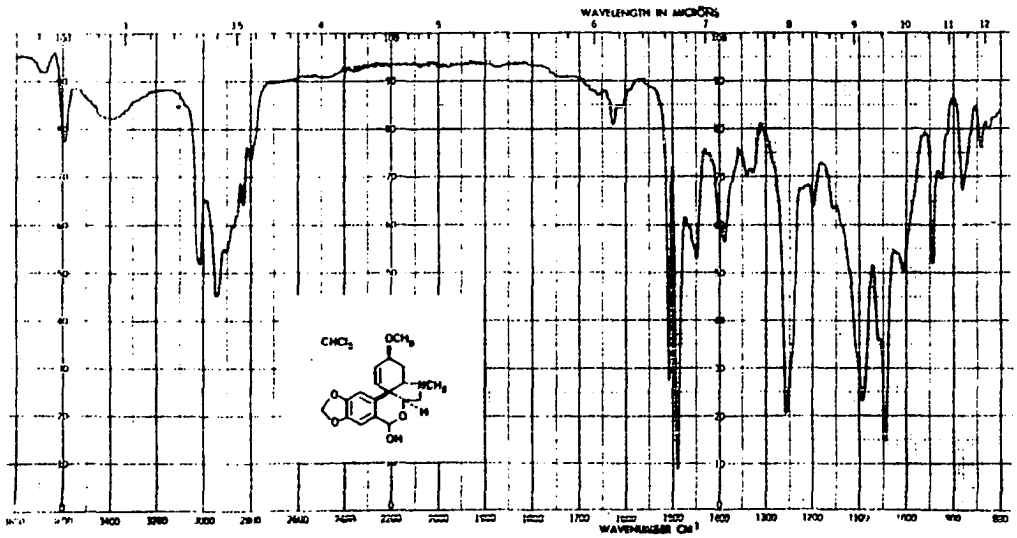
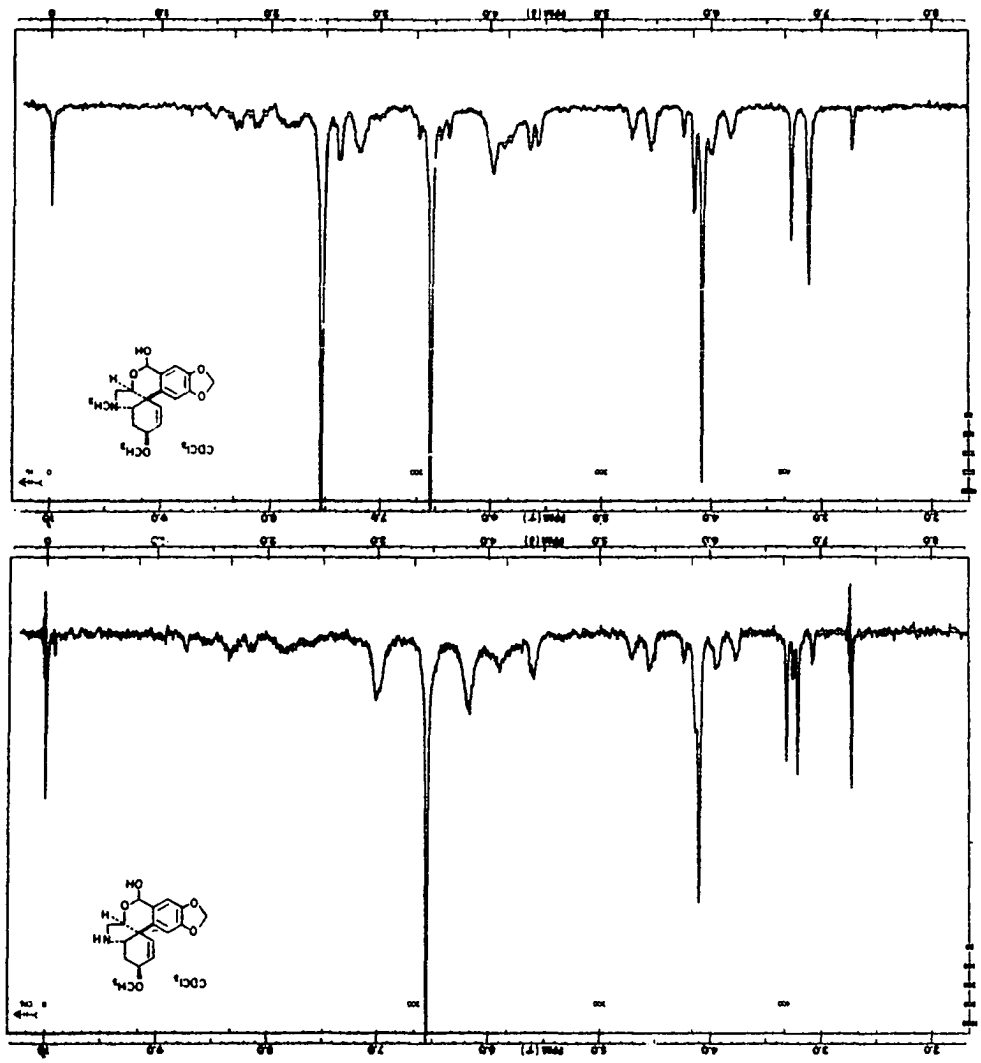

WAVELENGTH IN MICRONS
WAVENUMBER CM⁻¹
CHCl₃
OCH₃
NCH₃
H
OH

Fig. 25: Nuclear magnetic resonance spectra

a: N-Demethyl 6a-epipretazettine (69)

b: 6a-Epipretazettine (70)



hydrochloric acid. Extraction with chloroform after the aqueous solution had been made basic (pH 10) with potassium carbonate afforded 6a-epipretazettine (70) as the sole product. The ir [Fig. 24] and nmr [Fig. 25] spectra of 70 were almost identical with those of the compound assigned initially the structure 68.

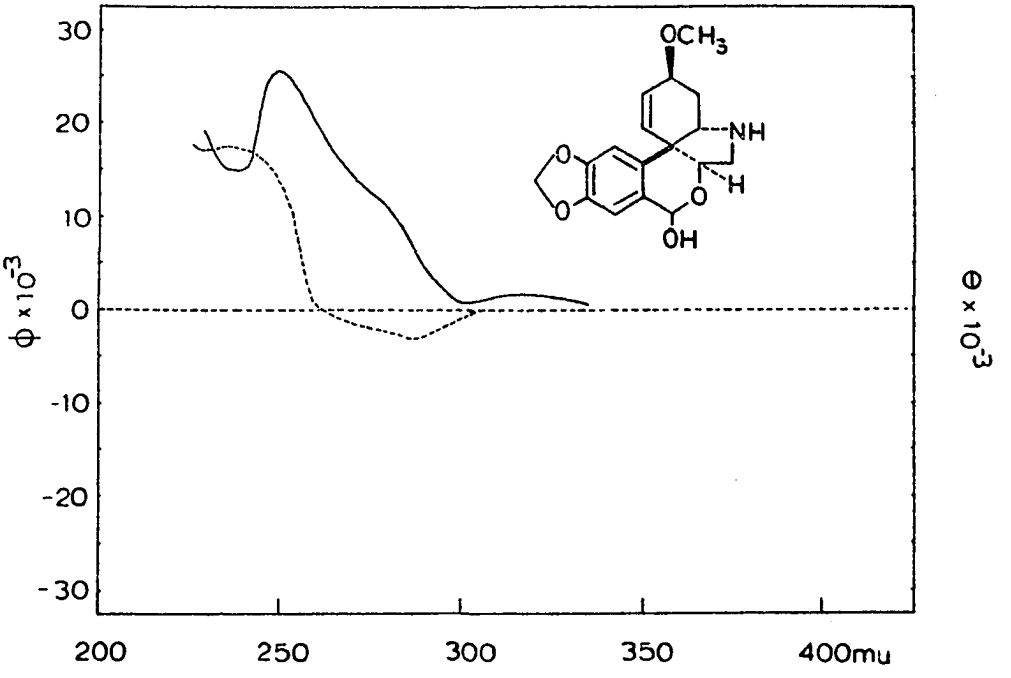
The nmr of 6a-epipretazettine (70) had two singlets at 6.89 and 6.71 ppm which are attributed to the two aromatic protons. Integration of these peaks indicated that they accounted for 1.2 and 0.8 protons respectively. Expansion of these peaks on a 100 MHz nmr spectrometer revealed that the low field peak actually contained a small singlet which is due to the same aromatic proton as the higher field singlet. This double peak, as well as the large and a small singlet associated with the benzylic proton, provides evidence that the benzylic hydroxyl group exists in solution as a mixture of C_8-hydroxyl epimers.

