week. Work up in the usual manner gave 1.4 g. of pure amine hydrochloride XI, m.p. 198–200°, $(\alpha)_D^{27°} = -0.17$, infrared spectrum: broad 3297 cm.$^{-1}$ (—OH); 2700–2400 cm.$^{-1}$ (—N$^+$—H); 1719 cm.$^{-1}$ (s) (—C=O).

Anal. Calcd. for $C_{24}H_{40}ClNO_2$: C, 70.30; H, 9.76. Found: C, 69.90; H, 9.89.

The free base (0.5 g.) of the above compound was dissolved in 10 ml. of acetone and then treated with 1 g. of methyl iodide. An immediate reaction occurred followed by the precipitation of the *2α-pyrrolidinomethyl-17β-hydroxy-5α-androstan-3-one methiodide* (XII). Recrystallization from ethyl alcohol yielded white crystalline substance, m.p. 248–250°, $(\alpha)_D^{27°}$ 3.72 (methyl alcohol), infrared spectrum: 3404 cm.$^{-1}$ (—OH); 1714 cm.$^{-1}$ (—C=O).

Anal. Calcd. for $C_{25}H_{42}INO_2$: C, 58.24; H, 8.21. Found: C, 58.24; H, 8.20.

2-(Pyrrolidinomethylene)-17β-hydroxy-5α-androstan-3-one (X). Ten grams of 2-hydroxymethylene-17β-hydroxy-5α-androstan-3-one[7] (VII) was dissolved in 500 ml. of dry benzene. Five grams of pyrrolidine were added and the solution was refluxed for 4 hr. as the water formed was collected in a water trap. The benzene was then removed *in vacuo* and the residue was recrystallized from ethyl acetate–ethyl alcohol. The resulting yellow crystals melted at 280–281°, $(\alpha)_D^{27°} = -124.86$ (chloroform), $\lambda_{max}^{C_2H_5OH}$ 339 mμ (ε 23,750), infrared spectrum: 3390 cm.$^{-1}$ (—OH); 1624 cm.$^{-1}$ (N—C=C).

Anal. Calcd. for $C_{24}H_{37}NO_2$: C, 77.58; H, 10.02; N, 3.78. Found: C, 77.66; H, 10.24; N, 3.82.

Reduction of X *to* XI. Compound X (4.5 g.) dissolved in 100 ml. of tetrahydrofuran was added slowly to a suspension of 3.5 g. of lithium aluminum hydride in 200 ml. of ether in a 1 l. flask connected with a stirrer, dropping funnel, and reflux condenser; the mixture was refluxed for 3 hr. A saturated solution of sodium potassium tartrate was added slowly to the solution. The mixture was filtered and the filtrate was extracted with ether and methylene chloride. The combined extract dried over magnesium sulfate, was filtered, and the filtrate evaporated to dryness *in vacuo*. The residue was taken up in a small amount of ethyl alcohol and then treated with ethyl acetate saturated with hydrogen chloride gas. The resulting viscous material was triturated well with ether and then recrystallized twice from ethyl alcohol–ether acetone to give one gram of product, m.p. 200°. This substance was identical with compound XI prepared *via* the Mannich reaction. The two samples gave superimposable infrared spectra and mixture melting point gave no depression.

The methiodide salt (m.p. 250–251°) of this compound was also identical with XII.

Anal. Calcd. for $C_{25}H_{42}INO_2$: C, 58.24; H, 8.21. Found: C, 58.20; H, 8.14.

Reduction of 2α-pyrrolidinomethyltestosterone XIV *to* XI. 2α-Pyrrolidinomethyltestosterone[8] (0.5 g.) prepared *via* the enamine intermediate was dissolved in a mixture of 12 ml. of dry dioxane and 6 ml. of dry ether. This solution was then added over a 10-min. period to a solution of 100 mg. of lithium dissolved in 50 ml. of liquid ammonia. An additional 50 mg. of lithium was added to maintain the blue color for an additional 30 min. The lithium amide formed was neutralized by the addition of 1.2 g. of ammonium chloride and the ammonia was allowed to evaporate. The residue was dissolved in chloroform, the solution was washed with water, dried over sodium sulfate and concentrated *in vacuo*. The resulting solid was dissolved in a small amount of ethyl alcohol and treated with ethyl acetate saturated with hydrogen chloride; a semicrystalline substance was obtained which was recrystallized from ethyl alcohol–ether to yield 90 mg. of substance, m.p. 198–200°, identical in all respects with XI.

