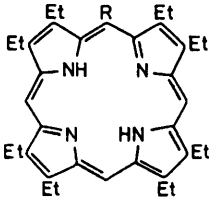
meso (Methine) Functionalization of Octa-alkylporphyrins

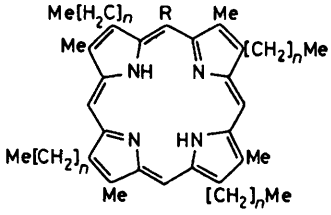
By **Kevin M. Smith** * and **Graham M. F. Bisset**, Department of Chemistry, University of California, Davis, California 95616, USA

meso-Acetoxymethylocta-alkylporphyrins [*e.g.* (1), (7), and (8)] react with a variety of nucleophiles such as alcohols (to give the corresponding alkoxymethylporphyrins), amines (yielding aminomethylporphyrins), and Grignard reagents (to give *meso*-alkylporphyrins). Treatment of the *meso*-acetoxymethylporphyrins with thiol reagents accomplishes reduction to give the *meso*-methylporphyrin rather than the sulphide. Making use of these *meso*-functionalization reactions, potential cytochrome P450 models and a model for the tense form of hemoglobin are synthesized.

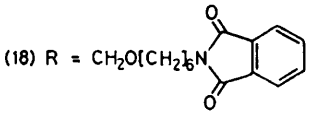
We have previously shown [1-3] that octa-alkylporphyrins which are substituted at their *meso* (methine) positions with an acetoxymethyl substituent are particularly susceptible to nucleophilic displacement reactions at the 'benzylic' methylene carbon atom. Specifically, porphyrins such as (1) reacted with water (during chromatography) to give the corresponding carbinol (2), and with alcohols (during crystallization) to give ethers [*e.g.* (3) and (4)]. Moreover, borohydride reagents transformed [1,2] the *meso*-acetoxymethylporphyrin (1) into the corresponding *meso*-methylporphyrin (5), and the same compound could be obtained by hydrogenolysis. We proposed that these reactions were favoured by the inherent stability of the 'benzylic' carbocation (6) and its various resonance forms; in support of this, Ponomarev [4] has published details of the unusual electronic absorption spectrum of one such cation, generated by treatment of copper(II) methoxymethyl-, hydroxymethyl-, or dimethylaminomethyl-porphyrins with Lewis or strong acids in polar aprotic solvents. The yellow colour of the cation was discharged immediately upon addition of a nucleophile, and in this way *meso*-methoxyetioporphyrin-I copper(II) complex was prepared on a preparative scale. In the present paper we describe preparative routes to a variety of novel *meso*-functionalized porphyrins by exploitation of the reactions of metal-free *meso*-acetoxymethylporphyrins with oxygen-, nitrogen-, and carbon-nucleophiles.

The acetoxymethylporphyrins (1), (7), and (8) were prepared [1-3] from the corresponding *meso*-unsubstituted porphyrins (9)—(11) by Vilsmeier formylation of the copper(II) complexes, followed by demetallation and borohydride reduction (to give the carbinols) and treatment with acetic anhydride in pyridine. Alcohols such as benzyl alcohol and isopropyl alcohol were successfully coupled with the octaethylporphyrin derivative (1) to give the ethers (12) and (13) respectively. These displacement reactions were more sluggish (typically 3 h heating under reflux for quantitative conversion) than the analogous reactions with methanol, ethanol, or water (15 min heating under reflux). t-Butyl alcohol did not react at all with (1), presumably because of its steric bulk. Hexane-1,6-diol was also successfully condensed with the acetoxymethylporphyrins (1), (7), and (8); initial attempts to carry out this reaction at high dilution (in order to avoid dimer formation by reaction of porphyrin at both ends of the diol) were unsuccessful, so the porphyrins were heated in a melt of the 1,6-diol. Under these conditions high yields of the products (14)—(16) were obtained, with no trace of the corresponding dimers being detected. As might be expected, the long-chain alcohols (15) and (16) derived from the lipophilic porphyrins (7) and (8)[3] could not be crystallized because of their high solubility in almost all organic solvents. The products (15) and (16) were judged pure by high-pressure liquid chromatography and were characterized by mass and n.m.r. spectroscopy.

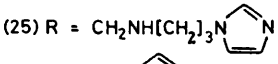


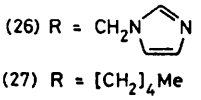


(1) R = CH_2OAc
(2) R = CH_2OH
(3) R = CH_2OMe
(4) R = CH_2OEt
(5) R = Me
(6) R = CH_2^+
(9) R = H
(12) R = CH_2OCH_2Ph
(13) R = CH_2OCHMe_2
(14) R = $CH_2O[CH_2]_6OH$
(17) R = $CH_2O[CH_2]_6Br$



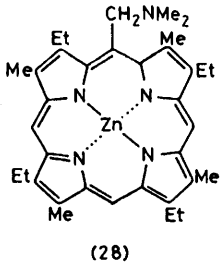
(19) R = $CH_2O[CH_2]_6\overset{+}{S}{=}C(NH_2)_2;Br^-$
(20) R = $CH_2O[CH_2]_6SH$
(21) R = $CH_2O[CH_2]_6S\rightarrow_2$





(27) R = $[CH_2]_4Me$

(7) R = CH_2OAc; n = 4
(8) R = CH_2OAc; n = 6
(10) R = H; n = 4
(11) R = H; n = 6
(15) R = $CH_2O[CH_2]_6OH$; n = 4
(16) R = $CH_2O[CH_2]_6OH$; n = 6
(22) R = $CH_2O[CH_2]_6S\rightarrow_2$; n = 4
(23) R = Fe^{III} Cl complex of (22)
(24) R = Me; n = 4



(28)

