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Position of the Aromatic Methoxyl in Alkaloids Related to Powelline[1]

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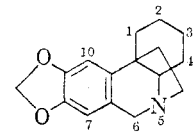
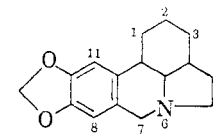
The methoxyl group of powelline and related alkaloids is assigned to the 7- position of the crinane nucleus on the basis of infrared and nuclear magnetic resonance spectra and the identity of a degradation product with synthetic material of known structure.

Alkaloids of the Amaryllidaceae bear either two or three oxygen atoms on the aromatic ring.[3] The most facile means of demonstrating the structure of the trioxygenated series has been by reduction with sodium in amyl alcohol to remove the methoxyl group representing the third oxygen, producing a dioxygenated alkaloid or derivative. Thus, powelline has been converted into dihydroepicrinine,[4a] buphanidrine into buphanisine,[4b] and fiancine into haemultine.[5,6] By appropriate transformations of substituents in the C-ring, it was possible to demonstrate that buphanamine,[7] crinamidine,[8] undulatine,[8,9] and nerbowdine[10] possessed the same ring system and aromatic oxygenation as powelline and buphanidrine. In the lycorine series, reduction has converted falcatine[4] and parkamine[11] into caranine, while nerispine is converted into caranine and α-dihydrocaranine.[5] These transformations have made it possible to elucidate the structures of alkaloids which occur in only very small quantities, but the single point of uncertainty has remained, that the methoxyl group could be in either of two positions: at position 7 or 10 of the crinane nucleus (I), and 8 or 11 of the lycorane nucleus (II).

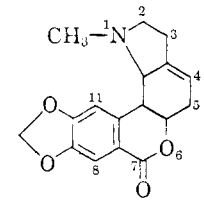
Recent speculation has placed the methoxyl at position 10 of the crinane system. Warnhoff and Wildman observed that the biogenetic scheme of Barton and Cohen[12] readily accommodated the intermediate IV which, by oxidative coupling,



I



II



III

would lead to the tetracyclic derivative V, corresponding to 10-methoxy crinane derivatives.[9] The corresponding intermediate VI required to produce a 7-methoxy crinane is a 2,3,4-trihydroxybenzyl type that is less familiar in nature. A compilation of the ultraviolet absorptions of 26 powellane derivatives and related compounds revealed that compounds without a substituent at C-1 showed a maximum at 286–288 mμ with a normal extinction coefficient of 1700–1800, while those with a C-1 substituent had extinction coefficients of 1320–1500. At that time, the reduced absorption was attributed to steric interaction between C-1 substituents and the methoxyl group at C-10. Similar effects were noted in alkaloids of the hemiacetal-lactone series (III), and the methoxyl was assigned to the corresponding hindered position 11. Subsequently, a similar interpretation and assignment were made by Jeffs and Warren[13] for the aromatic methoxyl of krigenamine. In view of the results described in the present paper, it must be concluded that no evidence actually exists which will warrant positive assignment of the methoxyl

(1) Paper XXIV of a series on Amaryllidaceae alkaloids. A preliminary communication of this work appeared in *Tetrahedron Letters*, 105 (1961). Previous paper: R. J. Highet, *J. Org. Chem.*, **26**, 4767 (1961).

(2) Visiting Scientist, National Heart Institute, 1957–1958, on leave from the University of Osaka, Osaka, Japan. Present address: Kyoto University, Kyoto, Japan.

(3) For a recent review of the alkaloids of this family, see W. C. Wildman in *The Alkaloids*, Vol. VI, R. H. F. Manske, ed., Academic Press, N. Y., p. 289.

(4)(a) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 4395 (1958). (b) The relation among these alkaloids had been deduced earlier from other evidence; *cf.*, W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).

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

(6) The occurrence of haemultine has been questioned recently by H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 1617 (1961).

(7) H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 881 (1961).

(8) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 3369 (1960).

