Pyrroles and Related Compounds. Part XVI.[1] Synthesis of Protoporphyrin-IX by the *a*- and *b*-Oxobilane Routes †

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2-Ethyl-2-devinylprotoporphyrin-IX dimethyl ester has been synthesised by the *a*-oxobilane route, the 4-vinyl group being introduced by a new method, *viz.* transformation of a β-acetoxyethyl side-chain present in one of the intermediate pyrroles. Protoporphyrin-IX dimethyl ester has also been prepared by both the *a*- and *b*-oxobilane routes, again with β-acetoxyethyl groups as precursors of the two vinyl groups in the porphyrin. The use of a pentachlorophenyl pyrromethane ester in the *a*-oxobilane synthesis and of a t-butyl pyrromethane ester in the *b*-oxobilane route enables these syntheses to be carried out in an entirely rational fashion without involving symmetrical intermediates, because the nuclear pentachlorophenyl ester can be selectively cleaved by mild alkaline hydrolysis, and the nuclear t-butyl ester by trifluoroacetic acid in the presence of nuclear benzyl esters. The intermediate oxophlorin formed in the *b*-oxobilane route undergoes exchange with tritium at the *meso*-position opposite the oxo-group, and thus the oxo-function facilitates the synthesis of δ-*meso*-tritiated protoporphyrin-IX required for biosynthetic experiments in the chlorophyll field. Attempts to prepare the 2,4-divinyl-β-oxophlorin were frustrated by preferential formation of a cyclic ether from the 4-substituent and the β-oxygen atom.

One of the main objects of our studies [2] in the porphyrin field is to investigate the later stages of chlorophyll biosynthesis with specifically labelled porphyrins related to protoporphyrin-IX, the precursor of both the blood and plant pigments. Fischer's classical synthesis [3] is not capable of being adapted to the preparation of protoporphyrin-IX specifically labelled in the C and D rings, because this part of the molecule is derived from a symmetrical pyrromethane. This drawback also

† Preliminary communication: R. P. Carr, P. J. Crook, A. H. Jackson, and G. W. Kenner, *Chem. Comm.*, 1967, 1027.

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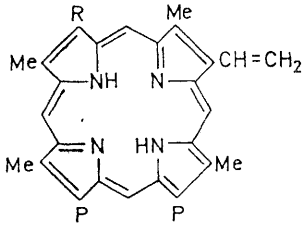
[1] Part XV, P. J. Crook, A. H. Jackson, and G. W. Kenner, preceding paper.

[2] A. H. Jackson and G. W. Kenner, *Nature*, 1967, **215**, 1126.

[3] H. Fischer and H. Orth, ' Die Chemie des Pyrrols,' Akademische Verlag, Leipzig, 1937, vol. II (i).

applied to our own early syntheses by the recently developed *a*- and *b*-oxobilane routes.[4,5] More recently [1] we have overcome this limitation by the use of 5,5′-pyrromethane-dicarboxylates differentially esterified with benzyl, pentachlorophenyl, and t-butyl groups (and which can be removed selectively by hydrogenation, mild alkaline hydrolysis, or mild acidic hydrolysis respectively). In this paper we describe their use in the synthesis of protoporphyrin-IX and its 2-ethyl-2-devinyl analogue.

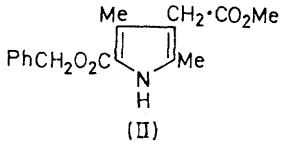
Another problem remaining to be solved was the introduction of vinyl groups into the porphyrin nucleus. The earlier methods,[3] *e.g.* reduction of an acetyl group followed by dehydration and Hofmann elimination of a β-aminoethyl side-chain, were not suitable for either of the oxobilane routes for a number of reasons (see below), and we accordingly sought another substituent which could be carried through these syntheses from monopyrrolic starting materials to the porphyrin stage and finally transformed into vinyl. The α-hydroxyethyl group appeared to be one possibility but this was ruled out because of the relative ease of elimination in porphyrins under acidic conditions, and we turned to the β-hydroxyethyl group and its acetyl derivative. Initially, we set out to synthesise the model monovinyl porphyrin (Ia) by the *a*-oxobilane route.[4] The acetoxyethyl pyrrole (IIIb) was first prepared by diborane reduction of the pyrroleacetic ester (II) to the alcohol



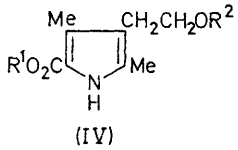
(I) a; R = Et
b; R = CH=CH$_2$
P = [CH$_2$]$_2$CO$_2$Me

(IIIa), followed by acetylation. The ester (II) could also be reduced to the alcohol (IIIa) by lithium borohydride but in somewhat lower yield. The acetoxyethyl pyrrole (IIIb) was then hydrogenolysed over palladium charcoal to the acid (IV), which was decarboxylated thermally and coupled with the phosphoryl chloride complex of the pyrrole amide (Va). After alkaline hydrolysis of the intermediate imine initially formed, the pyrroketone (VIa) was isolated in good yield and converted by 1 molar equivalent of t-butyl hypochlorite into its chloromethyl derivative (VIIa). The pyridinium salt of the latter was condensed in formamide with the lithium salt of the pyrromethane-carboxylic acid (VIIIa) and gave the *a*-oxobilane (IXa).

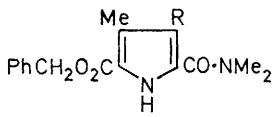
Application of the usual sequence [4] of reactions to this *a*-oxobilane, *viz.* diborane reduction of the oxo-group, hydrogenolysis of the benzyl esters, oxidation with t-butyl hypochlorite, and finally cyclisation of the intermediate bilene salt with methyl orthoformate–trichloroacetic acid and aerial oxidation then gave the desired mono-acetoxyethyl porphyrin (Xa), in 25% overall yield, free from contamination with any other



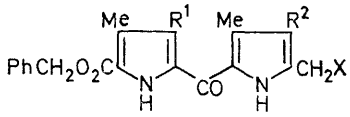
(II)



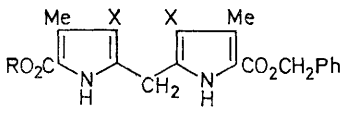
(IV)
R^1 = H, R^2 = Ac
(III) R^1 = CH$_2$Ph
a; R^2 = H
b; R^2 = Ac
c; R^2 = Xanthate
d; R^2 = CS·SMe
e; R^2 = Mesyl



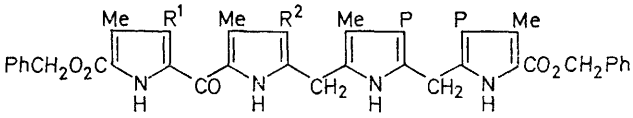
(V)
a; R = Et
b; R = CH$_2$·CH$_2$·OAc
c; R = CH$_2$·CH$_2$·OH



(VI) X = H (VII) X = Cl
a; R^1 = Et, R^2 = CH$_2$·CH$_2$·OAc
b; R^1 = R^2 = CH$_2$·CH$_2$·OAc

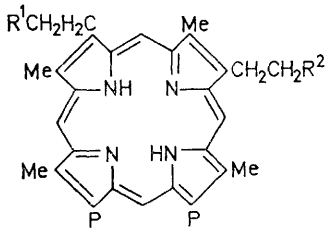


(VIII)
a; X = P, R = CH$_2$Ph
b; X = P, R = H
c; X = P, R = C$_6$Cl$_5$
d; X = CH$_2$·CH$_2$·CO$_2$H, R = H



(IX) a; R^1 = Et, R^2 = CH$_2$·CH$_2$·OAc
b; R^1 = R^2 = CH$_2$·CH$_2$·OAc

porphyrin, as shown by t.l.c., analysis, n.m.r. and mass spectroscopy.



(X) a; R^1 = H; R^2 = OAc
b; R^1 = R^2 = OAc

(XI) a; R^1 = H; R^2 = OH
b; R^1 = R^2 = OH

(XII) a; R^1 = H; R^2 = Cl
b; R^1 = R^2 = Cl

Model experiments on the conversion of the acetoxyethyl group into a vinyl group carried out on the starting pyrrole (IIIa) were unfruitful. For example, conversion to the xanthate (IIIc) followed by pyrolysis gave the dithiocarbonic ester (IIId) and treatment with mesyl chloride in pyridine gave a mixture of the chloride and mesylate (IIIe). The mesyl ester was very readily hydrolysed to the alcohol and attempts to convert it or

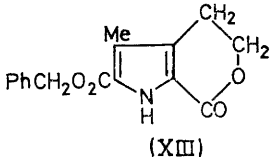
[4] A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc.* (*C*), 1967, 2045.

[5] A. H. Jackson, G. W. Kenner, G. McGillivray, and K. M Smith, *J. Chem. Soc.* (*C*), 1968, 294.

the chloride into the iodide or quaternary ammonium salt (for Hofmann elimination) were unsuccessful.

In the porphyrin series methanolysis of the acetoxyethyl group to hydroxyethyl was readily effected with methanolic sulphuric acid, thus leaving the side-chain esters unchanged, but attempts to eliminate the elements of water from the hydroxyethyl porphyrin (XIa) by heating it with sulphuric acid or toluene-*p*-sulphonic acid were unsuccessful. In contrast, haematoporphyrin could be converted into protoporphyrin quite readily in this manner. The hydroxy-group could, however, be replaced by chloride in a number of ways, *e.g.* by phosphoryl chloride, thionyl chloride, or with a large excess of mesyl chloride in pyridine. (Unless an excess of mesyl chloride was used, some starting material was recovered, presumably owing to formation of an unstable mesylate which hydrolysed during work-up or chromatography). Attempts to convert this chloroethyl porphyrin into the *N*-methylmorpholine quaternary salt were unsuccessful, nor did boiling collidine cause elimination of hydrogen chloride. However, treatment with hot potassium t-butoxide in t-butyl alcohol did effect the required transformation to vinyl porphyrin although the product was contaminated with traces of the t-butyl ether. Elimination also occurred with potassium t-butoxide in dimethyl sulphoxide at 20°, but again the vinyl porphyrin was contaminated with a by-product probably arising from the dimethyl sulphoxide (see Experimental section). Finally, it was found (in collaboration with Dr. J. Wass) that the zinc or ferric complex of the chloroethyl porphyrin cleanly eliminated hydrogen chloride when treated with potassium t-butoxide in t-butylalcohol at 20°. The zinc complex gave the pure vinyl porphyrin in good yield after re-esterification and removal of the zinc with methanolic sulphuric acid. The zinc complex was preferred as the reactions would be more easily followed spectroscopically and the zinc could be much more easily inserted and removed from the macrocycle than iron. The final product was fully characterised by analytical and spectroscopic methods.

The way was now clear for the synthesis of protoporphyrin-IX, which was readily effected by the same route starting from pyrroles (IIIb) and (Vb) and proceeding *via* the pyrro-ketones (VIb) and (VIIb) and the *a*-oxobilane (IXb). Some difficulty was experienced initially in the preparation of the amide (Vb) from the corresponding α-methylpyrrole by chlorination followed by

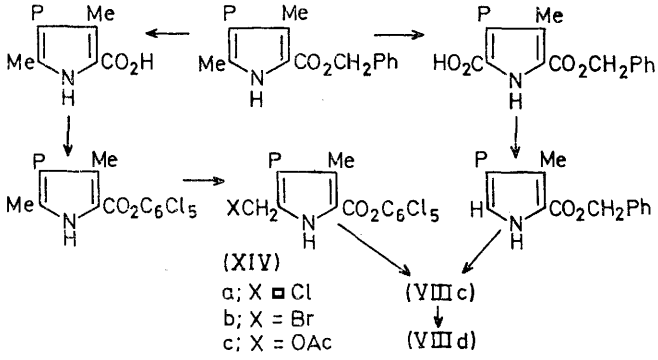


(XIII)

treatment of the trichloromethyl compound with gaseous dimethylamine. Yields varied from 25 to 70% and considerable amounts of the hydroxyethylpyrrole amide (Vc) and the lactone (XIII) were also formed in some experiments. Eventually it was found that reproducible yields (75—80%) of the desired amide (Vb) could be obtained by treatment of a tetrahydrofuran solution of the intermediate trichloromethyl pyrrole with aqueous dimethylamine.

In the conversions of the acetoxyethyl side-chains to vinyl groups it was found that a more satisfactory method of preparing the bischloroethyl porphyrin (in over 80% yield) was the use of thionyl chloride in the presence of dimethylformamide at room temperature. The elimination stage required a somewhat longer time for completion of reaction than for the monochloroethyl analogue. With these improvements and modifications conversion of the bisacetoxyethyl porphyrin into protoporphyrin-IX dimethyl ester could be effected in 65% overall yield.

As described, the foregoing synthesis suffers from the limitation that a symmetrical pyrromethane was used for the synthesis of the carboxylic acid (VIIIb). To overcome this limitation we synthesised the pyrromethane pentachlorophenyl ester (VIIIc) as shown schematically (Scheme 1). This ester was partially hydrolysed with dilute aqueous sodium hydroxide in tetrahydrofuran and the corresponding mono-ester tri-acid (VIIId) was isolated in 75% yield. The tri-lithium

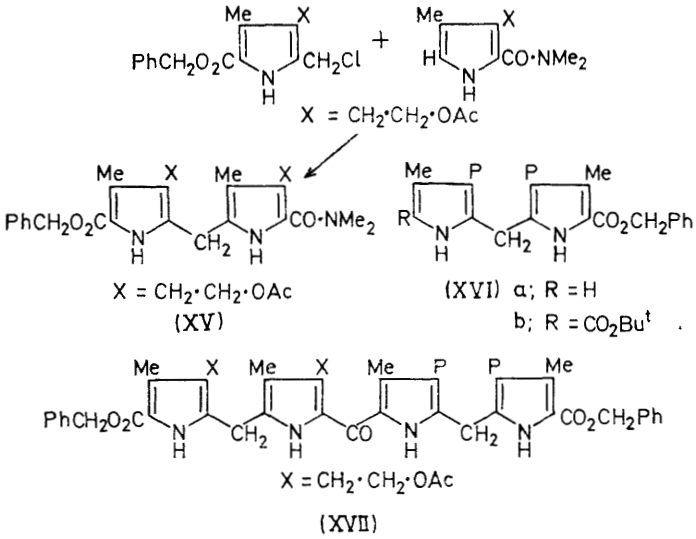


SCHEME 1

salt was then condensed with the pyridinium-methyl pyrroketone to give the *a*-oxobilane dipropionic acid. Esterification of the latter with diazomethane then gave the *a*-oxobilane dimethyl ester (IXb) which was identical in all respects with the material prepared by the earlier method.

