Synthetic and Biosynthetic Studies of Porphyrins. Part 9.[1] Synthesis of Isocoproporphyrin, Dehydroisocoproporphyrin, and De-ethylisocoproporphyrin

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The title compounds, which were excreted by patients suffering from porphyria cutanea tarda or rats poisoned with hexachlorobenzene have been synthesized by the *b*-oxobilane route. Isocoproporphyrin tetramethyl ester (**7a**) was prepared from pyrromethanes corresponding to rings DA and BC of the macrocycle, and the de-ethyl analogue (**7b**) was prepared in a similar fashion; acetylation of the latter followed by reduction and dehydration then afforded dehydroisocoproporphyrin tetramethyl ester (**7d**). Minor by-products arising in the syntheses have been shown to arise by rearrangement of the BC pyrromethane.

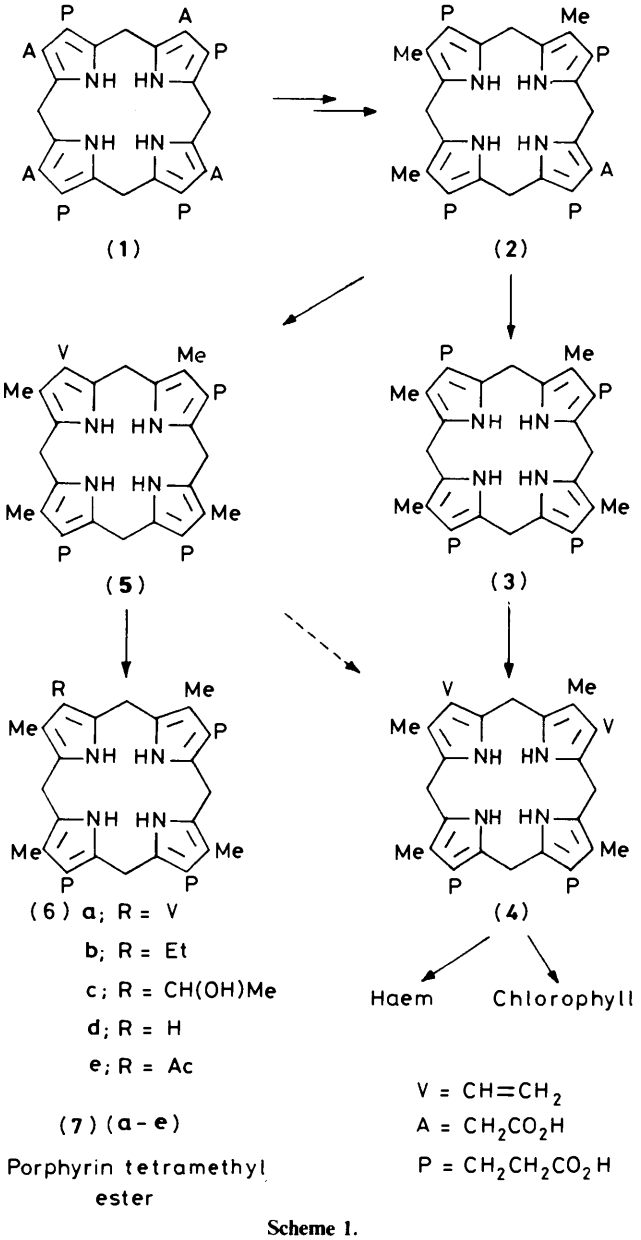
During the normal process of haem biosynthesis, uroporphyrinogen-III (**1**) is converted into coproporphyrinogen-III (**3**) by a series of four consecutive decarboxylations of the acetic acid side-chains (Scheme 1).[2] However, in the abnormal metabolic condition porphyria cutanea tarda (whether of genetic origin, or caused by poisoning, *e.g.* by hexachlorobenzene or other drugs), the uroporphyrinogen decarboxylase enzyme appears to be impaired, and the intermediate pentacarboxylic porphyrinogen (**2**) accumulates and undergoes an alternative series of transformations.[3] The enzyme, coproporphyrinogen oxidative decarboxylase, which normally converts coproporphyrinogen-III (**3**) into protoporphyrinogen-IX (**4**) acts upon the A-ring propionate side-chain of the pentacarboxylic porphyrinogen (**2**) to form dehydroisocoproporphyrinogen (**5a**). The latter then undergoes further transformations into isocoproporphyrin (**6b**) and its hydroxyethyl (**6c**) and de-ethyl (**6d**) analogues. [It is not yet known whether these modifications to the side-chains take place at the porphyrinogen stage, or after oxidation to the porphyrin (**6a**)].

The structures of these compounds had previously been deduced by a combination of spectroscopic and analytical methods,[4] and in order to confirm the structures of these four porphyrins (**6a**—**d**) and to provide further material for biosynthetic studies with the corresponding porphyrinogens, we undertook their synthesis.

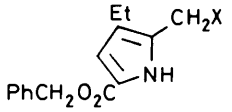
The method chosen was the *b*-oxobilane[5] route since neither the Fischer nor the MacDonald procedures is suitable for unsymmetrical porphyrins of this type.[6] Initially we set out to synthesize isocoproporphyrin tetramethyl ester (**7b**) *via* coupling of a pyrromethane amide (**10a**) (corresponding to the CD rings of the porphyrin) since the appropriate pyrroles were all readily accessible (Scheme 2).

The pyrromethane amide (**10a**) was prepared[7] in 60% yield by condensation of the pyridinium methylpyrrole (**8a**) with the lithium salt of the amido acid (**9a**); a small amount of the symmetrical pyrromethane (**11**) derived from the pyridinium methyl pyrrole (**8a**) was also formed as a by-product.

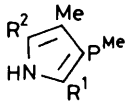
The pyrrolic precursor (**13a**) of ring C had previously been prepared in Cardiff.[8] but the original method was not entirely suitable for large-scale syntheses as the preparation of one of the aliphatic intermediates (**16a**) involved coupling the magnesium complex of benzyl hydrogen malonate with 3-methoxycarbonylpropionyl chloride in tetrahydrofuran; it was difficult to prepare pure benzyl hydrogen malonate and very large amounts of solvent were needed to solubilize its magnesium complex. Several alternative routes were investigated, and eventually the mixed ethyl methyl ester (**16b**) of β-oxoadipic acid was prepared *via* acylation of the magnesium complex of diethyl malonate with 3-methoxycarbonylpropionyl chloride followed by hydrolysis;[9] the mixed benzyl methyl ester (**16a**) was obtained by selective transesterification with benzyl alcohol at 165 °C, no catalyst being required (Scheme 3).



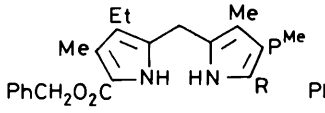
Scheme 1.



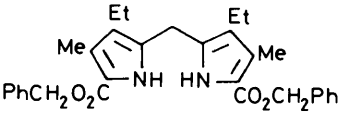
(8) a; R = Py^+Br^-
b; R = OAc



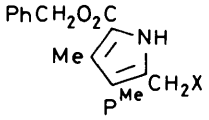
(9) a; R^1 = $CONMe_2$, R^2 = CO_2H
b; R^1 = CO_2Bu^t, R^2 = H
c; R^1 = CO_2Bu^t, R^2 = CO_2H



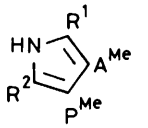
(10) a; R = $CONMe_2$
b; R = CO_2Bu^t
c; R = H



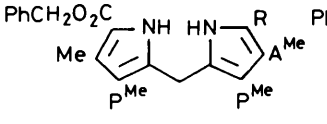
(11)



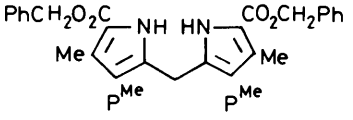
(12) a; R = OAc
b; R = Py^+Br^-



(13) a; R^1 = CO_2Bu^t, R^2 = H
b; R^1 = $CONMe_2$, R^2 = I
c; R^1 = $CONMe_2$, R^2 = H
d; R^1 = $CONMe_2$, R^2 = CO_2H

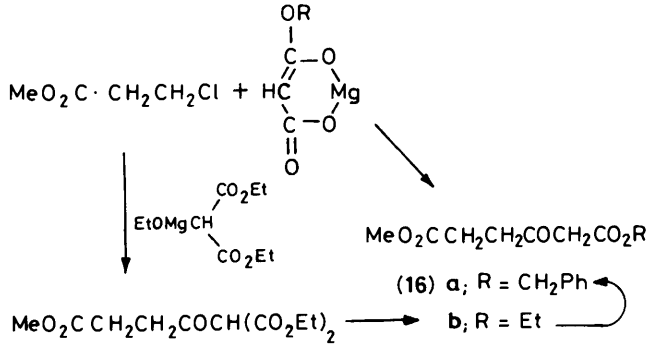


(14) a; R = CO_2Bu^t
b; R = H
c; R = $CONMe_2$



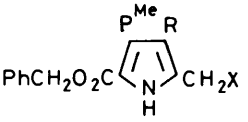
(15)

Scheme 2.

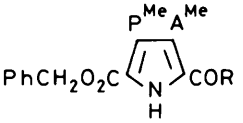


Scheme 3.

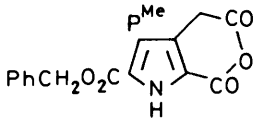
Oximation of the oxo-diester (**16a**) followed by Knorr condensation with acetylacetone then afforded the required acetylpyrrole (**17a**) in 60% yield. The latter was converted into the pyrrole acetate (**17b**) by thallium nitrate oxidative rearrangement in methanolic nitric acid.[10] Halogenation of the α-methyl group followed by hydrolysis afforded the α-carboxylic acid (**18a**), which was then transformed into the t-butyl ester (**18c**) *via* treatment of the acid chloride (**18b**), with t-butyl alcohol in the presence of dimethylaniline; a small amount of the cyclic anhydride (**19**) was also obtained as a by-product. The



(17) a; R = COMe, X = H
b; R = A^{Me}, X = H
c; R = Me, X = H
d; R = A^{Me}, X = OAc



(18) a; R = OH
b; R = Cl
c; R = OBu^t
d; R = NMe_2

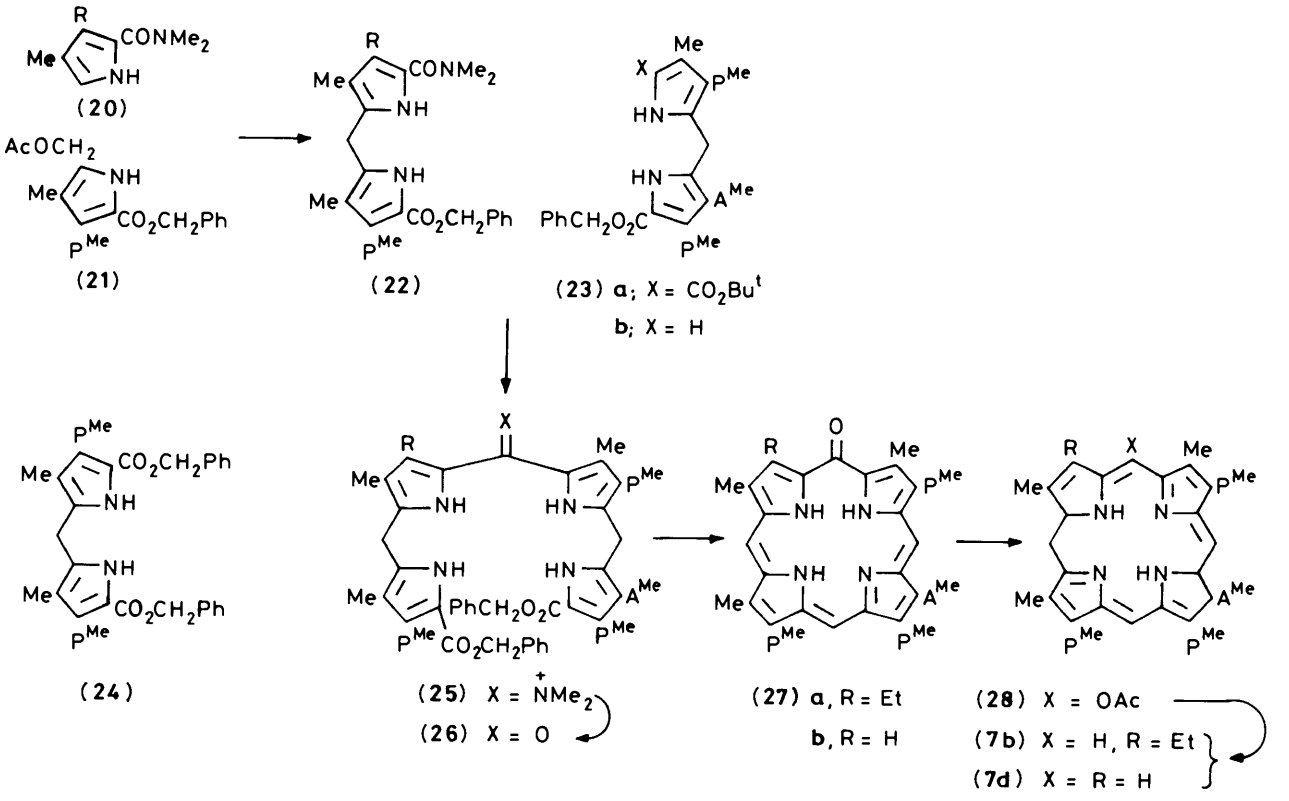


(19)

overall yield of the t-butyl ester (**18c**) was rather low, in contrast to experience with similar transformations of other pyrroles, but this was attributed in part to a deactivating effect by the neighbouring β-acetate residue (whereas in other cases the β-substituent was methyl, ethyl or propionate). Attempts to prepare the trichloroethyl ester analogue also gave low yields. For these reasons we abandoned the preparation of the pyrromethane (**14a**) and investigated the preparation of a pyrromethane amide (**14c**) corresponding to the CD rings of the isocoproporphyrin, and a pyrromethane t-butyl ester (**10b**) corresponding to the AB rings (Scheme 2). The latter was readily prepared in 60% yield by coupling the acetoxymethylpyrrole (**8b**) with the α-free pyrrole (**9b**) in acetic acid containing toluene-*p*-sulphonic acid as catalyst.[11] The precursor (**17a**) of the C-ring pyrrole amide (**13b**) was prepared from the acid chloride (**17b**) and dimethylamine, and then hydrogenolysed and iodinatively decarboxylated to the iodopyrrole amide (**13b**). The latter was hydrogenated over platinum oxide to form the α-free pyrrole (**13c**) and coupled with the acetoxymethylpyrrole (**12**) to give the desired pyrromethane amide (**14c**).

