772. *Pyrroles and Related Compounds. Part I. Syntheses of Some Unsymmetrical Pyrrolylmethylpyrroles (Pyrromethanes).*

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Unsymmetrical pyrrolylmethylpyrroles (pyrromethanes) (III) can be prepared from 5-bromomethylpyrroles (as I) and pyrrole-2-carboxylic acids (as II), either by brief heating in chloroform solution or by prolonged reaction between an alkali-metal salt of the acid and the pyridinium derivative of the halide (I). The analogous reaction with bicyclic carboxylic acids (III; R = H) is much less successful owing to formation of adducts with the probable structure (VII). The benzyl esters, from which the acids (II) are available, are conveniently prepared by alkoxide-catalysed transesterification of the ethyl esters.

Recent biochemical studies [1] with isotopes have demonstrated that natural compounds of both the porphyrin and the chlorophyll series arise from porphobilinogen and, while the precise mechanism of this process is still being discussed, there is general agreement that the four pyrrole nuclei are linked by methylene groups before cyclisation and dehydrogenation. In contrast, the classical porphyrin syntheses [2] proceed through pyrromethenes, in which the link is a methine group. A notable exception is the method of Siedel and Winkler,[3] but this is not fully controllable and indeed it leads, somewhat unexpectedly, to type III porphyrins.[4] Hence further examination of controlled stepwise linking of pyrrole nuclei by methylene groups [5] seemed to us desirable.

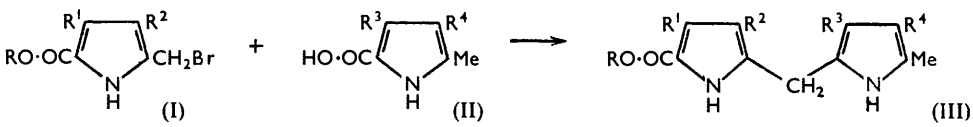
This paper is mainly concerned with the first stage of such syntheses, namely, the linking of two pyrrole nuclei to afford a pyrromethane (systematically named pyrrolylmethylpyrroles). Reaction between an α-halogenomethylpyrrole and the Grignard derivative of another pyrrole is a method of achieving this condensation,[6] but we chose a slightly different plan permitting possible future extension to stepwise syntheses employing blocking groups. An obvious blocking group for a 2-position, which is to be substituted later by a cationoid reagent, is benzyloxycarbonyl since a 2-carboxyl group is very easily displaced by proton and by bromine.[7] 2-Benzyloxycarbonylpyrroles have

[1] CIBA Foundation, " Porphyrin Biosynthesis and Metabolism," Ed. Wolstenholme and Millar, Churchill, London, 1955.
[2] Fischer and Orth, " Chemie des Pyrrols," Akademische Verlag, Leipzig, 1937, Vol. II, Part 1, p. 160.
[3] Siedel and Winkler, *Annalen*, 1943, **554**, 162.
[4] Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.
[5] A related study has been reported by Corwin and Coolidge, *J. Amer. Chem. Soc.*, 1952, **74**, 5196.
[6] Fischer, Baumann, and Riedel, *Annalen*, 1929, **475**, 205.
[7] Fischer and Orth, " Die Chemie des Pyrrols," Akademische Verlag, Leipzig, 1934, Vol. I, pp. 85, 235.

been prepared from benzyl acetoacetate by the Knorr method,[8] but we found it convenient to prepare them from the usual ethyl esters by alkoxide-catalysed transesterification; this reaction does not seem to have been used before, perhaps because the carbonyl group is inert and fairly drastic conditions are necessary, but the yields are good. Hydrogenolysis of the benzyl link is normal and this sequence provides clean preparations of, for instance, 4-ethyl-3 : 5-dimethylpyrrole-2-carboxylic acid and, by decarboxylation with acid, cryptopyrrole.

For coupling with these carboxylic acids, the esters derived from oxy-acids and hydroxymethylpyrroles were expected to be suitable and there seemed to be an easy route through the acetoxymethyl compounds, prepared from the methylpyrroles and lead tetra-acetate.[3] However, we were unable to prepare ethyl 4-ethyl-5-hydroxymethyl-3-methylpyrrole-2-carboxylate by alkaline hydrolysis of its acetyl derivative; only gums were obtained from most of the varied experiments, but some 25% of the crystalline methoxymethyl derivative was isolated after treatment with potassium hydroxide in aqueous methanol. Incidentally, it was shown by acetyl analysis and infrared spectroscopy that the material described by Siedel and Winkler [3] as the hydroxymethylpyrrole is actually its acetyl derivative, as indeed would be expected from its formation by action of lead tetra-acetate on ethyl 4-ethyl-3 : 5-dimethylpyrrole-2-carboxylate. Moreover, the 2-benzyloxymethylpyrrole proved quite inert during attempted hydrogenolysis, and no crystalline product could be isolated from reactions between either silver diphenyl phosphate or silver toluene-*p*-sulphonate with ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate. Accordingly this approach was abandoned in favour of more direct use of α-bromomethylpyrroles and, in fact, two good methods of condensing them with pyrrole-2-carboxylic acids were discovered; several examples of each method are given in the Experimental section. Incidentally, bromination of α-methylpyrroles in cold dilute ethereal solution gave more reliable preparations of these intermediates than the usual method with warm acetic acid.

The simpler and usually preferable method is to boil a solution of the reagents, (I) and (II), in dry chloroform for 10 minutes, whereupon hydrogen bromide and carbon dioxide are evolved and the pyrromethane is obtained in about 75% yield; the reaction is favoured



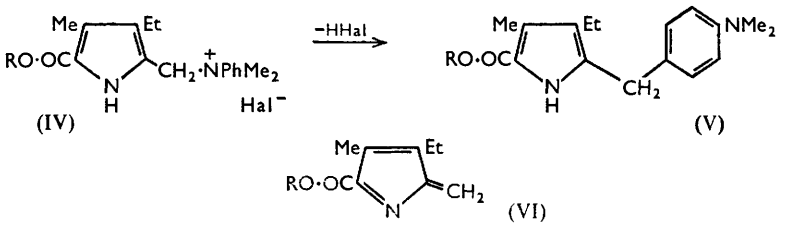
by a low dielectric constant, being faster in benzene and slower in nitromethane. As pyrrole-2-carboxylic acids lose carbon dioxide very easily, particularly under acidic conditions, it seemed possible that decarboxylation preceded condensation. But reaction between 3-ethyl-2 : 4-dimethylpyrrole (cryptopyrrole) and a bromomethylpyrrole (I; R = CH_2Ph, R^1 = Me, R^2 = Et) gave less than 6% of the pyrromethane under conditions which produced 80% from the carboxylic acid. Evidently the carboxylic acid is the true reagent, and indeed it is natural that it should be more reactive in cationoid substitution than the product of its decarboxylation, which is itself a cationoid substitution, and likewise salts of the carboxylic acid should be even more easily substituted. However, while lithium 4-ethyl-3 : 5-dimethylpyrrole-2-carboxylate did react moderately well with a bromomethylpyrrole (I; R = R^2 = Et, R^1 = Me), the reaction was slow and it may actually have gone through gradual liberation of some hydrogen bromide and hence the free acid.

