THE ALKALOIDS OF THE AMARYLLIDACEAE:

The Isolation of the Alkaloids of Boöphone disticha Herb., the Structure of Buphanitine and Contributions to the Chemistry of Buphanidrine.

BY

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A Thesis

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SUMMARY.

The alkaloid content of the bulbs of Boöphone disticha Herb., has been reinvestigated and five crystalline bases isolated. Distichine and its sublimate have been identified as hydrated forms of buphanidrine and Lewin's derivatives of his "oily" haemanthine are shown to be derivatives of buphanamine. "Crystalline" haemanthine has been identified with Tutin's buphanitine and the formula corrected to $C_{17}H_{21}O_5N$.

Buphanidrine, $C_{18}H_{21}O_4N$, has been hydrogenated to the dihydro base and a new derivative, the oxalate, prepared. The base was degraded by the Hofmann reaction to give two methines for which structures are proposed. A zinc dust distillation of the methine mixture has afforded phenan--thridine which was compared with a specimen synthesised from carbazole. Ozonolysis of the methine mixture gave formaldehyde which was isolated as a dimedone complex. The hydrolysis of buphanidrine to powelline, previously reported by Wildman, has been confirmed and powelline was degraded to powellane which was required for comparison studies.

Buphanitine, $C_{17}H_{21}O_5N$, has been shown to contain an aromatic methoxyl and methylenedioxy group. The aliphatic hydroxyl groups were concluded to be 1 : 3 from a Meerwein

Pondorff Verley reaction which gave buphanitenone. Sodium in boiling butanol containing buphanitine gave demethoxy--buphanitine, $C_{16}H_{19}O_4N$, for which two derivatives have been prepared.

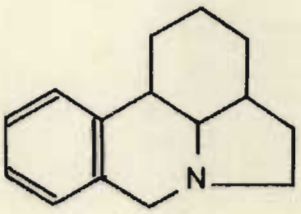
A Hofmann degradation of Buphanitenone gave powellenone methine. From this observation and oxidation and degradation reactions it has been conclusively proved that the alkaloid contains the 5 : 10b-ethanophenanthridine skeleton. However, further degradation to the unsubstituted aliphatic skeleton gave a compound which was not identical with powellane or its mirror image. This compound was named buphanitane and was concluded to have the previously unknown cis B/C ring fusion as opposed to the trans B/C ring system of the crinane series of alkaloids. Buphanitenone has been reduced by way of buphanitenol and buphanitanone to α-buphanitan-3-ol and directly to β-buphanitan-3-ol. Buphanitenol has been oxidised to buphanitenone with manganese dioxide and thus it has been shown that no allylic rearrangement has occurred during the reduction. Hence a structure for buphanitine has been proposed.

I N T R O D U C T I O N

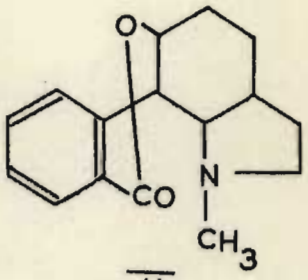
The poisonous and medicinal properties of the alkaloids of the Amaryllidaceae aroused an interest in their study as far back as 1877 when Gerrard [25] isolated an alkaloid which he named "narcissa" from the bulbs of Narcissus pseudonarcissus.L. Since then a large number of workers have isolated over fifty bases from wild, cultivated and hybrid plants of this family. However, confusion has arisen, in many cases, due to the complex nature of the alkaloidal mixture obtained from many plants. Often the same alkaloid was obtained in different crystalline form by different workers and insufficient characterisation has led to the renaming of many alkaloids. Structural studies are however eliminating many of these confusions.

The basic structures of the alkaloids of this family have so far been divided into six fundamental ring systems (Chart I). Within each ring system a number of alkaloids may stem from simple variations in the substitution of aliphatic and aromatic rings.

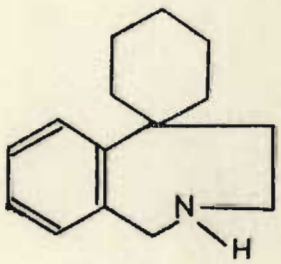
— CHART 1 —



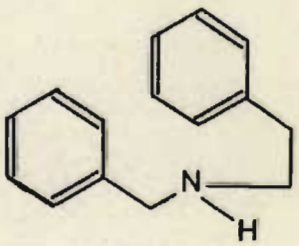
I



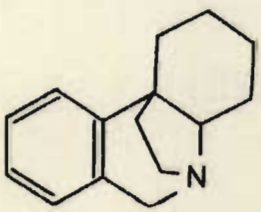
II



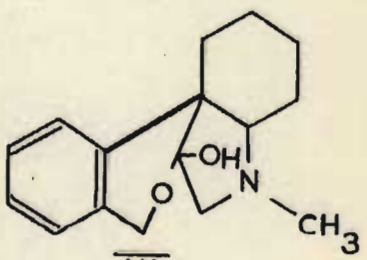
III



IV



V

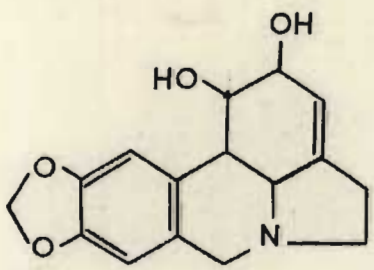


VI

THE SIX FUNDAMENTAL RING SYSTEMS OF THE ALKALOIDS OF AMARYLLIDACEAE

THE PYRROLO(DE)PHENANTHRIDINE ALKALOIDS.— The different alkaloids within this group may be grouped as differently oxygenated compounds as shown in Chart 2.

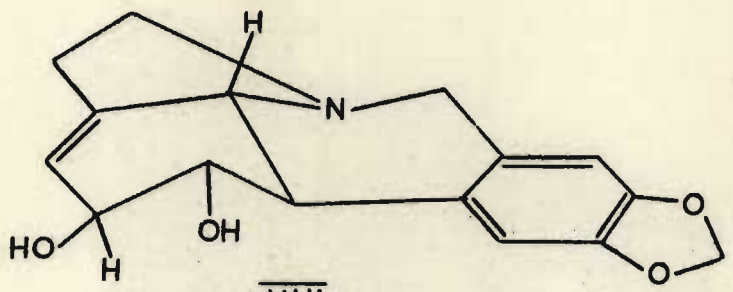
Lycorine, $C_{16}H_{17}O_4N$, the main alkaloid of this group and of the Amaryllidaceae has been known for sixty years. The most valuable evidence for its structure was published in 1955 through joint efforts of research groups in Japan and New Brunswick.[30] They showed that the chemistry can best be expressed by structure (VII) which was originally proposed by Cooke and Loudon.[18] The proof of



VII

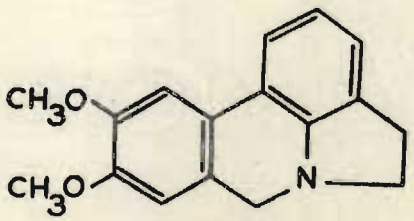
this structure was formulated on the basis of Hofmann and Emde degradations and the synthesis of the degradation products. Furthermore lycorine was treated with a large number of reagents and the degradation products which were obtained proved useful in the inter-relation of these bases. The main contribution was due to Fales, Warnhoff and Wildman[22] who studied a series of oxidation reactions.

The stereochemical structure advanced for this base is either (VIII) or its mirror image. [30]



VIII

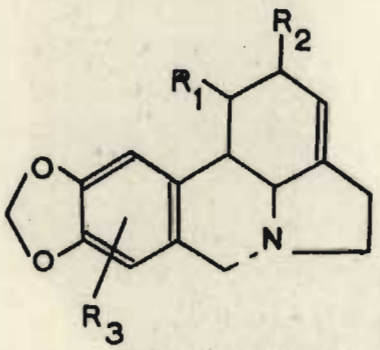
Methylpseudolycorine, $C_{17}H_{21}O_4N$, was first isolated in 1956 [23] and was shown to possess a double bond, two methoxyl and two hydroxyl groups. Periodic acid titration showed that the hydroxyl groups were vicinal and no enolic properties were observed. Preliminary characterisations paralleled similar reactions of lycorine and it was suspected that the alkaloid was the dimethoxy analog of lycorine. Methylpseudolycorine was readily dehydrated to (IX) and so



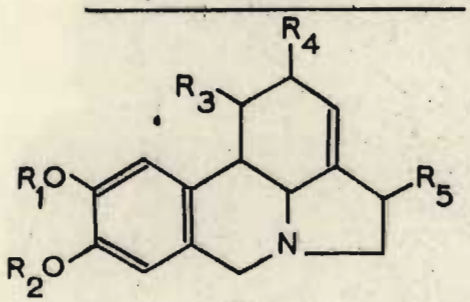
IX

established the ring system and location of two methoxyl

— CHART 2 —



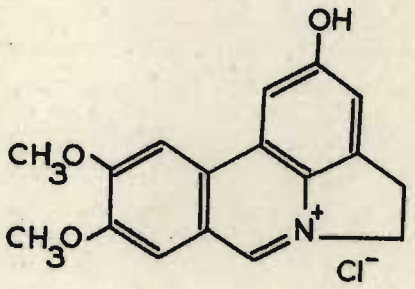
	R_1	R_2	R_3
VII Lycorine	OH	OH	H
XV Caranine	OH	H	H
XXX Falcatine	OH	H	OCH_3



	R_1	R_2	R_3	R_4	R_5
XI Methylpseudolycorine	Me	Me	OH	OH	H
XIII Pseudolycorine	H	Me	OH	OH	H
XVIII Galanthine	Me	Me	OH	OMe	H
XXIVb Narcissidine	Me	Me	OH	OH	OMe
XIX Pluviine	Me	Me	OH	H	H
XXVII Norpluviine	H	Me	OH	H	H

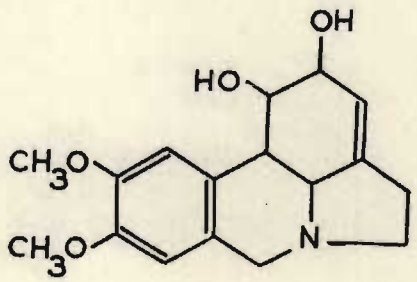
THE PYRROLO(DE)PHENANTHRIDINE GROUP OF ALKALOIDS

groups. Oxidation of methylpseudolycorine with selenium dioxide gave hydroxyphenanthridium chloride (X) which showed similar physical and spectral properties with



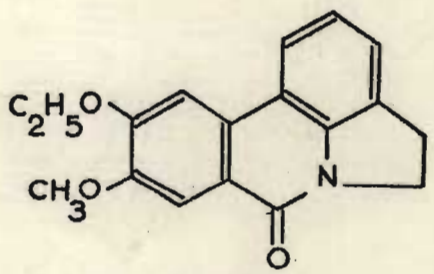
X

those of the lycorine products.[22] The positions of the hydroxyl groups and double bond were assigned on similar evidence for that presented for lycorine[30] and furthermore molecular rotation correlations justified the formula (XI) for methylpseudolycorine.



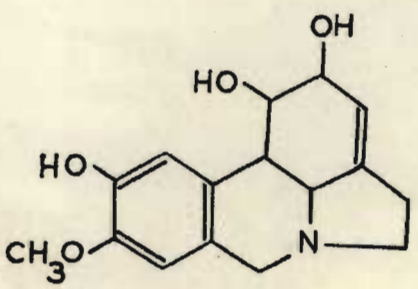
XI

Pseudolycorine [38] was established as a phenolic alkaloid which on treatment with diazomethane [23] gave a product which was identical with methylpseudolycorine. In a recent paper the Japanese workers Uyeo and Yanaihara [61] proposed that the formula for pseudolycorine be changed from $C_{16}H_{17}O_4N$ to $C_{16}H_{19}O_4N$. The position of the phenolic hydroxyl group [44] was found by ethylating this position with diazoethane and chlorinating the product which was oxidised to a phenanthridone (XII), which formula was confirmed by synthesis.



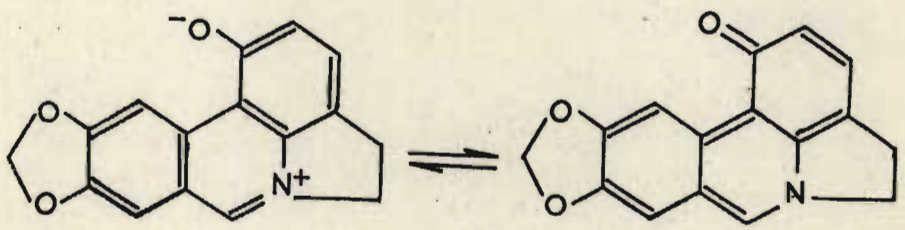
XII

Hence the structure (XIII) was established for pseudolycorine.



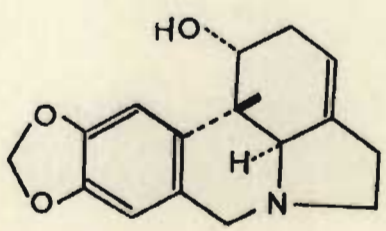
XIII

Caranine, a minor alkaloid of the Amaryllidaceae, was shown by Mason, Puschett and Wildman [47] to be a pentacyclic base of molecular formula $C_{16}H_{17}O_3N$. Compound (XIV) was formed as the sole product of a modified Openauer oxidation of this base and since compound (XIV) was formed from lycorine the basic skeleton



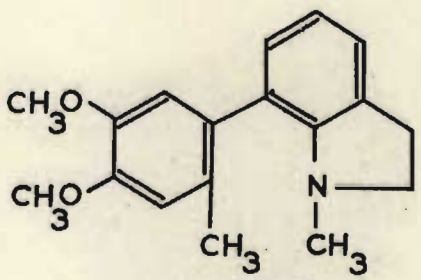
XIV

of caranine was established. Later experiments [66] substantiated the structure (XV) for this alkaloid. In fact even the absolute configuration has now been advanced.



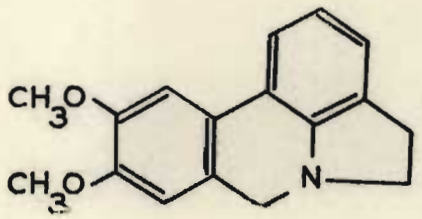
XV

Galanthine was first isolated by the Russian workers [54] who later [12] revised its formula to $C_{18}H_{23}O_4N$. While galanthine appears to undergo Hofmann and Emde degradations with the formation of a second aromatic ring,[54] as in the case of lycorine, no chemical proof of the double bond or hydroxyl group was given although such groups are usually present on ring C if aromatisation occurs. The Emde degradation of galanthine gave (XVI) which product was identical with the Emde degradation of lycorine and subsequent removal of the methylene group followed by



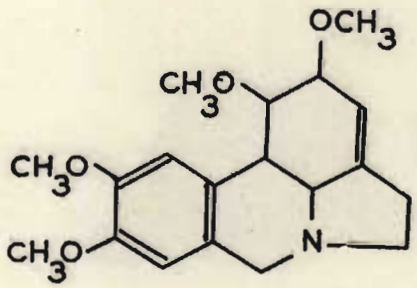
XVI

methylation.[63] An alternate proof of the galanthine ring system and the position of the aromatic methoxyl groups was found in the pyrolysis of galanthine which gave product (XVII). This product (XVII) was identical with a product obtained by a similar treatment of methylpseudolycorine. Oxidation and spectral studies



XVII

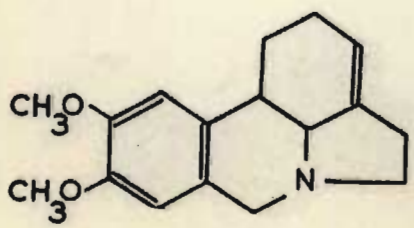
established the position of the double bond as 3 : 3a and the hydroxyl group was placed in the 1-position. Hence the structure of galanthine was formulated as (XVIII).



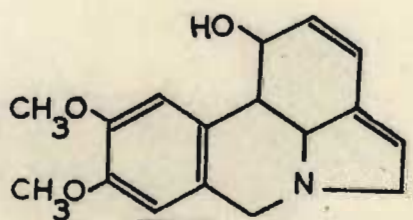
XVIII

Narcissidine was first isolated by Boit [6] who expanded the formula to $C_{15}H_{12}N(OCH_3)_3(OH)_2$ and also established the presence of a reduceable double bond. Further studies by Fales and Wildman [21] established the pyrrolo(de)phenan-

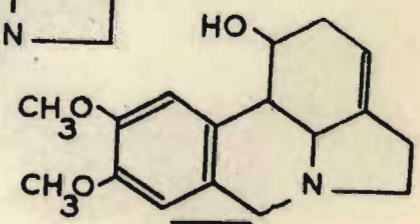
-thridine ring system beyond doubt. They observed that the infrared spectrum of narcissidine showed many bands in common with methylpseudolycorine (XI) and it also turned yellow in the presence of light and air. Hofmann and Emde degradations under conditions by which lycorine gave anhydro compounds were unsuccessful but like methylpseudolycorine and galanthine, narcissidine was oxidised by selenium dioxide and mercuric acetate but the initial yellow products soon resinified to intractible material. However, O, O-diacetyl-dihydronarcissidine was oxidised by potassium permanganate to a neutral conjugated lactam. This type of reaction is characteristic of alkaloids derived from pyrrolo(de)phenanthridine and does not occur in alkaloids of the 5 : 10b-ethanophenanthridine ring system. Furthermore, upon treatment with sodium and amyl alcohol narcissidine gave pluviine (XIX) and products (XX) and (XXI). Hence it was concluded that narcissidine contains



XX

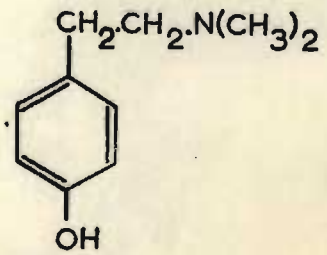


XXI

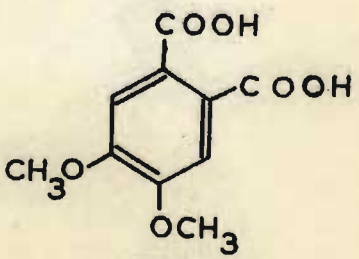


XIX

the 9 : 10-dimethoxypyrrolo(de)phenanthridine nucleus and a hydroxyl group in the 1-position. Since the hydroxyl groups in dihydronarcissidine and therefore narcissidine are vicinal the second hydroxyl group must be in the 2- or 11b-position. The latter position is unlikely since narcissidine is stable towards acid and catalytic hydrogenolysis, and it forms a diacetate with ease. The position of the third methoxyl group is ambiguous since it was shown that aliphatic and aromatic methoxyl groups may be removed with sodium and amyl alcohol. The ultraviolet spectrum is identical with that of methylpseudolycorine (XI) and the difference between the spectra of these alkaloids and that of anhaline (XXII) is quite small. Since narcissidine gave metahemipinic acid (XXIII) on oxidation with potassium permanganate the



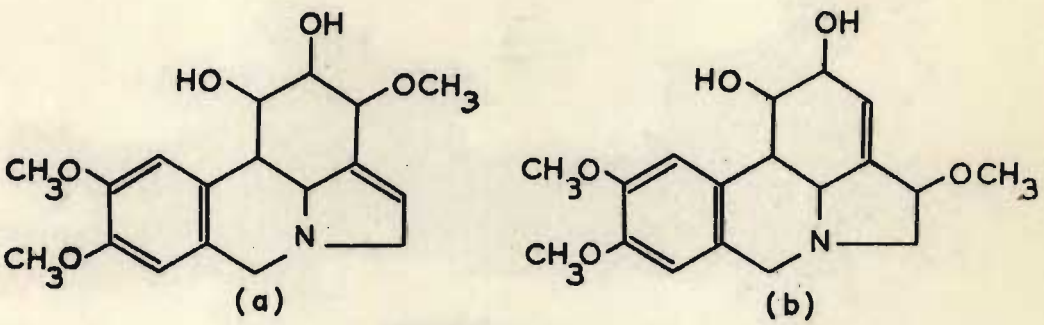
XXII



XXIII

aromatic methoxyl groups are in the 9- and 10- positions. Therefore the two hydroxyl groups and aromatic methoxyl

groups are in the same position as in methylpseudolycorine (XI). Hence the possible structures for narcissidine are (XXIVa) or (XXIVb). The position of the double

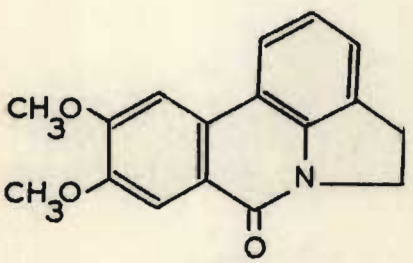


XXIV

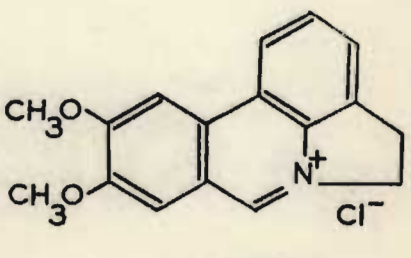
bond and aliphatic methoxyl group were placed by infrared and biogenetic considerations. Further, only structure (XXIVb) could give structures (XIX) and (XX) upon treatment with sodium and amyl alcohol and (XXIVb) would be expected to be stable to dilute acid whereas (XXIVa) would isomerise. Hence structure (XXIVb) was proposed for narcissidine.

Pluviine was studied by Boit, Ehmke, Uyeo and Yajima [7] who found that this base gave metahemipinic acid (XXIII) when oxidised with potassium permanganate. Hence it was suspected that pluviine was a dimethoxy analog of caranine (XV). Openauer oxidation of pluviine gave a red phenol betaine which had an identical ultra-

violet curve with that of caranine betaine and different from the lycorine betaine curve. Following the Japanese workers investigation of lycorine, pluviine was acetylated and the diacetylpluviine separated from the chloroform insoluble material which formed a hydrochloride, $C_{17}H_{16}O_2N.Cl$. This product was identical with anhydro--methylpseudolycorinium chloride. The hydrochloride was oxidised to the known phenanthridone (XXV) which product was also prepared from lycorine by consecutive demethylation and methylation of the methylenedioxy--phenanthridone. Reduction of the phenanthridone (XXV) and subsequent dehydration gave, on treatment with hydrochloric acid, anhydromethylpseudolycorinium chloride (XXVI). From spectral studies the double bond was

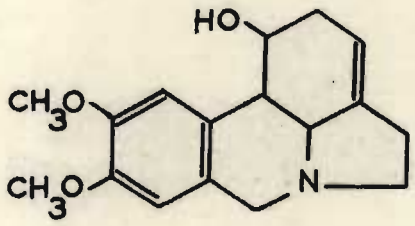


XXV



XXVI

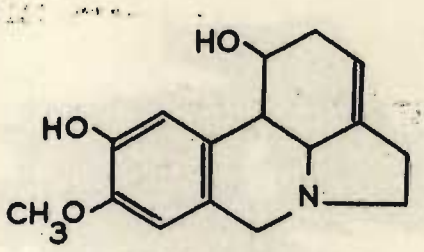
placed in the 3 :3a-position and hence structure (XIX) was proposed for pluviine.



XIX

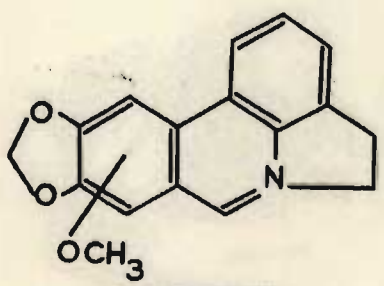
Recently, in the Osaka laboratory, tetrahydromolycorine was transformed to pluviine and a new alkaloid norpluviine was isolated.

Norpluviine, a phenolic alkaloid, with molecular formula $C_{15}H_{16}O_2N.OMe$, was isolated from Lycoris radiata.[61] Diazomethane treatment of this base afforded the non-phenolic pluviine (XIX). The position of the aromatic methoxyl and hydroxyl groups was established by degradation of O-ethyl-norpluviine to the phenanthridone (XII) which was previously isolated from pseudolycorine and synthesised. Hence the structure for norpluviine may be represented by (XXVII).

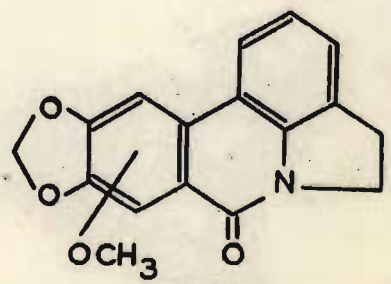


XXVII

Falcatine, $C_{17}H_{19}O_4N$, was isolated by Wildman and Kaufman [72] who noted that it was isomeric with powelline. Further studies [21] showed that the alkaloid possessed one hydroxyl group and a double bond. The aromatic ring contains both a methylenedioxy and a methoxyl group. Degradative studies, however, showed that falcatine had a different basic skeleton to powelline. Oxidation with selenium dioxide afforded a phenanthridinium nitrate (XXVIII) which was oxidised to the phenanthridone (XXIX). Analytical data and spectral comparisons of (XXVIII) and (XXIX) with

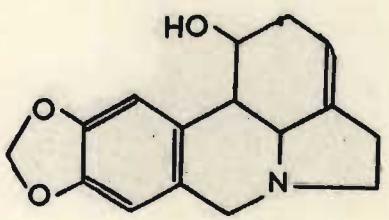


XXVIII



XXIX

compounds of analogous structure derived from lycorine [72] methylpseudolycorine [23] supported the assignment of the pyrrolo(de)phenanthridine system to falcatine. Due to similar infrared spectra, comparable rotations and occurrence in N. falcata and N. lacticoma, Wildman postulated that falcatine was ar-methoxycaranine. This postulation was supported by the fact that both alkaloids decomposed in light and air and both did not react with manganese dioxide. Hence falcatine (XXX) was treated with sodium and isoamyl alcohol and caranine (XV) was isolated. This experiment is convincing evidence that falcatine is ar-methoxycaranine.

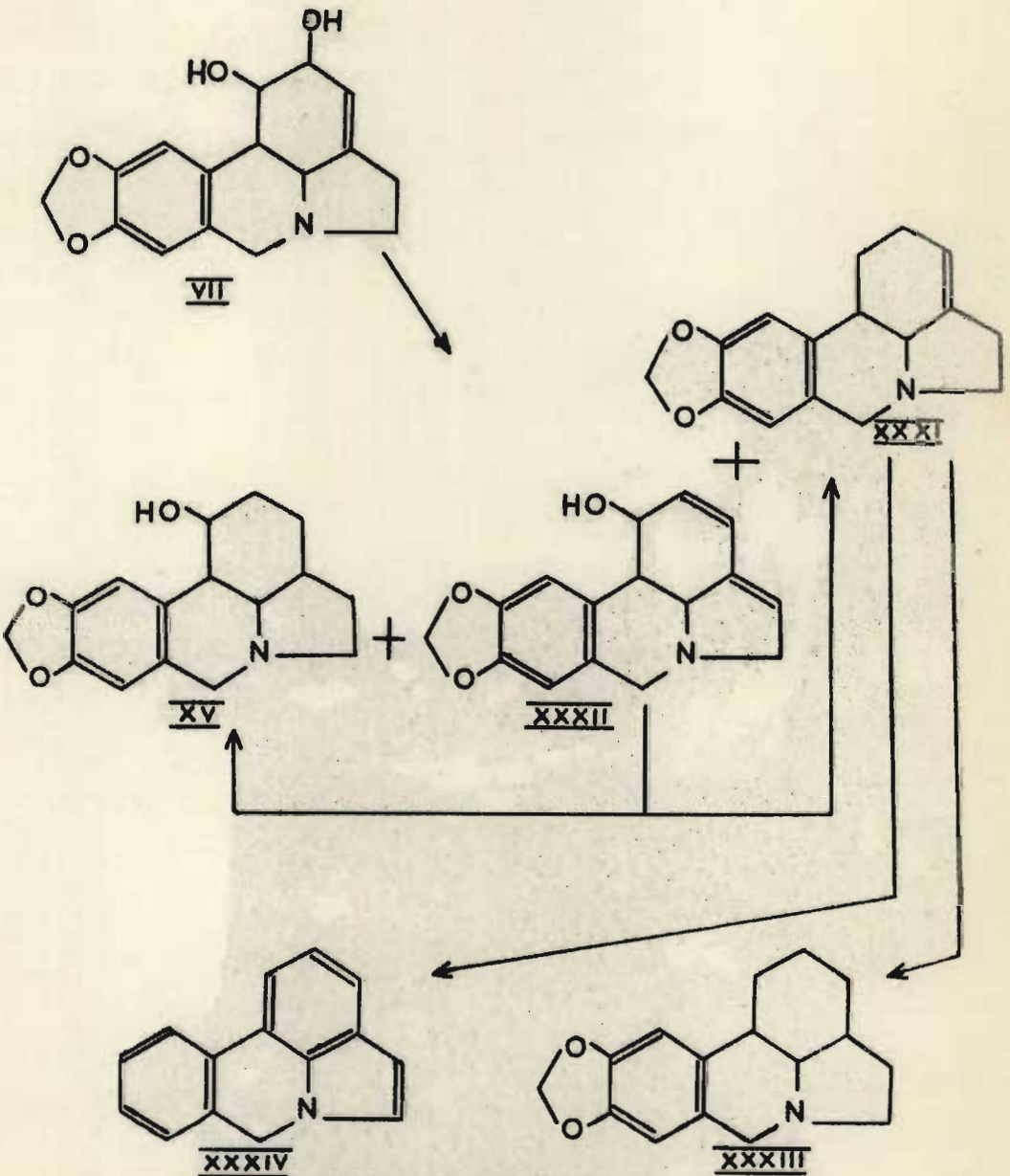


XXX

In studying the scope of the sodium and amyl alcohol reaction Wildman [21] converted lycorine (VII) and its O,O-diacetyl derivative to caranine (XV), lycorene (XXXI) and dehydrolycorine (XXXII). Catalytic reduction of lycorene (XXXI) gave the saturated basic ring system,

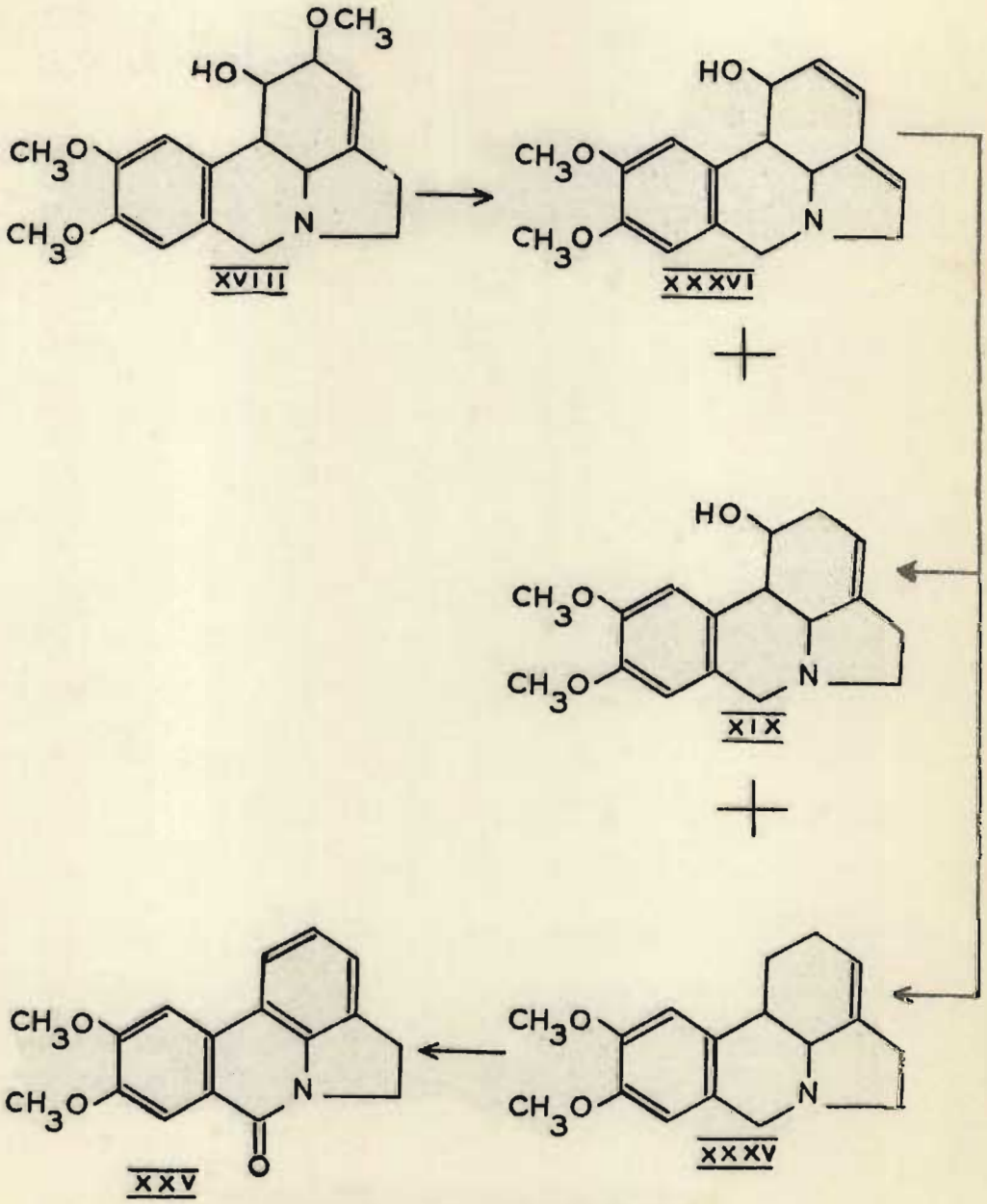
lycorane (XXXIII), and lycorene was readily dehydrogenated to the indole (XXXIV). Furthermore a solution of dehydrolycorine in n amyl alcohol gave caranine (XV) and lycorene (XXXI) (see Chart 3). A similar series of reactions on galanthine (XVIII) gave pluviine (XIX), methylpseudolycorene (XXXV) and dehydromethylpseudolycorene (XXXVI). The known phenanthridone (XXV) was obtained when methylpseudolycorene was heated above its melting point in air (see Chart 4).

