The solution was cooled to 10–15° and oxygen containing ozone (0.0051 mole of ozone per hour by thiosulfate titration of liberated iodine) was bubbled through the solution for 2 hours (100% excess). Two such batches were combined and a solution of 25 ml. of 30% H_2O_2 in 100 ml. of H_2O was added to it. The resulting yellow solution was left at room temperature for 4 hours and was then warmed on the steam-bath for 2 hours. The solvent was distilled *in vacuo* until 25 ml. of yellow oil remained. To this oil was added 45 ml. of H_2O and 5 ml. of 30% H_2O_2. After the solution was allowed to stand overnight at room temperature a solid deposit was formed. The solid was collected, washed well with water containing a little sodium bisulfite and dried, 1.7 g. The filtrate was treated with solid sodium bisulfite until all hydrogen peroxide was reduced and was extracted with 150 g. of $CHCl_3$ in 6 portions. After drying of the $CHCl_3$ extract over Na_2SO_4 and removal of the solvent, there was left 0.2 g. of crystalline solid; combined yield, 1.9 g. (58.5%). The combined solids were treated with a small amount of $CHCl_3$. From these $CHCl_3$ washings there was obtained 0.1 g. of a substance, m.p. 321–325°, which was identified as oxostrychnine epoxide by comparison of its infrared spectrum with that of an authentic sample. The residual solid melted at 285–292°. It was recrystallized 3 times from absolute MeOH, m.p. 288–292°, when heated on a Kofler block, or 314–317° when the capillary was placed in the bath above 250°.

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.65; H, 4.97; N, 8.64. Found: C, 66.06, 65.99, 66.29; H, 4.93, 4.93, 4.75; N, 8.26, 8.40.

The substance was saturated to 1% $KMnO_4$, was insoluble in 10% $NaHCO_3$, but dissolved slowly in 10% NaOH or 6 *N* HCl; $[\alpha]^{24}D$ +139 ± 2° (*c* 1.288, glac. HOAc); ultraviolet spectrum (absolute EtOH): λ_{max} 252 mμ, log ε 4.11. The infrared spectrum (Nujol mull) had bands at 3.08 and 5.65 μ in addition to the two lactam bands.

Acid VIII.—To 20 ml. of absolute MeOH containing 0.61 mmole of Na was added 200 mg. (0.62 mmole) of lactone VII. Within a few minutes the lactone dissolved to form a yellow solution. After standing for one hour the solvent was removed *in vacuo* at room temperature. The residual solid was dissolved in 5 ml. of H_2O and extracted with $CHCl_3$. This extract when worked up contained only a slight oily film. The aqueous basic solution was cooled and acidified by dropwise addition of 1 *N* HCl. The resulting white precipitate was filtered off, washed with H_2O and dried. It was crystallized from MeOH, forming fern-like leaves which sintered to fine needles above 200° and melted at 279–285°. After further recrystallization from MeOH the m.p. was raised to 299–302°. The substance liberated CO_2 from 10% $NaHCO_3$ and was unsaturated to 1% $KMnO_4$; mol. wt. calcd. for monobasic acid, 324; found by titration in 50% EtOH against 0.01116 *N* NaOH: mol. wt., 327 ± 5; ultraviolet spectrum (absolute EtOH): λ_{max} 292 mμ, log ε 3.61 (see Fig. 1).

Acid IX.—To a solution of 0.30 mmole of Na in 10 ml. of absolute MeOH was added 100 mg. (0.31 mmole) of lactone VII. The yellow solution was left at room temperature for 46 hours. The solution was worked up as above. No basic or neutral products were isolated and acidification produced only a small amount of yellow gum which was insoluble in $CHCl_3$. Extraction of the aqueous acidic phase with 60 ml. of $CHCl_3$ in 4 portions, followed by drying over Na_2SO_4 and removal of the solvent, left a transparent glassy residue. After drying *in vacuo*, this glass could be crystallized from MeOH furnishing 5.6 mg. of rectangular plates arranged in radial clusters, m.p. 255–259°. The compound dissolved readily in 10% $NaHCO_3$ with evolution of CO_2 and was unsaturated to 1% $KMnO_4$; ultraviolet spectrum (absolute EtOH): λ_{max} 254 mμ, log ε 4.06 (see Fig. 2).

Acknowledgment.—It is a pleasure to express my gratitude to Prof. R. B. Woodward, who suggested this problem, for his invaluable advice throughout the course of this work and in the preparation of the manuscript.

CAMBRIDGE 38, MASS.

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

The Structures of Haemanthamine and Crinamine[1]

BY H. M. FALES AND W. C. WILDMAN

RECEIVED JUNE 3, 1959

Degradative and spectral evidence is presented to show that structures XXVa and XXVIa represent the alkaloids haemanthamine and crinamine, respectively.

The alkaloid haemanthamine (natalensine) ranks second only to lycorine in abundance within the family Amaryllidaceae. It was reported first as a constituent of the *Haemanthus* hybrid "Konig Albert" by Boit.[2] Within the last five years it has been isolated from a number of *Haemanthus*,[3,4] *Narcissus*,[5–8] *Crinum*,[9] *Hippeastrum*,[10,11] *Hymenocallis*[12,13] and *Zephyranthes*[9,10,14] species and from *Calostemma purpureum* R. Br.,[13] *Elisena longipetala* Lindl.,[13] *Galanthus elwesii* Hook. F.,[14] *Sprekelia formosissima* (L.) Herb.,[14] *Urceolina miniata* (Herb.) Benth. and Hook,[13] and *Vallota purpurea* (Ait.) Herb.[11] In contrast, crinamine, which was isolated first by Tanaka[15] from *Crinum asiaticum* var. *japonicum* Bak., occurs in trace amounts in *Ammocharis coranica* (Ker.) Herb.,[16] *Brunsvigia cooperi* Baker,[17] a few *Crinum* spp.[9,14,16] and *Nerine bowdenii* W. Wats.[18]

The quantity of crinamine at our disposal was so limited that degradation was limited to critical experiments which were performed after the struc-

(1) Paper XIII in a series concerning alkaloids of the Amaryllidaceae; previous paper, H. M. Fales and W. C. Wildman, THIS JOURNAL, **80**, 4395 (1958). Part of the present paper has appeared in communication form: (a) H. M. Fales and W. C. Wildman, *Chemistry & Industry*, 561 (1958); (b) W. C. Wildman and H. M. Fales, THIS JOURNAL, **80**, 6465 (1958).

(2) H.-G. Boit, *Chem. Ber.*, **87**, 1339 (1954).

(3) W. C. Wildman and C. J. Kaufman, THIS JOURNAL, **77**, 1248 (1955).

(4) F. L. Warren and W. G. Wright, *J. Chem. Soc.*, 4696 (1958).

(5) H.-G. Boit, W. Stender and A. Beitner, *Chem. Ber.*, **90**, 725 (1957).

(6) H.-G. Boit and W. Döpke, *ibid.*, **89**, 2462 (1956).

(7) H.-G. Boit and H. Ehmke, *ibid.*, **89**, 163 (1956).

(8) H.-G. Boit, W. Döpke and A. Beitner, *ibid.*, **90**, 2197 (1957).

(9) H.-G. Boit, W. Döpke and W. Stender, *ibid.*, **90**, 2203 (1957).

(10) H.-G. Boit, W. Döpke and W. Stender, *Naturwissenschaften*, **45**, 390 (1958).

(11) H.-G. Boit, *Chem. Ber.*, **89**, 1129 (1956).

(12) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **45**, 315 (1958).

(13) H.-G. Boit and W. Döpke, *Chem. Ber.*, **90**, 1827 (1957).

(14) H.-G. Boit and H. Ehmke, *ibid.*, **88**, 1590 (1955).

(15) K. Tanaka, *J. Pharm. Soc. Japan*, **57**, 139 (1937).

(16) L. H. Mason, E. R. Puschett and W. C. Wildman, THIS JOURNAL, **77**, 1253 (1955).

(17) L. J. Dry, M. Poynton, M. E. Thompson and F. L. Warren, *J. Chem. Soc.*, 4701 (1958).

(18) The alkaloids of *N. bowdenii* will be discussed in a future paper of this series.

