Synthetic and Biosynthetic Studies of Porphyrins. Part 7.[1,2] The Action of Coproporphyrinogen Oxidase on Coproporphyrinogen-IV: Syntheses of Protoporphyrin-XIII, Mesoporphyrin XIII, and Related Tricarboxylic Porphyrins

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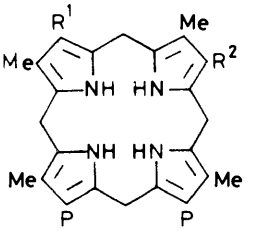
Coproporphyrinogen-IV (**2a**) is converted by an enzyme system from chicken blood into a tricarboxylic porphyrinogen (**2b**) and protoporphyrinogen-XIII (**2c**). The corresponding porphyrins were isolated as their methyl esters (**3b**) and (**3c**) and their structures were deduced by mass and n.m.r. spectrometry (including the use of shift reagents). Confirmation of these conclusions was obtained by total synthesis of the new porphyrins by the MacDonald and *ac*-biladiene routes. The vinyl groups were introduced either *via* acetoxyethyl side-chains derived from precursor pyrroles, or by reduction and dehydration of acetyl groups inserted into the porphyrins during the final stages of the syntheses. Mesoporphyrin-XIII dimethyl ester (**3m**) and the ethyl analogue (**3n**) of the vinyl tripropionate porphyrin (**3b**) were also synthesized by the MacDonald route.

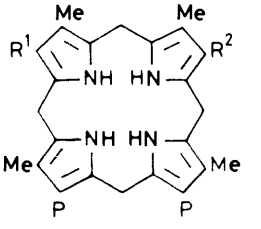
In the later stages of porphyrin biosynthesis, coproporphyrinogen-III (**1a**) is converted by coproporphyrinogen oxidase into protoporphyrinogen-IX (**1c**) by successive oxidative decarboxylation of the propionic acid groups on rings A and B into vinyl groups.[3] The protoporphyrinogen then undergoes a stereospecific dehydrogenation[4-6] to form protoporphyrin-IX, the branch point for the haem and chlorophyll pathways.

Coproporphyrinogen-IV (**2a**) has also long been known[7] to be metabolized by coproporphyrinogen oxidase, but before we began this work, the structures of the products were unknown. On the other hand coproporphyrinogen isomers I and II are inert to the enzyme.[7] It was, therefore, of considerable interest to us, in connection with our studies of the specificity of coproporphyrinogen oxidase[8] to determine the precise structure of the final product from coproporphyrinogen-IV. Our earlier work had shown that the required sequence of substituents in the neighbourhood of the propionic acid group (P) being degraded was R, Me, P, Me (where R = Me, Et, vinyl or H) and we therefore predicted that the product from coproporphyrinogen-IV would be protoporphyrinogen-XIII (**2c**). This prediction has now been vindicated as shown by the studies described in this paper.

Incubation of coproporphyrinogen-IV (**2a**) (prepared by sodium amalgam reduction of coproporphyrin-IV) with chicken red cell haemolysates afforded a dicarboxylic porphyrin as the end product; time course studies revealed that an intermediate tricarboxylic porphyrinogen was also formed and the corresponding porphyrin could be isolated from shorter incubations. Both the dicarboxylic and tricarboxylic porphyrins were converted into their methyl esters for analytical and spectroscopic studies, and the dimethyl ester of the dicarboxylic porphyrin was identified as protoporphyrin-XIII dimethyl ester (**3c**), essentially on the basis of n.m.r. spectrometry. The latter showed in particular that one of the *meso*-proton resonances moved markedly downfield on addition of europium shift reagent, whereas the other three *meso*-proton resonances were little affected; this behaviour is due to bidentate complexing[9] of the europium by neighbouring ester side-chains, and protoporphyrin-XIII dimethyl ester (**3c**) is the only one of the four possible protoporphyrin isomers which can be formed from coproporphyrinogen-IV by degradation of two of the propionic acid side-chains and which possesses two vicinal propionate groups. The quantities of tricarboxylic porphyrin isolated were essentially only sufficient for mass spectrometric and h.p.l.c.

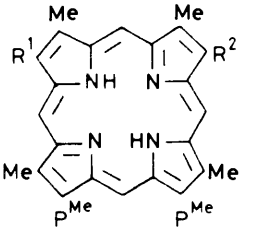


(1) a; $R^1 = R^2 = P$
b; $R^1 = CH{=}CH_2$, $R^2 = P$
c; $R^1 = R^2 = CH{=}CH_2$
d; Trimethyl ester of the porphyrin corresponding to (1b)
e; Dimethyl ester of the porphyrin corresponding to (1c)



(2) a; $R^1 = R^2 = P$
b; $R^1 = CH{=}CH_2$, $R^2 = P$
c; $R^1 = R^2 = CH{=}CH_2$

($P = CH_2CH_2CO_2H$)



(3) a; $R^1 = R^2 = P^{Me}$
b; $R^1 = CH{=}CH_2$, $R^2 = P^{Me}$
c; $R^1 = R^2 = CH{=}CH_2$
d; $R^1 = R^2 = CH_2CH_2OH$
e; $R^1 = R^2 = CH_2CH_2Cl$
f; $R^1 = H$, $R^2 = P^{Me}$
g; $R^1 = Ac$, $R^2 = P^{Me}$
h; $R^1 = CH(OH)CH_3$, $R^2 = P^{Me}$
i; $R^1 = R^2 \equiv H$
j; $R^1 \equiv R^2 = Ac$
k; $R^1 = H$, $R^2 = Ac$
l; $R^1 = R^2 = CH(OH)CH_3$
m; $R^1 = R^2 = Et$
n; $R^1 = Et$, $R^2 = P^{Me}$

($P^{Me} = CH_2CH_2CO_2Me$)

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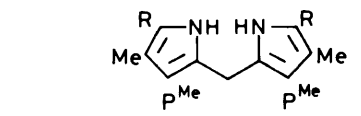
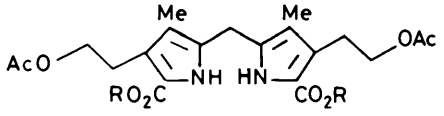
studies, but as both coproporphyrinogen-IV and protoporphyrinogen-XIII have a plane of symmetry there was little doubt of its structure (**3b**). These conclusions were borne out by total syntheses of both protoporphyrin-XIII dimethyl ester (**3c**) and the tricarboxylic porphyrin trimethyl ester (**3b**), which are described in detail below.

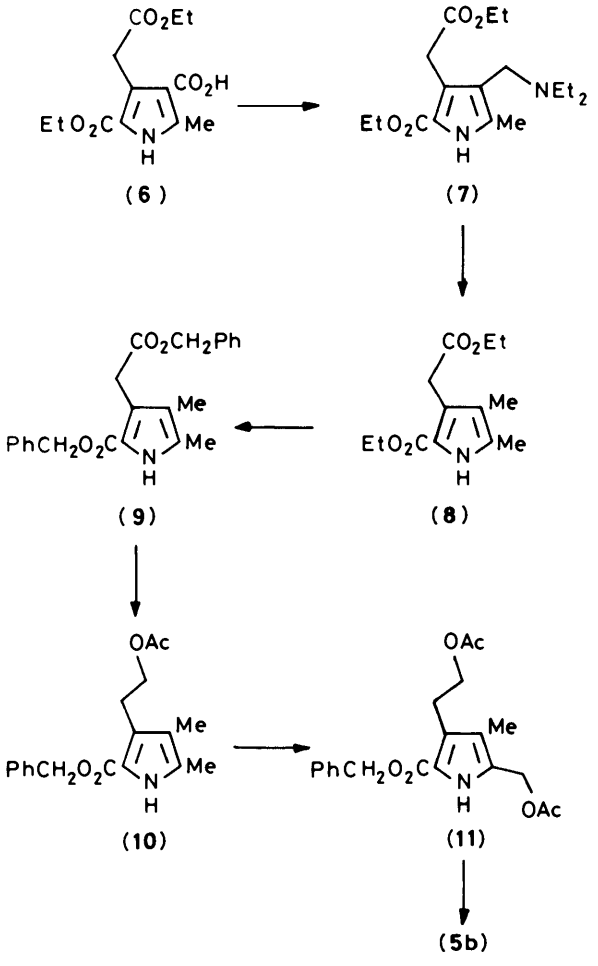
For the synthesis of both porphyrins the MacDonald route[10] was chosen initially because the readily available symmetrical diformylpyrromethane (**4a**) could be utilized in each case for construction of the C and D rings. For protoporphyrin-XIII our strategy required the bis(acetoxyethyl)pyrromethanedicarboxylic acid (**5b**), the side-chains of which, it was anticipated, could be transformed into vinyl groups at the porphyrin stage. This pyrromethane was synthesized by the route shown in Scheme 1, the initial pyrrole (**6**) being prepared by a Knorr condensation between diethyl oximinoacetone dicarboxylate and benzyl acetoacetate. Hydrogenolysis of the benzyl group followed by treatment with diethylamine and hydrochloric acid then gave the pyrrole Mannich base (**7**), which was reduced to the dimethylpyrrole (**8**) by hydrogenation over Raney nickel at high pressure and temperature. Two successive alkoxide-catalysed transesterifications, firstly with benzyl alcohol, and then a brief treatment with methanol gave the monomethyl monobenzyl ester (**9**). The latter was reduced with diborane and the product acetylated to give the acetoxyethylpyrrole (**10**). Treatment with lead tetra-acetate afforded the acetoxymethyl derivative (**11**) which underwent self-condensation to the pyrromethane (**5a**) when heated in acetic acid containing a trace of toluene-*p*-sulphonic acid. Hydrogenolysis of the benzyl groups then gave the desired bis(acetoxyethyl)pyrromethanedicarboxylic acid (**5b**), which was condensed with the diformylpyrromethane (**4a**) in methanol containing toluene-*p*-sulphonic acid as catalyst. Unfortunately, however, the desired bishydroxyethylporphyrin (**3d**) was only formed in very low yield (estimated at 3% spectroscopically); this was attributed to the probable formation of the unreactive bis-lactone (**12**) by acid-catalysed cyclization of the side-chains



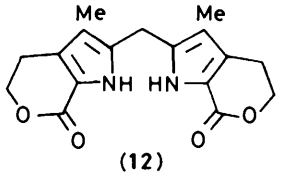
(4) a; R = CHO
b; R = CO_2H



(5) a; R = CH_2Ph
b; R = H



Scheme 1.



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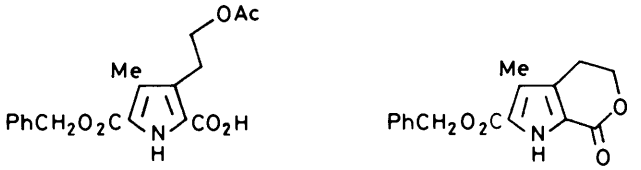
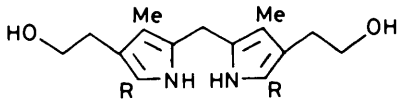


(13) (14)

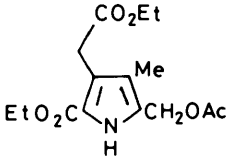
onto the terminal carboxyl groups. [A similar monopyrrolic lactone (**14**) had been observed[11] to result when the acetoxyethylpyrrole carboxylic acid (**13**) was heated in chloroform containing a trace of toluene-*p*-sulphonic acid.]

