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THE C—D RING CLEAVAGE OF DIHYDROCORYNANTHEINE DERIVATIVES

THE PARTIAL SYNTHESIS OF DIHYDROBURNAMICINE[1]

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Abstract—Two methods are described for the preparation of 3,4-*seco*-dihydrocorynantheine derivatives bearing an oxygen function at C-3. The first is the cyclization by Ac_2O–AcONa of dihydrocorynantheic acid and its derivative lacking the methoxymethylene group. This cyclization yields acetoxylactams in which lactam formation has taken place between N_b and the carboxyl group accompanied by cleavage of the C-3-N_b bond with the introduction of an acetoxy group at C-3. The structures of the lactams are supported by spectroscopic evidence and degradative studies.

The second method required 7-acetoxy-7H-dihydrocorynantheine methiodide prepared by treating dihydrocorynantheine successively with lead tetraacetate and methyl iodide. 7-Acetoxy-7H-dihydrocorynantheine-N_b-methiodide is converted by the action of hot aqueous acetic acid-sodium acetate and extraction from strongly basic solution to 3-keto-3,4-*seco*-N_b-methyldihydrocorynantheine. Dihydroburnamicine was obtained by a three-step sequence from 3-keto-3,4-*seco*-N_a-methyldihydrocorynantheine and its mass spectrum is reported.

RECENT investigations have disclosed a surprisingly large number of indole alkaloids bearing an oxygen function at C-3. The majority of these are 2-acylindole derivatives which have been the subject of a recent review.[3] The ring systems of several 2-acylindole alkaloids are closely related to other indole alkaloids bearing the tetrahydro-β-carboline moiety. Thus the skeleton of vobasine[4] and its congeners is a 3-keto-3,4-*seco*-derivative of the ring system found in vellosimine,[5] macusine,[6] periclivine,[7] mauiensine[8] and sarpagine.[9] A similar relationship exists between burnamicine[10,11] and dihydrocorynantheol methochloride which were obtained from the same plant.[12] Another interesting example is picraphylline and akuammigine which also occur in the same plant.[13]

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[3] J. A. Weisbach and B. Douglas, *Chem. & Ind.* 623 (1965).

[4] U. Renner, D. A. Prins, A. L. Burlingame and K. Biemann, *Helv. Chim. Acta.* **46**, 2186 (1963); M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas, *Tetrahedron Letters* No. 2, 53 (1963).

[5] H. Rapoport and R. E. Moore, *J. Org. Chem.* **27**, 2981 (1962).

[6] A. T. McPhail, J. M. Robertson and G. A. Sim, *J. Chem. Soc.* 1832 (1963).

[7] M. Cava, S. Talapatra, J. Weisbach, B. Douglas, R. Raffauf and J. Beal, *Tetrahedron Letters* No. 14, 931 (1965).

[8] P. J. Scheuer, M. Y. Chang and H. Fukami, *J. Org. Chem.* **28**, 2641 (1963).

[9] M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. Amai, P. Beak, N. V. Bringi and E. Wenkert, *J. Amer. Chem. Soc.* **84**, 622 (1962).

[10] M. F. Bartlett and W. I. Taylor, *J. Amer. Chem. Soc.* **85**, 1203 (1963).

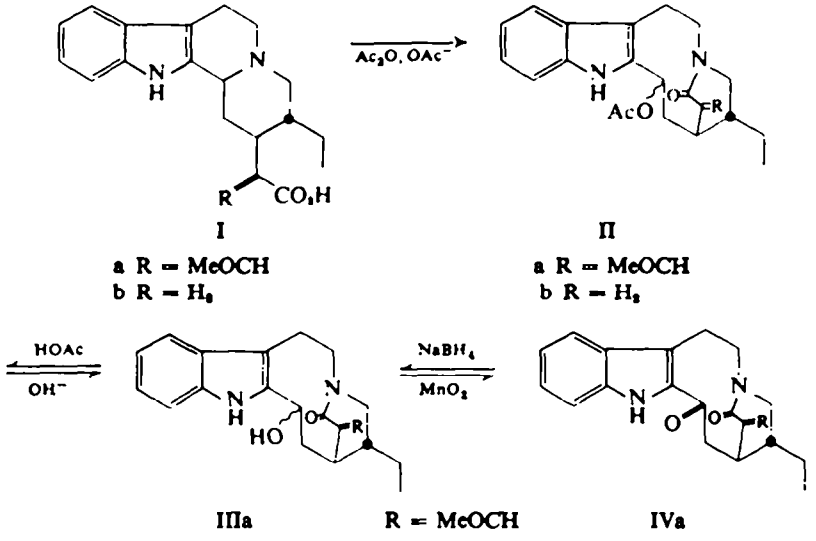
[11] M. F. Bartlett, R. Sklar, A. Smith and W. I. Taylor, *J. Org. Chem.* **28**, 2197 (1963).