On the other hand carboxylate salts are employed in the second method together with α-pyridiniummethylpyrrole bromides, prepared by quaternisation of α-bromomethylpyrroles. This reaction, in contrast to the other, requires a very polar medium and even

[8] MacDonald, *J.*, 1952, 4176.

aqueous mixtures containing 65% dimethylformamide or 50% acetone or 90% methyl cyanide were unsatisfactory. Good results were obtained with pure formamide but aqueous methanol is the most generally useful solvent; if the reagents are mixed in aqueous solution, there is immediate precipitation of an oil and therefore the best practice is to use the minimum proportion of methanol which prevents this precipitation. In order to reduce side-reactions, a moderate temperature is advisable despite the slowness of the reaction. It was expected that the rate would increase when a weaker base than pyridine was used for quaternisation and decrease when a stronger base was used; in fact the reaction proceeded less satisfactorily with 2-chloropyridine, 2 : 4-dimethylthiazole, triethylamine, or 4-methylmorpholine. When cryptopyrrole was substituted for the corresponding carboxylate salt, the yield fell by more than half. While this effect is less marked than in the first method, it seems that here again carbon dioxide is expelled during cationoid substitution.

An attempted modification of the second, quaternary salt method was unsuccessful because of an interesting rearrangement. Our idea was to employ the 2-methylphenylaminomethyl group as a comparatively inert substituent which could be activated by quaternisation at a suitable stage in a polypyrrole synthesis. This was frustrated by the very ready conversion by bases of the quaternary salts (IV) into the *p*-dimethylaminophenylmethylpyrroles (V). Oxidation with dichromate or permanganate produced the expected reddish-purple (Ehrlich) colour from these rearranged materials. Their structures were shown in infrared spectra, dissociation constants, and, in the instance of the benzyl ester (V; R = CH_2Ph), alternative synthesis from *p*-dimethylaminobenzoic acid and benzyl 4-ethyl-5-methoxy-3-methylmethylpyrrole-2-carboxylate. The analogous reactions took place with derivatives of diethylaniline. Presumably the base removes a proton from the cyclic nitrogen atom and thus decomposes the quaternary salt to the highly reactive intermediate (VI). Bearing this hypothesis in mind, we have sought alkaline catalysis of the reaction between α-bromomethylpyrroles and pyrrole-2-carboxylate salts, but without noteworthy result.

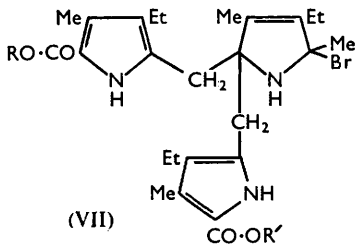


One serious limitation of both synthetical methods is that they apparently fail completely when α-methoxymethyl- or α-acetoxymethyl-pyrroles are used instead of the α-methylpyrroles (II). Coupling with 3-2′-carboxyethyl-4 : 5-dimethylpyrrole-2-carboxylic acid (II; $R^3 = CH_2{\cdot}CH_2{\cdot}CO_2H$, R^4 = Me) and its derivatives was also unexpectedly difficult. Both methods were tried unsuccessfully with the diacid, its salts, and its monomethyl ester. The nitrile (II; $R^3 = CH_2{\cdot}CH_2{\cdot}CN$, R^4 = Me) seemed to be a hopeful alternative, but the intermediate amide, benzyl 3-2′-carbamoylethyl-4 : 5-dimethylpyrrole-2-carboxylate, was obtained in only 25% yield from the diester; the 2-carboxylic acid derived from it also failed to react with benzyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (I; R = CH_2Ph, R^1 = Me, R^2 = Et). During the preparation of this series of pyrroles, the β-methyl group was introduced by Treibs and Zinsmeister's method [9] with the convenient modification that the Mannich base was prepared directly from the β-carboxylic acid.

Another limitation is that side-reactions become important, or overwhelming, when the process is extended to reaction between a pyrromethane acid (III; R = H) and an

[9] Treibs and Zinsmeister, *Chem. Ber.*, 1957, **90**, 87.

α-bromomethylpyrrole (I). Coupling by the first method of the pyrromethane acid (III; R = H, $R^1 = R^3 = Me$, $R^2 = R^4 = Et$) with both the ethyl and the benzyl ester



(VII)

(I; R = Et or CH_2Ph, $R^1 = Me$, $R^2 = Et$) led to crystalline substances with the composition of simple adducts. Brief treatment of these adducts with boiling ethanolamine gave small amounts of the pyrromethane esters (III; R = Et or CH_2Ph, $R^1 = R^3 = Me$, $R^2 = R^4 = Et$). Further an adduct was still obtained when a pyrromethane ester was used instead of the free acid. Provisionally we assign to these adducts the structure (VII), or the ionic equivalent; their reaction with alcoholic silver nitrate is rapid but scarcely decisive.

The second, quaternary salt method was more successful. A minute yield of the " tripyrrane " (pyrrolylmethylpyrrolylmethylpyrrole) was obtained from the lithium salt (III; R = Li, $R^1 = R^3 = Me$, $R^2 = R^4 = Et$) and the pyridinium derivative of the bromomethylpyrrole (I; R = CH_2Ph, $R^1 = Me$, $R^2 = Et$), but another lithium salt (III; R = Li, $R^1 = R^3 = Me$, $R^2 = Et$, $R^4 = CO_2Et$) yielded 23% of the crystalline " tripyrrane." Very likely the reactions with quaternary salts and with bromomethylpyrroles have the same side path and this is made less accessible by an appropriately placed ethoxycarbonyl substituent.