To exclude the possibility of lactone formation we therefore sought to prepare the di-α-free bis(hydroxyethyl)pyrromethane (**15b**). This could, in theory, have been prepared by hydrolysis and decarboxylation of the pyrromethane dibenzyl ester (**5a**), but a shorter route was developed from the pyrrole ester (**8**). Treatment of the latter with lead tetra-acetate, and acid-catalysed condensation of the intermediate acetoxymethylpyrrole (**16**), gave the bis(methoxycarbonylmethyl)pyrromethane (**17**). Diborane reduction to the bis(hydroxyethyl)pyrromethane (**15a**) followed by alkaline hydrolysis and decarboxylation in a sealed tube at 170 °C then afforded the desired α-free pyrromethane (**15b**). Acid-catalysed condensation of the latter with the diformylpyrromethane (**4a**) gave the bis(hydroxyethyl)porphyrin (**3d**) in 29% yield. The latter was converted by phosphoryl chloride in dimethylformamide into the bis(chloroethyl)porphyrin (**3e**), the zinc complex of which on treatment with potassium t-butoxide in t-butyl alcohol afforded protoporphyrin-XIII dimethyl ester (**3c**) in excellent yield. This product proved to be identical chromatographically and spectroscopically (n.m.r. spectral



(15) a; R = CO_2Et

b; R = H



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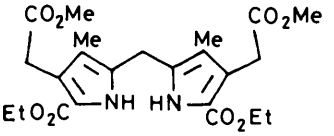

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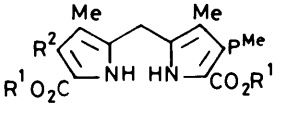
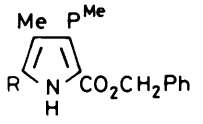


(18) a; R^1 = CH_2Ph, R^2 = H

b; R^1 = R^2 = H

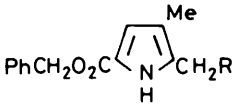
c; R^1 = H, R^2 = P^{Me}



(19) a; R = Me

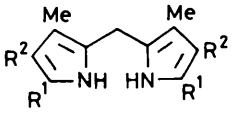
b; R = CO_2H

c; R = H



(20) a; R = H

b; R = OAc



(21) R^2 = H (22) R^2 = COMe

a; R^1 = CO_2CH_2Ph

b; R^1 = CO_2H

c; R^1 = CHO

titrations with europium shift reagent) and by mixed m.p. with the ester of the product derived enzymically from coproporphyrinogen-IV (**2a**).

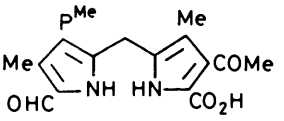
For the synthesis of the tricarboxylic porphyrin (**3b**) we adopted a slightly different approach to that used for protoporphyrin-XIII involving introduction of the vinyl substituent at a late stage into the porphyrin (**3f**). Thus for the A and B rings of the latter we required the pyrromethane dibenzyl ester (**18a**). The pyrrole propionic ester (**19a**) was converted into the carboxylic acid (**19b**) by trichlorination of the α-methyl group with sulphuryl chloride, followed by hydrolysis. Iodinative decarboxylation, followed by hydrogenolysis of the intermediate iodopyrrole over platinum then afforded the α-free pyrrole (**19c**). Acid-catalysed condensation of the latter with the acetoxymethylpyrrole (**20b**) [prepared by lead tetra-acetate treatment of the corresponding α-methylpyrrole (**20a**)] then gave the desired pyrromethane (**18a**) which was separated chromatographically from a small amount of the symmetrical pyrromethane (**21a**) formed by self-condensation of the acetoxymethylpyrrole (**20b**).

Hydrogenolysis of the dibenzyl ester (**18a**) over palladium-charcoal in tetrahydrofuran then afforded the corresponding dicarboxylic acid (**18b**), which was condensed directly with the diformylpyrromethane (**4a**) in methylene chloride–methanol containing toluene-*p*-sulphonic acid to give the desired porphyrin (**3f**). The iron complex of the latter was treated with acetic anhydride in presence of tin(IV) chloride, and after removal of the iron gave the acetyl porphyrin (**3g**); the reaction was monitored by h.p.l.c. and was shown to be complete within 5 min. The acetyl porphyrin was reduced with sodium borohydride to give the hydroxyethylporphyrin (**3h**) the progress of the reactions being monitored spectroscopically by the Soret band which shifted from 410 to 400 nm; the yield was *ca.* 60% owing to some over-reduction (possibly of the propionate ester groups), and traces of several other porphyrins were observed on t.l.c. or h.p.l.c. Dehydration of the hydroxyethyl group was effected by heating the compound with toluene-*p*-sulphonic acid in boiling *o*-dichlorobenzene, and the desired monovinylporphyrin triethyl ester (**3b**) was obtained in good yield. It proved to be identical with the triester of the product obtained from incubations of coproporphyrinogen-IV with chicken red cell haemolysates as shown by its chromatographic properties (t.l.c. and h.p.l.c.) and mass spectrum. Insufficient of the enzymically derived material was available for crystallization and mixed m.p. comparisons, but careful h.p.l.c. studies[12] distinguished it and the synthetic material from harderoporphyrin trimethylester (**1d**) the type III tricarboxylic porphyrin derived from the normal intermediate[3] between coproporphyrinogen-III (**1a**) and protoporphyrinogen-IX (**1c**). Protoporphyrin-XIII dimethyl ester (**2c**) could also be distinguished from protoporphyrin-IX (**1f**) dimethyl ester by h.p.l.c.[12]

The possiblity of synthesizing protoporphyrin-XIII by a similar route to the above was also investigated. The acetoxymethylpyrrole (**20b**) self-condensed in acetic acid to give the pyrromethane (**21a**) and the latter was hydrogenolysed to the dicarboxylic acid (**21b**). Condensation of the latter with diformylpyrromethane (**4a**) in presence of toluene-*p*-sulphonic acid, however, afforded deuteroporphyrin-XIII dimethyl ester (**3c**) but in only 3.5% yield. The yield was raised to 8% by use of hydriodic acid as in the original MacDonald method.[10] The low yields were attributed to the lower reactivity of the pyrromethane (**21b**) owing to the two β-free positions, whereas in most pyrromethanes previously utilized all the β-positions were substituted with alkyl or alkoxycarbonylalkyl groups. (β-Alkyl groups would be expected to activate the neighbouring α-positions towards electrophilic attack in the same way as alkyl groups in a benzene ring, and indeed our experience of the behaviour of pyrroles clearly indicates that as the number of alkyl groups in the ring increases, so does the reactivity both towards electrophiles, and towards atmospheric oxidation.)

The diacetylpyrromethane (**22a**) was also synthesized in good yield by direct acetylation of the diester (**21a**), and hydrogenolysed to the corresponding di-acid (**22b**). However, condensation of the latter with the diformylpyrromethane (**4a**) afforded only a trace of the desired diacetylporphyrin (**3j**). This was presumably due to the low reactivity of the di-acid (**22b**) engendered by the β-acetyl groups, although we had expected some porphyrin to be formed following an earlier report[13] that the acetyl pyrromethane (**23**) underwent self condensation to give a diacetyl deuteroporphyrin in 12% yield. An alternative approach to the porphyrin (**3i**) *via* the diformylpyrromethane (**21c**) was also investigated but unfortunately attempts to decarboxylate and formylate the di-acid (**21b**) using trifluoroacetic acid and triethylorthoformate[14] gave only traces of the required intermediate.

The biladiene route[15] to protoporphyrin-XIII was also investigated. Condensation of the pyrromethane di-acid (**21b**) with 2 mol equiv. of the formylpyrrole (**24**) gave a non-crystalline product with a pyrromethene-type visible spectrum, but attempts to cyclize the latter with copper(II) acetate in pyridine gave only traces of porphyrin. On the other hand Russian workers[16] have reported that reactions of the same formylpyrrole (**24**) with the pyrromethane di-acid (**25**) gave a biladiene (**26**), which was cyclized to deuteroporphyrin-III dimethyl ester (**27**) in 22% yield. It appears that vacant β-



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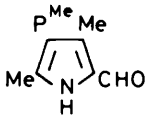

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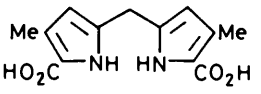

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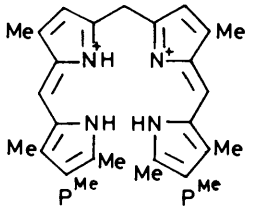

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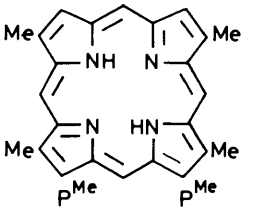

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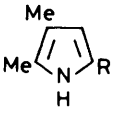
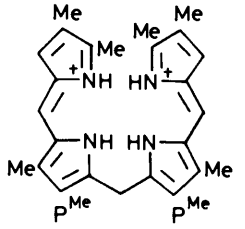


(28) a; R = CO_2H

b; R = CHO



(29)

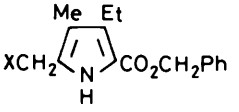
positions have a deleterious effect in both the biladiene and MacDonald syntheses, if adjacent to the α-position where it is desired to effect methene formation; however, high yields have been obtained in analogous couplings of formylpyrroles and pyrroles with unsubstituted β-positions.[17]

An alternative approach was, therefore, investigated involving condensation of the pyrromethane dicarboxylic acid (**4b**) with 2 mol equiv. of the formylpyrrole (**28c**) [the latter having been prepared by hydrogenolysis of the benzyl ester (**28a**) followed by decarboxylation and formylation of the intermediate acid (**28b**)]. The resulting biladiene (**29**) (obtained in 28% yield) was cyclized in the presence of copper(II) acetate and gave the copper complex of deuteroporphyrin-XIII dimethyl ester (**3i**) in 29% yield. Acetylation of the copper(II) or the corresponding iron(III) complex in the presence of tin(IV) chloride afforded a mixture of the mono- and di-acetylporphyrins (**3k**) and (**3j**) respectively. Borohydride reduction of the diacetyl derivative followed by toluene-*p*-sulphonic acid-catalysed dehydration then gave protoporphyrin-XIII dimethyl ester (**3c**) identical in all respects with material prepared *via* the MacDonald route, and with the 'natural' product derived from coproporphyrinogen-IV (**2a**).

Protoporphyrin-XIII and the related tricarboxylic porphyrin have also been characterized by the Cambridge[18] and Buenos Aires[19] groups in relation to their studies of enzymic incorporations of amino(methyl)pyrromethane into uroporphyrinogens.[20,21] Whilst our work was in progress Frydman[19] also described the synthesis of the methyl esters (**3c**) and (**3b**) of protoporphyrin-XIII and the tricarboxylic porphyrin and a further synthesis of protoporphyrin-XIII dimethyl ester has been reported by Clezy.[22] The melting point of our sample of the latter was 211—213 °C (slightly higher than that given by Frydman,[19] 208—210 °C) but lower than Clezy's, m.p. 228—229 °C. However, the n.m.r. spectra of our material and Clezy's were identical, and we are grateful to Professor Clezy for sending us a copy of the original spectrum. We conclude that this may be another example of the well-known polymorphism of porphyrins.

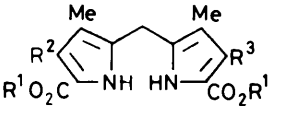
During the course of our work we also took the opportunity of synthesizing mesoporphyrin-XIII dimethyl ester (**3m**) and a related monoethylporphyrin tripropionic ester (**3n**) for further studies of the specificity of coproporphyrinogen oxidase. These two porphyrins are of course the ethyl analogues of protoporphyrin-XIII dimethyl ester (**3c**) and of the related monovinylporphyrin (**3b**).

