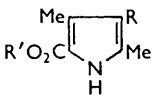
689. *Colouring Matters Derived from Pyrroles. Part II.* Improved Syntheses of Some Dipyrromethenes and Porphyrins.*

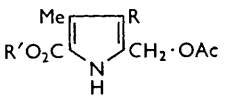
By A. W. Johnson, I. T. Kay, E. Markham, R. Price, and K. B. Shaw.

Esters of 4-substituted 3,5-dimethylpyrrole-2-carboxylic acids, for which an easy synthesis is available, have been used to prepare a variety of dipyrromethanes, dipyrromethenes, and porphyrins. The special properties of the t-butyl and benzyl esters have led to improved methods for the preparation of several dipyrromethenes.

In a previous paper,[1] we described a simple one-stage synthesis of pyrroles of the general structure (I) which made these compounds readily accessible for the preparation of certain porphyrins as well as of dipyrromethane and dipyrromethene intermediates. Some of these reactions are described in the present paper in which emphasis is placed on the special properties of benzyl and t-butyl esters (I; R′ = CH_2Ph or Bu^t) in the pyrrole series.



(I)



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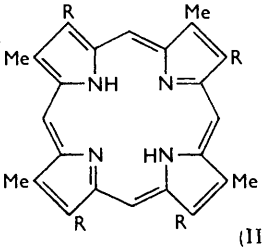


(III)

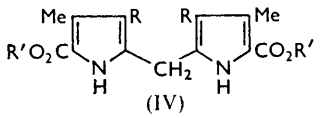
An ester of this type was used as the starting point for a convenient synthesis [2] of the esters of coproporphyrin III (III; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$); the ester (I; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$, R′ = CH_2Ph) was oxidised with lead tetra-acetate to the 5-acetoxymethyl derivative (II; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$, R′ = CH_2Ph) and then hydrogenolysed to the corresponding acid (II; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$, R′ = H). Acid-catalysed polymerisation of this acid gave the coproporphyrin III ester (III; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$) in 22% yield. By a similar process the acid (II; R = $CH_2{\cdot}CH_2{\cdot}CO_2Me$, R′ = H) has now given coproporphyrin III tetramethyl ester in 29% yield, but the interesting observation has been made that the yield can be increased to 52% if the polymerisation is carried out in the presence of cobaltous chloride, the cobalt complex of the porphyrin being obtained. In an alternative synthesis (cf. ref. 2), coproporphyrin III tetraethyl ester has been obtained directly from the t-butyl ester (II; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$, R′ = Bu^t) by heating its solution in ethylene glycol under reflux, and ætioporphyrin (probably III; R = Et) has been prepared in 22% yield by a similar method from the t-butyl ester (II; R = Et, R′ = Bu^t). In the latter case the yield of porphyrin (as zinc complex) was appreciably diminished by adding zinc acetate to the reaction mixture. Ætioporphyrin was obtained in one stage from the pyrrole t-butyl ester (I; R = Et, R′ = Bu^t) by heating its solution in acetic acid with one mol. of bromine. Although the yield was low in the single experiment performed, the preparation is nevertheless remarkable in that it represents a two-stage synthesis of ætioporphyrin from aliphatic intermediates. It is presumed that the bromine causes substitution at the α-methyl group, to give an α-bromomethyl derivative which then polymerises in the same manner as the α-acetoxymethyl compound. In this case, addition

* "A Synthesis of Coproporphyrin III" by Bullock, Johnson, Markham and Shaw (*J.*, 1958, 1430) is taken to be Part I of this series.

[1] Johnson, Markham, Price, and Shaw, *J.*, 1958, 4254.
[2] Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.

of zinc acetate had no effect on the reaction as the hydrogen bromide formed removed the metal from the porphyrin complex.

Treatment of the acetoxymethylpyrrole esters (II) with dilute acid gave good yields of the dipyrromethanes (IV; R′ = Et, and R = Me; R′ = CH_2Ph, and R = Et, $CH_2{\cdot}CH_2{\cdot}CO_2Me$, or $CH_2{\cdot}CH_2{\cdot}CO_2Et$). The benzyl esters were readily converted into the corresponding acids (IV; R′ = H) by hydrogenolysis, which causes fewer side reactions than hydrolyses of the ethyl esters. Treatment of the dipyrromethane-5,5′-dicarboxylic acid (IV; R = Et, R′ = H) with bromine in acetic acid [3] gave the 5,5′-dibromodipyrromethene hydrobromide (V; R = Et), and by use of a slightly modified procedure involving bromine in formic acid [4] the analogous compound (V; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$) was obtained. These 5,5′-dibromodipyrromethenes are useful porphyrin intermediates, *e.g.*, in the synthesis of mesoporphyrin IX.[5]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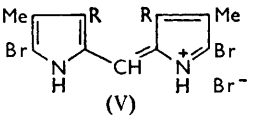
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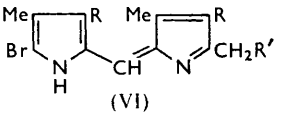
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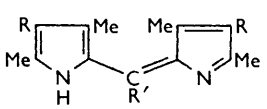
Another important group of dipyrromethenes (VI; R′ = H or Br) which contain an unsymmetrical arrangement of the β-substituents has been prepared in a novel manner by the direct action of bromine on the pyrrole t-butyl ester (I; R = Et, R′ = Bu^t). The mixed products (VI; R′ = H or Br) were separated by extraction with chloroform in which the former, present as a perbromide, was insoluble. Fischer, Baumann, and Riedl [6] had obtained the same mixture of dipyrromethenes (VI; R = Et, R′ = H or Br) by bromination of cryptopyrrole, but the present method avoids the preparation of the unstable cryptopyrrole and thus eliminates at least one preparative stage. In another example of this type of synthesis the pyrrole ester (I; R = CO_2Et, R′ = Bu^t) was converted by bromine into the dipyrromethene (VI; R = CO_2Et, R′ = H).[7]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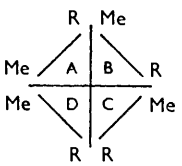
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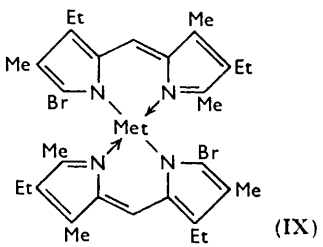
(IX)