Molecular models indicated that the *meso*-substituent in compounds (14)—(16) was sufficiently long to be able to wrap over the porphyrin core and co-ordinate with metal ions placed in the centre. Two potential cytochrome P450 models [5] were therefore synthesized as follows. Treatment of compound (14) with carbon tetrabromide–triphenylphosphine gave the bromoalkyl derivative (17). The terminal bromine atom could be readily displaced with mild nucleophiles such as phthalimide [to form (18)], so treatment with thiourea in refluxing ethanol and tetrahydrofuran smoothly gave the thiouronium salt (19) which was decomposed with 10% aqueous sodium hydroxide to give the presumed thiol (20). During the work-up it seems likely that the thiol was oxidized to give the disulphide (21) which was isolated in 95% overall yield from (17). Iron was successfully inserted into the disulphide using iron(II) chloride in methanol and tetrahydrofuran.[6] Similarly, the n-pentyl disulphide (22) was synthesized from (15) and this gave a crystalline iron(III) chloride complex (23). Attempts to generate the characteristic cytochrome P450.CO electronic absorption spectrum from (21; iron complex) and (23) have so far been unsuccessful. Traylor and Mincey [7] have recently synthesized a similar sulphide-bound cytochrome P450 model by way of a disulphide which was readily cleaved by simple reduction with dithionite.

Under anaerobic conditions, *meso*-acetoxymethylporphyrins treated with sulphur nucleophiles such as ethanedithiol, hexane-1,6-dithiol, and thiourea yielded only the corresponding *meso*-methylporphyrin [*e.g.* (24)] and not the expected sulphides. Substitution of sulphides (generated by pretreatment of thiols with sodium hydride/18-crown-6) in the above reactions gave essentially the same products. Presumably thiol or thiolate oxidation to disulphide occurs with concomitant reduction of the *meso*-acetoxymethyl substituent to methyl.

Traylor *et al.*[8] have described the synthesis of T-state hemoglobin models by treating activated derivatives of mesohemin with 3-(2-methylimidazol-1-yl)propylamine or other imidazole derivatives with shorter connecting arms. Through intramolecular ligation of the imidazole with the central iron atom it was possible to introduce strain into the iron–imidazole link which was not present in the unstrained 3-imidazol-1-ylpropylamine derivative and thereby cause reduced affinity in the binding of carbon monoxide and oxygen to the iron(II) atom. A somewhat similar but more symmetrical T-state hemoglobin model, currently undergoing independent binding studies,[9] was synthesized from the *meso*-acetoxymethylporphyrin (1); it was felt that the doming of the porphyrin ring caused by *meso*-methyl substituents [10] would add to the strain present in such an intramolecularly chelated heme. When excess of 3-imidazol-1-ylpropylamine was heated under reflux in 1,2-dichloroethane with porphyrin (1) during 24 h only a minute amount of a new compound was observed. Similarly, when the amine and (1) were heated together in a melt for several hours, little reaction took place. A 64% yield of the coupled product (25) was obtained however when the *meso*-acetoxymethylporphyrin (1) was heated under reflux in tetrahydrofuran containing 3-imidazol-1-ylpropylamine and a suspension of sodium hydride; a by-product from this reaction was the *meso*-imidazol-1-ylmethylporphyrin (26), presumably formed from small amounts of imidazole impurity present in the 3-imidazol-1-ylpropylamine; the identity of (26) was confirmed by synthesis of an authentic sample by heating imidazole and porphyrin (1) in a melt. Iron was inserted into (25) by treatment with iron(II) chloride in methanol and tetrahydrofuran to give the heme model.

The final reaction attempted with the *meso*-acetoxymethylporphyrin (1) was treatment with Grignard reagents. Addition of n-butylmagnesium bromide in ether to the porphyrin (1) in tetrahydrofuran caused an instantaneous colour change to bright red (anion formation?). Work-up and preparative thick layer chromatography gave a 64% yield of *meso*-n-pentyloctaethylporphyrin (27).

Very recently, Ponomarev [11] has shown that the zinc(II) complex of *meso*-dimethylaminoetioporphyrin-I (28) [the zinc complex of the Mannich base equivalent of compound (1)] undergoes displacement reactions with alcohols, enolates, malonates, and with nitromethane.

EXPERIMENTAL

Melting points were measured on a microscopic hot-stage apparatus. T.l.c. monitoring of all reactions was performed using Merck silica gel 60 F-254 precoated sheets (0.2 mm), and preparative t.l.c. was carried out on 20 × 20 cm glass plates coated with Merck GF 254 silica gel (1.5 mm); it was occasionally necessary to wash porphyrins extracted from these plates with 1M-HCl in order to remove zinc which had been scavenged by metal-free porphyrins from the fluorescer. Column chromatography was carried out using Merck neutral alumina 90 (70—230 mesh), and all reactions and chromatographic separations were carried out in the dark (aluminium foil). Electronic absorption spectra were determined using a Cary 15 or Cary 17 spectrophotometer (solutions in methylene chloride), and ^{1}H n.m.r. spectra were measured at 360 MHz (Nicolet NT-360) usually in $CDCl_3$ with tetramethylsilane as internal calibrant. Mass spectra (direct insertion probe, 70 eV, 50 μA, source temperature *ca.* 200 °C) were measured using a Finnegan 3200 spectrometer.

