A solution of this oil in methanol (50 ml.) was cooled in an ice-bath and saturated with dry ammonia. The mixture was allowed to stand at room temperature for 30 minutes and the solvent removed as before, giving an oil which crystallized on treatment with ether. Recrystallization from ethanol gave colorless needles (2.8 g., 93.5%), m.p. 193–200°, raised to 200–215° (placed on Kofler block at 190°), undepressed by admixture with the product of the previous reaction (XIII) and giving identical infrared and ultraviolet spectra (Baddiley[14] quotes colorless needles from 1:1 methanol–ethanol, m.p. 200–215°).

Methylation of Cyclic Sulfide XVI to 5′-Deoxy-5′-methylthio-2′,3′-O-isopropylideneuridine (X).—To a solution of 255 mg. (11.1 mmoles) of sodium in 50 ml. of dry ethanol, cooled to room temperature, was added 1.0 g. (33.3 mmoles) of the cyclic sulfide XVI, which dissolved readily on swirling by hand, followed by a solution of 1.42 g. (0.63 ml., 10 mmoles) of methyl iodide in 20 ml. of dry ethanol. After standing overnight, the colorless solution was cooled in ice-water, and neutralized by the careful addition of 1 *N* sulfuric acid.

The neutral reaction product was extracted thoroughly with chloroform, the extract washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent on a rotating evaporator at 40° (15 mm.) gave 1.102 g. of a colorless oil, which crystallized from methanol solution, giving 688 mg. (66%) of colorless prisms, m.p. 158–159°, undepressed on admixture with an authentic sample of 5′-deoxy-5′-methylthio-2′,3′-O-isopropylideneuridine (X), m.p. 158–158.5°. The ultraviolet spectrum of this material (λ_{max} 258 mμ, a_M 10,150) corresponded to that of X, and its infrared spectrum was indistinguishable from that of the authentic material.

A repetition of this reaction under identical conditions but with the omission of methyl iodide led to a pale yellow solution which was neutralized carefully with 1 *N* sulfuric acid. Extraction with chloroform followed by washing the extract with water and drying over anhydrous sodium sulfate gave a colorless solid residue (985 mg.) on removal of the solvent on a rotating evaporator at 30° (15 mm.). Crystallization from ethanol gave 889 mg. of colorless needles, m.p. 215–230°, undepressed on admixture with the starting material, and giving an identical infrared spectrum.

5′-Deoxy-2′,3′-O-isopropylidene-5′-thiocyanatouridine (XVIII).—To a solution of 5.15 g. (636 mmoles) of sodium thiocyanate in 100 ml. of methyl ethyl ketone was added 5.0 g. (12.7 mmoles) of 5′-deoxy-5′-iodo-2′,3′-O-isopropylideneuridine (II), and the mixture was heated under reflux on the steam-bath for 18 hours. Removal of the solvent from the cooled solution on the rotating evaporator at 30° (15 mm.) gave a pale yellow semi-solid residue, which was dissolved in a mixture of water and chloroform. The combined chloroform extracts were washed three times with water, dried over anhydrous sodium sulfate, and the solvent removed as above, giving 3.98 g. of an amorphous solid. Two crystallizations from methanol gave 3.42 g. (83%) of XVIII as colorless prisms, m.p. 170.5–171.5°; infrared spectrum (cm.$^{-1}$): —NH at 3120; C=O at 1760, 1707, 1685, 1670, 1665 and 1652; C=C at 1625; ultraviolet spectrum λ_{max} 256 mμ, a_M 10,150.

Anal. Calcd. for $C_{13}H_{15}O_5N_3S$: C, 47.99; H, 4.65; N, 12.92; S, 9.86. Found: C, 47.94; H, 4.44; N, 13.08; S, 10.17.

Acknowedgments.—We should like to express our thanks to the staffs of Dr. J. L. Johnson and Mr. W. A. Struck of The Upjohn Co. for the analytical and physical data recorded and to Dr. B. R. Baker, Stanford Research Institute, for helpful suggestions.

KALAMAZOO, MICH.

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

The Stereochemistry of Amaryllidaceae Alkaloids Derived from 5,10b-Ethanophenanthridine[1]

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

RECEIVED NOVEMBER 20, 1959

The Amaryllidaceae alkaloids crinine, powelline, buphanisine, buphanidrine, buphanamine, crinamidine and undulatine have been related to the (−)-crinane nucleus. Vittatine, haemanthamine, haemanthidine, haemultine, crinamine, 6-hydroxycrinamine and (+)-epicrinine are shown to be based on the enantiomorphic (+)-crinane nucleus. A method for the O-methylation of several of these alkaloids without concurrent N-methylation is described.

In 1951, the known alkaloids of the Amaryllidaceae were comprised of twelve bases in varying degrees of characterization and purity.[2] At the present time, the number of pure alkaloids isolated from plants of this family approaches one hundred. One of the most rapidly expanding groups of alkaloids within the family is that derived from a 5,10b-ethanophenanthridine (crinane) nucleus (I). This ring system was demonstrated first for the alkaloid crinine (II) in 1956.[3] Since that time, powelline (VI),[4,5] buphanisine (III),[4,5] buphanidrine (VII),[4,5] buphanamine (IX),[4] undulatine (XI),[6] haemanthamine (XVIIa),[7] crinamine (XVIIc),[7] haemanthidine (XVIIb),[8] haemultine (XXII),[9] vittatine (XIXa),[10] (+)-epicrinine (XIXb)[1] and 6-hydroxycrinamine (XVIId)[11] have been added to it. Because subsequent papers of this series will expand the group by at least four more alkaloids, it seems desirable to pause at this point and classify the known alkaloids of this ring system according to the enantiomorphic nature of the basic ring system and to complete the stereochemistry of the functional groups in the light of recent experimental evidence.

