900. *Pharmacodynamic Compounds. Part I. Some Antispasmodics derived from Substituted 2-Pyrrolidinylalkanols.*

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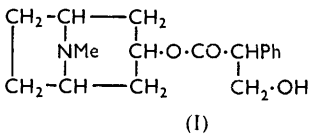
The preparation of some 1-alkyl-2-pyrrolidinylalkanols is described. These have been used to prepare a number of esters of diphenylacetic, benzilic, fluorene-9-carboxylic, and xanthen-9-carboxylic acid. Acid addition and quaternary ammonium salts of these esters have been prepared. Some have antispasmodic (antiacetylcholine) activity.

Numerous compounds modelled on the structure of atropine (I) have been synthesised in attempts to find compounds with the same desirable effects on the gastro-intestinal tract, but without some of the side-effects possessed by the parent alkaloid. In nearly all these compounds, the basic nitrogen atom forms part of either a substituted amino-group as in (II) or a simple heterocyclic group (pyrrolidine, piperidine, morpholine) in which the alkyl side chain is attached to the heterocyclic nitrogen atom as in (III).

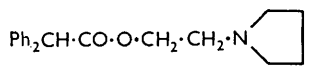
The structure of the tropine moiety of atropine bears an obvious relation to the

piperidinol (IV) and pyrrolidinylalkanols (V), noted by Burtner and Brown.[1] However, although a number of workers [2] have prepared atropine-like esters incorporating the piperidinol structure, it is only recently that Blicke and Lu [3] have prepared esters incorporating the pyrrolidinylmethanol (V; $R^1 = H$, $R^2 = Me$; $n = 1$). Their publication appeared during a systematic study of esters of (V) which was carried out in these Laboratories during the last four years and part of which is the subject of this communication.

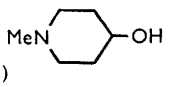


(I)

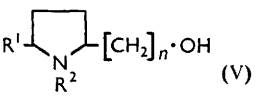
$Ph_2CH\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot NEt_2$ (II)



(III)



(IV)



(V)

Methyl pyrrole-2-carboxylate was prepared by diazomethane from pyrrole-2-carboxylic acid which was obtained by a modification of Oddo's method.[4] The direct preparation of the ethyl ester by the method of Maxim *et al.*,[5] gave only small yields of an impure product. The potassium derivative of the methyl ester with excess of methyl iodide in toluene gave methyl 1-methylpyrrole-2-carboxylate which on reduction with lithium aluminium hydride gave, in excellent yield, 2-hydroxymethyl-1-methylpyrrole, obtained recently by Ryskiewicz and Silverstein [6] by reduction of 2-formyl-1-methylpyrrole with sodium borohydride. However, on attempting to dissolve the alcohol in glacial acetic acid for hydrogenation, it polymerised explosively: Ryskiewicz and Silverstein [6] also comment on the ease of polymerisation of this alcohol under comparatively mild conditions such as shaking its ethereal solution with aqueous sodium hydrogen sulphite. Hydrogenation in methanol (platinic oxide catalyst) under pressure did not proceed at room temperature, and at 168° after 21 hr. a very small amount of the required 2-hydroxymethyl-1-methylpyrrolidine was obtained, identified as a picrate identical with that obtained by Renshaw and Cass.[7]

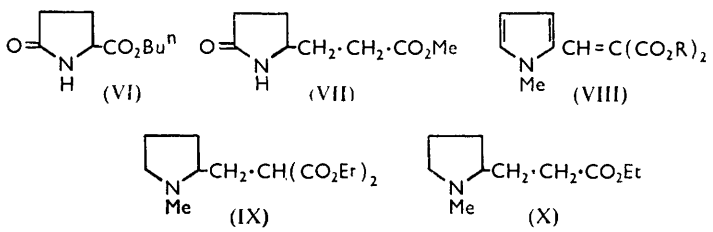
This alcohol was finally obtained directly by the reduction of diethyl pyrrolidine-1 : 2-dicarboxylate [8] with lithium aluminium hydride by analogy with the work of Dannley *et al.*[9] who reported excellent yields of methylated amines on reduction of the corresponding urethanes.

As an alternative route, butyl 5-oxopyrrolidine-2-carboxylate (VI) prepared from L-glutamic acid was reduced with lithium aluminium hydride in ether to 2-hydroxymethylpyrrolidine (V; $R^1 = R^2 = H$; $n = 1$) in 70% yield.[10] Methylation by formaldehyde and formic acid then gave 2-hydroxymethyl-1-methylpyrrolidine (V; $R^1 = H$, $R^2 = Me$; $n = 1$). Blicke and Lu [3] have described a similar method for the preparation of this alcohol.

2-(2-Hydroxyethyl)-1-methylpyrrolidine (V; $R^1 = H$, $R^2 = Me$; $n = 2$) was prepared by Hess, Merck, and Ulbrig,[11] but in view of the difficulties experienced in the preparation

