Studies related to the Chemistry of Melanins. Part VI.[1] Syntheses of 3-Carboxypyrrole-2-acetic Acid, 3,5-Dicarboxypyrrole-2-acetic Acid, and Related Compounds

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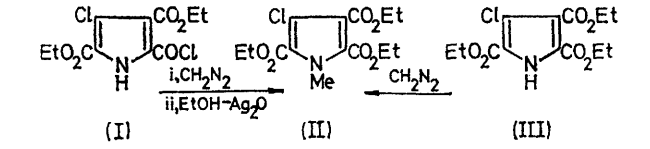
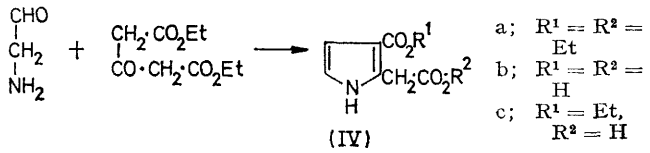
The acids named in the title were synthesised. In the case of pyrroles already containing an ester group, a carboxylic function can be introduced by use of phosgene, but better by use of oxalyl chloride; an acetic ester group can be introduced by use of diazoacetic ester. Some pyrroles containing carboxy- or ester groups are *N*-methylated by diazomethane.

OXIDATION by alkaline hydrogen peroxide of melanins formed by *in vitro* oxidation of 3,4-dihydroxyphenylalanine or 3,4-dihydroxyphenethylamine yields pyrrole-2,3-dicarboxylic acid and pyrrole-2,3,5-tricarboxylic acid, which were detected by paper chromatography.[2] However, other unidentified spots appear on the chromatograms; and in connection with experiments using specifically ^{14}C-labelled precursors, it was important to identify some of these. We therefore investigated the synthesis of 3-carboxypyrrole-2-acetic acid (IVb), 3,5-dicarboxypyrrole-2-acetic acid (Vb), and related acids, which could conceivably arise by the oxidation of indole-5,6-quinone units present in the melanin polymer.

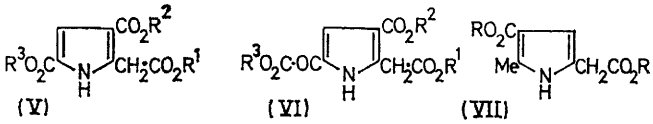


(I) (II) (III)



(IV)

a; $R^1 = R^2 =$ Et
b; $R^1 = R^2 =$ H
c; $R^1 =$ Et, $R^2 =$ H

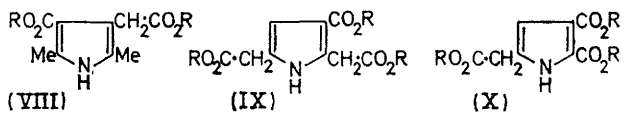


(V) (VI) (VII)

(V): a; $R^1 = R^2 = R^3 =$ Et; b; $R^1 = R^2 = R^3 =$ H; c; $R^1 = R^2 =$ Et, $R^3 =$ H

(VI): a; $R^1 = R^2 = R^3 =$ Et; b; $R^1 = R^2 = R^3 =$ H

(VII): a; R = Et; b; R = H

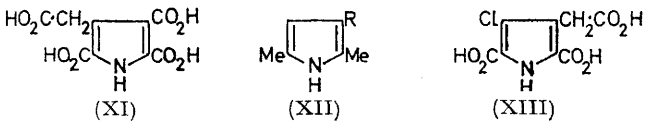


(VIII) (IX) (X)

(VIII): a; R = Et; b; R = H

(IX): a; R = Et; b; R = H

(X): a; R = Me; b; R = H



(XI) (XII) (XIII)

(XII): a; $R = CH_2 \cdot CO_2Et$; b; R = CN

An attempt to synthesise 3,5-dicarboxypyrrole-2-acetic acid by Arndt–Eistert homologation of diethyl 3-chloro-5-chloroformylpyrrole-2,4-dicarboxylate (I) was unsuccessful. The product isolated proved to be triethyl 4-chloro-1-methylpyrrole-2,3,5-tricarboxylate (II), identical with the product of the action of diazomethane on triethyl 4-chloropyrrole-2,3,5-tricarboxylate (III), formed by esterification of 4-chloropyrrole-2,3,5-tricarboxylic acid.[3] Prolonged action of excess of diazomethane on pyrrole-2,3,5-tricarboxylic acid,[3] and on pyrrole-2,3-dicarboxylic acid,[4] also resulted in *N*-methylation, as well as attack on the carboxylic acid groups.

Incidentally, condensation of aminoacetaldehyde with ethyl acetoacetate under alkaline conditions as described by Rinkes[5] gave only a low yield of 3-ethoxycarbonylpyrrole-2-carboxylic acid, the main product being pyrrole-2,3-dicarboxylic acid. The monoester was better obtained by reaction at room temperature, instead of at 35° as specified by Rinkes; it could also be prepared by treatment of the dicarboxylic acid with diazoethane, followed by mild alkaline hydrolysis. However, attempts to effect the homologation of 3-ethoxycarbonylpyrrole-2-carboxylic acid by the Arndt-Eistert method failed.