(1) Paper XVI in a series on the alkaloids of the plant family Amaryllidaceae; for the previous paper see: R. E. Lyle, E. A. Kielar, J. R. Crowder and W. C. Wildman, THIS JOURNAL, **82**, 2620 (1960).

(2) J. W. Cook and J. D. Loudon in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 331.

(3) W. C. Wildman, THIS JOURNAL, **78**, 4180 (1956).

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

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

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

(7) H. M. Fales and W. C. Wildman, *ibid.*, 561 (1958); THIS JOURNAL, **82**, 197 (1960).

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

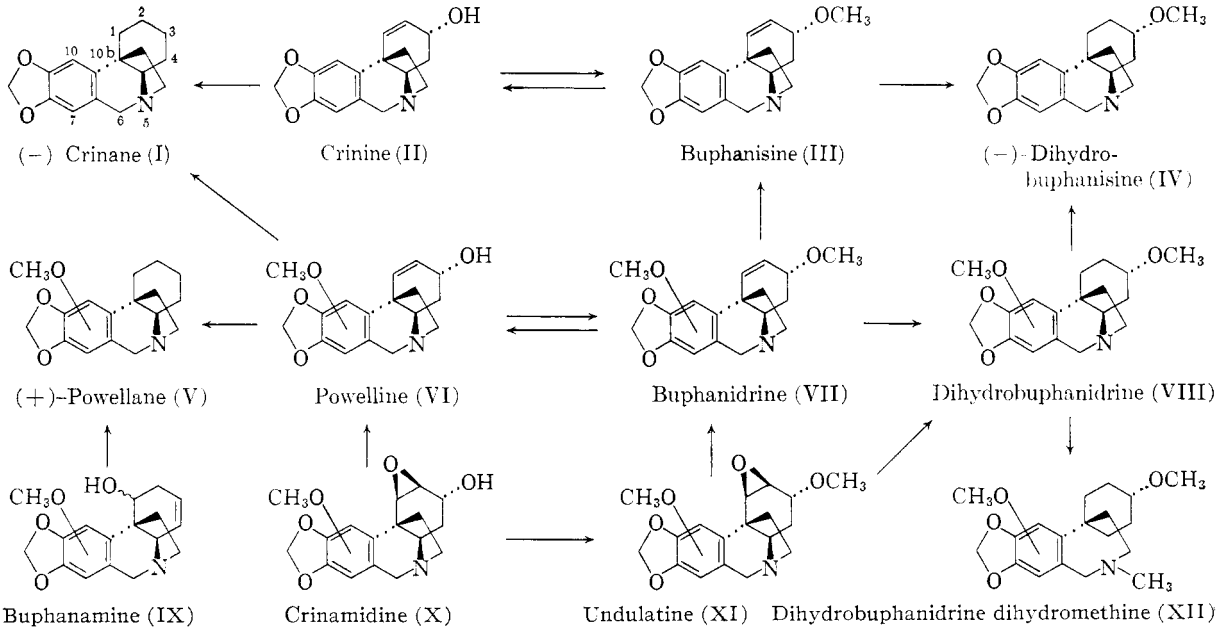
(9) H.-G. Boit, W. Döpke and W. Stender, *Naturwissenschaften*, **45**, 262 (1958); H.-G. Boit and W. Döpke, *Chem. Ber.*, **91**, 1965 (1958).

(10) H.-G. Boit and H. Ehmke, *ibid.*, **90**, 369 (1957).

(11) H. M. Fales, D. H. S. Horn and W. C. Wildman, *Chemistry & Industry*, 1415 (1959).

CHART 1

INTERRELATIONSHIPS OF ALKALOIDS DERIVED FROM (−)-CRINANE



In previous papers,[4,5] the structures of crinine and powelline (without stereochemical implications) were established as II and VI, respectively. In addition, preliminary evidence for the structures of the methyl ethers, buphanisine (III) and buphanidrine (VII), was presented. These four alkaloids have been interconverted by (1) aromatic demethoxylation with sodium and amyl alcohol,[12] and (2) mild acid hydrolysis of the allylic methoxyl group to afford the corresponding allylic alcohol.[5] The latter method was part of structure proof for the methoxy ethers III and VII. Although allylic rearrangement seemed unlikely in these particular reactions, this method of structure proof for III and VII appeared considerably less than unequivocal. Since that time, several alternate routes have been found to show that these structures are correct. The first proof was the Hofmann degradation of dihydrobuphanidrine (VIII) to the optically inactive dihydromethine (XII).[6] This paper reports a second proof which is concerned with the direct O-methylation of II and VI.