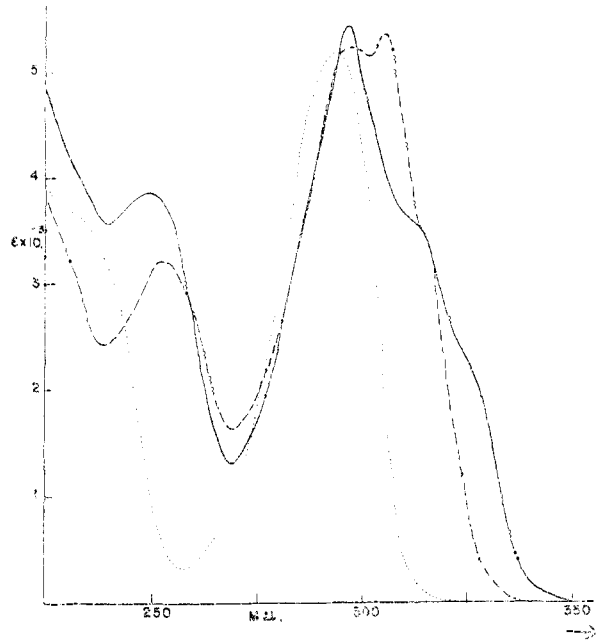
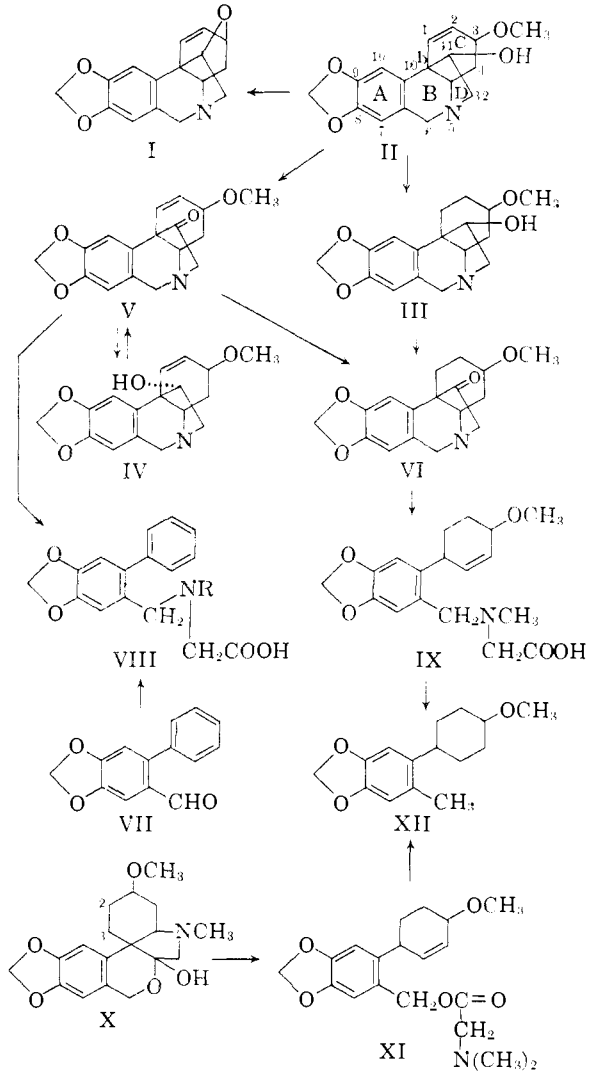


Fig. 1.—Ultraviolet absorption spectra of: dihydrohaemanthamine (III) in ethanol, ...; oxodihydrohaemanthamine (VI) in ethanol, ——; VI in ethanolic hydrochloric acid, -----.

ture of haemanthamine had been determined. This paper presents evidence to establish stereostructures for haemanthamine and crinamine.

Both alkaloids possess the molecular formula $C_{17}H_{19}NO_4$ and contain one methylenedioxy group, one methoxyl and one hydroxyl. Each contains one double bond which may be saturated by either catalytic or chemical methods. This unsaturation is not conjugated with the aromatic ring in either alkaloid, since the ultraviolet absorption spectrum of each shows normal methylenedioxyphenyl absorption (λ_{max}^{EtOH} 297 mμ, ε 5100) which is not altered appreciably in the dihydro derivatives. The ultraviolet spectra indicate also that the methoxyl group is not on the aromatic ring, a fact that is substantiated by the lack of infrared absorption at 1613 cm.$^{-1}$ [19] and by subsequent chemical degradations. The hydroxyl group of each base gave a normal ester derivative.

O-Acetyldihydrohaemanthamine was stable to oxidation by a saturated solution of potassium permanganate in acetone at room temperature. Since similar conditions oxidize acetyldihydro derivatives of the lycorine type to lactams,[20,21] it was considered unlikely that haemanthamine is a methyllycorine. This was supported by the observation that haemanthamine was not oxidized by selenium dioxide, a reagent which usually oxidizes alkaloids containing the lycorine ring system. Although haemanthamine was not affected by manganese dioxide, it was oxidized by chromic acid in pyridine. The product, oxohaemanthamine (V), showed carbonyl absorption at 1748 cm.$^{-1}$. Since saturated ring C ketones have been found to absorb near 1712 cm.$^{-1}$, [22,23] the high frequency of carbonyl absorption in oxohaemanthamine is compatible with a ketone on a five-membered ring. The ultraviolet spectrum (Fig. 1) deviated from that of haemanthamine but not in a manner to suggest conjugation of the carbonyl group with either the aromatic ring or the double bond. Oxodihydrohaemanthamine (VI) prepared by either the catalytic reduction of V or the oxidation of dihydrohaemanthamine (III), showed carbonyl absorption at 1748 cm.$^{-1}$ and the same unusual ultraviolet spectrum. Compatible with the assigned structure VI, oxodihydrohaemanthamine formed a monofluorenylidene derivative. An epimeric alcohol (IV) was formed when V was reduced with sodium borohydride.



This product differs from haemanthamine only in the configuration of the hydroxyl group since oxohaemanthamine was formed upon oxidation with chromic acid in pyridine. Catalytic hydrogenation of epihaemanthamine afforded a dihydro derivative.

(19) W. C. Wildman and C. J. Kaufman, THIS JOURNAL, **77**, 4807 (1955).

(20) E. W. Warnhoff and W. C. Wildman, *ibid.*, **79**, 2192 (1957).

(21) S. Takagi, W. I. Taylor, S. Uyeo and H. Yajima, *J. Chem. Soc.*, 4003 (1955).

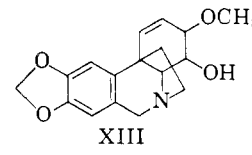
(22) W. C. Wildman, THIS JOURNAL, **80**, 2567 (1958).

(23) E. W. Warnhoff and W. C. Wildman, *Chemistry & Industry*, 1293 (1958).

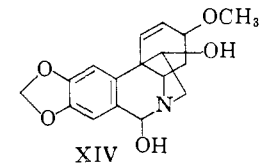
The alkaline degradation products of V and VI provided most valuable information supporting structure II for haemanthamine. When a solution of V in *t*-butyl alcohol was heated under reflux with potassium *t*-butoxide, an amino acid was formed which was shown by synthesis to have structure VIII (R = H). Condensation of 6-phenylpiperonal (VII) with ethyl glycinate gave a Schiff base which was reduced catalytically and then hydrolyzed to VIII (R = H), identical in all respects with the product derived from oxohaemanthamine. Under similar alkaline conditions, VI did not react, but the methiodides of V and VI when warmed in aqueous alkali afforded VIII (R = CH_3) and IX, respectively, in good yield. The structure of VIII (R = CH_3) was verified by the methylation of synthetic VIII (R = H) with formaldehyde and formic acid. The proposed structure IX is supported by the analytical data, solubility in acid and base, and infrared spectrum. The ultraviolet absorption spectrum showed that the double bond was not conjugated with the aromatic ring, while the stability of this product to acid precluded an isomeric enol ether structure. As required by structure IX, the substance was found to be optically active. Catalytic hydrogenation of IX proceeded with the absorption of two equivalents of hydrogen to form an optically inactive, neutral substance (XII) which proved to be identical with a degradation product of dihydrotazettine (X). Hofmann degradation of dihydrotazettine methiodide afforded a methine which has been shown to possess structure XI.[24,25] Catalytic hydrogenation of XI proceeded with the uptake of two equivalents of hydrogen to yield the same neutral product XII.[26] Comparison of XII derived from dihydroöxohaemanthamine and from dihydrotazettine showed no differences in ultraviolet or infrared spectra and no mixture melting point depression.

