ether (2:1) eluted a crystalline product, which on recrystallization from ether afforded 40 mg. of colorless needles, m.p. 104–105°, $[\alpha]^{21}D$ −77.3° (*c* 0.99, benzene). This substance was found to be identical with anhydrodihydrolycorine (XVII) by melting point determination and by comparison of the ultraviolet spectra.

Dehydration of Caranine (III).—A mixture of 180 mg. of caranine (III), 1 g. of phosphoryl chloride and 3 ml. of pyridine was worked up by a procedure analogous to that used for isocaranine (XII) as described above. The residue obtained by evaporation of the benzene extract afforded on recrystallization from ether 110 mg. of colorless needles, m.p. 153–154°, identical with the diene derivative XV obtained by the alkaline double bond migration of the diene derivative XIII.

Manganese Dioxide Oxidation of Isocaranine (XII).—A solution of 100 mg. of isocaranine (XII) in 33 ml. of benzene was shaken with 1.0 g. of manganese dioxide[25] at room temperature (25–30°) for ten hours. After removal of manganese dioxide by filtration, the benzene solution was extracted with dilute hydrochloric acid. The acidic aqueous layer was basified with 10% sodium carbonate and extracted with benzene. This benzene layer afforded 20 mg. of the starting material. The original benzene solution containing nonbasic substances was worked up in the usual manner. In trituration with ethanol, the residue afforded a small amount of crystalline product, which was purified by sublimation in high vacuum. Though this compound melted at 264–265°, not enough was obtained to carry out an analysis. Its ultraviolet spectrum was similar to that of dihydrolycorinone[26] and its infrared spectrum showed peaks at 2.95 μ (–OH) and 6.11 μ (–C(=O)–N–). Moreover, using manganese dioxide prepared by Attenburrow's method,[27] oxidation was carried out in chloroform solution changing the reaction temperature or reaction time as follows: 5°, 20°, 25° or 0.25, 0.5, 0.75, 1, 6 hours, respectively. However, the anticipated α,β-unsaturated ketone was not obtained.

Reduction of Lycorine Chlorohydrin (IV) with Lithium Aluminum Hydride in Ether.—A solution of 40 mg. of the chlorohydrin IV in 130 ml. of dry ether with 40 mg. of lithium aluminum hydride was heated under reflux for four hours. Water was added and the reaction mixture was filtered. The ethereal layer was separated, evaporated to dryness, and dissolved in 15 ml. of benzene. The residue was chromatographed on 10 g. of alumina. A mixture of benzene and ether (5:1) eluted a crystalline product, which on recrystallization from ethanol afforded 20 mg. of colorless prisms, m.p. 176–177°, undepressed on admixture with an authentic sample of caranine (III).

Acknowledgment.—We are indebted to Prof. S. Uyeo, Dr. W. I. Taylor, Dr. W. C. Wildman and Dr. H. M. Fales for valuable discussions.

(25) O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(26) S. Takagi, W. I. Taylor, S. Uyeo and H. Yajima, *ibid.*, 4003 (1955).

(27) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *ibid.*, 1094 (1952).

IMAFUKU, AMAGASAKI, JAPAN

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

Alkaloids of the Amaryllidaceae. XI. The Structures of Alkaloids Derived from 5,10b-Ethanophenanthridine[1,2]

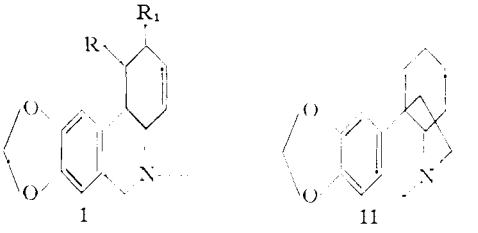
BY W. C. WILDMAN

RECEIVED DECEMBER 2, 1957

A combination of degradative and synthetic evidence has proved that the alkaloids crinine, powelline, buphanidrine and buphanisine are represented by structures IX, XVI, XX and XXIV, respectively.

The isolation and characterization of the alkaloid crinine from two unidentified *Crinum* species was reported by this Laboratory in 1955.[3] In a paper submitted after our communication, Boit[4] independently reported the isolation of an alkaloid, crinidine, from *Crinum moorei* J. D. Hook. Crinine and crinidine possessed identical molecular formulas and functional groups. Direct comparison of the two alkaloids by infrared spectra and mixture melting point determination showed them to be identical. Since that time, crinine has been isolated from *Boöphone fischeri* Baker,[5] *Crinum powellii* Hort.[6,7] and *Nerine bowdenii* W. Watson.[7]

Sharing with caranine (I, R = OH, R_1 = H)[1] the relatively simple molecular formula $C_{16}H_{17}NO_3$, crinine was found to contain the same functional groups, *viz.*, one methylenedioxyphenyl group, one hydroxyl and one aliphatic double bond. The latter is neither conjugated with the aromatic ring



1 11

nor contiguous with the hydroxyl function. Since crinine occurs frequently in bulbs which are rich also in lycorine (I, R, R_1 = OH),[8,9] a tentative hypothesis was advanced that crinine might possess the isomeric structure I (R = H, R_1 = OH). Support for this was obtained from the facile oxidation of crinine to a ketone, oxocrinine, by manganese dioxide. The infrared spectrum of oxocrinine showed no hydroxyl absorption but pos-

(1) Paper X, E. W. Warnhoff and W. C. Wildman, THIS JOURNAL, **79**, 2192 (1957).

(2) Preliminary reports of this work appeared in communication form: (a) W. C. Wildman, *ibid.*, **78**, 4180 (1956); (b) W. C. Wildman, *Chemistry & Industry*, 1090 (1956).

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

(4) H.-G. Boit, *Chem. Ber.*, **87**, 1704 (1954).

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

(6) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **88**, 1590 (1955).

(7) H.-G. Boit and H. Ehmke, *ibid.*, **89**, 2093 (1956).

(8) L. G. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima and N. Yanaihara, *J. Chem. Soc.*, 4622 (1954).

(9) Y. Nakagawa, S. Uyeo and H. Yajima, *Chemistry & Industry*, 1238 (1956).

sessed a strong band at 5.98 μ, characteristic of an α,β-unsaturated cyclohexenone. In agreement with this structural feature, the ultraviolet spectrum of oxocrinine showed intense absorption at 226 mμ. When the contribution of the methylenedioxyphenyl group was subtracted from the spectrum, the cyclohexenone chromophore showed a maximum at 227 mμ (ϵ 14,400). Although the wave length of this maximum was more in accord with that anticipated from a β-unsubstituted cyclohexenone, this conclusion was not deemed infallible since anomalous absorptions have been reported for certain amino and aromatic cyclohexenones.[10,11]

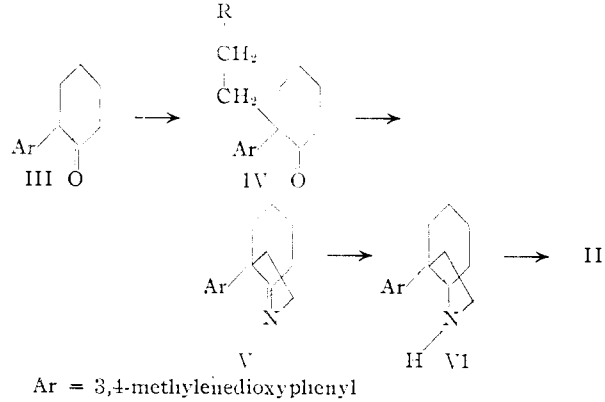
Lithium aluminum hydride reduction of oxocrinine afforded a crystalline alcohol which possessed the same melting point as crinine but differed from crinine in its infrared spectrum and molecular rotation. A mixture melting point was depressed 40°. This product was epimeric with crinine and differed from it only in the configuration of the hydroxyl group, since this epicrinine afforded oxocrinine in good yield upon manganese dioxide oxidation.

