Analogues of Hepatotoxic Pyrrolizidine Alkaloids: Synthesis and Esterification of 1-Methyl-2,3-bishydroxymethyl-pyrrolidines and -3-pyrrolines (Synthanecines) and Corresponding Pyrrole Derivatives

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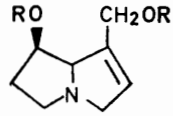
Several 2,3-bishydroxymethyl-pyrrolidine and -3-pyrroline derivatives (synthanecines) have been prepared as monocyclic analogues of the bicyclic necine bases which constitute the alcohol portions of many pyrrolizidine alkaloids. Thus, reduction of 2,3-bisethoxycarbonyl-1-methyl-3-pyrroline (IX) and of 2,3-bisethoxycarbonyl-4-methoxy-1-methyl-3-pyrroline (XII) with lithium aluminium hydride gives mainly the pyrrolidine (XI) (synthanecine B) while reduction using di-isobutylaluminium hydride gives the pyrrolines (X) and (XIII) (synthanecines A and C, respectively). Some of the unsaturated synthanecine esters, such as the carbamate (XVII) have biological effects similar to those of the toxic pyrrolizidine alkaloid monocrotaline (IV). Dehydrogenation of the 3-pyrroline diesters (IX) and (XII) and reduction of the resulting pyrrole diesters (XXI) and (XXII) provides the corresponding bishydroxymethylpyrroles (XXIII) and (XXV), which behave as bifunctional alkylating agents.

MANY pyrrolizidine alkaloids which are esters of unsaturated necine bases such as retronecine (I) [1] are toxic to various animal species, causing damage to the liver and sometimes the lungs and other organs.[2,3] The acid portions of the natural alkaloids are often complex, as in monocrotaline (IV) but simpler, semisynthetic esters such as di-isovalerylretronecine (II) [4] can cause similar toxic effects when given in larger doses [5] and the dicarbamate (III) is more active, having about the same toxicity to rats as monocrotaline.[6]

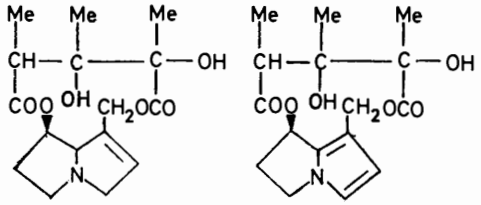
Synthetic analogues of the toxic alkaloids were required for metabolic and toxicological studies. A synthesis of retronecine (I) has been described [7] but it is lengthy and the overall yield is poor (<1%). There is much evidence that many or all of the toxic effects of pyrrolizidine alkaloids in animals are due to dihydropyrrolizine esters formed by metabolic dehydrogenation of the unsaturated (pyrroline) ring.[3,8] Thus, monocrotaline (IV) would be metabolised in rat liver to labile didehydromonocrotaline (monocrotaline pyrrole) (V).[9] The saturated ring in the didehydropyrrolizidine nucleus is not involved in metabolism to a toxic pyrrolic intermediate and hence could be omitted. This has led, as mentioned in a preliminary report,[6] to the preparation of a series of monocyclic analogues of the necine bases, which have been called synthanecines.[10] Thus, synthanecine A is 2,3-bishydroxymethyl-1-methyl-3-pyrroline (X), synthanecine B is the corresponding saturated

[1] F. L. Warren in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, London, 1970, vol. XII, p. 245.
[2] E. K. McLean, *Pharmacol. Rev.*, 1970, **22**, 429.
[3] A. R. Mattocks in 'Phytochemical Ecology,' ed. J. B. Harborne, Academic Press, London, 1972, p. 179.
[4] A. R. Mattocks, *J. Chem. Soc.* (*C*), 1969, 2698.
[5] R. Schoental and A. R. Mattocks, *Nature*, 1960, **185**, 842.
[6] A. R. Mattocks, *Nature*, 1971, **232**, 476.
[7] T. A. Geissman and A. C. Weiss, *J. Org. Chem.*, 1962, **27**, 139.
[8] A. R. Mattocks, *Chem.-biol. Interactions*, 1972, **5**, 227.
[9] A. R. Mattocks, *J. Chem. Soc.* (*C*), 1969, 1155.
[10] A. R. Mattocks in 'Proceedings of 5th International Congress on Pharmacology,' ed. T. A. Loomis, Karger A.G., Basel, 1973, vol. 2, p. 114.

(pyrrolidine) compound (XI), and synthanecine C is the 4-methoxy-derivative (XIII).

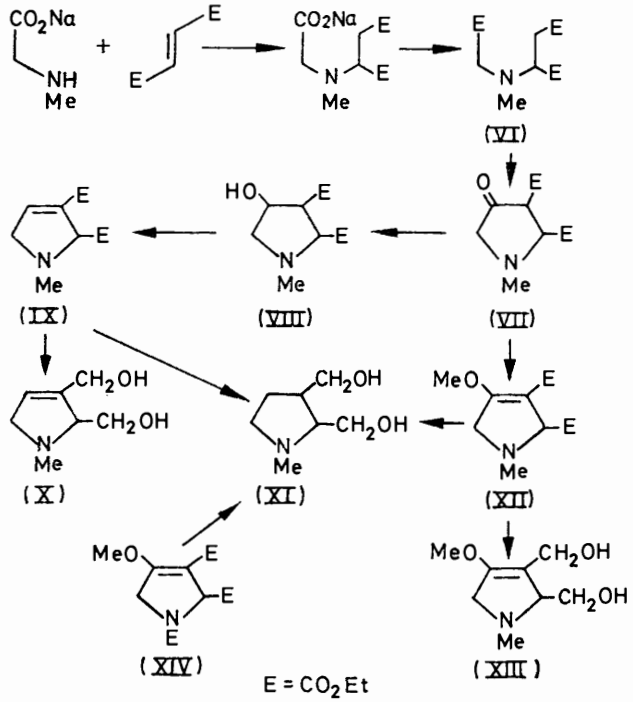


(I) R=H
(II) R=$COCH_2CHMe_2$
(III) R=CONHEt



(IV) (V)

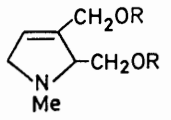
The key intermediate, 2,3-diethoxycarbonyl-1-methyl-4-pyrrolidone (VII), resulted from Dieckmann cyclisation of the triester (VI), which was prepared by reaction of diethyl fumarate with sodium sarcosinate followed by



E = CO_2Et

esterification (sarcosine ester failed to react with diethyl fumarate). The overall yield of crude (VII) was 40%. Reduction of (VII) with sodium borohydride gave the hydroxypyrrolidine (VIII) which was dehydrated in pyridine using phosphoryl chloride or (better) tosyl chloride to the pyrroline diester (IX). The latter, when crude, always contained some starting material which was readily distinguished and assayed by its *N*-methyl n.m.r. signal (δ 2·44 compared with 2·53 for the required product) and separated by fractional distillation. With diazomethane, (VII) gave the enol ether (XII) which was isolated as its picrate.

