56. 2,2′-*Bipyrroles.*

By R. Grigg, A. W. Johnson, and J. W. F. Wasley.

2-Iodopyrroles containing at least one ester substituent have been subjected to the Ullmann reaction, 2,2′-bipyrrole esters being obtained in good yield. Hydrolysis and decarboxylation of the esters has given a variety of alkyl-2,2′-bipyrroles. Some unsuccessful ring-synthetic methods designed to produce 2,2′-bipyrroles are also described.

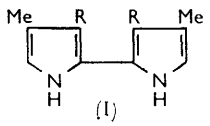
For an investigation [1] into the synthesis of modified porphyrin ring systems we required as intermediates 2,2′-bipyrroles which were unsubstituted in the 5- and 5′-positions. At the outset of our work there appeared to be no general method for the preparation of such 2,2′-bipyrroles. The available syntheses had been reviewed by Webb and Threlkeld,[2] who had selected the Ullmann method from 2-bromo- or 2-iodo-pyrroles for their preparations but had concluded that two carboxylic ester groupings were necessary on each pyrrole for the successful coupling of the rings. Rapoport and his co-workers [3] recently prepared some 2,2′-bipyrroles by dehydrogenation of 2-2′-pyrrolylpyrrolidine [4] or, preferably, 2-2′-pyrrolyl-1-pyrroline, itself obtained by condensation of pyrrole and 2-pyrrolidone in the presence of phosphorus oxychloride. These methods are of special value for the preparation of unsymmetrical 2,2′-bipyrroles.

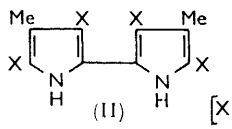
We have subjected the Ullmann coupling of pyrroles to further study and have developed methods by which a wide variety of 2,2′-bipyrroles can be obtained. The requisite 2-iodopyrroles, each of which contained at least one ester grouping, were prepared by decarboxylation of the corresponding 2-carboxylic acids in the presence of iodine.[5] Several of the acids have been obtained from the corresponding 2-methyl compounds by halogenation with bromine (1 mol.), then treatment with sulphuryl chloride (3 mol.) and hydrolysis. The experimental conditions for the Ullmann condensations have been modified by use of *NN*-dimethylformamide as solvent,[6] the reaction temperature necessary being then appreciably lower than when no solvent was used. In most cases the condensations could be effected even at room temperature. Several examples of the preparation of di- and tetra-carboxylic esters of 2,2′-bipyrrole by this method have been provided, the principal side-reaction being the replacement of nuclear iodine by hydrogen. These by-products were also prepared for reference by direct hydrogenolysis of the iodopyrroles. The 2,2′-bipyrrole esters were readily hydrolysed to the corresponding acids and these could be decarboxylated to the parent 2,2′-bipyrroles; by this method the compounds (I; R = Me or Et) have been obtained. We have also obtained the analogous compound (I; R = CO_2Et) from the corresponding tetracarboxylic ester [2] (II) by preferential hydrolysis of the α-ester groups followed by decarboxylation, whereas 4,4′-dimethyl-2,2′-bipyrrole (I; R = H) was obtained by complete hydrolysis and decarboxylation of

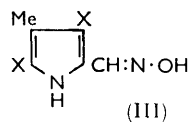
[1] Johnson and Price, *J.*, 1960, 1649; Johnson and Kay, *Proc. Chem. Soc.*, 1961, 168; Johnson, Kay, and Rodrigo, *J.*, in the press.
[2] Webb and Threlkeld, *J. Org. Chem.*, 1953, **18**, 1406, 1413.
[3] Rapoport and Holden, *J. Amer. Chem. Soc.*, 1960, **82**, 5510; 1962, **84**, 635; Rapoport and Castagnoli, *ibid.*, p. 2178.
[4] Fulhage and Vander Werf, *J. Amer. Chem. Soc.*, 1958, **80**, 6249.
[5] Kleinspehn and Corwin, *J. Amer. Chem. Soc.*, 1953, **75**, 5295.
[6] Kornblum and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5782.

this ester (II). 4,4′-Diethyl-2,2′-bipyrrole has been prepared by a similar method. The alkyl-2,2′-bipyrroles are colourless solids which should be kept out of contact of air. In solution they are very unstable (development of colour), particularly in the presence of acid. In contact with skin, the 2,2′-bipyrroles give a characteristic green colour which changes to blue in a few hours. The ultraviolet absorption of the substituted 2,2′-bipyrroles is markedly dependent on the number, nature, and positions of the substituents. Thus the 4,4′-dialkyl derivatives absorb at *ca.* 286 mμ whereas the 3,3′,4,4′-tetra-alkyl derivatives absorb at *ca.* 260 mμ, possibly because of the steric effects of the 3,3′-dialkyl groups. The bathochromic effect of ester groups in the 5,5′-positions was also very marked in comparisons with spectra of 4,4′-esters. The tetracarboxylic esters show three pronounced maxima, whereas the dicarboxylic esters and the alkyl derivatives mostly show only one main maximum.