Treatment of the haemopyrrole benzyl ester (**30a**) with lead tetra-acetate afforded the acetoxymethylpyrrole (**30b**) which underwent self-condensation in methanolic hydrochloric acid to afford the symmetrical pyrromethane (**31a**). Hydrogenolysis of the latter over palladium charcoal gave the corresponding di-acid (**32a**) which was condensed with the diformylpyrromethane (**4a**) in methanol containing toluene-*p*-sulphonic acid. After aeration and re-esterification the desired mesoporphyrin-XIII dimethyl ester (**3m**) was obtained in 25% yield. The acetoxymethylpyrrole (**30b**) was also coupled with the α-free pyrrole benzyl ester (**19c**) in methanol in the presence of a trace of toluene-*p*-sulphonic acid, and gave the pyrromethane (**31c**) in good yield. The latter was hydrogenolysed to the di-acid and



(30) a; X = H

b; X = OAc



(31) R^1 = CH_2Ph (32) R^1 = H

a; R^2 = R^3 = Et

b; R^2 = Et, R^3 = P^{Me}

coupled with diformylpyrromethane (**4a**) in the same way as in the mesoporphyrin-XIII synthesis to afford the desired tripropionate porphyrin (**32**). As in earlier MacDonald syntheses a small amount of coproporphyrin-11 tetramethyl ester was formed as a by-product, which presumably arose by self-condensation of the diformylpyrromethane (**33**).

Experimental

M.p.s were determined on a hot-stage apparatus and are uncorrected. Column chromatography was carried out on Woelm or Merck alumina (Grade III). T.l.c. monitoring was performed on silica plates (Merck GF 254 silica). H.p.l.c. separations of pyrromethanes and porphyrins were carried out with a Waters Associates 6000 pump with a Cecil variable wavelength detector; using 100 cm × 3 mm columns of Corasil II initially, but later shorter columns of μ-Porasil, or μ-Partisil. Visible absorption spectra were measured on Unicam SP800 and Carey 17 spectrophotometers, and ^1H n.m.r. spectra were determined on Perkin-Elmer R14 (100 MHz) and 32 (90 MHz) instruments. Mass spectra, electron impact (70 eV, 50 μA, source *ca.* 200 °C) and field desorption (wire currents 10—20 μA) were measured with a Varian CH5 double-focussing instrument with a Spectrosytems 100 data system.

Pyrroles

Ethyl 4-Diethylaminomethyl-3-ethoxycarbonylmethyl-5-methylpyrrole-2-carboxylate (**7**).—5-Ethoxycarbonyl-4-ethoxy-

carbonylmethyl-2-methylpyrrole-3-carboxylic acid[23] (20 g), diethylamine (16 g), 40% formaldehyde solution (10 ml) and ethanol (30 ml) were heated under reflux for 4 h. The reaction mixture was cooled, acidified with dilute hydrochloric acid and unchanged starting material recovered by filtration. The filtrate was made alkaline with aqueous sodium hydroxide whereupon the *pyrrole* (15.1 g, 65%) crystallized out and was filtered off; after being dried *in vacuo* it had m.p. 53 °C (Found: C, 63.1; H, 8.5; N, 8.5. $C_{17}H_{28}N_2O_4$ requires 62.9; H, 8.7; N, 8.6%); τ($CDCl_3$) 0.8 (1 H, br, NH), 5.62—5.97 (4 H, m, 2 × OCH_2CH_3), 6.05 (2 H, s, CH_2CO_2Et), 6.70 (2 H, s, CH_2N), 7.60 (4 H, q, 2 × NCH_2CH_3), 7.77 (3 H, s, 5-CH_3), 8.69 (3 H, t, $CO_2CH_2CH_3$), 8.76 (3 H, t, $CO_2CH_2CH_3$), and 9.02 (6 H, 2 × NCH_2CH_3).

Ethyl 3-Ethoxycarbonylmethyl-4,5-dimethylpyrrole-2-carboxylate (**8**).—Ethyl 4-dimethylaminomethyl-3-ethoxycarbonylmethyl-5-methylpyrrole-2-carboxylate (13 g) and Raney nickel (*ca.* 3 g) in ethanol (150 ml) were stirred with hydrogen (100 atmospheres) at 130 °C overnight in an autoclave. The cooled mixture was filtered and the residue washed with chloroform. The combined filtrates were evaporated to yield the *pyrrole* (8.1 g, 81%) which crystallized from aqueous ethanol as needles, m.p. 106 °C (Found: C, 61.8; H, 7.9; N, 5.6. $C_{13}H_{18}NO_4$ requires C, 61.6; H, 7.6; N, 5.5%); τ($CDCl_3$) 0.9, (1 H, br, NH), 5.62—5.95 (4 H, m, 2 × OCH_2CH_3), 6.20 (2 H, s, CH_2CO_2Et), 7.81 (3 H, s, 5-CH_3), 8.08 (3 H, s, 4-CH_3), 8.68 (3 H, t, $CO_2CH_2CH_3$), and 8.76 (3 H, t, $CO_2CH_2CH_3$).

Benzyl 3-Benzyloxycarbonylmethyl-4,5-dimethylpyrrole-2-carboxylate (**9**).—The diethyl ester (**7**) (4.5 g) in dry benzyl alcohol (25 ml) containing sodium (0.1 g) was heated on a water-bath under a partial vacuum of 14 mmHg for 3 h, after which the remaining benzyl alcohol was removed by distillation (60 °C at 1 mmHg). The residue was dissolved in ethanol and the solution saturated with carbon dioxide and diluted with water to provide the *dibenzyl ester* (5.2 g, 80%) as prisms, m.p. 86—87 °C (Found: C, 72.9; H, 5.9; N, 3.7. $C_{23}H_{23}NO_4$ requires C, 73.2; H, 6.1; N, 3.7%); τ ($CDCl_3$) 0.95 (1 H, br, NH), 2.70 (10 H, br s, 2 × Ph), 4.79 (2 H, s, CH_2Ph), 4.94 (2 H, s, CH_2Ph), 6.13 (2 H, s, CH_2CO_2), 7.86 (3 H, s, 5-CH_3), and 8.10 (3 H, s, 4-CH_3).

Benzyl 3-(2-Acetoxyethyl)-4,5-dimethylpyrrole-2-carboxylate (**10**).—Diborane generated by the addition of boron trifluoride–diethyl ether (30 ml) to sodium borohydride (6 g) in diglyme (20 ml) was passed, in a slow stream of nitrogen, through a solution of benzyl 3-benzyloxycarbonylmethyl-4,5-dimethylpyrrole-2-carboxylate (4.5 g) in tetrahydrofuran (25 ml) during 4 h. Methanol was carefully added to quench the reaction mixture, which was then evaporated to dryness. Crystallization of the residue from aqueous ethanol gave the *2'-hydroxyethylpyrrole* (3.1 g, 95%) as prisms, m.p. 74—75 °C (Found: C, 70.1; H, 6.9; N, 5.5 $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%); τ($CDCl_3$) 1.10 (1 H, NH), 2.63 (5 H, C_6H_5), 4.74 (2 H, CH_2Ph), 6.26 (2 H, t, CH_2OH), 7.00 (2 H, t, CH_2CH_2O), 7.84 (3 H, s, 5-CH_3), and 8.06 (3 H, s, 4-CH_3).

The foregoing hydroxyethylpyrrole (3 g) in pyridine (15 ml) was treated with acetic anhydride (3 ml) and stirred at 20 °C for 2 h. Dilution with ice-cold water precipitated the *acetoxyethylpyrrole* which crystallized from light petroleum (b.p. 60—80 °C) as needles (3.3 g, 92%), m.p. 79—80 °C (Found: C, 68.5; H, 6.6; N, 4.6. $C_{18}H_{21}NO_4$ requires C, 68.6; H, 6.7; N, 4.4%); τ($CDCl_3$) 1.03 (1 H, br, NH), 2.65 (5 H, s, Ph), 4.71 (2 H, s, CH_2Ph), 5.84 (2 H, t, CH_2OAc), 6.95 (2 H, t, CH_2CH_2O), 7.83 (3 H, s, 5-CH_3), 8.02 (3 H, s, OAc), and 8.05 (3 H, s, 4-CH_3).

Benzyl 5-Acetoxymethyl-4-methylpyrrole-2-carboxylate (**20b**).—Lead tetra-acetate (3.95 g) was added slowly to a stirred solution of benzyl 4,5-dimethylpyrrole-2-carboxylate (1.86 g) in glacial acetic acid (80 ml). The solution was stirred for a further 3 h and then poured into ice–water (600 ml). The precipitate was filtered off, washed with distilled water until neutral, dried *in vacuo*, and crystallized from methylene chloride–light petroleum (b.p. 40—60 °C) to give benzyl 5-acetoxymethyl-4-methylpyrrole-2-carboxylate (2.04 g, 87%) as 'fluffy' needles, m.p. 114—115 °C (lit.,[24] 115 °C) (Found: C, 67.0; H, 6.0; N, 5.1. Calc. for $C_{16}H_{17}NO_4$: C, 66.9; H, 5.2; N, 4.9%); $\lambda_{max.}$(EtOH) 218, 240, and 278 nm; τ($CDCl_3$) 0.70 (1 H, br, NH), 2.67 (5 H, s, Ph), 3.30 (1 H, s, 3-H), 4.75 (2 H, s, CH_2Ph), 4.99 (2 H, s, CH_2OAc), 7.93 (3 H, s, 4-CH_3) and 7.98 (3 H, s, OAc).

Benzyl 3-(2-Acetoxyethyl)-5-acetoxymethyl-4-methylpyrrole-2-carboxylate (**11**).—This was prepared in the same manner as (**20b**) from the corresponding 5-methylpyrrole (**10**) in 84% yield, and crystallized from dichloromethane–light petroleum as needles, m.p. 133—134 °C (Found: C, 64.5; H, 6.2; N, 3.9. $C_{20}H_{23}NO_6$ requires C, 64.3; H, 6.2; N, 3.75%); τ($CDCl_3$) 0.8 (1 H, br, NH), 2.62 (5 H, s, Ph), 4.70 (2 H, s, OCH_2Ph), 4.98 (2 H, s, 2-CH_2OAc), 5.85 (2 H, t, CH_2CH_2OAc), 6.95 (2 H, t, CH_2CH_2OAc), 7.95 (6 H, s, 2 × CH_3CO), and 8.03 (3 H, s, 4-CH_3).

Ethyl-5-acetoxymethyl-3-ethoxycarbonylmethyl-4-methylpyrrole-2-carboxylate (**16**).—Ethyl 4,5-dimethyl-3-ethoxycarbonylmethylpyrrole-2-carboxylate (7.5 g) was treated with lead tetra-acetate (14.5 g) following the procedure described for the pyrrole (**11**), to afford the *acetoxymethylpyrrole* (8.7 g, 94%), m.p. 136—137 °C after recrystallization from (methylene chloride–light petroleum) (Found: C, 57.9; H, 6.3; N, 4.3. $C_{15}H_{21}NO_6$ requires C, 57.9; H, 6.8; N, 4.5%); τ($CDCl_3$) 0.7 (1 H, br, NH), 4.97 (2 H, s, CH_2OAc), 5.87 (4 H, m, 2 × OCH_2CH_3), 6.20 (2 H, s, CH_2CO_2Et), 7.97 (3 H, s, OAc), 8.00 (3 H, s, 4-CH_3), 8.70 (3 H, t, $CO_2CH_2CH_3$), and 8.77 (3 H, t, $CO_2CH_2CH_3$).

2-Formyl-4-(2-methoxycarbonylethyl)-3,5-dimethylpyrrole (**24**).—Benzyl 4-(2-methoxycarbonylethyl)-3,5-dimethylpyrrole-2-carboxylate (5.0 g) was dissolved in acetone (100 ml) containing 10% Pd–C (100 mg) and hydrogenated at 1 atm until uptake of hydrogen (380 ml) was complete, the solution was filtered, the residue washed with hot acetone and the combined solutions evaporated to dryness. The corresponding pyrrole acid (3.7 g, 110%) was obtained as a solid which turned pink on standing. τ[$CDCl_3$ + 3 drops $(CD_3)_2SO$] 0.43 (1 H, br, NH), 1.75 (1 H, br, CO_2H), 6.38 (3 H, s, CO_2CH_3), 7.32 (2 H, t, CH_2CH_2CO), 7.62 (2 H, t, CH_2CH_2CO), 7.75 (3 H, s, CH_3), 7.83 (3 H, s, CH_3).