Oxocrinine absorbed one equivalent of hydrogen under catalytic conditions to give dihydroöxocrinine. Consistent with its formulation as a substituted cyclohexanone, dihydroöxocrinine showed infrared absorption at 5.84 μ and an ultraviolet spectrum resembling that of crinine itself. Dihydroöxocrinine could be obtained from dihydrocrinine by Oppenauer oxidation. Finally, the formation of a dibenzylidenedihydroöxocrinine by the condensation of dihydroöxocrinine with two equivalents of benzaldehyde showed that the carbonyl function of dihydroöxocrinine was flanked by two methylene groups.

Although the foregoing evidence was compatible with structure I (R = H, R_1 = OH) for crinine, several specific reactions which were invaluable in the characterization of many alkaloids in the lycorine group[12] were negative when applied to crinine. Selenium dioxide and mercuric acetate were without effect on crinine.[13] In contrast to the alkaloids derived from pyrrolo[de]phenanthridine,[1,14-16] O-acetyldihydrocrinine gave no neutral lactam when oxidized with potassium permanganate. Most convincingly, if crinine were represented by I (R = H, R_1 = OH), ring C of oxocrinine should become aromatic under rather mild conditions. However, not only did oxocrinine resist aromatization by the mild oxidizing agents mercuric acetate or selenium dioxide, but also was recovered unchanged from an attempted dehydrogenation with palladium-on-charcoal in boiling *p*-cymene.

From this comparison of the reactions of crinine with those of alkaloids of the lycorine series, it was apparent that ring C in the latter becomes aromatic under the mildest conditions while the six-membered ring of crinine (which contains the double bond and hydroxyl group) resists aromatization. The presence in crinine of a spiro ring system which prevents aromatization was an obvious conclusion derived from these preliminary experiments.

From biogenetic considerations and by analogy with the structure of tazettine, it seemed quite likely that crinine was derived from 5,10b-ethano-8,9-methylenedioxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (II). Indeed, this ring system was suggested previously[17] for lycorine on biogenetic grounds. A promising test of this hypothesis would be the conversion of crinine to a derivative lacking the double bond and the hydroxyl group which then could be compared with II. Fortunately, simple degradative and synthetic routes were available to implement such a plan. The carbonyl group of dihydroöxocrinine was removed by Wolff-Kishner reduction to afford a derivative of crinine which possessed the basic ring system of crinine without the complicating factors of the double bond and the hydroxyl group. This derivative was given the trivial name crinane. The synthesis of II was facilitated by the findings of many research groups who were concerned with the synthesis of morphine-like structures. The requisite starting ketone (III) was obtained from



Ar = 3,4-methylenedioxyphenyl

the 4-(3,4-methylenedioxyphenyl)-5-nitrocyclohexene by the Nef reaction.[18] The intermediate cyclohexenone was not crystalline, and the crude Nef reaction mixture was hydrogenated directly to give III. In the presence of acrylonitrile and Triton B catalyst, III afforded a monocyanoethyl derivative which was assigned the structure IV (R = CN) in accord with observations[19-21] that cyanoethylation of 2-phenylcyclohexanones and structurally related compounds occurs in the 2-position. Methanolysis of this product gave the corresponding methyl ester IV (R = $COOCH_3$) which was converted to the hydrazone hydrazide on refluxing with 85% hydrazine hydrate. The ac-

(10) V. Georgian, *Chem. and Ind.*, 930 (1954); 1480 (1957).

(11) W. C. Wildman, R. B. Wildman, W. T. Norton and J. B. Fine, THIS JOURNAL, **75**, 1912 (1953).

(12) Alkaloids of the lycorine group include all those possessing a structure based on the pyrrolo[de]phenanthridine ring system.

(13) *Cf.* H. M. Fales, E. W. Warnhoff and W. C. Wildman, THIS JOURNAL, **77**, 5885 (1955).

(14) H. Kondo and K. Katsura, *Ber.*, **73**, 112 (1940).

(15) K. Wiesner, W. I. Taylor and S. Uyeo, *Chemistry & Industry*, 46 (1954).

(16) H. M. Fales and W. C. Wildman, THIS JOURNAL, in press.

(17) R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, London, England, 1955, p. 92.

(18) W. C. Wildman and R. B. Wildman, *J. Org. Chem.*, **17**, 581 (1952). A review of this synthetic method has been presented by W. E. Noland in *Chem. Revs.*, **55**, 137 (1955).

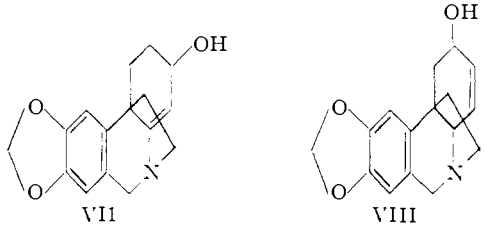
(19) W. E. Bachmann and L. B. Wick, THIS JOURNAL, **72**, 3388 (1950).

(20) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 1524 (1953).

(21) V. Boekelheide, THIS JOURNAL, **72**, 712 (1950).

tion of nitrous acid on the hydrazone hydrazide gave 2,3,4,5,6,7-hexahydro-3a-(3,4-methylenedioxyphenyl)-indole (V).[22] The double bond was assigned to the 1,7a-position by spectral means. The free base (V) in chloroform solution showed infrared absorption at 6.06 (s) μ but none in the 3 μ region attributable to the N–H stretching vibration. The perchlorate of V showed strong absorption at 5.94 μ. These bands are in good agreement with those found for hexahydroindole.[23] Catalytic hydrogenation of V gave an octahydroindole (VI) which was cyclized in good yield to the desired base (II) by the Pictet–Spengler method. The infrared spectra (in chloroform solution and as a liquid film) of II and the (−)-crinane obtained by the Wolff–Kishner reduction of dihydroöxocrinine were identical. Also, the infrared spectra (in chloroform solution) of the respective picrates were superimposable. From this evidence it was concluded that the basic ring system of crinine is that of II. The subsequent preparation of lycorane[16,24] (I, R, R_1 = H, no double bond at 3,3a) and its non-identity with (−)-crinane may be considered additional, though negative, evidence for the same conclusion.

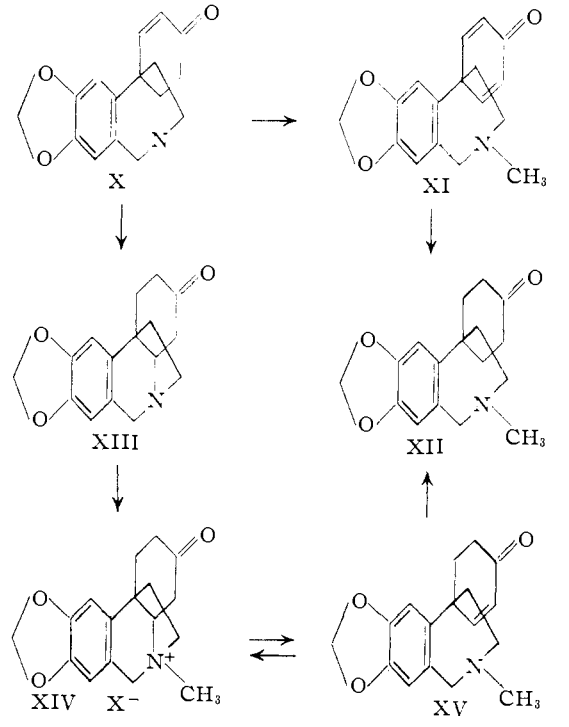
Within the basic ring system of crinine, three possible structures (VII, VIII, IX) are compatible with the requirements that the double bond and hydroxyl group are allylic and the carbon atoms adjacent to the hydroxyl group are unsubstituted. An attempt to correlate the basicities of crinine (pK_a 7.95) and dihydrocrinine (pK_a 8.70) with these three structures has proved to be misleading



VII VIII

IX

in the light of recent degradative studies which show, unequivocally, that crinine is represented by IX. Although no satisfactory yield of methine could be obtained from crinine methohydroxide, Hofmann degradations proceeded with extreme ease and excellent yields in the cases of both oxocrinine (X) and dihydroöxocrinine (XIII). When an aqueous solution of oxocrinine methiodide was treated with dilute sodium hydroxide and warmed on the steam-bath for a few minutes, a 95% yield of oxocrinine methine (XI) was obtained. Oxocrinine methine showed carbonyl absorption at 6.0 μ and an intense band at 230 mμ in the ultraviolet. It absorbed two equivalents of hydrogen under catalytic conditions to give a tetrahydro derivative (XII) which showed carbonyl absorption at 5.81 μ. The ultraviolet absorption spectrum of the tetrahydroöxocrinine methine was in accord with that expected from an isolated methylenedioxyphenyl chromophore. Most significantly, neither oxocrinine methine nor its tetrahydro derivative showed any trace of optical activity. Under similar Hofmann conditions, the methiodide of dihydrooxocrinine (XIV, X = I) afforded a non-crystalline,



optically active methine (XV). Catalytic reduction of XV proceeded with the absorption of one equivalent of hydrogen to yield XII, identical in all respects with inactive tetrahydroöxocrinine methine prepared from XI. Only structure IX for crinine is consistent with these findings.

