Pyrroles and Related Compounds. Part XXV.[1] Pemptoporphyrin, Isopemptoporphyrin, and Chlorocruoroporphyrin (*Spirographis* Porphyrin)

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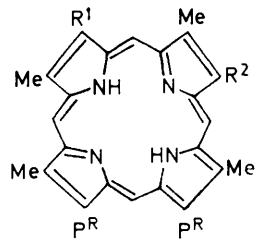
Pemptoporphyrin (4-vinyldeuteroporphyrin-IX dimethyl ester) and its 2-vinyl isomer have been synthesised by application of the *b*-oxobilane and *a*-oxobilane routes, respectively, thus providing a definitive proof of structure for the natural material. The vinyl groups in each case were introduced through transformation of acetoxyethyl side-chains. Formylation of one of the intermediates (4-chloroethyldeuteroporphyrin), followed by base-catalysed elimination of hydrogen chloride, afforded the dimethyl ester of chlorocruoroporphyrin (2-formyl-4-vinyldeuteroporphyrin-IX).

In earlier papers of this series we have described the application of our *a*- and *b*-oxobilane routes to the synthesis of porphyrins containing alkyl, propionate, and vinyl side-chains. We now describe the extension of these methods to the elaboration of vinyl-substituted porphyrins with vacant peripheral positions, and to the introduction of formyl substituents into the nucleus at a late stage of the synthesis. These studies were necessary preliminaries to investigations of possible routes to haem-*a*, which contains three labile side-chains (*viz.* hydroxyalkyl, vinyl, and formyl groups).[2] At the time when this work was begun, a new faecal porphyrin, pemptoporphyrin, had recently been isolated by French,[3] and Sano and French and their co-workers [4] had concluded, on the basis of biogenetic reasoning and analytical and spectral data, that its structure was either (1a) or (1b). The only satisfactory way of resolving this ambiguity was by total synthesis, and the preparation of these two isomers seemed a worthwhile target for our initial studies.



(1) $P^R = CH_2 \cdot CH_2 \cdot CO_2H$
(2) $P^R = CH_2 \cdot CH_2 \cdot CO_2Me$

V = CH_2:CH
a; R^1 = H, R^2 = V
b; R^1 = V, R^2 = H
c; R^1 = H, R^2 = Et
d; R^1 = R^2 = V
e; R^1 = CHO, R^2 = Et
f; R^1 = CHO, R^2 = V
g; R^1 = V, R^2 = CHO

In the event, we decided to apply the *b*-oxobilane route to the synthesis of the 4-vinyl isomer (2a), and this was shown to be identical with the dimethyl ester

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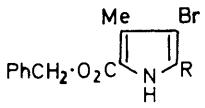
[1] Part XXIV, G. W. Kenner, S. W. McCombie, and K. M. Smith, *J.C.S. Perkin I*, 1973, 2517.

[2] G. A. Smythe and W. S. Caughey, *Chem. Comm.*, 1970, 809.

[3] J. M. French and E. Thonger, *Clinical Sci.*, 1966, **31**, 337.

[4] S. Sano, T. Shingu, J. M. French, and E. Thonger, *Biochem. J.*, 1965, **97**, 250.

of the natural material, as described in a preliminary communication.[5] The presence of a free peripheral position in the final porphyrin was a new problem to be solved, and we decided to use bromine as a protecting substituent throughout the early stages of the synthesis. As a simpler model, our initial efforts centred on the synthesis of dihydropemptoporphyrin dimethyl ester (2c). Originally, we had hoped to apply the *a*-oxobilane route[6] to the synthesis, but this foundered in the very early stages owing to problems encountered in the preparation of the pyrrole amide (3b), which was eventually to provide ring A of the porphyrin. The dibromo-derivative (3a) [readily available from (4) by direct bromination] was treated with sulphuryl chloride in carbon tetrachloride, and the product treated with dimethylamine (as in previous preparations of analogous amides). However, no amide was obtained, nor could the corresponding acid (3c) be isolated if alkaline hydrolysis was carried out in place of the dimethylamine treatment. Subsequently it was found that chlorination with sulphuryl chloride in glacial acetic acid gave



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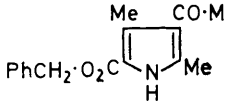
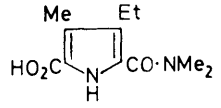


(4)

a; R = CH_2Br
b; R = $CO\cdot NMe_2$
c; R = CO_2H
d; R = $CH_2(NC_5H_5)^+Br^-$
e; R = $CH_2\cdot NH\cdot CHO$

the 2-formyl derivative directly, in 40% yield, without any hydrolytic step. It thus seemed likely that the β-bromine substituent was adversely affecting the reactivity of the neighbouring α-carbon substituent, and we therefore turned our efforts to the *b*-oxobilane route.[7]

The 2-bromomethylpyrrole (3a) was converted into the corresponding pyridinium salt (3d) and the crystalline product was heated with the lithium salt of the pyrrole-2-carboxylic acid (5) at 100° in formamide, to



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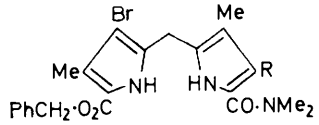
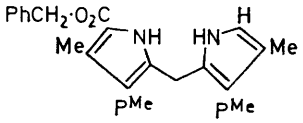


(6)

a; R = Et
b; R = $CH_2\cdot CH_2\cdot OAc$

afford the desired pyrromethane amide (6a) in 48% yield; a minor by-product was the formamidomethylpyrrole (3e). The phosphoryl chloride complex of the pyrromethane amide (6a) was then coupled with the 5-unsubstituted pyrromethane (7) in boiling methylene chloride, to afford the tetrapyrrolic imine salt (8a) ($\lambda_{max.}$ 360 nm), which was hydrolysed with aqueous



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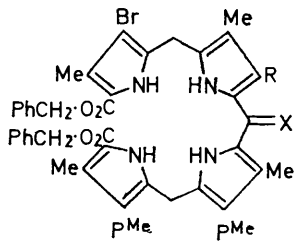
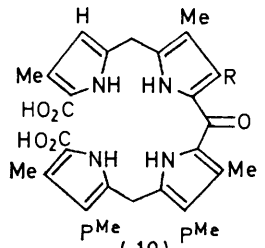
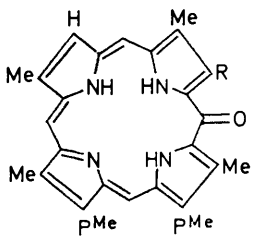


(8) X = $\overset{+}{N}Me_2$ Cl^-
(9) X = O
a; R = Et
b; R = $CH_2\cdot CH_2\cdot OAc$



(10) P^{Me} = $CH_2\cdot CH_2\cdot CO_2Me$

sodium carbonate to give the *b*-oxobilane (9a). The latter was characterised by elemental analysis, n.m.r., and mass spectrometry. The benzyl ester groups were smoothly cleaved by hydrogenation over palladised charcoal, and by extending the reaction time to 4 days, the bromine substituent was also removed, affording (10a) which was shown by its elemental analysis and spectral data to be free of bromine. Compound (10a) was then cyclised with trimethyl orthoformate and trichloroacetic acid in methylene chloride, and aerial oxidation gave the required oxophlorin (11a) in moderate yield. The crude oxophlorin (11a) was then converted into the corresponding *meso*-acetoxyporphyrin (12a) by



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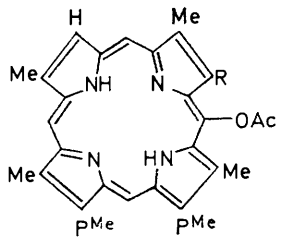


(12)

a; R = Et
b; R = $CH_2\cdot CH_2\cdot OAc$

treatment with acetic anhydride in pyridine. The crystalline product was ultimately obtained in 46% overall yield from the *b*-oxobilane (10a) [without isolation of the oxophlorin] and was shown to be uncontaminated with any other porphyrins by t.l.c. and spectral and elemental analysis. The *meso*-acetoxyporphyrin (12a) was readily converted into the corresponding *meso*-unsubstituted porphyrin (2c) in good overall yield by catalytic hydrogenation over palladised charcoal to the colourless porphyrinogen, followed by re-oxidation in air, or oxygen (*cf.* ref. 7). We have since

[5] A. H. Jackson, G. W. Kenner, and J. Wass, *Chem. Comm.*, 1967, 1027.

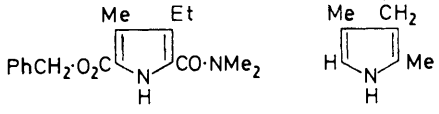
[6] A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc.* (*C*), 1967, 2045.

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

found [8] that the re-oxidation step can be carried out with greatly increased efficiency by using dichlorodicyanobenzoquinone in place of oxygen.