The free base of XI (0.5 g.) was treated with sodium methoxide (0.3 g.) dissolved in 50 ml. of methanol for 2 hr. The starting material was recovered quantitatively.

Acknowledgment. We would like to take this opportunity to thank Dr. Schlittler for his interest and encouragement. We are indebted to Mr. Louis Dorfman and his microanalytical group for their diligent cooperation.

SUMMIT, N. J.

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Haemultine and the Alkaloids of *Haemanthus multiflorus* Martyn[1]

H. M. FALES AND W. C. WILDMAN

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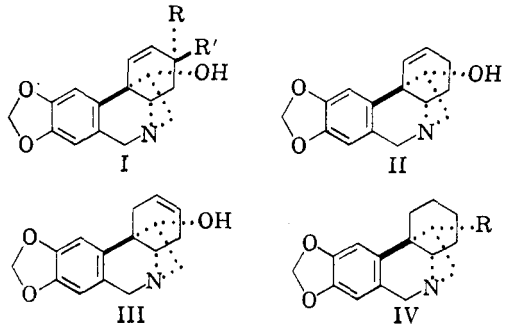
An investigation of the alkaloids of *Haemanthus multiflorus* Martyn has shown the presence of lycorine and montanine. No haemultine, previously reported by other workers to occur in this source, could be detected. Demethoxylation of either crinamine or haemanthamine with sodium and amyl alcohol affords two isomeric demethoxy derivatives (II and III) as well as the respective dihydro compounds.

A previous investigation of the alkaloids of *Haemanthus multiflorus* Martyn reported the presence of chlidanthine, haemanthidine, haemultine, hippeastrine and lycorine.[2a,2b] Of these alkaloids, only haemultine was of unknown structure. This alkaloid, $C_{16}H_{17}NO_3$, contained a basic, tertiary nitrogen, one reducible double bond, one hydroxyl and one methylenedioxy group. The hydroxyl was considered to be located in a five-membered ring and secondary since dihydrohaemultine was oxidized by chromic acid to a ketone hydroiodide showing absorption at 5.71 μ (1751 cm.$^{-1}$). It was reported that haemultine was obtained also from the action of sodium and *n*-amyl alcohol on either haemanthamine or crinamine.[2a] With the determination of the structures of

(1) Paper XXI on the alkaloids of the Amaryllidaceae; previous paper, H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 881 (1961). For a recent review of the alkaloids of this family, see W. C. Wildman in *The Alkaloids*, R. H. Manske, ed., Academic Press, New York, 1960, Vol. VI, p. 289.

(2)(a) H.-G. Boit and W. Döpke, *Chem. Ber.*, **91**, 1965 (1958); (b) H.-G. Boit, W. Döpke, and W. Stender, *Naturwissenschaften*, **45**, 390 (1958).



haemanthamine (I, R′ = OCH_3, R = H) and crinamine (I, R = OCH_3, R′ = H),[3,4] it appeared reasonable to Boit and Döpke to assume that haemultine was demethoxyhaemanthamine (I, R,R′ = H) or demethoxycrinamine which would be identical.[2a,5] The degradations reported for haemultine were consistent with such a structure and demethoxylation of allylic 3-hydroxy alkaloids of this ring system has been reported.[6] Investigations in our laboratory have demonstrated that both hydroxyl epimerization and double bond migration may occur when Amaryllidaceae alkaloids are treated with sodium and amyl alcohol.[6] Because of these uncertainties and the fact that derivatives of I can be rearranged under mild conditions to compounds containing the 5,11-methanomorphanthridine nucleus,[7] it seemed desirable to prove the structure of haemultine in a more unequivocal manner.

