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Synthesis of the Tricarboxylic Porphyrin Enzymically Formed from Coproporphyrinogen IV

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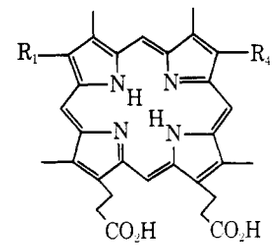
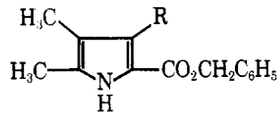
The synthesis of 1-vinyl-4,6,7-(β-methoxycarbonylethyl)-2,3,5,8-tetramethylporphyrin (**3**) was achieved; the product was identical with the tricarboxylic porphyrin isolated by the incubation of duck blood hemolysate with coproporphyrinogen IV. The precursor benzyl 2,3-dimethyl-4-(β-benzyloxycarbonylmethyl)-5-pyrrolecarboxylate was obtained by reductive C-methylation of the β-free pyrrole. It was reduced to the corresponding β-hydroxyethylpyrrole, which was transformed into the corresponding benzyl ester of the β-chloroethylpyrrole. The 2-acetoxymethyl derivative of the latter was condensed with the benzyl 4-methyl-3-(β-methoxycarbonylmethyl)-2-pyrrolecarboxylate and afforded the 5,5′-dibenzyloxycarbonyldipyrrylmethane. The latter was converted by hydrogenolysis into the corresponding 5,5′-dicarboxydipyrrylmethane, which was condensed with the 5,5′-diformyldipyrrylmethane **20** to afford 1-(β-chloroethyl)-4,6,7-(β-methoxycarbonylethyl)-2,3,5,8-tetramethylporphyrin (**19**). Treatment of the latter with potassium *tert*-butoxide afforded the tricarboxylic acid porphyrin **3** (as its trimethyl ester). The porphyrin can be distinguished from harderoporphyrin and from isoharderoporphyrin by its visible and NMR spectra.

We have recently shown[1] that coproporphyrinogen IV—the metabolically active hexahydro form of coproporphyrin IV (**1**)—was transformed by duck blood erythrocytes into a tricarboxylic acid porphyrin which was the main reaction product, and into a protoporphyrin isomeric with the natural protoporphyrin IX. The enzymatic transformation took place in high yields, higher even than the oxidative decarboxylation of the natural substrate coproporphyrinogen III to protoporphyrin IX. These results were at variance with previous results,[2] which reported that coproporphyrinogen IV underwent oxidative decarboxylation only one-tenth as fast as the natural isomer III, and that the reaction took place only to a slight extent.[3] The efficient enzymatic transformation of coproporphyrinogen IV into its reaction products added a new complexity to the studies on type III porphyrin biosynthesis.[4] These results found a prompt confirmation when the enzymatic reaction was carried out with chicken hemolysates,[5] and with beef liver mitochondria.[6] From biosynthetic considerations we reasoned that the protoporphyrin formed by the oxidative decarboxylation of coproporphyrinogen IV must be protoporphyrin XIII (**2**).[7] Jackson independently reached the same conclusion, and confirmed it by comparing the obtained product (as its dimethyl ester) with a synthetic sample of protoporphyrin XIII dimethyl ester.[5] Battersby lent support to this result by a study of the lanthanide shift of the meso protons in the NMR spectrum of the protoporphyrin isolated from beef liver mitochondria.[6] We now report the synthesis of the trimethyl ester of the tricarboxylic porphyrin **3**, which was found to be identical with the tricarboxylic trimethyl ester obtained by the esterification of the major reaction product formed during the enzymatic oxidation.[1]

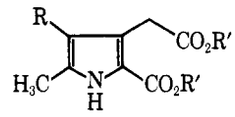


1, $R_1 = R_4 = CH_2CH_2CO_2H$
2, $R_1 = R_4 = CH{=}CH_2$
3, $R_1 = CH{=}CH_2$; $R_4 = CH_2CH_2CO_2H$
19, $R_1 = CH_2CH_2Cl$; $R_4 = CH_2CH_2CO_2H$ (trimethyl ester)

