Pyrrolizidine Alkaloid Analogues. Part 2.[1] Further Hydroxymethyl-1-methyl-3-pyrrolines (Synthanecines), and the Preparation and Esterification of Some Hydroxymethylpyrroles

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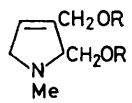
The preparation is described of 2-(2-hydroxyethyl)-3-hydroxymethyl-1-methyl-3-pyrroline (synthanecine D) (11) and 3-hydroxymethyl-1,2-dimethyl-3-pyrroline (synthanecine E) (21), esters of which behave as analogues of pyrrolizidine alkaloids which can be metabolically dehydrogenated in animals to pyrrole derivatives which are monofunctional alkylating agents. The corresponding pyrroles (15) and (23) and several other new hydroxymethylpyrroles have been prepared and the esterification of some of these is described. The electrophilic reactivities of a number of hydroxymethyl-pyrrole and -indole derivatives towards 4-*p*-nitrobenzylpyridine are compared, and the base-catalysed conversion of diethyl (*N*-ethoxycarbonylmethyl)-3-methylaminoglutarate (5) to 3-ethoxycarbonyl-4-hydroxy-1-methylpyrrole (45) is described.

In Part 1 [1] the preparation was described of some esters and carbamoyl derivatives of 2,3-bishydroxymethyl-1-methyl-3-pyrroline (synthanecine A) (1) which have cytotoxic effects similar to those of some naturally occurring pyrrolizidine alkaloids when administered to animals.[2,3] Just as alkaloids such as monocrotaline are dehydrogenated to dihydropyrrolizine esters by the hepatic microsomal system *in vivo*,[4,5] synthanecine derivatives such as the carbamate (2) are dehydrogenated



(1) R = H
(2) R = CONHEt

to the corresponding pyrroles which behave as bifunctional alkylating agents through activation of the two ester groups by conjugation with the pyrrole nitrogen.[6,7] Toxic effects result from the generation of such reactive compounds within the tissues.[5] Thus (2) is hepatotoxic and pneumotoxic to rats and is being used to study mechanisms of pyrrolizidine toxicity.[3]

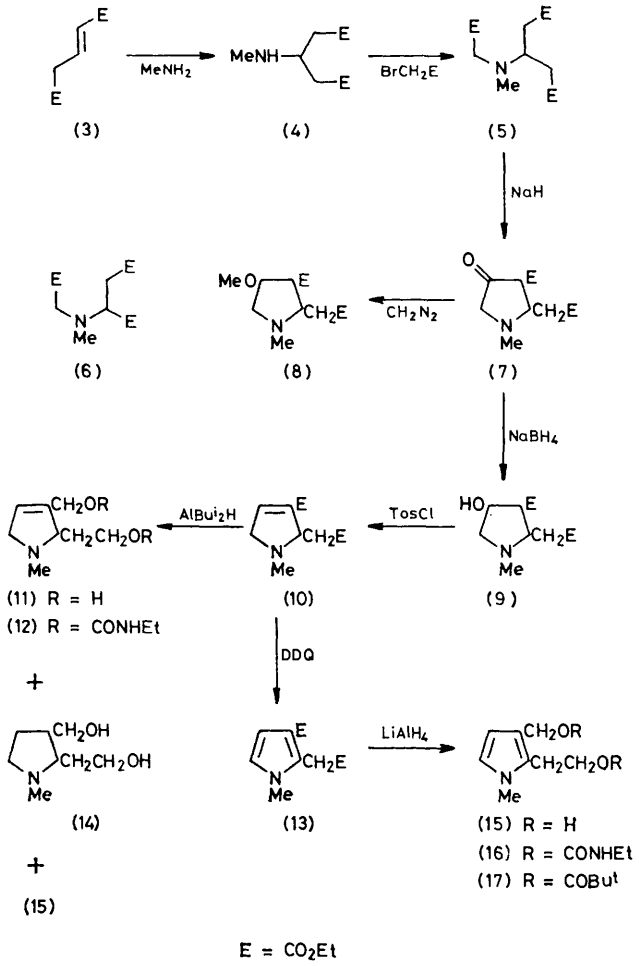
To define more precisely the structural features necessary to direct the metabolism of 3-pyrroline derivatives to the corresponding pyrroles, and for the latter to exert specific cytotoxic effects (antimitotic, antitumour, and carcinogenic activity, and the ability to cause cell necrosis), 3-pyrroline derivatives were required whose pyrrolic dehydrogenation products would be monofunctional alkylating agents. In addition to an oxymethylene group, a second ring substituent was required following our earlier unpublished observations that 3-pyrrolines having only one ring substituent were not readily metabolised to pyrroles in rat liver. Esters of 3-hydroxymethyl-1,2-dimethyl-3-pyrroline (synthanecine E) (21) meet these requirements; so also do esters of 2-(2-hydroxyethyl)-3-hydroxymethyl-1-methyl-3-pyrroline (synthanecine D) (11) because in the pyrroles (15)—(17) only the oxygen function in the 3-position is activated by the pyrrole nitrogen.

RESULTS AND DISCUSSION

For the preparation of synthanecine D, diethyl glutaconate (3) was allowed to react with methylamine

[1] Part 1, A. R. Mattocks, *J.C.S. Perkin I*, 1974, 707.
[2] A. R. Mattocks, *Nature*, 1971, **232**, 476.
[3] A. R. Mattocks and I. N. H. White, *Chem.-Biol. Interactions*, 1976, **15**, 173.
[4] A. R. Mattocks in 'Phytochemical Ecology,' ed. J. B. Harborne, Academic Press, London, 1972, p. 179.
[5] A. R. Mattocks, *Chem.-Biol. Interactions*, 1972, **5**, 227.
[6] A. R. Mattocks, *J. Chem. Soc.* (*C*), 1969, 2698.
[7] C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Austral. J. Chem.*, 1970, **23**, 1853.

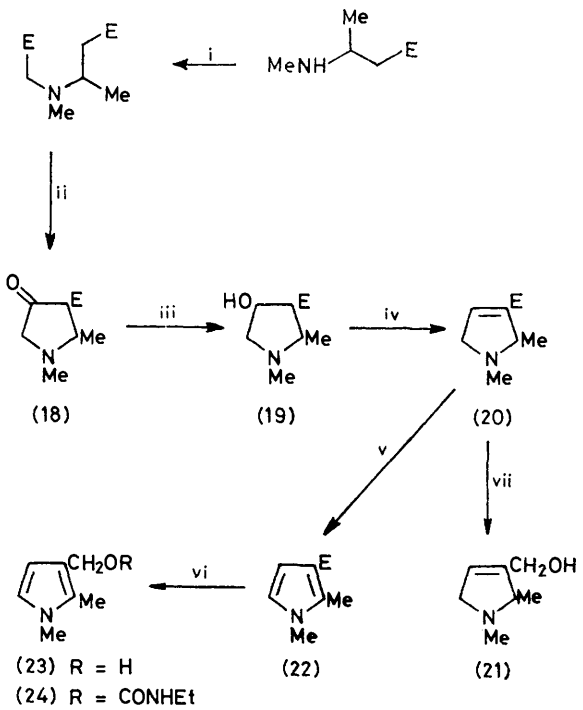
to give diethyl 3-methylaminoglutarate (4), which with ethyl bromoacetate gave the triester (5) in 67% overall



yield. A similar sequence starting with diethyl fumarate gave the previously described diethyl *N*-(ethoxycarbonylmethyl)-2-methylaminosuccinate (6), the starting material for synthanecine A, more conveniently and in similar yield (60%) to the more costly earlier procedure starting with sarcosine.[1] Dieckmann cyclisation of (5) at room temperature using sodium hydride gave the pyrrolidin-3-one (7) in 47% yield, along with some 3-ethoxycarbonyl-4-hydroxy-1-methylpyrrole (45b) (discussed later). Use of sodium or sodium ethoxide as condensing agent, especially at elevated temperatures, gave more of the pyrrole and a poor yield of (7). The i.r. spectrum of (7) (liquid) showed it to be entirely in the keto-form. It reacted slowly with diazomethane to give the enol ether (8). Reduction of (7) with borohydride gave the hydroxypyrrolidine (9) the best yield (62%) being obtained using aqueous sodium hydroxide as solvent rather than ethanol (44%); a similar improvement was achieved in the reduction of the 2-ethoxycarbonyl homologue [1]. Dehydration of (9) with toluene-*p*-sulphonyl chloride in pyridine gave the pyrroline (10) which was reduced with di-isobutylaluminium hydride. The reaction furnished the required pyrroline (synthanecine D) (11) together with the corresponding pyrrolidine (14) and pyrrole (15) in *ca.* 59, 17, and 19% yields respectively as determined from their *N*-methyl n.m.r. signals. Synthanecine D (37%) was extracted from the mixture and was converted into its *N*-ethylcarbamoyl derivative (12) using ethyl isocyanate. Like synthanecine A (1) and its carbamate (2) the compounds (11) and (12) were viscous oils, characterised as their crystalline picrolonates, from which the pure bases could be recovered using anion-exchange resin.

3-Hydroxymethyl-1,2-dimethyl-3-pyrroline (synthanecine E) (21) was prepared in a similar manner to (11), *via* the intermediates (18)—(20).