This acid was immediately dissolved in trifluoroacetic acid (20 ml) and stirred at 40 °C for 10 min under nitrogen. Chloroform (100 ml) was added to the orange solution and this was washed with distilled water. The aqueous layer was back extracted with chloroform (2 × 100 ml) and the combined organic fractions washed with aqueous sodium carbonate (10%; 200 ml) and distilled water (10 ml) and then dried ($MgSO_4$). After filtration, the chloroform was removed under reduced pressure to afford 3-(2-methoxycarbonylethyl)-2,4-dimethylpyrrole as a yellow oil (2.8 g, 97%); τ($CDCl_3$) 2.5 (1 H, v br, NH), 3.64 (1 H, s, 5-H), 6.47 (3 H, s, CO_2CH_3), 7.30 (2 H, t, CH_2CH_2CO), 7.60 (2 H, t CH_2CH_2CO), 7.87 (3 H, s, CH_3), and 8.02 (3 H, s, CH_3). The foregoing pyrrole (2.8 g) was dissolved in trifluoroacetic acid (120 ml) and the pale yellow solution was cooled to 0 °C in a salt–ice bath before triethyl orthoformate (freshly distilled; 3 ml) was added dropwise over 10—15 min. The dark solution was stirred for a further 5 min, poured into ice–water (150 ml), and the resulting precipitate extracted with chloroform. The combined solutions were washed with aqueous ammonia (10%; 50 ml) and distilled water (50 ml), dried

($MgSO_4$), filtered, and evaporated to dryness. Crystallization from chloroform–light petroleum (b.p. 60—80 °C) afforded the formylpyrrole (2.7 g), 83%) as a pale yellow solid, m.p. 123—125 °C (lit.,[13] m.p. 128—129 °C); τ($CDCl_3$) 0.1 (1 H, NH), 0.53 (1 H, s, CHO), 6.36 (3 H, s, CO_2CH_3), 7.30 2 H, t, CH_2CH_2CO), 7.58 (2 H, t, CH_2CH_2CO), 7.76 (3 H, s, CH_3), and 8.03 (3 H, s, CH_3).

Subsequently it was found more convenient to treat the preceding pyrrolecarboxylic acid directly with trifluoroacetic acid and triethyl orthoformate without isolation of the α-free pyrrole; the solution of the pyrrole acid was stirred for 10 min at 40 °C and then cooled to 0 °C and treated with triethyl orthoformate to give the formylpyrrole in equally good yield.

5-Benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylic Acid (**19b**) (*with P. J. Crook*).—Benzyl 4,5-dimethyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (15 g) (**19a**) was dissolved in sodium dried ether (280 ml) and to the stirred solution was added freshly distilled sulphuryl chloride (12 ml) dropwise over a period of 15 min at 20 °C. The solution was stirred for a further 72 h at 20 °C and then evaporated to dryness. The resulting brown oil was dissolved in dioxane (50 ml) and a solution of sodium acetate trihydrate (60 g) in water (80 ml) was added. The mixture was heated with stirring at 70 °C for 1.5 h and then cooled. Ether (50 ml) was added and a white crystalline solid separated. Aqueous sodium carbonate (10%; 250 ml) was then added and the mixture was agitated until all the solid had dissolved. The aqueous layer was separated, washed with ether (100 ml), and then saturated with sulphur dioxide. The white crystalline precipitate was collected, washed well with hot water, and dried overnight *in vacuo*. The product was recrystallized from chloroform–light petroleum to give the *pyrrolecarboxylic acid* (12.63 g, 77%) as crystals, m.p. 205—206 °C (decomp.) (Found: C, 62.4; H, 5.6; N, 4.0. $C_{18}H_{19}NO_6$ requires C, 62.6; H, 5.6; N, 4.0%).

Benzyl 5-Iodo-3-(2-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (*with P. J. Crook*).—A suspension of the foregoing pyrrole-2-carboxylic acid (10.25 g) in methanol (65 ml) was treated with a solution of sodium hydrogen carbonate (7.75 g) in water (75 ml) and the mixture was heated until a colourless solution was obtained. The solution was then heated at 65 °C and a solution of iodine (7.75 g) and potassium iodide (15 g) in water (125 ml) was added dropwise, with stirring, over a period of 30 min. A white crystalline solid separated from the reaction mixture. The last traces of iodine disappeared after stirring for a further 30 min at 65 °C. The mixture was left overnight at 0 °C and the product was collected, washed well with hot water, and dried *in vacuo*. The *iodopyrrole* (12.44 g, 98%) was obtained as long needles, m.p. 119—120 °C, from dichloromethane–light petroleum (Found: C, 47.8; H, 4.3; N, 3.1. $C_{17}H_{18}INO_4$ requires C, 47.9; H, 4.2; N, 3.3%); τ($CDCl_3$) 0.61 (1 H, br s, NH), 2.64 (5 H, s, Ph), 4.67 (2 H, s, CH_2Ph), 6.37 (3 H, s, OCH_3), 6.92 and 7.54 (4 H, 2 t, CH_2CH_2CO), and 8.02 (3 H, s, CH_3).

Benzyl 3-(2-Methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (**19c**) (*with P. J. Crook*).—The foregoing iodopyrrole (9.1 g) was added to a solution of anhydrous sodium acetate (3.13 g) in methanol (125 ml). Adams platinum oxide catalyst (30 mg) was added and the suspension was shaken in hydrogen at 760 mmHg/20 °C for 2 h (uptake of hydrogen, 537 ml). As the reaction proceeded the pyrrole went into solution. The catalyst was filtered off on Celite and the filtrate was evaporated. The residue was partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer was separated, washed with 10% aqueous sodium carbonate (100 ml), and water (100 ml), dried ($MgSO_4$), and evaporated to give a colourless oil. This crystallized from benzene–light petroleum to give the *pyrrole* (6.13 g, 96%) as long thin colourless needles, m.p. 57—58 °C (Found: C, 67.6; H, 6.2; N, 4.8. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7%); τ($CDCl_3$) 0.98 (1 H, br s, NH), 2.63 (5 H, s, Ph), 3.36 (1 H, d, pyrrole-H), 4.71 (2 H, s, CH_2Ph), 6.39 (3 H, s, OCH_3), 6.94 and 7.51 (4 H, 2 t, CH_2CH_2CO), and 7.98 (3 H, s, CH_3).

Pyrromethanes

Diethyl 4,4′-Bismethoxycarbonylmethyl-3,3′-dimethylpyrromethane-5,5-dicarboxylate (**17**).—Ethyl 5-acetoxymethyl-3-ethoxycarbonylmethyl-4-methylpyrrole-2-carboxylate (**18**) (5.0 g) was dissolved in methanol (50 ml) containing concentrated hydrochloric acid (4.0 ml) and heated under reflux for 2 h. As the mixture cooled the *pyrromethane* (2.6 g, 70%) crystallized out and was then filtered off and dried *in vacuo*. It had m.p. 121—122 °C unchanged on recrystallization from methylene chloride–light petroleum (Found: C, 59.5; H, 6.3; N, 5.95. $C_{23}H_{30}N_2O_8$ requires C, 59.7; H, 6.5; N, 6.1%); τ($CDCl_3$) 0.38 (2 H, br, 2 × NH), 5.75 (4 H, q, 2 × OCH_2CH_3), 6.14 (2 H, s, $=CCH_2C=$), 6.21 (4 H, s, 2 × CH_2CO_2Me), 6.32 (6 H, s, 2 × OCH_3), 8.07 (6 H, s, 2 × CH_3), and 8.74 (6 H, t, 2 × OCH_2CH_3).

Diethyl 4,4′-Bis(2-hydroxyethyl)-3,3′-dimethylpyrromethane-5,5′-dicarboxylate (**15a**).—Diborane generated externally from sodium borohydride (3.0 g) in diglyme (25 ml) and boron trifluoride–diethyl ether (16 ml), was passed in a slow stream of nitrogen through a solution of diethyl 4,4′-dimethoxycarbonylmethyl-3,3′-dimethylpyrromethane-5,5′-dicarboxylate (**17**) (2.0 g) in tetrahydrofuran (25 ml) during 4 h. Methanol was then cautiously added until the effervescence ceased. The solvents were evaporated under reduced pressure and the required *pyrromethane* (1.6 g, 91%) crystallized from aqueous ethanol as prisms, m.p. 168—170 °C (Found: C, 62.1; H, 7.2; N, 6.8. $C_{21}H_{30}N_2O_6$ requires C, 62.05; H, 7.4; N, 6.9%); τ($CDCl_3$) 1.1 (2 H, br, 2 × NH), 5.72 (4 H, q, 2 × OCH_2CH_3), 6.14 (2 H, s, $=CCH_2C=$), 6.24 (4 H, t, 2 × CH_2OH), 7.00 (4 H, t, 2 × CH_2CH_2OH), 8.05 (6 H, s, 2 × CH_3), and 8.72 (6 H, t, 2 × OCH_2CH_3).

4,4′-Bis(2-hydroxyethyl)-3,3′-dimethylpyrromethane (**15b**).—The foregoing pyrromethane (800 mg) was heated under pressure in a sealed glass tube with 3% sodium hydroxide (5 ml) and 3 drops of hydrazine for 3 h (air-bath temperature 170—172 °C). The cooled reaction mixture was then extracted with chloroform (3 × 50 ml) and the combined extracts were dried (Na_2SO_4) and evaporated to leave the desired *pyrromethane* (370 mg, 72%) as an amber oil which could not be induced to crystallize and was used directly for porphyrin synthesis; τ($CDCl_3$) 2.12 (2 H, br, 2 × NH) 3.65 (2 H, s, 5- and 5′-H), 6.28 (2 H, s, $=CCH_2C=$), 6.35 (4 H, t, 2 × CH_2OH), 7.40 (4 H, s, 2 × CH_2CH_2OH), and 8.08 (6 H, s, 2 × CH_3).

Dibenzyl 4,4′-Bis(2-acetoxyethyl)-3,3′-dimethylpyrromethane-5,5′-dicarboxylate (**5a**).—A solution of benzyl 3-(2-acetoxyethyl)-5-acetoxymethyl-4-methylpyrrole-2-carboxylate (**11**) (1.00 g) in acetic acid (8 ml) containing toluene-*p*-sulphonic acid hydrate (30 mg) was stirred and heated at 40—45 °C for 6 h (under N_2). Methylene chloride (50 ml) was then added and the solution was washed with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on alumina, eluting first with toluene–ethyl acetate (1:1, v:v). The desired product was eluted in methylene chloride and, since evaporation to dryness it could not be induced to crystallize, was collected as a thick yellowish oil (0.71g, 86%); τ($CDCl_3$) 0.6 (2 H, br, 2 × NH), 2.71 (10 H, s, 2 × Ph), 4.77 (4 H, s, 2 × OCH_2Ph),

5.87 (4 H, t, 2 × CH_2OAc), 6.20 (2 H, s, $=CCH_2C=$), 6.98 (4 H, t, 2 × CH_2CH_2O), 8.03 (6 H, s, 2 × CH_3), and 8.05 (6 H, s, 2 × CH_3); *m/z* (f.d.) 614 (M^+, 100%).

