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Structure and Stereochemistry of Buphanamine[1]

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Degradative evidence is presented to show that buphanamine possesses the stereostructure II.

Investigations of the alkaloids of *Boöphone disticha* Herb. (*Haemanthus toxicarius* Herb.) were among the first to be reported in the family Amaryllidaceae.[2-4] Unfortunately, the crude amorphous, basic fractions which were isolated were considered to be pure alkaloids and were named accordingly, *e.g.*, "buphanine"[3] and "haemanthine."[4] Recent attempts[5-8] to retain these names for products of current isolations has led to considerable confusion concerning the alkaloids of *B. disticha* since no authentic samples from the original isolations were available for comparison. Thus Warren and coworkers[5-8] have reported the isolation from *B. disticha* of "haemanthine," "distichine," "buphanitine" and lycorine. To account for the multiplicity of crystalline salts from "haemanthine,"[7] Goosen and Warren[8] have divided Lewin's "haemanthine" into "oily haemanthine" and "crystalline haemanthine." "Oily haemanthine" now[8] is considered the same as buphanamine,[9] since buphanamine forms a hydrochloride and a hydronitrate with the same melting points as those reported by Lewin for the corresponding derivatives of haemanthine.[10] "Crystalline haemanthine" is considered identical with buphanitine from a comparison of the melting points reported for buphanitine and its hydrochloride (but not the methiodide) and those found for "crystalline buphanitine."[8] No actual sample of buphanitine was available for comparison, however.[11] Finally, Warren's "distichine" is claimed to be a hydrate of buphanidrine.[8]

Earlier, buphanidrine, buphanamine, and lycorine had been reported to occur along with ambelline, buphanisine, and crinine in *B. fischerii* Baker.[9] Concurrently, the alkaloids of *Boöphone* spp. were being investigated in our laboratory and that of Dr. W. I. Taylor, then at the University of New Brunswick. The alkaloid, m.p. 189°, from *B. disticha*[12] and our material, m.p. 184–185°, also isolated from a *Boöphone* sp. were found to be identical with each other and with buphanamine.

Buphanamine, $C_{17}H_{19}NO_4$, has been shown to possess one methylenedioxy group, one methoxyl, one hydroxyl, and one double bond.[9,12] The ultraviolet absorption spectra of buphanamine and dihydrobuphanamine placed the methylenedioxy and the methoxy groups in the aromatic ring and showed that the double bond was not conjugated with the aromatic ring.[12] We have confirmed these observations.

The nature of the hydroxyl group was uncertain. Although buphanamine was acetylated easily, dihydrobuphanamine was reported not to be oxidized by chromic acid.[12] A reinvestigation in our laboratory of the oxidation of buphanamine and dihydrobuphanamine revealed that buphanamine was not oxidized by manganese dioxide when a chloroform solution of the alkaloid was stirred overnight with the reagent. However, the Oppenauer conditions which had been successful for dihydroundulatine[13] and dihydrocaranine[14] converted dihydrobuphanamine to a ketone, oxodihydrobuphanamine, in good yield. Subsequent studies showed that dihydrobuphanamine can be oxidized

(1) Paper XX in a series on alkaloids of the Amaryllidaceae; previous paper, H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 181 (1961).

(2) For a recent review of the alkaloids of this family, see W. C. Wildman, *The Alkaloids*, Vol. VI, R. H. F. Manske, ed., Academic Press, Inc., New York, 1960, p. 289.

(3) F. Tutin, *J. Chem. Soc.*, 1240 (1911).

(4) L. Lewin, *Arch. Exptl. Pathol. Pharmacol.*, **68**, 333 (1912).

(5) J. K. Cooke and F. L. Warren, *J. S. African Chem. Inst.*, **6**, 2 (1953).

(6) A. N. Bates, J. K. Cooke, L. J. Dry, A. Goosen, H. Krüsi, and F. L. Warren, *J. Chem. Soc.*, 2537 (1957).

(7) A. Goosen and F. L. Warren, *Chem. & Ind. (London)*, 267 (1957).

(8) A. Goosen and F. L. Warren, *J. Chem. Soc.*, 1094 (1960).

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

(10) *Cf.* ref. 2, p. 292.

(11) There is a distinct possibility that buphanitine (m.p. 234° and 240°, $[\alpha]_D^{20}$ −102°; hydrochloride, m.p. 265°; hydronitrate, m.p. 222–224°) and nerbowdine[1] (m.p. 232° and 244°, $[\alpha]_D^{23}$ −108.8°; hydrochloride, m.p. 254–265°, $[\alpha]_D^{23}$ −86.1°; hydronitrate, m.p. 227–240° dec.) eventually will be found identical.[11a] Both alkaloids occur in *Boöphone* species. Nerbowdine has been assigned structure IV unequivocally,[1] while buphanitine, on the basis of less compelling evidence, is claimed to be a 1,3-dihydroxypowellane with a *cis* B:C ring fusion.[8]

(11a) NOTE ADDED IN PROOF: A comparison of nerbowdine with buphanitine, provided by the South African workers, has shown the two substances to be identical. The infrared spectra (potassium bromide) of the two samples were identical, and a mixture melting point determination gave no depression.