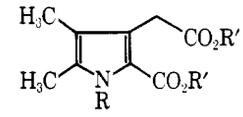
The visible absorption spectrum of the natural compound and its chromatographic mobility,[1] as well as biosynthetic considerations, suggested that **3** was its most probable structure. The synthetic sequence developed by Kenner and Jackson[8] to obtain vinylporphyrins—through β-chloroethylpyrroles—was adopted to prepare the synthetic precursors of ring A. This in turn required an efficient synthesis of pyrrole **4**. In our first attempts we made use of the Fischer–Fink method,[9] which was used[10] to prepare benzyl 2,3-dimethyl-5-pyrrolecarboxylate (**5a**)—a possible synthetic precursor of **4**—by condensation of (α-hydroxymethylenethyl) methyl ketone with the benzyl ester of 2-oximinoacetoacetate. However, the main reaction product was found to be **6a** (see also ref 11) and the purification of **5a** proved difficult. Hence the diethyl ester **5** was chosen as a starting product, and it was submitted to a reductive methylation with paraformaldehyde and hydriodic acid.[12] The unprotected NH group was found to be less reactive than the β carbon, and **6** was obtained in



4, R = $CH_2CO_2CH_2C_6H_5$
5a, R = H
6a, R = CH_3



5, R = H; R′ = C_2H_5
6, R = CH_3; R′ = C_2H_5
8, R = H; R′ = $CH_2C_6H_5$
9, R = H; R′ = H
11, R = CH_3; R′ = H



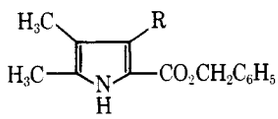
7, R = CH_3; R′ = C_2H_5
10, R = CH_2OH; R′ = $CH_2C_6H_5$

good yield. Only a small amount of the trimethyl derivative **7** was obtained, which could be easily separated from **6**.

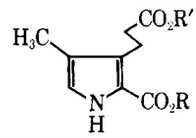
The dibenzyl ester **8** was then prepared by saponification of the diethyl ester **5** to the diacid **9**, followed by treatment of the latter with α-diazotoluene. Reductive methylation of **8** afforded the dibenzyl ester **4**, which was separated from a small amount of its *N*-hydroxymethyl derivative **10**. The dibenzyl ester **4** was also prepared from the diethyl ester **6** by saponification to **11**, followed by esterification of **11** with α-diazotoluene.

The dimethylpyrrole **4** was reduced with diborane,[8] and was transformed into the β-hydroxyethylpyrrole **12** in 83% yield; and by treatment of **12** with thionyl chloride the β-chloroethylpyrrole **13** was obtained.

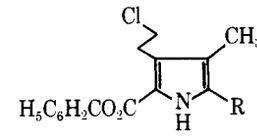
In a first attempt the benzyl ester was cleaved by hydrogenolysis, and the resulting acid **21** (65%) was treated with trifluoroacetic acid to give the 5,5′-free dipyrrylmethane. After an alkaline wash it was condensed with **20** in methylene chloride in the presence of *p*-toluenesulfonic acid.[8] An inseparable mixture of porphyrins was obtained. Hence, the dipyrrylmethane **18** was first treated with trifluoroacetic acid, and the resulting monobenzyl ester (87%) was transformed into its acid by hydrogenolysis and then condensed with **20** as mentioned above. Again a mixture of porphyrins was obtained; it was obvious that a randomization took place during the condensation process. The synthesis was then directed toward the preparation of the 5,5′-dibenzylcarbonyldipyrrylmethane **22**, which could be transformed into a 5,5′-dicarboxydipyrrylmethane **23**. The usefulness of this type of derivatives for the synthesis of uroporphyrins had already been noted.[14]



12, R = CH_2CH_2OH
13, R = CH_2CH_2Cl



17, R = $C(CH_3)_3$; R′ = C_2H_5
24, R = R′ = H
25, R = R′ = $CH_2C_6H_5$
26, R = $CH_2C_6H_5$; R′ = CH_3

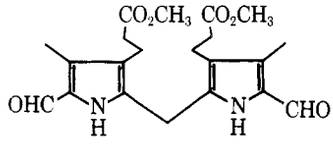


14, R = CH_2OOCCH_3
15, R = CHO
16, R = CH_2Cl

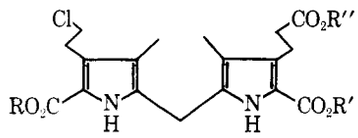
When **13** was treated with 1 equiv of lead tetraacetate in acetic acid to prepare the α-acetoxymethylpyrrole **14**, the latter was obtained in only 11% yield, since the major product (36%) was the aldehyde **15**. The pyrrole **13** was then transformed into its α-chloromethyl derivative **16** by treatment with sulfuryl chloride in carbon tetrachloride; and **16** was transformed into the desired α-acetoxymethyl **14** by treatment with sodium acetate in acetic acid.