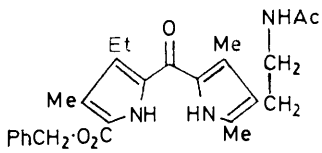
Having shown that a porphyrin with vacant peripheral position could be prepared by the *b*-oxobilane route, we turned our attention to the monovinyl analogue (1b). Dr. Sach, in Liverpool, had made some preliminary studies of the use of acetamidoethyl substituents as precursors for the vinyl group (by Hofmann degradation) in a projected *a*-oxobilane synthesis of a vinyl porphyrin, but coupling of the pyrrole (13) with the amide (14) under Vilsmeier conditions gave a very low yield of the corresponding ketone (15), presumably owing to interference by the side-chain. Furthermore, the acetamidoethyl group was readily reduced by diborane, an essential reagent for reduction of the pyrroketone carbonyl function in the later stages of the *a*-oxobilane route. We therefore decided to use the acetoxyethyl side-chain as a precursor of the vinyl group of pemptoporphyrin; this method had only recently been developed [9] at that time.

The acetoxyethylpyrrole (16) was converted into the corresponding amide (17a) by trichlorination with t-butyl hypochlorite, followed by treatment with dimethylamine and hydrolysis. Hydrogenolysis of the benzyl ester group then afforded the carboxylic acid (17b), the lithium salt of which was coupled with the pyridiniomethylpyrrole (3d) in hot formamide, to give the pyrromethane amide (6b). Thereafter, the synthesis paralleled closely that described for the ethylporphyrin (2c), and the (2-acetoxyethyl)porphyrin (18a) was obtained



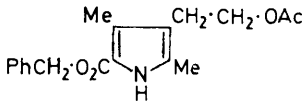
(13)

(14)

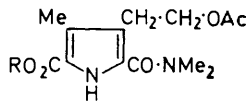


(15)

via the analogous intermediates (8b), (9b), (10b), (11b), and (12b). In this case, however, the *b*-oxobilane (9b) was not isolated in crystalline form, but was purified at the imine (8b) stage by chromatography [7] before hydrolysis to the *b*-oxobilane. In the final hydrogenation of the *meso*-acetoxyporphyrin (12b), small amounts of a green by-product were observed, and this was separated chromatographically after re-oxidation of the porphyrinogen to porphyrin. The visible absorption spectrum was consistent with that expected for a chlorin and the mass spectrum fitted a '*meso*-acetoxychlorin'



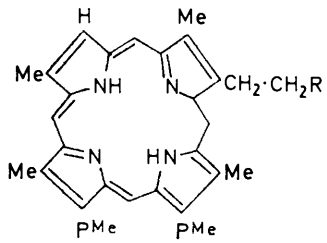
(16)



(17)

a; R = CH_2Ph

b; R = H



(18)

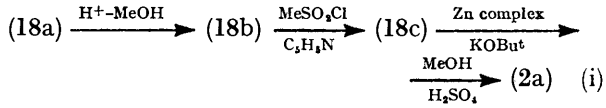
a; R = OAc

b; R = OH

c; R = Cl

formulation; however, insufficient material for proper characterisation was available. A similar by-product was also obtained in the ethyl series, but in much lower quantity. It is, however, interesting that no chlorin formation is observed during the reduction of *meso*-acetoxyporphyrins substituted in all eight peripheral positions, and that Clezy [10] has recently reported that hydrogenation of *meso*-acetoxyporphyrins with four neighbouring peripheral positions unsubstituted affords *meso*-acetoxychlorins.

Transformation of the acetoxyethyl side-chain of the porphyrin (18a) into vinyl was then effected by the



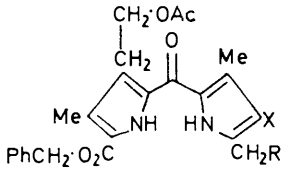
sequence (i) as described previously [9] for other analogous examples [*e.g.* protoporphyrin-IX dimethyl ester (2d)].

The n.m.r. spectrum of the 4-vinyldeuteroporphyrin-IX dimethyl ester (2a) (in $CDCl_3$) produced, was identical with the published spectrum [4] of pemptoporphyrin dimethyl ester, but there was a small difference in the m.p.s of the natural and synthetic materials (215—218 and 213—214°, respectively). Furthermore, in an earlier preparation of this compound described by Fischer and Wecker,[11] the m.p. was given as 264° 'falling to 225° after some time.' A pure sample of the natural product was no longer available, but a small amount of an impure preparation made available by Dr. Sano to the Nottingham group (who synthesised

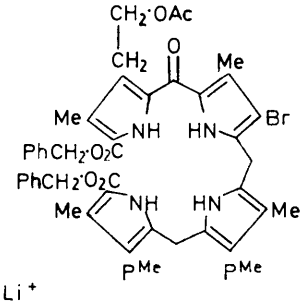
[8] S. W. McCombie, Ph.D. Thesis, Liverpool, 1972.
[9] R. P. Carr, A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc.* (*C*), 1971, 487.
[10] P. S. Clezy, V. Diakiw, and A. J. Liepa, *Austral. J. Chem.* 1972, **25**, 201.
[11] H. Fischer and G. Wecker, *Z. physiol. Chem.*, 1942, **272**, 1.

pemptoporphyrin independently by a different route [12a]) was given to us by Professor Johnson. This did not depress the m.p. of our material on admixture, nor that of the Nottingham synthetic sample, and moreover, the two synthetic products were compared directly in each laboratory and found to be identical. These results thus provided a fairly conclusive proof of structure (1a) for pemptoporphyrin, but we felt that in view of the m.p. recorded by Fischer and Wecker,[11] and the unsatisfactory nature of the comparisons with crude material from natural sources, a synthesis of the 2-vinyl isomer (2b) was desirable.

Bearing in mind the accessibility of the required pyrrolic intermediates, we decided to develop our synthesis of (2b) by the *a*-oxobilane route. The phosphoryl chloride complex of the pyrrole amide (17a) was coupled with 2,4-dimethylpyrrole to give the pyrroketone (19a) in excellent yield. As two of the projected subsequent reactions involved the use of t-butyl hypochlorite, the free β-position was blocked with bromine at this stage in the synthesis, to give (20a). (Nuclear chlorination was regarded as undesirable, because Dr. R. Fletcher, in these laboratories, had shown that subsequent removal of chlorine from similar compounds by hydrogenolysis, was considerably more difficult than removal of bromine.) Chlorination of the bromopyrroketone (20a) with t-butyl hypochlorite then gave the



(19) X = H
(20) X = Br
a; R = H, b; R = Cl



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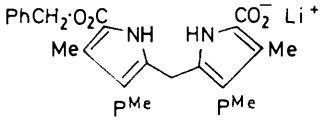
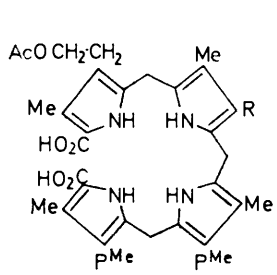


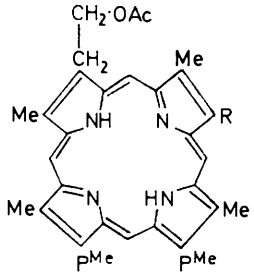
(21)

required chloromethyl derivative (20b) which was converted into the corresponding pyridinium salt and coupled with the pyrromethane carboxylate (21). Unfortunately, the resulting *a*-oxobilane (22) could not be obtained crystalline, but it was purified chromatographically and characterised spectroscopically before conversion into porphyrin. Diborane reduction of the oxo-function, followed by hydrogenolysis, afforded the dicarboxylic acid (23a), which was oxidised to the corresponding bilene with t-butyl hypochlorite, and this was cyclised with trimethyl orthoformate in methylene chloride containing trichloroacetic acid, and then oxidised with air to porphyrin in the usual fashion.[6] N.m.r. spectroscopy and mass spectrometry of the



(23)

a; R = H
b; R = Br



(24)

product clearly indicated that it was a mixture of the required porphyrin (24a) and the 4-bromoporphyrin (24b), thus showing that hydrogenolysis of the bromine had been incomplete; some of the bromo-compound (23b) must have remained after the hydrogenolysis step, though the mass spectrum of the diacid (23a) had not shown its presence (perhaps because of lower volatility).

Shortage of time and materials precluded repetition of the whole synthesis, and so the residual bromine was removed by exhaustive hydrogenation of the mixture of porphyrins (24) to the corresponding porphyrinogens. After re-oxidation in air, the single bromine-free porphyrin (24a) was obtained in reasonable yield and fully characterised by spectral and elemental analysis. Transformation of the 2-acetoxyethyl group into vinyl was effected in the same manner as described for the isomer, and the 2-vinylporphyrin (2b) was obtained with m.p. 220—221°. This m.p. was depressed when the material was mixed with the synthetic 4-vinylporphyrin (2a) or with the crude preparations of natural pemptoporphyrin dimethyl ester. Furthermore the n.m.r. spectrum of (2b) was significantly different from those of naturally derived material and (2a) (comparable concentrations in $CDCl_3$). These experiments thus clearly define the structure of pemptoporphyrin as (1a). Since the appearance of our preliminary publication [5] and during the preparation of this paper, further syntheses of pemptoporphyrin [12b,c] and of isopemptoporphyrin [12b] have been reported, confirming our assignments of the two isomers.