Because of the expensive nature of *H. multiflorus*, we sought to obtain haemultine by the demethoxylation of haemanthamine and crinamine, alkaloids with which we were amply supplied. When haemanthamine was treated with sodium and *n*-amyl alcohol, we obtained three substances: two isomeric demethoxyhaemanthamines, $C_{16}H_{17}NO_3$, and dihydrohaemanthamine. The demethoxyhaemanthamines were designated as α- and β-; the former was eluted first during chromatography on Florisil. β-Demethoxyhaemanthamine and dihydrocrinamine were obtained when crinamine was treated similarly. Apohaemanthamine gave the α-isomer only.[8] The isomers could be differentiated either by their distinctive infrared spectra in chloroform or Nujol or by reverse-phase paper chromatography. Neither isomer possessed the physical properties reported for haemultine, and the correlations of Table I are compatible with the assumption that haemultine is a mixture of α- and β-demethoxyhaemanthamine. Because of this divergence we have retained the names α- and β-demethoxyhaemanthamine for the sodium and amyl alcohol products although α-demethoxyhaemanthamine will be shown to have the structure which has been postulated by Boit and Döpke for haemultine.[9]

The analytical data indicated that neither α- nor β-demethoxyhaemanthamine possessed a methoxyl group. The isomers differed only in the position of the double bond because catalytic hydrogenation of either isomer gave the same dihydro derivative. Thionyl chloride followed by lithium aluminum hydride converted dihydrodemethoxyhaemanthamine to (+)-crinane (IV, R = H_2). This series of transformations provides unequivocal evidence that no skeletal rearrangement occurs when either haemanthamine or crinamine is demethoxylated with sodium and amyl alcohol, since both of these alkaloids have been related to the (+)-crinane nucleus.[4]

The hydroxy group may be assigned position 11 because oxodihydrodemethoxyhaemanthamine showed carbonyl absorption at 1746 $cm.^{-1}$ (chloroform) and the corresponding hydroiodide showed a band at 1759 $cm.^{-1}$ (potassium bromide). This is in good agreement with the values found for oxodihydrohaemultine hydroiodide (5.71 μ; 1751 $cm.^{-1}$),[2] oxodihydrohaemanthamine (1748 $cm.^{-1}$)[3] and oxocrinamine (1748 $cm.^{-1}$)[3]. Based on previous experience with 1-oxocrinane,[1] 2-oxopowellane[10] and 3-oxocrinane,[11] saturated ring C ketones appear to absorb near 1712 $cm.^{-1}$ The ultraviolet spectrum of oxodihydrohaemanthamine showed the characteristic abnormalities due to the close spacial proximity of the carbonyl group to the aromatic ring.[3] These data permit oxodihydrodemethoxyhaemanthamine to be assigned structure IV (R = O). The configuration of the hydroxyl group of dihydrodemethoxyhaemanthamine was determined by the method used in the haemanthamine and crinamine series. A hydroxyl at C_{11} oriented toward the aromatic ring (as in V, R′ = OH, R = H) would be expected to hydrogen bond intramolecularly to the π-electrons of the aromatic ring. Such bonding has been reported for epihaemanthamine, epicrinamine and their dihydro derivatives.[3] The fact that dihydrodemethoxyhaemanthamine shows only unbonded hydroxyl absorption at 3629 $cm.^{-1}$ establishes the normal configuration at C_{11} (*i.e.*, with

(3) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 197 (1960); *Chem. & Ind. (London)*, 561 (1958).

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

(5) Prior to the appearance of ref. 3, haemultine was considered to be 4-hydroxy-1-crinene.[2b]

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

(7) Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

(8) The conversion of apohaemanthamine to α-demethoxyhaemanthamine may be considered additional support for the structure assigned to apohaemanthamine.

(9) A sample of haemultine, kindly supplied by Prof. H.-G. Boit, was found by paper chromatography to be a mixture of α- and β-demethoxyhaemanthamine. Since this sample might well have come from the synthetic procedure rather than from isolation, it is not possible for us to state that haemultine does not exist.

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

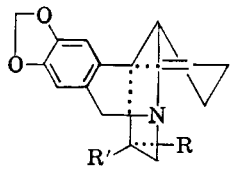
(11) W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).