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

(13) E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 1472 (1960).

(14) E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **79**, 2192 (1957).

equally well by pyridine–chromic acid. The ketone showed carbonyl absorption at 1694 cm.$^{-1}$ The ultraviolet absorption spectrum was only slightly altered from that of the starting alcohol, and it was concluded that the carbonyl group was part of a six-membered ring and not adjacent to the aromatic nucleus. Oxodihydrobuphanamine was reduced by sodium borohydride to a mixture of dihydrobuphanamine and epidihydrobuphanamine; the epimeric nature of the hydroxyl group of the latter was determined by reoxidation to oxodihydrobuphanamine.

The basic ring system of buphanamine was shown to be that of (+)-powellane (VIII) by the Wolff-Kishner reduction of oxodihydrobuphanamine.[15,16] Within this nucleus, the hydroxyl group must be located at either C_1 or C_4 since oxodihydrobuphanamine is not identical with either 2-oxopowellane[13] or 3-oxopowellane (oxodihydropowelline).[15,17] Proof that the hydroxyl group of buphanamine is at C_1 was obtained from degradations which led ultimately to IV and XII, the structures of which were known. Buphanamine was oxidized by pyridine–chromic acid complex[18] to an α,β-unsaturated ketone, oxobuphanamine (VI). Proof of the α,β-unsaturation was found in the infrared (ν_{max} 1669 cm.$^{-1}$) and ultraviolet spectra [differential curve between oxobuphanamine and dihydrobuphanamine, $\lambda_{max}^{C_2H_5OH}$ 228 mμ (ϵ 7470)]. Catalytic hydrogenation of VI afforded oxodihydrobuphanamine (V) identical with that obtained from the oxidation of dihydrobuphanamine. Epoxidation of VI with alkaline hydrogen peroxide gave an epoxy ketone (VII) as shown by analysis, the shift in the carbonyl absorption to 1695 cm.$^{-1}$, and the decrease in ultraviolet absorption at 230 mμ to nearly that of V. Proof that the epoxide of VII is *cis* to the phenyl can be obtained from mechanistic considerations and by degradation. Attack of OOH^- would most reasonably occur on that side of C_3 which is unhindered by the 5,10b-ethano bridge to yield VII. As was anticipated from earlier studies on epoxyoxopowelline,[1] sodium borohydride reduced VII to a mixture of two epimeric epoxy alcohols (III and XI). The structures were proved by reoxidation of the epoxy alcohols to VII and by further reduction with lithium aluminum hydride. Lithium aluminum hydride converted III and XI to nerbowdine (IV) and dihydrocrinamidine (XII) respectively, the structures of which had been elucidated earlier.[1] The isolation of IV and XII from this reaction series proved the configuration of the epoxide group of VII and established the hydroxyl group of

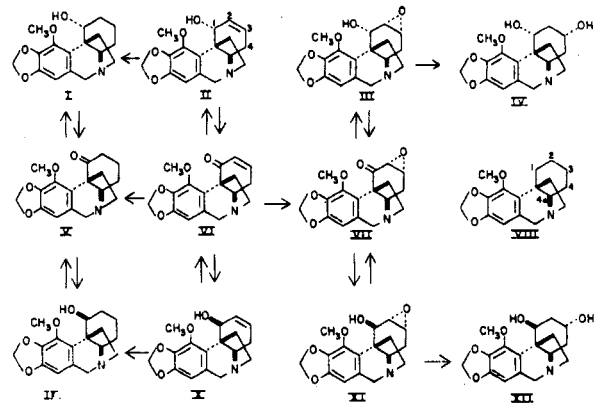


Figure 1

buphanamine at C_1 because the C_3-hydroxyl could not have existed in buphanamine itself.[19]

With the certainty of the hydroxyl group of buphanamine at C_1, four positions for the double bond were possible. A $\Delta^{1,2}$-system would require buphanamine to be an enol, a postulate not in keeping with the chemical properties of the alkaloid. A $\Delta^{4,4a}$-unsaturated system seemed unlikely from the observation that buphanamine is a relatively strong base and saturation of the double bond increased the basicity by only 0.65 pK units.[21] A choice between $\Delta^{2,3}$- and $\Delta^{3,4}$- unsaturation was impossible from the existing data. The establishment of structure VI for oxobuphanamine did not constitute proof that the double bond was at C_2—C_3 in buphanamine itself, since C_3—C_4 unsaturation could easily shift to C_2—C_3 once the carbonyl group at C_1 was formed.[22] To compound the problem, epibuphanamine (X), the only product formed when VI was reduced with sodium borohydride, was oxidized by manganese dioxide to VI although buphanamine was unaffected by the same reagent. Assignment of structure II to buphanamine

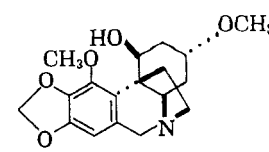
(15) W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).

(16) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 3368 (1960).

(17) Part of this material has been presented in Communication form, W. C. Wildman, *Chem. & Ind. (London)*, 1090 (1956).

(18) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 427 (1953).