Reduction of the pyrroline (IX) with lithium aluminium hydride (LAH), lithium borohydride, or sodium dihydrobis-(2-methoxyethoxy)aluminate led to mixtures containing predominantly synthanecine B (XI). However, reduction with di-isobutylaluminium hydride gave good yields of the required synthanecine A (X). Similarly, when the methoxy-compound (XII) was treated with lithium aluminium hydride the main product was (XI), whereas reduction with di-isobutylaluminium hydride gave synthanecine C (XIII). The overall yields of crude synthanecines A and C from the crude pyrrolidone (VII) were *ca.* 21 and 40%, respectively.



(XV) R = COC(Me)(Et)OMe
(XVI) R = $PO(OEt)_2$
(XVII) R = CONHEt
(XVIII) R = $CONMe_2$
(XIX) R = $CONEt_2$
(XX) R = CO_2Ph

Synthanecine B (XI) was also made by lithium aluminium hydride reduction of 4-methoxy-1,2,3-trisethoxycarbonyl-3-pyrroline (XIV), which was prepared from diazomethane and 1,2,3-trisethoxycarbonyl-4-pyrrolidone. The latter, previously described as an oil,[11,12] was obtained crystalline.

Synthanecines A—C and their esters were intractable gums which were best separated on alumina by ascending dry column chromatography (*cf.* ref. 13) and purified and characterised as their picrolonates. A series of esters of synthanecine A prepared by conventional methods, for biological studies, included the bis-2-methoxy-2-methylbutyrate (XV) and the bis(diethyl phosphate) (XVI). The carbamates (XVII)—(XIX) were prepared from the bis(phenyl carbonate) (XX) and the appropriate amines, while the dicarbamate (XVII) was also formed from synthanecine A and ethyl isocyanate, the amino-alcohol itself acting as basic catalyst.

Spectra.—In their n.m.r. spectra the unsaturated synthanecines and their esters were easily distinguished from the saturated derivatives by their lower field *N*-methyl signals (δ 2·45—2·52 compared with 2·32—2·40 for the pyrrolidines), and by the characteristic H-4 signal at δ 5·7—6·0 (except synthanecine C which showed an OMe singlet at 3·71). In synthanecine A (X) the 3-CH_2 signal was a singlet, δ 4·20, changed to 4·6—4·9 in the esters [and split to a doublet (*J* 8 Hz) in the phosphate (XVI)]. The 2-CH_2 group gave a doublet, δ 3·66 (*J* 3 Hz) changed to 4·1—4·4 (*J* 4—5 Hz) in the esters [two pairs of doublets in (XV) and (XVII) *]. The H-2 and -5 signals were multiplets, δ 3·1—3·6, often very difficult to distinguish in 60 MHz spectra.

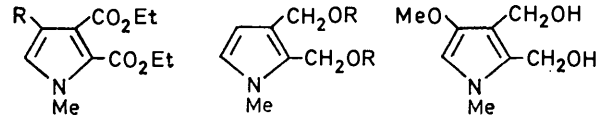
* These are attributed to non-equivalence of these protons due to restricted rotations of the C–CH_2– ester system (J_{AB} 11 Hz). Similar splittings have been observed for the 9-protons in some pyrrolizidine ester alkaloids (L. B. Bull, C. C. J. Culvenor, and A. T. Dick, 'The Pyrrolizidine Alkaloids,' North Holland, Amsterdam, 1968, p. 44).

[11] R. Kuhn and G. Osswald, *Chem. Ber.*, 1956, **89**, 1423.
[12] H. Rapoport and C. D. Willson, *J. Amer. Chem. Soc.*, 1962, **84**, 630.
[13] B. Loev and M. M. Goodman, *Chem. and Ind.*, 1967, 2026.

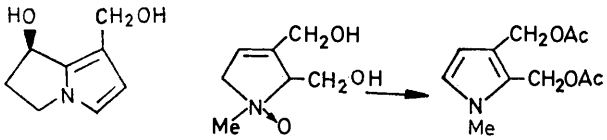
In the i.r. spectra, all the *N*-alkyl-pyrrolidines and -pyrrolines examined showed a characteristic band at 2790—2800 cm^{-1}. This was not seen in the corresponding pyrroles or *N*-acyl derivatives, or in the pyrrolizidine series, and was attributed to the 5-methylene group.

Pyrrole Derivatives.—The unsaturated synthanecines (A and C) and their esters could be converted into the corresponding pyrrole derivatives by the methods previously employed for dehydrogenation of unsaturated pyrrolizidine alkaloids.[9,14] When their chloroform solutions were treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), or heated with chloranil, and then Ehrlich reagent [15] was added, intense magenta colours were produced. They could be detected on t.l.c. by spraying with Ehrlich reagent following dehydrogenation to pyrroles with iodine vapour.[14]

The best preparative route to the bishydroxymethylpyrroles (XXIII) and (XXV) was lithium aluminium hydride reduction of the 2,3-bisethoxycarbonyl-1-methylpyrroles (XXI) and (XXII) which were made by dehydrogenation of the pyrrolines (IX) and (XII) with DDQ. Like didehydroretronecine (retronecine pyrrole) (XXVI),[9] the pyrrole alcohols (XXIII) and (XXV) gave intense colours with Ehrlich reagent ($\lambda_{max.}$ 570 and 546 nm respectively), formed red polymers in the presence of acid, and alkylated 4-*p*-nitrobenzylpyridine to blue derivatives. Their esters were more reactive alkylating agents than the alcohols and were unstable in the presence of acids and moisture. The bis-(*N*-ethylcarbamate) (XXIV) was prepared from the alcohol and ethyl



(XXI) R = H (XXIII) R = H (XXV)
(XXII) R = OMe (XXIV) R = CONHEt



(XXVI) (XXVII) (XXVIII)

isocyanate, while the labile diacetate (XXVIII) was prepared from synthanecine A *N*-oxide (XXVII) and acetic anhydride (*cf.* refs. 9 and 14). Like the pyrrolic derivatives of pyrrolizidine alkaloids, these esters were capable of cross-linking DNA *in vitro* [16] and of causing cytotoxic effects in rats.[3,6,10]

Several of the synthanecine esters including the carbamates (XVII)—(XIX) and the phosphate (XVI) were metabolically dehydrogenated to pyrrolic derivatives by rat liver *in vivo* and caused toxic effects in animals similar to if not identical with those produced by pyrrolizidine alkaloids.[6]

[14] C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Austral. J. Chem.*, 1970, **23**, 1853.

