805. *A General Route to ββ'-Substituted Pyrrole Intermediates for Porphyrin Synthesis.*

By S. F. MacDonald.

New pyrrole intermediates, (VIII*d*) and (X*d*), have been prepared by modifications of standard methods, the essential step being the substitution of benzyl acetoacetate for ethyl acetoacetate in the Knorr syntheses. As already briefly reported (MacDonald, *Chem. and Ind.*, 1951, 759) these should lead to the hitherto unknown pyrroles related to the uroporphyrins, with acetic and propionic acid residues in the ββ'-positions.

A new synthesis of hæmopyrrolecarboxylic acid has been carried out through (X*d*). The ambiguity in its previous syntheses extended to those of the coproporphyrins II and III, and there had consequently been no general method for preparing their homologues.

An earlier alternative solution to these problems had failed when it proved impossible to introduce appropriate β-substituents into the pyrroles by the usual methods. This can be attributed to the effect of α-carbethoxy-groups in diminishing the reactivity of adjacent free β-positions.

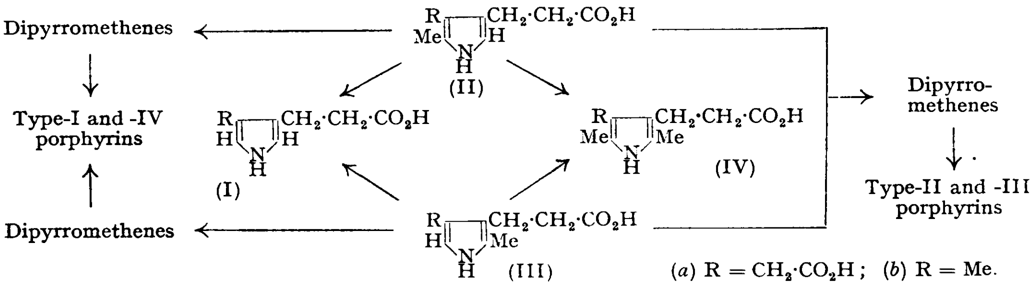
The uroporphyrins were formulated as porphintetra-acetic-tetrapropionic acids by Fischer and Orth ("Chemie des Pyrrols," Leipzig, 1937, Vol. II/i, pp. 504 *et seq.*) and the synthesis of pyrroles with acetic acid and propionic acid residues in the ββ'-positions had consequently been attempted. This was a necessary preliminary to the confirmation of the structures by synthesis, both of these porphyrins and of their oxidation product, a carboxylated hæmatinic acid. Such pyrroles have remained unknown; they could not be isolated from the reduction products of uroporphyrin I, as they did not form picrates (Fischer, *Z. physiol. Chem.*, 1916, **98**, 78; Fischer and Andersag, *Annalen*, 1927, **458**, 117). Were their properties known through synthesis, their isolation should not be difficult.

It was apparent from Fischer's work on analogous porphyrins that all the pyrroles (I*a*), (II*a*), (III*a*), and (IV*a*), and their α-carbethoxy-derivatives, had some importance, either for synthetic work or as probable reduction products of the uroporphyrins. However, the general question of applying his methods systematically to the synthesis of any such set of pyrroles and porphyrins was confused. This was largely because ambiguous reactions had sometimes been used in the syntheses of analogous sets, either for convenience or of necessity, and this obscured the question of their generality. Such reactions also implied indirect methods and proofs of structure which would involve greater difficulties in the present case.

A survey of the extensive literature showed that pyrroles can only be converted unambiguously into pure porphyrins by the routes indicated in Scheme 1. Here, as in Scheme 2, the α-carbethoxy-groups which are necessary for some transformations of the pyrroles are ignored for simplicity. Only those porphyrin syntheses are considered which proceed through dipyrromethenes; the other syntheses cannot be relied on to give porphyrins which are unmixed in type (Fischer, *Ber.*, 1927, **60**, 2649). As indicated in Scheme 1, type-I and type-IV porphyrins can be obtained unambiguously from either of the pyroles (II) and (III) (Fischer and Orth, *op. cit.*, p. 193, methods *b* and *a*; p. 202, "preparation" and method *a*). However, unambiguous methods for preparing pure type-II and type-III porphyrins require both the pyrroles (II) and (III) (Fischer and Andersag, *loc. cit.*; Fischer and Lamatasch, *Annalen*, 1928, **462**, 240; Fischer and Orth, *op. cit.*, p. 200, methods *c* and *b*; the second of the two coproporphyrin II syntheses employs a 5 : 5'-dibromopyrromethene obtained from (I*b*), rather than unambiguously from (II*b*) through the dipyrrylmethane of Fischer and Csukas, *Annalen*, 1934, **508**, 167). These methods avoid the ambiguity introduced by the use of (I) or the aldehyde obtained from it in dipyrromethene synthesis. The four other syntheses of type-II and type-III porphyrins used or implied by Fischer, would also require both the pyrroles (II) and (III) for unambiguous syntheses of the necessary dipyrromethenes.

Scheme 1 also indicates the most direct and general method of obtaining all four pyrroles of a set, using the interconversions developed by Fischer (Scheme 2) (Fischer and Orth, *op. cit.*, Vol. I, p. 47 *et seq.*, 278 *et seq.*). Generally, independent syntheses of the key pyrroles (II) and (III) are necessary; their mutual interconversions through the *symmetrical* intermediates (I) and (IV) will not always be possible, and the direction in which interconversion is possible cannot be predicted.

Scheme 1.



(*a*) R = $CH_2{\cdot}CO_2H$; (*b*) R = Me.