From the structures of these degradation products (VIII, IX and XII), the substitution pattern of the aromatic ring and the position of the methoxyl in ring C were established in haemanthamine. Furthermore, the environment of the amino group has been defined more clearly.[27] It is most reasonable to assume that the double bond of IX is introduced in the Hofmann degradation of VI and that the carboxyl group of IX is derived from the carbonyl group of oxodihydrohaemanthamine. If the carbonyl absorption at 1748 cm.$^{-1}$ is indicative of a five-membered ring, only structures V and VI are acceptable for oxohaemanthamine and oxodihydrohaemanthamine. An alternative structure with the ethano bridge linking the nitrogen to position 4 would result in the lycorine ring system which is unlikely for the reasons mentioned earlier. Finally, the double bond is placed in the 1,2-position since the alkaloid does not behave like an enol ether or a blocked enamine (*e.g.*, $\Delta^{4,4a}$).

The degradative evidence presented above is sufficient to establish the structure of haemanthamine as shown in formula II and to eliminate the necessity for considering an alternative structure XIII proposed at one time by Boit and co-workers.[28] The placement of functional groups in haemanthamine as shown in II is compatible with the structure XIV assigned recently to haemanthidine, an alkaloid of this family which has been converted to tazettine,[29,30] dihydroapohaemanthamine (I, no double bond),[31] and most recently, to dihydrohaemanthamine (*vide infra*). The conversion of haemanthamine to (+)-dihydrobuphanisine (III, no OH at C_{11})[1b] offers additional proof of the 5,10b-ethanophenanthridine nucleus in haemanthamine and will be discussed in a subsequent paper in this series.

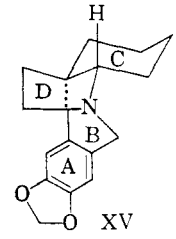


XIII

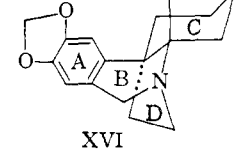


XIV

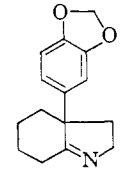
The parent ring system of haemanthamine can be constructed in either of two ways, XV and XVI, which differ in the mode of C:D ring fusion, *i.e.*, *trans* in the former and *cis* in the latter. In terms of the B:C ring junction, it is *cis* in XV and *trans* in XVI. It was reasoned by Sugimoto and Kugita[32] that when 3,3a,4,5,6,7-hexahydro-3a - (3,4 - methylenedioxyphenyl)- pseudoindole (XVII), a key intermediate in the synthesis of (±)-crinane,[22] is reduced catalytically, hydrogen from the catalyst surface adds from the side opposite that occupied by the phenyl to produce a *trans* B:C (octahydroindole) ring fusion (XVIII).



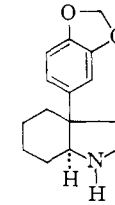
XV



XVI



XVII



XVIII

(24) R. J. Highet and W. C. Wildman, *Chemistry & Industry*, 1159 (1955).

(25) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo and H. Yajima, *J. Chem. Soc.*, 4749 (1956).

(26) This reduction was first carried out by Dr. R. J. Highet of this Laboratory.

(27) The difficulties encountered in the Hofmann degradation of haemanthamine have been reported recently.[4] While these degradations locate the position of the methylenedioxy group, the location of the methoxyl and the nature of the ring system could not be assigned rigorously.

(28) H.-G. Boit, W. Döpke and W. Stender, *Naturwissenschaften*, **45**, 262 (1958). In a more recent paper [*Chem. Ber.*, **91**, 1965 (1958)], Boit accepted structure II for haemanthamine. However, no new experimental evidence was cited in support of either structure.

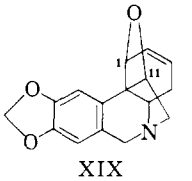
(29) H.-G. Boit and W. Stender, *ibid.*, **89**, 161 (1956).

(30) W. C. Wildman, *Chemistry & Industry*, 123 (1956).

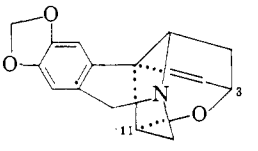
(31) S. Uyeo, H. M. Fales, R. J. Highet and W. C. Wildman, THIS JOURNAL, **80**, 2590 (1958).

(32) N. Sugimoto and H. Kugita, *Pharm. Bull.*, **5**, 378 (1957).

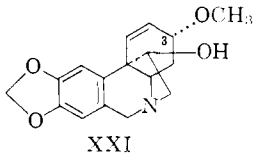
This ring fusion would lead to XV after Pictet–Spengler cyclization with formaldehyde. Such a structure also might be thought to explain the analgesic activity of several of the Amaryllidaceae alkaloids, since there is a strong geometrical similarity between XV, morphine and codeine.[33] We have obtained proof that all Amaryllidaceae alkaloids known to be derived from 5,10b-ethanophenanthridine have a *cis* B:C ring fusion as in XVI.[34] In the presence of 6 *N* hydrochloric acid, haemanthamine was converted in good yield to apohaemanthamine, $C_{16}H_{15}NO_3$. From the following evidence, we feel that apohaemanthamine is represented correctly by I. The molecular formula indicates that apohaemanthamine must contain either an additional ring or point of unsaturation beyond that of haemanthamine. The correctness of the former possibility is demonstrated by the infrared spectrum of I which shows no absorption bands from 5000–1500 cm.$^{-1}$ attributable to hydroxyl or carbonyl groups. Apohaemanthamine possesses no methoxyl group as shown by analysis and infrared spectrum. An unconjugated double bond is present since apohaemanthamine absorbed one equivalent of hydrogen under catalytic conditions. The ultraviolet spectrum of apohaemanthamine indicates that this unsaturation is not conjugated with the aromatic ring since the same spectrum was found for dihydroapohaemanthamine. The infrared spectrum (CCl_4) of I showed a sharp peak at 3116 cm.$^{-1}$, a frequency slightly higher than that characteristic of a disubstituted double bond[35]; this band was missing in the dihydro derivative. These data require that a new, oxygen-containing ring be present in apohaemanthamine. In addition to I, structure XIX, the allylic isomer of I, must be considered as an alternative structure for apohaemanthamine. By converting ring C of XVI to the boat form, an ether bridge between C_3 and C_{11} can be formed. Molecular models of such a product (XX) and its dihydro



XIX



XX



XXI

derivative are compact and possess very little strain. However, a C_1–C_{11} ether bridge as in XIX cannot be constructed with these models using either mode of B:C ring fusion (XV or XVI), and it must be concluded that structure XIX is either impossible or extremely strained. If the latter possibility is granted, it would be expected that such a linkage would be relatively prone toward ring opening. The fact that apohaemanthamine is stable to hot 6 *N* hydrochloric acid and to lithium aluminum hydride in refluxing tetrahydrofuran practically eliminates the consideration of XIX as the structure of apohaemanthamine in favor of the nearly strainless alternative structure. Apohaemanthamine cannot be formed if the C:D ring fusion is *trans* (as in XV), regardless of the conformation of ring C.