Both pyrromethanes (**10b**) and (**14c**) were also prepared[7] by coupling the pyridinium methylpyrroles (**8a**) and (**12b**) with the lithium salts of the pyrrolecarboxylic acids (**9c**) and (**13d**) respectively but the yields were lower in both cases and larger amounts of the symmetrical pyrromethanes (**11**) and (**15**) were formed as by-products.

The pyrromethane amide (**14c**) was then converted into its phosphoryl chloride complex ($\lambda_{max.}$ 275 and 378 nm) and heated with the α-free pyrromethane (**10c**) obtained by trifluoroacetic acid-catalysed hydrolysis and decarboxylation of the t-butyl ester. Unfortunately, in spite of numerous attempts under a variety of conditions none of the expected tetrapyrrolic imine salt was detected; the failure of this reaction was attributed to the β-acetate residue neighbouring the activated amide residue in the phosphoryl chloride complex (**23b**), combined perhaps with steric hindrance to substitution by the bulky propionate group in the β-position of the other pyrromethane. Interestingly, a literature survey[12] showed that none of the other *b*-



Scheme 4.

oxobilanes previously described was prepared from a pyrromethane amide bearing an acetate residue at the β-position next to the amide residue.

For these reasons we sought an alternative approach *via* pyrromethanes corresponding to the AD and BC rings of the isocoproporphyrin as shown in Scheme 4; the objective was to minimise steric effects on *b*-oxobilane formation by coupling at the position between two β-alkyl side-chains rather than the more bulky ester side-chains. This choice was also favoured by the relative accessibility of the required pyrroles. The BC pyrromethane t-butyl ester (**23a**) was synthesized as described in the preceding paper, and the AD pyrromethane (**22**) from the acetoxymethyl pyrrole (**21**) and the α-free pyrrole (**20a**) by heating in glacial acetic acid containing toluene-*p*-sulphonic acid as catalyst. A small amount of the symmetrical pyrromethane (**24**) was formed as a by-product.

Hydrolysis and decarboxylation of the pyrromethane t-butyl ester (**23a**) afforded the α-free pyrromethane (**23b**) which was immediately coupled with the phosphoryl chloride complex of the pyrromethane amide (**22**). The intermediate imine salt (**25a**) formed had $\lambda_{max.}$ 413 nm and on hydrolysis afforded the b-oxobilane (**26a**) in 21% overall yield. The latter was hydrogenolysed to the corresponding di-acid over palladium–charcoal and cyclized with trimethyl orthoformate in the presence of trichloroacetic acid. The resulting blue-green oxophlorin (**27a**) was acetylated to form the α-acetoxyisocoproporphyrin tetramethyl ester (**28a**), and the structure was confirmed by visible, mass, and n.m.r. spectral analyses including titrations with the europium shift reagent [Eu(fod)$_3$]; two of the three *meso*-proton resonances (at the β- and δ-positions) moved markedly to lowfield, as expected due to bidentate chelation with the shift reagent.[3b] Hydrogenolysis of the α-acetoxyporphyrin over palladium–charcoal followed by careful reoxidation with DDQ then afford isocoproporphyrin tetramethyl ester (**7a**) which proved to be identical in all respects (spectra, t.l.c., and h.p.l.c.) with naturally derived material, especially its behaviour on n.m.r. spectral titration with europium shift reagent.[3b] Our material was also shown to be identical (m.p. and mixed m.p.) with another sample of synthetic material, kindly provided by the late Professor G. W. Kenner, which had been synthesized by the tripyrrene biladiene route.[13] Isocoproporphyrin has also been synthesized by Clezy by the *b*-bilene route.[14]

A by-product formed in the oxobilane cyclization and separated by chromatography at the acetoxyporphyrin stage was shown by n.m.r. and mass spectra to be an isomeric acetoxyporphyrin; in contrast in the titration with europium shift reagent only one of the three *meso*-proton resonances moved to very lowfield, and this led us to the conclusion that the B-ring of this isomer was reversed, *i.e.* it had structure (**29a**). This was confirmed by conversion into the corresponding *meso*-unsubstituted porphyrin (**30a**) by hydrogenolysis followed by reoxidation, when n.m.r. shift reagent titrations again showed that only one *meso*-proton resonance moved to very lowfield.

It was clear that a rearrangement had occurred during the synthesis, and h.p.l.c. analysis of the *b*-oxobilane showed that it was a mixture of two components which field desorption mass spectrometry showed each had the same molecular weight (986); the two starting pyrromethanes (**22a**) and (**23b**) were, however, each shown by n.m.r. and h.p.l.c. to be single isomerically pure compounds. The reason for the formation of two oxobilanes was thought to be that traces of acid derived from unchanged phosphoryl chloride caused rearrangement of the α-free pyrromethane (**23b**) to the isomer (**31b**) prior to coupling with the amide (**22b**). This has now been confirmed by later work.[15]

The strategy adopted for the synthesis of the congeners (**7a**), (**7c**), and (**7d**) of isocoproporphyrin tetramethyl ester (**7b**) was very similar to that of isocoproporphyrin itself (Scheme 4) and our initial target was the de-ethyl isocoproporphyrin ester (**7d**). The pyrromethane amide (**22b**) required for the synthesis was prepared by coupling the acetoxymethyl pyrrole (**21**) with the 4-methylpyrrole amide (**20b**). The latter was prepared *via* hy-

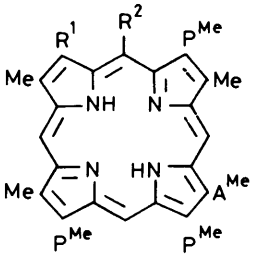
drolysis of the known methyl 4-methylpyrrole-2-carboxylate,[16] followed by conversion into the acid chloride and treatment with dimethylamine; attempts to convert the pyrrole ester directly into an amide by heating with dimethylamine, or even with morpholine under forcing conditions in a sealed tube were unsuccessful. The amide (**20b**) was coupled with the acetoxymethyl pyrrole (**21**) in dichloromethane containing tin(IV) chloride at −20 °C and afforded the required DA pyrromethane amide (**22b**), as well as the two symmetrical pyrromethanes (**24**) and (**32**), which were readily separated by chromatography. Improved yields of the unsymmetrical pyrromethane (**22b**) were formed when the coupling reaction was carried out in methanol containing toluene-*p*-sulphonic acid, and only a trace of the symmetrical pyrromethane (**24**) was observed as a by-product. The formation of the symmetrical pyrromethane (**24**) was an expected side-reaction, but the formation of the other by-product (**32**) was unexpected and it must have arisen as a result of acid or tin chloride-catalysed cleavage of the unsymmetrical pyrromethane (**22b**).

An alternative synthesis of the pyrromethane (**22b**) from the acetoxymethylpyrrole (**34b**) and the α-free pyrrole (**33**) was also investigated. Attempts to prepare the dimethyl pyrrole amide (**34a**) by the Fischer and Fink procedure[17] from the oxime derived from *N*,*N*-dimethylacetoacetamide and hydroxymethylenebutanone afforded only the trimethyl pyrrole amide (**35**) whereas with benzyl oximinoacetoacetate the dimethyl pyrrole ester is the major product, *i.e.* (**36**). The desired dimethylpyrrole (**37a**) was, therefore, prepared from the benzyl ester (**36**) by hydrogenation, conversion into the acid chloride, and treatment with dimethylamine. The pyrrole amide was converted into the acetoxymethyl derivative (**37b**) with lead tetra-acetate in dichloromethane, although interestingly when the reaction was carried out in acetic acid the symmetrical pyrromethane (**32**) was formed in high yield; similar reactions were observed with the amide (**37b**) derived from cryptopyrrole, the acetoxymethyl pyrrole (**37b**) being formed in dichloromethane, and the pyrromethane (**38**) in acetic acid.

The pyrrole (**33**) was prepared from the dimethylpyrrole (**17c**) by chlorination and hydrolysis to the α-carboxylic acid, followed by iodinative decarboxylation and hydrogenolysis over platinum. Coupling of the acetoxymethylpyrrole amide (**34b**) with the α-free pyrrole (**33**) in methanol containing toluene-*p*-sulphonic acid then afforded the desired (AD) pyrromethane (**22b**) in good yield, and this proved to be identical with material prepared by the alternative route.

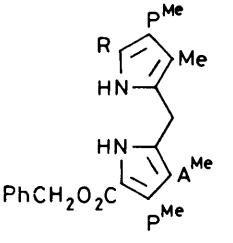
Coupling of the phosphoryl chloride complex of the pyrromethane amide (**22b**) with the α-free pyrromethane (**23b**) then afforded the imine salt (**25b**) which was purified by chromatography, hydrolysed to the *b*-oxobilane (**26b**) and cyclised to the oxophlorin (**27b**) in the same way as in the earlier series. The latter was converted into the acetoxyporphyrin (**28b**), and as in the previous case a small amount of an isomeric acetoxyporphyrin (**29b**) was also found, due to reversal of the B-ring pyrrole in the BC pyrromethane. Hydrogenolysis of the acetoxyporphyrin (**28b**) followed by reoxidation with DDQ then afforded de-ethylisocoproporphyrin tetramethyl ester (**7d**).

The structure of the minor by-products isolated in the syntheses of the *meso*-acetoxyporphyrin (**28a**) and (**28b**) was confirmed by an alternative synthesis of (**29b**) involving coupling of the pyrromethane (**31b**) with the pyrromethane amide (**22b**)–phosphoryl chloride complex. The *b*-oxobilane (**39**) prepared in this way was converted into the corresponding

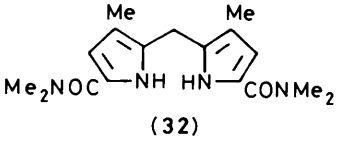


(**29**) a; R^1 = Et, R^2 = OAc
b; R^1 = H, R^2 = OAc

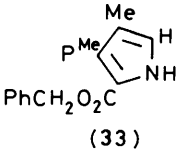
(**30**) a; R^1 = Et, R^2 = H
b; R^1 = R^2 = H



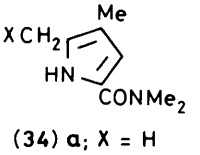
(**31**) a; R = CO_2Bu^t
b; R = H



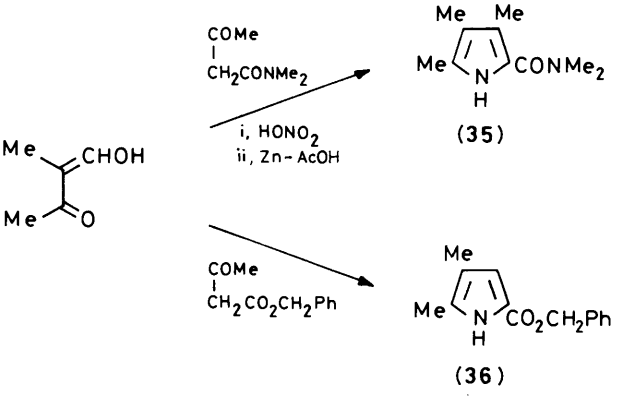
(**32**)



(**33**)

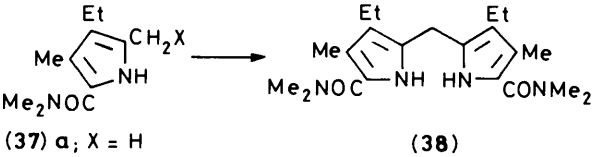


(**34**) a; X = H
b; X = OAc



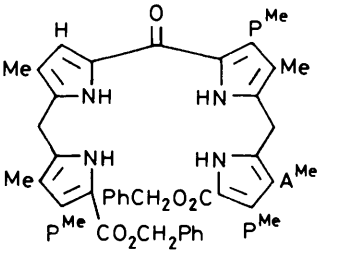
(**35**)

(**36**)



(**37**) a; X = H
b; X = OAc

(**38**)



(**39**)

oxophlorin, and thence into the acetoxyporphyrin (**29b**) in the same way as for the analogues described above. The product was again contaminated with a small amount of another acetoxyporphyrin as shown by h.p.lc. and spectral analyses; this proved to be identical with the acetoxyporphyrin precursor (**28b**) of de-ethylisocoproporphyrin (**7d**) by direct comparisons (mixed m.p., h.p.l.c., and spectra). This result conclusively proved that the rearrangements observed in both the isocoproporphyrin and de-ethylisocoproporphyrin syntheses were occurring at the pyrromethane stage.