In the course of our studies on the alkaloids of this family, we hoped to find a method for the methylation of secondary hydroxyl groups which would not quaternize the tertiary amino group at the same time. Such a reagent has been found in methyl *p*-toluenesulfonate. When this reagent was added to the potassium salt of powelline, a 57% yield of buphanidrine was obtained. Under identical reaction conditions, crinine (II) was converted to buphanisine (III). The reaction appears to proceed with retention of configuration since the potassium salts of crinine and powelline afforded only the respective free alkaloids when treated with ethanol instead of methyl *p*-toluenesulfonate. No trace of epicrinine or epipowelline could be found by spectrophotometric means. There was no evidence of epimeric methyl ethers in the methylation reaction products. O-Methylation of crinamidine by this method gave a 22% yield of undulatine (XI), providing an alternate structure proof for crinamidine (X).[13]

Since inversion has been demonstrated not to occur in either the methylation or demethylation reactions and undulatine (XI) has been converted to buphanidrine (VII) and dihydrobuphanidrine (VIII) by procedures which do not permit epimerization of the C_3-methoxyl,[6] the configuration of the C_3 substituent in the alkaloids VI, VII, X and XI with respect to the aromatic ring must be the same. Finally, these interrelationships require the alkaloids to be elaborated on the same enantiomorph of the crinane nucleus. In a manner analogous to the conversion of II to (−)-crinane (I), powelline (VI) has been transformed to the basic ring system (+)-powellane (V).[5] The conversion of buphanamine (IX) to (+)-powellane (V)[4] makes it evident that buphanamine also is a member of this group of alkaloids.

The isolation from natural sources of vittatine, the optical antipode of crinine,[10] and (+)-epicrinine,[1] which is also based on the (+)-crinane nucleus, makes it necessary to prove that the basic ring systems of (+)-powellane and (−)-crinane have the same absolute configuration.

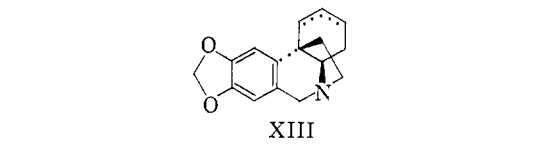
That buphanisine (III) and crinine (II) have the same absolute configuration is certain since they have been interconverted both by acid hydrolysis[5] (III→II) and by O-methylation (II→III). By standard degradative routes crinine has been converted to (−)-crinane [(−)-I] and buphanisine has been reduced to (−)-dihydrobuphanisine (IV).[5] Compounds I–IV show plain

(12) H. M. Fales and W. C. Wildman, THIS JOURNAL, **80**, 4395 (1958).

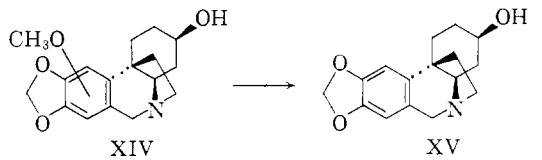
(13) Independent degradative proof for the structure and stereochemistry of crinamidine (X) will be presented in a later paper of this series.

negative rotatory dispersion curves in chloroform.[14] It was quite unexpected that (+)-powellane (V) showed a plain positive rotatory dispersion curve. The reason for this discrepancy is unknown at present.[15] However, we feel that the existing chemical evidence indicates that (+)-powellane (V) and (−)-crinane (I) possess the same absolute configuration.

Very little is known about the mechanism of aromatic demethoxylation beyond that proposed originally by Clayson.[17] In our extension of the method to certain Amaryllidaceae alkaloids,[12] three competing side reactions were observed: (1) epimerization of allylic hydroxyl (but not methoxyl) groups with concurrent reduction of the allylic unsaturation, (2) base-catalyzed E_2-elimination of allylic alcohols and methyl ethers to form 1,3-dienes which might be reduced further in a 1,4-manner, and (3) hydrogenolysis of the allylic ethers or alcohols to yield olefins.[18] From each of three different derivatives of powelline, either (−)-crinane or a derivative thereof has been obtained. Because of side reactions (1) and (3), powelline is converted by sodium and isoamyl alcohol not to crinine, but to a mixture of α- and β-crinenes (XIII) and dihydroepicrinine (XV).[12] All three of these compounds show simple negative rotatory dispersion curves, and both the α- and β-crinenes were reduced to (−)-crinane which was identified by mixture melting point, infrared spectrum and optical rotation. The dihydroepicrinine obtained in this reaction was identical by the same criteria with dihydroepicrinine prepared from crinine. No evidence for the side reaction was found in three remaining cases. Dihydroepipowelline (XIV) was demethoxylated to dihydroepicrinine (XV) only. Buphanidrine (VII) gave only buphanisine (III) in the presence of sodium and isoamyl alcohol and, under the same conditions, dihydrobuphanidrine (VIII) was partially converted to (−)-dihydrobuphanisine (IV). If the nucleus of VI and VII were the antipode of that of II and III, the aromatic demethoxylation reaction must occur with complete inversion of at least two centers (C_{4a} and C_{10b}), and in the cases of dihydroepipowelline, buphanidrine and dihydrobuphanidrine, C_3 must be inverted as well. To us, such a possibility is extremely remote.



XIII



XIV XV

Additional evidence for the same absolute configuration of the ring system of crinine and powelline can be derived from a comparison of the changes in rotation in certain transformations of the two alkaloids. If it is reasoned that powelline is an *ar*-methoxyvittatine,[19] oxidation to the α,β-unsaturated ketone, oxopowelline (VI, =O instead of OH), should give a product with a large positive rotation. Similarly, epipowelline (VI, OH epimeric at C_3) should be strongly dextrorotatory also. Such rotations would be in agreement with those observed for (+)-oxocrinine (oxovittatine) and (+)-epicrinine (epivittatine).[1] The fact that the conversion of powelline to both oxopowelline and epipowelline is accompanied by a levorotatory shift is additional evidence for the (−)-crinane nucleus in powelline, and therefore in VII, IX, X and XI as well.