meso-(*Benzyloxymethyl*)*octaethylporphyrin* (12).—*meso*-Acetoxymethyloctaethylporphyrin (1) [1] (50 mg) was dissolved in 1,2-dichloroethane (20 ml) and benzyl alcohol (5 ml) was added. The mixture was heated under reflux for 1 h before being evaporated to dryness under reduced pressure; the residue was chromatographed on alumina (Brockmann Grade III, elution with methylene chloride). The red eluates were evaporated to dryness and the residue was crystallized from methylene chloride–methanol to give the *porphyrin* (53 mg, 98%), m.p. 205—206 °C (Found: C, 80.15; H, 8.15; N, 8.9. $C_{44}H_{54}N_4O$ requires C, 80.69; H, 8.31; N, 8.56%); δ 1.85 (24 H, t, CH_2CH_3), 3.93—4.18 (16 H, m, CH_2CH_3), 4.95 (2 H, s, CH_2Ph), 6.56 (2 H, s, CH_2OCH_2Ph), 7.35, 7.52 (5 H, 2 × m, $C_6H_5CH_2$), 9.91 (1 H, s, γ-*meso*-H), and 10.09 (2 H, s, β,δ-*meso*-H); *m/e* (%) 654 (46), 548

(100), 533 (27), and 520 (14); $\lambda_{max.}$ 407 (ε 173 000), 505 (10 000), 540 (9 300), 576 (7 600), and 628 nm (3 800).

meso-(*Isopropoxymethyl*)*octaethylporphyrin* (13).—This compound was prepared in quantitative yield by treatment of the porphyrin (1) with isopropyl alcohol as described above; it had m.p. 198—199 °C (Found: C, 78.9; H, 9.1; N, 9.4. $C_{40}H_{54}N_4O$ requires C, 79.16; H, 8.97; N, 9.23%); δ −2.85 (2 H, bd s, NH), 1.65 (6 H, d, $CH(Me)_2$), 1.96 (24 H, t, CH_2CH_3), 3.74—4.47 (17 H, m, CH_2CH_3 and $CH(Me)_2$) 6.51 (2 H, s, CH_2OCH), 9.94 (1 H, s, γ-*meso*-H), and 10.14 (2 H, s, β,δ-*meso*-H); *m/e* (%) 606 (40), 548 (100), 534 (42), and 519 (22); $\lambda_{max.}$ 404 (ε 173 000), 506 (13 000), 541 (9 500), 577 (7 400), and 628 nm (3 700).

meso-(6-*Hydroxyhexyloxymethyl*)*octaethylporphyrin* (14).—Hexane-1,6-diol (5 g) was melted at 100 °C and to this was added a solution of *meso*-acetoxymethyloctaethylporphyrin (1) (1.007 g) in dry 1,2-dichloroethane (10 ml). The mixture was stirred at 100 °C for 2 h and then cooled, diluted with methylene chloride (100 ml), washed with 20% sodium hydrogen carbonate solution (3 × 50 ml), and then dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on alumina (Brockmann Grade IV, elution with methylene chloride) and the red eluates were evaporated and the residue was crystallized from methylene chloride–hexane to give the *alcohol* as purple needles (893 mg, 81%), m.p. 170 °C (Found: C, 77.6; H, 8.95; N, 8.1. $C_{43}H_{60}N_4O_2$ requires C, 77.67; H, 9.10; N, 8.43%); δ −3.03 (2 H, bd s, NH), 1.34—1.48 (2 H, m, 5′-CH_2), 1.48—1.65 (4 H, m, 3′,4′-CH_2), 1.80—2.00 (26 H, m, CH_2CH_3, 2′-CH_2), 3.55 (2 H, t, 6′-CH_2OH), 3.95—4:20 (18 H, m, CH_2-CH_3, 1′-CH_2), 6.44 (2 H, s, $CH_2O(CH_2)_6$), 9.93 (1 H, s, γ-*meso*-H), and 10.10 (2 H, s, β,δ-*meso*-H); *m/e* (%), 644 (81), 548 (100), 534 (42), 519 (26), and 504 (21); $\lambda_{max.}$ 404 (ε 165 000), 506 (11 500), 541 (8 400), 575 (6 300), and 628 nm (3 900).

Zinc(II) *complex*. A solution of porphyrin (14) (30 mg) in methylene chloride (50 ml) was treated with a solution of zinc(II) acetate (100 mg) in t-butyl alcohol (30 ml), and the volume was reduced to *ca.* 20 ml by evaporation under reduced pressure, whereupon the product crystallized. It was redissolved and chromatographed on alumina (Brockmann Grade IV, elution with methylene chloride); evaporation of the appropriate eluates gave a bright red residue which was crystallized from methylene chloride–hexane to give the *zinc complex* (28 mg; 85%), m.p. 174 °C; δ (in $CDCl_3$ + excess pyrrolidine),[12] 1.35—1.70 (6 H, m, 5′,4′,3′-CH_2), 1.74—1.99 (2 H, m, 2′-CH_2); 1.90 (24 H, t, CH_2CH_3), 2.68 (2 H, m, 6′-CH_2OH), 3.86—4.17 (18 H, m, CH_2CH_3, 1′-CH_2), 6.55 [2 H, s, $CH_2O(CH_2)_6$], 10.00 (1 H, s, γ-*meso*-H), and 10.09 (2 H, s, β,δ-*meso*-H); *m/e* (%), (^{64}Zn ions), 726 (12), 623 (3), 610 (100), 596 (38), and 582 (10); $\lambda_{max.}$ 407, 539, and 580.