Attempts to condense aminoacetaldehyde with diethyl acetonedicarboxylate under the conditions of Rinkes' experiments with ethyl acetoacetate afforded only ethyl 2-methylpyrrole-3-carboxylate in low yield. However, under modified conditions, at pH 9—10 throughout the reaction, ethyl 3-ethoxycarbonylpyrrole-2-acetate (IVa) was obtained (13·5%). Its n.m.r. spectrum showed a singlet at τ 5·58 (CH_2). Use of dimethyl acetonedicarboxylate instead of the diethyl ester (under Rinkes' conditions) afforded only a low yield of methyl 2-methylpyrrole-3-carboxylate, together with a compound, $(C_3H_4O_2)_n$, m.p. 114—116°, isolated from the acidified reaction mixture by extraction with ether, followed by chromatography on silica, thought

[1] Part V, S. N. Mishra and G. A. Swan, *J. Chem. Soc.* (*C*), 1967, 1431.
[2] F. Binns and G. A. Swan, *Chem. and Ind.*, 1957, 396.
[3] R. A. Nicolaus, *Gazzetta*, 1953, **83**, 239.
[4] R. A. Nicolaus and L. Mangoni, *Gazzetta*, 1956, **86**, 757.
[5] I. J. Rinkes, *Rec. Trav. chim.*, 1937, **56**, 1224.

to be an orcinol derivative.[6] Attempts to effect a similar condensation with dibenzyl acetonedicarboxylate failed.

Reaction of ethyl 2-methylpyrrole-3-carboxylate with phosgene, followed by treatment of the product with ethanol yields diethyl 5-methylpyrrole-2,4-dicarboxylate.[7] Similarly ethyl 3-ethoxycarbonylpyrrole-2-acetate (IVa), afforded ethyl 3,5-bisethoxycarbonylpyrrole-2-acetate (Va) (35%). The u.v. spectrum of ester (Va) was similar to that of diethyl 5-methylpyrrole-2,4-dicarboxylate; its n.m.r. spectrum showed a singlet at at τ 5·80 (CH_2), and the aromatic proton gave a signal at τ 2·78, split by NH.

Table 1

Substituents in pyrrole					R_F		
1	2	3	4	5	A	B	Colour when sprayed
H	$CH_2{\cdot}CO_2H$	CO_2Et	H	H	0·67	0·8	Red-brown
H	$CH_2{\cdot}CO_2H$	CO_2H	H	H	0·27	0·62	Red-brown
H	$CO{\cdot}CO_2H$		CO_2H	$CH_2{\cdot}CO_2H$	0·12	0·17	None
H	$CH_2{\cdot}CO_2H$	CO_2H	H	CO_2H	0·15	0·6	Red-brown
H	$CH_2{\cdot}CO_2H$	H	CO_2H	Me	0·27	0·70	Faint red-brown
H	$CH_2{\cdot}CO_2H$	H	CO_2H	CO_2H	0·4	0·72	Red-brown
H	$CH_2{\cdot}CO_2H$	CO_2H	H	$CH_2{\cdot}CO_2H$	0·37	0·67	Red-brown
H	Me	$CH_2{\cdot}CO_2H$	CO_2H	Me	0·37	0·87	None
H	CO_2H	$CH_2{\cdot}CO_2H$	CO_2H	CO_2H	0·1	0·3	Faint yellow
H	CO_2H	$CH_2{\cdot}CO_2H$	Cl	CO_2H	0·25	0·42	None
Me	CO_2H	CO_2H	H	CO_2H	0·2	0·7	Yellow

Table 2

Solvent	Substituents in pyrrole 2	3	4	5	Chemical shift (τ) α-H	β-H	NH
$CDCl_3$	H	H	H	H	3·18	3·64	ND
Me_2SO	H	H	H	H	3·17	3·82	−0·8
$CDCl_3$	Me	CO_2Et	H	H	3·35	3·39	0·94
	Me	CO_2Et	H	Me		3·64	1·35
	$CH_2{\cdot}CO_2Et$	H	CO_2Et	Me		3·70	0·77
	$CH_2{\cdot}CO_2Et$	CO_2Et	H	H	3·29	3·29	0·02
	$CH_2{\cdot}CO_2Et$	CO_2Et	H	CO_2Et		2·78	3·40
	CO_2Et	H	CO_2Et	Me		2·90	
	$CO{\cdot}CO_2Et$	H	CO_2Et	$CH_2{\cdot}CO_2Et$		2·13	
	Me	$CH_2{\cdot}CO_2Et$	CO_2Et	Me			1·6
	$CH_2{\cdot}CO_2Et$	CO_2Et	H	$CH_2{\cdot}CO_2Et$		3·63	−0·02
Dioxan	CO_2H	H	CO_2H	Me		2·79	
Dioxan	$CH_2{\cdot}CO_2H$	CO_2H	H	H	3·10	3·32	
D_2O	$CH_2{\cdot}CO_2H$	CO_2H	H	H	3·17	3·39	
D_2O	$CH_2{\cdot}CO_2H$	CO_2H	H	CO_2H		2·62	
D_2O	$CO{\cdot}CO_2H$	H	CO_2H	$CH_2{\cdot}CO_2H$		2·11	

Reaction of ethyl 2-methylpyrrole-3-carboxylate with oxalyl chloride, followed by treatment with ethanol gave a high yield of ethyl 4-ethoxycarbonyl-5-methylpyrrole-2-glyoxylate, and a similar reaction with ester (IVa) afforded ethyl 4-ethoxycarbonyl-5-ethoxycarbonylmethylpyrrole-2-glyoxylate (VIa) (80%) (*cf.* ref. 8). The u.v. spectrum of ester (VIa) showed absorption at 313 mμ (*cf.* ref. 9), and its n.m.r. spectrum contained signals at τ 5·76 (s, CH_2) 2·13 (aromatic proton, coupled to NH) (*cf.* ref. 10). We were unable to induce diethyl pyrrole-2,3-dicarboxylate to react with either phosgene or oxalyl chloride.