Pyrrole Derivatives.—A number of new hydroxymethylpyrroles have been prepared which are potentially interesting as biological alkylating agents and in some cases as synthanecine metabolities. They were made using established methods but special precautions were necessary during isolation and handling owing to their instability and toxicity. The pyrrolic alcohols (15) and (23) were accessible by dehydrogenation of (11) and (21) with chloranil,[1,7] but they were more conveniently made by dehydrogenating the 3-pyrroline esters (10) and (20) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and reducing the resulting pyrroles (13) and (22) with



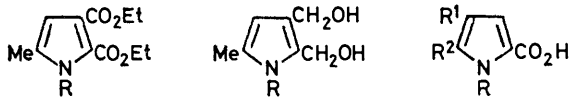
Reagents: i, $BrCH_2E$; ii, NaH; iii, $NaBH_4$; iv, TosCl; v, DDQ; vi, $LiAlH_4$; vii, $AlBu^i_2H$

lithium aluminium hydride (LAH). Similarly the alcohol (28) was prepared from the ester (26). The latter could be converted to (27) using chloranil, but less efficiently (82%) than with DDQ (95%). Reduction with

LAH of the known [8] diethyl 5-methyl-1-phenylpyrrole-2,3-dicarboxylate (29) and the similarly prepared 1-methylpyrrole (30) afforded the dialcohols (31) and (32),

(25) (26) (27) (28)

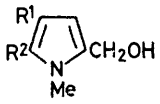
while 1-methylpyrrole-2,4- and 2,5-dicarboxylic acids (33) and (34) [9] were reduced with LAH to the 2,4- and 2,5-bishydroxymethyl-1-methylpyrroles (35) and (36). 3-Hydroxymethyl-1-methylindole (37) was made by reduction of 1-methylindole-3-carbaldehyde with sodium borohydride.



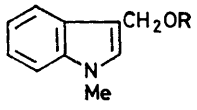
(29) R = Ph
(30) R = Me

(31) R = Ph
(32) R = Me

(33) R^1 = CO_2H, R^2 = H
(34) R^1 = H, R^2 = CO_2H



(35) R^1 = CH_2OH R^2 = H
(36) R^1 = H, R^2 = CH_2OH

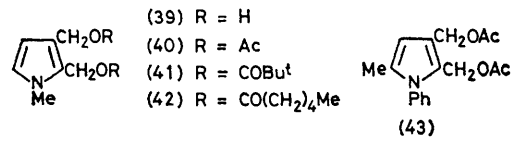


(37) R = H
(38) R = CONHEt

The compound 2,3-bishydroxymethyl-1-methylpyrrole (39) previously reported [1] as prisms with m.p. 56—57 °C after several recrystallisations from ether, has now been obtained as plates, m.p. 74 °C, from the same solvent. The two forms are spectroscopically identical, and either can be obtained by seeding the ether solution with the appropriate crystals.

All the hydroxymethylpyrroles and the indole (37) underwent acid-catalysed alkylation reactions with 4-*p*-nitrobenzylpyridine and other nucleophiles, and tended to polymerise in aqueous solution. All except (31) gave a red colour with Ehrlich reagent.

Esterification of hydroxymethylpyrroles is difficult owing to the extreme sensitivity to acids of both starting materials and products, and of the latter to moisture, and earlier attempts to prepare derivatives of 2-hydroxymethylpyrrole and similar compounds were reported to be unsuccessful.[10] One approach is through dehydrogenation of the relatively stable acyloxymethyl-3-pyrrolines, as with the preparation of didehydro-derivatives of some pyrrolizidine alkaloids.[6,7] The diacetyl ester (40) of 2,3-bishydroxymethyl-1-methylpyrrole, previously prepared by the simultaneous acetylation and dehydration of synthanecine A *N*-oxide,[1] has now been made in high yield (93%) by direct acetylation of the dialcohol (39) with acetyl chloride. The pivaloyl esters (17) and (41) and the n-hexanoyl ester (42) were similarly made using the appropriate acid chlorides.

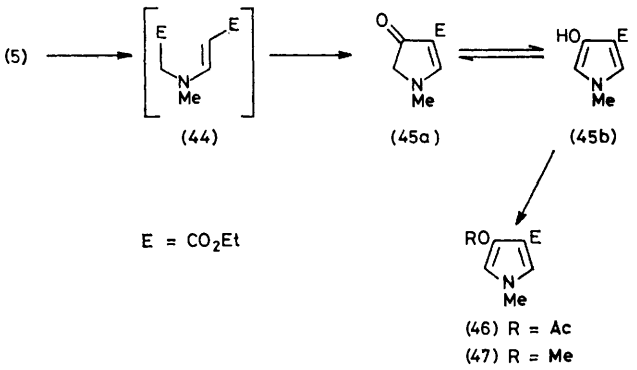


(39) R = H
(40) R = Ac
(41) R = $COBu^t$
(42) R = $CO(CH_2)_4Me$

(43)

These esters are both toxic and very reactive, and success in preparing them lies in rigorous exclusion of moisture and acids by use of excess of tertiary base, to prevent polymerisation. The preparation of esters (17), (41), (42), and (43) led to reasonably pure products, whereas attempted further purification by molecular distillation led largely to decomposition and polymerisation, with recovery of small amounts of less pure material. The crystalline *N*-ethyl carbamates (16), (24), and (38), prepared from the alcohols using ethyl isocyanate, are more stable to moisture than the acyl esters because acid is not liberated on hydrolysis; nevertheless they are highly reactive electrophilic agents (see Table) and similar precautions are needed when handling them.

As mentioned earlier 3-ethoxycarbonyl-4-hydroxy-1-methylpyrrole (45) was formed as a by-product during the preparation of (7) from the triester (5), especially at elevated temperatures. It was obtained in higher yield (45%) by heating (5) with ethanolic potassium hydroxide, and its formation apparently involves elimination of CH_2CO_2Et in a reverse Michael reaction [11] with cyclisation of the intermediate (44). The structure of (45) was evident from its i.r., n.m.r., and u.v. spectra. The i.r.



(44) (45a) (45b)

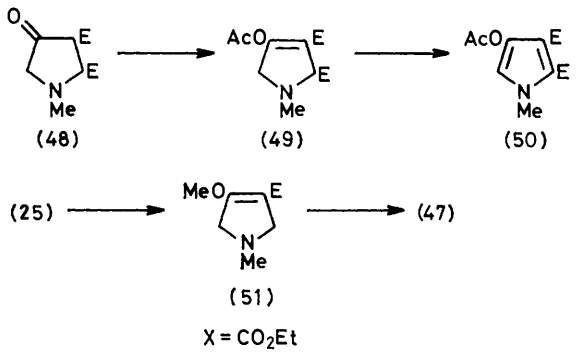
E = CO_2Et

(46) R = Ac
(47) R = Me

spectrum showed that in $CHCl_3$ it exists in the hydroxy-form (45b), having OH and ester bands (3 400 and 1 710 cm^{-1}) but no ketone CO band. This agrees with the

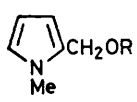
[8] R. G. Jones, *J. Amer. Chem. Soc.*, 1955, **77**, 4069.
[9] D. J. Chadwick, *J.C.S. Chem. Comm.*, 1974, 790.
[10] R. M. Silverstein, E. E. Ryskiewicz, and S. W. Chaikin, *J. Amer. Chem. Soc.*, 1954, **76**, 4485.
[11] E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, 1959, **10**, 179.

conclusion of Davoll [12] that 3-oxopyrrolines with unsubstituted 2- and 5-positions exist in the enol form. The

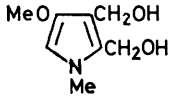


n.m.r. spectrum ($CDCl_3$) of (45) showed that the OH proton exchanged rapidly with D_2O at 33 °C while H-5 exchanged slowly (several minutes). The crystalline acetate (46) was readily prepared from (45) but an alternative synthesis failed: whereas the oxopyrrolidine (48) [1] was readily acetylated and the enol-acetate (49) dehydrogenated by DDQ to the acetoxypyrrole (50), the oxopyrrolidine (25) was very unstable, especially in aqueous alkali, and could not be acetylated. However, with diazomethane (25) gave the enol ether (51) which was dehydrogenated to the methoxypyrrole (47). The hydroxypyrrole (45) did not react with diazomethane, but with methyl sulphate it gave a methoxy-derivative, identical (spectra) with (47), in poor yield.

Alkylation Reactions.—The alkylating activities of some hydroxymethylpyrroles and their esters were compared by allowing them to react with 4-*p*-nitrobenzylpyridine in aqueous acetone. The reagent was in excess (230 ×) and the reactions followed approximately first-order kinetics. The results are given in the Table. Caution is needed when comparing monofunctional with bifunctional agents, but the following general conclusions can be drawn. (*a*) The electrophilic activities of the esters, including carbamates, are greater than the corresponding alcohols. (*b*) The reactivity of CH_2OR in the 2-position is much greater than in the 3-position [compare (52) and (28)]. (*c*) The reactivity is enhanced by the presence of other substituents on the pyrrole ring in the order Me > CH_2CH_2-OR > OMe [compare (28) with (15) and (23); (39) with (54) and (32)]. (*d*) Reactivity is decreased by substituting *N*-Ph for *N*-Me [compare (31) with (32)]. (*e*) The alkylating activity decreases with increasing size of the acyl ester group: the lower reactivity of (41)



(52) R = H
(53) R = CONHEt



(54)

compared with (40) is likely to be due to steric hindrance, rather than to the slightly higher basicity of the trimethylacetyl anion (pK_a 5.05) compared with acetate (pK_a 4.76). (*f*) The 3-CH_2OR position on indole is similar in reactivity to the 2-position on pyrrole [compare (37) and (38) with (52) and (53)].