meso-(6-*Hydroxyhexyloxymethyl*)-1,3,5,7-*tetramethyl*-2,4,6,-8-*tetra*-(*n-pentyl*)*porphyrin* (15).—This compound was prepared from the *meso*-acetoxymethyl-n-pentylporphyrin (7) and hexane-1,6-diol as described above for compound (14). The yield was 88% and the product was obtained as an evaporate. All attempts to crystallize the product were unsuccessful; δ −3.23 and −3.03 (each 1 H, bd s, NH), 0.97, 0.99, and 1.06 (6 H, 3 H, 3 H, each t, 5′-CH_3), 1.40—1.50 (2 H, m, 5″-CH_2), 1.50—1.67 (12 H, m, 4′,3″,4″-CH_2), 1.67—1.76 and 1.76—1.86 (6 H, 2 H, each m, 3′-CH_2), 1.91—2.02 (2 H, m, 2″-CH_2), 2.13—2.22 and 2.22—2.35 (2 H, 6 H, 2′-CH_2), 3.61 (2 H, t, 6″-CH_2OH), 3.54, 3.61, 3.62, and 3.63 (each 3 H, s, 1,3,5,7-CH_3), 3.93—4.14 (10 H, m, 1′,1″-CH_2), 6.36 [2 H, s, $CH_2O(CH_2)_6$], 9.92 (1 H, s, γ-*meso*-H), and 10.10 (2 H, s, β,δ-*meso*-H); *m/e* (%), 776 (26), 660 (100), 646 (41), 589 (18), 532 (6), 475 (5), 417 (3), and 388 (2); $\lambda_{max.}$ (peak ratio), 405 (100), 506 (7.9), 541 (5.2), 576 (3.6), 600 (1.0), and 629 nm (2.6).

Zinc(II) *complex*. Using the same method as described for zinc(II) complex of compound (14), the yield was 74% of non-crystalline material; δ 0.99 and 1.19 (9 H, 3 H, each t, 5′-CH_3), 1.40—1.58 (10 H, m, 5″-CH_2, 4′-CH_2), 1.58—1.76 (12 H, m, 3′,3″,4″-CH_2), 1.78—1.95 (2 H, m, 2″-CH_2), 1.98—2.28 (8 H, m, 2′-CH_2), 3.06—3.26 (2 H, m, 1′-CH_2), 3.31, 3.40, and 3.48 (6 H, 3 H, 3 H, each s, 1,3,5,7-CH_3), 3.60—3.82 and 3.83—4.05 (6 H, 2 H, each m, 1′-CH_2), 5.96 (2 H, s, $CH_2O(CH_2)_6$), and 9.35, 9.40, and 9.56 (each 1 H, s, *meso*-H); *m/e* (%) (^{64}Zn ions), 838 (13), 722 (100), 708 (32), 651 (12), 594 (5), 537 (5), and 480 (5); $\lambda_{max.}$ 408, 539, and 580 nm.

meso-(6-*Hydroxyhexyloxymethyl*)-1,3,5,7-*tetramethyl*-2,4,-6,8-*tetra*-(*n-heptyl*)*porphyrin* (16).—This compound was prepared from the *meso*-acetoxymethyl-n-heptylporphyrin (8) and hexane-1,6-diol as described above for compound (14). The yield was 74% and the product was isolated as an evaporate which could not be induced to crystallize; δ 0.80—1.14 (12 H, m of t, 7′-CH_3), 1.14—1.50 (18 H, 5′,5″,-6′-CH_2), 1.50—1.64 (12 H, m, 4′,3″,4″-CH_2), 1.64—1.84 (8 H, m, 3′-CH_2), 1.84—2.05 (2 H, m, 2″-CH_2), 2.06—2.44 (8 H, m, 2′-CH_2), 3.55, 3.59, and 3.60 (6 H, 3 H, 3 H, each s, 1,3,5,7-CH_3), 3.50—3.69 (2 H, m, 6″-CH_2), 3.80—4.19 (10 H, m, 1′,1″-CH_2), 6.19 [2 H, s, $CH_2O(CH_2)_6$], 9.89 (1 H, s, γ-*meso*-H), and 10.17 (2 H, s, β,δ-*meso*-H); *m/e* (%) 888 (20), 772 (100), 758 (50), 673 (20), 588 (10), 503 (10), and 386 (20); $\lambda_{max.}$ (peak ratio), 405 (100), 506 (8.0), 541 (5.3), 576 (3.6), and 629 nm (2.6).

meso-(6-*Bromohexyloxymethyl*)*octaethylporphyrin* (17).—The octaethylporphyrin alcohol (14) (400 mg) in methylene chloride (50 ml) was treated with carbon tetrabromide (800 mg) and triphenylphosphine (560 mg). The resulting green solution was heated under reflux for 3 h before being evaporated to dryness to give a residue which was chromatographed three times on alumina (Brockmann Grade III, elution with 25% hexane in toluene). The appropriate eluates were evaporated to give a residue which was crystallized from methylene chloride–methanol to give the *bromoalkylporphyrin* as purple needles (386 mg; 88%), m.p. 158 °C (Found: C, 70.9; H, 8.3; N, 7.8. $C_{43}H_{59}BrN_4O$ requires C, 70.95; H, 8.17; N, 7.70%), δ −3.05 (2 H, bd s, NH), 1.45—1.55 (4 H, m, 3′,4′-CH_2), 1.80—2.00 (28 H, m, CH_2-CH_3, 2′,5′-CH_2), 3.36 (2 H, t, 6′-CH_2Br), 3.93—4.20 (18 H, m, CH_2CH_3, 1′-CH_2), 6.44 [2 H, s, $CH_2O(CH_2)_6$], 9.94 (1 H, s, γ-*meso*-H), and 10.12 (2 H, s, β,δ-*meso*-H); *m/e* (%) (^{79}Br ions), 726 (35), 564 (12), 548 (57), 534 (100), and 519 (18); $\lambda_{max.}$ 404 (ε 164 000), 506 (11 200), 541 (8 300), 574 (6 500), and 628 nm (3 900).