TABLE I

COMPARISON OF HAEMULTINE WITH α- AND β-DEMETHOXYHAEMANTHAMINE

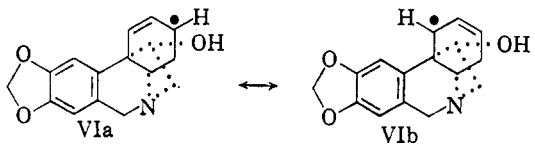
Compound	M.P.	$[\alpha]_D$	H_2·B	B·HI	B·CH_3I	B·picrate	O-Acetyl B·$HClO_4$	Oxodihydro Base·HI
Haemultine	174–175	+147°	218–220°	102°	263–264°	208–210°	192° dec.	178°
α-Demethoxyhaemanthamine	194–194.5	+10°	225–227°	140–150°	274–275°	260–264° dec.	—	178–180°
β-Demethoxyhaemanthamine	201–202	+199°	225–227°	—	263–264°	205–212°	130–160°	178–180°

respect to ring D, *trans* to the phenyl) for it and for α- and β-demethoxyhaemanthamine.



V

The position of the double bond in α- and β-demethoxyhaemanthamine was assigned also by spectral studies. Both isomers showed absorption at 3030 cm.$^{-1}$, due to the disubstituted double bond. This absorption disappeared on hydrogenation. Presumably, the demethoxylation process involves a free radical intermediate which may be stabilized by resonance (VIa ⟷ VIb). The positions of the double bond in VIa and VIb should



VIa VIb

represent the most probable positions of unsaturation in α- and β-demethoxyhaemanthamine. Since α-demethoxyhaemanthamine showed bonded hydroxyl absorption at 3590 cm.$^{-1}$, identical with the value found for haemanthamine and crinamine, it was assigned structure II. The β-isomer (III) showed both bonded and unbonded hydroxyl absorption at 3625 and 3585 cm.$^{-1}$. Such doublet absorption was not unexpected because the conditions for hydrogen bonding may be less favorable in III than in II, depending on the conformation of ring C.

An alkaloid possessing either structure II or III would be the first alkaloid of the Amaryllidaceae that does not have an oxygen-containing ring C and therefore does not fit well with the existing biogenetic theories.[12,13] Indeed, we have examined recently two different samples of *Haemanthus multiflorus* and can find neither haemultine nor α- or β-demethoxyhaemanthamine. Only lycorine and montanine could be isolated. Using the sensitive techniques of gas phase chromatography and paper chromatography, it was possible to demonstrate that neither sample contained detectable amounts of either II or III.

EXPERIMENTAL[14]

Isolation of alkaloids. The bulbs of *H. multiflorus* (2.1 kg.), purchased from C. C. vanTubergen, Haarlem, were extracted in the usual manner.[15] Trituration of the crude alkaloid fraction gave 0.10 g. of lycorine, m.p. 245–250° dec. A small portion of the filtrate was spotted on Whatman No. 1 paper (impregnated with formamide) and eluted with 3% methylene chloride in carbon tetrachloride. No alkaloids were detected near R_f 0.48 (α-demethoxyhaemanthamine) or R_f 0.36 (β-demethoxyhaemanthamine). Gas phase chromatography[16] at 204° of a small sample of the crude filtrate showed the presence of compounds with retention times of 9.1 and 17.6 min.; α- and β-demethoxyhaemanthamine have retention times of 5.85 and 6.0 min., respectively. Montanine, under these conditions, showed a retention time of 9.2 min. Chromatography of the remaining crude alkaloid fraction gave 220 mg. of montanine. A portion of the montanine was converted to its methiodide, m.p. 270–272° dec.; $[\alpha]^{25}_{589}$ +10.7°, $[\alpha]^{25}_{436}$ +5.3° (*c* 0.54, water); reported[7]: m.p. 269–272° dec.; $[\alpha]^{23}_{589}$ +10°. The remainder was converted to the picrate, m.p. 225–227°; reported[7]: m.p. 225–226°.