Attention was next turned to the synthesis of protoporphyrin-IX by the *b*-oxobilane route,[5] and for convenience in preparation of the pyrrolic intermediates the pyrromethane amide (XV) was synthesised as shown schematically (Scheme 2). It was then coupled as its phosphoryl chloride complex with the α-unsubstituted pyrromethane (XVIa), and after purification and hydrolysis of the intermediate imine salt, gave the noncrystalline *b*-oxobilane (XVII). The pyrromethane (XVIa) was prepared initially by thermal or acid-catalysed decarboxylation of the carboxylic acid (VIIIb), obtained by semi-hydrogenolysis of the corresponding symmetrical dibenzyl ester (VIIIa), but later it was also

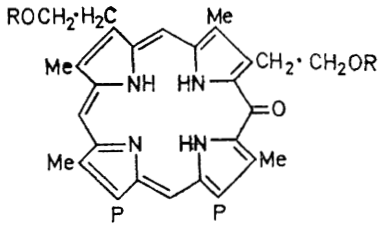
prepared by trifluoroacetic acid-catalysed de-esterification and decarboxylation of the unsymmetrical mixed t-butyl benzyl pyrromethane diester (XVIb). The latter

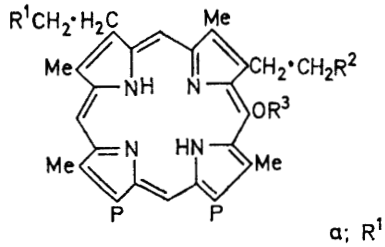


SCHEME 2

was prepared by a very similar method to that described for the analogous pentachlorophenyl benzyl diester (VIIIc).

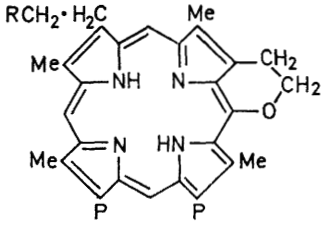
The *b*-oxobilane (XVII) was hydrogenolysed and the resulting diacid was cyclised with methyl orthoformate–trichloroacetic acid. Addition of pyridine and aeration then afforded the desired oxophlorin (XVIIIa) which could be isolated directly, or converted by acetic anhydride into the *meso*-acetoxyporphyrin (XIXa); a by-product in the cyclisation reaction was the monoacetoxyethyl cyclic ether (XIIIa). The structures of these three compounds were confirmed by analytical and spectroscopic methods, and the acetoxyporphyrin (XIXa) was transformed into the parent porphyrin (Xb) by catalytic hydrogenation to porphyrinogen followed by re-oxidation.[5]



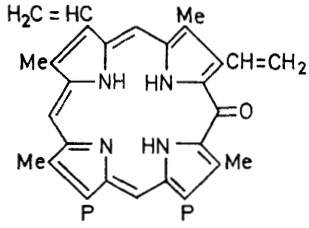


(XX)

a; $R^1 = R^2 = OH$, $R^3 = CH_2 \cdot OMe$
b; $R^1 = OAc$, $R^2 = OH$, $R^3 = Ac$



The *b*-oxobilane route to protoporphyrin-IX had an additional interest, because it was thought that the intermediate β-oxophlorin (XVIIIa) might be converted into its 2,4-divinyl derivative (XXII). This compound would be an isomer of 'α-oxyprotoporphyrin-IX', an iron complex of which is believed to be an intermediate in the metabolism of haem to bile pigments.[6,7] The synthesis of 'β-oxyprotoporphyrin-IX' (XXII) would be a useful model for our current studies in the α-series,[6] and therefore we devoted some effort to this task. In the event, unexpected difficulties were encountered and the desired conversion was not achieved.[8]

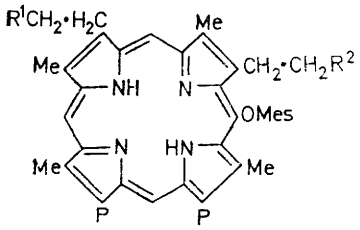


Treatment of the oxophlorin (XVIIIa) with benzyl chloroformate in pyridine (or in acetone in presence of potassium carbonate) gave the desired benzyl carbonate ester (XIXb) in moderate yield, together with traces of cyclic ether (XXIa). Unfortunately, however, the carbonate proved to be unstable to mild base (*e.g.* 0·5% potassium hydroxide in methanol) during attempts to hydrolyse the side-chain acetoxy-groups, and the blue colour which developed within a few minutes showed that an oxophlorin, either (XVIIIa) or its hydrolysis product (XVIIIb) had been formed. With chloromethyl methyl ether the zinc complex of the oxophlorin (XVIIIa) gave a low yield of a noncrystalline porphyrin, presumably the zinc complex of (XIXc), and the latter was hydrolysed to the zinc complex of the bishydroxyethyl porphyrin (XXa) with dilute methanolic sodium hydroxide. (Citric acid was required to neutralise the alkali for even dilute acetic acid cleaved the methoxymethyl group.) Attempts to convert the latter porphyrin into the corresponding bischloroethylporphyrin with thionyl chloride in dimethylformamide were, however, unsuccessful (even in presence of dicyclohexylamine as base) and the product was shown spectroscopically and by

[6] A. H. Jackson, G. W. Kenner, and K. M. Smith, *J. Chem. Soc.* (*C*), 1968, 302.
[7] *Cf.* R. Lemberg, *Rev. Pure Appl. Chem.*, 1956, **6**, 1.
[8] Preliminary account of this work has been given by A. H. Jackson and G. W. Kenner in 'Porphyrins and Related Compounds,' ed. T. W. Goodwin, Academic Press, London and New York, 1968.

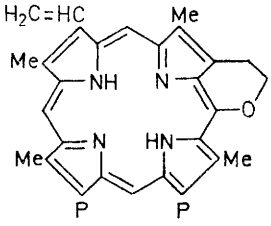
t.l.c. to be the zinc complex of the chloroethyl porphyrin cyclic ether (XXIb).

Acid-catalysed methanolysis of the bisacetoxyethyloxophlorin (XVIIIa) gave the corresponding bishydroxyethyloxophlorin (XVIIIb) and some of the numerous attempts to convert the latter into 'β-oxyprotoporphyrin-IX' (XXII) are enumerated below. (i) Treatment with methane sulphonyl chloride in pyridine gave a mixture of the bis-(chloroethyl)mesyloxyporphyrin (XXIIIa) in 30% yield together with the cyclic ether (XXIb). (ii) Treatment with methane sulphonyl chloride in pyridine, followed by exchange with sodium iodide in acetone gave various products depending on the precise reaction conditions; these products included the chloroethyl cyclic ether (XXIb), the iodoethyl dimesylate probably (XXIIIb), the iodoethyl cyclic ether (XXIc), and the hydroxy-ethyl cyclic ether (XXId). (iii) Treatment with thionyl chloride in dimethylformamide gave largely the chloroethyl cyclic ether (XXIb).



(XXIII)

a; $R^1 = R^2 = Cl$
b; $R^1 = I, R^2 = OMes$
c; $R^1 = R^2 = OH$



(XXIV)

Other experiments involving the green anion generated from the zinc complex of the oxophlorin were also carried out, these were as follows. (i) Addition of mesyl chloride gave a red product, presumably the *meso*-mesylate (XXIIIc) as its zinc complex, and this was then treated with mesyl chloride in pyridine; under these conditions the zinc was removed and the only product obtained was the chloroethyl cyclic ether (XXIb). (ii) Methylation with methyl iodide appeared to be rather slower than decomposition of the oxophlorin, and with dimethyl sulphate some methylation of the side-chain hydroxy-groups had also occurred. (iii) With benzyl chloroformate a mixture of at least two porphyrinic products was obtained (t.l.c.) and the n.m.r. spectrum showed that partial esterification of the side-chain hydroxy-groups had also occurred in addition to the oxo-function. (iv) Titration with acetic anhydride in acetone gave the acetoxyethylacetoxyporphyrin (XXb), even in presence of methanol, added to inhibit side-chain acetylation. (v) Neither diazomethane, nor diphenyldiazomethane underwent reaction with the oxophlorin anion.

Further studies showed that treatment of the zinc complexes of either the bischloroethyl mesylate (XXIIIa) or the iodoethyl mesylate (XXIIIb) with potassium t-butoxide in t-butyl alcohol gave the monovinylporphyrin cyclic ether (XXIV) in good yield. The bischloroethyl mesylate (XXIIIa) also underwent elimination to give the vinyl ether (XXIV) when heated with sodium fluoride and sodium carbonate in hexamethylphosphoramide; if the carbonate was omitted the product was the chloroethyl porphyrin (XXIb). The high degree of nucleophilicity of the oxo-function, even when apparently protected, was somewhat surprising, but electrophilic attack by the halogeno- or mesyloxy-ethyl group in the neighbouring 4-position is, of course, facilitated by their close proximity and by formation of the favoured six-membered ring. Further experiments to obviate this difficulty are in progress.

Versatile syntheses of protoporphyrin-IX, by both *a*- and *b*-oxobilane routes, have been described above and, in principle, they permit specific isotopic labelling of any position in the structure. In practice, labelling of the side-chains would be a major undertaking, because there are so many steps from aliphatic or monopyrrolic precursors. We have, however, taken advantage of one facet of oxophlorin chemistry,[6] to prepare protoporphyrin-IX labelled with tritium in the δ-position, by exchanging the δ-*meso*-hydrogen of the oxophlorin (XVIIIb) (asterisked in the formula) with tritiated acetic acid.* The tritiated oxophlorin was then converted into protoporphyrin dimethyl ester by following the same sequence of reactions as previously described. A small loss of tritium occurred during the hydrogenation and reoxidation of the acetoxyporphyrin (XIXa) to the porphyrin (Xb) as expected, but the primary tritium isotope effect kept this loss at a fairly low level. With this material, conditions have been found for the conversion by chloroplasts of the magnesium complex of protoporphyrin-IX into chlorophyll.

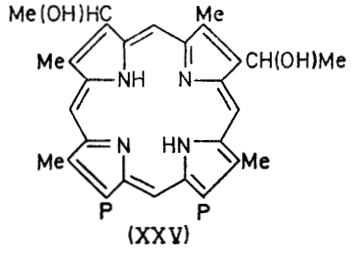
The active protoporphyrin dimethyl ester was then converted into the dipotassium salt of its magnesium complex by Granick's procedure,[9] and a number of attempts to incorporate the latter into chlorophyll *in vivo* were carried out, *e.g.* by standing aetiolated maize shoots in solutions of the porphyrin, or by injection into the hollow stems of broad bean plants. However, these experiments all failed, and finally we turned to the use of isolated chloroplasts.[10] The preliminary results were quite encouraging and further extensive studies by Dr. M. T. Cox have now confirmed [11] that the active protoporphyrin-IX is incorporated into chlorophyll in this system; full details will be described in a later paper.

In the course of these feeding experiments inactive protoporphyrin was required for diluting the radioactive material, but the commercially available samples proved to be of rather poor quality, *e.g.* esterification

* Preliminary experiments involving deuterium labelling were carried out with deuterioacetic acid, and the product analysed for deuterium by n.m.r. and mass spectrometry.

[9] S. Granick, *J. Biol. Chem.*, 1948, **175**, 333.
[10] J. M. Charlton, K. J. Treharne, and T. W. Goodwin, *Biochem. J.*, 1967, **105**, 205.
[11] M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J. Amer. Chem. Soc.*, 1969, **91**, 1232.

followed by chromatography gave only a 30% yield of somewhat impure dimethyl ester. The n.m.r. spectrum showed low intensity ethyl resonances, presumably due to partial reduction of the vinyl groups of protoporphyrin during the reductive removal of iron from haem. The impurities were difficult to remove chromatographically, and consequently we turned to commercial haematoporphyrin (XXV) as an alternative source of protoporphyrin. Fischer's procedure [3] for dehydrating the hydroxyethyl groups of haematoporphyrin (*i.e.* heating at 110° *in vacuo*) did not prove to be very satisfactory as only partial elimination occurred even after 5 hr. However, by heating haematoporphyrin in a high boiling solvent (*e.g.* xylene or *o*-dichlorobenzene) in presence of toluene-*p*-sulphonic acid a good yield of protoporphyrin was obtained. *o*-Dichlorobenzene was the preferred solvent as a minor by-product was formed in xylene solution; the mass spectrum of the latter showed that it was a mixture of porphyrins containing one or two $-CH(C_8H_9)CH_3$ side-chains, presumably formed by electrophilic substitution into xylene of the intermediate porphyrin carbonium ions (derived by loss of hydroxyl ion from the haematoporphyrin).



(XXV)

EXPERIMENTAL

M.p.s were determined on a hot-stage apparatus and are uncorrected. Neutral alumina (Woelm : Brockmann grade III) was used for all chromatographic separations, and reactions were followed where possible by t.l.c. and spectrophotometry, as described in earlier papers of this series. Electronic spectra were determined with a Unicam SP 800 spectrophotometer, n.m.r. spectra with Varian A-60 and HA-100 instruments, and mass spectra with an A.E.I. MS9 spectrometer at (50 μa. and 70 eV).