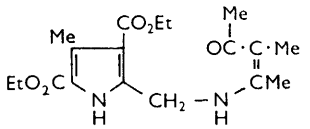
Several other possible routes to 2,2′-bipyrroles have been investigated. Thus, although the action of lead tetra-acetate [7] on ethyl 3,4-dimethylpyrrole-2-carboxylate gave only unchanged starting material, oxidation of crytopyrrole with potassium ferricyanide gave only unidentified oils. An attempt to carry out a modified Knorr reaction [8,9] with the oximes of 5-acetyl-3-ethoxycarbonyl-2,4-dimethylpyrrole and 3-methylpentane-2,4-dione failed to yield any bipyrrole, and the sole product recognised was the parent ketone formed by hydrolysis of the oxime. A similar reaction with the oxime (III) of 3,5-diethoxy-

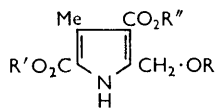

(I)

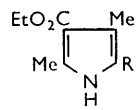

(II) [X = CO_2Et]


(III)

carbonyl-2-formyl-4-methylpyrrole gave a compound, $C_{18}H_{26}N_2O_5$, which was identified as (IV) by means of its infrared and nuclear magnetic resonance spectra and was clearly formed by reduction, Schiff's base formation, and prototropic shift; the infrared spectrum showed bands at 3460 and 3445 (2 NH bands) and 1700 cm.$^{-1}$ (αβ-unsaturated ketone); the principal bands in the nuclear magnetic resonance spectrum and their assignments were as follows: τ 8·63 (2 resolved triplets assigned to the methyl groups of the two ethoxycarbonyl groups); τ 8·1, 7·98, and 7·8 (3 singlets assigned to the three methyl groups in the 2-side chain); τ 7·3 (singlet assigned to the 4-methyl group); τ 5·6 (2 resolved quartets assigned to the methylenic protons of the two ethoxycarbonyl groups); τ 5·12 (resolved doublet, J = 4·25 c./sec., assigned to the protons of the methylene group adjacent to the pyrrole ring); τ −0·41 (broad singlet assigned to the pyrrolic NH proton); and τ −1·88 (a resolved triplet, J = 4·25 c./sec., assigned to the NH proton adjacent to the methylene group).


(IV)


(V)


(VI)

Similar reactions with each of the two isomeric monobenzyl monoethyl esters corresponding to (III) failed to yield condensation products with the diketone; instead, products of type (V) were obtained, the nature of the ether depending on the particular alcohol ROH used for the crystallisation. The structures (V) were in accord with the observed nuclear magnetic resonance spectra. It appears that the primary product was the 2-aminomethyl or 2-hydroxymethyl (V; R = H) derivative. A crystalline product,

[7] Cf. Siedel and Möller, *Z. physiol. Chem.*, 1939, **259**, 113.
[8] Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.
[9] Johnson, Markham, Price, and Shaw, *J.*, 1958, 4254.

m. p. 117—119°, isolated from the condensation of the dibenzyl ester corresponding to (III) with 3-methylpentane-2,4-dione has not yet been identified fully.

Other condensations also designed to produce 2,2'-bipyrroles included reaction of ethyl α-amino-β-oxobutyrate with ethyl β-(4-ethoxycarbonyl-3,5-dimethylpyrrol-2-yl)-β-oxopropionate (VI; R = $CO{\cdot}CH_2{\cdot}CO_2Et$),[10] and of ethyl 5-glycolloyl-2,4-dimethylpyrrole-3-carboxylate [11] with ethyl β-aminocrotonate, but in each case the starting materials were recovered unchanged.

Experimental

Ultraviolet absorption spectra were determined for ethanol solutions except where otherwise stated. Molecular weights were determined by the Rast method.

(*A*) *Pyrrole-2-carboxylic Acids.*—*5-Benzyloxycarbonyl-3-ethoxycarbonyl-4-methylpyrrole-2-carboxylic acid and 2-benzyl 4-ethyl 5-formyl-3-methylpyrrole-2,4-dicarboxylate.* 2-Benzyl 4-ethyl 3,5-dimethylpyrrole-2,4-dicarboxylate [9] (100 g.) was suspended in glacial acetic acid (650 c.c.), stirred, and cooled to 15°. Bromine (17·7 c.c., 1 mol.) was added in one lot, and then sulphuryl chloride (80·5 c.c., 3 mol.) was added dropwise in 2½ hr., the temperature being kept as low as possible (0—12°). The red solution was kept at 0—5° for 6 hr., then water (200 c.c.) was added, dropwise with stirring until the vigorous reaction had subsided and then the remainder rapidly. The solution was heated at 60—65° for 25 min. and then poured into ice–water (2 l.). The precipitate was separated, washed with water until neutral, and dissolved (still moist) in the minimum volume of hot ethanol, and solid sodium hydrogen carbonate was added until the effervescence ceased. The solution was poured into cold water (3·5 l.) with stirring and kept for 1—2 hr., and the by-product (see below) was separated. The filtrate was heated to 60° and acidified with dilute hydrochloric acid. The precipitated *acid* was separated, washed with water, and dried at 80° (66 g., 60%; m. p. 153—155°). Crystallisation from ethanol gave colourless needles, m. p. 156—157° (Found: C, 61·5; H, 4·9; N, 4·55. $C_{17}H_{17}NO_6$ requires C, 61·6; H, 5·15; N, 4·25%). The by-product (above; 40·5 g.) formed colourless needles (from ethanol), m. p. 112—114°, and was identified as the corresponding *aldehyde* (Found: C, 64·4; H, 5·2; N, 4·3. $C_{17}H_{17}NO_5$ requires C, 64·75; H, 5·45; N, 4·45%), whose *oxime* formed colourless needles (from aqueous ethanol), m. p. 141—143° (Found: C, 62·2; H, 5·05. $C_{17}H_{18}N_2O_5$ requires C, 61·8; H, 5·5%).