Pseudo-first-order rate constants (k) and approximate half-lives for reactions of electrophilic pyrrole and indole derivatives with 4-*p*-nitrobenzylpyridine in aqueous acetone at 50 °C

Compound	Ref.	*N*-substituent	Position(s) of CH_2OR	R	Other ring substituents	k/min^{-1}	$t_{\frac{1}{2}}$/min
(52)	13	Me	2	H		0.12	5.9
(28)		Me	3	H		0.014	49.5
(15)		Me	3	H	2-CH_2CH_2OH	0.31	2.2
(23)		Me	3	H	2-Me	0.74	0.94
(53)	14	Me	2	G		3.97	0.17
(16)		Me	3	G	2-CH_2CH_2O G	0.80	0.87
(17)		Me	3	Piv	2-CH_2CH_2O Piv	0.33	2.1
(24)		Me	3	G	2-Me	11.4	0.06
(39)	1	Me	2,3	H		0.10	6.9
(54)	1	Me	2,3	H	4-OMe	0.24	2.9
(32)		Me	2,3	H	5-Me	1.68	0.41
(31)		Ph	2,3	H	5-Me	0.40	1.7
(43)		Ph	2,3	Ac	5-Me	7.5	0.09
(55)	1	Me	2,3	G		1.24	0.56
(40)	1	Me	2,3	Ac		2.03	0.34
(41)		Me	2,3	Piv		0.44	1.58
(42)		Me	2,3	Hex		0.43	1.61
(37)	3-Hydroxymethyl-1-methylindole					0.14	4.9
(38)	3-*N*-Ethylcarbamoyloxymethyl-1-methylindole					2.92	0.24

* G = CONHEt; Piv = $COBu^t$; Hex = $CO(CH_2)_4Me$.

Toxicological studies on the synthanecine and hydroxymethylpyrrole derivatives will be reported in detail elsewhere. Compounds behaving *in vivo* as monofunctional alkylating agents caused acute cytotoxic effects (tissue necrosis) in animals, but not the delayed (antimitotic) effects in the liver or the progressive lung damage characteristic of bifunctional agents like synthanecine A bis-*N*-ethylcarbamate and pyrrolizidine alkaloids such as monocrotaline. The esters and carbamates of the hydroxymethylpyrroles and indoles are

[12] J. Davoll, *J. Chem. Soc.*, 1953, 3802.
[13] E. E. Ryskiewicz and R. M. Silverstein, *J. Amer. Chem. Soc.*, 1954, **76**, 5802.
[14] R. Plestina, H. B. Stoner, G. Jones, W. H. Butler, and A. R. Mattocks, *J. Pathology*, 1977, **121**, 9.

powerful acute lung poisons when given intravenously to rats,[2,14] the indole derivative (38) being the most potent with acute LD_{50} *ca.* 2 mg kg^{-1}. The hydroxymethylpyrroles (31) and (39) had a powerful antimitotic effect on rat liver, while (39) and (54) had antitumour activity when tested against the Walker tumour in rats.

EXPERIMENTAL

M.p.s were determined with a Mettler FP52 hot-stage or FP51 automatic melting-point apparatus. I.r. spectra were recorded with a Perkin-Elmer model 457 spectrophotometer, in $CHCl_3$ unless otherwise indicated; n.m.r. spectra were recorded at 60 MHz with a Perkin-Elmer R12B instrument, in $CDCl_3$ unless otherwise stated. Extracts were dried with anhydrous sodium sulphate. The Ehrlich reaction and qualitative alkylation reactions using 4-*p*-nitrobenzylpyridine were as described previously.[1]

Measurement of Alkylation Rates.—A solution of the pyrrole derivative (0.25 μmol) in 1,2-dimethoxyethane (0.05 ml) was mixed rapidly with 4-*p*-nitrobenzylpyridine reagent [6] (1 ml) at 50 °C. After a period of time at 50 °C the mixture was removed to an ice–water bath and a mixture of triethylamine and acetone (1 : 1; 1 ml) was added immediately. The blue solution was diluted to 10 ml with acetone and the absorbance measured at $\lambda_{max.}$ 555—570 nm. The procedure was repeated for different time intervals and the pseudo-first-order rate constant was determined graphically in the usual way.

Diethyl 3-*Methylaminoglutarate* (4).—A mixture of diethyl glutaconate (Aldrich Chemical Co., tech. grade; 62 g), ethanol (100 ml), and methylamine (33% solution in ethanol; 150 ml) was heated under reflux for 1 h, and the ethanol and methylamine were removed under reduced pressure. The residue was dissolved in dilute HCl and the solution washed twice with ether, basified with ammonia, and extracted with ether (×3). The combined basic extracts were dried and concentrated to give an oil (56 g, 77%). Distillation gave the *product*, b.p. 84—86 °C at 0.08—0.1 mmHg, n_D^{21} 1.440 3 (Found: C, 55.3; H, 9.3. $C_{10}H_{19}NO_4$ requires C, 55.3; H, 8.8%); $\nu_{max.}$ (film) 1 730s (ester) and 3 330 cm^{-1} (NH); δ 1.27 (6 H, t, ester Me), 1.70 (1 H, s, NH), 2.43 (3 H, s, NMe), 2.53 (4 H, d, CH_2), 3.32 (1 H, quintet, CH), and 4.16 (4 H, q, ester CH_2). The *picrolonate* formed yellow leaflets (from ethanol), m.p. 159 °C (Found: C, 50.3; H, 6.0; N, 14.6. $C_{20}H_{27}N_5O_9$ requires C, 49.9; H, 5.6; N, 14.6%).

Diethyl (N-*Ethoxycarbonylmethyl*)-3-*methylaminoglutarate* (5).—A mixture of diethyl 3-methylaminoglutarate (4) (35 g), ethyl bromoacetate (30 g), ethanol (150 ml), and powdered potassium carbonate (30 g) was heated under reflux for 1.5 h; the alcohol was then removed under reduced pressure. Sufficient ice-cold dilute HCl was added to the residue to give an acidic solution, which was washed with ether (×3), basified with ammonia solution, and extracted with ether (×3). The combined basic extracts were dried and concentrated to give an oil (42.6 g, 87%). Distillation gave the *triester* as a colourless oil, b.p. 130—132 °C at 0.1 mmHg, n_D^{22} 1.447 9 (Found: C, 55.8; H, 8.7; N, 4.7. $C_{14}H_{25}NO_6$ requires C, 55.4; H, 8.3; N, 4.6%); $\nu_{max.}$ 1 720s cm^{-1} (ester); δ 1.26 (9 H, t, ester Me), 2.40 (3 H, s, NMe), 2.46, 2.55 (4 H, 2 d, *J* 7 Hz, CH_2), 3.33 (2 H, s, NCH_2), 3.68 (1 H, t, *J* 7 Hz, CH), and 4.15 (6 H, q, ester CH_2). The compound formed a *picrolonate*, yellow leaflets (from ethanol), m.p. 122 °C (Found: C, 51.3; H, 5.8; N, 12.3. $C_{24}H_{33}N_5O_{11}$ requires C, 50.8; H, 5.8; N, 12.35%).

Diethyl (N-*Ethoxycarbonylmethyl*)-2-*methylaminosuccinate* (6).—A mixture of diethyl 2-methylaminosuccinate [15] (165 g), powdered anhydrous potassium carbonate (170 g), ethyl bromoacetate (138 g), and ethanol (600 ml) was heated under reflux for 24 h, cooled to room temperature, filtered (pump), and the filtrate evaporated to dryness (rotary). The residue was dissolved in 2M-HCl sufficient to give an acidic solution; this was washed with ether (×2), made basic with ammonia solution, and extracted with ether (×3). The extracts were dried and concentrated to give a product (165 g, 70%) identical (i.r. and n.m.r.) with the material previously described.[1]

3-*Ethoxycarbonyl*-2-*ethoxycarbonylmethyl*-1-*methylpyrrolid*-4-*one* (7).—The triester (5) (5.2 g) in benzene (30 ml) was stirred with powdered sodium hydride (0.6 g) at room temperature under dry N_2 for 5 h. The solution was extracted with water (3 × 15 ml). The aqueous extracts were combined, washed with ether, acidified with HCl (ice-cooling) to pH < 1, again washed with ether (×3), then adjusted to pH 6 with ammonia solution, and extracted with chloroform (×3). The combined chloroform extracts were dried and concentrated under reduced pressure to give the *pyrrolidone* as an oil (2.09 g, 47.5%), which later crystallised. After molecular distillation it was colourless, m.p. 69—70 °C (Found: C, 56.3; H, 7.35; N, 5.4. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.4; N, 5.45%); $\nu_{max.}$ (film) 1 730s (ester), 1 770s (C=O), and 2 790m cm^{-1} (N-CH_2); δ 1.25, 1.29 (6 H, 2 t, ester Me), 2.46 (3 H, s, NMe), 2.73 (2 H, 2 d, *J* 2 Hz, CH_2CO), 3.45 (2 H, m, H-5), and 4.15, 4.23 (4 H, 2 q, ester CH_2)

The acidic ether extracts from the above reaction contained pyrrolic material which gave a red colour with the Ehrlich reagent.