Methyl 3-*Acetyl*-4-*oxopentanoate* (with Mr. P. B. Hulbert).—Methyl bromoacetate (690 g.) was added to a stirred mixture of acetylacetone (450 g.), anhydrous potassium carbonate (570 g.), and dry acetone (510 ml.). When the mixture had ceased refluxing, it was heated under reflux for a further 1 hr. The mixture was filtered when cool, and the acetone removed under reduced pressure. The residual oil was fractionated twice under reduced pressure and the product (275 g., 42%) had b.p. 137—141°/14 mm. or 96°/0·9 mm. (lit.,[12] 130—132°/21 mm.), $n_D^{22} = 1{\cdot}455$ (Found: C, 55·8; H, 7·0. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%); n.m.r. ($CDCl_3$): (*a*) keto-form, CH_3, τ 7·73, 7·86; CH_2–CH_2, 5·82t, 7·15d; OCH_3, 6·23; (*b*) enol-form (*ca.* 30%), CH_3, 7·73; $-CH_2CO_2CH_3$, 6·70, 6·30; =C(OH), —6·2.

The residues from this preparation gave on distillation at 216°/1 mm. *dimethyl* 3,3-*diacetylglutarate* (7·5%) n_D^{22} 1·462 (Found: C, 54·2; H, 6·4. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6%); n.m.r. ($CDCl_3$): $CH_2CO_2CH_3$, τ 6·74, 6·33; CH_3CO, 7·82.

Pyrroles

Benzyl 4-*Methoxycarbonylmethyl*-3,5-*dimethylpyrrole*-2-*carboxylate* (II) (with Mr. P. B. Hulbert).—A solution of sodium nitrite (144 g.) in water (500 ml.) was slowly added to a well stirred solution of benzyl acetoacetate (384 g.) in glacial acetic acid (600 ml.), the temperature being kept below 10°. After being set aside in a refrigerator for 2 hr. the solution was slowly added to a solution of methyl 3-acetyl-4-oxopentanoate (344 g.) in glacial acetic acid (400 ml.), and a mixture of zinc dust (370 g.) and anhydrous sodium acetate (370 g.) was added simultaneously. When the addition was complete the reaction mixture was further heated under reflux for 1 hr. and then poured into water. The solid product was filtered off, and recrystallised twice from methanol to give fine, colourless needles of the desired *pyrrole* (218 g, 46%), m.p. 93—94° (Found: C, 68·0; H, 6·3; N, 4·7. $C_{17}H_{19}NO_4$ requires C, 67·8; H, 6·4; N, 4·7%); n.m.r. ($CDCl_3$): CH_3, τ 7·83, 7·69; $-CH_2CO_2CH_3$, 6·63, 6·38; $C_6H_5CH_2$, 2·68, 4·71; NH, 0·1.

Benzyl 4-(2-*Hydroxyethyl*)-3,5-*dimethylpyrrole*-2-*carboxylate* (IIIa).—(*a*) Diborane, generated externally by adding boron trifluoride–ether (127 ml.) dropwise to sodium borohydride (25 g.) in diglyme (50 ml.), was passed in a slow stream of nitrogen through a solution of the foregoing methoxycarbonylmethylpyrrole (20 g.) in tetrahydrofuran (100 ml.) during 45 min. Methanol was then carefully added until the vigorous effervescence ceased. The solvents were removed on a rotary evaporator, and the *hydroxyethylpyrrole* (16·7 g., 95%) was crystallised from benzene–light petroleum (b.p. 60—80 °C) to give pale buff needles, m.p. 120—121·5° (Found: C, 70·5; H, 7·1; N, 5·05. $C_{16}H_{19}NO_3$ requires C, 70·3; H, 7·0; N, 5·1%); n.m.r. ($CDCl_3$): NH, τ 0·6; $C_6H_5CH_2$, 2·66, 4·72; $HOCH_2$-CH_2, 6·39(t), 7·40(t); CH_3, 7·73, 7·85.

(*b*) The foregoing methoxycarbonylmethylpyrrole (19 g.) was dissolved in tetrahydrofuran (150 ml.) and lithium chloride (3·1 g.) and potassium borohydride (3·75 g.) added to the resulting solution. The mixture was stirred for 30 min. during which time the temperature rose 6°. The mixture was then heated under reflux for 5 hr. Water (200 ml.) was added and the mixture was extracted with chloroform. The solvents of the combined chloroform extracts were removed on a rotary evaporator and the *hydroxyethylpyrrole* (10·6 g., 65%) was crystallised from benzene–light petroleum (b.p. 60—80°) to give pale buff needles, m.p. 120—121°, identical with the product obtained in (*a*) above.

Benzyl 4-(2-*Acetoxyethyl*)-3,5-*dimethylpyrrole*-2-*carboxylate* (IIIb).—Acetic anhydride (16·7 ml.) was added to a solution of the foregoing hydroxyethylpyrrole (16·7 g.) in pyridine (75 ml.) and the mixture was stirred for 2 hr. at room temperature. The solution was then added dropwise with stirring to water (2 l.) and the precipitated solid was filtered off. Crystallisation from benzene–light petroleum (b.p. 60—80°) gave the 2-*acetoxyethylpyrrole* (19·15 g., 98%) as colourless needles, m.p. 73·5—74·5° (Found: C, 68·3; H, 6·8; N, 4·3. $C_{18}H_{21}NO_4$ requires C, 68·55; H, 6·7; N, 4·4%); n.m.r. ($CDCl_3$): $C_6H_5CH_2$, τ 2·67, 4·72; CH_2CH_2-$OCOCH_3$, 5·91t, 7·38t, 8·02; CH_3, 7·71, 7·82; NH, ~0·5.

4-(2-*Acetoxyethyl*)-3,5-*dimethylpyrrole*-2-*carboxylic Acid* (IV).—10% Palladium–charcoal (0·6 g.) and a few drops of triethylamine were added to a solution of the preceding 2-acetoxyethylpyrrole (6·0 g.) in tetrahydrofuran (60 ml.).

[12] F. March, *Ann. Chim. France*, 1902 (7), **26**, 317.

The mixture was hydrogenated at 20° and 1 atm. for 45 min. when hydrogen absorption had ceased. The solution was then filtered and the catalyst was washed with hot tetrahydrofuran. Evaporation of the combined washings and filtrate gave the required *pyrrole-carboxylic acid* (3·95 g., 96%) as a white amorphous solid, m.p. 168° (with decomp.) (Found: C, 55·3; H, 6·3; N, 9·8. $C_{13}H_{18}N_2O_5$ requires C, 55·3; H, 6·4; N, 9·9%).

Attempted Preparation of Benzyl 4-(2-*Acetoxyethyl*)-5-*dimethylamido*-3-*methylpyrrole*-2-*carboxylate*.—A solution of t-butyl hypochlorite (28·6 ml.) in carbon tetrachloride (100 ml.) was added during 45 min. to an ice-cooled, stirred solution of the acetoxyethyl-5-methylpyrrole (22·0 g.) in carbon tetrachloride (320 ml.). Immediately after addition the solution was evaporated to dryness and the residual oil was dissolved in dry benzene (100 ml.). Dimethylamine gas, generated by heating a 40% solution in water, was passed through the ice-cooled benzene solution for 1½ hr. Water (400 ml.) was then added and the mixture was stirred, under reflux on a boiling water-bath for 1 hr. The benzene layer was then washed with water until the washings were neutral, dried ($MgSO_4$), and evaporated to dryness. On the addition of ether (100 ml.) and trituration, the desired pyrrole-amide was obtained as colourless needles (4·65 g., 18·4%), m.p. 89—90°. Trituration of the mother liquors gave a second product obtained as colourless needles (1·5 g., 7·5%), m.p. 151—153°. The product was identified by n.m.r. and mass spectra as the *pyrrole-lactone* (XIII) (Found: C, 67·1; H, 5·3; N, 4·9. $C_{16}H_{15}NO_4$ requires C, 67·4; H, 5·3; N, 4·9%); n.m.r. spectrum ($CDCl_3$): N*H*, τ +0·08; $C_6H_5CH_2$, 2·65, 4·65; O–CH_2CH_2, 5·48(t), 7·24(t); CH_3, 7·73.

The mother liquors were evaporated to dryness and chromatographed on alumina (500 g.). The pyrrole-lactone (1·4 g., 7·0%) was eluted in benzene, the pyrrole-amide (1·5 g., 6·0%) in 5% ethyl acetate–benzene and a product which was identified as hydroxyethylpyrroleamide (Vc) (2·6 g., 13·6%) was eluted in 50% v/v ethyl acetate–benzene. Treatment with pyridine (20 ml.) and acetic anhydride (5 ml.) converted this into the desired acetoxyethylpyrroleamide (2·8 g.).

Benzyl 4-(2-*Acetoxyethyl*)-5-*dimethylamido*-3-*methylpyrrole*-2-*carboxylate* (Vb).—A solution of t-butyl hypochlorite (14·3 ml.) in carbon tetrachloride (50 ml.) was added during 45 min. to an ice-cooled, stirred solution of the acetoxyethyl-5-methylpyrrole (11 g.) in carbon tetrachloride (160 ml.). Immediately after addition the solution was evaporated to dryness and the residual oil was dissolved in dry tetrahydrofuran (100 ml.). The solution was added dropwise to a stirred 40% aqueous solution of dimethylamine (100 ml.) during 10 min. The mixture was stirred for a further 10 min. and then extracted with methylene chloride. The organic extracts were evaporated to dryness and the oil was taken up in benzene (100 ml.). Water (100 ml.) was then added and the mixture stirred and heated under reflux on a boiling water-bath for 2 hr. The benzene layer was separated and evaporated to dryness; the desired *dimethylamidopyrrole* (10·4 g., 77%) was obtained as colourless needles, m.p. 109—110° by trituration of the residue with ether. This was in a different crystalline form to that previously prepared (Found: C, 64·8; H, 6·6; N, 7·6. $C_{20}H_{24}N_2O_5$ requires C, 64·5; H, 6·5; N, 7·5%); n.m.r. spectrum ($CDCl_3$): N*H*, τ −0·13; $C_6H_5CH_2$, 2·65, 4·71; OCH_2CH_2, 5·89(t); $N(CH_3)_2$, 7·0; CH_3, 7·69; $COCH_3$, 8·02.

Benzyl 3,5-*Dimethyl*-4-(2-*xanthoxyethyl*)*pyrrole*-2-*carboxylate* (IIIc).—The corresponding hydroxyethylpyrrole (4 g.) was added to a solution of sodium t-butoxide in t-butyl alcohol obtained by dissolving sodium (0·5 g.) in t-butyl alcohol (7·5 ml.). The mixture was stirred for 5 min. at 18° before the addition of carbon disulphide (5 ml.), whereupon the solution became a pale yellow paste. Methyl iodide (5 ml.) was added after 15 min. with stirring to give a yellow solution which suddenly went solid. The product was filtered, washed with water, and dried. Crystallisation from benzene–light petroleum (b.p. 60—80°) gave the required *pyrrole* as fibrous needles (4·8 g., 93%), m.p. 121—123 (Found: C, 59·4; H, 5·8; N, 3·7. $C_{18}H_{21}NO_3S_2$ requires C, 59·5; H, 5·8; N, 3·85%); n.m.r. spectrum ($CDCl_3$): N*H*, τ 0·9; C_6H_5, 2·67; $C_6H_5CH_2$, 4·72; CH_2CH_2O, 7·17(t), 5·43- (t); SCH_3, 7·48; β-CH_3, 7·70, 7·80.

Pyrolysis of the Pyrrole Xanthate.—The foregoing xanthate derivative (0·8 g.) was heated under nitrogen in an oil-bath at 170° for 4 hr. After cooling the product was chromatographed on alumina (100 g.) in benzene. Each fraction was tested by t.l.c. and developed with iodine. The pyrrole-containing fractions were combined and evaporated to dryness and the isomeric *dithiocarbonic ester* (IIId) (0·4 g., 50%) was obtained as fine colourless needles, m.p. 137—138°, by crystallisation from benzene–light petroleum (b.p. 60—80°) (Found: C, 59·8; H, 6·0; N, 4·0. $C_{18}H_{21}NO_3S_2$ requires C, 59·5; H, 5·8; N, 3·9%); n.m.r. spectrum ($CDCl_3$), NH, τ 1·3; $C_6H_5CH_2$, 2·68, 6·75; $-CH_2CH_2-$ 7·0, 7·35(m); CH_3, 7·62, 7·74, 7·82.

Benzyl 3,5-*Dimethyl*-4-(2-*iodoethyl*)*pyrrole*-2-*carboxylate*.—Methanesulphonyl chloride (1·9 ml.) was added to a solution of 4-(2′-hydroxyethyl)pyrrole (5 g.) in pyridine (12 ml.) and the solution was stirred for 30 min. After removal of the pyridine on a rotary evaporator, the oil was dissolved in methylene chloride (50 ml.) and the solution was washed with water (2 × 50 ml.). The organic layer was evaporated to dryness and the product heated under reflux in acetone (150 ml.) with sodium iodide (5 g.) for 3 hr. After filtration and evaporation to dryness the product was chromatographed on alumina (50 g.), with benzene as eluant. Crystallisation from benzene–light petroleum (b.p. 60—80°) gave the required 2-*iodoethylpyrrole* (4·1 g., 50%) as colourless needles, m.p. 128—219° (Found: C, 50·25; H, 4·8; N, 3·9. $C_{16}H_{18}IO_2$ requires C, 50·3; H, 4·8; N, 3·7%); n.m.r. spectrum ($CDCl_3$): N*H* τ 1·1—1·3; $C_6H_5CH_2$, 2·69, 6·77; CH_2CH_2I, 6·87—7·13; CH_3. 7·77, 7·82.