[12] M. F. Bartlett, B. Korzun, R. Sklar, A. Smith and W. I. Taylor, *Ibid*, **28**, 1445 (1963).

[13] J. Levy, G. Ledouble, J. Le Men and M.-M. Janot, *Bull. Soc. chim. Fr.* 1917 (1964).

This relationship between these two classes of indole alkaloids suggests that tetrahydro-β-carbolines may be intermediates in the biosynthesis of some 2-acylindole alkaloids and perhaps the reverse is true as well. Several biogenetic proposals suggest 2-acylindoles as important intermediates.[13,14]

The synthesis of 2-acylindole alkaloid derivatives from the corresponding tetrahydro-β-carbolines is attractive for two reasons. This transformation might provide a model or at least an analogy for the biological process and tetrahydro-β-carbolines are relatively easy to synthesize. One method we find for effecting the desired transformation is the cyclization reaction shown below.



I
a R = MeOCH
b R = H

II
a R = MeOCH
b R = H

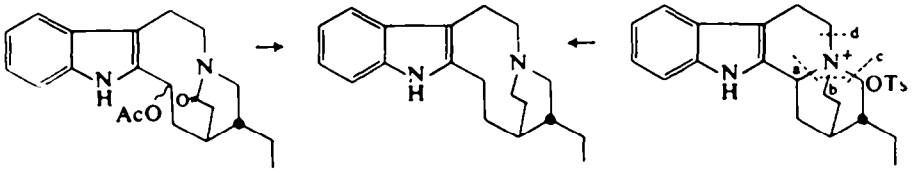
IIIa IVa

The acetoxylactams, IIa and b, were obtained in 46 and 35% yields respectively from dihydrocorynantheic acid and its derivative Ib. The proposed structures of IIa and b are supported by the following observations. The UV spectrum of IIa shows a combination of indole and α-methoxymethylene carbonyl chromophores as observed for dihydrocorynantheine and IIb shows a typical indole UV spectrum. Both the IR and NMR spectra of IIa and b are consistent with the proposed structures (Experimental). Saponification of IIa and b yielded the corresponding hydroxylactams, IIIa and b, but only the one derived from dihydrocorynantheic acid was obtained in crystalline form. The hydroxyl group of the hydroxylactam IIIa proved to be extremely reactive. Acetylation of the hydroxyl group took place in 10% AcONa–AcOH at room temperature to regenerate IIa and the action of 5% AcOH–MeOH converted IIIa to the corresponding methyl ether. The hydroxyl group in both hydroxy lactams was placed at C-3 since both compounds afforded 2-acylindoles upon manganese dioxide oxidation, but again only the compound derived from dihydrocorynantheic acid was obtained in crystalline form. The action of sodium borohydride on the ketolactam IVa yielded the parent alcohol in nearly quantitative yield.

The location of the acetoxy group of the acetoxylactams IIa and b establishes that the action of acetic anhydride on these dihydrocorynantheine derivatives results in cleavage of the C—D ring juncture. The nature of the ring system in these compounds

[14] G. F. Smith, *Chem. & Ind.* 1120 (1961).

was established by LAH reduction of the acetoxylactam IIb. This reaction afforded an oxygen-free base which was also obtained from LAH reduction of the known quaternary ammonium salt 6.[15] Structure V is proposed for this new base from its



IIa V VI

method of synthesis and its NMR spectrum. The LAH reduction of the quaternary ammonium salt VI could have cleaved any one of the four bonds a, b, c, or d. Cleavage of bond b would have produced dihydrocorynantheane but this possibility was ruled out by direct comparison of VI with an authentic sample of dihydrocorynantheane.[16] Of the three remaining possibilities, rupture of bonds c or d would have produced a second C-methyl group whereas cleavage of bond a is the only pathway that does not result in a new C-methyl group. The NMR spectrum of the base V shows a triplet at τ 9·05 corresponding to only three protons using the aromatic proton absorption (four protons) as an internal standard. The presence of two methyl groups in dihydrocorynantheane was readily apparent from its NMR spectrum.