Another objective, discussed briefly at the beginning of this paper, was to develop a route to formyl-substituted porphyrins. In preliminary studies, Dr. G. S. Sach (at Liverpool) investigated the possibility of carrying a protecting group through the *a*-oxobilane synthesis, with the intention of regenerating the formyl group after macrocycle formation. However, these experiments were unsuccessful owing partly to the

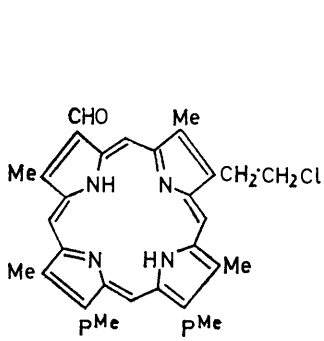
[12] (*a*) P. Bamfield, R. Grigg, R. W. Kenyon, and A. W. Johnson, *Chem. Comm.*, 1967, 1029; P. Bamfield, R. Grigg, A. W. Johnson, and R. W. Kenyon, *J. Chem. Soc.* (*C*), 1968, 1259; (*b*) R. Grigg, A. W. Johnson, and M. Roche, *J. Chem. Soc.* (*C*), 1970, 1928; (*c*) G. V. Ponomarev, S. M. Nasralla, A. G. Bybnova, and R. P. Evstigneeva, *Khim. geterotsikl. Soedinenii*, 1973, 202.

lability of the protecting groups towards diborane, a reagent required in one of the steps immediately preceding macrocycle formation in the *a*-oxobilane route.[6] We therefore decided to postpone introduction of the formyl group until after porphyrin formation, and to protect the vacant position required, with bromine (as described above) during the early stages of the syntheses.

The target formylporphyrin was chlorocruoroporphyrin (*Spirographis* porphyrin), the iron complex of which is the prosthetic group of the oxygen-carrying pigment of the polychaete worm *Spirographis spallanzanii*, found in the Adriatic.[13] The dimethyl ester of this compound had been synthesised previously (*a*) from deuteroporphyrin-IX,[11] (*b*) from protoporphyrin-IX by partial oxidation with permanganate,[14] and (*c*) more recently, by an ingenious photo-oxidation of protoporphyrin-IX and subsequent transformation, by Inhoffen and his colleagues.[15] However, none of these methods completely defines the structure (1f), and the alternative (1g) is only excluded by circumstantial evidence based largely on the synthesis of certain degradation products.[11]

In a series of model reactions, direct formylation of the copper complex of the 4-ethylporphyrin (2c) using the phosphoryl chloride complex of dimethylformamide was first investigated, as this had proved to be a useful method for the introduction of formyl groups into pyrroles. However, in the event, two formylated porphyrins were obtained by Dr. R. Fletcher, who also showed that similar formylations of the copper complex of deuteroporphyrin-IX dimethyl ester gave mixtures of products which included a *meso*-formylporphyrin. At this stage of our investigations, Professor Inhoffen kindly informed us of his results on the Vilsmeier formylation of porphyrin copper complexes,[16] and in the light of this information and our own results, we decided to revert to the original Fischer procedure.[17] Treatment of the iron(III) complex of the 4-ethylporphyrin (2c) with dichloromethyl methyl ether and tin(IV) chloride, followed by hydrolysis and removal of the iron, afforded the expected 4-ethyl-2-formylporphyrin (2e) in good yield.

Because of the well known sensitivity of vinyl-substituted porphyrins, we did not attempt to formylate the iron(III) complex of pemptoporphyrin directly, but instead formylated the iron complex of the chloroethyl derivative (18c) with dichloromethyl methyl ether and tin(IV) chloride. To hydrolyse the intermediate and eliminate hydrogen chloride directly from the 2-chloroethyl side-chain in the iron complex proved experimentally difficult and we therefore removed the iron to obtain the pure 4-(2-chloroethyl)-2-formylporphyrin (25). Attempts to eliminate hydrogen chloride from either the zinc complex or the free porphyrin, with potassium t-butoxide in t-butyl alcohol, gave mixtures of porphyrins, some of 'aetio'-type visible absorption spectra (rather than the expected 'rhodo'-type), and mass spectral evidence was compatible with the presence



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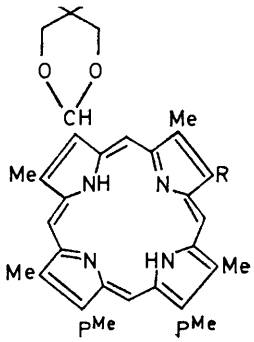

(26)

a; R = $CH_2 \cdot CH_2Cl$
b; R = $CH{:}CH_2$

of mixtures of pemptoporphyrin and dihydropemptoporphyrin dimethyl esters, showing that the formyl group had been eliminated. This difficulty was therefore overcome by protection of the formyl group by conversion into its relatively stable 2,2-dimethyltrimethylene acetal. The zinc complex of the resulting porphyrin (26a) underwent smooth elimination of hydrogen chloride on treatment with t-butoxide. Acidic hydrolysis of the acetal and removal of zinc then gave the 2-formyl-4-vinylporphyrin (1f), m.p. 281—283°, undepressed by admixture with one of the porphyrins obtained [15] from photo-oxidation of protoporphyrin-IX. The m.p. was also in satisfactory agreement with that reported [13] (285°) for the natural product. The Nottingham group also synthesised chlorocruoroporphyrin by another route [12] and direct comparison of the samples prepared by both routes confirmed their identity.

We had originally hoped to complete the series by synthesis of the 2-vinyl-4-formyl isomer (1g), but this was prevented by shortage of time and materials. However, this has now been achieved by the MacDonald route, as well as another synthesis of isopemptoporphyrin, which will be described in a later paper.[18]

EXPERIMENTAL

M.p.s were determined for samples in capillaries, except for those of the porphyrins, which were determined on a microscope hot-stage and are corrected. Neutral alumina (Brockmann grade III; Woelm) was used for all chromatographic separations, and reactions were followed by t.l.c. and spectrophotometry as described in earlier parts of this series. Electronic spectra were measured with a Unicam SP 800 spectrophotometer, ^1H n.m.r. spectra (solutions in deuteriochloroform with tetramethylsilane as internal reference) with Varian A-60 and HA-100 spectrometers,

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[14] H. Fischer and K. O. Dielmann, *Z. physiol. Chem.*, 1944, **280**, 186; R. Lemberg and A. Parker, *Austral. J. Exptl. Biol. Med. Sci.*, 1952, **30**, 163.

[15] H. H. Inhoffen, K. M. Bliesener, and H. Brockmann, *Tetrahedron Letters*, 1966, 3779.

[16] H. Brockmann, K. M. Bliesener, and H. H. Inhoffen, *Annalen*, 1968, **718**, 148.

[17] H. Fischer and A. Schwarz, *Annalen*, 1934, **512**, 239.

[18] D. E. Games, P. J. O'Hanlon, and A. H. Jackson, unpublished results.

and mass spectra with an A.E.I. MS9 instrument (at 50 μA and 70 eV; direct insertion probe; source temperature between 220 and 280°).

Pyrroles

Benzyl 4-Ethoxycarbonylmethyl-3,5-dimethylpyrrole-2-carboxylate (16).—A stirred solution of benzyl acetoacetate (356 g) in acetic acid (560 ml) was cooled to 0° and sodium nitrite (134 g) in water (465 ml) was added at such a rate that the temperature of the mixture did not exceed 10°. The solution was then stirred for 1 h at 0°, set aside at the same temperature overnight, and added slowly, with vigorous stirring to a solution of ethyl 3-acetyl-4-oxopentanoate (*cf.* ref. 9) (372 g) (b.p. 146—150° at 17 mmHg) in acetic acid (400 ml) which had been warmed to 60°. A mixture of zinc dust (350 g) and anhydrous sodium acetate (350 g) was added slowly at the same time, the zinc mixture being kept in excess. The temperature of the mixture was allowed to rise during the initial additions and was maintained at 70—80° by adjusting the rate of addition of reactants. After complete addition the mixture was heated under reflux during 30 min before being poured into iced water (20 l) and left overnight at room temperature. The precipitated *pyrrole* (404 g, 64%) was filtered off, washed with water, and recrystallised from aqueous methanol, giving pale yellow needles, m.p. 87—88° (Found: C, 68·6; H, 6·8; N, 4·4. $C_{18}H_{21}NO_4$ requires C, 68·6; H, 6·7; N, 4·4%), τ 0·4 (NH), 2·70 and 4·72 ($PhCH_2$), 5·92 (q) and 8·81 (t) ($OCH_2{\cdot}CH_3$), 6·67 ($CH_2{\cdot}CO$), and 7·85 and 7·71 (3- and 5-Me).

4-(2-Acetoxyethyl)-5-(dimethylcarbamoyl)-3-methylpyrrole-2-carboxylic Acid (17b).—Benzyl 4-(2-acetoxyethyl)-5-dimethylcarbamoyl-3-methylpyrrole-2-carboxylate [9] (12·8 g) in tetrahydrofuran (150 ml) containing triethylamine (4 drops) and 10% palladised charcoal (1 g) was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen had ceased (30 min). The catalyst was filtered off on Celite and the solvent was evaporated off to give the *pyrrolecarboxylic acid* (9·5 g, 98%) as a crystalline solid, m.p. 173—175° (decomp.). This material was used without further purification; a sample recrystallised from ethyl acetate had m.p. 181—182° (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%). It was not sufficiently soluble for its n.m.r. spectrum to be determined.