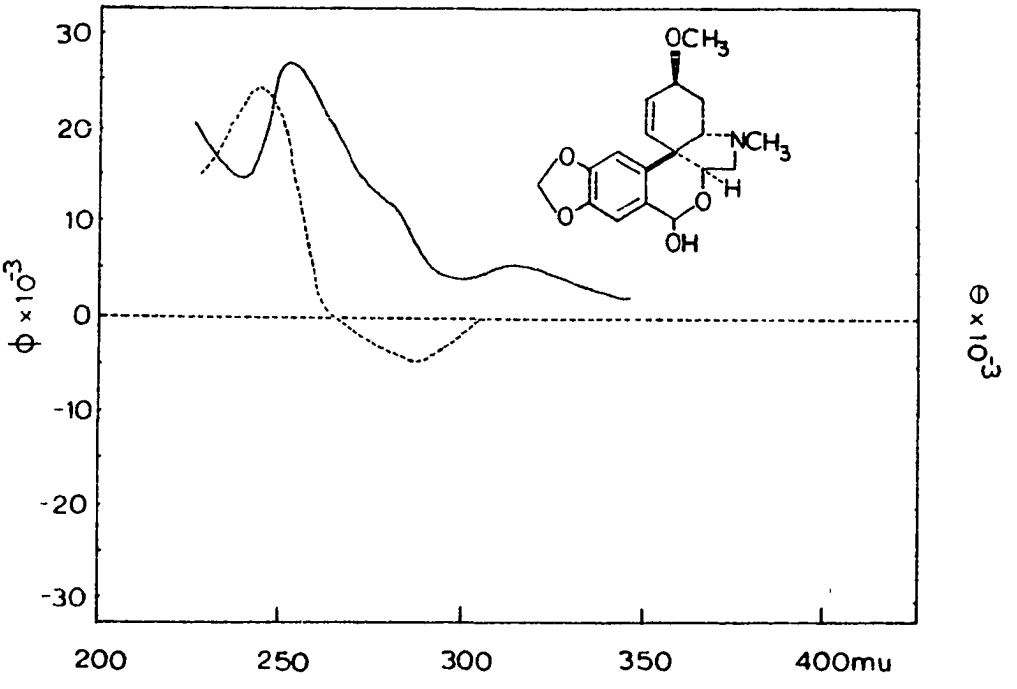
The ord and cd spectra of 6a-epipretazettine and its pregenitor [Fig. 26] are almost identical. These data suggest that both compounds possess the same ring system and that this system is not the 5,10b-ethanophenanthridine as originally anticipated. Although 11-epi-haemanthidine (68) must have been the initial product from the lithium aluminum hydride reduction of 6-acetyl 11-oxohaemanthidine (66), the compound in solution underwent a facile isomerization to N-demethyl 6a-epipretazettine (69). The complex aromatic and benzylic absorptions in the nmr spectrum of 69 must be due either to a small concentration of the 11-epihaemanthidine isomer (68) or to the compound's existence in solution as a mixture of C_8-hydroxyl group epimers (as 70 was described) or a combination of both effects. The ord and cd of

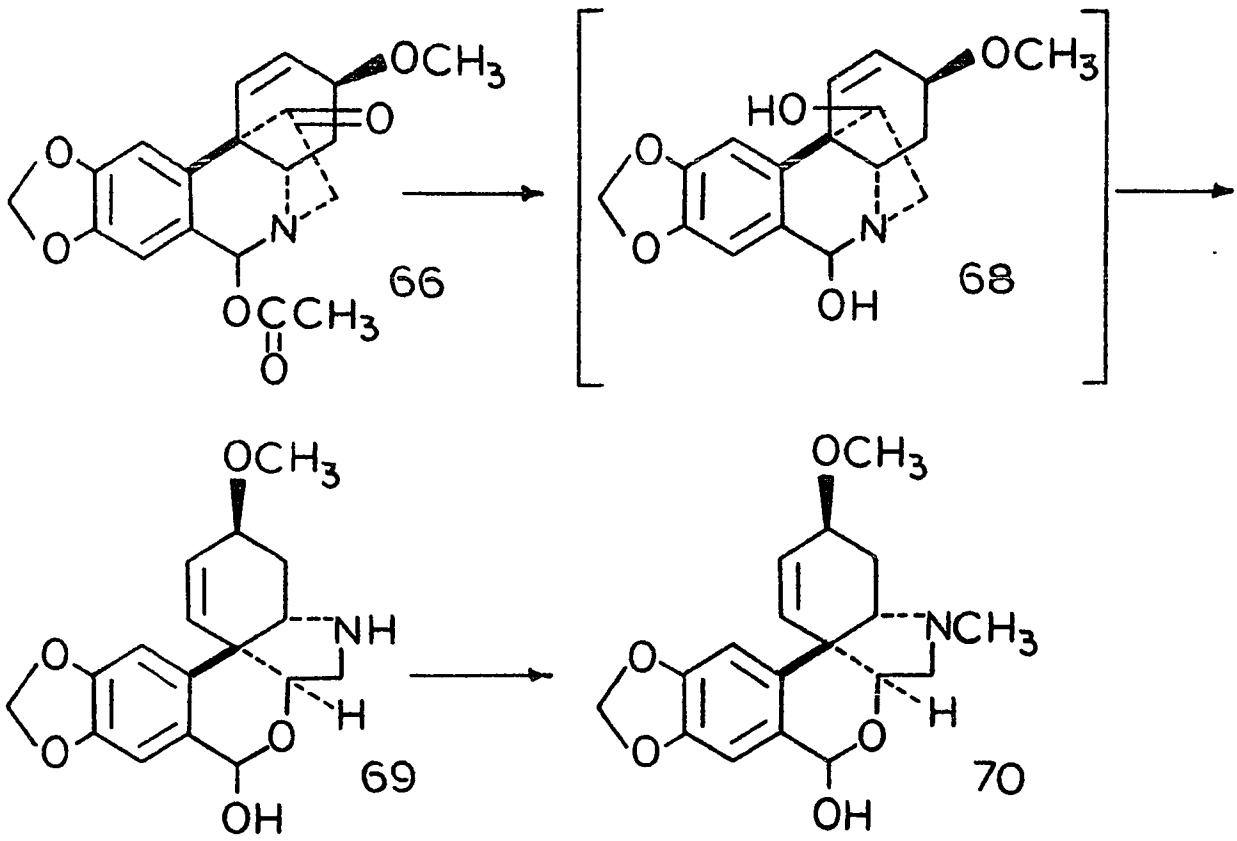
Fig. 26: Optical rotatory dispersion (———) and circular dichroism (----) spectra

a: N-Demethyl 6a-epipretazettine (69)

b: 6a-Epipretazettine (70)