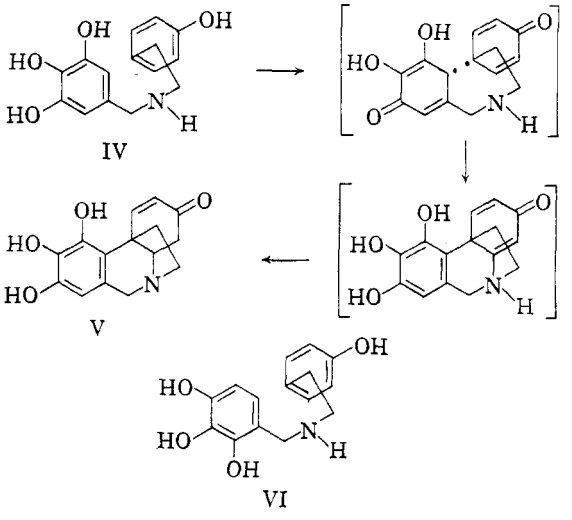
(9) E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 1472 (1960).

(10) H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 181 (1961).

(11) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **47**, 470 (1960).

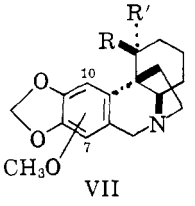
(12) D. H. R. Barton and T. Cohen, *Festschrift Arthur Stoll*, Birkhäuser, Basel, 1957, p. 117.

(13) P. W. Jeffs and F. L. Warren, *Chem. and Ind.*, 468 (1961).



group to C-8 or C-11 in either the lycorine or lactone series.[14,14a]

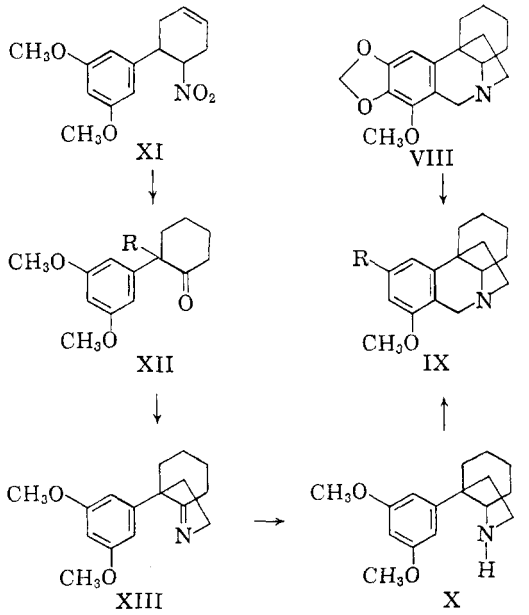
Recent studies of the hydroxyl stretching frequencies of 1-hydroxycrinane and powellane derivatives are not in agreement with the assignment of a C-10 methoxyl.[15] Molecular models show that a C-10 methoxyl and a C-1 hydroxyl are close enough to allow hydrogen bonding between the groups in either configuration of the hydroxyl. Such bonding may be anticipated to produce a hydroxyl stretching frequency of ca. 3550 cm.$^{-1}$ [15] However, dihydrobuphanamine (VII. R = OH, R′ = H)[7] shows a weakly bonded hydroxyl (3599 cm.$^{-1}$) while epidihydrobuphanamine (VII. R = H, R′ = OH)[7] shows an even more weakly bonded hydroxyl (3616 cm.$^{-1}$). When it was observed that the corresponding Ar-demethoxy derivatives[7] showed nearly identical hydroxyl stretching frequencies (3602 and 3616 cm.$^{-1}$, respectively), it was evident that the hydrogen bonding was between the



hydroxyl and the aromatic π electrons rather than between the hydroxyl and a C-10 methoxyl. Consequently, a C-7 assignment for the methoxyl is preferred on spectral grounds.

