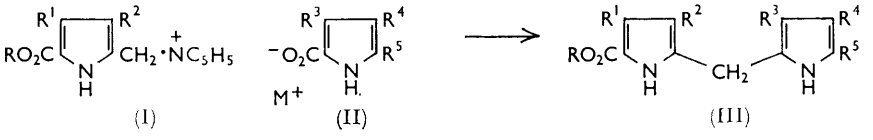
808. *Pyrroles and Related Compounds. Part VI.*[1] *Pyrrolylethylenes*

By A. Hayes, A. H. Jackson, J. M. Judge, and G. W. Kenner

1,2-Di-2′-pyrrolylethylenes are formed in low yield by alkaline treatment of α-pyridinium-methyl- and α-aminomethyl-pyrroles. In contrast with the pyridinium-methylpyrroles, the aminomethylpyrroles could not be coupled with pyrrole-α-carboxylic acids to give pyrromethanes.

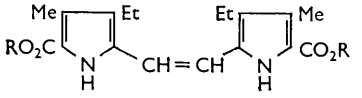
During the course of investigations [2] into the coupling of α-pyridinium-methylpyrroles (I) with the alkali-metal salts of pyrrole-α-carboxylic acids (II) to give pyrromethanes (III), Dr. N. R. Williams observed [3] that the pyridinium-methylpyrrole (I) was rapidly decomposed by dilute alkali to a brown gummy product. Treatment of this gummy



(I) (II) (III)

(a) R = R^2 = Et, R^1 = Me
(b) R = CH_2Ph, R^1 = Me, R^2 = Et

material with warm acetic anhydride yielded a pale yellow crystalline solid, which exhibited a marked fluorescence in ethanol solution. Elemental analysis gave the empirical formula $C_{11}H_{15}NO_2$, and further investigations [4] have now shown that this yellow compound is the pyrrolylethylene (IVa), a derivative of the systematically named 1,2-di-2′-pyrrolylethylene.



(IV)

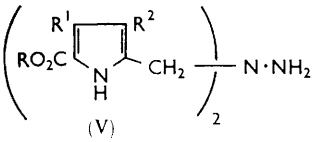
(a) R = Et
(b) R = CH_2Ph

Evidence for the pyrrolylethylene structure is as follows: (i) molecular-weight determination, (ii) the intense long-wavelength absorption (387 mμ) and violet fluorescence, which are indicative of a more extended conjugated system than in the parent pyrrole, (iii) bands at 3300 (N–H) and 1660 (C=O) cm.$^{-1}$ in the infrared spectrum, and (iv) the proton magnetic resonance spectrum which clearly shows in particular a singlet for the ethylenic protons at 3·1 τ.

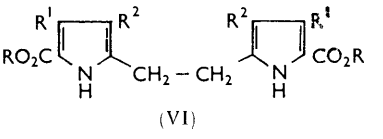
Pyrrolylethylenes were previously unknown,[5] but Fischer and Scheyer [6] synthesised

[1] Part V, A. H. Jackson, G. W. Kenner, and D. Warburton, *J.*, 1965, 1328.
[2] A. Hayes, G. W. Kenner, and N. R. Williams, *J.*, 1958, 3779.
[3] N. R. Williams, Ph.D. Thesis, Cambridge, 1956.
[4] J. M. Judge, M.Sc. Thesis, Liverpool, 1963.
[5] Cf. H. Fischer and H. Orth, " Die Chemie des Pyrrols," Akademische Verlag, Leipzig, 1934, Vol. I, p. 378.
[6] H. Fischer and H. Scheyer, *Annalen*, 1924, **439**, 185.

the pyrrolylethane (VIc) by oxidation of the 1,1-di-2'-pyrrolylmethylhydrazine (Vc) with cuprammonium salts. The pyrrolylethylene (IVa) was therefore reduced catalytically



(V)

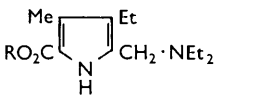


(VI)