A second shipment (795 g.) of *H. multiflorus* (M. Wittbolt, Holly Hill, Fla.), processed in the same way, gave 15 mg. of lycorine and 60 mg. of montanine. Neither paper nor gas phase chromatography gave any evidence of α- or β-demethoxyhaemanthamine.

α- and β-Demethoxyhaemanthamine (II and III). (a) *From haemanthamine.* A solution of 500 mg. of haemanthamine in 50 ml. of *n*-amyl alcohol was stirred vigorously under reflux in an atmosphere of nitrogen. Sodium (1.50 g.) was added in small portions over a 45-min. period. The solution was cooled, acidified with 10% sulfuric acid and washed with ether. The ether extracts were washed with acid, and the wash was combined with the original solution. The acid extracts were made basic and extracted with chloroform. Evaporation of the solvent left 300 mg. of an oil

(12) D. H. R. Barton and T. Cohen, *Festschrift Arthur Stoll*, Birkhäuser, Basel, 1957, p. 117.

(13) E. Wenkert, *Experientia*, **15**, 165 (1959).

(14) All melting points were obtained on a Kofler microscope hot stage and are corrected. Infrared spectra were recorded on either a Perkin-Elmer Model 21 or a Beckman IR-7 double-beam spectrophotometer. All comparisons and identifications of alkaloids and the products of their degradation were verified by the identity of the infrared spectra and by mixture melting point determinations with authentic reference compounds. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

(15) R. E. Lyle, E. A. Kielar, J. R. Crowder, and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 2620 (1960).

(16) H. A. Lloyd, H. M. Fales, P. F. Highet, W. J. A. VandenHeuvel, and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 3791 (1960).

which was chromatographed over Florisil with chloroform–methanol. Elution with 1% methanol produced 22 mg. (4.9%) of *α-demethoxyhaemanthamine* (II). Elution of the column with 2–4% methanol in chloroform produced 94 mg. (21%) of *β-demethoxyhaemanthamine* (III). Elution with 5% methanol in chloroform yielded 84 mg. (19%) of dihydrohaemanthamine, m.p. 231–232°.

Under the same conditions but employing *n*-butyl alcohol as the solvent, 1.00 g. of haemanthamine gave 20 mg. (2.2%) of II, 398 mg. (44%) of III, and 434 mg. (49%) of dihydrohaemanthamine.

When *n*-propyl alcohol was employed as above, the yields were 6.0% of II, 36% of III, and 42% of dihydrohaemanthamine.

Substitution of ethanol for the *n*-amyl alcohol furnished no α-isomer, 6.2% of III, 34% of dihydrohaemanthamine, and 34% of recovered haemanthamine.

(b) *From crinamine.* A solution of 500 mg. of crinamine was treated under the same conditions with 100 ml. of *n*-amyl alcohol and 3 g. of sodium to yield 275 mg. of basic residue. This was separated by chromatography into 79 mg. (18%) of III, 120 mg. (27%) of dihydrocrinamine and 90 mg. of a residue which appeared from its infrared spectrum to be a mixture of dihydrocrinamine and crinamine. Neither the α-isomer nor haemanthamine was detected.

(c) *From apohaemanthamine.* By the same method, 262 mg. of apohaemanthamine and 2.20 g. of sodium in 50 ml. of *n*-amyl alcohol provided 113 mg. of basic residue. This was chromatographed on alumina with ethyl acetate to give 39 mg. (15%) of recovered apohaemanthamine. Elution with 5% methanol in ethyl acetate gave 38 mg. (16%) of impure α-demethoxyhaemanthamine (II), m.p. 177–185°, which was converted first to the hydriodide, m.p. 140–150°, and then to the picrate, m.p. 260–264°. Regeneration over alumina with chloroform yielded the pure free base, m.p. 195–196°.

α-Demethoxyhaemanthamine crystallized from ethyl acetate as plates, m.p. 195–195.5°; $[\alpha]^{25}_{589}$ +10°, $[\alpha]^{25}_{436}$ +26° (*c* 0.19); $\lambda^{C_2H_5OH}_{max}$ 295 mμ (ε 4840); $\nu^{CCl_4}_{max}$ 3590 cm.$^{-1}$ (π-bonded OH).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; OCH_3 0.00; neut. equiv., 271. Found: C, 71.02; H, 6.14; OCH_3, 0.00; neut. equiv., 275.