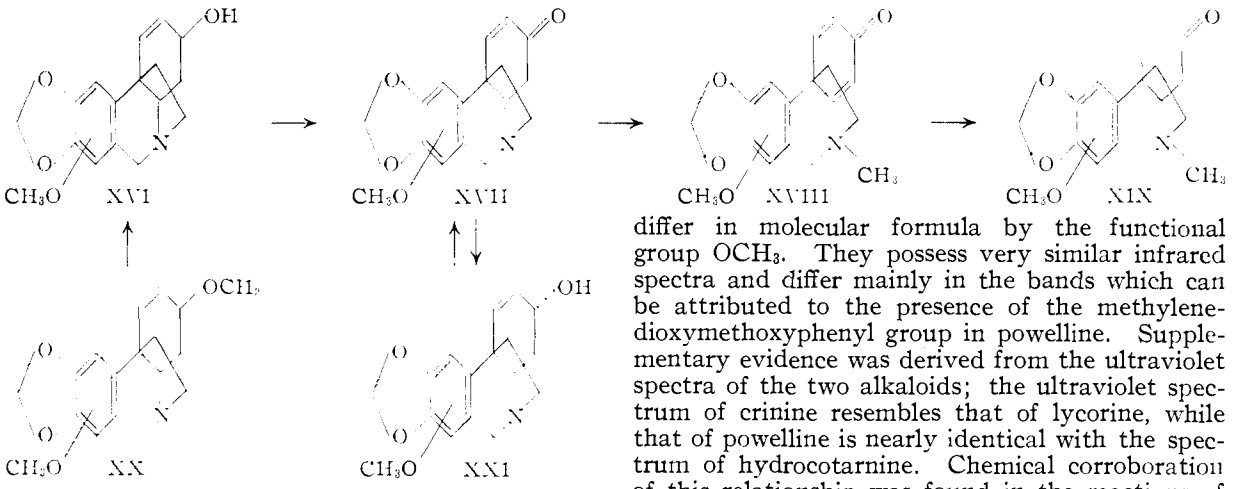
An interesting transannular effect[25] was observed in some reactions of dihydroöxocrinine methine (XV). In ethanol, at a concentration of 75 μg./ml., the ultraviolet spectrum of XV shows rising end absorption (ϵ_{235} mμ ~8000) (Fig. 1.) Upon dilution to a concentration of 25 μg./ml., however, no such rise is observed in this region (ϵ_{235} mμ 3650.) In fact, the curve is reminiscent of that found for XII or XIII. A similar change in the ultraviolet absorption of XV could be produced by variations in the *p*H of the solvent medium (Fig. 2). In alkali, the spectrum was that of an α,β-unsaturated ketone superimposed on an independent methylenedioxyphenyl chromophore. In acid, no absorption attributable to the former chromophore was present and the spectrum was nearly identical with that of XIII. It seems most reasonable to view

(22) *Cf.* W. E. Bachmann and E. J. Fornefeld, THIS JOURNAL, **73**, 51 (1951).

(23) B. Witkop, *ibid.*, **78**, 2873 (1956).

(24) K. Takeda, K. Kotera and S. Miznkami, *ibid.*, **80**, 2562 (1958).

(25) N. J. Leonard, *Rec. Chem. Progr. (Kresge-Hooker Sci. Lib.)*, **17**, 243 (1956).



the loss of cyclohexenone absorption upon dilution or acidification of XV as a transannular Michael addition of the amino group, which is held in a relatively fixed stereochemical position, to the β-carbon atom of the cyclohexenone (XV → XIV). The reverse reaction, which first was considered to be of the Hofmann type, is merely a special case of β-elimination from a β-aminoketone. Chemical proof of this hypothesis is derived from the observation that the picrate of dihydroöxocrinine methine is identical in every respect with the methopicrate of dihydroöxocrinine.

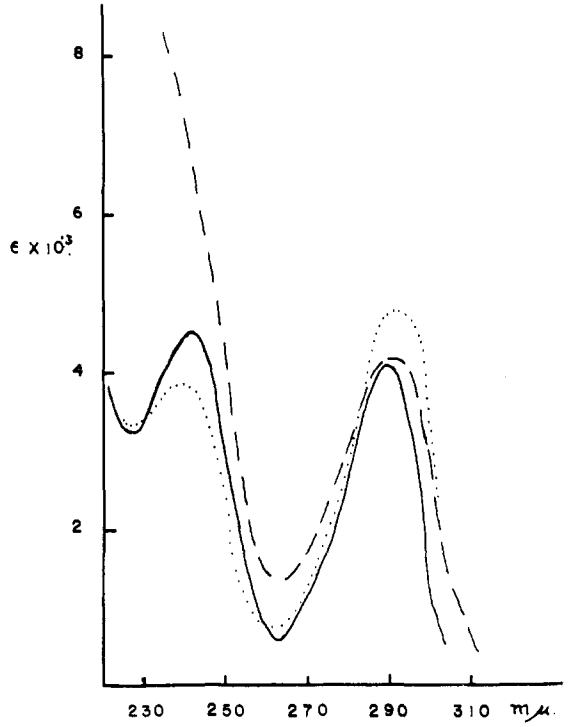


Fig. 1.—Ultraviolet absorption spectra in ethanol of: XV, c = 75 μg./ml., - - - - -; XV, c = 25 μg./ml., ...; XII, ———.

In a previous paper[2b] it was suggested that powelline, a minor alkaloid of *Crinum xpowellii* Hort., is *ar*-methoxycrinine. In support of this relationship, it was pointed out that crinine and powelline differ in molecular formula by the functional group OCH_3. They possess very similar infrared spectra and differ mainly in the bands which can be attributed to the presence of the methylenedioxymethoxyphenyl group in powelline. Supplementary evidence was derived from the ultraviolet spectra of the two alkaloids; the ultraviolet spectrum of crinine resembles that of lycorine, while that of powelline is nearly identical with the spectrum of hydrocotarnine. Chemical corroboration of this relationship was found in the reactions of powelline, all of which parallel those observed for crinine. Oxopowelline, dihydroöxopowelline, epipowelline, dihydroepipowelline and (+)-powellane were prepared in yields comparable to those in the crinine series. Moreover, there are excellent rotational correlations (observed at 589 mμ) between the two alkaloids and their corresponding degradation products. Unequivocal proof that powelline possesses the structure XVI may be derived from