4,4′-Bis(2-acetoxyethyl)-3,3′-dimethylpyrromethane-5,5′-dicarboxylic Acid (**5b**).—Hydrogenation of the foregoing dibenzyl ester was carried out in tetrahydrofuran containing triethylamine (3 drops) over palladium–charcoal at 20 °C and 1 atm for 16 h. The catalyst was filtered off through Celite, and the latter was washed with methylene chloride; the combined filtrates were evaporated to dryness and the required *pyrromethane* (76%) was obtained from methylene chloride–light petroleum as an off-white powder, m.p. 130—132 °C (decomp.) with softening at 110 °C (Found: C, 58.3; H, 5.9; N, 6.4. $C_{21}H_{26}N_2O_8$ requires C, 58.1; H, 6.0; N, 6.45%); τ[$(CD_3)_2SO$] −1.30 (2 H, br s, CO_2H), 0.6 (2 H, br s, NH), 6.21 (2 H, s, pyrCH_2pyr), 5.85 (2 H, t, OCH_2CH_2), 6.96 (2 H, t, OCH_2CH_2), 8.03 and 8.05 (12 H, 2 s, 2 × pyrCH_3 and 2 × CH_3CO).

Dibenzyl 3,3′-Dimethylpyrromethane-5,5′-dicarboxylate (**21a**).—Benzyl 5-acetoxymethyl-4-methylpyrrole-2-carboxylate (**20b**) (1.00 g) was boiled under reflux in acetic acid (30 ml) under nitrogen for 2 h. After cooling, the solution was poured into ice–water and the resulting precipitate washed with water until neutral. This material was dried *in vacuo*, extracted into absolute ethanol, and the solution evaporated to dryness and crystallized from chloroform–light petroleum to give dibenzyl-3,3′-dimethyl-2,2′-pyrromethane-5,5′-dicarboxylate (0.48 g, 62%), m.p. 185—187 °C. For analysis a sample was recrystallized from ethanol to give needles, m.p. 186—188 °C (lit.,[24] 187—189 °C) (Found: C, 73.0; H, 5.8; N, 6.2. Calc. for $C_{27}H_{26}N_2O_4$: C, 73.3; H, 5.9; N, 6.3%); τ($CDCl_3$) 0.70 (2 H, s, 2 × NH), 2.95 (10 H, s, 2 × Ph), 3.50 (2 H, s, 2 × 4- and 4′-H), 5.02 (4 H, s, 2 × CO_2CH_2Ph), 6.42 (2 H, s, $=CCH_2=$), 8.20 (6 H, s, 2 × CH_3).

3,3′-Dimethylpyrromethane-5,5′-dicarboxylic Acid (**21b**).—The foregoing dibenzyl pyrromethane (200 mg) was dissolved in tetrahydrofuran (20 ml) and triethylamine (5 drops) and shaken at 20 °C and 1 atm with 10% palladium on charcoal (150 mg) in hydrogen for 3 h. After uptake was complete the solution was filtered, the residue washed with hot ethyl acetate, and the combined filtrates evaporated to dryness to give the dicarboxylic acid which was used immediately for porphyrin synthesis.

Dibenzyl 4-(2-Methoxycarbonylethyl)-3,3′-dimethylpyrromethane-5,5′-dicarboxylate (**18a**).—Benzyl 3-(2-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (**19c**) (2.80 g), benzyl 5-acetoxymethyl-4-methylpyrrole-2-carboxylate (**20b**) (2.70 g), and toluene-*p*-sulphonic acid (0.95 g) were dissolved in methanol (50 ml) and stirred at 40 °C for 3 h under nitrogen. The solution turned pink and a white precipitate formed. Aqueous sodium hydrogen carbonate (10%; 5 ml) was added to the reaction mixture and the flask cooled to 0 °C. The resulting precipitate was filtered off, dried *in vacuo*, chromatographed on alumina (Merck Grade III; 350 g) eluting with increasing concentrations of ethyl acetate in benzene. T.l.c. of the fractions collected showed incomplete separation of the desired pyrromethane from the symmetrical pyrromethane (**21a**) formed by self-condensation of the acetoxymethylpyrrole. The desired *pyrromethane* (2.98 g, 63%) was obtained as white needles, m.p. 120—121 °C after recrystallization from chloroform–light petroleum (b.p. 60—80 °C). A small amount of material was further purified by preparative layer chromatography and recrystallized from chloroform–light petroleum for analysis (m.p. 121–122 °C) (Found: C, 70.4; H, 5.9; N, 5.2. $C_{31}H_{32}N_2O_6$ requires C, 70.9; H, 6.1; N, 5.3%); τ($CDCl_3$) 0.55 (1 H, s, NH), 0.76 (1 H, s, NH), 2.96 (10 H, s, 2 × Ph), 3.50 (1 H, s, 4′-H), 5.02 (4 H, s, 2 × CH_2Ph), 6.57 (2 H, s, $=CCH_2C=$), 6.63 (3 H, s, CO_2CH_3), 7.22 (2 H, t, CH_2CH_2CO), 7.78 (2 H, t, CH_2CH_2CO), 8.20 (3 H, s, CH_3), and 8.27 (3 H, s, CH_3); *m/z* (f.d.) 528 (M^+, 100%).

4-(2-Methoxycarbonylethyl)-3,3′-dimethylpyrromethane-5,5′-dicarboxylic Acid (**18b**).—The foregoing dibenzyl ester (500 mg) was dissolved in methanol (60 ml) and triethylamine (15 drops) and shaken at 20 and 1 atm with 10% Pd–C (300 mg) under hydrogen for 18 h. The solution was filtered, the solid washed with hot ethyl acetate, and the combined filtrates evaporated to dryness to give the desired pyrromethanedicarboxylic acid as a colourless oil (325 mg, 100%) which slowly crystallized with time and was used directly for porphyrin synthesis.

Dibenzyl 4-Ethyl-4′-(2-methoxycarbonylethyl)-3,3′-dimethyl pyrromethane-5,5′-dicarboxylate (**31b**).—Benzyl 5-acetoxymethyl-3-ethyl-4-methylpyrrole-2-carboxylate (**30b**) (222 mg) and benzyl 3-(2-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (**19c**) (212 mg) were stirred in methanol (15 ml) with toluene-*p*-sulphonic acid (40 mg) at 50 °C for 3 h after which chloroform (50 ml) was added to the mixture. The latter was then washed with aqueous sodium hydrogen carbonate (10%; 15 ml) and water (50 ml), dried ($MgSO_4$), and evaporated to dryness. The resulting residue was chromatographed on silica eluting first with benzene, and then with increasing concentrations of ethyl acetate in benzene. The early fractions afforded dibenzyl 4,4′-diethyl-3,3′-dimethylpyrromethane-5,5′-dicarbonylate (**31a**) (20 mg), m.p. 137.5—139 °C; after crystallization from chloroform–light petroleum (b.p. 60—80 °C). The second (main) fraction afforded the desired pyrromethane (**31b**) (296 mg, 76%) as a pale yellow oil which failed to crystallize, and was used directly for porphyrin synthesis. τ($CDCl_3$) 0.10 (1 H, s, NH), 0.23 (1 H, s, NH), 2.00 (10 H, s, 2 × Ph), 4.82 (4 H, s, 2 × CH_2Ph), 6.28 (2 H, s, $=CCH_2C=$), 6.46 (3 H, s, CO_2CH_3), 7.06 (2 H, q, CH_2CH_3) 7.35 (2 H, t, CH_2CH_2CO), 7.55 (2 H, t, CH_2CH_2CO), 8.06 (6 H, s, 2 × CH_3), 8.95 (3 H, t, CH_2CH_3); *m/z* (f.d) 556 (M^+, 100%).

Porphyrins

1,4-Bis(2-hydroxyethyl)-6,7-bis(2-methoxycarbonylethyl)-2,3,5,8-tetramethylporphyrin (**3d**).—4,4′-Bis(2-hydroxyethyl)-3,3′-dimethylpyrromethane (**15b**) (200 mg) and 5,5′-diformyl-3,3′-bis(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane (**4a**) (210 mg) were dissolved in methylene chloride (150 ml) with toluene-*p*-sulphonic acid (280 mg) in methanol (10 ml) and stirred for 24 h at 20 °C with the exclusion of light. A saturated solution of zinc acetate in methanol (20 ml) was added to the resulting deep red solution and the mixture stirred in air until the Soret band in the u.v. spectrum had reached a maximum. The solvents were then removed under reduced pressure and the residue re-esterified with methanol containing 5% concentrated H_2SO_4 (100 ml) overnight. The acid was neutralized with concentrated ammonia and the porphyrin taken up in chloroform, and the solution washed with water, dried, and evaporated to dryness under reduced pressure. The residue was chromatographed twice on alumina eluting with chloroform. Recrystallization from chloroform–methanol gave the required *porphyrin* (138 mg, 29%) as red prisms, m.p. 219—221 °C (lit.,[18] m.p. 214—216 °C) (Found: C, 68.8; H, 6.5; N, 9.2. $C_{36}H_{42}N_4O_6$ requires C, 69.0; H, 6.8; N, 8.9%); $\lambda_{max.}$($CHCl_3$) 398 (log $\varepsilon_{max.}$ 5.27), 498 (4.18), 533 (3.99), 570 (3.83), and 624 nm (3.64); $\lambda_{max.}$($CHCl_3$/TFA) 400 (5.62), 549 (4.23), and 595 nm (3.79); τ($CDCl_3$) −0.03 (2 H, s, =CH), −0.01 (2 H, s, =CH), 5.5—5.8

(12 H, m, 2 × CH_2CH_2OH + 2 × CH_2CH_2CO), 6.37 (6 H, s, 2 × CO_2CH_3), 6.44 (12 H, s, 4 × β-CH_3), 6.78 (4 H, t, 2 × CH_2CH_2CO), and 13.9 (2 H, br, 2 × NH); *m/z* (f.d.) 626 (M^+, 100%).

In preliminary experiments the pyrromethanedicarboxylic acid (**5b**) and the diformylpyrromethane (**4a**) were condensed in the same way, but the yield of porphyrin estimated spectroscopically was only 3%. Little improvement in yield was obtained by using hydriodic acid in acetic acid, as in MacDonald's original method.[10]

1,4-*Bis*(2-*chloroethyl*)-6,7-*bis*(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (**3e**).—The foregoing 1,4-bis(2-hydroxyethyl)porphyrin (110 mg) was dissolved in chloroform (50 ml) and dimethylformamide (8 ml) was added followed by anhydrous potassium carbonate (6 g). Thionyl chloride (2.5 ml) was then added and the mixture stirred for 3 h with protection from moisture. Dilute aqueous ammonia was added until the mixture was alkaline. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The resulting product was chromatographed on alumina in methylene chloride–hexane to yield the desired *porphyrin* (78 mg, 66%) as purple hair-like needles, m.p. 201—203 °C (Found: C, 65.6; H, 6.1; N, 8.2. $C_{36}H_{40}Cl_2O_4N_4$ requires C, 65.15; H, 6.1; N, 8.4%); $\lambda_{max.}$($CHCl_3$) 400 ($\log_{10}$ ε 5.27), 498 (4.17), 532 (4.02), 567 (3.82), and 621 nm (3.67); $\lambda_{max.}$($CHCl_3$–TFA) 403 (5.56), 548 (4.21), and 592 nm (3.80); τ −0.02 (2 H, s, *meso*-H), −0.04 (2 H, s, *meso*-H), 5.54—5.77 (12 H, m, 2 × CH_2CH_2Cl + 2 × CH_2CH_2CO), 6.36 (6 H, s, 2 × CO_2CH_3), 6.43 (6 H, s, 2 × β-CH_3), 6.48 (6 H, s, 2 × β-CH_3), 6.76 (4 H, t, 2 × CH_2CO_2Me), and 13.95 (2 H, br, 2 × NH) (lit.,[19,22] 204—206 °C, 201—203 °C).