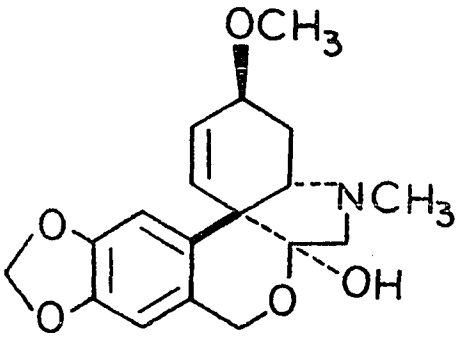

30
20
10
0
-10
-20
-30
200
250
300
350
400mu
φ x10-3
Θ x10-3
OCH3
NH
H
O
OH


30
20
10
0
-10
-20
-30
200
250
300
350
400mu
φ x10-3
Θ x10-3
OCH3
NCH3
H
O
OH

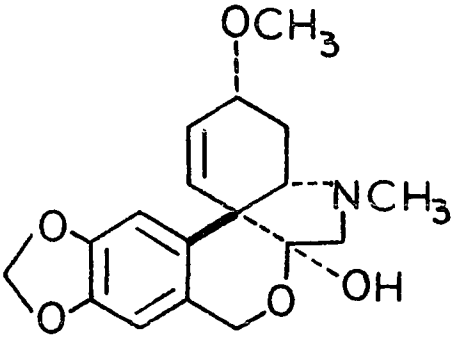


69 [Fig. 26] in various solvents and pH conditions indicate that the change from the 5,10b-ethanophenanthridine nucleus was not reversible.

Tazettine (22) has been proposed to contain a cis B-D ring fusion on the basis of spectral characteristics of certain degradation products of the base.[13] The results of this study have been challanged.[14] By our method of synthesis, 6a-epipretazettine (70) must have a cis B-D ring fusion. Although pretazettine and 6a-epipretazettine differ only in the stereochemistry of the B-D ring fusion, the ord and cd spectra make these two ring fusions easily distinguishable. The similarity between the ord and cd spectra of tazettine [Fig. 12] and 6a-epipretazettine [Fig. 26] lends strong support to the cis B-D ring fusion



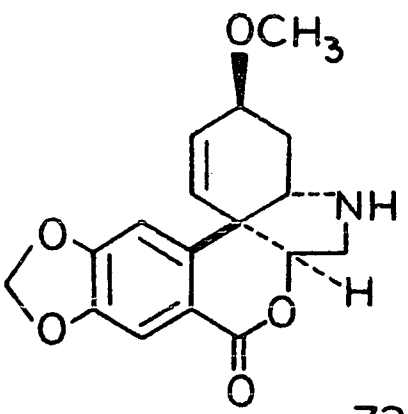
71



72

for tazettine. Therefore, on the basis of this spectral data and the evidence for the greater stability of dihydrotazettine as compared with 6a-epidihydrotazettine, the complete structure of tazettine is as shown in 71. By the interconversions outlined in the historical section, criwelline (31) must have the same C_{6a}-configuration and possess the structure 72.

Further evidence that 11-epihaemanthidine (68) exists as N-demethyl 6a-epipretazettine (69) was found in the isolation of only one oxidation



73

product upon treatment of the base with manganese dioxide. The product was identified as 6a-epi N-demethyl 3-epimacronine (73). No trace of 11-epi 6-oxohaemanthamine was detected.

11-Epihaemanthidine (68) undergoes a facile rearrangement to N-demethyl 6a-epipretazettine (69). In solution 68 should undergo a B-ring opening similar to that found for haemanthidine.[22] However, once the intermediate amino aldehyde has formed, the molecule can either reclose to the strained skeleton (68), or more favorably, form the more flexible molecule (69). The configuration of the C_{11}-hydroxyl group in 68 minimizes C and D ring torsional modifications required in hemiacetal formation. The proximity of the C_{11}-hydroxyl group to the aldehyde of the intermediate makes hydroxyl group participation more favorable and decreases the interaction of the amine with the aldehyde.

To investigate the rearrangement of pretazettine to tazettine in more detail, an attempt was made to rearrange 6a-epipretazettine (70) by base. Compound 70 is comparable with pretazettine (39) except that the strain inherent in the trans B-D ring is reduced. The rearrangement to tazettine was readily carried out, but stronger base and a longer reaction time were required. 6a-Epipretazettine (70) has gained the less reactive tazettine skeleton without the usual crossed-Cannizzaro reaction. However, it still undergoes the base catalyzed rearrangement to tazettine but much less readily than pretazettine. This can be rationalized if the strain in the molecules is primarily responsible for the rate of formation of the amino aldehyde intermediate. When the strain is reduced, this opening is slowed considerably, but

not stopped. Both the ring opened intermediates from 6a-epipretazettine and pretazettine can orient equally well for the hydride shift leading to tazettine.

SUMMARY

Five new Amaryllidaceae alkaloids containing the [2]benzopyrano-[3,4c]indole nucleus have been isolated and their structures established. The structure and reactivity of two of these bases, pretazettine and precriwelline, have led to the conclusion that tazettine and criwelline (reported to occur widely in this plant family) are probably rearrangement artifacts and not true alkaloids. A study of the interconversion of the 5,10b-ethanophenanthridine nucleus to the [2]benzopyrano[3,4c]-indole ring system provided partial syntheses of pretazettine, precriwelline, and a variety of closely related compounds. Evidence is cited that haemanthidine, 6-hydroxycrinamine, and several derivatives of these alkaloids undergo a reversible rearrangement to the [2]benzopyrano-[3,4c]indole nucleus under mild conditions. Variations in temperature, solvent, or pH are often sufficient to alter the basic ring system. Evidence is presented which confirms the alpha-configuration for the C_{6a}-hydroxyl group of tazettine, criwelline, and related compounds. A new biosynthetic scheme is postulated to account for all of the [2]benzopyrano[3,4c]indole alkaloids which have been isolated to date.

EXPERIMENTAL

Melting points were observed on a Kofler hot-stage apparatus and are corrected. Infrared spectra were obtained with a Beckman Model IR-12 spectrometer. Ultraviolet spectra were recorded on a Cary Model 14 spectrometer. Proton nuclear magnetic resonance spectra were obtained using Varian A-60 and HA-100 spectrometers. Mass spectra were recorded with an Atlas CH-4 mass spectrometer operating at 70 ev. Optical rotations, optical rotatory dispersion, and circular dichroism spectra were determined with a modified Jasco Model 5 spectrometer. Thin-layer (0.25 mm) and preparative thin-layer (1.0 mm) chromatography was carried out using Silica Gel PF 254 + 366 (Merck). Ultraviolet light of the appropriate wavelength was used for identification. All chromatograms were developed in chloroform-methanol-diethylamine (92:3:5) unless otherwise stated. The proof of identity of two compounds was carried out, when possible, by comparison of melting points and mixed melting points and always by infrared spectra and chromatographic characteristics. Elemental analyses of several compounds which could not be crystalized and were too sensitive to survive sublimation were obtained by high resolution studies using an A.E.I. MS-9 mass spectrometer.

Total Alkaloid Isolation

Sprekelia formosissima

Dormant bulbs (17.8 kg) were ground in 95% ethanol in a Waring Blendor. The plant material was extracted three times using ten gallons

of 95% ethanol each time. The ethanolic solution was evaporated *in vacuo* to a volume of approximately three liters, made acidic (pH 4) with tartaric acid, and extracted four times with benzene to remove the neutral material. The acidic solution was extracted four times with chloroform to provide 8.0 g of chloroform-soluble alkaloid hydrotartrates. The aqueous acidic solution was made basic (pH 8) with concentrated ammonium hydroxide and extracted four times with chloroform. The chloroform solution was evaporated *in vacuo* to give 46.0 g of crude alkaloids. Finally, the aqueous solution was raised to pH 10 with ammonium hydroxide and extracted three times with chloroform. This chloroform extract afforded 4.1 g of crude alkaloids. Thin-layer chromatography of each alkaloid fraction on silica gel plates developed in chloroform-methanol-diethylamine (92:3:5) failed to show the presence of any tazettine.