2,4-Dimethylpyrrole.—Dibenzyl 3,5-dimethylpyrrole-2,4-dicarboxylate [19] (25 g) in methanol (500 ml) containing 10% palladised charcoal (1 g) was hydrogenated at 100 atm and 180° for 12 h. The solution was filtered and evaporated, the resultant oil being dissolved in ether (100 ml) and washed with aqueous M-sodium hydrogen carbonate (2 × 100 ml). The organic layer was washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated to give an oil, which was distilled under vacuum, giving the pyrrole (3·8 g, 58%) as an oil, b.p. 70—85° at 20 mmHg, τ 3·58 (m) and 4·22 (m) (3- and 5-H), and 7·78 and 7·90 (2- and 4-Me).

Benzyl 4-Bromo-5-bromomethyl-3-methylpyrrole-2-carboxylate (3a).—Benzyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate (13·5 g) in hot (70°) carbon tetrachloride (500 ml) was cooled to 55° before dropwise addition of bromine (10·5 ml, 4 equiv.) in carbon tetrachloride (25 ml).[20] The resulting suspension was stirred during 3 h at 55° and, after cooling to 20°, the product was filtered off; a further crop was obtained by concentration of the filtrate, and the combined product was recrystallised from chloroform–light petroleum (b.p. 60—80°) to give the *bromomethylpyrrole* (11·2 g, 58%) as needles, m.p. 145—155° (decomp.) (Found: C, 43·5; H, 3·2; N, 3·8. $C_{14}H_{13}Br_2NO_2$ requires C, 43·5; H, 3·4; N, 3·6%). The corresponding pyridiniomethyl bromide (3d), prisms, m.p. 153—154°, was prepared by dissolution in the minimum volume of hot pyridine, followed by dilution with ether.

Attempted Preparation of Benzyl 4-Bromo-5-dimethylcarbamoyl-3-methylpyrrole-2-carboxylate.—Benzyl 4-bromo-5-bromomethyl-3-methylpyrrole-2-carboxylate (0·77 g) was suspended in acetic acid (30 ml) and sulphuryl chloride (0·36 ml) was added. The solution was stirred overnight under anhydrous conditions; evaporation then afforded a pink solid. Recrystallisation from benzene gave *benzyl 4-bromo-5-formyl-3-methylpyrrole-2-carboxylate* (0·25 g, 40%) as needles, m.p. 148—150° (Found: C, 51·9; H, 4·0. $C_{14}H_{12}BrNO_3$ requires C, 52·2; H, 3·8%), τ 0·0 (NH), 0·32 (CHO), 2·60 and 4·61 ($PhCH_2$), and 7·68 (Me).

Pyrromethanes

Benzyl 3-Bromo-5'-dimethylcarbamoyl-4'-ethyl-3',4-dimethylpyrromethane-5-carboxylate (6a).—5-Dimethylcarbamoyl-4-ethyl-3-methylpyrrole-2-carboxylic acid [21] (7·9 g) and lithium methoxide (1·34 g) were suspended in formamide (70 ml) and the mixture was shaken until all solids had dissolved. Benzyl 4-bromo-3-methyl-5-pyridiniomethylpyrrole-2-carboxylate bromide (16·4 g) was then added and the solution was heated under nitrogen at 100° during 18 h. A viscous oil separated and on cooling a solid crystallised from the formamide solution. The crystals were filtered off, washed well with water, and dried (7·1 g). The oil was dissolved in methylene chloride (100 ml) which was then washed successively with water, 1% v/v hydrochloric acid, and water again until the washings were neutral, and dried ($MgSO_4$). Evaporation gave a brown oil which crystallised after trituration with ether (2·4 g). The two crops were combined and recrystallised from chloroform–ether to give the *pyrromethane* (8·3 g, 48%) as needles, m.p. 202—203° (Found: C, 59·3; H, 6·0; N, 8·5. $C_{24}H_{28}BrN_3O_3$ requires C, 59·3; H, 5·8; N, 8·6%), τ 2·75 and 4·77 ($PhCH_2$), 6·20 (CH_2), 6·99 (NMe_2), 7·58 (q) and 8·91 (t) ($CH_2{\cdot}CH_3$), and 7·70 and 7·92 (2Me).

An insoluble impurity (0·3 g, 2%), m.p. 221—223°, filtered off during the recrystallisation was shown to be benzyl 4-bromo-5-formamidomethyl-3-methylpyrrole-2-carboxylate (3e) (Found: C, 51·4; H, 4·5; N, 7·5. $C_{15}H_{15}BrN_2O_3$ requires C, 51·3; H, 4·3; N, 8·0%), which was not sufficiently soluble in $CDCl_3$ for its n.m.r. spectrum to be measured.

Benzyl 4'-(2-Acetoxyethyl)-3-bromo-5'-dimethylcarbamoyl-3,4'-dimethylpyrromethane-5-carboxylate (6b).—4-(2-Acetoxyethyl)-5-dimethylcarbamoyl-3-methylpyrrole-2-carboxylic acid (9·5 g), lithium methoxide (1·4 g), formamide (75 ml), and benzyl 4-bromo-3-methyl-5-pyridiniomethylpyrrole-2-carboxylate bromide (17·7 g) were treated as in the foregoing experiment. The *pyrromethane* (8·2 g, 45%) was obtained as needles from methylene chloride–ether, m.p. 192—194° (Found: C, 57·3; H, 5·8; N, 7·5. $C_{26}H_{30}BrN_3O_3$ requires C, 57·4; H, 5·6; N, 7·7%), τ −0·5 and −0·4 (2NH), 2·69 and 4·72 ($PhCH_2$), 6·16 (CH_2), 5·89 and 7·21

[19] P. A. Burbidge, M.Sc. Thesis, Liverpool, 1963.
[20] *Cf.* H. Fisher and H. Scheyer, *Annalen*, 1923, **434**, 247.
[21] A. H. Jackson, G. W. Kenner, and D. Warburton, *J. Chem. Soc.*, 1965, 1328.

(O·CH_2·CH_2), 6·98 (NMe_2), 7·76 (COMe), and 7·90 and 8·00 (2Me). An insoluble impurity (1·1 g, 8%), m.p. 221—223°, was shown to be the formamidomethylpyrrole (3e).

Pyrroketones

Benzyl 3-(2-Acetoxyethyl)-3′,4,5′-trimethylpyrroketone-5-carboxylate (20a).—Benzyl 4-(2-acetoxyethyl)-5-dimethylcarbamoyl-3-methylpyrrole-2-carboxylate (8·9 g) in dry 1,2-dichloroethane (25 ml) was treated with phosphoryl chloride (2·5 ml); the mixture was stirred for 1 h at 20°, and then heated under reflux at 88° for 1 h. (The original u.v. absorption at 285 nm disappeared and was replaced by a new maximum at 368 nm.) 2,4-Dimethylpyrrole (2·4 g) in 1,2-dichloroethane (5 ml) was added with stirring over 15 min under nitrogen at 20° and the mixture was then refluxed for 2 h ($\lambda_{max.}$ 400 nm). Aqueous 10% sodium carbonate (60 ml) was added and the mixture was stirred vigorously and heated under reflux during 2 h. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to afford a light brown oily residue. Crystallisation from chloroform–ether gave the *pyrroketone* (7·8 g, 77%) as prisms, m.p. 142—143° (Found: C, 68·3; H, 6·3; N, 6·5. $C_{24}H_{26}N_2O_5$ requires C, 68·2; H, 6·2; N, 6·6%), τ 0·4 and 0·5 (2NH), 2·66 and 4·74 ($PhCH_2$), 4·21 (d, β-H), 5·90 and 7·06 (OCH_2·CH_2), and 7·70, 7·80, 8·05, and 8·12 (4Me), τ (CF_3·CO_2H) 2·55 and 4·51 ($PhCH_2$), 3·48 (β-H), 5·58 and 6·80 (O·CH_2·CH_2), and 7·44, 7·55, 7·65, and 7·87 (4Me), $\nu_{max.}$ (Nujol) 1580, 1680, and 1745 cm^{-1} (C:O).

Benzyl 3-(2-Acetoxyethyl)-4′-bromo-3′,4,5′-trimethylpyrroketone-5-carboxylate (21a).—The foregoing pyrroketone (1·8 g) in carbon tetrachloride (140 ml) was treated as rapidly as possible (without causing precipitation) with bromine (0·24 ml, 1·1 equiv.) in carbon tetrachloride (72 ml). The solvent was evaporated off and the residual red oil was chromatographed on alumina, the product being eluted with 8% ethyl acetate–benzene. Crystallisation from ether gave the *pyrroketone* (1·6 g, 75%) as pale yellow prisms, m.p. 96—98° (Found: C, 57·6; H, 5·2; N, 5·5. $C_{24}H_{25}BrN_2O_5$ requires C, 57·5; H, 5·0; N, 5·6%), τ −0·2 and 0·3 (2NH), 2·64 and 4·72 ($PhCH_2$), 5·88 (t) and 7·03 (t) (OCH_2·CH_2), and 7·69, 7·77, 8·07, and 8·11 (4Me).