6,7-*Bis*(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethyl*-1,4-*divinylporphyrin* (*Protoporphyrin XIII Dimethyl Ester*) (**3c**).—(*a*) The foregoing 1,4-bis(2-chloroethyl)porphyrin (50 mg) was dissolved in methylene chloride (30 ml) and a few drops of a saturated solution of zinc acetate in methanol were added. The mixture was warmed for a short time after which the visible spectrum showed zinc insertion to be complete. The mixture was then evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (5 ml). A solution of potassium t-butoxide in t-butylalcohol (30 ml) was then added and the mixture set aside in the dark for 4 days before addition of acetic acid (2 ml) and chloroform (50 ml). The organic phase was washed with water, dried (Na_2SO_4), and then evaporated to dryness. The residue was treated with 5% (v:v) sulphuric acid in methanol (50 ml) overnight after which the solution was neutralized with aqueous ammonia and extracted with chloroform. After work-up, the product was chromatographed on alumina with chloroform as eluant, to give the required *porphyrin* (31 mg, 70%) as shiny purple needles, m.p. 211—213 °C after crystallization from methylene chloride–hexane (lit.,[17–19,22] m.p. 198—200, 210—212, 208—210, and 228—229 °C) (Found: C, 73.45; H, 6.3; N, 9.0. Calc. for $C_{36}H_{38}O_4H_4$: C, 73.2; H, 6.5; N, 9.5%); $\lambda_{max.}$($CHCl_3$) 403 (log ε 5.20), 504 (4.16), 539 (4.04), 577 (3.80), 631 nm (3.65); $\lambda_{max.}$($CHCl_3$/TFA) 405 (5.44), 555 (4.11), and 597 nm (3.67); τ($CDCl_3$) 0.08 (2 H, s, β- and δ-*meso*-CH), 0.18 (1 H, s, α-*meso*-CH), 0.30 (1 H, s, γ-*meso*-CH), 1.87 (2 H, m, 2 × CH=CH_2), 3.82 (4 H, m, 2 × CH=CH_2), 5.73 (4 H, t, 2 × CH_2CH_2CO), 6.37 (6 H, s, 2 × CO_2CH_3), 6.53 (6 H, s, 5- and 8-CH_3), 6.57 (6 H, s, 2- and 3-CH_3), 6.82 (4 H, t, 2 × CH_2CH_2CO), and 14.20 (2 H, br, 2 × NH); *m/z* (f.d.) 590 (M^+).

(*b*) Finely powdered sodium borohydride (300 mg) was added to a stirred solution of diacetyldeuteroporphyrin-XIII dimethyl ester (**3j**) (30 mg) (see below) in dichloromethane (12 ml) containing methanol (0.5 ml). The mixture was stirred, in the dark, at 20 °C for 15 min; u.v. monitoring showed disappearance of absorption at $\lambda_{max.}$ 418 nm and appearance of absorption at $\lambda_{max.}$ 400 nm. The solution was washed with 0.5% hydrochloric acid (15 ml), the aqueous phase back extracted with dichloromethane (2 × 15 ml), and the combined extracts evaporated to dryness. The residue was chromatographed on alumina (Merck grade 4; 30 g) with dichloromethane and then with increasing proportions of acetone in dichloromethane as eluant. The red porphyrin band was collected and evaporated to give haematoporphyrin-XIII dimethyl ester (**3l**) as a purple solid (19 mg, 62%); $\lambda_{max.}$($CHCl_3$) 400, 498, 533, 572, and 623 nm; τ($CDCl_3$) 0.12 (2 H, s), 0.35 (1 H, s), and 0.43 (1 H, s) (=CH), 5.92 (4 H, t, 2 × CH_2CH_2CO), 6.15 [2 H, q, 2 × $CH(OH)CH_3$], 6.37 (6 H, s, 2 × CO_2CH_3), 6.72 (6 H, s, 2 × CH_3), 6.90 (6 H, s, 2 × CH_3), 6.90 (4 H, t, 2 × CH_2CH_2CO), and 8.15 [6 H, d, $CH(OH)CH_3$].

A solution of haematoporphyrin-XIII dimethyl ester (**3l**) (22 mg) and toluene-*p*-sulphonic acid (60 mg) in chlorobenzene (15 ml) was refluxed, in the dark, for 30 min. The chlorobenzene was removed under reduced pressure and the residue taken up in 5% sulphuric acid–methanol (30 ml) and allowed to stand, in the dark, overnight. The resulting solution was partitioned between dichloromethane (30 ml) and water (60 ml) and the aqueous phase extracted with dichloromethane (3 × 20 ml). The combined extracts were washed with 5% aqueous ammonia (40 ml) and water (50 ml) and evaporated to dryness. The residue was chromatographed on alumina (Merck grade 3; 20 g) and the major porphyrin fraction was collected, evaporated to dryness, and crystallized from dichloromethane–methanol to afford protoporphyrin-XIII dimethyl ester (16.2 mg, 76%) as lustrous purple needles, m.p. 212—214 °C, identical with the sample prepared as in (*a*).

1,6,7-*Tris*(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (**3f**).—Toluene-*p*-sulphonic acid (600 mg) in methanol (10 ml) was added to a solution of 4-(2-methoxycarbonylethyl)-3,3-dimethylpyrromethane-5,5-dicarboxylic acid (**18b**) (310 mg) and 5,5-diformyl-3,3-bis(2-methoxycarbonylethyl)-4,4-dimethylpyrromethane (**4a**) (420 mg) in methanol (10 ml) and dichloromethane (100 ml). The mixture was stirred for 18 h, in the dark, after which time u.v. spectral examination showed absorption at $\lambda_{max.}$ 411, 466, 503, and 530 nm.

A saturated solution of zinc acetate in methanol (10 ml) was then added and the solution stirred in the air for 3 h; u.v. spectral examination showed absorption of $\lambda_{max.}$ 411, 481, 510, and 538 nm, the Soret band at 411 nm being markedly enhanced. The solution was evaporated to dryness and the residue in 5% sulphuric acid–methanol (50 ml) set aside with exclusion of light. The resulting solution was partitioned between water (150 ml) and chloroform (50 ml) and the aqueous phase extracted further with chloroform (3 × 50 ml). The combined chloroform extracts were washed with 10% ammonia solution (100 ml) and water (100 ml). The organic phase was evaporated to dryness and water removed by azeotroping with ethanol. The residue was chromatographed on alumina (Merck Grade 3; 100 g) in dichloromethane, the combined porphyric eluants being collected, evaporated to dryness, and the residue rechromatographed on alumina (Merck Grade 3; 200 g) with increasing concentrations of dichloromethane in benzene. The first fraction from the column was evaporated to dryness to give an etio-type spectrum with an R_F on t.l.c. identical with that of deuteroporphyrin-XIII dimethyl ester (**3i**) (see below). This was attributed to contamination of the pyrromethane diacid (**18b**) with a small amount of the symmetrical pyrromethane (**18c**). The second (major) fraction contained a porphyrin which had an R_F value on t.l.c. identical with harderoporphyrin trimethyl ester (**1d**). The fraction was evaporated to dryness and the residue was crystallized from dichloromethane–light petroleum

to give 1,6,7-*tris*(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (92 mg, 14%) as purple microneedles, m.p. 213 °C (Found: C, 69.7; H, 6.2; N, 8.9; $C_{36}H_{40}N_4O_6$ requires C, 69.2; H, 6.4; N, 9.0%); $\lambda_{max.}$($CHCl_3$) 400 (log ε 5.22), 499 (3.93), 534 (3.87), 572 (3.73), 625 nm (3.54); τ($CDCl_3$) 0.10 (1 H, s, =CH), 0.15 (1 H, s, =CH), 0.17 (2 H, s, 2 × =CH), 1.10 (1 H, s, 4-CH=), 5.70 (6 H, m, 3 × $CH_2CH_2CO_2Me$), 6.38 (9 H, s, 3 × CO_2CH_3), 6.44 (3 H, s, CH_3), 6.48 (3 H, s, CH_3), 6.53 (3 H, s, CH_3), 6.62 (3 H, s, CH_3), 6.80 (6 H, m, 3 × $CH_2CH_2CO_2Me$), and 14.0 (2 H, vbr, NH); *m/z* (f.d.) 624 (M^+, 100%).

A third porphyrin fraction was obtained which had an R_F value (t.l.c.) corresponding to coproporphyrin tetramethyl ester due to self condensation of the diformylpyrromethane (**4a**). After evaporation of the eluates and recrystallization of the residue from dichloromethane–light petroleum coproporphyrin-II tetramethyl ester (45 mg) was obtained as purple microneedles, m.p. 284—286 °C; $\lambda_{max.}$($CHCl_3$) 400, 498, 533, 572, and 626 nm; τ($CDCl_3$) −0.09 (4 H, s, =CH), 5.60 (8 H, t, 4 × $CH_2CH_2CO_2Me$), 6.37 (24 H, br s, 4 × ring CH_3 and 4 × CO_2CH_3), 6.75 (8 H, t, 4 × $CH_2CH_2CO_2Me$), and 13.84 (2 H, br, 2 × NH); *m/z* (f.d.) 710 (M^+, 100%).

4-*Acetyl*-1,6,7-*tris*-(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (**3g**).—(*a*) Ferrous acetate was prepared by dissolving iron powder in boiling acetic acid, under reflux in a nitrogen atmosphere. A few drops of water were added and the mixture allowed to settle. The foregoing porphyrin (84 mg) was dissolved in refluxing acetic acid and the water-cleared aqueous ferrous acetate added with a Pasteur pipette. The solution was heated under reflux for a further 5 min, allowed to cool, poured into water, and extracted with chloroform. The haemin solution was evaporated to dryness and dried by azeotroping with ethanol to give a brown solid. Tin(IV) chloride (0.54 g) was added dropwise under anhydrous conditions to a stirred solution of the foregoing haemin in acetic anhydride (8 ml) which had been cooled to −10 °C in a salt–ice bath. After 10 min, the reaction mixture was poured into ice–water, the haemin extracted into chloroform, and the extracts evaporated to dryness. The residue was dissolved in methanol (25 ml) containing ferrous sulphate (500 mg) and potassium hydroxide (5 pellets), and dry hydrogen chloride was bubbled through the stirred solution for 40 min. The mixture was then partitioned between water (100 ml) and dichloromethane (50 ml), and the aqueous phase further extracted with dichloromethane until no fluorescence remained. The combined extracts were evaporated to dryness, the residue dissolved in 5% sulphuric acid–methanol (50 ml), and the solution set aside in the dark overnight. It was then partitioned between dichloromethane (50 ml) and water (150 ml) and extracted as before. The combined extracts were washed with 10% aqueous ammonia (50 ml) and water (50 ml) and then evaporated to dryness. The residue was chromatographed on alumina (Merck Grade 3; 100 g) with increasing concentrations of methylene chloride in benzene. The first (minor) fraction contained the β-free porphyrin (1 mg) whilst the second (major) fraction when evaporated to dryness and the residue recrystallized from dichloromethane–light petroleum gave 4-*acetyl*-1,6,7-*tris*-(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (35.9 mg, 40%) as purple needles, m.p. 214 °C (Found: C, 68.4; H, 6.3; N, 7.4. $C_{38}H_{42}N_4O_7$ requires C, 68.5; H, 6.3; N, 8.41%); $\lambda_{max.}$($CHCl_3$) 410 (log ε 5.18), 512 (3.89), 552 (3.97), 582 (3.79), and 640 nm (3.06); τ($CDCl_3$) −0.70 (1 H, s, =CH), 0.12 (1 H, s, =CH), 0.22 (1 H, s, =CH), 0.33 (3 H, 3 s, 3 × =CH), 5.70 (6 H, m, 3 × $CH_2CH_2CO_2Me$), 6.31 (3 H, s, CH_3), 6.35 (3 H, s, CH_3), 6.39 (6 H, s, 2 × CH_3), 6.50 (6 H, s, 2 × CH_3), 6.65 (3 H, s, CH_3), 6.75 (6 H, m, 3 × $CH_2CH_2CO_2Me$), 6.81 (3 H, s, $COCH_3$), and 14.15 (2 H, br s, 2 × NH); *m/z* (f.d.) 666 (M^+, 100%).