Apohaemanthamine was formed by the action of 6 *N* hydrochloric acid on crinamine. It was this reaction which provided the first indication that crinamine is closely related to haemanthamine. Crinamine formed a ketone, oxocrinamine, when oxidized by chromic acid in pyridine. This substance was not identical with V but showed similar carbonyl absorption at 1748 cm.$^{-1}$ and a comparable, abnormal ultraviolet spectrum. If the conversion of crinamine to apohaemanthamine does not involve an allylic rearrangement, oxocrinamine must be the 3-methoxy epimer of V and crinamine may be assigned the structure XXI. Such a formulation is supported by rotational data. In agreement with the earlier observation of Mills,[36] allylic 3-methoxy or 3-hydroxy epimers of tazettine,[25] powelline[22,37] and crinine[22,37] differ in specific rotation by at least 100°. The effect of replacing the 3-hydroxyl by methoxyl of the same configuration in these alkaloids does not appear to affect the specific rotations to a significant extent (*cf.* crinine, $[\alpha]_D$ −11.1°; buphanisine, $[\alpha]_D$ −26°; powelline, $[\alpha]_D$ 0°: buphanidrine, $[\alpha]_D$ −6.9°). A difference of 124° in the specific rotations of crinamine and haemanthamine is in accord with the epimeric nature of the methoxyl group in the alkaloids. Furthermore, this change is in the right direction. It will be shown in this and subsequent papers[18] that the allylic methoxyl or (hydroxyl) groups of crinine, powelline, buphanidrine, buphanisine, haemanthamine and haemanthidine are *cis* with respect to the aryl group. Epimerization of these groups causes this relationship to become *trans*. In crinine and powelline, which are based on the (−)-crinane nucleus, this epimerization of the hydroxyl from a *cis* to a *trans* relationship with respect to the aryl group causes a levorotatory increase of at least 100°.[22,37] Since haemanthamine is derived from the enantiomorphic (+)-crinane nucleus,[1b] a change in the configuration of the methoxyl to that of crinamine should and does provide a dextrorotatory increase of a similar amount (haemanthamine, $[\alpha]_D$ +33°: crinamine, $[\alpha]_D$ +157°).[38]

From the foregoing data, structures II and XXI may be assigned to haemanthamine and crinamine, respectively. From the structure of apohaemanthamine, these formulas may be refined to XXII. Except for determination of the absolute configuration of the alkaloids, it has been possible to expand

(33) H. Rapoport and J. B. Lavigne, THIS JOURNAL, **75**, 5329 (1953).

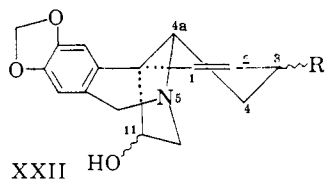
(34) This paper is limited to the proof of such a ring fusion for alkaloids hydroxylated in position 11; alkaloids not hydroxylated in this position will be discussed in a future paper.

(35) W. H. Tallent and I. J. Siewers, *Anal. Chem.*, **28**, 953 (1956).

(36) J. A. Mills, *J. Chem. Soc.*, 4976 (1952).

(37) W. C. Wildman, *Chemistry & Industry*, 1090 (1956).

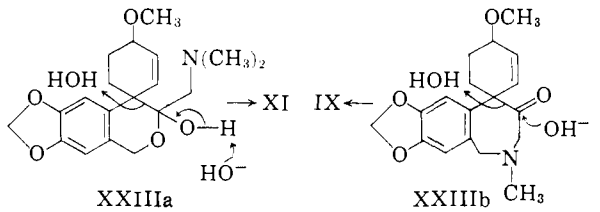
(38) Alternate chemical evidence that XXI is the correct formula for crinamine and that no allylic rearrangement has occurred in the preparation of apohaemanthamine has been obtained from other investigations of Amaryllidaceae alkaloids currently under study in this Laboratory. These data will be reported shortly.



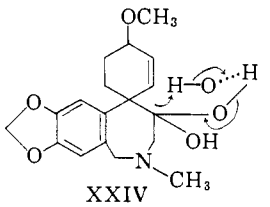
XXII

XXII to the complete stereostructures of both haemanthamine and crinamine.

The process by which IX and XI are obtained from the methohydroxides of VI and X, respectively, is uncertain. In the latter case, it was suggested[25] that the reaction proceeds by normal Hofmann elimination to produce the intermediate XXIIIa which by a rate-controlled displacement of water at the benzylic carbon atom would afford XI. A similar mechanism (XXIIIb → IX) may be proposed in the present case. Alternatively, both reactions may proceed *via* a cyclic intermediate such as XXIV. Such a course would require that the stereochemical relationship existing between



XXIIIa XXIIIb

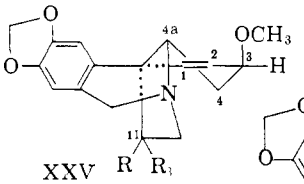


XXIV

the aryl and methoxyl groups in ring C of the precursors (VI and X) be retained in the product (XII). Since this need not be true of displacement mechanisms involving XXIIIa and XXIIIb, the degradation of haemanthamine and tazettine to a common product XII does not prove that the phenylmethoxyl relationship is the same in both alkaloids. However, we have been able to prove this to be true by another method.

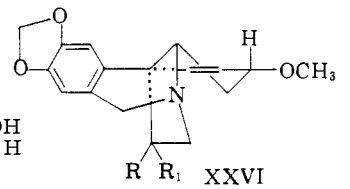
From degradative data,[25] it was suggested that the methoxyl and aryl groups of tazettine (X, double bond 1,2) are *cis*. Recently,[39] this has been proved by synthesis. Since haemanthidine methiodide is converted instantaneously to tazettine by extremely mild conditions[29,40] (cold, dilute ammonium hydroxide), there is no reason to doubt that these groups are *cis* in haemanthidine also. Thus the conversion of either tazettine or haemanthidine to haemanthamine (or a derivative thereof) by a process which does not involve either of these two centers would provide evidence for the stereochemical relationship of the methylenedioxyphenyl and methoxyl groups in haemanthamine. Both routes have been successful. Uyeo recently has achieved the conversion of tazettine to epihaemanthamine methiodide (methiodide of IV).[40] We have been able to convert haemanthidine to dihydrohaemanthamine in 3–5% yield by catalytic hydrogenation–hydrogenolysis. Since neither of these conversions involves C_{10b} or C_3, the methylenedioxyphenyl and methoxyl groups have the same configurations as in tazettine, *i.e.*, *cis*. Since crinamine is the C_3-epimer of haemanthamine it follows that these groups are *trans* in crinamine, and the structures of haemanthamine and crinamine may be expanded to XXV and XXVI, respectively.

The configuration of the C_{11}-hydroxyl group of haemanthamine and crinamine was determined by spectral studies emanating from the unique position occupied by this group between two unsaturated centers, the aromatic ring A and the 1,2-unsaturation. Since haemanthamine (II) and epi-



XXV

Series a, R = H, R_1 = OH
b, R = OH, R_1 = H



XXVI

haemanthamine (IV) are C_{11}-epimers, they may now be represented by structures XXVa and XXVb. Similarly, XXVIa and XXVIb represent crinamine and epicrinamine. When models were made of these structures, it became apparent that the hydroxyl group at C_{11} was situated favorably for hydrogen bonding with the π-electrons of the C_{1-2} double bond in series a (R = H, R_1 = OH). In the alternative series b (R = OH, R_1 = H), the hydroxyl group may bond readily with the π-electrons of the aromatic ring. It was reasoned that hydrogenation of the isolated double bond at C_{1-2} should alter the frequency of the OH stretching band of that epimer in which R_1 = OH, while such a hydrogenation would not change the frequency of a hydroxyl group bonded to the aromatic ring in this manner.

The normal absorption frequency for free secondary alcohols is approximately 3620 cm.$^{-1}$.[41] As shown in Table I, the alkaloids crinine (XXV, R,R_1 = H, OH instead of OCH_3), epicrinine (XXVI, R,R_1 = H, OH instead of OCH_3), and the dihydro derivatives of crinine, crinamine and haemanthamine absorb in the range 3620–3625 cm.$^{-1}$. However, the hydroxyl absorptions of crinamine and haemanthamine show bathochromic shifts of 34 and 27 cm.$^{-1}$, respectively, from the value of 3625 cm.$^{-1}$ found for their dihydro derivatives, which we attribute to a hydrogen bond between the C_{11}-hydroxyl group and the C_{1-2} unsaturation.[42,43] This evidence indicates that haemanthamine and crinamine possess the stereostructures XXVa and XXVIa, or the mirror images thereof, respectively. In contrast, epihaemanthamine shows a bathochromic shift of 60 cm.$^{-1}$ from the norm of 3620

(39) H. Irie, Y. Tsuda and S. Uyeo, *J. Chem. Soc.*, 1446 (1959).
(40) S. Uyeo, personal communication.
(41) M. St. C. Flett, *Spectrochim. Acta*, **10**, 21 (1957).
(42) Similar examples have been reported recently by P. von R. Schleyer, D. S. Trifan and R. Bacskai, THIS JOURNAL, **80**, 6691 (1958), and in references cited therein. Hydrogen bonding between phenols and benzenoid systems has been investigated recently by A. W. Baker and A. T. Shulgin, *ibid.*, **80**, 5358 (1958).
(43) R. West, *ibid.*, **81**, 1614 (1959).

