836. *Buxus Alkaloids. Part V.*[1] *The Constitution of Cyclobuxoxazine, a New Skeletal Alkaloid Containing a Tetrahydro-oxazine Ring*

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Partition chromatography of the strong bases from *Buxus microphylla* Sieb. *et* Zucc. *var. suffruticosa* Makino yielded cyclobuxoxazine (I; $R^1 = R^2 = H$), $C_{27}H_{46}N_2O_2$, as a minor alkaloid. This alkaloid is unique in that it possesses a tetrahydro-oxazine ring. The structure elucidation of this alkaloid and its synthesis from dihydrocyclomicrophylline-F (II; $R^1 = R^2 = R^3 = H$) are described.

CYCLOBUXOXAZINE (I; $R^1 = R^2 = H$), $C_{27}H_{46}N_2O_2$, m. p. 245—246°, $[\alpha]_D$ +29°, is one of the minor alkaloids,* which were isolated by partition chromatography[1] on alumina deactivated with aqueous ethylamine of the strong-base fraction from *Buxus microphylla* Sieb. *et* Zuzz. *var. suffruticosa* Makino, and whose polarity is between those of cyclomicrophylline-B and -C.[1] This alkaloid had infrared bands for an intramolecularly hydrogen-bonded hydroxyl (2·92 μ, broad in carbon tetrachloride), a secondary amino (3·01 μ, sharp in potassium bromide disc), and a cyclopropyl methylene (3·28 μ in carbon tetrachloride), but its ultraviolet spectrum did not show any selective absorption above 205 mμ. The structural similarity of this alkaloid to the other known groups of alkaloids,

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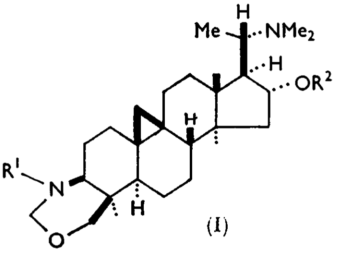
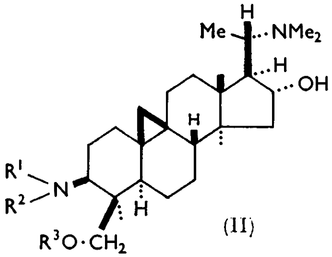
* Cyclobuxine-D[1] appeared in the same fraction as cyclobuxoxazine in this chromatography.

[1] Part IV, preceding Paper.

such as dihydrocyclomicrophylline-A (II; $R^1 = R^2 =$ Me, $R^3 =$ H), -C (II; $R^1 =$ Me, $R^2 = R^3 =$ H), and -F (II; $R^1 = R^2 = R^3 =$ H),[1] was indicated by its n.m.r. spectrum which showed peaks assignable to the 16β-proton (τ 5·92, septet, $J = 3·0$, 7·0, and 9·5 c./sec.) on the carbon attached to a secondary hydroxyl group, a 21-tertiary *C*-methyl (τ 9·12, $J = 7$ c./sec.), a cyclopropyl methylene (τ 9·68 and 9·38, AB doublets of $J = 4$ c./sec.), three quaternary *C*-methyls (τ 9·05, 8·97, and 8·86), and no olefinic protons. However, of interest was the observation that this spectrum did not contain any absorption due to hydroxymethylene protons, but instead showed four proton signals which appeared as a pair of AB quadruplets centred at τ 6·48 ($J = 11$ c./sec.) and 5·55 ($J = 10$ c./sec.), respectively. These signals are suggestive of a pair of methylene protons adjacent to the oxygen atom, and the greater deshielding of the methylene protons at τ 5·55 may be due to their proximity to both oxygen and nitrogen functions. This assumption was further supported by the fact that, while a quadruplet at τ 6·48 does not move appreciably to lower field (~0·02 p.p.m.) upon addition of monochloroacetic acid, that at τ 5·55 undergoes a great paramagnetic shift of ~0·39 p.p.m. under the same condition. Thus, one of the two oxygen atoms in cyclobuxoxazine must be present as an ether linkage, and the structure of cyclobuxoxazine is probably (I; $R^1 = R^2 =$ H).