— CHART 3 —



REACTIONS OF LYCORINE

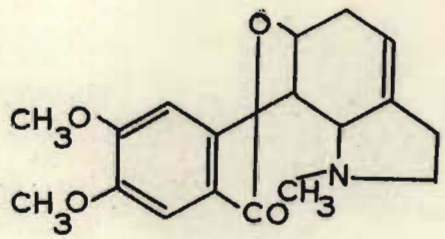
— CHART 4 —



REACTIONS OF GALANTHINE

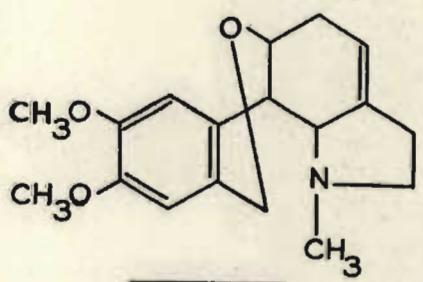
THE LACTONE OR SEMIACETAL GROUP OF ALKALOIDS.— The varying oxygenation observed in this group is exactly similar to that found in the previous group already described, namely (i) dimethoxy in place of methylenedioxy group, together with a possible further methoxylation in the aromatic ring, (ii) hydroxylation or methoxylation in ring C, and (iii) lactone or semiacetal grouping replace ring B of the previously considered structure. (Chart 5).

Homolycorine was isolated twenty five years ago by Kondo and Tomimura.[39] Recently Boit[8] corrected the formula to $C_{18}H_{21}O_4N$, which was confirmed by the Japanese workers.[36] The latter authors found that homolycorine was insoluble in cold sodium carbonate or sodium hydroxide but dissolved in hot sodium hydroxide to yield a salt which could not be extracted from aqueous solution with organic solvents. After acidification homolycorine was isolated as its hydrochloride in quantitative yield. In order to explain this they proposed that two oxygen atoms were present in a lactone. This proposition found support from ultraviolet and infrared determinations which indicated a δ-lactone system. Hence structure (XXXVII) was proposed for homolycorine.



XXXVII

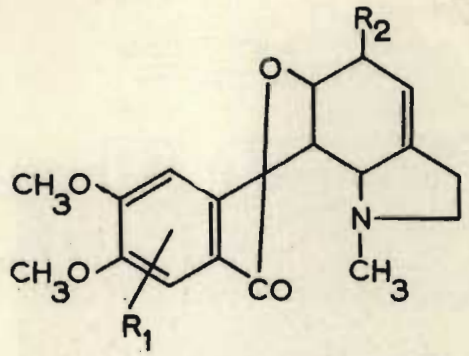
Lycorenine,[40,41,42,43] $C_{18}H_{23}O_4N$, was reduced electrolytically to desoxylycorenine (XXXVIII) by Kondo and Ikeda.[40] This cyclic ether was identical to the



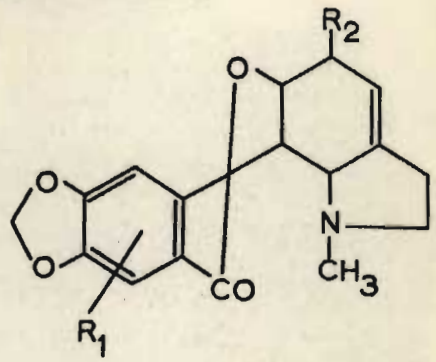
XXXVIII

product obtained from tetrahydrohomolycorine (XXXIX) by recyclisation with acid. Tetrahydrohomolycorine (XXXIX) was obtained as the lithium aluminium hydride reduction product of homolycorine (XXXVII). Further experiments

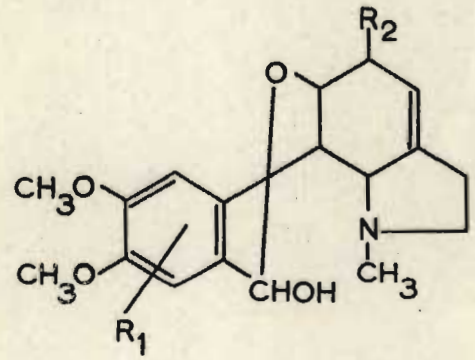
— CHART 5 —



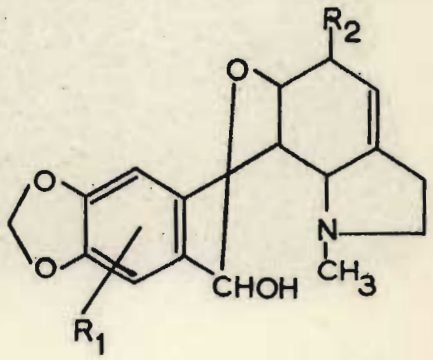
	R_1	R_2
XXXVII Homolycorine	H	H
LIII Albomaculine	OMe	H*
LXI Urminine	OMe	H*



	R_1	R_2
LV Clivonine (no at 3a-4)	H	OH*
Hippeastrine	H	OH
LVI Nivaline	H	OMe
XLI Neronine	OMe	OH



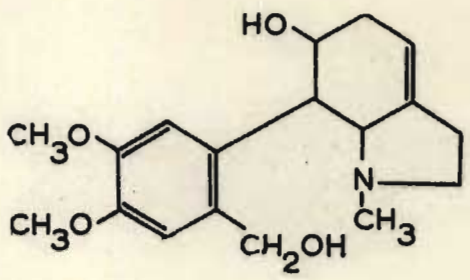
	R_1	R_2
XL Lycorenine	H	H
LVII Nerinine	OMe	H*
LX Urceoline	OMe	H*



	R_1	R_2
XLVIII Krigeine	OMe	OH

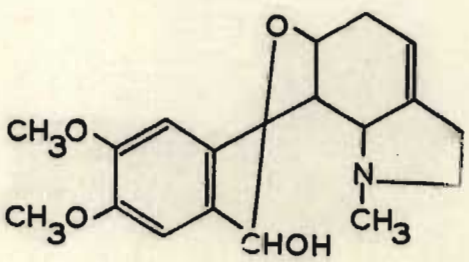
[* indicates stereoisomers]

THE LACTONE AND SEMIACETAL GROUP OF ALKALOIDS



XXXIX

showed a close relation between these alkaloids. Lithium aluminium hydride reduction of lycorenine gave tetrahydro--homolycorine (XXXIX) and although lycorenine was stable to potassium ferricyanide oxidation, it readily oxidised with chromic acid to homolycorine (XXXVII). Furthermore, when lycorenine was treated with hot alcoholic potassium hydroxide it underwent disproportionation to homolycorine and tetrahydrohomolycorine. Hence lycorenine has a cyclic hemiacetal structure (XL). The last experiment, however,

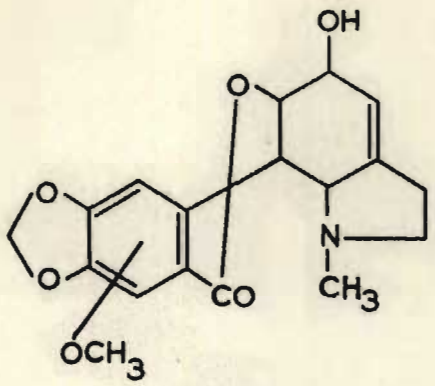


XL

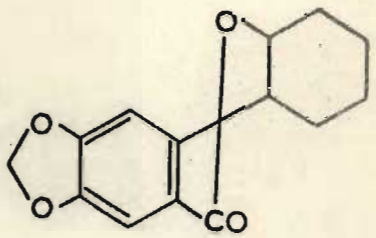
suggested that homolycorine could be produced from lycorenine during the isolation procedure.

The American group [17] extracted a series of plants and isolated five new alkaloids, four of which contained the lactone group and were thus related to homolycorine. The fifth new base was named Krigeine and contained a hemiacetal group which could readily be oxidised to a lactone. The facile identification of the lactone groups in these alkaloids was accomplished by spectrographic and chemical means. The presence of a lactone rather than an ester function in the readily abundant albomaculine, clivonine and neronine was demonstrated by their ready solution in warm alkali and relactonisation upon acidification, and the hydrochlorides of the bases were extracted into chloroform. Similar solubility of homolycorine was reported by Kitagawa, Taylor, Uyeo and Yajima.[36]

Neronine showed a maxima at 228 mμ (log ε 4.41) and 285 mμ (log ε 3.85) and a shoulder at 310 mμ (log ε 3.55). The first two bands are good evidence for the lactone structure proposed in (XLI). The absence of a distinct maximum near 305 mμ and the shifted wavelength of the 285 mμ band differentiate neronine from the possible spectral model (XLII). The spectral model shows three distinct maxima



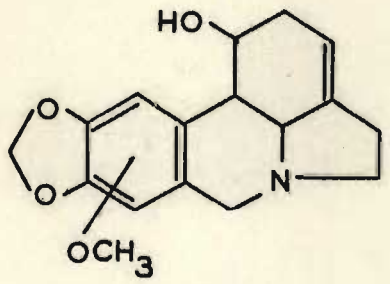
XLI



XLII

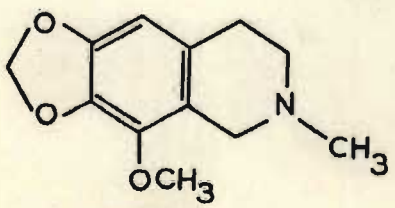
at 225 mμ (log ε 4.39), 263 mμ (log ε 3.72) and 307 mμ (log ε 3.73). These studies together with the infrared spectral analysis allowed the assignment of the methoxyl group to the 8-position of the aromatic ring.

If neronine has the homolycorine ring system only the double bond and the hydroxyl group remain to be located. From the chemical and spectral properties of neronine and its derivatives it may not be formulated as either an aldehyde-ammonia or an enol. Reduction of neronine with lithium aluminium hydride gave tetrahydroneronine which showed no carbonyl absorption in the infrared spectrum and the ultraviolet absorption curve was similar to that of falcatine (XXX), ambelline (XLIII) and hydrocotarnine (XLIV). This spectral relation in conjunction with the strong absorption at 6.2 μ, affords more evidence that the aromatic

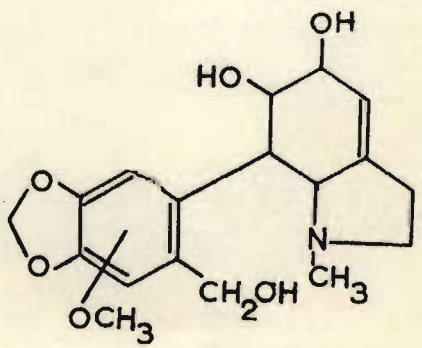


XXX

ring is substituted with both the methylenedioxy and methoxy groups. A qualitative test showed the presence of a vicinal glycol function in tetrahydroneronine and this was confirmed by the quantitative method of Siggia.[57] Hence tetrahydroneronine may be represented by structure (XLV). The alternate 6 : 7-dihydroxy structure is excluded from considerations of acetylation and oxidation experiments on the parent alkaloid.



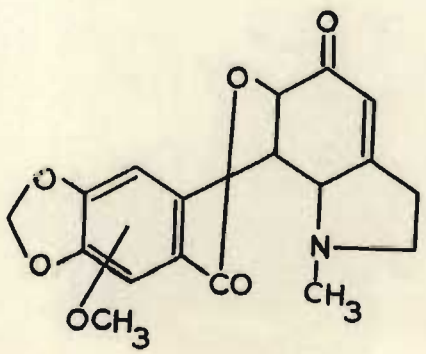
XLIV



XLV

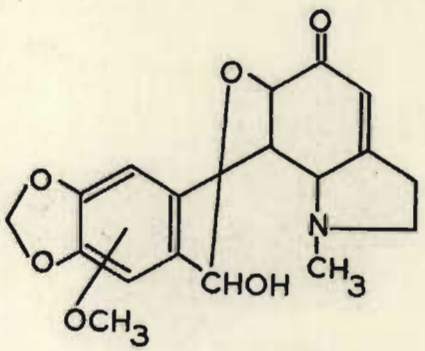
A manganese dioxide oxidation of neronine gave a compound, $C_{18}H_{17}O_6N$, which was found to contain no hydroxyl group and an absorption at 5.95 μ appeared. Further evidence for the α,β-unsaturated function in oxoneronine (XLVI) was found in its ultraviolet spectrum. The difference between the extinction coefficient of oxoneronine and neronine showed a maximum of 10800 at 245 mμ. Hence these considerations place the hydroxyl group in the 5-position and the double bond at 3a : 4-position.

Krigeine, $C_{18}H_{21}O_6N$, was disproportionated by an alkaline column of alumina to neronine (XLI) and tetrahydroneronine (XLV). A similar conversion of lycorenine (XL) occurred, the products being homolycorine (XXXVII) and tetrahydrolycorine. The ultraviolet absorption curve for krigeine showed a broad maximum of low intensity similar to that found for tetrahydroneronine (XLV), falcatine (XXX) and ambelline. Since it seemed possible that krigeine



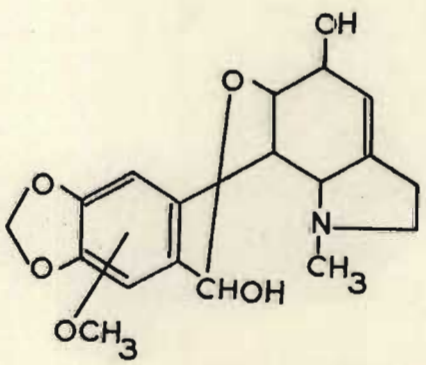
XLVI

was a hemiacetal type of dihydroneronine, Wildman et al. oxidised it with manganese dioxide and isolated oxoneronine (XLVI) which was previously obtained from neronine (XLI). This reaction oxidised first the allylic hydroxyl group to give compound (XLVII) and then the benzylic hydroxyl group



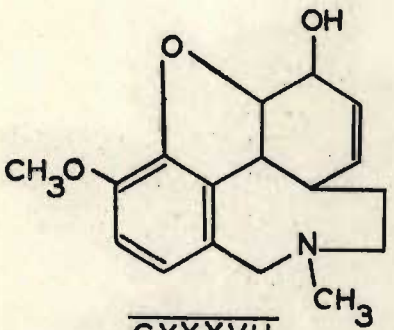
XLVII

to give oxoneronine (XLVI). Hence krigeine may be represented as structure (XLVIII).

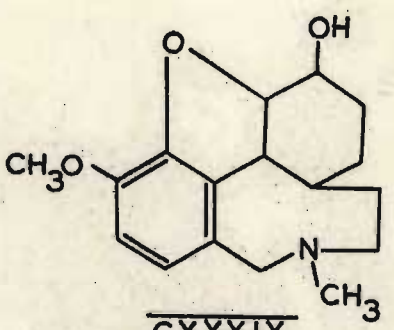


XLVIII

Albomaculine, $C_{19}H_{23}O_5N$, has three methoxyl groups two of which are placed on the aromatic ring since its infrared spectrum shows a strong band at 6.28 μ in contrast to the monomethoxyl aromatic substituted alkaloids of this family viz. galanthamine (CXXXVII) and lycoramine (CXXXIX) and their derivatives which invariably show a doublet near 6.15 and 6.27 μ. The third methoxyl group was also placed

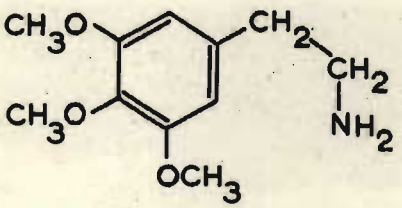


CXXXVII

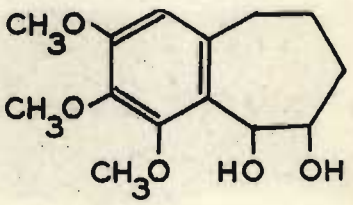


CXXXIX

on the aromatic ring since the ultraviolet spectrum of albomaculine was not similar to that of homolycorine (XXVII). Furthermore, the ultraviolet spectrum of tetrahydro--albomaculine resembled the curves of mescaline (LI) and 2 : 3 : 4-trimethoxybenzsuberane-5 : 6-diol (LII) and was dissimilar to the curve obtained for lycorenine (XL) or its dihydrodesoxy derivatives. Wildman does however recognise that this argument does not exclude the alternate 9,10,11 arrangement of the three methoxyl groups. Hence, if the

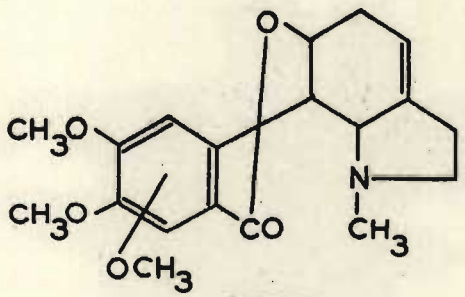


LI



LII

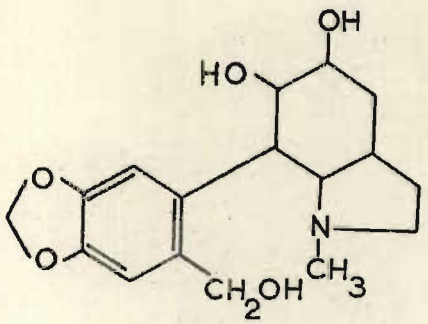
basic ring system of homolycorine is considered to be present in albomaculine then it may be represented as (LIII).



LIII

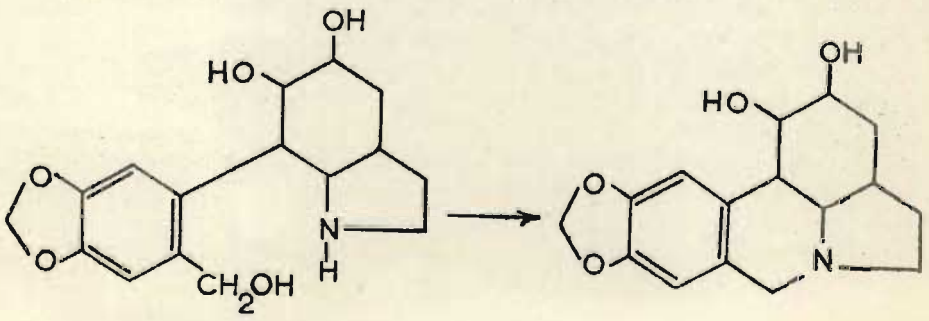
Clivonine, $C_{17}H_{19}O_5N$, has no methoxyl groups and the methylenedioxy function is placed in the 9-10 position since its ultraviolet absorption curve is nearly identical with that of the spectral model (XLII). Catalytic hydrogenation of clivonine with either palladium or platinum as catalysts failed but the base was reduced with lithium

aluminium hydride to tetrahydroclivonine (LIV). Tetrahydroclivonine shows no carbonyl absorption in the



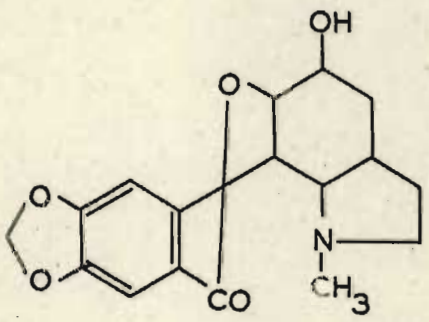
LIV

infrared and the vicinal glycol was confirmed by periodic acid titration. By analogy with neronine (XLI) and krigeine (XLVIII) the hydroxyl groups were placed in the 5- and 6- positions. It is of interest to note that the dihydroxy system of tetrahydroclivonine (LIV) would relate clivonine to dihydrolycorine for dihydrolycorine would result from a hypothetical ring closure involving the benzylic hydroxyl group and the N-H of nor-clivonine (LIVb). Hence structure (LV) was proposed for clivonine

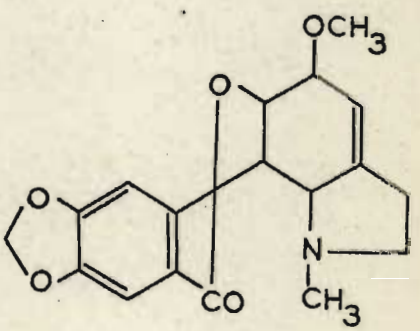


LIV b

Nivaline, $C_{18}H_{19}O_5N$, has been obtained in low yield and since its ultraviolet spectrum could almost be superimposed on that of clivonine it is likely that the methoxyl group is on position 3 or 5 or 11(b). Wildman favours the 5-position since this position is oxygenated in krigeine (XLVIII), neronine (XLI) and clivonine (LV). Hence structure (LVI) was proposed for this base but as yet nothing has been conclusively proved.



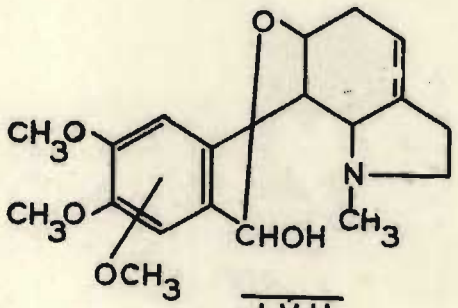
LV



LVI

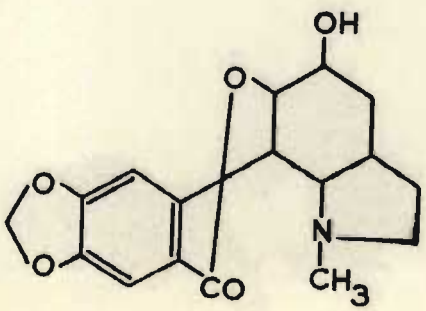
Nerinine, $C_{15}H_{12}O(OH)(OCH_3)_3(NCH_3)$ was plausibly suggested to be methoxylycorenine by Boit [13] since both alkaloids gave intense yellow colourations with mineral acids and furthermore both bases gave lactones when oxidised with chromic acid. Briggs, Highnet, Highnet and Wildman[17] proposed structure (LIII) for albomaculine and suggested it was related to nerinine in the same manner as homolycorine (XXXVII) was related to lycorenine (XL). Support for this

suggestion was found by comparison of molecular rotational differences. Boit [29] oxidised nerinine and identified the product with albomaculine (LIII). Hence the semiacetal structure (LVII) was proposed for nerinine.



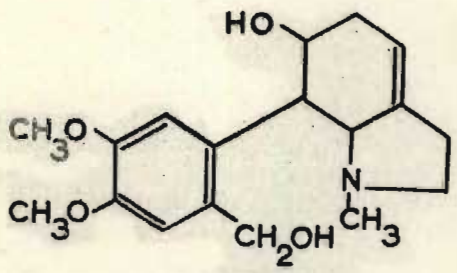
LVII

Hippeastrine, $C_{17}H_{17}O_5N$, was compared with clivonine (LV) by the American workers [17] since it was suggested that the only difference was the presence of a double bond in hippeastrine. Hydrogenation of hippeastrine, however, afforded a dihydro base (LVIII) which was similar but not identical with clivonine (LV). Boit [9] suggested that dihydrohippeastrine was possibly a diastereoisomer of clivonine.

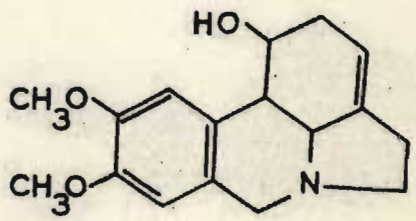


LVIII

Demethylhomolycorine, $C_{17}H_{19}O_4N$, a phenolic alkaloid recently isolated by the Osaka group [61] was converted to homolycorine (XXXVII) by methylation. In order to establish the positions of the aromatic methoxyl and hydroxyl groups, demethylhomolycorine was ethylated and reduced with lithium aluminium hydride. The diol product was treated with p-toluenesulphonyl chloride and the product processed in the manner used for the conversion of tetrahydrohomo--lycorine (XXXIX) into pluviine (XIX).[37] Distillation in

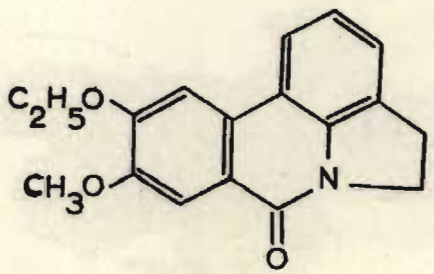


XXXIX



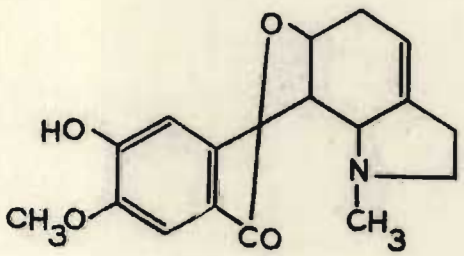
XIX

vacuo of the crude methochloride and purification of the



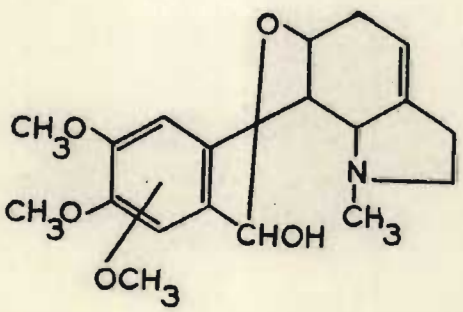
XII

distillate did not give, as expected, ethylnorpluviine but the only isolable product being the phenanthridone (XII). Hence the structure of demethylhomolycorine may be represented by (LIX).

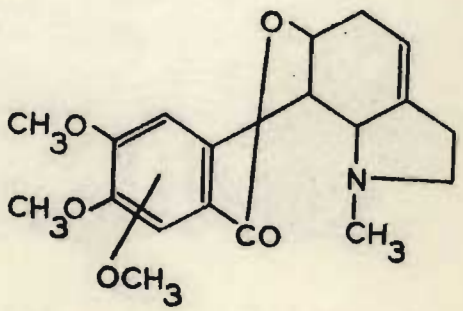


LIX

Recently Boit [5] proposed that Urceoline (LX) and Urminine (LXI) are stereoisomers of nerinine (LVII) and albomaculine (LIII) respectively.

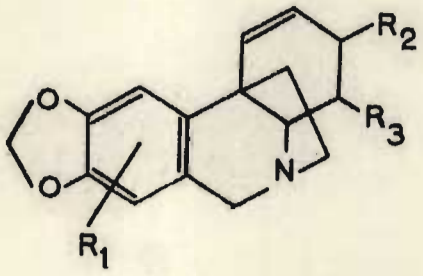


LX

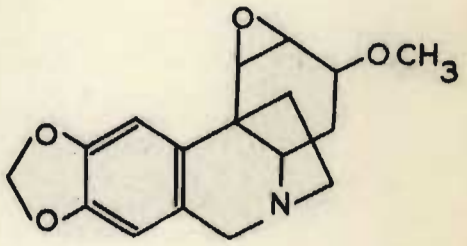


LXI

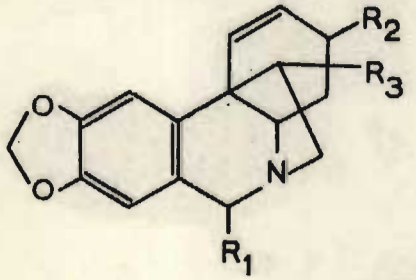
— CHART 6 —



		R_1	R_2	R_3
LXXII	Crinine	H	OH	H
CXIX	Vittatine	H	OH	H
LXXXV	Buphanisine	H	OCH_3	H
XCIV	Crinamidine	H	OH	OH
LXXXI	Powelline	OCH_3	OH	H
LXXXIV	Buphanidrine	OCH_3	OCH_3	H



LXXXVI Undulatine

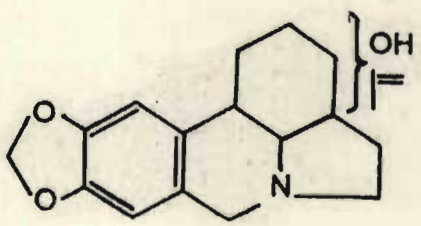


		R_1	R_2	R_3
CXV	Haemultine	H	H	OH
XCVI	Haemanthamine	H	OMe	OH
CVIII	Crinamine	H	OMe	OH
CXI	Haemanthidine	OH	OMe	OH

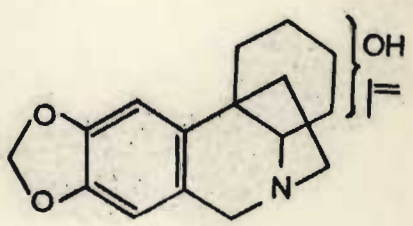
THE 5:10b-ETHANOPHENANTHRIDINE ALKALOIDS

THE 5 : 10b-ETHANOPHENANTHRIDINE ALKALOIDS.—— The different alkaloids of the 5 : 10b-ethanophenanthridine group are, as in the previous groups, variations of aliphatic and aromatic substitution, and in addition optical antipodes and possibly diastereoisomeric forms are encountered.