Pentachlorophenyl 3,5-*Dimethyl*-4-(2-*methoxycarbonylethyl*)*pyrrole*-2-*carboxylate* (VIIIc).—A solution of benzyl 3,5-dimethyl-4(2-methoxycarbonylethyl)pyrrole-2-carboxylate (20 g.) in tetrahydrofuran (100 ml.) was hydrogenated over 10% palladium–charcoal (1 g.) with triethylamine (0·1 ml.) as an accelerator. When hydrogen absorption had ceased the catalyst was removed by filtration through Celite and phosgene was passed through the ice-cooled filtrate for 30 min. The solvent was then evaporated off under reduced pressure and a solution of pentachlorophenol (14·6 g.) in pyridine (40 ml.) was added. Methanol (150 ml.) was added to the oil obtained by evaporation of the pyridine and the required *pentachlorophenyl ester* crystallised as pinkish plates, m.p. 174—176° (Found: C, 42·9; H, 2·95; N, 2·9. $C_{17}H_{14}Cl_5NO_4$ requires C, 43·1; H, 3·0; N, 3·0%); n.m.r. spectrum ($CDCl_3$): N*H*, τ 0·8—1·1; CO_2CH_3, 6·33; CH_2CH_2CO, 7·23—7·60: CH_3, 7·67, 7·78.

Pentachlorophenyl 5-Bromomethyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate (XIVb).—A solution of bromine (0·35 ml.) in ethanol-free chloroform (12 ml.) was added during 15 min. to a vigorously stirring solution of the 5-methylpyrrole (3 g.) in ethanol-free chloroform (60 ml.) containing potassium carbonate (5 g.) in suspension. After the addition, the mixture was stirred for a further 1 hr. The inorganic material was filtered off and the solvent was removed under reduced pressure. Trituration of the oil obtained by this procedure, gave the required 5-bromomethylpyrrole as pinkish microcrystals, (3·4 g., 97%), m.p. 136—138°; n.m.r. spectrum ($CHCl_3$): N*H*, τ 0·25—0·5; C*H*$_2$Br, 5·55; C*H*$_2$C*H*$_2$CO, 7·15—7·6(m); β-C*H*$_3$, 7·67.

For analysis the bromomethylpyrrole was converted into its *pyridinium salt* by treatment with pyridine. The salt was obtained as colourless needles by trituration with ether (Found: C, 42·0; H, 3·7; N, 4·3. $C_{22}H_{18}BrCl_5N_2O_4$ requires C, 41·8; H, 2·9; N, 4·4%).

Pentachlorophenyl 5-Acetoxymethyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate (XIVc).—Lead tetraacetate (3·65 g.) was added to a stirred solution of the 5-methylpyrrole (3 g.) in glacial acetic acid (90 ml.). After 3 hr. the mixture was poured into water (200 ml.) and extracted with chloroform. The combined chloroform extracts were washed with aqueous sodium carbonate and then water. The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure; the oil obtained was triturated in ether to give the desired *acetoxymethylpyrrole* as colourless needles (2·8 g., 83·2%), m.p. 144—145° (Found: C, 42·7; H, 3·0; N, 2·6: $C_{16}H_{16}Cl_5NO_6$ requires C, 42·9; H, 3·0; N, 2·6%); n.m.r. spectrum ($CDCl_3$): N*H*, τ 0·37; C*H*$_2$–O, 4·75; OC*H*$_3$, 6·22; C*H*$_2$C*H*$_2$, 7·09(t), 7·43(t); C*H*$_3$, 7·58; COC*H*$_3$, 7·86.

3-(2-*Acetoxyethyl*)-5-*benzyloxycarbonyl*-4-*methylpyrrol*-2-*ylpyridinium Bromide*.—A solution of bromine (1·6 ml.) in dry ether (304 ml.) was added during 3 min. to a stirred solution of benzyl 4-(2-acetoxyethyl)-3,5-dimethylpyrrole-2-carboxylate (8·7 g.) in dry ether (348 ml.). The solution obtained was stirred at 18° for a further 2 hr. and then evaporated to low bulk. The bromomethylpyrrole was induced to crystallise by scratching and cooling the solution after it had been decanted from the insoluble gummy impurities. The solution was cooled at 0° for 15 min. and then the product was filtered off and washed with ice-cold 1 : 1 ether–light petroleum (b.p. 40—60°). The bromo-derivative was dissolved in pyridine and the solution was diluted with a large volume of ether. The precipitated oil was washed by decantation with ether and on scratching the solution with a glass rod, it finally crystallised. After recrystallisation from ethanol–ether the *pyridinium salt* was obtained as prisms (10·6 g., 81%), m.p. 147—148° (Found: C, 58·0; H, 5·4; N, 5·6. $C_{23}H_{25}BrN_2O_4$ requires C, 58·3; H, 5·3; N, 5·9%); n.m.r. spectrum (CF_3CO_2H): N*H*, τ −0·55; $C_5H_5\overset{+}{N}$–, 1·05—2·1; –C*H*$_2$–N^+, 3·95; C_6H_5–, 2·6.

Pyrromethanes and Pyrroketones

Pentachlorophenyloxycarbonyl-5-benzyl 4,4′-Dimethyl-3,3′-di-(2-methoxycarbonylethyl)pyrromethane-5-carboxylate. (VIIIa).—A glacial acetic acid solution (32 ml.) containing pentachlorophenyl-5-bromomethyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate (1·5 g.), benzyl 4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate (0·9 g.), and sodium acetate (0·25 g.) was heated on a boiling water-bath for 2 hr. The mixture was poured into water, the organic products were extracted with methylene chloride, and the extracts were washed with 10% sodium carbonate solution, and then water; the solution was dried ($MgSO_4$) and evaporated to dryness. The dark brown oil obtained was chromatographed on alumina (150 g.) with benzene–light petroleum (b.p. 60—80°) mixtures as the initial eluants. The pyrromethane fraction was eluted in 100% benzene, the last traces coming off in a mixture of 5% ethyl acetate in benzene. Evaporation of the solvent under reduced pressure gave the product as a pale yellow oil which crystallised from methanol. Recrystallisation from benzene–light petroleum (b.p. 60—80°) gave the required *pyrromethane* (0·62 g., 29·5%), as colourless prisms, m.p. 158—160° (Found: C, 52·9; H, 4·1; N, 3·7. $C_{34}H_{31}Cl_5N_2O_8$ requires C, 52·8; H, 4·0; N, 3·6%); n.m.r. ($CDCl_3$): N*H*, τ 0·56, 0·94br; $C_6H_5CH_2$, 2·68, 4·75; C*H*$_2$–, 6·0; –C*H*$_2$C*H*$_2$–CO$_2$C*H*$_3$, 7·2—7·5m; β-C*H*$_3$, 7·66, 7·75.

5′-*Benzyloxycarbonyl*-4,4′-*dimethyl*-3,3′-*di*-(*carboxyethyl*)-*pyrromethane*-5-*carboxylic Acid* (VIIId).—The preceding pentachlorophenyl benzyl ester was dissolved in tetrahydrofuran (120 ml.) and the solution was diluted with water (120 ml.). 1M-Sodium hydroxide solution (18 ml.) was added to give a clear solution which was left under nitrogen in the dark for 72 hr. The tetrahydrofuran was removed under reduced pressure and sulphur dioxide was passed through the aqueous solution. The precipitated oil was extracted with methylene chloride and the extracts were evaporated to dryness. The required *pyrromethane-tricarboxylic acid* (0·45 g., 75%), was obtained as pinkish prisms by crystallisation from ether, m.p. 140—141° (decomp.) (Found: C, 62·65; H, 5·7; N, 5·7. $C_{26}H_{28}N_2O_8$ requires C, 62·9; N, 5·7; N, 5·6%).

Benzyl 3,4′-Di-(2-acetoxyethyl)-3′,4-dimethyl-5′-dimethylamidopyrromethane-5-carboxylate.—3-(2-Acetoxyethyl)-2-dimethylamido-3-methylpyrrole-5-carboxylic acid (4·4 g.) was shaken with lithium methoxide (0·605 g.) in formamide (22·8 ml.) until a clear solution was obtained. 3-(2-Acetoxyethyl)-5-benzyloxycarbonyl-4-methylpyrrol-2-ylpyridinium bromide salt (7·2 g.) was added and the mixture was swirled until all had dissolved. The solution was heated under nitrogen at 100° for 20 hr. The cool reaction mixture was diluted with water (100 ml.) and extracted with methylene chloride. The extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The required *pyrromethane* (4·2 g., 49%) was obtained as colourless prisms by trituration with ether, m.p. 142—143° (Found: C, 65·5; H, 6·9; N, 7·8. $C_{30}H_{37}N_3O_7$ requires C, 65·3; H, 6·8; N, 7·6%); n.m.r. ($CDCl_3$): $C_6H_5CH_2$, τ 2·72, 4·76; C*H*$_2$C*H*$_2$O, 5·91t, 6·02t; C*H*$_2$, 6·20; CON(C*H*$_3$)$_2$, 7·02; C*H*$_2$C*H*$_2$O, 7·21t, 7·29t; C*H*$_3$, 7·73, 8·03; COC*H*$_3$, 8·00.

5-*Benzyl* 5′-t-*Butyl* 4,4′-*Dimethyl*-3,3′-*di*-(2-*methoxycarbonylethylethyl*)-*pyrromethane*-5,5′-*dicarboxylate* (XVI).—The α-free pyrrole t-butyl ester (3·2 g.) and sodium acetate (2·5 g.) were dissolved in glacial acetic acid. The bromomethylpyrrole benzyl ester (5·6 g.) was then added and dissolved with warming. After heating under reflux on an oil-bath at 145—150° for 40 min. the mixture was poured onto ice and then extracted with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and then evaporated to dryness. The residual oil was chromatographed on alumina (200 g.) elution being first with light petroleum (b.p. 60—80°) until movement of the band ceased, then with 1 : 1 benzene–light petroleum and finally with benzene. The desired *pyrromethane* was then eluted in

benzene and was obtained as colourless needles (3·4 g., 47·5%), m.p. 114—115° by crystallisation from ether–light petroleum (b.p. 40—60°).

Benzyl 4′-(2-Acetoxyethyl)-3-ethyl-3′,4,5′-trimethylpyrroketone-5-carboxylate (VIa).—Benzyl 5-dimethylamido-4-ethyl-3-methylpyrrole-2-carboxylate (6·28 g.) in ethylene dichloride (25 ml.) was treated with phosphoryl chloride (2·5 ml.) and stirred and heated gently under reflux for 2 hr. At the end of this time the new absorption at 368 nm. had reached a maximum, and the solution was allowed to cool to 20° before the addition of 3-(2-acetoxyethyl)-2,4-dimethylpyrrole [obtained by heating 3-(2-acetoxyethyl)-2,4-dimethylpyrrole-5-carboxylic acid (4·5 g.) to 160° under nitrogen for 30 min.] in ethylene dichloride (5 ml.) over 10 min. The solution was boiled and a slow stream of nitrogen was passed through the mixture to remove traces of hydrogen chloride produced. The mixture was heated under reflux for 2 hr., and then boiled and stirred vigorously under reflux with sodium acetate (18 g.) in water (30 ml.) and more ethylene dichloride (15 ml.). The organic layer was separated and the aqueous layer was washed with ethylene dichloride. The combined organic layer and washings were dried ($MgSO_4$) and evaporated to dryness on a rotary evaporator. Trituration of the oil with ether yielded the desired *pyrroketone* (7·30 g., 81%) as fine needles, m.p. 137—138° (from methanol) (Found: C, 69·6; H, 6·8; N, 6·2. $C_{26}H_{28}N_2O_5$ requires C, 69·3; H, 6·7; N, 6·5%); n.m.r. ($CDCl_3$): N*H*, τ 0·35, 0·66; $C_6H_5CH_2$, 2·60, 4·68; OCH_2, 5·92t; CH_2CO, 7·28t; CH_2CH_3, 7·36q, 8·92t; CH_3, 7·68, 7·74, 7·98, 8·03.

Benzyl 3,4′-Di-(2-acetoxyethyl)-3′,4,5′-trimethylpyrroketone-5-carboxylate (VIb).—This was synthesised from the amide (Vb) (8·0 g.) and 4-(2-acetoxyethyl)-3,5-dimethylpyrrole-2-carboxylic acid (3·9 g.) in the same manner as the preceding preparation. The *product* (8·4 g.; 77%) crystallised as fine needles, m.p. 114—116°, from ether (Found: C, 66·2; H, 6·4; N, 5·3. $C_{28}H_{32}N_2O_7$ requires C, 66·1; H, 6·3; N, 5·5%); n.m.r. ($CDCl_3$): N*H*, τ −0·04, 0·34; $C_6H_5CH_2$, 2·62, 4·69; $-CH_2-O$, 5·85t, 5·93t; $-CH_2-CH_2-$, 7·01t, 7·33t; β-CH_3, 7·66, 7·97; α-CH_3, 7·97; $COCH_3$, 8·07.

Benzyl 4′-(2-Acetoxyethyl)-5′-chloromethyl-3-ethyl-3′,4-dimethylpyrroketone-5-carboxylate. (VIIa).—t-Butyl hypochlorite (1·26 ml.) in ether (50 ml.) was added, with stirring, during 5 min. to an ice-cooled solution of the (2-acetoxyethyl)pyrroketone (5·5 g.) in tetrahydrofuran (50 ml.) and ether (200 ml.). After a test had been made for disappearance of all the hypochlorite with starch–iodide paper, the solution was evaporated to dryness. Trituration with ether gave the required *chloromethylpyrroketone* (3·7 g., 63%). It crystallised from ether as a pink solid, m.p. 111—112° (Found: C, 64·2; H, 6·2. $C_{26}H_{29}ClN_2O_5$ requires C, 64·4; H, 6·0%); n.m.r. ($CDCl_3$): $C_6H_5CH_2$, τ 2·61, 4·69; CH_2Cl, 5·37; $O-CH_2-CH_2-$, 5·87t, 7·22t; 3′,4-CH_3, 7·68, 7·98; $-CH_2CH_3$, 7·32q, 8·92t; $COCH_3$, 7·98.