Finally, dehydroisocoproporphyrin tetramethyl ester (**7b**) was prepared from the de-ethylisocoproporphyrin (**7a**) by the route outlined schematically below. Acetylation of the copper complex with acetic anhydride/tin(IV) chloride in dichloromethane followed by demetallation afforded the β-acetylporphyrin (**7e**) which was reduced with sodium borohydride to form the hydroxyethylporphyrin (**7c**); the latter was then dehydrated to the vinylporphyrin (**7b**) by heating in chlorobenzene in the presence of toluene-*p*-sulphonic acid. The products formed in this series of reactions were shown to have chromatographic (t.l.c. and h.p.l.c.) and mass spectral characteristics identical with naturally derived material, and their properties corresponded closely with those synthesized by other routes.

Biosynthetic experiments with the porphyrinogens (**6a**), (**6b**), and (**6d**) have already been described elsewhere[18] and these show that all three are converted by chicken red cell haemolysates into dihydroprotoporphyrin, protoporphyrin and pemptoporphyrin respectively. This raises the interesting possibility that there may be an alterative pathway[18] from dehydroisocoproporphyrinogen (**5**) to protoporphyrinogen (**4**) in abnormal metabolism (*cf.* Scheme 1).

Experimental

M.p.s were determined on a Kofler block and are uncorrected. Reactions were monitored by t.l.c., h.p.l.c., and by u.v. and visible spectra as appropriate. In a number of instances, especially with pyrromethanes and oxobilanes, the intermediates in porphyrin synthesis were only obtained as gums or foams; however, the purity of all these intermediates was confirmed in each case by t.l.c. or h.p.l.c. and by spectroscopic methods (usually n.m.r.) before proceeding to the next stages in the syntheses. ^{1}H n.m.r. spectra were determined with a Perkin-Elmer R32 90 MHz instrument, and ^{13}C-spectra on a Bruker 360 MHz instrument in $CDCl_3$ solution unless otherwise stated. Chemical shifts are given as δ values from internal $SiMe_4$. Mass spectra were measured with a Varian CH5D spectrometer either by field desorption (wire currents 10-20 μA) or by electron impact at 50 μA and 70 eV with source temperatures in the range 200—250 °C.

Pyrroles

t-Butyl 3-(2-*Methoxycarbonylethyl*)-4-*methylpyrrole*-2-*carboxylate* (**9b**).—t-Butyl 3-(2-methoxycarbonylethyl)-5-iodo-4-methypyrrole-2-carboxylate (500 mg, 1.27 mmol) and anhydrous sodium acetate (0.3 g) were dissolved in methanol (5 ml) and platinum oxide (5 mg) was added; the mixture was then hydrogenated at 20 °C and 760 mmHg until uptake was complete. The catalyst was filtered off through Celite and the filtrate evaporated to dryness. The residue was partitioned between ethyl acetate (10 ml) and aqueous sodium carbonate (10%; 10 ml). The organic layer was separated and washed with water (2 × 5 ml) and dried ($MgSO_4$). Removal of the solvent gave the desired pyrrole (320 mg, 94%) as an oil which could not be induced to crystallise; $\nu_{max.}$(Nujol) 3 360 (NH), 1 736 (methyl ester C=O), and 1 695 cm^{-1} (t-butyl ester C=O); δ 9.30 (1 H, s, NH), 6.56 (1 H, d, 5-H), 3.58 (3 H, 2-OCH_3), 2.95 (2 H, t, 3-CH_2CH_2CO), 2.43 (2 H, t, 3-CH_2CH_2CO), 1.95 (3 H, s, 4-CH_3), and 1.48 [9 H, 2, $OC(CH_3)_3$]; *m/z* (f.d.) 267 (M^+, 100%).

t-Butyl 5-*Benzyloxycarbonyl*-4-(2-*methoxycarbonylethyl*)-3-*methoxycarbonylmethylpyrrole*-2-*carboxylate* (**18c**).—(*a*) 5-Benzoyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylic acid (1.00 g) obtained by hydrogenolysis of the corresponding benzyl ester over Pd–C was stirred with thionyl chloride (5 ml) at 20 °C for 1 h. The excess of thionyl chloride was removed under reduced pressure and t-butyl alcohol (5 ml) and *N*,*N*-dimethylaniline (2.5 ml) were slowly added. The mixture was heated at 70 °C for 2 h and then left overnight at 20 °C. Dichloromethane (15 ml) was added and the solution washed with sulphuric acid (2M; 2 × 5 ml), aqueous sodium carbonate (10%; 2.5 ml), and water (10 ml) and then dried ($MgSO_4$). Removal of the solvent gave a green oil (0.62 g) which was found to be a mixture by t.l.c. separation was achieved on silica preparative layer chromatography plates, developed with dichloromethane–ethyl acetate (9:1) yielding the desired pyrrole (0.20 g, 17%) as a yellow oil, which crystallized with time, m.p. 38—41 °C; δ 9.63 (1 H, s, NH), 7.43 (5 H, s, *Ph*CH_2O), 5.37, (2 H, s, PhCH_2O), 3.86 (2 H, s, 3-CH_2CO), 3.70 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), 3.04 (2 H, t, 4-CH_2CO), 2.54 (2 H, t, 4-CH_2CH_2CO), and 1.54 [9 H, s, $OC(CH_3)_3$].

(*b*) 5-Benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylic acid (0.5 g) was treated with oxalyl chloride (2 ml) for 2 h. The excess of oxalyl chloride was removed under reduced pressure and the resulting oil treated with t-butyl alcohol (2.5 ml) and *N*,*N*-dimethylaniline (1.25 ml) at 70 °C for 2 h and then left overnight at 20 °C. Dichloromethane (8 ml) was added to the blue solution and the whole then washed with dilute sulphuric acid (2M; 2 × 5 ml), aqueous sodium carbonate (10%; 2 × 5 ml), and water (2 × 5 ml) and dried ($MgSO_4$). Removal of the solvent gave a blue oil which was purified on silica preparative plates developed with dichloromethane–ethyl acetate (9:1, v/v). The t-butyl ester pyrrole (49 mg, 9%) was isolated as fine white needles, m.p. 39—42 °C, identical with the sample prepared as in (*a*).

Benzyl 3-(2-*Methoxycarbonylethyl*)-4-*methoxycarbonylmethyl*-5-(2,2,2-*trichloroethoxycarbonyl*)*pyrrole*-2-*carboxylate*.—5-Benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylic acid (250 mg), trichloroethanol (105 mg), and dicyclohexylcarbodi-imide (128 mg) were dissolved in dry ether (50 ml) and stirred at 20 °C for 20 h. The dicyclohexylurea formed was then filtered off and the ether removed under reduced pressure. The residual yellow oil was dissolved in acetone and filtered. Removal of the acetone gave a yellow oil which was dissolved in ether (25 ml), and the solution washed with aqueous sodium carbonate (10%; 10 ml) and dried ($MgSO_4$). Removal of the solvent gave a yellow solid which crystallized from dichloromethane–light petroleum (b.p. 40–60 °C) to give the desired pyrrole (34 mg, 10%) as yellow needles, m.p. 211—214.5 °C (Found: M^+, 533.037. $C_{22}H_{22}Cl_3NO_8$ requires *M*, 533.041); *m/z* (e.i.) 533 (M^+, 4.6%), 535 (3.9), 537 (1.0), 442 (2.75), 444 (3.3), and 91 (100).

Benzyl 5-*Dimethylcarbamoyl*-4-*methoxycarbonylmethyl*-3-(2-*methoxycarbonylethyl*)*pyrrole*-2-*carboxylate* (**18d**).—5 Benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylic acid (1.00 g) was treated with freshly distilled thionyl chloride (5 ml) at 20 °C for 1.5 h. Removal of the excess of thionyl chloride under reduced pressure gave a yellow oil which was dissolved in dry benzene (50 ml). Dimethylamine gas was passed through the solution for 30 min and the resulting solution washed with water (2 × 20 ml)

and dried ($MgSO_4$). Removal of the benzene gave a yellow solid which was recrystallized from dichloromethane–light petroleum (b.p. 60—80 °C) to give *benzyl 5-dimethylcarbamoyl-4-methoxycarbonylmethyl-3-(2'-methoxycarbonylethyl)pyrrole-2-carboxylate* (1.00 g, 94%) as needles, m.p. 133—134 °C (Found: C, 60.8; H, 6.25; N, 6.7; $C_{22}H_{26}N_2O_7$, requires C, 61.4; H, 6.0; N, 6.5%); δ 9.75 (1 H, s, NH), 7.36 (5 H, s, $PhCH_2O$), 5.39 (2 H, s, $PhCH_2O$), 3.67 (3 H, s, OCH_3), 3.60 (3 H, s, OCH_3), 3.00 [6 H, s, $CON(CH_3)_2$], 3.00 (2 H, t, 3-CH_2CO), 2.50 (2 H, t, 3-CH_2CH_2CO); *m/z* (f.d.) 430 (100); *m/z* (e.i.) 430 (M^+, 13), 385 (15), 91 (100), and 45 (20).

5-Dimethylcarbamoyl-4-methoxycarbonylmethyl-3-(2'-methoxycarbonylmethyl)pyrrole-2-carboxylic acid (**13d**).—Benzyl 5-dimethylcarbamoyl-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (5.0 g) was dissolved in dry tetrahydrofuran (100 ml) and hydrogenated over 10% palladium–charcoal (0.5 g) with a trace of triethylamine, until hydrogen uptake was complete (280 ml). The catalyst was filtered off through Celite and evaporation of the filtrate gave a colourless oil. This was dissolved in chloroform (100 ml) and extracted with aqueous sodium carbonate (10%; 4 × 50 ml) and the combined extracts saturated with sulphur dioxide. The aqueous solution was extracted with chloroform (4 × 50 ml) and the chloroform extracts dried ($MgSO_4$) and evaporated to give the desired *pyrrole-2-carboxylic acid* (3.0 g, m.p. 198—201 °C (Found: C, 52.7; H, 6.1; N, 8.2. $C_{15}H_{20}N_2O_7$, requires C, 52.9; N, 8.2%); δ 10.5 (1 H, s, CO_2H), 9.10 (1 H, s, NH), 3.66 (6 H, s, 2 × OCH_3), 3.64 (2 H, s, 4-CH_2CO), 3.04 [6 H, s, $CON(CH_3)_2$], 3.00 (2 H, t, 3-CH_2CH_2CO), and 2.60 (2 H, t, 3-CH_2CH_2CO); *m/z* (f.d.) 340 (M^+, 100%).

5-Iodo-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-dimethylcarbamoylpyrrole (**13b**).—The foregoing pyrrole-2-carboxylic acid (**13d**) (1.0 g) was dissolved in methanol (5 ml) and a solution of anhydrous sodium hydrogen carbonate (0.25 g) in water (5 ml) was added and the mixture heated until a clear solution was obtained. A solution of iodine (0.738 g) and potassium iodide (1.60 g) in water (9 ml) was added slowly to the stirred mixture at 65 °C. After the addition the mixture was stirred for a further 30 min at 60 °C. The mixture was then kept at 0 °C overnight. The off-white solid was filtered off and washed with hot water and recrystallised from aqueous methanol to give the desired iodopyrrole (0.70 g, 56%) as needles, m.p. 130.5—131 °C (lit.,[19] 129—131 °C), δ 0.09 (1 H, s, NH), 6.36 (6 H, s, 2 × OCH_3), 6.42 (2 H, s, 3-CH_2CO), 7.00 [5 H, s, $CON(CH_3)_2$], and 7.2—7.6 (4 H, m, 4-CH_2CH_2CO); *m/z* (f.d.) 422 (M^+, 100%), 844 ($2M^+$, 4), and 845 (15).