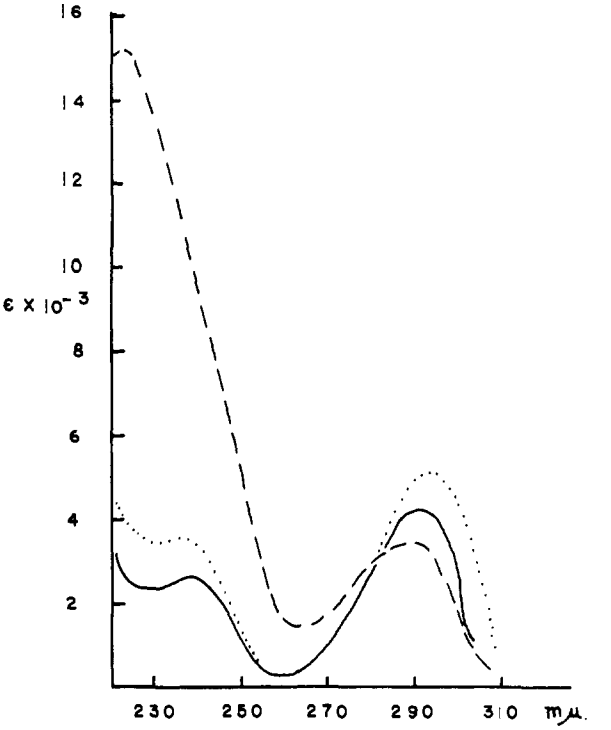
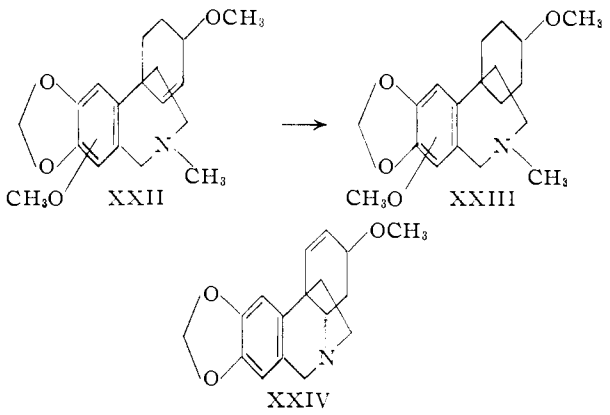


Fig. 2.—Ultraviolet absorption spectra of: XV in alkaline ethanol, - - - - -; XV in acidic ethanol, ———; XIII in ethanol, ...

two different chemical methods. One of these, the conversion of powelline or dihydroepipowelline (XXI, no double bond 1,2) to dihydroepicrinine by sodium and isoamyl alcohol, is the subject of another paper.[16] The second proof is analogous in its method to that employed for crinine. The action

of mild alkali on oxopowelline methiodide gave a methine (XVIII) which was optically inactive. The methine absorbed two equivalents of hydrogen to yield a tetrahydroöxopowelline methine (XIX) which was optically inactive also.

Buphanidrine, $C_{15}H_{13}N(O_2CH_2)(OCH_3)_2$, was isolated first from *Boöphone fischeri* Baker.[5] In this Laboratory, the alkaloid has been found to be a constituent of the bulbs of an unidentified *Brunsvigia* species of South African origin and of an *Amaryllis bella-donna* hybrid ($^3/_4$ *A. bella-donna* L. × $^1/_4$ *Brunsvigia gigantea* Heist.).[26] Buphanidrine is considered to be the methyl ether of powelline from the observations that the alkaloid contains the methylenedioxymethoxyphenyl group (infrared absorption at 6.2 μ; hydrocotarnine-like ultraviolet spectrum of the alkaloid and its derivatives), one double bond (shown by catalytic hydrogenation), and one reactive, aliphatic methoxyl group (evidenced by the hydrolysis of buphanidrine to powelline using dilute hydrochloric acid).[2b] Dihydrobuphanidrine methine



(XXII) affords an optically inactive dihydro derivative (XXIII) upon catalytic hydrogenation,[27] proving that no allylic rearrangement occurred during the acid hydrolysis of buphanidrine. These results establish with certainty the structure of buphanidrine as XX.

Since buphanisine[5] has been shown to be *ar*-demethoxybuphanidrine[16] and affords crinine on acid hydrolysis, the alkaloid can be represented only by structure XXIV.

With the structural determination of dihydroundulatine[27] and the four alkaloids discussed in this paper, degradative products and techniques are available to aid materially in the studies of other alkaloids containing this ring system. Buphanamine[2b,5,28] and crinamidine[4] most certainly belong to this group and studies on their structures will be reported shortly.

Acknowledgment.—The author is indebted to Dr. B. G. Schubert of the Section of Plant Introduction, U. S. Department of Agriculture, for her help in obtaining the plant material used in this study and to Messrs. D. L. Rogerson, Jr., and J. D. Link for the isolation of the crude alkaloid mixture. The skillful assistance of Miss Patricia Wagner and Mrs. L. C. Warren in the instrumental aspects of the work is acknowledged gratefully.

(26) The yield of buphanidrine from the latter source is 0.0008%. Details of the isolations from this plant material will be reported in another paper.

(27) E. W. Warnhoff and W. C. Wildman, unpublished data.

(28) L. G. Humber and W. I. Taylor, *Can. J. Chem.*, **33**, 1268 (1955).

Experimental[29]

Isolation of Alkaloids.—Crinine, lycorine, powelline and crinamine were isolated from *Crinum xpowellii* Hort. by the methods described previously.[3] The yields agreed well with those reported by Boit and Ehmke[6,7] in a study of the alkaloids of the same plant. Buphanidrine was isolated from an unidentified *Brunsvigia* species by the excellent procedure of Renz, Stauffacher and Seebeck.[5] Accurate yield data on this isolation are unavailable due to accidental loss in the processing of the bulbs.

Basicity Measurements.—In dimethylformamide–water (3:7), these pK_a values were obtained: crinine, 7.95; dihydrocrinine, 8.70; oxocrinine, 6.33; and buphanidrine, 7.75.

Crinine.—Crinine, isolated by chromatography, was purified through its picrate, m.p. 237–239°. Regeneration of the alkaloid by alkali and recrystallization from acetone gave colorless needles, m.p. 209–210°. Analytical and spectral data have been presented earlier.[3]

Dihydrocrinine.—A solution of 517 mg. of crinine in 10 ml. of ethanol was reduced with 130 mg. of 10% palladium-on-charcoal catalyst at room temperature and atmospheric pressure. Hydrogen absorption stopped after the uptake of one equivalent of hydrogen. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was crystallized from acetone to give 390 mg. (75%) of colorless prisms, m.p. 220–221°, $[\alpha]^{26}_{589}$ −28.8°, $[\alpha]^{26}_{436}$ −64.0° (*c* 1.27); reported m.p. 212–214°,[3] 212–213°.[4]

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.41; H, 7.00; N, 5.08.

O-Acetyldihydrocrinine.—Acetylation of 60 mg. of dihydrocrinine in the usual manner with acetic anhydride and pyridine gave 52 mg. of O-acetyldihydrocrinine, m.p. 152–153° after recrystallization from cyclohexane.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.66; H, 6.79; N, 4.42.

Powelline.—The alkaloid crystallized from acetone or ethyl acetate as colorless prisms, m.p. 200–201°, $[\alpha]^{25}_{589}$ 0° (*c* 0.5), λ_{max} 288 mμ (log ϵ 3.23); reported[6] m.p. 197–198°, $[\alpha]^{22}_{589}$ 0° (chloroform).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65; OCH_3, 10.30. Found: C, 67.59; H, 6.23; N, 4.63; OCH_3, 10.06.

Powelline Picrate.—Prepared in aqueous ethanol and recrystallized from the same solvent, the picrate was obtained as yellow plates, m.p. 228–231° dec. (reported[6] 223–224°).

Powelline Methiodide.—Prepared in acetone and recrystallized from the same solvent, the methiodide formed colorless prisms, m.p. 273–275° dec. (reported[6] 273–274° dec.).

Dihydropowelline.—In the manner reported for dihydrocrinine, 110 mg. of powelline afforded 92 mg. of colorless prisms, m.p. 209–212°. One recrystallization from ethyl acetate gave pure dihydropowelline, m.p. 211–212°, $[\alpha]^{26}_{589}$ −11.9° (*c* 1.27), λ_{max} 287 mμ (log ϵ 3.25).

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.06; H, 6.79; N, 4.63.

Buphanidrine.—The alkaloid crystallized from ether to give massive prisms, m.p. 88–89°, $[\alpha]^{23}_{589}$ −6.93° (*c* 1.01), $[\alpha]^{23}_{589}$ +0.8° (*c* 0.63, ethanol), (reported[5] oil, $[\alpha]^{20}_{589}$ +1.8° (*c* 0.54, ethanol). The infrared spectrum was iden-

(29) 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 by a Rudolph photoelectric spectropolarimeter, model 200 S-80, in chloroform solution using a 2-dm. tube. Ultraviolet spectra were obtained in absolute ethanol solution with a Cary model 11MS 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.

tical with that of authentic buphanidrine,[30] and a mixture melting point showed no depression.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44; 2 OCH_3, 19.68. Found: C, 68.58; H, 6.65; N, 4.57; OCH_3, 20.22.