Crinine is a structural isomer of caranine $C_{16}H_{17}O_3N$, and hence could be depicted as (LXII) or (LXIII). Wildman,[70] however, found that the reactions, which were



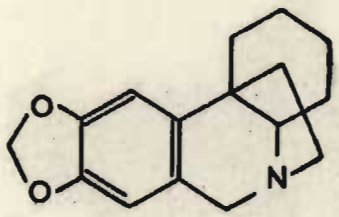
LXII



LXIII

invaluable for the characterisation of many alkaloids in the pyrrolo(de)phenanthridine group were negative when applied to crinine. The structure of crinine thus had an inherent factor which prevented aromatisation of ring C and the obvious conclusion was a spiro-ring system as in (LXIII). This ring system was suggested by Robinson [58] for lycorine on biogenetic grounds. In order to test this hypothesis crinine was degraded to an unsubstituted ring C product,

crinane (LXIV), and compared with a synthetic specimen.

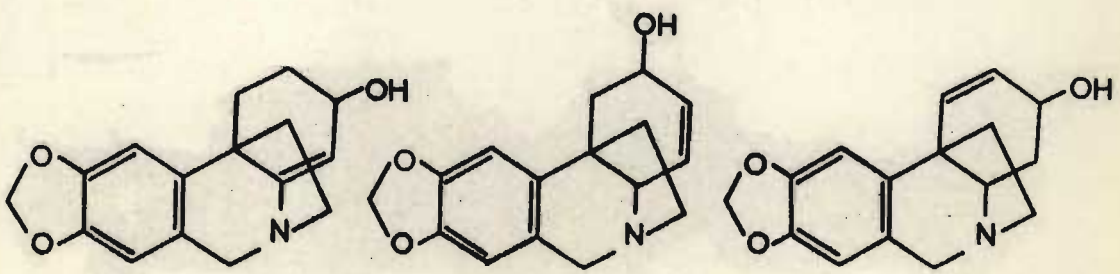


LXIV

This degradation was accomplished by oxidising the allylic hydroxyl group to a ketone by the selective oxidising agent manganese dioxide and then reducing the double bond catalytically. The carbonyl oxygen was replaced by two hydrogen atoms in a modified Wolff-Kishner reduction and the product Crinane was obtained. The starting product (LXV) for the synthesis was obtained from 4-(3,4-methylenedioxyphenyl)-5-nitrocyclohexene by the Nef reaction. In the presence of acrylonitrite and Triton B catalyst, (LXV) afforded a monocyanoethyl derivative which could be assigned structure (LXVI). Methanolysis of this product gave the corresponding methyl ester (LXVII) which was converted to the hydrazone hydrazide on refluxing with 80% hydrazine hydrate. The action of nitrous acid on the hydrazone hydrazide gave 2,3,4,5,6,7-hexahydro-3a-(3,4-methylenedioxyphenyl)-indole (LXVIII). Catalytic

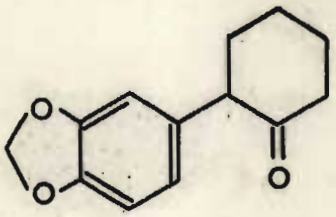
hydrogenation of (LXVIII) gave an octahydra-indole (LXIX) which was cyclicised in good yield to (LXIV) by the Pictet-Spengler method (Chart 7).

The infrared spectrum of synthetic (LXIV) and (-)-crinane obtained by the Wolff-Kishner reduction of dihydro-oxocrinine were identical. Also the infrared spectra of their respective picrates in chloroform solution were superimposable. Furthermore, the subsequent preparation of lycorane by Fales and Wildman and Takeda [59] et al. and its non identity with (-)-crinane may be considered as additional evidence that crinine has the ethano-5 : 10b-phenanthridine type of skeleton. With the basic ring system of crinine three possible structures, (LXX), (LXXI) and (LXXII) are compatible with the require--ments that the double bond and hydroxyl group are allylic and the carbon atoms adjacent to the hydroxyl group are unsubstituted. Hofmann degradation of crinenone (LXXIII)

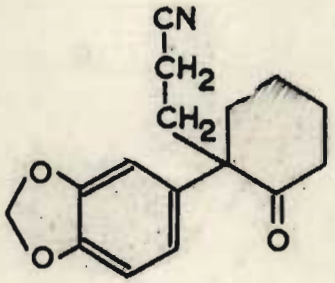


LXX LXXI LXXII

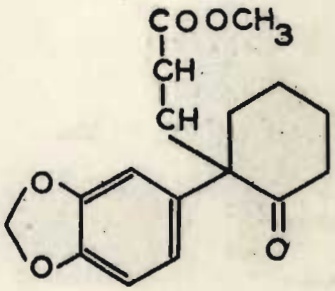
— CHART 7 —



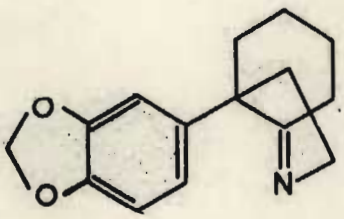
LXV



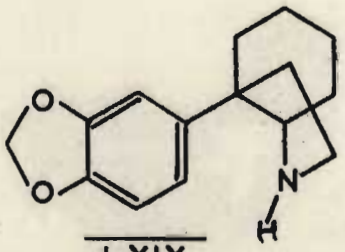
LXVI



LXVII



LXVIII



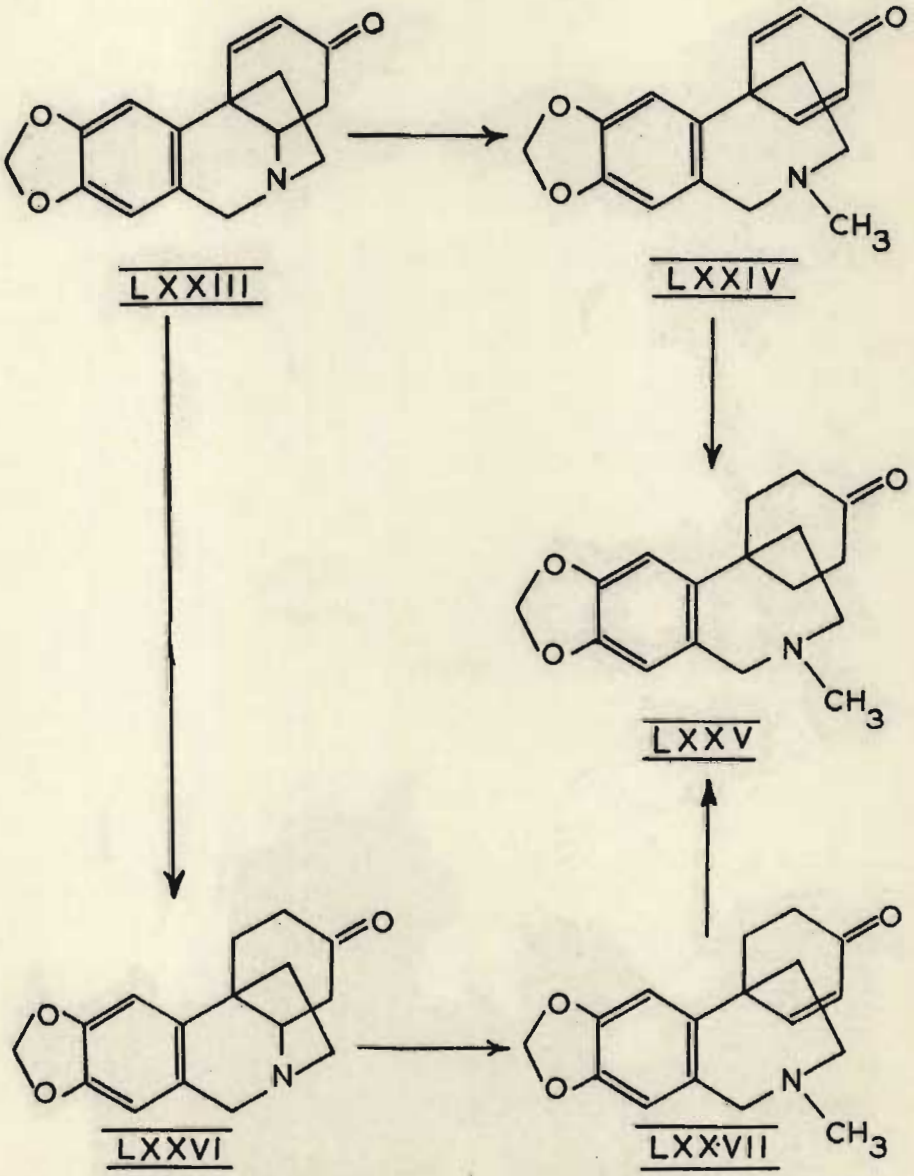
LXIX

THE SYNTHESIS OF CRINANE

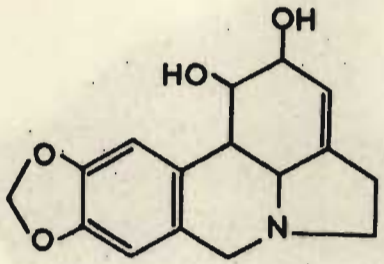
gave a methine (LXXIV) which absorbed two equivalents of hydrogen to give an optically inactive dihydrocrinanone methine (LXXV). Similarly, crinanone (LXXVI) gave a methine (LXXVII) which absorbed one equivalent of hydrogen to give the same optically inactive methine (LXXV) (Chart 8). Hence structures (LXX) and (LXXI) were eliminated and (LXXII) was proposed for crinine.

Powelline and crinine possess very similar infrared spectra and differ mainly in the bands which can be attributed to the methylenedioxy and methoxyl substituents on the benzene ring in powelline. Supplementary evidence about the differences was obtained from ultraviolet spectral comparisons. The curve of crinine resembles that of lycorine (VII) but the powelline curve resembles more closely that of hydrocotarnine (XLIV). However, the similarity in the basic skeleton of crinine and powelline was corroborated by chemical evidence in that powellenone, powellanone, epipowelline, dihydroepipowelline, and (+)-powellane were prepared in yields comparable with those of the crinine series. Furthermore this basic skeletal similarity hypothesis was enhanced by excellent molecular rotational differences at 589 mμ. Since the difference between powelline and crinine (LXXII) seems to be the aromatic methoxyl substituent in powelline, it was treated with

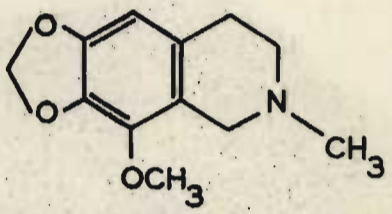
— CHART 8 —



HOFMANN DEGRADATION OF CRINENONE AND CRINANONE

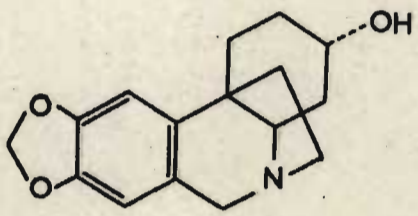


VII

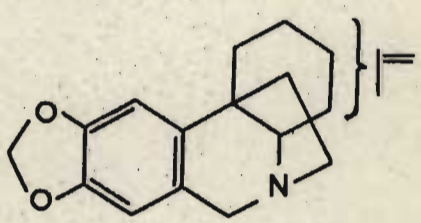


XLIV

sodium and amyl alcohol. The crude reaction mixture had a weak band at 6.2 μ in the infrared spectrum but no crinine was isolated. The most strongly adsorbed substance was identified as dihydroepicrinine (LXXVIII) and preceding this material, two isomeric non-crystalline substances, $C_{16}H_{17}O_2N$ (LXXIX), were eluted. Each of these isomers gave



LXXVIII



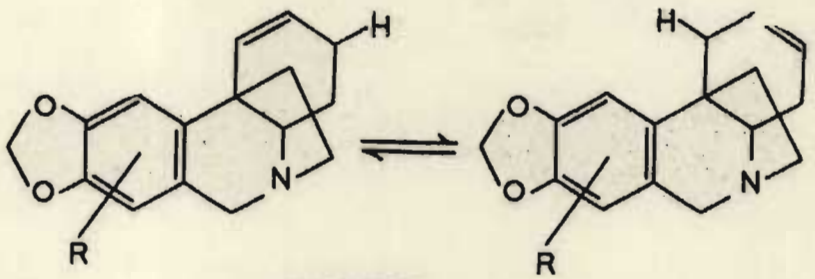
LXXIX

(a) α-isomer

(b) β-isomer

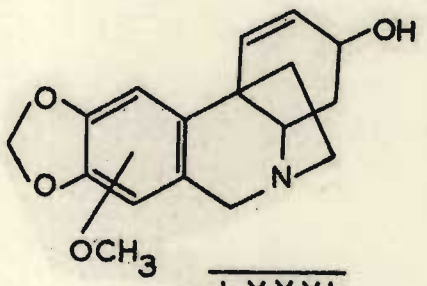
(-)-crinane upon absorption of one equivalent of hydrogen under catalytic conditions. The nature of these products

is chemical evidence that (i) powelline is derived from the 5 : 10b-ethanophenanthridine ring system of crinine, (ii) the methylenedioxy group is attached to the 8 : 9-position as in crinine, and (iii) the hydroxyl group of powelline is in the same position as in crinine. The isomeric desoxycrinines (LXXIX(a) and (b)) may be derived from the hydrogenolysis of the allylic 3-OH group. The formation of the intermediate radical (LXXX, R = OCH_3 or H)



LXXX

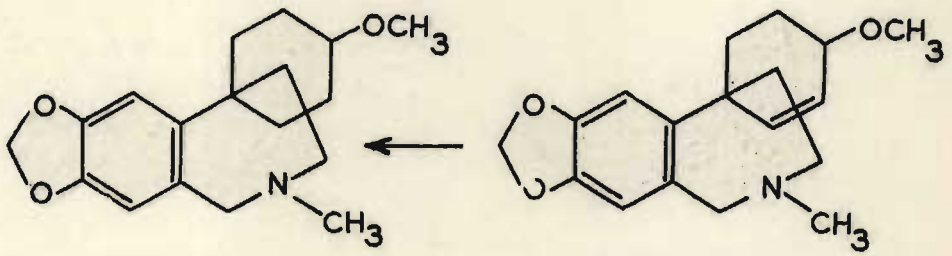
followed by reduction of the resonance hybrid would explain the formation of two isomers. However, dihydroepipowelline on treatment with sodium and isoamyl alcohol gave dihydroepicrinine (this supports the mechanism proposed for the formation of the desoxycrinines) and the position of the hydroxyl group in powelline was established beyond doubt when it was observed that oxopowelline methine as well as the tetrahydro- derivative were optically inactive. Hence structure (LXXXI) was proposed for powelline.



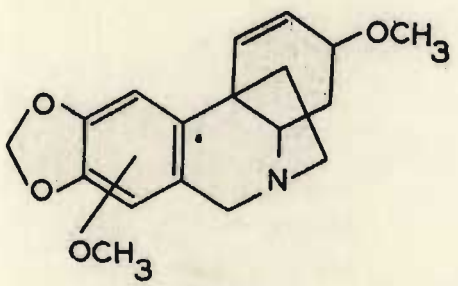
LXXXI

Buphanidrine was first isolated by Rens et al.[56] who established the formula $C_{18}H_{21}O_4N$. The ultraviolet spectrum of this base is very similar to hydrocotarnine (XLIV) and hence it was assumed the molecule had a methylene--dioxy and a methoxyl group substituted on the benzene ring. The constitution of this base was readily shown since hydrochloric acid hydrolysis [70] removed the methyl from the aliphatic methoxyl group and the product was found to be powelline (LXXXI)

The possibility that the hydrolysis was accompanied by allylic rearrangement has been minimised by the discovery that the dihydro derivative (LXXXII) of dihydrobuphanidrine methine (LXXXIII) was optically inactive. Hence buphanidrine is methoxypowelline and has structure (LXXXIV).



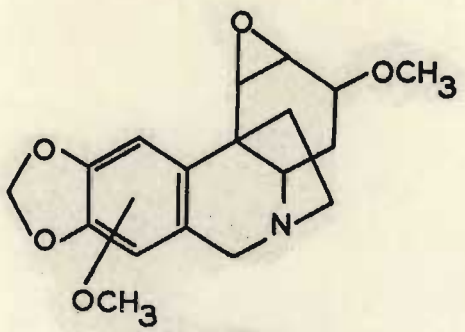
LXXXII LXXXIII



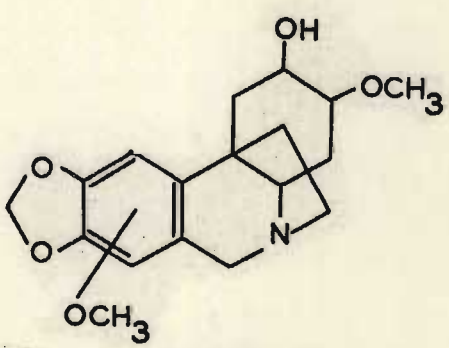
LXXXIV

Buphanisine, $C_{17}H_{19}O_4N$, a companion alkaloid of buphanidrine, in B. fischeri,[60] was isolated from the sodium isoamyl alcohol reaction mixture of buphanidrine. Hence the de-Ar-methoxybuphanidrine structure (LXXXV) was proposed for buphanisine. Further evidence for the structure of buphanidrine (LXXXIV) and buphanisine (LXXXV) was obtained from the hydrochloric acid hydrolysis of buphanisine which gave crinine (LXXII) as product.

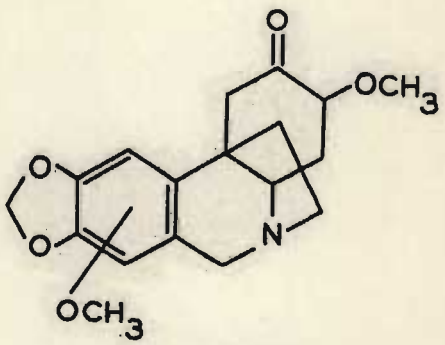
Undulatine, $C_{18}H_{21}O_5N$, was shown [71] to have structure (LXXXVI) since the epoxide ring could be opened with lithium aluminium hydride to give α-dihydroundulatine (LXXXVII) which was oxidised to the ketone (LXXXVIII) which had the



LXXXVI

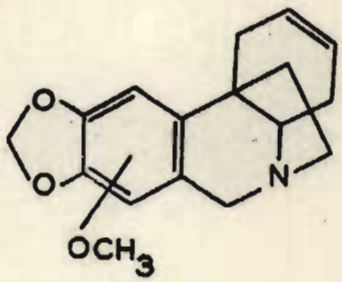


LXXXVII

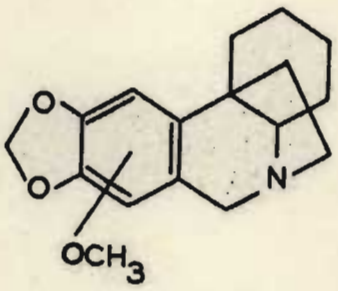


LXXXVIII

α-configuration for the methoxyl group. The β-methoxyl ketone formed when the α-isomer was treated with alkali and it was reduced by the Wolff-Kishner reaction to give Δ^2 powellene (LXXXIX). Δ^2-Powellene was catalytically reduced to (+)-powellane (XC). Furthermore, the mesylate

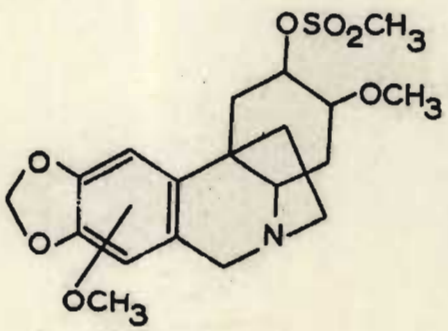


LXXXIX

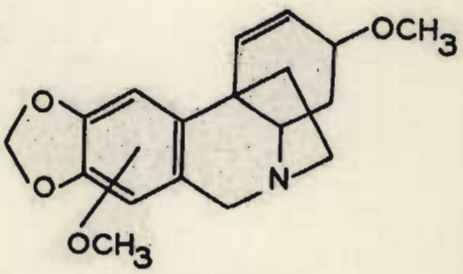


XC

of α-dihydroundulatine (XCI) upon treatment with potassium tert-amyl alcohol gave an almost quantitative yield of buphanidrine (LXXXIV).



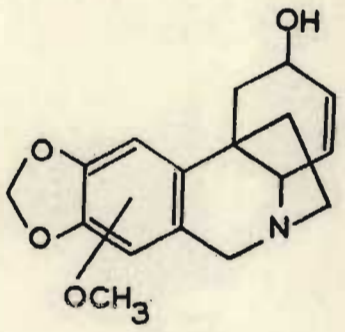
XCI



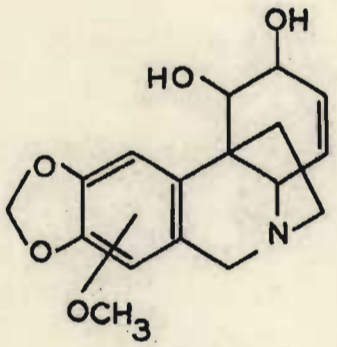
LXXXIV

Crinamidine was first isolated by Boit who studied it further.[16] The base formed mono and diacetyl derivatives, hence the formula was expanded to $C_{15}H_{12}(OH)_2(OCH_3)(O_2CH_2)(\equiv N)$. Since the infrared spectrum was similar to that of powelline, which was thought to have structure (XCII), structure (XCIII)

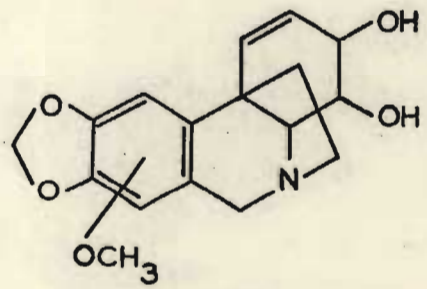
was proposed for crinamidine. In the light of recent work which established the structure (LXXXI) for powelline, crinamidine would more likely have structure (XCIV).



XCII



XCIII



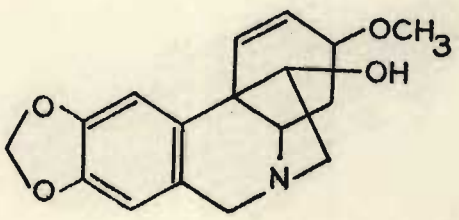
XCIV

Haemanthamine (Natalensine), $C_{17}H_{19}O_4N$, did not contain an allylic hydroxyl group or belong to the pyrro(de)phenan--thridine group since it was not oxidised by either manganese dioxide or selenium dioxide. Dilute hydrochloric acid converted haemanthamine to the demethoxy ether, apohaemanthamine (XCV) which was reduced catalytically to

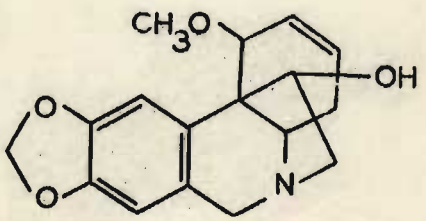
dihydroapohaemanthamine. From this reaction it was concluded that the methoxyl group was not on the benzene ring, which conclusion found support from spectral analysis. Haemanthamine (XCVI) and its dihydro derivative (XCVII) were oxidised to their respective five ring ketones (XCVIII) and (XCIX). Sodium borohydride reduction of the ketone (XCVIII) derived from haemanthamine, afforded the epimeric alcohol (C) and the C ring of the ketone (XCVIII) was aromatised upon treatment with potassium tertiary butoxide to give N-(6-phenylpiperonyl)-glycine (CI) which was synthesised from ethylglycinate and 6-phenylpiperonaldehyde. Methylation of N-(6-phenylpiperonyl)-glycine with formaldehyde and formic acid gave the N-methyl base (CVII) which was also obtained from the ketone (XCVIII), by Hofmann degradation. Analogous to the transformation of tazettine [49] tazettine methiodide [71,29,40] and dihydro--tazettine methiodide [71,29] to 6-phenylpiperonyl alcohol, N : N-dimethyl-6-phenylpiperonylglycinate and compound (CII) respectively, the methiodide of (XCIX) was degraded by alkali to (CIII). The structure of (CIII) was proved by catalytic hydrogenation and hydrogenolysis to (CIV) which was also obtained from dihydrotazettine methine (CII) under similar conditions. The isolation of compound (CIV) from these two sources and the formation of the methine (CIII)

and (CII) indicates identical stereochemistry of ring C in tazettine (CV) and haemanthamine (XCVI) (Chart 9).

Crinamine, $C_{17}H_{19}O_4N$, is isomeric with haemanthamine and possesses the same expanded formula.[47] Since crinamine is also converted to apohaemanthamine (XCV) by acid and is not identical with the epimer of haemanthamine (C) it may be postulated as either the 3 methoxy epimer (CVIII) or the 1-methoxy-Δ^2-allylic isomer (CIX) of haemanthamine.



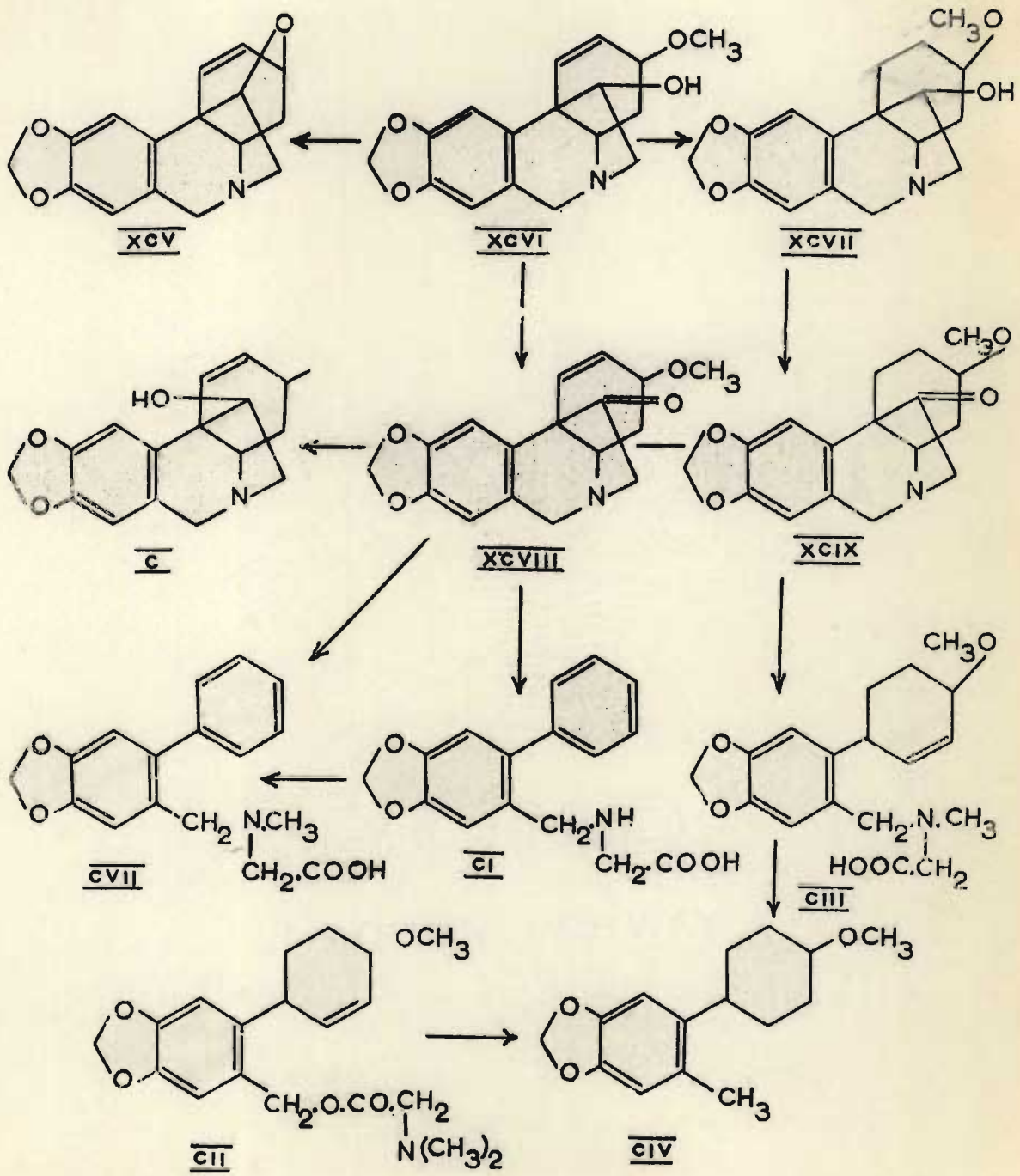
CVIII

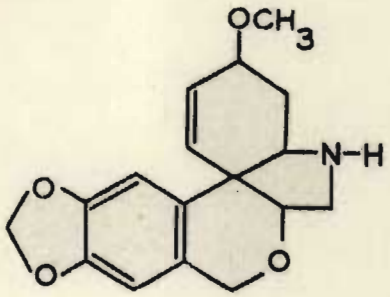


CIX

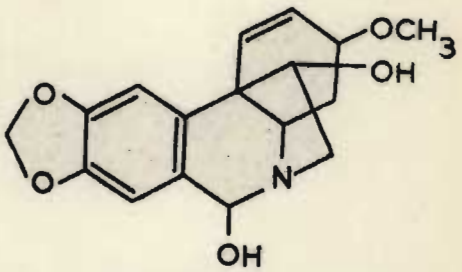
Haemanthidine, $C_{17}H_{19}O_5N$, upon treatment with methyl iodide and formaldehyde gave tazettine (CV). Hence Boit and Wildman [68] concluded that its structure may be represented as (CX). Later, however, Wildman [64] et al. revised his structure to (CXI) which forms an O,O-diacetate and not a O,N-acetate as was previously reported. Furthermore, 6N hydrochloric acid at 90° converted haemanthidine to apohaemanthidine (CXII). Catalytic hydrogenation of

— CHART 9 —



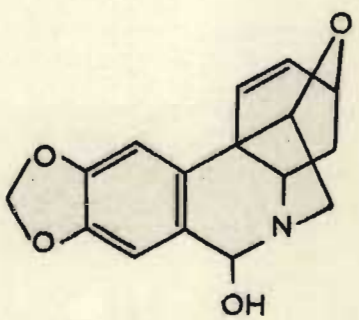


CX

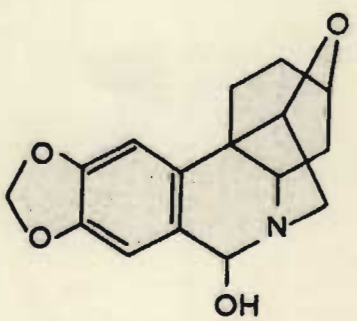


CXI

apohaemanthidine gave the dihydro base (CXIII). The benzylic hydroxyl group of dihydroapohaemanthidine (CXIII) was removed

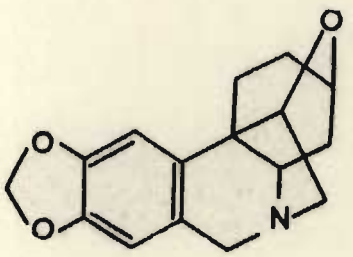


CXII



CXIII

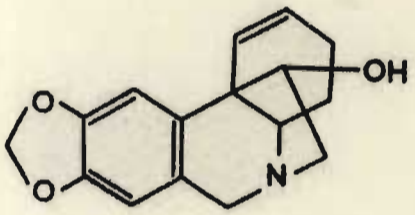
by chlorination and subsequent reduction with lithium aluminium hydride to give a base which was identical with dihydroapohaemanthamine (CXIV), prepared from haemanthamine by Wildman.[24]



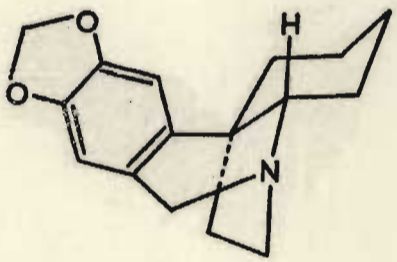
CXIV

Haemultine, $C_{16}H_{17}O_3N$, was studied by the German group[15] who demonstrated the presence of a tertiary nitrogen atom, a double bond, a methylenedioxy function and an acetylatable hydroxyl group. The hydroxyl group was secondary since oxidation of dihydrohaemultine gave a ketone, $C_{16}H_{17}O_3N$. Haemultine was isolated with dihydrohaemanthine from the sodium and amyl alcohol reaction on haemanthamine (XCVI). The same reaction on crinamine (CVIII) gave haemultine and dihydrocrinamine as products. Hence it followed that haemultine as well as haemanthamine and crinamine contain the crinane basic skeleton. The double bond was placed in the same position as that of haemanthamine and crinamine, hence structure (CXV) was proposed for haemultine.