TABLE I

HYDROXYL STRETCHING FREQUENCIES OF AMARYLLIDACEAE ALKALOIDS[a]

Compound	Hydroxyl frequency, cm.$^{-1}$	Hydroxyl frequency of dihydro derivative, cm.$^{-1}$
Haemanthamine	3598	3625
Crinamine	3591	3625
Epihaemanthamine	3560	3560
Crinine	3620	3621
Epicrinine	3622	..

[a] The compounds were observed at high dilution in carbon tetrachloride with a Beckman IR-7 double-beam, prism-grating spectrophotometer. The spectral slit width was approximately 4 cm.$^{-1}$ and the wave length was accurate to ± 3 cm.$^{-1}$. Only one sharp band was observed in each case, presumably because variations of the OH–π-bond distance are minimized due to the compact structures of these compounds; *cf.* cyclohexanol-1-alkanol.[41]

cm.$^{-1}$, which is not altered by reduction of the double bond. We consider this an example of the hydrogen of a hydroxyl group bonded to an aromatic ring. The marked extent of this bonding (and consequent shift in frequency) may be attributed to the methylenedioxy substitution of the aromatic ring and the rigidly fixed position of the C_{11}-hydroxyl group toward the aromatic ring. Accordingly, we assign the structure XXVb to epihaemanthamine. It is interesting to note that this configuration is in agreement with the observation that epihaemanthamine fails to form apohaemanthamine (XX) on treatment with acid. Presumably XX is formed by attack of the C_{11}-hydroxyl on the allylic carbonium ion at C_3. Since III also fails to yield XX, it seems likely that the carbonium ion is generated at C_3 and that the oxygen atom of XX is derived from the C_{11}-hydroxyl.

The unusual ultraviolet spectra of VI in acid and base as compared to dihydrohaemanthamine (Fig. 1) may be attributed to the unique location of the carbonyl function.[44] We believe that the inflexions at 313 and 324 mμ are due to the two longest wave length bands of the cyclopentanone chromophore [310 mμ (ϵ 15.9) and 323 mμ (ϵ 5.0)],[45] the intensities of which have been augmented by π-electron overlap with the methylenedioxyphenyl ring. A similar explanation has been given for the anomalous spectra of several derivatives of 9,10-dihydro-9,10-ethano-11-ketoanthracene (XXVII) in which a similar situation exists.[46] These anomalous bands at 313 and 324 mμ in V and VI undergo a hypsochromic shift of 7 mμ and an increase in extinction coefficient in acid solution, which may be attributed to an increase in the energy required for polarization of the carbonyl group adjacent to the positively charged nitrogen atom.

XXVII

Acknowledgment.—The authors are indebted to Messrs. D. L. Rogerson and J. D. Link for the processing of plant material and to Miss Elizabeth Kielar and Mr. Harry Mueller for the isolation of the pure alkaloids. The skillful assistance of Miss Patricia Wagner and Mrs. L. C. Warren in the instrumental aspects of the work is acknowledged gratefully.

Experimental[47]

Isolation and Characterization of the Alkaloids.—Haemanthamine was isolated, along with tazettine and haemanthidine, from the bulbs of *Sprekelia formosissima* (L.) Herb. by methods described earlier.[16] The yields were comparable to those reported by Boit and Ehmke[14] from the same source. Crinamine was obtained from the bulbs of *Nerine bowdenii* W. Wats. Isolations from this source will be described in detail elsewhere. Haemanthamine and crinamine were purified by the methods described in previous papers of this series[3,16] to give the physical constants reported therein.

The dissociation constants of the alkaloids and several of their degradation products are listed in Table II. In general, structural alterations change the dissociation constant in agreement with well-established principles.[48] Measurements were obtained in 60% dimethylformamide–water at 25° with a Beckman model G *p*H meter equipped with micro glass and calomel electrodes. The pK_a was considered equal to the *p*H at the mid-point of the titration curve.

TABLE II

DISSOCIATION CONSTANTS

Compound	pK_a	Compound	pK_a
Haemanthamine	6.95	Oxohaemanthamine	~4.34
Dihydrohaemantha-mine	7.55	Dihydroöxohaemanthamine	4.93
O-Acetyldihydro-haemanthamine	6.40	Apohaemanthamine	7.10
Crinamine	6.75	Dihydroapohaemanthamine	7.75

Haemanthamine was recovered unchanged from treatment with manganese dioxide and chloroform at 25° overnight, selenium dioxide in refluxing ethanol, *p*-toluenesulfonyl chloride and pyridine, sodium borohydride in ethanol, and 2,4-dinitrophenylhydrazine in dilute sulfuric acid. Haemanthamine methiodide was recovered from an attempted Emde degradation.

Dihydrohaemanthamine (III).—To a solution of 200 mg. of haemanthamine in 7 ml. of tetrahydrofuran was added 200 mg. of lithium aluminum hydride. The mixture was refluxed for 24 hours without protection from atmospheric moisture. The complex was destroyed by the addition of ethyl acetate followed by ethanol, water and 25% sodium hydroxide. The tetrahydrofuran was decanted and concentrated. The residue was dissolved in dilute hydrochloric acid, washed with benzene, basified and again extracted with chloroform. The chloroform solution was evaporated and the residue chromatographed on alumina. Elution with ethyl acetate gave a 53% yield of dihydrohaemanthamine, m.p. 229–230°, $[\alpha]^{25}_{589}$ +103° (*c* 2.9), +83° (*c* 0.25), identical in all respects with that obtained *via* catalytic reduction.[3] Dihydrohaemanthamine was recovered unchanged after refluxing with 6 *N* hydrochloric acid for 1 hour or 1 *N* acid overnight.

O-Acetyldihydrohaemanthamine.—A solution of 300 mg. of dihydrohaemanthamine in 12 ml. of 0.1 *N* perchloric acid and 5 ml. of acetic anhydride was allowed to stand overnight, poured into ice-water and neutralized with sodium bicarbonate. The aqueous solution was extracted with chloroform and the extracts were dried over sodium sulfate.

(44) Identical spectra were obtained from V and oxocrinamine.

(45) G. Förster, R. Skrabal and J. Wagner, *Z. Elektrochem.*, **43**, 291 (1937).

(46) W. E. Noland, M. S. Baker and H. I. Freeman, THIS JOURNAL, **78**, 2233 (1956).

(47) All melting points were observed on a *Kofler* microscope hot-stage and are corrected. The boiling points are uncorrected. Unless otherwise noted, rotations were measured in chloroform with a Rudolph photoelectric spectropolarimeter using a 2-dm. tube, and ultraviolet spectra were obtained in absolute ethanol solution on a Cary model 11 MS recording spectrophotometer. Infrared spectra were recorded on either a Perkin–Elmer model 21 or a Beckman IR-7 double-beam spectrophotometer in chloroform solution unless noted to the contrary. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

(48) H. C. Brown, D. H. McDaniel and O. Häfliger in E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 567.

Evaporation of the solvent left 284 mg. (83%) of the oily acetate. Chromatography on alumina failed to produce crystalline material. The oil was evaporatively distilled at 130° (2 μ) for analysis. The infrared spectrum (CCl_4) exhibited a typical acetate band at 1739 cm.$^{-1}$ but no absorption in the 5000–3125 cm.$^{-1}$ region.

Anal. Calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.70; H, 6.76; N, 3.99.

The base was recovered in 83% yield from treatment with a saturated solution of 2 moles of potassium permanganate in acetone at 25°.