A synthesis [8] of symmetrical dipyrromethenes (VII; R′ = H) containing 5,5′-dimethyl groups involves the action of formic and hydrobromic acid on the 2-ethoxycarbonylpyrroles (I; R = Me, Et, or $CH_2{\cdot}CH_2{\cdot}CO_2Et$, R′ = Et), although in the case of the product from the pyrrole containing the β-propionic ester side-chain, some hydrolysis of the ester groups occurred and re-esterification was necessary. Acetic acid cannot replace formic acid for the preparation of *meso*-methyl analogues of (VIII; R′ = Me), but it has now been found that these compounds can be obtained easily from the 2-t-butoxycarbonylpyrroles (I; R = Me or $CH_2{\cdot}CH_2{\cdot}CO_2Me$, R′ = Bu^t) by the action of acetyl chloride in acetic acid. It is, of course, necessary that the intermediate pyrrole-2-carboxylic acids in these reactions should be decarboxylated readily; the pyrrole (I; R = CO_2Et, R′ = Bu^t)

[3] Fischer, Halbig, and Walach, *Annalen*, 1927, **452**, 268.
[4] Cf. MacDonald and Michl, *Canad. J. Chem.*, 1956, **34**, 1768.
[5] Fischer and Stangler, *Annalen*, 1928, **462**, 251.
[6] Fischer, Bauman, and Riedl, *ibid.*, 1929, **475**, 205.
[7] Fischer and Bäumler, *ibid.*, 1929, **468**, 58.
[8] Fischer *et al.*, *ibid.*, 1928, **466**, 147; 1930, **483**, 251; 1932, **492**, 128.

merely formed the corresponding monocarboxylic acid after reaction with acetyl chloride. As in the brominative decarboxylation described above, this synthesis of dipyrromethenes avoids the preparation of trialkylpyrroles.

In considering dipyrromethene intermediates for the synthesis of III-type porphyrins, abbreviated as (VIII) where only the β-pyrrole substituents are indicated, the union to be effected can be either AB ⟶ CD or AD ⟶ BC, where AB is the same as BC. The preparation, from the pyrroles (I), of all three types of dipyrromethene required for these syntheses has now been described: (V) corresponds to CD, (VI) to AB or BC, and (VII) to AD. There remains, of course, the problem of having the necessary α-substituents present on the dipyrromethenes in order to form the remaining *meso*-carbons of the porphyrin.

Although metal salts are frequently added to the reaction mixtures in syntheses of phthalocyanins and benzoporphyrins,[9] it is usual to employ the free dipyrromethenes in the preparation of the porphyrins themselves. After it had been observed that the action of palladium–strontium carbonate on 5-bromo-5′-bromomethyl-3,4′-diethyl-4,3′-dimethyldipyrromethene hydrobromide (VI; R = Et, R′ = Br) in ethanolic solution gave the palladium complex of ætioporphyrin I (without the metal the reaction can be effected by formic acid [10]), it was decided to assess the effect of different metals in this type of synthesis.[11] The dipyrromethene used was 5-bromo-3,4′-diethyl-4,5,3′-trimethyldipyrromethene and the cobalt, nickel, copper, and zinc derivatives (IX) were prepared by standard methods. Solutions of the metal complexes were not affected by aqueous potassium hydroxide, but the metal was rapidly and quantitatively removed by treatment with aqueous potassium cyanide. Each of these metal complexes as well as the free dipyrromethene was heated under reflux in *o*-dichlorobenzene for 60 min. and the amount of porphyrin (either the metal derivative or the free base) was estimated spectroscopically. Yields were as follows: cobalt, 17%; zinc, 15%; nickel, 14%; copper, 7%; and free base, 11%. It is clear that the presence of the metal results only in a modest increase of yield under these conditions. A determination of the magnetic susceptibility ($\mu_{eff.}$ = 4·5) of the green cobalt complex of (VII; R = Et, R′ = H), kindly carried out by Professor R. Nyholm and Mr. D. J. Machin, indicated that it was tetrahedral and all of the above metal complexes are probably of this type. There is thus an appreciable energy barrier to be overcome before the rearrangement to the planar metalloporphyrin can take place and this approach would not appear to offer any advantage over the conventional methods, *e.g.*, heating the dipyrromethene hydrobromide in succinic acid. In another attempt to utilise the dipyrromethene–metal complexes, the possibility of preparing a mixed metal complex from two dipyrromethenes was examined in order to assess the possibility of preparing porphyrins of the mesoporphyrin IX type. This approach would be of practical value if the mixture of symmetrical and unsymmetrical metallo-dipyrromethenes was more easily separated than the mixed porphyrins. Equimolecular quantities of 3,3′,4,4′,5,5′-hexamethyldipyrromethene and 4,4′-diethyl-3,3′,5,5′-tetramethyldipyrromethene were treated with cobalt acetate, and the resulting mixture was separated by solvent-extraction and crystallisation. An *X*-ray powder photograph of the mixed cobalt complex, taken by Dr. R. B. Elliott of the Geology Department, University of Nottingham, confirmed that it differed from both of the symmetrical cobalt complexes. In other cases, however, the mixed dipyrromethene–metal complex could not be isolated conveniently and this approach has consequently been abandoned.