Most of the pyrrole esters could be hydrolysed satisfactorily by treatment with a mixture of equal volumes of 5% aqueous lithium hydroxide and ethanol. The use of sodium or potassium hydroxide often gave rise to the precipitation of alkali metal salts, which were sometimes difficult to decompose to the free acid. In the case of compounds containing ester groups in both α- and β-positions it was often possible to hydrolyse the former selectively.

Hydrolysis of ester (VIa), and subsequent oxidation with alkaline hydrogen peroxide of the resulting acid (VIb), yielded 3,5-dicarboxypyrrole-2-acetic acid (Vb), which was also obtained by hydrolysis of the ester (Va). Treatment of the acid (Vb) with diazoethane led to the reformation of ester (Va). The n.m.r. spectrum of the acid (Vb) in deuterium oxide consisted of only two sharp singlets, at τ 2·62 (aromatic) and 5·88 (CH_2), apart from the HOD peak at τ 5·15.

Hydrolysis of ester (IVa) afforded the acid (IVb), τ (D_2O) 5·9 (s, CH_2) and 3·21, (ABq, J 3·5 c./sec., aromatic).

The use of ethyl diazoacetate for the introduction of the acetic ester side chain into the pyrrole nucleus appears to be hitherto unknown in the case of derivatives containing electron-withdrawing substituents. However, the reaction was found to proceed with ethyl 2-methylpyrrole-3-carboxylate, ethyl 2,5-dimethylpyrrole-3-carb-

[6] V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, 1947, **30**, 675.

[7] H. Fischer and M. Hussong, *Annalen*, 1931, **492**, 128.

[8] C. D. Nenitzescu, I. Necşoiu, and M. Zalman, *Commun. Acad. Rep. populare Romîne*, 1958, **8**, 659; J. L. Archibald and M. E. Freed, *J. Heterocyclic Chem.*, 1967, **4**, 335.

[9] V. Eisner and P. H. Gore, *J. Chem. Soc.*, 1958, 922.

[10] H. H. Wasserman, J. E. McKeon, L. A. Smith, and P. Forgione, *Tetrahedron*, 1968, Suppl. 8, 647.

oxylate, ethyl 3-ethoxycarbonylpyrrole-2-acetate (IVa), and dimethyl pyrrole-2,3-dicarboxylate (with methyl diazoacetate) giving ethyl 4-ethoxycarbonyl-5-methylpyrrole-2-acetate (VIIa), ethyl 4-ethoxycarbonyl-2,5-dimethylpyrrole-3-acetate (VIIIa), diethyl 3-ethoxycarbonylpyrrole-2,5-diacetate (IXa), and methyl 4,5-bismethoxycarbonylpyrrole-2-acetate (Xa), respectively, the latter in very low yield. The esters (IXa) and (Xa) were hydrolysed to the acids (IXb) and (Xb), respectively, which on oxidation afforded pyrrole-2,3,5-tricarboxylic acid.

When ester (VIIIa) was treated with sulphuryl chloride, then hydrolysed, it gave 2,4,5-tricarboxypyrrole-3-acetic acid (XI). The reaction of 2,5-dimethylpyrrole with ethyl diazoacetate yielded an oil, believed to be ethyl 2,5-dimethylpyrrole-3-acetate (XIIa), a crystalline solid, identical with authentic 3-cyano-2,5-dimethylpyrrole (XIIb), and ammonia. Treatment of ester (XIIa) with sulphuryl chloride, followed by hydrolysis gave 2,5-dicarboxy-4-chloropyrrole-3-acetic acid (XIII).

Table 1 shows the R_F values of various acids in ascending paper chromatography with the systems propan-1-ol–ammonium hydroxide (*d* 0·88)–water (6 : 3 : 1) (A), and butan-1-ol–acetic acid–water (4 : 1 : 5; organic phase) (B); the papers were sprayed with diazotised sulphanilic acid, followed by alkali.

Table 2 shows the chemical shifts of the aromatic and *N*-protons of a number of esters and acids. In agreement with earlier work,[10] the resonance due to the β-hydrogen atom of pyrrole is moved downfield by electron-withdrawing groups, and upfield by alkyl groups.

EXPERIMENTAL

I.r. spectra of liquids and solids were measured for liquid films and potassium bromide discs, respectively. N.m.r. spectra were obtained with a Perkin-Elmer R10 instrument, operating at 60 MHz, and, except where otherwise stated, for solutions in deuteriochloroform. U.v. spectra were measured for solutions in ethanol. Light petroleum refers to the fraction of b.p. 60—80°. Potentiometric titrations were done with a Radiometer Titrator, type TTT1a, in conjunction with a Titrigraph type SBR2c.