Benzyl 3,4′-Di-(2-acetoxyethyl)-5′-chloromethyl-3′,4-dimethylpyrroketone-5-carboxylate (VIIg).—This compound was synthesised in 76% yield from the corresponding 5′-methylpyrroketone by treatment with t-butyl hypochlorite following the same procedure as for the analogue above, and crystallised from ether as a pink solid, m.p. 110—111° (Found: C, 61·7; H, 5·8; N, 4·9. $C_{28}H_{31}ClN_2O_7$ requires C, 61·9; H, 5·7; N, 52%); n.m.r. ($CDCl_3$): $C_6H_5CH_2$ τ −2·62, 4·68; $-CH_2-Cl$, 5·39; 5·85t, 5·89t; $-CH_2-CH_2-$, 7·01t, 7·25t; β-CH_3, 7·67, 7·97; $COCH_3$, 8·00, 8·09.

Oxobilanes

Dibenzyl 4-(2-Acetoxyethyl)-2-ethyl 6,7-di-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-a-oxobilane-1′,8′-dicarboxylate (IXa).—Benzyl 4-(2-acetoxyethyl)-5′-chloroethyl-3-ethyl-3′,4-dimethylpyrroketone-5-carboxylate (1·2 g.) in pyridine (2·6 ml.) was added to a solution of 5′-benzyloxycarbonyl-3,3′-di-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5-carboxylic acid (1·47 g.) and lithium methoxide (0·11 g.) in formamide (100 ml.) under nitrogen during which time a viscous greenish oil separated out. The formamide was decanted from the cool solution, and the oil taken up in methylene chloride and washed with water (3 × 50 ml.). The organic layer was dried ($MgSO_4$) evaporated to dryness and the residual oil crystallised from dry peroxide-free ether (25 ml.) to give the a-*oxobilane* (1·02 g., 44%) as a yellowish solid, which was recrystallised from methylene chloride–light petroleum (b.p. 40—60°) to give light yellow prisms, m.p. 118—120° (Found: C, 68·7; H, 6·7; N, 6·25. $C_{53}H_{60}N_4O_{11}$ requires C, 68·5; H, 6·5; N, 6·0%).

Dibenzyl 2,4-Di-(2-acetoxyethyl)-6,7-di-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-a-oxobilane-1′,8′-dicarboxylate. (IXb).—(*a*) A suspension of 5′-benzyloxycarbonyl-3,3′-di-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5-carboxylic acid (2·0 g.) and lithium methoxide (0·15 g.) in formamide (50 ml.) was shaken to give complete dissolution. This solution was added to benzyl 3,4′-di-(2-acetoxyethyl)-2′-chloromethyl-4,3′-dimethylpyrroketone-5-carboxylate (1·9 g.) in pyridine (3·2 ml.) and the mixture was heated at 50° for 18 hr. under nitrogen. During the heating period an oil separated from the solution and formed a viscous lower layer. After a further 3 hr. at 20° the formamide solution was decanted from the gum, and the latter was washed by decantation with formamide (2 × 5 ml.), then with water (2 × 5 ml.); it was then taken up in methylene chloride (50 ml.). After being washed with water (3 × 50 ml.) the methylene chloride solution was dried ($MgSO_4$) and evaporated to dryness. The residue was evaporated twice with 20-ml. portions of dry peroxide-free ether to remove traces of pyridine, and the foam remaining was taken up in ether (100 ml.) and kept overnight at 20° under nitrogen. The a-*oxobilane* (1·49 g., 41·5%), crystallised as yellow prisms, m.p. 132—134° (Found: C, 67·0; H, 6·4; N, 5·75. $C_{55}H_{62}N_4O_{13}$ requires C, 66·9; H, 6·3; N, 5·7%); n.m.r. ($CDCl_3$): N*H*, τ 0·4—0·6, 1·25; $C_6H_5CH_2$, 2·68, 2·82, 4·72, 4·92; CH_2-O, 5·8—6·35m; CH_2-CH_2 and CH_2-CO, 6·9—7·7m, β-CH_3, 7·70, 7·79; 8·09, 8·16; OCH_3, 6·44; $COCH_3$, 8·03, 8·04.

(*b*) A suspension of 5′-benzyloxycarbonyl-4,4′-dimethyl-3,3′-di-(carboxyethyl)pyrromethane-5-carboxylic acid (400 mg.) and lithium methoxide (96 mg.) in formamide (10·4 ml.) was shaken to give complete dissolution. The solution was added to benzyl 3,4′-di-(2-acetoxyethyl)-5′-chloromethyl-3′,4-dimethylpyrroketone-5-carboxylate (400 mg.) in pyridine (0·67 ml.) and the mixture was heated at 50° for 18 hr. under nitrogen. The solution was then poured into water (200 ml.) and sulphur dioxide was passed through until it was acid to litmus. The product precipitated as a colourless oil. The aqueous mixture was extracted with chloroform and the organic fractions were combined and evaporated to dryness. The oily residue was methylated with an ether solution of diazomethane and then chromatographed on a column of alumina (100 g.) with ethyl acetate–benzene as eluant. After evaporation to dryness of the combined oxobilane-containing fractions, the product (172 mg., 25%)

was obtained as yellow microcrystals by trituration with ether, m.p. 132—133°. The i.r. was identical with that of the a-oxobilane prepared by the previous route.

Dibenzyl 2,4-*Di*-(2-*acetoxyethyl*)-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethyl*-b-*oxobilane*-1′,8′-*dicarboxylate* (XVII).—Benzyl 3,4′-di-(2-acetoxyethyl)-3′,4-dimethyl-5′-dimethylamidopyrromethane-5-carboxylate (2·5 g.) was dissolved in phosphoryl chloride (10 ml.) and heated at 50° for 30 min. Meanwhile, 5-benzyloxycarbonyl-3,3′-di-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5′-carboxylic acid was decarboxylated by being heated to its melting point *in vacuo*. The pyrromethaneamide–phosphoryl chloride complex solution was evaporated to dryness under reduced pressure, the last traces of phosphoryl chloride being scavenged with ethylene dibromide (20 ml.); the yellow oil produced was dissolved in methylene chloride (10 ml.). The α-free pyrromethane dissolved in methylene chloride (10 ml.) was added to the solution which was then stirred in an oil-bath at 50°, under reflux, with a slow passage of nitrogen through it. After 20 hr. the reaction mixture was diluted with methylene chloride (50 ml.) and washed with water (2 × 50 ml.). The solution was dried ($MgSO_4$) and evaporated to dryness under reduced pressure, the last traces of ethylene dibromide being scavenged with benzene. The oil was then chromatographed on alumina (150 g.) first with benzene as eluant until no further material was eluted from the column. The column was then eluted with 100-ml. portions of ethyl acetate–benzene mixtures increasing to 50% ethyl acetate, and then with pure ethyl acetate until the eluate was colourless. The bilane *b*-imine salt was then stripped from the column with methanol and the solution was evaporated to dryness. Hydrolysis to oxobilane was then carried out by heating a stirred methylene chloride (100 ml.) solution of the imine under reflux with 10% aqueous sodium carbonate (100 ml.) for 4 hr. The organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure; the oil produced was chromatographed on alumina (150 g.) with first benzene as eluant and then with gradually increasing proportions of ethyl acetate in benzene. The product started to be eluted in 10% (v/v) ethyl acetate–benzene but required 50% of ethyl acetate to remove the last traces from the column. The combined eluates were evaporated to dryness under reduced pressure and finally under high vacuum. The required product was obtained as a pale yellow foam (2·17 g., 48%) which could not be crystallised. T.l.c. on silica gel in benzene–ethyl acetate mixtures showed a single spot, after development with iodine; n.m.r. ($CDCl_3$): N*H*, τ −0·16 −0·8, −0·8, 0·17; $C_6H_5CH_2$, 2·75, 4·82; CH_2–O, 5·9—6·3m; OCH_3, 6·35, 6·39; CH_2CH_2 and CH_2CO, 7·0—7·6m; β-CH_3, 7·75, 7·77, 8·05, 8·19; $COCH_3$, 8·02, 8·05.

Porphyrins

4-(2-*Acetoxyethyl*)-2-*ethyl*-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (Xa).—The monoacetoxyethyl-*a*-oxobilane (856 mg.) in tetrahydrofuran (25 ml.) and ethyl acetate (25 ml.) was treated under nitrogen with a slow stream of diborane generated externally from sodium borohydride (0·45 g.) in diglyme by addition of boron trifluoride–etherate in diglyme during a few min. Spectroscopic sampling showed that reduction of the oxo-function was complete in 1·5 hr. (the maximum at 350 nm. having completely disappeared), and the solution was evaporated to dryness. The residue was taken up in methanol (25 ml.) and after 10 min. tetrahydrofuran (25 ml.) was added and the yellowish solution was hydrogenated overnight at 20° and 1 atm. over palladium–charcoal (10%; 500 mg.) in presence of 0·1 ml. triethylamine as promoter. After removal of catalyst and solvent (under nitrogen) the residual bilane diacid (673 mg.) was taken up in tetrahydrofuran (50 ml.) and ether (200 ml.) and cooled to −15° before addition of t-butyl hypochlorite (0·112 ml., 96%) in ether (50 ml.) during 2 hr. at −10 to −15°. The deep red solution was concentrated to small bulk (under nitrogen) and left overnight to crystallise. The b-*bilene* (618 mg.) crystallised out as dark red needles, and a further 57 mg. was obtained by trituration of the mother liquors with ether.

This product (675 mg.) was dissolved in methylene chloride (175 ml.) and methyl orthoformate (1·87 ml.) and added to a freshly prepared solution of 1M-trichloroacetic acid in methylene chloride (53 ml.) diluted to 175 ml. by addition of methylene chloride (122 ml.). The mixture was stirred in oxygen overnight in the dark (17 hr.) (spectroscopic yield of porphyrin 33%) then washed with 10% sodium carbonate (500 ml.) and water (3 × 500 ml.), and dried ($MgSO_4$). After removal of solvent *in vacuo* the residue was chromatographed twice on alumina (grade III) first in methylene chloride and then in benzene–methylene chloride (1 : 1 v/v). The porphyrine fractions were collected, evaporated to dryness, and crystallised from methylene chloride–methanol to give the desired *acetoxyethylporphyrin* (157 mg., 26%) as violet needles, m.p. 207—208° (corr.) (Found: C, 69·9; H, 6·7; N, 8·6. $C_{38}H_{44}N_4O_6$ requires C, 69·9; H, 6·8; N, 8·6%).

2,4-*Di*-(2-*acetoxyethyl*)-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphyrin* (Xb).—(*a*) The di-(acetoxyethyl)-*a*-oxobilane dibenzyl ester (1·05 g.) in dry tetrahydrofuran (35 ml.) and dry ethyl acetate (35 ml.) was reduced with diborane, generated from sodium borohydride (0·525 g.) in diglyme (19·5 ml.) and boron trifluoride–ether (5·25 ml.) in diglyme (19·5 ml.) during 5 min., in an apparatus similar to that previously described. The diborane was swept into the reaction vessel by a slow stream of nitrogen. The absorption at 350 nm. due to the pyrroketone moiety had completely disappeared after 70 min. The resulting colourless solution was evaporated to dryness under reduced pressure of nitrogen, taken up in methanol (22 ml.), and tetrahydrofuran (75 ml.) and hydrogenated over palladium–charcoal (0·48 g., 10%) in the presence of a trace of triethylamine (as promoter) at 20° and 1 atm. The uptake of hydrogen was complete in 18 hr. As a check on the completeness of hydrogenation a sample was removed from the flask (by means of a hypodermic syringe inserted through a serum cap in a side-neck) and diluted to a concentration of 50 μmole/l. with ethanol; the rapid disappearance of the absorption at 282 nm. (due to the terminal pyrrole-carboxylic acid groups) on addition of a few drops of concentrated hydrochloric acid to the sample cell then confirmed that the benzyl groups had been successfully removed. The catalyst was removed by filtration through ' Hyflo Supercel ' under nitrogen, and the solvents were removed under reduced pressure of nitrogen. The last traces of tetrahydrofuran and methanol were removed by evaporation of the residue with dry peroxide-free ether (25 ml.) and the bilane diacid was obtained as a buff, gummy solid.

This bilane di-acid was dissolved in tetrahydrofuran (60 ml.) and the solution was diluted with ether (240 ml.). This solution was stirred under nitrogen and cooled to

—15° during the addition of t-butyl hypochlorite (0·129 ml.) in ether (12·6 ml.) during 1 hr. in the dark. A starch–iodide test was negative 5 min. after the end of the addition, and the bilene solution formed was allowed to warm up to room-temperature. The solution was evaporated to dryness and ether added (50 ml.). The purple bilene was scraped from the sides of the flask and the suspension filtered.