The *hydriodide of α-demethoxyhaemanthamine* was prepared with dilute acetic acid and sodium iodide and recrystallized from water as fine, hydrated prisms which melted from 140–150°, forming an opaque glass.

Anal. Calcd. for $C_{16}H_{18}NO_3I$: C, 48.13; H, 4.54; neut. equiv., 399. Found after drying at 137° (vac.): C, 47.95; H, 4.63; neut. equiv., 394.

The *methiodide* was recrystallized from acetone–ethanol, m.p. 274–275°.

Anal. Calcd. for $C_{17}H_{20}NO_3I$: C, 49.40; H, 4.88; I, 30.71. Found: C, 49.27; H, 4.95; I, 30.76.

The *picrate* was prepared with aqueous picric acid and recrystallized from water as fine prisms, m.p. 260–264°.

Anal. Calcd. for $C_{22}H_{20}N_4O_{10}$: C, 52.80; H, 4.03. Found: C, 52.61; H, 4.22.

β-Demethoxyhaemanthamine (III) was recrystallized from acetone as rectangular plates, m.p. 201–202°; $[\alpha]^{24}_{589}$ +199°, $[\alpha]^{24}_{436}$ +437° (*c* 0.17), $[\alpha]^{25}_{589}$ +167°, $[\alpha]^{25}_{436}$ +361° (*c* 0.5); $\lambda^{C_2H_5OH}_{max}$ 295 mμ (ε 5170), $\nu^{CCl_4}_{max}$ 3625 cm.$^{-1}$ (free OH), 3585 cm.$^{-1}$ (bonded OH).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; OCH_3, 0.00; neut. equiv., 271. Found: C, 70.85; H, 6.36; OCH_3, 0.00; neut. equiv., 273.

A mixture melting point with the α-isomer showed a depression of 30°.

β-Demethoxyhaemanthamine did not form a crystalline hydriodide, but a *picrate* crystallized from water as short yellow prisms, m.p. 205–212°.

Anal. Calcd. for $C_{22}H_{20}N_4O_{10}$: C, 52.80; H, 4.03. Found: C, 52.75; H, 4.27.

β-Demethoxyhaemanthamine methiodide was recrystallized from water as short prisms, m.p. 263–266°.

Anal. Calcd. for $C_{17}H_{20}NO_3I$: C, 49.40; H, 4.88; I, 30.71. Found: C, 49.09; H, 4.9 1;I, 30.54.

O-Acetyl-β-demethoxyhaemanthamine hydroperchlorate monohydrate was prepared by acetylation of the β-isomer with pyridine and acetic anhydride at room temperature in the usual manner, followed by treatment with aqueous perchloric acid. After recrystallization from water, fine, hydrated needles were obtained, m.p. 130–160°; ν^{Nujol}_{max} 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}NO_8Cl \cdot H_2O$: C, 50.06; H, 5.14. Found: C, 50.29; H, 5.07.

O-3,5-Dinitrobenzoyl-β-demethoxyhaemanthamine was prepared from III and 3,5-dinitrobenzoyl chloride in the usual manner. It crystallized from ethyl acetate as yellow prisms, m.p. 217–218°; ν_{max} 1739 cm^{-1} (potassium bromide).

Anal. Calcd. for $C_{23}H_{19}N_3O_8$: C, 59.35; H, 4.12. Found: C, 59.38; H, 3.96.

Dihydrodemethoxyhaemanthamine. A solution of 100 mg. of either the α- or β-isomer of demethoxyhaemanthamine in acetic acid was stirred with 200 mg. of pre-reduced platinum oxide in a hydrogen atmosphere. After 1 mole was absorbed, the uptake of hydrogen ceased. The solution was filtered, evaporated, made basic and extracted with chloroform. The residue on evaporation was crystallized from ethyl acetate to yield fine prisms, m.p. 225–227°; $[\alpha]^{25}_{589}$ +40°, $[\alpha]^{25}_{436}$ +89° (*c* 0.65); $\lambda^{C_2H_5OH}_{max}$ 295 mμ (ε 5240), $\nu^{CCl_4}_{max}$ 3629 cm.$^{-1}$ (free OH). The materials obtained by reduction of the α- and β-isomers were identical.