5-Methylpyrrole-2,4-dicarboxylic Acid.—Diethyl 5-methylpyrrole-2,4-dicarboxylate [7] (1·5 g.) was boiled under reflux for 2 hr. with a mixture of aqueous lithium hydroxide (5%; 100 ml.) and ethanol (20 ml.). The ethanol was removed and the residual solution was acidified (Congo Red) with hydrochloric acid. The precipitate was collected and dissolved in hot water; the solution was cooled in ice and treated with hydrochloric acid dropwise. The precipitated acid was collected, and dried; m.p. 232° (decomp.) (lit.,[11] 234—235°) (0·75 g.).

Diethyl 3-Chloro-5-chloroformylpyrrole-2,4-dicarboxylate (I).—A mixture of acetic acid (46 ml.), acetic anhydride (6 ml.), and diethyl 3-bromo-5-methylpyrrole-2,4-dicarboxylate [7] (3·62 g.) at 10° was treated successively with bromine (6 ml.) and sulphuryl chloride (9 ml.), dropwise with stirring and cooling in ice. The mixture was kept overnight at 0°, then added to water (60 ml.), heated for 30 min. at 60—70°, and then poured into ice–water (500 ml.). The precipitate was collected and washed with water; a warm ethanolic solution of it was treated with sodium hydrogen carbonate until evolution of carbon dioxide ceased, then poured into water (60 ml.). The resulting solution was filtered and acidified (hydrochloric acid), and the precipitated 3,5-bisethoxycarbonyl-4-chloropyrrole-2-carboxylic acid, m.p. 177—178° (lit.,[4] 180—181°) was collected, washed with water, and dried. This (0·43 g.) was heated at 50—60° under reflux with thionyl chloride (2 g.) until gas evolution ceased. The excess of thionyl chloride was removed under reduced pressure, and the residual oil was diluted with light petroleum, and kept overnight in a refrigerator. The resulting solid was recrystallised twice from light petroleum, yielding the *product*, m.p. 50° (0·36 g.) (Found: N, 4·55. $C_{11}H_{11}ClNO_5$ requires N, 4·55%).

Triethyl 4-Chloro-1-methylpyrrole-2,3,5-tricarboxylate (II).—(*a*) The chloride (I) (0·5 g.), was kept at room temperature overnight with an excess of ethereal diazomethane solution, and the mixture was then evaporated below 5°. The residue was stirred for 20 hr. with silver oxide (from 10 ml. of 6·25% silver nitrate solution) in ethanol (300 ml.). The ethanol was removed from the filtered solution, and the residue was chromatographed on alumina (100 g.). The material (0·2 g.) eluted by benzene was heated in a sublimation apparatus at 120°/0·2 mm., giving the *ester* as an oil (Found: C, 50·35; H, 5·35; Cl, 10·05; N, 4·35. $C_{14}H_{18}ClNO_6$ requires C, 50·70; H, 5·45; Cl, 10·7; N, 4·2%).

(*b*) A solution of 4-chloropyrrole-2,3,5-tricarboxylic acid [3] (0·73 g.) in absolute ethanol (150 ml.) was saturated with hydrogen chloride at 0°, heated under reflux for 2 hr., cooled, poured on ice (250 g.), and neutralised with sodium hydrogen carbonate. The solution was evaporated under reduced pressure to two thirds of its original volume and extracted with ether (4 × 50 ml.). The residue (III) obtained by evaporation of the dried ($MgSO_4$) extract was kept at room temperature overnight with an excess of ethereal diazomethane solution. The mixture was evaporated; the residue when chromatographed yielded an oil, identical (i.r. spectrum) with that obtained in (*a*).

Trimethyl 4-Chloro-1-methylpyrrole-2,3,5-tricarboxylate.—Treatment of trimethyl 4-chloropyrrole-2,3,5-tricarboxylate [3] with diazomethane in ether afforded the *1-methyl compound*, m.p. 68° (from benzene–light petroleum) (Found: C, 45·25; H, 3·9; N, 4·55. $C_{11}H_{12}ClNO_6$ requires C, 45·6; H, 4·2; N, 4·8%).

Trimethyl 1-Methylpyrrole-2,3,5-tricarboxylate.—Pyrrole-2,3,5-tricarboxylic acid [3] (0·2 g.) was treated three times successively for periods of 24 hr. at room temperature with excess of diazomethane in ether. The resulting *ester*, after sublimation at 70°/0·001 mm., had m.p. 61—62° (0·23 g.) (Found: C, 51·8; H, 5·1; N, 5·6. $C_{11}H_{13}NO_6$ requires C, 51·75; H, 5·1; N, 5·5%).

Dimethyl 1-Methylpyrrole-2,3-dicarboxylate.—Pyrrole-2,3-dicarboxylic acid [4] (0·2 g.) when treated six times successively with diazomethane, then sublimed at 50°/0·001 mm. afforded the *ester*, m.p. 48—50° (0·08 g.) (Found: C, 54·8; H, 5·7; N, 7·15. $C_9H_{11}NO_4$ requires C, 54·8; H, 5·6; N, 7·1%). The residue, when sublimed at 70°/0·001 mm., yielded dimethyl pyrrole-2,3-dicarboxylate, m.p. 70° (lit.,[4] 72—73°) (0·15 g.) (Found: C, 52·3; H, 4·95. $C_8H_9NO_4$ requires C, 52·45; H, 4·9%).

[11] R. A. Nicolaus and L. Mangoni, *Ann. Chim.* (*Italy*), 1956, **46**, 847.