[1] Burtner and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 630.
[2] Burtner and Cusic, *ibid.*, 1943, **65**, 262; Burtner, U.S.P. 2,387,879/1945; Biel, Friedman, Leiser, and Sprengler, *J. Amer. Chem. Soc.*, 1952, **74**, 1485; Biel, Drukker, Friedman, Horner, Leiser, and Sprengler, *ibid.*, 1955, **77**, 2250; Feldkamp, Faust, and Cushman, *ibid.*, 1952, **74**, 3831; Lands, *J. Pharmacol.*, 1951, **102**, 210.
[3] Blicke, U.S.P. 2,695,301/1954; Blicke and Lu, *J. Amer. Chem. Soc.*, 1955, **77**, 29.
[4] Oddo, *Gazzetta*, 1912, **42**, 257.
[5] Maxim, Zugravescu, and Fulga, *Bull. Soc. chim. France*, 1938, **5**, 44.
[6] Ryskiewicz and Silverstein, *J. Amer. Chem. Soc.*, 1954, **76**, 5802; *J. Org. Chem.* 1955, **20**, 668.
[7] Renshaw and Cass, *J. Amer. Chem. Soc.*, 1939, **61**, 1195.
[8] Signaigo and Adkins, *ibid.*, 1936, **58**, 1122.
[9] Dannley, Lukin, and Shapiro, *J. Org. Chem.*, 1955, **20**, 92.
[10] Cf. Karrer and Portman, *Helv. Chim. Acta*, 1948, **31**, 2088.
[11] Hess, Merck, and Ulbrig, *Ber.*, 1915, **48**, 1886.

of the starting material 2-(2-hydroxyethyl)pyrrole (by the action of ethylene oxide on pyrrylmagnesium bromide), as well as in its subsequent hydrogenation, an alternative route utilising the more readily available ethyl α-(1-methyl-2-pyrryl)acetate [12] was adopted. Hydrogenation of this ester in acetic acid at room temperature under pressure gave ethyl α-(1-methyl-2-pyrrolidinyl)acetate, which on reduction with lithium aluminium hydride gave 2-(2-hydroxyethyl)-1-methylpyrrolidine (V; $R^1 = H$, $R^2 = Me$; $n = 2$).



1-Ethyl-2-(2-hydroxyethyl)pyrrolidine (V; $R^1 = H$, $R^2 = Et$, $n = 2$), 1-*n*-propyl-2-(2-hydroxyethyl)-1-*n*-propylpyrrolidine (V; $R^1 = H$, $R^2 = Pr$; $n = 2$), and 2-(2-hydroxyethyl)-1 : 5-dimethylpyrrolidine (V; $R^1 = R^2 = Me$; $n = 2$) were obtained by analogous reactions. 1-Benzyl-2-(2-hydroxyethyl)pyrrolidine (V; $R^1 = H$, $R^2 = CH_2Ph$; $n = 2$) was obtained by reduction, with lithium aluminium hydride, of ethyl α-(1-benzyl-2-pyrrolidinyl)acetate which was itself obtained by the action of benzyl bromide on ethyl 2-pyrrolidinylacetate.[13] The same alcohol (V; $R^1 = H$, $R^2 = CH_2Ph$; $n = 2$) was prepared by Baker, Schaub, and Williams [14] by similar reduction of ethyl α-(1-benzyl-5-oxo-Δ^2-pyrrolinyl)acetate.

2-(3-Hydroxypropyl)-1-methylpyrrolidine (V; $R^1 = H$, $R^2 = Me$; $n = 3$) has been prepared by two routes. In the first methyl β-(5-oxo-2-pyrrolidinyl)propionate (VII) was prepared from dimethyl γ-nitropimelate by the method of Leonard *et al.*[15] Reduction with lithium aluminium hydride gave 2-(3-hydroxypropyl)pyrrolidine (V; $R^1 = R^2 = H$; $n = 3$) which on methylation with formaldehyde and formic acid then gave the desired alcohol (V; $R^1 = H$, $R^2 = Me$; $n = 3$). The second route utilised the condensation of 2-formyl-1-methylpyrrole with diethyl malonate to give the ester (VIII; R = Et) which was readily hydrolysed to the dicarboxylic acid (VIII; R = H). Since attempts to decarboxylate this acid failed, the diester was hydrogenated under pressure at room temperature in acetic acid (platinic oxide catalyst) to the reduced ester (IX) which on hydrolysis with alcoholic potassium hydroxide solution (0·5 equiv.) was converted into ethyl β-(1-methyl-2-pyrrolidinyl)propionate (X). Reduction with lithium aluminium hydride then gave the desired alcohol (V; $R^1 = H$, $R^2 = Me$; $n = 3$).

Esters of diphenylacetic, fluorene-9-carboxylic, and xanthen-9-carboxylic acid incorporating the *N*-alkyl-2-pyrrolidinylalkanol were prepared by conventional treatment of the acid chlorides with the alkanol in benzene, chloroform, or ether. Esters of benzilic acid were prepared by King and Holmes's method [16] in which benzilic acid was converted by phosphorus pentachloride into α-chlorodiphenylacetyl chloride which was then allowed to react with the basic alkanol, the resulting α-chlorodiphenylacetate hydrochloride, which was sometimes isolated, being hydrolysed with water to the diphenylglycollate hydrochloride. This was then either isolated directly or converted into the free base, and the hydrochloride was prepared from this as a separate experiment. Quaternary salts of the basic esters were prepared and isolated by the usual techniques.

The diphenylglycollate, its hydrochloride, and its methiodide prepared from the

[12] Sohl and Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 3828; Nenitzescu and Solomonica, *Ber.*, 1931, **64**, 1924.
[13] Clemo and Melrose, *J.*, 1942, 424.
[14] Baker, Schaub, and Williams, *J. Org. Chem.*, 1952, **17**, 117.
[15] Leonard, Hruda, and Long, *J. Amer. Chem. Soc.*, 1947, **69**, 690.
[16] King and Holmes, *J.*, 1947, 164.

2-hydroxymethyl-1-methylpyrrolidine derived from L-glutamic acid did not depress the melting points of the corresponding compounds prepared from the racemic form of the alcohol, although the melting points differed by several degrees. Blicke and Lu [3] obtained a diphenylglycollate hydrochloride by the reaction of 2-chloromethyl-1-methylpyrrolidine with benzilic acid in propan-2-ol, but give a melting point lower than that observed by us.