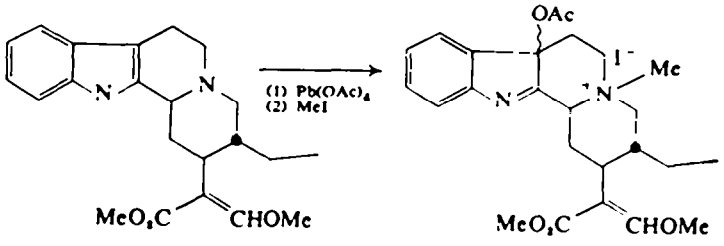
The combined chemical and spectroscopic evidence provides firm support for the proposed structures IIa and b. However, we have no basis on which to assign the stereochemistry of the C-3 acetoxy groups in these materials. The detailed mechanism of the lactamization reaction is also open to question although the reaction is clearly related to the cleavage of tertiary benzyl amines by the action of acetic anhydride[17] or ethyl chlorocarbonate.[18] A very similar reaction is the cleavage of the quinuclidine ring of cinchonamine by acetic anhydride to yield a N_b-acetyl-2-vinylindole derivative.[19] One possible pathway for the lactamization reaction involves a 2-alkylidene-2H-indole intermediate and we propose that the lithium aluminum hydride reductions of the acetoxylactam IIb and the quaternary ammonium salt VI do involve elimination to 2-alkylidene-2H-indole intermediates which suffer reduction to regenerate the indole system. Evidence regarding the lithium aluminum hydride hydrogenolysis of 2-indolecarbinol derivatives has been presented elsewhere.[20]

The ketolactam IVa appeared to be an attractive intermediate for the synthesis of dihydroburnamicine. The conversion to dihydroburnamicine would necessarily involve hydrolysis of the lactam ring which we were not able to bring about. We thought that the keto group would have to be protected or hydrolysis of the lactam ring would be followed by reclosure of the C—D ring to give 3-dehydro-19,20-dihydrocorynantheic acid. Accordingly the C-3 carbonyl group was converted to the ethylenedioxy derivative in the usual manner but all efforts to hydrolyze the lactam ring of this material met with failure. The development of another method for effecting the C—D

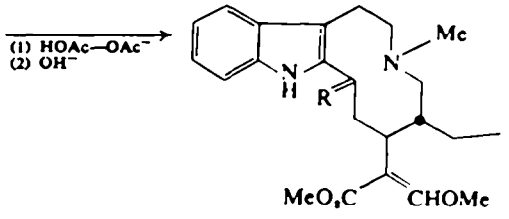
[15] E. Wenkert and N. V. Bringi, *J. Amer. Chem. Soc.* **81**, 1474 (1959).
[16] Prepared by the procedure of M.-M. Janot and R. Goutarel, *Bull. Soc. Chim. Fr.* 588 (1951).
[17] M. Tiffeneau, *Bull. Soc. Chim. Fr.* [4] **9**, 825 (1911).
[18] J. Knabe and U. R. Shulka, *Arch. Pharmaz.* **295**, 871 (1962), and Refs. cited therein.
[19] R. Goutarel, M.-M. Janot, V. Prelog and W. I. Taylor, *Helv. Chim. Acta.* **33**, 150 (1950).
[20] L. J. Dolby and D. L. Booth, *J. Org. Chem.* **30**, 1550 (1965).

ring cleavage of dihydrocorynantheine made the route from the ketolactam appear unattractive.

The second approach to the synthesis of 3-keto-3,4-*seco*-dihydrocorynantheine derivatives is outlined below. The action of lead tetraacetate in benzene solution



VII



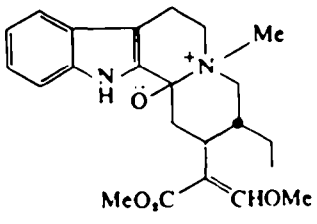
VIII R = O
IX R = OH, H

converts dihydrocorynantheine to the expected 7-acetoxy-7H-dihydrocorynantheine in 25% yields based on unrecovered dihydrocorynantheine. The acetoxyindolenine affords the N_b-methiodide VII upon exposure to methyl iodide in benzene solution. The desired 3-keto-3,4-*seco*-N_b-methyldihydrocorynantheine VIII was obtained in 55% yield from the acetoxyindolenine methiodide after treatment with boiling aqueous acetic acid containing sodium acetate and extraction from strongly alkaline solution.

The 2-acylindole VIII has several interesting properties. Its UV spectrum in ether solution shows normal 2-acylindole absorption (307 mμ; ε 14,800) which is changed to a dihydrocorynantheine spectrum upon the addition of acetic acid. In ethanol solution the material shows only the absorption expected for a combination of indole and α-methoxymethylenecarbonyl chromophores (dihydrocorynantheine). This spectacular solvent effect is ascribed to the formation of a dipolar species such as X in polar solvents. Such an interaction is expected from the elegant studies of Leonard *et al.*[21] The IR spectrum of VIII (chf) shows a strong band at 1640 cm^{-1} which is consistent with the 2-acylindole structure. The NMR spectrum ($CDCl_3$) exhibits a sharp signal at τ 8·36 attributed to the N-methyl group. That the N-methyl group should appear at such high field is not unexpected since the N-methyl group of protopine[22] appears at τ 8·08 and the N-methyl group of picraphylline[13] is found at τ 8·0.