In addition to the alkaloids described above, there exists a group of at least four alkaloids which have been shown to contain a similarly substituted crinane nucleus but with an additional hydroxyl substituent at C_{11} (Chart 2). The structures assigned to haemanthamine (XVIIa),[7] haemanthidine (XVIIb),[8] crinamine (XVIIc)[7] and 6-hydroxycrinamine (XVIId)[11] have been discussed in previous papers. As part of the structure proof of these alkaloids, XVIIa and XVIIc were converted by 6 *N* hydrochloric acid to apohaemanthamine (XXIa) while XVIIb and XVIId, under the same conditions, afforded apohaemanthidine (XXIb). Since both XXIa and XXIb have been converted to the common degradation product, dihydroapohaemanthamine (XXIa, no double bond), it is evident that XVIIa–XVIId are based on the same crinane enantiomorph. Haemultine,[9] which has been obtained from the sodium and amyl alcohol reduction of either XVIIa or XVIIc, as well as from *Haemanthus multiflorus* Martyn, probably is a member of this group of alkaloids and has been assigned structure XXII.[20]

(14) A recent review of the use of optical rotatory dispersion in organic chemistry has been published by C. Djerassi, *Record Chem. Prog. (Kresge-Hooker Sci. Lib.)*, **20**, 101 (1959).

(15) Extremely subtle changes in molecular structure have been found to reverse the direction of rotatory dispersion curves; *cf.* the optical rotatory dispersion curves of 3-methylcyclohexanone and 3-methylcycloheptanone of the same absolute configuration are opposite in direction; C. Djerassi and G. W. Krakower, THIS JOURNAL, **81**, 237 (1959); see also C. Djerassi and L. E. Geller, *ibid.*, **81**, 2789 (1959). A possible explanation involves the position of the aromatic methoxyl group, which has not been determined by positive evidence. Biogenetic theories[16] suggest that the aromatic methoxyl group is in position 10 of the crinane nucleus. In the only other possible position (C_7) the methoxyl group presents no steric hindrance to either adjacent positions, C_8 or C_6. A C_{10}-methoxyl, however, can cause considerable interference with the hydrogen(s) at C_1. Distortion of the molecule due to such an interaction may be responsible for the observed rotation of (+)-powellane.

(16) E. W. Warnhoff, *Chemistry & Industry*, 1385 (1957).

(17) D. B. Clayson, *J. Chem. Soc.*, 2016 (1949).

(18) Side reaction 3 has been reported recently in the conversion by sodium and *n*-amyl alcohol of either crinamine (XVIIc) or haemanthamine (XVIIa) to haemultine (XXII); H.-G. Boit and W. Döpke, *Chem. Ber.*, **91**, 1965 (1958)

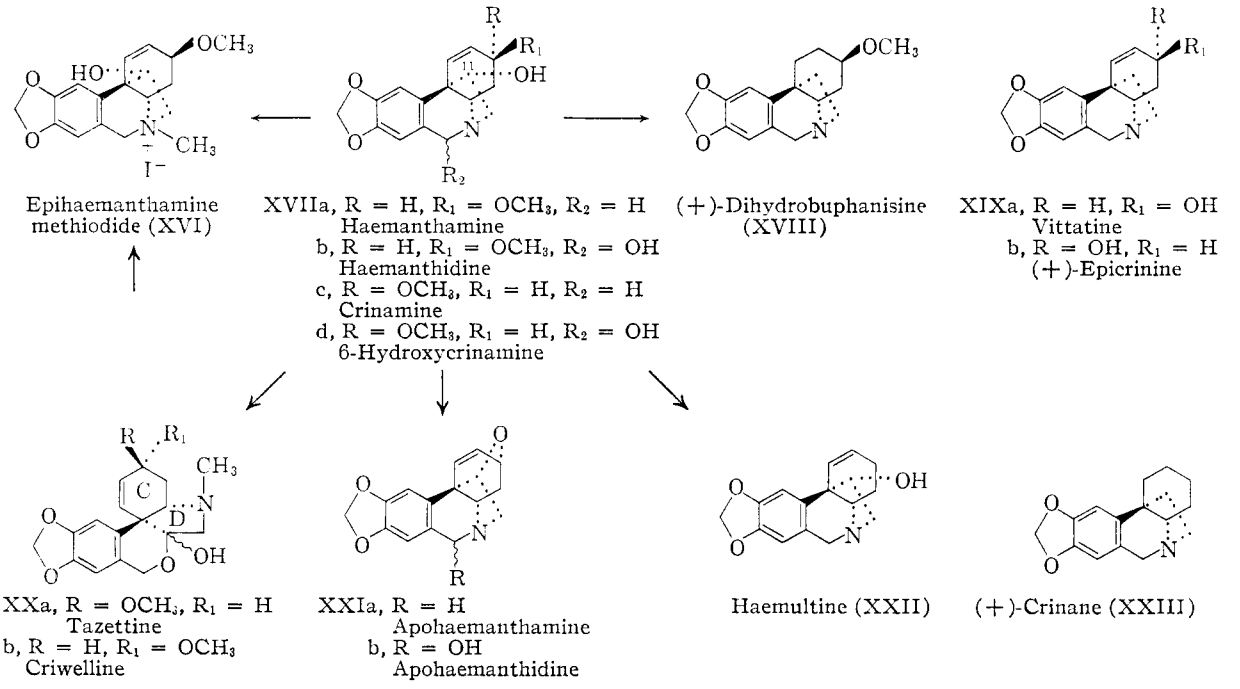
(19) Vittatine has been shown to be the optical antipode of crinine; H.-G. Boit and H. Ehmke, *ibid.*, **90**, 369 (1957).