Buphanidrine Hydroperchlorate.—Prepared in glacial acetic acid and recrystallized from acetone–ether, buphanidrine hydroperchlorate formed colorless prisms, m.p. 250–252° dec., $[\alpha]^{23}_{589}$ +5.4° (*c* 0.75, ethanol), (reported[6] m.p. 240–242°, $[\alpha]^{20}_{589}$ +5.5°). The infrared spectrum (Nujol) of this material and that of authentic buphanidrine hydroperchlorate were identical.

Anal. Calcd. for $C_{18}H_{21}NO_4 \cdot HClO_4$: C, 51.99; H, 5.33; 2 OCH_3, 14.92. Found: C, 51.90; H, 5.35; OCH_3, 14.78.

Buphanidrine Hydrorhodanide.—Prepared in the manner described by Renz, Stauffacher and Seebeck, the hydrorhodanide formed colorless prisms from acetone–ether, m.p. 204–205°, $[\alpha]^{25}_{589}$ + 10.2° (*c* 0.9, ethanol), (reported[5] m.p. 200–202°, $[\alpha]^{20}_{589}$ +8.1° (*c* 0.87, ethanol). The infrared spectrum (Nujol) was identical with that of buphanidrine hydrorhodanide, and a mixture melting point showed no depression.

Buphanidrine Picrate.—A solution of 48 mg. of buphanidrine in ethanol was treated with excess ethanolic picric acid. The picrate precipitated as a gum but turned crystalline on the addition of a few drops of water. Recrystallization from ethanol–acetone afforded yellow prisms, m.p. 238–239°.

Anal. Calcd. for $C_{18}H_{21}NO_4 \cdot C_6H_3N_3O_7$: C, 52.94; H, 4.44; N, 10.29. Found: C, 52.93; H, 4.41; N, 10.14.

Dihydrobuphanidrine.—An ethanolic solution of 204 mg. of buphanidrine absorbed one equivalent of hydrogen when stirred at room temperature and atmospheric pressure with 100 mg. of 10% palladium-on-charcoal catalyst. The resulting dihydrobuphanidrine was an oil that could not be induced to crystallize. It was converted in the usual manner to the crystalline **picrate** which was recrystallized from ethanol–acetone to give 236 mg. of yellow plates, m.p. 281–283° dec.

Anal. Calcd for $C_{18}H_{23}NO_4 \cdot C_6H_3N_3O_7$: C, 52.74; H, 4.80; N, 10.25. Found: C, 52.71; H, 4.75; N, 10.25.

Oxocrinine (X).—To a stirred solution of 500 mg. of crinine in 200 ml. of chloroform was added 3.0 g. of manganese dioxide.[31] The reaction mixture was stirred for 6 hours and then filtered to remove the manganese dioxide. The oxide was washed twice with warm ethanolic chloroform. The combined filtrates were concentrated under reduced pressure to give a colorless oil that was crystallized from ether, 427 mg., m.p. 180–185°. Recrystallization from ether afforded pure oxocrinine, m.p. 184–186°, $[\alpha]^{24}_{589}$ −307°, $[\alpha]^{24}_{436}$ −848° (*c* 1.2); λ_{max} 5.98 μ, 226 mμ (log ε 4.25) and 296 mμ (log ε 3.63). On several occasions, a polymorph was obtained, m.p. 168–169°, which recrystallized at 170° when seeded with the higher melting form and then showed a m.p. 183–185°.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.15; H, 5.52; N, 5.21.

By the same technique, 72 mg. of epicrinine afforded 60 mg. of product, m.p. 184–186°, which was identical in all respects with oxocrinine.

Oxopowelline (XVII).—Under the conditions described for oxocrinine, oxopowelline, m.p. 171–173°, was obtained in 92% yield. Recrystallization from ether afforded pure oxopowelline, m.p. 177–178°, $[\alpha]^{25}_{589}$ −258°, $[\alpha]^{25}_{436}$ −697° (*c* 0.5); λ_{max} 5.96 μ, λ_{inf} 280 mμ (log ε 3.29).

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.14; H, 5.75; N, 4.74.

Dihydroöxocrinine (XIII).—A solution of 193 mg. of oxocrinine in 20 ml. of ethanol was added to a pre-reduced ethanolic suspension containing 100 mg. of 10% palladium-on-charcoal. At atmospheric pressure and room temperature, the compound rapidly absorbed 93% of the calculated amount of hydrogen. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residual oil was crystallized twice from benzene–cyclohexane to give 163 mg. of dihydroöxocrinine, m.p. 158–159°, $[\alpha]^{26}_{589}$ −67.7°, $[\alpha]^{26}_{436}$ −178° (*c* 1.35); λ_{max} 5.84 μ, 237 mμ (log ε 3.56) and 294 mμ (log ε 3.72).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.96; H, 6.17; N, 5.12.

An alternative method of preparation for dihydroöxocrinine involved the Oppenauer oxidation of dihydrocrinine. To a dried powder of potassium *t*-butoxide, prepared from 130 mg. of potassium in an excess of *t*-butyl alcohol, was added 20 ml. of dry, thiophene-free benzene, 250 mg. of fluorenone and 130 mg. of dihydrocrinine, m.p. 221°. The reaction mixture was covered with nitrogen and stirred magnetically at room temperature for 1 hour. The dark brown reaction mixture was diluted with water, and the benzene layer was washed twice with dilute (2%) potassium hydroxide solution, then four times with 2% hydrochloric acid. The combined acidic extracts were washed twice with ether and then basified with solid sodium hydroxide. The basic material was extracted with chloroform until a silicotungstic acid test indicated that no alkaloids remained in the aqueous solution. The combined chloroform solutions were washed with water and concentrated to yield 124 mg. of yellow oil which crystallized on trituration with ether. Recrystallization from ether afforded 66 mg. (51%) of dihydroöxocrinine, m.p. 157–159°, identical in all respects with the compound prepared by the catalytic reduction of oxocrinine.

Dihydroöxocrinine Methopicrate.—A solution of 110 mg. of dihydroöxocrinine in 3 ml. of ethanol was warmed with an excess of methyl iodide for several minutes. The solvent and excess methyl iodide were removed by evaporation under reduced pressure. The residual oil was dissolved in aqueous ethanol and treated with aqueous lithium picrate. The precipitate was washed several times with water and recrystallized twice from acetone, m.p. 209–211°, $[\alpha]^{22}_{589}$ −20.6°, $[\alpha]^{22}_{436}$ −30.2° (*c* 1.31, acetone–water, 90:10); λ^{Nujol}_{max} 5.84 μ.

Anal. Calcd. for $C_{16}H_{17}NO_3 \cdot CH_3 \cdot C_6H_2N_3O_7$: C, 53.70; H, 4.31; N, 10.89. Found: C, 53.63; H, 4.49; N, 10.96.

Dibenzylidenedihydroöxocrinine.—A solution of 84 mg. of dihydroöxocrinine and 127 mg. of freshly distilled benzaldehyde in 2 ml. of absolute ethanol was treated with 5 drops of piperidine and boiled under reflux for 17 hours. The solution was concentrated in an air jet to a yellow solid which was recrystallized from ethanol to give 40 mg. of product, m.p. 120°. Repeated recrystallizations gave 20 mg. of analytical purity, m.p. 124–125°; λ_{max} 6.01, 6.24, 6.35 μ, 232 mμ (log ε 4.27), 305 mμ (log ε 4.33) and 325 mμ (log ε 4.36).

Anal. Calcd. for $C_{30}H_{25}NO_3$: C, 80.51; H, 5.63. Found: C, 80.31; H, 5.88.

Dihydroöxopowelline.—In a manner analogous to the preparation of dihydroöxocrinine by catalytic hydrogenation, dihydroöxopowelline was obtained from oxopowelline in 63% yield, m.p. 165–166°, $[\alpha]^{25}_{589}$ −42°, $[\alpha]^{25}_{436}$ −103° (*c* 1.3); λ_{max} 5.83 μ, 287 mμ (log ε 3.22).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.48; H, 6.10; N, 4.58.