The hydroperchlorate was prepared in ethanol–ether and recrystallized from ethanol as plates, m.p. 231–241° dec.

Anal. Calcd. for $C_{19}H_{23}NO_5 \cdot HClO_4$: C, 51.18; H, 5.43. Found: C, 51.07; H, 5.49.

Apohaemanthamine (I). (a) From Haemanthamine.—A solution of 1.00 g. of haemanthamine in 20 ml. of 6 *N* hydrochloric acid was heated on the steam-bath for 1 hour. The cooled solution was extracted with benzene, basified with sodium hydroxide and again extracted with chloroform. Evaporation of the chloroform extracts left an oil which was chromatographed on alumina. Ethyl acetate–benzene (1:1) eluted apohaemanthamine which was recrystallized from cyclohexane as prisms, m.p. 146–148°, $[\alpha]^{25}_{589}$ +204°, $[\alpha]^{25}_{436}$ +449° (*c* 1.03, ethanol). The infrared spectrum (CCl_4) showed a maximum at 3067 cm.$^{-1}$ (—CH=CH—C) but no methoxyl band at 2849 cm.$^{-1}$ or hydroxyl at 3700–3300 cm.$^{-1}$. The ultraviolet spectrum showed a maximum at 296 mμ (ϵ 5420). A sample was sublimed at 120° (25μ) for analysis.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61. Found: C, 71.36; H, 5.61; OCH_3, 0.00.

The free base was recovered essentially unchanged from treatment with lithium aluminum hydride in tetrahydrofuran.

The hydroperchlorate crystallized as prisms from aqueous ethanol, m.p. 202–203°.

Anal. Calcd. for $C_{16}H_{15}NO_3 \cdot HClO_4$: C, 51.97; H, 4.36; OCH_3, 0.00. Found: C, 52.21; H, 4.70; OCH_3, 0.00.

Apohaemanthamine picrate was recrystallized from ethanol as yellow prisms, m.p. 193–195°.

Anal. Calcd. for $C_{16}H_{15}NO_3 \cdot C_6H_3N_3O_7$: C, 53.01; H, 3.64; N, 11.24. Found: C, 53.05; H, 3.73; N, 10.95.

(b) **From Crinamine.**—A solution of 152 mg. of crinamine in 5 ml. of 6 *N* hydrochloric acid was heated on a steam-bath for 1 hour. The yellow solution was poured into 150 ml. of water, basified with ammonium hydroxide and extracted with chloroform. The chloroform extracts were washed with water and concentrated under reduced pressure to yield 150 mg. of pale yellow oil. Chromatography of this material on alumina (15 g.) and elution with ethyl acetate–benzene (1:1) gave 60 mg. of crude apohaemanthamine which was purified by sublimation, 50 mg., m.p. 140–145°. Recrystallization from cyclohexane and sublimation gave pure material, m.p. 146–147°, $[\alpha]^{24}_{589}$ +198°, $[\alpha]^{24}_{436}$ +438° (*c* 0.94, ethanol). The melting point was not depressed when this material was mixed with apohaemanthamine prepared from haemanthamine. The infrared spectra (KBr) of the two materials were identical. Apohaemanthamine picrate, m.p. 193–195°, prepared from apohaemanthamine derived from crinamine, was identical in all respects with that obtained from haemanthamine.

Dihydroapohaemanthamine.—A solution of 204 mg. of apohaemanthamine in ethanol was hydrogenated at atmospheric pressure in the presence of 100 mg. of prereduced platinum oxide. The solution absorbed 87% of the theoretical amount of hydrogen. The catalyst was removed by filtration, and evaporation of the solvent left 200 mg. of dihydroapohaemanthamine, m.p. 156–159°. The compound showed no absorption at 3067 cm.$^{-1}$ (CCl_4), and the ultraviolet spectrum was identical with that of apohaemanthamine. A sample was sublimed at 120° (5 μ) for analysis, m.p. 160–161°, $[\alpha]^{24}_{589}$ +110°, $[\alpha]^{24}_{436}$ +243° (*c* 0.58, ethanol).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16; neut. equiv., 271. Found: C, 70.76; H, 6.22; N, 5.20; neut. equiv., 270.

Oxohaemanthamine (V).—A solution of 1.430 g. of haemanthamine in 5 ml. of dry pyridine was added in one portion to a yellow suspension of 1.50 g. of chromic anhydride in 15 ml. of dry pyridine. The mixture was allowed to stand overnight, poured into ice-water and filtered through a wad of glass wool. The precipitate was washed with chloroform, and these washings were used to extract the aqueous pyridine filtrates. The chloroform extracts were dried over sodium sulfate and evaporated under reduced pressure. The remaining gum was extracted with hot benzene and concentrated to 1.112 g. of an oil which was chromatographed on alumina. Elution with 7% ethyl acetate in benzene produced the oxohaemanthamine. Further elution with ethyl acetate yielded 0.465 g. (32%) of recovered haemanthamine. The ketone crystallized readily from ether or cyclohexane furnishing 465 mg. (32%) of prisms, m.p. 163–165°, $[\alpha]^{23}_{589}$ +142°, $[\alpha]^{23}_{436}$ +558° (*c* 0.55). The infrared spectrum ($CHCl_3$) showed absorption at 1748 cm.$^{-1}$ (5-membered ketone). The ultraviolet spectrum was identical with that of the dihydro derivative shown in Fig. 1.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; neut. equiv., 300. Found: C, 68.47; H, 5.71; neut. equiv., 300.

The ketone was recovered unchanged from treatment with hydroxylamine hydrochloride or semicarbazide hydrochloride in a sodium acetate buffer and from 2,4-dinitrophenylhydrazine in dilute sulfuric acid.

Oxohaemanthamine Picrate.—Prepared in ethanol and recrystallized from acetic acid, the picrate formed yellow bladed prisms, m.p. 242–244°.

Anal. Calcd. for $C_{17}H_{17}NO_4 \cdot C_6H_3N_3O_7$: C, 52.27; H, 3.81; OCH_3, 5.87. Found: C, 52.13; H, 3.76; OCH_3, 6.18.

Oxohaemanthamine Methiodide.—Prepared in ether and recrystallized from water, the methiodide formed prisms, m.p. 243–245°,

Anal. Calcd. for $C_{17}H_{17}NO_4 \cdot CH_3I$: C, 48.99; H, 4.57; I, 28.76. Found: C, 48.91; H, 4.68; I, 28.65.

Oxodihydrohaemanthamine (VI).—(a) A solution of 600 mg. of dihydrohaemanthamine in dry pyridine was combined with 600 mg. of chromic anhydride in the same solvent and treated according to the method developed for the preparation of oxohaemanthamine. Chromatography on alumina produced 405 mg. (68%) of crystalline oxodihydrohaemanthamine, bladed prisms from cyclohexane, m.p. 179–180°, $[\alpha]^{24}_{589}$ +272°, $[\alpha]^{24}_{436}$ +842° (*c* 0.47). The ultraviolet spectra in acid and base are shown in Fig. 1. The infrared spectrum ($CHCl_3$) showed a band at 1748 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; neut. equiv., 301. Found: C, 67.68; H, 6.24; neut. equiv., 302.

(b) A solution of 123 mg. of oxohaemanthamine in ethanol absorbed 1 mole of hydrogen in the presence of 50 mg. of 5% palladium-on-charcoal. The catalyst was removed and the solvent evaporated to leave prisms of oxodihydrohaemanthamine, m.p. 175–178°. After recrystallization from cyclohexane the melting point was 179–180°, as was that of a mixture with the material obtained in (a).

Oxodihydrohaemanthamine Methiodide.—Prepared in ethyl acetate and recrystallized from water, the methiodide formed fine prisms, m.p. 195–200°.

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot CH_3I$: C, 48.77; H, 5.00. Found: C, 48.52; H, 5.17.