(20) The structure of haemultine has not been proved rigorously. There is no evidence for the position of the double bond. It is assumed by the German workers that the cleavage of XVIIa or XVIIc occurs without rearrangement of the crinane nucleus. Sole evidence for representing haemultine as XXII is based on the infrared carbonyl absorption of oxohaemultine at 5.71 μ. In view of the ease with which XVIIa and XVIIc are converted to derivatives of 5,11-methanomorphanthridine,[21] further studies on the structure of haemultine seem warranted.

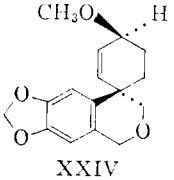
(21) Y. Inubushi, H. M. Fales, E. W. Warnhoff and W. C. Wildman, Abstr., p. 48P, 136th Meeting, Amer. Chem. Soc., Atlantic City, N. J., 1959.

CHART 2

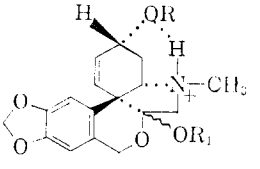
INTERRELATIONSHIPS OF ALKALOIDS DERIVED FROM (+)-CRINANE



Although tazettine (XXa)[22] and criwelline (XXb)[11] do not possess a crinane nucleus, the fact that haemanthidine (XVIIb) and 6-hydroxycrinamine (XVIId) may be converted to tazettine and criwelline, respectively, under very mild conditions (methyl iodide followed by dilute alkali) establishes the close relationship between the two types of alkaloids.[23] Degradative evidence for the structure and stereochemistry of XXa has been presented in an elegant paper by Taylor, Uyeo and co-workers.[22] More recently, the *cis* relationship of the methoxyl and methylenedioxyphenyl groups of tazettine with respect to ring C has been verified by the synthesis of XXIV, a degradation product of tazettine.[24] The *cis* C:D ring fusion of XXa was advanced to explain the increased basicities of isotazettine derivatives when compared with



XXIV



XXV

comparable compounds of tazettine,[22] since in the iso series (XXV), hydrogen bonding between the proton of the conjugate acid and the C_3-oxygen is possible. Recently, the last necessary feature to complete the structure of tazettine, the absolute configuration, has been proposed as depicted in XXa.[25] Since tazettine has been converted to epihaemanthamine methiodide[25] and haemanthidine and 6-hydroxycrinamine are converted to tazettine and criwelline, respectively, all the alkaloids and their degradation products depicted in Chart 2 have the absolute configurations shown.

With the structural and stereochemical studies of crinamine, haemanthidine and haemanthamine completed, we sought to find a method whereby the C_{11}-hydroxylated alkaloids of Chart 2 and the C_{11}-unsubstituted alkaloids of Chart 1 might be interrelated. The most obvious route appeared to be the removal of the C_{11}-hydroxyl group of haemanthamine (XVIIa). Although the conversion of –CHOH to $-CH_2-$ is one of the most common in the field of organic chemistry, a number of obvious methods were unsuccessful in our hands. Thus, haemanthamine was recovered from an attempted tosylation in pyridine, in spite of the ease with which the base formed an O-acetate, an O-*m*-nitrobenzoate and an O-3,5-dinitrobenzoate. Since oxohaemanthamine (XVIIa, =O instead of OH) did not form carbonyl derivatives, it was not unexpected that the Wolff–Kishner and Clemmensen reductions failed or that a bis-ethylene mercaptole could not be obtained. A conversion was achieved by the method which had been successful in the conversion of dihydroapohaemanthidine to dihydroapohaemanthamine.[8] Thionyl chloride converted dihydrohaemanthamine (XVIIa, no double bond 1,2) to a chloro compound which was not isolated, but was reduced directly with lithium aluminum hydride. The product XVIII was identical in infrared spectrum (KBr), crystalline form and melting point with (−)-dihydrobuphanisine (IV). However, a mixture melting point was depressed more than 20°. From an examination of the optical rotatory dispersion curves, it became obvious that the product

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

(23) This facile rearrangement of the 11-hydroxylated crinane nucleus to the skeleton of tazettine and criwelline leads us to speculate that XXa and XXb are produced by the plant from a comparable precursor.

(24) H. Irie, Y. Tsuda and S. Uyeo, *J. Chem. Soc.*, 1446 (1959).

(25) T. Kitagawa, S. Uyeo and N. Yokoyama, *ibid.*, 3741 (1959).

derived from dihydrohaemanthamine was the optical antipode of (−)-dihydrobuphanisine. Since buphanisine is one of the alkaloids shown in Chart 1 derived from the (−)-crinane nucleus, the absolute configuration of the alkaloids of Chart 1 is antipodal to that of the alkaloids in Chart 2. Thus haemanthamine, haemanthidine, crinamine and 6-hydroxycrinamine are derived from the (+)-crinane nucleus. To this group of four alkaloids must be added vittatine (XIXa),[18] (+)-epicrinine (XIXb)[1], and probably haemultine.[26]

In addition to establishing the stereochemical series of the known alkaloids derived from 5,10b-ethanophenanthridine, the conversion of haemanthamine to (+)-dihydrobuphanisine places the stereochemistry of the non-hydroxylated alkaloids derived from this nucleus on a more certain basis. Since the methoxyl and phenyl groups of haemanthamine are *cis* with respect to ring C,[7] the same relationship must exist in (+)-dihydrobuphanisine. From the interrelationships derived earlier, it follows that all 3-oxy substituents in the naturally occurring alkaloids shown in Chart 1 are *cis* to the phenyl also.