Benzyl 3-(2-Acetoxyethyl)-4′-bromo-3′-chloromethyl-3′,4-dimethylpyrroketone-5-carboxylate (21b).—A stirred solution of the pyrroketone (21a) (1·7 g) in tetrahydrofuran (21 ml) and carbon tetrachloride (68 ml) at 0—3° was treated with t-butyl hypochlorite (0·44 ml, 1·1 equiv.) in carbon tetrachloride (17 ml). The solvents were evaporated off and the residue was crystallised from benzene–light petroleum (b.p. 60—80°) to give the *chloromethylpyrroketone* (1·5 g, 83%) as pale cream needles, m.p. 131—133° (Found: C, 53·8; H, 4·7; N, 4·9. $C_{24}H_{24}BrClN_2O_5$ requires C, 53·8; H, 4·5; N, 5·2%), τ −0·8 and 0·0 (2NH), 2·61 and 4·68 ($PhCH_2$), 5·43 (CH_2Cl), 5·86 (t) and 7·02 (t) (OCH_2·CH_2), and 7·68, 8·04, and 8·10 (3Me).

Oxobilanes

Dibenzyl 2-(2-Acetoxyethyl)-4-bromo-1,3,5,8-tetramethyl-6,7-bis-(2-methoxycarbonylethyl)-a-oxobilane-1′,8′-dicarboxylate (22).—5′-Benzyloxycarbonyl-3,3′-bis-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5-carboxylic acid [6] (1 g) was suspended in formamide (20 ml), lithium methoxide (0·072 g) was added, and the suspension was shaken until the solids had passed into solution. The pyrroketone (21b) (1 g) in pyridine (1·6 ml) was then added and the solution was heated at 50° under nitrogen for 18 h. An oily viscous lower layer formed, and this slowly became a gummy solid when kept at 20° for a further 18 h. The upper layer was decanted off, and the residual gum washed with water before dissolving in methylene chloride (15 ml). The solution was washed with water, dried ($MgSO_4$), and evaporated to dryness to give a buff gum, which could not be crystallised, but was used directly for conversion into porphyrin.

Dibenzyl 2-Bromo-4-ethyl-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-b-oxobilane-1′,8′-dicarboxylate (9a).—Benzyl 3-bromo-5′-dimethylcarbamoyl-4′-ethyl-3′,4-dimethylpyrromethane-5-carboxylate (5·4 g) in phosphoryl chloride (36 ml) was kept at 50° for 10 min ($\lambda_{max.}$ 390 nm). The excess of solvent was removed by distillation *in vacuo* and dry ethylene dibromide (2 × 20 ml) was then added and evaporated off. The residual orange-brown oil was taken up in methylene chloride (36 ml) and mixed with a solution of benzyl 3,3′-bis-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5-carboxylate [obtained by decarboxylation of the corresponding 5′-carboxylic acid (6·5 g) [6]] in methylene chloride (36 ml). The mixture was heated under reflux in the dark and a slow stream of nitrogen was bubbled through it until spectroscopic analysis showed that the new band developing at 410 nm had reached its maximum intensity (24 h). The flow of nitrogen was stopped and aqueous 10% sodium carbonate (100 ml) was added. The heterogeneous mixture was heated under reflux with vigorous stirring for 1·5 h ($\lambda_{max.}$ 360 nm), the organic layer was separated, and the aqueous layer was extracted with fresh methylene chloride (30 ml). The combined extracts were washed thoroughly with water before evaporation to give a brown oil which was taken up in ether–methanol and kept under nitrogen at room temperature. After 48 h the b-*oxobilane* (4·5 g, 44%) was obtained as tiny yellow needles, m.p. 168—170° (Found: C, 63·6; H, 6·0; N, 6·1. $C_{49}H_{53}BrN_4O_9$ requires C, 63·8; H, 5·8; N, 6·1%), τ 0·1, 0·2, 0·5, and 1·2 (4NH), 2·71 and 4·87 ($2PhCH_2$), 6·20 and 6·25 ($2CH_2$), 6·42, 6·53, and 7·2—7·8 ($2MeO_2C$·CH_2·CH_2), 7·4 (m) and 9·18 (t) (CH_2·CH_3), and 7·75, 7·79, 7·95, and 8·04 (4Me), $\nu_{max.}$ (Nujol) 1560, 1650, and 1725 cm^{-1} (C:O).

Dibenzyl 4-(2-Acetoxyethyl)-2-bromo-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-b-oxobilane-1′,8′-dicarboxylate (9b).—Benzyl 4′-(2-acetoxyethyl)-3-bromo-5′-dimethylcarbamoyl-3′,4-dimethylpyrromethane-5-carboxylate (4·2 g) in phosphoryl chloride (15 ml) was treated as in the foregoing experiment. It was then condensed with benzyl 3,3′-bis-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5-carboxylate (from 4·8 g of the corresponding 5′-carboxylic acid [6]) and the reaction was carried out as described above. The *b*-oxobilane could not be induced to crystallise, and so it was obtained as a brown solid foam (3·1 g, 41%) by addition of light petroleum (b.p. 60—80°) and evaporation. The product was shown to be homogeneous by t.l.c. and was used without further purification.

4-Ethyl-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-b-oxobilane-1′,8′-dicarboxylic Acid (10a).—Dibenzyl 4-ethyl-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-*b*-oxobilane-1′,8′-dicarboxylate (1·0 g) in tetrahydrofuran (125 ml) containing triethylamine (4 drops) and 10% palladised charcoal (300 mg) was hydrogenated at room temperature and atmospheric pressure during 4 days. The catalyst was filtered off on Celite, which was washed with hot tetrahydrofuran. The combined filtrates were

evaporated to dryness; the residual yellow oil was taken up in the minimum volume of methanol and ether was added. The b-*oxobilane* (0·61 g, 84%) separated as tiny needles, m.p. 153—154° (decomp.) (Found: C, 63·8; H, 6·1; N, 8·1. $C_{35}H_{41}N_4O_9$ requires C, 64·1; H, 6·3; N, 8·5%).

Porphyrins

β-*Acetoxy*-4-*ethyl*-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (12a).—4-Ethyl-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-*b*-oxobilane-1′,8′-dicarboxylic acid (140 mg) was treated successively with M-trichloroacetic acid in methylene chloride (12·6 ml) and trimethyl orthoformate (0·45 ml) in methylene chloride (71·5 ml). The deep red solution ($\lambda_{max.}$ 505 nm) was stirred in the dark for 3·5 h before addition of pyridine (0·9 ml), and the mixture was then stirred overnight. The resulting green solution was evaporated and the residue was taken up in pyridine (39 ml) and acetic anhydride (11·2 ml). After stirring at room temperature for 1 h the red solution was evaporated and the residue was dissolved in methylene chloride (50 ml) and washed successively with aqueous 10% sodium carbonate (50 ml) and water until the washings were neutral; the solution was then dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on alumina (elution with methylene chloride first, and then 1 : 1 methylene chloride–benzene). The porphyrinic eluates were evaporated and the residue was crystallised from methylene chloride–methanol to furnish the *acetoxyporphyrin* (61 mg, 46%) as red-brown needles, m.p. 181—183° (Found: C, 69·2; H, 6·6; N, 8·9. $C_{36}H_{40}N_4O_6$ requires C, 69·2; H, 6·6; N, 9·0%), $\lambda_{max.}$ (CH_2Cl_2) 402·5 (log ε 5·26), 500 (4·10), 532·5 (3·67), 571 (3·71), and 622 nm (3·07), τ (0·1M) 0·18, 0·24, and 0·48 (3 *meso*-H), 1·30 (β-H), 5·9 (m), 6·9 (m), 6·44, and 6·51 ($2CH_2{\cdot}CH_2{\cdot}CO_2Me$), 6·62, 6·67 (2), and 6·78 (4Me), 7·19 (COMe), 8·26 (t) and 5·9 (m) ($CH_3{\cdot}CH_2$), and 14·0 (2NH), *m/e* 624 (45%) and 582 (100), *m** 542 (624 ⟶ 582).

4-*Ethyl*-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (2c).—The *meso*-acetoxyporphyrin (12a) (100 mg) in tetrahydrofuran (80 ml) containing triethylamine (4 drops) and 10% palladised charcoal (100 mg) was hydrogenated at room temperature and atmospheric pressure for 16 h (overnight). The catalyst was filtered off on Celite and tetrahydrofuran (300 ml) and pyridine (2·5 ml) were added to the filtrate before aeration overnight with a stream of compressed air. The solution was concentrated to small volume before addition of benzene and re-evaporation. The residue was chromatographed twice on alumina (elution with methylene chloride–benzene, 1 : 1) and the porphyrinic eluates were evaporated to give a red residue which was crystallised from methylene chloride–methanol to give the porphyrin (46 mg, 51%) as red-violet needles, m.p. 215—218° (lit.,[22] 213°). T.l.c. confirmed that the product was homogeneous; $\lambda_{max.}$ (CH_2Cl_2) 400, 496, 531, 566, and 619 nm, τ (0·1M) 0·20 (2), 0·25, and 0·28 (4 *meso*-H), 1·22 (β-H), 5·80 (t), 5·81 (t), 6·88 (t), 6·90 (t), 6·45, and 6·48 ($2CH_2{\cdot}CH_2{\cdot}CO_2Me$), 6·54, 6·59, and 6·65 (2) (4Me), 8·30 (t) and 6·17 (q) ($CH_3{\cdot}CH_2$), and 14·2 (2NH), *m/e* 566 (100%), 493 (25), 470 (3), and 469 (5), *m** 429 (566 ⟶ 493).