Scheme 2.

$$\text{(I)} \underset{\textit{via}\ \text{CBrCl}_3\ \text{for Me}}{\overset{\textit{via}\ \text{CHO for H}}{\rightleftharpoons}} \text{(II) or (III)} \underset{\textit{via}\ \text{phthalide}}{\overset{\textit{via}\ \text{CHO for H}}{\rightleftharpoons}} \text{(IV)}$$

More direct syntheses of the symmetrical (I) and (IV) have no advantage when (II) or (III) is available, and their usefulness is limited as discussed above. When carbethoxy-groups are used to block the α-positions, more direct syntheses of (I) will be very restricted; the effect of these groups is discussed below. Direct syntheses of (IV), where no such blocking is required, should be most general. Though little developed, the steps here have been indicated (Fischer and Orth, *op. cit.*, Vol. I, pp. 155, 164, 263, 287, 289), but the removal of a methyl group to free an α-position requires conditions inappropriate when easily decarboxylated acetic acid side-chains are present as in (IV*a*) (Scheme 2).

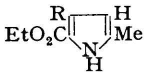
It was apparent that independent syntheses of (II*a*) and (III*a*) would have to be found; only thus could straightforward syntheses of all the required pyrroles and uroporphyrins be projected according to Fischer's methods. The known methods were inadequate.

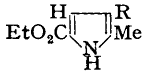
The same problem in pyrrole synthesis had arisen in connection with the coproporphyrins, but had received no general solution. The material (III*b*), the coproporphyrins I and IV, and homologues of these are available by general methods. However, the synthesis of hæmopyrrolecarboxylic acid (II*b*) (Fischer and Treibs, *Ber.*, 1927, **60**, 377), and consequently those of authentic coproporphyrins II and III, depended on the fortunate course of ambiguous reactions involving (I*b*) or (IV*b*); authentic homologues of these are unknown.

General methods had led to all the purely alkyl analogues of (II) and (III) and to all the ætioporphyrins and their homologues. Here, the convenient but unnecessary use of the α-aldehyde obtained from 3-ethyl-4-methylpyrrole has led to confusion; its structure is still in doubt (Fischer, Baumann, and Riedl, *Annalen*, 1930, **475**, 240; Siedel, *Z. physiol. Chem.*, 1935, **231**, 186; Fischer and Hoefelmann, *ibid.*, 1938, **251**, 187; Siedel and Winkler, *Annalen*, 1943, **554**, 169).

One obvious approach to (II*a*), (III*a*), (II*b*), and homologues of the last, was to introduce the second β-substituent into (V; R = $CH_2{\cdot}CO_2H$ or R = $CH_2{\cdot}CH_2{\cdot}CO_2H$), for (V; R = alkyl) had thus been the only important primary source of pyrrole- and porphin-propionic acids. However, the required intermediates could not be prepared by available methods. Numerous attempts had therefore been made to introduce the second substituent into (VI) which, unlike (V), could be obtained without restriction on R. These failed because of the unrecognized effect of an α-carbethoxy-group in blocking the adjacent β-position to substitution by the Gattermann–Hoesch reaction or by use of $MeO{\cdot}CH_2{\cdot}CH(CO_2Et)_2$, the reactions through which $CH_2{\cdot}CH_2{\cdot}CO_2H$ and $CH_2{\cdot}CO_2H$ had been introduced into (V; R = alkyl). Thus (VI; R = Me or $CH_2{\cdot}CH_2{\cdot}CO_2H$) (Fischer and Hussong, *Annalen*, 1932, **492**, 141; Fischer and Kutscher, *ibid.*, 1930, **481**, 193) had failed to give aldehydes leading to (II*b*) or (III*a*), and (VI; R = CN or CO_2Et) (Fischer and Hussong, *loc. cit.*; Fischer and Elhardt, *Z. physiol. Chem.*, 1939, **257**, 61) was likewise unreactive. The description of the 4-glyoxylic ester derivative of (VI; R = CHO) refers to [VI; R = $CH{:}C(CN){\cdot}CO_2Et$] (Fischer and Orth, *op. cit.*, Vol. I, pp. 228, 308). However, substitution in (VI) by the Friedel–Crafts method and its condensation with formaldehyde is still possible (Fischer and Orth, *op. cit.*, Vol. I, pp. 192, 197, 348). The effect of an α-cyano-group in preventing substitution had been recognized (Fischer and Elhardt, *loc. cit.*).

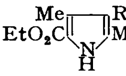
(V)





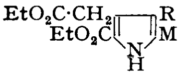
(VI)

The necessary reactivity was therefore not to be expected in (VI), and that in (V) was uncertain. Although (V; R = alkyl) had given aldehydes and glyoxylic esters and reacted with $MeO{\cdot}CH_2{\cdot}CH(CO_2Et)_2$ (Fischer and Orth, *op. cit.*, Vol. I, pp. 163, 165, 293, 295, 308), the only example of interest here (V; R = $CH_2{\cdot}CN$) had not (Fischer and Elhardt, *loc. cit.*; Fischer and Mueller, *Z. physiol. Chem.*, 1937, **246**, 31). However, the only route to (II*a*), (III*a*), and the homologues of (II*b*) by these methods lay in the assumption that (V) generally would show the desired reactivity, (V; R = $CH_2{\cdot}CN$) being incorrectly formulated. This finds some justification, as it had failed to give the pine-splint and Ehrlich reactions (Fischer and Mueller, *loc. cit.*; Benary, *Ber.*, 1919, **53**, 2218), in contrast to (V; R = alkyl) (see below), and its mode of formation was obscure.