Previous papers[7,27] have shown that the C:D ring fusion of the alkaloids based on the crinane nucleus is *cis*. With ring C in the half-boat conformation, ether formation between C_{11} and C_3 (as in XXI) becomes possible. In the half-chair conformation (presumably the more stable) the C_3-substituent is *quasi* axial in all alkaloids except (+)-epicrinine (XIXb), crinamine (XVIIc) and 6-hydroxycrinamine (XVIId). Consistent with this conformation, oxocrinine and oxopowelline are reduced by sodium borohydride or lithium aluminum hydride to the more stable C_3-*quasi* equatorial epimers[5] and oxodihydroundulatine is isomerized by alkali to epi oxodihydroundulatine.[6]

Experimental[28]

Conversion of Crinine to Buphanisine.—Molten potassium (275 mg.) in 100 ml. of hot benzene was converted to a fine, bluish suspension by high-speed stirring in a nitrogen atmosphere. The mixture was cooled to 30–40° and 300 mg. of crinine was added in one portion. The alkaloid was allowed to metalate for 10 minutes; then 190 mg. of methyl *p*-toluenesulfonate in 10 ml. of benzene was added dropwise. The mixture was stirred for 1–3 hours at room temperature, then cooled to 0° and decomposed with excess ethanol. Evaporation of the solvents left a yellow mass which was taken up in 1 *M* sulfuric acid and washed with benzene to remove neutral compounds. The acidic layer was basified with sodium hydroxide and extracted with chloroform. Evaporation of the extracts left an oil which was chromatographed over alumina with benzene–ethyl acetate. Pure ethyl acetate eluted 45 mg. (15%) of a solid which possessed the same infrared spectrum as buphanisine in chloroform. Two recrystallizations from ether gave material melting 125–127° alone or on admixture with authentic buphanisine. An infrared spectrum (KBr) of the product was identical with that of authentic buphanisine; $[\alpha]^{25}_{589}$ −28.9°, $[\alpha]^{25}_{436}$ −88.6° (*c* 0.46, ethanol); reported[12] $[\alpha]^{25}_{589}$ −24° (*c* 1.00, 95% ethanol).

Further elution of the column with ethanol–ethyl acetate furnished 100 mg. (36%) of unchanged crinine.

In order to rule out the possibility of epimerization of the secondary hydroxyl group under the strongly basic conditions encountered in the above sequence, a duplicate experiment was performed with omission of the methyl *p*-toluenesulfonate. The reaction afforded 275 mg. of crude basic product which was recrystallized to yield 145 mg. (48%) of pure crinine, m.p. 207–209° alone or on admixture with authentic crinine (reported[29] m.p. 209–210°). An infrared spectrum (KBr) confirmed the identity of the product. The filtrates were then chromatographed over alumina with ethanol–ethyl acetate. Early fractions yielded 43 mg. (14%) of a compound possessing an infrared spectrum ($CHCl_3$) identical with that of **dihydroöxocrinine**.[5] Further elution added 27 mg. (9%) of crinine to bring the total recovery of starting material to 56%. No evidence for the presence of epicrinine could be found in the infrared spectrum of any fraction.

Conversion of Powelline to Buphanidrine.—A solution of 300 mg. of powelline in benzene was treated with 275 mg. of potassium and 190 mg. of methyl *p*-toluenesulfonate under the above conditions. A yield of 267 mg. of crude basic product was obtained. Chromatography over alumina, as in the preceding example, furnished 171 mg. (57%) of buphanidrine, identical in infrared spectrum ($CHCl_3$) with authentic material. The product was converted to the **hydroperchlorate** and recrystallized from water, m.p. 244–247° dec. alone or on admixture with authentic buphanidrine hydroperchlorate, $[\alpha]^{24}_{589}$ +5.3°, $[\alpha]^{25}_{436}$ +4.20° (*c* 0.71, 95% ethanol); reported[5] m.p. 250–252° dec., $[\alpha]^{23}_{589}$ +5.4° (*c* 0.75, ethanol); reported[30] m.p. 240–242°, $[\alpha]^{20}_{589}$ +5.5°.

In addition, a 23% recovery of powelline was realized by further elution of the column with ethanol–ethyl acetate.

A duplicate experiment with powelline, omitting the methyl *p*-toluenesulfonate, furnished a 93% yield of recovered powelline, m.p. 193–196°. The filtrate (15 mg.) from the powelline contained no epipowelline as determined by inspection of the infrared spectrum.

Conversion of Crinamidine to Undulatine.—A solution of 300 mg. of crinamidine in benzene was combined with 275 mg. of potassium and 190 mg. of methyl *p*-toluenesulfonate under the above conditions to yield 219 mg. of crude reaction product. Chromatography, as before, gave 12 mg. of fine needles which were recrystallized from aqueous ethanol, m.p. 145–147°. Admixture with undulatine depressed the melting point. The compound was not investigated further.