The condensation of **14** and of the known[13] *tert*-butyloxycarbonylpyrrole **17** was carried out in acetic acid–*p*-toluenesulfonic acid,[8] and the dipyrrylmethane **18** was obtained (47%).

To prepare the porphyrin **19** the cleavage of the 5,5′ protecting groups of **18** was required in order to achieve its condensation with the known diformylpyrrylmethane **20**.[8]



20



18, R = $CH_2C_6H_5$; R′ = $C(CH_3)_3$; R″ = C_2H_5
21, R = H; R′ = $C(CH_3)_3$; R″ = C_2H_5
22, R = R′ = $CH_2C_6H_5$; R″ = CH_3
23, R = R′ = H; R″ = CH_3

The pyrrole **17** was saponified to the diacid **24**; the latter was treated with α-diazotoluene to afford the dibenzyl ester **25**, which was in turn transesterified with methanol–20% sulfuric acid.[14] The obtained methyl benzyl ester **26** was condensed with the acetate **14** and the dipyrrylmethane **22** was thus prepared (70%). Hydrogenolysis of **22** in acetic acid over Pd/C gave the diacid **23**, which was condensed with the diformyldipyrrylmethane **20** with the usual technique.[8,14] TLC analysis of the reaction mixture indicated the presence of a main porphyrin, which after isolation was found to be **19**. Vinylation of the β-chloroethyl side chain with potassium *tert*-butoxide gave a porphyrin in 65% yield which proved to be **3** (isolated as trimethyl ester). Its visible and NMR spectra were identical with those of the natural product, and different in several features from those of harderoporphyrin and isoharderoporphyrin.[15] A sample of the synthetic ester **3** was hydrolyzed to the triacid; the latter was reduced to its porphyrinogen, which was then incubated with duck blood hemolysate as described elsewhere.[1] It was transformed into protoporphyrin XIII at a rate similar to that of protoporphyrin XIII formation from coproporphyrinogen IV. Hence the rate-limiting step in the transformation of coproporphyrinogen IV into protoporphyrinogen XIII seems to be the decarboxylation of the tricarboxylic acid intermediate.

Experimental Section[16]

Benzyl 5-Methyl-3-(β-benzyloxycarbonylmethyl)-2-pyrrolecarboxylate (8). The diethyl ester **5**[17] (5 g) was dissolved in a solution containing 60 mL of ethanol and 60 mL of a 10% sodium hydroxide solution, and the mixture was evaporated to dryness in an open flask at 110 °C. The residue was dissolved in 60 mL of water, and

the solution was adjusted to pH 3 with concentrated hydrochloric acid. The precipitated acid **9** was filtered, dried (3.4 g, mp 148–150 °C), suspended in 300 mL of methanol, and esterified at 20 °C by a dropwise addition of freshly distilled α-diazotoluene.[18] A few drops of acetic acid were added to destroy the excess α-diazotoluene after Ehrlich's reaction was negative in the cold and all the acid had dissolved. The solution was evaporated to dryness in vacuo, and the residue was crystallized from cyclohexane, 6.7 g (90%), mp 92–94 °C.

Anal. Calcd for $C_{22}H_{21}O_4N$: C, 72.7; H, 5.9; N, 3.9. Found: C, 72.8; H, 5.8; N, 3.8.

