Syntheses of Monofunctional Porphyrinyl Peptides containing Glycine and Leucine

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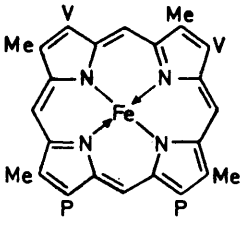
4,6,8-Triethyl-2-(2-methoxycarbonylethyl)-1,3,5,7-tetramethylporphyrin is synthesised using the *a,c*-biladiene route. Activated derivatives of the corresponding porphyrin free carboxylic acid were coupled with glycine ethyl ester, and the resulting porphyrinyl-glycine ester was hydrolysed and coupled with L-leucine methyl ester to give a porphyrinyl dipeptide; an isomer of this dipeptide was prepared by direct coupling of the activated porphyrin with L-leucyl-glycine methyl ester. A porphyrinyl tripeptide was also prepared in low yield by coupling the porphyrinyl-glycine with L-leucyl-glycine methyl ester. Attempts to synthesise porphyrinyl peptides containing unprotected histidine (which would have yielded haem protein models) were largely unsuccessful. Mass-spectral fragmentation patterns for the synthetic porphyrinyl peptides are reported.

SIGNIFICANT amounts of recent research have been devoted to understanding the mode of action of various haem proteins.[1] Of central importance is the way in which the polypeptide modifies the function of these haem proteins such that with (usually) the same prosthetic group [*i.e.* haem, iron(II) protoporphyrin-IX, (1)] the composite of haem and polypeptide can uniquely accomplish the various diverse functions associated with the haemoglobins, myoglobins, cytochromes, catalases, or peroxidases. In this paper we describe preliminary studies of a general approach to the synthesis of porphyrinyl peptides ultimately to be used as models for the



(1)

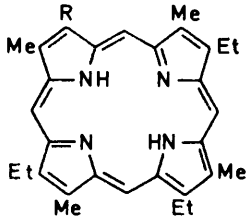
V = $CH{=}CH_2$

P = $CH_2CH_2CO_2H$

haem protein systems. Our approach involves stepwise coupling of individual amino-acids and peptides to a model monofunctionalised porphyrin.

Several examples of attachment of amino-acid residues to difunctional derivatives of natural porphyrins have been reported. For example, Warme and Hager [2] synthesised histidyl and methionyl mesohaemins, whereas van der Heijden *et al.*[3] coupled histidine and histidine dipeptides to protohaemin. More recently, Radhyukin *et al.*[4] prepared histidine-containing di- and tri-peptides by amidation of one of the two propionic side-chains in protohaemin.

The porphyrin chosen as the substrate in our studies was the monofunctional ester derivative (2) of aetioporphyrin-I. This choice was influenced by its ease of synthesis from simple monopyrrole precursors using Johnson's *a,c*-biladiene route.[5] Thus, 'brominated kryptopyrromethene-I'[6] (3) was synthesised from t-butyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (4) *via*



(2) R = $CH_2CH_2CO_2Me$

(11) R = $CH_2CH_2CO_2H$

(12) R = CH_2CH_2CO-N 

(13) R = CH_2CH_2CO–Gly–OEt

(14) R = CH_2CH_2CO–Leu–Gly–OMe

(15) R = CH_2CH_2CO–Gly–OH

(16) R = CH_2CH_2CO–Gly–N 

(17) R = CH_2CH_2CO–Gly–Leu–OMe

(18) R = CH_2CH_2 CO–Gly–Leu–Gly–OMe

(19) R = CH_2CH_2 CO–His–OMe

(20) R = CH_2CH_2 CO–Leu–Gly–OH

(5).[7] The second pyrromethene half, (6), was obtained by hydrogenolysis of the formylpyrrole benzyl ester (7) to give (8) which, as the semicarbazone (9), was treated with pyrrole (4) in 48% HBr in methanol.[8] The pyrromethenes (3) and (6) were coupled in a Friedel–Crafts reaction catalysed by tin(IV) chloride,[5] and gave a 97% yield of the *a,c*-biladiene dihydrobromide (10) after treatment with HBr in methanol. This material was cyclised directly by heating in *o*-dichlorobenzene to give a 46% yield of the required aetioporphyrin-I