Experimental

Preparation of Pyrrole Intermediates.

t-Butyl 4-Ethyl-3,5-dimethylpyrrole-2-carboxylate (I; R = Et, R′ = Bu^t).—Redistilled t-butyl acetoacetate (260 g.) in glacial acetic acid (300 c.c.) was treated with aqueous sodium

[9] Linstead and Weiss, *J.*, 1950, 2975.
[10] Fischer and Klarer, *Annalen*, 1926, **450**, 181.
[11] Corwin and Sydow, *J. Amer. Chem. Soc.*, 1953, **75**, 4484.

nitrite (135 g. in 300 c.c.) with stirring during 75 min. at 10—12° (ice-cooling). The product was kept for a further hr. at 4°, then overnight at room temperature. The following day, 3-ethylpentane-2,4-dione [1] (210 g.) and acetic acid (60 c.c.) were added with stirring, followed by zinc dust (210 g.) at such a rate as to keep the temperature at 80—85°. Next, the mixture was stirred for a further 30 min., then heated at 100° for 2 hr. The hot solution was poured, with stirring, into cold water (5 l.), and the precipitated solid was separated and dissolved in hot ethanol (500 c.c.). The clarified solution was diluted with water to produce a faint turbidity and then kept, the *ester* being obtained as colourless needles (118 g., 31%, m. p. 134—135°) (Found: C, 69·6; H, 9·8; N, 6·3. $C_{13}H_{21}O_2N$ requires C, 69·9; H, 9·5; N, 6·3%).

t-Butyl 3-2′-*Methoxycarbonylethyl*-2,4-*dimethylpyrrole*-2-*carboxylate* (I; R = CH_2·CH_2·CO_2Me, R′ = Bu^t).—Prepared in a similar manner from t-butyl acetoacetate and methyl 4-acetyl-5-oxohexanoate,[1] this *ester* (35%) formed colourless needles, m. p. 99—100° (Found: C, 64·0; H, 8·2; N, 5·15. $C_{15}H_{23}O_4N$ requires C, 63·8; H, 7·8; N, 5·0%).

A similar reaction between t-butyl acetoacetate and ethyl 4-acetyl-5-oxohexanoate gave *t-butyl* 3-2′-*ethoxycarbonylethyl*-2,4-*dimethylpyrrole*-2-*carboxylate* (I; R = CH_2·CH_2·CO_2Et, R′ = Bu^t) as colourless needles (37%), m. p. 69° (Found: C, 65·3; H, 8·3; N, 5·0. $C_{16}H_{25}O_4N$ requires C, 65·05; H, 8·5; N, 4·75%).

Ethyl 5-*Acetoxymethyl*-3,4-*dimethylpyrrole*-2-*carboxylate* (II; R = Me, R′ = Et).—Lead tetra-acetate (24·5 g.) was added to a solution of ethyl 2,3,4-trimethylpyrrole-5-carboxylate [2] (10 g.) in glacial acetic acid (250 c.c.) at room temperature during 15 min. with stirring. Stirring was continued for a further 2 hr., after which most of the solvent was removed under reduced pressure, and the residue poured into water (500 c.c.). The precipitated solid was separated, washed with water, and crystallised from aqueous acetone, forming colourless needles, m. p. 131—132° (lit.,[12] 132°) (11·5 g., 87%).

Benzyl 5-*Acetoxymethyl*-4-*ethyl*-3-*methylpyrrole*-2-*carboxylate* (II; R = Et, R′ = CH_2Ph).—Obtained (19 g., 66%) from benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate [1] (24·5 g.) by a similar process, and after crystallisation from acetone, this *compound* formed colourless needles, m. p. 122° (Found: C, 68·7; H, 6·75; N, 4·7. $C_{18}H_{21}O_4N$ requires C, 68·55; H, 6·7; N, 4·45%).

Benzyl 5-*Acetoxymethyl*-4-2′-*methoxycarbonylethyl*-3-*methylpyrrole*-2-*carboxylate* (II; R = CH_2·CH_2·CO_2Me, R′ = CH_2Ph).—This *diester* was obtained from benzyl 4-2′-methoxycarbonylethyl-3,5-dimethylpyrrole-2-carboxylate [1] in 69% yield by a similar process. It formed colourless needles, m. p. 111—112°, from aqueous acetone (Found: C, 64·2; H, 6·2; N, 3·7. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·75%).

t-Butyl 5-*Acetoxymethyl*-4-2′-*ethoxycarbonylethyl*-3-*methylpyrrole*-2-*carboxylate* (II; R = CH_2·CH_2·CO_2Et, R′ = Bu^t).—Prepared (50%) likewise from t-butyl 4,2′-ethoxycarbonylethyl-3,5-dimethylpyrrole-2-carboxylate (above) with lead tetra-acetate, this *butyl derivative* formed colourless needles, m. p. 84—85° (Found: C, 61·3; H, 7·4; N, 4·3. $C_{18}H_{27}O_6N$ requires C, 61·2; H, 7·7; N, 3·95%).

Preparation of Dipyrromethanes.

Diethyl 3,3′,4,4′-*Tetramethyldipyrromethane*-5,5′-*dicarboxylate* (IV; R = Me, R′ = Et).—Ethyl 5-acetoxymethyl-3,4-dimethylpyrrole-2-carboxylate (7 g.) was dissolved in ethanol (200 c.c.) containing concentrated hydrochloric acid (5 c.c.) and heated under reflux for 1 hr. On cooling, the product crystallised. When separated, washed with ethanol, and dried, it had m. p. 196—198° (lit.,[13] 198°), unchanged after recrystallisation from ethanol.

Dibenzyl 3,3′-*Diethyl*-4,4′-*dimethyldipyrromethane*-5,5′-*dicarboxylate* (IV; R = Et, R′ = CH_2Ph).—Prepared (66%) similarly from benzyl 5-acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate, this *analogue* formed colourless needles (from ethanol), m. p. 126—127° (Found: C, 74·5; H, 6·75; N, 5·8. $C_{31}H_{34}O_4N_2$ requires C, 74·65; H, 6·85; N, 5·6%).

Dibenzyl 3,3′-*di*-(2-*ethoxycarbonylethyl*)-4,4′-*dimethyldipyrromethane*-5,5′-*dicarboxylate* (IV; R = ·CH_2·CH_2·CO_2Et; R′ = CH_2Ph), prepared (72%) in a similar manner from benzyl 5-acetoxymethyl-4-2′-ethoxycarbonylethyl-3-methylpyrrole-2-carboxylate,[2] formed colourless needles (from ethanol), m. p. 102—103° (Found: C, 69·1; H, 6·5; N, 4·65. $C_{37}H_{42}O_8N_2$ requires C, 69·15; H, 6·6; N, 4·35%).