meso-(6-*Bromohexyloxymethyl*)-1,3,5,7-*tetramethyl*-2,4,6,8-*tetra*-(*n-pentyl*)*porphyrin*.—This compound was similarly prepared from the porphyrin alcohol (15). The yield was 82%, isolated as an evaporate; δ −3.23 and −3.03 (each 1 H, s, NH), 0.97, 0.99, and 1.06 (6 H, 3 H, 3 H, each t, 5′-CH_3), 1.50—1.67 (12 H, m, 3″,4″,4′-CH_2), 1.67—1.85 (6 H, 2 H, each m, 3′-CH_2), 1.85—1.93 (2 H, m, 5″-CH_2), 1.93—2.01 (2 H, m, 2″-CH_2), 2.13—2.24 and 2.22—2.35 (2 H, 6 H, each m, 2′-CH_2), 3.38 (2 H, t, 6″-CH_2Br), 3.56, 3.61, 3.62, and 3.63 (each 3 H, s, 1,3,5,7-CH_3), 3.93—4.17 (10 H, m, 1′,1″-CH_2), 6.37 (2 H, s, $CH_2O(CH_2)_6$), 9.91 (1 H, s, γ-*meso*-H), and 10.11 (2 H, s, β,δ-*meso*-H); *m/e* (%) (^{79}Br ions), 838 (21), 660 (10), 646 (41), 589 (83), 532 (41), and 475 (75);

$\lambda_{max.}$ (peak ratio), 404 (100), 505 (7.8), 541 (5.1), 575 (3.5), 600 (1.0), and 629 nm (2.6).

Bis-[6-(meso-*octaethylporphyrinylmethoxy)hexyl*] *Disulphide* (21).—The octaethylporphyrin bromide (17) (100 mg) in tetrahydrofuran (5 ml) and absolute ethanol (5 ml) was treated with thiourea (200 mg). The mixture was heated under reflux for 3 h and then hydrolysed by addition of 10% aqueous sodium hydroxide (10 ml) for 5 min. The product immediately crystallized and was filtered off, washed with water (2 × 20 ml), and then dried *in vacuo*. The product was chromatographed on alumina (Brockmann Grade III, elution with 25% hexane in toluene) and the appropriate eluates were evaporated to dryness and the residue was crystallized from methylene chloride–hexane to afford brown crystals (89 mg, 95%), m.p. 153—154 °C (Found: C, 75.8; H, 8.85; N, 8.5. $C_{86}H_{118}N_8O_2S_2$ requires C, 75.95; H, 8.75; N, 8.24%); δ −3.05 (2 H, bd s, NH), 1.45—1.60 (8 H, m, 3′, 4′-CH_2), 1.65—1.75 (4 H, m, 5′-CH_2), 1.75—2.00 (52 H, m, CH_2CH_3), 2.64 (4 H, t, 6′-CH_2SSCH_2), 3.88—4.00 (4 H, m, 1′-CH_2), 3.95—4.20 (32 H, m, CH_2CH_3), 6.39 [4 H, s, $CH_2O(CH_2)_6$], 9.92 (2 H, s, γ-*meso*-H), and 10.10 (4 H, s, β,δ-*meso*-H); *m/e* (%), 680 (8), 564 (18), 548 (100), 534 (78), and 519 (34); though there was no firm evidence from the mass spectrum to suggest that this material is a dimer, chromatographic R_F data (the compound had a much greater R_F value than the corresponding alcohol), the ease of oxidation of thiols to give disulphides in air, and other literature results on porphyrin disulphides [7] indicate that this is so; $\lambda_{max.}$ 406 (ε 164 00), 507 (13 000), 542 (9 000), 576 (6 000), and 629 nm (4 400).

Bis-[6-(meso-1,3,5,7-*tetramethyl*-2,4,6,8-*tetra*-*n*-*pentylporphyrinylmethoxy)hexyl*] *Disulphide* (22).—This compound was prepared in 74% yield from the corresponding bromoalkylporphyrin using the procedure described above for compound (21). It was isolated as an evaporate; δ −3.28 (4 H, bd s, NH), 0.95, 0.96, and 1.02 (6 H, 3 H, 3 H, each t, 5′-CH_2), 1.43—1.64 (24 H, m, 3″,4″,4′-CH_2), 1.63—1.79 (20 H, m, 3′,5″-CH_2), 1.82—1.93 (4 H, m, 2″-CH_2), 2.00—2.12 and 2.12—2.29 (8 H, 8 H, each m, 2′-CH_2), 2.69 (4 H, t, 6″-CH_2SSCH_2), 3.45, 3.48, 3.50, and 3.51 (each 6 H, s, 1,3,5,7-CH_3), 3.80—4.00 (20 H, m, 1′,1″-CH_2), 5.98 [4 H, s, $CH_2O(CH_2)_6$], 9.81 (2 H, s, γ-*meso*-H), and 9.97 (4 H, s, β,δ-*meso*-H); *m/e* (%), 792 (6), 660 (100), 646 (68), 589 (60), 531 (28), and 475 (52); $\lambda_{max.}$ (peak ratio) 405 (100), 507 (8.3), 541 (5.4), 577 (3.8), 601 (1.1), and 629 nm (2.7).