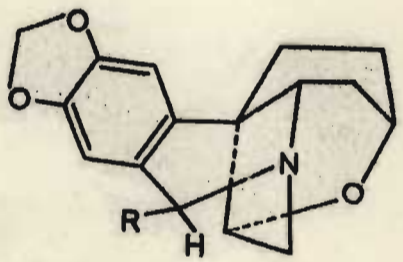
It was found that haemanthamine [24] (XCVI) and haemanthidine [64] (CXI) although possessing the 5, 10b-ethanophenanthridine nucleus are devoid of such activity. These alkaloids must possess the nucleus represented by



CXV

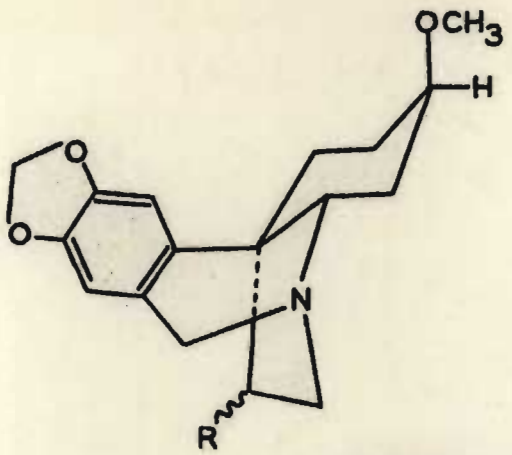


CXVI



CXVII

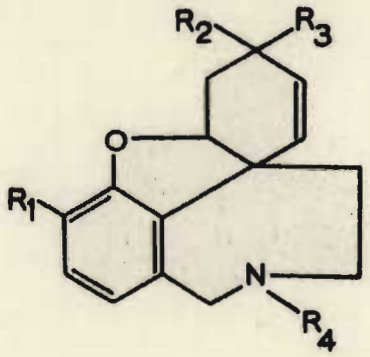
(CXVI) to permit the formation of apohaemanthamine (CXVII, R = H) and apohaemanthidine (CXVII, R = OH). It has been shown that all alkaloids known to possess the 5 : 10b-ethanophenanthridine nucleus are based on the stereostructure (CXVI) and its mirror image. Dihydrohaemanthamine (CXVIII, R = OH) upon treatment with thionyl chloride and the product hydrogenated with lithium aluminium hydride gave desoxydihydrohaemanthamine which was found to be the optical isomer of dihydrobuphanisine (CXVIII, R = H). This transformation identifies the alkaloids hydroxylated in the



CXVIII

5 membered D ring [haemanthamine (XCVI), haemanthidine (CXI), crinamine (CVIII), and haemultine (CXV)], with the (+)-crinane nucleus (CXVI) while the alkaloids not hydroxylated in this position, crinine (LXXII), powelline (LXXXI), buphanidrine (LXXXIV), buphanisine (LXXXV), undulatine (LXXXVI) and buphanamine with the (-)-crinane nucleus. These observations should not, however, be interpreted as a general rule since the occurrence of vittatine [10] (CXIX), the optical antipode of crinine (LXXII) has been reported.

CHART 10



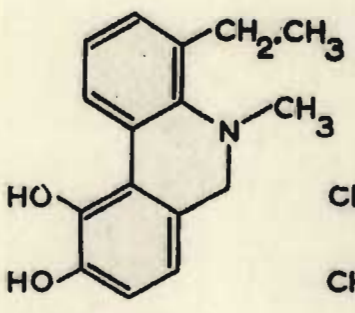
	R_1	R_2	R_3	R_4	
Galanthamine	CH_3O	H	OH	CH_3	
Lycoramine (no |=)	CH_3O	H	OH	CH_3	*
Irenine (no |=)	CH_3O	H	OH	CH_3	*
Narwedine	CH_3O	O		CH_3	
Chlidanthine	HO	H	CH_3O	CH_3	
Narcissamine	CH_3O	H	OH	H	

* diastereoisomers

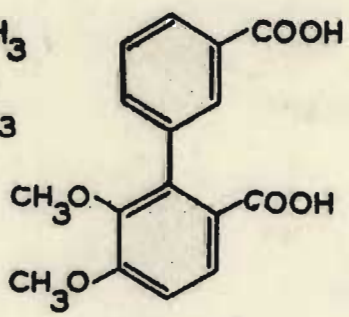
THE SPIROHEXANETETRAHYDROBENZAZEPINE ALKALOIDS

THE 5-SPIROHEXANETETRAHYDROBENZAZEPINE ALKALOIDS.— As in the previous groups of alkaloids in this family the alkaloids of this group are the different oxygenated, methylated and hydrogenated members of 5-spirohexanetetrahydrobenzazepine ring system.

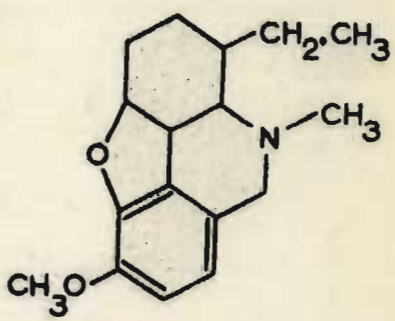
Galanthamine (lycoramine), $C_{17}H_{21}O_3N$, upon treatment with hydrobromic acid gave a dihydric phenol, apogalanthamine. which structure was elucidated by Emde degradation of O : O-dimethyl derivative followed by oxidation to galanthamic acid, $C_{16}H_{14}O_6$. On the basis of structure (CXXIX) for this acid Proskurnina and Yakovleva.[51] proposed structure (CXXX) for apogalanthamine and hence structure (CXXXI) for



CXXX



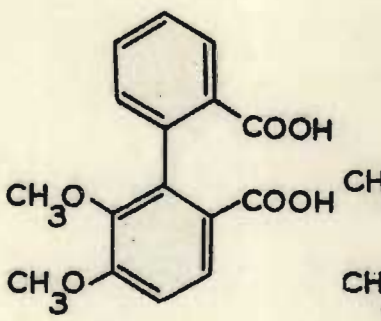
CXXIX



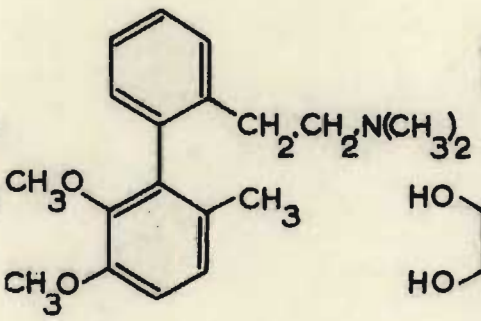
CXXXI

galanthamine. This series of experiments was repeated by Kobayashi, Shingu and Uyeo [37] who obtained two acids from the oxidation. The synthesis of galanthamic acid revealed that it is 2 : 3-dimethoxydiphenyl-6 :2′-dicarboxylic acid (CXXXII). On this basis it was concluded that the Emde

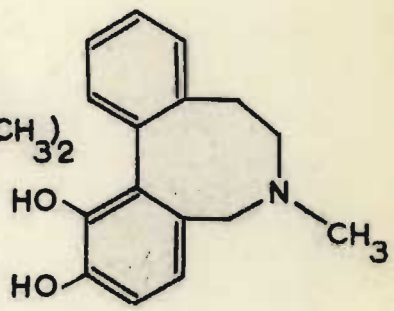
base and apogalanthamine are structures (CXXXIII) and (CXXXIV) respectively. Therefore galanthamine must be



CXXXII

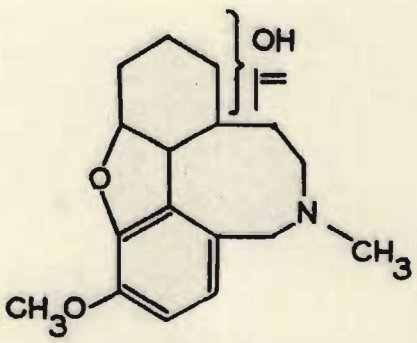


CXXXIII

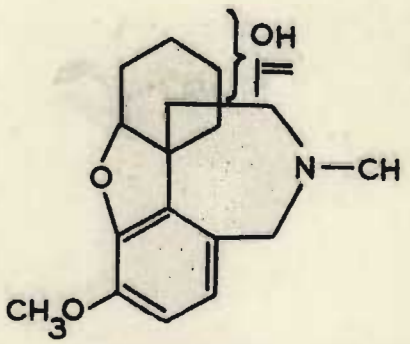


CXXXIV

structure (CXXXV) if treatment with hydrobromic acid is not accompanied by rearrangement. If rearrangement does occur then (CXXXVI) must be considered. Recently,[10]

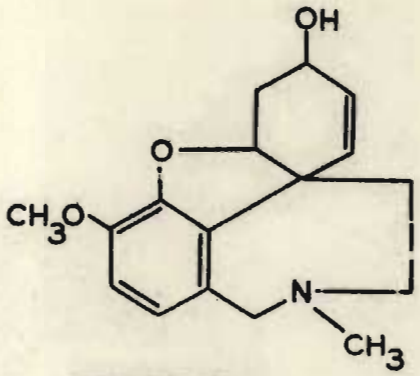


CXXXV



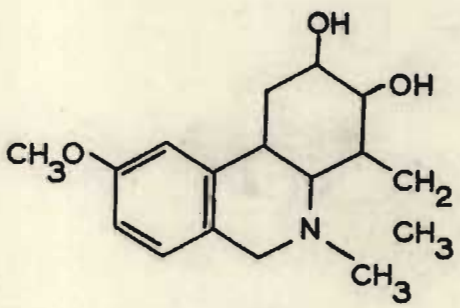
CXXXVI

however, it was established that the structure of galanthamine may be represented by (CXXXVII).



CXXXVII

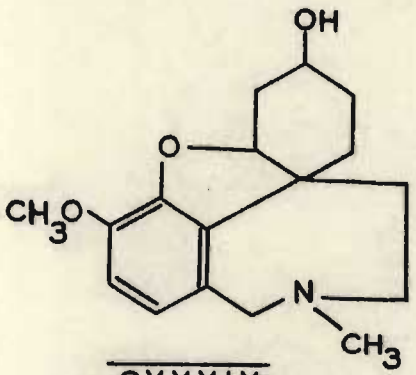
Lycoramine, $C_{17}H_{25}O_3N$, was isolated from Lycoris radiata by Kondo [38] in 1932. On the basis of a series of degradation studies Kondo proposed structure (CXXXVIII) for this base. Wildman [69] synthesised desethylycoramine and



CXXXVIII

related compounds which confirmed the above structure. Furtherm re it was established that lycoramine (CXXXVIII) had the trans diol system. Later, however, Uyeo and Koizumi,[62] found that lycoramine contained only one hydroxyl group

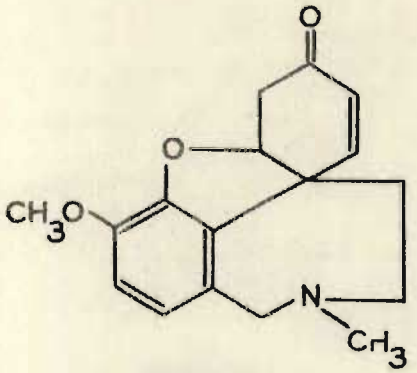
replaceable by hydrogen using hydrogen bromide followed by reduction with zinc-alkali or by reducing with Raney nickel the mercaptol from the ketone obtained by Openauer oxidation of the hydroxyl group. The inert oxygen atom in the alkaloid appeared to exist in an oxide ring fused to the C-ring of the hydrophenanthridine skeleton. Later, however, since the structure of galanthine was elucidated and it was known that lycoramine was dihydrogalanthamine the structure (CXXXIX) was proposed for this base.



CXXXIX

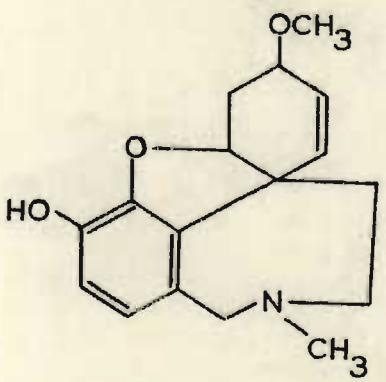
Narwedine,[10] $C_{17}H_{23}O_3N$, was found to be identical with the oxidation product of galanthamine (CXL). Hence since galanthamine has been established as structure (CXXXVII), narwedine must have structure (CXL). Hydrogenation of narwedine (CXL) gave as products lycoramine (CXXXIX) and Irenine (CXLI). Hence Irenine is identical with lycoramine (dihydrogalanthamine)(CXXXIX) except for the

configuration of the hydroxyl group.



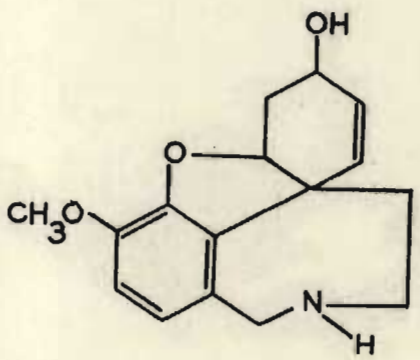
CXL

Chlidanthine, $C_{17}H_{21}O_3N$, is a phenolic base of this family. Kobayashi, Shingu and Uyeo [37] gave evidence for a double bond and ether linkage. Proskurnina and Jakowlawa [66] hydrolysed chlidanthine with bromine water and isolated a compound which was identical with apogalanthamine (CXXXIV). Since the structure of apogalanthamine was proved Boit [9] proposed structure (CXLII)for chlidanthine.



CXLII

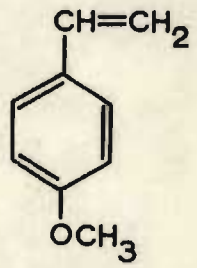
Narcissamine was isolated by Boit and Ehmke [14] and its formula established as $C_{16}H_{19}O_3N$ by Wildman et al. [23] who expanded it to $C_{15}H_{14}O(OCH_3)(NH)(OH)$. On this basis narcissamine was suspected to be either N- demethylgalanth--amine or N- demethylbase 9 (Base 9 is an unnamed alkaloid of this family). Comparison of N- methylnarcissidine methiodide and perchlorate with the corresponding salts of galanthamine confirmed that narcissidine was N- desmethyl--galanthamine and accordingly has structure (CXLIII).



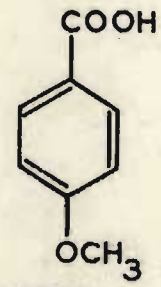
CXLIII

MISCELLANEOUS ALKALOIDS WITH DIFFERENT RING SYSTEMS.

Belladine,[67] $C_{19}H_{25}O_3N$, was degraded by the Hofmann reaction to p-methoxystyrene (CXX) which was readily oxidised to p-anisic acid (CXXI). Another product

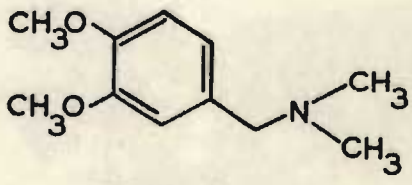


CXX

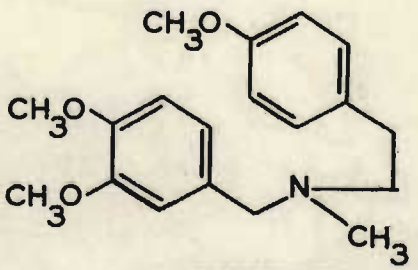


CXXI

from the Hofmann reaction was identified as N : N dimethylveratrylamine (CXXII). Hence structure (CXXIII)



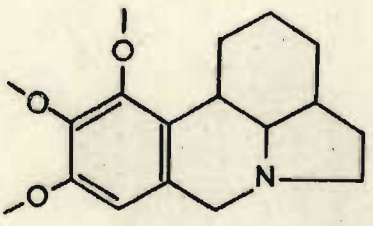
CXXII



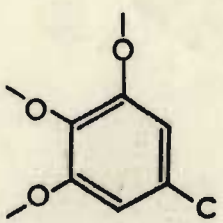
CXXIII

was proposed for belladine. This structure (CXXIII) is consistent with the absence of optical asymmetry. Belladine is a simple structure from which other Amaryllidaceae

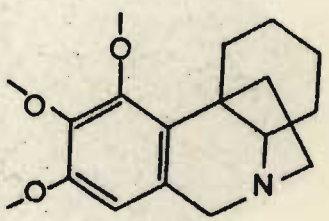
alkaloids could be constructed, according to the biogenetic postulates of Barton and Cohen.[2] An interesting consequence of Barton and Cohen's suggestions is that in those Amaryllidaceae alkaloids with three oxygens attached to the aromatic ring, the position of these atoms should always be as is shown in (CXXIV), (CXXV) and (CXXVI) (even if (CXXVI) were formed by oxidative coupling of two separate molecules) since the aromatic ring of the alkaloid will be derived from



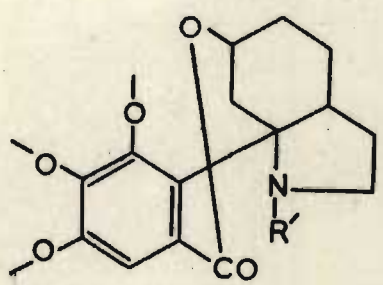
CXXIV



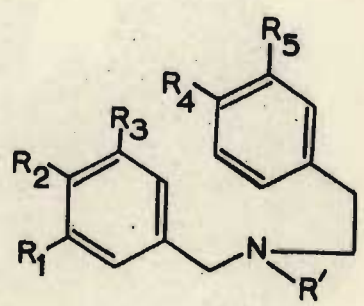
CXXVII



CXXV

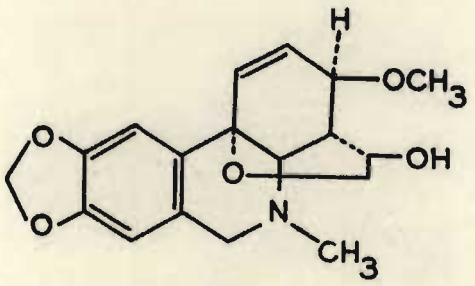


CXXVI



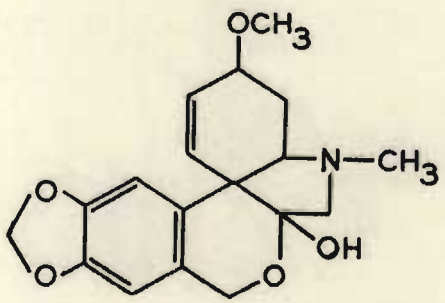
CXXVIII

a fragment containing skeleton (CXXVII). The intermediate postulated may be represented as (CXXVIII)(R = H or OH;R′= H).



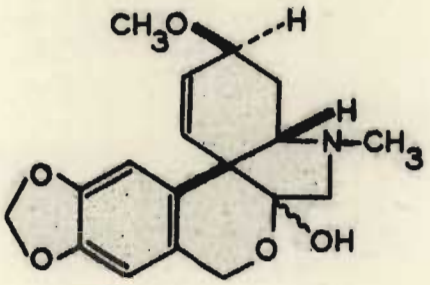
CXLIV

Tazettine, $C_{18}H_{21}O_5N$, recently had its structure elucidated by the combined efforts of the Canadian and Japanese workers.[32] Wenkert [65] correlated the work of previous investigators and proposed a structure (CXLIV). This structure, however, could not account for the methine, $C_{18}H_{19}O_4N$. From the investigation of the Hofmann reaction on deoxytazettine Ikeda, Taylor, Tsuda, Uyeo and Yajima [32] proposed structure (CV) for tazettine which satisfactorily



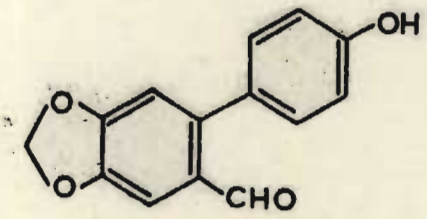
CV

explained the reactions of this base. Wildman arrived at the same conclusion by investigation of the degradation products of dihydrotazettamide.



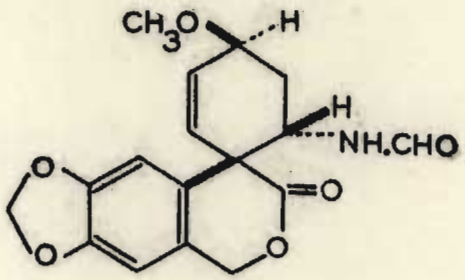
CV

In a recent communication Ihrie, Tsuda and Uyeo [49] synthesised (CXLIV) by a stereospecific route (Chart 11) and identified it with the Emde degradation product of an amine derived from tazettamide (CXLV) (Chart 12) and hence provided further confirmation of the detailed structure of tazettine (CV). Furthermore, it was found that two more



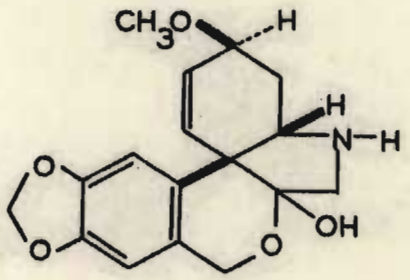
CXLVI

compounds were formed during the initial oxidation of tazettine viz., 6-(p-hydroxyphenyl)-piperonaldehyde (CXLVI) and N- demethyltazettamide (CXLVII), which was identical



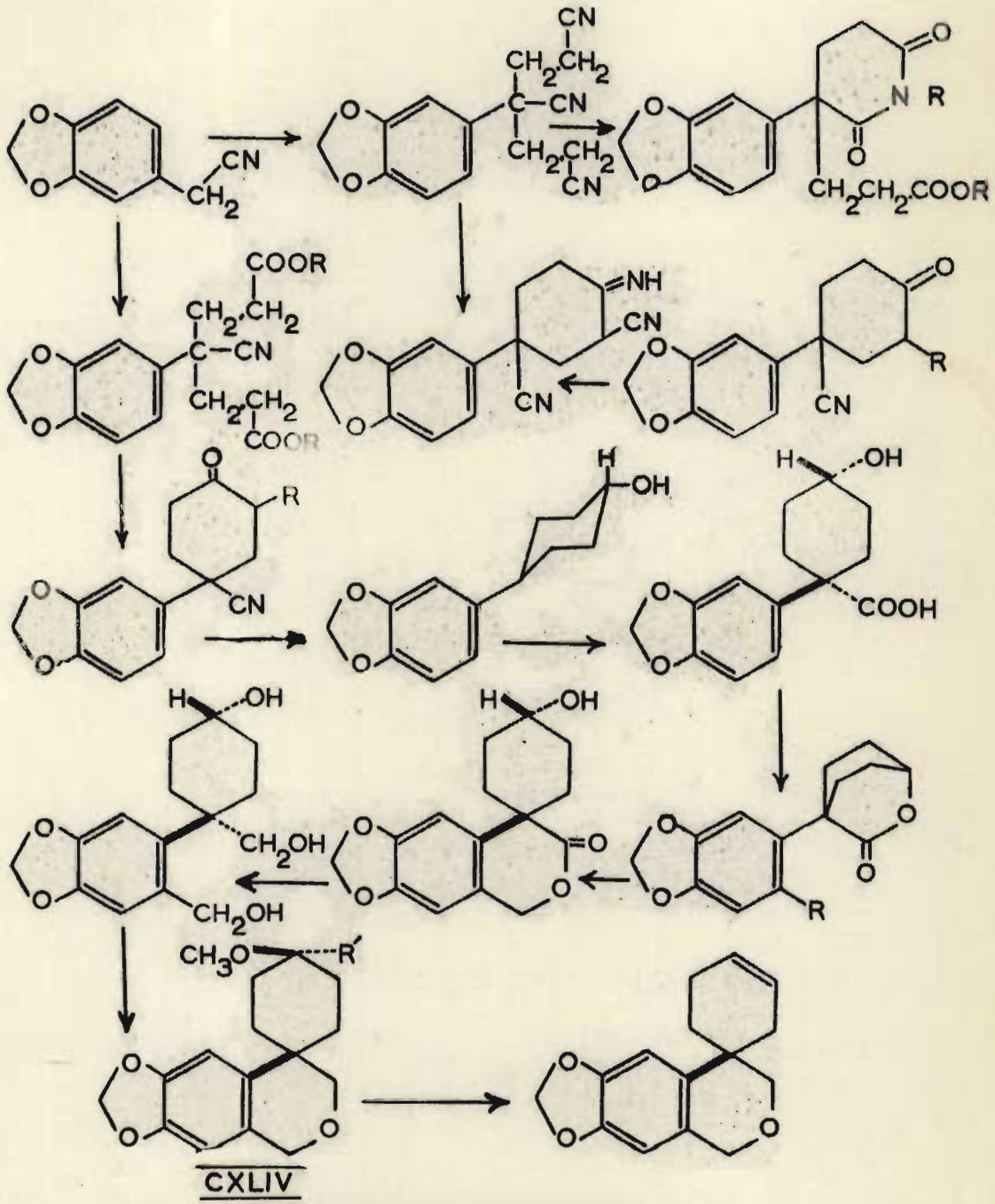
CXLVII

with the product obtained by manganese dioxide oxidation of nortazettine (CXLVIII) which in turn was prepared by alkaline rearrangement of haemanthidine (CXI).



CXLVIII

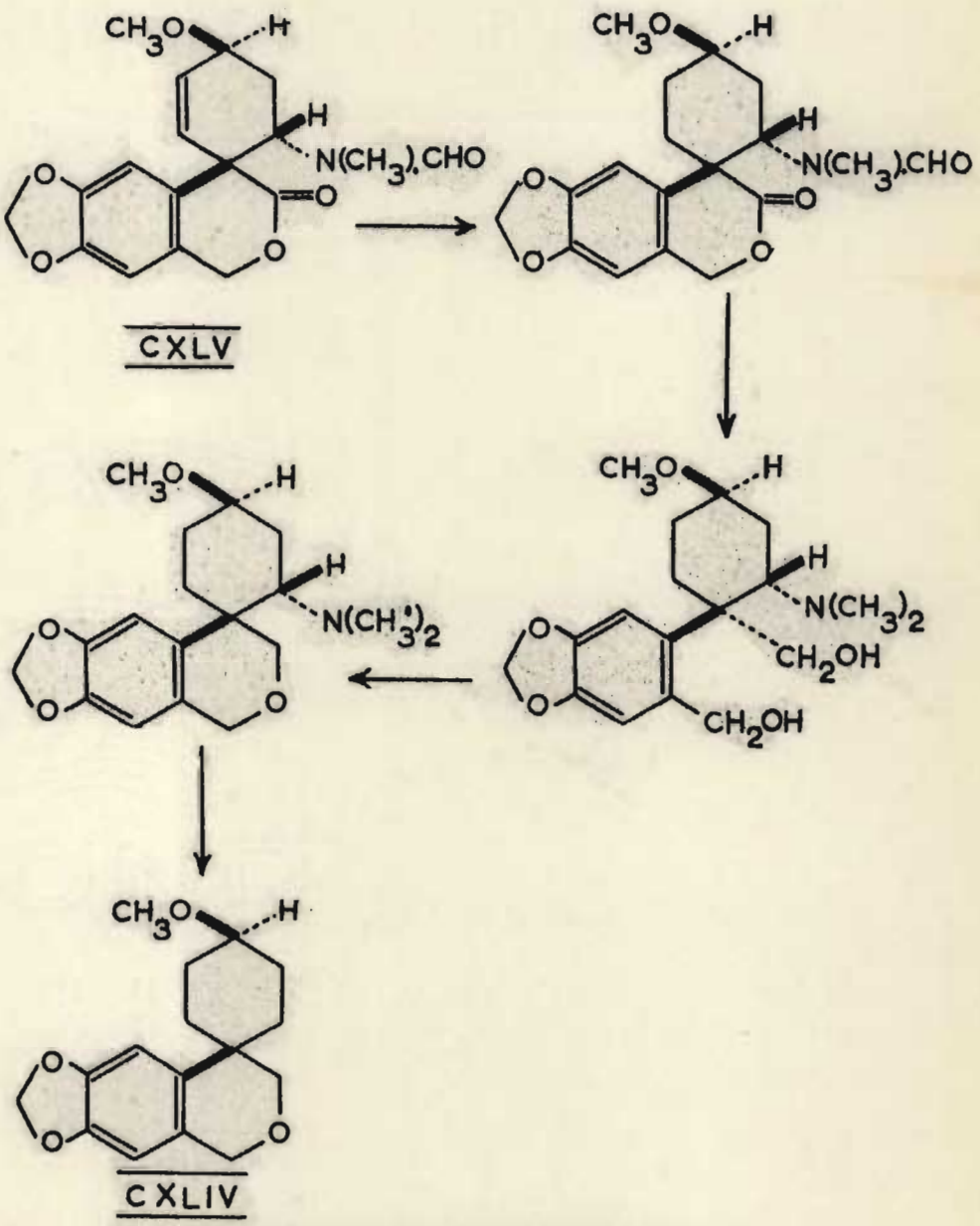
— CHART 11 —



CXLIV

THE STEREOSPECIFIC SYNTHESIS OF A TAZETTINE PRODUCT

— CHART 12 —



DEGRADATION OF TAZETTAMIDE TO COMPOUND CXLIV

D I S C U S S I O N

The first chemical study of the bulbs of Boophone disticha was performed by Juritz [35] who showed that these bulbs contained alkaloids. However the isolation of the constituents of the mixture has proved extremely difficult. Since 1910 many different workers have isolated different individuals from the complex mixture of alkaloids. The author has reinvestigated this mixture and isolated the alkaloids which are found to exist in several different forms and thus correlated the findings of the previous investigators.