The pharmacological properties of the ester hydrochlorides and their quaternary salts have been investigated by Mr. D. M. Brown of these Laboratories and the results, which demonstrate the high antispasmodic activity of some of the benzilic acid esters, have been published.[17]

Experimental

Pyrrole-2-carboxylic Acid.—The following modification of Oddo's method [4] gave reproducible results: Freshly distilled pyrrole (99 g.) was added to a boiling solution of the Grignard reagent from magnesium turnings (34 g.) and ethyl bromide (157 g.) in ether (450 ml.), during 0·5 hr. with stirring. The mixture was then refluxed for 2 hr. and poured with stirring on a large excess of powdered solid carbon dioxide. After evaporation of excess of carbon dioxide the residue was acidified with 5N-sulphuric acid and filtered. The ether layer was separated and the aqueous layer extracted with ether (4 × 100 ml.). The combined ether layers were washed with water (3 × 75 ml.), dried ($MgSO_4$), and evaporated. The unchanged pyrrole (32 g.) was removed at 100° (bath)/3 mm., and the residual solid then dissolved in aqueous ammonia solution (*d* 0·88) and extracted with ether. This ether extract was rejected and the ammonia solution on acidification with concentrated hydrochloric acid gave pyrrole-2-carboxylic acid (53 g., 47%), m. p. 180—181°, sufficiently pure for esterification.

The acid (11 g.) in dry methanol (140 ml.) with diazomethane [400 ml. from nitrosomethylurea (40 g.)] gave the pale yellow methyl ester (10 g., 74%), m. p. 70—72° (Blicke and Blake [18] give m. p. 73°).

Methyl 1-Methylpyrrole-2-carboxylate.—A solution of methyl pyrrole-2-carboxylate (21 g.) in dry toluene (25 ml.) was added during 0·5 hr. to a boiling, stirred suspension of " molecular potassium " (6·5 g.) in dry toluene (150 ml.). After refluxing for 23 hr. the solvent was removed under reduced pressure and the residual solid refluxed, with stirring, with excess of methyl iodide (101 ml.) for 36 hr. The inorganic material was collected and washed with dry ether. After evaporation of the filtrate the residual liquid, on distillation *in vacuo*, gave *methyl 1-methylpyrrole-2-carboxylate* (28 g., 77%), b. p. 62°/1 mm., $n_D^{18\cdot5}$ 1·5222 (Found: C, 60·7; H, 6·5; N, 10·2. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1%).

2-Hydroxymethyl-1-methylpyrrole.—The preceding ester (37 g.) in dry ether (*ca.* 150 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (10 g.) in dry ether (300 ml.) during 0·5 hr. (gentle ebullition). The mixture was then refluxed for 2·5 hr. and thereafter cooled. Ice-cold water (35 ml.) was cautiously added, the solution filtered, and the inorganic residue washed with ether. The combined washings and the filtrate were dried ($MgSO_4$) and evaporated and the residual liquid was distilled *in vacuo* to give 2-hydroxymethyl-1-methylpyrrole (23 g., 87%), b. p. 82°/2 mm., $n_D^{15\cdot5}$ 1·5308 (Found: C, 65·0; H, 8·4; N, 12·0. Calc. for C_6H_9ON: C, 64·9; H, 8·1; N, 12·6%). The product dissolved in acetic acid to a deep yellow solution, from which a yellow solid began to separate. This quickly became red and a rapid exothermic polymerisation resulted in a violent explosion.

Diethyl Pyrrolidine-1 : 2-dicarboxylate.—Diethyl pyrrole-1 : 2-dicarboxylate [8] (30 g.) in glacial acetic acid (75 ml.) was hydrogenated at an initial pressure of 100 atm. in the presence of platinic oxide (3 g.) at room temperature for 2 hr.: up-take (6 atm.) of hydrogen was by then complete. The catalyst was removed and the acetic acid neutralised with saturated aqueous potassium carbonate. Potassium acetate separated and sufficient anhydrous potassium carbonate (66 g.) was added to saturate the aqueous layer. The inorganic material was collected and washed with ether (4 × 50 ml.). The ether was separated from the filtrate, and the aqueous layer was further extracted with ether (4 × 250 ml.). The combined ether extracts were dried ($MgSO_4$) and evaporated and the residual oil distilled *in vacuo* to give diethyl pyrrolidine-1 : 2-dicarboxylate (25 g., 83%), b. p. 131—133°/4 mm., n_D^{23} 1·4545 (Signaigo and Adkins [8] give b. p. 133—134°/8 mm., n_D^{25} 1·4530).

[17] Acred, Atkins, Bainbridge, Brown, Quinton, and Turner, *Brit. J. Pharmacol.*, 1957, **12**, 447.
[18] Blicke and Blake, *J. Amer. Chem. Soc.*, 1930, **52**, 235.

Butyl 5-Oxopyrrolidine-2-carboxylate.—This was prepared by esterification of L-glutamic acid (Segel's procedure [19]) in 55—65% yield and had b. p. 180°/6·5 mm., $n_D^{19\cdot5}$ 1·4739 (Found: C, 58·2; H, 8·1; N, 8·0. Calc. for $C_9H_{15}O_3N$: C, 58·4; H, 8·1; N, 7·6%) (lit.; [10] yield 65%; b. p. 157—160°/1·3 mm.).