Bis-[6-(meso-*octaethylporphyrinylmethoxy)hexyl*] *Disulphide–Iron*(III) *Chloride*.[6]—The octaethylporphyrin disulphide (21) (70 mg) in dry tetrahydrofuran (20 ml) was carefully degassed by bubbling N_2 gas through it. The solution was then added to a degassed solution of iron(II) chloride (500 mg) in dry methanol (20 ml) at 25 °C with stirring under an atmosphere of N_2. After 30 min the solution was exposed to the atmosphere and stirred for 10 min before addition of methylene chloride (50 ml); the mixture was then washed with 0.1M-HCl (3 × 100 ml). The organic phase was dried (Na_2SO_4), evaporated to dryness, and the residue was chromatographed on alumina (Brockmann Grade III, elution with 10% methylene chloride in toluene). The major band was collected, washed with 0.1M-HCl, dried (Na_2SO_4), and evaporated to dryness; the residue was then crystallized from methylene chloride–heptane to give purple-brown crystals (58 mg, 77%), m.p. 112 °C (Found: C, 67.1; H, 8.05; N, 7.3. $C_{86}H_{114}Cl_2Fe_2N_8O_2S_2$ requires C, 67.13; H, 7.47; N, 7.28%); δ (in CD_3OD–KCN), using internal DSS as calibrant, −9.10 (4 H, s, β,δ-*meso*-H), −1.90 (2 H, s, γ-*meso*-H), 1.34 and 1.60 (each 12 H, t, 1,4,5,8-CH_2CH_3), 1.49—1.70 (4 H, m, 4′-CH_2), 1.70—1.93 (8 H, m, 3′,5′-CH_2), 2.27 (4 H, t, CH_2SSCH_2), 2.38—2.51 (4 H, m, 4′-CH_2), 2.52—2.79 (24 H, m, 2,3,6,7-CH_2CH_3), 3.93 (4 H, t, 1′-CH_2), 5.98 (8 H, q, 6,7-CH_2CH_3), 7.22 and 7.47 (each 8 H, q, 1,4,5,8-CH_2CH_3), 7.92—8.50 (8 H, bd q, 2,3-CH_2CH_3), and 21.90 (4 H, s, $CH_2O(CH_2)_6$); *m/e* (%), *ca.* 1 450 (1), 733 (4), 602 (100), 587 (48), 572 (27), 558 (8), 542 (21), 527 (10), 513 (6), and 497 (8); $\lambda_{max.}$ 383 (ε 213 000), 406 (148 000), 515 (18 300), 544 (18 300), and 645 nm (9 100).

Bis-[6-(meso-1,3,5,7-*tetramethyl*-2,4,6,8-*tetra*-(*n*-*pentyl*)*porphyrinylmethoxy)hexyl*] *Disulphide–Iron*(III) *Chloride* (23).—This compound was prepared from compound (22) in 55% yield using the procedure described above. It was crystallized from methylene chloride–heptane and had m.p. 101 °C (Found: C, 69.75; H, 8.45; N, 6.6. $C_{102}H_{146}Cl_2Fe_2N_8O_2S_2$ requires C, 69.49; H, 8.35; N, 6.36%), δ (in CD_3OD–KCN, using internal DSS as calibrant) −7.95 and −7.85 (each 2 H, s, β,δ-*meso*-H), −0.79 (2 H, s, γ-*meso*-H), 0.72, 0.78, 1.15, 1.18 (each 6 H, t, 5′-CH_3), 1.44—1.56, 1.64—1.78, 1.78—1.79, and 2.01—2.60 (8 H, 8 H, 16 H, 12 H, each m, 3′,3″,-4′,4″,5″-CH_2), 2.21—2.37 and 2.41—2.60 (8 H, 12 H, each m, 2′,2″-CH_2), 2.44 (4 H, t, CH_2SSCH_2), 4.10 (4 H, t, 1″-CH_2), 6.28, 7.55, and 7.65 [each 4 H, t, 4,6,8-(1′-CH_2)], 8.25—8.75 [4 H, bd s, 2-(1′-CH_2)], 10.01 (6 H, bd s, 3-CH_3), 13.75, 14.20, and 14.35 (each 6 H, s, 1,5,7-CH_3), and 18.65 [4 H, s, $CH_2O(CH_2)_6$]; *m/e* (%), 846 (2), 714 (57), 700 (100), 643 (53), 585 (30), 529 (24), and 473 (13); $\lambda_{max.}$ 380 (ε 188 000), 407 (112 000), 515 (17 000), 541 (16 100), and 648 nm (8 000).

meso-(*Phthalimidohexyloxymethyl*)*octaethylporphyrin* (18).—Anhydrous potassium carbonate (500 mg) and phthalimide (100 mg) were stirred together in dry dimethylformamide (10 ml) for 5 min at 90 °C. A solution of octaethylporphyrin bromide (17) (20 mg) in dry dimethylformamide (2 ml) was then added and the mixture was stirred at 90 °C for 30 min. Upon addition of water (100 ml) the porphyrin was precipitated and this was taken into methylene chloride (3 × 50 ml) by extraction. The combined organic extracts were washed with water (50 ml), dried (Na_2SO_4), and evaporated to give a residue which was chromatographed twice on alumina (Brockmann Grade III, elution with methylene chloride). The appropriate eluates were evaporated and the residue was crystallized from methylene chloride–methanol to give purple crystals (22 mg, 100%), m.p. 114—115 °C (Found: C, 77.25; H, 7.95; N, 8.85. $C_{51}H_{63}N_5O_3$ requires C, 77.14; H, 7.80; N, 8.82%), δ 1.56—1.76 (4 H, m, 3′,4′-CH_2), 1.77—1.97 (28 H, m, CH_2CH_3, 2′,5′-CH_2), 3.70 (2 H, t, 6′-CH_2), 3.95—4.17 (18 H, m, CH_2CH_3, 1′-CH_2), 6.37 (2 H, s, $CH_2O(CH_2)_6$), 7.55, 7.76 (AA′BB′ 4 H, phth-H), 9.91 (1 H, s, γ-*meso*-H), 10.10 (2 H, s, β,δ-*meso*-H); *m/e* (%), 793 (17), 563 (22), 548 (100), 534 (49), and 519 (21); $\lambda_{max.}$ 404 (ε 238 000), 506 (12 700), 541 (8 500), 576 (5 600), and 628 nm (4 200).