3-Benzyloxycarbonyl-5-ethoxycarbonyl-4-methylpyrrole-2-carboxylic acid and 4-benzyl 2-ethyl 5-formyl-3-methylpyrrole-2,4-dicarboxylate. Prepared from 4-benzyl 2-ethyl 3,5-dimethylpyrrole-2,4-dicarboxylate [12] in a manner similar to that described in the previous experiment, the *acid* (27%) formed colourless needles, m. p. 167°, from aqueous ethanol (Found: C, 61·2; H, 5·3; N, 4·2%). The *aldehyde* (23%) crystallised from ethanol as colourless prisms, m. p. 145—147° (Found: C, 64·7; H, 5·2; N, 4·2%), and the corresponding *oxime* (90%) from aqueous ethanol as needles, m. p. 163—165° (Found: C, 61·4; H, 5·75%).

3,5-Dibenzyloxycarbonyl-4-methylpyrrole-2-carboxylic acid and 2,4-dibenzyl-5-formyl-3-methylpyrrole-2,4-dicarboxylate. Prepared similarly from dibenzyl 3,5-dimethylpyrrole-2,4-dicarboxylate [13] by a similar method except that the temperature of the reaction was maintained at 15—20° throughout, this *acid* (25%) formed colourless needles, m. p. 135—136°, from ethanol (Found: C, 67·1; H, 5·15; N, 3·7. $C_{22}H_{19}NO_6$ requires C, 67·15; H, 4·85; N, 3·55%). The *aldehyde* (51%) crystallised from ethanol as colourless needles, m. p. 115° (Found: C, 69·9; H, 5·15; N, 3·75. $C_{22}H_{19}NO_5$ requires C, 70·0; H, 5·05; N, 3·7%), and the corresponding *oxime* (85%) formed colourless needles (from aqueous ethanol), m. p. 128—130° (Found: C, 67·5; H, 5·2; N, 6·9. $C_{22}H_{20}N_2O_5$ requires C, 67·35; H, 5·15; N, 7·15%).

3,5-Diethoxycarbonyl-4-ethylpyrrole-2-carboxylic acid and diethyl 3-ethyl-5-formylpyrrole-2,4-dicarboxylate. Diethyl 3-ethyl-5-methylpyrrole-2,4-dicarboxylate [14] (38·3 g.) in glacial acetic acid (180 c.c.) was treated as above with bromine (7·45 c.c.) and then sulphuryl chloride (38 c.c.). The acidic *product* (31·5 g., 73·5%) formed colourless flat needles (from ethanol), m. p. 141—143° (Found: N, 4·95. $C_{13}H_{17}NO_6$ requires N, 5·0%). As a by-product, the corresponding *formyl*

[10] Fischer and Schneller, *Z. physiol. Chem.*, 1923, **128**, 240.
[11] Nenitzescu, Necsoiu, and Zalman, *Comm. acad. rep. populare, Romîne*, 1957, **7**, 421 *Chem. Abs.*, 1958, **52**, 16,330.
[12] MacDonald, *J.*, 1952, 4176.
[13] Treibs and Ott, *Annalen*, 1958, **615**, 137.
[14] Fischer and Stangler, *Annalen*, 1927, **459**, 53.

compound (5·6 g.) was obtained. It formed colourless needles, m. p. 102—104°, from ethanol (Found: C, 58·5; H, 6·0; N, 5·25. $C_{13}H_{17}NO_5$ requires C, 58·4; H, 6·4; N, 5·25%).

5-Ethoxycarbonyl-3,2′-ethoxycarbonylethyl-4-methylpyrrole-2-carboxylic acid (with R. Rodrigo). Ethyl 4-2′-ethoxycarbonylethyl-3,5-dimethylpyrrole-2-carboxylate [8] (50 g.) was dissolved in dry ether (500 c.c.), and bromine (9·6 c.c., 1 mol.) was added in 10 min. The mixture was kept for 1 hr., during which the bromo-derivative separated, and then, with stirring, sulphuryl chloride (40 c.c., 2·65 mol.) was added during 2 hr. The resulting red solution was kept at room temperature for 15 hr., then evaporated under reduced pressure, and the residual red oil was hydrolysed on a steam-bath for 5—10 min. with 30% aqueous sodium acetate (500 c.c.). The crude acid solidified on cooling and, after purification through the sodium salt, the *acid* (37·5 g., 67%), m. p. 146—150°, was crystallised from ethanol, forming colourless needles, m. p. 146° (Found: C, 56·7; H, 6·2; N, 4·65. $C_{14}H_{19}NO_6$ requires C, 56·55; H, 6·45; N, 4·7%).

(*B*) *2-Iodopyrroles.—2-Benzyl 4-ethyl 5-iodo-3-methylpyrrole-2,4-dicarboxylate.* 5-Benzyloxycarbonyl-3-ethoxycarbonyl-4-methylpyrrole-2-carboxylic acid (59 g.) was dissolved in ethanol (254 c.c.) and water (365 c.c.) containing sodium hydrogen carbonate (43·6 g.). The solution was warmed to 60—65°, and a solution of iodine (47·1 g.) and potassium iodide (69 g.) in water (545 c.c.) was added dropwise as fast as it was decolorised. After being stirred for a further 10 min., the hot solution was filtered. The *product* (75·2 g., 91·3%), m. p. 132—134°, was washed with water (4 × 250 c.c.) and dried at 80°. It formed colourless needles, m. p. 134—135·5°, from ethanol (Found: C, 46·8; H, 3·8; N, 3·25; I, 30·2. $C_{16}H_{16}INO_4$ requires C, 46·5; H, 3·95; N, 3·4; I, 30·7%).