(19) Alternative evidence for the C_1-hydroxyl was reported in the conversion of oxoisodihydroundulatine (i) to VI.[13] At that time VI was considered a product of the oxidation and concurrent double bond isomerization of buphanamine and was called oxoisobuphanamine.[20] In view of the results cited in this paper, VI is correctly named oxobuphanamine.



i

(20) *Cf.* ref. 2, p. 360.

(21) A $\Delta^{4,4a}$-double bond would be expected to exert a significant weakening effect on the basicity since it would be α,β to the amine function. The quaternary salt cannot form a Schiff's base because such a structure would violate Bredt's Rule. *Cf.* strychnine-neostrychnine, V. Prelog and O. Häfliger, *Helv. Chim. Acta*, **32**, 1851 (1949).

(22) The first attempt to oxidize buphanamine to VI gave a crude product showing two carbonyl bands (1666 and 1700 cm.$^{-1}$). This was interpreted as both $\Delta^{2,3}$- and $\Delta^{3,4}$-unsaturation, the $\Delta^{2,3}$-isomer being derived from isomerization.

suggests that the configuration of the C_1-hydroxyl determined the outcome of the manganese dioxide oxidation. This has not been found true in related cases.[1,15] Several incidental observations, however, can be cited in support of structure II for buphanamine. It has been reported that isocaranine, an allylic alcohol, is not oxidized by manganese dioxide.[23] Isocaranine is quite similar to a $\Delta^{2,3}$-structure for buphanamine. With additional steric hindrance provided by the aromatic methoxyl, which has been assigned to C_{10},[13] a negative result in the oxidation of buphanamine with manganese dioxide might not be unexpected. Positive indication for C_2—C_3 unsaturation was obtained in the isolation of α- and β-crinene from the demethylation of buphanamine with sodium and 3-methyl-1-butanol. The same crinenes had been obtained previously from similar degradation of powelline, an allylic alcohol.[24] C_2—C_3 unsaturation seemed likely from deuteration studies. Deuteration of buphanamine in the presence of platinum oxide gave a dideuterio compound which was oxidized to the ketone. Equilibration with alkali caused the loss of nearly half the deuterium content. This observation can be explained only if buphanamine has $\Delta^{2,3}$-unsaturation. Unequivocal proof of the double bond position was provided by the reduction of VI to buphanamine and epibuphanamine by lithium aluminum hydride.

Since the preceding degradations showed that buphanamine and epibuphanamine are allylic alcohols epimeric at C_1 rather than double bond isomers, it seemed possible to determine the configuration of the hydroxyl group by the rotational method of Mills.[25] Several *Amaryllidaceae* alkaloids possess either allylic alcohol or allylic methoxyl groups, and this technique has been applied to assign absolute configurations to tazettine,[26,27] lycorine,[28] and the alkaloids derived from 5,10b-ethanophenanthridine.[16,29] The absolute configuration of the powellane nucleus is known, and if these rules are valid, the epimer with the more positive rotation (epibuphanamine) should be assigned structure X.[30]

The preceding degradations establish stereostructure II for buphanamine. Because many alkaloids derived from the 5,10b-ethanophenanthridine nucleus differ only in the type of aromatic substitution,[2] it was of interest to examine the demethoxylation of buphanamine and its derivatives, since the products might be alkaloids in their own right or derivatives thereof. The demethoxylations were effected by sodium and 3-methyl-1-butanol. The use of this reagent for demethoxylation of Amaryllidaceae alkaloids was reported first in our laboratory.[24] Subsequent adaptation of this technique by others has led to tentative structures for haemultine,[31] fiancine[32] and nerispine.[32,33] Demethoxylation of dihydrobuphanamine (I) afforded a demethoxydihydrobuphanamine (I, no OCH_3) which could be oxidized to a ketone (V, no OCH_3). Reduction of V (no OCH_3) gave a C_1 epimer (IX, no OCH_3) which also could be prepared by the action of sodium and 3-methyl-1-butanol on IX. Evidence that the crinane skeleton remained intact was provided by the conversion of V (no OCH_3) to (−)-crinane. The fact that I and IX gave different products is indicative that the hydroxyl groups were not epimerized in the process. Their configuration is confirmed by the close relationship between their rotations and those of the methoxylated precursors.[30]

EXPERIMENTAL[34]

Isolation of alkaloids. Buphanamine, buphanidrine, nerbowdine, and ambelline were isolated from an unidentified *Brunsvigia* species of South African origin in yields of 0.007, 0.013, 0.01, and 0.0005%, respectively. An unidentified *Boöphone* species, collected in the Orange Free State, afforded a 0.015% yield of buphanamine along with traces of lycorine. Isolation procedures followed the methods described in previous papers of this series.

Buphanamine (II). The alkaloid crystallized from ethyl acetate as prisms, m.p. 183–185°, $[\alpha]^{24}_{589}$ −195°, $[\alpha]^{24}_{436}$ −408° (*c* 0.97); λ_{max} 287 mμ (ε 1495); reported:[9] m.p. 184–186°, $[\alpha]^{20}_{589}$ −205°.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65; (1) OCH_3, 10.30. Found: C, 67.52; H, 6.20; N, 4.62; OCH_3, 10.23.