1-*Methylpyrrole*-2,3,5-*tricarboxylic Acid*.—Trimethyl 1-methylpyrrole-2,3,5-tricarboxylate (62 mg.) was heated under reflux for 2 hr. with ethanol (1 ml.) and 5% aqueous lithium hydroxide (2 ml.), poured on ice (10 g.), and acidified (Congo Red) with hydrochloric acid. Extraction with ether (3 × 10 ml.) afforded the *acid*, which crystallised from a small volume of water containing a little ethanol; m.p. 244° (Found: C, 45·15; H, 3·5. $C_8H_7NO_6$ requires C, 45·05; H, 3·3%).

Diethyl Pyrrole-2,3-*dicarboxylate*.—Prepared from pyrrole-2,3-dicarboxylic acid (1·04 g.) and diazoethane in ether, the *ester* (1·38 g.) had b.p. 110° (bath)/0·08 mm. (Found: C, 56·7; H, 6·3; N, 6·8. $C_{10}H_{13}NO_4$ requires C, 56·85; H, 6·2; N, 6·65%).

3-*Ethoxycarbonylpyrrole*-2-*carboxylic Acid*.—The diethyl ester (2·0 g.) was kept for 24 hr. at 37° with ethanol (10 ml.) and 5% aqueous lithium hydroxide (10 ml.), diluted with water (100 ml.), and acidified. The precipitated product, recrystallised from ethanol–water (1 : 1) had m.p. 145° (lit.,[5] 146—147°) (0·83 g.). Extraction with ether of the solution from which this had been precipitated yielded pyrrole-2,3-dicarboxylic acid, m.p. 224° (decomp.) (lit.,[4] 225°) (0·65 g.).

Ethyl 3-*Ethoxycarbonylpyrrole*-2-*acetate* (IVa).—A mixture of diethyl acetonedicarboxylate (15·2 g.) and water (90 ml.) was stirred, while a solution in water (10 ml.) of syrupy aminoacetaldehyde hydrochloride, prepared from aminoacetal (10 g.) by Fischer's method,[12] and simultaneously sodium hydroxide solution (10%) were added so as to maintain the pH of the mixture between 9 and 10 (pH meter). The mixture was then kept for 24 hr. at 40°, cooled, and extracted with ether (3 × 50 ml.). The ether was removed from the dried ($MgSO_4$) extract, and the residue (7·5 g.) was chromatographed on neutral alumina (100 g.). Light petroleum eluted diethyl acetonedicarboxylate, and mixtures of light petroleum and benzene eluted the *carboxyester* (IVa) which gave a positive Ehrlich reaction and formed leaflets, m.p. 56—56·5° (2·21 g.) (from benzene–light petroleum), $\nu_{max.}$ 1725 and 1700 cm.$^{-1}$ (Found: C, 58·85; H, 6·45; N, 6·25. $C_{11}H_{15}NO_4$ requires, C, 58·65; H, 6·7; N, 6·2%). The residual alkaline reaction mixture was acidified and extracted again with ether (3 × 50 ml.). The residue from the dried extract was chromatographed on Hopkin and Williams silica (60 g.). Elution with benzene–ether (1 : 1) afforded 3-*ethoxycarbonylpyrrole*-2-*acetic acid* (IVc), m.p. 104° (1·06 g.), $\nu_{max.}$ 1720, 1700 and 1665 cm.$^{-1}$, pK_a 4·5 (Found: C, 54·95; H, 5·75; N, 7·0. $C_9H_{11}NO_4$ requires C, 54·8; H, 5·6; N, 7·1%).

3-*Carboxypyrrole*-2-*acetic Acid* (IVb).—Ethyl 3-ethoxycarbonylpyrrole-2-acetate (IVa) (0·7 g.) was heated under reflux for 4 hr. with a mixture of ethanol (15 ml.) and 5% aqueous lithium hydroxide (15 ml.). The diluted solution was then acidified and extracted continuously with ether for 4 hr. to afford the crude acid, m.p. 175—177° (decomp.) (0·35 g.). This (15 mg.) was purified by two-dimensional chromatography on prewashed Whatman no. 4 paper, run successively with solvents A and B. The required spot, revealed by u.v. light, was cut out and the *acid* was eluted by Reith's method,[13] and dried ($CaCl_2$); m.p. 184° (decomp.) (10 mg.), p*K*a 4·2 and 6·4 (Found: C, 49·7; H, 4·3. $C_7H_7NO_4$ requires, C, 49·7; H, 4·2%).

3-*Methoxycarbonylpyrrole*-2-*acetic Acid*.—Methyl 3-methoxycarbonylpyrrole-2-acetate, prepared like the diethyl ester, was an oil, b.p. 80° (bath) /0·001 mm. The alkaline reaction mixture from its preparation yielded the *carboxyester*, m.p. 131—133° (from benzene) (Found: C, 52·2; H, 5·1; N, 7·75. $C_8H_9NO_4$ requires C, 52·45; H, 4·9; N, 7·65%).