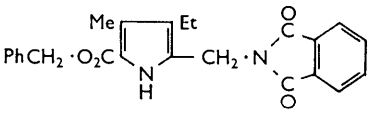
(a) R = R^2 = Et, R^1 = Me
(b) R = CH_2Ph, R^1 = Me, R^2 = Et
(c) R = Et, R^1 = Me, R^2 = CO_2Et

to the corresponding pyrrolylethane, and the latter was shown to be identical with the pyrrolylethane (VIa) prepared *via* the hydrazine (Va). The pyrrolylethane (VIa) could be reoxidised to the pyrrolylethylene (IVa) by treatment with bromine, followed by triethylamine.

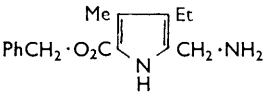
Alkaline treatment of another pyridinium-methylpyrrole (Ib) also yielded a pyrrolylethylene (IVb), and the same product was obtained in other investigations [7] which involved heating a benzene solution of the pyrrole Mannich base (VIIb) over solid sodium hydroxide. The corresponding pyrrolylethane (VIb) was synthesised by Fischer and Scheyer's method;[6] in this case the intermediate hydrazine (Vb) was not isolated since, on recrystallisation, it decomposed to give the pyrrolylethane.



(VII) (a) R = Et
(b) R = CH_2Ph



(VIII)



(IX)

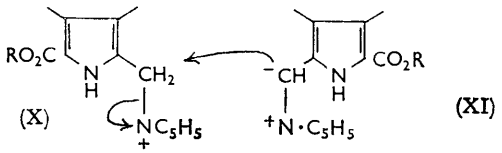
The pyrrole Mannich base (VIIb) was originally prepared in order to study its use in pyrromethane syntheses (cf. ref. 2) instead of pyridinium-methylpyrroles (I). However, attempts to condense it [or the corresponding ethyl ester (VIIa)] with pyrrole-α-carboxylic acids were unsuccessful, only gummy products being obtained under a variety of different conditions. The possibility of synthesising phthalimidomethylpyrromethanes was also considered, but this was frustrated by our inability to prepare the appropriate phthalimidomethylpyrrole-α-carboxylic acid (required for coupling with a pyridinium-methylpyrrole), as the benzyl ester (VIII) proved remarkably resistant to hydrogenolysis (*e.g.*, no reduction occurred over palladium or Raney nickel at 100 atm., whilst at 100° decomposition occurred). Treatment of the phthalimidomethylpyrrole (VIII) with hydrazine readily gave the corresponding aminomethylpyrrole (IX), but the latter did not appear to react with pyrrole-α-carboxylic acids under either alkaline or acidic conditions. The stability of this aminomethylpyrrole (IX) is in marked contrast with that of porphobilinogen and is presumably due to the deactivating influence of the alkoxycarbonyl grouping.[8]

The formation of pyrrolylethylenes from pyridinium-methylpyrroles or aminomethylpyrroles is paralleled by the well-known formation of stilbenes by alkaline treatment of benzyl halides or benzylammonium salts, and the mechanism is probably similar.[9]

Initial loss of a proton would form an anion, *e.g.*, in the case of a pyridinium salt (X) the ylid (XI) (cf. ref. 10); the latter could then react with a second molecule of pyridinium salt in a simple displacement reaction (as shown), and elimination of the second molecule

[7] A. Hayes, Ph.D. Thesis, Cambridge, 1958.
[8] Cf. A. H. Jackson and S. F. MacDonald, *Canad. J. Chem.*, 1957, **35**, 715.
[9] Cf. W. Kirmse, " Carbene Chemistry," Academic Press, New York, 1964, p. 81 ff.

of pyridine would give the pyrrolylethylene. Formation of ylids from pyridinium salts is well known,[10] but attempts to trap intermediate ylids were unsuccessful.