Benzyl 2,3-Dimethyl-4-(β-benzyloxycarbonylmethyl)-5-pyrrolecarboxylate (4). Procedure A. Freshly distilled 57% hydriodic acid (85 mL) was dropwise added at 5 °C to a mixture of 85 mL of acetic anhydride and 35 mL of 50% hypophosphorous acid, and the mixture was kept at 20 °C during 10 min after the addition was completed. A solution of 2 g of paraformaldehyde in 300 mL of glacial acetic acid was then added, followed by 5 g of the dibenzyl ester **8**. The solution was further kept during 2 h at 20 °C, when 500 mL of ether and 500 mL of a cold saturated sodium carbonate solution were added, and the ethereal layer was separated after a thorough mixing. The aqueous solution was further extracted with ether (3 × 200 mL), and the ethereal extracts were pooled, washed with a 5% sodium carbonate solution (100 mL), then with a 2% sodium thiosulfate solution (100 mL), and finally with water. The dried (Na_2SO_4) extracts were evaporated to dryness, and the oily residue dissolved in a small volume of 2% methanol in benzene was adsorbed on a column (4.5 × 35 cm) of TLC silica gel packed and prewashed with the same solvent. The pyrrole **4** was eluted by applying a small pressure, and its complete elution was monitored by TLC (R_f, 0.60, 2% methanol in benzene). Evaporation in vacuo of the eluates afforded 2 g (38%) of **4**: mp 94–95 °C (cyclohexane); NMR ($CDCl_3$) 1.88 (s, 3, C_3CH_3), 2.15 (s, 3, C_2CH_3), 3.8 (s, 2, CH_2), 5.03, 5.2 (s, 4, CH_2Ph), 7.26 ppm (b, 10, C_6H_5).

Anal. Calcd for $C_{23}H_{23}O_4N$: C, 73.2; H, 6.1; N, 3.7. Found: C, 73.1; H, 6.1; N, 3.7.

Further elution of the column with the same solvent afforded the *N*-hydroxymethylpyrrole **10** (R_f, 0.50; 2% methanol in benzene): 0.45 g (9%); mp 57–58 °C (cyclohexane); NMR ($CDCl_3$) 2.0 (s, 3, C_3CH_3), 2.3 (s, 3, C_2CH_3), 3.8 (s, 2, CH_2), 4.85 (t, J = 9 Hz, OH, exchanges with D_2O), 5.12 (s, 2, CH_2OPh side chain), 5.30 (s, 2, CH_2OPh nucleus), 5.6 ppm (d, J = 9 Hz, 2, CH_2OH, was transformed into a s after exchange with D_2O); MS *m/e* 407 (M^+, 20).

Procedure B. A solution of 2.1 g of the 2,3-dimethylpyrrole **6** (see below) in 25 mL of ethanol and 25 mL of a 10% sodium hydroxide solution was saponified to the acid **11** following the procedure described for the diester **5**. The obtained acid (1.26 g, 75%) was esterified with α-diazotoluene as described for the preparation of **8**. The reaction product was filtered through a TLC silica gel column following procedure A, and 1.8 g (60%) of the dibenzyl ester **4** was thus obtained.

Ethyl 2,3-Dimethyl-4-(β-ethoxycarbonylmethyl)-5-pyrrolecarboxylate (6). A solution of 2 g of paraformaldehyde in 300 mL of acetic anhydride and 5 g of the diethyl ester **5** were added to a mixture of 85 mL of hydriodic acid (57%), 85 mL of acetic anhydride, and 35 mL of hypophosphorous acid as described for the preparation of **4**. Following the same working procedure as described for **4** except for the use of 2.5% methanol in benzene for the elution purposes, 2.1 g (39%) of **6** (R_f, 0.60, 2.5% methanol in benzene) was obtained: mp 113–114 °C (methanol); NMR ($CDCl_3$) 1.25 (m, 6, CH_3CH_2), 1.94 (s, 3, C_3CH_3), 2.2 (s, 3, C_2CH_3), 3.8 (s, 2, CH_2), 4.2 (m, 4, CH_2CH_3), 9.1 ppm (b, 1, NH).

Anal. Calcd for $C_{13}H_{19}O_4N_1$: C, 61.7; H, 7.5; N, 5.5. Found: C, 61.6; H, 7.6; N, 5.6.

During the elution of the column the eluates which preceded the fraction containing the diethyl ester **6** contained the minor reaction product **7** (R_f, 0.70, 2.5% methanol in benzene) which was recovered after evaporating the eluates in vacuo: 0.35 g (6%); mp 55–57 °C (methanol–water); NMR ($CDCl_3$) 1.2 (m, 6, CH_3CH_2), 1.9 (s, 3, C_3CH_3), 2.05 (s, 3, NCH_3), 2.2 (s, 3, C_4CH_3), 3.8 (s, 2, CH_2), 4.2 ppm (m, 4, CH_2CH_3).