Ethyl 2-*Methylpyrrole*-3-*carboxylate*.—Benary's[14] method of preparation was improved as follows. Ammonium hydroxide (10%; 450 ml.) was added dropwise during 30 min. to a stirred mixture of ethyl acetoacetate (65 g.) and 1,2-dichloroethyl ethyl ether (71·5 g.). The mixture was stirred for a further 2 hr., then kept in a refrigerator overnight. The lower, oily layer was separated and filtered, and the resulting crystals were washed with water. The oily filtrate was stirred for 2 hr. with sodium hydroxide solution (10%), kept in a refrigerator overnight, and filtered, affording a second crop of crystals. The combined crystals (23·5 g.) were dried ($CaCl_2$) for 12 hr. *in vacuo*, then chromatographed on alumina (500 g.). Elution with benzene gave the ester, m.p. 75° (lit.,[14] 78—79°) (22·9 g.), τ 5·63 (q, *J* 1·2 c./sec., $CH_3{\cdot}CH_2$), 7·47 (s, CMe), and 8·67 (t, *J* 1·2 c./sec., $CH_3{\cdot}CH_2$). Sublimation at 100°/0·04 mm. gave a form, m.p. 68° (Found: C, 62·65; H, 7·25; N, 9·1. Calc. for $C_8H_{11}NO_2$: C, 62·7; H, 7·25; N, 9·15%). Hydrolysis with aqueous ethanolic lithium hydroxide yielded the acid, m.p. 166° (decomp.) (lit.,[11] 168°).

4-*Ethyl* 2-*Methyl* 5-*Methylpyrrole*-2,4-*dicarboxylate*.—This was prepared from the ester just described by the method previously used for the 2,4-bisethoxycarbonyl compound,[7] but by use of methanol instead of ethanol. When sublimed at 120°/0·05 mm. this had m.p. 161—162° (Found: C, 56·8; H, 6·3; N, 6·55. $C_{10}H_{13}NO_4$ requires, C, 56·85; H, 6·2; N, 6·65%).

Ethyl 3,5-*Bisethoxycarbonylpyrrole*-2-*acetate* (Va).—Ethyl 3-ethoxycarbonylpyrrole-2-acetate (IVa) (2·1 g.) was kept for 2 days at 37° in a solution of phosgene in toluene (12·5%; 90 ml.). The excess of phosgene was removed at 11 mm. and the solution was then heated under reflux for 30 min. with ethanol (100 ml.); the solvents were then removed at 11 mm. The residue (2·5 g.) was chromatographed on neutral alumina (100 g.) with gradient elution [light petroleum (250 ml.) and benzene (250 ml.), then benzene (250 ml.) and chloroform (250 ml.); fractions (25 ml.) were collected]. Fractions 15—30 were combined to yield a residue (1·54 g.), which was recrystallised twice from benzene–light petroleum, and then sublimed at 140°/0·002 mm., affording the *ester*, m.p. 66° (0·95 g.), $\nu_{max.}$ 1718 and 1690 cm.$^{-1}$ (Found: C, 56·45; H, 6·35; N, 4·8. $C_{14}H_{19}NO_6$ requires C, 56·55; H, 6·45; N, 4·7%).

3,5-*Dicarboxypyrrole*-2-*acetic Acid* (Vb).—*Method* 1. The ester (Va) (0·5 g.) was hydrolysed as for the preparation of 3-carboxypyrrole-2-acetic acid, but with 2 hr. heating. The crude product was recrystallised three times from water, affording the *acid*, m.p. 260—261° (decomp.), after drying ($CaCl_2$) (Found: C, 44·8; H, 3·6; N, 6·65. $C_8H_7NO_4$ requires C, 45·05; H, 3·3; N, 6·55%).

4-*Ethoxycarbonyl*-5-*ethoxycarbonylmethylpyrrole*-2-*carboxylic Acid* (Vc).—*Method* 1. Ethyl 3,5-bisethoxycarbonylpyrrole-2-acetate (0·5 g.) was heated under reflux for 2 hr. with a saturated, ethanolic solution of lithium hydroxide (50 ml.); the solution was poured on ice (100 g.), acidified, and extracted with ether. The residue (0·32 g.; m.p. 137—140°) from the dried extract, when recrystallised twice from

[12] E. Fischer, *Ber.*, 1908, **41**, 1021.
[13] W. S. Reith, *Nature*, 1957, **179**, 580.
[14] E. Benary, *Ber.*, 1911, **44**, 495.

chloroform gave the *product*, m.p. 140° (Found: C, 53·3; H, 5·7; N, 5·15. $C_{12}H_{16}NO_6$ requires C, 53·5; H, 5·6; N, 5·2%).