(23) K. Takeda, K. Kotera, and S. Mizukami, *J. Am. Chem. Soc.*, **80**, 2562 (1958).

(24) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 4395 (1958).

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

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

(27) T. Kitagawa, S. Uyeo, and N. Yokoyama, *J. Chem. Soc.*, 3741 (1959).

(28) Y. Nakagawa and S. Uyeo, *J. Chem. Soc.*, 3736 (1959).

(29) P. W. Jeffs, F. L. Warren, and W. G. Wright, *J. Chem. Soc.*, 1090 (1960).

(30) Spectral evidence supporting the hydroxyl configurations assigned to I, II, III, IX, X, and XI and their *ar*-demethoxy derivatives will be presented elsewhere.

(31) H.-G. Boit and W. Döpke, *Chem. Ber.*, **91**, 1965 (1958).

(32) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **47**, 109 (1960).

(33) The structures assigned to these alkaloids must be regarded as tentative until evidence is presented that no skeletal rearrangement, double bond migration, or hydroxyl epimerization has occurred in the strenuous demethoxylation step. Rearrangements of the latter two types have been reported.[24]

(34) All melting points were observed on a Kofler microscope hot-stage and are corrected. Unless otherwise noted, rotations were measured in chloroform with a Rudolph photoelectric spectropolarimeter using a 2-dm. tube, and ultraviolet spectra were obtained in absolute ethanol solution on a Cary model 11 MS recording spectrophotometer. Infrared spectra were recorded on either a Perkin-Elmer model 21 or a Beckman IR-7 double-beam spectrophotometer in chloroform solution unless noted to the contrary. All comparisons and identifications of alkaloids and the products of their degradation were verified by the identity of the infrared spectra (potassium bromide) and by mixture melting point determinations with authentic reference compounds. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

The *hydrochloride* formed colorless prisms from ethanol-ether containing a trace of water, m.p. 180°. A sample was dried at 100° (1 mm.) for 4 hr. for analysis. The sample proved to be hygroscopic and on equilibration with air had an analysis corresponding to the monohydrate.

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot HCl \cdot H_2O$: C, 57.38; H, 6.23; N, 3.94. Found: C, 57.57; H, 6.27; N, 4.08.

An unhydrated sample was obtained by redrying at 130° and analyzing immediately.

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot HCl$: C, 60.44; H, 5.97; N, 4.15. Found: C, 60.34; H, 6.06; N, 4.16.

The *hydronitrate* formed colorless prisms from water, m.p. 136–140°.

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot HNO_3 \cdot 2H_2O$: C, 50.99; H, 6.04. Found: C, 50.89; H, 5.79.

Dihydrobuphanamine (I). An ethanolic solution of 336 mg. of buphanamine absorbed 104% of the theoretical amount of hydrogen at room temperature and atmospheric pressure in the presence of 100 mg. of 10% palladium-on-charcoal. Concentration of the filtrate and crystallization from acetone gave 257 mg. of colorless prisms, m.p. 201–202°, $[\alpha]^{24}_{589}$ −83.4°, $[\alpha]^{24}_{436}$ −170.4° (*c* 0.99); reported:[12] m.p. 200°.

Oxobuphanamine (VI). A solution of 500 mg. of pure buphanamine in 10 ml. of pyridine was combined with a suspension of 400 mg. of chromium trioxide in 10 ml. of pyridine. After standing at room temperature overnight, the mixture was poured into water, made basic with potassium carbonate, and extracted with chloroform. Evaporation of the solvent left 480 mg. (96%) of crystalline oxobuphanamine, m.p. 200–212°. The infrared spectrum showed only one band at 1669 cm.$^{-1}$ which was unchanged on further purification.[35] One recrystallization from ethyl acetate furnished octahedra, m.p. 211–213°, $[\alpha]^{25}_{589}$ −43°, $[\alpha]^{25}_{436}$ −187° (*c* 0.28); λ_{max} 279 mμ (ε 1438), λ_{min} 261 mμ (ε 960), λ 225 mμ (ε 20,000). The ultraviolet spectrum of oxobuphanamine was determined versus the same concentration of oxodihydrobuphanamine in the reference cell to permit the observation of a maximum at 228 mμ (ε 7470) due to the unsaturated ketone alone.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; neut. equiv., 299. Found: C, 68.44; H, 5.94; neut. equiv., 295.

Oxodihydrobuphanamine (V). A solution of 14.5 mg. of oxobuphanamine and 20 mg. of palladium-on-charcoal in ethanol rapidly absorbed 1 mole of hydrogen at atmospheric pressure. Filtration and evaporation left an oil exhibiting only one carbonyl band at 1694 cm.$^{-1}$ The spectrum was unchanged on purification. Crystallization from ether afforded prisms, m.p. 140–141.5°, $[\alpha]^{24}_{589}$ −133°, $[\alpha]^{24}_{436}$ −281° (*c* 1.11); λ_{max} 284 mμ (ε 1435), λ 228 mμ (ε 9630).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.88; H, 6.39; N, 4.65.