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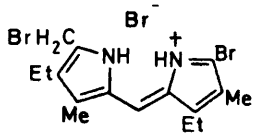
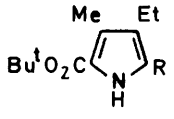
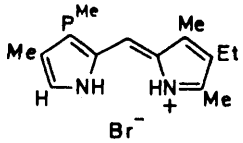
derivative (2). Fischer [9] had previously synthesised this same porphyrin in 3% yield using succinic acid fusion of two pyrromethene hydrobromides. Hydrolysis of the propionic ester was efficiently accomplished using potassium hydroxide in methanol, and afforded



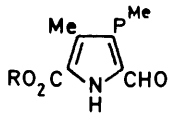
(3)



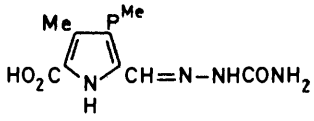
(4) R = Me
(5) R = CH_2Br



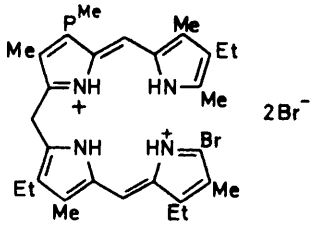
(6)



(7) R = CH_2Ph
(8) R = H



(9)



(10)

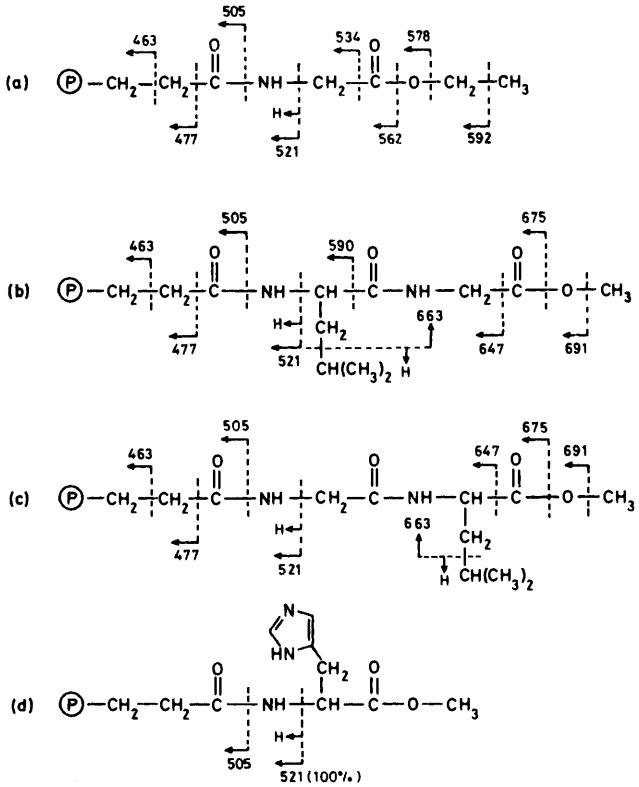
P^{Me} = $CH_2CH_2CO_2Me$

the porphyrincarboxylic acid (11) in virtually quantitative yield.

Coupling Reactions with Amino-acids and Peptides.— In initial experiments the porphyrincarboxylic acid (11) was activated using either the acid chloride (produced using oxalyl chloride) or the pivaloyl mixed anhydride (from pivaloyl chloride). These methods were eventually superseded by use of the imidazolide (12), obtained by treatment of (11) with *NN'*-carbonyldi-imidazole. This imidazolide was considerably less stable than the analogues obtained [10] from porphyrin nuclear carboxylic acids (which could even be chromatographed), but formation of (12) could be readily monitored by t.l.c. sampling of the reaction mixture.