(VII)

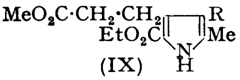
(*a*; R = CO_2Et)
(*b*; R = $CO_2{\cdot}CH_2Ph$)
(*c*; R = CO_2H)
(*d*; R = H)
(*e*; R = COCl)
(*f*; R = $CO{\cdot}NH{\cdot}NH_2$)
(*g*; R = $CH_2{\cdot}NMe_2$)



(VIII)

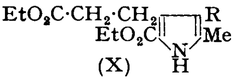
(a; R = CO_2Et)
(*b*; R = $CO_2{\cdot}CH_2Ph$)
(*c*; R = CO_2H)
(*d*; R = H)
[*e*; R = $CH_2{\cdot}CH(CO_2Et)_2$]
(*f*; R = CHO)

(IX)



(*a*; R = CO_2Et)
(*b*; R = $CO_2{\cdot}CH_2Ph$)
(*c*; R = CO_2H)
(*d*; R = H)

(X)



(*b*; R = $CO_2{\cdot}CH_2Ph$)
(*c*; R = CO_2H)
(*d*; R = H)
(*e*; R = CHO)

The most direct route to (V; R = alkyl) is typified by the condensation of oximinoacetoacetic ester and acetoacetic ester to (VII*a*) (Knorr), its partial hydrolysis in concentrated sulphuric acid at 40° to (VII*c*), and decarboxylation to (VII*d*) (Fischer and Wallach, *Ber.*, 1925, **58**, 2820; Fischer and Orth, *op. cit.* Vol. I, p. 239; cf. *Org. Synth.*, Coll. Vol. II, p. 198). Similarly, oximinoacetonedicarboxylic ester and β-keto-α-oximinoadipic ester with acetoacetic ester gave (VIII*a*) (Fischer and Mueller, *loc. cit.*; Fischer Neumann, and Hirschbeck, *Z. physiol. Chem.*, 1943, **279**, 1) and (IX*a*) (this paper; Professor A. Treibs, personal communication) respectively, but these did not thus yield (VIII*d*) or (IX*d*). The substitution of the readily available benzyl acetoacetate (Bacon, *Amer. Chem. J.*, 1905, **33**, 79) for ethyl acetoacetate in the Knorr syntheses has led to a sufficiently general synthesis of (V). Thus (VII*b*), (VIII*b*), (IX*b*), and (X*b*) were prepared, hydrogenated to (VII*c*), (VIII*c*), (IX*c*), and (X*c*), and decarboxylated to (VII*d*), (VIII*d*), (IX*d*), and (X*d*).

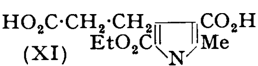
The substance (VII*b*) was used to explore the reaction, for it gave the known pyrroles (VII*c*) and (VII*d*) which are better prepared from (VII*a*).

The structure of (VIII*d*) was confirmed by its hydrolysis to (V; R = $CH_2{\cdot}CO_2H$) followed by decarboxylation to the known (VII*d*); its reactivity is illustrated by the formation of (VIII*e*) with $MeO{\cdot}CH_2{\cdot}CH(CO_2Et)_2$, and further by formation of (VIII*f*) by the Gattermann-Hoesch method (MacDonald, *loc. cit.*), leading to transformations completely establishing its structure, and to (III*a*).

The benzyl ester (X*b*) has been a preferred alternative to (IX*b*), because it can be prepared from a more reliable β-ketoadipic ester, obtained from the crystalline acid (Eisner, Elvidge, and Linstead, *J.*, 1950, 2226). The pyrrole (X*d*) also proved reactive, giving the aldehyde (X*e*), the structure of which was confirmed by Wolff–Kishner reduction to hæmopyrrolecarboxylic acid (II*b*), previously synthesised by Fischer and Treibs (*loc. cit.*). The conversion of (X*d*) into (II*a*) is being studied.

This synthesis of hæmopyrrolecarboxylic acid makes Fischer's syntheses of the coproporphyrins II and III unambiguous throughout, and the same methods should now give the homologues of these (cf. Fischer and Stangler, *Annalen*, 1928, **462**, 253, 261). The pyrrole (X*d*) also provides a route to (II; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$) and porphinoctapropionic acid.

After (IX*c*) had been precipitated by carbon dioxide from an alkaline solution of the crude product (see below), sulphur dioxide precipitated much (XI) which had remained in solution. Decarboxylation of (XI) gave (V; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$), the structure of which was confirmed by comparison with the same product obtained by the alkaline hydrolysis of (X*d*); it gave (X*d*) in good yield on esterification. (XI) also arose as a by-product in the preparation of (X*c*). Fortunately, the acetic ester group in (VIII*c*) is more resistant to hydrolysis, for the free acetic acid group, unlike the propionic acid group would not survive the subsequent decarboxylation.


(XI)

All these pyrroles give a positive Ehrlich's reaction, those of the series (VIII), (IX), and (X) behaving like the analogous members of the series (VII). It is interesting that (VI; R = Me or $CH_2{\cdot}CH_2{\cdot}CO_2H$) do not give a positive Ehrlich's reaction in the cold (Fischer and Hussong, *loc. cit.*; Fischer and Fink, *Z. physiol. Chem.*, 1948, **283**, 152); the more reactive isomers (V; R = Me or $CH_2{\cdot}CH_2{\cdot}CO_2H$) do. The behaviour of the alleged (V; R = $CH_2{\cdot}CN$) remains unexplained; an approach to such a structure is being made through (V; R = $CH_2{\cdot}CO{\cdot}NH_2$) obtained from (VIII*d*).