Monofluorenylideneoxodihydrohaemanthamine.—A solution of 48.3 mg. of oxodihydrohaemanthamine and 25 mg. of fluorenone in 3 ml. of *t*-butyl alcohol was combined with a solution of 35 mg. of potassium in 1 ml. of *t*-butyl alcohol and refluxed for 5 minutes. After standing at room temperature for 1.5 hours, the reaction mixture was treated with water, and the resulting precipitate was collected by filtration. The compound crystallized as orange prisms from ethanol, m.p. 229–231°. A carbonyl stretching band at 1718 cm.$^{-1}$ was found in the infrared spectrum ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{25}NO_4$: C, 77.73; H, 5.44; N, 3.02; OCH_3, 6.70; mol. wt., 463.5. Found: C, 77.72; H, 5.41; N, 3.02; OCH_3, 6.96; mol. wt. (Rast), 445; neut. equiv., 467.

Epihaemanthamine (XXVb).—A solution of 200 mg. of oxohaemanthamine in 5 ml. of methanol was treated with 200 mg. of sodium borohydride and allowed to stand overnight. Dilute acetic acid was added, and the solution was boiled gently for 15 minutes. The cooled solution was basified with dilute sodium hydroxide and allowed to cool at 0°. Fine prisms of epihaemanthamine precipitated and

were removed by filtration; 168 mg. (84%), m.p. 205–215°. A sample was recrystallized from ethyl acetate, m.p. 216–217°, $[\alpha]^{25}_{589}$ −24°, $[\alpha]^{25}_{436}$ −15° (*c* 0.23). The compound showed an ultraviolet spectrum identical with that of haemanthamine.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.78; H, 6.30.

The methiodide was prepared in ethyl acetate and recrystallized from water as fine prisms, m.p. 265–268° (previous dec.), $[\alpha]^{23}_{589}$ −20°, $[\alpha]^{23}_{436}$ −26° (*c* 0.81, dimethylformamide).

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot CH_3I$: C, 48.77; H, 5.00. Found: C, 48.40; H, 5.00.

Epihaemanthamine was recovered in 58% yield by chromatography on alumina after refluxing with 6 *N* hydrochloric acid for 1 hour. No apohaemanthamine was detected. A solution of 95 mg. of epihaemanthamine was treated with 100 mg. of chromic anhydride in 3 ml. of pyridine in the manner described above for the conversion of haemanthamine to oxohaemanthamine. Evaporation of the chloroform extracts left 80 mg. (84%) of an oil possessing an infrared spectrum that was identical with oxohaemanthamine. Chromatography on alumina furnished crystalline material, m.p. 162–165°; admixture with authentic V did not depress this melting point.

Dihydroepihaemanthamine.—A solution of 95 mg. of epihaemanthamine in 10% acetic acid–ethanol was combined with 56 mg. of prereduced palladium-on-charcoal. The mixture absorbed slightly more than one equivalent of hydrogen in 5 minutes. The catalyst was removed by filtration. Evaporation of the solvent left an oil which was dissolved in dilute hydrochloric acid, washed with benzene and basified with sodium hydroxide. The free base was extracted with chloroform, dried with magnesium sulfate and evaporated to yield 59 mg. (62%) of prisms which were recrystallized from ethyl acetate, m.p. 187–188°, $[\alpha]^{23}_{589}$ +35°, $[\alpha]^{23}_{436}$ +90° (*c* 0.68).

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; neut. equiv., 303. Found: C, 67.23; H, 6.88; neut. equiv., 304.

Cleavage of Oxohaemanthamine by Potassium *t*-Butoxide.—Oxohaemanthamine (130 mg.) was added to a solution of 134 mg. of potassium in 10 ml. of *t*-butyl alcohol. The mixture was refluxed under nitrogen for 2 hours. Excess *t*-butyl alcohol was removed under reduced pressure, and the residue was dissolved in a small amount of water. Careful neutralization with acetic acid caused precipitation of 60 mg. (45%) of the free amino acid VIII (R = H). This was identical in melting point, mixture melting point and ultraviolet and infrared (Nujol) spectra with N-(6-phenylpiperonyl)-glycine obtained by synthesis.

Hofmann Degradation of Oxohaemanthamine Methiodide.—A solution of 38 mg. of oxohaemanthamine methiodide was heated with 1 ml. of 10% sodium hydroxide on a steam-bath for 30 minutes. A heavy precipitate of the hydrated sodium salt of VIII (R = CH_3) appeared as the solution cooled. The precipitate was removed by filtration and dried to give 31 mg. of hydrated sodium N-methyl-N-(6-phenylpiperonyl)-glycinate. One recrystallization from water afforded material which was identical in all respects with the synthetic sodium salt.

N-(6-Phenylpiperonyl)-glycine (VIII, R = H).—A solution of 128 mg. of 6-phenylpiperonal and 500 mg. of ethyl glycinate in benzene was slowly distilled for 10 minutes to remove the water produced during the formation of the Schiff base. The solvent was removed under reduced pressure, and the oil was dissolved in ethanol and added to 150 mg. of prereduced palladium-on-charcoal. The solution absorbed 12 ml. of hydrogen very slowly and stopped. Addition of 5 ml. of dilute acetic acid caused the absorption of an additional 4 ml. of hydrogen. The catalyst was removed, and the solution was treated with a large excess of sodium hydroxide and refluxed for 12 hours. The reaction mixture was cooled, filtered and brought to *p*H 7 with acetic acid. The free amino acid VIII (R = H) precipitated as colorless plates, 98 mg. (62%), m.p. 200–205° dec. Recrystallization from water raised the melting point to 205–209° dec. The infrared spectrum (Nujol) showed absorption at 2778–2381 cm.$^{-1}$ (bonded $-\overset{+}{N}H_2$) and 1587 cm.$^{-1}$ ($-COO^-$), characteristic of dipolar amino acids. The ultraviolet spectrum exhibited maxima at 252 mμ (ε 7020) and 293 mμ (ε 5130), typical of the 6-phenylpiperonyl chromophore.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.21; H, 5.48; N, 4.95.

N-(6-Phenylpiperonyl)-glycine picrate crystallized from aqueous ethanol as irregular prisms, m.p. 173–180° dec.

Anal. Calcd. for $C_{16}H_{15}NO_4 \cdot C_6H_3N_3O_7$: C, 51.36; H, 3.53. Found: C, 51.66; H, 3.61.

Sodium N-Methyl-N-(6-phenylpiperonyl)-glycinate.—A solution of 95 mg. of N-(6-phenylpiperonyl)-glycine in 2 ml. of formic acid and 0.5 ml. of formalin was heated on a steam-bath overnight. The resulting solution was made strongly basic with 20% sodium hydroxide causing large flakes of the sodium salt of VIII (R = CH_3) to precipitate. Recrystallization from hot water produced 31 mg. (29% of pure product. The infrared spectrum (Nujol) strongly resembled that of the original amino acid, but the region from 3800–3125 cm.$^{-1}$ was clear and a maximum remained at 1587 cm.$^{-1}$ ($-COO^-$). The ultraviolet spectrum showed maxima at 252 mμ (ε 5440) and 293 mμ (ε 4350).

Anal. Calcd. for $C_{17}H_{16}NO_4Na$: C, 63.54; H, 5.02; neut. equiv., 161. Found: C, 63.33; H, 5.06; neut. equiv., 161.

Hofmann Degradation of Oxodihydrohaemanthamine Methiodide.—A solution of 150 mg. of oxodihydrohaemanthamine methiodide in 25 ml. of 25% sodium hydroxide was refluxed overnight in a nitrogen atmosphere. Lustrous plates appeared even when the solution was hot, and on cooling 224 mg. of the crude hydrated sodium salt of IX was collected. This material exhibited normal methylenedioxophenyl absorption in the ultraviolet and possessed a sharp maximum at 1603 cm.$^{-1}$ ($-COO^-$) in the infrared. The material was extremely hygroscopic and could be crystallized from 25% sodium hydroxide only. The crystals were dissolved in a minimum of water and acidified with perchloric acid whereupon long prisms of the **hydroperchlorate of IX** formed. Recrystallization from water gave colorless prisms, m.p. 202–207° dec., $[\alpha]^{23}_{589}$ +27.2°, $[\alpha]^{23}_{436}$ +37.6° (*c* 1.11, 5% sodium hydroxide). The infrared spectrum (Nujol) exhibited maxima at 3636 cm.$^{-1}$ (N^+–H, unbonded), 2778–2439 cm.$^{-1}$ (N^+–H, bonded) and 1739 cm.$^{-1}$ (COOH). The ultraviolet spectrum was that of a simple methylenedioxyphenyl chromophore, λ_{max} 247 mμ (ε 5630) and 292 mμ (ε 4230).