2-*Hydroxymethylpyrrolidine.*—The foregoing butyl ester (80 g.) in ether (3·5 l.) was reduced with lithium aluminium hydride (40 g.) in dry ether (3·5 l.). The mixture was refluxed for 18—22 hr. and then worked up as described previously to give after careful fractionation 2-hydroxymethylpyrrolidine (67%), b. p. 89°/6 mm., n_D^{20} 1·4846 (Found: C, 59·2; H, 10·7. Calc. for $C_5H_{11}ON$: C, 59·4; H, 10·9%). Its *picrate*, prepared in ether, crystallised from ethyl acetate–ether as prisms, m. p. 106—107° (Found: C, 40·2; H, 4·4; N, 17·2. $C_{11}H_{14}O_8N_4$ requires C, 40·0; H, 4·2; N, 17·0%).

2-*Hydroxymethyl*-1-*methylpyrrolidine.*—(*a*) 2-Hydroxymethylpyrrolidine (50 g.) was added with cooling to anhydrous formic acid (95 ml., *d* 1·2), followed by 40% aqueous formaldehyde (65 ml.). When the initial vigorous evolution of carbon dioxide had subsided, the whole was refluxed for 16—20 hr., cooled, acidified with 5N-hydrochloric acid (230 ml.), and evaporated *in vacuo* to dryness, a dark gum being obtained which on cooling set to needles. These were dissolved in a minimum quantity of water (*ca.* 150 ml.), saturated with sodium hydroxide, and extracted with chloroform (7 × 50 ml.). The combined extracts were dried (K_2CO_3), the chloroform removed at 400 mm., and the residual oil distilled *in vacuo*. The fraction, b. p. 49—50°/2 mm., on redistillation gave 2-hydroxymethyl-1-methylpyrrolidine (35 g., 61%), b. p. 57°/4 mm., $n_D^{19\cdot5}$ 1·4692 (Found: C, 62·1; H, 11·1. Calc. for $C_6H_{13}ON$: C, 62·6; H, 11·3%). Blicke and Lu [3] give b. p. 67—69°/12 mm.

(*b*) Diethyl pyrrolidine-1 : 2-dicarboxylate (25 g.) in ether (1 l.) was reduced by dropwise addition during 0·5 hr. to a stirred suspension of lithium aluminium hydride (9 g.) in dry ether (2 l.). The mixture was refluxed for 22 hr. and then worked up as described previously to give 2-hydroxymethyl-1-methylpyrrolidine (9 g., 65%), b. p. 68—70°/14 mm., n_D^{23} 1·4678 (Renshaw and Cass [7] report b. p. 77°/15 mm.). The picrate, prepared in ether, crystallised from ethanol as needles, m. p. 173—174° (lit.,[7] m. p. 173°).

1 : 2-*Dimethylpyrrole.*—This was obtained by Rapoport and Jorgensen's method.[20] It was also obtained as follows by Wolff–Kishner reduction of 2-formyl-1-methylpyrrole (cf. King and Nord [21]). 2-Formyl-1-methylpyrrole (23 g.), ethylene glycol (170 ml.), and 60% aqueous hydrazine hydrate (63 ml.) were heated in a bath to 160° (internal temperature) and the water removed by distillation. The whole was then allowed to cool to 60° and potassium hydroxide (pellets) (42 g.) added. Heating was then continued at an internal temperature of 130° for 1 hr. until nitrogen ceased to be evolved. After cooling, the mixture was extracted with ether (6 × 50 ml.), the ether extracts were dried (KOH) and evaporated, and the residual oil (10 g., 48%) was distilled, to give 1 : 2-dimethylpyrrole, b. p. 138°, n_D^{27} 1·4898 (Rapoport and Jorgensen [20] give b. p. 139—140°, n_D^{25} 1·4913).

α-(1-*Alkyl*-2-*pyrryl*)*acetates.*—These were obtained following the general method described by Sohl and Shriner [12] for ethyl 1-methyl-2-pyrrylacetate: Ethyl 1-ethyl-2-pyrrylacetate (41%), b. p. 102—110°/3 mm. Ethyl 1-*n*-propyl-2-pyrrylacetate (36%), b. p. 79—87°/0·05 mm., n_D^{24} 1·4847. *Ethyl* 1 : 2-*dimethyl*-5-*pyrrylacetate* (71%), b. p. 98°/1 mm., n_D^{16} 1·4950 (Found: C, 66·0; H, 8·5; N, 8·3. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%).

α-(1-*Substituted* 2-*pyrrolidinyl*)*acetates.*—These were obtained by the following modification of Sohl and Shriner's method: [12]

Ethyl 1-*methyl*-2-*pyrrolidinylacetate.* Hydrogenation of ethyl 1-methyl-2-pyrrylacetate in glacial acetic acid at 100 atm. for 16 hr. at room temperature in the presence of platinic oxide gave ethyl 1-methyl-2-pyrrolidinylacetate (65%), b. p. 65—66°/2·5 mm., $n_D^{18\cdot5}$ 1·4464 (Found: C, 63·1; H, 9·8; N, 8·4. Calc. for $C_9H_{17}O_2N$: C, 63·2; H, 9·9; N, 8·2%) (Sohl and Shriner [12] report b. p. 88—89°/10 mm., n_D^{20} 1·4465).

Similarly were prepared:

Ethyl 1-*ethyl*-2-*pyrrolidinylacetate* (75%), b. p. 83—84°/4 mm., n_D^{20} 1·4487 (Found: C, 64·5; H, 10·6; N, 7·3. $C_{10}H_{19}O_2N$ requires C, 64·9; H, 10·3; N, 7·6%).