4-(2-Methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-dimethylcarbamoylpyrrole (**13c**).—The foregoing iodopyrrole (**13b**) (500 mg) was dissolved in a solution of anhydrous sodium acetate (0.30 g) in methanol (5 ml) and hydrogenated over platinum oxide (5 mg) at 760 mmHg and 20 °C until hydrogen uptake was complete (26.5 ml). The catalyst was filtered off, the methanol removed, and the residue partitioned between ethyl acetate (15 ml) and aqueous sodium carbonate (10%; 15 ml). The organic layer was separated, washed with water (2 × 15 ml), and dried ($MgSO_4$). Removal of the solvent gave a clear oil (350 mg, 100%) shown to be the desired α-free pyrrole (**13c**) by its spectra and used directly in pyrromethane preparations without further purification; δ 9.20 (1 H, s, NH), 6.68 (1 H, d, 5-CH_2CO), 3.06 [6 H, s, $N(CH_3)_2$], and 2.4—2.8 (4 H, m, CH_2CH_2CO).

4,5-N,N-Tetramethylpyrrole-2-carboxamide (**34a**).—A solution of 4,5-dimethylpyrrole-2-carboxylic acid (2.80 g) in methanol was neutralized to litmus with methanolic potassium hydroxide. Methanol was removed under reduced pressure and the residue dried *in vacuo* overnight. The potassium salt was suspended in dry benzene (60 ml) and freshly distilled oxalyl chloride (1.78 ml) was added to the stirred mixture over several minutes. The mixture was stirred for a further 1 h (with exclusion of moisture) and then dry dimethylamine gas bubbled through the solution for 5 min. The mixture was stirred for a further 1 h and the dark solution then washed with water (2 × 60 ml), dried ($MgSO_4$) and, with charcoal, filtered, and evaporated to give a dark residue. Two crystallizations from methanol gave 4,5,*N*,*N*-tetramethylpyrrole-2-carboxamide (1.78 g, 53%) as pale straw coloured crystals, m.p. 175—175.5 °C (lit.,[20] m.p. 173—175 °C); 10.10 (1 H, br, NH), 6.34 (1 H, d, *J* 2 Hz, pyrrolic H), 3.17 [6 H, s, $N(CH_3)_2$], 2.18 (3 H, s, CH_3), and 1.99 (3 H, s, CH_3).

5-Acetoxymethyl-4,N,N-trimethylpyrrole-2-carboxamide (**34b**).—Lead tetra-acetate (6.0 g) was added, over several minutes, to a stirred solution of the foregoing pyrrole-2-carboxamide (**34a**) (2.0 g) in dichloromethane (70 ml) and the mixture stirred at 20 °C for 16 h. The solution was washed with water (70 ml), dried ($MgSO_4$), filtered, and evaporated to dryness. Crystallisation of the residue from dichloromethane–light petroleum (b.p. 60—80 °C) afforded the *2-carboxamide* (2.32 g, 87%) as needles, m.p. 137—140 °C; δ 10.13 (1 H, NH), 7.33 (1 H, d, *J* 2 Hz, pyrrolic H), 5.04 (2 H, s, CH_2), 3.18 [6 H, s, $N(CH_3)_2$], 2.08 (3 H, s, CH_3), and 2.00 (3 H, s, CH_3) (Found: M^+, 224.1165. $C_{11}H_{16}N_2O_3$ requires *M*, 224.1161).

5-Acetoxymethyl-4-ethyl-3,N,N-trimethylpyrrole-2-carboxamide (**37b**).—Lead tetra-acetate (1.33 g) was added, over several minutes, to a stirred solution of 4-ethyl-3,5,*N*,*N*-tetramethylpyrrole-2-carboxamide[21] (0.50 g) in dichloromethane (28 ml), and a white precipitate of lead(II) acetate precipitated after a few minutes. The mixture was stirred overnight, washed with distilled water, and dried ($MgSO_4$), filtered, and evaporated to dryness; the residue crystallised from dichloromethane–light petroleum (b.p. 60—80 °C) to give 5-acetoxymethyl-4-ethyl-3,*N*,*N*-trimethylpyrrole-2-carboxamide (0.56 g, 84%) as a pale yellow solid, m.p. 119—121 °C (softening at 110 °C); (Found: M^+, 252.1486. $C_{13}H_{20}N_2O_3$ requires *M*, 252.14738); δ 9.25 (1 H, NH), 4.98 (2 H, s, CH_2OCO), 3.03 [6 H, s, $N(CH_3)_2$], 2.43 (2 H, q, CH_2CH_3), 2.00 (3 H, s, pyrrolic CH_3), and 1.05 (3 H, t, CH_2CH_3); *m/z* (e.i.) 252 (19%), 236 (36), 208 (18), 193 (44), 176 (61), and 149 (100).

4,N,N-Trimethylpyrrole-2-carboxamide (**20b**).—A solution of 4-methylpyrrole-2-carboxylic acid (2.30 g) in methanol (20 ml) was neutralised to litmus with methanolic potassium hydroxide and then evaporated under reduced pressure and the residue dried *in vacuo* overnight.

The potassium salt was suspended in dry benzene (60 ml) and freshly distilled oxalyl chloride (2.35 g) added over several minutes. The mixture was stirred for 1 h after which dry dimethylamine gas was bubbled through it for 5 min. The solution was then stirred for a further 30 min after which it was washed with water (2 × 60 ml), dried ($MgSO_4$ and with decolourising charcoal), filtered through Celite, and evaporated to dryness under reduced pressure. Crystallisation from dichloromethane–light petroleum (b.p. 60—80 °C) afforded 4,N,N-trimethylpyrrole-2-carboxamide (1.34 g, 48%) as needles, m.p. 95—97 °C (Found: M^+, 152.0947. $C_8H_{12}N_2O$ requires *M*, 152.0950); δ 9.8 (1 H, vbr, NH), 6.70 (1 H), 6.41 (1 H, pyrrolic H), 3.19 [6 H, s, $N(CH_3)_2$], and 2.09 (3 H, s, CH_3); *m/z* (e.i.) 152 (23%) and 108 (100).

t-Butyl 3-(2'-Methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate [*Precursor of* (**31**)].—A suspension of t-butyl 5-iodo-3-(2'-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate[22]

(500 mg), anhydrous sodium acetate (0.30 g), and Adams catalyst (2 mg) in methanol was shaken at 20 °C and 1 atm in hydrogen for 3 h. The mixture was partitioned between ethyl acetate (30 ml) and 10% aqueous sodium carbonate (30 ml), the organic phase separated, washed with water (2 × 50 ml), dried ($MgSO_4$), filtered, and evaporated (rotary evaporator) to afford the desired pyrrole (330 mg, 98%) as a colourless oil. This could not be induced to crystallise and was used directly for pyrromethane preparation.

Pyrromethanes

Benzyl 5'-Dimethylcarbamoyl-3-ethyl-4'-(2-methoxycarbonylethyl)-3',4-dimethylpyrromethane-5-carboxylate (**10a**).—5-Dimethylcarbamoyl-4-(2'-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylic acid[23] (**9a**) (1.41 g) was shaken with lithium methoxide (0.19 g) in dry formamide (40 ml) until a clear solution was obtained. This solution was then added to a stirred solution of 1-(5-benzyloxycarbonyl-3-ethyl-4-methyl-2-pyrrolylmethyl)pyridinium bromide[7] (**8a**) (2.075 g) in dry formamide (40 ml) and stirred for 24 h at 100 °C under dry nitrogen. The reaction mixture was then cooled and filtered to give the symmetrical pyrromethane, dibenzyl 3,3'-diethyl-4,4'-dimethylpyrromethane-5,5'-dicarboxylate (**11**) (0.70 g, 28%), m.p. 201—203 °C (lit.,[24] m.p. 202—203 °C); δ 9.39 (2 H, s, 2 × NH), 7.27 (10 H, s, 2 × $PhCH_2O$), 5.20 (4 H, s, 2 × $PhCH_2O$), 3.79 (2 H, s, 2-CH_2), 2.42 (4 H, q, 3- and 3'-CH_2CH), 2.27 (6 H, s, 4- and 4'-CH_3), and 1.02 (6 H, t, 3- and 3'-CH_2CH_3).

The filtrate was evaporated under reduced pressure and the residue extracted with dichloromethane (4 × 25 ml); the combined extracts were washed with water (2 × 25 ml), dried ($MgSO_4$), and evaporated to give a brown oil which crystallised from ether–light petroleum (b.p. 40—60 °C) to give the desired *pyrromethane* (1.44 g, 59%) as needles, m.p. 184—186 °C; δ 10.30 (1 H, s, NH), 9.89 (1 H, s, NH), 7.32 (5 H, s, $PhCH_2O$), 3.77 (2 H, s, 2-CH_2), 3.70 (3 H, s, OCH_3), 3.00 [6 H, s, $CON(CH_3)_2$], 2.3—2.9 (6 H, m, 4'-CH_2CH_2CO, 3-CH_2CH_3), 2.27 (3 H, s, 4-CH_3), 1.99 (3 H, s, 3'-CH_3), and 1.01 (3 H, t, 3-CH_2CH_3).

Benzyl 5'-Dimethylcarbamoyl-3,3'-bis-(2''-methoxycarbonylethyl)-4'-methoxycarbonylmethyl-4-methylpyrromethane-5-carboxylate (**14c**).—(*a*) 5-Dimethylcarbamoyl-4-methoxycarbonylmethyl-3-(2'-methoxycarbonylethyl)pyrrole-2-carboxylic acid (**13d**) (1.0 g) was shaken with lithium methoxide (90 mg) in dry formamide (25 ml) until a clear solution was obtained. This solution was then added to a stirred solution of 1-[5'-benzyloxycarbonyl-4'-methyl-3'-(2-methoxycarbonylethyl)pyrrol-2'-yl]methylpyridinium bromide[25] (**12b**) (1.39 g) in dry formamide (25 ml) and the mixture heated at 100 °C, with stirring, for 24 h under nitrogen. The reaction mixture was cooled and extracted with dichloromethane (4 × 50 ml). The combined extracts were washed with water (2 × 50 ml), dried ($MgSO_4$), and evaporated to give a red oil which was chromatographed on alumina (Merck grade III) eluting with chloroform–light petroleum (b.p. 60—80 °C) [initially 1:19 (v/v) and finally 2:3 (v/v)] giving the required *pyrromethane* (405 mg, 23%) as a pale yellow oil which could not be induced to crystallise; δ 9.98 (1 H, s, NH), 9.80 (1 H, s, NH), 7.27 (5 H, s, $PhCH_2O$), 5.21 (2 H, s, $PhCH_2O$, 3.80 (2 H, s, 2-CH_2), 3.5 (11 H, br s, 3 × OCH_3, 4'-CH_2CO), 2.86 [6 H, s, $CON(CH_3)_2$], 2.2—2.8 (8 H, m, 2 × CH_2CH_2CO), and 2.2 (3 H, s, 4-CH_3); *m/z* (f.d.) 609 (M^+, 100%).

(*b*) Benzyl 5-acetoxymethyl-4-(2'-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate (**12a**) (440 mg) and 2-dimethylcarbamoyl-3-methoxycarbonylmethyl-4-(2'-methoxycarbonylethyl)pyrrole (**13c**) (350 mg) were dissolved in glacial acetic acid (10 ml). Toluene-*p*-sulphonic acid (20 mg) was added and the mixture heated at 45 °C for 3 h under dry nitrogen. The mixture was poured into ice–water (500 ml) and extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with water (3 × 25 ml), dried ($MgSO_4$), and evaporated to give a red oil which after column chromatography (alumina, Merck grade III) eluting with chloroform–light petroleum (b.p. 60—80 °C) (2:3, v/v) gave the required pyrromethane (61 mg, 84%) as a colourless oil with spectral and chromatographic properties identical with those of the previous sample.

(*c*) When the preparation was carried out in methanol instead of acetic acid but otherwise in the same way as in (*b*) the required pyrromethane (248 mg, 34%) was obtained as a pale yellow oil.