[21] N. J. Leonard, J. A. Adamacik, C. Djerassi and O. Halpern, *J. Amer. Chem. Soc.* **80**, 4858 (1958) and previous papers in the series.

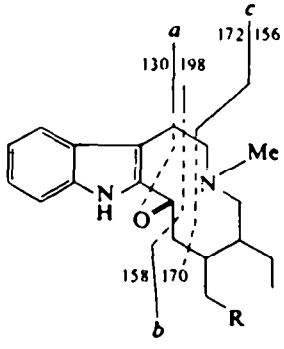
[22] N. S. Bhacca, L. F. Johnson and J. N. Shoolery, *NMR Spectra Catalog* No. 339. Varian Associates, Palo Alto, California (1962).



X

The 3-keto-3,4-*seco*-N_b-methyldihydrocorynantheine was quite resistant to sodium borohydride reduction in aqueous methanol. This inertness is ascribed to the formation of the dipolar species X in polar solvents. In accord with this hypothesis the keto group was easily reduced by the action of sodium borohydride in 1,2-dimethoxyethane to afford the corresponding alcohol IX. The alcohol shows the expected dihydrocorynantheine UV spectrum and the absorption at 1640 cm^{-1} is absent. The NMR spectrum of the alcohol shows the N-methyl group shifted downfield to a normal value of τ 7·76.

Saponification and acid-catalyzed hydrolysis of 3-keto-3,4-*seco*-N_b-methyldihydrocorynantheine was accompanied by decarboxylation to furnish the ketoaldehyde XI. The IR spectrum of the ketoaldehyde XI showed carbonyl absorptions at 1720 and 1640 cm^{-1} and it was used for the next step without deliberate purification. Dihydroburnamicine[23] XII was obtained from the ketoaldehyde in 50% yield by the action of sodium borohydride in aqueous methanol. The strong nitrogen —C-3 carbonyl interaction protects the keto group from reduction as previously observed. The dihydroburnamicine obtained in this manner shows a typical 2-acylindole UV absorption spectrum in ether solution and the spectrum is changed to that of an indole upon addition of acetic acid. In ethanol solution the spectrum appears to be a combination of 2-acylindole and indole spectra. The IR spectrum shows absorption at 1640 cm^{-1} and the NMR spectrum shows a sharp signal at τ 8·06 ascribed to the



XI R = CHO
XII R = CH_2OH

[23] A direct comparison of our material with the reduction product of authentic burnamicine was not possible since no burnamicine remained from structural studies. We wish to thank Dr. Taylor for a helpful discussion of this problem. It is not certain that dihydroburnamicine prepared from dihydrocorynantheine has the same absolute configuration at C-15 as authentic burnamicine but biogenetic considerations suggest that this should be the case.

N-methyl group. Dihydroburnamicine shows a pK_a' of 9·02 (50% MeOH–H_2O) which is very close to that reported for burnamicine.[10]

The mass spectrum of dihydroburnamicine[24] provides further confirmation of the proposed structure and it bears important similarities to the mass spectrum of the parent compound.[10] However, the mass spectrum of dihydroburnamicine is substantially simpler than that of burnamicine probably because the isolated double bond facilitates additional modes of fragmentation.

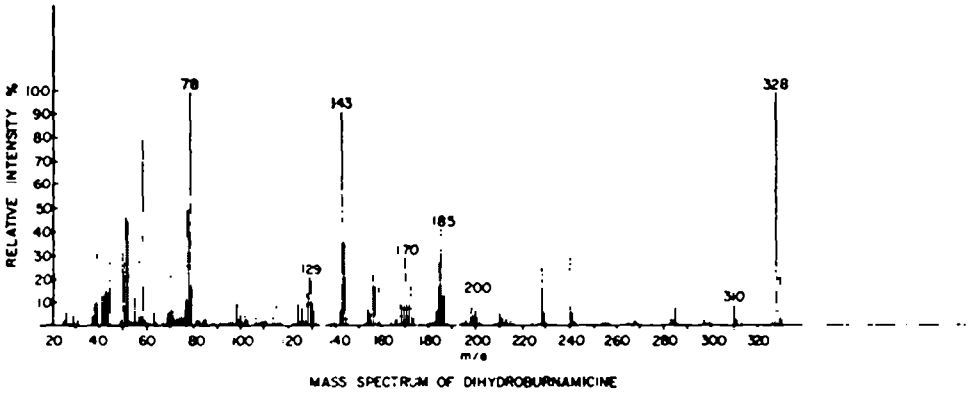


FIG. 1.