3-*Ethoxycarbonyl*-4-*hydroxy*-1-*methylpyrrole* (45).—The triester (5) (0.6 g) and potassium hydroxide (0.13 g) dissolved in absolute ethanol (15 ml) were heated under reflux for 20 min, and then evaporated under reduced pressure. The yellow gum was dissolved in water (20 ml) and the solution washed once with ether, then acidified (HCl), and extracted with ether (3 × 15 ml). The combined acidic extracts were dried and concentrated to give the *hydroxypyrrole* as a viscous orange-yellow oil (0.15 g, 45%); $\lambda_{max.}$ (EtOH) 214 (ε 11 000) and 242.5 nm (12 580); $\nu_{max.}$ 1 720s (ester) and 3 400m, br cm^{-1} (OH); δ 1.33 (3 H, t, ester *Me*), 3.58 (3 H, s, NMe), 4.32 (2 H, q, ester CH_2), 6.15 (1 H, d, *J* 3 Hz, H-5: slowly exchangeable with D_2O), 6.86 (1 H, d, *J* 3 Hz, H-2: becomes a singlet after D_2O exchange of H-5), and 7.4 br (1 H, OH). The Ehrlich reaction gave $\lambda_{max.}$ 534 nm (ε 55 000), with an inflexion at 510 nm. The hydroxypyrrole was recovered unchanged after treatment with excess of diazomethane in ether (with a little methanol) at room temperature for 18 h. With dimethyl sulphate in aqueous ethanolic sodium hydroxide it gave 3-ethoxycarbonyl-4-methoxy-1-methylpyrrole (47), identical (i.r. and n.m.r.) with the authentic compound prepared by dehydrogenation of 3-ethoxycarbonyl-4-methoxy-1-methyl-3-pyrroline (see below). Acetylation of the hydroxypyrrole with acetic anhydride (100 °C, 1 h) gave 4-*acetoxy*-3-*ethoxycarbonyl*-1-*methylpyrrole* (46) which after molecular distillation formed prisms, m.p. 47—48 °C (Found: C, 57.1; H, 6.2; N, 6.9. $C_{10}H_{13}NO_4$ requires C, 56.9; H, 6.2; N, 6.6%); $\nu_{max.}$ ($CHCl_3$) 1 700s (ester) and 1 753 cm^{-1} (vinyl ester); δ 1.30 (3 H, t, ester Me), 2.29 (3 H, s, acetyl-

[15] R. L. Augustine, Z. S. Zelawski, and D. H. Malarek, *J. Org. Chem.*, 1967, **32**, 2257.

Me), 3.62 (3 H, s, NMe), 4.25 (2 H, q, ester CH_2), 6.55 (1 H, d, *J* 3 Hz, H-5), and 7.13 (1 H, d, *J* 3 Hz, H-2); $\lambda_{max.}$ (EtOH) 210 (ε 14 550) and 234 nm (9 960); the acetoxypyrrole gave no colour with the Ehrlich reagent.

3-*Ethoxycarbonyl*-2-*ethoxycarbonylmethyl*-4-*methoxy*-1-*methyl*-3-*pyrroline* (8).—The pyrrolidone (7) (0.24 g) was dissolved in anhydrous ether and treated with an excess of diazomethane for 18 h at room temperature. The ether and excess of reagent were evaporated off giving an oil (0.24 g) which contained some starting material. This was dissolved in dilute HCl and the solution washed with ether (×3); it was then made strongly basic with NaOH, and extracted with ether (×3). The combined basic extracts were dried and concentrated to give the methoxypyrroline as a colourless oil (76 mg); $\nu_{max.}$ 1 640s (conjugated C=C), 1 690s (conjugated ester), 1 725s (ester), and 2 790w cm^{-1} (NCH_2); δ 1.26, 1.27 (6 H, 2 t, ester Me), 2.49 (3 H, s, NMe), 2.7 (2 H, m, 2-CH_2), 3.85 (3 H, s, OMe), and 4.16, 4.21 (4 H, 2 q, ester CH_2).

The *picrate* formed blades (from ethanol), m.p. 152 °C (Found: C, 45.65; H, 5.05; N, 11.2. $C_{19}H_{24}N_4O_{12}$ requires C, 45.6; H, 4.8; N, 11.2%).

3-*Ethoxycarbonyl*-2-*ethoxycarbonylmethyl*-4-*hydroxy*-1-*methylpyrrolidine* (9).—To an ice-cold solution of the oxopyrrolidine (7) (10 g) in aqueous sodium hydroxide (2%, 75 ml) was added a solution of sodium borohydride (0.8 g) in water (5 ml). The mixture was kept at 0 °C for 1.5 h, then acidified with HCl, washed with ether (×2), basified with ammonia solution, and extracted with ether (×4). The combined basic extracts were dried and concentrated under reduced pressure to give the hydroxypyrrolidine as an oil (6.3 g, 62%), n_D^{21} 1.470 7, which crystallised below room temperature; $\nu_{max.}$ 1 720s (ester), 2 790m (NCH_2), and 3 400 br cm^{-1} (OH), δ 1.26, 1.29 (6 H, 2 t, ester *Me*), 2.39 (3 H, s, NMe), 2.7 (2 H, m, 2-CH_2), 2.9 (1 H, br s, OH), and 4.16, 4.23 (4 H, 2 q, ester CH_2). Its *picrolonate* formed pale yellow blades (from ethanol), m.p. 189 °C (Found: C, 50.2; H, 5.7; N, 13.2. $C_{22}H_{29}N_5O_{10}$ requires C, 50.5; H, 5.5; N, 13.4%).

3-*Ethoxycarbonyl*-2-*ethoxycarbonylmethyl*-1-*methyl*-3-*pyrroline* (10).—To a solution of the hydroxypyrrolidine (9) (10 g) in pyridine (30 ml) was added a solution of toluene-*p*-sulphonyl chloride (30 g) in pyridine (70 ml). The mixture was heated on a steam-bath in a stoppered flask for 2 h, after which most of the solvent was removed under reduced pressure. The residue was dissolved in ice-cold dilute HCl sufficient to give an acidic solution which was washed with ether (4 × 50 ml), basified with ammonia solution, and extracted with ether (3 × 50 ml). The combined basic extracts were dried, and concentrated under reduced pressure to a brown oil (7 g, 75%) which was distilled, the fraction with b.p. 100—130 °C at 1 mmHg being collected. The distillate was redissolved in dilute HCl and the solution washed with ether, basified with sodium hydroxide, and extracted with light petroleum (×3; b.p. 60—80 °C). The combined petroleum extracts were dried, boiled with charcoal, concentrated under reduced pressure, and the residue distilled to give the pure *pyrroline*, b.p. 96—100 °C at 0.1 mmHg, n_D^{20} 1.469 0 (Found: C, 59.8; H, 7.9; N, 5.5. $C_{12}H_{19}NO_4$ requires C, 59.8; H, 7.9, N, 5.8%); $\nu_{max.}$ (film) 1 635w (C=C), 1 717s (conjugated ester), 1 737s (ester), and 2 780m cm^{-1} (NCH_2), δ 1.25, 1.30 (6 H, 2 t, ester Me), 2.48 (3 H, s, NMe), 2.7 (2 H, m, 2-CH_2), 3.0—3.9 (3 H, m, H-1 and H-5), 4.22, 4.14 (4 H, 2 q, ester CH_2), and 6.75 (1 H, m, H-4).

2-(2-*Hydroxyethyl*)-3-*hydroxymethyl*-1-*methyl*-3-*pyrroline* (*Synthanecine D*) (11).—To the pyrroline diester (10) (4 g) in toluene (30 ml) was added during 15 min, under N_2, a solution of di-isobutylaluminium hydride (13.7 g) in toluene (60 ml) with stirring and cooling to 20—25 °C (ice–water bath). The mixture was then set aside without external cooling for 45 min. Ethyl acetate (5 ml) was added with stirring and then, after 5 min, acetone (100 ml) and Hyflo Supacel (20 g), followed by methanol (15 ml) were added slowly with external cooling to 30—35 °C. The mixture was shaken vigorously until gelling occurred (5—6 min), after which it was set aside for 1 h and then filtered (pump) and the residue rinsed with hot methanol (3 × 20 ml). The combined filtrates were diluted with water (30 ml), then evaporated (rotary, 70 °C) to a gum which was dissolved in chloroform (30 ml), and the solution dried and concentrated (rotary) to a viscous oil (1.37 g, A). The residue from filtration was stirred with water (100 ml) for 30 min, filtered (pump), and the residue rinsed with hot water (2 × 20 ml) and the combined filtrates concentrated under reduced pressure (rotary) to a brown gum, which was re-extracted with chloroform, and the dried extract again concentrated to a viscous oil (1.12 g, B). Analysis of the n.m.r. spectra of mixtures (A) and (B) gave the approximate compositions: (A) pyrroline (11) (78%), pyrrolidine (14) (0%), and pyrrole (15) (22%); and (B) pyrroline (11) 41%, pyrrolidine (14) 41%, and pyrrole (15) 18%. Crude (A) (714 mg) was dissolved in citrate–phosphate buffer, pH 4 (30 ml) and the solution was washed with chloroform (6 × 10 ml), basified with KOH, saturated with K_2CO_3, and extracted with chloroform (8 × 10 ml). The combined basic extracts were dried and concentrated to give the pyrroline [509 mg, 71% of (A)] as a viscous oil, $\nu_{max.}$ 2 790m (NCH_2) and 3 330s, br cm^{-1} (OH), δ 1.9 (2 H, m, 2-CH_2), 2.46 (3 H, s, NMe), 3.71 (2 H, t, CH_2O), 4.11 (2 H, s, 3-CH_2), 4.5 (2 H, s, OH), and 5.75 (1 H, s, H-4). This formed a *picrolonate* as orange-yellow microcrystals (from ethanol), m.p. 155 °C (Found: C, 51.5; H, 5.6; N, 16.85. $C_{18}H_{23}N_5O_7$ requires C, 51.3; H, 5.5; N, 16.6%).

2-(2-N-*Ethylcarbamoyloxyethyl*)-3-(N-*ethylcarbamoyloxymethyl*)-1-*methyl*-3-*pyrroline* (12).—The dialcohol (11) (0.47 g), 1,4-diazabicyclo[2.2.2]octane (2 mg), and freshly redistilled ethyl isocyanate (3 ml) were heated together under reflux for 4 min. The excess of reagent was removed under reduced pressure, benzene (5 ml) was added, and the solvent removed as before. The gum was dissolved in dilute HCl and the solution washed with chloroform (×5), basified with ammonia solution, and extracted with chloroform (×3). The combined basic extracts were dried and concentrated under reduced pressure to a gum, which was redissolved in anhydrous ether and the solution boiled with charcoal, filtered, and concentrated to give the carbamate as a viscous gum (0.72 g, 81%); $\nu_{max.}$ 1 710s (CO), 2 790m (NCH_2), 3 030w (C=C), and 3 450m cm^{-1} (NH); δ 1.14 (6 H, t, CH_2*Me*), 1.87 (2 H, d of t, *J* 5 and 7 Hz, 2-CH_2), 2.43 (3 H, s, NMe), 3.21, 3.23 (4 H, 2 d, C*H*$_2$Me), 4.66 (2 H, s, 3-CH_2), *ca.* 5 (2 H, br, NH), and 5.70 (1 H, m, H-4). The base formed a *picrolonate* as pale yellow prisms (from ethanol), m.p. 146 °C (Found: C, 51.0; H, 5.9; N, 17.45. $C_{24}H_{33}N_7O_9$ requires C, 51.15; H, 5.9; N, 17.4%).