It should be remarked that the self-condensation of porphobilinogen may follow, at any rate partly, similar " side-paths " and that these could lead to type III porphyrins, which are actually formed, instead of the type I porphyrins expected from the " normal " elimination of ammonia. However, the factors controlling the relative importance of the various reactions are uncertain and the schemes which we have drawn do not lead inevitably to the type III porphyrins; accordingly we refrain from adding yet another speculation in this field.

Experimental

Benzyl 4-Ethyl-3 : 5-dimethylpyrrole-2-carboxylate.—A mixture of ethyl 4-ethyl-3 : 5-dimethylpyrrole-2-carboxylate [10] (100 g.), sodium (2 g.), and benzyl alcohol (250 c.c.) was kept at 100° with exclusion of moisture during 1 hr., then ethanol was distilled away at 12 mm. This operation was repeated periodically until, after 4 hr. in all, the solution was evaporated on a water-bath at 1 mm. The residue was taken up in ether (500 c.c.), which was washed with water and then kept overnight in the refrigerator. The *benzyl ester* which crystallised was combined with the second crop and recrystallised from light petroleum (b. p. 80—100°) in colourless needles (115 g., 87%), m. p. 104—105° (Found: C, 75·0; H, 7·2; N, 5·7. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4; N, 5·4%).

Benzyl 3 : 5-Dimethylpyrrole-2-carboxylate.—Sodium (0·5 g.) and ethyl 3 : 5-dimethylpyrrole-2-carboxylate [11] (21 g.) in benzyl alcohol (150 c.c.) were manipulated as in the preceding experiment. Recrystallisation of the *benzyl ester* as above afforded 17 g. (60%) having m. p. 102—104° (Found: C, 73·3; H, 6·7; N, 6·3. $C_{14}H_{15}O_2N$ requires C, 73·3; H, 6·6; N, 6·1%).

2-Benzyl 4-Ethyl 3 : 5-Dimethylpyrrole-2 : 4-dicarboxylate.—The usual Knorr synthesis was carried out with benzyl acetoacetate (40 g.) in glacial acetic acid (60 c.c.) and sodium nitrite (15 g.) in water (20 c.c.), ethyl acetoacetate (27 g.) in glacial acetic acid (110 c.c.), and zinc

[10] Signaigo and Adkins, *J. Amer. Chem. Soc.*, 1936, **58**, 709.
[11] Chu and Chu, *J. Org. Chem.*, 1954, **19**, 266.

dust (40 g.). Two recrystallisations from ethanol of the crude *diester* (44 g.) afforded 23 g. (40%), m. p. 122—123° (Found: C, 68·1; H, 6·5; N, 4·9. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4; N, 4·65%).

Ethyl 4-Diethylaminomethyl-3-(2-ethoxycarbonylethyl)-5-methylpyrrole-2-carboxylate.—5-Ethoxycarbonyl-4-(2-ethoxycarbonylethyl)-2-methylpyrrole-3-carboxylic acid was prepared from its benzyl ester according to MacDonald's directions;[8] in large-scale working it was preferable to dissolve the product of hydrogenolysis in boiling ethanol (3 l. for 200 g.), filter off the catalyst, and allow crystallisation to occur instead of forming the sodium salt. A mixture of the acid (149 g.), diethylamine (102 c.c.), 40% aqueous formaldehyde (59 c.c.), and ethanol (400 c.c.) was boiled under reflux during 5 hr., before being filtered and poured into water (4·5 l.). A little unchanged acid (3·5 g.) was collected when the pH had been brought down to 2 with dilute hydrochloric acid, and the filtrate was then made alkaline with aqueous ammonia. The *Mannich base* (149 g., 90%) having m. p. 57—58°, which crystallised out of the cooled solution, was sufficiently pure for hydrogenolysis, but recrystallisation from aqueous methanol furnished material with m. p. 66—67° (Found: C, 63·0; H, 8·9; N, 7·9%; equiv., 328. $C_{18}H_{30}O_4N_2$ requires C, 63·9; H, 8·9; N, 8·3%; equiv., 338).

Ethyl 3-(2-Ethoxycarbonylethyl)-4 : 5-dimethylpyrrole-2-carboxylate.—The foregoing Mannich base (79·3 g.) and Raney nickel (20 c.c.) in ethanol (500 c.c.) were stirred with hydrogen (100 atm.) at 150° during 10½ hr. The filtered solution was combined with another batch and concentrated under reduced pressure to 300 c.c. The solution was boiled and brought to the point of crystallisation by addition of water. A portion of the *diethyl ester*, m. p. 88—90° (94 g., 80%), recrystallised from aqueous ethanol in chunky crystals, m. p. 91° (Found: C, 63·0; H, 7·9; N, 5·4. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·2%).

Benzyl 3-(2-Benzyloxycarbonylethyl)-4 : 5-dimethylpyrrole-2-carboxylate.—The foregoing diethyl ester (80 g.), sodium (4 g.), and benzyl alcohol (400 c.c.) were heated at 13 mm. on a boiling-water bath during 2½ hr. The residue from evaporation of the benzyl alcohol at 100°/2 mm. was dissolved in benzene (500 c.c.) and washed with water (4 × 75 c.c.). Dilution of the benzene solution, after it had been dried and concentrated to 200 c.c., with light petroleum furnished the *dibenzyl ester* (55 g., 47%), m. p. 130° unchanged by recrystallisation from methanol (in plates) (Found: C, 73·3; H, 6·8; N, 3·7. $C_{24}H_{25}O_4N$ requires C, 73·6; H, 6·4; N, 3·6%).

Acidification with acetic acid of the aqueous wash-liquor precipitated benzyl 3-(2-carboxyethyl)-4 : 5-dimethylpyrrole-2-carboxylate (38 g., 42%), m. p. 165—167° (Found: equiv., 307. Calc. for $C_{17}H_{19}O_4N$: equiv., 301). Presumably its sodium salt was formed while the benzene solution of the dibenzyl ester was washed, and this could have been avoided by previous addition of carbon dioxide.