Experimental

1,2-*Di*-(5-*ethoxycarbonyl*-3-*ethyl*-4-*methyl*-2-*pyrrolyl*)*ethylene* (IVa).—(*a*) (With Dr. N. R. Williams). Ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (2·0 g.) was treated with dry pyridine (2·3 ml., 4 mol.) and warmed on a steam-bath. The pyrrole dissolved with evolution of heat, and within a short time the corresponding 5-pyridinium-methylpyrrole bromide [2] (m. p. 150°) crystallised out; it was filtered off and washed with a little dry ether or dioxan (yield 90—95%).

2N-Sodium hydroxide was added slowly dropwise with stirring to a solution of this pyridinium salt (1·0 g.) in water (10 ml.). The solution became turbid after the addition of a few drops and then a brown oil separated out. When no more oil was produced, addition of sodium hydroxide was stopped and the aqueous layer was decanted from the oily residue. The latter was taken up in acetic anhydride (5 ml.) by warming on a steam-bath and, on cooling, brownish-yellow crystals were deposited. After recrystallisation from aqueous ethanol the *pyrrolylethylene* (0·080 g., 14%) was obtained as bright yellow needles with a greenish-blue lustre, m. p. 222°. The mixed m. p. with Dr. Williams's earlier sample, m. p. 213—215°, was 222° (Found: C, 68·5; H, 7·9; N, 7·2; OEt, 23·7%; *M* (Rast), 395. $C_{22}H_{30}N_2O_4$ requires C, 68·4; H, 7·8; N, 7·3; OEt, 23·4%; *M*, 386), $\nu_{max.}$ (Nujol) 3300 (NH), 1660 (CO), 1450, 1275 cm.$^{-1}$, $\lambda_{max.}$ (ethanol) 273 and 383 mμ (log ε 4·34 and 4·32). Proton magnetic resonance (p.m.r.) spectrum ($CDCl_3$): 4,4′–CH_3, singlet at 7·69; 3,3′–CH_2·CH_3, quartet at 7·44 and triplet at 8·89; 5,5′–CO_2·CH_2·CH_3, quartet at 5·63 and triplet at 8·62; CH=CH, singlet at 3·31 τ.

(*b*) 1,2-(5-Ethoxycarbonyl-3-ethyl-4-methyl-2-pyrrolyl)ethane (130 mg.) (see below) in dry ether (25 ml.) was treated with bromine (0·0084 ml., 1 mol.) in dry ether (5 ml.), set aside for 2 hr., and the faintly violet fluorescent solution treated with two drops of triethylamine (*i.e.*, excess). The immediately formed triethylamine hydrobromide was filtered off and the solution was evaporated to dryness. The residual mixture of pyrrolylethylene and unchanged pyrrolylethane was separated by fractional crystallisation from ether. The less-soluble pyrrolylethylene was obtained as yellow needles (29 mg., 23%), m. p. 219°, mixed m. p., with the sample prepared as described in (*a*), 219—220°.

1,2-*Di*-(5-*ethoxycarbonyl*-3-*ethyl*-4-*methyl*-2-*pyrrolyl*)*ethane* (VIa).—(*a*) The foregoing pyrrolylethylene (100 mg.) in methanol (75 ml.) was shaken with 10% palladium–charcoal (50 mg.) in hydrogen at 1 atm. and 25° for 3 hr. until uptake was complete (*ca.* 5 ml., 1 mol.). After removal of catalyst the methanol was evaporated to small bulk, whereupon the required *pyrrolylethane* (81 mg.; 81%) crystallised as colourless needles, m. p. 168° (Found: C, 68·2; H, 8·6; N, 7·4%; *M* (Rast), 364. $C_{22}H_{32}N_2O_4$ requires C, 68·0; H, 8·3; N, 7·2%; *M*, 388), principal $\nu_{max.}$ (Nujol) 3300 (NH), 1660 (CO), 1450 cm.$^{-1}$, $\lambda_{max.}$ (ethanol) 290 mμ (log ε 4·54). P.m.r. spectrum ($CDCl_3$): CO_2·CH_2·CH_3, 5·65 and 8·64; CH_3, 7·67; CH_2·CH_3, 7·63 and 8·97; CH_2·CH_2, 7·10; NH, ~1·1 τ.