3-*Ethoxycarbonyl*-2-*ethoxycarbonylmethyl*-1-*methylpyrrole* (13).—To the pyrroline diester (10) (2.7 g) in chloroform (20 ml) was added a hot solution of DDQ (4 g) in chloroform (120 ml). The mixture was allowed to cool to room temperature during 30 min, washed with aqueous potassium

carbonate (10%, 3 × 30 ml), water (30 ml), dilute HCl (10 ml), and again with K_2CO_3 (30 ml), dried (K_2CO_3), and concentrated under reduced pressure. The resulting red gum was dissolved in ether (30 ml), boiled with charcoal, filtered, and concentrated to give the pink crystalline *product* (2 g, 74%). Recrystallisation from ether gave colourless prisms, m.p. 58 °C (Found: C, 60.15; H, 7.0; N, 5.6. $C_{12}H_{17}NO_4$ requires C, 60.25; H, 7.1; N, 5.9%); $\nu_{max.}$ (film) 1 690s (3-ester), 1 730s (2-ester), and 3 105w cm^{-1} (pyrrole); δ 1.25, 1.31 (6 H, 2 t, ester Me), 3.56 (3 H, s, NMe), 4.10 (2 H, s, 2-CH_2), 4.17, 4.25 (4 H, 2 q, ester CH_2), and 6.54 (2 H, s, H-4 and H-5).

2-(2-*Hydroxyethyl*)-3-*hydroxymethyl*-1-*methylpyrrole* (15).—The pyrrole diester (13) (1 g) was heated under reflux with lithium aluminium hydride (0.7 g) in ether (120 ml) for 30 min. The solution was cooled, decomposed with 1M-sodium hydroxide solution (5 ml) during 20 min, filtered, and the residue washed with chloroform (4 × 10 ml). The combined filtrate and washings were concentrated to give the crystalline *product* (0.645 g, 99%) which formed blades (from ether–ethyl acetate), m.p. 93 °C (Found: C, 62.5; H, 8.3; N, 9.4. $C_8H_{13}NO_2$ requires C, 61.9; H, 8.4; N, 9.0%); δ 2.85 (2 H, t, *J* 5 Hz, 2-CH_2), 3.15 (2 H, s, OH), 3.55 (3 H, s, NMe), 3.70 (2 H, t, *J* 5 Hz, CH_2O), 4.45 (2 H, s, 3-CH_2), 6.08 (1 H, d, *J* 3 Hz, H-4), and 6.52 (1 H, d, *J* 3 Hz, H-5).

The Ehrlich reaction gave $\lambda_{max.}$ 568 nm ($\varepsilon_{max.}$ 91 390). This product (0.1 g) was heated under reflux with ethyl isocyanate (2 ml) and 1,4-diazabicyclo[2.2.2]octane (1 mg) for 20 min, excess of reagent removed under reduced pressure, and the residue recrystallised from ether–light petroleum (b.p. 60—80 °C) to give 2-(2-N-*ethylcarbamoyloxyethyl*)-3-N-*ethylcarbamoyloxymethyl*-1-*methylpyrrole* (16) (0.18 g, 94%) as needles, m.p. 78 °C (Found: C, 56.7; H, 7.7; N, 14.5. $C_{14}H_{23}N_3O_4$ requires C, 56.7; H, 7.7; N, 14.1%); $\nu_{max.}$ (KBr) 1 690s (C=O) and 3 325m cm^{-1} (NH), δ 1.10 (6 H, t, CH_2Me), 3.08 (4 H, d of q, CH_2Me), 3.30 (2 H, t, *J* 6 Hz, 2-CH_2), 3.58 (3 H, s, NMe), 4.12 (2 H, t, *J* 6 Hz, CH_2O), 4.85br (2 H, s, NH), 5.00 (2 H, s, 3-CH_2), 6.11 (1 H, d, *J* 3 Hz, H-4), and 6.52 (1 H, d, *J* 3 Hz, H-5). The Ehrlich reaction gave $\lambda_{max.}$ 568 nm ($\varepsilon_{max.}$ 101 000).

3-*Ethoxycarbonyl*-1,2-*dimethyl*-4-*pyrrolidone* (18).—Ethyl 3-methylaminobutyrate, prepared according to ref. 16, had b.p. 82—84 °C at 30 mmHg, n_D^{23} 1.422 9 (lit.,[16] b.p. 72 °C at 12.5 mmHg, n_D^{20} 1.4250); $\nu_{max.}$ 1 725s (ester), 2 800m (NCH_2), and 3 330w cm^{-1} (NH); δ 1.13 (2 H, d, Me), 1.26 (3 H, t, ester Me), 2.43 (3 H, s, NMe), and 4.17 (2 H, q, ester CH_2). This with ethyl bromoacetate [17] gave ethyl (*N*-ethoxycarbonylmethyl)-3-methylaminobutyrate (83%), b.p. 100 °C at 0.7 mmHg, n_D^{23} 1.439 1, $\nu_{max.}$ 1 725s (ester) and 2 800w cm^{-1} (NCH_2); δ 1.10 (3 H, d, Me), 1.27 (6 H, t, ester Me), 2.37 (3 H, s, NMe), 2.50 (2 H, d, CH_2), 3.27 (2 H, s, NCH_2), and 4.16, 4.20 (4 H, 2 q, ester CH_2). The latter (50 g) in benzene (120 ml) was stirred with powdered sodium hydride (6 g) under nitrogen with external cooling (water) for 1 h, then at room temperature for 3 h. The mixture was extracted with water (2 × 30 ml) and the combined aqueous phase back-washed with ether, acidified (HCl), and washed twice more with ether, then adjusted to pH 7—8 with ammonia solution and extracted with chloroform (3 × 50 ml). The combined chloroform extracts were dried and concentrated to give the *pyrrolidone* (26 g, 65%) as an oil which was distilled, b.p. 84—86 °C at 0.6—0.7 mmHg, n_D^{20} 1.451 8 (Found: C, 58.1; H, 8.0; N, 7.4. $C_9H_{15}NO_3$ requires C, 58.4; H, 8.1; N, 7.6%); $\nu_{max.}$ 1 725s (ester), 1 760s (C=O), and 2 790m cm^{-1} (NCH_2), δ 1.29 (3 H, t, CO_2CH_2Me), 1.32 (3 H, d, *J* 5 Hz, 2-Me), 2.42 (3 H, s, N-Me), *ca.* 3.0 (1 H, m, H-2), and 4.23 (2 H, q, ester CH_2).

3-*Ethoxycarbonyl*-4-*hydroxy*-1,2-*dimethylpyrrolidine* (19).—The pyrrolidone (18) (29.5 g) was reduced with sodium borohydride (3 g) in the way described above for the reduction of (7), to give the *product* as an oil (22 g, 74%), b.p. 88—90 °C at 0.2—0.3 mmHg, n_D^{20} 1.464 2 (Found: C, 58.2; H, 9.2; N, 7.3. $C_9H_{17}NO_3$ requires C, 57.8; H, 9.1; N, 7.5%); $\nu_{max.}$ (film) 1 730s (ester), 2 795m (NCH_2), and 3 400m, br cm^{-1} (OH).

3-*Ethoxycarbonyl*-1,2-*dimethyl*-3-*pyrroline* (20).—The hydroxypyrrolidine (19) (27 g) was dehydrated with toluene-*p*-sulphonyl chloride (80 g) in pyridine (250 ml) as described above for the dehydration of (9) to give the *pyrroline* as a colourless oil (16 g, 63%), b.p. 55—57 °C at 0.4 mmHg, n_D^{22} 1.463 0, which became yellow with time (Found: C, 64.1; H, 9.0; N, 8.0. $C_9H_{15}NO_2$ requires C, 63.9; H, 8.9; N, 8.3%); $\nu_{max.}$ 1 630m (C=C), 1 710s (ester), and 2 785m cm^{-1} (NCH_2); δ 1.29 (3 H, d, *J* 6 Hz, 2-Me), 1.30 (3 H, t, ester *Me*), 2.45 (3 H, s, NMe), 4.21 (2 H, q, ester CH_2), and 6.75 (1 H, m, H-4).

3-*Hydroxymethyl*-1,2-*dimethyl*-3-*pyrroline* (*Synthanecine E*) (21).—A solution of the pyrroline ester (20) (5.4 g) in toluene (50 ml) was added to di-isobutylaluminium hydride (10 g) in toluene (50 ml) under N_2 during 15 min with stirring and cooling (water-bath) to 15—20 °C. The mixture was then left for 1 h at room temperature. Ethyl acetate (5 ml) was added, followed after 5 min by acetone (250 ml), Hyflo Supacel (30 g), and methanol (15 ml) (with stirring). After 3 min the mixture was shaken vigorously until it gelled (about 3 min), left for 15 min, then shaken again and filtered (pump) through a pad of Hyflo Supacel prepared with acetone. The residue was washed with acetone (300 ml) and the filtrate and washings were evaporated (rotary) to an orange gum (3.3 g). This (3 g) was purified by dissolving it in citrate–phosphate buffer, pH 3 (75 ml). The solution was washed with chloroform (×6), basified (KOH), almost saturated with K_2CO_3, and extracted with chloroform (3 × 50 ml). The basic extracts were combined, dried, and concentrated to give the *product* as a viscous oil (2.4 g, 59%), n_D^{23} 1.487 5. Molecular distillation gave an analytical sample (Found: C, 65.6; H, 10.3; N, 10.8. $C_7H_{13}NO$ requires C, 66.1; H, 10.2; N, 11.0%); $\nu_{max.}$ 2 790m (NCH_2) and 3 350m, br cm^{-1} (OH); δ 1.16 (3 H, d, *J* 6 Hz, 2-Me), 2.43 (3 H, s, NMe), *ca.* 3.2 (1 H, m, H-2), 3.3 br (1 H, variable, OH), *ca.* 3.4 (2 H, m, H-5), 4.13 (2 H, s, CH_2O), and 5.63 (1 H, m, H-4).