Benzyl 3-Ethyl-4'-(2-methoxycarbonylethyl)-3',4-dimethyl-5'-t-butoxycarbonylpyrromethane-5-carboxylate (**10b**).—(*a*) 4-(2'-Methoxycarbonylethyl)-3-methyl-5-t-butoxycarbonylpyrrole-2-carboxylic acid (**9c**) (1.0 g) was shaken with lithium methoxide (0.122 g) in dry formamide (24 ml) with gentle warming until a clear solution was obtained. This solution was added to a stirred solution of 1-(5'-benzyloxycarbonyl-3'-ethyl-4'-methylpyrrol-2'-ylmethyl)pyridinium bromide (**8a**) (1.334 g) in dry formamide (24 ml) under nitrogen. The stirred mixture was heated at 100 °C under nitrogen for 24 h after which it was cooled and extracted with dichloromethane (3 × 25 ml). The combined extracts were washed with water (2 × 25 ml), dried ($MgSO_4$), and evaporated to give an orange oil which was chromatographed on alumina (Merck grade III); elution was first with light petroleum (40—60 °C) and then slowly increasing proportions of dichloromethane in petroleum. The desired *pyrromethane* (300 mg, 18%) was isolated as a pale brown oil, which would not crystallise; δ 9.10 (1 H, s, NH), 8.72 (1 H, s, NH), 7.26 (5 H, s, $PhCH_2O$), 5.21 (2 H, s, $PhCH_2O$), 3.80 (2 H, s, 2-CH_2), 3.64 (3 H, s, OCH_3), 2.97 (2 H, t, 4'-CH_2CH_2CO), 2.2—2.6 (4 H, m, 4'-CH_2CH_2CO and 3-CH_2CH_3), 2.25 (3 H, s, 4-CH_3), 1.94 (3 H, s, 3'-CH_3), 1.50 [9 H, s, $COOC(CH_3)_3$], and 1.00 (3 H, t, 3-CH_2CH_3); *m/z* (f.d.) M^+, 522 (100%).

(*b*) Benzyl 5-acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate (**8b**) (801 mg), t-butyl-3-(2'-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (**9b**) (680 mg) and toluene-*p*-sulphonic acid monohydrate (40 mg) were dissolved in glacial acetic acid (10 ml) and heated at 40 °C for 10 h under dry nitrogen. The mixture was then poured into water (250 ml) and extracted with dichloromethane (4 × 30 ml). The combined extracts were washed with aqueous sodium carbonate (5%, w/v; 2 × 25 ml) and water (2 × 25 ml), dried ($MgSO_4$), decolourised with charcoal, and evaporated to give a pale yellow oil, which was chromatographed on alumina (Merck grade III) eluting with ethyl acetate–light petroleum (b.p. 40—60 °C) (1:19, v/v) to give the required pyrromethane (808 mg, 60%) as a colourless oil which did not crystallise. Its spectral characteristics were identical with those of the previous sample.

(*c*) When the reaction was carried out in methanol (instead of acetic acid) in the same way as in (*b*) only benzyl 4-ethyl-5-methoxymethyl-3-methylpyrrole-2-carboxylate was isolated, m.p. 103 °C, δ 9.19 (1 H, s, NH), 7.38 (5 H, s, $PhCH_2O$), 4.70 (2 H, s, $PhCH_2O$), 5.62 (2 H, s, 5-CH_2OCH_3), 6.08 (3 H, s, 5-CH_2OCH_3), 7.59 (2 H, q, 4-CH_2CH_3), 7.70 (3 H, s, 3-CH_3), and 8.94 (3 H, t, 4-CH_2CH_3).

(*d*) When the reaction was carried out as in (*b*) but in methanol containing 1 mol equiv. of toluene-*p*-sulphonic acid the required pyrromethane was formed in 30% yields after chromatography.

Benzyl 4'-Ethyl-4-(2-methoxycarbonylethyl)-3,3'-dimethyl-5'-dimethylcarbamoylpyrromethane-5-carboxylate (**22a**).—Benzyl 5-acetoxymethyl-3-(2-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (**21**) (1.12 g) and 3-ethyl-4-methyl-2-

dimethylcarbamoylpyrrole (**20a**) (0.54 g) were dissolved in glacial acetic acid (15 ml), treated with toluene-*p*-sulphonic acid monohydrate (0.45 g), and heated at 40 °C for 9 h. The reaction mixture was poured into ice–water (300 ml) and the product extracted into dichloromethane (3 × 100 ml). The combined extracts were washed with aqueous sodium carbonate (10%; 3 × 50 ml) and water (3 × 50 ml), dried ($MgSO_4$), and evaporated to give a red oil which was chromatographed in toluene on alumina (grade III) eluting initially with toluene, then toluene–dichloromethane (3:2, v/v). The fraction containing the desired product was collected and evaporated to dryness to afford a pale yellow solid, which was recrystallised from methanol–ether to give the *pyrromethane* (0.60 g, 40%) as needles, m.p. 162—164 °C (Found: M^+, 493.2600. $C_{28}H_{35}N_3O_5$ requires *M*, 493.2577); δ 9.98 (1 H, s, NH), 9.89 (1 H, s, NH), 7.27 (5 H, s, $PhCH_2O$), 5.21 (2 H, s, $PhCH_2O$), 3.73 (2 H, s, 2-CH_2), 3.60 (3 H, s, OCH_3), 2.9—3.2 [8 H, m, 4-CH_2CH_2CO, $CON(CH_3)_2$], 2.3—2.6 (4 H, m, 4-CH_2CH_2CO, 4′-CH_2CH_3), 1.97 (6 H, s, 3-CH_3, 3′-CH_3), and 1.08 (3 H, t, 4′-CH_2CH_3); *m/z* 493 M^+, 100%).

A second fraction was isolated and shown to be the symmetrical pyrromethane derived from the acetoxymethylpyrrole.

Benzyl 4-(2-Methoxycarbonylethyl)-3,3′-dimethyl-5′-dimethylcarbonylpyrromethane-5-carboxylate (**22b**).—(*a*) 4,*N*,*N*-Trimethylpyrrole-2-carboxamide (**20b**) (50 mg) was dissolved in dichloromethane (25 ml) and cooled to −20 °C. Stannic chloride (3 drops) was added, followed by a cooled solution of benzyl 5-acetoxymethyl-3-(2-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (**21**) (135 mg) in dichloromethane (25 ml); the mixture was then allowed to warm to 20 °C over 3 h whilst being stirred. The solution was washed with aqueous sodium hydrogen carbonate (10%; 30 ml) and water (40 ml), dried ($MgSO_4$), filtered, and evaporated to dryness. The pale orange oily residue was chromatographed on alumina (Grade III; 10 g), eluting first with benzene and then with increasing proportions of ethyl acetate in benzene. The first fraction contained dibenzyl 4,4′-bis(2-methoxycarbonylethyl)-3,3′-dimethyl-2,2′-pyrromethane-5,5′-dicarboxylate (35 mg, 17%), m.p. 89—91 °C (lit.,[19] m.p. 90—91 °C).

A second fraction was crystallised from dichloromethane–light petroleum (b.p. 60—80 °C) to give the desired unsymmetrical *pyrromethane* (30 mg, 18%) as pale orange crystals, m.p. 154—156 °C; δ 10.87 (1 H, NH), 10.21 (1 H, NH), 7.21 (5 H, C_5H_5), 6.29 (1 H, d, *J* 2 Hz, pyrrolic H), 5.15 (2 H, s, CH_2Ph), 3.87 (2 H, s, bridge CH_2), 3.60 (3 H, s, CO_2CH_3), 3.08 [6 H, s, $N(CH_3)_2$], 6.97 (2 H, t, CH_2CH_2CO), 2.46 (2 H, t, CH_2CH_2CO), 2.05 (3 H, s, CH_3), and 7.99 (3 H, s, CH_3); *m/z* (e.i.) 465 (100%), 421 (14), 392 (10), 374 (18), 357 (8), 356 (20), 329 (81), 315 (36), and 314 (31).

Elution with methanol gave a third fraction which crystallised from ethanol to give 3,3′,N,N,N′,N′-*hexamethylpyrromethane-5,5′-dicarboxamide* (**32**) as needles, m.p. 266.5—269 °C; δ 9.95 (1 H, NH), 6.33 (2 H, d, *J* 2 Hz, pyrrolic H), 3.88 (2 H, s, bridge CH_2), 3.15 [12 H, s, 2 × $N(CH_3)_2$], 8.03 (6 H, s, 2 × CH_3) (see below).

(*b*) 4,*N*,*N*-Trimethylpyrrole-2-carboxamide (50 mg) and benzyl 5-acetoxymethyl-3-(2′-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (135 mg) were suspended in methanol (15 ml) with toluene-*p*-sulphonic acid monohydrate (25 mg) and stirred at 35 °C for 2 h. Aqueous sodium carbonate (10%; 15 ml) was added and the mixture extracted with chloroform (3 × 30 ml). The combined chloroform extracts were washed with water (40 ml), dried ($MgSO_4$), filtered, and evaporated to dryness. The residual yellow oil was chromatographed on alumina as above, giving 5′-benzyloxycarbonyl-4′-(2-methoxycarbonylethyl)-3,3,*N*,*N*-tetramethyl-2,2′-pyrromethane-5-carboxamide (99 mg, 61%) as needles, m.p. 155.5—157 °C.

(*c*) A solution of benzyl 3-(2′-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (151 mg) in dichloromethane (25 ml) containing 6 drops of stannic chloride was stirred at 0 °C whilst 5-acetoxymethyl-4,*N*,*N*-trimethylpyrrole-2-carboxamide (98.5 mg) in dichloromethane (25 ml) was added dropwise over 5 min. The mixture was stirred for 4 h at room temperature, and then washed with aqueous sodium hydrogen carbonate (10; 30 ml) and distilled water (50 ml), dried ($MgSO_4$), filtered, and evaporated to dryness. The mixture was chromatographed on alumina (10 g) as above and the desired pyrromethane amide was obtained as pale pink needles (57 mg, 24%), m.p. 155—156.5 °C from dichloromethane–light petroleum (b.p. 60—80 °C).

(*d*) 5-Acetoxymethyl-4,*N*,*N*-trimethylpyrrole-2-carboxamide (2.60 g) and benzyl 3-(2′-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (3.16 g) were heated in pyridine (50 ml) for 1 h under reflux. The mixture was partitioned between chloroform (100 ml) and water (100 ml) and the organic layer separated, washed with 5% hydrochloric acid (2 × 100 ml) and distilled water (100 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed on alumina (100 g) as previously. Crystallisation of the main fraction from dichloromethane–light petroleum (b.p. 60—80 °C) afforded the desired unsymmetrical pyrromethane as needles (1.88 g, 38%), m.p. 155.5—157 °C.

(*e*) 5-Acetoxymethyl-4,*N*,*N*-trimethylpyrrole-2-carboxamide (0.80 g) and benzyl 3-(2′-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (1.25 g) were stirred in methanol (25 ml) with toluene-*p*-sulphonic acid monhydrate (400 mg) at 40 °C for 1 h. A white precipitate formed after the first few minutes. Chloroform (50 ml) was added and the solution washed with sodium hydrogen carbonate (10%; 50 ml) and distilled water (50 ml) and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed on alumina (40 g) as above. Crystallisation of the product from dichloromethane–light petroleum (b.p. 60—80 °C) gave 5′-benzyloxycarbonyl-4′-(2-methoxycarbonylethyl)-3,3′,*N*,*N*-tetramethyl-2,2′-pyrromethane-5-carboxamide (1.12 g, 57%) as needles, m.p. 155.5—157 °C.

Benzyl 4,3′-Bis-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-4′-methylpyrromethane-5-carboxylate (**23b**).—The corresponding 5′-t-butoxycarbonylpyrromethane (0.850 g 1.33 mmol) was dissolved in dry trifluoroacetic acid (10 ml) under dry nitrogen and stirred at 20 °C for 2 h. The reaction mixture was poured onto ice and water (100 ml). The resulting red oil was extracted with dichloromethane (4 × 50 ml) and the combined extracts were washed with aqueous sodium carbonate (10%; 3 × 25 ml) and water (3 × 25 ml), dried ($MgSO_4$), and evaporated to give the desired α-free *pyrromethane* (0.62 g, 86%) as a colourless oil; δ 9.71 (1 H, s, NH), 8.94 (1 H, s, NH), 7.31 (5 H, s, $PhCH_2O$), 6.38 (1 H, d, 5-H), 5.22 (2 H, s, $PhCH_2O$), 3.88 (2 H, s, 2-CH_2), 3.72 (3 H, s, OCH_3), 3.59 (3 H, s, OCH_3), 3.52 (5 H, s, OCH_3 and 3-CH_2CO), 3.01 (2 H, t, 4-CH_2CH_2CO), 2.35—2.85 (6 H, m, 4-CH_2CH_2CO and 3′-CH_2CH_2O), and 2.00 (3 H, s, 4′-CH_3).