The nuclear magnetic resonance spectra of oxocrinine and oxopowelline and their dihydro derivatives corroborate this assignment. In the spectra of oxocrinine and dihydrooxocrinine, the peaks of the aromatic protons may be differentiated readily, for one is affected by hydrogenation and shifted upfield 0.17 p.p.m. (see Table I); this must correspond to the C-10 proton which is close to the π electrons of the double bond. The resonance of the sole aromatic proton of oxopowelline shows it to be at C-10, for the shift relative to the C-10 proton of oxocrinine corresponds to the anticipated effect of the aromatic methoxyl (0.23 p.p.m.).[16] In dihydrooxopowelline, this peak has been shifted 0.19 p.p.m. by hydrogenation of the bond. Furthermore, the resonance peaks of the olefinic protons are not affected by the addition of the methoxyl, although a C-10 methoxyl surely would affect the C-1 peak. The position of one of the peaks from the C-6 protons is shifted upfield 0.1 p.p.m. by the addition of the C-7 methoxyl.

Conclusive proof that the methoxyl is at C-7 came from degradation and synthesis. Reduction of (+)-powellane (VIII) with sodium in liquid ammonia[17] produced (+)-5,10b-ethano-9-hydroxy-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (IX. R = OH) which was converted by diazomethane to the dimethyl ether (IX. R = CH_3O). Synthetic material of this structure was available by the following route.[4b] Condensation of 3,5-



dimethoxybenzaldehyde with nitromethane in the

(14) A possible explanation for the decreased extinction coefficients of the trioxygenated alkaloids may be found in the work of Van Heldin, Verkade, and Wepster [R. Van Heldin, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **73**, 39 (1954)] who noted that 2,3-dimethyl-4-nitroaniline has a lower extinction coefficient than the isomeric 2,5-dimethyl-4-nitroaniline. This has been termed the "buttressing effect." In powellane derivatives, it would bring C-1 substituents into closer proximity with the C-10 proton.

(14)(a) NOTE ADDED IN PROOF: In contrast with our findings in powellane series, the aromatic methoxyl of falcatine, an alkaloid of the lycorine group, has been shown recently to be at C-8 (K. Torssell, *Acta Chem. Scand.*, **15**, 94F(1961).

(15) An extensive summation of such studies will be published shortly. H. M. Fales and W. C. Wildman, in preparation.

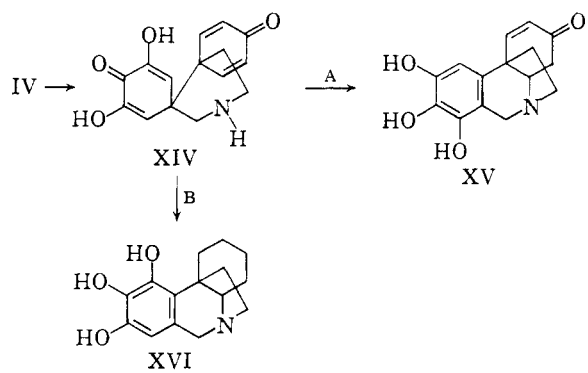
(16) L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, New York, 1959, p. 63.

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

presence of sodium hydroxide provided 3,5-dimethoxy-β-nitrostyrene. This was condensed with butadiene to provide the nitrocyclohexene XI, which was subjected to a Nef reaction[18] and reduced by catalytic hydrogenation to the cyclohexanone XII (R = H). Condensation with one mole of methyl acrylate in the presence of potassium *t*-butoxide converted this ketone to the oily keto ester XII (R = $CH_2CH_2COOCH_3$) in good yield. A Curtius degradation with simultaneous cyclization provided the imine XIII, which was isolated as the perchlorate. The base was reduced to the corresponding secondary amine (X) which was cyclized with formaldehyde to furnish the oily racemate of IX with an infrared spectrum, showing forty bands, that was identical with that of (+)-5,10b-ethano-7,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (IX). Similarly, the racemic picrate of IX exhibited an infrared spectrum (KBr) identical with that of the optically active material. The gas phase chromatographic behavior of the two bases was identical on a 3500-plate column.

With this body of evidence, the structures of crinamidine, flexinine, nerbowdine, undulatine, and buphanamine, which have been represented as 10-methoxy crinane derivatives,[7,10] must be revised to 7-methoxy derivatives.