Benzyl 3-(2-Methoxycarbonylethyl)-4 : 5-dimethylpyrrole-2-carboxylate.—(*a*) Sodium (0·1 g.) was added to a solution of the foregoing dibenzyl ester (5 g.) in methanol (50 c.c.). Solid carbon dioxide was added to the solution after it had been boiled during 20 min. and it was then concentrated to 15 c.c. and diluted with water (5 c.c.). The *methyl benzyl ester* (3·5 g., 87%) crystallised in needles, m. p. 93—95° raised to 95° by recrystallisation from methanol (Found: C, 68·3; H, 6·7; N, 4·5. $C_{18}H_{21}O_4N$ requires C, 68·5; H, 6·7; N, 4·4%).

(*b*) A solution of the foregoing monobenzyl ester (37 g.) in methanol (150 c.c.) was boiled during 1 hr. while being saturated with dry hydrogen chloride. Evaporation to 50 c.c., crystallisation, and recrystallisation from aqueous methanol (charcoal) furnished 26 g. (68%) of mixed ester, m. p. 94—95°.

Benzyl 3-(2-Carbamoylethyl)-4 : 5-dimethylpyrrole-2-carboxylate.—The foregoing methyl benzyl ester (2 g.) and methanol (30 c.c.) saturated with ammonia were kept in a sealed tube at 160° during 48 hr. Evaporation followed by recrystallisation from chloroform and then methanol afforded 0·5 g. (25%) of the *amide*, m. p. 210—212° raised to 214—215° by two further crystallisations from chloroform (Found: C, 67·9; H, 7·0; N, 9·0. $C_{17}H_{20}O_3N_2$ requires C, 68·0; H, 6·7; N, 9·3%). The infrared spectrum (Nujol mull) contained, as expected, major bands at 1672, 1660 cm.$^{-1}$ and a smaller one at 1625 cm.$^{-1}$.

Ethyl 4-(2-Benzyloxycarbonylethyl)-3 : 5-dimethylpyrrole-2-carboxylate.—Sodium (0·1 g.) was added to a solution of ethyl 4-(2-ethoxycarbonylethyl)-3 : 5-dimethylpyrrole-2-carboxylate (5 g.) in benzyl alcohol (50 c.c.). After the solution had been heated on a boiling-water bath at 13 mm. during 4 hr., it was evaporated at 2 mm. The residual *benzyl ethyl ester* was washed in ether with water before being crystallised from methanol; it had m. p. 68—70° (4·6 g., 75%)

and recrystallised from light petroleum (b. p. 80—100°) in needles, m. p. 69—71° (Found: C, 68·9; H, 7·5; N, 4·1. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·0; N, 4·25%).

Ethyl 4-(2-*Methoxycarbonylethyl*)-3 : 5-*dimethylpyrrole*-2-*carboxylate*.—This preparation from the foregoing benzyl ethyl ester followed preparation (*a*) above of benzyl 3-(2-methoxycarbonylethyl)-4 : 5-dimethylpyrrole-2-carboxylate. The *ethyl methyl ester*, m. p. 100—102°, was obtained in 85% yield and, recrystallised from aqueous methanol, had m. p. 102° (Found: C, 61·7; H, 7·5; N, 5·7. $C_{13}H_{19}O_4N$ requires C, 61·6; H, 7·6; N, 5·5%).

Benzyl 4-(2-*Benzyloxycarbonylethyl*)-3 : 5-*dimethylpyrrole*-2-*carboxylate*.—The foregoing ethyl methyl ester (1·2 g.), sodium (0·2 g.), and benzyl alcohol (30 c.c.) were heated on a boiling-water bath at 13 mm. during 7 hr. The *dibenzyl ester*, m. p. 86—88° (1·2 g., 84%), was isolated in the usual way and recrystallised from methanol in needles, m. p. 87—88° (Found: C, 73·8; H, 6·6; N, 3·7. $C_{24}H_{25}O_4N$ requires C, 73·6; H, 6·4; N, 3·6%).

Benzyl 4-(2-*Methoxycarbonylethyl*)-3 : 5-*dimethylpyrrole*-2-*carboxylate*.—This *benzyl methyl ester* was prepared from the foregoing dibenzyl ester in the same way as the isomeric ester; the yield of material with m. p. 97—99° was 87% and, recrystallised from methanol, had m. p. 99—100° (Found: N, 4·4%).

Ethyl 5-*Acetoxymethyl*-4-*ethyl*-3-*methylpyrrole*-2-*carboxylate*.—Treatment of ethyl 4-ethyl-3 : 5-dimethylpyrrole-2-carboxylate with lead tetra-acetate in glacial acetic acid at room temperature according to Siedel and Winkler's method [3] produced the 2-acetoxymethylpyrrole (43%), which was recrystallised from light petroleum (b. p. 80—100°) and sublimed at 110°/0·01 mm., then having m. p. 127—128° (Found: C, 61·6; H, 7·3; N, 5·8; Ac, 17·7. Calc. for $C_{13}H_{19}O_4N$: C, 61·6; H, 7·6; N, 5·5; Ac, 17·0%). A saturated solution of this substance in carbon tetrachloride had peaks of infrared absorption at 1745, 1721, 1701, 1678 $cm.^{-1}$, whereas a solution of the precursory 2-methylpyrrole had peaks at 1715, 1669 $cm.^{-1}$.

Hydrolysis of this 2-acetoxymethylpyrrole with potassium hydroxide in methanol or ethanol gave the 2-methoxymethyl- and 2-ethoxymethyl-pyrrole, which are described below. Hydrolysis with potassium hydroxide in cold 50% aqueous acetone or with sodium hydrogen carbonate in boiling 50% aqueous acetone yielded a brown gum together with small amounts of a colourless crystalline *substance*, m. p. 102—104°, possibly the symmetrical ether (Found: C, 64·8; H, 7·3; N, 6·4. $C_{22}H_{32}O_5N_2$ requires C, 65·3; H, 8·0; N, 6·9%).

Benzyl 5-*Acetoxymethyl*-3-*methylpyrrole*-2-*carboxylate*.—This *compound* was obtained from benzyl 3 : 5-dimethylpyrrole-2-carboxylate in only 8% yield by the procedure described [3] for reaction between ethyl 3 : 5-dimethylpyrrole-2-carboxylate and lead tetra-acetate. Crystallisation from light petroleum (b. p. 80—100°) and sublimation at 100°/10^{-2} mm. furnished colourless crystals, m. p. 121° (Found: C, 66·9; H, 5·8; N, 5·2. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 6·0; N, 4·9%).