Benzyl 5′-t-Butoxycarbonyl-4,4′-bis-(2-methoxycarbonyl)-3-methoxycarbonylmethyl-3′-methylpyrromethane-5,5′-dicarboxylate (**31a**).—t-Butyl 3-(2-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate (**9a**) (300 mg) and benzyl 5-acetoxymethyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate[26] (**17d**) (484 mg) were dissolved in glacial acetic acid (6 ml) and stirred with toluene-*p*-sulphonic acid monohydrate (17 mg) at 40 °C for 3 h. The red solution was poured into ice–water (100 ml), extracted with dichloromethane

(4 × 25 ml), and the combined extracts washed with distilled water, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was chromatographed on alumina (grade III; 20 g), eluting with 5% ethyl acetate–light petroleum (b.p. 60—80 °C) to give the title compound as prisms (439 mg, 61%), m.p. 147.5—148.5 °C; δ 9.13 (1 H, NH), 8.68 (1 H, NH), 7.37 (5 H, s, Ph), 5.27 (2 H, s, CH_2Ph), 3.83 (2 H, s, bridge CH_2), 3.70 (3 H, s), 3.65 (3 H, s), and 3.61 (3 H, s,) (3 × CO_2CH_3), 3.46 (2 H, s, acetate CH_2), 2.99 (4 H, t, 2 × CH_2CH_2CO–), 2.48 (4 H, t, 2 × CH_2CH_2CO), 1.96 (3 H, s, CH_3), and 1.51 [9 H, s, –$C(CH_3)_3$]; *m/z* (e.i.) 638 (13%), 547 (100), and 531 (78).

Benzyl 4,4′-Bis-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-3′-methyl-2,2′-pyrromethane-5-carboxylate (**31b**).—The foregoing pyrromethane t-butyl ester (**31a**) (150 mg) was dissolved in trifluoroacetic acid (2 ml) and stirred at 20 °C for 1 h under nitrogen. After addition of dichloromethane (10 ml), the solution was washed with 10% aqueous sodium carbonate (2 × 20 ml) and distilled water (2 × 30 ml), dried ($MgSO_4$), filtered, and evaporated to afford the desired α-free pyrromethane as a red oil (125 mg, 100%); δ 8.58 (1 H, NH), 8.34 (1 H, NH), 7.31 (5 H, s, C_6H_5), 6.38 (1 H, pyrrolic H), 5.24 (2 H, s, CH_2Ph), 3.77 (2 H, s, bridge CH_2), 3.65 (3 H, s), 3.62 (3 H, s), and 3.57 (3 H, s) (3 × CH_2CH_3), 3.44 (2 H, s, acetate CH_2), 2.97 (2 H, t, 4-CH_2CH_2CO), 2.63 (2 H, t, 4′-CH_2CH_2CO), 2.50 (4 H, m, 2 × CH_2CH_2CO), and 1.95 (3 H, s, CH_3).

3,3′-N,N,N′,N′-Hexamethyl-2,2′-pyrromethane-5,5′-dicarboxamide (**32**).—Lead tetra-acetate (1.50 g) was added over several minutes to a stirred solution of 4,5,*N*,*N*-tetramethylpyrrole-2-carboxamide (**34a**) (0.50 g) in acetic acid (20 ml) and the mixture stirred for a further 2 h at room temperature. It was then poured into water (300 ml) and extracted wiith chloroform (3 × 40 ml). The combined organic extracts were washed with aqueous sodium carbonate (10%; 50 ml) and distilled water (50 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to provide a residue which crystallised from ethanol to afford the title compound as needles, (0.30 g, 85%), m.p. 267—269 °C; δ 9.6 (2 H, 2 × NH), 6.70 (2 H, d, *J* 2 Hz, 2 × pyrrolic H), 3.85 (2 H, s, bridge CH_2), 3.14 [12 H, s, 2 × –$(CH_3)_2$], 2.01 (6 H, s, 2 × CH_3); *m/z* (e.i.) 316 (41), 272 (28), 228 (100), 199 (56), and 165 (48) (Found: M^+, 316.1900. $C_{17}H_{24}N_4O_2$ requires *M*, 316.1899).

3,3′-Diethyl-4,4′,N,N,N′,N′-hexamethyl-2,2′-pyrromethane-5,5′-dicarboxamide (**38**).—4-Ethyl-3,5,*N*,*N*-tetramethylpyrrole-2-carboxamide (**37a**) (0.50 g) was dissolved in glacial acetic acid (28 ml) and lead tetra-acetate (1.33 g) added portionwise, over several minutes, to the stirred solution. The mixture was stirred for a further 2 h, poured into water (200 ml), and extracted with chloroform (5 × 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to dryness, the residual yellow oil crystallising from dichloromethane–light petroleum (b.p. 60—80 °C) to give the title compound as colourless prisms (0.29 g, 79%), m.p. 255—257 °C; δ 9.45 (2 H, 2 × NH), 3.73 (2 H, s, bridge CH_2), 2.98 [12 H, s, 2 × $N(CH_3)_2$], 2.38 (4 H, q, 2 × CH_2CH_3), 1.97 (6 H, s, 2 × CH_3), 1.01 (6 H, t, 2 × CH_2CH_3); *m/z* (e.i.) 372 (18), 328 (14), 296 (30), 284 (71), 269 (53), 255 (100), and 239 (79) (Found: M^+, 372.2546. $C_{21}H_{32}N_4O_2$ requires *M*, 372.2525).

Oxobilanes

Dibenzyl 4-Ethyl-1,6,8-tris-(2-methoxycarbonylethyl)-7-methoxycarbonyl-2,3,5-trimethyl-b-oxobilane-1′,8′-carboxylate (**26a**).—Benzyl 4′-ethyl-4-(2-methoxycarbonylethyl)-3,3′-dimethyl-5′-dimethylcarbamoylpyrromethane-5-carboxylate (1.10 g) was dissolved in freshly distilled phosphoryl chloride (30 ml) and heated to 45 °C for 1 h, at which time the new band in the u.v. spectrum at $\lambda_{max.}$ 386 nm had reached a maximum. The excess of phosphoryl chloride was removed under reduced pressure and dry 1,2-dibromoethane (2 × 15 ml) added to chase out the last traces of phosphoryl chloride. The residual brown oil [$\lambda_{max.}$(CH_2Cl_2) 280 and 386 nm] was dissolved in dry dichloromethane (38 ml) and a solution of benzyl 4,3′-bis-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-4′-methylpyrromethane-5-carboxylate (1.20 g) in dry dichloromethane (38 ml) was added. The mixture was heated under reflux for 65 h in the dark and under dry nitrogen, until the new band at $\lambda_{max.}$ 414 nm had reached its maximum. Dichloromethane (150 ml) was added and the reaction mixture was washed with water (2 × 100 ml) and dried ($MgSO_4$). Removal of the solvent gave a brown oil which was chromatographed on alumina (grade III), eluting first with benzene and then with increasing proportions of ethyl acetate in benzene, and finally pure ethyl acetate. The column was then stripped with methanol and evaporation of the methanol fractions gave a light brown oil, which on dissolution in benzene and evaporation gave the desired imine salt (**28a**) (0.685 g, 29%) as a brown foam; $\lambda_{max.}$(CH_2Cl_2) 281 and 413 nm; δ 10.98 (2 H, s, 2 × NH), 10.35 (2 H, s, 2 × NH), 7.29 (10 H, m, 2 × *Ph*CH_2O), 5.23 (4 H, s, 2 × PhCH_2), 3.94 (4 H, br s, 2 × CH_2 methane bridge), 3.70 (2 H, s, 7-CH_2CO_2Me), 3.56 (3 H, s, 7-CH_2CO_2*Me*), 3.5 (9 H, s, 3 × CO_2Me), 3.26 [6 H, s, $N(CH_3)_2$], 2.8—3.1 (4 H, m, 2 × CH_2CH_2CO), 2.65—2.45 (2 H, t, 6-CH_2CH_2CO), 2.3—2.65 (8 H, m, 3 × CH_2CH_2CO, and 4-CH_2CH_3), 2.00 (3 H, s, 5-CH_3), 1.89 (6 H, s, 2 × CH_3), and 1.09 (3 H, t, 4-CH_2CH_3) (Found: M^+, 1 014.571. $C_{57}H_{68}N_5O_{11}$ requires 1 014.567).

The imine salt (665 mg) was dissolved in dichloromethane (40 ml) and hydrolysed by stirring under reflux with aqueous sodium carbonate (10%; 40 ml) for 8 h. The organic phase was separated, washed with water (2 × 20 ml), dried ($MgSO_4$), and evaporated to give an orange-brown oil which was chromatographed on alumina (grade III), eluting with benzene–ethyl acetate (7:3, v/v). The product was obtained as a yellow gum which re-chromatographed to give the *b-oxobilane* (400 mg, 64%) as a yellow foam; $\lambda_{max.}$($CHCl_3$) 280 and 348 nm; $\lambda_{max.}$($CHCl_3$ + HCl) 277 and 447 nm; δ 10.10 (1 H, s, NH), 10.00 (2 H, s, 2 × NH), 9.90 (1 H, s, N*H*), 7.25 (10 H, s, 2 × *Ph*CH_2O), 5.17 (4 H, s, 2 × PhCH_2O), 3.87 (2 H, s, methane bridge), 3.80 (2 H, s, methane bridge), 3.72 (2 H, s, 4-CH_2CO), 3.57 (6 H, s, 2 × OCH_3), 3.50 (3 H, s, OCH_3), 3.46 (3 H, s, OCH_3), 2.95 (4 H, m, 2 × CH_2CH_2O), 2.42 (10 H, m, 2 × CH_2CH_2CO, 6-CH_2CH_2CO, and 4-CH_2CH_3), 1.95 (9 H, s, 2-, 3-, 5-CH_3), and 1.20 (3 H, t, 4-CH_2CH_3); (Found: M^+, 986.505. $C_{55}H_{62}N_4O_{13}$ requires *M*, 986.510).

Dibenzyl 1,6,8-Tris-(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-2,3,5-trimethyl-b-oxobilane-1′,8′-dicarboxylate (**26b**).—5′-Benzyloxycarbonyl-4′-(2-methoxycarbonylethyl)-3,3′,*N*,*N*-tetramethyl-2,2′-pyrromethane-5-carboxamide (**22b**) (1.10 g) was converted into its phosphoryl chloride complex [$\lambda_{max.}$(CH_2Cl_2) 278 and 370 nm] and coupled with benzyl 3′,4-bis-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-4′-methyl-2,2′-pyrromethane-5-carboxylate (**23b**) (1.93 g) in the same manner as the preceding oxobilane synthesis. The product [$\lambda_{max.}$(CH_2Cl_2) 278, 361, and 412 nm] was purified by chromatography on alumina and afforded the imine salt (**25b**) (2.15 g, 88%) as a yellow foam; δ 7.35 (10 H, 2 × Ph), 6.30 (1 H, 4-H), 5.27 (4 H, s, 2 × $CH_2C_6H_5$), 3.95 (4 H, s, 2 × bridge CH_2), 3.60 (s), 3.58 (s), 3.54 (s), and 3.52 (s) [18 H, 4 × CO_2CH_3, =$N^+(CH_3)_2$], 3.44 (2 H, s, acetate CH_2), 2.5—3.3 (12 H, m, 3 × CH_2CH_2CO), 8.02 (3 H, s), and 1.78 (6 H, 3 × CH_3).

The imine salt was dissolved in benzene (120 ml) and stirred

vigorously with aqueous sodium acetate (10%; 120 ml) under gentle reflux for 12 h. The organic layer was separated and the aqueous phase extracted with chloroform (2 × 50 ml). The combined extracts were washed with water (100 ml), evaporated to dryness, and the residue dried *in vacuo*. The latter was then chromatographed on alumina (Merck grade III; 100 g) eluting with 50% ethyl acetate–benzene. The eluant was evaporated and the residue dried *in vacuo* to give the oxobilane as a yellow foam (1.635 g, 69% from pyrromethanes); $\lambda_{max.}$(EtOH) 273 and 357 nm; $\lambda_{max.}$(EtOH + HCl) 417 nm; δ 10.72 (1 H), 10.33 (1 H), 10.01 (1 H), 9.92 (1 H) (4 × N*H*), 7.24 and 7.46 (10 H, 2 × Ph), 6.53 (1 H, pyrrolic H), 5.18 (2 H, s), 5.13 (2 H, s) (2 × CH_2Ph), 3.87 (2 H, s, bridge CH_2), 3.74 (2 H, s, bridge CH_2), 3.57 (12 H, 4 × CO_2CH_3), 3.45 (2 H, s, acetate CH_2), 2.9 (6 H, m, 3 × C$H_2$$CH_2$CO), 2.45 (6 H, m, 3 × CH_2CH_2CO), 2.18 (3 H, s, CH_3), and 1.96 (6 H, 2 × CH_3).