With glycine ethyl ester in tetrahydrofuran, the imidazolide (12) gave a 92% yield of the porphyrinyl-glycine ethyl ester (13); by way of the acid chloride the best yield was only 70%. Treatment of the imidazolide (12) with L-leucyl-glycine methyl ester gave an 82% yield of the porphyrinyl-L-leucyl-glycine methyl ester (14). On the other hand, hydrolysis of the porphyrinyl-glycine ester (13) gave the carboxylic acid (15) which was successfully coupled, as the imidazolide (16), with L-leucine methyl ester hydrochloride to give a 60% yield of the porphyrinyl-glycyl-L-leucine methyl ester (17).

The stepwise procedure was less efficient when attempts were made to synthesise a porphyrinyl tripeptide. Thus, treatment of the imidazolide (16) with L-leucyl-glycine methyl ester gave only a 9% yield of the porphyrinyl tripeptide (18) which was not fully characterised. Similarly, attempts to prepare the porphyrinyl-histidine ester (19) gave only a 5% yield of incompletely characterised material. Molecular models indicated that the ideal peptide length for an imidazole-containing model would have three amino-acids, with the histidine at the terminus. However, attempts to couple the porphyrinyl-L-leucyl-glycine (20) with unprotected histidine methyl ester were completely unsuccessful, as were



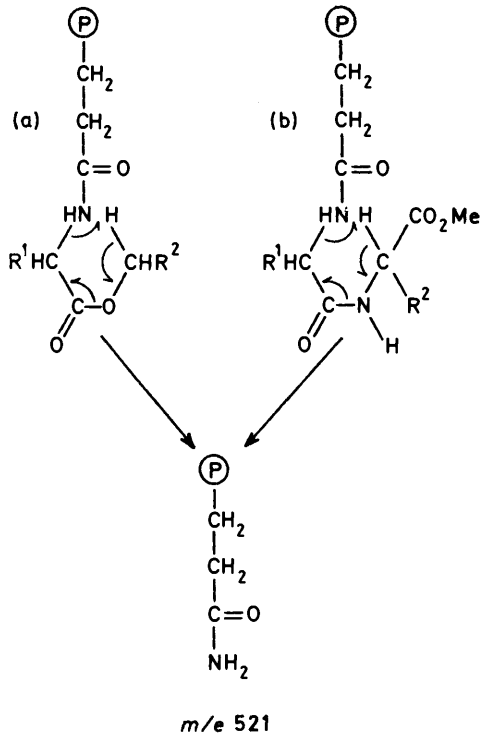
SCHEME 1 Mass spectral fragmentation patterns for porphyrinyl peptides, (a) compound (13), M^+ 607 (100%); (b) compound (14), M^+ 706 (100%); (c) compound (17), M^+ 706 (100%); and (d) compound (19), M^+ 673 (2%)

reactions involving the imidazolide (12) and L-leucyl-glycyl-L-histidine methyl ester or the imidazolide (16) with L-histidine methyl ester. It seems likely that controlled stepwise syntheses of histidine-containing

porphyrinyl peptides will require use of amino-acids or peptides in which the histidine imidazole is *N*-protected. *N*-Benzyl protection was used in a porphyrinyl peptide synthesised by Radhyukin *et al.*[4]

Mass Spectra of Porphyrinyl Peptides.—The mass-spectral characteristics of porphyrin systems have been discussed in detail elsewhere.[11] A major feature of such spectra is that, since the porphyrin nucleus fails to undergo any cleavage under normal circumstances, the fragmentations observed are almost solely those associated with the peripheral substituents. It therefore seemed that porphyrinyl-peptides should display fragmentation pathways characteristic only of the peptide portion, and such was the case.