The anticipated fragmentations along lines a, b, and c are those observed for burnamicine.[10] Fission along a gives rise to peaks at $m/e = 128$, 129, and 130 undoubtedly arising from the indole residue. Similar peaks are also found in the mass spectrum of the 2-acylindole alkaloid picraphylline.[13] The peak at $m/e = 170$ may be considered to arise by cleavage along b and loss of carbon monoxide (mass 28) from the fragment of mass 198 formed from fission along a. The 170 peak corresponds to the peak at $m/e = 168$ in the mass spectrum of burnamicine. The peaks at $m/e = 143$ and 144 also correspond to peaks found in the mass spectra of both burnamicine and picraphylline.[10,13] Both burnamicine and dihydroburnamicine show a peak ($m/e =$ 308 and 310 respectively) which can be considered to arise from the loss of water. The peak at $m/e = 78$ in the mass spectrum of dihydroburnamicine is undoubtedly due to the presence of benzene in the sample. Dihydroburnamicine could only be crystallized from benzene which it retains tenaciously.

EXPERIMENTAL[25]

Acetoxylactam IIa. Dihydrocorynantheine hydrochloride (5·0 g) was heated with 2N KOH (100 ml) in aqueous MeOH for 3 hr. The solvent was evaporated under red. press. and the mixture was acidified to pH 6 with dil HCl. The amino acid was extracted with chf and the aqueous residue evaporated and leached with dry EtOH. The EtOH and chf extracts were combined and evaporated to afford crude dihydrocorynantheic acid suitable for the next step. This was heated under reflux for 1·5 hr with Ac_2O (50 g) and freshly fused AcONa (5·0 g). The cooled reaction mixture was neutralized with NH_4OH and extracted with chf. Evaporation of the chf afforded 4·4 g of the crude

[24] We are indebted to Dr. Taylor for the mass spectrum and his helpful comments.

[25] All m.p.'s are uncorrected. IR spectra: $CHCl_3$ soln, Beckman IR-5 IR spectrophotometer and UV spectra: Cary Model II spectrophotometer. Rotations: Perkin–Elmer Model 141 polarimeter, $c \approx 0·4$. PMR spectra: $CDCl_3$ soln, TMS as internal standard. Microanalyses: by Micro-Tech Laboratories, Skokie, Illinois.

acetoxyactam which was chromatographed on 150 g of activity III Woelm neutral alumina. Fractions of 50 ml were collected. Fraction 1 contained a trace of amorphous material and fractions 2–8 contained 2·27 g (46%) of the crystalline acetoxylactam, m.p. 168–170°. Continued elution with CH_2Cl_2 removed only a trace of amorphous material and successive elution with 50% acetone–CH_2Cl_2 and 15% MeOH–CH_2Cl_2 yielded 652 mg amorphous material which was not investigated. The analytical sample of the acetoxylactam showed m.p. 176–177° (dec) softening at 169° $[\alpha]_{5890}$ +492 (MeOH) after recrystallization from acetone. The UV spectrum was virtually identical with that of dihydrocorynantheine and the IR spectrum showed absorption at 1720, 1665, and 1608 cm^{-1}. The NMR spectrum showed a sharp signal at τ 8·03 ascribed to an acetoxy group. (Found: C, 69·56, 69·36; H, 7·27, 7·12; N, 7·25; mol. wt. 414, 440 (osmometer). $C_{23}H_{28}N_2O_4$ requires: C, 69·68; H, 7·07; N, 7·09%; mol. wt. 396.)

Hydroxylactam IIIa. The acetoxylactam (1·70 g) was dissolved in 5% NaOH (100 ml) in 50% aqueous MeOH and stored at room temp for 2 hr. Most of the MeOH was removed under red. press. and the residue extracted with chf. The extracts were washed with water, dried over $MgSO_4$ and evaporated to yield 1·20 g of the crude hydroxylactam. Crystallization from acetone afforded 0·790 g (52%) pure hydroxylactam, m.p. 150° (foam), $[\alpha]_{5890}$ +431°, MeOH. (Found: C, 70·89, 70·91, H, 7·41, 7·38; N, 8·29. $C_{21}H_{26}N_2O_3$ requires: C, 71·16; H, 7·39; N, 7·90.)