Anal. Calcd. for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51. Found: C, 64.65; H, 7.51.

Further elution of the original column produced 69 mg. (22%) of undulatine, m.p. 152–153° alone or on admixture with authentic material, $[\alpha]^{25}_{589}$ −34°, $[\alpha]^{25}_{436}$ −62° (*c* 1.04, chloroform); reported[6] m.p. 151–152°, $[\alpha]_{589}$ −32°. The infrared spectrum (KBr) was identical with that of authentic undulatine.

A duplicate experiment with crinamidine, omitting the methyl *p*-toluenesulfonate, afforded 74% recovery of basic material which was chromatographed on Florisil with ethanol–chloroform. An oil (14 mg.) was removed with 2% methanol and examined in the infrared region. A solution ($CHCl_3$) spectrum failed to eliminate the possibility of epicrinamidine[31] because of a number of absorption bands common to both compounds, so recourse was made to paper chromatography in a solvent system containing 8 parts of *n*-amyl alcohol, 1 part of acetic acid and 1 part of water. This system has been shown to elute crinamidine with R_f 0.51 and epicrinamidine with R_f 0.39. The oil was found to consist mostly of crinamidine with no epicrinamidine.

Further elution of the original column with 2% methanol afforded a 47% recovery of pure crystalline crinamidine, m.p.

(26) This material was presented earlier in communication form; W. C. Wildman and H. M. Fales, THIS JOURNAL, **80**, 6465 (1958).

(27) P. F. Highet and W. C. Wildman, *J. Org. Chem.*, **25**, 287 (1960).

(28) 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 on a Rudolph photoelectric polarimeter 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 a Perkin–Elmer model 21 double-beam spectrophotometer, in chloroform solution unless noted to the contrary. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

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

(30) J. Renz, D. Stauffacher and E. Seebeck, *Helv. Chim. Acta*, **38**, 1209 (1955).

(31) Epicrinamidine will be fully described in a subsequent paper of this series.

235–236°, identical in infrared spectrum (KBr) with starting material. Finally, 10–100% methanol in chloroform eluted 34 mg. of an oil which on examination by paper chromatography appeared to consist of both crinamidine and epicrinamidine. Accordingly, it was carefully rechromatographed over Florisil with methanol–chloroform, and the two components were separated, One product was identified as crinamidine. With this crinamidine removed, the second component was found by infrared examination most nearly to resemble powelline, and the absence of epicrinamidine was established.

Conversion of Dihydrohaemanthamine to (+)-Dihydrobuphanisine.—A solution of 521 mg. of dihydrohaemanthamine in 5 ml. of thionyl chloride was refluxed for 1.5 hours. The solvent was removed under reduced pressure, and the resulting gum was taken up in 20 ml. of tetrahydrofuran. Lithium aluminum hydride (1.0 g.) was added, and the mixture was refluxed for 5 hours. The excess hydride was decomposed by the addition of ethanol, and 50% sodium hydroxide was added to destroy the complex. The tetrahydrofuran was decanted. The precipitate was washed with chloroform, and the washings were combined with the tetrahydrofuran. Evaporation of the dried solvents left 434 mg. of crude product which was chromatographed over alumina that had been deactivated with ethyl acetate. Pure benzene eluted a few milligrams of an odoriferous thio compound. Ethyl acetate in benzene (3–100%) afforded 344 mg. of crystalline (+)-dihydrobuphanisine. Further elution with 5% ethanol in ethyl acetate produced 46 mg. (9%) of dihydrohaemanthamine.

The (+)-dihydrobuphanisine was recrystallized from ether, m.p. 95–97°. On admixture with authentic (−)-dihydrobuphanisine, the melting point was depressed below 70° while the infrared spectrum (KBr) was identical with that of authentic (−)-dihydrobuphanisine. (+)-Dihydrobuphanisine showed $[\alpha]^{25}_{589}$ +27.9°, $[\alpha]^{25}_{436}$ +61.4°, $[\alpha]^{25}_{400}$ +83°, $[\alpha]^{25}_{350}$ +162° (*c* 0.59, chloroform). Authentic (−)-dihydrobuphanisine showed $[\alpha]^{25}_{589}$ −27.9°, $[\alpha]^{25}_{436}$ −61.7°, $[\alpha]^{25}_{400}$ −83.3°, $[\alpha]^{25}_{350}$ −164° (*c* 0.66, chloroform).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37. Found: C, 71.19; H, 7.38.

Crinine (II), R.D.: $[\alpha]^{25}_{650}$ −17°, $[\alpha]^{25}_{589}$ −23.5°, $[\alpha]^{25}_{436}$ −91.7°, $[\alpha]^{25}_{360}$ −302°, $[\alpha]^{25}_{330}$ −694° (*c* 0.64, chloroform).

Buphanisine (III), R.D.: $[\alpha]^{25}_{650}$ −24.7°, $[\alpha]^{25}_{589}$ −32.4°, $[\alpha]^{25}_{436}$ −102°, $[\alpha]^{25}_{360}$ −308°, $[\alpha]^{25}_{330}$ −639° (*c* 0.85, chloroform).

(−)-Crinane (I), R.D.: $[\alpha]^{25}_{589}$ −14°, $[\alpha]^{25}_{436}$ −32°, $[\alpha]^{25}_{370}$ −70°, $[\alpha]^{25}_{330}$ −221° (*c* 0.20, chloroform).