Standard conditions were found for the Knorr syntheses, the formation of the half-esters, and for their purification and decarboxylation. The Knorr syntheses were carried out at 60° (cf. Fischer and Orth, *op. cit.*, Vol. I, pp. 257, 258), the oximino-ester and zinc dust being added to the other components (Corwin and Quattlebaum, *J. Amer. Chem. Soc.*, 1936, **58**, 1081). The catalytic debenzylations were carried out over Raney nickel in dried ethanol, at 100°/100 atm. as the pyrroles were not easily soluble. These acids, (VII*c*), (VIII*c*), (IX*c*), and (X*c*), were insoluble in aqueous sodium hydrogen carbonate. They were purified by precipitation from cold dilute solutions of their sodium salts, by use of carbon dioxide instead of acid; the products were then much more easily filtered and were free from mineral acid. 3-Carbethoxy-2 : 4-dimethylpyrrole-5-carboxylic acid, the isomer of (VII*c*), is also insoluble in bicarbonate, but free propionic and acetic acids derived from (VIII), etc., are soluble in it. None of the published methods gave consistent results when applied to the decarboxylation of these acids to (VII*d*), (VIII*d*), (IX*d*), and (X*d*). Too little or too much heating results in incomplete decarboxylation or in extensive decomposition; the cessation of frothing is no guide here, even in the case of (VII*c*). It is probable that the thermal formation and decomposition of dimers complicates the reactions, and unchanged acids, particularly (VII*c*), may sublime to contaminate distilled products. It was found that heating to 230° in glycerol, followed as rapidly as foaming permitted by steam-distillation at 280° (steam not preheated), gave consistently maximal yields of products which crystallized directly in the receiver, high-melting impurities being then absent.

Much the best method of preparing (VII*d*) is that of Fischer and Wallach (*loc. cit.*) through (VII*a*) (see above). With these modifications in the Knorr synthesis of (VII*a*) and in the purification and decarboxylation of (VII*c*), pure (VII*d*) was obtained in 45% yield from ethyl acetoacetate. It was thought that the partial hydrolysis of (VII*a*) to (VII*c*) in concentrated sulphuric acid might be analogous to that of mesitoic esters (Treffers and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 1708), but (VII*a*) was recovered unchanged after treatment with 100% sulphuric acid at 10°.

Some experiments were begun on further methods for introducing acetic acid and propionic acid groups into (VII*d*). With carbonyl chloride (cf. Fischer and Orth, *op. cit.*, Vol. I, p. 313) it gave (VII*e*), identified by conversion into (VII*a*), and it also readily gave the Mannich base (VII*g*) (cf. Fischer and Nenitzescu, *Annalen*, 1925, **443**, 113). It did not react with cyanoacetic ester under Gattermann–Hoesch conditions (cf. Fischer and Orth, *op. cit.*, Vol. I, p. 310). An attractive alternative to decarboxylating (VII*c*) and its analogues was to utilize the carboxyl group to build up the side-chain, a method which should also be applicable in pyrroles where the free β-position would be inactivated by an adjacent α-carbethoxy-group (see above). Acetyl chloride converted (VII*c*) into the acid chloride (VII*e*), which gave (VII*a*) and (VII*f*) with ethanol and hydrazine respectively.

EXPERIMENTAL

M. p.s are uncorrected.

Diethyl 3 : 5-*Dimethylpyrrole*-2 : 4-*dicarboxylate* (VII*a*).—Acetoacetic ester (400 g.) in acetic acid (900 c.c.) was treated slowly with sodium nitrite (220 g.) in water (300 c.c.) at 4—7°, and the resulting solution run into a stirred mixture of acetoacetic ester (400 g.), acetic acid (1400 c.c.), and zinc dust (600 g.) in a 5-l. flask cooled in water. The addition wsa made at 60°, rising to 100°, to keep the product in solution; stirring at 100° was then continued 1·5 hours. The product was isolated as usual (Fischer and Orth, *op. cit.*, Vol. I, p. 255), giving 536 g. (73%) of vacuum-dried ester.

Benzyl 5-*Carbethoxy*-2 : 4-*dimethylpyrrole*-3-*carboxylate* (VII*b*).—Sodium nitrite (13·8 g.) in water (20 c.c.) was slowly added with stirring to ethyl acetoacetate (26 g.) in acetic acid (100 c.c.) at 4—8°. After 15 minutes, benzyl acetoacetate (38·4 g.) and anhydrous sodium acetate (25 g.) were added, followed by a mixture of zinc dust (35 g.) and sodium acetate (10 g.) during 30 minutes. To keep the product in solution, acetic acid (100 c.c.) was added, and the mixture allowed to boil. The mixture was refluxed for 1 hour and decanted from zinc into water. The *product* was filtered off and washed with water, giving 35 g. (58%), m. p. 140—145°. For analysis, it was crystallized from ethanol, distilled (150—170°/5 × 10^{-3} mm.), and recrystallized several times, forming colourless plates, m. p. 151—151·5° (Found : C, 67·3; H, 6·3; N, 4·8. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4; N, 4·6%). Ehrlich's reaction weakly positive in the hot.

5-*Carbethoxy*-2 : 4-*dimethylpyrrole*-3-*carboxylic Acid* (VII*c*).—(*a*) *By Fischer and Wallach's method* (loc. cit.). The crude diethyl ester (VII*a*) was treated with sulphuric acid and poured on ice. The precipitate was filtered off (cloth filter) and washed with water (500 c.c.; thorough washing is difficult and unnecessary). It was stirred in water (1 l.) for 30 minutes, 10% aqueous sodium hydroxide being added to alkalinity (phenolphthalein). The filtered solution was made up to 2·5 l. with ice and water and saturated with carbon dioxide; the product (67·6 g., 77%) was filtered off, washed with water, and vacuum-dried. When the diester (VII*a*) (100 g.) was treated with sulphuric acid (200 c.c.) at 10° and 20% oleum (200 c.c.) was added at 10°, the diester (95 g.) was recovered unchanged.