(I)



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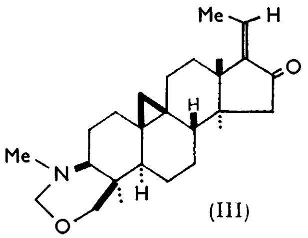

(III)

When treated with acetic anhydride–pyridine, cyclobuxoxazine yielded the *NO*-diacetate (I; $R^1 = R^2 =$ COMe), showing typical infrared bands for an *O*-acetyl (5·79 μ) and a tertiary *N*-acetyl (5·98 μ) group, and n.m.r. signals for the grouping CH_2–C*H*(OAc)–CH (τ 4·92, multiplet) and *N*-acetyl (τ 7·83). Hydrolysis of this *NO*-diacetate with aqueous methanolic potassium carbonate gave rise to the *N*-acetyl derivative (I; $R^1 =$ COMe, $R^2 =$ H). As is apparent from the n.m.r. spectra of the *NO*-diacetyl and the *N*-acetyl derivatives, introduction of the *N*-acetyl function causes a great downfield shift of 0·43 p.p.m. in the position of the methylene proton resonance at τ 5·55 in the parent alkaloid, whereas the corresponding methylene protons at τ 6·48 do not show any appreciable displacement (0·06 p.p.m.) to lower field.

Reduction of cyclobuxoxazine with lithium aluminium hydride in ether afforded dihydrocyclomicrophylline-C (II; $R^1 =$ Me, $R^2 = R^3 =$ H). Such a cleavage of the ether linkage[2] followed by the generation of a new methyl substituent at the nitrogen atom at C-3 and a primary hydroxyl group confirmed the presence of the grouping $-NH-CH_2-O-CH_2-$.

The absence of the 4-primary hydroxyl group in cyclobuxoxazine reflects itself on the alkaline hydrolysis of its *N*-acetyl derivative (I; $R^1 =$ COMe, $R^2 =$ H), which resulted in the recovery of starting material. This phenomenon is in marked contrast to the ease of the alkaline hydrolysis[1] of the *N*-acetyl derivatives of cyclomicrophylline-B and -C under the same conditions.

N-Methylation of cyclobuxoxazine with formic acid–formalin yielded the *N*-methyl derivative (I; $R^1 =$ Me, $R^2 =$ H), whose infrared spectrum showed the absence of the NH

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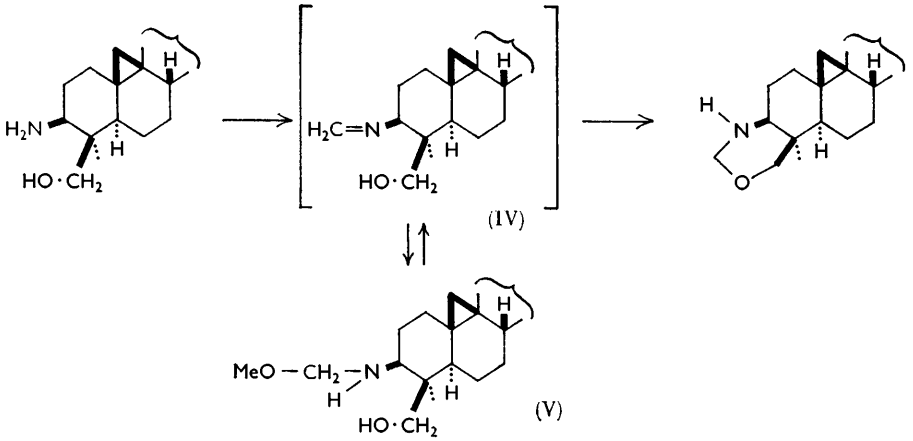
[2] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, 1956, pp. 807—817.

absorption. The formation of a new *N*-methyl group was clearly indicated by its n.m.r. signal at τ 7·82. Acetic anhydride–pyridine acetylation of this *N*-methyl derivative afforded the *O*-acetate (I; $R^1 = Me$, $R^2 = COMe$).

Oxidation of *N*-methylcyclobuxoxazine (I; $R^1 = Me$, $R^2 = H$) with chromium trioxide in acetic acid, and subsequent elimination of dimethylamine from the resultant amino-ketone by chromatography on alumina, furnished the *cis*-αβ-unsaturated cyclopentenone (III). On reductive cleavage with lithium aluminium hydride in ether, *N*-methylcyclobuxoxazine yielded dihydrocyclomicrophylline-A (II; $R^1 = R^2 = Me$, $R^3 = H$) in quantitative yield.