The same compound was formed in 48% yield when 300 mg. of dihydrobuphanamine was oxidized with chromium trioxide under conditions described for the oxidation of buphanamine. Under modified Oppenauer conditions,[13,14] 334 mg. of dihydrobuphanamine gave 194 mg. of V, m.p. 136–138°, $[\alpha]^{24}_{589}$ −136°, $[\alpha]^{24}_{436}$ −285° (*c* 1.04).

(+)-*Powellane* (VIII). Wolff-Kishner reduction of 240 mg. of oxodihydrobuphanamine (V) in the manner employed for oxodihydropowelline[15] gave 168 mg. of (+)-powellane which was purified *via* the picrate, m.p. 211–213°, $[\alpha]^{25}_{589}$ +24.8° (*c* 1.16); reported:[15] m.p. 213–215°, $[\alpha]^{25}_{589}$ +28.2°. The free base was regenerated by chromatography of the picrate on alumina, recrystallization from ether, and finally sublimation, m.p. 110–111°; reported:[15] m.p. 113.5–115°. The optical rotatory dispersion curve of the (+)-powellane was identical with that of authentic material.

(35) An earlier report (ref. 2, p. 360) noted the presence of an additional carbonyl band at 1700 cm.$^{-1}$ This probably resulted from an epoxy alcohol contaminant in the buphanamine employed at that time, since it did not appear when a pure sample of buphanamine from another source was used.

Lithium aluminum hydride reduction of oxobuphanamine. A solution of 266 mg. of oxobuphanamine and 300 mg. of lithium aluminum hydride in 25 ml. of tetrahydrofuran was refluxed for 1 hr. and then decomposed with 25% sodium hydroxide. Extraction with chloroform and evaporation of the solvents left 273 mg. of a mixture which was triturated with ethyl acetate and a drop of water to give 104 mg. (39%) of hydrated *epibuphanamine* (X). Recrystallization from ethyl acetate containing a trace of water produced analytically pure material which after drying at 70° (10 mm.) melted at 161–162°, $[\alpha]^{24}_{589}$ +23°, $[\alpha]^{24}_{436}$ +56° (*c* 1.03); λ_{max} 286 mμ (ε 1430).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; neut. equiv., 301. Found: C, 67.99; H, 6.33; neut. equiv., 304.

Chromatography of the filtrates over alumina with ethyl acetate furnished 20 mg. (8%) of *oxodihydrobuphanamine* (V). Further elution with 1% methanol in ethyl acetate furnished an additional 42 mg. of X to give a total yield of 68%. Elution with 2% methanol afforded 25 mg. (9.5%) of buphanamine (II), m.p. 182–184°.

In contrast to buphanamine which was not oxidized with manganese dioxide in chloroform, a solution of 51 mg. of epibuphanamine afforded 22 mg. (43%) of *oxobuphanamine* on stirring overnight with activated manganese dioxide in chloroform. The product was isolated by chromatography on alumina and elution with 2% ethyl acetate in benzene, m.p. 211–213° from ethyl acetate. Ethyl acetate eluted 7 mg. (14%) of *epibuphanamine*.

Action of sodium borohydride on oxobuphanamine. A methanolic solution of 355 mg. of oxobuphanamine was treated with 300 mg. of sodium borohydride in the usual manner. The oily product, 349 mg., gave 171 mg. (48%) of *epibuphanamine*, m.p. 161–162°, on trituration with wet ethyl acetate. Chromatography of the filtrates on ethyl acetate–deactiyated alumina with ethyl acetate afforded an additional 80 mg. of epibuphanamine. This was followed by 7 mg. of an insoluble product, m.p. 230–245°, which was not investigated further. Finally, 17 mg. (5%) of *dihydrobuphanamine* was eluted, m.p. 199–202°. No trace of buphanamine could be found in the mixture.

Dihydroepibuphanamine (IX). A solution of 16 mg. of X in ethanol was stirred under hydrogen with 15 mg. of palladium-on-charcoal for 3 hr. and filtered. Evaporation of the solvent left irregular prisms, m.p. 195–197°. One crystallization from ethyl acetate and sublimation at 150° (10 μ) produced bladed prisms, m.p. 195–197°, $[\alpha]^{25}_{589}$ +26°, $[\alpha]^{25}_{436}$ +55° (*c* 0.38); λ_{max} 286 mμ (ε 1445).

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; neut. equiv., 303. Found: C, 67.44; H, 6.83; neut. equiv., 306.

Action of sodium borohydride on oxodihydrobuphanamine. A solution of 300 mg. of oxodihydrobuphanamine in 30 ml. of methanol was reduced with 500 mg. of sodium borohydride to yield 330 mg. of crude product. Chromatography on alumina with 2% methanol in ethyl acetate afforded 85 mg. (28%) of *dihydroepibuphanamine* (IX), m.p. 195–197°. Further elution with 3–5% methanol produced 46 mg. of a mixture followed by 186 mg. (62%) of *dihydrobuphanamine* (I), m.p. 200°.