(b) *From benzyl* 5-*carbethoxy*-2 : 4-*dimethylpyrrole*-3-*carboxylate* (VII*b*). The benzyl ester (5 g.) was hydrogenated for 4 hours (50°/100 atm.) in ethanol (250 c.c.) with Raney nickel (7 g.). After filtration and removal of the solvent, the product was dissolved in dilute sodium hydroxide, precipitated with acid, and crystallized from ethanol, forming colourless plates (74%), m. p. 272° (lit., 273°) (Found : C, 56·6; H, 6·35; N, 6·6. Calc. for $C_{10}H_{13}O_4N$: C, 56·85; H, 6·2; N, 6·6%).

Ethyl 3 : 5-*Dimethylpyrrole*-2-*carboxylate* (VII*d*).—(*a*) The acid (VII*c*), from the benzyl ester (VII*b*), was decarboxylated by heating it over a free flame. The product was extracted from the melt with cold ethanol, crystallized from 50% ethanol, and distilled at 200°/30 mm. It had m. p. and mixed m. p. with authentic material 123—124° (Found : C, 64·6; H, 8·0; N, 8·6. Calc. for $C_9H_{13}O_2N$: C, 64·7; H, 7·8; N, 8·4%).

(*b*) *Preparative method.* The acid (VII*d*) (20 g.) was wetted with glycerol (50 g.) in a ½-l. flask with a short wide neck. The mixture was heated at 220—230° until the paste had liquefied, and two further 20-g. portions of the acid were added successively, the heating being repeated after each addition. The contents were then steam-distilled (260—300°, thermometer in mixture) until the distillate became dark and free from oil. The product was filtered off from the distillate, washed with water, crystallized from 95% ethanol (75 c.c.), and washed with ethanol (25 c.c.), giving 40·1 g. of m. p. 123°. The mother-liquiors yielded a further 1·6 g., m. p. 121—122° (total 87%).

5-*Carbethoxy*-2 : 4-*dimethylpyrrole*-3-*carbonyl Chloride* (VII*e*).—(a) *From* (VII*d*). The pyrrole (1 g.) in toluene (25 c.c.) was saturated with carbonyl chloride at 20° and set aside for 2 days. The crystalline acid chloride was filtered off and dried *in vacuo*. Boiling ethanol converted it into the diester (VII*a*), m. p. 134° undepressed when mixed with an authentic specimen (Found : C, 60·2; H, 7·35; N, 5·9. Calc. for $C_{12}H_{17}O_4N$: C, 60·2; H, 7·2; N, 5·9%).

(b) *From* (VII*c*). The half-ester (1 g.) was refluxed with acetyl chloride (40 c.c.) for 1 hour, then cooled, and the product (0·98 g.) filtered off; the *acid chloride* formed colourless needles, m. p. 203° (Found : C, 52·6; H, 4·8; N, 6·2; Cl, 14·4. $C_{10}H_{12}O_3NCl$ requires C, 52·3; H, 5·3 N, 6·1; Cl, 15·4%). Boiling ethanol converted it into the diester (VII*a*), m. p. 134—134·5°.

5-*Carbethoxy*-2 : 4-*dimethylpyrrole*-3-*carboxyhydrazide* (VII*f*).—The acid chloride (VII*g*) (0·98 g.) was dissolved in dioxan (10 c.c.) containing hydrazine hydrate (100%; 2 c.c.) at 0°. The *product* was precipitated with water, filtered off, dissolved in dilute acid, and re-precipitated with alkali, yielding needles (from ethanol), m. p. 220° (Found : C, 53·1; H, 6·9; N, 18·6. $C_{10}H_{15}O_3N_3$ requires C, 53·3; H, 6·7; N, 18·65%).

Ethyl 3 : 5-*Dimethyl*-4-*dimethylaminomethylpyrrole*-3-*carboxylate* (VII*g*).—The pyrrole (VII*d*) (16·7 g.) was heated under reflux for 3 hours with ethanol (50 c.c.), dimethylamine hydrochloride (10 g.), and 40% formaldehyde solution (10 g.). After concentration, addition of water (250 c.c.), and filtration warm, the *product* (21 g., 94%) was precipitated with aqueous sodium hydroxide. It was purified by precipitation as the hydrochloride from ethanol, and the regenerated base crystallized from 40% ethanol as colourless long plates, m. p. 121° (Found : C, 63·9; H, 8·85; N, 12·6. $C_{12}H_{20}O_2N_2$ requires C, 64·3; H, 9·0; N, 12·5%). Ehrlich's reaction was positive in the hot.

Benzyl 5-*Carbethoxy*-4-*carbethoxymethyl*-2-*methylpyrrole*-3-*carboxylate* (VIII*b*).—Amyl nitrite (117 g.; twice distilled) was added during 1 hour at 20° to a stirred and cooled mixture of ethyl acetonedicarboxylate (*Org. Synth.*, Coll. Vol. I, 2nd edn., p. 237) and concentrated hydrochloric acid (1·5 c.c.). After the addition, the temperature was allowed to rise spontaneously to 25°; the mixture was then heated to 40° and set aside at room temperature overnight. It was then run during 40 minutes into a vigorously stirred mixture of ammonium acetate (150 g.), acetic acid (1 l.), benzyl acetoacetate (192 g.), and zinc dust (50 g.) in a 2-l. flask cooled in ice-water. During the addition, zinc dust (100 g.) was added in small portions and the temperature was kept at 60—65°. The cooling-bath was then removed and, after the temperature rise ceased, the mixture was slowly heated to 95° during 2 hours, stirring being continued. The hot solution was decanted from zinc into well-stirred ice-water (12 l.), and the zinc washed with hot 50% acetic acid. The *product* was filtered off after 2 hours, washed with 50% ethanol (500 c.c.), and crystallized from absolute alcohol (280 c.c.) (charcoal), giving 203·5 g. (55%) of m. p. 120—123°; after several recrystallizations it formed colourless flat prisms, m. p. 123—124° (Found : C, 64·5; H, 6·2; N, 3·8. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·8%). Ehrlich's reaction was positive in the hot.