EXTRACTION.—— The bulbs and roots are not easily dried because the tough outer shells prevent drying and if the bulbs are sliced they become mouldy. The bulbs were stripped of the outer dry shells since a previous study reported that these contained only a small amount of lycorine. The fleshy portion was sliced and extracted with boiling ethanol which stopped enzyme action and prevented decomposition. The once extracted bulbs were easily dried, by exposure to the sun, crushed and re-extracted with ethanol.

The combined alcohol extracts were flash evaporated and steam distilled to remove the remaining alcohol and volatile compounds, reported by Tutin [60] to be furfuraldehyde and valeric acid. The cooled solution, which was acid due

to the presence of plant acids, was filtered and extracted with ether to remove the fats. The bases were liberated with sodium carbonate and extracted with chloroform (A). The precipitate which formed at the interface was filtered off, dissolved in acid and filtered. The filtrate which contained the alkaloidal material was washed with ether basified and extracted with butanol which was concentrated to a solid. The solid in ethanol deposited colourless prisms of lycorine, m. p. 253—4°.

The coloured phenolic impurities were washed from the chloroform extract (A) with aqueous sodium hydroxide. Carbon dioxide was passed into the sodium hydroxide washing in order to liberate phenolic bases which were extracted with chloroform (B). An acetone solution of the dark brown gum, obtained by evaporating off chloroform (B), deposited crystals which recrystallised from the same solvent as prisms of alkaloid I, m. p. 263° (Found: C, 66.9; H, 5.9. $C_{16}H_{17}O_4N$ requires C, 66.9; H, 6.0%). Alkaloid I was insoluble in carbon tetrachloride and chloroform and a nujol mull showed no free hydroxyl absorption in the 3μ region of the infrared. Hence if a phenolic hydroxyl were present it would be expected to be strongly hydrogen bonded but a ferric chloride test for phenols was negative. This water soluble alkaloid I developed an intense purple colouration with 80% sulphuric acid and chromotropic acid, characteristic

of a methylenedioxy group.

The chloroform extract (A) on concentration to a small volume deposited crystals which were separated and recrystallised from ethanol to give a further quantity of lycorine, m. p. 253—4°. The remaining alkaloids were contained in the chloroform filtrate which was concentrated to a gum. The constituents of this gum was separated by various procedures.

Alumina column adsorption chromatography provided a partial separation of a gum which crystallised from methanol water, m. p. ca. 130° (crude "distichine"), a small amount of material which crystallised from wet ether, m. p. ca. 110—120° and partially crystalline gums, m. p. ca. 175° (crude buphanamine) and m. p. ca. 225° (crude crystalline "haemanthine"), but most of the fractions were intractible gums.

A fractional hydrochloric acid extraction of a chloroform solution of the bases was proved to be impractic--able because "distichine" hydrochloride was soluble in chloroform. Therefore it seemed likely that a separation might be obtained if the chloroform solution of the bases be made turbid with ether prior to each hydrochloric acid extraction. "Distichine" hydrochloride would then readily be extracted in the final stages from a solvent which would

be mainly ether. However, investigation of this process gave mainly intractible gums except for the first few fractions which on regeneration gave crystals m. p. ca. 225° (crude crystalline "haemanthine").

Since hydrochloric acid proved unsuccessful a fractional sulphuric acid extraction was attempted but as in the previous case it proved unsuccessful.

The failure of the chromatographic separation seemed to be due to the close similarity and the number of components present. Therefore the chloroform soluble and insoluble hydrochlorides were separated by extracting a hydrochloric acid solution of the bases with chloroform. The chloroform insoluble hydrochlorides which were contained in the aqueous acid solution were regenerated with sodium carbonate and extracted with chloroform which in turn was fractionally extracted with enough sulphuric acid to remove half the alkaloidal material. The base from the sulphuric acid extract crystallised from acetone m. p. ca. 225° (crude crystalline "haemanthine"). The residue from the chloroform solution was chromatographed to give a series of gums, some of which crystallised from acetone, m. p. ca. 175° (crude buphanamine). The chloroform soluble hydrochlorides were regenerated by shaking the solution with aqueous sodium carbonate. Chromatography of the gum gave, in the early

fractions, alkaloid m. p. ca. 130° (crude "distichine") and the latter fractions gave a small quantity of crystals m. p. ca. 175° (crude buphanamine).

In order to obtain further partial separation the elegant method of Renz [56] was followed. The concentrated acetone solution of the crude alkaloid mixture deposited crystals m. p. ca. 225° (crude "haemanthine"). The gum from the decanted acetone solution in chloroform was extracted with hydrochloric acid to remove the chloroform insoluble hydrochlorides. The regenerated base from the chloroform solution was chromatographed to give a series of gums, some of which crystallised from methanol-water, m. p. ca. 130° (crude "distichine"). The hydrochloric acid extract was basified and extracted with chloroform which on concentration gave a gum. The gum in benzene was shaken out with buffer solutions pH 6.1 and 5 respectively. On concentration the benzene solution gave a small amount of gum which crystallised from methanol-water, m. p. ca. 130° (crude "distichine"). The base from buffer solution pH 6.1 on chromatography gave a series of gums, some of which crystallised upon trituration with acetone, m. p. ca. 175° (crude buphanamine) and m. p. ca. 225° (crude "haemanthine") respectively. The gum from the buffer solution pH 5 in acetone deposited a few crystals m. p. ca. 225° (crude

crystalline "haemanthine") and gave on chromatography a series of gums, some of which crystallised, m. p. ca. 112—120°, and m. p. ca. 175° (crude buphanamine). The crystals m. p. ca. 112—120° had the same infrared spectrum as those of m. p. ca. 110—120° but since this material was present in very low yield it was set aside and not investig-ated further. This method proved satisfactory but no undulatine or buphanidrine was separated. These bases were expected to be present because Wildman [67] stated that "Distichine" was in all probability a mixture of buphanidrine and undulatine. The author therefore decided to modify the extraction for the ready separation of crude "distichine", m. p. ca. 130°, crude "haemanthine", m. p. ca. 225°, and crude buphanamine, m. p. ca. 175°, and investigate these crude compounds.

The modified procedure consisted of the initial separation of the chloroform soluble hydrochlorides which were regenerated and chromatographed to give gums, some of which crystallised, m. p. ca. 130° (crude "distichine"). The gums which could not be induced to crystallise or give the crystalline derivatives of "distichine" were not studied further. The mixed bases which constituted the chloroform insoluble hydrochlorides were taken up in acetone and set aside. The solution deposited crystals, m. p. ca. 225°

(crude crystalline "haemanthine") and the gum from the decanted acetone was chromatographed into fractions. The early fractions gave crystals, m. p. ca. 175° (crude buphanamine) and the later crystals, m. p. ca. 225° (crude crystalline "haemanthine"). The initial crystallisation from acetone removed most of the crystalline "haemanthine" and thus only a small amount was eluted from the column.

BUPHANIDRINE.— Buphanidrine, $C_{18}H_{21}O_4N$, was first reported as a gum from B. fischeri [56] and characterised as the hydroperchlorate, m. p. 240—242° and hydrobromide, m. p. 195—197°. Undulatine, $C_{18}H_{21}O_5N$, m. p. 148—149°, was first isolated by Boit [11] who reported an N-CH_3 for this base but did not characterise it further. Aware of this existing knowledge we [4] published the existence of a new alkaloid "distichine", $C_{19}H_{21}O_5N.\frac{3}{4}H_2O$, m. p. 144° which we presumed sublimed to the anhydrous semi-crystalline gum, $C_{19}H_{21}O_5N$, m. p. 90—92°. The analytical figures of the picrate, styphnate, perchlorate, methiodide and platinichloride fitted well the calculated figures [4] (Table 1). Later, Boit reported the absence of an N-CH_3 group in undulatine and buphanidrine was obtained as crystals, m. p. 88—89°. [31] Warnhoff and Wildman [67] however suggested that "distichine"

TABLE I.

Analytical Figures Obtained for "DISTICHINE"

Derivative	Found		$C_{19}H_{21}O_5N$ requires:		
	C	H	Solvent of Crystallisation.	C	H
Methiodide	49.7	5.2	-	49.5	5.0
Picrate	52.9	4.5	-	52.5	4.2
Perchlorate	51.8	4.9	-	51.4	5.0
Styphnate	50.5	4.1	-	51.0	4.1
Platinichloride (Pt. 18.7%)	40.7	4.4	H_2O (Pt. 17.5%)	40.9	4.2

is in all probability undulatine contaminated with traces of buphanidrine since the infrared spectrum of a specimen (supplied by us) was identical with a 3 : 1 mixture of undulatine $C_{18}H_{21}O_5N$, and buphanidrine." Furthermore, in a private communication Wildman stated that undulatine and buphanidrine were readily separated by alumina chromatography. In an effort to resolve this the author chromatographed a specimen of crude "distichine", m. p. ca. 130° and found that the first few fractions gave crystals m. p. 135° and the latter fractions contained crystals which melted progressively lower and finally gums. Rechromatography of

the first few crystalline fractions gave a similar series of eluates. This process repeated gave the same results. Successive recrystallisations of the crystals m. p. ca. 130° (crude "distichine") raised the melting point to 144° which was unchanged by recrystallisation from ether; but when an ethereal solution was seeded with a sample of buphanidrine, kindly supplied by Dr. Wildman, it crystallised in prisms, m. p. 90—92°. Furthermore, when Dr. Wildman's sample of anhydrous buphanidrine was crystallised from aqueous methanol the melting point was raised, but once the anhydrous form had been obtained three or four crystallisations were necessary to reobtain m. p. 144°. Hence it was concluded that "distichine" is a hydrated form of buphanidrine. The analytical figures of "distichine", m. p. 144° and the sublimed "distichine", fit the formula $C_{18}H_{21}O_4N.1\frac{1}{2}H_2O$ and $C_{18}H_{21}O_4N.\frac{1}{2}H_2O$ respectively (see Table 2). Our analytical figures for the previously reported [4] derivatives of "distichine" as well as the recently prepared oxalate,[27] m. p. 187—188° fit equally well as derivatives of buphanidrine (see Table 2). Furthermore, the infrared spectra of the perchlorate, picrate and methiodide of buphanidrine (kindly supplied by Dr. Wildman) and of "distichine" all respectively were identical.

TABLE 2.

ANALYTICAL FIGURES OBTAINED FOR "DISTICHINE".

	Found. C.	H.	Formula.	Requires. C.	H.
Distichine	64.2	6.8	$C_{18}H_{21}O_4N.1\frac{1}{2}H_2O$	64.3	7.1
Distichine (sublimed)	66.8	6.4	$C_{18}H_{21}O_4N.\frac{1}{2}H_2O$	66.6	6.8
Methiodide	49.7	5.2	$C_{19}H_{24}O_4NI$	49.9	5.3
Picrate	52.9	4.5	$C_{24}H_{24}O_{11}N$	52.9	4.4
Perchlorate	51.8	4.9	$C_{18}H_{22}O_8NCl$	52.0	5.3
Styphnate	50.5	4.1	$C_{24}H_{24}O_{12}N_4.\frac{1}{2}H_2O$	50.6	4.4
Platinichloride	40.7 (Pt. 18.7%)	4.4	$C_{36}H_{44}O_8N_2Pt.Cl_6.H_2O$	40.9 (Pt.18.4%)	4.3
Oxalate	59.0	5.7	$C_{20}H_{23}O_8N$	59.25	5.7

Buphanidrine ("distichine"), $C_{18}H_{21}O_4N$, in 80% sulphuric acid was treated with chromotropic acid. The purple colouration which developed is indicative of a methylenedioxy group. Zeisel determination indicated the presence of two methoxyl groups. The alkaloid showed no characteristic N-H or OH absorption in the 3μ region of the infrared

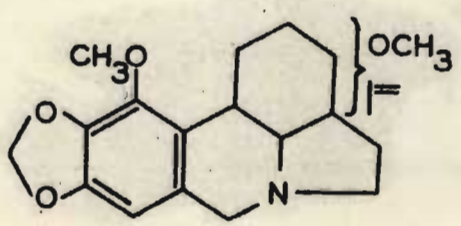
spectrum and readily formed a methiodide. One equivalent of hydrogen was absorbed when buphanidrine was hydrogenated over 10% palladium on charcoal catalyst. However, it is interesting to note that reduction did not occur with Adams's catalyst.

Buphanidrine may now be formulated as :

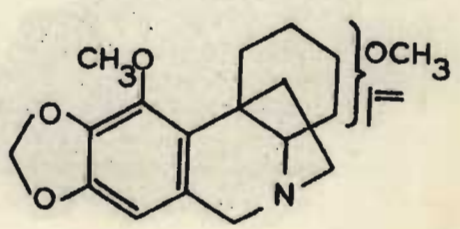
$C_{13}H_{13}(\ C = C)(\equiv N)(O_2CH_2)(OCH_3)_2$

A strong infrared absorption at 1622 $cm.^{-1}$ was evidence for a substituted aromatic ring. Hence one of the methoxyl groups was placed on the aromatic nucleus. From the above data it was concluded that the compound is tetracyclic excluding the methylenedioxy ring. This conclusion found support from a Kuhn-Roth determination which indicated the absence of a $C\text{-}CH_3$ group.

The possible structures are therefore the pyrrolo(de)phenanthridine type (I) or the 5 : 10b-ethano--phenanthridine type (II). The aromatic methoxyl group was placed according to the biogenetic postulates of Barton and Cohen.[2]

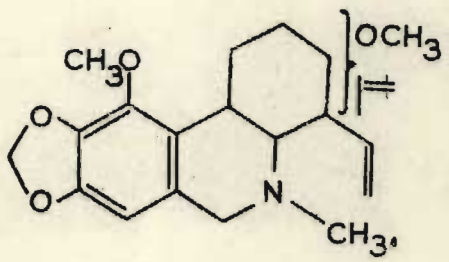


I

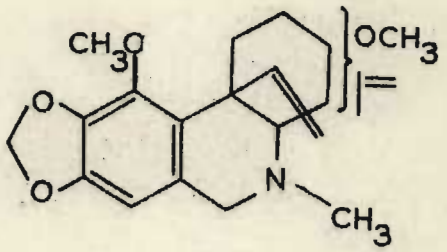


II

A Hofmann degradation of buphanidrine methiodide gave a gummy methine which with ozone gave formaldehyde. This aldehyde did not come from the methylenedioxy group, as is possible, because ozonisation of the alkaloid itself gave no detectable amount of formaldehyde. This experiment is indicative of the group $C = CH_2$ which could be accommodated in both the above formulae as shown in structures (III) and (IV).

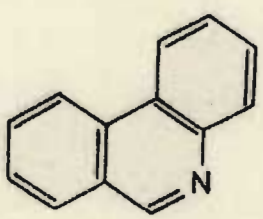


III



IV

Part of the methine was distilled over zinc dust to give phenanthridine (V) which was isolated as its mercuric

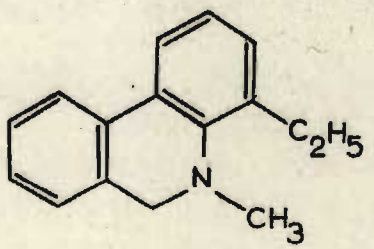


V

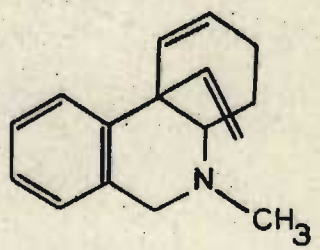
chloride double salt. The base from the mercuric chloride

double salt was converted to a picrate which infrared spectrum was identical with the corresponding curve of an authentic specimen of phenanthridine picrate, prepared from carbazole (Chart 1), and a mixed melt showed no depression. Again this product could arise from either (I) or (II).

A second product from the zinc dust distillation was a compound, $C_{22}H_{22}O_7N_4$ i.e. $C_{16}H_{19}N.C_6H_3O_7N_3$, from which all the oxygen atoms had seemingly been eliminated but the skeleton C_{16} remained. Again this could be accounted for by both (I) and (II) giving rise to (VI) and (VII) respectively, neither of which could be expected.



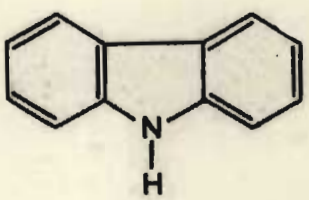
VI

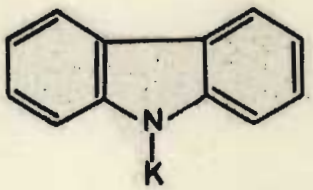


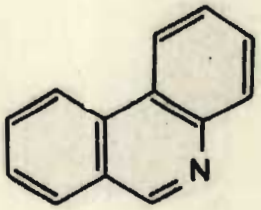
VII

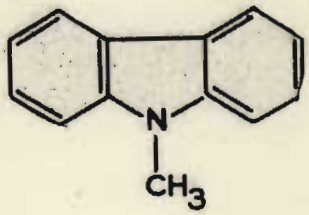
A third product isolated also as a picrate, $C_{24}H_{24}O_{11}N_4$, m. p. 229°, was seemingly the original alkaloid picrate, m. p. 235°. The fission of the methoxyl group with the elimination of methanol was indicative of the 5 : 10b-ethanophenanthridine type (II) since the pyrrolo(de)phenanthridine alkaloids are known in all cases

— CHART 1 —





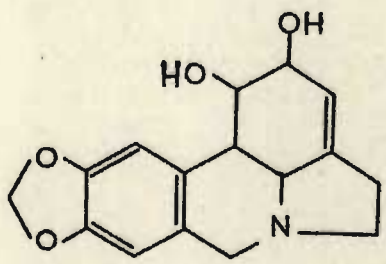




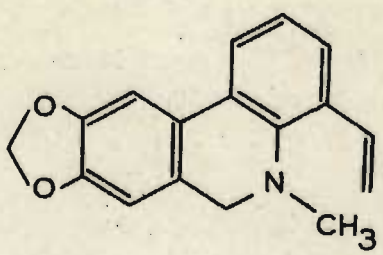
SYNTHESIS OF PHENANTHRIDINE

to undergo the Hofmann degradation. In fact a portion of the residue from the Hofmann reaction with hydriodic acid gave buphanidrine methiodide so that the reaction proceeded only with difficulty and partially with the elimination of methanol (Chart 2).

α-Buphanidrine methine (VIII), $C_{17}H_{21}O_4N$, has resulted from the elimination of the C_2 grouping from β-buphanidrine methine (IX), $C_{19}H_{23}O_4N$, isolated as its hydrochloride. This elimination has not previously been encountered in this group of alkaloids. The Hofmann reaction normally proceeds by the fission of the pyrrole ring in the pyrrole(de)phenan--thridines with aromatisation of ring C as in lycorine[30] (X).



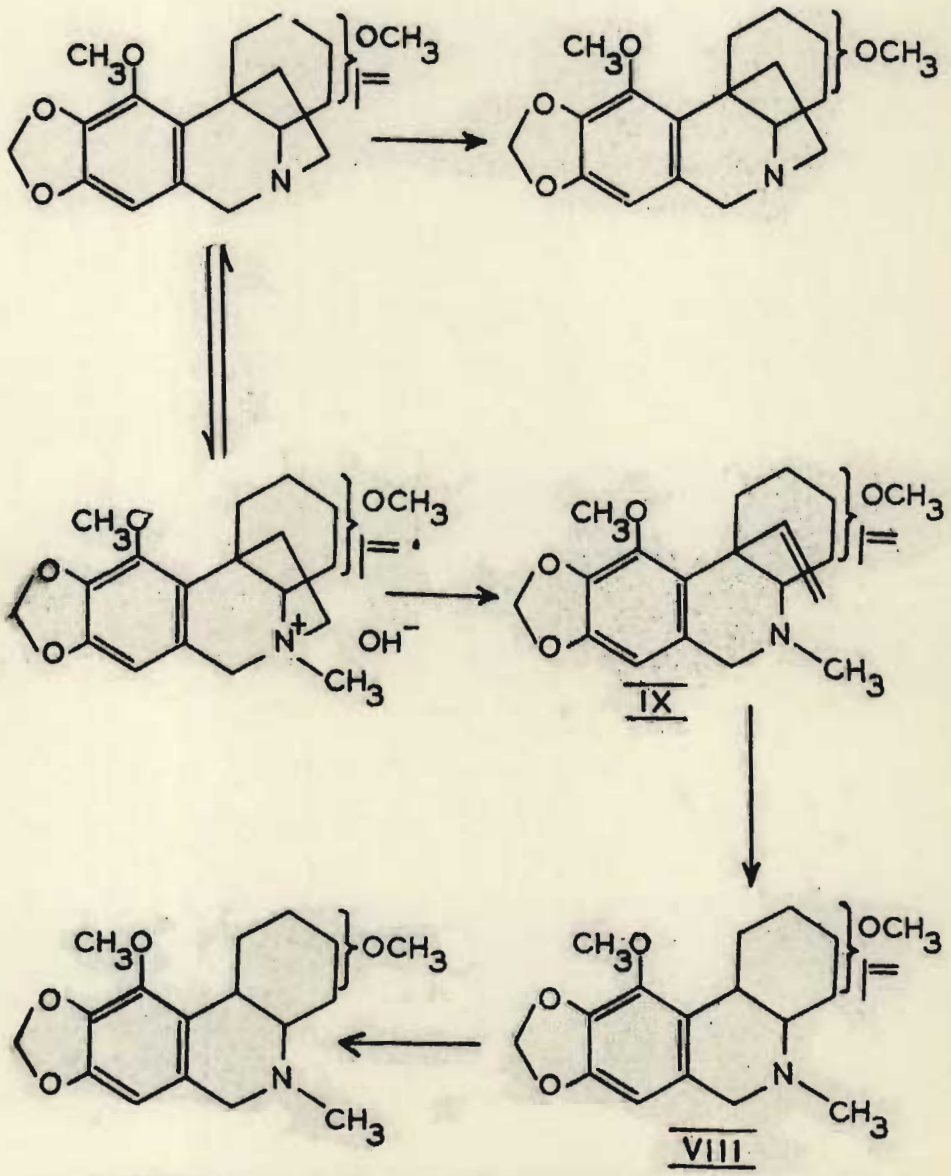
X



The present reaction was explicable as in the series shown in Chart 2.

The compound (VIII) was obtained as a crystalline solid, m. p. 117—119° and was characterised as the hydrochloride, $C_{17}H_{21}O_4N.HCl.H_2O$, m. p. 236°, and perchlorate,

— CHART 2 —

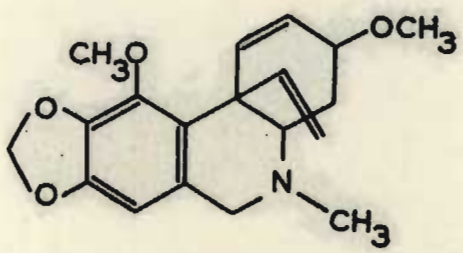


HOFMANN REACTION ON BUPHANIDRINE

$C_{17}H_{21}O_4N.HClO_4$, m. p. 230°. Further, the product was reduced catalytically to the dihydro form, $C_{17}H_{23}O_4N.\frac{1}{2}H_2O$, m. p. 154—156°, which was again characterised as the hydrochloride, $C_{17}H_{23}O_4N.HCl.H_2O$, m. p. 200—205°, the perchlorate, $C_{17}H_{23}O_4N.HClO_4.H_2O$, m. p. 220—230° (dec.), and the methiodide, $C_{17}H_{23}O_4N.CH_3I.H_2O$, m. p. 292—300° (dec.).

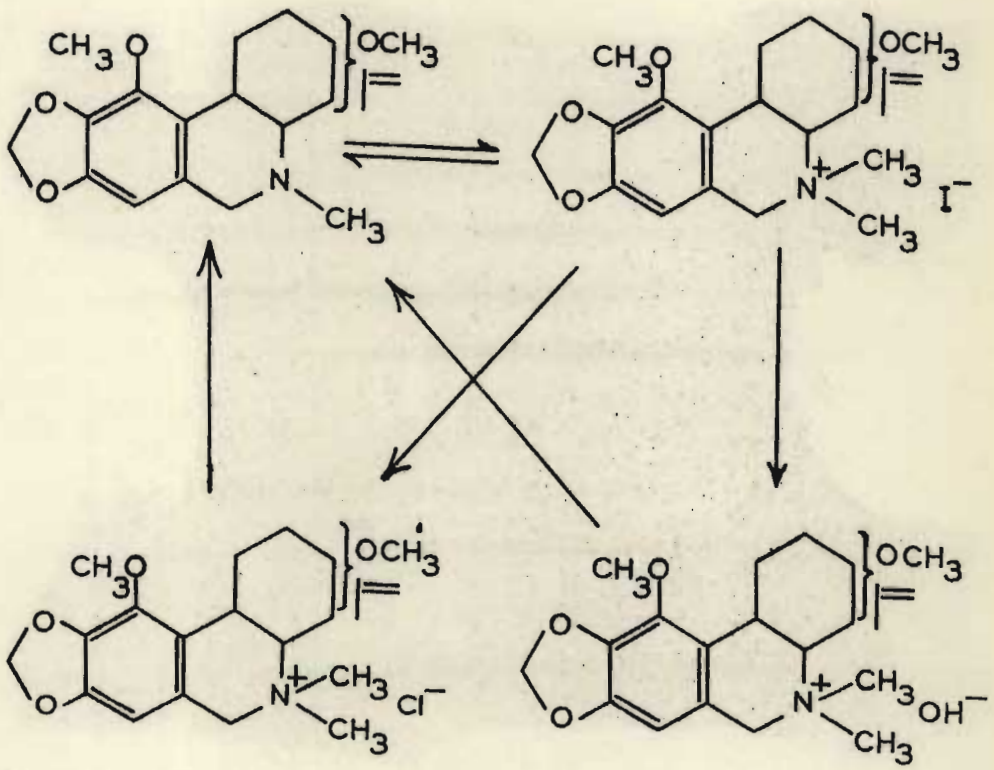
Attempts to degrade further compound (VIII) or its dihydro derivative by both Hofmann and Emde reactions on the methohydroxide and methochloride respectively gave back the starting material with the elimination of the methyl group (Chart 3).

The second product from the initial Hofmann reaction gave a hygroscopic β-methine hydrochloride, m. p. 160° in which the original number of carbon atoms in the skeleton had been preserved and accordingly is assigned structure (IX).

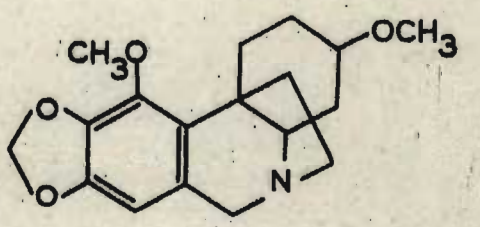


IX

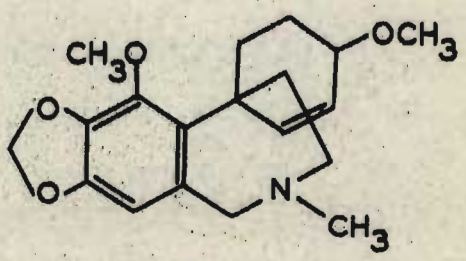
— CHART 3 —



At this stage of the investigation a paper appeared by Wildman in which he established the structural formula for buphanidrine. His work, however, gave further evidence that the author fissioned the C-N bond of the pyrrole ring during the Hofmann reaction since Wildman performed the degradation on dihydrobuphanidrine (XI) and obtained a methine[70] (XII) which absorbed an equivalent of hydrogen to become optically inactive. Hence the position of the aliphatic methoxyl group was established. Further evidence

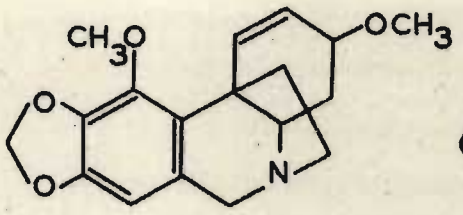


XI

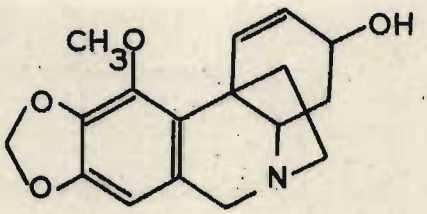


XII

for the structure of buphanidrine (XIII) was obtained by its interconversion to powelline (XXIX) by dilute acid hydrolysis. This experiment was confirmed by the author in order to obtain powelline for degradation to powellane which was required for comparison with the basic skeleton of buphanitine (see later).