Catalytic deuteration of buphanamine. A solution of 700 mg. of buphanamine in 8 ml. of acetic acid-H_4[2] was added to a suspension of 30 mg. of prereduced platinum oxide in the same solvent with 99% deuterium gas. The base absorbed approximately one mole of deuterium at atmospheric pressure in about 30 min. at 28°. After an additional hour of stirring, the suspension was filtered, evaporated under an air stream, made basic with a large excess of aqueous 20% sodium carbonate, and allowed to stir with chloroform for 30 min. The mixture was extracted with chloroform, and the dried extracts were evaporated to yield 716 mg. (~100%) of dihydrobuphanamine-2,3-H_2[2]. One crystallization from ethyl acetate produced material melting 199.5–200°. The compound exhibited a small band at 2183 cm.$^{-1}$ due to the C—D stretching vibration, but the infrared spectrum was not identical with that of dihydrobuphanamine.

Anal. Calcd. for $C_{17}H_{19}NO_4H_2^2$: 9.52 atom % excess deuterium. Found: 10.57 atom % excess deuterium (1.05% high).

A blank run conducted under the same conditions as above but employing dihydrobuphanamine (Found: 0.00 atom % excess deuterium) instead of buphanamine caused the incorporation of 0.33 atom % excess deuterium.

A solution of 300 mg. of the deuterated dihydrobuphanamine was oxidized with 300 mg. of chromium trioxide in pyridine under the conditions described earlier. The oxodihydrobuphanamine was stirred with a large excess of 20% sodium carbonate in a two-phase system with chloroform for 5 hr. Passage over a short alumina column with 50% benzene–ethyl acetate produced 143 mg. (48%) of oxodihydrobuphanamine-3-H_1^2 which was crystallized from ether, m.p. 140–141.5°, ν C—D 2175 cm.$^{-1}$ and ν C=O 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{18}NO_4H_1^2$: 5.26 atom % excess deuterium. Found: 6.26 atom % excess deuterium (1.00% high).

Epoxyoxobuphanamine (VII). An ethanolic solution of 115 mg. of oxobuphanamine was epoxidized by the procedure described in an earlier paper.[1] The crude product showed no carbonyl absorption at 1669 cm.$^{-1}$ but exhibited a new band at 1695 cm.$^{-1}$. One recrystallization from ethanol produced 80 mg. (63%) of epoxyoxobuphanamine, rectangular plates, m.p. 246–248°, $[\alpha]_{589}^{25}$ +108°, $[\alpha]_{436}^{25}$ +269° (*c* 0.52); λ 280 mμ (ϵ 1610), λ_{min} 266 mμ (ϵ 1338), λ 228 mμ (ϵ 8320).

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; neut. equiv. 315. Found: C, 64.76; H, 5.51; neut. equiv., 316.

Action of sodium borohydride on epoxyoxobuphanamine. A methanolic solution of 430 mg. of VII was treated with sodium borohydride in the usual manner. The oily product was triturated with ethyl acetate to yield 70 mg. (16%) of *epoxybuphanamine* (III), m.p. 232–237°. Recrystallization from ethyl acetate afforded flat plates, m.p. 248–251°, $[\alpha]_{589}^{24}$ −154°, $[\alpha]_{436}^{24}$ −308° (*c* 0.68); λ_{max} 286 mμ (ϵ 1495).

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; vic. glycol, 0.00 mole. Found: C, 64.41; H, 6.17; vic. glycol, 0.00.

On trituration of the filtrates with acetone, 110 mg. (26%) of *epiepoxybuphanamine* (XI), m.p. 185–187°, was obtained. Recrystallization from acetone gave irregular prisms, m.p. 180–182°, $[\alpha]_{589}^{25}$ −37°, $[\alpha]_{436}^{25}$ −72° (*c* 0.69); λ_{max} 286 mμ (ϵ 1415).

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04. Found: C, 64.15; H, 5.97.

The filtrates were chromatographed over silicic acid with 2% methanol in chloroform to yield an additional 10 mg. (2%) of epoxybuphanamine followed by 250 mg. (58%) of epiepoxybuphanamine.

A solution of 120 mg. of XI in 15 ml. of chloroform was stirred overnight with 120 mg. of activated manganese dioxide. An infrared spectrum of the filtered solution indicated the presence of two carbonyl bands at 1739 cm.$^{-1}$ and 1695 cm.$^{-1}$. Chromatography on alumina with ethyl acetate gave 20 mg. of *epoxyoxobuphanamine* (VII), m.p. 246–248°. Under the same conditions, epoxybuphanamine (III) was recovered unchanged, but when 6 mg. of III was oxidized with 6 mg. of chromium trioxide in pyridine in the usual manner, 4 mg. of epoxyoxobuphanamine, m.p. 246–248°, was isolated by chromatography on alumina with ethyl acetate.

Conversion of epoxybuphanamine to nerbowdine. A solution of 17 mg. of III in tetrahydrofuran was reduced with lithium aluminum hydride in the usual manner. The oily product (15 mg.) was chromatographed first on alumina and then on silicic acid. Elution with 5–10% methanol in chloroform gave a trace of material (<1 mg.), m.p. 183–185°, which was not investigated further. Further elution gave a trace of carbonyl-containing compound, m.p. 231–232°, not present in the original reduction product. Elution with 10% methanol produced 5 mg. (29%) of *nerbowdine* (IV), m.p. 229–232°. Finally, a fourth product (6 mg., 35%), m.p. 229–233°, was obtained which probably is the *cis*-1,2-dihydroxypowellane formed by fission of the epoxide ring in the opposite direction. Analysis of this product gave the following results.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; vic. glycol, 1 mole. Found: C, 63.97; H, 6.61; vic. glycol, 0.82 mole.