Epicrinine.—To a suspension of 567 mg. of lithium aluminum hydride in 100 ml. of dry ether was added dropwise an ethereal solution of 588 mg. of oxocrinine. The reaction mixture was boiled under reflux for 13 hours. The excess lithium aluminum hydride was decomposed with ethyl acetate, and the reaction mixture was hydrolyzed with water and 6 *N* sodium hydroxide. The aqueous solution was extracted three times with chloroform and the combined chloroform solutions were washed once with water and concentrated under reduced pressure. The oil residue was triturated with acetone to yield 412 mg. (73%) of epicrinine, m.p. 205–209°. Recrystallization from acetone afforded 321 mg. of pure epicrinine, m.p. 209–209.5°, $[\alpha]^{27}_{589}$ −142°, $[\alpha]^{27}_{436}$ −343° (*c* 1.03); λ_{inf} 237 mμ (log ε 3.31) and 295 mμ (log ε 3.47). A mixture melting point with crinine, m.p. 209–210°, was depressed to 170°. The material was much less soluble in chloroform than was crinine. Sodium borohydride reduction of oxocrinine in methanol afforded a 73% yield of epicrinine, m.p. 205–208°.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.89; H, 6.31; N, 5.35.

(30) Since the publication of ref. 5, the Swiss workers have obtained buphanidrine in crystalline form. We are indebted to Dr. J. Renz for this determination and for generous samples of buphanidrine hydroperchlorate, hydrobromide and hydrorhodanide.

(31) J. Altenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

Epicrinine Picrate.—Prepared in aqueous ethanol and recrystallized from the same solvent, the picrate formed yellow prisms, m.p. 227–229°. A mixture melting point with crinine picrate, m.p. 237–239° dec., was not depressed.

Anal. Calcd. for $C_{16}H_{17}NO_3 \cdot C_6H_3N_3O_7$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.96; H, 4.00; N, 11.16.

Dihydroepicrinine.—A solution of 229 mg. of epicrinine in 10 ml. of ethanol absorbed 0.86 equivalent of hydrogen at room temperature and atmospheric pressure with 188 mg. of 10% palladium-on-charcoal. The catalyst was removed by filtration and washed with ethanol. The combined ethanolic solutions were concentrated under reduced pressure to give 228 mg. of an oil which could be crystallized only from solvents containing some water. The material crystallized best from aqueous acetone to give fine, colorless prisms, m.p. 103–108°, $[\alpha]^{22}_{589}$ −23.0° (*c* 1.0).

Anal. Calcd. for $C_{16}H_{19}NO_3 \cdot H_2O$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.98; H, 7.13; N, 4.78.

The picrate crystallized from aqueous ethanol, m.p. 202–204°.

Anal. Calcd. for $C_{16}H_{19}NO_3 \cdot C_6H_3N_3O_7$: C, 52.59; H, 4.41; N, 11.15. Found: C, 52.32; H, 4.41; N, 11.10.

The hydroperchlorate was prepared by the addition of aqueous perchloric acid to the gummy base. Recrystallization from water afforded fine, colorless needles which lost birefringence and turned to a gum at 135–140°. The analytical sample was dried for 3 hours at 100° and for 12 hours at room temperature and 0.1 mm.

Anal. Calcd. for $C_{16}H_{19}NO_3 \cdot HClO_4 \cdot H_2O$: C, 49.04; H, 5.66; N, 9.05. Found: C, 48.87; H, 5.79; N, 9.13.

Epipowelline (XXI).—By the procedure reported for the preparation of epicrinine, epipowelline was obtained in 50% yield and recrystallized from ethyl acetate as colorless prisms, m.p. 177–178°, $[\alpha]^{26}_{589}$ −103°, $[\alpha]^{26}_{436}$ −229° (*c* 1.2); λ_{max} 287 mμ (log ε 3.21).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.57; H, 6.27; N, 4.60.

Dihydroepipowelline.—Catalytic hydrogenation of 460 mg. of epipowelline in ethanol with palladium-on-charcoal catalyst gave 360 mg. of dihydroepipowelline hydrate from aqueous acetone, m.p. 107–120°. A sample was dried for 48 hours at room temperature (0.1 mm.) for analysis.

Anal. Calcd. for $C_{17}H_{21}NO_4 \cdot H_2O$: C, 63.53; H, 7.21; N, 4.36; H_2O, 5.60. Found: C, 63.64; H, 7.26; N, 4.33; H_2O, 5.41.

A sample was dried at 130° (0.1 mm.) to constant weight; loss in weight 5.41%.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.24; H, 6.84; N, 4.57.

(−)-Crinane (II).—To a warm solution of 1.68 g. of potassium hydroxide in 10 ml. of diethylene glycol was added 3 ml. of hydrazine hydrate (85%) and 280 mg. of dihydrooxocrinine. The solution was refluxed at 150–160° for 2 hours. The reaction mixture was cooled, diluted with water and extracted three times with ether. The ethereal solution was washed once with water, dried and concentrated to 205 mg. of colorless oil. The oil was chromatographed on 20 g. of Merck aluminum oxide. Elution with 10% ethyl acetate in benzene afforded 141 mg. of colorless oil that showed no carbonyl band in the infrared spectrum. This material was evaporatively distilled at 130° (10 μ) for analysis, $[\alpha]^{24}_{589}$ −6.3°, $[\alpha]^{24}_{436}$ −16.2° (*c* 0.98).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.57; H, 7.63; N, 5.37.

This (−)-crinane crystallized upon seeding with crystalline (−)-crinane, m.p. 109–110°, which was obtained from catalytic hydrogenation of α-desoxycrinine.[16] Recrystallization from ether gave colorless prisms of (−)-crinane, m.p. 109–110°, $[\alpha]^{25}_{589}$ −6.1°, $[\alpha]^{24}_{436}$ −15.9° (*c* 0.61).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.78; H, 7.52; N, 5.39.

The picrate originally formed yellow prisms from acetone–ethanol, m.p. 206–207°.

Anal. Calcd. for $C_{16}H_{19}NO_2 \cdot C_6H_3N_3O_7$: C, 54.32; H, 4.56; N, 11.52. Found: C, 54.40; H, 4.52; N, 11.51.

Later preparations of this picrate from (−)-crinane, m.p. 109–110°, derived from the catalytic hydrogenation of α-desoxycrinine[16] melted at 211–212°. A liquid melt of the lower melting form crystallized when seeded with the higher melting polymorph and then melted at 211–212°. A mixture of the two polymorphs melted at 211–212°. Once the higher melting form had been obtained, it was impossible to isolate again the picrate melting at 206–207°. In chloroform solution, the infrared spectra of the two polymorphs were indistinguishable, although considerable differences existed in spectra obtained from Nujol mulls.

(+)-Powellane.—By the procedure given for the preparation of (−)-crinane, 169 mg. of dihydroöxopowelline afforded 103 mg. of colorless oil that showed no carbonyl absorption in the infrared. Conversion to the picrate in the usual manner gave 137 mg. of yellow prisms, m.p. 213–215°, $[\alpha]^{24}_{589}$ +28.2° (*c* 1.00).

Anal. Calcd. for $C_{17}H_{21}NO_3 \cdot C_6H_3N_3O_7$: C, 53.49; H, 4.68; N, 10.85. Found: C, 53.29; H, 4.68; N, 10.65.

The free base (162 mg.), obtained by passing a chloroform solution of 270 mg. of picrate over 10 g. of aluminum oxide and eluting with chloroform, was evaporatively distilled for analysis, b.p. 140° (5 μ), $[\alpha]^{25}_{589}$ +5.0° (*c* 1.0). The distilled (+)-**powellane** crystallized on standing and was purified by sublimation, m.p. 113.5–115°, $[\alpha]^{25}_{589}$ +11.1° (*c* 0.34).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.30; H, 7.44; N, 5.05.