Ethyl 4-Ethoxycarbonyl-5-methylpyrrole-2-glyoxylate.—Freshly distilled oxalyl chloride (2 ml.) in dry ether (30 ml.) was added gradually to a solution of ethyl 2-methylpyrrole-3-carboxylate (1·76 g.) in ether (30 ml.), cooled in methanol–solid carbon dioxide, and protected from moisture. The mixture was allowed to come to room temperature during 1 hr., kept there for 24 hr., and the ether was then removed at 11 mm. The residue was heated under reflux for 30 min. with ethanol (25 ml.) and the ethanol was removed at 11 mm.; the residue when recrystallised twice from benzene–light petroleum had m.p. 115—117° (2·5 g.). Sublimation at 110°/0·003 mm. afforded the *diester*, $\lambda_{max.}$ 317 mμ, $\nu_{max.}$ 1735 and 1710 cm.$^{-1}$ (Found: C, 56·35; H, 5·7; N, 5·55. $C_{12}H_{15}NO_5$ requires C, 56·9; H, 5·95; N, 5·55%). This gave a bright red colour with alcoholic sodium hydroxide. Hydrolysis, as for the preparation of 3,5-dicarboxypyrrole-2-acetic acid, gave *4-carboxy-5-methylpyrrole-2-glyoxylic acid*, m.p. 250° (decomp.) (Found: C, 48·75; H, 3·6; N, 7·1. $C_8H_7NO_5$ requires C, 48·75; H, 3·5; N, 7·2%). Hydrolysis of the diester, as for the preparation of 4-ethoxycarbonyl-5-ethoxycarbonylmethylpyrrole-2-carboxylic acid yielded *4-ethoxycarbonyl-5-methylpyrrole-2-glyoxylic acid*, m.p. 200—202° (decomp.) (from chloroform), $\lambda_{max.}$ 315 mμ, $\nu_{max.}$ 1740 and 1685 cm.$^{-1}$ (Found: C, 49·0; H, 5·3; N, 5·75. $C_{10}H_{11}NO_5{\cdot}H_2O$ requires C, 49·4; H, 5·35; N, 5·8%). Treatment of the diacid (100 mg.) with hydrogen peroxide (50 vols.; 25 ml.) for 24 hr. at room temperature, followed by continuous extraction with ether for 4 hr. yielded 5-methylpyrrole-2,4-dicarboxylic acid, m.p. 230° (decomp.) (75 mg.), identical (u.v. and i.r. spectra) with the same compound obtained before.

Ethyl 4-Ethoxycarbonyl-5-ethoxycarbonylmethylpyrrole-2-glyoxylate (VIa).—Ethyl 3-ethoxycarbonylpyrrole-2-acetate (IVa) (1 g.) was treated similarly with oxalyl chloride (5 ml.), followed by ethanol. The crude product was chromatographed on neutral alumina (30 g.) [gradient elution with light petroleum (50 ml.) and benzene (50 ml.), followed by benzene (50 ml.); fractions (5 ml.) were collected]. The residue obtained by evaporation of fractions 10—20 was recrystallised from benzene–light petroleum to give a product, m.p. 44—45° (1·4 g.), which on sublimation at 80°/0·001 mm. afforded the *ester*, m.p. 45°, $\nu_{max.}$ 1750—1730 and 1700 cm.$^{-1}$ (Found: C, 55·1; H, 5·85; N, 4·45. $C_{15}H_{19}NO_7$ requires C, 55·4; H, 5·9; N, 4·3%).

4-Carboxy-5-carboxymethylpyrrole-2-glyoxylic Acid (VIb).—The ester (VIa) (2 g.), when hydrolysed as for the preparation of 3,5-dicarboxypyrrole-2-acetic acid (method 1) yielded the *acid*, m.p. 120° (1·52 g.) (Found: C, 38·4; H, 3·95; N, 5·25. $C_9H_7NO_7,2H_2O$ requires C, 39·0; H, 4·0; N, 5·05%).

3,5-Dicarboxypyrrole-2-acetic Acid (Vb).—(*Method* 2).—The acid (VIb) (0·5 g.) in sodium carbonate solution (2N; 30 ml.), was kept for 1 hr. at room temperature with hydrogen peroxide (50 vols.; 2 ml.), then acidified and continuously extracted with ether for 12 hr. Recrystallisation of the product from water afforded the acid as needles, m.p. 257° (decomp.) (Found: C, 45·15; H, 3·45; N, 6·45%).

4-Ethoxycarbonyl-5-ethoxycarbonylmethylpyrrole-2-carboxylic Acid (Vc).—(*Method* 2). A mixture of ethyl 4-ethoxycarbonyl-5-ethoxycarbonylmethylpyrrole-2-glyoxylate (VIa) (0·5 g.), ethanol (5 ml.), water (5 ml.), hydrogen peroxide (50 vols.; 1 ml.), and sodium carbonate solution (2N; 5 ml.) was kept at room temperature for 2 hr., diluted with water (20 ml.), acidified, and extracted with ether (3 × 20 ml.). The residue left after removal of ether from the extract crystallised from ethanol–water (1 : 4; 6 ml.), affording the product, m.p. 140—142° (Found: C, 53·35; H, 5·65; N, 5·25%).

Ethyl 4-Ethoxycarbonyl-5-methylpyrrole-2-acetate (VIIa).—Ethyl diazoacetate (0·455 g., 1 mol.) was added dropwise during 1 hr. to a mixture of ethyl 2-methylpyrrole-3-carboxylate (0·5 g.) and copper powder (25 mg.) at 90°. After a further 4 hr. at 90° nitrogen evolution had ceased. The cooled material was chromatographed on alumina (30 g.). Elution with benzene–light petroleum (1 : 10; 50 ml.) gave the unchanged pyrrole (0·15 g.), and further elution with the same solvent (75 ml.) afforded the *product*, m.p. 61° (from benzene–light petroleum) (0·34 g.) (Found: C, 60·35; H, 7·2; N, 5·95. $C_{12}H_{17}NO_4$ requires C, 60·3; H, 7·15; N, 5·85%).

4-Carboxy-5-methylpyrrole-2-acetic Acid (VIIb).—The ester (VIIa) (0·3 g.) was boiled for 2 hr. with ethanol (5 ml.) and lithium hydroxide solution (5%; 10 ml.). The crude product, when recrystallised from water containing a little ethanol, gave the *acid*, m.p. 178—180° (decomp.) (0·16 g.) (Found: C, 52·85; H, 5·0. $C_8H_9NO_4$ requires C, 52·45; H, 4·9%).