Since the biogenetic path leading to powellane derivatives evidently does not proceed as previously considered, it is interesting to consider alternatives. One possibility is that cyclization of dioxygenated aromatic systems occurs to produce crinane precursors which subsequently are oxygenated to produce derivatives of powellane. Biological oxygenation of the C ring and ethano positions has been demonstrated recently[19-23]



(18) W. C. Wildman and R. B. Wildman, *J. Org. Chem.*, **17**, 581 (1952).

(19) A. R. Battersby, R. Binks, and W. C. Wildman, *Proc. Chem. Soc.*, 410 (1960).

(20) D. H. R. Barton and G. W. Kirby, *Proc. Chem. Soc.*, 392 (1960).

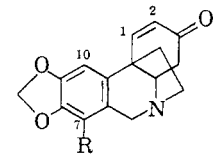
(21) D. H. R. Barton, G. W. Kirby, J. B. Taylor, and G. M. Thomas, *Proc. Chem. Soc.*, 254 (1961).

(22) A. R. Battersby, R. Binks, S. W. Breuer, H. M. Fales, and W. C. Wildman, *Proc. Chem. Soc.*, 243 (1961).

(23) A. R. Battersby, H. M. Fales, and W. C. Wildman, *J. Am. Chem. Soc.*, **83**, 4098 (1961).

TABLE I

NMR DATA



	C-7	C-10	C-1	C-2	C-6
Oxocrinine,[2b] R = H	3.52[a]	3.10	2.38	3.95	5.63; 6.23; J = 16
Dihydrooxocrinine,[2b] R = H, no double bond	3.50	3.27			5.65, 6.18; J = 17
Oxopowelline,[2b] R = OCH_3		3.34	2.38	3.91	5.78, 6.15; J = 17
Dihydrooxopowelline,[2b] R = OCH_3, no double bond		3.53			5.82, 6.16; J = 17

[a] Values are on the τ scale, relative to tetramethylsilane = 10 as an internal standard.

in the incorporation of either tyrosine or norbelladine into lycorine and haemanthamine. Another possibility is that such a trioxygenated intermediate as IV cyclizes through the bis-spiro system XIV, which may undergo a diene-phenol rearrangement to the required powellane precursor XV, although there appears to be no *a priori* reason for path A over path B.

EXPERIMENTAL[24]

Reduction of powelline. To a mixture of 0.312 g. of ammonium chloride in 25 ml. of ammonia was added an ethereal solution of 0.308 g. of powellane[4b] and 0.368 g. of sodium in small pieces, over a period of 15 minutes until a blue color developed. The solution was evaporated to dryness. The residue was dissolved in water, washed with ether, and neutralized with small pieces of Dry Ice. The aqueous solution was extracted three times with chloroform, and the combined extracts were evaporated. Recrystallization of the residue from chloroform provided 0.270 g. of (+)-5,10b-ethano-9-hydroxy-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (IX. R = OH) as prisms, m.p. 240–242°. Further crystallization from chloroform provided material, m.p. 245–247°, that was unchanged by sublimation

(24) Physical measurements of melting points, infrared and ultraviolet spectra and optical rotations were performed on the instruments used in our previous papers. Gas phase chromatographs were obtained on a Barber-Coleman Model 15 apparatus equipped with an argon ionization detector. The column was a 6 × 4 ft. U-tube packed with 3/4% SE-30 on Chromosorb W, 80–100 mesh. All comparisons and identifications of alkaloids and products of their degradation were verified by the identity of the infrared spectra (KBr) and by mixture melting point determinations with authentic reference compounds. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J. We are indebted to Dr. E. D. Becker and Mr. R. B. Bradley of the National Institute of Arthritis and Metabolic Diseases for the nuclear magnetic resonance spectra, which were obtained on a Varian-v-4300-2 nuclear magnetic resonance spectrometer operating at 60 mc. Frequencies were obtained relative to tetramethylsilane as an internal standard by interpolation using the audio sideband technique.