(*b*) Ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (2·0 g.) was warmed with hydrazine hydrate (0·9 ml.) on a steam-bath for 5 min. The upper layer containing hydrazine hydrobromide was decanted, and the residual gum was crystallised from absolute ethanol to give the pale yellow crystalline 1,1-di-2′-pyrrolylhydrazine (0·6 g.), which was then added to a hot aqueous ethanolic solution of cuprammonium sulphate [prepared from copper sulphate (0·23 g.) in water (4 ml.) by addition of a slight excess of concentrated aqueous ammonia followed by water (to make the volume up to 8 ml.), and ethanol (10 ml.)]. The resulting mixture was heated on a steam-bath, when the hydrazine dissolved, nitrogen was evolved, and the solution became green. The resulting clear solution was made just acid by addition of glacial acetic acid.

[10] F. Kröhnke, *Angew. Chem.*, 1953, **65**, 605.

A fawn-coloured solid crystallised from the cooled solution and it was recrystallised from aqueous methanol, giving the pyrrolylethane (100 mg., 14%) as pale yellow needles, m. p. 169°, mixed m. p. with the sample prepared as in (*a*), 168°. The infrared spectrum was identical with that of the previous sample.

1,2-*Di*-(5-*benzyloxycarbonyl*-3-*ethyl*-4-*methyl*-2-*pyrrolyl*)*ethylene* (IVb).—(*a*) This compound was prepared as for the diethyl analogue described above [method (*a*)], from benzyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (5·0 g.) except that the intermediate pyridinium salt was not obtained crystalline and the syrupy solution in pyridine was dissolved in water and treated directly with alkali. The *pyrrolylethylene dibenzyl ester* (0·36 g., 10%) crystallised from ethanol as greenish-yellow needles, m. p. 205—207° (Found: C, 75·2; H, 6·9; N, 5·3. $C_{32}H_{34}N_2O_4$ requires C, 75·3; H, 6·7; N, 5·5%), $\nu_{max.}$ (Nujol) 3300 (NH), 1660 (CO), 1450, 1275 cm.$^{-1}$, $\lambda_{max.}$ (ethanol) 265 and 387 mμ (log ε 4·15 and 4·44). P.m.r. spectrum ($CDCl_3$): $CO_2{\cdot}CH_2{\cdot}C_6H_5$, 4·72 and 2·63; CH_3, 7·72; $CH_2{\cdot}CH_3$, 7·48, 8·89; $CH{=}CH$, 3·31; NH, ~0·8 τ.

(*b*) The same compound was also obtained in very low yield from an experiment in which benzyl 5-diethylaminomethyl-4-ethyl-3-methylpyrrole-2-carboxylate was heated in boiling benzene over solid sodium hydroxide for several hours, followed by chromatography of the gummy product in benzene–light petroleum on alumina.

1,2-*Di*-(5-*benzyloxycarbonyl*-3-*ethyl*-4-*methyl*-2-*pyrrolyl*)*ethane* (VIb).—Benzyl 5-bromomethyl-3-ethyl-4-methylpyrrole-2-carboxylate (2·0 g.) was mixed with hydrazine hydrate (1·0 ml.). The resulting sticky solid was recrystallised from ethanol and gave the *pyrrolylethane* (0·6 g., 20%) directly as colourless needles, m. p. 183° (Found: C, 74·7; H, 7·3; N, 5·7%; *M* (Rast), 534. $C_{32}H_{36}N_2O_4$ requires C, 75·0; H, 7·1; N, 5·5%; *M*, 512), $\nu_{max.}$ (Nujol) 3280 (NH), 1650 (CO), 1435, 1300, 1270, 1235 cm.$^{-1}$, $\lambda_{max.}$ (ethanol) 290 mμ (log ε 38,800). P.m.r. spectrum ($CDCl_3$): $CO_2{\cdot}CH_2{\cdot}C_6H_5$, 4·72 and 2·69; CH_3, 7·72; $CH_2{\cdot}CH_3$, 7·65 and 9·01; $C_2{\cdot}HCH_2$, 7·17; NH ~1·0 τ.