Attempted oxidation of the porphyrinogen with 0·005% iodine in aqueous 3% sodium acetate gave a mixture (mass spectrum) of the required porphyrin and the 2-iodo-derivative.

4-*Ethyl*-2-*formyl*-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (2e).—The foregoing porphyrin (38 mg) in refluxing acetic acid (18 ml) was treated with a freshly prepared solution of iron(II) acetate in acetic acid. Conversion into the haem was almost instantaneous but refluxing was continued for a further 5 min before evaporation under vacuum. The residue was partitioned between methylene chloride (75 ml) and water (75 ml) and the organic phase was washed with aqueous 10% sodium carbonate (3 × 75 ml) and then water until the washings were neutral, before being dried ($MgSO_4$), treated briefly with hydrogen chloride gas, and evaporated to dryness. The residue was taken up in methylene chloride (18 ml), treated with tin(IV) chloride (0·36 ml) and dichloromethyl methyl ether (0·36 ml), and was set aside for 12 min (colour brown to green). The mixture was added to methylene chloride (150 ml) and water (150 ml) and the organic phase was washed with water until the washings were neutral, and then dried ($MgSO_4$) and evaporated to dryness. The residue was taken up in the minimum volume of pyridine and diluted with acetic acid (270 ml), and to this stirred solution, in an atmosphere of nitrogen, was added a fresh solution of iron(II) sulphate (1·08 g) in concentrated hydrochloric acid (10·8 ml); passage of the nitrogen was continued for 5 min. The mixture was poured into methylene chloride–saturated aqueous sodium acetate and the porphyrinic products were extracted into the organic phase. The combined organic extracts were washed with aqueous 10% sodium carbonate and water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed twice on alumina (elution first with methylene chloride and then 1 : 1 methylene chloride–benzene) and the porphyrinic eluates were evaporated to dryness to give a red residue which was crystallised from methylene chloride–methanol to give the *formylporphyrin* (26 mg, 64%) as violet needles, m.p. 243—246°, τ (0·05M) −1·11 (CHO), −0·44, 0·30, 0·32, and 0·63 (4 *meso*-H), 5·8 (m), 6·85 (m), 6·37, and 6·43 ($2CH_2{\cdot}CH_2{\cdot}CO_2Me$), 6·57 (2), 6·60, and 6·68 (4Me), 8·24 (t) and 6·11 (q) ($CH_3{\cdot}CH_2$), and 14·0 (2NH), *m/e* 594 (100%), 566 (35), 535 (6), 521 (30), 493 (7), and 448 (5), *m** 457 (594 ⟶ 521) (Found: M^+, 594·284. Calc. for $C_{35}H_{38}N_4O_5$ *M*, 594·284), $\lambda_{max.}$ (CH_2Cl_2) 417 (log ε 5·24), 515 (4·10), 555 (4·23), 560 (4·15), 583 (3·85), and 640 nm (3·35).

β-*Acetoxy*-4-(2-*acetoxyethyl*)-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (12b).—Dibenzyl 4-(2-acetoxyethyl)-2-bromo-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-*b*-oxobilane (2·7 g, foam) in tetrahydrofuran (300 ml) containing 10% palladised charcoal (350 mg) and triethylamine (10 drops) was hydrogenated at room temperature and atmospheric pressure during 4 days. The solution was evaporated after filtering off the catalyst on Celite, to give a yellow oil which was obtained as a buff foam by addition of light petroleum (b.p. 60—80°) and evaporation. The residue was dried at 60° during 3 h and the solid (1·6 g) was treated with M-trichloroacetic acid in methylene chloride (130 ml) and trimethyl orthoformate (4·64 ml) in methylene chloride (740 ml). The deep red solution ($\lambda_{max.}$ 505 nm) was stirred for 3·5 h before addition of pyridine (8·7 ml) and then stirred in air overnight. The resulting green solution ($\lambda_{max.}$ 404, 495, 610, and 700 nm) was evaporated and the residue taken up in pyridine (56 ml) and acetic anhydride (16 ml) and stirred at room temperature for 1 h. The solution was evaporated and the residue was taken up in methylene chloride (150 ml),

[22] H. Fischer and A. Kirstahler, *Z. physiol. Chem.*, 1931, **198**, 44, 58.

washed with aqueous 10% sodium carbonate and water, and then dried ($MgSO_4$) and evaporated. The residue was chromatographed on alumina (twice) (elution first with methylene chloride and then with 1 : 1 methylene chloride–benzene). The porphyrinic eluates were evaporated and the residue was crystallised from methylene chloride–methanol to give the meso-*acetoxyporphyrin* (550 mg, 29%) as red-brown needles, m.p. 224—225° (Found: C, 67·1; H, 6·2; N, 8·3. $C_{38}H_{42}N_4O_8$ requires C, 66·8; H, 6·2; N, 8·2%), $\lambda_{max.}$ (CH_2Cl_2) 401·5 (log ε 5·26), 499·5 (4·14), 530 (3·70), 571 (3·73), and 623·5 nm (3·14), τ (0·1M) 0·19, 0·26, and 0·54 (3 *meso*-H), 1·32 (β-H), 5·9 (m), 5·2 (m), and 7·92 (CH_2·CH_2·OAc), 5·8 (m), 6·87 (t), 6·39, and 6·45 ($2CH_2$·CH_2·CO_2Me), 6·53, 6·61, 6·65, and 6·77 (4Me), 7·09 (*meso*-OAc), and 14·0 (2NH), *m/e* 682 (5%), 640 (9), 636 (8), 624 (5), 580 (100), 549 (5), 521 (5), 507 (18), 434 (3), 290 (4), 237 (8), and 223 (6), *m** 601 (682 ⟶ 640), 526 (640 ⟶ 580), and 444 (580 ⟶ 507).

4-(2-*Acetoxyethyl*)-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (18a).—The porphyrin (12b) (200 mg) in tetrahydrofuran (150 ml) containing 10% palladised charcoal (200 mg) and triethylamine (10 drops) was hydrogenated at room temperature and atmospheric pressure during 16 h (overnight). The catalyst was filtered off on Celite and tetrahydrofuran (600 ml) containing pyridine (5 ml) was added to the filtrate before it was aerated overnight with a gentle stream of compressed air. The solution was concentrated to *ca.* 10 ml, benzene was added and evaporated off, and the residue was chromatographed twice on alumina (elution with methylene chloride and then 1 : 1 methylene chloride–benzene). The porphyrinic eluates were evaporated and the residue was crystallised from methylene chloride–methanol to afford the *porphyrin* (94 mg, 51%) as violet-red needles, m.p. 229—232° (Found: C, 69·1; H, 6·4; N, 9·0. $C_{36}H_{40}N_4O_6$ requires C, 69·2; H, 6·5; N, 9·0%), $\lambda_{max.}$ (CH_2Cl_2) 399·5 (log ε 5·25), 495·5 (4·28), 530 (4·02), 566 (3·88), and 620 nm (3·68), τ (0·1M) 0·21, 0·28 (2), and 0·35 (4 *meso*-H), 1·22 (β-H), 6·00 (t), 5·34 (t), and 7·94 (CH_2·CH_2·OAc), 5·75 (t), 5·83 (t), 6·18 (t), 6·84 (t), 6·38, and 6·40 ($2CH_2$·CH_2·CO_2Me), 6·52, 6·53, 6·66, and 6·69 (4Me), and 14·35 (2NH), *m/e* 624 (100%), 593 (4), 566 (7), 565 (5), 551 (18), 491 (5), and 312 (3), *m** 486 (624 ⟶ 551).