The synthesis of cyclobuxoxazine from a known related alkaloid was achieved in the following way. Addition of three molar equivalents of formalin to a suspension of dihydrocyclomicrophylline-F (II; $R^1 = R^2 = R^3 = H$) in warm dioxan produced a clear solution. After evaporation of the solution *in vacuo*, the residue was crystallised from methanol to yield the *O*-methyl ether (VI), whose n.m.r. spectrum showed a peak at τ 6·80 due to the methoxyl protons. This compound seems to have been formed by addition of methanol to the intermediate azomethine (V). Filtration of the *O*-methyl ether derivative (VI) in methylene chloride solution on alumina produced a mixture of cyclobuxoxazine and the azomethine (V), and the formation of the latter was clearly detected by a fairly strong sharp infrared band at 6·20 μ due to the C=N linkage. On the other hand, when the *O*-methyl ether (VI) in methylene chloride solution was allowed to stand in an alumina column for some time and then the product was eluted with ether, cyclobuxoxazine was obtained quantitatively.

Heating of dihydrocyclomicrophylline-F (II; $R^1 = R^2 = R^3 = H$) with formic acid–formalin yielded *N*-methylcyclobuxoxazine (I; $R^1 = Me$, $R^2 = H$) as the sole product, whereas treatment with formic acid–acetic anhydride furnished the corresponding *N*-formyl derivative (II; $R^1 = CHO$, $R^2 = R^3 = H$). The latter, on treatment with formic acid–formalin, gave *N*-methylcyclobuxoxazine and dihydrocyclomicrophylline-A (II; $R^1 = R^2 = Me$, $R^3 = H$) in a ratio of about 1 : 1. However, in this case, no less than 50% of starting material was recovered unchanged.

When the *N*-monoacetyl derivative (II; $R^1 = COMe$, $R^2 = R^3 = H$) was heated with formic acid–formalin in a sealed tube at 100° for 8 hours, the *O*-monoacetate (II; $R^1 = R^2 = Me$, $R^3 = COMe$) was obtained together with dihydrocyclomicrophylline-A. Apparently, the former was formed *via* the *N* ⟶ *O* acyl migration in the acidic medium. Heating of *N*-acetylcyclobuxoxazine (I; $R^1 = COMe$, $R^2 = H$) in a sealed tube at 100° for 48 hours provided, in good yield, *N*-methylcyclobuxoxazine (I; $R^1 = Me$, $R^2 = H$).

EXPERIMENTAL

Rotations are for chloroform solutions. Except where stated otherwise, infrared spectra were measured in potassium bromide discs. N.m.r. spectra were recorded on a Varian A-60 instrument at 60 Mc. for solutions in deuterochloroform with tetramethylsilane as internal reference; chemical shifts are quoted on the τ scale. Alumina for chromatography refers to Brockmann's standardised alumina.

Isolation of Cyclobuxoxazine (I; $R^1 = R^2 = H$) *and Cyclobuxine-D.*—The strong-base fraction[1] (150 g.) from *Buxus microphylla* Sieb. *et* Zucc. *var. suffruticosa* Makino was chromatographed on alumina deactivated with 10% (v/w) of 70% aqueous ethylamine, and the fraction eluted between cyclomicrophylline-B and -C was collected (5 g.). This fraction was rechromatographed in methylene chloride on alumina (activity grade III; 300 g.), and elution with methylene chloride–ether (4 : 1) gave a crystalline mass (860 mg.) which was shown to be a mixture of cyclomicrophylline-A and -B by the signal positions of the C-3 and C-20 *N*-methyl groups in its n.m.r. spectrum. Further elution with methylene chloride–ether (1 : 1) gave *cyclobuxoxazine* (380 mg.), m. p. 245—246° (from methylene chloride–hexane), $[\alpha]_D$ +29°, $\lambda_{max.}$ 2·92 (OH) and 3·01 μ (sharp, NH), $\lambda_{max.}$(CCl_4) 2·92 (broad, OH or NH) and 3·28 μ (CH stretching vibration due to cyclopropyl methylene), and no selective ultraviolet absorption in 95% ethanol down to 205 mμ. The n.m.r. spectrum exhibited peaks at τ 9·68 and 9·38 (2H, doublets, *J* 5 c./sec., cyclopropane), 9·05, 8·97, and 8·86 (9H, quaternary methyl), 9·12 (3H, doublet, *J* 7 c./sec., tertiary methyl), 7·76 (6H, *N*-dimethyl), 6·74 and 6·21 (2H, quadruplet centred at 6·48, *J* 11 c./sec., CH_2O), 5·94 (1H, multiplet, >C*H*–O), and 5·74 and 5·36 (2H, quadruplet centred at 5·55, *J* 10 c./sec., –N–C*H*$_2$–O) (Found: C, 75·2; H, 10·85; N, 6·3. $C_{27}H_{46}N_2O_2$ requires C, 75·3; H, 10·75; N, 6·5%).