Inferior ethyl acetonedicarboxylate gives once-recrystallized products which begin to melt at about 110°; they are quite satisfactory for the subsequent stages. Use of sodium nitrite and acetic acid in place of amyl nitrite lowered the yield considerably (cf. Fischer and Mueller, *loc. cit.*; Fischer, Neumann and Hirschbeck, *loc. cit.*).

5-*Carbethoxy*-4-*carbethoxymethyl*-2-*methylpyrrole*-3-*carboxylic Acid* (VIII*c*).—The benzyl ester (VIII*b*) (70 g.) was hydrogenated in absolute ethanol (800 c.c.) over Raney nickel (5 c.c.) for 3 hours at 100°/100 atm. The bulk of the product was filtered off and more obtained by evaporation of the ethanol. Three such lots (from 203 g. of benzyl ester) were combined, dissolved in cold aqueous sodium hydroxide, diluted to 0·1M (*ca.* 6 l.), filtered, and saturated with carbon dioxide at 0°. The precipitated *product* was filtered off, washed with water (3 l.), and dried at 100°, giving 139·5 g. (91%) of m. p. 238—239° (decomp.). After three recrystallizations from acetic acid, colourless prisms, m. p. 240° (decomp.), were obtained, which give Ehrlich's reaction very faintly in the hot (Found : C, 55·5; H, 6·2; N, 5·1. $C_{13}H_{17}O_6N$ requires C, 55·1; H, 6·05; N, 4·9%).

Batches of 125 g. were hydrogenated at 125°/150 atm. but with no increase in the amount of ethanol or nickel.

Ethyl 3-*Carbethoxymethyl*-5-*methylpyrrole*-2-*carboxylate* (VIII*d*).—The above carboxylic acid (15 g.) was wetted with glycerol (45 g.) in a ½-l. bolt-head flask fitted with a steam-inlet and a thermometer reaching to the bottom and with a downward air-condenser leading to a Liebig condenser. The mixture was heated with a moving free flame to 230° until foaming ceased. The temperature was then rapidly raised to 270—280° and a current of steam (not superheated) passed in until the distillate was highly coloured. After cooling and dilution with water, the *product* was filtered off from the distillates of three such runs and crystallized from light petroleum (200 c.c.; b. p. 80—100°) (charcoal) and then from 40% acetic acid (145 c.c.) (charcoal), giving 15·5 g. (41%) of m. p. 90·5—91°. After recrystallizing from 40% ethanol, colourless plates, m. p. 91—92°, were obtained, giving Ehrlich's reaction in the cold (Found : C, 60·2; H, 6·9; N, 6·0. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·2; N, 5·9%).

Ethyl 3-*Carboxymethyl*-5-*methylpyrrole*-2-*carboxylate* (V; R = $CH_2{\cdot}CO_2H$).—The diester (VIII*d*) was heated under reflux with a slight excess of 0·1N-sodium hydroxide to effect solution (about 15 minutes), filtered (charcoal), and acidified at 0°. The *product* was filtered off and recrystallized from water as large needles or (more stable form) plates, and from ether; it had m. p. 157° (Found : C, 57·2; H, 6·6; N, 6·55. $C_{10}H_{13}O_4N$ requires C, 56·9; H, 6·2; N, 6·6%).

Reconversion of the Half-ester (V; R = $CH_2{\cdot}CO_2H$) *into the Diester* (VIII*d*).—The half-ester with saturated ethanolic hydrogen chloride (18 hours at 15°) gave the diester; crystallized from 40% acetic acid it had m. p. 91—92°, unchanged when mixed with an authentic specimen.

Decarboxylation of the Half-ester (V; R = $CH_2{\cdot}CO_2H$) *to Ethyl* 3 : 5-*Dimethylpyrrole*-2-*carboxylate* (VII*d*).—The half-ester was refluxed for 3 minutes with a little resorcinol and poured into water. The precipitated ethyl 3 : 5-dimethylpyrrole-2-carboxylate, crystallized from ethanol, had m. p. 122—123°, unchanged when mixed with an authentic specimen.

Ethyl 3-*Carbamylmethyl*-5-*methylpyrrole*-2-*carboxylate* (V; R = $CH_2{\cdot}CO{\cdot}NH_2$).—The ester (VIII*d*) was set aside in concentrated aqueous ammonia (15 parts) for 10 days. The *product* was filtered off, washed with hot light petroleum (b. p. 80—100°), crystallized from water (200 parts) (charcoal), then from acetone, forming colourless needles, m. p. 205° (Found : C, 57·2; H, 7·0; N, 13·1. $C_{10}H_{14}O_3N_2$ requires C, 57·1; H, 6·7; N, 13·3%). Ehrlich's reaction was positive in the cold.

Ethyl 3-*Carbethoxymethyl*-3-(2 : 2-*dicarbethoxyethyl*)-5-*methylpyrrole*-2-*carboxylate* (VIII*f*).—The pyrrole (VIII*d*) (1·08 g.) was heated under reflux for 1 hour with methoxymethylmalonic ester (1·5 c.c.), ethanol (3 c.c.), and ethanolic hydrogen chloride (saturated at 0°; 1·5 c.c.). After cooling, the solution was poured into ice-water, and the oil separated and left to crystallize in a vacuum-desiccator over potassium hydroxide. The well-crystallized *product* (1·24 g.) remained after draining on tile; twice crystallized from light petroleum (b. p. 40—60°), it formed colourless needles, m. p. 58°, and did not give Ehrlich's reaction in the cold but did so strongly in the hot (Found : C, 58·0; H, 7·3; N, 3·6. $C_{20}H_{29}O_8N$ requires C, 58·4; H, 7·1; N, 3·4%).