Benzyl 4-*Ethyl*-3-*methyl*-5-*phthalimidomethylpyrrole*-2-*carboxylate*.—Potassium phthalimide (3·8 g.) was added to a solution of benzyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (6·6 g.) in dimethylformamide (40 ml.) during 5 min. in which the temperature of the solution rose from 22° to 30°. The mixture was shaken for 2 hr. until all the solid had dissolved and then set aside overnight. Chloroform (65 ml.) was added, and the solution was poured into water. The separated aqueous layer was extracted with more chloroform (2 × 20 ml.) and the combined organic extracts were washed with 0·2N-sodium hydroxide (40 ml.), followed by water (40 ml.). The dried (Na_2SO_4) solution was evaporated to give a brown oil, which crystallised from aqueous ethanol giving the *phthalimidomethylpyrrole* (3·0 g., 38%) as colourless needles m. p. 125—126° (Found: C, 71·0; H, 5·6; N, 7·0. $C_{24}H_{22}N_2O_4$ requires C, 71·6; H, 5·5; N, 7·0%).

Benzyl 5-*Aminomethyl*-4-*ethyl*-3-*methylpyrrole*-2-*carboxylate*.—Hydrazine hydrate (0·5 ml.) was added to the foregoing phthalimidomethylpyrrole (0·19 g.) in methanol (20 ml.). The solution was kept at 20° for 4 hr. and then evaporated to dryness. The residue was shaken with water, acidified to pH 5 with dilute acetic acid, and the insoluble phthalhydrazide (0·06 g., m. p. 335°) was filtered off. The filtrate was basified with aqueous ammonia to pH 10, and the desired *aminomethylpyrrole* (0·12 g., 91%) crystallised as needles, m. p. 89—91°, raised to 90—92° by recrystallisation from aqueous ethanol (Found: C, 70·4; H, 7·6; N, 10·2%; Equiv., 272. $C_{16}H_{20}N_2O_2$ requires C, 70·6; H, 7·4; N, 10·3%; Equiv., 272). The base had pK_a 7·8 (50% aqueous ethanol) and formed a *picrate*, m. p. 185—187° (Found: N, 14·0. $C_{22}H_{23}N_5O_9$ requires N, 14·0%).

Ethyl 5-*Diethylaminomethyl*-4-*ethyl*-3-*methylpyrrole*-2-*carboxylate*.—Finely powdered ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (1·6 g.) was added in portions to diethylamine (10 ml.) with stirring. After 1 hr. at 20° the mixture was poured into water (50 ml.) and the *diethylaminomethylpyrrole* (1·45 g., 93%) separated out. On recrystallisation from aqueous ethanol it formed plates, m. p. 62—64° (Found: C, 67·9; H, 9·8; N, 10·5%; Equiv., 271. $C_{15}H_{26}N_2O_2$ requires C, 67·6; H, 9·8; N, 10·5%; Equiv., 266), pK_a 7·4 in 50% aqueous ethanol. The *picrate* formed needles, m. p. 159°, from ethanol (Found: C, 51·3; H, 6·1. $C_{21}H_{29}N_5O_9$ requires C, 50·9; H, 5·9%).

Benzyl 5-*Diethylaminomethyl*-4-*ethyl*-3-*methylpyrrole*-2-*carboxylate*.—This compound was prepared, as for the foregoing ethyl ester, from the corresponding 5-bromomethylpyrrole benzyl ester, and it formed low-melting needles which were extremely soluble in all organic solvents and could not be recrystallised. However, the free base readily formed a *picrate*, m. p. 161—163°

from ethanol (Found: N, 13·0. $C_{26}H_{31}N_5O_9$ requires N, 12·6%). The *hydrochloride* was prepared by passing dry hydrogen chloride through a benzene solution of the free base, and had m. p. 183° (Found: C, 66·0; H, 8·2; N, 7·7. $C_{20}H_{29}ClN_2O_2$ requires C, 65·9; H, 8·0; N, 7·7%).

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