Ethyl 1-n-*propyl*-2-*pyrrolidinylacetate* (41%), b. p. 99°/4·5 mm., n_D^{23} 1·4488 (Found: C, 66·2; H, 10·5; N, 7·4. $C_{11}H_{21}O_2N$ requires C, 66·3; H, 10·6; N, 7·0%) [*hydrochloride* crystallised

[19] Segel, *J. Amer. Chem. Soc.*, 1952, **74**, 852.
[20] Rapoport and Jorgensen, *J. Org. Chem.*, 1949, **14**, 664.
[21] King and Nord, *ibid.*, 1949, **14**, 641.

from ethyl acetate–methanol–ether as prisms, m. p. 130—131° (Found: C, 55·9; H, 9·3; N, 5·9. $C_{11}H_{22}O_2NCl$ requires C, 56·1; H, 9·3; N, 5·9%)].

Ethyl 1 : 2-*dimethyl*-5-*pyrrolidinylacetate* (73%), b. p. 71°/1·5 mm., n_D^{20} 1·4462 (C, 64·2; H, 10·2; N, 7·8. $C_{10}H_{19}O_2N$ requires C, 64·9; H, 10·3; N, 7·6%) {*picrate* [from ethyl acetate–light petroleum (b. p. 40—60°)], needles, m. p. 119° (Found: C, 46·7; H, 5·5; N, 13·7. $C_{16}H_{22}O_9N_4$ requires C, 46·3; H, 5·3; N, 13·6%)}.

Ethyl 1-*Benzyl*-2-*pyrrolidinylacetate*.—Ethyl 2-pyrrolidinylacetate [13] (24 g.), anhydrous potassium carbonate (16 g.), and benzyl bromide (26 g.) in dry toluene (150 ml.) were refluxed for 1·5 hr. and then filtered. The inorganic residue was extracted with boiling toluene (*ca.* 30 ml.), and the combined toluene filtrates were evaporated. The residual liquid on distillation *in vacuo* gave *ethyl* 1-*benzyl*-2-*pyrrolidinylacetate* (25 g., 66%), b. p. 108°/0·02 mm., $n_D^{21·5}$ 1·5095 (Found: C, 72·9; H, 8·4; N, 5·9. $C_{15}H_{21}O_2N$ requires C, 72·9; H, 8·5; N, 5·7%). [*Picrate*, needles (from ethyl acetate–ether), m. p. 99—100° (Found: C, 53·2; H, 5·2; N, 11·9. $C_{21}H_{24}O_9N_4$ requires C, 53·0; H, 5·0; N, 11·8%).]

1-*Substituted* 2-(2-*Hydroxyethyl*)*pyrrolidines*.—The following were obtained by reduction of the corresponding esters in ether with lithium aluminium hydride in the usual manner:

2-(2-Hydroxyethyl)-1-methylpyrrolidene (65%), b. p. 77°/3·5 mm., n_D^{18} 1·4726 (Found: C, 64·7; H, 11·2; N, 11·2. Calc. for $C_7H_{15}ON$: C, 65·1; H, 11·6; N, 10·9%) (Hess *et al.*[11] give b. p. 110—120°/14 mm.). The *tri-iodophenylurethane*, prepared in light petroleum (b. p. 60—80°), crystallised from light petroleum (b. p. 110—120°)–chloroform (trace) as needles, m. p. 173—174° (decomp.) (Found: C, 27·2; H, 2·9. $C_{14}H_{17}O_2N_2I_3$ requires C, 26·8; H, 2·7%).

1-*Ethyl*-2-(2-*hydroxyethyl*)*pyrrolidine* (77%), b. p. 95°/3·5 mm., n_D^{20} 1·4742 (Found: C, 66·5; H, 11·9; N, 9·9. $C_8H_{17}ON$ requires C, 67·1; H, 11·9; N, 9·8%).

2-(2-*Hydroxyethyl*)-1-n-*propylpyrrolidine* (75%), b. p. 91°/1 mm., n_D^{24} 1·4685 (Found: N, 9·2. $C_9H_{19}ON$ requires N, 8·9%). The *tri-iodophenylurethane*, prepared in light petroleum (b. p. 60—80°), crystallised from light petroleum (b. p. 80—100°) as prisms, m. p. 79—80° (Found: C, 28·9; H, 3·3; N, 4·2. $C_{16}H_{21}O_2N_2I_3$ requires C, 29·4; H, 3·2; N, 4·3%).

5-(2-Hydroxyethyl)-1 : 2-dimethylpyrrolidine (78%), b. p. 68—72°/1·5 mm., n_{19}^D 1·4795 (analysis was unsatisfactory).

1-*Benzyl*-2-(2-*hydroxyethyl*)*pyrrolidine* (79%), b. p. 110°/0·05 mm., n_D^{24} 1·5370 (Found: C, 75·3; H, 9·6; N, 6·5. Calc. for $C_{13}H_{19}ON$: C, 76·1; H, 9·3; N, 6·8%) (Baker *et al.*[14] give b. p. 112—115°/0·05 mm.). The *picrate* crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 78—79° (Found: C, 52·5; H, 5·0; N, 13·3. $C_{19}H_{22}O_8N_4$ requires C, 52·5; H, 5·1; N, 12·9%).

2-(3-*Hydroxypropyl*)*pyrrolidine*.—A solution of methyl β-(5-oxo-2-pyrrolidinyl)propionate [15] (22 g.) in dry tetrahydrofuran (110 ml.) was added dropwise to a suspension of lithium aluminium hydride (15 g.) in dry ether (250 ml.) and tetrahydrofuran (110 ml.). Isolation in the usual manner gave 2-(3-*hydroxypropyl*)*pyrrolidine* (5 g., 31%), b. p. 118°/4·5 mm., m. p. *ca.* 30° (Found: C, 64·6; H, 11·7; N, 11·0. $C_7H_{15}ON$ requires C, 65·1; H, 11·6; N, 10·9%).