Diethyl 4-2'-*Carbomethoxyethyl*-2-*methylpyrrole*-3 : 5-*dicarboxylate* (IX*a*).—Sodium nitrite (0·35 g.) in a little water was added with stirring during 15 minutes to methyl δ-carbethoxylævulate (1 g.) in acetic acid (3 c.c.) at 4°. After ½ hour, ethyl acetoacetate (0·65 c.c.) was added. Anhydrous sodium acetate (2 g.) and zinc dust (2·5 g.) were then added with stirring during 15 minutes at 20—65°. After ½ hour's stirring at 95°, the solution was decanted from the zinc into water, and the zinc washed with hot 50% acetic acid. The *product* was filtered off, washed with water, and crystallized from ethanol (30 c.c. of 33%), giving 1 g. (64%) as colourless needles, m. p. 103—103·5° unchanged on recrystallization (Found : C, 58·3; H, 7·1; N, 4·7. $C_{15}H_{21}O_6N$ requires C, 57·9; H, 6·8; N, 4·5%). Ehrlich's reaction was weakly positive in the hot.

Benzyl 5-*Carbethoxy*-4-2'-*carbomethoxyethyl*-2-*methylpyrrole*-3-*carboxylate* (IX*b*).—Sodium nitrite (3 g.), in water (4 c.c.) was added at 0° to a stirred mixture of methyl δ-carbethoxylævulate (8·4 g.), acetic acid (30 c.c.), and water (1 c.c.). After 1·5 hours at 0°, ammonium sulphamate (1 g.), benzyl acetoacetate (8·5 g.), and acetic acid (20 c.c.) were added. A mixture of zinc dust (8 g.) and anhydrous sodium acetate (8 g.) was gradually added, together with acetic acid (100 c.c.) to the stirred mixture; the temperature rose to 100° and was kept thereat for ½ hour more. The *product* was isolated by pouring the mixture into water, etc., and had m. p. 168—169° (10·2 g., 66%). Twice crystallized from ethanol (500 c.c.) it formed pale yellow plates, m. p. 172° (Ehrlich's reaction positive in the hot) (Found : C, 64·1; H, 6·2; N, 3·9. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N. 3·8%).

5-*Carbethoxy*-4-2'-*carbomethoxyethyl*-2-*methylpyrrole*-3-*carboxylic Acid* (IX*c*).—The benzyl ester (6·4 g.) was hydrogenated in ethanol (350 c.c.) over Raney nickel (2 c.c.) for 5 hours at 100°/75 atm. The *product* (3 g.) was obtained as usual by precipitation from dilute aqueous sodium hydroxide with carbon dioxide and crystallized from acetone as colourless plates, m. p. 220° (Ehrlich's reaction positive in the hot) (Found : C, 55·1; H, 5·7; N, 5·2. $C_{13}H_{17}O_6N$ requires C, 55·1; H, 6·0; N, 4·9%).

Ethyl 4-2'-*Carbomethoxyethyl*-5-*methylpyrrole*-2-*carboxylate* (IX*d*).—The acid (IX*c*) (100 mg.) was sublimed at 235°/15 mm., and the *product* extracted with pentane, in which high-melting impurities are less soluble. After distilling at 110°/15 mm., it melted at 65—65·5° (Ehrlich's reaction positive in the cold) (Found : C, 60·5; H, 7·4; N, 5·85. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·2; N, 5·9%).

5-*Carbethoxy*-4-2'-*carboxyethyl*-2-*methylpyrrole*-3-*carboxylic Acid* (XI).—The aqueous alkaline mother-liquor from (IX*c*) was acidified with sulphur dioxide; the *product* (2·2 g.) formed small colourless needles, m. p. 253° (decomp.), from acetic acid (Found: C, 53·6; H, 5·5; N, 5·4. $C_{12}H_{15}O_6N$ requires C, 53·5; H, 5·6; N, 5·2%).

Ethyl 3-2′-*Carboxyethyl*-5-*methylpyrrole*-2-*carboxylate* (V; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$).—The crude acid (XI) was sublimed at 235°/20 mm. and the *product* purified by washing it with hot light petroleum (b. p. 80—100°), and crystallized from aqueous ethanol; it was dissolved in alkali, precipitated with acid, and crystallized from ether (thimble), forming colourless needles, m. p. 152° alone or mixed with the product obtained from (X*d*) (see below) (Found: C, 58·8; H, 6·9; N, 6·2. $C_{11}H_{15}O_4N$ requires C, 58·6; H, 6·7; N, 6·2%).

Ethyl β-Ketoadipate.—β-Ketoadipic acid (Eisner, Elvidge, and Linstead, *loc. cit.*) gave the ethyl ester (70%) by the method given for the esterification of acetonedicarboxylic acid (*Org. Synth., loc. cit.*).

Benzyl 5-*Carbethoxy*-4-2′-*carbethoxyethyl*-2-*methylpyrrole*-3-*carboxylate* (X*b*).—Amyl nitrite (30 g.; twice distilled) was added during 1 hour at 20—25° to ethyl β-ketoadipate (55·5 g.) containing concentrated hydrochloric acid (0·7 c.c.); the temperature was then allowed to rise spontaneously to 40°. Next day the mixture was run into a stirred and cooled mixture of benzyl acetoacetate (50 g.), acetic acid (250 c.c.), zinc dust (15 g.), and ammonium acetate (40 g.) at 60—65° during 1 hour; at the same time zinc dust (40 g.) was added in small portions. The bath was then removed and the mixture stirred for 3 hours at 75—100°. The solution was decanted into well-stirred ice-water (3 l.), the zinc washed, and the *product* filtered off, washed, and dried; crystallized from ethanol (350 c.c.), it had m. p. 140—142° (67·7 g., 68%). Recrystallized from light petroleum (b. p. 60—80°; thimble) and then from ethanol, it formed colourless plates, m. p. 142—143° (Ehrlich's reaction weakly positive in the hot) (Found: C, 65·15; H, 5·95; N, 3·7. $C_{21}H_{25}O_6N$ requires C, 65·1; H, 6·5; N, 3·6%).