EXPERIMENTAL

M.p.s are corrected. I.r. spectra were recorded with a Perkin-Elmer 457 spectrophotometer for liquid films unless otherwise stated. Only bands useful for characterisation are listed. N.m.r. spectra were recorded at 60 MHz using Perkin-Elmer R10 or R12B spectrometers, using deuteriochloroform solutions unless otherwise stated. Extracts were dried using anhydrous sodium sulphate. T.l.c. was run on silica gel plates (Macherey–Nagel G25) using ethyl acetate–acetone–ethanol–aqueous ammonia (*d* 0·88) (5 : 3 : 1 : 1 v/v) as solvent. Hydroxymethylpyrroles were detected by spraying with an Ehrlich reagent containing boron trifluoride.[15] Hydroxymethyl-3-pyrrolines and their esters were detected by exposing the dried plate to iodine vapour,[14] then spraying with the Ehrlich reagent. Synthanecine A derivatives gave blue spots; synthanecine C derivatives gave magenta spots. Synthanecine B gave a brown spot with iodine (no Ehrlich colour).

Ehrlich Reaction.—To the pyrrole derivative, in diethylene glycol dimethyl ether or ethanol (1 ml) was added Ehrlich reagent containing boron trifluoride.[15] The solution was heated at 55—60° for 5 min, cooled, diluted with acetone, and the absorption spectrum of the magenta solution was recorded using a Unicam SP 800 spectrophotometer.

Alkylation Reaction.—To the pyrrole derivative (0·2—1·0 mg) in acetone (1 ml) was added 4-*p*-nitrobenzylpyridine (0·2—0·5 g) and water (0·2—0·5 ml), and the mixture was heated in a water-bath at 80—95° for 1 min, cooled, and triethylamine added. Development of a mauve or blue colour showed that the pyrrole was acting as an alkylating agent.[9]

Diethyl (N-*Ethoxycarbonylmethyl*)-2-*methylaminosuccinate* (VI).—A solution of sarcosine (89 g, 1 mol) and sodium hydroxide (40 g, 1 mol) in water (120 ml) was evaporated under reduced pressure and the thoroughly dried sodium salt was suspended in absolute ethanol (150 ml) and diethyl fumarate (172 g, 1 mol). The mixture was heated under reflux for 4 h, cooled in ice, saturated ethanolic HCl (500 ml) was added, and the milky suspension (containing NaCl) was saturated with dry HCl and kept at room temperature for 7 days. Most of the ethanol and HCl were removed under reduced pressure, the residue was taken up in water (300 ml), and the solution washed with ether (2 × 100 ml), basified with ammonia solution (cooling), and extracted with ether (3 × 200 ml). The basic extracts were dried and the solvent evaporated to give the crude *product* (165 g, 57%). Distillation gave an oil, b.p. 128—130° at 0·6 mmHg, n_D^{22} 1·4438 (Found: C, 54·1; H, 8·0; N, 4·6. $C_{13}H_{23}NO_6$ requires C, 54·0; H, 8·0; N, 4·8%); $\nu_{max.}$ 1730s cm^{-1} (ester), δ 1·24, 1·27, and 1·29 (3 × 3H, t, ester Me), 4·15, 4·17, and 4·20 (3 × 2H, q, ester CH_2), 2·46 (3H, s, NMe), and 3·43 (2H, s, NCH_2).

Diethyl 1-*Methyl*-4-*oxopyrrolidine*-2,3-*dicarboxylate* (VII).—A suspension of powdered sodium (4·1 g) in benzene (300 ml) and the crude triester (VI) (50 g) was stirred for 1 h, heated under reflux for 1 h, then cooled and shaken with 3 lots of water (100 + 20 + 20 ml). The combined aqueous extracts were washed with ether (2 × 50 ml), adjusted to pH 6·5 with HCl, extracted with chloroform (3 × 100 ml), and the chloroform extracts dried and concentrated to give the crude *pyrrolidone* (29·5 g, 70%). Distillation gave an oil, b.p. 120—140° at 1—2 mmHg, n_D^{21} 1·4615, $\nu_{max.}$ ($CHCl_3$)

[15] A. R. Mattocks, *Analyt. Chem.*, 1968, **40**, 1749.

[16] I. N. H. White and A. R. Mattocks, *Biochem. J.*, 1972, **128**, 291.

1740s (ester) and 1780m cm^{-1} (C=O), δ 1·30 (6H, t, ester Me), 4·25 (4H, q, ester CH_2), and 2·55 (3H, s, NCH_3). The *picrate* formed yellow prisms, m.p. 108° (from ethanol–ether) (Found: C, 43·2; H, 4·2; N, 12·1. $C_{17}H_{20}N_4O_{12}$ requires C, 43·2; H, 4·2; N, 11·9%). The *picrolonate* formed yellow blades (from ethanol), m.p. 148—149° (Found: C, 49·3; H, 4·8; N, 14·0. $C_{21}H_{25}N_5O_{10}$ requires C, 49·7; H, 4·9; N, 13·8%).

Diethyl 4-Hydroxy-1-methylpyrrolidine-2,3-dicarboxylate (VIII).—To a stirred solution of the crude pyrrolidone (VII) (50 g) in ethanol (400 ml), maintained at −5 to 0°, was added a solution of sodium borohydride (9 g) in ethanol (150 ml), portionwise, during 30 min. The mixture was kept at −5 to 0° for 2 h, then acidified with HCl (80 ml in 200 ml water) below −5°, and the ethanol removed under reduced pressure (rotary evaporator). The aqueous liquor was washed with ether (3 × 50 ml), basified with ammonia solution, and extracted with ether (3 × 100 ml). The combined basic extracts were dried and concentrated to give a brown oil (22 g, 44%). Distillation gave the *hydroxy-ester* as an oil, b.p. 126° at 0·4—0·5 mmHg, n_D^{22} 1·4608 (Found: C, 54·1; H, 7·9; N, 5·5. $C_{11}H_{19}NO_5$ requires C, 53·9; H, 7·8; N, 5·7%), $\nu_{max.}$ 3420m (OH) and 1730s cm^{-1} (ester), δ 1·28 (6H, t, ester Me), 4·19 (2H, q, 3-ester CH_2), 4·24 (2H, q, 2-ester CH_2), and 2·44 (3H, s, NMe). The *picrolonate* formed blades (from ethanol), m.p. 159—160° (Found: C, 49·2; H, 5·2; N, 13·8. $C_{21}H_{27}N_5O_{10}$ requires C, 49·5; H, 5·3; N, 13·7%).