(+)-Crinane (IV, R = H). Dihydrodemethoxyhaemanthamine (233 mg.) was refluxed with excess thionyl chloride for 1 hr. The excess thionyl chloride was evaporated, and the residue was treated with 10 ml. of tetrahydrofuran and a large excess of lithium aluminum hydride. After refluxing overnight, the mixture was decomposed with alkali and extracted with chloroform. The crude product obtained on evaporation (185 mg.) exhibited an infrared spectrum (chloroform) identical with that of (−)-crinane. Chromatography on alumina and elution with 50% ethyl acetate in benzene produced 110 mg. (32%) of pure (+)-crinane which was distilled at 110° (vac.) and converted to a picrate which was recrystallized from ethanol-acetone, m.p. 199–200°. The compound depressed the melting point of (−)-crinane picrate (m.p. 202–204°) but exhibited an infrared spectrum (potassium bromide) which was identical with that of the latter material.

Anal. Calcd. for $C_{22}H_{22}N_4O_9$: C, 54.32; H, 4.56. Found: C, 54.44; H, 4.46.

(+)-Crinane was recovered from the picrate by elution with chloroform from a short column of alumina. It was recrystallized from ether as prisms, m.p. 108–110°; a mixture with (−)-crinane (m.p. 108–109°) melted at 80–98°; $[\alpha]^{24}_{589}$ +6.5°, $[\alpha]^{24}_{436}$ +15° (*c* 0.61); (−)-crinane, $[\alpha]^{25}_{589}$ −6.1°, $[\alpha]^{25}_{436}$ −16° (*c* 0.61). Infrared spectra of the (+) and (−) enantiomers were identical in either chloroform or potassium bromide.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; neut. equiv., 257. Found: C, 74.55; H, 7.40; neut. equiv., 263.

Oxodihydrodemethoxyhaemanthamine (IV, R = O). A solution of 140 mg. of dihydrodemethoxyhaemanthamine in 4 ml. of pyridine was treated with 100 mg. of chromium trioxide in 2 ml. of pyridine and allowed to remain overnight at room temperature. The mixture was decomposed with 10% sodium carbonate and extracted with chloroform. Evaporation of the solvents left a dark gum which was taken up in benzene, filtered and evaporated to a light oil which showed no hydroxyl absorption in the infrared. Chromatography on alumina with 50% benzene-ethyl acetate afforded 109 mg. (78%) of crystalline ketone. Recrystallization from ether produced prisms, m.p. 103–105°; $[\alpha]^{24}_{589}$ +278°, $[\alpha]^{24}_{436}$ +869° (*c* 1.01); $\nu^{CHCl_3}_{max}$ 1746cm.$^{-1}$; $\lambda^{C_2H_5OH}_{max}$ 250 mμ (ε 3470) and 296 mμ (ε 5140), $\lambda^{C_2H_5OH}_{inf}$ 313 mμ (ε 3310) and $\lambda^{C_2H_5OH}_{inf}$ 325 mμ (ε 2130). In acidic ethanol, maxima

were seen at 254 mμ (ε 3070), 298 mμ (ε 5250) and 306 mμ (ε 5370) and an inflection at 318 mμ (ε 2950).

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., 270.

The *hydriodide* was prepared with dilute acetic acid and potassium iodide and recrystallized from water as prisms, m.p. 178–180° (reported[2a] 178°); ν_{max}^{KBr} 1759 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{18}NO_3I$: C, 48.13; H, 4.54. Found: C, 48.26; H, 4.61.

BETHESDA 14, MD.