Ismeme calithina

Growing bulbs (1.5 kg) were processed in the same manner as cited for *S. formosissima*. The following weights of chloroform extractable material were obtained: pH 4 fraction, 1.8 g; pH 8 fraction, 2.5 g; pH 10 fraction, 0.5 g. Thin-layer chromatography of the alkaloid fractions on silica gel plates developed in chloroform-methanol-diethylamine (92:3:5) failed to show the presence of tazettine.

Crinum powellii

Dormant bulbs (16.5 kg) of *C. powellii* were processed in the same manner as *S. formosissima*. Extraction with chloroform at pH 4 provided 25.3 g of basic material. Similar extractions at pH 8 and pH 10

provided 33.2 g and 4.4 g respectively of alkaloidal mixtures. Lycorine (3.0 g) was removed from the pH 8 chloroform by filtration.

Crinum erubescens

Dormant bulbs (18.0 kg), processed as described for S. formosissima, provided 15.5 g of material by chloroform extraction at pH 2, 42.5 g from extraction at pH 8, and 7.8 g from extraction at pH 10. Lycorine (6.5 g) was removed from the pH 8 fraction by trituration with chloroform and filtration. Thin-layer investigation of the pH 8 fraction allowed the isolation of the following known alkaloids: lycorine, crinine, coranicine, crinamine, macronine, 6-hydroxycrinamine, powelline, buphanidrine, flexinine, crinamidine, nerbowdine, and deacetylbowdensine.

Alkaloid Isolation and Chemistry

Pretazettine (39)

Isolation Pretazettine is most easily isolated from the pH 8 S. formosissima extracts by column chromatography using silica gel packed in chloroform. Elution of the column with chloroform and 3% methanol in chloroform removed most of the alkaloids of the crude fraction leaving pretazettine on the column. Chloroform-methanol (1:1) elutes the pretazettine.

Synthesis via haemanthidine methiodide (27) To a solution of 100 mg of haemanthidine in 8 ml methanol was added two ml of methyl iodide. The solution was allowed to stand 2 hr at room temperature before evaporation to dryness. The resulting methiodide was dissolved in 10 ml of distilled water, previously made acidic (pH 5) with

hydrochloric acid. The aqueous solution was adjusted to pH 8 with potassium carbonate and extracted 4 times with chloroform. The chloroform extract was evaporated under reduced pressure to give 94 mg of pretazettine. Only trace impurities were present as detected by thin-layer chromatography. The synthetic material showed ir and nmr spectra as well as chromatographic characteristics identical with those of the naturally occurring alkaloid.

Synthesis by Eschweiler-Clarke reaction A solution of 100 mg of haemanthidine in 0.4 ml 88% formic acid and 0.5 ml 37% formaldehyde was heated at 90-100° for 6 hr. The mixture was cooled, diluted to 50 ml with water, made basic (pH 8) with potassium carbonate, and extracted 4 times with chloroform. The extract was evaporated under reduced pressure to give 95 mg pretazettine. Thin-layer chromatography indicated that pretazettine was the only compound present: (amorph); $[\alpha]^{24}\underline{D}$ + 180° (c 0.2, $CHCl_3$); λ_{max} (95% EtOH) 238 mμ(ε 5060), 291 mμ(ε 4300); ir ($CHCl_3$) [Fig. 1] 1508, 1489, 1045, 942 cm^{-1} (aromatic methylenedioxy), 3600 cm^{-1} (-OH), 2832 cm^{-1} ($-OCH_3$); nmr ($CDCl_3$) [Fig. 2] δ6.75 and 6.83 ppm (2s, aromatic protons), 2.47 ppm (s,$-NCH_3$), 3.42 ppm (s,$-OCH_3$), 5.91 ppm (s, 2, methylenedioxy); ord (MeOH) [Fig. 13] $[\Phi]_{320}$ + 4100°, $[\Phi]_{301}$ + 6600° pk, $[\Phi]_{275}$ + 2700° tr, $[\Phi]_{248}$ + 12,100° sh, $[\Phi]_{230}$ + 18,100° (last reading); cd (MeOH) $[\Theta]_{290}$ + 7400°, $[\Theta]_{240}$ + 16,000°, $[\Theta]_{225}$ + 26,800° (last reading).

Pretazettine hydrochloride Pretazettine affords a crystalline hydrochloride salt from ethanol: mp 224-225°; $[\alpha]^{24}\underline{D}$ + 30.3° (c 0.15, H_2O); λ_{max} (95% EtOH) 243 mμ(ε 3400), 290 mμ(ε 4000); nmr (D_2O) [Fig. 14] δ7.08, 7.05, 6.98, 6.95 ppm (4s, 2 aromatic protons), 6.53 ppm

(broad singlet, 2 olefinic protons), 6.08 ppm (s, 2, methylenedioxy), 3.48 ppm ($-OCH_3$), 3.32 ppm ($-NCH_3$); ord (MeOH) [Fig. 12] $[\Phi]_{320}$ + 1000°, $[\Phi]_{302}$ + 3200° pk, $[\Phi]_{280}$ - 4300°sh, $[\Phi]_{255}$ - 7100° tr, $[\Phi]_{230}$ + 8000° (last reading); cd (MeOH) $[\theta]_{284}$ + 8800°, $[\theta]_{248}$ - 4300°, $[\theta]_{225}$ + 8000° (last reading).

Anal. Calcd. for $C_{18}H_{21}NO_5 \cdot HCl$: C, 58.77; H, 6.03; N, 3.81. Found: C, 58.53; H, 6.18; N, 3.91.

Pretazettine hydrobromide Pretazettine hydrobromide crystallizes from ethanol as colorless prisms: mp 224-226°; $[\alpha]^{24}\underline{D}$ + 19.4° (c 0.16, H_2O).

Anal. Calcd. for $C_{18}H_{21}NO_5 \cdot HBr$: C, 52.44; H, 5.38; N, 3.40. Found: C, 52.29; H, 5.23; N, 3.43.

Manganese dioxide oxidation of pretazettine (39)

A suspension of 3.067 g of manganese dioxide and 302 mg pretazettine in 200 ml of chloroform (previously dried over K_2CO_3) was stirred at room temperature for 4 hr. The manganese dioxide was removed by filtration and the filter cake was washed with chloroform. The chloroform solution was evaporated to dryness under reduced pressure to give 260 mg of residue which was separated by preparative thin-layer chromatography on silica gel using chloroform-methanol-diethylamine (92:3:5). The band at R_f 0.8 yielded 108 mg of 3-epimacronine (41). The alkaloid afforded colorless prisms from acetone: mp 129-131°; $[\alpha]^{24}\underline{D}$ + 276° (c 0.95, $CHCl_3$); λ_{max} (95% EtOH) 227 mμ (ε 29,000), 267 mμ (ε 6100), 307 mμ (ε 6600); ir ($CHCl_3$) [Fig. 3] 1505, 1481, 1042, 940 cm^{-1} (aromatic methylenedioxy), 1720 cm^{-1} (C = O), 2832 cm^{-1}

($-OCH_3$); nmr ($CDCl_3$) [Fig. 4] δ6.75 and 7.51 ppm (2s, aromatic protons), 6.02 ppm (s, 2, methylenedioxy), 3.41 ppm (s,$-OCH_3$) 2.52 ppm (s,$-NCH_3$).