Diethyl 1-Methyl-3-pyrroline-2,3-dicarboxylate (IX).—(a) To a solution of crude hydroxypyrrolidine (VIII) (15 g) in pyridine (60 ml) was added toluene-*p*-sulphonyl chloride (15 g) in pyridine (60 ml). The mixture was heated on a steam-bath for 20 min, then about two thirds of the pyridine was evaporated under reduced pressure (water pump) at 100°. To the residue was added water (60 ml) and hydrochloric acid (20 ml) and the solution was washed with ether (4 × 50 ml), basified with ammonia solution, extracted with ether (4 × 50 ml), and the dried (K_2CO_3) basic extracts concentrated, finally at 100°, under reduced pressure to remove pyridine, leaving an oil (13·1 g, 94%). Distillation through a short column of glass helices gave the pure *pyrroline*, b.p. 115—120° at 0·2—0·3 mmHg, n_D^{22} 1·4660 (Found: C, 57·8; H, 7·5; N, 6·1. $C_{11}H_{17}NO_4$ requires C, 58·1; H, 7·5; N, 6·2%), $\nu_{max.}$ 2800m (5-CH_2), 1735s (ester), and 1650w cm^{-1} (C=C), δ 1·27 (6H, t, ester Me), 4·19 (2H, q, 3-ester CH_2), 4·21 (2H, q, 2-ester CH_2), 2·53 (3H, s, NMe), 4·20 (1H, s, H-2), 3·5—4·0 (2H, m, H-5), and 6·90 (1H, t, H-4). Higher boiling distillates contained some starting material, easily assayed by its NMe signal at δ 2·44. The *picrate* formed leaflets (from ethanol), m.p. 135° (Found: C, 44·8; H, 4·3; N, 12·4. $C_{17}H_{20}N_4O_{11}$ requires C, 44·7; H, 4·4; N, 12·3%).

(b) To the crude hydroxy-ester (VIII) (5·4 g) in pyridine (40 ml) was added at 0° a solution of phosphoryl chloride (5·5 ml) in pyridine (20 ml). The mixture was allowed to warm to room temperature during 5 min, heated on a steam-bath for 1 min, then kept 30 min at room temperature. About two thirds of the pyridine was removed at 100° under reduced pressure and the residue was shaken with saturated aqueous sodium hydrogen carbonate (50 ml), extracted with ether (3 × 50 ml), and the extracts combined, dried, and concentrated to a brown oil (3·5 g, 70%) which was distilled as for (a).

Diethyl 4-Methoxy-1-methyl-3-pyrroline-2,3-dicarboxylate (XII).—A solution of diazomethane in ether was added portionwise to the pyrrolidone (VII) (30 g), in ether, until an excess was present as shown by a blue colour when a drop of the mixture was added to 4-*p*-nitrobenzylpyridine in acetone. The mixture was kept at room temperature overnight, the presence of an excess of diazomethane was confirmed, and the solvent was removed under reduced pressure. The resulting oil (30 g) was dissolved in ethanol (100 ml), picric acid (27 g) in acetone (100 ml) was added, and after concentrating and cooling the solution the *picrate* of the methoxypyrroline was collected (38 g, 67%). Recrystallisation from ethanol gave yellow prisms, m.p. 122° (Found: C, 44·3; H, 4·5; N, 11·6. $C_{18}H_{22}N_4O_{12}$ requires C, 44·4; H, 4·5; N, 11·5%). The picrate (5 g) in acetone–methanol, was passed through a column (30 × 2·5 cm) of anion-exchange resin (AG1 × 10; OH form). Concentration of the eluate gave the pyrroline as an oil (2·64 g, 100%), n_D^{21} 1·4880, reaction neutral to wet pH paper, $\lambda_{max.}$ (water) 250 nm; $\nu_{max.}$ 2800m (5-CH_2), 1730s (2-ester), 1690s (3-ester), and 1650s cm^{-1} (C=C), δ 1·23 (3H, t, 3-ester Me), 1·28 (3H, t, 2-ester Me), 4·16 (2H, q, 3-ester CH_2), 4·21 (2H, q, 2-ester CH_2), 2·52 (3H, s, NMe), 3·92 (3H, s, OMe), and 4·21 (1H, s, H-2).

Triethyl 4-Methoxy-3-pyrroline-1,2,3-tricarboxylate (XIV).—Triethyl 4-oxopyrrolidine-1,2,3-tricarboxylate, prepared according to Kuhn and Osswald [11] as modified by Rapoport and Willson,[12] crystallised after being kept in a deep-freeze, forming rectangular plates [from ether–light petroleum (b.p. 40—60°)], m.p. 52—54° (Found: C, 51·8; H, 6·4; N, 4·6. Calc. for $C_{13}H_{19}NO_7$: C, 51·8; H, 6·3; N, 4·6%), $\nu_{max.}$ (KBr) 3400w (OH, enol), 1780m (C=O), 1745s, 1718s (CO_2Et), 1675m, and 1635w cm^{-1}, δ 1·30 (9H, t, ester Me), 4·1—4·3 (8H, ester CH_2 and H-5), and 5·08 (1H, H-2).

This keto-ester, in ether, was treated with a solution of diazomethane in ether until effervescence ceased and a slight excess of (yellow) diazomethane was present. After 30 min the ether was evaporated to give the *methoxypyrroline* as a viscous oil (100%) which crystallised on keeping in a deep-freeze and formed plates, m.p. 68—69° [from ether–light petroleum (b.p. 40—60°)] (Found: C, 53·6; H, 6·6; N, 4·6. $C_{14}H_{21}NO_7$ requires C, 53·3; H, 6·7; N, 4·4%), $\nu_{max.}$ (KBr) 1745s (2-ester), 1700—1701s (1- and 3-ester), and 1645m (conj. C=C) cm^{-1}, δ 1·26 (9H, t, ester Me), 4·17 (6H, q, ester CH_2), 3·95 (3H, s, OMe), 4·49 (2H, d, *J* 3 Hz, H-5), and 5·10 (1H, t, *J* 3 Hz, H-2).