(*b*) Copper(II) acetate (80 mg) in methanol (8 ml) was added to a solution of the tetramethyltripropionate porphyrin (**3f**) (20 mg) in chloroform (8 ml) and the mixture heated under reflux for 10 min. The solution was diluted with water (10 ml) and the porphyrin copper complex extracted into chloroform; the extract was dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized from methylene chloride–methanol and the copper(II) complex (20 mg) was taken up in dichloromethane (15 ml) and acetic anhydride (3 ml) and stirred at 0 °C for 2 min with stannic chloride (0.15 ml). The solution was poured into water (100 ml) shaken vigorously, and the organic layer separated; the latter was then washed with 5% aqueous ammonia (25 ml) and water 2 × 25 ml) and evaporated to dryness. Last traces of water were removed by azeotroping with absolute alcohol and the residue dried *in vacuo*. The product was taken up in concentrated sulphuric acid (5 ml) and the solution kept at room temperature for 15 min before it was poured into ice-cold methanol (95 ml). The solution was kept in the dark overnight, dichloromethane added (50 ml), and the mixture washed with water (50 ml), 5% aqueous ammonia (50 ml), and water (2 × 50 ml). The solvent was removed under reduced pressure and the residue chromatographed on a column of alumina (Merck grade 3; 15 g) eluting with dichloromethane. After a minor pre-fraction of non-acetylated porphyrin, a major porphyric fraction was collected. This was evaporated to dryness and crystallized from dichloromethane–light petroleum (b.p. 60—80 °C) to give the title porphyrin (14.1 mg, 71%) as purple needles, m.p. 214—215 °C identical with the product prepared as in (*a*); *m/z* (e.i.) 593 (14%), 594 (6.9), 595 (1), 635 (2), 666 (100), 667 (49), 668 (9), and 669 (2%).

4-(1-*Hydroxyethyl*)-1,6,7-*tris*-(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (**3h**).—Finely ground sodium borohydride was added to a stirred solution of the foregoing acetylporphyrin (36 mg) in dichloromethane (10 ml) containing methanol (0.5 ml). The solution was stirred at 0 °C in the dark, with monitoring in the u.v. region of the Soret band; this shifted completely from 410 to 400 nm in *ca.* 10 min. Hydrochloric acid (0.5; 10 ml) was added and the porphyrin extracted with dichloromethane. The extract was evaporated to dryness and the residue chromatographed on alumina (Merck Grade 3; 30 g) in dichloromethane. A trace of starting material was obtained, followed by the predominant band containing the desired hydroxyethylporphyrin. This second fraction was evaporated to dryness and the residue recrystallized from methylene chloride–light petroleum (b.p. 60—80 °C) to give 4-(1-*hydroxyethyl*)-1,6,7-*tris*-(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (23 mg, 63%) as purple needles, m.p. 160—162 °C (Found: C, 68.7; H, 6.3; N, 7.95. $C_{38}H_{44}N_4O_7$ requires C, 68.3; H, 6.6; N, 8.4%); $\lambda_{max.}$($CHCl_3$) 400 (log ε 5.26), 500 (4.07), 535 (3.93), 573 (3.77), and 626 (3.58); τ($CDCl_3$) 0.07 (1 H, s, =CH), 0.19 (1 H, s, =CH), 0.30 (1 H, s, =CH), 0.41 (1 H, s, =CH), 4.18 (1 H, q, $CHOHCH_3$), 5.80 (6 H, m, 3 × $CH_2CH_2CO_2Me$), 6.38 (9 H, 3 × CO_2CH_3), 6.59 (3 H), 6.65 (3 H) 6.76 (3 H), and 6.85 (3 H) (ring CH_3), 6.8 (6 H, m, 3 × $CH_2CH_2CO_2Me$), 8.13 (3 H, d, $CHOHCH_3$), and 14.35 (2 H, br s 2 × NH); *m/z* 669 (65%), 668 (100%), and 651 (M − OH, 28%).

1,6,7-*Tris*-(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethyl*-4-*vinylporphyrin* (**3b**).—A solution of the foregoing hydroxyethylporphyrin (22 mg) and toluene-*p*-sulphonic acid (50 mg) in *o*-dichlorobenzene (20 ml) was maintained at 140 °C for 30 min in the dark. The *o*-dichlorobenzene was removed under reduced pressure and the residue dissolved in 5% sulphuric acid–methanol (25 ml). After being set aside overnight, the resulting solution was partitioned beween dichloromethane (25 ml) and water (100 ml) and extracted with dichloromethane until the aqueous phase showed no fluorescence under u.v. light. The combined extracts were washed with 10% aqueous ammonium

hydroxide (50 ml) and water (50 ml), evaporated to dryness, and the residue chromatographed on alumina (Merck Grade 3; 15 g). The major porphyrin fraction was collected, evaporated to dryness, and the residue recrystallized from dichloromethane–light petroleum (b.p. 60—80 °C) to give 1,6,7-*tris*-(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethyl*-4-*vinylporphyrin* as purple needles (11.5 mg, 54%), m.p. 201—202 °C (lit.,[19] m.p. 197—199 °C; $\lambda_{max.}$($CHCl_3$) 404 (log ε 5.27), 504 (4.10), 540 (3.95), 557 (3.73), and 663 nm (3.52); τ($CDCl_3$) −0.06 (1 H, s, =CH), 0.04 (1 H, s, =CH), 0.08 (1 H, s, =CH), 0.10 (1 H, s, =CH), 1.80 (1 H, m, C*H*=CH_2), 3.80 (2 H, m, CH=C*H*$_2$), 5.67 (6 H, m, C*H*$_2$$CH_2CO_2Me$), 6.36 (9 H, s, 3 × CO_2CH_3), 6.45 (6 H, s, 2 × CH_3) 6.47 (3 H, s, CH_3), 6.53 (3 H, s, CH_3), 6.80 (6 H, m, 3 × CH_2C*H*$_2CO_2Me$), and 14.02 (2 H, s, NH); *m/z* (f.d.) 650 (M^+, 100%) (Found: M^+, 650.356. $C_{38}H_{42}N_4O_6$ requires *M*, 650.359).

6,7-*Bis*(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (*Deuteroporphyrin*-XIII *Dimethyl Ester*) (**3i**).—(*a*) Toluene-*p*-sulphonic acid (300 mg) in methanol (5 ml) was added to a solution of 3,3-dimethyl-2,2-pyrromethane-5,5-dicarboxylic acid (**21b**) (116 mg) and 5,5-diformyl-3,3-bis(2-methoxycarbonylethyl)-4,4-dimethyl-2,2-pyrromethane (**4a**) (178 mg) in methanol (3 ml) and dichloromethane (30 ml) and the resulting mixture was stirred for 18 h in the dark. A saturated solution of zinc acetate was then added and the solution stirred in air for 4 h. It was then evaporated to dryness and the mixture set aside overnight in 5% sulphuric acid–methanol (25 ml) with exclusion of light. The reaction was worked up in the same way as the corresponding preparation of protoporphyrin-XIII dimethyl ester (**3d**) and after chromatography; the first fraction contained a porphyrin whose R_F (t.l.c.) was identical with that of deuteroporphyrin-IX dimethyl ester. The solution was evaporated to dryness and the residue crystallized from dichloromethane–light petroleum (b.p. 60—80 °C) to give *deuteroporphyrin*-XIII *dimethyl ester* (8.4 mg, 3.5%) as small purple needles, m.p. 235—237 °C (lit.,[19] m.p. 236—238 °C) (Found: C, 71.4; H, 5.7; N, 11.65. Calc. for $C_{32}H_{34}N_4O_4$: C, 71.4; H, 6.3; N, 10.4%); $\lambda_{max.}$($CHCl_3$) 399 (log ε 5.23), 498 (4.03). 532 (3.88), 571 (3.70), and 624 nm (3.45); τ($CDCl_3$) 0.14 (1 H, s, =CH), −0.07 (1 H, s, =CH), 0.02 (2 H, s, 2 × =CH), 0.92 (2 H, s, 1- and 4-H), 5.60 (4 H, t, 2 × C*H*$_2$$CH_2CO_2Me$), 6.28 (6 H), 6.36 (6 H), 6.41 (6 H) (4 × ring CH_3, 2 × CO_2CH_3), 6.75 (4 H, t, 2 × CH_2C*H*$_2$-CO_2Me), and 13.9 (2 H, v br, NH); τ(CF_3CO_2D) 1.24 (1 H, s, =CH), −1.17 (1 H, s, =CH), −0.08 (2 H, s, =CH), 0.27 (2 H, s, 1- and 4-H), 5.25 (4 H, t, 2 × C*H*$_2$$CH_2CO$), 6.09 (6 H, s), 6.17 (6 H, s), 6.26 (6 H, s, 4 × ring CH_3 and 2 × CO_2CH_3), and 6.68 (4 H, t, 2 × CH_2C*H*$_2CO$); *m/z* (e.i.) 465 (17%), 466 (6), 538 (100), and 539 (15).

A second porphyric fraction was collected which was shown to be coproporphyrin-II tetramethyl ester due to self-condensation of the diformylpyrromethane. Copper(II) acetate (10 mg) in methanol (10 ml) was added to a solution of the deuteroporphyrin-XIII dimethyl ester (25 mg) in chloroform (10 ml) and the mixture refluxed for 10 min. The solution was washed with water, evaporated to dryness, and the residue crystallized from dichloromethane–methanol to yield the desired copper(II) complex as brick red microneedles, m.p. 253.5—254.5 °C (32 mg, quantitative).

(*b*) Dibenzyl 3,3′-bis(2-methoxycarbonylethyl)-4,4′-dimethyl-2,2′-pyrromethane-5,5′-dicarboxylate (1.60 g) was shaken with 10% palladium–charcoal (150 mg) in acetone solution containing triethylamine (3 drops), under an atmosphere of hydrogen, at 20 °C and 760 mmHg for 3 h. After uptake of hydrogen (150 ml) the catalyst was filtered off, the residue washed with hot acetone, and the combined filtrates evaporated to dryness. The residue was taken up in aqueous ammonia (10%; 10 ml) and acidification with glacial acetic acid afforded a white precipitate. This was filtered off and dried *in vacuo* to give 3,3′-bis(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5,5′-dicarboxylic acid (**4b**) as an amorphous solid, m.p. 188—190 °C (1.56 g, 96%); τ[$(CD_3)_2SO$] −1.20 (2 H, s, 2 × CO_2H), 6.18 (2 H, s, =CCH_2C=), 6.40 (6 H, s, 2 × CO_2CH_3), 7.46 (4 H, t, 2 × CH_2CH_2CO), 7.84 (10 H, overlapping s and t, 2 × CH_3 and 2 × CH_2C*H*$_2$CO).

A solution of the above pyrromethane diacid (1.10 g) in trifluoroacetic acid (5 ml) was added to a solution of 2-formyl-4,5-dimethylpyrrole (0.63 g) in methanol (20 ml) and the mixture immediately treated with hydrogen bromide in acetic acid (40%; 4 ml). The dark red solution was stirred for 30 min, and then the biladiene salt was precipitated by addition of ether (80 ml). After 2 h a brick red precipitate of the desired biladiene hydrobromide (1.49 g, 82%) was collected, washed with ether, dried *in vacuo*, and used immediately for porphyrin synthesis; $\lambda_{max.}$(EtOH) 445 nm; τ($CDCl_3$) 2.89—3.02 (4 H, m, 4 × =CH), 6.77 (2 H, s, =CCH_2=), 6.34 (3 H, s, CO_2CH_3), 6.58 (3 H, s, CO_2CH_3), 7.20 (4 H, m, CH_2CH_2CO), 7.32 (6 H, s, 2 × CH_3), 7.79 (6 H, s, 2 × CH_3), 7.93 (6 H, s, 2 × CH_3), and 8.02 (4 H, m, 2 × CH_2C*H*$_2$CO).