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.55; H, 5.90; N, 4.20.

The band at R_f 0.6 provided 124 mg of N-demethyl 3-epimacronine (40) which crystallized as prisms from ether-acetone: mp 154-155°; $[\alpha]^{24}D$ + 207° (c 0.36, $CHCl_3$); λ_{max} (95% EtOH) 228 mμ (ε 31,400), 268 mμ (ε 6000), 308 mμ (ε 6800); ir ($CHCl_3$)[Fig. 3] 1508, 1484, 1042, 941 cm^{-1} (aromatic methylenedioxy), 1721 cm^{-1} (C = O), 2838 cm^{-1} ($-OCH_3$); nmr ($CDCl_3$) [Fig. 4] δ6.71 and 7.50 ppm (2s, aromatic protons), 6.02 ppm (s, 2, methylenedioxy), 3.41 ppm (s,$-OCH_3$).

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.76; H, 5.43; N, 4.44. Found: C, 64.78; H, 5.51; N, 4.53.

N-Demethyl 3-epimacronine (40)

From 3-epimacronine (41) A suspension of 30 mg of 3-epimacronine (41) and 300 mg manganese dioxide in 25 ml of chloroform was stirred at room temperature for 4 hr. Thin-layer chromatography of the recovered residue showed that about half of the starting material had been converted to 40 in this time.

From 6-oxohaemanthamine (28) To a solution of 50 mg 6-oxohaemanthamine[19] dissolved in 3 ml of 95% ethanol was added a mixture of 0.45 ml glacial acetic acid and 1.15 g sodium acetate dissolved in 9 ml water. The mixture was refluxed for three hr and then cooled. The solution was diluted to approximately 50 ml with water, made basic

(pH 10) with ammonium hydroxide and extracted 4 times with chloroform. The chloroform was dried with potassium carbonate and evaporated to dryness to provide 44 mg of a light yellow oil which crystallized on standing. The compound crystallized from ether-acetone as prisms, mp 153-155°. The compound was identical to 40 prepared from manganese dioxide oxidation of pretazettine.

3-Epimacronine (41)

Isolation 3-Epimacronine was isolated from the pH 8 alkaloid fraction of S. formosissima. The separation was carried out using preparative thin-layer chromatography in a series of solvent systems with the successive recovery of the band corresponding to synthetic 3-epimacronine. The effects of each purification could be observed by increase of carbonyl absorption in the infrared spectrum. The chromatography was carried out on silica gel in chloroform-methanol-diethylamine (92:3:5); ether-methanol-diethylamine (85:10:5); and ethyl acetate-methanol (4:1). The R_f values were respectively 0.6, 0.8, and 0.5 for 3-epimacronine in the solvent systems.

From N-demethyl 3-epimacronine (40) To a solution of 50 mg of N-demethyl 3-epimacronine (40) in 5 ml of methanol was added 50 mg of boric acid and 0.5 ml of 37% formaldehyde. The solution was treated with 150 mg of sodium borohydride and allowed to stand for 30 min at room temperature. The reaction was stopped by the addition of 0.5 ml of acetic acid. The solution was diluted with water, made basic (pH 10) with ammonium hydroxide, and extracted three times with chloroform. The chloroform was dried with potassium carbonate and

evaporated to dryness *in vacuo*. The residue was crystallized from acetone to give 36 mg of 41, mp 130-131°.

Precriwelline (45)

Isolation Precriwelline was separated from the other alkaloids of the pH 8 fraction of *C. powellii* by preparative thin-layer silica gel chromatography by elution in methanol-ethyl acetate (50:50). The precriwelline essentially remained at the origin while all other alkaloids migrated to a significant extent. The band of lowest R_f was removed and eluted with a large volume of methanol. The free base is amorphous.

Synthesis To a solution of 329 mg of 6-hydroxycrinamine in 20 ml of methanol was added 6 ml of methyl iodide. The solution was allowed to stand 3 hr at room temperature before evaporation to dryness. The residue was dissolved in 10 ml of distilled water previously made acidic (pH 5) with hydrochloric acid. On standing overnight, the aqueous solution yielded 240 mg of precriwelline hydrochloride as needles: mp 199-200°. The free base was recovered by adjusting the pH of an aqueous solution containing the hydrochloride to pH 8 with potassium carbonate and extracting 4 times with chloroform. Evaporation of this extract under reduced pressure yielded 308 mg of amorphous precriwelline. The synthetic base had ir and nmr spectra and chromatographic behavior identical with the naturally occurring compound: $[\alpha]^{24}_{D}$ + 228° (c 0.18, $CHCl_3$); λ_{max} (95% EtOH) 242 mμ (ε 3010), 291 mμ (ε 3200); ir ($CHCl_3$) [Fig. 7] 1509, 1489, 1047, 942 cm^{-1} (aromatic methylenedioxy), 2835 cm^{-1} ($-OCH_3$), 3600 cm^{-1} (-OH); nmr

($CDCl_3$) [Fig. 8] δ6.61 and 6.83 ppm (2s, two aromatic protons), 5.90 ppm (s, 2, methylenedioxy), 2.48 ppm (s,-NCH_3), 3.41 ppm (s,-OCH_3).

Precriwelline hydrochloride Precriwelline hydrochloride crystallized from water as needles: mp 199-201°; $[\alpha]^{24}_{D}$ + 82° (c 0.2, H_2O).

Anal. Calcd. for $C_{18}H_{21}NO_5 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 57.37; H, 6.15; N, 3.72. Found: C, 57.29; H, 6.36; N, 3.81.

Manganese dioxide oxidation of precriwelline (45)

A solution of 20 mg of precriwelline in 30 ml dry chloroform was stirred with 200 mg of manganese dioxide for 4 hr. The manganese dioxide was removed by filtration and the chloroform was evaporated to yield 11 mg of an oil. Thin-layer chromatography indicated the presence of N-demethylmacronine (42) and macronine (43) in about equal amounts.

O-Methylprecriwelline (46)

A solution of 180 mg of precriwelline (45) in 10 ml of methanol was made acidic (pH 2) with gaseous HCl and refluxed overnight. The solution was evaporated to dryness under reduced pressure. To the resulting oil was added 100 ml of water previously adjusted to pH 10 with ammonium hydroxide. The solution was extracted 4 times with chloroform. The chloroform extract was evaporated to dryness under reduced pressure to give 138 mg of an oil. Separation by preparative thin-layer chromatography allowed the recovery of 84 mg of O-methylprecriwelline (R_f 0.8) and 35 mg of precriwelline. The O-methylprecriwelline (46) gave identical ir and nmr spectra with the

previously reported material.[27]

N-Demethylmacronine (42)

The most non-polar major compound of the pH 8 fraction from C. erubescens was recovered by preparative thin-layer chromatography using silica gel developed in chloroform-methanol-diethylamine (91:4:5). The desired band was removed and the material was recovered from the silica gel by elution with methanol. The compound crystallized from acetone mp 176-177° was identical with N-demethylmacronine prepared by synthesis.[27]

N-Demethyl N-carboethoxymacronine (47)

Isolation From the non-polar trace compounds of the pH 8 fraction from C. erubescens, a compound was isolated which had an R_f 0.8 on silica gel in chloroform-methanol-diethylamine (91:4:5). Although thin-layer chromatography in several solvent systems testified to the compound's purity, it remained amorphous.