2,3-Bishydroxymethyl-1-methyl-3-pyrroline (*Synthanecine A*) (X).—To a solution of the diester (IX) (9·5 g) in toluene (60 ml) was added with stirring and cooling to 30—35° during 15 min a solution of di-isobutylaluminium hydride (DIBAH) (36 g) in toluene (75 ml). The solution was kept at room temperature for 1 h, ethyl acetate (15 ml) was added to consume the excess of DIBAH, followed after 5 min by acetone (150 ml) and Hyflo supacel filter-aid (30 g), then, very slowly with cooling to 30—35°, methanol (30 ml). The mixture was shaken vigorously until gelling occurred (*ca.* 5 min), then filtered (pump) and the residue washed with acetone (100 ml). The filtrates and washings were discarded. The solid residue was freed from solvents under reduced pressure, stirred with water (150 ml) during 30 min, then the water was evaporated (rotary) and the solids were extracted with hot chloroform containing 25% methanol (5 × 100 ml). The combined extracts were concentrated under reduced pressure to a gum which was re-extracted repeatedly with ether. The combined ether extracts were concentrated to give the crude amino-alcohol as a gum (4·28 g, 72%). The base formed a *picrolonate* as leaflets

(from ethanol), m.p. 176° (decomp.) (Found: C, 50·1; H, 5·4; N, 17·0. $C_7H_{13}NO_2,C_{10}H_8N_4O_5$ requires C, 50·1; H, 5·2; N, 17·2%). The *base*, recovered from the picrolonate using anion-exchange resin and purified by molecular distillation, was a gum, R_F 0·34 (Found: N, 9·8. $C_7H_{13}NO_2$ requires N, 9·8%), $\nu_{max.}$ 3330s,br (OH), 2790s (5-CH_2), and 1650w cm^{-1} (C=C), δ 2·46 (3H, s, NMe), 3·1 (1H, H-2), 3·4 (2H, H-5), 3·6—4·2 variable (2H, OH), 3·66 (2H, d, *J* 3 Hz, 2-CH_2), 4·20 (2H, s, 3-CH_2), and 5·75 (1H, H-4).

The *diacetyl* derivative, prepared from the base and acetyl chloride, was an oil, n_D^{20} 1·4640, b.p. 175—180° at 0·9—1·0 mmHg, R_F 0·81 (Found: N, 5·7. $C_{11}H_{17}NO_4$ requires N, 6·2%), $\nu_{max.}$ 2780m (5-CH_2) and 1740s cm^{-1} (ester), δ 2·08 (6H, s, acetyl Me), 2·52 (3H, s, NMe), 4·17 (2H, d, *J* 5 Hz, 2-CH_2), 4·67 (2H, s, 3-CH_2), and 5·85 (1H, s, H-4).

2,3-*Bis*-(*N*-*ethylcarbamoyloxymethyl*)-1-*methyl*-3-*pyrroline* (XVII).—(a) Synthanecine A (X) (0·5 g) was heated under reflux with ethyl isocyanate (3·5 ml) for 1 h, then the excess of reagent was removed under reduced pressure. The residue was dissolved in dilute HCl, the solution washed with ether, basified with ammonia solution, and extracted four times with ether. The combined basic extracts were dried and concentrated to give a viscous oil (0·7 g, 70%). This formed a *picrolonate* as needles (from ethanol), m.p. 122—123° (efferv.) (Found: C, 48·9; H, 5·6; N, 17·4. $C_{13}H_{23}N_3O_4,C_{10}H_8N_4O_5,H_2O$ requires C, 48·7; H, 5·8; N, 17·3%). The *base*, recovered from the picrolonate using anion exchange resin and purified by molecular distillation, was a water soluble gum, R_F 0·73 (Found: N, 14·3. $C_{13}H_{23}N_3O_4$ requires N, 14·7%), $\nu_{max.}$ 3330m (NH), 2790m (5-CH_2), and 1700s cm^{-1} (CO), δ 1·12 (6H, t, ethyl Me), 2·50 (3H, s, NMe), 3·20 (4H, double q, *J* 7, 7 Hz, reduced to q by deuterium exchange, ethyl CH_2), 3·5—3·7 (3H, m, H-2, -5), 4·01 and 4·27 (2H, 2 × 2d, *J* 4 Hz, 2-CH_2), 4·61 (2H, s, 3-CH_2), 5·35br (2H, NH), and 5·75 (1H, s, H-4).

(b) This carbamate was also prepared (30% yield) by the action of ethylamine on the bisphenylcarbonate (XX) (below).

Bis-(NN-*diethylcarbamate*) (XIX).—Phenyl chloroformate (2·5 ml) was added with stirring to a solution of compound (X) (1 g) in pyridine (12 ml). After 1 h at room temperature the mixture was diluted with water (20 ml) (ice-cooling), made acid (HCl), washed with 3 lots of ether, basified with ammonia solution (cooling), and extracted with ether (3 × 30 ml). The combined basic extracts were dried and concentrated under reduced pressure to give the crude bisphenylcarbonate (XX) as a viscous oil (2·8 g, 100%), R_F 0·76, $\nu_{max.}$ 3070w (arom.), 2790m (5-CH_2), and 1763s cm^{-1} (CO), δ 2·52 (3H, s, NMe), 3·4—3·8 (2H, m, H-5), 4·37 (2H, d, *J* 5 Hz, 2-CH_2), 4·90 (2H, s, 3-CH_2), 6·0 (1H, H-4), and 7·2—7·4 (10H, arom.).

This crude product (1·3 g) was dissolved in diethylamine (8 ml), kept 16 h at room temperature, then heated under reflux for 2 h, and the excess of amine removed at 100° under reduced pressure. The residue was dissolved in ether and the solution shaken for 1 min with N-sodium hydroxide (to remove phenol), then with water. The combined aqueous phases were re-extracted with ether and the extract combined with the original ether solution, dried, charcoaled, and concentrated under reduced pressure to give the *bis-diethylcarbamate* as an oil (0·865 g, 73%), R_F 0·80 (Found: C, 59·8; H, 9·3; N, 11·5. $C_{17}H_{31}N_3O_4$ requires C, 59·8; H, 9·1; N, 12·3%); $\nu_{max.}$ 2780m (5-CH_2) and 1700s cm^{-1} (CO); δ 1·12 (12H, t, ethyl CH_3), 2·49 (3H, s, N-Me), 3·28 (8H, q, ethyl CH_2), 4·10 (2H, d, *J* 5 Hz, 2-CH_2), 4·62 (2H, s, 3-CH_2), and 5·73 (1H, H-4). The *picrolonate* formed prisms (from ethanol), m.p. 116° (Found: C, 53·7; H, 6·4; N, 16·3. $C_{17}H_{31}N_3O_4,C_{10}H_8N_4O_5$ requires C, 53·6; H, 6·4; N, 16·2%).