Acid Hydrolysis of Buphanidrine.—A solution of 373 mg. of buphanidrine in 10 ml. of 10% hydrochloric acid was boiled under reflux for 1 hour. The solution was cooled to room temperature, diluted with water, basified with ammonia and extracted with chloroform. The chloroform solution was washed once with water and concentrated under reduced pressure to give 315 mg. of oil that was chromatographed on 10 g. of aluminum oxide (Merck). Elution with 5% ethyl acetate in benzene afforded 113 mg. of unreacted buphanidrine which was identified by its infrared spectrum and by conversion to the hydroperchlorate, m.p. 250° dec. Elution with chloroform and 5% ethanol in chloroform afforded crude powelline which was recrystallized twice from ethyl acetate to give 52 mg. of pure powelline, m.p. 200–201°. The infrared spectrum (Nujol) was identical with that of an authentic sample.

Acid Hydrolysis of Buphanisine.—From the hydrolysis of 176 mg. of buphanisine under conditions identical to those reported for buphanidrine, there was obtained after chromatography 52 mg. of unreacted buphanisine, m.p. 122–124°, and 23 mg. of crinine, m.p. 209–210°.

2-(3,4-Methylenedioxyphenyl)-cyclohexanone (III).—An ethanolic solution of 9.4 g. of 4-(3,4-methylenedioxyphenyl)-5-nitrocyclohexene[32] was treated with a solution of sodium ethoxide prepared from 1.7 g. of sodium and 150 ml. of ethanol. The reaction mixture was covered with nitrogen, allowed to stand 10 hours at room temperature and then added over 10 minutes to a stirred solution of 50 ml. of concentrated hydrochloric acid, 500 ml. of water and 400 ml. of ethanol at 0–10°. The reaction mixture was maintained at this temperature for 30 minutes and then allowed to come to room temperature over 2.5 hours. The yellow solution was diluted with an equal volume of water and extracted exhaustively with ether. The combined ether extracts were washed three times with water, dried and concentrated under reduced pressure to give a red-brown oil that was reduced in ethanolic solution with 1.0 g. of 10% palladium-on-charcoal catalyst at room temperature and a pressure of 3 atmospheres. The catalyst was removed by filtration, and on concentration the ethanolic solution afforded 4.66 g. (56%) of product, m.p. 92–93°. An analytical sample was prepared by sublimation at 90° (1 μ), m.p. 93–94°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.33; H, 6.55.

2-β-Cyanoethyl-2-(3,4-methylenedioxyphenyl)-cyclohexanone (IV, R = CN).—To a stirred solution of 2.85 g. of III in 20 ml. of peroxide-free dioxane was added 3 ml. of Triton B followed by a solution of 0.9 g. of acrylonitrile in 10 ml. of dioxane. The reaction mixture was warmed to 70° and maintained at this temperature for 1.5 hours. The orange-red solution was stirred overnight at room temperature and then diluted with 200 ml. of water and acidified with dilute hydrochloric acid. The cloudy aqueous solution

(32) L. H. Mason and W. C. Wildman, THIS JOURNAL, **76**, 6194 (1954).

was extracted three times with ether. The combined ether extracts were washed once with water, dried over magnesium sulfate and concentrated to an orange oil that was chromatographed on 150 g. of acid-washed alumina. Elution with benzene gave a total of 2.51 g. (71%) of colorless product which could not be crystallized. A portion of the material was evaporatively distilled at 150° (1 μ) for analysis.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.91; H, 6.28; N, 5.02.

2-Carbomethoxyethyl-2-(3,4-methylenedioxyphenyl)-cyclohexanone (IV, R = $COOCH_3$).—A solution of 2.67 g. of the nitrile IV (R = CN) in 200 ml. of dry methanol was saturated with dry hydrogen chloride and heated under reflux for 12 hours. The methanol was removed by distillation under reduced pressure, and the residue was diluted with 500 ml. of water, basified with saturated sodium bicarbonate solution and extracted three times with ether. The ether extracts were washed once with sodium bicarbonate solution and once with water and dried with magnesium sulfate. The ether was removed by distillation, and the residue was crystallized from methanol to give 1.33 g. of keto-ester, m.p. 87–89°. A second crop, 0.45 g., m.p. 72–85°, was obtained from the filtrates. A portion was recrystallized twice from methanol for analysis, m.p. 88–89°.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.15; H, 6.51.

2,3,4,5,6,7-Hexahydro-3a-(3,4-methylenedioxyphenyl)-indole (V).—By the procedure of Bachmann and Fornefeld,[21] it was possible to obtain 1.07 g. (48%) of crude V from 2.79 g. of the keto-ester IV (R = $COOCH_3$). The base could not be obtained in crystalline form and was converted to the **hydroperchlorate** salt with aqueous perchloric acid. Recrystallization from water gave 1.0 g. of the salt, m.p. 227–229°. The free base showed strong absorption at 6.06 μ. As a Nujol mull, the hydroperchlorate showed an intense band at 5.94 μ.

Anal. Calcd. for $C_{15}H_{17}NO_2 \cdot HClO_4$: C, 52.41; H, 5.28; Cl, 10.32. Found: C, 52.51; H, 5.27; Cl, 10.14.

***dl*-5,10b-Ethano-8,9-methylenedioxy-1,2,3,4,5,6,10b,10c-octahydrophenanthridine, (±)-Crinane (II).**—A solution of 997 mg. of the hydroperchlorate of V in 30 ml. of aqueous ethanol was treated with 8 drops of 10% perchloric acid and hydrogenated at room temperature and atmospheric pressure in the presence of 270 mg. of 10% palladium-on-charcoal catalyst. Hydrogenation ceased after the absorption of one equivalent of hydrogen. The catalyst was removed by filtration, and the filtrate was concentrated in an air jet. Neither the free base VI nor its hydroperchlorate could be crystallized, and the free base was cyclized directly.

A mixture of 713 mg. of VI in 10 ml. of water was treated with 5 ml. of formalin and 1.0 g. of sodium bicarbonate. The reaction mixture was heated on the steam-bath for 30 minutes, then cooled. The aqueous solution was decanted from the gummy organic material. This water-insoluble residue was washed three times with water. The gum was dissolved in 5 ml. of 20% hydrochloric acid, and the reaction mixture was heated on the steam-bath for 30 minutes. The solution was cooled, diluted with water and washed with ether. The aqueous solution was basified with concentrated ammonium hydroxide and extracted three times with ether. The combined ether extracts were washed with water, dried over magnesium sulfate and concentrated to 698 mg. of basic oil. The crude product was dissolved in benzene and chromatographed on 30 g. of aluminum oxide. Elution with benzene–ethyl acetate (95:5) gave 405 mg. of oil which was crystallized from ether, m.p. 97–99°. The infrared spectra (in chloroform solution and as a liquid film) of this material were identical in all respects with the corresponding spectrum of (−)-crinane derived from the Wolff–Kishner reduction of dihydroöxocrinine.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.69; H, 7.27; N, 5.41.

The picrate was prepared in ethanol and recrystallized from acetone–ethanol, m.p. 218–220°. In chloroform solution, its infrared spectrum was identical with that of (−)-crinane picrate, m.p. 206–207°.

Anal. Calcd. for $C_{16}H_{19}NO_2 \cdot C_6H_3N_3O_7$: C, 54.32; H, 4.56; N, 11.52. Found: C, 54.49; H, 4.35; N, 11.60.

Oxocrinine Methine (XI).—To a solution of 200 mg. of oxocrinine in methanol–acetone (1:3) was added 5 ml. of methyl iodide. After standing a few minutes, the solution was concentrated under reduced pressure to give a crystalline residue. This residue was dissolved in 6 ml. of water, heated on the steam-bath to approximately 80° and treated with 3 ml. of 10% sodium hydroxide solution. An insoluble oil formed immediately, and the hot reaction mixture was mixed thoroughly with 5 ml. of benzene. The benzene layer was removed through a pipet, and this benzene extraction procedure was repeated five times. The combined benzene extracts were concentrated in an air jet, and the residue was dissolved in ether. The ether solution was dried with magnesium sulfate. The methine crystallized on concentration to give 175 mg. of colorless prisms, m.p 107–109°. A second crop (24 mg., m.p. 100–106°) was obtained from the filtrate. Two recrystallizations from ether gave pure oxocrinine methine, m.p. 109–110°, $[\alpha]^{24}_{589,436,405}$ 0.0 ± 0.3° (*c* 1.08). The infrared spectrum (CCl_4) showed strong absorption at 6.00 μ and a band of moderate intensity at 6.15 μ. No hydroxyl absorption was present. The ultraviolet absorption spectrum showed maxima at 230 mμ (log ε 4.27) and 290 mμ (log ε 3.59).