Ethyl 4-*Ethyl*-5-*methoxymethyl*-3-*methylpyrrole*-2-*carboxylate*.—The corresponding 2-bromomethylpyrrole, prepared as described below, was dissolved in hot methanol, which was promptly diluted with water till the appearance of turbidity. The methyl ether, which separated from the cooled solution in quantitative yield, was recrystallised from light petroleum (b. p. 80—100°) and sublimed at 60°/0·001 mm.; it had m. p. 75—77° (Found: C, 63·9; H, 8·4; N, 6·4. Calc. for $C_{12}H_{19}O_3N$: C, 64·0; H, 8·5; N, 6·2%). Fischer and Adler [12] give m. p. 73°.

Ethyl 5-*Ethoxymethyl*-4-*ethyl*-3-*methylpyrrole*-2-*carboxylate*.—This ethyl ether was obtained from the 2-acetoxymethylpyrrole and potassium hydroxide in cold ethanol, or better sodium ethoxide in boiling ethanol; it had m. p. 59—60° (Found: C, 65·0; H, 8·7; N, 5·9. Calc. for $C_{13}H_{21}O_3N$: C, 65·2; H, 8·8; N, 5·85%). Fischer and Adler [12] give m. p. 54° and Bullock *et al.*[4] give m. p. 56—58°.

Ethyl 5-*Benzyloxymethyl*-4-*ethyl*-3-*methylpyrrole*-2-*carboxylate*.—Ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (4·0 g.) was dissolved in a solution of sodium (0·35 g.) in benzyl alcohol (25 c.c.). After removal of the sodium bromide, most of the benzyl alcohol was evaporated at 2 mm. Recrystallisation of the crystalline residue (2·45 g., 56%) from light petroleum (b. p. 80—100°) furnished the colourless *benzyl ether*, m. p. 85—86° (Found: C, 71·4; H, 7·2; N, 4·6. $C_{18}H_{23}O_3N$ requires C, 71·7; H, 7·7; N, 4·65%). This was recovered unchanged after attempted hydrogenolysis at room temperature and pressure in ether catalysed by platinic oxide, palladium black, or palladised charcoal, and in ethanol catalysed by Raney nickel.

Benzyl 4-*Ethyl*-5-*methoxymethyl*-3-*methylpyrrole*-2-*carboxylate*.—This *ether* was prepared like the ethyl ester in 90% yield with m. p. 85—86°, raised to 86—87° by recrystallisation from light

[12] Fischer and Adler, *Z. physiol. Chem.*, 1931, **197**, 266.

petroleum (b. p. 80—100°) (Found: C, 71·1; H, 7·3; N, 5·2. $C_{17}H_{21}O_3N$ requires C, 71·0; H, 7·4; N, 4·9%).

Benzyl 5-Benzyloxymethyl-4-ethyl-4-methylpyrrole-2-carboxylate.—This *benzyl ether* was made in 39% yield in the same way as the corresponding ethyl ester, and it had m. p. 99—100° after distillation at 120°/0·01 mm. (Found: C, 75·7; H, 6·9. $C_{23}H_{25}O_3N$ requires C, 76·0; H, 6·9%).

α-Bromomethylpyrroles (I).—A solution of bromine (2·8 c.c., one mol.) in dry ether (500 c.c.) was added rapidly to a vigorously stirred solution of ethyl 4-ethyl-3 : 5-dimethylpyrrole-2-carboxylate (10 g.) in dry ether (500 c.c.). After 1 hr. the colour had faded to pale yellow, and the solution was then concentrated in a vacuum to about 200 c.c. The mass of crystals and liquor was left overnight in a refrigerator before being filtered; the colourless needles (11·7—13·2 g., 83—93%) of ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate, which easily became red in air, had m. p. 128—130° (Fischer and Ernst [13] record m. p. 128—132°). The analogous benzyl ester, m. p. 137—138°, was prepared in yields of 74—92%. Smaller-scale preparations were made of ethyl 5-bromomethyl-4-(2-ethoxycarbonylethyl)-3-methyl- (77%), m. p. 126—128°, ethyl 4-(2-benzyloxycarbonylethyl)-5-bromomethyl-3-methyl- (56%), m. p. 121—123°, benzyl 5-bromomethyl-4-(2-methoxycarbonylethyl)-3-methyl- (80%), m. p. 116—118°, and benzyl 5-bromomethyl-3-(2-methoxycarbonylethyl)-4-methyl-pyrrole-2-carboxylate (84%), m. p. 137—139°, which were intermediates in the preparations of pyrromethanes 6, 7, 8, and 9 respectively.

As the starting material was insufficiently soluble in ether, diethyl 5-bromoethyl-3-methylpyrrole-2 : 4-dicarboxylate was prepared according to ref. 14.

Pyrrole-2-carboxylic Acids (II).—(a) *From benzyl esters.* A solution of the benzyl pyrrole-2-carboxylate (3 g.) in methanol (150 c.c.) was shaken at room temperature and pressure with hydrogen and catalyst [15] (0·3 g.) containing 10% palladium–charcoal which had been washed with 10% nitric acid. Uptake of hydrogen was complete in about 4 hr. and the product was obtained as a cream-coloured powder by evaporation of the filtered solution under reduced pressure (nitrogen) at 40°; it was normally used immediately.

Alternatively, commercial ether containing two drops of triethylamine was substituted for the methanol. Then the course of hydrogenation could not be observed accurately, but it was complete in 2 hr. and the pure product was easily obtained by evaporation at 15°. In this way *4-ethyl-3 : 5-dimethylpyrrole-2-carboxylic acid*, previously described [16] as exceptionally unstable, was obtained with m. p. 102—103° (92%) and, recrystallised from 70% ethanol, had m. p. 104° with decarboxylation (Found: C, 65·0; H, 7·7; N, 8·7. $C_9H_{13}O_2N$ requires C, 64·65; H, 7·8; N, 8·4%). When a lithium salt was required, the ethereal solution was neutralised with N-methanolic lithium methoxide; in some cases the salt crystallised and in others the risk of decarboxylation during evaporation was reduced.