(200°/0.001 mm.) or crystallization from methanol-acetone. $[\alpha]^{25}_{589}$ +8.6°; $[\alpha]^{25}_{436}$ +27.0° (*c*, 0.64). λ_{max} 279–284 mμ (ϵ = 1770); addition of dilute base caused a shift to 293 mμ (ϵ = 1700). ν^{Nujol}_{max} 2600 (broad), 1595, 1060, 980, 850 cm.$^{-1}$

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; OCH_3, 11.96. Found: C, 73.93; H, 8.12; OCH_3, 11.85.

Methylation was effected by treating the above product (0.110 g.) in 15 ml. of methanol with distilled ethereal diazomethane solution prepared from 3.375 g. of *N*-nitroso-*N*-methyl-*N*-nitroguanidine. After standing for 5 days, the solution was evaporated. The residue was taken up in dilute hydrochloric acid, extracted once with benzene, made alkaline with sodium hydroxide, and extracted three times with benzene. The combined benzene extracts were dried over magnesium sulfate and distilled to dryness, leaving 72 mg. of *(+)-5,10b-ethano-7,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine* (IX. R = OCH_3) as an oil. This was converted to its *picrate* and crystallized twice from ethanol-chloroform to provide 95 mg., m.p. 238–239°.

Anal. Calcd. for $C_{23}H_{26}N_4O_9$: C, 54.97; H, 5.22; N, 11.15. Found: C, 55.09; H, 5.15; N, 11.24.

The *free base* was regenerated by chromatography over alumina and distilled at 170°/0.001 mm. $[\alpha]^{24}_{589}$ +11.4°; $[\alpha]^{24}_{436}$ +32.5° (*c*, 0.69). λ_{max} 276–282 mμ (ϵ = 1850). $\nu^{CCl_4}_{max}$ 1595, 1200, 1150, 1080, 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; 2 OCH_3, 22.71. Found: C, 74.25; H, 8.43; OCH_3, 22.95.

The *methiodide* crystallized as plates from acetone, m.p. 186–188° dec.

Anal. Calcd. for $C_{18}H_{26}NO_2I$: C, 52.05; H, 6.31; I, 30.56. Found: C, 52.05; H, 6.25; I, 30.38.

3,5-Dimethoxy-β-nitrostyrene was prepared in 70% yield from 3,5-dimethoxybenzaldehyde and nitromethane by the procedure of Worrall[25] for nitrostyrene. A sample was recrystallized from methanol to yield lemon-yellow needles m.p. 133.5–134.5°.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.62; H, 5.25; N, 6.47.

4-(3,5-Dimethoxyphenyl)-5-nitrocyclohexene (XI) was prepared by reaction of 3,5-dimethoxy-β-nitrostyrene with excess butadiene[18] to give a 75% yield of product that was, recrystallized from ethanol-water as colorless prisms, m.p. 73–75°.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51. Found: C, 63.55; H, 6.42.

6-(3,5-Dimethoxyphenyl)-3-cyclohexen-1-one was obtained from XI by the Nef reaction.[18] A sample was recrystallized from ethanol-water to give a short, colorless needles, m.p. 65.5–66.6°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.44; H, 6.95.

2-(3,5-Dimethoxyphenyl)cyclohexanone (XII. R = H). The cyclohexenone was reduced in ethanol at room temperature and a pressure of 3 atm. in the presence of 10% palladium-on-charcoal catalyst. The product was recrystallized from ethanol-water as rectangular plates, m.p. 62.5–63°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.64; H, 8.01; OCH_3, 26.82. Found: C, 71.77; H, 7.74; OCH_3, 26.49.

2-Carbomethoxyethyl-2-(3,5-dimethoxyphenyl)cyclohexanone (XII. R = $CH_2CH_2CO_2CH_3$). To a dried powder of potassium *t*-butoxide, prepared from 0.6 g. of potassium and dry *t*-butyl alcohol, was added a solution of 3.7 g. (0.0158 mole) of ketone (XII. R = H) in 100 ml. of dry benzene. The mixture was cooled in ice water and covered with nitrogen. A solution of freshly distilled methyl acrylate (1.5 g., 0.0175 mole) in 30 ml. of dry benzene was added with vigorous stirring over a period of 30 minutes at 5–10°. The mixture was stirred for 1 hr. at this temperature and then allowed to warm gradually to room temperature. After standing overnight, the solution was acidified with dilute acetic acid. The aqueous layer was extracted twice with benzene. The extracts were combined with the organic layer, washed with water, dried over magnesium sulfate, and evaporated to yield 4.9 g. of thick yellow sirup. Examination of the product by gas-phase chromatography showed that it consisted mostly of monoester and a small amount of unreacted ketone.