3-*Hydroxymethyl*-1,2-*dimethylpyrrole* (23).—Dehydrogenation of 3-ethoxycarbonyl-1,2-dimethyl-3-pyrroline (20) (2.5 g) by the method described above for (13) using DDQ (3.5 g) gave 3-ethoxycarbonyl-1,2-dimethylpyrrole (22) (2.2 g, 89%), b.p. 89—90 °C at 0.1—0.2 mmHg, n_D^{23} 1.509 0, m.p. 24 °C (lit.,[18] b.p. 136 °C at 9 mmHg, m.p. 24 °C); $\nu_{max.}$ 1 690s cm^{-1} (ester); δ 1.33 (3 H, t, ester Me), 2.50 (3 H, s, 2-Me), 3.50 (3 H, s, NMe), 4.26 (2 H, q, ester CH_2), 6.49 (1 H, d, *J* 2.5 Hz, H-4), and 6.51 (1 H, d, *J* 2.5 Hz, H-5). This ester (1 g) in anhydrous ether (100 ml) was heated under reflux with lithium aluminium hydride (0.6 g) for 1 h, then water (2 ml) was added portionwise with stirring.

[16] K. Morsch, *Monatsh.*, 1932, **60**, 50.

[17] J. F. Cavalla, J. Davoll, M. J. Dean, C. S. Franklin, D. M. Temple, J. Wax, and C. V. Winder, *J. Medicin. Pharm. Chem.*, 1961, **4**, 1.

[18] H. Shinohara, S. Misaki, and E. Inoto, *Nippon Kagaku, Zasshi*, 1962, **87**, 1167 (*Chem. Abs.*, 1963, **59**, 3867g).

After stirring under reflux for 1 h, the mixture was filtered (pump) and the residue washed with chloroform. The combined filtrates were dried and concentrated, and the residue distilled on a steam-bath at 0.1—0.2 mmHg to give 3-*hydroxymethyl*-1,2-*dimethylpyrrole* as a colourless oil (0.67 g, 89%) which crystallised, m.p. 28 °C (Found: C, 67.3; H, 8.8; N, 11.3. $C_7H_{11}NO$ requires C, 67.2; H, 8.8; N, 11.2%); $\nu_{max.}$ (film) 3 380s, br cm^{-1} (OH); δ 1.6 (1 H, br, variable, OH), 2.20 (3 H, s, 2-Me), 3.50 (3 H, s, NMe), 4.50 (2 H, s, CH_2O), 6.10 (1 H, d, *J* 3 Hz, H-4), and 6.52 (1 H, d, *J* 3 Hz, H-5). This compound was unstable at room temperature, rapidly becoming red. The Ehrlich reaction gave $\lambda_{max.}$ 565 nm (ε 59 000). It was refluxed for 1 h with an excess of ethyl isocyanate and 1,4-diazabicyclo[2.2.2]-octane (2 mg), the solution concentrated and the residue recrystallised from anhydrous ether–light petroleum (b.p. 60—80 °C) to give 3-(N-*ethylcarbamoyloxymethyl*)-2,3-*dimethylpyrrole* (24) as colourless leaflets, m.p. 57—58 °C (Found: C, 61.3; H, 8.3; N, 14.3. $C_{10}H_{16}N_2O_2$ requires C, 61.2; H, 8.2; N, 14.3%); δ 1.10 (3 H, t, *J* 7 Hz, NCH_2Me), 2.21 (3 H, s, 2-CH_2), 3.21 (2 H, 2 q, *J* 7 + 7 Hz, NCH_2Me), 3.51 (3 H, s, NMe), 4.6 (1 H, br, variable, NH), 5.0 (2 H, s, CH_2O), 6.13 (1 H, d, *J* 3 Hz, H-4), and 6.55 (1 H, d, *J* 3 Hz, H-5). This compound was unstable in water and alkylated 4-(*p*-nitrobenzyl)pyridine.

4-*Ethoxycarbonyl*-1-*methyl*-3-*pyrrolidone* (25).—Ethyl *N*-ethoxycarbonylmethyl-2-methylaminopropionate, prepared according to Cavalla *et al.*,[17] had b.p. 89 °C at 0.5 mmHg, n_D^{23} 1.436 5 (lit.,[17] b.p. 110 °C at 1.5 mmHg, n_D^{20} 1.435 6). This (20 g) was added to a suspension of sodium hydride (3 g) in benzene (110 ml) and the mixture was stirred (magnetic) under N_2 for 3 h without external heating, then extracted with water (3 × 25 ml). The combined extracts were quickly washed with ether, acidified (HCl) (with cooling), washed again with ether (×3), then adjusted with ammonia solution to pH 7—7.5 and immediately extracted with chloroform (4 × 20 ml). The combined chloroform extracts were dried and concentrated under reduced pressure to a pale brown oil (7.4 g, 47%) which quickly crystallised, m.p. 87—88 °C. Recrystallisation from ether gave the *pyrrolidone* (25) as colourless prisms, m.p. 94 °C (Found: C, 56.2; H, 7.5; N, 7.8. $C_8H_{13}NO_3$ requires C, 56.1; H, 7.6; N, 8.2%); $\nu_{max.}$ (KBr) 1 675s (C=C), 1 690s (conjugated ester), 2 380m (NCH_2), and 3 440m, br cm^{-1} (OH); before recrystallisation additional bands were present at 1 730s (ester) and 1 765m cm^{-1} (C=O); δ 1.29 (3 H, t, ester Me), 2.48 (3 H, s, NMe), 3—3.5 (5 H, ring protons), and 4.25 (2 H, q, ester CH_2). The *picrolonate* formed yellow prisms (from ethanol), m.p. 155 °C (decomp.) (Found: C, 49.8; H, 5.05; N, 16.0. $C_{18}H_{21}N_5O_8$ requires C, 49.7; H, 4.8; N, 16.1%). The *picrate*, yellow needles (from acetone–ethanol), had m.p. 151 °C (decomp.) (Found: C, 42.3; H, 4.0; N, 13.7. $C_{14}H_{16}N_4O_{10}$ requires C, 42.0; H, 4.0; N, 14.0%).

3-*Ethoxycarbonyl*-4-*methoxy*-1-*methyl*-3-*pyrroline* (51).—The pyrrolidone (25) (1.1 g) was treated with diazomethane in ether containing a few drops of methanol and the reaction set aside for 2 days at room temperature; the product was isolated as described above for (8), to give the *methoxypyrroline* (51) as an oil (0.54 g, 45%); $\nu_{max.}$ 1 648s (C=C), 1 698s (conjugated ester), and 2 790m cm^{-1} (NCH_2); δ 1.26 (3 H, t, ester *Me*), 2.47 (3 H, s, NMe), 3.68 (4 H, m, H-2 and H-5), 3.88 (3 H, s, OMe), and 4.18 (2 H, q, ester CH_2). The *picrolonate* formed orange-yellow prisms (from ethanol), m.p. 156 °C (Found: C, 50.4: H, 5.15; N, 15.2. $C_{19}H_{23}N_5O_8$ requires C, 50.8; H, 5.1; N, 15.6%).

3-*Ethoxycarbonyl*-4-*methoxy*-1-*methylpyrrole* (47).—The methoxypyrroline (51) (0.25 g) was dehydrogenated as described (above) for (13) using DDQ (0.28 g) to give the *methoxypyrrole* (0.15 g, 61%) which formed prisms, m.p. 48—50 °C, after molecular distillation at 80—95 °C (bath) and 0.008 mmHg (Found: C, 58.9; H, 7.2; N, 7.8. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.1; N, 7.7%); $\nu_{max.}$ 1 700s cm^{-1} (ester); δ 1.31 (3 H, t, ester Me), 3.57 (3 H, s, NMe), 3.74 (3 H, s, OMe), 4.26 (2 H, q, ester CH_2), 6.11 (1 H, d, *J* 2.5 Hz, H-5), and 7.02 (1 H, d, *J* 2.5 Hz, H-2).

3-*Ethoxycarbonyl*-1-*methyl*-3-*pyrroline* (26).—To a solution of 4-ethoxycarbonyl-1-methyl-3-pyrrolidone (25) (12 g) in ethanol (200 ml), cooled to 0 to −5 °C was added portionwise with stirring a solution of sodium borohydride (7 g) in ethanol (200 ml). The reaction was set aside for 2 h below 0 °C and then acidified with HCl, evaporated (rotary), and the residue redissolved in water (50 ml). The solution was washed with ether, basified with ammonia solution, and extracted with chloroform (4 × 30 ml). The combined extracts were dried and concentrated to give crude 3-ethoxycarbonyl-4-hydroxy-1-methylpyrrolidine (9.4 g, 77%) as a brown oil. To this, dissolved in pyridine (25 ml), was added a solution of *p*-tosyl chloride (29 g) in pyridine (100 ml), the mixture was heated on a steam-bath for 2.5 h, then worked up as described for (10) to give an oil (6 g, 71%). Distillation gave the pyrroline, b.p. 42—43 °C at 0.5 mmHg, n_D^{21} 1.466 4; $\nu_{max.}$ 1 635w (C=C), 1 710s (ester), and 2 790m cm^{-1} (NCH_2); δ 1.29 (3 H, t, ester Me), 2.48 (3 H, s, NMe), 3.65 (4 H, s, H-2 and H-5), 4.21 (2 H, q, ester CH_2), and 6.71 (1 H, s, H-4). Its *picrate* formed blades (from ethanol), m.p. 118 °C (Found: C, 43.6; H, 4.0; N, 14.9. $C_{14}H_{16}N_4O_9$ requires C, 43.8; 4.2; N, 14.6%).