(b) *From ethyl esters.* When the sodium salt was required, the usual hydrolysis with sodium hydroxide (1·3 mols.) in boiling aqueous methanol (finally 50%) during 7 hr. was convenient; at first only two-thirds of the aqueous sodium hydroxide solution were added to the methanolic solution of the ester. An 80% yield was assumed and the solution was neutralised (phenolphthalein) with acetic acid before direct reaction with a pyridinium salt. The exceptionally stable 4-ethyl 2-hydrogen 3 : 5-dimethylpyrrole-2 : 4-dicarboxylate was prepared in this way [m. p. 203° (decomp.) after precipitation with dilute hydrochloric acid] in preference to hydrogenolysis of the benzyl ester, which gave colourless needles with m. p. 205—207° (decomp.).

Pyrrolylmethylpyrroles (*Dipyrromethanes*) (III).—*Method A.* Apart from variations in scale all the tabulated preparations were made as follows. The α-bromomethylpyrrole (I) (0·01 mol.) was added to a solution of the carboxylic acid (II) prepared directly from 1·05 mols. of the benzyl ester in chloroform (100 c.c. distilled from phosphoric oxide). Air was then displaced by nitrogen from the flask and reflux condenser, which was capped with a Bunsen valve. Immediately after the solution had been boiled during 10 min., it was evaporated under reduced pressure (nitrogen bubbler) to a light brown syrup, which was taken up in methanol (30 c.c.), treated with the appropriate small amount of water, and left in a refrigerator. The crystals, which were formed overnight in the tabulated yield, were fawn-coloured, and their m. p. was about 2° below that of the analytical specimen.

[13] Fischer and Ernst, *Annalen*, 1926, **447**, 139.
[14] Fischer and Stangler, *Annalen*, 1927, **459**, 53.
[15] Mozingo, *Org. Synth.*, 1946, **26**, 77.
[16] Fischer and Walach, *Ber.*, 1925, **58**, 2818.

Preparations of pyrromethane 2 in different solvents (boiling for stated time) gave the following yields: chloroform (30 min.) 41%; chloroform *not* dried with phosphoric oxide (10 min.) 56%; benzene (1 min.) 47%; nitromethane (30 min.) 50%, (60 min.) 68%, (90 min.) 38%; nitromethane *not* dried with phosphoric oxide (30 min.), 29% of impure material; methyl cyanide (30 min.), 50% of impure material. A preparation under the standard conditions from 3-ethyl-2 : 4-dimethylpyrrole, instead of the carboxylic acid, gave 5·5%.

Variations in the preparation of pyrromethane 1 gave the following yields: benzene (1 min.) 50%, (30 min.) 38%, (120 min.) 15%; methanol (30 min.) 31%. Under the standard conditions 44% was obtained from ethyl 5-chloromethyl-4-ethyl-3-methylpyrrole-2-carboxylate (from the 2-methylpyrrole and sulphuryl chloride [17] in 7% yield). The α-bromomethylpyrrole and the lithium salt of the carboxylic acid dissolved together in boiling benzene and then lithium bromide began to separate; after 2 hr. the solution contained a 43% yield of pyrromethane 1 and these seemed to be the optimum conditions. Lower yields were obtained from methanolic reaction mixtures.

Method B. Ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (12 g.) dissolved exothermically in dry pyridine (15 c.c.), and this solution was used directly in reactions. Crystallisation of the quaternary salt from the cooled solution was assisted by addition of dioxan; after recrystallisation from dioxan, 1-(*5-ethoxycarbonyl-3-ethyl-4-methyl-2-pyrrolylmethyl*)*pyridinium bromide* had m. p. 151—154° (Found: C, 54·1; H, 6·0; N, 7·7. $C_{16}H_{21}O_2N_2Br$ requires C, 54·4; H, 5·9; N, 7·9%). Slightly more pyridine (20 c.c.) was used to dissolve the corresponding benzyl ester (14·8 g.). The pyridine solution of either quaternary salt was diluted with 200 c.c. of the aqueous-alcoholic solvent (see below) and then mixed with a solution of either the sodium or the lithium salt (one mol.) in the same solvent (100 c.c.). The flask was flushed with nitrogen and capped with a Bunsen valve. The product usually crystallised during the reaction period; it was collected from the cooled mixture and washed with 50% and then 100% methanol. The tabulated preparations were carried out with the following solvents and times of heating: no. 1 in 25% methanol for 24 hr. at 40°; no. 2 in 50% methanol for 21 hr. at 40°; no. 3 in 50% methanol for 24 hr. at 40°; no. 4 in 50% ethanol for 9 hr. under reflux; no. 5 in 50% ethanol for 20 hr. under reflux.

Numerous trial preparations of pyrromethanes 1 and 2 were made on 1/10 scale. In addition to the points mentioned in the Introduction, it was found that reaction at room temperature yielded more than 50% after one week, that the excess of pyridine was valuable, and that reaction in 3 : 1 formamide–methanol gave a very impure product.

TABLE 1. *Pyrrolylmethylpyrroles* (*pyrromethanes*) (III).

No.	R	R¹	R²	R³	R⁴	Method	Yield (%)	M. p.[a]	Formula[d]
1	Et	Me	Et	Me	Et	A	68	141—142°[b]	$C_{19}H_{28}O_2N_2$
						B	75		
2	CH_2Ph	Me	Et	Me	Et	A	80	123—125	$C_{24}H_{30}O_2N_2$
						B	74		
3	Et	Me	Et	Me	H	B	69	129[c]	$C_{17}H_{24}O_2N_2$
4	Et	Me	Et	Me	CO_2Et	B	82	133—134	$C_{20}H_{22}O_4N_2$
5	CH_2Ph	Me	Et	Me	CO_2Et	B	78	164—165	$C_{25}H_{30}O_4N_2$
6	Et	Me	$CH_2{\cdot}CH_2{\cdot}CO_2Et$	Me	Et	A	83	116—118	$C_{22}H_{32}O_4N_2$
7	Et	Me	$CH_2{\cdot}CH_2{\cdot}CO_2{\cdot}CH_2Ph$	Me	Et	A	68	123—125	$C_{27}H_{34}O_4N_2$
8	CH_2Ph	Me	$CH_2{\cdot}CH_2{\cdot}CO_2Me$	Me	Et	A	40	125	$C_{26}H_{32}O_4N_2$
9	CH_2Ph	$CH_2{\cdot}CH_2{\cdot}CO_2Me$	Me	Me	Et	A	79	133—135	$C_{26}H_{32}O_4N_2$

[a] Recryst. from light petroleum (b. p. 80—100°) or ethanol. [b] Undepressed by a sample prepared according to ref. 6. [c] Fischer *et al.*[6] give m. p. 129°. [d] Analysis of the products for carbon, hydrogen, and nitrogen gave the following results (%) (figures required by the formulæ being in parentheses): no. 2, 76·3 (76·2), 7·8 (8·0), 7·4 (7·4); no. 4, 66·4 (66·6), 7·6 (7·8), 8·0 (7·8); no. 5, 71·3 (71·1), 7·1 (7·2), 6·7 (6·6); no. 6, 67·8 (68·0), 8·4 (8·3), 7·2 (7·2); no. 7, 72·1 (72·0), 7·9 (7·6), 6·3 (6·2); no. 8, 71·5 (71·5), 7·4 (7·4), —; no. 9, 71·3 (71·5), 7·4 (7·4), 6·4 (6·4).