Major fragment ions observed in the porphyrinyl peptides (13), (14), (17), and (19) are indicated in Scheme 1. All compounds showed molecular ions which, for (13), (14), and (17), were the base (100%) peaks. Ions at *m/e* 505 and 521 were common to all compounds, the latter arising presumably from McLafferty rearrangements of the type shown in Scheme 2. In addition to the



SCHEME 2 Mass spectral McLafferty rearrangement to produce ions at *m/e* 521 for: (a) compound (13), where R^1 = H, R^2 = Me, and compound (19), where R^1 = Im·CH_2, R^2 = H; and (b) compound (14), where R^1 = Bu^i, R^2 = H, and compound (17) where R^1 = H, R^2 = Bu^i

fragments shown in Scheme 1, compound (13) possessed a peak at *m/e* 561 due to loss of ethanol (Por-CONHCH=C=O$^+$) and losses of methanol were observed for compound (14) at *m/e* 674 (Por-CO-Leu-NHCH=C=O$^+$) and for compound (17) at *m/e* 674 [Por-CO-Gly-NHC(Bu^i)=C=O$^+$].

EXPERIMENTAL

M.p.s were measured on a microscopic hot-stage apparatus. Reactions were monitored by t.l.c. using glass slides coated with Merck GF 254 silica gel. All reactions were performed under an atmosphere of nitrogen, in the dry, and usually also in the dark (aluminium foil). Electronic absorption spectra were measured using a Unicam SP-800 spectrophotometer, usually on solutions in methylene chloride. Proton n.m.r. spectra were measured on a Varian XL-100 instrument, usually in deuteriochloroform as solvent with tetramethylsilane as internal standard. Mass spectra (direct insertion probe, 70 eV, 50 μA, source temperature *ca.* 200 °C) were measured using an AEI MS-9 or AEI MS-12 instrument.

Semicarbazone (9) *of 5-Formyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylic Acid* (8).—Benzyl 2-formyl-3-(2-methoxycarbonylethyl)-4-methylpyrrole-5-carboxylate [12] (7) (16 g) in tetrahydrofuran (400 ml) and triethylamine (1 ml) was hydrogenated over 10% palladium–charcoal (1.6 g) at room temperature and atmospheric pressure until uptake of hydrogen ceased. The catalyst was filtered off on Celite and the filtrate was evaporated to dryness at room temperature to give a residue of 5-formyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylic acid (8) which was used immediately. Meanwhile, semicarbazide hydrochloride (16 g) and sodium acetate (27 g) were dissolved with warming in methanol (100 ml) and water (50 ml). After cooling, a fine white precipitate of sodium chloride was filtered off on Celite. The 2-formylpyrrolecarboxylic acid (7) in warm methanol (20 ml) was then added to the solution of semicarbazide acetate and the mixture was set aside for 2 min. Addition of cold water produced a yellow flocculent precipitate of the semicarbazone, which was filtered off, washed with water, methanol, and then dried in air (9.7 g, 76%). A sample recrystallised from acetic acid had m.p. 213 °C (lit.,[8] 213 °C), τ([$^2H_6$]DMSO) 0.00, 2.20, and 3.40 (2 H, C*H*=NN*H*CONH_2), 6.40 (3 H, OMe), 7.35 (4 H, m, CH_2CH_2CO), and 7.75 (3 H, Me), $\nu_{max.}$ (Nujol) 1 650, 1 690, and 1 720 cm^{-1}.