4-Benzyl 2-ethyl 5-iodo-3-methylpyrrole-2,4-dicarboxylate. Prepared as above but from the isomeric benzyl ethyl ester, this *iodo-derivative* (65%) formed colourless needles, m. p. 194—195°, from aqueous ethanol (Found: C, 46·8; H, 4·1; N, 3·1; I, 31·0%).

Dibenzyl 5-iodo-3-methylpyrrole-2,4-dicarboxylate. Prepared similarly from the dibenzyl ester, this *iodo-derivative* (65%) formed colourless needles, m. p. 148—149°, from ethanol (Found: C, 53·3; H, 4·0; N, 3·2; I, 26·8. $C_{21}H_{18}INO_4$ requires C, 53·05; H, 3·8; N, 2·95; I, 26·7%).

Diethyl 3-ethyl-5-iodopyrrole-2,4-dicarboxylate. 3,5-Diethoxycarbonyl-4-ethylpyrrole-2-carboxylic acid (29·8g.) and sodium hydrogen carbonate (25·5 g.) in ethanol (92 c.c.) and water (154 c.c.) were stirred at 70—75°. A solution of iodine (27·4 g.) and potassium iodide (42 g.) in water (320 c.c.) was added as fast as it was decolorised (50 min.). The precipitate (35·5 g., 92%) was separated, washed with water (4 × 150 c.c.), and dried at 80°, then having m. p. 166·5—170°. On crystallisation from ethanol it formed colourless needles, m. p. 165—167° (Found: C, 39·5; H, 4·3; N, 4·1; I, 35·0. $C_{12}H_{16}INO_4$ requires C, 39·45; H, 4·4; N, 3·85; I, 34·75%).

Ethyl 3,4-dimethyl-5-iodopyrrole-2-carboxylate. Prepared from 5-ethoxycarbonyl-3,4-dimethylpyrrole-2-carboxylic acid [15] as above in a yield of 90·6%, this *product* was obtained as colourless needles, m. p. 134—136°, from ethanol (Found: C, 36·7; H, 4·4; N, 4·5; I, 43·5. $C_9H_{12}INO_2$ requires C, 36·9; H, 4·15; N, 4·8; I, 43·35%).

Similarly from 5-ethoxycarbonyl-3-ethyl-4-methylpyrrole-2-carboxylic acid,[16] there was obtained *ethyl 4-ethyl-5-iodo-3-methylpyrrole-2-carboxylate* (85%), m. p. 114—115°, as colourless needles (from ethanol) (Found: C, 39·0; H, 4·5; N, 4·7; I, 41·3. $C_{10}H_{14}INO_2$ requires C, 39·1; H, 4·6; N, 4·55; I, 41·35%); and from 5-ethoxycarbonyl-3-2′-ethoxycarbonylethyl-4-methylpyrrole-2-carboxylic acid by reaction with iodine there was obtained *ethyl 4-2′-ethoxycarbonylethyl-5-iodo-3-methylpyrrole-2-carboxylate* (85%), m. p. 106—107°, flat needles (from ethanol) (Found: C, 41·4; H, 4·9; N, 3·8; I, 33·0. $C_{13}H_{18}INO_4$ requires C, 41·2; H, 4·8; N, 3·7; I, 33·5%).

(*C*) *2,2′-Bipyrrolecarboxylic Esters.—General procedure for Ullmann condensations.* The iodopyrrole (10 g.; crystallisation not necessary) was dissolved in *NN*-dimethylformamide (50 c.c.), powdered copper bronze (10 g.) was added, and the mixture was stirred at room temperature for 17 hr. The copper bronze was then separated and washed with hot chloroform (4 × 50 c.c.). The filtrate and washings were washed with N-hydrochloric acid (2 × 100 c.c.) and with water (2 × 100 c.c.) and dried, and the solvent was removed under reduced pressure. When the crude products were oils, the excess of solvent was removed at a water pump for 1 hr.

Tetraethyl 4,4′-dimethyl-2,2′-bipyrrole-3,3′,5,5′-tetracarboxylate. This was prepared as above

[15] Fischer and Hierneis, *Annalen*, 1931, **492**, 21.
[16] Fischer, Sturm, and Friedrich, *Annalen*, 1928, **461**, 244.

from diethyl 5-iodo-3-methylpyrrole-2,4-dicarboxylate.[5] The reaction could also be carried out by stirring the reactants under reflux for ½ hr. The crude product was triturated with light petroleum (b. p. 60—80°; 30 c.c.), filtered off, washed with light petroleum (2 × 15 c.c.), and dried at 80° (4·04 g., 63%); it had m. p. 178—180°. After crystallisation from chloroform–ethanol, it formed colourless needles, m. p. 184—186° (Webb and Threlkeld [2] give m. p. 178—179°), with a faint blue fluorescence (Found: C, 59·0; H, 6·35; N, 6·15%; *M*, 443. Calc. for $C_{22}H_{28}N_2O_8$: C, 58·9; H, 6·3; N, 6·25%; *M*, 448), $\lambda_{max.}$ 252, 282, and 352 mμ (ε 26,500, 15,100, and 21,300, respectively).

Evaporation of the light petroleum mother-liquors gave crude diethyl 3-methylpyrrole-2,4-dicarboxylate [17] (1·4 g., 22%) which after sublimation at 110°/0·2 mm. formed colourless prisms, m. p. 87—90° (lit.,[17] 91°), and was identical with the sample obtained by hydrogenolysis of diethyl 5-iodo-3-methylpyrrole-2,4-dicarboxylate (below).