Alkyl 5-Alkylanilinomethyl-4-ethyl-3-methylpyrrole-2-carboxylates.—A solution of either *N*-methylaniline or *N*-ethylaniline (2·0 mmol.) in dry ether (10 c.c.) was mixed with one of either ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate or the analogous benzyl ester (2·0 mmol.) in dry ether (30 c.c.). The hydrobromide of the product was rapidly

[17] Fischer, Sturm, and Friedrich, *Annalen*, 1928, **461**, 244.

precipitated and the solution was concentrated to 15 c.c. and washed with 1% ammonia solution. The brown gum obtained from the ether, after it had been washed with water and dried (K_2CO_3), was crystallised from ethanol. The *alkylanilinomethylpyrroles* (Table 2), obtained in good yield, were insoluble in cold ethanol but dissolved on the addition of dilute mineral acid.

TABLE 2. *Alkyl 5-Alkylanilinomethyl-4-ethyl-3-methylpyrrole-2-carboxylates.*

					Found (%)			Reqd. (%)		
Cpd.	*N*-Alkyl	Ester	M. p.	Formula	C	H	N	C	H	N
A	Me	Et	89—90°	$C_{18}H_{24}O_2N_2$	72·1	8·0	9·1	72·0	8·0	9·3
B	Me	CH_2Ph	91—92	$C_{23}H_{26}O_2N_2$	76·5	7·5	7·6	76·2	7·2	7·7
C	Et	Et	91—92	$C_{19}H_{26}O_2N_2$	72·9	8·5	8·6	72·6	8·3	8·9
D	Et	CH_2Ph	69—70	$C_{24}H_{28}O_2N_2$	76·8	7·8	7·2	76·6	7·5	7·4

Alkyl 5-Dialkylaminophenylmethyl-4-ethyl-3-methylpyrrole-2-carboxylates.—(*a*) A mixture of ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate or the benzyl ester (2 mmol.) and *NN*-dimethyl- or *NN*-diethyl-aniline (3 c.c.) was warmed on a water-bath for 2 min., then poured into 3N-hydrochloric acid (50 c.c.). The oily salt precipitated was taken up in 70% ethanol (10 c.c.) and decomposed with 10% ammonia solution (5 c.c.). The precipitated *dialkylaminophenylmethylpyrrole* (Table 3) was recrystallised from ethanol.

(*b*) The *NN*-dialkyl-*N*-(2-pyrrolylmethyl)anilinium salts were prepared from methyl or ethyl iodide and the compounds described in Table 2, or from the dialkylaniline and α-bromomethylpyrrole in cold ether. They formed colourless crystals, soluble in aqueous ethanol, and easily decomposed to gums. On being kept in 50% methanol with lithium 4-ethyl-3 : 5-dimethylpyrrole-2-carboxylate, they were converted into substances identified by mixed m. p. with those prepared by method (*a*).

(*c*) Concentrated hydrochloric acid (2 drops) was added to a solution of benzyl 4-ethyl-5-methoxymethyl-3-methylpyrrole-2-carboxylate (0·1 g.) and *p*-dimethylaminobenzoic acid (0·2 g.) in methanol (5 c.c.). After the solution had been boiled during 5 min., it was poured into dilute hydrochloric acid. Addition of ammonia solution to a solution of the precipitated solid in aqueous ethanol precipitated compound B′ (0·1 g.), m. p. 133—135° undepressed by material prepared by method (*a*). A similar yield was obtained from dimethylaniline (0·3 c.c.).

Physical Properties of Compounds Described in Tables 2 and 3.—Dissociation constants were determined by titration in 80% ethanol at 25°. Compound A′, pK_a' 4·2, like *NN*-dimethyl-*p*-toluidine pK_a' (4·2); compound C′, pK_a' 5·6; compound D′ pK_a' 5·3. The " unrearranged bases " were notably weaker and the following values are less accurate; compound A, pK_a' 1·8; compound C, pK_a' 3·8; compound D, pK_a' 3·6.

TABLE 3. *Ethyl or benzyl 5-dialkylaminophenylmethyl-4-ethyl-3-methylpyrrole-2-carboxylates.*

					Found (%)			Reqd. (%)		
Cpd.	*N*-Dialkyl	Ester	M. p.	Formula	C	H	N	C	H	N
A′	Me	Et	114—115°	$C_{19}H_{26}O_2N_2$	72·8	8·3	8·6	72·6	8·3	8·9
B′	Me	CH_2Ph	133—134	$C_{24}H_{28}O_2N_2$	76·4	7·3	7·7	76·6	7·5	7·4
C′	Et	Et	86—87	$C_{21}H_{30}O_2N_2$	73·8	8·5	7·9	73·6	8·8	8·2
D′	Et	CH_2Ph	87—88	$C_{26}H_{32}O_2N_2$	77·1	8·0	6·7	77·2	8·0	6·9

The infrared absorption of solutions in CCl_4 of all eight compounds was examined with Perkin-Elmer 21 machines (NaCl prism). The spectra in the " rearranged " series (Table 3) had a sharp peak (N–H) between 3430 and 3420 cm.$^{-1}$, a broad one (bonded N–H) at 3295—3285 cm.$^{-1}$, and a double peak at 1707—1705 and 1687—1680 cm.$^{-1}$. Spectra taken at various dilutions of compound A′ showed the diminution of the bonded N–H band expected for intermolecular hydrogen-bonding, but there was little change in the relative intensities of the twin peaks. The bonded N–H band was almost absent from the spectra in the " unarranged " series (Table 2), which were otherwise similar with peaks at 3430—3428, 1708—1707, 1690—1685 cm.$^{-1}$.