4′-Ethyl-3-(2-methoxycarbonylethyl)-3′,4,5′-trimethylpyrromethene Hydrobromide (6).—The semicarbazone (9) (12 g) and t-butyl 3-ethyl-2,4-dimethylpyrrole-5-carboxylate [13] (9.2 g) in 48% (w/v) hydrobromic acid (12 ml) and methanol (250 ml) were heated under reflux for 5 h. The dark green solution was cooled, evaporated to dryness, and the residue was dissolved in methylene chloride leaving light brown crystals of semicarbazide hydrobromide. The methylene chloride solution was washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was crystallised from methanol [m.p. 118 °C (lit.,[8] 118—119 °C)] or else used directly (6.7 g, 41%), τ 2.52 (d, 5-H), 2.62 (methine), 6.42 (3 H, OMe), 6.98 (2 H, t) and 7.5 (2 H, m) (CH_2CH_2CO), 7.5 (2 H, m) and 8.90 (3 H, t) (CH_2CH_3), and 7.30 (3 H), 7.64 (3 H), and 7.92 (3 H) (3 × Me).

4,6,8-Triethyl-2-(2-methoxycarbonylethyl)-1,3,5,7-tetramethylporphyrin (2).—To an intimately ground mixture of 5-bromo-5′-bromomethyl-3,4′-diethyl-3′,4-dimethylpyrromethene hydrobromide [7] (3) (4.8 g) and 4′-ethyl-3-(2-methoxycarbonylethyl)-3′,4,5′-trimethylpyrromethene hydrobromide (6) (3.8 g) in methylene chloride (500 ml) was added distilled tin(IV) chloride (10 ml) and the solution was stirred for 4 h at room temperature. The mixture was evaporated to dryness and the residue was dissolved in chloroform (400 ml) and washed three times with an aqueous

solution containing equal volumes of 48% (w/v) HBr, methanol, and water. The chloroform layer was separated, dried ($MgSO_4$), filtered, and evaporated to dryness to give a brown powder of the *a,c*-biladiene dihydrobromide (10) (7.6 g, 97%). This was added to refluxing *o*-dichlorobenzene (500 ml) and heating was continued for a further 15 min. The mixture was cooled and the *o*-dichlorobenzene was distilled off under vacuum. The residue was dissolved in 5% (v/v) concentrated sulphuric acid in methanol (100 ml) and set aside for 3 h. Chloroform (50 ml) was then added and the organic layer was washed with water until neutral, then separated, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was chromatographed (Brockmann Grade III alumina, elution with methylene chloride) and the red eluates were evaporated to dryness and the residue was crystallised from methylene chloride–methanol to give purple needles (2.3 g, 46%), m.p. 239—240 °C (lit.,[9] 237 °C) (Found: C, 75.9; H, 7.5; N, 10.2. Calc. for $C_{34}H_{40}N_4O_2$: C, 76.1; H, 7.5; N, 10.4%), τ 0.02 (4 H, *meso*-H), 5.74 (2 H, t) and 6.75 (2 H, t) (CH_2CH_2CO), 6.04 (6 H, m), and 8.24 (9 H, t) (3 × CH_2CH_3), 6.42 (3 H, OMe), and 6.50 (12 H, 4 × Me), $\lambda_{max.}$ 396 (ε 137 000), 497 (11 000), 531 (8 000), 566 (5 000), and 622 nm (3 000), $\lambda_{max.}$ (CH_2Cl_2 + 5% CF_3CO_2H) 403 (ε 368 000), 547 (14 500), and 592 nm (6 000); *m/e* 536 (100%), 521 (6), 477 (31), 463 (42), and 449 (15).

2-(2-*Carboxyethyl*)-4,6,8-*triethyl*-1,3,5,7-*tetramethylporphyrin* (11).—To 4,6,8-triethyl-2-(2-methoxycarbonylethyl)-1,3,5,7-tetramethylporphyrin (2) (500 mg) in pyridine (2 ml) was added a solution of 10% (w/v) potassium hydroxide in methanol (100 ml), and the mixture was heated under reflux for 3 h before being cooled, neutralised with an excess of citric acid solution, and then the porphyrin extracted into chloroform (100 ml). This was washed with water (× 3), dried ($MgSO_4$), filtered, and then evaporated to dryness. The residue was taken into tetrahydrofuran and crystallised by addition of benzene to give the *porphyrin* (446 mg, 96%), m.p. >325 °C (Found: C, 75.7; H, 7.4; N, 10.7. $C_{33}H_{38}N_4O_2$ requires C, 75.8; H, 7.3; N, 10.7%).