The bilene (868 mg.) was dissolved in methylene chloride (225 ml.) and trimethyl orthoformate (2·4 ml.) and a normal solution of trichloroacetic acid in methylene chloride (68·3 ml.) added. The mixture was stirred overnight in an atmosphere of oxygen in the dark. The methylene chloride solution was washed with 10% sodium carbonate solution and twice with water and was then dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was chromatographed on alumina in benzene–methylene chloride (1 : 1 v/v). The porphyrin eluates were collected and evaporated to dryness under reduced pressure. The product crystallised from methylene chloride–methanol and gave the *porphyrin* (229 mg., 30%) as purple needles, m.p. 167—168° (Found: C, 67·6; H, 6·3; N, 8·1. $C_{40}H_{46}N_4O_8$ requires C, 67·6; H, 6·5; N, 7·9%); n.m.r. (0·1M in $CDCl_3$): N*H*, τ 14·17; *meso-H*, 0·18 (2H), 0·27, 0·31; CH_2O, 5·25t, 5·34t; β-CH_2, 5·6—6·1m; OCH_3, 6·43, 6·45, CH_3, 6·53, 6·60, 6·63, 6·71, CH_2–CO, 6·81t, 6·85t; COCH_3, 7·0, 7·02; $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 397(5·23), 498(4·11), 535(3·94), 568(3·80), 623(3·57), in $CHCl_3$ + HCl gas, 420(5·37), 557(4·18), 598(3·76) nm; mass spectrum, *m/e* (%): 710(M^+)(100), 652(5), 651(5), 650(4), 637(8), 577(4); *m**, 595(710 → 651), 561(710 → 577).

(*b*) The corresponding β-acetoxyporphyrin [(XIX) see below] (104 mg.) in tetrahydrofuran (80 ml.) solution containing a few drops of triethylamine was hydrogenated over 10% palladium–charcoal (100 mg.) until the solution was colourless (2·5 hr.). After removal of the catalyst by filtration through ' Supercell ' the solution was diluted with tetrahydrofuran (150 ml.) and pyridine (5 ml.) was added. Oxidation was effected by bubbling a slow stream of air through the solution for 22 hr. After removal of the solvent under reduced pressure the product was chromatographed on alumina (100 g.) in methylene chloride. After evaporation of the combined porphyrin fractions to dryness, the desired porphyrin (70 mg., 73%) was obtained as purple plates, m.p. 166—167°. This was shown to be identical in all respects with that obtained by the *a*-oxobilane route.

2-*Ethyl*-4-(2-*hydroxyethyl*)-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (XIa).—The 4-(2-acetoxyethyl)-porphyrin (100 mg.) was dissolved in sulphuric acid (5% w/v) in methanol (100 ml.) and left overnight in the dark. The solution was poured into ice-cold water, the last traces being washed in with chloroform; the solution was neutralised with dilute ammonia solution before extraction with chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give the required product (85 mg., 91%) as purple needles, m.p. 227—228° (from methylene chloride–ether) (Found: C, 70·5; H, 6·7; N, 9·3. $C_{36}H_{42}N_4O_2$ requires C, 70·8; H, 6·9; N, 9·2%); n.m.r. ($CDCl_3$: 0·05M): *meso-H*, τ 0·06 (3H), 0·09 (1H); β-CH_2 and CH_2–O, 5·6—5·9m; OCH_3, 6·42(s); CH_3, 6·50; CH_2–CO–, 6·80t; CH_2CH_3, 6·02q, 8·18t; $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 3q 7(509) 498(400), 533(3·83), 568(3·68), 621(3·45); in $CHCl_3$ + HCl gas, 420(5·25), 557(4·07), 590(3·69) nm.; mass spectrum, *m/e* (%): 610(M^+)(100), 592(26), 579(24), 551(24), 549(17), 537(25).

2,4-*Di*-(2-*hydroxyethyl*)-6,7-*di*-(2-*methoxycarbonyl ethyl*)-1,3,5,8-*tetramethylporphin* (XIb).—The corresponding 2,4-di-(2-acetoxyethyl)porphyrin (237 mg.) was treated with sulphuric acid in methanol as above. The required *product* (196 mg., 94%) was obtained as feather-like needles, m.p. 225—226·5° (from pyridine–ether) (Found: C, 68·7; H, 6·8. $C_{36}H_{24}N_4O_6$ requires C, 69·0; H, 6·8%); n.m.r. (CF_3CO_2H): *meso-H*, 1·0; CH_3, 6·19(2), 6·22, 6·24; CH_2CH_2CO_2CH_3, 5·25t, 6·65t, 6·16; CH_2CH_2O, 5·3m, 4·8t, $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 397(5·20), 498(410), 533(3·94), 568(3·79), 623(3·57); in $CHCl_3$ + HCl gas, 420(5·37), 559(4·18), 598(3·76) nm.; mass spectrum, *m/e* (%): 626(M^+) (100), 595(39), 567(4), 566(3), 565(4), 564(3), 559(15), 521(4); *m**, 566(626 → 595).

4-(2-*Chloroethyl*)-2-*ethyl*-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (XIIa).—The 2-ethyl-4-(2-hydroxyethyl)porphin (70 mg.) was treated with methanesulphonyl chloride (3·0 ml.) in pyridine (9·0 ml.) and heated under nitrogen at 75° for 35 min. Water (30 ml.) was added and the mixture was extracted with methylene chloride. The combined extracts after being dried ($MgSO_4$) were evaporated to dryness under reduced pressure and the residue was chromatographed on alumina in benzene–methylene chloride (1 : 1 v/v). The porphyrin fraction was collected, and after evaporation to dryness, the residue was crystallised from methylene chloride–methanol to give the *chloroethylporphin* as purple plates (45 mg., 63%), m.p. 238·5—239·5° (Found: C, 68·7; H, 6·5; N, 8·8. $C_{36}H_{41}ClN_4O_4$ requires C, 68·7; H, 6·6; N, 8·9%); n.m.r. ($CDCl_3$): *meso-H*, 0·19 (1H), 0·24 (2H), 0·35 (1H); CH_2 and CH_2Cl, τ 5·6—6·0m; OCH_3, 6·43; CH_3, 6·58, 6·63, 6·63, 6·66; CH_2–CO–, 6·89t; CH_2CH_3, 6·18q, 8·29t; $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 397(5·12), 498(4·01), 533(3·86), 568(3·69), 623(3·48); in $CHCl_3$ + HCl gas, 420(5·23), 559(4·08), 590(3·73) nm. mass spectrum, *m/e* (%): 628(M^+)(100), 592(*M* — HCl)(46), 555(11), 519(8); *m**, 491(628 → 555), 456(592 → 519).

2,4-*Di*-(2-*chloroethyl*)-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (XIIb).—(*a*) Methanesulphonyl chloride (6·0 ml.) was added to a solution of 2,4-di-(2-hydroxyethyl)porphyrin (140 mg.) in pyridine (18·0 ml.). The resulting solution was heated at 75° under nitrogen for 35 min. Water (50 ml.) was added and the mixture was extracted with methylene chloride. The combined extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure; the residue was chromatographed on alumina in benzene–methylene chloride (1 : 1 v/v). The porphyrin fraction was collected and, after evaporation to dryness, was crystallised from methanol–methylene chloride to give purple plates (82·5 mg., 55%) m.p. 216—217° (Found: C, 65·0; H, 6·1; N, 8·1. $C_{36}H_{40}Cl_2N_4O_4$ requires C, 65·15; H, 6·1; N, 8·4%); n.m.r. (0·1M in $CDCl_3$): *meso-H*, τ 0·30 (1H), 0·50 (2H), 0·67 (1H), CH_2Cl and CH_2, 5·7—6·2m; –OCH_3, 6·44, 6·46; β-CH_3 and CH_2CO, 6·6—7·0m; $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 397(5·26), 498(4·14), 532(3·96), 568(3·80), 623(3·62); in $CHCl_3$ + HCl gas, 420(5·36), 557(4·20), 575(3·78) infl., 598(3·83) nm.; mass spectrum, *m/e* (%); 662(M^+)(100), 628(15), 627(15), 626(13), 613(10), 589(9); *m**, 568(662 → 613), 525(662 → 589).

(*b*) The corresponding 2,4-di-(2-acetoxyethyl)porphyrin (74 mg.) was hydrolysed as previously described and the di-(hydroxyethyl)porphyrin produced was dissolved in chloroform (64 ml.). Dimethylformamide (32 ml.) was added to the solution followed by anhydrous potassium

carbonate (6·4 g.) to absorb moisture. Thionyl chloride (1·6 ml.) was then added and the mixture was stirred for 1 hr. before addition of excess dilute aqueous ammonia. The chloroform layer was washed with water and after being dried ($MgSO_4$) solvent was removed under reduced pressure; the product was chromatographed on alumina (100 g.) in methylene chloride. Crystallisation from methanol–methylene chloride yielded the desired porphyrin (53 mg., 76%) from the di-(acetoxyethyl)porphyrin as purple needles m.p. 215—217°. The n.m.r. mass spectra and m.p. showed the product to be identical with that prepared with methanesulphonyl chloride in pyridine.

2-*Ethyl*-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethyl*-4-*vinylporphin* (Ia).—The corresponding 4-(2-chloroethyl)porphyrin (60 mg.) was dissolved in methylene chloride (25 ml.) and a few drops of a saturated solution of zinc acetate in methanol were added to it. After the mixture had been warmed on a steam-bath the visible spectrum showed zinc insertion to be complete. The solvent was removed under reduced pressure and the metalloporphyrin was dissolved in tetrahydrofuran (2 ml.). N-potassium t-butoxide in t-butyl alcohol (35 ml.) was then added and the solution was left in the dark under nitrogen for 72 hr. The solution was then poured into ethyl acetate (100 ml.) and, after neutralisation with glacial acetic acid, was washed with water. The ethyl acetate layer was then evaporated to dryness and the porphyrin was dissolved in tetrahydrofuran (5 ml.) before the addition of 5% (w/v) concentrated sulphuric acid in methanol (70 ml.). After being set aside overnight the acid was neutralised with dilute aqueous ammonia and the mixture was extracted with methylene chloride. Chromatography on alumina in benzene–methylene chloride, followed by crystallisation from methylene chloride–methanol then gave the desired *vinylporphin* (42 mg., 66%) as purple needles, m.p. 234—235° (Found: C, 73·0; H, 6·75; N, 9·7. $C_{36}H_{40}N_4O_4$ requires C, 73·0; H, 6·8; N, 9·45%); n.m.r. (0·1M in $CDCl_3$): *meso-H*, τ 0·18(1H), 0·31 (3H); $CH{=}CH_2$, 1·95q, 3·91q; CH_2CH_2, 5·85t, 6·88t; CH_2CH_3, 6·24q, 8·29t; β-CH_3, 6·55, 6·63, 6·64, 6·66; OCH_3, 6·4, 6·42; NH 14·2; mass spectrum *m/e* (%): 592(M^+)(100), 519(15), *m**, 457(592 → 519).

A number of preliminary attempts were made to effect elimination of hydrogen chloride from the chloroethylporphyrin without prior conversion to the zinc complex, and the following describes a typical experiment. Potassium (1·9 g.) was dissolved in butanol (100 ml.) distilled from potassium, and 20 ml. of this solution was evaporated to dryness under reduced pressure. Dimethyl sulphoxide (20 ml.) was then added and the mixture was swirled to give complete dissolution. Chloroethylporphyrin (68 mg.) was added and the mixture was swirled again to assist dissolution. The solution was left in a dry box for 6 hr. and then poured into ethyl acetate. The pH was brought to 7 with acetic acid and the ethyl acetate solution was washed with water. After evaporation of the solution to dryness the porphyrin was re-esterified with diazomethane and then chromatographed on alumina (60 g.) in 50% (v/v) benzene–methylene chloride. Two porphyrins were obtained and crystallised from methanol–methylene chloride. The first (23 mg.) was shown by the n.m.r. spectrum to be the desired vinyl porphyrin contaminated with the second porphyrin. The second porphyrin (7 mg.) could not be identified, but the mass spectrum showed the parent peak at *m/e* 652, whilst the n.m.r. spectrum showed both acetyl-methyl and vinyl resonances.

6,7-*Di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethyl*-2,4-*divinylporphin* (*Protoporphyrin*-IX *Dimethyl Ester*) (Ib).—(*a*) The corresponding 2,4-di-(2-chloroethyl)porphyrin (70 mg.) was converted into its zinc complex and treated with potassium t-butoxide, *etc.* as in the preceding preparation. Protoporphyrin-IX dimethyl ester (52 mg., 73%) was obtained and crystallised from methylene chloride–methanol as purple needles, m.p. 228—229° (lit.,[3] 230°) (Found: C, 73·4; H, 6·2; N, 9·2. Calc. for $C_{36}H_{38}N_4O_4$: C, 73·2; H, 6·5; N, 9·5%); n.m.r. (0·1M in $CDCl_3$): *meso-H*, τ 0·39, 0·49, 0·53, 0·61; $CH{=}CH_2$, *ca.* 2·1m, *ca.* 4·0m; CH_2–CH_2, 5·88t, 690t; OCH_3, 6·39; β-CH_3, 6·67, 6·70, 6·74, 6·74. The mass spectrum was identical with that of a sample of natural origin.

(b) *From Haematoporphyrin*.—Haematoporphyrin (200 mg.) was heated with toluene-*p*-sulphonic acid (500 mg.) in *o*-dichlorobenzene (150 ml.) at 140° for 2 hr. The solution was shaken with dilute ammonium hydroxide, and much of the porphyrin went into the aqueous layer. Glacial acetic acid was added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were evaporated to dryness. The residue was taken up in sulphuric acid (5% v/v) in methanol and after being set aside overnight, the solution was neutralised and worked up. After chromatography a single porphyrin product was obtained, and this was crystallised from methylene chloride–methanol to give protoporphyrin-IX dimethyl ester (105 mg., 55%) as purple needles, m.p. 227—228°, identical in all respects with the synthetic material.

In a similar experiment in which haematoporphyrin dimethyl ester was heated with toluene-*p*-sulphonic acid in boiling xylene, a 42% yield of protoporhyrin dimethyl ester was obtained. However, a minor by-product was also formed the mass spectrum of which indicated that the porphyrin had reacted with the xylene. The molecular weight was 802 showing that a molecule of xylene had added to each of the double bonds in protoporphyrin. A similar reaction has been observed previously in resorcinol fusion reactions.