Copper(II) acetate (5 g) was added to a solution of the foregoing *a,c*-biladiene hydrobromide (1.20 g) in pyridine (35 ml) and the mixture stirred for 10 min at room temperature and for a further 1 h at 70 °C. Dilution with methanol failed to precipitate the desired copper porphyrin and the mixture was dispersed between chloroform (60 ml) and water (60 ml). The organic layer was separated and the aqueous phase extracted with chloroform (4 × 20 ml). The combined chloroform fractions were washed with dilute hydrochloric acid (2 × 60 ml), water (2 × 60 ml) and evaporated to dryness on a rotary evaporator, the last traces of water by being azeotroped with ethanol. The residue was chromatographed on alumina (Merck Grade 3; 20 g) eluting first with benzene and then with increasing proportions of dichloromethane in benzene. The eluants were evaporated to dryness and crystallized from dichloromethane–methanol to yield deuteroporphyrin-XIII dimethyl ester copper(II) complex as red crystals, m.p. 253—254 °C (207 mg, 21%); $\lambda_{max.}$($CHCl_3$) 397, 524, and 560 nm. The foregoing copper(II) complex (10.1 mg) was taken up in concentrated sulphuric acid (5 ml), the mixture kept at room temperature, in the dark, for 15 min and then poured into ice-cold methanol (95 ml). After the mixture had been set aside overnight, it was partitioned between dichloromethane (50 ml) and water (300 ml) and the aqueous phase extracted with chloroform (4 × 30 ml). The combined extracts were washed with aqueous ammonia (5%; 50 ml) and water (2 × 50 ml) and then evaporated to dryness. The residue was passed down an alumina column (Merck grade 3; 5 g) eluting with 25% dichloromethane–benzene. The combined porphyric fractions were evaporated to dryness and the residue crystallized from dichloromethane–methanol to afford deuteroporphyrin-XIII dimethyl ester (5.9 mg; 61%) as purple microneedles, m.p. 236—237 °C identical with the previous sample prepared as in (*a*) $\lambda_{max.}$ 399, 498, 532, 571, and 624 nm.

1,4-*Diacetyl*-6,7-*bis*(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (*Diacetyldeuteroporphyrin*-XIII *Dimethyl Ester*) (**3j**).—The copper(II) complex of deuteroporphyrin-XIII dimethyl ester (34.2 mg) was taken up in acetic anhydride (20 ml) and dichloromethane (20 ml) and stirred for 15 min with stannic chloride (0.25 ml). The reaction mixture was washed with water (40 ml) and the organic layer separated, washed with 5% aqueous ammonia (40 ml) and water (2 × 40 ml), and evaporated under reduced pressure. The last traces of water were removed by azeotroping with absolute alcohol and the product was dried *in vacuo*. The residue was taken up in

concentrated sulphuric acid (8 ml) and the green solution kept at room temperature for 15 min before being poured into ice-cold methanol (150 ml). The mixture was set overnight in the dark, after which it was diluted with dichloromethane (100 ml), washed with water (100 ml), and evaporated. The residue was chromatographed on alumina (Merck grade 3; 50 g), eluting first with 30% dichloromethane–benzene and then with 5% acetone–dichloromethane.

A trace of deuteroporphyrin-XIII dimethyl ester was eluted first followed by a second porphyrin band which exhibited a rhodo-type visible spectrum. Solvent was evaporated off and the residual porphyrin crystallized from dichloromethane–methanol to afford 1-*acetyl*-6,7-*bis*(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (**3k**) (2.6 mg, 8%), m.p. 199—202 °C (Found: M^+, 580.308. $C_{34}H_{36}N_4O_5$ requires M, 580.312); $\lambda_{max.}$(CHCl$_3$) 411, 510, 546, 582, and 636; τ(CF$_3$CO$_2$D) −1.56 (1 H, s, =CH), −1.23 (1 H, s, =CH), −1.11 (1 H, s, =CH), 0.96 (1 H, s, =CH), 0.35 (1 H, s, 4-H), 5.30 (4 H, t, 2 × CH_2CH$_2$CO), 5.85 (3 H, s), 6.12 (3 H, s), 6.25 (12 H, s), and 6.42 (3 H, s) (4 × ring CH$_3$, COCH$_3$, and 2 × CO$_2$CH$_3$), and 6.70 (4 H, t, 2 × CH$_2$CH$_2$CO). A third fraction was then eluted and crystallized from dichloromethane–methanol giving *diacetyldeuteroporphyrin-XIII dimethyl ester* as purple crystals, m.p. 222—223 °C (20.7 mg, 61%) (Found: M^+, 622.331. $C_{36}H_{38}N_4O_6$ requires M, 622.327); $\lambda_{max.}$(CHCl$_3$) 419 (log ε 5.07), 516 (4.11), 550 (3.86), 587 (3.82), and 639 nm (3.46); τ(CF$_3$CO$_2$D) −1.42 (2 H, s, =CH), −1.28 (1 H, s, =CH), −0.95 (1 H, s, =CH), 5.39 (4 H, t, CH$_2$CH$_2$CO), and 5.90 (6 H, s), 6.20 (6 H, s), 6.28 (6 H, s), and 6.44 (6 H, s) (4 ring CH$_3$, 2 × CO$_2$CH$_3$, 2 × COCH$_3$), and 6.72 (4 H, t, 2 × CH$_2$CH$_2$CO); *m/z* 622 (100%) and 549 (10%).

1,4-*Diethyl*-6,7-*bis*(2-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (*Mesoporphyrin-XIII Dimethyl Ester*) (**3m**).—Dibenzyl 4,4′-diethyl-3,3′-dimethyl-2,2′-pyrromethane-5,5′-dicarboxylate (115 mg) was dissolved in acetone (10 ml) containing triethylamine (5 drops) and shaken with a suspension of 10% palladium–charcoal (50 mg) for 3 h under hydrogen at 1 atm and 20 °C. The catalyst was filtered off and washed with hot acetone and the combined filtrates evaporated to dryness to give 4,4′-diethyl-3,3′-dimethyl-2,2′-pyrromethane-5,5′-dicarboxylic acid (74 mg, 100%) as a colourless oil which slowly solidified; τ(CDCl$_3$) −1.12 (2 H, br, 2 × CO$_2$H), 1.33 (2 H, br, 2 × NH), 6.18 (2 H, s, =CCH$_2$C=), 7.05 (4 H, q, 2 × CH_2CH$_3$), 7.97 (6 H, s, 3- and 3′-CH$_3$), and 8.85 (6 H, t, 2 × CH$_2$CH_3).

Toluene-*p*-sulphonic acid (120 mg) in methanol was added to a solution of the pyrromethane diacid and 5,5′-diformyl-3,3′-bis(2′-methoxycarbonyl)-4,4′-dimethyl-2,2′-pyrromethane (79 mg) in methanol (1 ml) and dichloromethane (15 ml) and the resulting mixture was stirred for 18 h in the dark. A saturated solution of zinc acetate in methanol (2 ml) was then added and the mixture stirred in air for 4 h. The reaction mixture was worked up for porphyrin in the same manner as in the preparation of deuteroporphyrin-XIII described above, and chromatographed twice on alumina. The major porphyrin fraction was collected, evaporated to dryness and crystallized from dichloromethane–methanol to give mesoporphyrin-XIII dimethyl ester (29 mg, 25%) as fluffy red needles, m.p. 216—217 °C (lit.,[17] m.p. 217 °C); $\lambda_{max.}$(CHCl$_3$) 399, 497, 532, 568, and 622 nm; τ(CDCl$_3$) 0.01 (1 H, s, =CH), 0.03 (3 H, s, 3 × =CH), 5.65 (4 H, t, 2 × CH_2CH$_2$CO), 6.02 (4 H, q, 2 × CH_2CH$_3$), 6.40 (6 H, s), 6.45 (6 H, s), and 6.50 (6 H, s) (4 × ring CH$_3$ and 2 × CO$_2$CH$_3$), 6.78 (4 H, t, 2 × CH$_2$CH_2CO), 8.22 (6 H, t, 2 × CH$_2$CH_3), and 3.87 (2 H, br, 2 × NH); δ(CF$_3$CO$_2$D) 1.14 (1 H), 10.97 (3 H) (meso-protons), 5.32 (4 H, t, 2 × CH_2CH$_2$CO), 5.72 (4 H, q, 2 × CH_2CH$_3$), 6.22 (12 H, s) and 6.28 (6 H, s, 4 × ring CH$_3$ and 2 × CO$_2$CH$_3$), 6.73 (4 H, t, CH$_2$CH_2CO), and 8.20 (6 H, t, 2 × CH$_2$CH_3). A second minor fraction was shown to be coproporphyrin-II tetramethyl ester.

1-*Ethyl*-4,6,7-*tris*(2′-*methoxycarbonylethyl*)-2,3,5,8-*tetramethylporphyrin* (**3n**).—Dibenzyl 4-ethyl-4′-(2-methoxycarbonylethyl)-3,3′-dimethyl-2,2′-pyrromethane-5,5′-dicarboxylate (**31b**) (100 mg) was dissolved in methanol (10 ml) containing triethylamine (5 drops) and shaken with palladium–charcoal (20 mg, 10%) under an atmosphere of hydrogen (1 atm) for 18 h, at 20 °C. The catalyst was filtered off through Celite and the residue washed with hot acetone. The combined filtrates were then evaporated to dryness to afford the pyrromethane-5,5′-dicarboxylic acid as an unstable, pale green oil which was used without further purification. The n.m.r. spectrum showed the loss of signals at 2.80 and 4.82 due to the benzyl ester groups.

Toluene-*p*-sulphonic acid (120 mg) in methanol (2 ml) was added to a stirred solution of the above pyrromethane diacid and 5,5′-diformyl-3,3′-bis(2-methoxycarbonylethyl)-4,4′-dimethyl-2,2′-pyrromethane (72 mg) in methanol (1 ml) and dichloromethane (15 ml). The mixture was stirred for 18 h, in the dark, after which time spectral examination showed absorption at $\lambda_{max.}$ 411, 466, 503, and 530 nm. Zinc acetate in methanol was then added and the reaction mixture worked up for porphyrin and chromatographed as in the preceding preparation. Fractions were analysed by t.l.c. and those containing the major porphyrin were combined and evaporated to dryness. Crystallization of the residue from dichloromethane–methanol afforded the *title compound* (**3n**) (17.5 mg, 15%) as lustrous purple needles, m.p. 182.5—184 °C (Found: M^+, 652.374. $C_{38}H_{44}N_4O_6$ requires M, 652.375); $\lambda_{max.}$(CHCl$_3$) 400 (log$_{10}$ ε 5.24), 500 (4.15), 533 (4.00), 570 (3.83), and 622 nm (3.67); τ(CDCl$_3$) −0.03 (1 H, s, =CH), 0.01 (1 H, s, =CH), 0.03 (2 H, s, 2 × =CH), 5.65 (6 H, m, 3 × CH_2CH$_2$CO), 5.97 (2 H, q, CH_2CH$_3$), 6.36 (9 H, s, 3 × CO$_2$CH$_3$), 6.40 (3 H, s), 6.43 (3 H, s), and 6.46 (6 H, s) (4 × ring CH$_3$), 6.75 (6 H, m, 3 × CH$_2$CH_2CO) 8.19 (3 H, t, CH$_2$CH_3), and 3.84 (2 H, s, 2 × NH).

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