Ethyl 4-Ethoxycarbonyl-2,5-dimethylpyrrole-3-acetate (VIIIa).—Ethyl diazoacetate (15·9 g., 2 mol.) was added during 2 hr. to ethyl 2,5-dimethylpyrrole-3-carboxylate [15] (11·5 g.) containing copper powder (0·1 g.) at 80°, and the mixture was kept at 80° for a further 2 hr. The product was chromatographed on alumina (500 g.). Elution with benzene–light petroleum (1 : 1; 3·5 l.) yielded the unchanged pyrrole (6·5 g.), and elution with benzene (2 l.) afforded the *diester* (1·83 g.), m.p. 93—95° (from benzene–light petroleum); after sublimation at 120°/0·001 mm., m.p. 94—96° (Found: C, 61·2; H, 7·55; N, 5·7. $C_{13}H_{19}NO_4$ requires C, 61·4; H, 7·3; N, 5·5%). Hydrolysis, as for the preparation of (VIIb), afforded acid (VIIIb), m.p. 158°, shown by potentiometric titration to be a diacid, $\nu_{max.}$ 1715, 1700, and 1660 cm.$^{-1}$.

Sulphuryl chloride (16·6 g., 6 mol.) was added during 1 hr. to a solution of (VIIIa) (4·62 g.) in a mixture of acetic acid (500 ml.) and acetic anhydride (60 ml.) at 5°. After 7 hr. at room temperature the mixture was diluted with water (500 ml.), boiled under reflux for 1 hr., then cooled. The liquid was decanted, and the residual tar was heated under reflux for 2 hr. with sodium hydroxide solution (10%; 25 ml.). The cooled solution was acidified (Congo Red) with hydrochloric acid, and extracted continuously with ether for 10 hr. The residue (0·26 g.) left after removal of ether from the extract gave 2,4,5-tricarboxypyrrole-3-acetic acid (XI), m.p. 140° (decomp.) (from water), $\nu_{max.}$ 1720, 1700 and 1650 cm.$^{-1}$. Oxidation of this with a large excess of hydrogen peroxide in 2N-sodium carbonate for 24 hr., yielded pyrrole-2,3,4,5-tetracarboxylic acid, chromatographically identical with an authentic sample.[16]

Reaction of 2,5-Dimethylpyrrole with Ethyl Diazoacetate.—The products from the reaction of 2,5-dimethylpyrrole [17] (7·6 g.) with ethyl diazoacetate (16·0 g., 2 mol.) in the presence of copper (50 mg.) at 60° were chromatographed on

[15] W. Küster, *Z. physiol. Chem.*, 1922, **121**, 144.
[16] R. A. Nicolaus, *Rass. Med. sper.*, 1960, VII, Suppl. 2, 18.
[17] D. M. Young and C. F. H. Allen, *Org. Synth.*, **16**, 25.

neutral alumina (500 g.). Benzene–light petroleum mixtures, and benzene eluted the unchanged pyrrole and diethyl fumarate. Gradient elution with benzene–chloroform mixtures gave an oil, b.p. 90° (bath)/0·001 mm., thought to be (XIIa), $\nu_{max.}$ 1740 cm.$^{-1}$, followed by a fraction which, after sublimation at 50°/0·001 mm., had m.p. 80—82° (0·19 g.), $\nu_{max.}$ 3400 and 2230 cm.$^{-1}$ (Found: C, 69·85; H, 6·8; N, 23·5. Calc. for C_7H_8N: C, 70·0; H, 6·85; N, 23·3%), identical (i.r. and u.v. spectra) with an authentic sample of 3-cyano-2,5-dimethylpyrrole.[18]

During the reaction ammonia was evolved, as shown by sweeping it out with nitrogen and collecting it in an ethanolic solution of picric acid, to give ammonium picrate.

Sulphuryl chloride (6·7 g., 7 mol.) was added during 1 hr. to a solution of (XIIa) (1·16 g.) in a mixture of acetic acid (250 ml.) and acetic anhydride (30 ml.), and the product (XIII), worked up as for (XI), had m.p. 184° (decomp.) (53 mg.) and i.r. absorption similar to that of (XI). Oxidation with hydrogen peroxide yielded 4-chloropyrrole-2,3,5-tricarboxylic acid, chromatographically identical with an authentic sample.[3]

Methyl 4,5-Bismethoxycarbonylpyrrole-2-acetate (Xa).—Dimethyl pyrrole-2,3-dicarboxylate (1·7 g.) was treated with methyl diazoacetate (6·0 g., *ca.* 8 mol.) as before, and the product, when chromatographed on alumina (250 g.), afforded, by elution with benzene–light petroleum (1 : 1; 200 ml.), the *ester*, m.p. 134° after sublimation at 110°/0·001 mm. (47 mg.) (Found: C, 51·35; H, 5·1; $C_{11}H_{13}NO_6$ requires C, 51·75; H, 5·1%). Hydrolysis and oxidation, as before, yielded pyrrole-2,3,5-tricarboxylic acid, chromatographically identical with an authentic sample.[3]

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[18] R. Justoni, *Gazzetta*, 1941, **71**, 375.