Synthesis A solution of 20 mg of N-demethylmacronine in 0.5 ml of chloroform was added to 4 ml of freshly distilled ethyl chloroformate. The solution was allowed to stand overnight at room temperature. The reaction mixture was evaporated to dryness under reduced pressure with the recovery of 22 mg of an oil. Thin-layer chromatography on silica gel developed in ethyl acetate-methanol (90:10) showed that the residue was pure. This material was identical with natural 47 by comparison of infrared spectra and chromatographic data: $[\alpha]_D^{24}$ + 313° (c 0.17, $CHCl_3$); λ_{max} (95% EtOH) 288 mμ (ε 29,300), 268 mμ (ε 5140), 308 mμ (ε 5840); ir ($CHCl_3$) [Fig. 9] 1508, 1482, 1041, 940 cm^{-1}

(aromatic methylenedioxy), 1721 cm^{-1} (C = O lactone), 1695 cm^{-1} (C = O carbamate), 2830 cm^{-1} ($-OCH_3$); nmr ($CDCl_3$) [Fig. 10] δ 6.66 and 7.52 ppm (2s, aromatic protons), 6.05 ppm (s, 2, methylenedioxy), 3.34 ppm (s, $-OCH_3$), 4.16 ppm (q, 2, $CH_3\underline{CH_2}OCO-$), 1.28 ppm (t, 3, $\underline{CH_3}CH_2O-$).

Anal. Calcd. for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.24; H, 5.63; N, 3.61.

N-Demethyl O-methylpretazettine (58)

A solution of 100 mg haemanthidine in 8 ml methanol was acidified (pH 4) with 0.1 ml conc. hydrochloric acid and refluxed overnight. The methanolic solution was evaporated to dryness. Distilled water (20 ml), previously adjusted to pH 10 with ammonium hydroxide was added to the residue. The resulting aqueous solution was extracted 4 times with chloroform and the extract was evaporated under reduced pressure to dryness to give 104 mg of an oil. Thin-layer chromatography indicated the presence of haemanthidine (R_f 0.2) and N-demethyl O-methylpretazettine (R_f 0.6). Components of the mixture were separated on preparative thin-layer plates to give 28 mg of haemanthidine and 66 mg of N-demethyl O-methylpretazettine: (amorph); $[\alpha]_{\underline{D}}^{24}$ + 82° (c 0.18, CH_3OH); λ_{max} (95% EtOH) 242 mμ (ε 5650), 291 mμ (ε 4050); ir ($CHCl_3$) [Fig. 15] 1508, 1488, 1050, 942 cm^{-1} (aromatic methylenedioxy), 2838 cm^{-1} ($-OCH_3$), 3382 cm^{-1} (-N-H); nmr ($CDCl_3$) [Fig. 16] δ 6.79 and 6.70 ppm (2s, aromatic protons), 5.90 ppm (s, 2, methylenedioxy), 3.55 and 3.41 ppm (2s, $-OCH_3$).

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.26; H, 6.39; N, 4.23. Found:

C, 65.28; H, 6.64; N, 4.39.

N-Demethyl O-methylprecriwelline (59)

In an analogous manner, 100 mg of 6-hydroxycrinamine was converted to a mixture of 44 mg starting material and 48 mg of N-demethyl O-methylprecriwelline: (amorph); $[\alpha]^{24}_{D}$ + 193° (c 0.14, $CHCl_3$); λ_{max} (95% EtOH) 243 mμ (ε 6850), 292 mμ (ε 4700); ir ($CHCl_3$) [Fig. 15]; nmr ($CDCl_3$) [Fig. 16] δ 6.80 and 6.56 ppm (2s, aromatic protons), 5.90 ppm (s, 2, methylenedioxy), 3.54 and 3.40 ppm (2s, $-OCH_3$).

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.26; H, 6.39; N, 4.23. Found: C, 65.53; H, 6.55; N, 4.24.

O-Methylpretazettine (44)

From pretazettine (39) A solution of 100 mg of pretazettine hydrochloride in 8 ml of methanol was acidified with 0.1 ml of conc. hydrochloric acid and refluxed overnight. The solution was evaporated to dryness under reduced pressure. Water (10 ml), made basic to pH 10 with potassium carbonate, was added to the residue. The resulting aqueous mixture was extracted 4 times with chloroform. Evaporation of the chloroform gave 94 mg of residue which was chromatographed on a silica gel column packed in chloroform. Elution with chloroform afforded 32 mg of O-methylpretazettine. Further elution with 15% methanol in chloroform eluted 38 mg of pretazettine. The O-methylpretazettine defied all attempts at crystallization. The material probably consists of the two C_8-methoxyl epimers. Two substances were detected on silica gel thin-layer chromatography plates developed in chloroform-methanol-diethylamine (92:3:5) (R_f 0.8).

From N-Demethyl O-methylpretazettine (58) To a solution of 50 mg N-demethyl O-methylpretazettine in 10 ml methanol was added 2 ml methyl iodide. The solution was allowed to stand at room temperature for 2 hr before evaporation to dryness under reduced pressure. The residue was dissolved in 10 ml of dilute hydrochloric acid (pH 4). The resulting solution was adjusted to pH 10 with potassium carbonate and extracted 4 times with chloroform. The extract, upon evaporation, gave 48 mg of O-methylpretazettine: (amorph); $[\alpha]^{24}\underline{D}$ + 180° (c 0.24, $CHCl_3$); λ_{max} (95% EtOH) 242 mμ(ε 5950), 589 mμ(ε 3600), ir ($CHCl_3$) [Fig. 5]; nmr ($CDCl_3$) [Fig. 6] δ 6.76 ppm (s, 2, aromatic protons), 5.88 ppm (s, 2, methylenedioxy), 3.53 and 3.41 ppm (2s, $-OCH_3$), 2.48 ppm (s,$-NCH_3$); ord (MeOH) [Fig. 13] $[\Phi]_{320}$ + 5000°, $[\Phi]_{300}$ + 9500° pk, $[\Phi]_{282}$ + 4000° tr, $[\Phi]_{250}$ + 21,700° sh, $[\Phi]_{230}$ + 24,800° (last reading); cd (MeOH) $[\Theta]_{293}$ + 11,200°, $[\Theta]_{240}$ + 28,000°, $[\Theta]_{225}$ + 30,500° (last reading).

Anal. Calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.22; H, 6.96; N, 4.07.

Hydrolysis of O-methylpretazettine (44) A solution of 100 mg of O-methylpretazettine in 10 ml of dilute aqueous hydrochloric acid (pH 2) was allowed to stand at room temperature for two hr. The solution was made basic (pH 10) with potassium carbonate and extracted 3 times with chloroform. The extraction recovered 94 mg of pretazettine which was characterized and shown to be pure by the ir spectrum and thin-layer chromatography.

Dihydropretazettine (62)

From pretazettine (39) A solution of 300 mg pretazettine in 10 ml glacial acetic acid was added to a suspension of 110 mg of previously reduced Adam's catalyst in 15 ml acetic acid and hydrogenated at room temperature and atmospheric pressure. The compound absorbed slightly more than one equivalent of hydrogen in 2 hr. When the reduction was complete, the solvent was removed by evaporation under reduced pressure and the resulting oil was dissolved in approximately 50 ml of water. The aqueous solution was made basic (pH 10) with ammonium hydroxide and extracted 4 times with chloroform. The extract yielded 280 mg of dihydropretazettine which was pure by thin-layer chromatographic criteria.