2,4-*Di*-(2-*acetoxyethyl*)-β-*hydroxy*-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin*.*—A solution of 2,4-di-(2-acetoxyethyl)-1,3,5,8-tetramethyl-*b*-oxobilane (1·81 g.) in tetrahydrofuran (100 ml.) was hydrogenated over 10% palladium–charcoal (200 mg.) for 2 hr. Three drops of concentrated hydrochloric acid were added to a spectroscopic sample in ethanol. The complete disappearance of the absorption at 285 nm. in the u.v. spectrum during 30 min. indicated that complete hydrogenation had occurred. The catalyst was removed by filtration through Supercel and the *b*-oxobilane di-acid was obtained as a pale yellow foam by removal of the solvent under reduced pressure. The di-acid was dissolved in methylene chloride (375 ml.) and a solution (121 ml.) of 1M-trichloroacetic acid in methylene chloride was added, followed by methyl orthoformate (4·22 ml.). The mixture was stirred for 3 hr. after which pyridine (15·0 ml.) was added; the mixture was stirred overnight. After this time examination of the intensity of the Soret absorption indicated that cyclisation had occurred to the extent of 60%. The solvent was removed under reduced pressure, and benzene (150 ml.) was added. The insoluble pyridinium trichloroacetate was filtered off and, after

* As in previous papers,[5,6] oxophlorins are systematically named, for simplicity, as derivatives of the tautomeric hydroxyporphyrins in the Experimental section.

evaporation of the solvent under reduced pressure, the product was chromatographed on alumina (150 g.) in chloroform. The blue oxophlorin band was eluted after a large band of green material. After the evaporation to dryness of the combined blue fractions the *oxophlorin* (210 mg., 16%) was obtained as a blue microcrystalline solid. It formed blue needles, m.p. 164—165° (from tetrahydrofuran–ether) (Found: C, 66·3; H, 6·6; N, 7·6. $C_{40}H_{46}N_4O_9$ requires C, 66·1; N, 6·4; N, 7·7%), $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, *403(5·0)*, *550(3·66)* infl., 586(3·98), 633(4·22); in $CHCl_3$ + HCl gas (dication,) 421(5·41), 524(3·67), 562(4·02), 618(4·08); in $CHCl_3$ + HCl gas + trace pyridine (*i.e.* green monocation), 4·09(4·86), 502(3·52) infl., 536(3·64), 580(3·60), 650(3·87) infl., 697(4·19).

The green band from the above chromatography after removal of the solvent was stirred and treated with acetic anhydride (5 ml.) in pyridine (30 ml.) for 30 min. After removal of the pyridine and acetic anhydride under reduced pressure (oil pump) the product was chromatographed on alumina (150 g.) in 10% (v/v) benzene–methylene chloride. Together with a large green band there were two porphyrin bands. The slower moving band after crystallisation from methanol–methylene chloride was identified as the *meso*-acetoxydi-(2-acetoxyethyl)porphyrin (37 mg.) m.p. 209—211° (see below). The faster-moving porphyrin after crystallisation from methanol–methylene chloride was identified as the *porphyrin* (XXIa) (11 mg.), m.p. 212—214° (Found: C, 68·6; H, 6·1; N, 8·1. $C_{38}H_{42}N_4O_7$ requires C, 68·5; H, 6·35; N, 8·4%); n.m.r. (0·04M in $CDCl_3$): *meso-H*, τ 0·22, 0·31, 0·48; O–CH_2CH_2, 4·82t, 6·15t; $CH_2CH_2OCOCH_3$, 5·82t, 5·28t, 8·01; $CH_2CH_2CO_2CH_3$, 5·82t, 6·86t, 6·40; CH_3, 6·50, 6·59, 6·61, 6·64; N*H*, *ca.* 13·0b; $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 409(5·32), 517(4·18), 540(3·60), 575(3·67), 6·29(3·52); in $CHCl_3$ + HCl gas, 425(5·46), 566(3·99), 620(4·16), nm.; mass spectrum, *m/e* (%): 666(M^+)(100), 635(4), 608(7), 607(8), 606(8), 593(12), 534(6); *m**, 529(666 → 593).

Deuterium exchange: the oxophlorin (15 mg.) was dissolved in deuteriochloroform (0·3 ml.) in a n.m.r. tube. Deuterioacetic acid (0·1 ml.) was added and the tube was left in the dark overnight. A drop of deuteriotrifluoroacetic acid was added and the n.m.r. spectrum was run: *meso-H*, τ −0·31, −0·09, 0·32; $CH_2CH_2OCOCH_3$, *ca.* 5·2m, *ca.* 5·9m, (methyl signals obscured by acetic acid); $CH_2CH_2CO_2CH_3$, *ca.* 5·9m, 5·95t and 6·10t, 6·41 and 6·48; CH_3, 6·61, 6·62, 6·65, 6·73. The intensity of the signal for the δ-*meso* hydrogen (at τ 0·32) showed a decrease of *ca.* 50%, showing that *ca.* 50% exchange had occurred at the δ-position.

The sample was then converted into the *meso*-acetoxyporphyrin as described below and the mass spectrum of this indicated that about 40% exchange had occurred.

β-*Acetoxy*-2,4-*di*-(2-*acetoxyethyl*)-6,7-*di*-(2*methoxycar bonylethyl*)-1,3,5,8-*tetramethylporphin*.—The corresponding *b*-oxobilane (4·16 g.) was hydrogenated and cyclised as before with the same proportions of reagents. The solvent was then removed under reduced pressure and the product was stirred in pyridine (300 ml.) with acetic anhydride (96 ml.) for 45 min. After evaporating the solution to dryness under reduced pressure, the product was chromatographed on alumina (400 g.) with benzene–methylene chloride (1 : 1 v/v) as eluant. The porphyrin fractions were combined and evaporated to dryness and the required *acetoxyporphyrin* (1·78 g., 48·3%) was obtained as fine red needles, m.p. 209—211° (from methylene chloride–methanol) (Found: C, 65·85; H, 6·5; N, 7·3. $C_{42}H_{48}N_4O_{10}$ requires C, 65·6; H, 6·3; N, 7·3%); n.m.r. (0·1M in $CDCl_3$): *meso-H*, τ 0·20, 0·22, 0·61; n.m.r. (0·1M in $CDCl_3$): *meso-H*, τ 0·20, 0·22, 0·61; $CH_2CH_2OCOCH_3$, 6·0—6·2m, 5·1—5·5m, 7·92 and 8·05; $CH_2CH_2CO_2CH_3$, 5·6—6·0m, 6·88t, 6·40 and 6·46; CH_3, 6·47, 6·59, 6·79, 6·88; *meso*-$OCOCH_3$, 7·09; N*H*, 13·94; $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 405(5·27), 501·(4·21), 533(3·76), 572(3·78), 624(3·23); in $CHCl_3$ + HCl gas, 425(5·63), 561(4·19), 580(3·74) infl., 602(3·61) nm.; mass spectrum, *m/e* (%): 768(M^+)(9), 726(16), 666(100), 607(5), 593(13); *m**, 686(768 → 726), 611(726 → 666), 553(666 → 607), 528(666 → 593).

2,4-*Di*-(2-*acetoxyethyl*)-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin*-β-*benzylcarbonate* (XIXb).—The corresponding *b*-oxobilane (XVII) (200 mg.) was cyclised as described above. After evaporation of the reaction mixture to dryness, the residue was dissolved in acetone (100 ml.) and sodium carbonate was added to the solution. The mixture was stirred at room temperature and benzyl chloroformate (1 ml.) was added, whereupon the solution slowly turned reddish brown. A further addition of benzyl chloroformate (0·5 ml.) after 45 min. resulted in no increase in the Soret absorption. The reaction mixture was evaporated to dryness, dissolved in methylene chloride, and washed with water. The methylene chloride solution was dried ($MgSO_4$) and evaporated to dryness; the product was chromatographed on alumina (150 g.). The excess of benzyl chloroformate was removed by elution initially with benzene; the porphyrin was eluted with benzene–methylene chloride (1 : 1 v/v). After the evaporation of the eluates the residue on crystallisation from methylene chloride–methanol gave the desired meso-*benzyloxycarbonyloxyporphyrin* (72 mg, 33%) as brick-red prisms, m.p. 187—188° (Found: C, 67·2; H, 5·9; N, 6·35. $C_{48}H_{52}N_4O_{11}$ requires C, 66·95; H, 6·1; N, 6·5%), n.m.r. spectrum ($CDCl_3$: 0·1M): *meso-H*, τ 0·09, 0·11, 0·47; $C_6H_5OH_2$, 2·54, 4·51; CH_2O, 5·0—5·5m; $-CH_2CH_2CO$, 5·5—6·1m; 6·7—7·0m; CCH_3, 6·36, 6·43; $-CH_3$, 6·46, 6·63, 6·70, 6·80; $-COCH_3$, 7·99, 8·03. The mass spectrum did not show a parent ion, and the base peak (arising by fragmentation of the *meso*-benzyl group and one mole of acetic acid) was presumably due to the formation of the cyclic ether (XXIa), *m/e* (%): 666(100), 593(10); $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 403(5·25), 500(4·21), 531(3·79), 571(3·79), 624(3·28): in $CHCl_3$ + HCl gas, 424(5·46), 567(3·96), 620(4·16) nm. A minor by-product was shown by visible and mass spectra, as well as t.l.c. to be the cyclic ether (XXIa).

β-*Hydroxy*-2,4-*di*-(2-*hydroxyethyl*)-6,7-*di*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (XVIIIb).—The corresponding di-(acetoxyethyl)-β-acetoxyporphyrin (500 mg.) was dissolved in sulphuric acid (5% v/v) in methanol (250 ml.). After 18 hr. in the dark the solution was poured into an ice-water (200 ml.) and methylene chloride (200 ml.) mixture and was neutralised with dilute aqueous ammonia. The deep-blue methylene chloride layer was separated and the aqueous layer was washed with more methylene chloride. The combined methylene chloride fractions were then washed with water and, after being dried ($MgSO_4$), were evaporated to dryness. Titration with ether gave the desired β-*oxophlorin* (385 mg., 93%) as a blue-green solid, m.p. 221—223° (Found: C, 66·6; H, 6·2; N, 8·7. $C_{36}H_{42}N_4O_7$ requires C, 67·3; H, 6·6; N, 8·7%). This oxophlorin could be recrystallised only with difficulty, and appeared to decompose slowly in solution to a red product; n.m.r. (CF_3CO_2H): meso-*H*, τ −0·66(2H), −0·12; $-CH_2OH$, 4·8—5·2m; $CH_2CH_2CO_2CH_3$; 5·25—5·75m, 6·6—6·9m,

6·18, 6·26; CH_3, 6·47 (6H), 6·49, 6·68; N*H*, 11·2 (2H), 12·9 (2H); mass spectrum *m/e* (%): 642(5), 624(100), 608(25), 593(15), 551(20). The base peak here again was presumably due to cyclic ether formation following loss of water; $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 420(5·19), 580(3·93), 628(4·18); in $CHCl_3$ + HCl gas, 421(5·38), 532infl. (3·62), 568(3·90), 621(4·18). The dication could not be completely converted into the monocation even with a large excess of pyridine. Some of the reactions carried out with this oxophlorin are detailed below: (*a*) The di-(hydroxyethyl)-β-oxophlorin (55 mg.) was dissolved in pyridine (6 ml.) and methanesulphonyl chloride (2 ml.) was added. The mixture was heated under nitrogen at 75° for 35 min. Water was then added, and the mixture was extracted with methylene chloride; the combined extracts were then washed with more water. The extract was dried ($MgSO_4$) and evaporated to dryness; the product was chromatographed on alumina (50 g.) with benzene–methylene chloride (1 : 1 v/v) as eluant. The porphyrin product separated into two bands which were collected separately and, after removal of the solvents *in vacuo*, each was crystallised from methylene chloride–methanol.

The product (11 mg.) eluted first was obtained as red-brown fibrous needles, m.p. 207—209°, and was characterised as the *chloroethylporphyrin* (XXIb) (Found: C, 67·4; H, 5·9; N, 9·0; $C_{36}H_{39}ClN_4O_5$ requires C, 67·2; H, 6·1; N, 8·7%); n.m.r. ($CDCl_3$: 0·04M): *meso-H*; τ 0·27, 0·51, 0·54; OCH_2CH_2, 4·84t, 6·17t; CH_2CH_2Cl, 5·6—6·0m; CH_2CH_2-CO_2CH_3, 5·7—6·0m, 6·84t, 6·37; CH_3, 6·50, 6·60 (6H), 6·69; N*H* 13·0b; mass spectrum *m/e* (%); 644(35), 642(100), 608(40), 606(46), 571(5), 569(10), 535(8), 533(10), *m**: 2505(644 → 571, 642 → 569), 470(608 → 535, 606 → 533); $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 410(5·32), 508(4·16), 541(3·59), 577(3·65), 630(3·52); in $CHCl_3$ + HCl gas: 425(5·46), 565(3·96), 620(4·16) nm.

The second product (9 mg.) was obtained as brick-red fibrous needles, m.p. 181—182°, and was characterised as the *di-(chloroethyl)*-meso-*mesyloxyporphyrin* (XXIIIa) (Found: C, 58·7; H, 5·55; N, 6·9; $C_{37}H_{42}Cl_2N_4O_7S$ requires C, 58·65; H, 5·6; N, 7·4%); n.m.r. spectrum ($CDCl_3$, 0·03M): *meso-H*, τ −0·04, 0·10, 0·19; CH_2CH_2Cl, 5·6—6·0 m; $CH_2CH_2CO_2CH_3$, 5·7m, 6·81t, 6·38; OSO_2CH_3, 7·00; N*H*, 13·5. The mass spectrum was closely similar to that of the other product, showing that cyclisation had occurred in the mass spectrometer to form the chloroethyl-cyclic ether (XXIb) by elimination of chlorine (from the 4-substituent) and the mesyl group; $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 407(5·16), 506(4·08), 540(3·83), 576(3·79), 628(3·48); in $CHCl_3$ + HCl gas, 427(5·36), 532infl. (3·48),564 (4·11), 608(3·84) nm.