meso-*Methyl*-1,3,5,7-*tetramethyl*-2,4,6,8-*tetra*-n-*pentylporphyrin* (24).—The *meso*-acetoxymethyl-n-pentylporphyrin (7) (46 mg) in dry 1,2-dichloroethane (40 ml) was treated with hexane-1,6-dithiol (500 mg). The mixture was then heated under reflux for 4 d, after which the solution was diluted with water (200 ml) and extracted with methylene chloride (3 × 100 ml). The extract was then washed with saturated aqueous sodium hydrogen carbonate and water, and dried (Na_2SO_4). After evaporation to dryness, the residue was chromatographed on alumina (Brockmann Grade III, elution with toluene) and then further purified by preparative thick layer chromatography (silica gel, plate

development with methylene chloride). The red band was scraped off and extracted with methylene chloride containing 2% methanol; the extract was evaporated to dryness and the residue was then crystallized from methylene chloride–methanol to give (unexpectedly, see text) the meso-*methylporphyrin* as purple crystals (27 mg, 63%), m.p. 169 °C. The same compound could also be prepared by reduction of the *meso*-acetoxymethylporphyrin with sodium borohydride in t-butyl alcohol (80%) or by reduction with tetra-n-butylammonium borohydride in 1,2-dichloroethane (87%).[1,2] The structure of the hexane-1,6-dithiol product was finally established by comparison with these rationally produced materials (Found: C, 81.8; H, 9.55; N, 8.75. $C_{45}H_{64}N_4$ requires C, 81.76; H, 9.76; N, 8.48%); δ 0.82—1.07 (12 H, m, 5′-CH_3), 1.42—1.64 (8 H, m, 4′-CH_2), 1.66—1.83 (8 H, m, 3′-CH_2), 2.09—2.37 (8 H, m, 2′-CH_2), 3.52, 3.53, 3.56, and 3.57 (each 3 H, s, 1,3,5,7-CH_3), 4.49 (3 H, s, *meso*-CH_3), 9.78 (1 H, s, γ-*meso*-H), and 9.96 (2 H, β,δ-*meso*-H); *m/e* (%), 660 (100), 647 (47), 589 (13), 532 (4), 475 (4), 417 (4), and 330 (24); $\lambda_{max.}$ 409 (ε 177 000), 508 (14 000), 542 (6 000), 578 (6 000), and 629 nm (1 400).

meso-(3-*Imidazol*-1-*ylpropyl*-1-*aminomethyl*)*octaethylporphyrin* (25).—3-Imizadol-1-ylpropylamine (530 mg) [obtained [13] by Raney nickel reduction of 2-imidazol-1-ylethyl cyanide, the adduct derived from Michael addition of imidazole to acrylonitrile] [8] was dissolved in dry tetrahydrofuran (2 ml) and then added to a suspension of sodium hydride (265 mg; 50% dispersion in oil) in dry tetrahydrofuran (8 ml). After the mixture had been heated at reflux for 15 min the supernatant liquid was syringed into a solution of *meso*-acetoxymethyloctaethylporphyrin (1) (183 mg) in dry tetrahydrofuran (10 ml); this was then heated under reflux for 30 min. The solution was then carefully poured into water (50 ml) and washed with methylene chloride (3 × 50 ml); partition into the organic phase was facilitated by addition of aqueous sodium chloride solution. The combined organic phases were washed sequentially with 1% aqueous potassium hydroxide (50 ml) and water (50 ml), and then dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed twice on alumina (Brockmann Grade V, elution with methylene chloride) and the appropriate eluates were evaporated to give a residue which was crystallized from methylene chloride–hexane to give the *porphyrin* as purple needles (130 mg, 64%), m.p. 203—204 °C (Found: C, 76.7; H, 8.6; N, 14.6. $C_{43}H_{57}N_7$ requires C, 76.86; H, 8.55; N, 14.60%), δ −2.95 (2 H, bd s, NH), 1.60—2.20 (26 H, m, CH_2CH_3, 2′-CH_2), 2.73 (2 H, t, 1′-CH_2), 3.58—4.33 (18 H, m, CH_2CH_4, 3′-CH_2), 5.98 [2 H, s, $CH_2NH(CH_2)_3$], 6.70, 6.92, and 7.38 (each 1 H, s, Im-4,5,2-H), 9.83 (1 H, s, γ-*meso*-H), and 10.04 (2 H, s, β,δ-*meso*-H); *m/e* (%) 671 (14), 548 (100), 534 (40), 520 (18), and 505 (19); $\lambda_{max.}$ 406 (ε 172 000), 507 (13 600), 541 (7 600), 575 (5 900), and 627 nm (3 000). A second fraction from the column chromatography described above was shown to be the *meso*-imidazol-1-ylmethylporphyrin (26); the identity of this material was established by comparison with an authentic synthetic sample (*vide infra*).

Iron(III) *complex*. The foregoing porphyrin was treated with iron(II) chloride as described above for the preparation of the iron(III) complex of porphyrin (21), and gave a 57% yield of red-brown crystals, m.p. >300 °C (crystallized from methylene chloride–heptane); δ (in CD_3OD–KCN, with internal DSS as calibrant), −12.49 (2 H, s, β,δ-*meso*-H), −5.71 (1 H, s, γ-*meso*-H), 1.77—1.89 (2 H, m, 2′-CH_2), 1.75, 2.05, 2.90, and 3.19 (each 6 H, t, CH_2CH_3), 3.20—3.30 (2 H, m, 1′-CH_2), 3.75—4.40 (2 H, bd m, 3′-CH_2), 5.65—6.40 (8 H, bd q, CH_2CH_3), 6.43, 6.71, and 7.11 (each 1 H, s, Im-4,5,2-H), 6.55—7.30, 7.68—8.35, 11.50—12.30 (4 H, 2 H, 2 H, each bd q, CH_2CH_3), and 22.21 [2 H, s, $CH_2NH(CH_2)_3$]; *m/e* (%), 725 (40), 602 (100), 588 (40), 573 (26), and 559 (20); $\lambda_{max.}$ 388 (ε 69 000), 409 (51 000), 548 (6 000), and 646 nm (2 400).