A mixture of 4.9 g. of ketoester and 10% sodium hydroxide solution was heated on the steam bath for 1.5 hours. The cooled, basic solution was extracted several times with benzene, acidified, and extracted exhaustively with benzene. The organic extracts were dried and evaporated in the usual manner to yield 4.4 g. of *2-carboxyethyl-2-(3,5-dimethoxyphenyl)cyclohexanone* (XII. R = CH_2CH_2COOH) as a frothy white residue which crystallized when triturated with ether. An analytical sample was recrystallized from benzene and sublimed under reduced pressure, m.p. 152–154°.

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; neut. equiv., 306. Found: C, 66.68; H, 7.25; neut. equiv., 301.

To a suspension of 4.2 g. of the above acid (XII. R = CH_2CH_2COOH) in ether was added a large excess of diazomethane solution in ether. The mixture was allowed to stand at room temperature for 2 hours. The excess diazomethane was destroyed by addition of dilute acetic acid. The ether layer was washed with sodium bicarbonate solution, then water, and was dried and evaporated to yield 4.2 g. of a thick, pale yellow oil. A colorless sample was obtained by evaporative distillation under reduced pressure.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.61; H, 7.71.

2,3,4,5,6,7-Hexahydro-3a-(3,5-dimethoxyphenyl)indole (XIII) was prepared from 2.3 g. of the ketoester (XII, R $CH_2CH_2COOCH_3$) by the method of Bachmann and Fornefeld.[26] The crude base (1.09 g., 58%) was obtained as a thick, yellow oil.

The *picrate* was prepared and recrystallized from ethanol, m.p. 164–168° dec.

Anal. Calcd. for $C_{22}H_{24}N_4O_9$: C, 54.10; H, 4.95; N, 11.47. Found: C, 54.05; H, 4.97; N, 11.46.

The free base could not be obtained in crystalline form, and it was converted to the perchlorate with aqueous perchloric acid. Recrystallization from acetone-ether gave small prisms, m.p. 137–139°.

Anal. Calcd. for $C_{16}H_{22}NO_6Cl$: C, 53.39; H, 6.17; N, 3.89; Cl, 9.86; neut. equiv., 360. Found: C, 53.27; H, 6.22; N, 3.94; Cl, 10.11; neut. equiv., 362.

2,3,3a,4,5,6,7,7a-Octahydro-3a-(3,5-dimethoxyphenyl)indole (X). A solution of 800 mg. of the perchlorate of XIII in 30 ml. of ethanol, to which a few drops of 10% aqueous perchloric acid had been added, was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium-on-charcoal catalyst. The reduction stopped in 30 minutes after one equivalent of hydrogen was absorbed. The catalyst was removed and the solution concentrated *in vacuo* to yield an oily perchlorate which could not be obtained in crystalline form. The free base (515 mg.) was a pale yellow oil which gave one peak in gas phase chromatography; retention time, 2.9 minutes at 175°. The infrared spectrum in chloroform or carbon tetrachloride did not show any absorption for an NH band, but the base gave a bright blue Simon test for secondary amines. Attempts to prepare a picrate yielded an oil.

The *tosylate* was prepared in the usual manner and purified by evaporative distillation at 200°/0.1 mm. It showed a retention time of 8.3 minutes at 245° in gas phase chromatography.

Anal. Calcd. for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03; N, 3.37. Found: C, 66.85; H, 7.29; N, 3.51.

dl-5,10b-Ethano-7,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (IX. R = OCH_3). A solution of 490 mg.