Ethyl α-*Ethoxycarbonyl*-β-(1-*methyl*-2-*pyrryl*)*acrylate*.—2-Formyl-1-methylpyrrole [6] (100 g.), diethyl malonate (155 ml.), ethanol (920 ml.), and piperidine (64 ml.) were refluxed for 4 hr. A part of the solvent (*ca.* 500 ml.) was evaporated and the residual solution cooled to give pale pink crystals which were filtered off and washed with a small amount of light petroleum (b. p. 80—100°)–ethanol (3 : 1), to give crystals (76 g.), m. p. 72°. The combined washings and the filtrate were further evaporated to give an oil which crystallised to a second crop of crystals (86·5 g.), m. p. 71°. Repetition of this procedure gave a further crop of crystals (13·5 g.), m. p. 68—69°, the total yield of *ethyl* α-*ethoxycarbonyl*-β-(1-*methyl*-2-*pyrryl*)*acrylate* being 176 g. (76%). Crystallisation from light petroleum (b. p. 80—100°)–ethanol (3 : 1) gave prisms, m. p. 73° (Found: C, 62·0; H, 6·5; N, 5·7. $C_{13}H_{17}O_4N$ requires C, 62·2; H, 6·8; N, 5·6%).

α-*Carboxy*-β-(1-*methyl*-2-*pyrryl*)*acrylic Acid*.—The above ester (5 g.) was warmed with potassium hydroxide (4·3 g.) in water (15 ml.) to give complete solution, which was then refluxed for 0·25 hr. Evaporation to half volume *in vacuo*, followed by ether-extraction (3 × 10 ml.), gave an aqueous layer which was acidified with concentrated hydrochloric acid (8 ml.). The separated solid (3 g., 81%) was filtered off and crystallised from acetone–light petroleum (b. p. 60—80°) to give α-*carboxy*-β-(1-*methyl*-2-*pyrryl*)*acrylic acid* as yellow prisms, m. p. 167° (Found: C, 55·4; H, 4·8; N, 7·5. $C_9H_9O_4N$ requires C, 55·3; H, 4·6; N, 7·2%).

Ethyl α-Ethoxycarbonyl-β-(1-methyl-2-pyrrolidinyl)propionate.—Ethyl α-ethoxycarbonyl-β-(1-methyl-2-pyrryl)acrylate (64 g.) in glacial acetic acid (250 ml.) was hydrogenated at room temperature at an initial pressure of 100 atm. in the presence of platinic oxide (5 g.). After being stirred for 16 hr. the mixture was worked up as previously described. A fraction (58 g.,

Esters, etc., $Ph_2C(OH)\cdot CO\cdot O\cdot[CH_2]_n$–N(R)

No.	*n*	R	Salt	Yield (%) †	M. p.	Form and solvent ‡
1	1	Me	—	53	100—101°,[a] 104° [b]	Needles, Pet
2	1	Me	HCl	61 67	* 170—171,[a] 182—183 [b]	Needles, COMeEt
3	1	Me	MeI	97 84	192,[a] 184 [b]	Prisms, EtOAc–MeOH–Et_2O
4	1	Me	MeBr	—	171 [a]	Needles, $COMe_2$
5	1	Me	Me_2SO_4	84	154—155 [a]	Needles, COMeEt–EtOH–Et_2O
6	1	Me	EtI	40	148—150 [a]	Needles, EtOAc–MeOH–Et_2O
7	2	H [d]	—	38	125	Needles, Pet
8	2	H	HCl	—	143—144	Needles, EtOH–Et_2O
9	2	Me	—	56	82—83	Needles, Pet
10	2	Me	HCl	58	134	Prisms, EtOH–Et_2O
11	2	Me	MeI	66	153	Needles, EtOH–Et_2O
12	2	Me	MeBr	78	148—149	Needles, COMeEt–Et_2O
13	2	Me	EtI	56	176—177	Prisms, COMeEt–EtOH
14	2	Me	*n*-PrI	71	178	Needles, COMeEt–EtOH
15	2	Et	HCl	89	151	Prisms, EtOH–Et_2O
16	2	Et	EtI	80	162	Needles, COMeEt–EtOH
17	2	*n*-Pr	—	42	B. p. 156—157°/5 × 10^{-4} mm., n_D^{23} 1·5491	—
18	2	*n*-Pr	HCl	—	149—150	Needles, EtOAc–MeOH–Et_2O
19	3	Me	—	88	84	Needles, Pet
20	3	Me	HCl	—	122	Needles, COMeEt–Pet
21	3	Me	MeI	85	130	Needles, EtOAc–EtOH