Anal. Calcd. for $C_{18}H_{23}NO_5 \cdot HClO_4$: C, 49.83; H, 5.58; Cl, 8.17; OCH_3, 7.15. Found: C, 49.82; H, 5.70; Cl, 8.04; OCH_3, 7.35.

2-(4-Methoxycyclohexyl)-4,5-methylenedioxytoluene (XII).—A solution of 150 mg. of the hydroperchlorate of IX in 30 ml. of 5% acetic acid in ethanol was added to 200 mg. of prereduced platinum oxide. The solution absorbed 2 moles of hydrogen over a period of 24 hours. The filtered solution was poured into water, acidified to *p*H 2 and extracted with benzene. The dried extracts were evaporated, leaving 20 mg. of a neutral oil which was crystallized and recrystallized from aqueous ethanol to yield plates, m.p. 84–85°, $[\alpha]^{25}_{589}$ 0°, $[\alpha]^{25}_{400}$ 0° (*c* 1.26). The infrared spectrum of XII (KBr) exhibited no absorption from 3850–3130 cm.$^{-1}$ and from 2780–1640 cm.$^{-1}$ while the ultraviolet spectrum was identical with that of the starting material. A negative test for unsaturation was obtained with a dilute solution of potassium permanganate.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; OCH_3, 12.50. Found: C, 72.77; H, 8.25; OCH_3, 12.50.

The same material (XII) was obtained when 317 mg. of dihydrotazettine methine[24,25] was hydrogenated with 180 mg. of prereduced platinum oxide in 5% acetic acid in ethanol. Slightly more than 2 moles of hydrogen was absorbed, and after treatment in the manner described above, 214 mg. of non-basic material was obtained. After distillation at 70° (1 μ) and recrystallization from aqueous ethanol, crystals were obtained which melted at 84–85° alone or on admixture with XII from IX. The infrared (KBr) and ultraviolet spectra also were identical.

Oxocrinamine.—A solution of 95 mg. of crinamine in 5 ml. of dry pyridine was combined with 90 mg. of chromic anhydride in 6 ml. of pyridine and treated according to the method outlined above for the conversion of haemanthamine to oxohaemanthamine. Chromatography over alumina and recrystallization from ethanol furnished 55 mg. (58%) of

oxocrinamine as short-bladed prisms, m.p. 165–167°, $[\alpha]^{24}_{589}$ + 203°, $[\alpha]^{24}_{436}$ +640° (*c* 0.56, ethanol). This compound depressed the melting point of oxohaemanthamine (m.p. 164–165°) nearly 20°. Oxocrinamine showed a band at 1748 cm.$^{-1}$ ($CHCl_3$) in the infrared and had an ultraviolet spectrum identical with that of oxohaemanthamine.

Catalytic Hydrogenation–Hydrogenolysis of Diacetylhaemanthidine.—A solution of 424 mg. of diacetylhaemanthidine[2,31] in 60 ml. of absolute ethanol was added to a suspension of 100 mg. of platinum oxide and 200 mg. of palladium-on-charcoal which had been equilibrated with hydrogen. The solution absorbed 1 mole of hydrogen at 28° in 30 minutes and absorption ceased. The temperature was raised to reflux the ethanol, and the solution absorbed another 23 ml. of hydrogen over a 2-hour period. The mixture was cooled and filtered. The solvent was removed under reduced pressure to yield 400 mg. of an oil. The residue was warmed with 10% sodium hydroxide for 4 hours, extracted with chloroform and dried over sodium sulfate. The chloroform was removed under reduced pressure to yield 350 mg. of a viscous oil which was dissolved in chloroform and chromatographed over alumina. Elution with 1% ethanol in chloroform produced 13 mg. (3.5%) of crystals which were sublimed at 150° (10 μ) to afford dihydrohaemanthamine, m.p. 228–230°, $[\alpha]^{25}_{589}$ +78 ± 2° (*c* 0.25, chloroform). The melting point of a mixture with authentic dihydrohaemanthamine prepared from haemanthamine was not depressed. The infrared absorption spectra (KBr) of the two materials were identical.

Further elution with 10% ethanol in chloroform yielded 250 mg. of dihydrohaemanthidine, identical in all respects with authentic material.

Many conditions were employed without success in an effort to improve the yield of dihydrohaemanthamine. In one case a 5% yield of dihydrohaemanthamine was obtained by conducting the reduction in hot glacial acetic acid with a small amount of perchloric acid in the presence of palladium-on-charcoal alone. The yield of dihydrohaemanthamine was so low in all of these reactions that it was felt necessary to ascertain that the haemanthidine used in the reactions contained no haemanthamine. To this end a 300-mg. mixture of 5% haemanthamine in haemanthidine was chromatographed over alumina and easily separated into its components with chloroform and 10% ethanol–chloroform, respectively. Haemanthidine purified in this manner was used in subsequent hydrogenations without affecting the results.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

The Synthesis of 9-(2-Amino-2-deoxy-β-D-allopyranosyl)-6-dimethylaminopurine, an Analog of the Aminonucleoside Derived from Puromycin

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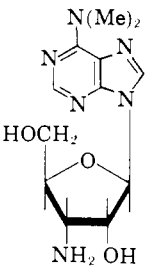
RECEIVED JUNE 9, 1959

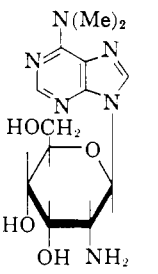
The subject nucleoside was prepared by a fifteen-step synthesis from N-anisylidene-D-glucosamine.

Analogs of the aminonucleoside[2] I derived from the antibiotic puromycin are of interest because of the antitumor[3] and trypanocidal[4] properties exhibited by I in experimental animals. Previous reports from this Laboratory have described the preparation of various analogs of I containing variations in the aminosugar moiety. These have included the 9-β 3-aminoarabinofuranosyl,[5] 3-aminoxylofuranosyl,[6] 5-aminoribofuranosyl[7] and 2-aminoribofuranosyl[8] derivatives of 6-dimethylaminopurine. In this paper we wish to report the synthesis of another such analog, 9-(2-amino-2-deoxy-β-D-allopyranosyl)-6-dimethylaminopurine (II).[9]

In principle, it was anticipated that the synthesis of a 2-aminoalloside could be achieved conveniently from a 2-aminoglucosyl nucleoside by inversion of the hydroxy group at C-3. Nucleosides containing the 2-aminoglucosyl sugar have been reported,[10]



I



II

and inversion of an hydroxy group adjacent and *trans* to an amino group *via* the N-acetyl-*O*-mesylate has been described in the carbohydrate field for both glycosides[11,12] and nucleosides.[13]

Previous reports from this Laboratory have described the synthesis in 47% yield of 9-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-6-dimethylamino-2-methylmercaptopurine (VI) from chloroacetoglucosamine (III) and chloromercuri-6-dimethylamino-2-methylmercaptopurine (V).[10,14] However, in the present investigation,

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(9) The synthesis of 9-(3-amino-2-deoxy-β-D-allopyranosyl)-6-dimethylaminopurine will be reported at a later date (R. E. Schaub and M. J. Weiss).

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(11) B. R. Baker and R. E. Schaub, *ibid.*, **19**, 646 (1954).

(12) B. R. Baker, R. E. Schaub and J. H. Williams, THIS JOURNAL, **77**, 7 (1955).

(13) B. R. Baker and R. E. Schaub, *ibid.*, **77**, 2396 (1955).

(14) The chloromercuri derivative of 6-dimethylamino-2-methylmercaptopurine was used rather than that of 6-dimethylaminopurine since it has been shown that reaction of the chloromercuri derivative of the latter purine with chloroacetoglucose gives a 7-substituted nucleoside, whereas condensation with the derivative of the former purine gives a 9-substituted nucleoside.[15] It was assumed that a similar course of reaction would obtain with a 1-chloro-2-acetamido-