Conversion of epiepoxybuphanamine to dihydrocrinamidine. A solution of 22 mg. of XI was reduced with lithium aluminum hydride in the standard manner. The glassy product (17 mg., 77%) was crystallized by evaporation with ethanol. One recrystallization from ethanol produced prisms of pure dihydrocrinamidine (XII), m.p. 260–261°.

Demethoxydihydrobuphanamine (I, no OCH_3). A solution of 400 mg. of I was demethoxylated in the usual manner.[24] The product (293 mg.) contained no methylenedioxymethoxy band at 1626 cm.$^{-1}$. Chromatography over alumina and elution with 4% methanol in ethyl acetate furnished 218 mg. (60%) of fine prisms which melted at 210–212° after crystallization from ethyl acetate and depressed the m.p. of dihydrobuphanamine 30°, $[\alpha]_{589}^{24}$ −75°, $[\alpha]_{436}^{24}$ −163° (*c* 0.68); λ_{max} 235 mμ (ϵ 3410), λ_{max} 293 mμ (ϵ 4860).

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; neut. equiv., 273; OCH_3, 0.00. Found: C, 70.34; H, 6.96; neut. equiv., 271; OCH_3, 0.00.

Demethoxydihydroepibuphanamine (IX, no OCH_3). By the same technique employed above, 60 mg. of dihydroepibuphanamine (IX) yielded 30 mg. (55%) of crystalline demethoxydihydroepibuphanamine. Recrystallization from ethyl acetate afforded fine prisms, m.p. 224–225°, $[\alpha]_{589}^{24}$ +33.7°, $[\alpha]_{436}^{24}$ +70° (*c* 0.42); λ_{max} 235 mμ (ϵ 3520), λ_{max} 293 mμ (ϵ 4810).

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; OCH_3, 0.00. Found: C, 69.98; H, 7.00; OCH_3, 0.00.

The same compound, m.p. 223–224°, was obtained in 50% yield from the reduction of 30 mg. of oxodemethoxydihydrobuphanamine (V, no OCH_3) with sodium borohydride.

Oxodemethoxydihydrobuphanamine (V, no OCH_3). A pyridine solution of 152 mg. of I (no OCH_3) was oxidized with 100 mg. of chromium trioxide in 5 ml. of pyridine in the usual manner. The crude product, oxodemethoxydihydrobuphanamine (111 mg., 73%), showed a carbonyl band at 1706 cm.$^{-1}$. Chromatography over alumina with ethyl acetate produced crystalline material with an infrared spectrum that was identical with that of the crude product. Crystallization from ether afforded prisms, m.p. 182–183°, $[\alpha]_{589}^{24}$ −158°, $[\alpha]_{436}^{24}$ −335° (*c* 0.75); λ_{inf} 235 mμ (ϵ 4230), λ_{max} 292 mμ (ϵ 4740).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; neut. equiv., 271. Found: C, 71.11; H, 6.31; neut. equiv., 267.

(−)-Crinane. A solution of 1.67 g. of potassium hydroxide and 3 ml. of anhydrous hydrazine in 10 ml. of diethylene glycol was combined with 200 mg. of V (no OCH_3). The mixture was refluxed for 2 hr., cooled, and poured into water. Extraction with benzene and evaporation of the solvents left an oil (150 mg., 79%) which was passed over a small alumina column and eluted with benzene–ethyl acetate (1:1). Evaporative distillation at 100° (30 μ) and crystallization from ether gave pure (−)-crinane, m.p. 109–110°, $[\alpha]_{589}^{25}$ −5.7°, $[\alpha]_{436}^{25}$ −16.8° (*c* 0.63); reported:[15] $[\alpha]_{589}^{24}$ −6.3°, $[\alpha]_{436}^{24}$ −16.2°.

Action of sodium and 3-methyl-1-butanol on buphanamine. In the manner described for the preparation of demethoxydihydrobuphanamine, 500 mg. of buphanamine was demethoxylated with 800 mg. of sodium and 3-methyl-1-butanol. The chloroform extracts yielded 312 mg. of a yellow oil which showed no hydroxyl absorption in the infrared region. Chromatography on alumina and elution with 10% ethyl acetate in benzene gave 89 mg. (21%) of an oil which was distilled at 120° (<1 μ) and identified by its infrared spectrum as α-crinene, $[\alpha]_{589}^{25}$ −74°, $[\alpha]_{436}^{25}$ −192° (*c* 0.78); reported:[23] $[\alpha]_{589}^{25}$ −76.3°, $[\alpha]_{436}^{25}$ −193°. It formed a picrate in ethanol which melted at 220–223°; reported:[23] m.p. 225–226°.