The hydroxylactam (40 mg) was stirred at room temp with AcOH (1 ml) and AcONa (100 mg) for 30 min. The usual workup yielded IIa in quantitative yield.

Ketolactam IVa. Active MnO_2 (10 g) was added to a stirred solution of 1·30 g hydroxylactam in 200 ml CH_2Cl_2 and 50 ml chf at room temp. After 15 hr, an additional 7·0 g MnO_2 was added and stirring was continued for 18 hr. The Mn_4O_9 was filtered off and evaporation of the solvent afforded the crude ketolactam which was crystallized from acetone to yield 660 mg (51%) pure material, m.p. 241° (dec) turning green at ca. 200°, $[\alpha]_{5890}$ +260° (MeOH); UV spectrum (EtOH) 313 μm (ε 12,700), 238 μm (25,500), 217 μm (26,900); IR maxima, 1667, 1640, and 1610 cm^{-1}. TLC showed the ketone to be free from starting material. (Found: C, 71·53; H, 6·84; N, 8·25. $C_{21}H_{24}N_2O_3$ requires: C, 71·57; H, 6·86; N, 7·95%.)

Acetoxylactam IIb. Dihydrocorynantheine (5·35 g) was hydrolyzed to the aldehyde ester[26,27] (3·0 g, 57%). The crude aldehyde ester was deformylated as described for the deformylation of geissoschizine[28] by the action of hot 2N KOH to yield 2·10 g Ib isolated as the hydrochloride. The amino acid hydrochloride was cyclized as described for dihydrocorynantheic acid to yield 1·80 g crude IIb which was chromatographed on 50 g grade III Woelm neutral alumina. Fractions of 20 ml were collected. Elution with CH_2Cl_2 yielded 83 mg amorphous material in the first 4 fractions Fraction 5, 200 mg, was partially crystalline and continued elution with CH_2Cl_2 yielded 750 mg (9·2% from dihydrocorynantheine) IIb, m.p. 194–195°. After crystallization from CH_2Cl_2–ether, the analytical sample had m.p. 197·5–198·5°, UV (EtOH), 294 mμ (ε 6,800), 290 μm (8,900) 283 μm (8,700) 224 μm (36,100), and IR maxima (chf) 1750 and 1640 cm^{-1}. The NMR spectrum showed a sharp signal at τ 7·97 ascribed to an acetoxy group. (Found: C, 71·36, 7·39; H, 7·13, 7·23; N, 7·87, 8·03. $C_{21}H_{26}N_2O_3$ requires: C, 71·16; H, 7·39; N, 7·90%.)

LAH reduction of the acetoxylactam IIb. Compound IIb (100 mg) was heated under reflux for 2·5 hr with 300 mg LAH in 20 ml THF. The reaction mixture was hydrolyzed and extracted with CH_2Cl_2 to afford 85 mg crude product which was chromatographed on 10 g grade II Woelm neutral alumina. Elution with 30% pet. ether (30–60°)–benzene removed a trace of amorphous material and yielded 16 mg (20%) V m.p. 178·5–179° after two crystallizations from MeOH. Elution with chf and 50% acetone–chf removed 11 mg amorphous material. The UV spectrum of V showed normal indole absorption and the NMR spectrum exhibited a triplet at τ 9·05 corresponding to 3 protons using the aromatic absorption (4 protons) in the region τ 2–3 as an internal standard. (Found: C, 80·81; H, 9·09; N, 9·75. $C_{19}H_{24}N_2$ requires: C, 80·80, H, 9·28, N, 9·92%.)

Quaternary ammonium salt VI. Dihydrocorynantheol was converted to VI, m.p. 315–317° (dec), after crystallization from dimethylformamide and MeOH–chf (lit.[16] m.p. 315–316°) as previously described.[16] (Found: C, 69·22; H, 7·10; N, 5·99. $C_{36}H_{38}N_2O_6S$ requires: C, 69·00; H, 7·13; N, 6·19%.)

LAH reduction of the quaternary ammonium salt VI. The quaternary ammonium tosylate (100 mg)

[26] J. P. Kutney and R. T. Brown, *Tetrahedron Letters* No. 26, 1815 (1963).

[27] A. Chatterjee and P. Karrer, *Helv. Chim. Acta.* **33**, 802 (1955).

[28] F. Pusieux, R. Goutarel, M.-M. Janot and A. LeHir, *C.R. Acad. Sci. Paris* **249**, 1369 (1959).

was heated under reflux with 300 mg LAH in anhydrous N-methylmorpholine. The usual workup afforded 55 mg (90%) of V m.p. 169–171° after crystallization from MeOH. The material was chromatographed as previously described to yield pure V, m.p. 178·5–179°, identical with the material prepared by reduction of IIb.