From dihydrohaemanthidine A solution of 90 mg dihydrohaemanthidine in 8 ml methanol and 2 ml of methyl iodide was allowed to stand at room temperature for 4 hr. The solution was evaporated to dryness under reduced pressure and 10 ml of dilute hydrochloric acid (pH 6) was added. The residue dissolved slowly upon warming on a steam bath. The aqueous solution was made basic (pH 10) with potassium carbonate and extracted 4 times with chloroform. The chloroform extract upon evaporation gave 94 mg of dihydropretazettine identical with that obtained by the reduction of pretazettine. The compound is amorphous; $[\alpha]_{\underline{D}}^{24}$ + 39° (c 0.22, $CHCl_3$); λ_{max} (95% EtOH) 238 mμ (ε 4050), 291 mμ (ε 4300); ir ($CHCl_3$) [Fig. 18]; nmr ($CDCl_3$) [Fig. 19] δ 6.96 and 6.88 ppm (2s, aromatic protons), 5.92 ppm (s, 2, methylenedioxy), 3.40 ppm ($-OCH_3$), 2.45 ppm ($-NCH_3$); nmr (D_2O) [Fig. 19] δ 6.81 and 6.76 ppm (2s, aromatic protons), 5.96 ppm (s, 2,

methylenedioxy), 3.41 ppm ($-OCH_3$), 3.03 ppm ($-NCH_3$).

Anal. Mass Calcd. for $C_{18}H_{23}NO_5$: 333.155. Found (by high resolution mass spec.): 333.157.

6a-Epidihydrotazettine (65)

A solution of 150 mg of dihydropretazettine in 8 ml of chloroform and 0.2 ml water was refluxed for 24 hr. The solution was evaporated under reduced pressure. The residue was separated by preparative thin-layer chromatography using chloroform-methanol (90:10). Isolation of the major band (R_f 0.5) gave 82 mg of 6a-epidihydrotazettine: (amorph): λ_{max} (95% EtOH) 234 mμ (ϵ 3880), 295 mμ (ϵ 4350); ir ($CHCl_3$) [Fig. 20]; nmr ($CDCl_3$) [Fig. 21] δ 6.89 and 6.38 ppm (2s, aromatic protons), 5.90 ppm (s, 2, methylenedioxy), 4.69 ppm (s, 2, benzylic), 3.30 ppm ($-OCH_3$), 2.36 ppm ($-NCH_3$).

Anal. Mass Calcd. for $C_{18}H_{23}NO_5$: 333.155. Found: 333.155.

Dihydrotazettine (64)

From dihydropretazettine (62) Sufficient methanol was added to dissolve 50 mg dihydropretazettine in 1 ml water. This solution was made basic with 1 ml of 40% sodium hydroxide solution and refluxed 3 hr. The aqueous solution was cooled, diluted to 50 ml with water, and extracted 4 times with chloroform. The chloroform extract was evaporated to dryness under reduced pressure to give 42 mg of dihydrotazettine, identical in all respects to the compound prepared by the hydrogenation of tazettine. The residue crystallized as prisms from ethyl acetate: mp 164-166° (lit.[52] mp 168-169°).

From 6a-epidihydrotazettine By the same procedure which was used to convert dihydropretazettine to dihydrotazettine, 15 mg of 6a-epidihydrotazettine was converted to 9 mg of product which gave an infrared spectrum and had chromatographic characteristics identical with dihydrotazettine.

6-Acetyl 11-oxohaemanthidine (66)

A solution of 312 mg haemanthidine, 3 ml dimethyl sulfoxide, and 2 ml acetic anhydride was allowed to stand at room temperature for 10 hr. The mixture was diluted to 30 ml with water, made basic (pH 10) with ammonium hydroxide and extracted four times with benzene. The organic layer was reextracted 3 times with dilute ammonium hydroxide (pH 8). The benzene solution was evaporated to dryness to provide a green oil. The color and residual dimethyl sulfoxide were removed by column chromatography using silica gel packed in chloroform. Elution with chloroform provided 301 mg of product. Although thin-layer chromatography indicated only one compound was present, it remained amorphous: $[\alpha]^{24}_{D}$ + 64° (c 0.26, CH_3OH); λ_{max} (95% EtOH) 251 mμ(ε 3930), 296 mμ (ε 4400), shoulders at 314 mμ (ε 2640), 325 mμ (ε 1850); ir ($CHCl_3$) [Fig. 22] 1751 cm^{-1} (C = O); nmr ($CDCl_3$) [Fig. 23] δ 5.93 ppm (s, 2, methylenedioxy), 3.38 ppm ($-OCH_3$), 2.22 and 2.17 ppm (two portions of $-OCOCH_3$ due to the epimeric nature of the C_6-position).

Anal. Calcd. for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.64; H, 5.42; N, 4.04.

11-Oxohaemanthidine (67)

A solution of 100 mg of 6-acetyl 11-oxohaemanthidine in 8 ml methanol was made basic with one drop of 40% sodium hydroxide solution and allowed to stand at room temperature for 30 min. The solution was neutralized with dilute hydrochloric acid and evaporated to dryness under reduced pressure. The residue was dissolved in approximately 50 ml water, the solution adjusted to pH 8 with ammonium hydroxide, and extracted 4 times with chloroform. Evaporation of the organic solvent provided 88 mg of an oil. The product was purified by preparative thin-layer chromatography. The major band (R_f 0.5) was recovered as an amorphous material. $[\alpha]^{24}_{D}$ + 60° (c 0.20, $CHCl_3$); λ_{max} (95% EtOH) 251 mμ (ε 3920), 295 mμ (ε 4600), shoulders at 314 mμ (ε 2740), 326 mμ (ε 2000); ir ($CHCl_3$) [Fig. 22] 1765 cm^{-1} (C = O), 3600 cm^{-1} (hydroxyl group); nmr ($CDCl_3$) [Fig. 23].

Anal. Mass Calcd. for $C_{17}H_{17}NO_5$: 315.111. Found: 315.111.

N-Demethyl 6a-epipretazettine (69)

From 6-acetyl 11-oxohaemanthidine (66) To a solution of 301 mg of 6-acetyl 11-oxohaemanthidine in 15 ml of tetrahydrofuran was added 300 mg lithium aluminum hydride. The reaction was allowed to proceed at room temperature for 2 hr. Excess hydride was destroyed by the addition of a few drops of water saturated with sodium sulfate and the inorganic solids were removed by filtration. The solvent was evaporated to dryness under reduced pressure. The residue (231 mg) was shown by thin-layer chromatography to be a mixture of haemanthidine and one other major compound. Preparative thin-layer chromatography

recovered 38 mg of haemanthidine (R_f 0.3) and 182 mg of N-demethyl 6a-epipretazettine (R_f 0.5).

From 11-oxohaemanthidine (67) To a solution of 30 mg of 11-oxohaemanthidine in 10 ml tetrahydrofuran was added 40 mg lithium aluminum hydride. The reduction was allowed to proceed at room temperature for 1 hr. The reaction was quenched and the product was isolated in the same manner as reported in the preceding paragraph. Thin-layer chromatography provided 8 mg of haemanthidine and 18 mg of N-demethyl 6a-epipretazettine: (amorph); $[\alpha]^{24}\underline{D}$ + 133° (c 0.22, CH_3OH); λ_{max} (95% EtOH) 241 mμ(ε 4230), 292 mμ(ε 3120); ir ($CHCl_3$) [Fig. 24] 1508, 1490, 1043, 941 cm^{-1} (aromatic methylenedioxy), 2835 cm^{-1} ($-OCH_3$), 3600 cm^{-1} (-OH); nmr ($CDCl_3$) [Fig. 25] δ 6.79 and 6.69 ppm (two major aromatic singlets), 6.90 and 6.75 ppm (two minor aromatic singlets), 5.90 ppm (s, 2, methylen[illegible], 5.85 and 5.76 ppm (2 parts of benzylic protons), 3.44 ppm [illegible] MeOH) [Fig. 26] $[\Phi]_{320}$ + 2000°, $[\Phi]_{312}$ + 2400° pk, $[\Phi]_{[illegible]}$ [illegible]0° tr, $[\Phi]_{280}$ + 9450° sh, $[\Phi]_{250}$ + 25,200° pk, $[\Phi]_{236}$ + 14, 600° tr, $[\Phi]_{228}$ + 18,000° (last reading); cd (MeOH) $[\Theta]_{283}$ - 2600°, $[\Theta]_{240}$ + 16,900°, $[\Theta]_{225}$ + 16,300° (last reading).