Dibenzyl 3,3′-*Di*-(2-*methoxycarbonylethyl*)-4,4′-*dimethyldipyrromethane*-5,5′-*dicarboxylate* (IV;

[12] Siedel and Winkler, *Annalen*, 1943, **554**, 162.
[13] Fischer and Walach, *ibid.*, 1926, **450**, 109.

R = CH_2·CH_2·CO_2Me, R′ = CH_2Ph).—(i) Prepared similarly (65%) from benzyl 5-acetoxymethyl-4,2′-methoxycarbonylethyl-3-methylpyrrole-2-carboxylate, this *dipyrromethane* formed colourless needles, m. p. 96—97°, from ethanol (Found: C, 68·2; H, 6·0; N, 4·85. $C_{35}H_{38}O_8N_2$ requires C, 68·4; H, 6·25; N, 4·55%).

(ii) The same acetoxy-pyrrole (1 g.) was dissolved in methanol (30 c.c.) containing concentrated hydrochloric acid (3 drops) and kept at room temperature for one month. The solution was reduced to 10 c.c., and the resulting colourless solid separated and crystallised from ethanol; it was obtained as colourless needles, m. p. alone and mixed with the product from the previous experiment, 96—97°.

Preparation of Dipyrromethenes.

5,5′-Dibromo-3,3′-diethyl-4,4′-dimethyldipyrromethene (V; R = Et).—Dibenzyl 3,3′-diethyl-4,4′-dimethyldipyrromethane-5,5′-dicarboxylate (above; 9·1 g.) was dissolved in methanol (100 c.c.), and methanol-washed Raney nickel (5 g.) was added. The mixture was hydrogenated at 100—110°/140 atm. for 2 hr., after which the catalyst and solvent were removed. The residual oil was treated in glacial acetic acid (40 c.c.) with bromine (3·0 c.c.) in glacial acetic acid (10 c.c.) for 2 hr. at room temperature. The precipitated hydrobromide was separated, washed with light petroleum, and dried (5·7 g., 67%). The free base was prepared by treating a methanolic solution of the hydrobromide with ammonia. It crystallised from methanol in yellow needles, m. p. 181—182° (lit.,[3] 184°) (Found: C, 46·35; H, 4·5; N, 7·1. Calc. for $C_{15}H_{18}N_2Br_2$: C, 46·65; H, 4·7; N, 7·25%), $\lambda_{max.}$ 325, 491 mμ (log ε 3·56, 4·5).* The *cobalt complex* was prepared by treating the hydrobromide (1 g.) in ethanol (50 c.c.) and aqueous ammonia (0·5 c.c.; *d* 0·88) with a saturated solution (2·5 c.c.) of cobalt acetate in aqueous ammonia. After removal of the solvent, the residue was dissolved in chloroform, washed several times with water, and dried ($MgSO_4$). The solvent was removed and the cobalt complex (800 mg.) crystallised as green needles from chloroform–methanol (Found: C, 43·3; H, 4·1; N, 6·85. $C_{30}H_{34}N_4Br_4Co$ requires C, 43·45; H, 4·15; N, 6·75%), $\lambda_{max.}$ at 239, 319, 377, 515, 710, and 770 mμ (log ε 4·42, 3·8; 4·86, 3·6, 2·8 and 2·91) with an inflection at 585 mμ (log ε 3·55).

5,5′-Dibromo-3,3′-di-(2-ethoxycarbonylethyl)-4,4′-dimethyldipyrromethene (V; R = CH_2·CH_2·CO_2Et).—Dibenzyl 3,3′-di-(2-ethoxycarbonylethyl)-4,4′-dimethyldipyrromethane-5,5′-dicarboxylate (above; 3 g.) was hydrogenated in methanol (150 c.c.) over Adams catalyst. The solvent was then removed under reduced pressure and the resulting off-white solid, decomp. >160°, washed with ether, dried (2·0 g., 80%), and treated with bromine (3 c.c.) in 90% formic acid (15 c.c.). The mixture was kept for 1 hr. before being left overnight in a desiccator over solid sodium hydroxide at *ca.* 30 mm. The product was separated, washed with formic acid, and dried (yield 3 g., 75%). The *hydrobromide* crystallised from ethanol as violet needles, m. p. 188—189° (Found: C, 41·7; H, 4·35; N, 4·25. $C_{21}H_{27}O_4N_2Br_3$ requires C, 41·3; H, 4·45; N, 4·55%), $\lambda_{max.}$ 455 mμ (log ε 4·46).

The hydrobromide (2·4 g.) was dissolved in methanol (50 c.c.), and the solution made alkaline with dilute ammonia. The precipitated orange *base* was separated, washed with water, dried (1·9 g., 90%), and crystallised from ethanol, forming orange needles, m. p. 92—94° (Found: N, 5·4. $C_{21}H_{26}O_4N_2Br_2$ requires N, 5·3%). The *cobalt complex* crystallised from chloroform–methanol in green needles, m. p. 175—176° (Found: C, 45·2; H, 4·4; N, 5·3. $C_{42}H_{50}O_8N_4Br_4Co$ requires C, 45·15; H, 4·5; N, 5·0%). The *nickel complex* crystallised from chloroform–methanol in olive-green needles, m. p. 178—179° (Found: C, 44·8; H, 3·90; N, 5·15. $C_{42}H_{50}O_8N_4Br_4Ni$ requires C, 45·15; H, 4·48; N, 5·0%).