Bis(*diethyl phosphate*) (XVI).—Diethylphosphoryl chloride [17] (5 g) was added slowly, with stirring, to a solution of compound (X) (1·5 g) in pyridine (20 ml). After standing at room temperature for 1·5 h the pyridine was removed at 100° under reduced pressure, benzene (20 ml) was added, and again evaporated under reduced pressure. The residue was dissolved in dilute HCl (30 ml) and the solution washed with chloroform (4 × 20 ml) (**Caution:** the extract contained highly toxic tetraethyl pyrophosphate). The aqueous phase was basified with ammonia solution, extracted with chloroform (3 × 20 ml) and the combined basic extracts dried and concentrated under reduced pressure to give a brown oil. This was dissolved in ether (30 ml), charcoaled, filtered, and the solvent removed to give the *bis*(*diethyl phosphate*) as a slightly viscous oil (Found: N, 3·9; P, 14·1. $C_{15}H_{31}NO_8P_2$ requires N, 3·4; P, 14·9%), $\nu_{max.}$ 2780m (5-CH_2), 1260s (P=O), 1165m (POEt), and 1020vs,br cm^{-1} ($POCH_2$), δ 1·34 (12H, t, ethyl Me), 2·51 (3H, s, NMe), 4·14 (8H, m, ethyl CH_2), 4·63 (2H, d, *J* 8 Hz, $3CH_2$), and 5·90 (1H, s, H-4).

Bis-(2-*methoxy*-2-*methylbutyrate*) (XV).–A suspension of sodium hydride (5·4 g) in dimethyl sulphoxide (120 ml) was stirred at 35—45° for 1 h before adding methyl 2-hydroxy-2-methylbutyrate [18] (10 g) and stirring at room temperature for 2 h. Methyl iodide (45 g) was added slowly, and the mixture stirred for 48 h at room temperature, then shaken with water (100 ml), and extracted with ether (3 × 80 ml). The combined extracts were dried, the ether removed at atmospheric pressure, and the residue distilled. The fraction, b.p. 152—160° (6 g), contained *ca.* 80% methyl 2-methoxy-2-methylbutyrate (i) and 20% unchanged hydroxy-ester (ii), δ 0·88 [t, Me, (i) + (ii)], 1·38 [s, C-Me, (i)], 1·40 [s, C-Me, (ii)], 3·28 [s, OMe, (i)], 3·76 [s, ester Me, (i)], and 3·80 [s, ester Me, (ii)].

This mixture was heated under reflux with sodium hydroxide solution (50 ml, 10%) for 1 h, cooled, washed once with ether, made acid (HCl), extracted with ether (3 × 50 ml), and the combined acid extracts dried and concentrated to give the mixed acids (4·2 g) as a viscous liquid. This was dissolved in benzene (5 ml), oxalyl chloride (4 ml) was added, and the mixture kept at 35—45° for 2·5 h, then fractionally distilled under reduced pressure to give 2-methoxy-2-methylbutyryl chloride (1·5 g, 32%), b.p. 63° at *ca.* 30 mmHg, n_D^{21} 1·4300, $\nu_{max.}$ ($CHCl_3$) 1780s cm^{-1} (CO), δ 0·94 (3H, t, Me), 1·46 (3H, s, CMe), 1·88 (2H, q, CH_2), and 3·35 (3H, s, OMe).

To a solution of compound (X) (0·2 g) in pyridine (5 ml) was added the above acid chloride (0·7 g). The mixture was kept 1 h at room temperature, then 20 min at 80—90°, poured into ice–water, made acid with HCl and washed with 3 lots of ether. The aqueous solution was basified with ammonia solution (cooling), extracted with chloroform (3 × 20 ml), the combined basic extracts dried, and the chloroform and pyridine removed at 100° under reduced pressure. The brown residue was dissolved in ether, charcoaled, and the solvent evaporated to give the bis-(2-methoxy-2-methylbutyrate) (XV) as an oil (0·29 g, 56%), $\nu_{max.}$ 2780m (5-CH_2) and 1735s cm^{-1} (CO), δ 0·88 (6H, t, Me), 1·39 (6H, s, CMe), 1·79 (4H, q, CH_2), 2·51 (3H, s, NMe), 3·28

[17] F. R. Atherton, H. T. Howard, and A. R. Todd, *J. Chem. Soc.*, 1948, 1106.
[18] A. R. Mattocks, *J. Chem. Soc.*, 1964, 1918.

(6H, s, OMe), 4·12 and 4·39 (2H, 2 × 2d, *J* 4 Hz, 2-CH_2), 4·75 (2H, s, 3-CH_2), and 5·85 (1H, s, H-4). The *picrolonate* formed blades (from ethanol–ether), m.p. 126—127° (Found: N, 11·3. $C_{19}H_{33}NO_6,C_{10}H_8N_4O_5$ requires N, 11·0%).

2,3-*Bishydroxymethyl*-4-*methoxy*-1-*methyl*-3-*pyrroline* (*Synthanecine C*) (XIII).—To a solution of 2,3-bisethoxycarbonyl-4-methoxy-1-methyl-3-pyrroline (4·9 g) in toluene (15 ml) was added portionwise, during 10 min, a solution of di-isobutylaluminium hydride (15·4 g, 6 equiv.) in toluene (55 ml). During the addition, spontaneous heating to reflux occurred. The mixture was heated for 20 min on a steam-bath, then decomposed with methanol (15 ml) with shaking and cooling to 25—35° until gelling occurred. The gel was broken up, the solvent removed under reduced pressure, and the solid powdered and washed twice with ethanol (pump), and the washings discarded. The powder was stirred with water (20 ml) for 30 min, dried under reduced pressure, and extracted with 4 lots of chloroform. The combined chloroform extracts were concentrated to give the crude amino-alcohol as a gum (2 g, 61%). T.l.c. showed the main component, synthanecine C, R_F 0·40, with small amounts of its corresponding pyrrole, R_F 0·48, as well as another pyrroline, R_F 0·33 and another pyrrole, R_F 0·71. The *picrolonate* formed blades (from ethanol), m.p. 143° (decomp.) (Found: C, 49·7; H, 5·3; N, 16·2. $C_8H_{15}NO_3,C_{10}H_8N_4O_5$ requires C, 49·4; H, 5·3; N, 16·0%), δ [$(CD_3)_2SO$–$CDCl_3$] 2·41 (3H, s, picrolonate Me), 3·02 (3H, s, NMe), and 3·76 (3H, s, OMe).