Methoxylactam. Compound IIa (800 mg) was heated under reflux for 3 hr with 1 ml AcOH and 20 ml MeOH. The soln was made alkaline with NH_4OH and extracted with chf. The combined extracts were washed to neutrality, dried over $MgSO_4$ and evaporated to yield 750 mg crude ether. This product was chromatographed on activity III Woelm neutral alumina. Elution with CH_2Cl_2 yielded 400 mg (52%) crystalline ether, m.p. 220–221° after crystallization from acetone. The IR spectrum showed no hydroxyl or acetate absorption and the UV spectrum was unchanged from that of the starting material. (Found: C, 71·23; H, 7·57; N, 7·46; OCH_3, 17·12; mol. wt. 343 (osmometer). $C_{22}H_{28}N_2O_3$ requires: C, 71·71; H, 7·66; N, 7·60; OCH_3, 16·85%; mol. wt. 368.)

Dioxolane derivative of IVa. The IVa (195 mg) was dissolved in 10 ml ethylene glycol and 50 ml dry benzene and treated with 15 mg *p*-toluenesulfonic acid monohydrate. The resulting soln was refluxed under a water take-off separator for 1 hr. The reaction mixture was then poured into 100 ml 3% Na_2CO_3aq and extracted with ether. The combined ether soln was washed with water, dried over $MgSO_4$ and evaporated to afford 184 mg crude dioxolane. This product was chromatographed over 10 g activity III Woelm neutral alumina. Fractions of 10 ml were collected. Elution with 50% benzene–CH_2Cl_2 (fractions 1–5) yielded 38 mg amorphous material which was not identified. Elution with pure CH_2Cl_2 (fractions 6–13) removed 110 mg (50%) of crystalline dioxolane, m.p. 156–158°, after recrystallization from abs EtOH or MeOH–water and drying at 80° *in vacuo*. The UV spectrum showed dihydrocorynantheine absorption. (Found: C, 69·78; H, 7·07; N, 7·09. $C_{23}H_{30}N_2O_4$ requires: C, 69·68; H, 7·12; N, 7·07%.)

7-Acetoxy-7-H-dihydrocorynantheine. Dihydrocorynantheine (4·75 g) in 100 ml dry benzene was treated with 6·06 g lead tetraacetate. The reaction mixture was stirred for 10 min after which it was filtered and washed with Na_2CO_3aq. The crude product was chromatographed on 200 g grade III Woelm neutral alumina and fractions of 100 ml were collected. Elution with 400 ml benzene yielded 1·046 g dihydrocorynantheine. Fractions 5 and 6 contained amorphous material (480 mg) and fractions 7–13 contained 7-acetoxy-7-H-dihydrocorynantheine, (1·621 g) which was crystallized twice from ether–pet. ether (30–60°) to yield 956 mg (23%) 7-acetoxy-7-H-dihydrocorynantheine, m.p. 180–181°, $[\alpha]_{5890}$ +142° (MeOH). Continued elution with benzene afforded some amorphous material which was not investigated. (Found: 67·65; H, 7·21; N, 6·85. $C_{24}H_{30}N_2O_5$ requires: C, 67·59; H, 7·09; N, 6·57%.)

7-Acetoxy-7-H-dihydrocorynantheine methiodide. The free base (1·0 g) in benzene (20 ml) was treated with 3 ml MeI. After 2 days the soln deposited 1·30 g (97%) crystalline methiodide, m.p. 206° (dec), $[\alpha]_{5890}$ +141 (MeOH), after 2 crystallizations from MeOH–ether. (Found: C, 52·15; H, 6·13; N, 4·78. $C_{24}H_{33}IN_2O_5$ 0·5 H_2O requires: C, 52·00; H, 5·94; N, 4·85%.)