No.	Formula	Found (%) C	H	N	Hal	Required (%) C	H	N	Hal
1	$C_{20}H_{23}O_3N$	73·9 73·6	7·2 7·2	4·3 4·1	—[a] —[b]	73·8	7·1	4·3	—
2	$C_{20}H_{24}O_3NCl$	66·4 66·2	6·7 6·7	4·3 4·1	9·9[a] 10·0[b]	66·4	6·6	3·9	9·8
3	$C_{21}H_{26}O_3NI$	53·8 54·2	5·7 5·8	— —	26·8[a] 27·2[b]	54·0	5·6	—	27·2
4	$C_{21}H_{26}O_3NBr$	60·5	6·6	—	19·4	60·0	6·2	—	19·0
5	$C_{22}H_{29}O_7NS$	58·9	6·5	—	6·9[c]	58·5	6·4	—	7·1[c]
6	$C_{22}H_{28}O_3NI$	54·7	5·6	—	26·0	54·9	5·8	—	26·4
7	$C_{20}H_{23}O_3N$	74·1	7·2	4·4	—	73·8	7·1	4·3	—
8	$C_{20}H_{24}O_3NCl$	66·5	7·0	—	9·3	66·4	6·6	—	9·8
9	$C_{21}H_{25}O_3N$	74·3	7·2	4·2	—	74·4	7·4	4·1	—
10	$C_{21}H_{26}O_3NCl$	66·9	6·8	4·0	—	67·1	6·9	3·7	—
11	$C_{22}H_{28}O_3NI$	55·0	5·9	2·3	—	54·9	5·8	2·9	—
12	$C_{22}H_{28}O_3NBr$	60·6	6·4	3·3	—	60·8	6·5	3·2	—
13	$C_{23}H_{30}O_3NI$	55·8	6·0	3·2	—	55·7	6·1	2·8	—
14	$C_{24}H_{32}O_3NI$	55·8	6·2	—	—	56·7	6·3	—	—
15	$C_{22}H_{28}O_3NCl$	68·1	7·3	3·8	—	67·8	7·2	3·6	—
16	$C_{24}H_{32}O_3NI$	56·6	6·5	—	24·7	56·6	6·3	—	24·9
17	$C_{23}H_{29}O_3N$	75·2	8·0	4·1	—	75·2	7·9	3·8	—
18	$C_{23}H_{30}O_3NCl$	68·1	7·3	—	8·7	68·4	7·4	—	8·8
19	$C_{22}H_{27}O_3N$	74·9	7·8	4·3	—	74·8	7·7	4·0	—
20	$C_{22}H_{28}O_3NCl$	67·6	7·1	—	9·4	67·8	7·2	—	9·1
21	$C_{23}H_{30}O_3NI$	55·4	6·2	—	25·9	55·8	6·1	—	25·7

[a] Product obtained from 2-hydroxymethyl-1-methylpyrrolidine derived from L-glutamic acid. [b] Product obtained from 2-hydroxymethyl-1-methylpyrrolidine derived from diethyl pyrrolidine-1 : 2-dicarboxylate. [c] Analysis for sulphur. [d] Prepared by the hydrogenation of 1-benzyl-2-[2-(αα-diphenylglycolloyloxy)ethyl]pyrrolidine (crude) in acetic acid at an initial pressure of 66 lb./sq. in. with 10% palladium–charcoal. The benzilic ester was prepared, by the described general method, from 1-benzyl-2-(2-hydroxyethyl)pyrrolidine.

* Blicke and Lu [3] give m. p. 161—162°. † Yields of hydrochlorides given only where they were isolated directly from the reaction mixture. ‡ Pet = light petroleum.

88%) of b. p. 93—100°/0·5 mm. was collected, which on redistillation gave *ethyl α-ethoxycarbonyl-β-(1-methyl-2-pyrrolidinyl)propionate*, b. p. 88°/0·1 mm., n_D^{21} 1·4524 (Found: C, 60·8; H, 9·2; N, 5·5. $C_{13}H_{23}O_4N$ requires C, 60·8; H, 9·0; N, 5·5%).

Ethyl β-(1-Methyl-2-pyrrolidinyl)propionate.—Ethanolic 1·25N-potassium hydroxide (125 ml., 1 equiv.) was added to a solution of the above ester (40 g., 2 equiv.) in ethanol (40 ml.). After 16 hr. at room temperature the solvent was removed *in vacuo* and 1·18N-hydrochloric acid (132 ml.) was added. The mixture was evaporated to dryness *in vacuo*, ethanol (50 ml.) added, and the mixture again evaporated to dryness to ensure complete removal of water. Dry ethanol (50 ml.) was added to the residue, the ethanolic solution filtered, and the inorganic material (2·7 g.) washed with dry ethanol (25 ml.). Evaporation of the filtrate followed by distillation of the residue gave a fraction (23 g., 79%) of b. p. 48—50°/0·05 mm. which on redistillation gave *ethyl β-(1-methyl-2-pyrrolidinyl)propionate*, b. p. 48°/0·04 mm., n_D^{22} 1·4520 (Found: C, 64·9; H, 10·5; N, 7·9. $C_{10}H_{19}O_2N$ requires C, 64·8; H, 10·3; N, 7·6%). Its *picrate*, prepared in ethyl acetate, crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 106° (Found: C, 46·1; H, 5·3; N, 13·4. $C_{16}H_{22}O_9N_4$ requires C, 46·4; H, 5·3; N, 13·5%).

2-(3-*Hydroxypropyl*)-1-*methylpyrrolidine.*—(*a*) Reduction of ethyl β-(1-methyl-2-pyrrolidinyl)propionate (28 g.) in dry ether (300 ml.) with lithium aluminium hydride (6 g.) gave 2-(3-*hydroxypropyl*)-1-*methylpyrrolidine* (18 g., 86%), b. p. 60°/0·03 mm., n_D^{20} 1·4741 (Found: C, 67·0; H, 12·2; N, 9·6. $C_8H_{17}ON$ requires C, 67·1; H, 11·9; N, 9·8%) [*picrate*, needles, m. p. 53°, from chloroform–*cyclo*hexane (Found: N, 15·3. $C_{14}H_{20}O_8N_4$ requires C, 45·2; H, 5·4; N, 15·0%)].

(*b*) 2-(3-Hydroxypropyl)pyrrolidine (8 g.) was methylated with 90% formic acid (13·5 ml.) and 40% aqueous formaldehyde (7 ml.) as previously described. 2-(3-Hydroxypropyl)-1-methylpyrrolidine (5 g., 60%) was obtained as a liquid, b. p. 103—104°/2·5 mm., n_D^{21} 1·4720 [picrate, m. p. and mixed m. p. 54° (Found: C, 45·2; H, 5·7; N, 14·7%)].