Dibenzyl 1,5,8-Tris-(2-methoxycarbonylethyl)-7-methoxycarbonylmethyl-2,3,6-trimethyl-b-oxobilane-1′,8′-dicarboxylate (**39**).—5′-Benzyloxycarbonyl-4′-(2-methoxycarbonylethyl)-3,3′,*N*,*N*-tetramethyl-2,2′-pyrromethane-5-carboxamide (80 mg) was converted into its phosphoryl chloride complex, and coupled with benzyl 4,4′-bis-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-4′-methyl-2,2′-pyrromethane-5-carboxylate (**31**) (120 mg) in the same way as in the previous *b*-oxobilane synthesis. The crude imine formed had $\lambda_{max.}$ 275, 366 and 406 nm, and after chromatography the imine salt (73 mg) was obtained as a yellow foam and converted into the *b*-oxobilane (65 mg); δ 11.0, 10.9, 10.56, and 10.10 (4 × NH), 7.29 (10 H, 2 × CH_2*Ph*), 6.49 (1 H, 2-H), 5.16 (2 H, s), and 5.10 (2 H, s) (2 × CH_2Ph), 3.4—3.85 (6 H, m, 2 × CH_2 and acetate CH_2), 3.73 (12 H, 4 × CO_2CH_3), 2.84 (6 H, m, 3 × C$H_2$$CH_2$CO), 2.45 (6 H, m, 3 × CH_2CH_2CO), and 1.90 (9 H, pyrrolic CH_3's).

Porphyrins

α-Acetoxy-2-ethyl-4,6,7-tris-(2-methoxycarbonylethyl)-5-methoxycarbonylmethyl-1,3,8-trimethylporphyrin (**28a**).—The corresponding dibenzyl *b*-oxobilane-1′,8′-dicarboxylate (400 mg) was dissolved in dry tetrahyrofuran (50 ml) and hydrogenolysed over 10% palladium–charcoal (200 mg), with a trace of triethylamine (2 drops), at 20 °C and 1 atm. The catalyst was filtered off after hydrogen uptake had ceased, and removal of the solvent gave the required *b*-oxobilane-1′,8′-dicarboxylic acid (326 gm, 100%) as a yellow–brown foam [$\lambda_{max.}$(CH_2Cl_2) 285 and 373 nm; $\lambda_{max.}$(CH_2Cl_2 + HCl) 285 and 447 nm] The *b*-oxobilane-1′,8′-dicarboxylic acid was treated consecutively with solutions of trichloroacetic acid (5.00 g) in dichloromethane (33 ml) and trimethyl orthoformate (1.40 g) in dichloromethane (120 ml). The resulting deep red solution was stirred for 3 h in the dark, after which pyridine (1.4 ml) was added and the mixture stirred overnight in the presence of air in the dark. The resulting green solution of the oxophlorin ($\lambda_{max.}$ 424 nm) was evaporated to dryness under reduced pressure and the residue taken up in pyridine (12 ml) and acetic anhydride (4 ml). The mixture was stirred at 20 °C in the dark for 1 h after which the deep red solution was evaporated to dryness and the residue dissolved in dichloromethane (50 ml) and the solution washed with 10% sodium carbonate (2 × 30 ml), and then with water until the washings were neutral, and dried ($MgSO_4$). Removal of the solvent gave a deep red oil, which was chromatographed on alumina (Grade III), eluting with dichloromethane. The combined porphyrin containing fractions were re-chromatographed eluting with dichloromethane–benzene (1:1, v/v). N.m.r., t.l.c., and h.p.l.c. analyses of the eluates showed that two porphyrins were present and these were separated on preparative silica t.l.c. plates eluting with ethyl acetate–benzene–ethanol (20:80:1, v/v).

The lower band (R_F 0.40) was eluted with acetone, and the extract evaporated to dryness and the residue crystallised from dichloromethane–methanol to give α-acetoxyisocoproporphyrin tetramethyl ester (78 mg, 26%), m.p. 185—186 °C; $\lambda_{max.}$ 403 (log ε 5.19), 502 (4.10), 535 (3.66), 576 (3.66), and 630 nm (3.11); δ 10.05 (1 H, s, *meso-H*), 9.95 (1 H, s, *meso-H*), 9.80 (1 H, s, *meso*-H), 4.97 (2 H, s, 5-CH_2CO), 3.8—4.5 (8 H, m, 3 × C$H_2$$CH_2$CO and 2-C$H_2$$CH_3$), 3.72 (3 H, s, OCH_3), 3.66 (6 H, s, 2 × OCH_3), 3.48 (9 H, br s, 3 × CH_3), 3.0—3.4 (6 H, m, 3 × CH_2CH_2CO), 2.91 (3 H, s, $OCOCH_3$), and 1.75 (3 H, t, 2-CH_2CH_3); *m/z* (f.d.) 768 (M^+, 100%); *m/z* (e.i.) 768 (M^+, 21%), 726 (100), and 710 (22) (Found: M^+, 768.330. $C_{42}H_{48}N_4O_{10}$ requires *M*, 768.336).

The higher band (R_F 0.45) was again eluted with acetone, and the extract evaporated and the residue crystallised from dichloromethane–methanol–light petroleum (b.p. 60—80 °C), to give the acetoxyporphyrin (**29a**), m.p. 214—215 °C; $\lambda_{max.}$ 403 (log ε 5.18), 502 (4.050), 535 (3.653), 577 (3.634), and 630 nm (3.10); δ 10.12 (1 H, s, *meso-H*), 9.99 (1 H, s, *meso-H*), 9.83 (1 H, s, *meso-H*), 4.98 (2 H, s, 5-CH_2CO), 3.85—4.5 (8 H, m, 3 × C$H_2$$CH_2$CO and 2-C$H_2$$CH_3$), 3.78 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 3.65 (3 H, s, OCH_3), 3.60 (6 H, s, OCH_3 and CH_3), 3.52 (3 H, s, CH_3), 3.50 (3 H, s, CH_3), 3.05—3.5 (6 H, m, 3 × $CH_2$$CH_2$CO), 2.96 (3 H, s, $OCOCH_3$), 1.75 (3 H, t, 2-CH_2CH_3); *m/z* (f.d.) 768 (M^+, 100%); *m/z* (e.i.) 768, (M^+, 18%), 740 (52), and 726 (100) (Found: M^+, 768.334. $C_{42}H_{48}N_4O_{10}$ requires *M*, 768.336).

α-Acetoxy-4,6,7-tris-(2-methoxycarbonylethyl)-5-methoxycarbonylmethyl-1,3,8-trimethylporphyrin (*α-Acetoxyde-ethylisocoproporphyrin Tetramethyl Ester*) (**28b**).—The dibenzyl *b*-oxobilane-1′,8′-dicarboxylate (**25b**) (1.63 g) in acetone (40 ml) containing triethylamine (20 drops) was shaken with 10% palladium–charcoal (200 mg) in hydrogen at 20 °C and 1 atm for 12 h. The solution was filtered through Celite, washed well with hot methanol, acetone and ethyl acetate, and the combined filtrates evaporated to dryness to yield the b-*oxobilane diacid* as a pale yellow solid (1.03 g, 82%); $\lambda_{max.}$(EtOH) 285 and 364 nm; $\lambda_{max.}$(EtOH + 2 drops HCl) 446 nm; δ[$CDCl_3$ + 4 drops $(CD_3)_2SO$] 11.3 (1 H), 10.9 (1 H), 10.8 (1 H), and 10.67 (1 H) (pyrrolic NH's), 6.48 (1 H, pyrrolic *H*), 6.0 (2 H, br, 2 × CO_2H), 5.49 (2 H, acetate-CH_2), 4.87 and 4.82 (4 H, 2 × bridge CH_2), 3.64 and 6.41 (12 H, 4 × CO_2CH_3), 2.95 (6 H, m, 3 × C$H_2$$CH_2$CO), 2.50 (6 H, m, 3 × CH_2CH_2CO), 7.80 (3 H, s), 2.06 (3 H, s), and 1.99 (3 H, s) (3 × pyrrolic CH_3).

The *b*-oxobilanedicarboxylic acid (0.61 g) was treated consecutively with trichloroacetic acid (10 g) in dichloromethane (66 ml) and freshly distilled trimethyl orthoformate (2.5 ml) in dichloromethane (240 ml) and a dark red colour slowly developed. The mixture was stirred for 3 h in the dark. Pyridine was then added (5.6 ml) and the mixture stirred, open to the atmosphere, overnight. The dark green solution was evaporated to dryness and stirred with pyridine (24 ml) and acetic anhydride (8 ml) for 1 h in the dark. The deep red solution was evaporated to dryness and the residue taken up in dichloromethane (60 ml), washed with 10% aqueous sodium carbonate (40 ml) and distilled water (40 ml), and again reduced to dryness. The residual red oil was chromatographed on alumina (30 g; grade III) eluting with dichloromethane and the combined porphyric fractions evaporated to dryness. T.l.c. [silica plates; developed with ethyl acetate–benzene–ethanol (20:80:1)] showed that two porphyrins were present. Careful chromatography on silica (Kieselgel 60; 100 g) eluting with benzene–ethyl acetate–ethanol (170:30:1) gave partial separation and fractions were analysed by t.l.c. to determine purity. Mixed fractions were re-chromatographed in a similar fashion.

The more polar porphyric fraction (R_F 0.30) crystallised from dichloromethane–methanol to yield the title compound as a

purple solid (47 mg, 8%), m.p. 214.5—216 °C; $\lambda_{max.}$($CHCl_3$) 405 (log ε 5.49), 503 (4.33), 536 (3.97), 575 (3.95), and 627 nm (3.26); δ 9.96 (1 H), 9.80 (2 H) (meso-*H*) 8.80 (1 H, 2-H), 4.91 (2 H, s, acetate CH_2), 4.25 (6 H, m, 3 × CH_2CH_2CO), 3.73 (3 H), 3.67 (6 H), 3.58 (3 H), 3.44 (5 H), and 3.40 (6 H) (3 × ring CH_3 and 4 × CO_2CH_3), 3.25 (6 H, m, 3 × CH_2CH_2CO), 2.90 (3 H, s, $OCOCH_3$); *m/z* (e.i.) 740 (18%) and 697 (100) (Found: M^+, 768.408. $C_{42}H_{48}N_4O_{10}$ requires *M*, 768.405.

The least polar porphyrin (upper spot on t.l.c., R_F 0.35) crystallised from dichloromethane–methanol to afford a rearranged porphyrin (6.1 mg, 1%) as purple needles, m.p. 227.5—299.5 °C; $\lambda_{max.}$($CHCl_3$) 405 (log ε 5.37), 503 (4.25), 535 (3.86), 574 (3.86), and 626 nm (3.14); δ 10.11 (1 H), 9.99 (2 H), (meso-H), 8.88 (1 H, s-H), 5.00 (2 H, s, acetate CH_2), 4.33 (6 H, m, 3 × CH_2CH_2CO), 3.80 (3 H, s), 6.25 (3 H, s), 3.66 (3 H, s), 3.61 (9 H, s), 3.53 (3 H, s) (3 × ring CH_3, and 4 × CO_2CH_3), 3.29 (6 H, m, 3 × CH_2CH_2CO), 7.00 (3 H, s, $OCOCH_3$), and −4.00 (2 H, vbr, NH) (Found: M^+, 768.409. $C_{42}H_{48}N_4O_{10}$ requires *M*, 768.405).

α-*Acetoxy*-3,6,7-*tris*-(2′-*methoxycarbonylethyl*)-5-*methoxycarbonylmethyl*-1,4,8-*trimethylporphyrin* (**29b**).—The dibenzyl *b*-oxobilane-1′-8′-dicarboxylate (**39**) (45 mg) in acetone (10 ml) containing triethylamine (3 drops) was shaken with 10% palladium–charcoal (20 mg) under an atmosphere of hydrogen at s.t.p. for 12 h. The solution was filtered through Celite, the catalyst washed well with hot acetone, and the combined filtrates evaporated under reduced pressure to afford the *b*-oxobilanedicarboxylic acid as a yellow solid foam (33 mg, 96%); $\lambda_{max.}$(CH_2Cl_2) 273 and 262 nm; $\lambda_{max.}$(CH_2Cl + HCl gas) 444 nm; δ 11.53, 10.82, and 10.50 (NH), 6.52 (1 H, 4-H), 3.85 (4 H, 2 × bridge CH_2), 3.64, 3.62, 3.58, and 3.56 (12 H, 4 × CO_2CH_3), 3.50 (2 H, acetate CH_2), 2.97 (6 H, m, 3 × CH_2CH_2CO), 2.50 (6 H, m, 3 × CH_2CH_2CO), 2.09, 2.03, and 2.00 (9 H, 3 × CH_3).

The oxobilane diacid (32 mg) was then converted by the same method as in the preceding two preparations into the oxophlorin, and then into the *acetoxyporphyrin* (**29b**) (3.2 mg, 10%), m.p. 227.5—229.5 °C. This was shown by mixed m.p. and spectral comparison to be identical with the minor product formed in the preceding synthesis of the acetoxyporphyrin (**28a**).

A minor fraction separated chromatographically was shown to be the α-acetoxyde-ethylisocoproporphyrintetramethyl ester (**28a**) (0.8 mg, 2%), m.p. 213—215.5 °C (not lowered by admixture with the major component of the preceding synthesis).