3-Keto-3,4-seco-N$_b$-methyldihydrocorynantheine VIII. A soln of 1·14 g 7-acetoxy-7-H-dihydrocorynantheine methiodide in 40 ml 10% AcOH containing 164 mg AcONa was heated under reflux for 3 hr. The soln was made strongly alkaline with 50% NaOHaq and then extracted with benzene. The extracts were washed with water and evaporated to yield 513 mg crude VIII which was crystallized from ether to yield 432 mg (55%) pure VIII, m.p. 208–209°, $[\alpha]_{5890}$ −43° (dioxan). Another form, m.p. 153–155°, was sometimes obtained. The IR spectra (chf soln) of the two forms were indistinguishable. The IR spectrum showed maxima at 1695 and 1640 cm^{-1}. The UV spectrum (ether) 307 mμ (ε 14,800) 227 μm (36,400) changed to a typical indole spectrum upon addition of AcOH. In EtOH the UV spectrum was that of an indole derivative: 291 mμ (ε = 6,600) 282 (8,020) 221 (47,200) λ_{sh} 240 mμ (ε = 14,500). The compound had pK_a' 9·02 (50% MeOH–water). The NMR spectrum exhibited a sharp signal at τ 8·36 attributed to the N-methyl group. (Found: C, 69·41, 69·36; H, 7·60, 7·71; N, 7·27, 7·13; mol. wt. 385, 381 (potentiometric titration). $C_{23}H_{30}N_2O_4$ requires: C, 69·32; H, 7·59; N, 7·03%; mol. wt. 398·5.)

Sodium borohydride reduction of VIII. The 2-acylindole (50 mg) was treated with 50 mg $NaBH_4$ in 1,2-dimethoxyethane (10 ml) and stored at room temp for 2 hr. The usual workup afforded 45 mg (90%) IX, m.p. 179–180°, after crystallization from EtOH or acetone–pet ether (30–60°). The UV spectrum in EtOH or ether showed dihydrocorynantheine absorption and the N-methyl group appeared at τ 7·76 in the NMR spectrum ($CDCl_3$). (Found: C, 69·15; H, 8·01; N, 7·22. $C_{23}H_{32}N_2O_4$ requires: C, 68·97; H, 8·05; N, 6·99%.)

Ketoaldehyde XI. Compound VIII (1·30 g) was heated under reflux for 2·5 hr with 50 ml 2N KOH in 80% MeOH–water. The solvent was evaporated under red. press. and the residue treated with 110 ml 1N HCl with cooling. The resulting soln was heated under reflux for 3·5 hr after which it was cooled and made alkaline with 10% NaOH. The mixture was extracted with chf. The combined extracts were washed to neutrality, dried over $MgSO_4$ and the chf evaporated to yield 400 mg (38%) crude ketoaldehyde which was used without further purification. The IR spectrum showed absorption at 1720 and 1640 cm^{-1}.

Dihydroburnamicine. The ketoaldehyde (400 mg) was dissolved in 25 ml 80% MeOH–water and added during 10 min to a soln of $NaBH_{21}$ (400 mg) in 10 ml 80% MeOH–water with stirring at room temp and stirring was continued for 10 min. The mixture was diluted with water and extracted with chf. The soln was washed with water, dried over $MgSO_4$ and evaporated to yield 325 g crude dihydroburnamicine. This was chromatographed over 30 g Woelm basic alumina activity IV and 10 ml fractions collected. Fractions 1–17 eluted with CH_2Cl_2 contained 14 mg oil. Fractions 18–37, eluted with 1% MeOH–CH_2Cl_2, yielded 31 mg amorphous material. Elution with 1–5% MeOH–CH_2Cl_2 yielded 212 mg (53%) crystalline dihydroburnamicine contained in fractions 38–100. Continued elution with 5% MeOH–CH_2Cl_2 yielded 6 mg amorphous material contained in fractions 100–120. Fractions 38–100 were combined and crystallized from benzene to yield pure dihydroburnamicine, m.p. 101–103° $[\alpha]_{4886}$ +·245° (dioxan). The material retains benzene which is not removed by extended drying *in vacuo* at 60° (0·1 mm). The presence of benzene is apparent in the NMR spectrum which shows a sharp signal at τ 2·63 and the N-methyl group appears at τ 8·06. The UV spectrum (ether) shows normal 2-acylindole absorption, 307 mμ (ε 13,900), changed to a typical indole spectrum upon addition of AcOH. The UV (EtOH) shows 291 mμ (ε 7230) 282 (8,400) 274 (8,150) 220 (39,100) λ_{sh} 310 mμ (2,020). Two determinations of the pK_a' gave values of 8·96 and 9·08 (50% MeOH-water). Carbon analyses gave uniformly high values and N values were always low. This result is undoubtedly caused by the presence of benzene in the material. A representative analysis is presented below. (Found: C, 73·84; H, 8·52; N, 7·98. $C_{20}H_{28}N_2O_2$ requires: C, 73·14; H, 8·59; N, 8·53%.)

The picrate was prepared in the usual manner and crystallized from EtOH. It showed m.p. 216–220° (dec) with darkening from 190°. (Found: C, 55·85; H, 5·78; N, 12·30. $C_{26}H_{31}N_5O_9$ requires: C, 56·01; H, 5·60; N, 12·56%.)