5-Bromo-5′-bromomethyl-3,4′-diethyl-4,3′-dimethyldipyrromethene Hydrobromide (VI; R = Et, R′ = Br).—t-Butyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (36 g.) in glacial acetic acid (250 c.c.) was treated with bromine (20 c.c.) in glacial acetic acid (100 c.c.). After the vigorous reaction had subsided, the mixture was kept for 1 hr. and the steel-blue crystals (18 g.) were separated and washed with light petroleum (b. p. 60—80°). The mixed product (5 g.) was separated by extraction with chloroform at <40°, the above dipyrromethene hydrobromide [6] being obtained from the extract as red prisms (3 g.), m. p. >350° (Found: C, 39·8; H, 4·4; N, 5·6. Calc. for $C_{16}H_{21}N_2Br_3$: C, 39·9; H, 4·4; N, 5·8%).

5-Bromo-3,4′-diethyl-4,3′,5′-trimethyldipyrromethene Hydrobromide Perbromide (as VI; R = Et, R′ = H).—The chloroform-insoluble fraction from the above separation was obtained as a brick-red powder (1·4 g.), m. p. 147° (lit.,[6] 149°), which was the above-named perbromide.

* Absorption maxima are for chloroform solution, throughout.

Metal complexes. (i) The methene hydrobromide perbromide (3 g.) was dissolved in ethanol (15 c.c.) containing aqueous ammonia (2·5 c.c.; *d* 0·88), and a saturated solution of cobaltous acetate in aqueous ammonia (10 c.c.) was added. The mixture was boiled gently for 5 min., then cooled, and water (100 c.c.) was added. The solution was extracted with chloroform (3 × 25 c.c.), and the combined extracts were washed and dried. After concentration of the chloroform solution to 10 c.c., crystallisation was induced by gradual addition of methanol. The *cobalt complex* so obtained formed green plates, m. p. 174° (Found: C, 54·8; H, 6·0; N, 8·0. $C_{32}H_{40}N_4Br_2Co$ requires C, 54·9; H, 5·8; N, 8·0%), $\lambda_{max.}$ 376, 509, 705 and 765 mμ (log ε 4·25, 5·14, 2·66, and 2·72, respectively) with inflections at 400 and 615 mμ (log ε 4·14 and 3·51). (ii) Prepared in an analogous manner by using ammoniacal nickel chloride, the *nickel complex* (850 mg.) formed olive-green needles, m. p. 174° (Found: C, 54·9; H, 5·9; N, 7·6. $C_{32}H_{40}N_4Br_2Ni$ requires C, 54·95; H, 5·8; N, 8·0%). (iii) Prepared similarly by using ammoniacal cupric acetate, the *copper complex* (1 g.) formed green prisms, m. p. 156°, which could not be recrystallised satisfactorily (Found: N, 7·95. Calc. for $C_{32}H_{40}N_4Br_2Cu$: N, 7·25%), $\lambda_{max.}$ at 338, 397, 491, and 800 mμ (log ε 4·03, 4·14, 4·69, and 3·51 respectively) with inflections at 380 and 520 mμ (log ε 4·12 and 4·29). (iv) Prepared similarly by using ethanolic zinc acetate, the *zinc complex* (900 mg.), m. p. 177°, formed brown needles with a golden metallic sheen (Found: C, 54·6; H, 5·55; N, 8·05. $C_{32}H_{40}N_4Br_2Zn$ requires C, 54·45; H, 5·7; N, 7·95%), $\lambda_{max.}$ at 233, 291, 365, and 507 mμ (log ε 4·29, 3·75, 4·01, and 5·06) with inflections at 310 and 480 mμ (log ε 3·67 and 4·82).

These metal complexes (100 mg.) were all converted into the metal derivatives of ætioporphyrin I by suspending them in *o*-dichlorobenzene (2 c.c.), raising the temperature of the suspension to the b. p. during ½ hr., then heating the solutions under reflux for 1 hr. A similar reaction was carried out with the free base. After cooling, chloroform (5 c.c.) was added to each mixture, which was chromatographed on alumina (Spence type H; 30 × 2·5 cm.). The porphyrin band was eluted (hand spectroscope), and the eluate made up to 100 c.c. An aliquot part was diluted (1 : 5) and examined spectroscopically over the range 350—430 mμ. The yields of metal porphyrin were calculated from the intensity of the strong band near 400 mμ, after measurement of the intensity of absorption of each of the porphyrin derivatives: ætioporphyrin I, log ε 5·23 at 396 mμ; cobalt complex log ε 5·35 at 393 mμ; nickel complex, log ε 5·26 at 392 mμ; copper complex, log ε 5·59 at 398 mμ; zinc complex, log ε 5·43 at 402 mμ. On this basis the percentage conversions were: cobalt, 17%; nickel, 14%; copper, 7%; zinc, 15%; free base, 11%.

5-Bromo-3,4′-di(ethoxycarbonyl)-4,3′,5′-trimethyldipyrromethene (VI; R = CO_2Et, R′ = H).—t-Butyl 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylate [1] (2·59 g.) was suspended in glacial acetic acid (5 c.c.), and bromine (0·9 c.c.) in acetic acid (10 c.c.) was added. The mixture was kept for 15 min. with occasional stirring, then the hydrobromide (1·65 g.) was separated and washed with light petroleum. It crystallised from chloroform–light petroleum as brick-red felted needles which decomposed before melting [$\lambda_{max.}$ 295 mμ (log ε 3·63)].

The hydrobromide (1·5 g.) was suspended in methanol (50 c.c.), and aqueous ammonia (5 c.c.; *d* 0·88) was added. The mixture was boiled gently for 5 min., then cooled, the free base (1·1 g.) separating. It crystallised from acetone as brown needles with a golden reflex, m. p. 151° (lit.,[7] 153°) (Found: N, 5·4. Calc. for $C_{18}H_{21}O_4N_2Br$: N, 5·65%).

The *cobalt complex* (750 mg.) from this base (1 g.) formed green needles, m. p. 233° (Found: C, 49·8; H, 4·8; N, 6·1. $C_{36}H_{40}O_8N_4Br_2Co$ requires C, 49·5; H, 4·6; N, 6·4%), $\lambda_{max.}$ 376 and 522 mμ (log ε 3·08 and 5·11).