(*b*) The di-(hydroxyethyl)-β-oxophlorin (100 mg.) was dissolved in pyridine and methanesulphonyl chloride was added. The mixture was set aside at room temperature and then heated and extracted as in (*a*) above. Only a trace of the chloroethylporphyrin (XXIb) was formed and the desired di-(chloroethyl)-*meso*-mesyloxyporphyrin (XXIIIa) (35 mg., 30%) was obtained as brick-red fibrous needles, m.p. 181—182° (from methylene chloride–methanol).

(*c*) The di-(hydroxyethyl)-β-oxophlorin (30 mg.) was dissolved in pyridine (2 ml.) and methanesulphonyl chloride (0·3 ml.) was added. The solution was set aside at room temperature in the dark for 2 hr. and then a solution of sodium iodide (3 g.) in acetone (30 ml.) was added; the solution was set aside for a further period (3 days). The product was extracted and chromatographed in a similar manner to previous experiments. The porphyrin product (11 mg.) was obtained as a reddish solid, tentatively identified as the iodoethyl mesyloxyethyl β-mesyloxyporphyrin (XXIIIb) from its n.m.r. spectrum ($CDCl_3$): *meso-H*, τ 0·05, 0·30, 035; CH_2–O, 4·9—5·4m; $-CH_2CH_2-$ and CH_2I, 5·5—6·1m, 5·6—5·9m; OCH_3, 6·37, 6·39; CH_3, 5·31, 5·37, 5·39, 5·45; *meso*-OSO_2CH_3, 6·98; side-chain OSO_2CH_3, 7·30.

(*d*) The di-(hydroxyethyl)-β-oxophlorin (30 mg.) was dissolved in chloroform (20 ml.) and a few drops of a saturated solution of zinc acetate in methanol were added. The mixture was warmed on a steam-bath, whereupon the solution went red. The solution was washed with water (40 ml.), dried ($MgSO_4$), and evaporated to dryness. The oxophlorin zinc complex was then dissolved in acetone (10 ml.) and mixed with a suspension of potassium carbonate (1 g.) in acetone (20 ml.). The solution slowly turned green showing that the anion had been formed;[6] on the addition of methanesulphonyl chloride (0·1 ml.) the solution immediately turned red. After 15 min. water (5 ml.) was added and the acetone was removed under reduced pressure. The product was extracted into methylene chloride, washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue (23 mg.) which was difficult to crystallise, and did not appear homogeneous on t.l.c. was taken up in pyridine (3 ml.) and treated with further methanesulphonyl chloride (1 ml.) to complete conversion of the side-chain hydroxy-groups. The reaction mixture was heated briefly on a steam-bath and worked up as above. The product was shown by visible spectra both of its free base and dication and by t.l.c. to be identical with the chloroethylporphyrin (XXIb). The zinc was removed under the reaction conditions, the product being metal-free porphyrin.

(*e*) An acetone solution of the anion of the zinc complex was prepared from the di-(hydroxyethyl)oxophlorin (100 mg.) as above. On the addition of benzyl chloroformate (0·3 ml.) the solution slowly turned red (over 5 min.) and was stirred for a further 15 min. Water (30 ml.) was then added and the acetone was removed *in vacuo*. The product was then extracted as above, but defied attempts at crystallisation; t.l.c. of the product showed two porphyrins. The product was dissolved in pyridine (9 ml.) and methanesulphonyl chloride (3 ml.) was added. The reaction mixture was heated briefly and extracted as above. The product (27 mg.) chromatographed as one band but could not be crystallised and the n.m.r. spectrum showed the benzyl aromatic signal was approximately equivalent to 12 protons.

(*f*) The zinc complex of the di-(hydroxyethyl)-β-oxophlorin (50 mg.) was dissolved in acetone (100 ml.) and potassium carbonate (10 g.) in acetone (20 ml.) was added. Immediately afterwards dimethyl sulphate (1·5 ml.) was added and the mixture was stirred and heated under reflux for 15 min. The solution turned green and then slowly turned red. The visible spectrum indicated that *meso*-methylation had not gone to completion and so a further portion of dimethyl sulphate (0·5 ml.) was added and the solution was heated for a further 20 min. after which reaction was complete. The product was extracted and the zinc was removed as previously described. The product was then chromatographed on alumina; methylene chloride being the initial eluant and then chloroform. Three porphyrins were obtained and were collected separately and crystallised from methylene chloride. The first product

(A) (10 mg.) eluted was shown by mass spectrometry to be a tri-*O*-methylated porphyrin. The second porphyrin (11 mg.) was identified by mass spectrometry as a di-*O*-methylated porphyrin (B) and the third component was shown to be a mixture, probably containing some mono-*O*-methylated porphyrin; mass spectra, *m/e* (%): A, 684(100), 669(20), 654(11), 653(11), 639(8), 638(7), 637(6), 625(5), 609(7), *m**: 655(684 → 669). B, 670(100), 655(27), 640(25), 625(20).

(*g*) An acetone solution of the zinc complex anion was prepared from the di-(hydroxyethyl)oxophlorin (25 mg.) as above. Methanol (20 ml.) was added to the solution. A solution of acetic anhydride (1·5 ml.) in acetone (30 ml.) was titrated into the anion solution and the reaction was followed spectroscopically by the disappearance of the maximum at 628 nm. The reaction did not go to completion and required the addition of two portions (0·5 ml. each) of neat acetic anhydride before the peak at 628 nm. had completely disappeared. Water (40 ml.) was then added and the acetone and methanol were removed *in vacuo*. The product was extracted as previously described but could not be crystallised. The oil (25 mg.) was dissolved in methylene chloride (5 ml.) and added to sulphuric acid (1%) in methanol (23 ml.). After 3 min. solid potassium carbonate (5 g.) followed by water (10 ml.) and methylene chloride (10 ml.) was added. The layers were separated and the methylene chloride fraction was washed with water, dried ($MgSO_4$), and evaporated to dryness. The red solid product (5 mg.) was tentatively identified as the 2-acetoxy-*meso*-acetoxyporphyrin (XXb) from its n.m.r. and mass spectrum; n.m.r. spectrum ($CDCl_3$, 0·02M): *meso-H*, τ 0·1, 0·25, 0·4; CH_2CH_2CO and CH_2O, 5·6—6·1m, 6·7—7·0m; OCH_3, 6·41, 6·46; $-CH_3$, 6·55, 6·60 (6H), 6·65; *meso*-$OCOCH_3$, 7·12; side-chain $OCOCH_3$, 6·95. The mass spectrum [*m/e* (%): 726(10), 666(100), 624(22)], showed that cleavage of the *meso*-acetyl group had occurred in the spectrometer with concomitant cyclic-ether formation, and this confirmed the location of the side-chain acetyl group.

Elimination Reactions of Halogeno-ethyl Porphyrin Derivatives.—(*a*) The porphyrin (10 mg.) was dissolved in methylene chloride (5 ml.) and a few drops of a saturated solution of zinc acetate in methanol were added. The solution was warmed for a few minutes and checked spectroscopically that the zinc insertion was complete (by the disappearance of the peak at 502 nm. and the emergence of peaks at 540 and 572 nm.). The solution was evaporated to dryness, dissolved in tetrahydrofuran (1 ml.), and 1N-t-butoxide in t-butyl alcohol (10 ml.) was added. The resulting solution was set aside in the dark for 3·5 hr. under nitrogen. The product was extracted and re-esterified with methanolic sulphuric acid, and was obtained as dark purple needles (5 mg., 53%), m.p. 258—259° from methylene chloride–methanol. The product was a porphyrin indicating that the ether link had not been cleaved.

Similar elimination reactions with the di-(chloroethyl)-*meso*-mesyloxyporphyrin (XXIIIa) and the iodoethyl-*meso*-mesyloxyporphyrin (XXIIIb) gave an identical product in approximately the same yield (60%). This product was characterised as the *vinyl porphyrin cyclic ether* (XXIV) (Found: C, 71·5; H, 6·6; N, 9·1. $C_{36}H_{38}N_4O_5$ requires C, 71·3; H, 6·3; N, 9·2%); n.m.r. spectrum (CF_3CO_2H): *meso-H*, τ −0·29, −0·19, 0·07; $CH{=}CH_2$, *ca.* 1·9q, *ca.* 3·6q; $-OCH_2CH_2$, 4·18t, 5·90t; $CH_2CH_2CO_2CH_3$, *ca.* 5·8m, *ca.* 6·7m, 6·25, 6·26; CH_3, 6·35 (6H), 6·41, 6·55; mass spectrum *m/e*; M^+, 606 (only a very weak spectrum could be obtained), $\lambda_{max.}$ (log $\varepsilon_{max.}$): in $CHCl_3$, 414(5·30), 5·2(4·15), 547(3·73), 581(3·67), 534(3·52); in $CHCl_3$ + HCl gas, 428(5·39), 570(3·93), 625(4·15) nm.

(*b*) The di-(chloroethyl)-*meso*-mesyloxyporphyrin (5 mg.) was dissolved in hexamethylphosphoric triamide (2 ml.) and sodium fluoride (7 mg.) and sodium carbonate (7 mg.) were added; the mixture was heated for 17 hr. at 100°. (Some of the inorganic salts still remained out of solution.) Water was then added and the mixture was extracted with methylene chloride. The methylene chloride extract was washed with water (×3), dried ($MgSO_4$), and evaporated to dryness. Chromatography of the product on alumina in methylene chloride afforded two porphyrins. The major fraction (*ca.* 3 mg.) had an identical visible spectrum to that of the vinyl porphyrin (XXIV). The minor fraction (*ca.* 1 mg.) was not identified.

A similar reaction was carried out in the absence of sodium carbonate. Only one porphyrin was produced with rather less overall porphyrin recovery, and this was identified as the chloroethyl porphyrin cyclic ether (XXIb).

In a further attempt with an excess sodium hydride in hexamethylphosphoric triamide the product was again the chloroethyl porphrin (XXIb).

Tritiation of Oxophlorins for Conversion into Protoporphyrin.—(*a*) The di-(acetoxyethyl)-β-oxophlorin (XVIIIa) (88 mg.) was dissolved in a solution containing tritiated water (20 mg.: 20 mCi), glacial acetic acid (0·12 ml.), and chloroform (0·4 ml.) and the resulting solution was set aside in the dark for 4 days. The active solvent mixture was removed by vacuum transfer techniques and the residue was dissolved in pyridine (2·5 ml.). Acetic anhydride (1·0 ml.) was then added and, after 30 min. the solution was evaporated to dryness. The desired δ-tritiated β-acetoxyporphyrin (80·5 mg.; activity 0·29 mCi $mmole^{-1}$) was obtained by crystallisation from methylene chloride–methanol.

(*b*) The di-(hydroxyethyl)-β-oxophlorin (XVIIIb) (200 mg.) was dissolved in a solution of tritiated water (20 mg.; 200 mCi), glacial acetic acid (1·0 ml.), and chloroform (2·0 ml.). After 118 hr. in the dark the oxophlorin was converted into δ-tritiated di-(acetoxyethyl)-β-acetoxyporphyrin (220 mg.; activity 3·5 mCi $mmole^{-1}$) with pyridine (5·0 ml.) and acetic anhydride (2·0 ml.) as above.

Tritiated Magnesium Protoporphyrin-IX Dipotassium Salt.—Ethyl bromide (15 ml.) was added to magnesium turnings (1·0 g.) in dry ether (30 ml.) and the mixture was warmed. When the reaction had subsided the ether and excess of ethyl bromide were distilled off and dry propanol (70 ml.) was added in small portions (vigorous reaction).

Active protoporphyrin (5 mg.; 0·17 mCi $mmole^{-1}$) (prepared from the foregoing tritiated β-acetoxyporphyrin) together with inactive protoporphyrin (10 mg.) were added to 7·5 ml. of the above suspension and heated at 70° for 5 hr. under a stream of nitrogen. After evaporating the mixture almost to dryness, the product was dissolved in ether and water. The ether layer was washed with a solution of ammonium acetate (5 g.) and disodium hydrogen phosphate (5 g.) in water (50 ml.) and was then washed several times with water. After being dried (Na_2SO_4) the solution was evaporated to dryness. Potassium hydroxide (30% w/v) in methanol (3 ml.) was then added and the solution was warmed at 45° for 1 hr. Dilution with water (7 ml.) gave a flocculent red precipitate which was dissolved in hot methanol (1 ml.); the solution was cooled and three drops of a solution obtained by diluting the potassium hydroxide–methanol solution with nine times its volume of water, were

added and the precipitate was centrifuged out. The supernatant liquors were discarded and the solid (13 mg.; activity 0·05 mCi mmole^{-1}) was dried in a vacuum oven.

Counting of Tritiated Porphyrins.—Approximately 0·1 mg. of sample was accurately weighed into a counting tube. Tetrahydrofuran (0·2 ml.) was added and then benzoyl peroxide (*ca.* 4 mg.) was added to the resulting solution. Care was taken that the cap of the counting tube was screwed tightly to prevent losses by evaporation and the sample was left in sunlight until completely decolourised (*ca.* 8 hr.). The sample was diluted with organic scintillator solution (6 ml.) and counted with a scintillation counter. When a steady count was obtained, the average of *ca.* six 100-sec. counts was taken. A weighed quantity of standard tritiated decalin (*ca.* 80 mg.) was then added and a second series of counts were taken. From the difference in mean counts the efficiency of counting was calculated and thence the activity of the sample.

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