2-(2-*Acetoxyethyl*)-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (24a).—The aforementioned crude *a*-oxobilane (22) (1·6 g) was taken up in dry tetrahydrofuran (50 ml) and dry ethyl acetate (50 ml) and reduced with an excess of diborane [generated from sodium borohydride (0·75 g) and boron trifluoride–ether complex (7·5 ml)] as described earlier.[6] The resulting colourless solution was evaporated and the residue was taken up in methanol (30 ml), tetrahydrofuran (30 ml), and triethylamine (20 drops) containing 10% palladised charcoal (800 mg). The mixture was hydrogenated at room temperature and atmospheric pressure during 24 h before filtering off the catalyst on Celite and evaporation to dryness. The resulting bilane-1′,8′-dicarboxylic acid (23) was taken up in tetrahydrofuran (200 ml) and ether (200 ml) and the solution at −15° was stirred under nitrogen during the addition of t-butyl hypochlorite (0·19 ml) in ether (65 ml). The red suspension was allowed to warm to room temperature before evaporation and trituration of the residue with ether. The purple solid ($\lambda_{max.}$ 505 nm) was filtered off and taken up in methylene chloride (300 ml) containing trimethyl orthoformate (3·5 ml) and treated with a solution of trichloroacetic acid (16·5 g) in methylene chloride (300 ml). The mixture was stirred in oxygen overnight in the dark before being washed with dilute aqueous sodium carbonate (4 × 100 ml) and water (5 × 100 ml), dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on alumina (elution with 1 : 1 methylene chloride–benzene) and the porphyrinic eluates were evaporated. The residue was crystallised from methylene chloride–methanol. The product (80 mg) was shown (mass spectra) to be a mixture of two porphyrins (24a and b), and it was therefore taken up in tetrahydrofuran (60 ml) containing triethylamine (3 drops) and 10% palladised charcoal, and hydrogenated overnight. After the usual oxidative work-up of the porphyrinogen, and chromatography of the porphyrin, the *product* (24a) (38 mg) crystallised from methylene chloride–methanol as red violet needles, m.p. 213—215° (Found: C, 69·3; H, 6·7; N, 8·6. $C_{36}H_{40}N_4O_6$ requires C, 69·2; H, 6·5; N, 9·0%), $\lambda_{max.}$ (CH_2Cl_2) 400 (log ε 5·27), 497 (4·14), 530 (3·93), 566 (3·80), and 620 nm (3·60), τ (0·14M) 0·22 (3) and 0·32 (4 *meso*-H), 1·13 (β-H), 6·07 (t), 5·39 (t) and 8·09 (CH_2·CH_2·OAc), 5·85 (t), 6·91 (t), and 6·46 ($2CH_2$·CH_2·CO_2Me), 6·64, 6·68 (2), and 6·76 (4Me), and 14·3 (2NH), *m/e* 624 (100%), 593 (3), 566 (5), 565 (4), 551 (24), 537 (6), 491 (6), 478 (3), 477 (2), 418 (2), 417 (2), and 312 (2), *m** 510 (624 ⟶ 565), 485 (624 ⟶ 551), and 438 (551 ⟶ 491).

4-(2-*Hydroxyethyl*)-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (18b).—4-(2-Acetoxyethyl)-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin (200 mg) was set aside overnight in 5% w/v sulphuric acid–methanol (200 ml) in the dark. The solution was poured into ice-cold aqueous 6% sodium acetate (400 ml) and methylene chloride (600 ml) and the pH of the aqueous phase was adjusted to 7 with ammonium hydroxide. The organic phase was separated and the aqueous phase was re-extracted with methylene chloride (4 × 50 ml); the combined extracts were washed with aqueous 10% sodium carbonate (2 × 100 ml) and water, dried ($MgSO_4$) and evaporated to dryness to give a residue which was chromatographed on alumina (elution first with methylene chloride and then with methylene chloride containing 2% methanol). The porphyrinic eluates were evaporated and the residue was crystallised from methylene chloride–methanol–ether to give the *porphyrin* (183 mg, 98%) as red-violet needles, m.p. 215—217° (Found: C, 70·4; H, 6·7; N, 9·2. $C_{34}H_{38}N_4O_5$ requires C, 70·1; H, 6·6; N, 9·6%), $\lambda_{max.}$ (CH_2Cl_2) 399 (log ε 5·22), 497 (4·10), 530 (3·89), 566 (3·76), 592sh (3·13), and 620 nm (3·55), τ (0·1M) 0·41, 0·43 (2), and 0·52 (4 *meso*-H), 1·26 (β-H), 6·2 (m) (CH_2·CH_2O), 5·96 (t), 6·03 (t), 6·97 (t), 7·00 (t), and 6·45 (2) ($2CH_2$·CH_2·-CO_2Me), 6·47, 6·74, 6·80, and 6·84 (4Me), and 14·5 (2NH), *m/e* 582 (100%), 551 (40), 523 (5), 509 (7), 477 (7), 449 (8), 436 (8), 419 (9), and 404 (4), *m** 522 (582 ⟶ 551) and 445 (582 ⟶ 509).

2-(2-*Hydroxyethyl*)-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin*.— 2-(2-Acetoxyethyl)-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin (38 mg) was subjected to the conditions described for the foregoing analogue. The *porphyrin* (33 mg, 93%) crystallised from methylene chloride–methanol as violet-red needles, m.p. 210—212° (Found: C, 69·9; H, 6·8; N, 9·2. $C_{34}H_{38}N_4O_5$ requires C, 70·1; H, 6·6; N, 9·6%), $\lambda_{max.}$ (CH_2Cl_2) 398 (log ε 5·23), 497 (4·09), 530 (3·88), 566 (3·75), 595sh (3·08), and 619 nm (3·55), τ (0·11M) 0·28 (2), 0·31, and 0·35 (4 *meso*-H), 1·17 (β-H), 5·91 (t), 5·96 (t), 6·94 (t) (2),

and 6·44 (2) ($2CH_2{\cdot}CH_2{\cdot}CO_2Me$), 6·2 (m) ($CH_2{\cdot}CH_2{\cdot}O$), and 6·54, 6·66 (2), and 6·78 (4Me), *m/e* 582 (100%), 551 (25), 523 (3), 509 (18), 478 (5), 477 (4), 405 (7), 291 (3), 238 (7), 209 (7), and 202 (5), *m** 522 (582 ⟶ 551) and 445 (582 ⟶ 509).

4-(2-*Chloroethyl*)-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (18c).—4-(2-Hydroxyethyl)-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin (90 mg) in pyridine (9 ml) and methanesulphonyl chloride (2·6 ml) was heated at 75° during 30 min under nitrogen. After pouring into methylene chloride (150 ml) and water (150 ml) the aqueous phase was re-extracted with methylene chloride (4 × 30 ml) and the combined organic fractions were washed with aqueous 10% sodium carbonate solution (3 × 100 ml), followed by water until the washings were neutral, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on alumina (elution first with methylene chloride and then 1 : 1 methylene chloride–benzene). The porphyrinic eluates were evaporated and the residue was crystallised from methylene chloride–methanol to give the *porphyrin* (69 mg, 75%) as red-violet needles, m.p. 215—218° (Found: C, 68·1; H, 6·0; N, 9·4. $C_{34}H_{37}ClN_4O_4$ requires C, 67·9; H, 6·2; N, 9·3%), $\lambda_{max.}$ (CH_2Cl_2) 400 (log ε 5·22), 499 (4·08), 529·5 (3·89), 566 (3·75), 595sh (3·14), and 619·5 nm (3·55), τ (0·1M) 0·16, 0·21, 0·31, and 0·39 (4 *meso*-H), 1·26 (β-H), 5·73 (t), 5·79 (t), 6·81 (2), and 6·37 (2) ($2CH_2{\cdot}CH_2{\cdot}CO_2Me$), 5·88 (m) ($CH_2{\cdot}CH_2Cl$), 6·46, 6·54, 6·59, and 6·67 (4Me), and 14·3 (2NH), *m/e* 600 (^{35}Cl) (35%), 564 (100), 527 (6), 491 (17), and 417 (7), *m** 428 (564 ⟶ 491).

2-(2-*Chloroethyl*)-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin*.— 2-(2-Hydroxyethyl)-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin (33 mg) was subjected to the reaction conditions described for the isomer; the *porphyrin* (25 mg, 73%) crystallised from methylene chloride–methanol as red-violet needles, m.p. 199—201° (Found: C, 68·0; H, 5·9; N, 9·1. $C_{34}H_{37}ClN_4O_4$ requires C, 67·9; H, 6·2; N, 9·3%), $\lambda_{max.}$ (CH_2Cl_2) 400 (log ε 5·24), 497 (4·10), 529 (3·89), 566·5 (3·76), 595sh (3·09), and 620 nm (3·55), τ (0·06M) 0·10, 0·14 (2), and 0·26 (4 *meso*-H), 1·07 (β-H), 5·80 (m) ($CH_2{\cdot}CH_2Cl$), 5·75 (t), 6·80 (t), and 6·38 ($CH_2{\cdot}CH_2{\cdot}CO_2Me$), 6·40, 6·51 (2), and 6·59 (4Me), and 14·2 (2NH), *m/e* 600 (100%), 565 (12), 564 (14), 527 (25), 491 (8), 417 (7), and 405 (8), *m** 463 (600 ⟶ 527).