The base, recovered from the picrolonate using anion exchange resin in methanol, was a gum, $\nu_{max.}$ 3340s (OH) and 1690s cm^{-1} (C=C), δ 2·45 (3H, s, NMe), 3·3 (OH), 3·42 (H-5), 3·63 (2H, d, *J* 3 Hz, 2-CH_2), 3·71 (3H, s, OMe), and 4·2 (2H, m, 3-CH_2), no u.v. absorption above 215 nm (in H_2O).

2,3-*Bishydroxymethyl*-1-*methylpyrrolidine* (*Synthanecine B*) (XI).—(a) Compound (XII) (8·4 g) and lithium aluminium hydride (17 g) in ether (300 ml) were heated under reflux for 1 h. The cooled mixture was decomposed with dilute sodium hydroxide solution, the ether was decanted, and the wet solids stirred with hot ethanol (150 ml). Chloroform (50 ml) and Hyflo supacel (15 g) were added, the mixture filtered, and the filtrate concentrated to a gum which was re-extracted with hot chloroform. This extract together with the original ether was dried and the solvents evaporated to give a brown gum (4·8 g). This was converted to a *picrolonate* (7·6 g) which formed yellow needles (from ethanol), m.p. 192° (Found: C, 49·9; H, 5·7; N, 17·1. $C_7H_{15}NO_2,C_{10}H_8N_4O_5$ requires C, 49·9; H, 5·6; N, 17·1%). The *base*, recovered from the picrolonate using anion-exchange resin and purified by molecular distillation, was a gum, R_F 0·27 (Found: C, 57·9; H, 10·1; N, 9·8 $C_7H_{15}NO_2$ requires C, 57·9; H, 10·3; N, 9·7%), $\nu_{max.}$ 3340s (OH) and 2800s cm^{-1} (5-CH_2), δ 2·32 (3H, s, NMe), 3·5—3·6 (4H, 2- and 3-CH_2), and 4·3 (2H, s, OH). The *diacetate* was an oil, n_D^{22} 1·4580, b.p. 90° at 0·25 mmHg (Found: C, 57·3; H, 8·4; N, 6·4. $C_{11}H_{19}NO_4$ requires C, 57·6; H, 8·3; N, 6·1%), $\nu_{max.}$ 2780m (5-CH_2) and 1740s cm^{-1} (ester), δ 2·08 (6H, s, acetyl Me), 2·40 (3H, s, NMe), 4·04 (2H, d, *J* 6 Hz, 3-CH_2), and 4·15 (2H, d, *J* 5 Hz, 2-CH_2).

(b) Triethyl 4-methoxy-3-pyrroline-1,2,3-tricarboxylate (3 g) and lithium aluminium hydride (2 g) in tetrahydrofuran (THF) (30 ml) were heated under reflux for 4 h after the initial reaction had subsided. The mixture was cooled, decomposed with dilute sodium hydroxide solution, and filtered (pump). The solids were extracted with hot ethanol (20 ml), then chloroform (10 ml), the combined extracts evaporated to dryness, and the residue re-extracted with hot THF. This extract was combined with the THF filtrate from the reaction mixture and the solvent removed under reduced pressure to give the product as a gum (1 g, 73%), essentially the same (t.l.c. and spectra) as the crude product of (a).

Reduction of Pyrroline (IX).—(a) *With lithium aluminium hydride.* The pyrroline (IX) (1 g) was reduced in the way already described for the 4-methoxy-analogue to give a gum (0·39 g, 63%) which contained about equal amounts of 2,3-bishydroxymethyl-1-methyl-3-pyrroline and 2,3-bishydroxymethyl-1-methylpyrrolidine (synthanecines A and B) as shown by n.m.r. spectra (*N*-methyl signals at δ 2·46 and 2·32 respectively).

(b) *With lithium borohydride.* Anhydrous lithium bromide (1·2 g) was added to a solution of sodium borohydride (0·5 g) in diethylene glycol dimethyl ether (diglyme; 15 ml) and the mixture stirred for 10 min. The pyrroline (IX) (1 g) was added and the mixture was heated on a steam-bath for 1 h, cooled, poured into water (15 ml), and acidified dropwise with HCl. The solution was washed with ether, basified (Na_2CO_3), washed again with ether, evaporated to dryness, and the residue extracted with 3 lots of warm chloroform. The combined chloroform extracts were concentrated to give a gum which was re-extracted with ether. Evaporation of the ether gave a gum (0·23 g, 36%), shown to be 2,3-bishydroxymethyl-1-methylpyrrolidine (i.r. and n.m.r. spectra). The picrolonate had m.p. 189°, not depressed by mixing with the authentic synthanecine B picrolonate.

(c) *With sodium dihydrobis*-(2-*methoxyethoxy*)*aluminate.* To the pyrroline (IX) (1 g) in ether (50 ml) was added an excess of the reagent (5 ml of 70% solution in benzene). After the initial exothermic reaction, the solution was kept 15 min at room temperature and decomposed with enough dilute HCl (shaking) to give an acidic aqueous layer which was separated, washed with ether, made basic (Na_2CO_3), and evaporated to dryness under reduced pressure. The residue was extracted with chloroform (×3) and the combined extracts concentrated to a gum (0·36 g, 56%) which was found (i.r. and n.m.r.) to be mainly 2,3-bishydroxymethyl-1-methylpyrrolidine together with a small amount of unreduced starting material.

Diethyl 1-*Methylpyrrole*-2,3-*dicarboxylate* (XXI).—The pyrroline (IX) (3 g) was added to a part-solution, part-suspension of powdered DDQ (4 g) in warm chloroform (80 ml) and the mixture stirred at *ca.* 50° for 10 min. The chloroform solution was washed with aqueous potassium carbonate (10%; 4 × 20 ml), dried and concentrated under reduced pressure, and the residue distilled to give the *pyrrole* as a pale yellow oil (2·86 g, 96%), b.p. 128—131° at 0·6 mmHg, n_D^{22} 1·5020 (Found: C, 58·7; H, 6·5; N, 6·6. $C_{11}H_{15}NO_4$ requires C, 58·7; H, 6·7; N, 6·2%), $\nu_{max.}$ 3120w (ring) and 1703s cm^{-1} (ester), δ 1·31 (3H, t, ester Me), 1·33 (3H, t, ester Me), 3·81 (3H, s, NMe), 4·29 (2H, q, ester CH_2), 4·32 (2H, q, ester CH_2), 6·48 (1H, d, *J* 3 Hz, H-4), and 6·67 (1H, d, *J* 3 Hz, H-5).