meso-*Imidazol*-1-*ylmethyloctaethylporphyrin* (26).—Imidazole (600 mg) was melted at 100 °C and to this was added *meso*-acetoxymethyloctaethylporphyrin (1) (60 mg). The mixture was stirred for 30 min at 100 °C and then cooled and diluted with methylene chloride (50 ml) and water (50 ml). The aqueous phase was extracted with methylene chloride (2 × 50 ml) and the combined organic phases were washed with water (3 × 50 ml), dried (Na_2SO_4), and then evaporated to dryness. The residue was chromatographed on alumina (Brockmann Grade V, elution with 25% methylene chloride in toluene) and the appropriate eluates were evaporated to dryness and the residue was crystallized from methylene chloride–hexane to give the *imidazolylporphyrin* as purple crystals (56 mg, 92%), m.p. 196—197 °C, identical with the by-product mentioned above (Found: C, 78.35; H, 7.9; N, 14.05. $C_{40}H_{50}N_6$ requires C, 78.13; H, 8.20; N, 13.67%), δ −3.04 and −2.85 (each 1 H, s, NH), 1.87 (24 H, t, CH_2CH_3), 3.68 (4 H, q, 2,3-CH_2CH_3), 4.12 (12 H, q, 1,4,5,6,7,8-CH_2CH_3), 6.95, 7.04, and 7.36 (each 1 H, s, Im-4,5,2-H), 7.49 (2 H, s, CH_2Im), 9.94 (1 H, s, γ-*meso*-H), and 10.16 (2 H, s, β,δ-*meso*-H); *m/e* (%) 614 (24), 548 (100), 534 (49), 519 (19), and 505 (22); $\lambda_{max.}$ 402 (ε 152 000), 505 (13 700), 541 (10 600), 574 (7 000), and 628 nm (5 300).

meso-*n*-*Pentyloctaethylporphyrin* (27).—1-Bromobutane (680 mg) and clean dry magnesium turnings (240 mg) were warmed in dry ether (15 ml) and reaction was initiated by addition of a little 1,2-dibromoethane. After the mixture had been heated under reflux for 15 min, a sample (5 ml) of the Grignard solution was syringed into a solution of *meso*-acetoxymethyloctaethylporphyrin (1) (60 mg) in dry tetrahydrofuran (10 ml) at 25 °C. The porphyrinic solution immediately became bright red in colour and was quenched by addition of water (20 ml). The porphyrin was extracted into methylene chloride (150 ml) which was washed with water (2 × 50 ml), dried (Na_2SO_4), and evaporated to dryness. After preparative thick layer chromatography (silica gel, development with 2% ethyl acetate in toluene) and crystallization of the appropriate extract from methylene chloride–hexane, the *product* was obtained as purple crystals (38 mg, 64%), m.p. 180—181 °C (Found: C, 81.23; H, 9.4; N, 9.1. $C_{41}H_{56}N_4$ requires C, 81.41; H, 9.33; N, 9.26%), δ −2.80 (2 H, bd s, NH), 0.83 (3 H, t, 5′-CH_3), 1.23—1.43 (2 H, m, 4′-CH_2), 1.45—1.64 (2 H, m, 3′-CH_2), 1.76—1.98 (24 H, m, CH_2CH_3), 3.92—4.18 (18 H, m, CH_2CH_3, 2′-CH_2), 5.05 (2 H, t, 1′-CH_2), 9.80 (1 H, s, γ-*meso*-H), and 10.04 (2 H, s, β,δ-*meso*-H); *m/e* (%), 604 (100), 548 (62), 534 (23), 519 (23), 504 (19); $\lambda_{max.}$ 409 (ε 178 000), 508 (13 600), 542 (5 400), 578 (5 400), and 628 nm (1 300).

This research was supported by grants from the National Science Foundation (CHE-78-2557) and the National Institutes of Health (HL 22252).

[1/424 *Received*, 16*th March*, 1981]

REFERENCES

[1] K. M. Smith, G. M. F. Bisset, and M. J. Bushell, *Bio-org. Chem.*, 1980, **9**, 1.
[2] M. J. Bushell, B. Evans, G. W. Kenner, and K. M. Smith, *Heterocycles*, 1977, **7**, 67.

[3] K. M. Smith and G. M. F. Bisset, *J. Org. Chem.*, 1979, **44**, 2077.
[4] G. V. Ponomarev, *Khim. Geterotsikl. Soedin.*, 1977, 90.
[5] For discussion of the requirements for a successful cytochrome P450 model see, J. O. Stern and J. Peisach, *J. Biol. Chem.*, 1974, **249**, 7495; J. P. Collman, T. N. Sorrell, and B. M. Hoffman, *J. Am. Chem. Soc.*, 1975, **97**, 913; C. K. Chang and D. Dolphin, *J. Am. Chem. Soc.*, 1975, **97**, 5948; 1976, **98**, 1607; S. C. Tang, S. Koch, G. C. Papaefthymiou, S. Foner, R. B. Frankel, J. A. Ibers, and R. H. Holm, *J. Am. Chem. Soc.*, 1976, **98**, 2414.
[6] K. C. Langry, Ph.D. Thesis, University of California, Davis, 1981.
[7] T. G. Traylor and T. Mincey, *Acta Biol. Med. Germ.*, 1979, **38**, 351.
[8] J. Geibel, J. Cannon, D. Campbell, and T. G. Traylor, *J. Am. Chem. Soc.*, 1978, **100**, 3575.
[9] T. G. Traylor, work in progress.
[10] W. R. Scheidt in 'Porphyrin Chemistry Advances,' ed. F. R. Longo, Ann Arbor Science Press, Ann Arbor, 1979, p. 225.
[11] G. V. Ponomarev, *Khim. Geterotsikl. Soedin.*, 1980, 943.
[12] R. J. Abraham, S. C. M. Fell, H. Pearson, and K. M. Smith, *Tetrahedron*, 1979, **35**, 1759.
[13] T. J. Schwan, *J. Heterocycl. Chem.*, 1967, **4**, 633.