(25) D. E. Worrall in *Org. Syntheses*, Coll. Vol. I, 413 (1947).

(26) W. E. Bachmann and J. Fornefeld, *J. Am. Chem. Soc.*, **73**, 51 (1951).

of X in 6 ml. of 3% acetic acid was treated with 4 ml. of 36% formaldehyde solution and 0.8 g. of solid sodium bicarbonate. The mixture was warmed on the steam bath for 15 minutes, then cooled. A thick, gummy material separated from the aqueous solution. It was washed several times with water and dissolved in benzene. The benzene solution was washed twice with water and evaporated. The thick, oily residue was dissolved in 5 ml. of 3*N* hydrochloric acid, and the solution was heated on the steam bath for 15 minutes. The solution was cooled, diluted with water, extracted with ether, made basic with ammonium hydroxide, and extracted with chloroform. The extract was dried and evaporated to yield 460 mg. of thick, pale yellow oil. Examination of the product by gas-phase chromatography (¾% SE-30 column, 177°) showed that it consisted of approximately 1 part of unreacted secondary amine (retention time 5.15 minutes) and 2 parts of another compound with the same retention time as the product obtained by degradation (7.9 minutes). The two compounds were separated by Hinsberg's method through reaction with *p*-toluenesulfonyl chloride. The final product was distilled at 140°/0.01 mm. to yield 196 mg. of colorless oil. The infrared spectra (carbon tetrachloride solution and liquid film) of this material were identical with the spectra of the degradation product of powellane.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; neut. equiv., 273. Found: C, 74.77; H, 8.58; neut. equiv., 280.

The *picrate* was obtained as rectangular plates m.p. 209–212°, after recrystallization from chloroform-ethanol. The infrared spectrum (KBr) was identical with that of the picrate of IX (R = OCH_3) obtained by the degradation of powellane.

Anal. Calcd. for $C_{23}H_{26}N_4O_9$: C, 54.97; H, 5.22; N, 11.15. Found: C, 54.68; H, 5.11; N, 11.06.

BETHESDA 14, MD.

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Synthetical Experiments Related to the Indole Alkaloids. II.[1a] The Synthesis of Hexadehydroyohimbane

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Lithium aluminum hydride reduction of 2-(2-3′-indolyl-2-oxoethyl)isoquinolinium iodide (III), obtained from 3-acetylindole, isoquinoline, and iodine, gave directly 5,7,8,13,13b,14-hexahydrobenz[*g*]indolo[2,3-*a*]quinolizine (II), hexadehydroyohimbane. This is the simplest and most direct method of obtaining the yohimbine ring skeleton.

Interest in the synthesis of alkaloids of the indole group has been very intense over the last few years, and many notable successes have been achieved, especially the synthesis of reserpine,[2] strychnine,[3] and yohimbine,[4] and more recently a simulated biogenetic route to the strychnine-type ring skeleton.[5] The early methods of synthesis used in this field have been thoroughly discussed in *The Alkaloids*.[6] Our approach to the synthesis of the yohimbine ring skeleton has been developed in two stages. In part I of this series known methods were evaluated, and in a new method an intermediate 2-(2-3′-indolylethyl)isoquinolinium iodide (I) was reduced with lithium aluminum hydride to hexadehydroyohimbane (II) in good yield. Alstonilinol[7] has since been synthesized by this method and apart from an application to the berberine group[8] no others have been reported.

We now wish to report a more direct route to the yohimbine ring skeleton. An isoquinolinium salt that is capable of undergoing reduction and ring closure to the quinolizine is still the key intermediate, and the pentacyclic base is available from indole itself in three steps. Use is made of the two different ways in which 3-acetylindole can react. It possesses normal ketonic properties, readily forming a phenylhydrazone,[9] an oxime,[10] a thiosemicarbazone,[11] and a Mannich base with paraformaldehyde and dimethylamine hydrochloride.[12a] As it is analogous to acetophenone, it should condense with iodine and a tertiary organic base forming the corresponding salt, a reaction that is general for a methyl ketone group directly attached to an aromatic nucleus.[13]

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