Elution with ether–methanol (9 : 1) gave a material (2·3 g.) which crystallised from acetone to afford a crystalline mass (724 mg.). This was rechromatographed in methylene chloride on alumina (100 g.) deactivated with 70% aqueous ethylamine (5 ml.), and elution with methylene chloride and crystallisation from acetone furnished cyclobuxine-D, identified by m. p., mixed m. p., and infrared spectrum.

Elution with methylene chloride–methanol (9 : 1) gave, after crystallisation from acetone, cyclomicrophylline-C (260 mg.), identified by m. p., mixed m. p., and infrared spectrum.

Acetylation of Cyclobuxoxazine.—The alkaloid (50 mg.) was treated with acetic anhydride–anhydrous pyridine (1 : 4; 2·5 ml.) and the solution kept at room temperature overnight. After removal of the solvent *in vacuo*, the residue (62 mg.) was chromatographed on alumina (activity grade I; 3 g.), and elution with methylene chloride afforded the NO-*diacetyl derivative* (I; $R^1 = R^2 =$ COMe) (42 mg.) as needles, m. p. 240° (from acetone–hexane), $[\alpha]_D$ −35°, $\lambda_{max.}$ 5·84 (O·COMe) and 5·99 μ (N·COMe), τ 9·57 and 9·36 (2H, doublets, *J* 4·5 c./sec., cyclopropane), 9·03 (3H) and 8·90 (6H) (quaternary methyl), 9·19 (3H, doublet, *J* 6 c./sec., tertiary methyl), 8·03 (3H, *O*-acetyl), 7·86 (6H, *N*-dimethyl), 7·83 (3H, *N*-acetyl), 6·70 and 6·14 (2H, quadruplet centred at 6·42, *J* 11 c./sec., CH_2O), 5·62 and 4·70 (2H, quadruplet centred at 5·12, *J* 11 c./sec., Ac–N–C*H*$_2$–O), and 4·92 (1H, multiplet, >C*H*OAc) (Found: C, 72·45; H, 9·7; N, 5·25. $C_{31}H_{50}N_2O_4$ requires C, 72·35; H, 9·8; N, 5·45%).

Hydrolysis of NO-*Diacetylcyclobuxoxazine* (I; $R^1 = R^2 =$ COMe).—The diacetyl derivative (30 mg.) was heated under reflux with 3% methanolic potassium carbonate solution (10 ml.) for 30 min. Usual working up of the product and crystallisation from ethanol afforded the N-*acetyl derivative* (I; $R^1 =$ COMe, $R^2 =$ H) (23 mg.), m. p. 284—285°, $[\alpha]_D$ −28°, $\lambda_{max.}$ 2·94 (OH) and 6·00 μ (N·COMe), τ 9·60 and 9·38 (2H, doublets, *J* 4 c./sec., cyclopropane), 9·03, 8·90, and 8·88 (9H, quaternary methyl), 9·12 (3H, doublet, *J* 7 c./sec., tertiary methyl), 7·86 (3H, *N*-acetyl), 7·76 (6H, *N*-dimethyl), 6·71 and 6·16 (2H, quadruplet centred at 6·43, *J* 11 c./sec., CH_2O), 5·62 and 4·70 (2H, quadruplet centred at 5·16, *J* 11 c./sec., Ac–N–C*H*$_2$–O), and 6·00 (1H, multiplet, >C*H*OH) (Found: C, 73·55; H, 10·4; N, 5·7. $C_{29}H_{48}N_2O_3$ requires C, 73·7; H, 10·25; N, 5·95%).