3-*Ethoxycarbonyl*-1-*methylpyrrole* (27).—(*a*) 3-Ethoxycarbonyl-1-methyl-3-pyrroline (26) (1.6 g) was dehydrogenated with DDQ (2.8 g) in chloroform (100 ml) as described above for the preparation of (13) to give the *pyrrole* as an oil (1.5 g, 95%) which was distilled, b.p. 68 °C at 0.5 mmHg, n_D^{20} 1.504 3 (Found: C, 63.1; H, 7.0; N, 9.0. $C_8H_{11}NO_2$ requires C, 62.75; H, 7.2; N, 9.15%); $\nu_{max.}$ (film) 1 703s cm^{-1} (ester); δ 1.30 (3 H, t, ester Me), 3.65 (3 H, s, NMe), 4.26 (2 H, q, ester CH_2), 6.57 (2 H, d, *J* 2 Hz, H-4, 5), and 7.25 (1 H, s, H-2). (*b*) The pyrroline ester (26) (4.3 g) was heated under reflux with chloranil (12 g) in chloroform (150 ml) for 1.5 h. The solution was cooled (ice), excess of chloranil was filtered off and the filtrate was shaken with dilute potassium carbonate solution (×5). The chloroform phase was dried, diluted with an equal volume of light petroleum (b.p. 60—80 °C), boiled with charcoal, and concentrated to give 3-ethoxycarbonyl-1-methylpyrrole (3.5 g, 82%), identical with the above product.

3-*Hydroxymethyl*-1-*methylpyrrole* (28).—The pyrrole ester (27) (0.51 g) was reduced with lithium aluminium hydride (0.3 g) as described for (15), to give the *hydroxymethylpyrrole* as an oil (0.357 g, 96%), n_D^{24} 1.525 0 (Found: C, 65.1; H, 8.3. C_6H_9NO requires C, 64.9; H, 8.1%); $\nu_{max.}$ 3 430 cm^{-1} (OH); δ 1.75 (1 H, s, OH), 3.60 (3 H, s, NMe), 4.51 (2 H, s, CH_2O), 6.16 (1 H, t, H-4), 6.57 (1 H, d, H-5), and 6.60 (1 H, d, H-2). This compound, unlike other hydroxymethylpyrroles, did not polymerise readily; with dilute HCl it gave a white opalescence and with dilute HNO_3 an orange colour slowly developed.

Diethyl 1,5-*Dimethylpyrrole*-2,3-*dicarboxylate* (30).—A mixture of ethyl 2-ethoxalyl-4-oxovalerate [8] (25 g) and a solution of methylamine in ethanol (33%; 50 ml) was kept for 15 min at 20—30 °C (water cooling). The ethanol was

removed under reduced pressure, concentrated sulphuric acid (75 ml) was added, and after 15 min the mixture was poured into ethanol (150 ml) with ice-cooling. Then ethyl acetate (500 ml) and ice-cold water (1 l) were added with stirring. The organic phase was separated, the aqueous phase washed with ethyl acetate (200 ml), and the combined ethyl acetate extracts back-washed with water (100 ml) and with aqueous sodium hydrogencarbonate (100 ml), dried, and concentrated to a brown oil (13.5 g). Distillation gave the *pyrrole*, b.p. 126 °C at 0.15 mmHg, n_D^{21} 1.503 5 (Found: C, 60.0; H, 7.3; N, 6.1. $C_{12}H_{17}NO_4$ requires C, 60.25; H, 7.1; N, 5.9%); $\nu_{max.}$ (film) 1 700s cm^{-1} (ester); δ 1.29, 1.30 (6 H, 2 t, ester Me), 2.21 (3 H, s, 5-Me), 3.70 (3 H, s, NMe), 4.26, 4.31 (4 H, 2 q, ester CH_2), and 6.23 (1 H, s, H-4).

2,3-*Bishydroxymethyl*-1,5-*dimethylpyrrole* (32).—The pyrrole diester (30) (1.5 g) was reduced with lithium aluminium hydride (1.2 g) to give the crude *pyrrole* (0.9 g, 93%), m.p. 67—69 °C. Two recrystallisations from ethyl acetate–ether (charcoal) gave colourless needles, m.p. 71 °C (Found: C, 62.2; H, 8.0; N, 9.4. $C_8H_3NO_3$ requires C, 61.9; H, 8.4; N, 9.0%); $\nu_{max.}$ (KBr) 3 300s cm^{-1} (OH); δ 2.20 (3 H, s, 5-Me), 3.1 (2 H, br, variable, OH), 3.50 (3 H, s, NMe), 4.42 (2 H, s, 3-CH_2O), 4.50 (2 H, s, 2-CH_2O), and 5.85 (1 H, s, H-4). The compound decomposed slowly to a red polymer at room temperature. With the Ehrlich reagent it gave $\lambda_{max.}$ 528 nm (ε 35 800).

2,3-*Bishydroxymethyl*-5-*methyl*-1-*phenylpyrrole* (31).—Diethyl 5-methyl-1-phenylpyrrole-2,3-dicarboxylate [8] (29) (1.2 g) was reduced with lithium aluminium hydride (1.5 g) to give the *bishydroxymethylpyrrole* (0.7 g, 81%), m.p. 83—84 °C. Recrystallisation from ether–light petroleum (b.p. 60—80 °C) gave colourless leaflets, m.p 84 °C (Found: C, 72.3; H, 7.2; N, 6.75. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 6.9; N, 6.45%); $\nu_{max.}$ 3 300s, br cm^{-1} (OH); δ 2.01 (3 H, s, 5-Me), 2.78 (2 H, s, variable, OH), 4.31 (2 H, s, 3-CH_2O), 4.57 (2 H, s, 2-CH_2O), 6.0 (1 H, s, H-4), and *ca.* 7.4 (5 H, m, phenyl). The compound polymerised rapidly in the presence of acids and alkylated 4-(*p*-nitrobenzyl)pyridine; it gave practically no colour with the Ehrlich reagent.

2,4-*Bishydroxymethyl*-1-*methylpyrrole* (35).—1-Methylpyrrole-2,4-dicarboxylic acid (33) [9] (0.5 g) was reduced with lithium aluminium hydride (1.5 g) and the *product* (0.19 g, 45%) was recrystallised from ether–light petroleum (b.p. 60—80 °C) to give prisms, m.p. 102 °C (Found: C, 60.3; H, 8.1; N, 10.1. $C_7H_{11}NO_2$ requires C, 59.6; H, 7.8; N, 9.9%); $\nu_{max.}$ 3 400m, br cm^{-1} (OH); δ 1.45 (2 H, s, OH) 3.66 (3 H, s, NMe), 4.52 (2 H, s, 4-CH_2O), 4.59 (2 H, s, 2-CH_2O), 6.17 (1 H, d, *J* 2 Hz, H-3), and 6.67 (1 H, d, *J* 2 Hz, H-5). The Ehrlich reaction gave $\lambda_{max.}$ 565 nm (ε 5 750). After similar reduction of crude starting material containing also the 2,5-dicarboxylic acid (34) [9] the product contained 2,5-bishydroxymethyl-1-methylpyrrole (36), which was purified by fractional crystallisation from ether–light petroleum, m.p. 87—89 °C, $\nu_{max.}$ 3 400m, br cm^{-1} (OH); δ 1.56 (2 H, s, OH), 3.71 (3 H, s, NMe), 4.62 (4 H, s, CH_2O), and 6.05 (2 H, s, H-3 and H-4). The Ehrlich reaction gave $\lambda_{max.}$ 526 nm (ε 19 200), with an inflexion at 497 nm. Both the above compounds alkylated 4-(*p*-nitrobenzyl)pyridine.

3-*Hydroxymethyl*-1-*methylindole* (37).—To a solution of 1-methylindole-3-carbaldehyde (1.5 g), m.p. 68 °C (lit.,[19] 65 °C), in methanol (10 ml) was added sodium borohydride (1.5 g) in methanol (10 ml). After 45 min at room temperature water (30 ml) was added and the solution was saturated with K_2CO_3 and extracted with ether (3 × 30 ml). The combined extracts were dried (K_2CO_3) and concentrated to give the *product* (1.5 g, 100%) as needles, m.p. 30 °C (Found: C, 74.6; H, 7.2. $C_{10}H_{11}NO$ requires C, 74.5; H, 6.8%); δ 1.88 (1 H, s, OH), 3.66 (3 H, s, NMe), 4.80 (2 H, s, CH_2O), 6.96 (1 H, s, H-2), 7.25 (3 H, m, H-5, H-6, and H-7), and 7.5—7.8 (1 H, m, H-4).

This alcohol was heated under reflux with ethyl isocyanate for 10 min, the excess of reagent removed under reduced pressure, and the residue recrystallised from ether to give 3-N-*ethylcarbamoyloxymethyl*-1-*methylindole* (38) as prisms, m.p. 113—114 °C (Found: C, 66.8; H, 7.0; N, 11.8. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.9; N, 12.1%); δ 1.05 (3 H, t, NCH_2Me), 3.16 (2 H, dq, NCH_2Me), 3.71 (3 H, s, NMe), 4.6 (1 H, br, NH), 5.30 (2 H, s, CH_2O), 7.10 (1 H, s, H-2), 7.25 (3 H, m, H-5, H-6, and H-7), and 7.6—7.8 (1 H, m, H-4).