2-[2-(αα-*Diphenylacetoxy*)*ethyl*]-1-*methylpyrrolidine.*—Reaction of 2-(2-hydroxyethyl)-1-methylpyrrolidine (7 g.) with diphenylacetyl chloride (13 g.) in benzene (60 ml.) at room temperature for 18 hr. gave a crude ester hydrochloride (13 g., 65%) which on basification with 30% aqueous potassium hydroxide gave 2-[2-(αα-*diphenylacetoxy*)*ethyl*]-1-*methylpyrrolidine* (9 g., 48%) as an amber oil, b. p. 165°/0·05 mm., n_D^{23} 1·5521 (Found: C, 77·8; H, 7·7; N, 4·3. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·7; N, 4·3%).

2-[2-(αα-*Diphenylacetoxy*)*ethyl*]-1-*ethylpyrrolidine* was prepared similarly from 1-ethyl-2-(2-hydroxyethyl)pyrrolidine as an amber viscous oil (55%), b. p. 168°/0·03 mm., $n_D^{19\cdot5}$ 1·5511 (Found: C, 78·1; H, 8·0; N, 4·3. $C_{22}H_{27}O_2N$ requires C, 78·4; H, 8·0; N, 4·2%).

2-[2-(αα-*Diphenylacetoxy*)*ethyl*]-1 : 1-*dimethylpyrrolidinium Iodide.*—2-[2-(αα-Diphenylacetoxy)ethyl]-1-methylpyrrolidine (2 g.) was treated with methyl iodide (1·5 ml.) in toluene (25 ml.) for 18 hr. at room temperature. Crystallisation from butanone gave the *iodide* as pale yellow needles (2 g., 80%), m. p. 143—144° (Found: C, 56·5; H, 6·3; N, 2·7. $C_{22}H_{28}O_2NI$ requires C, 56·8; H, 6·0; N, 3·0%).

2-[2-(*Fluorene*-9-*carbonyloxy*)*ethyl*]-1-*methylpyrrolidine Hydrochloride.*—2-(2-Hydroxyethyl)-1-methylpyrrolidine (5 g.) with fluorene-9-carbonyl chloride (9 g.) in chloroform (80 ml.) at room temperature for 0·5 hr. gave the *ester hydrochloride* (4 g., 25%) as prisms, m. p. 164° (decomp.) (from ethanol–ether) (Found: C, 69·9; H, 6·6; N, 3·9. $C_{21}H_{24}O_2NCl$ requires C, 70·5; H, 6·7; N, 3·9%).

2-[2-(*Xanthen*-9-*carbonyloxy*)*ethyl*]-1-*methylpyrrolidine Hydrochloride.*—2-(2-Hydroxyethyl)-1-methylpyrrolidine (2·5 g.) with xanthen-9-carbonyl chloride (4·5 g.) in dry ether (400 ml.) for 18 hr. at room temperature gave a solid (5 g., 80%) which on crystallisation from ethanol–ether gave the *ester hydrochloride*, m. p. 197—198° (decomp.), as needles (Found: C, 67·1; H, 6·5; N, 3·5. $C_{21}H_{24}O_3NCl$ requires C, 67·5; H, 6·4; N, 3·8%).

2-[2-(*Xanthen*-9-*carbonyloxy*)*ethyl*]-1 : 1-*dimethylpyrrolidinium Iodide.*—The free base (4 g.) [liberated from the preceding hydrochloride (5 g.)] was allowed to react with methyl iodide (3·3 ml.) in toluene (50 ml.) at room temperature to give the *iodide* (4·5 g., 69%) as rods, m. p. 165° (from ethanol) (Found: C, 54·8; H, 5·7; N, 3·1. $C_{22}H_{26}O_3NI$ requires C, 55·1; H, 5·4; N, 2·9%).

2-[2-(αα-*Diphenylglycolloyloxy*)*ethyl*]-1 : 5-*dimethylpyrrolidine Hydrochloride.*—A solution of 2-(2-hydroxyethyl)-1 : 5-dimethylpyrrolidine (5 g.) in dry ether (100 ml.) was added with stirring to a solution of α-chlorodiphenylacetyl chloride (10 g.) in dry ether (300 ml.) during

0·5 hr. After being kept overnight at room temperature, the ethereal layer was decanted. The residual gum on trituration with dry ethanol (*ca.* 20 ml.) solidified and was collected (4 g.). This hydrochloride (4 g.) was dissolved in water (80 ml.) and left at room temperature for 30 min. Sodium chloride (30 g.) was added and the solution extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and evaporated to a gum, which crystallised from propan-2-ol–ether (1 : 6) to give the *ester hydrochloride* (3 g., 24%) as rods, m. p. 179—180° (Found: C, 67·4; H, 7·4; N, 3·5. $C_{22}H_{28}O_3NCl$ requires C, 67·8; H, 7·2; N, 3·6%).

2-[2-(αα-*Diphenylglycolloyloxy*)*ethyl*]-1 : 1 : 5-*trimethylpyrrolidinium iodide* was obtained by the previous procedure (89% yield) as a gum which solidified on trituration with butanone and crystallisation from ethanol–butanone (1 : 4) as needles, m. p. 154—155° (Found: C, 55·6; H, 6·1; N, 3·4. $C_{23}H_{30}O_3NI$ requires C, 55·8; H, 6·1; N, 2·9%).

Other Esters and Salts.—The Table records other *compounds* prepared by analogous methods.

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