5,5′-Dibenzyl 3,3′-*diethyl* 4,4′-*dimethyl*-2,2′-*bipyrrole*-3,3′,5,5′-*tetracarboxylate*. This preparation could also be carried out at 100° by stirring for 1¾ hr. The crude *product* was triturated with light petroleum, filtered off, washed with more solvent, and dried at 80° (5·35 g., 77%). After crystallisation from chloroform–ethanol it formed colourless needles with a faint blue fluorescence (4·35 g.), m. p. 197—199° (Found: C, 67·1; H, 5·35; N, 4·7%; *M*, 559. $C_{32}H_{32}N_2O_8$ requires C, 67·1; H, 5·6; N, 4·9%; *M*, 572·6), $\lambda_{max.}$ 253, 293, and 352 mμ (ε 27,300, 15,650, and 21,800, respectively). From the mother-liquors there was obtained crude 2-benzyl 4-ethyl 3-methylpyrrole-2,4-dicarboxylate (1·7 g., 24·4%) which crystallised from methanol as needles, m. p. 117—120°, identical with the product obtained by hydrogenolysis of 2-benzyl 4-ethyl 5-iodo-3-methylpyrrole-2,4-dicarboxylate (below).

3,3′-*Dibenzyl* 5,5′-*diethyl* 4,4′-*dimethyl*-2,2′-*bipyrrole*-3,3′,5,5′-*tetracarboxylate*. 4-Benzyl 2-ethyl 5-iodo-3-methylpyrrole-2,4-dicarboxylate (8 g.) in *NN*-dimethylformamide (40 c.c.) was treated with copper bronze (9 g.) in the usual way at room temperature overnight. The *product* (1·5 g., 27%) formed needles, m. p. 221—222°, from chloroform–ethanol (Found: C, 66·9; H, 5·4; N, 5·2%; *M*, 552. $C_{32}H_{32}N_2O_8$ requires C, 67·1; H, 5·6; N, 4·9%; *M*, 573), $\lambda_{max.}$ (in $CHCl_3$) 253, 291, and 354 mμ (ε 30,200, 15,490, and 22,390, respectively).

Tetrabenzyl 4,4′-*dimethyl*-2,2′-*bipyrrole*-3,3′,5,5′-*tetracarboxylate*. Prepared similarly from dibenzyl 5-iodo-3-methylpyrrole-2,4-dicarboxylate, this *bipyrrole* (56%) formed long colourless needles, m. p. 211—213°, from chloroform–ethanol (Found: C, 72·5; H, 5·15; N, 3·85%; *M*, 651. $C_{42}H_{36}N_2O_8$ requires C, 72·4; H, 5·2; N, 4·0%; *M*, 697), $\lambda_{max.}$ (in $CHCl_3$) 255, 294, and 355 mμ (ε 30,200, 16,600, and 22,390, respectively).

Tetraethyl 4,4′-*diethyl*-2,2′-*bipyrrole*-3,3′,5,5′-*tetracarboxylate*. This condensation was also carried out by stirring the refluxing reactants for 5 min. The crude *product* was triturated with light petroleum, filtered off, washed, and dried at 80° (4·25 g.; 65%), then having m. p. 163—166°. Crystallisation from chloroform–ethanol gave colourless needles, m. p. 167—168°, with a faint blue fluorescence (Found: C, 60·5; H, 6·4; N, 6·0%; *M*, 477. $C_{24}H_{32}N_2O_8$ requires C, 60·5; H, 6·75; N, 5·9%; *M*, 476·5), $\lambda_{max.}$ 252, 293, and 352 mμ (ε 26,000, 15,600, and 22,300, respectively). From the light petroleum mother-liquors there was obtained crude diethyl 3-ethylpyrrole-2,4-dicarboxylate (38%) which formed colourless prisms, m. p. 81—84° (from aqueous ethanol), and was identical with the sample obtained by hydrogenolysis of diethyl 3-ethyl-5-iodopyrrole-2,4-dicarboxylate (below).

Diethyl 3,3′,5,5′-*tetramethyl*-2,2′-*bipyrrole*-4,4′-*dicarboxylate*. The dark brown oily product was sublimed at 100°/0·2 mm. for 8 hr. in a cold-finger apparatus. Ethyl 2,4-dimethylpyrrole-3-carboxylate was obtained as a colourless sublimate (1·0 g., 17·6%), m. p. 74—76° (lit.,[18] 75—76°) alone or mixed with an authentic specimen obtained by hydrogenolysis of the corresponding iodide (see below). The semisolid residue from the sublimation was triturated with an ether (5 c.c.)–light petroleum (25 c.c.) mixture, filtered, and washed with light petroleum, to give a colourless solid (1·8 g., 31·7%), m. p. 208—211°, which formed colourless plates, m. p. 203—205° from ethanol (Found: C, 64·8; H, 7·3; N, 8·35%; *M*, 337. $C_{18}H_{24}N_2O_4$ requires C, 65·05; H, 7·3; N, 8·43%; *M*, 332·4), $\lambda_{max.}$ 260 mμ (ε 14,950).