Esterification of 2,3-*Bishydroxymethyl*-1-*methylpyrrole*.—A batch of 2,3-bishydroxymethyl-1-methylpyrrole (39) prepared as previously described [1] formed platelets, m.p. 74 °C (from ether). It was otherwise identical (i.r., n.m.r., t.l.c.) with previous batches, m.p. 56 °C (prisms, from ether).[1] Material of m.p. 56 °C when melted or dissolved in ether, then seeded with the product of m.p. 74 °C, crystallised with m.p. 74 °C.

(*a*) *With acetyl chloride*. To a solution of acetyl chloride (2.5 ml) in benzene (5 ml) was added, with shaking and cooling to 10—20 °C, first a solution of triethylamine (1.5 ml) in benzene (3 ml), then, portionwise, a solution of 2,3-bishydroxymethyl-1-methylpyrrole (0.5 g) in benzene (2 ml) and triethylamine (2 ml). After 15 min at room temperature, the mixture was concentrated under reduced pressure on a steam-bath. Benzene (10 ml) and triethylamine (1 ml) were added and again removed under reduced pressure. This was repeated. The residue, a brown powder, was warmed with benzene (5 ml); anhydrous ether (50 ml) and light petroleum (b.p. 60—80 °C) were added and the mixture was shaken, boiled with charcoal, filtered, and the filtrate concentrated at up to 100 °C under reduced pressure to give an oil (0.745 g, 93%), n_D^{21} 1.499 0, which crystallised, m.p. 30 °C, and was identical (i.r., n.m.r.) with 2,3-bisacetoxymethyl-1-methylpyrrole (40).[1] The Ehrlich reaction gave $\lambda_{max.}$ 570 nm (ε 68 400).

(*b*) *With trimethylacetyl chloride*. To a solution of trimethylacetyl chloride (2 ml) in benzene (5 ml) was added, with shaking, triethylamine (0.5 ml) followed by a solution of 2,3-bishydroxymethyl-1-methylpyrrole (0.28 g) in benzene (5 ml) and triethylamine (3 ml). The mixture was kept in a closed flask for 0.5 h, then worked up as for (*a*) to give 2,3-*bistrimethylacetoxymethyl*-1-*methylpyrrole* (41) as a viscous oil (0.38 g, 61%) (Found: C, 66.4; H, 8.7; N, 4.3. $C_{17}H_{27}NO_4$ requires C, 66.0; H, 8.7; N, 4.5%); $\nu_{max.}$ (film) 1 725s cm^{-1} (ester); δ 1.20 (18 H, s, Me), 3.62 (3 H, s, NMe), 5.08 (2 H, s, 3-CH_2), 5.16 (2 H, s, 2-CH_2), 6.16 (1 H, d, *J* 3 Hz, H-4), and 6.64 (1 H, d, *J* 3 Hz, H-5). The compound partially polymerised on attempted molecular distillation at 100 °C (bath) and 0.01 mmHg.

(*c*) *With n-hexanoyl chloride*. To a solution of 2,3-bishydroxymethyl-1-methylpyrrole (0.14 g) and 1,4-diazabicyclo[2.2.2]octane (0.6 g) in benzene (10 ml) was added n-hexanoyl chloride (0.6 g) in benzene (3 ml) with vigorous shaking. The mixture was set aside at room temperature for 30 min, heated to 50—60 °C for 5 min, then worked up as for (*a*) except that several portions of xylene (5 ml) were added to the crude residue and removed at 100 °C under

[19] H. Wieland and G. Hesse, *Annalen*, 1934, **513**, 1.

reduced pressure to remove n-hexanoic anhydride impurity. 2,3-*Bis-n-hexanoyloxymethyl-1-methylpyrrole* (42) (0.3 g, 89%) was obtained as a viscous oil, n_D^{22} 1.481 0 (Found: N, 4.0. $C_{19}H_{31}NO_4$ requires N, 4.15%); $\nu_{max.}$ (film) 1 730s cm^{-1} (ester); δ 0.90 (6 H, t, Me), 1.4 (12 H, m, CH_2), 2.31 (4 H, t, CH_2CO), 3.63 (3 H, s, NMe), 5.09 (2 H, s, 3-CH_2), 5.19 (2 H, s, 2-CH_2), 6.18 (1 H, d, *J* 3 Hz, H-4), and 6.64 (1 H, d, *J* 3 Hz, H-5).

2-(2-*Trimethylacetoxyethyl*)-3-*trimethylacetoxymethyl*-1-*methylpyrrole* (17).—2-(2-Hydroxyethyl)-3-hydroxymethyl-1-methylpyrrole (15) (0.13 g) was allowed to react with trimethylacetyl chloride (1.5 ml) in benzene (2 ml) in the presence of triethylamine (1.5 ml) in a similar way to (*b*) (above) to give the *ester* as a viscous oil (0.16 g, 58%), n_D^{21} 1.480 0 (Found: C, 67.0; H, 9.0; N, 4.2. $C_{18}H_{29}NO_4$ requires C, 66.9; H, 9.0; N, 4.3%); $\nu_{max.}$ (film) 1 725s cm^{-1} (ester); δ 1.20 (18 H, s, Me), 2.95 (2 H, t, *J* 8 Hz, 2-CH_2), 3.61 (3 H, s, NMe), 4.15 (2 H, t, *J* 8 Hz, CH_2-O), 5.00 (2 H, s, 3-CH_2), 6.12 (1 H, d, *J* 3 Hz, H-4), and 6.54 (1 H, d, *J* 3 Hz, H-5).

2,3-*Bisacetoxymethyl-5-methyl-1-phenylpyrrole* (43).—Prepared from 2,3-bishydroxymethyl-5-methyl-1-phenylpyrrole (31) (0.5 g) and acetyl chloride (2.5 ml) in benzene (10 ml) and triethylamine (2 ml) by the method described under (*a*) (above), the *ester* was a viscous oil (yield 97%), n_D^{22} 1.537 0 (Found: C, 67.8; H, 6.4; N, 4.9. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.3; N, 4.65%); $\nu_{max.}$ (film) 1 735 cm^{-1} (ester); δ 1.92 (3 H, s, 3-Ac), 2.07 (3 H, s, 2-Ac), 2.02 (3 H, s, 5-Me), 4.90 (2 H, s, 3-CH_2), 5.10 (2 H, s, 2-CH_2), 6.10 (1 H, s, H-4), and 7.4 (5 H, m, Ph).

Diethyl 4-*Acetoxy-1-methyl-3-pyrroline-2,3-dicarboxylate* (49).—Diethyl 1-methyl-4-oxopyrrolidine-2,3-dicarboxylate (48) [1] (2.43 g) was dissolved in aqueous sodium hydroxide (0.4 g), the solution was evaporated to dryness (rotary), and the residue redissolved in *NN*-dimethylformamide (20 ml). Acetyl chloride (4 ml) was added and the mixture was stirred for 15 min, then poured with stirring into aqueous disodium phosphate (30%, 120 ml). After 5 min the solution was extracted with ether (3 × 30 ml) and the combined extracts back-washed with dilute aqueous sodium hydrogencarbonate, then with water, dried, and concentrated to give a viscous oil (0.6 g, 21%). This formed a *picrolonate*, as yellow blades (from ethanol), m.p. 150 °C (Found: C, 50.4; H, 5.15; N, 12.7. $C_{23}H_{27}N_5O_{11}$ requires C, 50.3; H, 4.9; N, 12.75%). The base, recovered from the picrolonate using anion-exchange resin (Dowex I) had $\nu_{max.}$ (film) 1 670m (C=C), 1 715—1 740s, br (esters), 1 780s (enol acetate), and 2 890m cm^{-1} (NCH_2); δ 1.25, 1.28 (6 H, 2 t, CH_2Me), 2.26 (3 H, s, acetyl Me), 2.55 (3 H, s, NMe), 3.8 (2 H, m, H-5), and 4.18, 4.23 (4 H, 2 q, CH_2Me).

Diethyl 4-*Acetoxy-1-methylpyrrole-2,3-dicarboxylate* (50).—To the pyrroline (49) (0.4 g) in chloroform (10 ml) was added a solution of DDQ (0.4 g) in chloroform (30 ml). The reaction was set aside for 1 h at room temperature, and the crude product was isolated in the same way as (13) to give a brown oil (0.26 g, 66%). This was dissolved in ether (5 ml), light petroleum (b.p. 60—80 °C) (50 ml) was added, and the solution shaken in turn with dilute aqueous potassium carbonate, water, and dilute HCl, dried, and concentrated. Molecular distillation of the residue (bath, 140—150 °C) gave the *pyrrole* as a viscous oil (Found: C, 55.0; H, 6.1; N, 4.8. $C_{13}H_{17}NO_6$ requires C, 55.1; H, 6.0; N, 4.95%); $\nu_{max.}$ (film) 1 710s (ester), 1 760s (acetyl), and 3 140w cm^{-1} (pyrrole); δ 1.33 (6 H, t, CH_2Me), 2.25 (3 H, s, MeCO), 3.81 (3 H, s, NMe), 4.26, 4.28 (4 H, 2 q, CH_2Me), and 6.80 (1 H, s, H-5).

Dimethyl 4-*acetoxy-1-methylpyrrole-2,3-dicarboxylate*, similarly prepared, formed colourless leaflets, m.p. 60—62 °C (Found: C, 52.2; H, 5.5; N, 5.3. $C_{11}H_{13}NO_6$ requires C, 51.8; H, 5.1; N, 5.5%); δ 2.25 (3 H, s, MeCO), 3.82, 3.83 (6 H, 2 s, ester Me), 3.85 (3 H, s, NMe), and 6.80 (1 H, s, H-5).

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