Anal. Mass Calcd. for $C_{17}H_{19}NO_5$: 317.126. Found: 317.125.

6a-Epipretazettine (70)

A solution of 112 mg of 11-epihaemanthidine in 10 ml methanol and 3 ml methyl iodide was allowed to stand at room temperature for 2 hr. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in 6 ml of dilute (pH 5) hydrochloric acid.

The aqueous solution was then adjusted to pH 10 with potassium carbonate and extracted 4 times with chloroform. The chloroform extract, upon evaporation, gave 90 mg of 6a-epipretazettine: (amorph); $[\alpha]^{24}_{D}$ + 188° (c 0.20, CH_3OH); λ_{max} (95% EtOH) 242 mμ(ε 6000), 291 mμ (ε 4500); ir ($CHCl_3$) [Fig. 24]; nmr ($CDCl_3$) [Fig. 25] δ 6.89 and 6.72 ppm (2s, aromatic protons), 5.91 ppm (s, 2, methylenedioxy), 5.83 and 5.75 ppm (2 parts of benzylic proton), 3.46 ppm ($-OCH_3$), 2.48 ppm ($-NCH_3$); ord (MeOH) [Fig. 26] $[\Phi]_{320}$ + 4000°, $[\Phi]_{310}$ + 4500° pk, $[\Phi]_{300}$ + 3200° tr, $[\Phi]_{280}$ + 10,800° sh, $[\Phi]_{253}$ + 26,200° pk, $[\Phi]_{240}$ + 16,000° tr, $[\Phi]_{225}$ + 26,000° (last reading); cd (MeOH) $[\Theta]_{238}$ - 4000°, $[\Theta]_{245}$ + 24,000°, $[\Theta]$ + 15,000° (last reading).

Anal. Mass Calcd. for $C_{18}H_{21}NO_5$: 331.142. Found: 331.140.

Tazettine (71)

From pretazettine (39) A solution of 10 mg of pretazettine in 1 ml of 0.1 N sodium hydroxide was allowed to stand at room temperature. Thin-layer chromatographic examination of the mixture after 30 min indicated more than half of the pretazettine had rearranged to tazettine. In 1 hr the rearrangement was complete.

A solution of 50 mg of pretazettine in 1 ml of chloroform was allowed to stand overnight at room temperature. Thin-layer chromatographic examination of the mixture after standing 12 hr indicated that the rearrangement was approximately half completed.

A solution of 10 mg of pretazettine in 1 ml of distilled water was heated at 70°. The rearrangement was complete in less than 1 hr.

Pretazettine was stable in dilute aqueous acid. A solution of

20 mg of pretazettine in 2 ml of 0.2 N hydrochloric acid was refluxed for 12 hr. Examination of the solution indicated the presence of only pretazettine. Thin-layer examination in all cases was carried out in chloroform-methanol-diethylamine (92:3:5), pretazettine (R_f 0.5), tazettine (R_f 0.7).

From 6a-epipretazettine (70) A solution of 40 mg of 6a-epipretazettine in 10 ml of methanol was made basic with 1 ml of 40% sodium hydroxide and refluxed for 2 hr. The solution was cooled, diluted to 100 ml with water and extracted 3 times with chloroform. Evaporation of the solvent under reduced pressure gave 35 mg tazettine after crystallization from acetone, mp 209-210° (lit.[3] 210-211°); ord (MeOH) [Fig. 12] $[\Phi]_{320}$ + 3000°, $[\Phi]_{298}$ + 1000° tr, $[\Phi]_{280}$ + 10,700° sh, $[\Phi]_{251}$ + 30,000° pk, $[\Phi]_{238}$ + 10,000° tr, $[\Phi]_{225}$ + 14,800° (last reading); cd (MeOH) $[\Theta]_{290}$ - 5500°, $[\Theta]_{242}$ + 32,000°, $[\Theta]_{225}$ + 17,000° (last reading).

6a-Epi N-demethyl 3-epimacronine (73)

A solution of 105 mg of 11-epihaemanthidine was stirred at room temperature for 2 hr in 100 ml chloroform containing 1 g manganese dioxide. The reaction mixture was filtered and the filter cake was washed repeatedly with chloroform. Evaporation of the combined chloroform filtrates under reduced pressure afforded 88 mg of oil. Two components of this residue were separated by preparative thin-layer chromatography. The band at R_f 0.7 provided 23 mg of a compound which was found to be a decomposition product of the material with R_f 0.65. The major band at R_f 0.65 provided 62 mg of 6a-epi N-demethyl

3-epimacronine (73): (amorph); $[\alpha]^{24}_{D}$ + 79° (c 0.14, $CHCl_3$); λ_{max} (95% EtOH) 228 mμ (ε 25,000), 268 mμ (ε 5800), 310 mμ (ε 5850); ir ($CHCl_3$) [Fig. 18] 1711 cm^{-1} (C = O); nmr ($CDCl_3$) [Fig. 14] δ 6.84 and 7.55 ppm (2s, aromatic protons), 6.04 ppm (s, 2, methylenedioxy), 3.46 ppm (s, $-OCH_3$).

Anal. Mass Calcd. for $C_{17}H_{19}NO_5$: 315.111. Found: 315.111.

Haemanthamine (26)

Ord (MeOH) [Fig. 11] $[\Phi]_{320}$ + 3100°, $[\Phi]_{305}$ + 7600° pk, $[\Phi]_{275}$ - 6300° sh, $[\Phi]_{252}$ - 10,200° tr, $[\Phi]_{230}$ + 12,100° (last reading); cd (MeOH) $[\Theta]_{290}$ + 13,100°, $[\Theta]_{245}$ - 10,200°, $[\Theta]_{225}$ + 15,000° (last reading).

Haemanthamine methiodide

Ord (MeOH) [Fig. 11] $[\Phi]_{320}$ + 2000°, $[\Phi]_{305}$ + 4300° pk, $[\Phi]_{280}$ - 5100° sh, $[\Phi]_{255}$ - 8600° tr, $[\Phi]_{230}$ + 20,000° (last reading); cd (MeOH) $[\Theta]_{295}$ + 6300°, $[\Theta]_{245}$ - 7000°, $[\Theta]_{230}$ + 8000° (last reading).

Haemanthidine (32)

Ord (MeOH) [Fig. 17] $[\Phi]_{320}$ + 3000°, $[\Phi]_{303}$ + 5000° pk, $[\Phi]_{280}$ - 5000° sh, $[\Phi]_{254}$ - 13,600° tr, $[\Phi]_{230}$ + 5000° (last reading); cd (MeOH) $[\Theta]_{294}$ + 11,400°, $[\Theta]_{244}$ - 7600°, $[\Theta]_{225}$ + 6000° (last reading).

Dihydrohaemanthidine

Ord (MeOH) [Fig. 17] $[\Phi]_{370}$ + 2500°, $[\Phi]_{302}$ + 3300° pk, $[\Phi]_{280}$ - 2700° sh, $[\Phi]_{250}$ - 4500° tr, $[\Phi]_{235}$ 0° (last reading); cd (MeOH) $[\Theta]_{290}$ + 6400°, $[\Theta]_{240}$ - 3700°, $[\Theta]_{225}$ + 2000° (last reading).

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