5-*Carbethoxy*-4-2′-*carbethoxyethyl*-2-*methylpyrrole*-3-*carboxylic Acid* (X*c*).—The benzyl ester (X*b*) (65 g.) in dried ethanol (500 c.c.) was heated under reflux with Raney nickel (2·5 c.c.), more nickel added (2·5 c.c.), and the whole hydrogenated at 100°/100 atm. for 5 hours. The residue on evaporation was extracted with 10% aqueous sodium hydroxide (160 c.c., diluted with ice and water to 4 l.); the solution was filtered and saturated with carbon dioxide at 0°. The *product* was filtered off, washed well with water, and dried *in vacuo* [42 g., 84%; m. p. 230° (decomp.)]. Crystallized from acetone (thimble) and dried ($90°/2 \times 10^{-2}$ mm.) it formed flat colourless needles, m. p. 230° (decomp.) (Ehrlich's reaction positive in the hot) (Found: C, 57·6; H, 6·6; N, 4·5. $C_{14}H_{19}O_6N$ requires C, 56·6; H, 6·4; N, 4·7%).

Ethyl 3-2′-*Carbethoxyethyl*-5-*methylpyrrole*-2-*carboxylate* (X*d*).—The acid (X*c*) (15 g.) was rapidly heated in glycerol (45 g.), with a free flame to 260° until frothing ceased; then a rapid current of steam was introduced at 280° until there was little oil in the condensate. The *product* was separated from the distillate by filtration, crystallized twice from pentane (thimble), and distilled ($110°/5 \times 10^{-4}$ mm.) (m. p. *ca.* 65—67°; yield, 51%). It was separated from granular material and obtained as very large colourless prisms by repeated crystallization from pentane, then having m. p. 66° or mixed with (IX*d*) 61°, Ehrlich's reaction being positive in the cold (Found: C, 61·8; H, 7·35; N, 5·5. $C_{13}H_{19}O_4N$ requires C, 61·6; H, 7·6; N, 5·5%). The apparent difficulty in purification has since been traced to polymorphism; resolidified melts may melt at either 56° or at 69°.

Ethyl 3-2′-*Carboxyethyl*-5-*methylpyrrole*-2-*carboxylate* (V; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$).—The crude ester (X*d*) (1 g.) was stirred for 15 minutes at 100° in 0·5N-sodium hydroxide (10 c.c.), cooled, filtered (charcoal), and acidified (Congo-red) with sulphur dioxide at 0°. The *product* was filtered off and crystallized from water (50 c.c.; charcoal), from ether (thimble) and again from water, forming colourless needles (0·23 g.), m. p. 153° [mixed m. p. with (V; R = $CH_2{\cdot}CO_2H$) 140°; Ehrlich's reaction positive in the cold] (Found: C, 58·85; H, 6·8; N, 6·4. $C_{11}H_{15}O_4N$ requires C, 58·6; H, 6·7; N, 6·2%).

5-*Carbethoxy*-4-2′-*carbethoxyethyl*-2-*methylpyrrole*-3-*aldehyde* (X*e*).—A solution of the ester (X*d*) (0·52 g.) in dry ether (1·5 c.c.) and dry chloroform (1·5 c.c.) containing anhydrous hydrogen cyanide (1 c.c.) was cooled in ice-salt, and dry hydrogen chloride passed in for 6 hours. After being kept at 0° overnight, the solvent was removed *in vacuo*, the residue washed with ether and dissolved in water (10 c.c.), and the solution filtered and adjusted to pH 4. The *product* (0·24 g., 41%) soon separated and was filtered off, washed with water, and dried (m. p. 118—120°). Crystallized from water (charcoal), then twice from ether–pentane (thimble), it formed colourless plates, m. p. 122° (Found: C, 59·6; H, 6·9; N, 5·0. $C_{14}H_{19}O_5N$ requires C, 59·8; H, 6·8; N, 5·0%).

Hæmopyrrolecarboxylic Acid (II*b*).—The crude aldehyde (X*e*) (0·24 g.) was heated at 100°

for 1 hour with N-sodium hydroxide (2 c.c.) and filtered. The filtrate was evaporated *in vacuo* and the dry residue heated with hydrazine hydrate (0·5 c.c.) and a solution of sodium (0·1 g.) in ethanol (1·5 c.c.) for 14 hours at 160°. Water (4 c.c.) was added, the ethanol removed at 100°, and the product (0·10 g.) precipitated from the filtered solution by sulphur dioxide at 0°. It was twice crystallized from ether–light petroleum, then once from water (15 parts), and sublimed (115°/5 × 10^{-4} mm.), forming colourless prisms, m. p. 129—130° (lit., 130—131°) (Found: C, 64·7; H, 7·7; N, 8·6. Calc. for $C_9H_{13}O_2N$: C, 64·6; H, 7·8; N, 8·4%). Ehrlich's reaction was positive in the cold.

This acid with ethereal diazomethane gave the methyl ester which, crystallized from ether–light petroleum and distilled at 100° *in vacuo*, had m. p. 54—55° (lit., 57°). This gave a picrate, chocolate brown needles, m. p. 119° (lit., 121—122°).

The author thanks Professor A. R. Todd, F.R.S., for his interest and the Wellcome Trust for a Fellowship, during tenure of which this work was carried out.

THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 17th,* 1952].