1,3,8-*Trimethyl*-4,6,7-*tris*-(2-*methoxycarbonylethyl*)-5-*methoxycarbonylmethyl*-2-*ethylporphyrin* (*Isocoproporphyrin Tetramethyl Ester*) (**7b**).—The acetoxyisocoproporphyrin (**28a**) (55 mg) was dissolved in dry tetrahydrofuran (200 ml) and hydrogenated over 10% palladium–charcoal (25 mg) in the presence of triethylamine (3 drops) for 14 h. The catalyst was filtered off and the filtrate concentrated in the dark. The porphyrinogen was dissolved in dry benzene (100 ml) containing 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ; 50 mg), and stirred for 15 min at 20 °C. The benzene was then removed and the residue chromatographed on alumina (Grade III), eluting initially with benzene to remove the excess DDQ, and then with chloroform–benzene (1:1, v/v). The porphyrinic fraction was isolated and crystallised from dichloromethane–light petroleum (b.p. 60—80 °C) to give isocoproporphyrin tetramethyl ester (32 mg, 69%), m.p. 179—181 °C. The m.p. was not depressed on admixture with a sample prepared by the *ac* biladiene route (kindly provided by the late Prof. G. W. Kenner and Prof. K. M. Smith (Found: M^+, 710.328. Calc. for $C_{40}H_{46}N_4O_8$: *M*, 710.331).

2-*Ethyl*-3,6,7-*tris*-(2-*methoxycarbonylethyl*)-5-*methoxycarbonylmethyl*-1,4,8-*trimethylporphyrin* (**30a**).—The acetoxyporphyrin (**29a**) (10 mg) isolated as a by-product in the synthesis of acetoxyisocoproporphyrin (**28a**) was converted into the *meso*-unsubstituted prophyrin in the same manner as in the preceding experiment. After chromatography and crystallisation from dichloromethane–light petroleum (b.p. 60—80 °C) the *porphyrin ester* (**30a**) (5 mg, 54%) crystallised as violet needles, m.p. 211—213 °C (Found: M^+, 710.325. $C_{40}H_{46}N_4O_8$ requires *M*, 710.331); $\lambda_{max.}$($CHCl_3$) 401 (log ε 5.213), 500 (4.141), 534 (3.957), 571 (3.806), and 625 nm (3.592); δ 10.15 (1 H, s, *meso*-H), 5.10 (2 H, s, $CH_2CO_2CH_3$), 4.25—4.60 (6 H, m, 3 × $CH_2CH_2CO_2CH_3$), 4.03 (2 H, q, CH_2CH_3), 6.26 (3 H, s, OCH_3), 6.36 (3 H, s, OCH_3), 6.39 (12 H, s, 2 × OCH_3, 2 × CH_3), 6.44 (3 H, s, CH_3), 6.56 (6 H, m, 3 × $CH_2CH_2CO_2Me$), and 8.17 (3 H, t, CH_2CH_3); *m/z* (f.d.) 710 (M^+, 100%); *m/z* (e.i.) 710 (M^+, 100%), 637 (26), 639 (13), 355 (M^{2+}, 1).

4,6,7-*Tris*-(2-*methoxycarbonylethyl*)-5-*methoxycarbonylmethyl*-1,3,8-*trimethylporphyrin* (*De-ethylisocoproporphyrin Tetramethyl Ester*) (**7d**).—This was prepared from the corresponding acetoxyporphyrin (**28b**) (10 mg) by hydrogenolysis over palladium–charcoal and re-oxidation with DDQ in the same manner as the preceding porphyrin. After chromatography the de-ethylisocoproporphyrin ester (18 mg, 84%) crystallised from dichloromethane–methanol as purple needles, m.p. 188—190 °C (lit.,[14] m.p. 190—191 °C); $\lambda_{max.}$($CHCl_3$) 402 (log ε 5.31), 499 (4.15), 535 (3.97), 568 (3.84), and 623 nm (3.57); δ 9.93 (2 H), 9.82 (1 H), 9.70 (1 H, *meso*-H), 8.73 (1 H, 2-H), 4.98 (2 H, s, acetate CH_2), 4.25 (6 H, m, 3 × CH_2CH_2CO), 3.72, 3.66, 3.61, 3.58, 3.55, 3.49, and 3.44 (3 × ring CH_3 and 4 × CO_2CH_3), 3.22 (6 H, m, 3 × CH_2CH_2CO), and 4.14 (2 H, 2 × NH): δ(CF_3CO_2D) 11.26 (1 H), 11.17 (1 H), 11.07 (1 H), 10.98 (1 H, meso-*H*), 9.65 (1 H, 2-H), 5.53 (2 H, s, acetate CH_2), 4.7 (6 H, m, 3 × CH_2CH_2CO), 4.75—4.85 (21 H, 3 × ring CH_3 and 4 × CO_2CH_3), and 3.30 (6 H, m, 3 × CH_2CH_2CO).

3,6,7-*Tris*-(2-*methoxycarbonylethyl*)-5-*methoxycarbonylmethyl*-1,4,8-*trimethylporphyrin* (**30b**).—This was prepared from the corresponding acetoxyporphyrin (**29b**) (14 mg) in the same manner as the analogues described above, and crystallised from dichloromethane–methanol as violet needles, m.p. 188—189 °C (10.6 mg, 82%); $\lambda_{max.}$($CHCl_3$) 402 (log ε 5.23), 499 (4.09), 535 (3.91), 568 (3.78), and 624 nm (3.49); δ 10.12 (2 H), 10.06 (1 H) *meso*-H), 9.01 (1 H, 2-H), 5.07 (2 H, s, acetate CH_2), 4.40 (6 H, m, 3 × CH_2CH_2CO), 3.74 (3 H, s), 3.67 (9 H, s), 3.61 (9 H, s) (3 × ring CH_3 and 4 × CO_2CH_3), 3.30 (6 H, m, 3 × CH_2CH_2-CO), and −3.85 (2 H, NH) (Found: M^+, 740.367. $C_{40}H_{44}N_4O_{10}$ requires *M*, 740.373).

2-*Acetyl*-4,6,7-*tris*-(2′-*methoxycarbonylethyl*)-5-*methoxycarbonylmethyl*-1,3,8-*trimethylporphyrin* (**7e**).—Copper acetate (60 mg) in methanol (6 ml) was added to a solution of de-ethylisocoproporphyrin tetramethyl ester (**7d**) (16 mg) in chloroform (6 ml) and the mixture heated under reflux for 10 min. The solution ($\lambda_{max.}$ 399, 524, and 563 nm) was washed with distilled water, evaporated to dryness, and the residue dried *in vacuo*. The red solid was taken up in dichloromethane (8 ml) and acetic acid (8 ml) and the solution stirred at room temperature for 5 min with tin(IV) chloride (0.1 ml). The solution was poured into water, vigorously shaken, and the organic layer separated, washed with 5% aqueous ammonia (20 ml) and distilled water (2 × 20 ml), and evaporated to dryness. Last traces of water were removed by azeotroping with absolute alcohol. The residue was taken up in 5% sulphuric acid–trifluoroacetic acid (10 ml) and kept at 20 °C, in the dark, for 20 min. Dichloromethane was then added and the resulting solution washed with

distilled water (50 ml), 5% aqueous ammonia (40 ml), and water (40 ml). The solvent was evaporated and the residue dried as before. This was taken up in 5% sulphuric acid–methanol (20 ml) and allowed to stand in the dark overnight. Dichloromethane (20 ml) was added and the solution washed with water (40 ml), 5% aqueous ammonia (30 ml) and distilled water (2 × 30 ml). The solvent was evaporated under reduced pressure and the residue chromatographed on alumina (10 g; grade III) eluting first with dichloromethane and then with increasing proportions of acetone in dichloromethane (up to 10%). A small fraction corresponding to starting material (1.5 mg) was collected, followed by a major band which was evaporated to dryness and crystallised from dichloromethane–methanol to afford 2-acetyl-4,6,7-tris-(2′-methoxycarbonylethyl)-5-methoxycarbonylmethyl-1,3,8-trimethylporphyrin (8 mg, 45%) as lustrous purple needles, m.p. 196—197 °C (lit.,[14] m.p. 194—195 °C); $\lambda_{max.}$($CHCl_3$) 411 (log ε 5.32), 512 (4.16), 551 (4.33), 578 (4.12), and 635 nm (3.37); δ 10.64 (1 H), 9.90 (1 H), 9.87 (1 H), 9.74 (1 H) (meso-*H*), 4.96 (2 H, s, acetate CH_2), 4.31 (6 H, m, 3 × CH_2CH_2CO), 3.74 (3 H, s), 6.32 (3 H, s), 3.61 (9 H, s), 3.59 (3 H, s), 3.44 (3 H, s) (3 × ring CH_3, 4 × CO_2CH_3), 3.24 (6 H, m, 3 × CH_2CH_2CO), 3.18 (3 H, s, $COCH_3$), and −4.1 (2 H, 2 × NH).

2-(1-*Hydroxyethyl*)-4,6,7-*tris*-(2-*methoxycarbonylethyl*)-5-*methoxycarbonylmethyl*-1,3,8-*trimethylporphyrin* (*Hydroxyisocoproporphyrin Tetramethyl Ester*) (**7c**).—Finely powdered sodium borohydride (25 mg) was added to a stirred solution of the foregoing acetylporphyrin (**7e**) (8.3 mg) in dichloromethane (6 ml) containing methanol (0.3 ml) and the mixture stirred in the dark at room temperature for 10 min. The progress of the reaction was monitored by u.v. spectroscopy (the Soret band at $\lambda_{max.}$ 411 nm was replaced by a new band at 400 nm). The solution was washed with 0.5% hydrochloric acid (8 ml), the aqueous phase back extracted with dichloromethane (2 × 10 ml), and the combined extracts evaporated to dryness. The residue was chromatographed on alumina (10 g; grade IV) with dichloromethane, and then with increasing proportions of acetone in dichloromethane. The major porphyrin fraction was evaporated to dryness and crystallised from dichloromethane–light petroleum (b.p. 60—80 °C) to give hydroxyisocoproporphyrin tetramethyl ester (7.0 mg, 84%) as purple needles, m.p. 165—167 °C (lit.,[14] m.p. 163—164 °C); $\lambda_{max.}$($CHCl_3$) 403 (log ε 5.30), 501 (4.17), 537 (4.03), 572 (3.86), and 625 (3.52); δ 10.30 (1 H), 9.98 (1 H), 9.88 (1 H), 9.85 (1 H) (meso H), 6.35 (1 H, q, $CHOHCH_3$), 4.96 (H, s, acetate CH_2), 4.27 (6 H, m, 3 × CH_2CH_2CO), 3.73 (3 H, s), 3.68 (3 H, s), 3.64 (3 H, s), 3.60 (3 H, s), 3.53 (3 H, s), 3.48 (3 H, s), 3.45 (3 H, s) (3 × ring CH_3 and 4 × CO_2CH_3), 3.24 (6 H, m, 3 × CH_2CH_2CO), 2.14 (3 H, d, $CHOHCH_3$), and −4.04 (2 H, br s, 2 × NH).

4,6,7-*Tris*-(2-*methoxycarbonylethyl*)-5-*methoxycarbonylmethyl*-1,3,8-*trimethyl*-2-*vinylporphyrin* (*Dehydroisocoproporphyrin Tetramethyl Ester*) (**7a**).—Hydroxyisocoproporphyrin tetramethyl ester (**7a**) (6.0 mg) and toluene-*p*-sulphonic acid (16 mg) were heated under reflux in chlorobenzene (5 ml), in the dark, for 30 min. The chlorobenzene was removed under reduced pressure and the residue taken up in 5% sulphuric acid–methanol (20 ml) and set aside overnight. The resulting solution was partitioned between dichloromethane (20 ml) and water (50 ml) and the aqeuous layer extracted with dichloromethane (2 × 20 ml). The combined extracts were washed with 5% aqueous ammonia (20 ml) and distilled water (30 ml) and evaporated to dryness. The residue was chromatographed on alumina (5 g; grade III), eluting with dichloromethane, and the porphyric fraction was evaporated to dryness. Crystallisation of the residue from dichloromethane–methanol gave dehydroisocoproporphyrin tetramethyl ester as purple needles, m.p. 172.5—174 °C (lit.,[14] m.p. 174—175 °C); $\lambda_{max.}$($CHCl_3$) 404 (log ε 5.26), 504 (4.12), 541 (4.10), 574 (3.85), and 627 nm (3.48); δ 10.11 (3 H, *meso*-H), 10.05 (1 H, *meso*-H), 8.17 (1 H, m, $CH{=}CH_2$), 6.20 (2 H, m, $CH{=}CH_2$), 5.06 (2 H, s, acetate CH_2), 4.40 (6 H, m, 3 × CH_2CH_2CO), 3.74 (3 H), 6.33 (3 H), 3.61 (15 H), (3 × ring CH_3 and 4 × CO_2CH_3), 3.28 (6 H, m, 3 × CH_2CH_2CO–), and −3.86 (2 H, 2 × NH).

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Received 23rd December 1986; *Paper* 5/2252