[2-(2-*Carbonylethyl*)-4,6,8-*triethyl*-1,3,5,7-*tetramethylporphyrinyl*]-*glycine Ethyl Ester* (13).—2-(2-Carboxyethyl)-4,6,8-triethyl-1,3,5,7-tetramethylporphyrin (522 mg) and *NN'*-carbonyldi-imidazole (243 mg) were stirred in refluxing tetrahydrofuran (10 ml) for 2 h. Glycine ethyl ester hydrochloride (420 mg) in tetrahydrofuran (7 ml) and triethylamine (2 ml) was stirred for 2 h before addition to the porphyrinyl imidazolide solution. The mixture was then heated under reflux for 36 h. After evaporation to dryness the residue was dissolved in chloroform which was then washed twice with water, dried ($MgSO_4$), filtered, and then evaporated to dryness. The residue was then dissolved in methylene chloride and chromatographed (Brockmann Grade III alumina, elution with methylene chloride) and the red eluates were evaporated to dryness. Crystallisation from methylene chloride gave flat red plates (561 mg, 92%), m.p. 220—221 °C (Found: C, 72.9; H, 7.4; N, 11.3. $C_{37}H_{45}N_5O_3$ requires C, 73.1; H, 7.5; N, 11.5%), τ 0.11 (2 H), 0.15, and 0.27 (*meso*-H), 5.95 (2 H, m, CONHCH_2CO), 6.14 (2 H, m), 7.43 (2 H, t), 6.1 (2 H, m), and 9.03 (3 H, t) (CH_2CH_2CONHCH$_2$CO$_2$$CH_2CH_3$), 6.14 (6 H, m) and 8.22 (9 H, t) (3 × CH_2CH_3), 6.55 (9 H) and 6.69 (3 H) (4 × Me), $\lambda_{max.}$ 397 (ε 153 000), 497 (12 000), 531 (8 000), 566 (5 000), and 622 nm (4 000), $\lambda_{max.}$ (CH_2Cl_2 + 5% CF_3CO_2H) 403 (ε 432 000), 547 (15 000), and 592 nm (5 000); *m/e* 607 (100%), 592 (7), 578 (2), 562 (4), 561 (5), 534 (4), 521 (2), 505 (3), 477 (20), 463 (40), and 449 (16)