Diethyl 3,3′,4,4′-*tetramethyl*-2,2′-*bipyrrole*-5,5′-*dicarboxylate*. This condensation was best carried out by stirring the reactants at 100° for 3 hr. The crude *product* was triturated with light petroleum, filtered off, and washed to yield a colourless solid (1·9 g., 34·5%), m. p. 187—189°, which after crystallisation from ethanol formed needles, m. p. 194·5—196° (Found: C,

[17] Corwin, Bailey, and Viohl, *J. Amer. Chem. Soc.*, 1942, **64**, 1267.
[18] Knorr and Lange, *Ber.*, 1902, **35**, 3007.

65·1; H, 7·0; N, 8·4%; *M*, 341. $C_{18}H_{24}N_2O_4$ requires C, 65·05; H, 7·3; N, 8·45%; *M*, 332·4), $\lambda_{max.}$ 325 mμ (ε 24,400). Evaporation of the mother-liquors gave crude ethyl 3,4-dimethylpyrrole-2-carboxylate (31·6%), which sublimed at 100°/0·2 mm. as colourless needles, m. p. 92—94°, identical with the sample obtained by hydrogenolysis of ethyl 5-iodo-3,4-dimethylpyrrole-2-carboxylate (below).

Diethyl 3,3′-*diethyl*-4,4′-*dimethyl*-2,2′-*bipyrrole*-5,5′-*dicarboxylate*. The reaction was best carried out by stirring the reactants at 100° for 1½ hr. The brown oily *product* solidified overnight (15 hr.) and was triturated with light petroleum, filtered off, and washed. Evaporation of the filtrate gave a brown oil and the process was repeated. The filtrate from the second crop of crystals was evaporated and kept for 5 days; a further treatment with light petroleum then gave a third crop of crystals (total yield, 3·35 g., 28·6%), m. p. 177—180°, which formed colourless needles, m. p. 182—183° from ethanol (Found: C, 66·4; H, 7·5; N, 7·75%; *M*, 355. $C_{20}H_{28}N_2O_4$ requires C, 66·65; H, 7·8; N, 7·75%; *M*, 360·4), $\lambda_{max.}$ 316 mμ (ε 21,000), with a shoulder at 291 mμ (ε 17,200).

Diethyl 3,3′-*diethoxycarbonylethyl*-4,4′-*dimethyl*-2,2′-*bipyrrole*-5,5′-*dicarboxylate*. The reddish-brown oil produced was triturated with light petroleum (30 c.c.) and kept overnight at room temperature. The precipitated solid was separated, washed, and dried at 70°. A second, smaller crop was obtained by keeping the mother-liquors for a further 2 days (total yield, 3·86 g.; 30%); this *product* had m. p. 110—120°, raised to 136—138° by crystallisation from ethanol (Found: C, 62·2; H, 7·4; N, 6·05%; *M*, 506. $C_{26}H_{36}N_2O_8$ requires C, 61·9; H, 7·2; N, 5·55%; *M*, 504·6), $\lambda_{max.}$ 325 mμ (ε 32,600).

Ethyl 2-*formyl*-4-*methylpyrrole*-3-*carboxylate*. Attempted Ullmann condensations of ethyl 2-formyl-5-iodo-4-methylpyrrole-3-carboxylate [19] at room temperature or under reflux yielded *ethyl* 2-*formyl*-4-*methylpyrrole*-3-*carboxylate* as the sole product. It formed colourless prisms, m. p. 141—143° after crystallisation from ethanol and sublimation at 146°/0·2 mm. (Found: C, 59·7; H, 6·05; N, 7·75%; *M*, 184. $C_9H_{11}NO_3$ requires C, 59·7; H, 6·1; N, 7·7%; *M*, 181).

(*D*) *Hydrolysis and Decarboxylation of* 2,2′-*Bipyrrole Esters*.—Complete hydrolysis of the esters was effected by hydrolysis under reflux with one mol. excess of sodium hydroxide in aqueous ethanol for 5 hr. Acidification of the product with dilute hydrochloric acid gave the free acid in high yield. These acids were decarboxylated without further purification by sublimation at 210°/0·2 mm., except where otherwise stated.

Diethyl 4,4′-*dimethyl*-2,2′-*bipyrrole*-3,3′-*dicarboxylate*. Tetraethyl 4,4′-dimethyl-2,2′-bipyrrole-3,3′,5,5′-*tetracarboxylate* (1·4 g.) was dissolved in hot ethanol (100 c.c.), and sodium hydroxide (250 mg., 2 mol.) in water (30 c.c.) was added. The mixture was heated under reflux for 5 hr. and the ethanol distilled off. The solution was cooled, diluted with water (100 c.c.), filtered, and acidified with hydrochloric acid; the product was precipitated as a gelatinous solid. This was separated, washed with water (30 c.c.), and dried *in vacuo*. The product (1·2 g.; 97%), m. p. 250—252°, was insoluble in common solvents and was decarboxylated without further purification. This 5,5′-dicarboxylic acid (1 g.) was decarboxylated at 210°/0·1 mm., the 3,3′-*diester* subliming as colourless needles (100 mg., 15%); when further sublimed at 195—200°/0·1 mm. it had m. p. 225—227° (decomp.) (Found: C, 63·2; H, 6·4; N, 8·9. $C_{16}H_{20}N_2O_4$ requires C, 63·1; H, 6·6; N, 9·2%). It gave a turquoise colour in the Ehrlich reaction.