3,3′,4,4′,5,5′-Hexamethyldipyrromethene (VII; R = Me, R′ = H).—Ethyl 3,4,5-trimethylpyrrole-2-carboxylate [2] (3·62 g.) was dissolved in hot 90% formic acid (5 c.c.), and 48% hydrobromic acid (4 c.c.) was added. The mixture was heated on the steam-bath for 3 hr., then cooled. The product (2·55 g., 83%) was separated and washed with water, methanol, and ether. The *hydrobromide* crystallised from a hot solution in chloroform–light petroleum (b. p. 60—80°; 3 : 1) as dark red prisms with a metallic sheen, m. p. 294—295° (Found: C, 58·3; H, 6·8; N, 9·1. $C_{15}H_{21}N_2Br$ requires C, 58·4; H, 6·95; N, 8·9%), $\lambda_{max.}$ 288, 363, and 487 mμ (log ε 3·12, 3·81, and 4·99). The hydrobromide (5 g.) was dissolved in chloroform (500 c.c.) and shaken with aqueous ammonia (equal vols. of water and *d* 0·88). The chloroform layer was separated and dried, and after removal of the solvent the residue was crystallised from ethanol. The free base (4 g.) was thus obtained as red prisms, m. p. 168° (decomp.) (lit.,[13] 172°) (Found: C, 78·9; H, 8·8; N, 12·3. Calc. for $C_{15}H_{20}N_2$: C, 78·9; H, 8·75; N, 12·3%), $\lambda_{max.}$ 326 and 445 mμ

(log ε 3·52 and 4·46). The cobalt complex [6] formed green needles from chloroform–methanol. It sublimed at >330° (Found: C, 70·3; H, 7·45; N, 10·6. Calc. for $C_{30}H_{38}N_4Co$: C, 70·2; H, 7·5; N, 10·9%) and had $\lambda_{max.}$ 375, 507, 610, 710, and 765 mμ (log ε 4·21, 5·12, 3·48, 2·62, and 2·71 respectively) with an inflection at 563 mμ (log ε 3·62).

4,4-*Diethyl*-3,3′,5,5′-*tetramethyldipyrromethene* (VII; R = Et, R′ = H) *Derivatives*.—By reaction with formic and hydrobromic acid as described in the foregoing experiment, ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate was converted into 4,4′-*diethyl*-3,3′,5,5′-*tetramethyldipyrromethene hydrobromide* (88%), m. p. 230—246° (decomp.) (Found: C, 60·6; H, 7·3; N, 8·35. $C_{17}H_{25}N_2Br$ requires C, 60·55; H, 7·45; N, 8·3%), $\lambda_{max.}$ 288, 364, and 488 mμ (log ε 3·14, 3·85, and 5·00 respectively).

The hydrobromide (1 g.) was dissolved in ethanol (50 c.c.) containing aqueous ammonia (1 c.c.; *d* 0·88), and to this a saturated solution (10 c.c.) of cobalt acetate in ammonia (*d* 0·88) was added. The cobalt complex which separated crystallised as green prisms (950 mg.), m. p. 198° (lit.,[3] 198°), from ethanol (Found: C, 71·4; H, 7·8; N, 10·3. Calc. for $C_{34}H_{46}N_4Co$: C, 71·7; H, 8·14; N, 10·15%); it had $\lambda_{max.}$ 373, 509, 710, and 770 mμ (log ε 4·22, 5·08, 2·66, and 2·70) with an inflection at 615 mμ (log ε 3·47).

The Mixed Cobalt Complex of 3,3′,4,4′,5,5′-*Hexamethyl- and* 4,4′-*Diethyl*-3,3′,5,5′-*tetramethyldipyrromethene*.—A saturated solution of cobalt acetate in aqueous ammonia (20 c.c.; *d* 0·88) was added to a solution of the hexamethyldipyrromethene hydrobromide (1·45 g.) and the diethyltetramethyldipyrromethene hydrobromide (1·58 g.) in hot ethanol (50 c.c.) containing aqueous ammonia (3 c.c.; *d* 0·88). The solution was boiled gently for 5 min. and cooled. A mixture of cobalt complexes (2·4 g.) separated. Extraction (thimble) of the mixture with hot ethanol gave the cobalt complex of 4,4′-diethyl-3,3′,5,5′-tetramethyldipyrromethene (490 mg.) which, after crystallisation from chloroform–methanol, had m. p. 198°, not depressed on admixture with the product from the previous experiment (Found: C, 71·8; H, 8·2; N, 10·0%).

The residue (1·5 g.) in the thimble was further extracted with hot light petroleum (b. p. 60—80°) and yielded green crystals (540 mg.) which sublimed at 240—260°, and were crystallised from chloroform–methanol. This was the mixed *complex* (Found: C, 70·8; H, 7·85; N, 10·0, 10·1. $C_{32}H_{42}N_4Co$ requires C, 70·95; H, 7·65; N, 10·35%), $\lambda_{max.}$ 375, 508, 615, 710, and 770 mμ (log ε 4·28, 5·21, 3·54, 2·66, and 2·77 respectively) with an inflection at 570 mμ (log ε 3·70). *X*-Ray powder diagrams showed that the 3 cobalt complexes differed from each other. The residue (0·8 g.) still remaining in the thimble was extracted with chloroform–methanol (1 : 1); then concentration of the extract gave the cobalt complex of hexamethyldipyrromethene as green needles which sublimed at >330°. It was recrystallised from chloroform–methanol (Found: C, 69·9; H, 7·6; N, 10·8%).