Lithium Aluminium Hydride Reduction of Cyclobuxoxazine.—A solution of the alkaloid (40 mg.) in anhydrous ether (30 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (30 mg.) in anhydrous ether (30 ml.). After the addition, stirring was continued at room temperature overnight. The excess reagent was decomposed by ethyl acetate and the complex was treated with aqueous sodium sulphate solution. The ether layer was separated by decantation and dried over anhydrous sodium sulphate. Evaporation of the ether and crystallisation of the product from acetone–hexane afforded dihydrocyclomicrophylline-C (II; R^1 = Me, R^2 = R^3 = H) (34 mg.), identified by m. p., mixed m. p., and infrared spectrum.

Attempted Hydroylsis of N-*Acetylcyclobuxoxazine* (I; R^1 = COMe, R^2 = H).—The *N*-acetyl derivative (18 mg.) was refluxed with 5% methanolic potassium hydroxide solution (10 ml.) for 6 hr. Usual working up afforded the starting material (15 mg.).

N-*Methylation of Cyclobuxoxazine*.—The alkaloid (120 mg.) was heated with formic acid–formalin (1 : 1; 1 ml.) on a boiling-water bath for 6 hr. The product obtained in the usual way was crystallised from acetone–hexane, giving N-*methylcyclobuxoxazine* (I; R^1 = Me, R^2 = H) as needles (110 mg.), m. p. 201—202°, $[\alpha]_D$ +40°, $\lambda_{max.}$ 2·92 (OH) and 3·56 μ (NMe), τ 9·66 and 9·37 (2H, doublets, *J* 4·5 c./sec., cyclopropane), 9·03 (3H) and 8·88 (6H) (quaternary methyl), 9·12 (3H, doublet, *J* 7 c./sec., tertiary methyl), 7·75 (6H, *N*-dimethyl), 7·89 (3H, *N*-methyl), 6·86 and 6·24 (2H, quadruplet centred at 6·55, *J* 11 c./sec., CH_2O), 6·42 and 5·55 (2H, quadruplet centred at 5·98, –N–CH_2–O), and 5·90 (1H, multiplet, $\rangle$*CH*OH) (Found: C, 75·5; H, 10·95; N, 6·2. $C_{28}H_{48}N_2O_2$ requires C, 75·6; H, 10·9; N, 6·3%).

Acetylation of N-*Methylcyclobuxoxazine* (I; R^1 = Me, R^2 = H).—The *N*-methyl derivative (23 mg.) in acetic anhydride–pyridine (1 : 2; 3 ml.) was allowed to stand at room temperature overnight. The product was crystallised from actone–hexane to give N-*methyl*-O-*acetylcyclobuxoxazine* (I; R^1 = Me, R^2 = COMe) as plates (20 mg.), m. p. 204—205°, $[\alpha]_D$ +19°, $\lambda_{max.}$ 5·80 μ (O·COMe), τ 9·64 and 9·35 (2H, doublets, *J* 4 c./sec., cyclopropane), 9·03, 8·92, and 8·88 (9H, quaternary methyl), 9·19 (3H, doublet, *J* 6 c./sec., tertiary methyl), 8·04 (3H, *O*-acetyl), 7·90 (3H, *N*-methyl), 7·86 (6H, *N*-dimethyl), 6·87 and 6·24 (2H, quadruplet centred at 6·56, *J* 11 c./sec., CH_2O), 6·41 and 5·55 (2H, quadruplet centred at 5·98, *J* 8 c./sec., –N–CH_2–O), and 4·91 (1H, multiplet, $\rangle$*CH*OAc) (Found: C, 74·25; H, 10·4; N, 5·65. $C_{30}H_{50}N_2O_3$ requires C, 74·05; H, 10·35; N, 5·75%).