XIII



XXIX

BUPHANITINE, m. p. 240° was isolated from B. disticha by Tutin [60] who reported a hydrochloride, m. p. 265°, and a methiodide, m. p. 278°. Lewin [46] held that buphanitine was a mixture, one component of which he reported as an oil haemanthine which gave a hydrochloride m. p. 175°, and a hydronitrate, m. p. 125°. The reisolation [20] of these salts confirmed the chemical individuality of Lewin's haemanthine. Confusion arose when buphanitine (crystalline "haemanthine") was obtained in a crystalline form, m. p. 230°, since the derivatives of Lewin's oily "haemanthine" were associated with this crystalline base.[3] Later, [28] this crystalline base, buphanitine, erroneously called "haemanthine" was obtained as solvated crystals, m. p. 240°, and thus identified with Tutin's buphanitine. The formula was corrected to $C_{18}H_{21}O_5N.\frac{1}{2}H_2O$ since it sublimed to a compound thought to be the anhydrous form, m. p. 197—199°. This

sublimate is best obtained by sublimation from alumina under reduced pressure, and does not give the crystalline "haemanthine" (buphanitine) derivatives. Further investigation of buphanitine showed that this base crystallises from chloroform in needles which change crystalline form at 210° and m. p. 234°, or prisms m.p. 232°. It is of interest to note that the above needles and rhombohedra sublime at 180°/0.1mm. to needles and rhombohedra respectively without changing their characteristic melting habits. Both forms when crystallised from acetone gave prisms m. p. 232°. Furthermore, both forms crystallise from ethanol in prisms which lose this solvent of crystallisation at 140° and m. p. 240°. Buphanitine hydrochloride and hydronitrate have m.p.'s 265 and 222—224° respectively. A new formula for buphanitine, $C_{17}H_{21}O_5N$, is accordingly proposed which fits well the reported analyses [26] (Table 3) as well as its degradation products. It is probable that Tutin's [60] "buphanitine" methiodide, m. p. 278°, is probably buphanidrine methiodide, m. p. 271°. This conclusion finds some support from Tutin's analytical figures for "buphanitine" methiodide (Found: C, 50.7; H, 5.2%) which approximate more closely to buphanidrine methiodide (C, 49.9; H, 5.3) than buphanitine methiodide (C, 46.7; H, 5.2).

Buphanitine, (crystalline "haemanthine") $C_{17}H_{21}O_5N$,

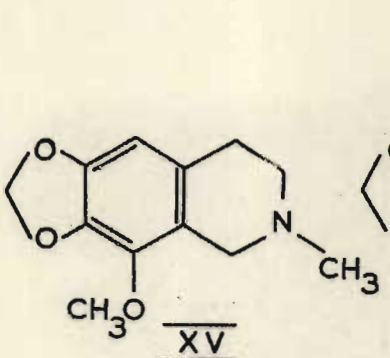
TABLE 3.

ANALYTICAL FIGURES FOR BUPHANITINE AND ITS DERIVATIVES.

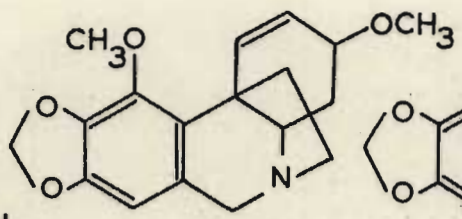
COMPOUND.	C H N	FORMULA.	REQUIRES C H N
Buphanitine	64.0, 6.4, 4.5	$C_{17}H_{21}O_5N$	63.9, 6.6, 4.4
Buphanitine (sublimed from alumina)	65.4, 6.8	$C_{34}H_{40}O_9N_2$	65.8, 6.5
Hydroperchlorate	46.8, 5.8	$C_{17}H_{22}O_9NCl.H_2O$	46.6, 5.5
Methiodide	46.7, 5.8, 2.6	$C_{18}H_{24}O_5NI$	46.7, 5.2, 3.0
Hydrochloride	57.4, 6.4 (Cl. 10.0)	$C_{17}H_{22}O_5NCl$	57.3, 6.2 (Cl. 10.0)
Hydronitrate	53.1, 5.9	$C_{17}H_{22}O_8N_2$	53.4, 5.8
Diacetylbuphanitine	62.2, 6.2 (COMe 21.3)	$C_{21}H_{25}O_7N$	62.5, 6.3 (2 COMe 21.3)
Demethoxybuphanitine	66.3, 6.8, 5.0	$C_{16}H_{19}O_4N$	66.4, 6.6, 4.8

contains a tertiary nitrogen atom since it readily forms a methiodide. The alkaloid in 80% sulphuric acid gave, upon treatment with chromotropic acid, a purple colour which is indicative of a methylenedioxy function. Acetylation of the alkaloid gave a diacetate which could be hydrolysed back to the original base. This experiment indicated that the alkaloid contained two aliphatic hydroxyl groups since it possessed no phenolic properties. Absorptions at 3550 and 3485 cms.$^{-1}$ in the infrared gave support for this deduction. Hence the formula was expanded to $C_{15}H_{14}(\equiv N)(O_2C H_2)(OCH_3)(OH)_2$. The methoxyl and methylenedioxy groups were seemingly in the benzene ring since the alkaloid showed a strong infrared absorption at 1622 cm.$^{-1}$. [21] Proof of this was obtained by treatment of buphanitine with sodium and n-butanol to give demethoxybuphanitine, $C_{16}H_{19}O_4N$, characterised further as a hydrochloride, m. p. 304—308°, and hydroperchlorate, m. p. 285—287°. Furthermore the ultraviolet absorption curves of buphanitine and buphanidrine (XIV), which was reported by Wildman to be similar to hydrocotarnine (XV), are similar and different to the curve of lycorine (X) (Chart 4). The aromatic methoxyl group is placed on the 10-position to fit the biogenetic postulates of Barton and Cohen who suggested that the alkaloids of this family containing three oxygen atoms attached to the aromatic ring

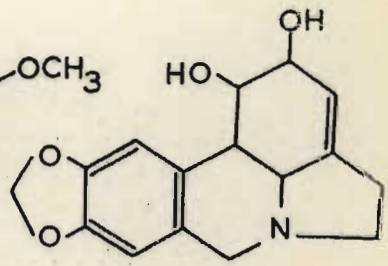
should always be in the positions as shown in (XVI), (XVII) and (XVIII) (even if (XVIII) were formed by oxidative coupling of two separate molecules).



XV

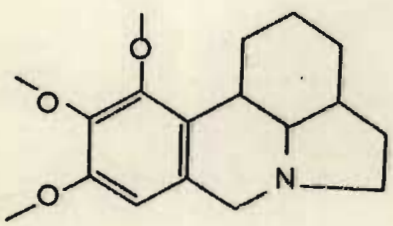


XIV

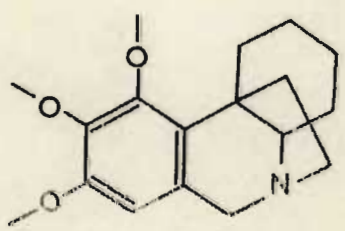


X

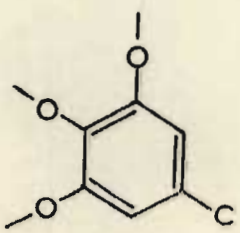
These skeletons, (XVI), (XVII) and (XVIII) were suggested to be derived from a fragment containing skeleton (XIX) and thus the intermediate may be represented as (XX).



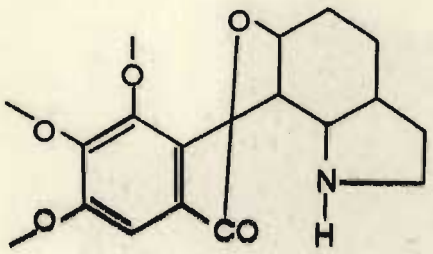
XVI



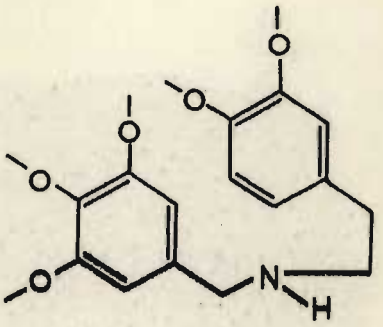
XVII



XIX

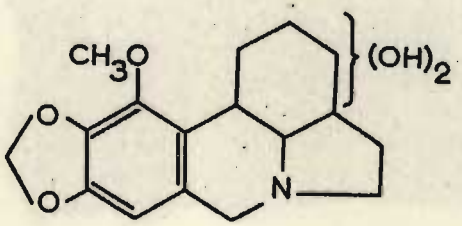


XVIII

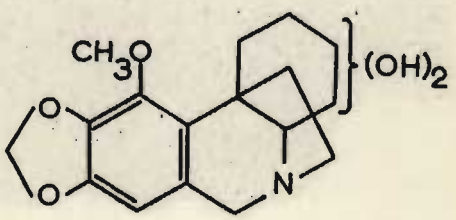


XX

The compound was not reduced by hydrogen and Adams's catalyst and hence it is tetracyclic excluding the methylenedioxy ring. From a Kuhn-Roth determination it was established that, excluding the methylenedioxy and methoxyl carbon atoms, all the carbon atoms are cyclic. Since all the oxygen atoms have been accounted for the compound possesses either the pyrrolo(de)phenanthridine (XXI) or the 5 : 10b-ethanophenanthridine structure (XXII).



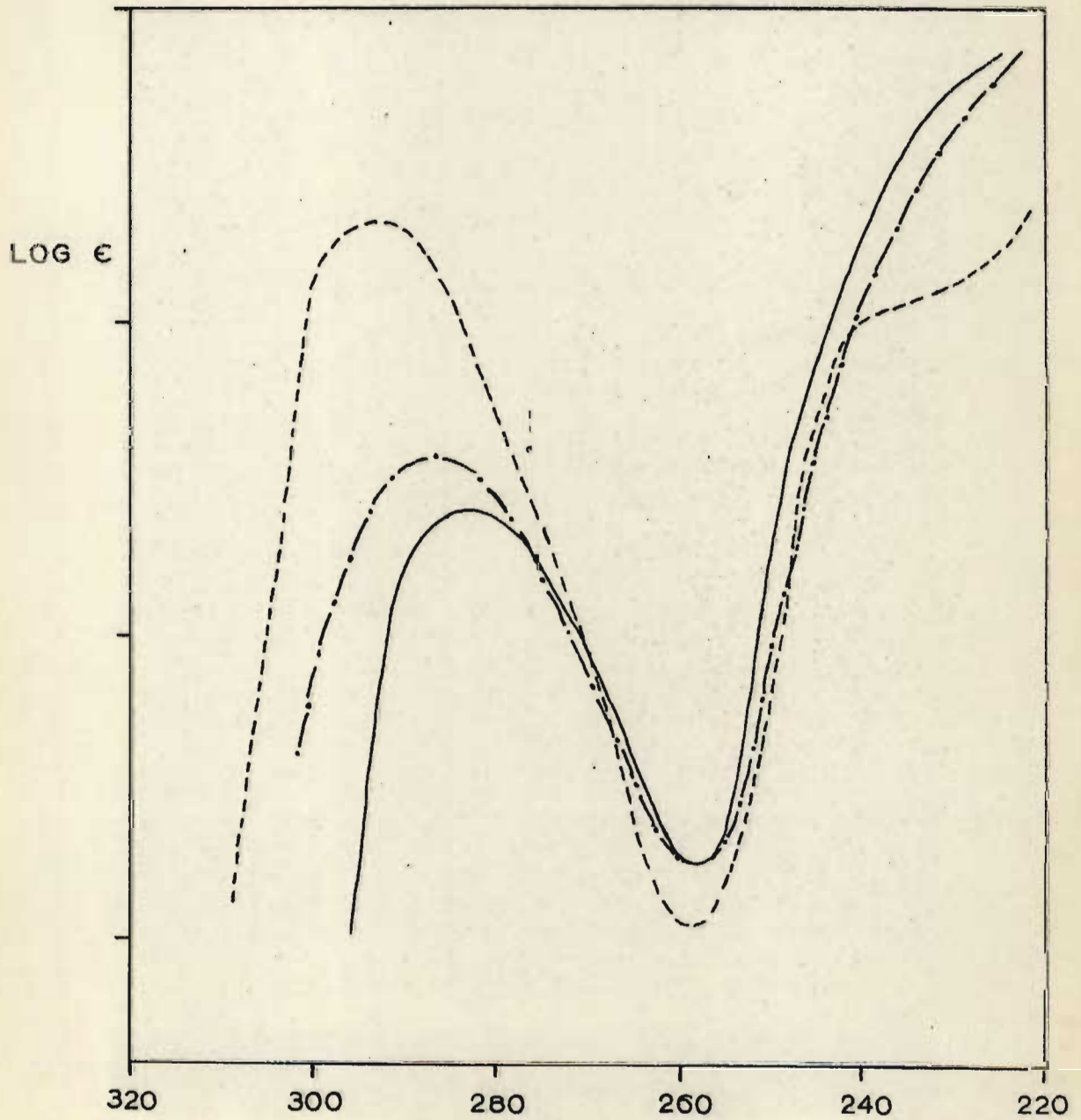
XXI



XXII

— CHART 4 —

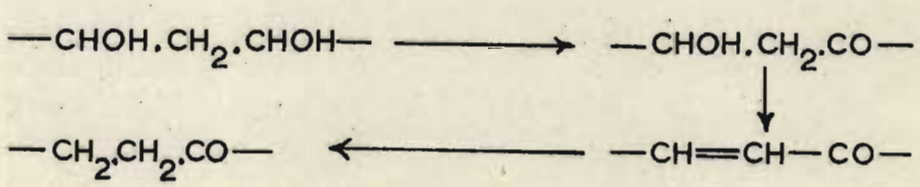
THE ULTRAVIOLET SPECTRA OF LYCORINE ------
BUPHANITINE ——
& BUPHANIDRINE —·—·—



The alkaloid seemingly had not the pyrrolo(de)phenan--thridine structure (XXI) since it was stable to oxidation with potassium ferricyanide and mercuric acetate [22] and both the Hofmann and von Braun reactions gave back the starting material. Hence it was suspected that buphanitine possessed the 5 : 10b-ethanophenanthridine structure (XXII).

The hydroxyl groups in buphanitine were secondary in that the alkaloid gave a diacetate and it was not readily dehydrated with phosphorus pentoxide in benzene. The hydroxyl groups were not on adjacent carbon atoms since Bates [3] reported that the compound was unattacked by periodic acid.

In order to establish the ring system it seemed desirable to oxidise the hydroxyl groups and then eliminate the oxygen atoms with a Wolff-Kishner reduction. Buphanitine was oxidised with the Meerwein-Pondorff-Verley reaction to buphanitenone which showed in the infrared an absorption at 1670 $cm.^{-1}$ indicative of a conjugated carbonyl. Catalytic hydrogenation of buphanitenone over 10% palladium on

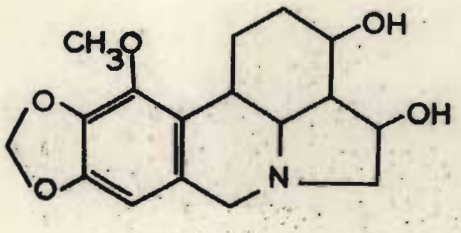


charcoal gave buphanitanone which showed in the infrared,

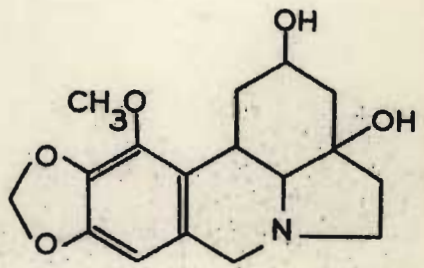
a strong absorption at 1718 cm.$^{-1}$, characteristic of a six ring ketone.[50] Hence it was concluded that buphanitine possessed a 1 :3-dihydroxy group and the possible structures are shown on Chart 5. Structure (XXIV) may be eliminated since it contains a tertiary hydroxyl group and structure (XXVIII) would not be expected to undergo this reaction with the elimination of a hydroxyl group.

The Huang-Minlon modification of the Wolff-Kishner reaction on buphanitanone gave buphanitane which showed no absorption in the 6 and 3μ regions of the infrared. Buphanitane was isolated as a picrate, m. p. 210—213°, which seemed to be identical with powellane picrate.[70] However, the base, regenerated by passing a chloroform solution of the picrate through an alumina column, gave a substance m. p. 143—144°, which was not identical with powellane, m. p. 113—116°. The powellane was prepared from buphanidrine (XIII) which was hydrolysed with 10% hydrochloric acid to powelline (XXIX). Powelline was oxidised with manganese dioxide to powellenone (XXX) which was catalytically reduced to powellanone (XXXI). Reduction of powellanone with the Huang-Minlon reaction gave powellane (XXXII) (Chart 6). A mixed melt of buphanitane and powellane gave m. p. 102—113°. Furthermore, powellane needles were different from buphanitane laminae

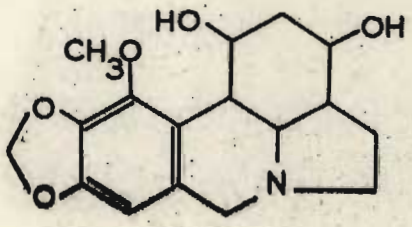
CHART 5



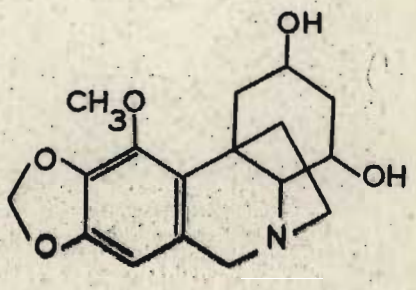
XXIII



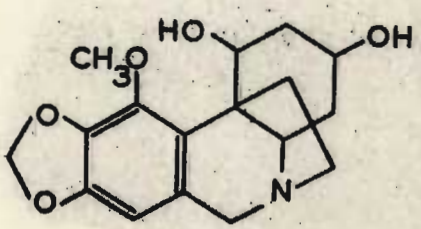
XXIV



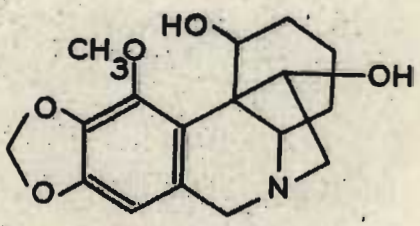
XXV



XXVI



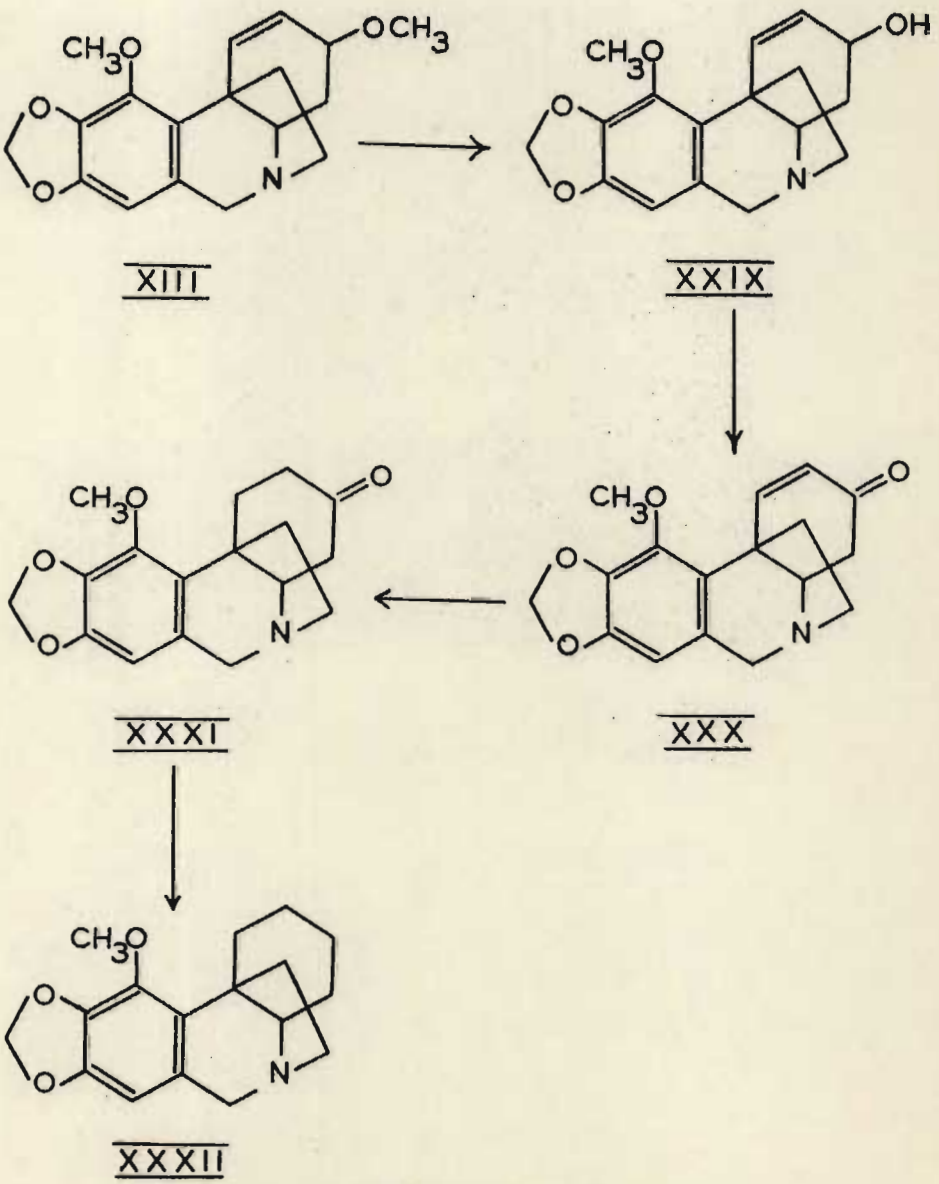
XXVII



XXVIII

POSSIBLE STRUCTURES OF BUPHANITINE

— CHART 6 —



DEGRADATION OF BUPHANIDRINE TO POWELLANE

and all efforts to obtain the same crystal shape failed. The rotation of buphanitane is $+4.6^{o}$ and hence it is not the optical antipode of powellane $[\alpha]_{D} = +11^{o}$.

A comparative study of the molecular rotations of powellane and crinane with their derivatives revealed the expected similarity between these two compounds. When molecular rotation differences for buphanitane and its derivatives were compared with those of powellane or crinane and their derivatives a similarity in sign was observed, as shown in Table 4.

TABLE 4.

COMPOUND.	$[\alpha]D$	FORMULA	M.W	MR
(P) Powellane	+11.1	$C_{17}H_{21}O_3N$	287	+31
(C) Crinane	-6.3	$C_{16}H_{19}O_2N$	257	-16
(B) Buphanitane	+4.6	$C_{17}H_{21}O_3N$	287	+13
(OH_2P) Powellanone	-42	$C_{17}H_{19}O_4N$	302	-126
(OH_2C) Crinanone	-67.7	$C_{16}H_{17}O_3N$	271	-183
(OH_2B) Buphanitanone	-5.6	$C_{17}H_{19}O_4N$	302	-17

P $\longrightarrow$ OH_2P $\Delta MR = -157$

C $\longrightarrow$ OH_2C $\Delta MR = -142$

B $\longrightarrow$ OH_2B $\Delta MR = -30$

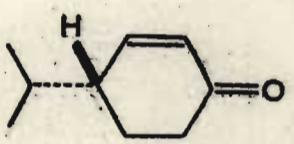
There is, however, a change in sign on conversion of the αβ-unsaturated ketone to the saturated ketone as shown in Table 5. This is indicative of a different asymmetric

TABLE 5.

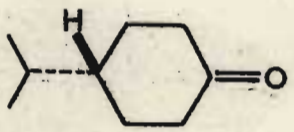
COMPOUND.	$[\alpha]_D$	FORMULA.	MW	MR
(OP) Powellenone	-258	$C_{17}H_{17}O_4N$	299	-772
(OC) Crinenone	-307	$C_{16}H_{15}O_3N$	269	-824
(OB) Buphanitenone	+34	$C_{17}H_{17}O_4N$	299	+102

OP ⟶ OH_2P	ΔMR = +641
OC ⟶ OH_2C	ΔMR = +646
OB ⟶ OH_2B	ΔMR = -119

configuration on a carbon vicinal to the double bond and probably in the γ-position to the carbonyl since a similar effect is observed on passing from cryptan (XXXIII) to dihydrocryptan (XXXIV).[48]

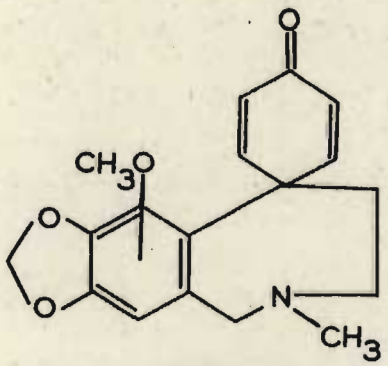


XXXIII



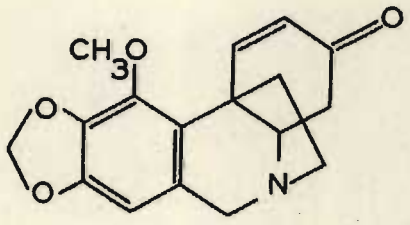
XXXIV

Therefore it seemed likely that buphanitine possessed the 5 : 10b-ethanophenanthridine skeleton with the previous unknown cis B/C ring fusion. In order to elucidate this problem buphanitenone was treated with methyl iodide and the methiodide warmed with sodium hydroxide. The product from this reaction, buphanitenone methine, m. p. 131—132°, was optically inactive and showed a strong band at 1663 $cm.^{-1}$ in the infrared which indicates a conjugated carbonyl group. The optical inactivity of the methine eliminates structures (XXIII), (XXV) and (XXVI) since the oxidation product of these compounds could not undergo the Hofmann degradation to furnish an optically inactive methine. The methine has the same properties as powellenone methine which has recently [70] been assigned structure (XXXV). The structure

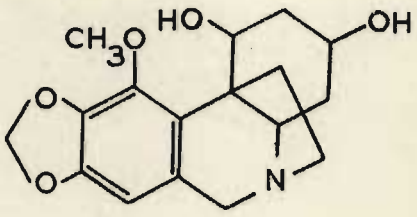


XXXV

(XXXV) for buphanitenone methine necessitates structure (XXXVI) for buphanitenone and hence (XXXVII) for buphanitine.

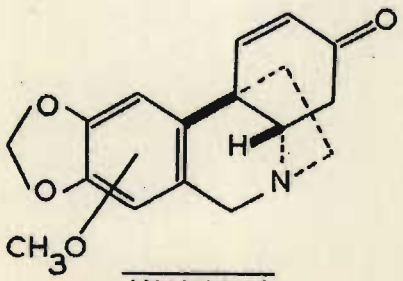


XXXVI

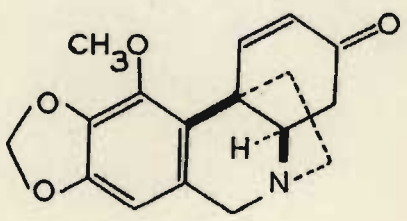


XXXVII

However, structure (XXXVI) is also the structure of powellenone and since buphanitenone is not identical with this ketone or its mirror image the only possible explanation is the difference in the B/C ring fusion. The stereochemistry of powellenone has recently been defined as (XXXVIII)[34] and the Hofmann reaction destroys the asymmetry to yield (XXXV). The structure of powellenone (XXXV) necessitates that buphanitenone is structure (XXXIX)

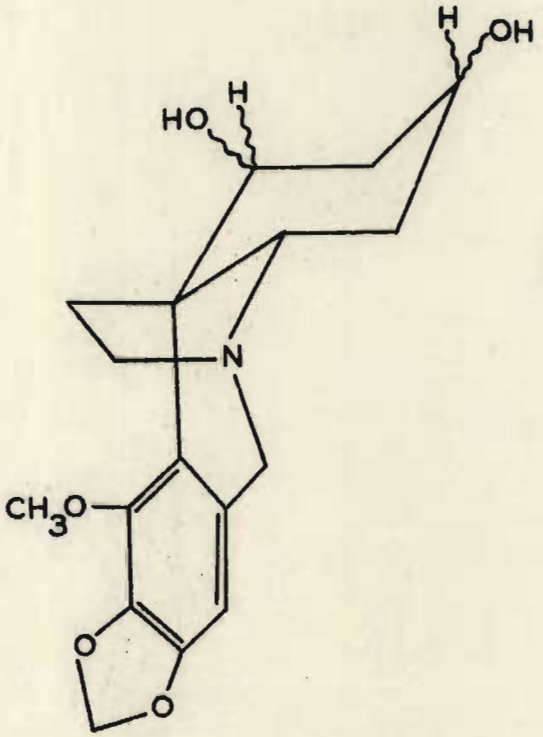


XXXVIII



XXXIX

or its mirror image. Hence buphanitine is 1 : 3-dihydroxy--buphanitane (XL) or its mirror image.



XL

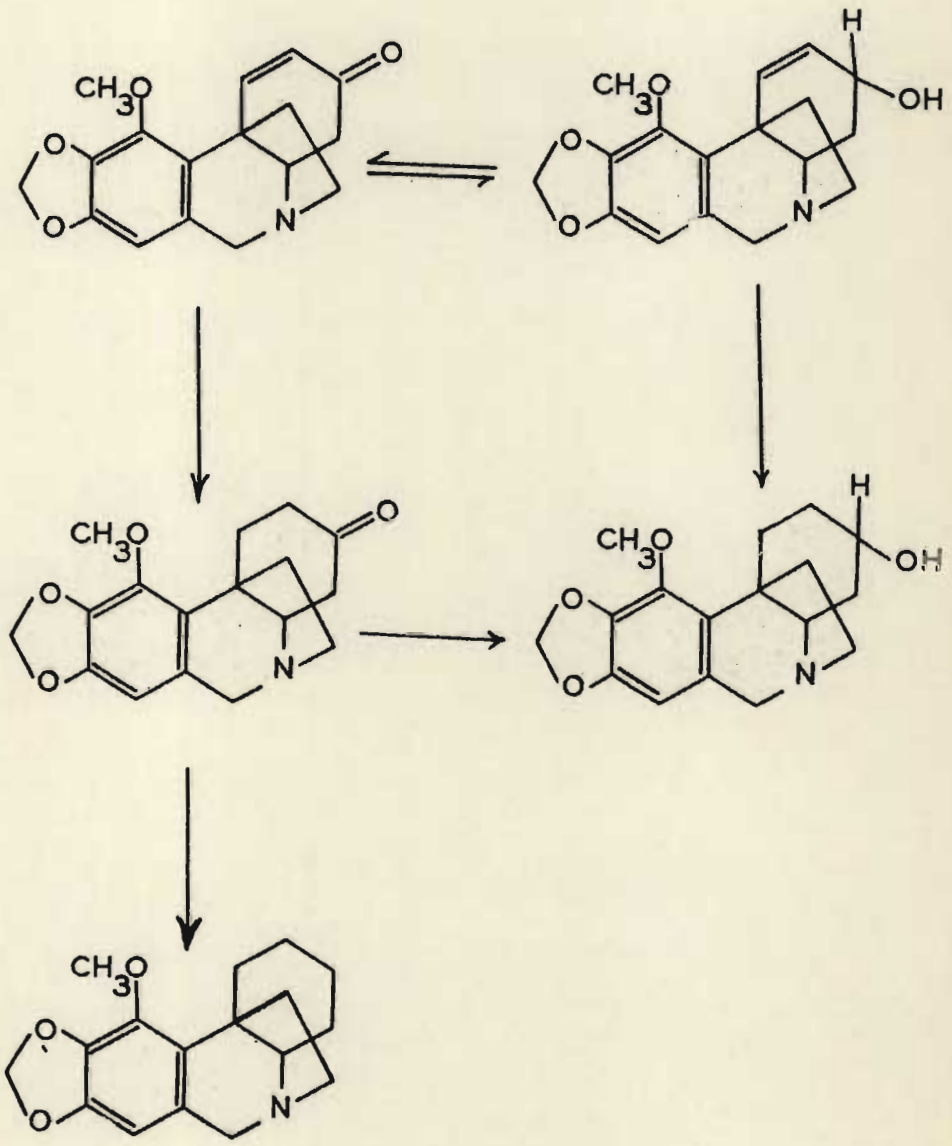
The reduction of buphanitenone (XLI) with lithium aluminium hydride gave α-buphanitenol (XLII) which was reoxidised to buphanitenone with manganese dioxide so that the reduction process was not accompanied by an allylic rearrangement. Reduction of buphanitanone (XLIII) with lithium aluminium hydride or catalytic reduction of α-buphanitenol (XLII) gave α-buphanitanol (XLIV). The one

stage catalytic reduction of buphanitenone in the presence of platinum gave β-buphanitanol (XLV). (Chart 7). Neither α- or β- buphanitanol were identical with dihydrobuphanamine or dihydroepipowelline or dihydropowelline. This observation provides further evidence for the cis B/C ring fusion in buphanitine as opposed to the trans fusion in the alkaloids which contain the crinane skeleton.