Diethyl 4-*Methoxy*-1-*methylpyrrole*-2,3-*dicarboxylate* (XXII).—The pyrroline (XII) (3 g) was dehydrogenated using DDQ (4 g) in the same way as described above to give the crude *pyrrole* as an oil (2·55 g, 86%), b.p. 137—40° at 0·2 mmHg, n_D^{23} 1·5120 (Found: C, 56·1; H, 6·8; N, 5·1. $C_{12}H_{17}NO_5$ requires C, 56·5; H, 6·7; N, 5·5%), $\nu_{max.}$ 3108w, 3120w (ring), and 1710s cm^{-1} (ester), δ 1·33 (6H, t, ester

Me), 3·73 (3H, s, OMe), 3·78 (3H, s, NMe), 4·29 (2H, q, ester CH_2), 4·31 (2H, q, ester CH_2), and 6·30 (1H, s, H-5).

2,3-*Bishydroxymethyl*-1-*methylpyrrole* (XXIII).—The pyrrole (XXI) (1·5 g) was added to a suspension of lithium aluminium hydride (1·2 g) in anhydrous ether (50 ml) and the mixture was heated under reflux for 1·5 h, cooled, and decomposed with water (3—4 ml). After 15 min the mixture was filtered (pump) and the solid washed several times with chloroform. The combined organic filtrates were dried, and concentrated under reduced pressure to give the *product* (0·85 g, 91%) as an oil which crystallised when kept in a deep-freeze. Recrystallisation from ether gave prisms, m.p. 56—57°, R_F 0·49 (Found: C, 60·2; H, 7·9; N, 10·1. $C_7H_{11}NO_2$ requires C, 59·6; H, 7·8; N, 9·9%), $\nu_{max.}$ 3320br,s cm^{-1} (OH), δ 3·3br variable (2H, s, OH), 3·62 (3H, s, NMe), 4·45 (2H, s, 3-CH_2), 4·50 (2H, s, 2-CH_2), 6·10 (1H, d, *J* 3 Hz, 4-H), and 6·58 (1H, d, *J* 3 Hz, H-5). The compound, in ethanol, gave a magenta Ehrlich reaction, $\lambda_{max.}$ 570 nm (ε 71,900). The alkylation reaction gave an intense mauve colour.

2,3-*Bishydroxymethyl*-4-*methoxy*-1-*methylpyrrole* (XXV).—The pyrrole (XXII) (1·2 g) was reduced with lithium aluminium hydride (1·2 g) in the same way as described above, to give the *product* as a gum (0·56 g, 70%) which crystallised on rubbing with ether. Recrystallisation from benzene–ether gave prisms, m.p. 92°, R_F 0·48 (Found: C, 56·1; H, 7·8; N, 8·0. $C_8H_{13}NO_3$ requires C, 56·1; H, 7·6; N, 8·2%), $\nu_{max.}$ (KBr) 3270s cm^{-1} (OH), δ 3·2br variable (2H, OH), 3·58 (3H, s, NMe), 3·70 (3H, s, OMe), 4·47 (4H, s, CH_2O), and 6·10 (1H, s, H-5). The compound gave an immediate bright red precipitate with aqueous HCl. The alkylation reaction gave a strong mauve colour, $\lambda_{max.}$ 560br nm. The Ehrlich reaction gave a magenta colour, $\lambda_{max.}$ 546 nm (ε 45,600).

2,3-*Bis*-(*N*-*ethylcarbamoyloxymethyl*)-1-*methylpyrrole* (XXIV).—The pyrrole (XXIII) (0·35 g) was heated under reflux with ethyl isocyanate (6 ml) for 2·5 h. 1,4-Diazabicyclo[2.2.2]octane (0·5 mg) was added and the mixture heated for a further 20 min. Excess of reagent was removed under reduced pressure, the residue was dissolved in anhydrous ether (10 ml) and the solvent again removed. The *dicarbamate* remained as a gum (0·65 g, 93%) which crystallised. Recrystallisation from anhydrous ether–light petroleum (b.p. 60—80°) gave blades, m.p. 85° (Found: C, 55·2; H, 7·4; N, 15·0. $C_{13}H_{21}N_3O_4$ requires C, 55·1; H, 7·4; N, 14·8%), $\nu_{max.}$ 3310s (NH) and 1690s,br cm^{-1} (CO); δ 1·10 (6H, t, ethyl Me), 3·19 (4H, 2q, ethyl CH_2), 3·61 (3H, s, NMe), 4·6br (NH), 5·05 (2H, s, 3-CH_2), 5·15 (2H, s, 2-CH_2), 6·16 (1H, d, *J* 3 Hz, H-4), and 6·60 (1H, d, *J* 3 Hz, H-5). The alkylation reaction gave an intense mauve colour without the addition of triethylamine. The Ehrlich reaction gave a magenta colour, $\lambda_{max.}$ 570 nm (ε 77,350). When a solution of the carbamate in *NN*-dimethylformamide was added to water, a pale yellow polymer was precipitated after a few min. When added to dilute HCl, a red polymer was precipitated immediately.

2,3-*Bisacetoxymethyl*-1-*methylpyrrole* (XXVIII).—Synthanecine A (0·25 g) in methanol (5 ml) and aqueous hydrogen peroxide (0·3 ml) was kept at room temperature for 16 h, then heated under reflux for 2 h. Excess of peroxide was decomposed by adding manganese dioxide, and the solution was filtered and concentrated under reduced pressure to give the crude *N*-oxide as a gum. This material was dissolved in acetic anhydride (2 ml) at 30—35°, and after 2 min triethylamine (10 ml) was added and the mixture kept at room temperature for 1·5 h in a stoppered flask. The triethylamine and the excess of acetic anhydride were removed with cautious warming at 5—0·5 mmHg, further triethylamine being added frequently to maintain basic conditions. The residue was dissolved in anhydrous ether (5 ml), the solution diluted with light petroleum (b.p. 40—60°; 60 ml), charcoaled, filtered, and the solvents removed under reduced pressure to give the diacetoxy-pyrrole derivative as an oil (148 mg, 38%) which was purified by molecular distillation, $\nu_{max.}$ 1735s cm^{-1} (ester), δ 2·03 and 2·04 (6H, s, 3- and 2-acetyl Me), 3·61 (3H, s, NMe), 5·04 (2H, s, 3-CH_2), 5·14 (2H, s, 2-CH_2), 6·13 (1H, d, *J* 3 Hz, H-4), and 6·60 (1H, d, *J* 3 Hz, H-5). The Ehrlich reaction gave an intense magenta colour, $\lambda_{max.}$ 570 nm. The alkylation reaction gave an intense mauve colour. The compound dissolved in water to give a clear solution which became cloudy and pink after a few min. It gave a red polymer with dilute HCl.

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