Oxidation of N-*Methylcyclobuxoxazine*.—The *N*-methyl derivative (25 mg.) in glacial acetic acid (5 ml.) was allowed to react with chromium trioxide (4 mg., 1·3 molar equivalents) in the minimum of water at room temperature for 2 days. The mixture was poured into water, made alkaline with solid potassium carbonate, and the product was extracted with methylene chloride. The extract after concentration was adsorbed on a column of alumina (activity grade I; 10 g.) and kept at room temperature for 30 min. Elution with methylene chloride afforded the cis-αβ-*unsaturated ketone* (III) (15 mg.) which formed needles, m. p. 201—203° (from methanol), $[\alpha]_D$ −67°, $\lambda_{max.}$ 5·82 (αβ-unsaturated five-membered-ring ketone) and 6·09 μ (double bond conjugated with carbonyl), $\lambda_{max.}$ (95% EtOH) 243 mμ (ε 9200), τ 9·56 and 9·26 (2H, doublets, *J* 4 c./sec., cyclopropane), 9·05, 8·86, and 8·67 (9H, quaternary methyl), 8·16 (3H, doublet, *J* 7·5 c./sec., vinyl methyl coupled with vinyl proton), 7·88 (3H, *N*-methyl), 6·85 and 6·22 (2H, quadruplet centred at 6·54, *J* 11 c./sec., CH_2O), 6·40 and 5·53 (2H, quadruplet centred at 5·97, *J* 8 c./sec., –N–CH_2–O), and 3·44 (1H, quadruplet, *J* 7·5 c./sec., vinyl proton coupled with vinyl methyl) (Found: C, 78·6; H, 9·75; N, 3·55. $C_{26}H_{39}NO_2$ requires C, 78·55; H, 9·9; N, 3·5%).

Lithium Aluminium Hydride Reduction of N-*Methylcyclobuxoxazine*.—The *N*-methyl derivative (40 mg.) in ether (30 ml.) was treated with lithium aluminium hydride (30 mg.) as described above, to give dihydrocyclomicrophylline-A (II; R^1 = R^2 = Me, R^3 = H) (35 mg.), identified by m. p. and infrared spectrum.

Synthesis of Cyclobuxoxazine.—To a suspension of dihydrocyclomicrophylline-F (II; R^1 = R^2 = R^3 = H) (70 mg.) in warm dioxan (10 ml.) was added 30% aqueous formaldehyde solution (0·01 ml., three molar equivalents). The mixture immediately turned to a clear solution, which was kept at 50—60° for a further 10 min. The solvent was removed *in vacuo* at 50—60°, and the residual solid was crystallised from methanol to afford the O-*methyl ether* (VI) (60 mg.) as plates, m. p. 203—205° (decomp.), τ 9·66 and 9·38 (2H, doublets, *J* 4 c./sec., cyclopropane), 9·03, 8·96, and 8·88 (9H, quaternary methyl), 9·12 (3H, doublet, *J* 7 c./sec., tertiary methyl), 7·75 (6H, *N*-dimethyl), 6·82 and 6·22 (2H, quadruplet centred at 6·52, *J* 11 c./sec., CH_2OH), 6·80 (3H, OCH_3), and 5·68 and 5·38 (2H, quadruplet centred at 5·53, *J* 8·5 c./sec., –N–CH_2–O) (Found: 72·4; H, 10·7; N, 6·25. $C_{28}H_{50}N_2O_3$ requires C, 72·7; H, 10·9; N, 6·05%). The *O*-methyl ether (45 mg.) in methylene chloride was filtered on a short column of alumina (activity grade I; 2 g.). Elution with ether gave a mixture of products whose infrared spectrum showed a fairly strong absorption band at 6·20 μ (N=C). This mixture presumably consisting of cyclobuxoxazine and the azomethine (V), was allowed to stand in methylene chloride on alumina (activity grade I; 10 g.) at room temperature for 1 hr. Elution with ether and crystallisation from hexane–methylene chloride gave cyclobuxoxazine (30 mg.), whose identity was established by direct comparison with a sample of natural cyclobuxoxazine (m. p., mixed m. p., and infrared spectrum).

Formation of N-*Methylcyclobuxoxazine from Dihydrocyclomicrophylline-F* (II; $R^1 = R^2 = R^3 = H$).—The alkaloid (100 mg.) in formic acid–formalin (9 : 1; 2 ml.) was heated on a boiling-water bath for 6 hr. The product was isolated by dilution with water, basification with solid potassium carbonate, and extraction with methylene chloride. It was dissolved in methylene chloride and the solution was filtered through alumina (10 g.). The solid product obtained crystallised from acetone–hexane to give *N*-methylcyclobuxoxazine (95 mg.), identified by m. p., mixed m. p., and infrared and n.m.r. spectra.