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94; CH_3N, 5.31. Found: C, 72.36; H, 6.01; N, 4.88; CH_3N, 5.23.

After standing for 3 weeks, the methine was found to melt at 125–127°. Recrystallization from ether raised the melting point to 128–129°. The infrared spectrum in chloroform solution was identical with that of the polymorph, m.p. 109–110°.

Anal. Found: C, 72.03; H, 6.25; N, 4.92.

Oxopowelline Methine (XVIII).—A solution of 198 mg. of oxopowelline methiodide in 5 ml. of hot water was treated with 2 ml. of 10% sodium hydroxide. The methine was removed by benzene extraction as in the case of oxocrinine methine. The benzene solution was concentrated to dryness in an air jet, and the residue was dissolved in ether. The ether solution was centrifuged to remove traces of insoluble material and concentrated to give 92 mg. (66%) of colorless prisms, m.p. 132–133°. An analytical sample was prepared by sublimation, m.p. 132–133°, $[\alpha]^{25}_{546,436}$ 0.0 ± 0.7° (*c* 0.85, ethanol); λ_{max} 6.00, 6.15 μ.

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47; OCH_3, 9.90. Found: C, 68.97; H, 6.24; N, 4.48; OCH_3, 9.92.

Tetrahydroöxocrinine Methine (XII).—A solution of 322 mg. of oxocrinine methine in 10 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 100 mg. of 10% palladium-on-charcoal catalyst. The absorption of hydrogen ceased after the uptake of two equivalents. The catalyst was removed by filtration, and the filtrate was concentrated to give 245 mg. of colorless prisms, m.p. 148–149°, $[\alpha]^{24.5}_{589,\ 436,\ 365.5}$ 0.0 ± 0.2° (*c* 1.01); λ_{max} 5.81 μ, 242 mμ (log ε 3.64) and 290 mμ (log ε 3.60).

In the same manner, 117 mg. of dihydroöxocrinine methine (XV) absorbed one equivalent of hydrogen to give, after several recrystallizations from ethanol, 50 mg. of tetrahydroöxocrinine methine, m.p. 148–149°.

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.11; H, 7.29; N, 4.87.

Tetrahydroöxopowelline Methine (XIX).—Catalytic hydrogenation of an ethanolic solution of 263 mg. of oxopowelline methine in the presence of 100 mg. of 10% palladium-on-charcoal catalyst afforded a quantitative yield of non-crystalline tetrahydro derivative that was evaporatively distilled for analysis, b.p. 180° (1 μ), $[\alpha]^{25}_{589,\ 500,\ 436,\ 400}$ 0.0 ± 0.3° (*c* 0.88); λ_{max} 5.83, 6.20 μ, 279 mμ (log ε 3.16).

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 67.95; H, 7.42; N, 4.53.

Dihydroöxocrinine Methine (XV).—In a manner identical to that described for oxocrinine methine, 226 mg. of dihydroöxocrinine was converted to 234 mg. of dihydroöxocrinine methine. It was not possible to prepare the methine in crystalline condition, and the material was purified through evaporative distillation at 150° (1 μ), $[\alpha]^{25}_{589}$ + 138.7°, $[\alpha]^{25}_{436}$ + 361.4° (*c* 1.3); λ_{max} 5.93 μ. The ultraviolet ab-

sorption spectrum showed maxima at 226 mμ (log ε 4.15) and 288 mμ (log ε 3.58) when run in ethanol containing one drop of sodium hydroxide.

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.46; H, 6.87; N, 4.98.

The picrate was prepared by the addition of ethanolic picric acid to an ethanolic solution of 64 mg. of the methine. The picrate was recrystallized from acetone to give 51 mg. of yellow prisms, m.p. 209–211°, $[\alpha]^{22}_{589}$ −19.4°, $[\alpha]^{22}_{436}$ −28.0° (*c* 1.25, acetone–water, 90:10). The infrared spectrum (Nujol) was identical with that of dihydroöxocrinine methopicrate. A mixture melting point was not depressed.

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

The Synthesis of 1-(Aminodeoxy-β-D-ribofuranosyl)-2-pyrimidinones. New 3′- and 5′-Aminonucleosides

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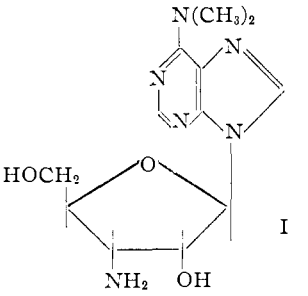
1-(3-Amino-3-deoxy-β-D-ribofuranosyl)-thymine (VII) was prepared *via* the condensation of dithyminylmercury (II) with 1-chloro-2,5-di-*O*-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranose (V). Condensation of N-acetylcytosinemercury (III) with V gave, after deblocking, 3′-amino-3′-deoxycytidine (IX). The versatile intermediate, 1-(2,3-di-*O*-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)-4-ethoxy-2-pyrimidinone (XVII) was prepared from chloromercuri-4-ethoxy-2-pyrimidinone (IV) and V. Ammonolysis of XVII afforded a second synthesis of IX. Treatment of XVII with butylamine or with dimethylamine gave the corresponding 4-butylamino- (XVIII) and 4-dimethylamino- (X) analogs of IX. Reaction of XVII with methanolic hydrogen chloride produced, after deblocking, 3′-amino-3′-deoxyuridine (XIX). 1-(5-Amino-5-deoxy-β-D-ribofuranosyl)-thymine (XXII) and 5′-amino-5′-deoxycytidine (XXIV) were prepared by similar procedures. Condensation of a mercury derivative of 4-dimethylamino-2(1H)-pyrimidinone (XI) with V gave the *O*-glycosyl derivative XV.

A considerable number of purine nucleosides have been prepared in this Laboratory as analogs of the aminonucleoside, 6-dimethylamino-9-(3-amino-3-deoxy-β-D-ribofuranosyl)-purine (I), derived from the antibiotic puromycin.[1] In the course of this work it was demonstrated that the carcinostatic[2a] and trypanocidal[2b] activities of the aminonucleoside were dependent on the presence of the 3-amino-3-deoxy-D-ribose portion and only to a lesser extent on the nature of the purine moiety. Thus, 3′-amino-3′-deoxyadenosine [6-amino-9-(3-amino-3-deoxy-β-D-ribofuranosyl)-purine[3]] was at least as active as the aminonucleoside, whereas 6-dimethylamino-9-β-D-ribofuranosylpurine[4] had no trypanocidal activity and showed antitumor activity only in tissue culture. Also, a large number of 9-(3-amino-3-deoxy-β-D-ribofuranosyl)-purines with variously substituted amino groups in the 6-position had trypanocidal and *in vivo* antitumor activity.[5] Therefore, it was of interest to determine the effect on the chemotherapeutic activity resulting from the substitution of nucleic acid pyrimidines for the purine portion of the aminonucleoside I. The preparation of several 1-(3-amino-3-deoxy-β-D-ribofuranosyl)-2-pyrimidinones is the subject of this paper.

The most commonly used method for the synthesis of pyrimidine nucleosides has been the one devised by Hilbert and Johnson[6] which involves the condensation of a 2,4-dialkoxypyrimidine with an acylated 1-halo sugar. Good results have been obtained on application of this method to the preparation of pyranosyl nucleosides,[7] but the procedure



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gave poor yields[8] or compounds of doubtful structure[9] when used with poly-O-acyl-D-ribofuranosyl halides for the synthesis of the naturally occurring pyrimidine nucleosides. No practical synthesis of these latter compounds was available until Fox and his co-workers[10–12] demonstrated the utility of the mercury derivatives of certain 2-pyrimidinones in condensation with suitably blocked glycofuranosyl halides for the preparation of the required 1-β-D-glycofuranosyl-2-pyrimidinone derivatives. Thus, dithyminylmercury (II) upon re-

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