(+)-Powellane (V), R.D.: $[\alpha]^{25}_{589}$ 0°, $[\alpha]^{25}_{436}$ +10°, $[\alpha]^{25}_{360}$ +44°, $[\alpha]^{25}_{320}$ +117° (*c* 0.25, chloroform).

Conversion of Dihydrobuphanidrine to Dihydrobuphanisine.—An ethanolic solution of 1.92 g. of buphanidrine, m.p. 90–91°, $[\alpha]^{26}_{589}$ −4.7° (*c* 1.1, chloroform), was hydrogenated in the presence of 330 mg. of 5% palladium-on-charcoal. After absorption ceased, the catalyst was removed by filtration. Concentration of the filtrate gave 2.0 g. of oil which was purified *via* the picrate, m.p. 284–285° dec. (reported[5] for dihydrobuphanidrine picrate, m.p. 281–283° dec.). The free base, 1.9 g., was regenerated from the picrate by passing a chloroform solution of the picrate through a column of alumina. The chloroform eluates were concentrated and a portion was purified by evaporative distillation at 130° (10 μ), $[\alpha]^{26}_{589}$ −10.6°, $[\alpha]^{26}_{436}$ −14.2° (*c* 0.85, chloroform). The remaining 1.7 g. of dihydrobuphanidrine was dissolved in 100 ml. of xylene and treated with 2.0 g. of sodium and 17 ml. of isoamyl alcohol by the procedure reported earlier.[12] From the alkaloids forming chloroform-insoluble hydrochlorides there was obtained a mixture of dihydrobuphanidrine and dihydrobuphanisine. The alkaloid fraction forming chloroform-soluble hydrochlorides (1.3 g.) appeared to consist entirely of dihydrobuphanidrine and this was retreated with 2.0 g. of sodium and 20 ml. of isoamyl alcohol.[32] The product appeared to be a mixture of dihydrobuphanidrine and dihydrobuphanisine. The combined products were partially separated by chromatography on alumina. Elution with benzene–ethyl acetate (1:1) and ethyl acetate gave first 188 mg. of dihydrobuphanidrine followed by 560 mg. of a mixture of dihydrobuphanidrine and dihydrobuphanisine. Elution with 20% ethanol in ethyl acetate gave 300 mg. of material with an infrared spectrum identical with that of dihydrobuphanisine. Crystallization from ether gave 180 mg. of IV, m.p. 94–95°, $[\alpha]^{24}_{589}$ −26°, $[\alpha]^{25}_{436}$ −61° (*c* 0.71, chloroform). A mixture melting point determination with authentic (−)-dihydrobuphanisine,[12] m.p. 95–96°, was not depressed.

(32) Quantitative estimates of the ratio of dihydrobuphanidrine and dihydrobuphanisine can be made from the intensity of the infrared absorption at 6.18 μ shown only by the former compound: *cf.* W. C. Wildman and C. J. Kaufman, THIS JOURNAL, **77**, 4807 (1955).

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE UNIVERSITY]

The Formation of 1-(2,4-Dinitrophenyl)-substituted Pyrazolines from α,β-Unsaturated 2,4-Dinitrophenylhydrazones

BY WILLIAM L. CHAMBERS AND M. L. WILLARD

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The formation of 1-(2,4-dinitrophenyl)-substituted pyrazolines from α,β-unsaturated 2,4-dinitrophenylhydrazones has been demonstrated. An alternate synthesis of 1-(2,4-dinitrophenyl)-substituted pyrazolines is presented.

The formation of 1-(2,4-dinitrophenyl)-substituted pyrazolines from α,β-unsaturated 2,4-dinitrophenylhydrazones has been proposed by several workers,[1] but experimental proof of this formation has not been presented.

When α-bromopropiophenone 2,4-dinitrophenylhydrazone is refluxed in glacial acetic acid, dehydrohalogenation takes place, and an orange product (I), m.p. 214–216°, is produced. Ramirez and Kirby[2] eliminated a pyrazoline structure for this compound on the basis that phenyl vinyl ketone DNPH was stable under ring closing conditions. These workers noted also that the ultraviolet absorption spectrum of compound (I) compared favorably with that of an azo structure.

We find, however, that when phenyl vinyl ketone DNPH is treated with boiling glacial acetic acid containing hydrobromic acid, the same orange product (I) was obtained.

To establish the presence of a pyrazoline structure, the heterocyclic was synthesized by an alternate route from 2,4-dinitrochlorobenzene (VI) and 3-phenyl-2-pyrazoline (IV). This reaction yielded

(1) (a) G. Morgan and C. F. Griffith, *J. Chem. Soc.*, 841 (1937); (b) C. F. H. Allen and J. H. Richmond, *J. Org. Chem.*, **2**, 222 (1937); (c) T. L. Jacobs in R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, Vol. 5, p. 64; (d) L. I. Braddock, K. Y. Garlow, L. I. Grim, A. F. Kirkpatrick, S. W. Pease, A. J. Pollard, E. F. Price, T. L. Reissman, N. A. Rose and M. L. Willard, *Anal. Chem.*, **25**, 301 (1953); (e) D. S. Tarbell and W. E. Lovett, THIS JOURNAL, **78**, 2259 (1956).

(2) Fausto Ramirez and Arthur F. Kirby, *ibid.*, **75**, 6026 (1953).