N-*Formylation of Dihydrocyclomicrophylline-F*.—The alkaloid (100 mg.) was heated with formic acid–acetic anhydride (1 : 5; 6 ml.) at 100° for 6 hr. The solution was poured into water and the extract was washed with 3% aqueous potassium carbonate and then water, dried over anhydrous sodium sulphate, and evaporated. The residue in methylene chloride was adsorbed on alumina (activity grade I; 10 g.) and elution with methylene chloride–ether (1 : 1) afforded the N-*formyl compound* (II; $R^1 = CHO$, $R^2 = R^3 = H$) (80 mg.) which crystallised from methanol to show m. p. 292—294°, $[\alpha]_D$ +7·1°, $\lambda_{max.}$ 2·96 and 3·10 (OH or NH), and 6·14 and 6·52 μ (NH·CHO), τ 9·66 and 9·45 (2H, doublets, *J* 4 c./sec., cyclopropane), 9·38, 9·02, and 8·86 (9H, quaternary methyl), 9·12 (3H, doublet, *J* 7 c./sec., tertiary methyl), 7·76 (6H, *N*-dimethyl), 7·01 and 6·58 (2H, quadruplet centred at 6·80, *J* 13 c./sec., CH_2OH), 6·00 (1H, multiplet, N*H*), and 1·83 (1H, singlet, N·C*H*O) (Found: C, 72·55; H, 10·45; N, 6·4. $C_{27}H_{46}N_2O_3$ requires C, 72·6; H, 10·4; N, 6·25%).

Reaction of N-*Formyldihydrocyclomicrophylline-F* (II; $R^1 = CHO$, $R^2 = R^3 = H$) *with Formic Acid–Formalin*.—The *N*-formyl compound (70 mg.) in formic acid–formalin (9 : 1; 1 ml.) was heated at 100° for 6 hr. The product was isolated by dilution with water and extraction with methylene chloride. Working up of the organic layer in the usual way afforded the starting material (30 mg.). The aqueous layer was basified with solid potassium carbonate and extracted with methylene chloride. Chromatography of the product on alumina (activity grade I; 3 g.) and elution with methylene chloride gave *N*-methylcyclobuxoxazine (14 mg.), identified by m. p., mixed m. p., and infrared spectrum. Further elution with ether afforded dihydrocyclomicrophylline-A (II; $R^1 = R^2 = Me$, $R^3 = H$) (12 mg.), identified by m. p., mixed m. p., and infrared spectrum.

Reaction of N-*Acetyldihydrocyclomicrophylline-F with Formic Acid–Formalin*.—A mixture of the *N*-acetyl derivative (110 mg.) and formic acid–formalin (9 : 1; 2 ml.) was heated in a sealed tube at 100° for 8 hr. The product was isolated by dilution with water, basification with aqueous ammonia, and extraction with methylene chloride. It was chromatographed in methylene chloride on alumina (activity grade I; 3 g.), and elution with the same solvent afforded the O-*monoacetate* (II; $R^1 = R^2 = Me$, $R^3 = COMe$) (40 mg.), m. p. 210—211° (from hexane–acetone), $[\alpha]_D$ −47°, $\lambda_{max.}$ 2·94 (OH) and 5·74 μ (O·COMe), τ 9·69 and 9·46 (2H, doublets, *J* 4 c./sec., cyclopropane), 9·23, 9·03, and 8·86 (9H, quaternary methyl), 9·12 (3H, doublet, *J* 7 c./sec., tertiary methyl), 7·94 (3H, *O*-acetyl), 7·76 and 7·73 (12H, *N*-dimethyl), 6·16 and 5·73 (2H, quadruplet centred at 5·95, *J* 10·5 c./sec., CH_2OAc), and 6·00 (1H, multiplet, $>CHOH$) (Found: C, 73·65; H, 10·85; N, 5·65. $C_{30}H_{52}N_2O_3$ requires C, 73·7; H, 10·7; N, 5·75%).

Further elution with ether gave dihydrocyclomicrophylline-A (II; $R^1 = R^2 = Me$, $R^3 = H$) (50 mg.), identified by m. p., mixed m. p., and infrared spectrum.

Reaction of N-*Acetylcyclobuxoxazine* (I; $R^1 = COMe$, $R^2 = H$) *with Formic Acid–Formalin*.—The *N*-acetyl derivative (15 mg.) and formic acid–formalin (9 : 1; 1 ml.) in a sealed tube were heated at 100° for 48 hr. Isolation of the product in the usual way gave *N*-methylcyclobuxoxazine (I; $R^1 = Me$, $R^2 = H$) (10 mg.), identified by m. p., mixed m. p., and infrared spectrum.

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