4,4′-*Di*-(2-*ethoxycarbonylethyl*)-3,3′,5,5′-*tetramethyldipyrromethene* (VII; R = CH_2·CH_2·CO_2Et, R′ = H).—Ethyl 4-2′-ethoxycarbonylethyl-3,5-dimethylpyrrole-2-carboxylate [2] (22·5 g.) was heated on the water-bath with formic acid (21 c.c.) and concentrated hydrochloric acid (21 c.c.) until effervescence ceased (*ca.* 2 hr.). The solution was cooled (ice-bath), and the dark red crystals (13·7 g.) were separated, washed with ether, and dried. The crude product (8 g.) was dissolved in dry ethanol (75 c.c.), cooled (ice), and saturated with dry hydrogen chloride. Next day, the solution was reduced to *ca.* 50 c.c. and cooled, and the dark red crystalline *hydrochloride* was separated and dried (7 g.). After crystallisation from ethanol it had m. p. 184—186° (Found: C, 63·9; H, 7·35; N, 6·1. $C_{23}H_{33}O_4N_2Cl$ requires C, 63·2; H, 7·6; N, 6·4%), $\lambda_{max.}$ 288, 360, and 484 mμ (log ε 3·10, 3·77, and 5·07 respectively). The corresponding free base, obtained from a chloroform solution of the hydrochloride by shaking with aqueous ammonia gave a *cobalt complex* which formed green needles, m. p. 137—138°, from ethanol (Found: C, 64·0; H, 7·2; N, 6·5. $C_{46}H_{62}O_8N_4Co$ requires C, 64·4; H, 7·3; N, 6·55%), having $\lambda_{max.}$ 374, 505, 610, 705, and 760 mμ (log ε 4·2, 5·19, 3·49, 2·63, and 2·71 respectively).

Zinc Complex of 3,3′,4,4′,5,5′,α-*Heptamethyldipyrromethene* (VII; R = R′ = Me).—t-Butyl 3,4,5-trimethylpyrrole-2-carboxylate [2] (2·09 g.) was mixed with acetyl chloride (2 c.c.) and glacial acetic acid (2 c.c.) and heated under reflux for 1·5 hr. The solution was cooled, diluted with water (250 c.c.), and neutralised with aqueous ammonia. The yellow solid thus obtained was separated, washed with water, and dried. The crude dipyrromethene (2·05 g.) was unstable and could not be crystallised. It (1 g.) was dissolved in warm ethanol (25 c.c.), and a saturated solution of zinc acetate in ethanol (10 c.c.) containing one drop of aqueous ammonia was added. The mixture was warmed for 5 min. and then cooled, the zinc complex (400 mg.) separating as

orange needles with a green metallic sheen. A further quantity of the complex was obtained by adding more zinc acetate solution to the filtrate. The *zinc complex*, crystallised from chloroform–methanol, had m. p. 288° after sintering at 260° (Found: C, 70·5; H, 7·8; N, 10·0. $C_{32}H_{42}N_4Zn$ requires C, 70·1; H, 7·7; N, 10·2%), $\lambda_{max.}$ 305, 367, and 505 mμ (log ε 3·91, 3·91, and 4·06 respectively).

Zinc Complex of 4,4′-*Di*-(2-*methoxycarbonylethyl*)-3,3′,5,5′,α-*pentamethyldipyrromethene* (VII; R = CH_2·CH_2·CO_2Me, R′ = Me).—Prepared from t-butyl 4-2′-methoxycarbonylethyl-3,5-dimethylpyrrole-2-carboxylate (above; 2 g.) in a similar manner, the free dipyrromethene (1·4 g.) was again unstable and was characterised as the bright orange *zinc complex* (0·7 g.) (from chloroform–methanol), m. p. 218° (decomp.) (Found: C, 62·9; H, 7·05; N, 6·75. $C_{44}H_{58}O_8N_4Zn$ requires C, 63·15; H, 7·0; N, 6·7%), $\lambda_{max.}$ 235, 304, 365, and 501 mμ (log ε 4·32, 3·89, 3·84, and 5·05 respectively).

A similar reaction with t-butyl 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylate [1] gave only the corresponding acid, 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylic acid [14] as colourless needles, m. p. 196° [lit., 202° (decomp.)] (from ethanol) (Found: C, 57·0; H, 5·8. Calc. for $C_{10}H_{13}O_4N$: C, 56·9; H, 6·2%).

Preparation of Porphyrins

Coproporphyrin III Tetramethyl Ester (III; R = CH_2·CH_2·CO_2Me).—This was prepared from benzyl 5-acetoxymethyl-4-2′-methoxycarbonylethyl-3-methylpyrrole-2-carboxylate by hydrogenolysis to the free acid and then polymerisation by acetic acid and methanol as described earlier.[2] The product (29%) crystallised from chloroform–methanol in red-brown needles, m. p. 151—154°. This compound has been reported to exist in dimorphic forms, and m. p.s over a wide range have been quoted for each of these, *e.g.*, lower-melting, 135°,[15] 145—146°,[16] 155—157°,[17] and higher-melting, 165°,[18] 170°,[16] 181—182°.[17] The higher-melting form was not observed in this experiment. Light absorption max. were at 400, 497, 531, 566, and 620 mμ (log ε 5·19, 4·10, 3·93, 3·76, and 3·62 respectively). The cobalt complex crystallised from chloroform–methanol in red-brown needles, m. p. 194—197°, $\lambda_{max.}$ 267, 327, 413, 520, and 555 mμ (log ε 4·15, 4·24, 5·11, 4·01, and 4·28 respectively).

The cobalt complex was also obtained (52%) by carrying out the polymerisation of 5-acetoxymethyl-4-2′-methoxycarbonylethyl-3-methylpyrrole-2-carboxylic acid (from 2·0 g. of the benzyl ester) in methanol (50 c.c.) containing glacial acetic acid (10 c.c.), the solution being heated under reflux in the presence of cobaltous chloride (4 g.) for 7 hr. The deep red solution so obtained was aerated for *ca.* 12 hr., then diluted with water (100 c.c.), made alkaline with ammonia, and extracted with chloroform (6 × 50 c.c.). The mixed chloroform extracts were dried ($MgSO_4$), reduced in volume, and chromatographed on alumina as before. The solvent was removed from the eluted main band, and the residue crystallised from chloroform–methanol, forming reddish-brown needles, m. p. 195—198° alone and mixed with the previous product (Found: C, 62·4; H, 5·9; N, 7·4. $C_{40}H_{44}O_8N_4Co$ requires C, 62·6; H, 5·8; N, 7·3%). The light absorption was similar to that of the previous product.