Further elution with 100% ethyl acetate yielded 59 mg. (14%) of an oil which also was distilled at 120° (<1 μ) and identified as β-crinene by its infrared spectrum, $[\alpha]_{589}^{25}$

$-92°$, $[\alpha]^{25}_{436}$ $-195°$ (*c* 1.13); reported:[23] $[\alpha]^{25}_{589}$ $-95.1°$, $[\alpha]^{25}_{436}$ $-206°$. It formed a picrate from ethanol, m.p. 201–202°; reported:[23] m.p. 201–202°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY, AND THE LABORATORIES OF THE MEMPHIS CHEMICAL CO.]

Experiments with Furochromones. Synthesis of Ammiol and Khellol

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The syntheses of ammiol (Va) from khellin (Ia), and of khellol (Vb) from visnagin (Ib) are given. Treatment of the 2-formyl derivatives of 5,8-dimethoxy- (IVa) and 5-methoxyfuro-4′,5′,6,7-chromone (IVb) with ammoniacal silver nitrate solution effected their oxidation to the corresponding carboxylic acid derivatives (VIa-b) respectively.

Demethylation of Ia and of Ib is now reported to occur upon prolonged treatment with aluminum isopropoxide, to give 5-norkhellin (XIa) and 5-norvisnagin (XIb) respectively.

Khellin (Ia), visnagin (Ib), and khellol (Vb), which can be obtained from the Egyptian plants *Ammi visnaga* (L.) are now available in quantity, and a number of degradations and similar reactions have been carried out with these three substances with the view of obtaining products which may be useful as medicinals or in further syntheses.[1a–c] Recently, Seitz,[2] upon a chromatographic fractionation of a crude khellin on alumina, has succeeded in isolating a new natural furochromone derivative, ammiol (Va), which displays the same relationship to Ia as Vb to Ib.

The present investigation deals with the synthesis of 2-hydroxymethyl-5,8-dimethoxyfuro-4′,5′,6,7-chromone (Va) by an unambiguous method, and with the study of its isolation as a free constituent in the total extracts of *Ammi visnaga* (L.) grown in Egypt.

In this synthesis, namely of Va, the route applied to 2-methylchromone by Schmutz, Hirt, and Lauener[3] for the synthesis of 2-oxochromones has been followed (*cf.* Chart 1). Treatment of Ia with iodine[4] in pyridine led to the formation of 1-(4-oxo-1,4H-5,8-dimethoxyfuro-4′,5′,6,7-chromene-2-ylmethyl)-pyridinium iodide (IIa). The latter, upon treatment with sodium carbonate, gave khellinone (VIIa), and, when heated with sodium sulfite solution, 4,7-dimethoxy-6-hydroxybenzofuran-5-carboxylic acid[1a] together with VIIa. IIa was then condensed with *p*-nitrosodimethylaniline in the presence of sodium carbonate to give 5,8-dimethoxyfuro-4′,5′,6,7-chromone-2-*p*-dimethylaminophenylazomethine (IIIa).[5] Attempts to prepare the Schiff bases directly from Ia and from Ib by the Ehrlich-Sachs reaction in aqueous ethanol in the presence of sodium carbonate, as well as in anhydrous methanol in the presence of anhydrous potassium carbonate[6] did not lead to the expected products. IIIa was treated with 10*N* sulfuric acid to yield 2-formyl-5,8-dimethoxyfuro-4′,5′,6,7-chromone (IVa), which gave with the common aldehyde reagents the corresponding derivatives.

Reduction of the formyl derivative IVa with aluminum isopropoxide led to an almost quantitative yield of ammiol (Va), proved to be identical with the natural product.[7] On the other hand, reduction of IVa with zinc dust and glacial acetic acid effected the formation of a poor yield of Va, together with a sparingly soluble substance as the main product. The latter gave the correct analytical values for a glycol derivative of IVa, and its structure is under further investigation.

The structurally related analog of Va, namely, khellol (Vb), now has been, similarly, synthesized *via* the sequence of reactions described above (*cf.*

(1) (a) A. Schönberg, N. Badran, and N. A. Starkovsky, *J. Am. Chem. Soc.*, **75**, 4992 (1953); (b) *J. Am. Chem. Soc.*, **77**, 5390 (1955). (c) For a review on this subject, *cf.* C. P. Huttrer and E. Dale, *Chem. Revs.*, **48**, 543 (1951), and H. Schmid, *Fortsch. Chem. organ. Naturstoffe*, II, 124 (1954).

(2) G. Seitz, *Arch. Pharm.*, **287**, 79 (1954).

(3) J. Schmutz, R. Hirt, and H. Lauener, *Helv. Chim. Acta*, **35**, 1168 (1952).

(4) *Cf.* N. A. Starkovsky, *Egyptian J. Chem.*, **2**, 111 (1959).

(5) 2-Methylchromone gives *N*-(*p*-dimethylaminophenyl)-α-(4-oxo-1,4H-benzopyran-2-yl)nitrone under similar conditions (*cf.* ref. No. 3).

(6) *Cf.* A. McGookin, *J. Appl. Chem., London*, **5**, 65 (1955).

(7) Both synthetic Va as well as its structural analog Vb gave an intense violet-red color with sodium hydroxide pellets (*cf.* A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 1611 (1950).