4,4′-*Dimethyl*-2,2′-*bipyrrole*. Tetraethyl 4,4′-dimethyl-2,2′-bipyrrole-3,3′,5,5′-tetracarboxylate (1·2 g.) was dissolved in methanol (150 c.c.), and an aqueous soution (75 c.c.) of sodium hydroxide (600 mg., 5 mol.) was added. The mixture was heated under reflux for 5 hr., the ethanol removed by distillation, and the residue diluted with water (200 c.c.), filtered, and acidified with hydrochloric acid. The precipitated acid (850 mg., 94%) was separated, washed with water, and dried *in vacuo*. Decarboxylation of the acid as above gave 4,4′-*dimethyl*-2,2′-*bipyrrole* as a sublimate of colourless needles (110 mg., 26%), m. p. 152—155° (decomp.) (Found: C, 74·6; H, 7·05; N, 17·8. $C_{10}H_{12}N_2$ requires C, 74·95; H, 7·55; N, 17·5%), $\lambda_{max.}$ 284 mμ (ε 13,320). In solution it became dark green in 1 hr. at room temperature and could not be recrystallised. It gave a green colour in the cold with the Ehrlich reagent, and royal blue when hot. The *dipicrate* formed pale yellow needles (from methanol), m. p. 165—167° (decomp.), but decomposed on attempted recrystallisation (Found: N, 17·9. $C_{22}H_{18}N_8O_{14}$ requires N, 18·1%). The *distyphnate* formed pale yellow needles (from methanol), m. p. 205—

[19] Corwin and Kleinspehn, *J. Amer. Chem. Soc.*, 1953, **75**, 2089.

206° (decomp.) but decomposed on attempted recrystallisation (Found: N, 16·7. $C_{22}H_{18}N_8O_{18}$ requires N, 16·4%).

4,4'-*Diethyl*-2,2'-*bipyrrole*. Prepared similarly from the corresponding 3,3',5,5'-tetraester by hydrolysis and decarboxylation of the tetracarboxylic acid at 210°/0·2 mm., this *bipyrrole* was purified by sublimation at 145°/0·2 mm., forming colourless plates, decomp. 164° (below the m. p.) (Found: C, 76·3; H, 8·65; N, 15·5%; *M*, 200. $C_{12}H_{16}N_2$ requires C, 76·55; H, 8·6; N, 14·9%; *M*, 188·3), $\lambda_{max.}$ 286 mμ (ε 13,650), Ehrlich reaction (cold) deep blue.

3,3'-*Diethyl*-4,4'-*dimethyl*-2,2'-*bipyrrole*. Prepared similarly from the corresponding 5,5'-diester, this *product* formed colourless prisms, m. p. 112—113° (Found: C, 77·8; H, 9·21; N, 13·5%; *M*, 226. $C_{14}H_{20}N_2$ requires C, 77·75; H, 9·3; N, 12·95%; *M*, 216), $\lambda_{max.}$ 256 mμ (ε 9780), Ehrlich reaction (cold) deep blue.

3,3',4,4'-*Tetramethyl*-2,2'-*bipyrrole*. Prepared similarly from the corresponding 5,5'-diester by hydrolysis and decarboxylation of the dicarboxylic acid at 210°/0·2 mm., this *compound* was purified by sublimation at 110°/0·2 mm.; it formed colourless prisms, m. p. 121—123° (Found: C, 76·8; H, 8·6; N, 15·4%; *M*, 199. $C_{12}H_{16}N_2$ requires C, 76·55; H, 8·6; N, 14·9%; *M*, 188·3), $\lambda_{max.}$ 263 mμ (ε 11,770), Ehrlich reaction (cold) deep blue.

(*E*) *Hydrogenolysis of* 2-*Iodopyrroles*.—The 2-iodopyrrole (5 g.; crystallisation not necessary), anhydrous sodium acetate (1·25 mol.), and Adams platinum catalyst (20 mg.) were suspended in ethanol (75 c.c.) and hydrogenated at room temperature until uptake ceased. The catalyst was separated and the filtrate concentrated under reduced pressure to *ca.* 20 c.c. The resulting solution was slowly diluted with water (230 c.c.), and the precipitated solid separated, washed, and dried. The following were thus obtained:

Diethyl 3-methylpyrrole-2,4-dicarboxylate (96%), m. p. 91—92° (Found: C, 58·5; H, 6·55 N, 6·35. Calc. for $C_{11}H_{15}NO_4$: C, 58·65; H, 6·7; N, 6·2%).

Diethyl 3-*ethylpyrrole*-2,4-*dicarboxylate* (100%), plates, m. p. 88·5—90° (from ethanol) (Found: C, 59·9; H, 7·03; N, 5·65. $C_{12}H_{17}NO_4$ requires C, 60·25; H, 7·15; N, 5·85%).

2-*Benzyl* 4-*ethyl* 3-*methylpyrrole*-2,4-*dicarboxylate* (98%), m. p. 121·5—122·5° (Found: C, 66·8; H, 5·6; N, 4·9. $C_{16}H_{17}NO_4$ requires C, 66·9; H, 5·95; N, 4·9%).

Ethyl 2,4-dimethylpyrrole-3-carboxylate (96%), m. p. 74—76° (lit.,[16] 75—76°) (Found: C, 64·4; H, 7·8; N, 8·6. Calc. for $C_9H_{13}NO_2$: C, 64·65; H, 7·85; N, 8·4%).

Ethyl 2-formyl-4-methylpyrrole-3-carboxylate (87%), m. p. 141—143°, as colourless prisms after sublimation at 146°/0·2 mm. The sample was identical with that obtained from the attempted Ullmann condensation (see above).

Ethyl 3,4-*dimethylpyrrole*-2-*carboxylate* (98%), m. p. 93—95° (Found: C, 64·4; H, 7·6; N, 8·25%).