Coproporphyrin III Tetraethyl Ester (III; R = CH_2·CH_2·CO_2Et).—t-Butyl 5-acetoxymethyl-4-2′-ethoxycarbonylethyl-3-methylpyrrole-2-carboxylate (1·5 g.) was heated in ethylene glycol (15 c.c.) under reflux for 1 hr., then cooled. Methanol (50 c.c.) was added and the solution aerated for 17 hr. Water (75 c.c.) was then added and the porphyrin extracted with chloroform until the extract showed no porphyrin absorption when viewed in the hand spectroscope. The chloroform extract was dried, concentrated to 20 c.c., and chromatographed on a column (30 × 2 cm.) of alumina. Elution of the product was followed by means of the hand spectroscope and, after removal of the solvent from the eluted porphyrin solution, the residue was crystallised from chloroform–methanol, to give coproporphyrin III tetraethyl ester as reddish-brown needles (150 mg., 19%), m. p. 146—148° (lit.,[2] 147—149°), $\lambda_{max.}$ 266, 401, 499, 534, 569, and 620 mμ (log ε 3·92, 5·28, 4·15, 3·99, 3·82, and 3·64 respectively).

Ætioporphyrin III (III; R = Et).—(i) t-Butyl 5-acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate (above; 1·0 g.) was suspended in ethylene glycol (10 c.c.) and heated under reflux

[14] Knorr, *Annalen.*, 1886, **236**, 290.
[15] Fischer and Andersag, *ibid.*, 1927, **458**, 117.
[16] Fischer, Platz, and Morgenroth, *Z. physiol. Chem.*, 1929, **182**, 284.
[17] Gray and Holt, *Biochem. J.*, 1948, **43**, 191.
[18] Fischer and Hiernis, *Z. physiol. Chem.*, 1931, **196**, 162.

for 30 min. The dark solution was cooled, diluted with methanol (40 c.c.), and aerated for 8 hr., further methanol being added as required to maintain constant volume. Water (200 c.c.) was added and the solution extracted with chloroform (3 × 20 c.c.). The chloroform extracts were washed with water, dried ($MgSO_4$), concentrated to *ca.* 5 c.c., and chromatographed on alumina (Spence type H; 30 × 1·5 cm.). The porphyrin fraction was collected (hand spectroscope), and, after removal of the solvent, the residue crystallised from chloroform–methanol as purple prisms (99 mg., 22·5%) (Found: C, 80·0; H, 7·75; N, 11·6. Calc. for $C_{32}H_{38}N_4$: C, 80·3; H, 8·0; N, 11·7%), $\lambda_{max.}$ 246, 269, 396, 497, 532, 566, 620, and 645 mμ (log ε 3·90, 3·89, 5·22, 4·13, 3·99, 3·81, 3·65, and 2·62 respectively).

(ii) The pyrrole t-butyl ester (10 g.) of the foregoing experiment was mixed with zinc acetate (2·5 g.), suspended in ethylene glycol (80 c.c.), and heated under reflux for 90 min. After cooling, the mixture was aerated for 5 hr., water (200 c.c.) was added, and the solution thoroughly extracted with chloroform. The combined chloroform extracts were dried and the solvent was removed, leaving a bright green solid (1·8 g.) which was extracted continuously from a thimble with ether (25 c.c.). The residue in the thimble was crystallised twice from chloroform–methanol, as orange-red needles (30 mg.) which showed the typical metal-porphyrin spectrum in chloroform solution. The other products from the reaction have not been identified.

(iii) t-Butyl 3-ethyl-2,4-dimethylpyrrole-5-carboxylate (2 g.) in glacial acetic acid (20 c.c.) was mixed with bromine (0·5 c.c., 1 mol.) and heated under reflux for 2 hr. On cooling, the mixture was diluted with water, neutralised with aqueous ammonia, and extracted with chloroform, and the chloroform extract was dried. After removal of most of the solvent, the concentrated solution (10 c.c.) was chromatographed on a column (30 × 2 cm.) of alumina (Spence type H), elution being followed by means of the hand spectroscope. The ætioporphyrin so obtained crystallised from chloroform–methanol as purple prisms (30 mg.), $\lambda_{max.}$ 399, 498, 534, 567, and 620 mμ (log ε 5·16, 4·09, 3·95; 4·78, and 3·63 respectively).

(iv) The previous experiment was repeated but with the addition of zinc acetate (500 mg.). The yield of ætioporphyrin, after isolation in a similar manner, was unchanged.

Ætioporphyrin I Palladium Complex.—(i) 5-Bromo-5′-bromomethyl-3,4′-diethyl-4,3′-dimethyldipyrromethene hydrobromide (above; 1·0 g.) and 3% palladium–strontium carbonate (6·0 g.) were heated in ethanol (400 c.c.) for 20 hr. After separation of the catalyst, the solvent was removed under reduced pressure. The residue was chromatographed in chloroform on alumina (Spence type H; 50 × 3 cm.), elution being followed by means of the hand spectroscope. The *product* crystallised from chloroform–methanol in purple needles (45 mg., 7·5%), m. p. 300—304° (Found: C, 65·8; H, 5·9; N, 9·85. $C_{32}H_{36}N_4Pd$ requires C, 65·9; H, 6·2; N, 9·6%), $\lambda_{max.}$ 231, 272, 335, 393, 512, and 547 mμ (log ε 4·39, 4·07, 4·18, 5·26, 4·11, and 4·58 respectively).

(ii) 5-Bromo-3,4′-diethyl-3′,4,5′-trimethyldipyrromethene hydrobromide perbromide (1·0 g.; above) and 3% palladium–strontium carbonate (6·0 g.) were heated in ethanol (400 c.c.) for 20 hr. The product (40 mg., 8%), isolated as in the foregoing experiment, was the same as the previous metal porphyrin.

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