[2-(2-*Carbonylethyl*)-4,6,8-*triethyl*-1,3,5,7-*tetramethylporphyrinyl*]-L-*leucyl-glycine Methyl Ester* (14).—2-(2-Carboxyethyl)-4,6,8-triethyl-1,3,5,7-tetramethylporphyrin (11) (156 mg) and *NN'*-carbonyldi-imidazole (73 mg) in tetrahydrofuran (3 ml) and benzene (0.1 ml) were heated under reflux for 1 h. Meanwhile, *N*-benzyloxycarbonyl-L-leucylglycine methyl ester[8] (1.01 g) in dioxan (20 ml) and a solution of 5 mmol HCl per ml of dioxan (1.5 ml) was hydrogenated over 10% palladium–charcoal (100 mg) at room temperature and atmospheric pressure until hydrogen uptake had ceased. The catalyst was filtered off on Celite, the filtrate was evaporated to dryness, and the residue was dissolved in tetrahydrofuran (12 ml) to give a solution of 0.25 mmol of L-leucyl-glycine methyl ester hydrochloride per ml of tetrahydrofuran. This solution (6 ml) was then added to the refluxing solution, followed by an excess of triethylamine (1.0 ml), and the mixture was heated under reflux for a further 48 h. After evaporation to dryness the residue was dissolved in chloroform, washed twice with water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed (Brockmann Grade V alumina, elution with 10% acetone in methylene chloride) and the red eluates were evaporated and recrystallised from methylene chloride–methanol to give a purple amorphous *powder* (172 mg, 82%), m.p. 174—176 °C (Found: C, 71.2; H, 7.9; N, 11.9. $C_{42}H_{54}N_6O_4$ requires C, 71.4; H, 7.7; N, 11.9%), τ(CF_3CO_2H) −0.03 (1 H) and 0.02 (3 H) (*meso*-H), 5.37 (2 H, m) and 6.79 (2 H, m) (CH_2CH_2CO), 5.83 (2 H, m, NHCH_2CO), 6.19 (3 H, OMe), 6.27 (12 H, 4 × Me), 5.83 (6 H, m) and 8.18 (9 H, t) (3 × CH_2CH_3), and 9.09 (6 H, d, CHMe_2), $\lambda_{max.}$ 397 (ε 163 000), 497 (12 000), 531 (8 000), and 566 nm (6 000), $\lambda_{max.}$ (CH_2Cl_2 + 5% CF_3CO_2H) 400 (ε 424 000), 546 (15 000), and 592 nm (5 000); *m/e* 706 (100%), 691 (4), 675 (3), 674 (4), 663 (8), 650 (5), 647 (2), 590 (14), 521 (11), 505 (6), 477 (31), and 463 (40); amino-acid analysis: Gly 1.01, Leu 0.99.

[2-(2-*Carbonylethyl*)-4,6,8-*triethyl*-1,3,5,7-*tetramethylporphyrinyl*]-*glycyl*-L-*leucine Methyl Ester* (17).—[2-(2-Carbonylethyl)-4,6,8-triethyl-1,3,5,7-tetramethylporphyrinyl]-glycine methyl ester (13) (490 mg) in tetrahydrofuran (100 ml) and 0.1M-aqueous sodium hydroxide (25 ml) was stirred at room temperature during 48 h. An excess of citric acid solution was then added and the product was extracted with chloroform. The chloroform layer was separated, washed twice with water, dried ($MgSO_4$), filtered, and evaporated to dryness, and the residue was recrystallised from tetrahydrofuran–n-hexane to give [2-(2-carbonylethyl)-4,6,8-trimethyl-1,3,5,7-tetramethylporphyrinyl]-glycine (15) in quantitative yield. A portion of this (29 mg) was heated under reflux in tetrahydrofuran (2 ml) with *NN'*-carbonyldi-imidazole (10 mg) during 1 h. L-Leucine methyl ester hydrochloride (27 mg) in tetrahydrofuran (1 ml) and di-isopropylethylamine (0.026 ml) was added to the refluxing solution and the mixture was then stirred during 24 h at room temperature. It was then evaporated to dryness, dissolved in chloroform, washed with water, dried ($MgSO_4$), and evaporated again to dryness to give a residue which was chromatographed (Brockmann Grade III alumina, elution with methylene chloride). The red eluates were evaporated and the residue was crystallised from methylene chloride–methanol to give a purple amorphous powder (20 mg; 60%), m.p. 192—194 °C (Found: C, 71.7; H, 7.6; N, 11.7. $C_{42}H_{54}O_4N_6$ requires C, 71.4; H, 7.7; N, 11.9%), $\lambda_{max.}$ 397 (ε 149 000), 497 (12 000), 531

(8 000), 567 (5 000), and 622 nm (4 000), $\lambda_{max.}$ (CH_2Cl_2 + 5% CF_3CO_2H), 402 (ε 426 000), 548 (14 000), and 592 nm (5 000); *m/e* 706 (100%), 691 (4), 675 (2), 674 (2), 663 (16), 650 (4), 647 (2), 521 (85), 505 (9), 477 (40), and 463 (66); amino-acid analysis: Gly 1.06, Leu 1.00.

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