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Structures Related to Morphine. XVII.[1] Further Stereochemical Studies with 9-Oxobenzomorphans

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Addition of methylmagnesium iodide to 2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (II) has afforded the 9-methylcarbinol methiodide (III) with the hydroxyl oriented toward the *cis*-fused iminoethano system as shown by degradation to the known *cis*-fused furan derivatives IV and VIII. Pyrolysis of III in boiling 1-nonanol yielded the base VII. Methyllithium and the free base VI on the other hand produced the diastereoisomer (X) which was also degraded to a nitrogen-free compound, presumably the *trans*-fused furan XI. A similar stereochemical pattern was followed in the addition of hydrogen to II and VI. Spectral data furnished additional proof of our assignments which are in conformity with and confirmatory of those made in the 2′-methoxy series (*cf.* References 1 and 2). Compounds VII, X, XIII, XV, and the *O*-acetyl derivative of XV have been tested for analgesic activity.

In a previous paper[2] we reported that the addition of methyl metallo reagents to 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (I) afforded only one of the two possible methylcarbinols in 75% yield; when the free base corresponding to I was used, the stereochemistry of addition was reversed. As one aspect of the determination of configuration of these methyl carbinols it was decided to degrade them to nitrogen-free products by two Hofmann elimination reactions. Somewhat unexpectedly,[3] in both instances, the two final products, obtained in good yield, exhibited characteristics of tetrahydrofurano compounds which were not identical. To help distinguish between these two it was deemed relevant to degrade similarly the methylcarbinol methiodide (III)[4] which, if the hydroxyl were *cis* (equatorial for the hydroaromatic ring) to the *cis*-fused iminoethano system, should lead to the known synthetic 1,2,3a,9b-tetrahydro-*cis*-3a,9b-dimethylnaphtho[2,1-b]furan (IV).[5] In the present report details of this degradation, of the addition of methyllithium to the base, VI, of the addition of hydrogen to II and VI and of an improved synthesis of II and VI are given.

Double Hofmann degradation of the methylcarbinol methiodide (III)[4] yielded a nitrogen-free product whose infrared and ultraviolet spectra corresponded with those of 1,2,3a,9b-tetrahydro-*cis*-3a,9b-dimethylnaphtho[2,1-b]furan (IV) synthesized by Fry.[5] Hydrogenation of the IV obtained by degradation gave VIII also identical with synthetic material.[5] Furthermore, the infrared spectrum of the base VII (prepared from III in boiling 1-nonanol) in chloroform was indicative of OH—N bonding (broad, strong band at 3450 cm.$^{-1}$). These facts confirm the assignments for III and VII as well as those made in the 2′-methoxy series as stated before.[2] Hydrogenation of II (platinum oxide) produced the carbinol XV (after cleavage of methyl iodide consistent with results in the 2′-methoxy series.[1]

Also in analogy with the 2′-methoxy series, reaction of the base VI with methyllithium or with platinum oxide-catalyzed hydrogen afforded the diastereoisomers X and XIII respectively of VII and XV. Degradation of X gave a nitrogen-free product whose infrared and ultraviolet absorption data were compatible with the *trans*-fused furan structure (XI)[2] and which absorbed one mole of hydrogen to give presumably XII.

In the course of the above work an improved synthesis of the ketone methobromide II[6] was developed. This improvement hinged largely on the use of 3,4-dihydro-1-methyl-2(1*H*)naphthalenone prepared by the method of Stork.[7] Further exploration of the pyrolysis of II to VI, previously carried out unsatisfactorily by dry distillation of II[6] has been made also. In boiling 1-hexanol, heptanol, octanol, or nonanol, the principal product

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(2) E. L. May and H. Kugita, *J. Org. Chem.*, 26, 188 (1961).

(3) Molecular models indicate unfavorable geometry for closure of a *trans*-fused tetrahydrofuran ring.

(4) E. L. May and E. M. Fry, *J. Org. Chem.*, 22, 1366 (1957).

(5) E. M. Fry, *J. Org. Chem.*, 22, 1710 (1957).

(6) E. L. May and J. G. Murphy, *J. Org. Chem.*, 20, 257 (1955).

(7) G. Stork, U. S. Pat. 2,773,099; *Chem. Abstr.*, 51, 9703d (1957).