BUPHANAMINE.— Buphanamine, $C_{17}H_{19}O_4N$, m. p. 184—186°, was isolated by Renz, Stauffacher and Seebeck [56] from B. fischeri and characterised as a hydroperchlorate, $C_{17}H_{20}O_8NCl$, m. p. 232—234°. The unnamed alkaloid, m. p. 189°, which formed a hydroperchlorate, $C_{17}H_{20}O_8NCl.1\frac{1}{2}H_2O$, m. p. 119°, previously isolated from B. disticha by Humber and Taylor [31] was shown by Wildman to be identical with buphanamine.[73] The author also isolated this base, m. p. 192—194°, from B. disticha and prepared its hydro--chloride, m. p. 180°, which was identical to the derivative prepared by Bates [3] and erroneously thought to be a derivative of buphanitine (crystalline "haemanthine"). Buphanamine formed a hydronitrate, m. p. 130°, and thus it seems likely that the hydronitrate and hydrochloride of buphanamine are identical with Lewin's [46] salts from his "oily haemanthine" and are not derivatives of buphanitine

(crystalline "haemanthine") as was previously reported.[4,28] In view of the confusion which has been associated with the name haemanthine it is proposed that Lewin's "oil haemanthine" be known as buphanamine.[26]

— CHART 7 —



REACTIONS OF BUPHANITENONE

E X P E R I M E N T A L

All melting points are uncorrected.

Extraction.

Seventy bulbs of Boöphone disticha Herb. collected on the outskirts of Pietermaritzburg were stripped of the outer dry shells, sliced and extracted with ethanol in a Soxhlet extractor. The once extracted bulbs were dried (7 kg.), milled and re-extracted with ethanol. The combined extracts were flash evaporated under reduced pressure and the concentrate (4 litres) steam distilled for four hours. The cooled solution was filtered, washed with ether (3 x 1 litre), rendered alkaline with sodium carbonate and extracted with chloroform (5 x 1 litre). The extract was concentrated to one-tenth of its original volume and the precipitated material (2 g.) filtered off. Recrystallisation of the solid from ethanol gave colourless crystals of lycorine, m. p. 253—4°.

Analysis:

Found: C, 67.3; H, 6.0

$C_{16}H_{17}O_4N$ requires C, 66.8; H, 6.0%

Tutin [60] gives m. p. 267° for lycorine.

The filtrate was extracted with 10% sodium hydroxide (3 x 100 ml.), washed with water and concentrated to a gum A. (60 g.).

Carbon dioxide was passed into the sodium hydroxide solution for 2 hours and the resultant carbonate solution

extracted with chloroform (3 x 100 ml.). The extract was washed with water (100 ml.), dried over anhydrous sodium sulphate and concentrated to a dark brown gum. The gum in acetone slowly deposited rhombohedra (14 mg.), m.p. 263°.

Analysis:

Found:	C, 66.9; H, 5.9
$C_{16}H_{17}O_4N$ requires	C, 66.9; H, 5.9%

The compound was completely soluble in a small volume of cold water and insoluble in chloroform and carbon tetra-chloride. A few crystals of the sample in 80% sulphuric acid gave, on treatment with chromotropic acid, a magenta colouration which did not develop with separate test solutions of the sample in 80% sulphuric acid, and chromo-tropic acid in 80% sulphuric acid.

Separation of the Constituents of Gum A.

(i) The alkaloid mixture (5 g.) in benzene was chromato-graphed on alumina (140 g; grade 1) and eluted with benzene, benzene-ethyl acetate mixtures, chloroform and methanol, 50 ml. fractions of each being taken. The first few benzene fractions eluted amorphous non-alkaloidal material which was discarded. The eluates of 10% ethyl acetate in benzene gave gums (crude buphanidrine, [crude "distichine"]). The 50% ethyl acetate in benzene fractions contained a small

amount of crystalline material, which recrystallised from wet ether, m. p. 110—120°. The 70% ethyl acetate in benzene and pure ethyl acetate in benzene gave partially crystalline gums, m. p. ca. 170° and ca. 225°, respectively (crude buphanamine and crude buphanitine [crude crystalline "haemanthine"] respectively).

(ii) A chloroform solution of the bases (5 g.) was made turbid with ether and extracted with N/5 hydrochloric acid (15 ml.). The above process was continued until the solution could no longer be made turbid with ether. The fractional hydrochloric acid extraction was then continued, without further addition of ether, until the solvent layer was negative to a Mayers test.

Each acid extract was basified, extracted with chloroform which was washed with a small volume of water, dried over anhydrous sodium sulphate and concentrated to a gum. The first few gums crystallised from chloroform-ether mixtures but all efforts to crystallise the other fractions failed. The crystals obtained showed m. p. ca. 225° (crude buphanitine [crude crystalline "haemanthine"]).

(iii) The gum (5 g.) in chloroform (50 ml.) was fractionally extracted with N/10 sulphuric acid (10 x 30 ml.). The bases from the first few aliquots gave partially crystalline

gums, m. p. ca. 225°, (crude buphanitine [crude crystalline "haemanthine"]). The bases from the other fractions could not be induced to crystallise.

(iv) The mixed bases (5 g.) in 2N hydrochloric acid (50 ml.) were extracted with chloroform B (5 x 10 ml.). The aqueous solution was basified with sodium carbonate and the free bases extracted with chloroform, dried over anhydrous sodium sulphate and concentrated to a gum D. The chloroform solution B was shaken with aqueous sodium carbonate, dried over anhydrous sodium sulphate and concentrated to a gum E.

Gum D in chloroform (50 ml.) was fractionally extracted with N/10 sulphuric acid (3 x 30 ml.). The chloroform solution was concentrated to a gum and chromatographed on alumina. Elution with benzene, benzene-ethyl acetate mixtures, chloroform and methanol gave gums. The gums from the 60% ethyl acetate-benzene fractions in acetone deposited crystals, m. p. ca. 170° (crude buphanamine). The acid extract was basified and extracted with chloroform which was dried over anhydrous sodium sulphate and concentrated to a gum. The gum in acetone deposited prisms m. p. ca. 225°, (crude buphanitine [crude crystalline "haemanthine"]).

Gum E in benzene was adsorbed on alumina and eluted as above. The benzene fractions eluted non-alkaloidal material which was discarded. The 10% ethyl acetate in

benzene fractions on concentration, gave gums (c... buphanidrine [crude "distichine"]). The 60% ethyl acetate in benzene fractions gave partially crystalline material, m. p. ca. 170° (crude buphanamine).

(v) Following the elegant method used by Renz [56] the mixed bases were dissolved in acetone and carefully set aside. The solution deposited crystals, m. p. ca. 225° (crude buphanitine). The liquor was concentrated to a gum which was dissolved in chloroform (50 ml.) and vigorously shaken with N hydrochloric acid (50 ml.), washed with water (10 ml.) and dried over anhydrous sodium sulphate. The gum thus obtained was dissolved in benzene and chromato--graphed on alumina (100 g.). The column was washed with benzene and eluted with 10% ethyl acetate in benzene. All the fractions on concentration gave gums (crude buphanidrine [crude "distichine"]).

The hydrochloric acid extract was combined with the water washing, basified with sodium carbonate and extracted with chloroform (5 x 50 ml.). The chloroform solution was washed with a little water and concentrated to a gum which was dissolved in benzene (100 ml.) and extracted with buffers pH 6.1 (3 x 30 ml.) and 5 (3 x 80 ml.).

The gum from the benzene solution in methanol was treated with one drop of 70% perchloric acid. Ether was

added and the solid which precipitated, recrystallised from the same solvents to give needles of buphanidrine ("distichine") perchlorate, m. p. 252°.

Analysis:

Found:	C, 51.8; H, 4.9
$C_{18}H_{21}O_4N$ requires	C, 52.0; H, 5.3%

The infrared spectrum was identical to the spectrum of an authentic sample of buphanidrine perchlorate.

The buffer extract (pH 6.1) was rendered alkaline with sodium carbonate and extracted with chloroform (4 x 50 ml.), which was dried over anhydrous sodium sulphate and concen-trated to a gum. The gum in acetone deposited crystals, m. p. ca. 225° (crude buphanitine [crude crystalline "haemanthine"]). The solution was decanted off and concentrated to a gum which was dissolved in benzene and chromatographed on alumina (100 g.). The column was eluted with benzene and benzene-ethyl acetate mixtures. The 60% ethyl acetate in benzene fractions gave semi-crystalline gums, m. p. ca. 170° (crude buphanamine). Later fractions eluted small amounts of crystalline material, m. p. ca. 225° (crude buphanitine [crude crystalline "haemanthine]).

The buffer extract (pH 5) was rendered alkaline with sodium carbonate and extracted with chloroform (4 x 50 ml.) which was dried over anhydrous sodium sulphate and

concentrated to a gum (0.7 g.). The gum in ether deposited a few crystals m. p. ca. 225° (crude buphanitine [crude crystalline "haemanthine]). The residue, from the decanted ether, in benzene was chromatographed on alumina. The column was eluted as in the previous cases. The 5% ethyl acetate in benzene fractions gave a small amount of material which crystallised from wet ether, m. p. 116—120°. These crystals had the same infrared spectrum as the compound, m. p. 110—120° isolated in separation (i). A small quantity of crystals m. p. ca. 170° (crude buphanamine) was also isolated from the later fractions.

(vi) The alkaloidal mixture (10 g.) in chloroform (50 ml.) was extracted with 0.2N hydrochloric acid (4 x 25 ml.) and washed with a small volume of water, which washing was combined with the hydrochloric acid extract F. The chloroform solution was shaken with aqueous sodium carbonate which in turn was extracted with chloroform. The combined chloroform extract was dried over anhydrous sodium sulphate, concentrated to a gum, and taken up in 0.5N hydrochloric acid (50 ml.). The ether extract, washed with a small volume of water, was concentrated under reduced pressure. The resulting gum, which partially solidified, was dissolved in benzene and chromatographed on alumina (100 g.).

Benzene, benzene-ethyl acetate mixtures and methanol were used as eluates. The 5% ethyl acetate in benzene fractions gave gums (crude buphanidrine [crude "distichine]). The later fractions contained non-crystalline material which was not studied further.

The hydrochloric acid extract F was basified with aqueous sodium carbonate and extracted with chloroform (4 x 30 ml.). The extract, washed with a small volume of water and dried over anhydrous sodium sulphate, gave a gum. The gum in acetone slowly deposited crystals, m. p. 230° (crude buphanitine [crude crystalline "haemanthine"]). The liquor was decanted off, concentrated to a gum and chromatographed on alumina (150 g.) using as eluates, benzene, benzene-ethyl acetate mixtures and ethyl acetate. All fractions were crystallised from acetone. The earlier fractions gave a substance, m. p. ca. 170° (crude buphanamine) and the latter fractions gave a substance m. p. ca. 225° (crude buphanitine [crude crystalline "haemanthine"]).

Dihydrolycorine.——

Lycorine (2 g.) in glacial acetic acid (70 ml.) was hydrogenated at atmospheric pressure over Adams' catalyst. After three hours the hydrogenation was complete, one mole of hydrogen per mole of lycorine. The solution was filtered, concentrated and poured into water. The aqueous

solution was washed with ether, basified with sodium carbonate and extracted with amyl alcohol (4 x 50 ml.) which was dried over anhydrous sodium sulphate, filtered and concentrated, under reduced pressure, to a gum. The gum crystallised from hot ethanol in colourless prisms of dihydrolycorine, m. p. 247° (1.4 g.).

(Literature : m. p. 246° and 247°)

Diacetyldihydrolycorine.—

A solution of dihydrolycorine (1.4 g.) in acetic anhydride (50 ml.) was refluxed for one hour, concentrated and poured into water. The aqueous solution was basified with a saturated solution of sodium carbonate and extracted with chloroform (4 x 50 ml.). The chloroform extract was dried over anhydrous sodium sulphate, filtered and concen--trated to a gum. The gum solidified upon trituration with ethanol. The solid crystallised from hot ethanol in colourless plates of diacetyldihydrolycorine, m. p. 171—2° (0.7 g.).

Buphanidrine ("distichine").—

(a) Crude buphanidrine in methanol, treated with water until the solution was turbid, gave colourless needles. After five such operations the needles showed m. p. 145°.

Analysis:

Found:	C, 64.2, 64.2, 63.7; H, 6.8, 6.4, 6.8
$C_{18}H_{21}O_4N.1\frac{1}{2}H_2O$ requires	C, 64.3; H, 7.1%

Sublimation of the crystals, m. p. 145°, gave a semi-crystalline mass.

Found:	C, 66.8, 66.7; H, 6.4, 6.2
$C_{18}H_{21}O_4N.\frac{1}{2}H_2O$ requires	C, 66.6; H, 6.8%

(NOTE: The sublimate formed a picrate identical to the picrate formed from the crystals, m. p. 145°, by comparison of analyses, infrared spectra and mixed melting point determinations).

Buphanidrine, m. p. 145°, in ether was concentrated and seeded with a sample of anhydrous buphanidrine, m. p. 90—92°, kindly supplied by Dr. Wildman. On setting aside, the solution deposited large prisms of unhydrated buphanidrine, m. p. 90—92°.

Analysis:

Found:	C, 68.1; H, 6.6
$C_{18}H_{21}O_4N$ requires	C, 68.5; H, 6.7%

The infrared spectrum of the unhydrated buphanidrine and the spectrum of buphanidrine supplied by Dr. Wildman were

identical.

The hydrated buphanidrine crystals, m. p. 145°, in ether were dried over anhydrous sodium sulphate and filtered into a sublimation tube. The ether was removed on a steambath and the base sublimed to give the hemi-hydrated form. The experiment was repeated using chloroform as solvent but the result was unaltered.

(b) Pure buphanidrine picrate in hot water was cooled, the base regenerated by the addition of 2N sodium hydroxide and extracted with ether. The ethereal solution was washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure at room temperature to give a pale yellow gum. The gum in ethanol was treated with picric acid and the picrate m. p. 235°, did not depress when admixed with buphanidrine picrate, m. p. 234°.

The gum was distilled at 140°/0.2 mm. $[\alpha]_D^{22}$ -34.5° (concentration 1, in chloroform).

Analysis:

Found:	C, 68.9;	H, 7.0
$C_{18}H_{21}O_4N$ requires	C, 68.5;	H, 6.7%

It was noticed that on leaving the gum open to the atmosphere it changed from colourless to a silky, semi-

colourless gum.

Analysis:

Found:	C, 67.4;	H, 7.0
$C_{18}H_{21}O_4N$ requires	C, 68.5;	H, 6.7%

Buphanidrine Styphnate.——

An alcoholic solution (1.5 ml.) of buphanidrine (0.01 g.) was treated with a few drops of saturated ethanolic styphnic acid. The yellow precipitate which formed immediately was filtered off and recrystallised from ethanol to give yellow rectangular laminae of buphanidrine styphnate, m. p. 239—241°.

Analysis:

Found:	C, 50.5, 50.6;	H, 4.1, 3.7
$C_{24}H_{24}O_{12}N_4 \cdot \frac{1}{2}H_2O$ requires	C, 50.6;	H, 4.4%

Buphanidrine Platinichloride.——

Buphanidrine (0.01 g.) in 2N hydrochloric acid was treated with an excess of an aqueous solution of platinum chloride. The yellow precipitate which formed was filtered off, washed with cold water and recrystallised from hot water. The solution deposited orange-yellow rods of buphanidrine platinichloride, m. p. 223°.

Analysis:

Found:	C, 40.7, 40.8;
	H, 4.4, 4.2;
	Pt, 18.7, 18.7
$C_{18}H_{21}O_4N.PtCl_6.H_2O$ requires	C, 40.9;
	H, 4.2;
	Pt, 18.4%

Hydrogenation of Buphanidrine.——

Method A: An ethanolic solution (20 ml.) of buphanidrine (200 mg.) absorbed one mole of hydrogen per mole of buphanidrine when stirred at room temperature and atmospheric pressure with 10% palladium on charcoal (100 mg.). The catalyst was filtered off and the filtrate concentrated to a gum. The gum in ethanol was treated with saturated picric acid and the amorphous precipitate crystallised from acetone-ethanol. Recrystallisation from acetone-ethanol gave yellow prisms of dihydrobuphanidrine picrate, m. p. 286°.

Analysis:

Found:	C, 52.6; H, 4.5
$C_{18}H_{23}O_4N.C_6H_3O_7N_3$ requires	C, 52.7; H, 4.75%

Method B: Buphanidrine (100 mg.) in distilled methanol was treated with a few milligrams of platinum oxide. The mixture was shaken in an atmosphere of hydrogen for 36 hours. The suspension was filtered off and the methanol removed under reduced pressure to give a

gum which was identified as buphanidrine by comparison of the infrared spectra of its picrate, m. p. 234°, and perchlorate, m. p. 252°, with the authentic curves of buphanidrine picrate and perchlorate respectively.

The experiment was repeated using glacial acetic acid, N hydrochloric acid and methanol containing a few drops of concentrated hydrochloric acid as solvents. In all cases unchanged buphanidrine was recovered.

Buphanidrine Methiodide.—

To a solution of buphanidrine (0.5 g.) in methanol (25 ml.), methyl iodide (1 ml.) was added. The solution was refluxed on a steam-bath for 30 minutes. The condenser was removed and the excess methyl iodide distilled off. On setting aside the solution deposited needle crystals which were recrystallised from methanol to give colourless needles of buphanidrine methiodide, m. p. 275°.

Analysis:

Found:	C, 49.6, 49.9;	H, 5.4, 5.5
$C_{18}H_{21}O_4N.CH_3I$ requires	C, 49.9;	H, 5.3%

The salt crystallised from acetone, m. p. 286°.

Found:	C, 49.4;	H, 5.4%

Buphanidrine Picrate.——

A few drops of saturated alcoholic picric acid was added to a solution of buphanidrine (100 mg.) in ethanol (5 ml.). The amorphous mass which precipitated was dissolved in boiling ethanol and set aside. The solution deposited yellow needles of buphanidrine picrate, m. p. 235°.

Analysis:

Found:	C, 52.6, 52.7, 52.7; H, 4.6, 4.0, 4.4; N, 10.1; OMe, 10.4
$C_{18}H_{21}O_4N.C_6H_3O_7N_3$ requires	C, 52.9; H, 4.4; N, 10.3; OMe, 11.2%

Buphanidrine Hydroperchlorate.——

Buphanidrine (100 mg.) in methanol (2 ml.) was treated with a few drops of 70% perchloric acid and the solution made turbid with ether. On setting aside the solution deposited a mass of fine needle crystals. Recrystallisation from the methanol-ether gave colourless needles of buphanidrine hydroperchlorate, m. p. 252°.

Analysis:

Found:	C, 52.0, 52.2, 51.8; H, 5.4, 5.2, 5.2;
$C_{18}H_{21}O_4N.HClO_4$ requires	C, 52.0; H, 5.3%

Colour Reactions of Buphanidrine.——

A few milligrams of buphanidrine was dissolved in a few drops of concentrated sulphuric acid and a magenta colour was obtained.

The experiment was repeated using concentrated nitric acid and a bright yellow colour developed.

Buphanidrine Oxalate.——

A saturated ethereal solution (7 ml.) of dihydrated oxalic acid was added to an ethereal solution (1 ml.) of buphanidrine (50 mg.). The white amorphous solid which immediately precipitated was washed with ether, dissolved in acetone and light petroleum added until the solution was turbid. On setting aside the solution deposited needles of buphanidrine oxalate, m. p. 187—188°.

Analysis:

Found:	C, 59.0; H, 5.7;
$C_{18}H_{21}O_4N.C_2H_2O_4$ requires	C, 59.25; H, 5.7%

Hofmann Degradation of Buphanidrine.——

Buphanidrine methiodide (7.4 g.) in hot distilled water, was cooled and treated with freshly precipitated silver oxide prepared from silver nitrate (9 g.). The solution was stirred for thirty minutes, filtered and concentrated on a steam-bath to a brown, very hygroscopic,

semi-crystalline gum. The gum was heated at 105°/40 mm., until bubbling ceased, cooled and lixiviated with ether. This process was repeated four times. The remaining dark brown residue in water was treated with one drop of hydriodic acid. On setting aside crystals deposited. The aqueous liquor was decanted off and the solid recrystallised from methanol in needles, m. p. 275°. The infrared spectra of these crystals and buphanidrine methiodide were identical.

The ether solutions were shaken with a small volume of water, dried over anhydrous sodium sulphate and concentrated to a gum (3 g.). The gum in benzene was chromatographed on alumina (100 g.). The column was eluted with benzene (7 x 50 ml.), 5% ethyl acetate in benzene (3 x 50 ml.), 10% ethyl acetate in benzene (4 x 50 ml.), 15% ethyl acetate in benzene (6 x 50 ml.), 20% ethyl acetate in benzene (5 x 30 ml.) and finally with methanol (500 ml.). The fluorescent benzene eluates gave gums β-buphanidrine methine. Fractions 15 to 21 on concentration gave gums which solidified upon lixiviation with ether. The solid in a small volume of ether deposited prisms of α-buphanidrine methine (0. 9 g.), m. p. 117—9°.

Analysis:

Found:	C, 65.4; H, 6.8; N, 4.2; OMe, 20.1; N-Me, 4.8
$C_{17}H_{21}O_4N.\frac{1}{2}H_2O$ requires	C, 65.4; H, 7.1; N, 4.5; 2OMe, 19.3; N-Me, 4.7%
$C_{17}H_{19}O_4N.\frac{1}{2}H_2O$ requires	C, 65.8; H, 6.5; N, 4.5; OMe, 19.4; N-Me, 4.7%

Ozonolysis of Buphanidrine Methine.——

A solution of crude buphanidrine methine (0.2 g.) in chloroform was cooled in ice and a steady stream of ozone was passed through the solution for 3 hours. The yellow gum which separated was dissolved in hot water and transferred to a distillation flask. The distillate was collected in a test tube containing an aqueous solution of dimedone and the needle crystals which formed, m. p. 188—9° did not depress when admixed with a specimen of formaldehyde dimedone.

Buphanidrine methine (0.2 g.) was ozonised as above, but the product was decomposed by reduction. The solid which separated in ethanol (25 ml.) was hydrogenated over platinum oxide for 30 hours. The solution was evaporated under reduced pressure at room temperature to a gum, which was taken up in alcohol and again evaporated to dryness. The residue which gave positive aldehyde tests with Fehling's solution and Schiff's base, failed to crystallise.

Zinc Dust Distillation of Buphanidrine Methine.——

Impure buphanidrine methine (1 g.) in ether was stirred with zinc dust (15 g.) until the mixture was a homogeneous paste. The ether was removed by evaporation in a vacuum dessicator. The resulting solid was crushed to a powder and packed into a combustion tube which contained zinc dust (50 g.). The organic material was distilled in a slow stream of hydrogen at red heat. The product in chloroform was chromatographed on alumina (25 g.) and eluted with ether (6 x 150 ml.) and finally with methanol (3 x 150 ml.). All the ether fractions gave white precipitates upon treatment with aqueous mercuric chloride. The mercuric chloride double salt from the second fraction was dissolved in hot water and hydrogen sulphide was bubbled through the solution for fifteen minutes. The mercuric sulphide was removed by filtration and the filtrate rendered alkaline with sodium carbonate. The precipitated material was extracted with ether (4 x 15 ml.), washed with a small volume of water and dried over anhydrous sodium sulphate. The filtered extract gave on concentration a gum which was dissolved in ethanol and treated with a few drops of a saturated ethanolic solution of picric acid. The amorphous precipitate crystallised again from ethanol in yellow prisms of phenanthridine picrate, m. p. 229°.

Analysis:

Found	C, 56.1; H, 3.0.
$C_{19}H_{12}O_7N$ requires	C, 55.9; H, 3.0%

The sample did not depress the melting point of an authentic specimen of phenanthridine picrate, m. p. 230°, prepared from carbazole, and the infrared spectra were identical. (Chart 1).

The mercuric chloride double salt of the fifth fraction was processed as above. The picrate crystallised from ethanol as needles, m. p. 235°.

Analysis:

Found	C, 58.2; H, 5.3.
$C_{22}H_{24}O_7N_4$ requires	C, 57.9; H, 5.3.
$C_{22}H_{22}O_7N_4$ requires	C, 58.1; H, 4.8.
$C_{22}H_{20}O_7N_4$ requires	C, 58.4; H, 4.5%

The first chloroform fraction gave a mercuric chloride double salt which was regenerated as above. The gum in ethanol was treated with a few drops of ethanolic picric acid and the precipitate crystallised from ethanol in yellow needles of buphanidrine picrate, m. p. 229°.

Analysis:

Found	C, 52.7; H, 3.9.
$C_{24}H_{24}O_{11}N_4$ requires	C, 52.6; H, 4.6%

α-Buphanidrine Methine Hydrochloride.——

To a solution of α-buphanidrine methine (0.03 mg.) in methanol (1 ml.) one drop of concentrated hydrochloric acid was added and the solution made turbid with ether. On setting aside needles deposited. The solution was decanted off and the solid recrystallised from methanol-ether, gave needles of α-buphanidrine methine hydrochloride, m. p. 236°. The salt also crystallised from acetone in needles m. p. 236°.

Analysis:

Found	C, 56.5, 56.4;	
	H, 6.5, 6.7;	Cl, 9.3.
$C_{17}H_{22}O_4NCl.H_2O$ requires	C, 56.9;	
	H, 6.7;	Cl, 9.9%

α-Buphanidrine Methine Hydroperchlorate.——

One drop of 70% perchloric acid was added to a methanolic solution (1 ml.) of α-buphanidrine methine (0.02 mg.). The solution was made turbid with ether and agitated. The mass of fine needles was separated by centrifuging and decantation of the liquor. Recrystallis--ation from methanol-ether gave colourless needles of α-buphanidrine methine hydroperchlorate, m. p. 230°.

Analysis:

Found	C, 50.4;	H, 5.5.
$C_{17}H_{22}O_8NCl$ requires	C, 50.4;	H, 5.4%

Catalytic Hydrogenation of α-Buphanidrine Methine.—

α-Buphanidrine methine (0.5 g.) in methanol (25 ml.) was hydrogenated at atmospheric pressure in the presence of platinum catalyst (20 mg.). The absorption of hydrogen was rapid and the reduction was complete in one hour, one mole of hydrogen per mole of α-buphanidrine methine having been absorbed. The platinum catalyst was removed by filtration and the filtrate concentrated to a gum under reduced pressure. The gum solidified on lixiviation with acetone. The solid in acetone on setting aside slowly deposited prisms of α-dihydrobuphanidrine methine, m. p. 154—156°.

Analysis:

Found	C, 65.0; H, 7.5.
$C_{17}H_{23}O_4N.\frac{1}{2}H_2O$ requires	C, 65.0; H, 7.7%

α-Dihydrobuphanidrine Methine Methiodide.—

To a solution of α-dihydrobuphanidrine methine (0.1 g.) in methanol (2 ml.), methyl iodide (0.5 ml.) was added. The solution was refluxed on a steam-bath for 3 hours and concentrated to a gum under reduced pressure. Lixiviation of the gum with acetone gave a solid mass which was recrystallised twice from acetone to give colourless needles of α-dihydrobuphanidrine methine methiodide, which discoloured at 214—216° and m. p. 292—300° (dec.).

Analysis:

Found	C, 47.0; H, 5.7.
$C_{18}H_{26}O_4NI.H_2O$ requires	C, 47.2; H, 6.0%

α-Dihydrobuphanidrine Methine Hydrochloride.——

α-Dihydrobuphanidrine methine (0.03 g.) in methanol (1 ml.) was treated with one drop of concentrated hydro--chloric acid and agitated. The solid which immediately separated, recrystallised from methanol-ether in a mass of fine colourless needles of α-dihydrobuphanidrine methine hydrochloride, m. p. 200—205° with recrystallisation and m. p. 240—3°.

Analysis:

Found	C, 56.2, 56.2;
	H, 7.2, 7.1.
$C_{17}H_{24}O_4NCl.H_2O$ requires	C, 56.7;
	H, 7.3%

α-Dihydrobuphanidrine Methine Hydroperchlorate.——

A solution of α-dihydrobuphanidrine methine (30 mg.) in methanol (1 ml.) was treated with one drop of 70% perchloric acid and made turbid with ether. On setting aside the solution deposited crystals which recrystallised from methanol-ether in fine needles of α-dihydrobuphanidrine methine hydroperchlorate, m. p. 220—230° (dec.).

Analysis:

Found	C, 48.0; H, 6.5.
$C_{17}H_{24}O_8NCl.H_2O$ requires	C, 48.2; H, 6.2%

β-Buphanidrine Methine Hydrochloride.—

Concentrated hydrochloric acid (0.1 ml.) was added to a solution of β-buphanidrine methine (0.1 g.) in methanol (2 ml.). Ether was added until the solution was turbid. The solid which separated, recrystallised twice from methanol-ether, gave colourless hygroscopic needles of β-buphanidrine methine hydrochloride, m. p. 160°.

Analysis:

Found	C, 58.4; H, 7.1; Cl, 8.4.
$C_{19}H_{24}O_4NCl.1\frac{1}{2}H_2O$ requires	C, 57.9; H, 6.8; Cl, 9.0%

α-Buphanidrine Methine Methiodide.—

To a solution of α-buphanidrine methine (1 g.) in methanol (10 ml.), methyl iodide (1 ml.) was added and the solution refluxed on a steam-bath for two hours. The solvent was removed under reduced pressure and the residue dissolved in hot acetone. On setting aside the solution deposited colourless crystals of α-buphanidrine methine methiodide, m. p. 210—14°.