The absorption of the four ethyl esters was also examined for CS_2 solutions. In agreement with the assigned structures, the spectra of A and C have peaks at 746—742 and 687—683 cm.$^{-1}$

(monosubstituted benzene), while those of A′ and C′ have peaks at 809—802 cm.$^{-1}$ (*para*-disubstituted benzene). A peak at 767—766 cm.$^{-1}$ is common to all four spectra, and it is probably connected with the heterocyclic ring. Maxima: with A at 3420, 3285, 3020, 2955, 1706, 1684, 1316, 1240, 1182, 1110, 1068, 1060, 1030, 995, 962, 927, 766, 687 cm.$^{-1}$; with A′ at 3425, 3290, 2960, 1702, 1680, 1347, 1318, 1242, 1190, 1160, 1150, 1108, 1068, 1062, 1024, 975, 947, 809, 766 cm.$^{-1}$; with C at 3428, 2960, 1705, 1685, 1318, 1233, 1182, 1106, 1068, 1060, 1035, 962, 762, 742, 683 cm.$^{-1}$; with C′ at 3425, 3290, 2960, 1700, 1678, 1315, 1260, 1238, 1190, 1146, 1103, 1092, 1068, 1060, 1018, 972, 802, 763 cm.$^{-1}$.

Adducts (VII) *from α-Bromomethylpyrroles and Pyrromethanes.*—(*a*) A solution of pyrromethane 2 (1·9 g.) in methanol (180 c.c.) was shaken with 10% palladised charcoal (0·3 g.) and hydrogen until absorption of gas ceased (3 hr.). The acid left after filtration and evaporation was dissolved in dry chloroform (170 c.c.), mixed with ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (1·23 g.), and boiled in an atmosphere of nitrogen during 10 min. The dark tar left after evaporation of the chloroform yielded 0·70 g. of crystals, m. p. 140—142, when its solution in ethyl acetate was chilled. Two recrystallisations from ethyl acetate–light petroleum furnished pink clusters of the *adduct* (VII; R = H, R′ = Et), m. p. 172—174° (Found: C, 60·0; H, 7·0; N, 7·1. $C_{28}H_{40}O_4N_3Br$ requires C, 59·8; H, 7·2; N, 7·5%). A solution of this adduct (0·3 g.) in 2-aminoethanol (2 c.c.) was boiled during 2 min. (slight effervescence), and was then poured into water (75 c.c.). Recrystallisation of the precipitate from aqueous methanol yielded pyrromethane 1 (0·05 g.), m. p. and mixed m. p. 140—142°.

(*b*) In the same manner benzyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (0·75 g.) and pyrromethane 2 (0·70 g.) yielded the *adduct* (VII; R = H, R′ = CH_2Ph) (0·8 g.) as fawn rosettes, m. p. 137—139° raised to 143—145° by recrystallisation from chloroform–light petroleum (Found: C, 63·6; H, 6·9; N, 6·65. $C_{33}H_{42}O_4N_3Br$ requires C, 63·5; H, 6·8; N, 6·7%). Treatment of this adduct with 2-aminoethanol as described in (*a*) produced pyrromethane 2, m. p. and mixed m. p. 123—125°.

(*c*) A solution of pyrromethane 2 (1·9 g.) and ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (1·03 g.) in dry chloroform (100 c.c.) was boiled during 10 min. in nitrogen. Evaporation and crystallisation from ethyl acetate furnished the *adduct* (VII; R = Et, R′ = CH_2Ph) (0·2 g.), m. p. 161—162° raised to 163—165° by recrystallisation from ethyl acetate–light petroleum (b. p. 80—100°) in brown plates (Found: C, 63·5; H, 7·1; N, 6·25. $C_{35}H_{46}O_4N_3Br$ requires C, 64·4; H, 7·1; N, 6·4%).

Benzyl 4-Ethyl-5-[5′-(4″-ethyl-3″ : 5″-dimethyl-2″-pyrrolylmethyl)-4′-ethyl-3′-methyl-2′-pyrrolylmethyl]-3-methylpyrrole-2-carboxylate.—Hydrogenolysis of pyrromethane 2 in ether by the method described above for the pyrrole series, followed by cautious recrystallisation from ethanol, yielded 83% of the carboxylic acid, m. p. 141—142° (decomp.) (lit.,[6] m. p. 145°). The lithium salt was obtained in the usual way in almost quantitative yield and was coupled with 1-(5-benzyloxycarbonyl-3-ethyl-4-methyl-2-pyrrolylmethyl)pyridinium bromide at 40° in 50% methanol. Within a few hours a dark brown oil has separated, and this also occurred under all the other conditions tried. When this oil was kept at 0° with a little ethanol the pale brown *product* separated in 1—5% yield; it had m. p. 120—122° after recrystallisation from ethanol (Found: C, 76·4; H, 8·0; N, 7·7. $C_{32}H_{41}O_2N_3$ requires C, 76·9; H, 8·3; N, 8·4%).

Ethyl 4-Ethyl-5-[5′-(4″-ethoxycarbonyl-3 : 5-dimethyl-2″-pyrrolylmethyl)-4′-ethyl-3′-methyl-2′-pyrrolylmethyl]-3-methylpyrrole-2-carboxylate.—Hydrogenolysis of pyrromethane 5 in ether was troublesome on account of its small solubility. While boiling during 1 hr., 150 c.c. of ether dissolved 1·35 g. of pyrromethane 5, and the rapidly cooled solution was used immediately. The acid, m. p. 155—157° (decomp.), was obtained in quantitative yield. Its lithium salt, prepared directly from the ethereal solution, was coupled in 50% methanol at 40° with 1-(5-ethoxycarbonyl-3-ethyl-4-methyl-2-pyrrolylmethyl)pyridinium bromide. This mixture yielded a yellow gum together with the pale brown *product* (23%), m. p. 151—153° (from ethanol) (Found: C, 69·8; H, 8·1; N, 8·9. $C_{26}H_{39}O_4N_3$ requires C, 69·8; H, 8·2; N, 8·7%).

We thank Sir Alexander Todd, F.R.S., for his encouragement, the Department of Scientific and Industrial Research for a Maintenance Grant (to N. R. W.), and Imperial Chemical Industries Limited, Pharmaceuticals Division, for a grant (to A. H.).

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[*Received, May 16th,* 1958.]