(*F*) *Other Attempted Bipyrrole Syntheses*.—*Diethyl* 5-N-(1,2-*dimethyl*-3-*oxobut*-1-*enyl*)*aminomethyl*-3-*methylpyrrole*-2,4-*dicarboxylate* (IV). The oxime [20] (7 g.) of diethyl 5-formyl-3-methylpyrrole-2,4-dicarboxylate was heated with 3-methylpentane-2,4-dione (7 c.c.), zinc dust (2 g.), and glacial acetic acid (200 c.c.) on a steam-bath for 2 hr., and the product was poured into water (2 l.), basified with aqueous ammonia and then extracted with ether (3 × 200 c.c.). The ethereal extract was dried ($MgSO_4$), the solvent removed under reduced pressure, and the residual *ketone* (IV) crystallised from aqueous methanol as colourless needles (4 g., 44%), m. p. 147—149° (Found: C, 61·7; H, 7·3; N, 8·35%; *M*, 324. $C_{18}H_{26}N_2O_5$ requires C, 61·7; H, 7·5; N, 8·0%; *M*, 350), $\nu_{max.}$ (in CCl_4) 3460, 3445, 3185, 3131, 3050, 2990, 2968, 2940, 2912, 2878, 1725, 1700, 1610, 1512, 1488, 1448, 1435, 1378, 1359, 1278, 1243, 1199, 1176, 1113, 1076, 1033, and 979 $cm.^{-1}$. The *picrate* formed yellow prisms, m. p. 230—232° (decomp.), from ethanol (Found: C, 49·9; H, 5·15; N, 11·6. $C_{24}H_{29}N_5O_{12}$ requires C, 49·7; H, 5·0; N, 12·05%).

4-*Benzyl* 2-*ethyl* 5-*methoxymethyl*-3-*methylpyrrole*-2,4-*dicarboxylate*. 4-Benzyl 2-ethyl 5-formyl-3-methylpyrrole-2,4-dicarboxylate (8 g.), 3-methylpentane-2,4-dione (5 c.c.), and zinc dust (3 g.) in acetic acid (200 c.c.) were heated on a steam-bath with stirring for 3 hr., poured into water (2 l.), and kept for 2 hr. The *methoxymethyl product* was isolated as in the previous experiment, forming colourless needles (4 g.; 50%), m. p. 69—70°, from aqueous methanol (Found: C, 65·0; H, 6·4; N, 4·15%; *M*, 320. $C_{18}H_{21}NO_5$ requires C, 65·25; H, 6·4; N, 4·25%; *M*, 331).

2-*Benzyl* 4-*ethyl* 5-*ethoxymethyl*-3-*methylpyrrole*-2,4-*dicarboxylate* was prepared similarly, as

[20] Fischer and Halbig, *Annalen*, 1926, **450**, 109.

needles (2 g., 38%), m. p. 122—124° (from aqueous ethanol) (Found: C, 66·3; H, 6·35%; *M*, 354. $C_{19}H_{23}NO_5$ requires C, 66·1; H, 6·7%; *M*, 345).

3-*Ethyl* 5-*iodoacetyl*-2,4-*dimethylpyrrole*-3-*carboxylate*. 5 Ethyl 5-chloroacetyl 2,4-dimethylpyrrole-3-carboxylate [10] (1·65 g.) was heated in acetone (60 c.c.) under reflux in the presence of sodium iodide (5 g.) for 15 min. The precipitated sodium chloride was separated and washed with acetone (2 × 10 c.c.), and the combined filtrate and washings were evaporated to dryness under reduced pressure. Water (100 c.c.) was added and the solid (2·25 g.) was separated, washed, and dried at 100°. On crystallisation from ethanol this *iodoacetyl derivative* formed pale yellow needles, m. p. 157—159° (Found: C, 39·4; H, 4·35; N, 4·3; I, 37·7. $C_{11}H_{14}INO_3$ requires C, 39·45; H, 4·2; N, 4·2; I, 37·9%), showing strong bands at 3450, 3260, 1690, and 1610 cm.$^{-1}$.

Ethyl 5-*glycolloyl*-2,4-*dimethylpyrrole*-3-*carboxylate and its monoacetate*. The foregoing iodo-compound (1 g.) and anhydrous potassium acetate (2 g.) were heated together in acetone (40 c.c.) under reflux for 4 hr. The solvent was removed under reduced pressure and the residue triturated with water (100 c.c.). The 2′-*acetoxyacetyl derivative* (0·8 g.) was separated, washed, and dried at 80°; crystallisation from ethanol gave colourless needles, m. p. 147—149° (Found: C, 58·3; H, 6·45; N, 4·95. $C_{13}H_{17}NO_5$ requires C, 58·4; H, 6·4; N, 5·25%), showing strong bands at 3500, 3300, 1750, 1700, and 1650 cm.$^{-1}$.

The acetyl derivative (3·61 g.) in ethanol (47 c.c.) containing N-sodium hydroxide (13·5 c.c.) was heated under reflux for 2 hr. Most of the solvent was removed under reduced pressure and water (150 c.c.) was added. The precipitated solid (2·81 g., 92·5%) was separated, washed, and dried at 80°. The *glycolloyl derivative* formed colourless needles, m. p. 153—155°, from ethanol (Found: C, 59·0; H, 6·6; N, 6·55. $C_{11}H_{15}NO_4$ requires C, 58·65; H, 6·7; N, 6·22%), and showed strong bands at 3500, 3300, 1700, and 1640 cm.$^{-1}$.

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Department of Chemistry,
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