Hofmann Degradation of α-Buphanidrine Methine.—

Buphanidrine methine methiodide (1 g.) in hot water was treated with silver oxide, freshly prepared from silver nitrate (2 g.), and the mixture stirred at room temperature for 30 minutes. The solid material was filtered off and the filtrate, which gave a negative iodide test, was concentrated under reduced pressure on a steam-bath. The concentrate deposited a white powder which was filtered off and dissolved in ether. On setting aside the solution deposited colourless rhombohedra of α-buphanidrine methine, m. p. 117°. A mixture of the product and an authentic specimen of α-buphanidrine methine showed no melting point depression.

Emde Degradation of α-Buphanidrine Methine.—

An aqueous solution of α-buphanidrine methine methiodide (0.7 g.) was stirred for 30 minutes with an excess of freshly prepared, acid free silver chloride. The precipitate was filtered off and the solution concentrated under reduced pressure on a steam bath. The white powder which deposited recrystallised from ether as rhombohedra of α-buphanidrine methine, m. p. 117°. The infrared spectra of the regenerated base and authentic α-buphanidrine methine were identical.

Sodium Hydroxide Treatment of α-Buphanidrine Methine.——

α-Buphanidrine methine methiodide (1 g.) was refluxed with 10% sodium hydroxide (20 ml.) for one hour. The cooled solution was extracted with ether E_1 (4 x 10 ml.), acidified with hydrochloric acid and extracted with ether E_2 (4 x 10 ml.). The ether extract E_1 was extracted with 1N hydro--chloric acid (4 x 10 ml.), washed with a small volume of water, dried over anhydrous sodium sulphate and on concentration gave a neglible amount of material. The hydrochloric acid extract was rendered alkaline with sodium carbonate and extracted with ether (4 x 10 ml.). The ether extract was dried and concentrated to a gum. The gum in methanol was treated with a few drops of concentrated hydro--chloric acid and the solution made turbid with ether. The solid which precipitated was recrystallised from the methanol -ether to give colourless needles of α-buphanidrine methine hydrochloride, m. p. 236°. The infrared spectrum of this sample was identical to the infrared spectrum of an authentic specimen of α-buphanidrine methine hydrochloride.

The ether extract E_2 was washed with a small volume of water, dried over anhydrous sodium sulphate and concentrated to give a small amount of gum which could not be induced to crystallise.

Hofmann Degradation of α-Dihydrobuphanidrine Methine.-

α-Dihydrobuphanidrine methine methiodide (1 g.) in hot water (30 ml.) was filtered, cooled rapidly and well washed silver oxide, prepared from silver nitrate (2 g.), added. The mixture was stirred for 20 minutes, filtered and concentrated under reduced pressure on a steam-bath to 15 ml. The white powder which deposited was filtered off and the filtrate concentrated under the above conditions to 5 ml. A further quantity of white solid which precipitated was filtered off and combined with the previously obtained material. An acetone solution of the solid gave prisms of α-dihydrobuphanidrine methine, m. p. 154—6°. The infrared spectra of an authentic specimen of α-dihydrobuphanidrine methine and the end product from the reaction, were identical.

Emde Degradation of α-Dihydrobuphanidrine Methine.——

α-Dihydrobuphanidrine methine methiodide (0.5 g.) in hot water (20 ml.) was stirred with an excess of freshly prepared, acid free, silver chloride for 30 minutes. The solid was filtered off and the solution concentrated under reduced pressure on a steam-bath. The white solid was removed by filtration and the filtrate on concentration deposited a further quantity of white material. The combined precipitates in acetone slowly deposited prisms of

α-dihydrobuphanidrine methine, m. p. 154—6°. The infrared spectrum of the regenerated base was identical with the spectrum of authentic α-dihydrobuphanidrine methine.

Hydrochloric Acid Hydrolysis of Buphanidrine.—

A solution of buphanidrine (1 g.) in 4N hydrochloric acid (35 ml.) was refluxed for one hour. The cooled solution was diluted with water, washed with ether (2 x 25 ml.), rendered alkaline with concentrated ammonium hydroxide and extracted with chloroform (4 x 25 ml.). The chloroform extract was washed with a small volume of water, dried over anhydrous sodium sulphate and concentrated to a gum. The gum in benzene was chromatographed on alumina (25 g.).

The 10% ethyl acetate in benzene eluates gave gums which were dissolved in methanol and treated with a few drops of 70% perchloric acid. Ether was added until the solutions were turbid. On setting aside the solutions deposited prisms which were recrystallised from methanol-ether. The prisms were identified by mixed melting point determinations and comparison of infrared spectra as buphanidrine perchlorate, m. p. 252°.

The first few chloroform fractions eluted gums which crystallised upon lixiviation with acetone. The solid material was recrystallised twice from ethyl acetate to give colourless prisms of powelline, m. p. 199—201°. Wildman [70] gives m. p. 200—201°.

The latter chloroform fractions gave gums which could not be induced to crystallise.

Powellenone.—

To a stirred solution of powelline (0.5 g.) in chloroform (200 ml.) was added active manganese dioxide (3 g.). The reaction mixture was stirred at room temper--ature for 6 hours, filtered and the precipitate washed with a warm (1 : 1) ethanol-chloroform solution. The combined filtrates were concentrated under reduced pressure to give a colourless oil.

Powellanone.—

Powellenone (0.2 g.) in ethanol (20 ml.) was hydrogen--ated over pre-reduced 10% palladium on charcoal (100 mg.) at atmospheric pressure and room temperature. The compound rapidly absorbed hydrogen (ca. 15 ml.). The catalyst was filtered off, washed with ethanol and the combined filtrates concentrated under reduced pressure. The residual oil crystallised from benzene-cyclohexanone in colourless prisms of powellanone, m. p. 150—152°. Further recrystallisations from the same solvents raised the m. p. to 157—9°. (Wildman [70] gives m. p. 158—9°.)

Powellane.——

Powellanone (50 mg.) was treated with 85% hydrazine hydrate (0.55 ml.). A warm solution of potassium hydroxide (300 mg.) in diethylene glycol (2 ml.) was added to the reaction mixture. The reactants were heated to 150—160° in an oil bath held at 175—185° for 2 hours. The cooled solution, diluted with water was extracted with ether (3 x 7 ml.). The ethereal solution was washed with a small volume of water, dried over anhydrous sodium sulphate, filtered and concentrated to an oil. The oil in ethanol was treated with a few drops of saturated ethanolic picric solution. The yellow solid which precipitated was recrystallised twice from ethanol to give needles of powellane picrate, m. p. 210—213°.

Powellane picrate in chloroform was chromatographed on alumina (5 g.). Elution with chloroform gave an oil which was sublimed on a Kofler hotplate. The oily sublimate readily crystallised upon agitation to give rhombohedra of powellane, m. p. 111°.

(Wildman [70] gives powellane picrate, m. p. 213—215°, and powellane, m. p. 113.5—115°).

Buphanitine ("Haemanthine").——

The crude buphanitine, m. p. ca. 225°, in chloroform was treated with ether until the solution was turbid. After a few hours the solution deposited needles, $[\alpha]_D$ -102°, and a small amount of prisms. The solution was decanted off, seeded with prisms, and set aside. After a few hours the solution deposited prisms, $[\alpha]_D$ -101°. The infrared spectra of the needle and rhombohedral forms were similar but showed differences in the infrared. The needles changed crystalline form at 210° and finally melted at 230°. The prisms showed m. p. 230° and a mixture of the two forms did not depress the melting point. The samples were dried at room temperature under high vacuum for 12 hours.

Analysis:

Found for needles	C, 64.0, 64.0; H, 6.4, 6.4; Active H, 0.63.
$C_{17}H_{21}O_5N$ requires	C, 63.9 ; H, 6.6 ; Active 2H, 0.65%
Found for prisms	C, 63.4, 63.5; H, 6.4, 6.5.
$C_{17}H_{21}O_5N$ requires	C, 63.9 ; H, 6.6.

The needles and prisms sublimed at 175—180°/0.1 mm. to give needles, which changed crystalline form at 210° and m. p. 230°, and rhombohedra, m. p. 230°, respectively. The sublimates were submitted for analysis.

Analysis:

Found for needles	C, 64.1, 63.3;	H, 5.4, 5.4.
$C_{17}H_{21}O_5N$ requires	C, 63.9 ;	H, 6.6%
Found for prisms	C, 63.5 ;	H, 5.2.
$C_{17}H_{21}O_5N$ requires	C, 63.9 :	H, 6.6%

The needles were converted to rhombohedra by crystallisation from lesser turbid solutions of chloroform and ether and the rhombohedra gave needles from more turbid solutions of chloroform and ether.

The crude buphanitine crystallised from a concentrated ethanolic solution in colourless prisms which lost solvent of crystallisation at 130° and m. p. 240°. On setting aside the colourless rhombohedra gradually changed to opaque white crystals. The sample was dried at 100° under high vacuum for 12 hours and submitted for analysis.

Analysis:

Found	C, 63.8;	H, 6.7.
$C_{17}H_{21}O_5N$ requires	C, 63.9;	H, 6.6%

A concentrated solution of buphanitine in acetone deposited colourless prisms, m. p. 230°. Both needles and rhombohedra crystallised from acetone as colourless prisms, m. p. 230° and all the forms of haemanthine gave identical hydrochlorides.

Buphanitine Hydroperchlorate.——

A solution of buphanitine (0.1 g.) in methanol was treated with two drops of 70% perchloric acid and ether added until the solution was turbid. All efforts to induce crystallisation failed. A large volume of ether was added and precipitated salt filtered off. The solid crystallised from hot water in colourless flat needles of buphanitine hydroperchlorate, m. p. 99—100°. A sample was dried under high vacuum at room temperature and submitted for analysis.

Analysis:

Found:	C, 46.8;	H, 5.8.	
$C_{17}H_{22}O_9NCl.H_2O$ requires	C, 46.6;	H, 5.5%	

Buphanitine Methiodide.——

Buphanitine (1 g.) in methanol (25 ml.) was treated with methyl iodide (5 ml.) and the solution refluxed on a steam-bath for two hours. The crystals which separated recrystallised from methanol in fine colourless needles of buphanitine methiodide, m. p. 248°.

Analysis:

Found	C, 46.7;	H, 5.8;	N, 2.6.
$C_{18}H_{24}O_5NI$ requires	C, 46.7;	H, 5.2;	N, 3.0%

Dehydrobuphanitine.——

Buphanitine (0.2 g.) was crushed in a mortar with alumina (1 g.) and then sublimed at 175—180°/0.1 mm. The sublimate was in the form of colourless needles of dehydrobuphanitine, m. p. 197—9°.

Analysis:

Found	C, 65.4; H, 6.8.
$C_{34}H_{40}O_9N_2$ requires	C, 65.8; H, 6.5%

Buphanitine Hydrochloride.——

To a solution of buphanitine (50 mg.) in methanol (1 ml.) a few drops of concentrated hydrochloric acid was added and the solution made turbid with ether. Immediately fine needle crystals deposited. Recrystallisation from methanol-ether gave colourless needle crystals of buphanitine hydrochloride, m. p. 265°, $[\alpha]_D^{22}$ +13° (c, 1 in chloroform).

Analysis:

Found	C, 57.4; H, 6.4; Cl, 10.0.
$C_{17}H_{21}O_5N.HCl$ requires	C, 57.3; H, 6.2; Cl, 10.0%

Buphanitine Hydronitrate.——

Buphanitine (80 mg.) was dissolved in methanol and a few drops of concentrated nitric acid added to the solution. Ether was added until the solution was turbid and on setting

aside a mass of fine needles deposited. The solid was recrystallised from methanol-ether to give colourless needles of buphanitine hydronitrate, m. p. 234—6°.

Analysis:

Found	C, 53.1; H, 5.9.
$C_{17}H_{22}O_8N_2$ requires	C, 53.4; H, 5.8%

Lewin [46] gives oily "haemanthine" hydronitrate (unanalysed) m. p. 118°.

Acetylation of Buphanitine.—

A solution of buphanitine (0.5 g.), benzene (20 ml.), acetyl chloride (4 ml.) and acetic anhydride (10 ml.) was refluxed for 40 minutes, cooled and poured into water. The organic layer was separated and discarded. The aqueous solution was made alkaline with a saturated sodium carbonate solution and extracted with chloroform (4 x 25 ml.). The extract was washed with a small volume of water and concen--trated under reduced pressure. The crude gum in chloroform was chromatographed on alumina (15 g.) and the column eluted with benzene (4 x 25 ml.) and chloroform (3 x 25 ml.). The chloroform fractions were concentrated to gums which were dissolved in methanol, treated with one drop of hydrochloric acid and the solutions made turbid with ether. The crystals which deposited had m. p. 263° and the melting points did not depress when the samples were mixed with buphanitine hydrochloride.

The concentrated benzene fractions were made turbid with light petroleum and set aside. The solutions deposited an amorphous white solid of diacetylbuphanitine.

Analysis:

Found	C, 62.2, 62.1; H, 6.2, 6.1; COMe, 21.3.
$C_{21}H_{25}O_7N$ requires	C, 62.5; H, 6.3 ; 2COMe, 21.3%

On one occasion a turbid light petroleum-ether solution of the gums from the latter benzene fractions deposited colourless needle crystals of monoacetylbuphanitine, m. p. 199°.

Analysis:

Found	C, 62.9; H, 6.3; COMe, 10.6.
$C_{19}H_{23}O_6N$ requires	C, 63.1; H, 6.4; 1 COMe, 11.9%

Hydrolysis of Diacetylbuphanitine.——

Diacetylbuphanitine (0.6 g.) was refluxed with 15% ethanolic potassium hydroxide (50 ml.) for one hour. The ethanol was distilled off under reduced pressure, water added and the basic solution extracted with chloroform. The washed extract was dried over anhydrous sodium sulphate, filtered and concentrated to a gum. The gum crystallised from chloroform-ether in needles of buphanitine, m. p. 230°.

Analysis:

Found	C, 63.8; H, 6.4.
$C_{17}H_{21}O_4N$ requires	C, 63.9; H, 6.6%

The infrared spectrum was identical to the spectrum of an authentic specimen of buphanitine.

Hydrogenation of Buphanitine.—

A solution of buphanitine (0.2 g.) in methanol (30 ml.) was hydrogenated at atmospheric pressure over Adams's catalyst for 12 hours. The platinum was removed by filtration and the methanol distilled off under reduced pressure. The gum crystallised from chloroform-ether in needles of buphanitine, m. p. 230°. The infrared spectrum was identical to the infrared spectrum of the starting material.

Mercuric Acetate Oxidation of Buphanitine.—

Mercuric acetate (5 g.) was added to a solution of buphanitine (1 g.) in 5% acetic acid (40 ml.) and the solution was stirred at 60° for 2 hours, at 70° for 90 minutes and finally set aside for four days. No deposit of mercurous acetate formed.

Von Braun Degradation of Buphanitine.—

Diacetylbuphanitine (2 g.) in benzene was treated with excess cyanogen bromide and the solution refluxed on a steam-bath for 75 minutes, washed with 1N hydrochloric acid,

water, dried over anhydrous sodium sulphate and concen--trated to a gum (2.3 g.). A small portion of the gum in 2N nitric acid gave a pale yellow precipitate on treatment with a solution of silver nitrate. The gum in 5% sodium hydroxide (30 ml.) was refluxed for one hour. Carbon dioxide was bubbled through the solution for three hours. The solution was extracted with chloroform which was dried over anhydrous sodium sulphate, filtered and concentrated to a gum. The gum crystallised from chloroform-ether in fine colourless needles of unchanged buphanitine, m. p. 236°.

Analysis:

Found	C, 64.0, 64.2;	H, 7.0, 7.1;	
	N, 4.7.		
$C_{17}H_{21}O_5N$ requires	C, 63.9	; H, 6.6	;
	N, 4.4%		

The infrared spectra of the end product and starting material were identical.

Phosphorus Pentoxide Dehydration of Buphanitine.——

Buphanitine (0.5 g.), benzene (40 ml.) and phosphorus pentoxide (5 g.) were refluxed for one hour. The mixture, which darkened in colour, was cooled, poured into water and the organic layer separated. The aqueous solution was rendered alkaline with sodium carbonate and extracted with chloroform (3 x 75 ml.). The extract was dried over

anhydrous sodium sulphate, filtered and concentrated to a gum which solidified on lixiviation with acetone. The solid recrystallised from acetone in prisms of buphanitine, m. p. 236° (0.2 g.).

The infrared spectra and melting points of the starting material and the end product were identical.

6N Hydrochloric Acid Hydrolysis of Buphanitine.——

A solution of buphanitine (0.5 g.) in 6N hydrochloric acid (50 ml.) was heated at 90° for 150 minutes. The reaction mixture was basified with a saturated sodium carbonate solution and extracted with chloroform (4 x 30 ml.). The washed extract was dried over anhydrous sodium sulphate, filtered and concentrated to a gum which crystallised from acetone. The solid recrystallised from acetone in colour--less prisms of buphanitine, m. p. 236°.

The infrared spectrum was identical to the spectrum of authentic buphanitine.

Ar-demethoxybuphanitine.——

Buphanitine (1 g.) in n-butanol (150 ml.) was heated to boiling and sodium (9.7 g.) added over a period of one hour. The cooled solution was treated with a solution of ammonium chloride (25 g.) in water (75 ml.), and then steam distilled. The remaining aqueous solution was rendered alkaline with sodium carbonate and extracted with chloroform

(5 x 50 ml.). The chloroform extract was washed with a small volume of water, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The gum thus obtained was chromatographed on alumina (10 g.). Elution with chloroform gave first a pale yellow ether-soluble gum (0.05 g.) which failed to crystallise. Later eluates gave, on evaporation to dryness, almost colourless, ether-insoluble gums, which were dissolved in chloroform and ether added until the solution was just turbid. On setting aside a mass of fine crystals deposited. The solvent was decanted off and the solid recrystallised from the same solvents in colourless needles of Ar-demethoxy-buphanitine, m. p. 258°, $[\alpha]_D$ -105°.

Analysis:

Found	C, 66.3; H, 6.8; N, 5.0; OMe, 0.
$C_{16}H_{19}O_4N$ requires	C, 66.4; H, 6.6; N, 4.8%

Ar-demethoxybuphanitine hydrochloride.—

A methanol solution (0.5 ml.) of Ar-demethoxy--buphanitine was treated with one drop of concentrated hydrochloric acid and made turbid with ether. The mass of fine needles which formed recrystallised from methanol-ether in colourless needles of Ar-demethoxybuphanitine hydrochloride, m. p. 304—308°.

Analysis:

Found	C, 58.9; H, 6.7.
$C_{16}H_{19}O_4N.HCl$ requires	C, 58.8; H, 6.2%

Ar-Demethoxybuphanitine Hydroperchlorate.—

One drop of 70% perchloric acid was added to a solution of Ar-demethoxybuphanitine (50 mg.) in methanol (1 ml.). Ether was added until the solution was turbid and crystallisation was initiated by agitation with a glass rod. The solid material which formed recrystallised from methanol-ether in needles of ar-demethoxybuphanitine hydroperchlorate, m. p. 285—287°.

Analysis:

Found	C, 48.8; H, 5.5.
$C_{16}H_{17}O_4N.HClO_4$ requires	C, 49.2; H, 5.2%

Buphanitenone.—

A mixture of buphanitine (0.5 g.), freshly distilled aluminium isopropoxide (3 g.) and cyclohexanone (16 ml.) was heated under reflux in an atmosphere of nitrogen. After heating for half an hour the solution gelled and cyclohexanone (5 ml.) was added. The resultant solution was refluxed for 18 hours, cooled, poured into water (50 ml.), treated with 6N sodium hydroxide (20 ml.) and extracted with chloroform (4 x 30 ml.). The chloroform solution was washed with a small volume of water and extracted with 2N

hydrochloric acid (4 x 30 ml.). The acid solution was washed with ether (2 x 30 ml.), basified with a saturated sodium carbonate solution and the precipitated material extracted with chloroform (4 x 40 ml.), which was washed with a small volume of water, dried over anhydrous sodium sulphate and concentrated to a gum. This intractible material in 2N hydrochloric acid (20 ml.) was filtered, washed with ether (3 x 10 ml.) and extracted with chloro--form (3 x 20 ml.) which was washed with water and dried over anhydrous sodium sulphate. The gum thus obtained solidified upon trituration with ether. An acetone solution of the solid was decolourised with active charcoal and concentrated to a small volume. On setting aside the solution deposited rhombohedra of buphanitenone, m. p. 184—5° $[\alpha]_D$ +34° (c, 0.5 in chloroform).

Analysis:

Found	C, 68.2; H, 6.0; N, 5.1.
$C_{17}H_{17}O_4N$ requires	C, 68.2; H, 5.7; N, 4.7%

The infrared absorption curve (nujol mull) showed a strong band at 1670 $cm.^{-1}$. A solution of buphanitenone in 80% sulphuric acid gave upon treatment with chromotropic acid a magenta colour which did not develop with a control solution of buphanitenone in 80% sulphuric acid.

Buphanitenone Methiodide.——

To a solution of buphanitenone (200 mg.) in methanol (10 ml.) methyl iodide (1 ml.) was added. The reaction mixture was refluxed for half an hour and the excess methyl iodide distilled off. On cooling the solution deposited a white precipitate which recrystallised from methanol to give fine colourless needles of buphanitenone methiodide, as needles m. p. 241—3°.

Analysis:

Found	C, 48.1; H, 5.1.
$C_{17}H_{17}O_4N.CH_3I.\frac{1}{2}H_2O$ requires	C, 47.9; H, 4.9%

Lithium Aluminium Hydride Reduction of Buphanitenone.——

To a suspension of lithium aluminium hydride (1 g.) in sodium dry ether (100 ml.) buphanitenone (300 mg.) was added. The reaction mixture was boiled under reflux for 12 hours. The excess lithium aluminium hydride was decomposed with ethyl acetate and the heterogeneous mixture hydrolysed with 6N sodium hydroxide (50 ml.). During this process the organic solvents were distilled off. The aqueous solution was diluted and extracted with chloroform (4 x 50 ml.) which was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue crystallised when triturated with acetone. Recrystallisation from acetone gave rhombohedra

of α-buphanitenol, m. p. 167—170°.

Analysis:

Found	C, 67.6;	H, 6.5.
$C_{17}H_{19}O_4N$ requires	C, 67.76;	H, 6.4%

The sample in carbon tetrachloride showed an infrared absorption band at 3650 $cm.^{-1}$.

Manganese Dioxide Oxidation of α-Buphanitenol.——

Attenburrow [1] oxide (1.5 g.) was added to a stirred solution of α-buphanitenol (100 mg.) in chloroform (100 ml.). The reaction mixture was stirred at room temperature for 6 hours. The precipitate was filtered off and washed twice with chloroform. The washings were combined with the filtrate and the solvent removed by reduced pressure distillation. The resultant gum was dissolved in acetone and solidified when the solution was agitated. The solid was recrystallised twice from acetone to give colourless rhombohedra of buphanitenone, m. p. 184—5°.

The infrared spectrum was identical to the spectrum of an authentic specimen of buphanitenone.

α-Buphanitanol.——

α-Buphanitenol (200 mg.) in methanol (30 ml.) was hydrogenated at atmospheric pressure over Adams's catalyst. After three hours the hydrogen absorption was complete. The catalyst was filtered off, washed with methanol and

the combined filtrates concentrated to a gum. The gum crystallised from acetone in rhombohedra of α-buphanitanol, m. p. 211—213°, $[\alpha]_D^{22}$ ±0° (c, 1 in ethanol).

Analysis:

Found	C, 63.6; H, 6.7.
$C_{17}H_{21}O_4N.H_2O$ requires	C, 63.5; H, 7.2%

Catalytic Hydrogenation of Buphanitenone.—

(A) Platinum Catalyst:

Buphanitenone (100 mg.) in methanol was hydrogenated at room temperature and pressure over Adams's catalyst. After the hydrogen absorption ceased the catalyst was filtered off and washed twice with methanol. The combined filtrates were concentrated under reduced pressure. The gum crystallised from acetone to give colourless rhombohedra of β-buphanitanol, m. p. 130—140° with recrystallisation and m. p. 209—212°, $[\alpha]_D^{22}$ ±0° (c, 1 in ethanol). A sample was dried at room temperature under high vacuum and submitted for analysis.

Analysis:

Found	C, 63.6; H, 7.4.
$C_{17}H_{21}O_4N.H_2O$ requires	C, 63.5; H, 7.2%

A sample sublimed at 170° under high vacuum showed m. p. 209—212°.

Analysis:

Found	C, 63.8; H, 6.8.
$C_{17}H_{21}O_4N.H_2O$ requires	C, 63.5; H, 7.2%

A nujol mull showed an absorption at 3650 $cm.^{-1}$.

(B) 10% Palladium on Charcoal Catalyst:

Pre-reduced 10% palladium on charcoal (100 mg.) was added to a ethanolic solution (40 ml.) of buphanitenone (200 mg.) and the mixture was shaken in an atmosphere of hydrogen at room temperature and pressure. The solution rapidly absorbed a mole of hydrogen per mole of buphanitenone. The catalyst was removed by filtration and washed with ethanol. The ethanol filtrates were combined and concentrated to a gum. The gum was crystallised from acetone to give colourless rhombohedra of buphanitanone, m. p. 174—7°, $[\alpha]_D$ -5.6° (c, 1 in chloroform).

Analysis:

Found	C, 68.0; H, 6.5.
$C_{17}H_{19}O_4N$ requires	C, 67.8; H, 6.4%

The infrared spectrum in a nujol paste showed a strong absorption band at 1718 $cm.^{-1}$.

Lithium Aluminium Hydride Reduction of Buphanitanone.——

A solution of buphanitanone (70 mg.) in ether was treated with lithium aluminium hydride (200 mg.). The mixture was refluxed for 12 hours, treated with ethyl acetate to decompose the excess lithium aluminium hydride and the contents hydrolysed with 6N sodium hydroxide (30 ml.). The organic solvents were removed by distillation and the diluted aqueous layer extracted with chloroform (4 x 15 ml.) which was washed with water and dried over anhydrous sodium sulphate. The filtered extract was concentrated under reduced pressure to a gum which solidified upon trituration with acetone. The solid recrystallised from acetone in rhombohedra of α-buphanitanol, m. p. 211—213°, which melting point was undepressed on admixture with α-buphanitanol obtained by catalytic reduction of α-buphanitenol. Furthermore, the infrared spectra were identical.

Buphanitenone Methine.——

Buphanitenone methiodide (300 mg.) in hot water (10 ml.) was treated with 10% sodium hydroxide (5 ml.). The mixture was heated on a waterbath for 10 minutes and the precipitated base removed by benzene extraction (3 x 5 ml.). This process was repeated until the aqueous solution was negative to a Mayers test. The benzene extract was washed with water, dried over anhydrous sodium sulphate and concentrated to a

gum which solidified on trituration with acetone. The solid was recrystallised twice from acetone to give colourless rhombohedra of buphanitenone methine, m. p. 131—2°, $[\alpha]_D^{20}$ ±0 (C, 1 in chloroform).

Analysis:

Found	C, 68.5; H, 6.1.
$C_{18}H_{19}O_4N$ requires	C, 68.99; H, 6.1%

The infrared absorption curve of the sample in nujol showed a strong band at 1663 cm.$^{-1}$.

Buphanitane.—

Oxobuphanitane (140 mg.) and 85% hydrazine hydrate (1.5 ml.) were added to a warm solution of potassium hydroxide (0.8 g.) in diethylene glycol (5 ml.). The reaction flask was placed in an oil bath, which was maintained at 175—185°, and the solution refluxed at 150—160° for 2 hours. The reaction mixture was cooled, poured into water (20 ml.) and extracted with ether (3 x 10 ml.), and chloroform (3 x 10 ml.), (A). The basic solution was acidified with 2N hydrochloric acid, then rendered alkaline with a saturated sodium carbonate solution and extracted with chloroform (3 x 15 ml.) (B).

The ethereal extract was washed with a small volume of water, dried over anhydrous sodium sulphate and concentrated to a gum. Alcoholic picric acid was added to the gum in

ethanol and the amorphous picrate, which precipitated immediately, separated. Three recrystallisations from ethanol gave pure buphanitane picrate, m. p. 210—213°, $[\alpha]_D$ +3 (c, 1 in chloroform).

Analysis:

Found	C, 53.6; H, 4.4.
$C_{17}H_{21}O_5N.C_6H_3O_7N_3$ requires	C, 53.5; H, 4.7%

The chloroform solutions (A) and (B) were separately washed with small volumes of water, dried over anhydrous sodium sulphate and concentrated to gums (A) and (B). The negligible quantity of gum (A) was discarded and gum (B) proved to be intractible.

Buphanitane picrate in chloroform was chromatographed on alumina (5 g.). Elution with chloroform gave an oil which solidified upon lixiviation with ether. The solid sublimed at 140°/0.1 mm. to give buphanitane as laminae, m. p. 143—144°, $[\alpha]_D^{18}$ +4.6 (c, 1 in chloroform).

Analysis:

Found	C, 70.7; H, 7.7.
$C_{17}H_{21}O_3N$ requires	C, 71.05; H, 7.4%

A mixture of buphanitane and powellane (needles, m. p. 113—115°) prepared from buphanidrine showed melting point 102—113°.

Buphanamine.——

Crude buphanamine crystallised from hot acetone in colourless prisms, m. p. 192—4°.

Analysis:

Found	C, 67.7;	H, 6.3.
$C_{17}H_{19}O_4N$ requires	C, 67.76;	H, 6.36%

Buphanamine Hydrochloride.——

Buphanamine (0.01 g.) in methanol (1 ml.) was treated with two drops of concentrated hydrochloric acid. The solution was made turbid with ether and on setting aside deposited a mass of fine needle crystals of buphanamine hydrochloride, m. p. 180°.

Analysis:

Found	C, 54.8;	H, 6.4.
$C_{17}H_{20}O_4NCl.2H_2O$ requires	C, 54.6;	H, 6.5%

Buphanamine Hydronitrate.——

To a solution of buphanamine (0.01 g.) in methanol (1 ml.) a few drops of concentrated nitric acid was added. Ether was added until the solution was turbid and on setting aside colourless prisms of buphanamine hydronitrate, m. p. 128—130°, deposited.

Analysis:

Found	C, 51.4;	H, 5.8.
$C_{17}H_{20}O_7N_2.2H_2O$ requires	C, 51.0;	H, 6.0%

Dihydrobuphanamine.—

Buphanamine (150 mg.) in methanol (25 ml.) was hydrogenated over Adams's catalyst at atmospheric pressure. When the hydrogen absorption was complete the catalyst was filtered off and the filtrate concentrated under reduced pressure. The gum solidified when triturated with acetone. The solid recrystallised from acetone in colourless prisms of dihydrobuphanamine, m. p. 200°.

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