4-*Vinyldeuteroporphyrin*-IX *Dimethyl Ester* (' *Pempto-porphyrin Dimethyl Ester* ') (2a).—4-(2-Chloroethyl)-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin (28 mg) in acetic acid (3 ml) was treated during 5 min with a hot solution of acetic acid (36 ml) saturated with zinc acetate. The solution was evaporated and the residue was dissolved in ethyl acetate (50 ml); the solution was washed with water, dried ($MgSO_4$), and evaporated to dryness. The zinc chelate was taken up in tetrahydrofuran (3 ml) and M-potassium t-butoxide in t-butyl alcohol (20 ml) and the solution was stirred under nitrogen during 5 h at 20°. The mixture was poured into ethyl acetate (150 ml) and water (50 ml) and the aqueous phase was adjusted to pH 4 with dilute sulphuric acid. The aqueous phase was re-extracted with more ethyl acetate and the combined organic phases were evaporated, azeotroped dry with a little dry benzene, dried at 55° during 4 h, and then set aside for 15 h in 5% w/v sulphuric acid–methanol. After pouring into ice cold methylene chloride (50 ml) and water (50 ml) the aqueous phase was adjusted to pH 6 with ammonium hydroxide, and the organic layer was separated, combined with methylene chloride from back-extraction of the aqueous phase, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed twice on alumina (elution with methylene chloride first, and then 3 : 1 methylene chloride–benzene) and the porphyrinic eluates were evaporated. The residue crystallised from methylene chloride–methanol to give the product (16 mg, 59%) as violet-red needles, m.p. 213—214° (lit.,[4] 215—218°; lit.,[12] 209—210°) (Found: C, 72·2; H, 6·4; N, 9·6. Calc. for $C_{34}H_{36}N_4O_4$: C, 72·3; H, 6·4; N, 9·9%), $\lambda_{max.}$ (CH_2Cl_2) 402·5 (log ε 5·15), 501 (4·05), 534 (3·91), 571 (3·71), 600sh (3·02), and 625 nm (3·50), τ (0·09M) 0·15, 0·26 (2), and 0·30 (4 *meso*-H), 1·20 (β-H), 2·04 (m) and 4·02 (m) ($CH{:}CH_2$), 5·91 (t), 6·96 (t), and 6·50 ($2CH_2{\cdot}CH_2{\cdot}CO_2Me$), 6·46, 6·53, and 6·69 (2) (4Me), and 14·35 (2NH), *m/e* 564 (100%), 491 (30), and 417 (5), *m** 428 (564 ⟶ 491).

2-*Vinyldeuteroporphyrin*-IX *Dimethyl Ester* (' *Isopempto-porphyrin Dimethyl Ester* ') (2b).—2-(2-Chloroethyl)-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin (25 mg) was subjected to the same conditions as described above; the *porphyrin* (14 mg, 59%) crystallised from methylene chloride–methanol as red-violet needles, m.p. 220—221° (lit.,[12b] 218—219°) (Found: C, 71·9; H, 6·4; N, 9·8. $C_{34}H_{36}N_4O_4$ requires C, 72·3; H, 6·4; N, 9·9%), $\lambda_{max.}$ (CH_2Cl_2) 401·5 (log ε 5·25), 500·5 (4·03), 536·5 (3·91), 570 (3·72), 600sh (3·08), and 625 nm (3·49), τ (0·09M) 0·08, 0·23, 0·25, and 0·30 (4 *meso*-H), 1·15 (β-H), 2·0 (q) and 3·9 (m) ($CH{:}CH_2$), 5·78 (t), 6·82 (t), 6·38, and 6·40 ($2CH_2{\cdot}CH_2{\cdot}CO_2Me$), 6·44, 6·54 (2), and 6·60 (4Me), and 14·3 (2NH), *m/e* 564 (100%), 491 (23), 418 (6), and 417 (6), *m** 428 (564 ⟶ 491).

4-(2-*Chloroethyl*)-2-*formyl*-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (25).—4-(2-Chloroethyl)-6,7-bis-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin (75 mg) in refluxing acetic acid (35 ml) was treated with a freshly prepared solution of iron(II) acetate in acetic acid. Refluxing was continued for a further 5 min before removal of the solvent under vacuum. The residue was dissolved in methylene chloride (150 ml) and water (150 ml) and the organic phase was washed with aqueous 10% sodium carbonate (3 × 150 ml) and then water until the washings were neutral. After drying ($MgSO_4$) the solution was treated with a little gaseous hydrogen chloride and evaporated, and the residue, in methylene chloride (36 ml), was treated with tin(IV) chloride (0·72 ml) and dichloromethyl methyl ether (0·72 ml) and set aside at room temperature for 12 min. The mixture was poured into methylene chloride (300 ml) and water (300 ml) and the organic phase was washed until the washings were neutral, then dried ($MgSO_4$) and evaporated to dryness. The residue, in pyridine (minimum volume) and acetic acid (540 ml) was treated with iron(II) sulphate (2·16 g) in concentrated hydrochloric acid (21·6 ml) and stirred for 5 min. The product was poured into methylene chloride (270 ml) and saturated aqueous sodium acetate (450 ml) and the porphyrinic products were extracted into the organic phase, which was washed with aqueous 10% sodium carbonate and water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed twice on alumina, first in methylene chloride, and then in methylene chloride–benzene (1 : 1 to 7 : 3). The porphyrinic eluates were evaporated and the residue was crystallised from methylene chloride–methanol to furnish the *porphyrin* (59 mg, 75%) as violet needles, m.p. 228—230° (Found: C, 67·1; H, 6·0; N, 8·5. $C_{35}H_{37}ClN_4O_5$ requires C, 66·8; H, 5·9; N,

8·9%), τ (0·08M) −0·42 (CHO), 0·32, 0·58, 0·89, and 1·52 (4 *meso*-H), 6·1 (m) (CH_2·CH_2Cl), 5·9 (m), 6·84 (t), 6·33, and 6·40 ($2CH_2$·CH_2·CO_2Me), 6·66, 7·00, 7·02, and 7·22 (4Me), and 15·35 (2NH), *m/e* 628 (100%), 600 (6), 592 (50), 555 (15), and 519 (9), *m** 490 (628 → 555).

2-*Formyl*-6,7-*bis*-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethyl*-4-*vinylporphin* (' *Chlorocruoroporphyrin Dimethyl Ester* ') (2f).—The porphyrin (25) (29 mg) in a minimal volume of methylene chloride was treated with 2,2-dimethylpropane-1,3-diol (51 mg) in benzene (30 ml) and a small crystal of toluene-*p*-sulphonic acid hydrate. The methylene chloride and a portion (*ca.* 10 ml) of the benzene were distilled off and the remaining solution was refluxed during 2 h before being poured into methylene chloride and saturated aqueous sodium acetate. The aqueous phase was then re-extracted with several portions of methylene chloride and the combined organic fractions were washed with aqueous 10% sodium carbonate (3 × 70 ml) and water (70 ml), dried ($MgSO_4$), and evaporated to dryness. The residual acetal (26a) was treated with methylene chloride (6 ml) and then a saturated solution of zinc acetate in methanol (12 ml) and warmed for 3 min. The solution was poured into ethyl acetate (50 ml) and saturated aqueous sodium acetate (50 ml) and the organic phase was separated, washed with water (50 ml), dried ($MgSO_4$), and evaporated; the residue was finally dried at 60° for 45 min. The resultant zinc chelate in tetrahydrofuran (3 ml) was treated with M-potassium t-butoxide in t-butyl alcohol (20 ml) with stirring at 20° during 5 h in the dark. The mixture was poured into ethyl acetate (150 ml) and water (150 ml) and the aqueous phase adjusted to pH 4 with dilute sulphuric acid. The organic phase was separated, combined with portions of ethyl acetate (4 × 20 ml) used for back-extraction of the aqueous phase, and washed with water. The solution was evaporated to dryness, a little dry benzene being added and evaporated to remove traces of water, and then dried for 4 h at 55°. The residue was taken up in 5% w/v sulphuric acid–methanol (30 ml) and set aside in the dark for 15 h, before being poured into ice-cold methylene chloride (50 ml) and water (50 ml), and the aqueous phase was adjusted to pH 6 with ammonium hydroxide after intimate mixing. The organic phase was separated and the aqueous phase was re-extracted with methylene chloride (4 × 20 ml). The combined extracts were washed with water, dried ($MgSO_4$), evaporated to dryness, and the residue was chromatographed twice on alumina with chloroform as eluant. The porphyrinic eluates were evaporated and the residue was crystallised from chloroform–ether to give the porphyrin (10 mg, 37%) as violet needles, m.p. 281—283° (lit.,[13] 285°; lit.,[15] 278—279°; lit.,[12a] 276—278°) (Found: C, 71·0; H, 6·3; N, 9·3. Calc. for $C_{35}H_{36}N_4O_5$: C, 70·9; H, 6·1; N, 9·5%), $\lambda_{max.}$ (CH_2Cl_2) 419 (log ε 5·24), 517 (4·11), 555 (4·24), 560 (4·15), 583 (3·86), and 642 nm (3·36), τ (accumulated spectrum) −1·12 (CHO), −0·46, 0·24, 0·30, and 0·40 (4 *meso*-H), *ca.* 3·6 (CH:CH_2), 5·7 (m), 6·7 (m), and 6·3 (2) ($2CH_2$·CH_2·CO_2Me), and 6·3 (2), 6·45, and 6·5 (4Me), *m/e* 592 (100%), 561 (4), 533 (3), 519 (26), 495 (2), 446 (5), 445 (4), 418 (2), and 296 (3), *m** 455 (592 → 519) and 383 (519 → 446).

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