Benzyl 2,3-Dimethyl-4-(β-hydroxyethyl)-5-pyrrolecarboxylate (12). By addition of 40 mL of boron trifluoride etherate to 12 g of sodium borohydride suspended in 40 mL of diglyme while the mixture was kept under a gentle nitrogen stream,[8] a diborane-carrying nitrogen flux was obtained and bubbled into a solution of 2 g of pyrrole **4** in 50 mL of dry tetrahydrofuran. After 3 h the reduction of the side chain was complete; methanol was added to the reaction mixture until the effervescence subsided, and the solution was evaporated to dryness. The residue was purified by filtration through a TLC silica gel column (3.5 × 30 cm) packed and eluted with 2% methanol in benzene. The eluates were evaporated to dryness and the residue was crystallized from benzene–petroleum ether (bp 60–80 °C): 1.2 g (83%); mp 84–85 °C; NMR ($CDCl_3$) 1.88 (s, 3, C_3CH_3), 2.1 (s, 3, C_2CH_3), 2.95 (t, J = 6 Hz, 2, CH_2OH), 3.7 (t, J = 6 Hz, 2, pyrr-CH_2), 4.6 (s, 1, OH), 5.25 (s, 2, CH_2Ph), 7.4 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{19}O_3N$: C, 70.3; H, 6.9; N, 5.1. Found: C, 70.4; H, 7.0; N, 5.0.

Benzyl 2,3-Dimethyl-4-(β-chloroethyl)-5-pyrrolecarboxylate (13). To a solution of the β-hydroxyethylpyrrole **12** (1.76 g) in 20 mL of methylene chloride and 0.6 mL of dry pyridine was added 0.52 mL of freshly distilled thionyl chloride. The mixture was heated under nitrogen at 70 °C for 90 min, when 180 mL of methylene chloride was added and the solution was washed with 2 N hydrochloric acid, followed by a 5% sodium bicarbonate solution and then by water. The organic layer was evaporated to dryness and the residue was filtered through a TLC silica gel column with the usual technique using 2% methanol in benzene as eluent. The eluates were evaporated to dryness, and the residue crystallized from cyclohexane: 0.9 g (47%); mp 113–115 °C; NMR ($CDCl_3$) 1.94 (s, 3, C_3CH_3), 2.17 (s, 3, C; $_2CH_3$), 3.1 (m, 2, CH_2Cl), 3.6 (m, 2, pyrr-CH_2), 5.3 (b, 2, CH_2Ph), 7.4 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{18}O_2NCl$: C, 65.9; H, 6.2; N, 4.8. Found: C, 65.8; H, 6.4; N, 4.7.

Benzyl 2-Chloromethyl-3-methyl-4-(β-chloroethyl)-5-pyrrolecarboxylate (16). To a solution of 900 mg of **13** in 100 mL of dry carbon tetrachloride was added 0.24 mL (1 mequiv) of freshly distilled sulfuryl chloride. The mixture was kept at 45 °C for 4 h, after which it was evaporated to dryness. The residue was crystallized from methylene chloride–petroleum ether (bp 60–80 °C): 1.0 g (100%); mp 118–120 °C; NMR ($CDCl_3$) 2.0 (s, 3, CH_3), 3.1 (m, 2, CH_2Cl), 3.56 (m, 2, pyrr-CH_2CH_2–), 4.5 (s, 2, CH_2), 5.3 (s, 2, CH_2Ph), 7.36 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{17}O_2NCl_2$: C, 65.6; H, 4.4; N, 3.6. Found: C, 65.7; H, 4.5; N, 3.7.

Benzyl 2-Acetoxymethyl-3-methyl-4-(β-chloroethyl)-5-pyrrolecarboxylate (14). The 2-chloromethylpyrrole **16** (1.0 g) was dissolved in 30 mL of 1% sodium acetate in glacial acetic acid, and the mixture was kept at 20 °C for 1 h. It was then poured over 300 mL of ice–water, the aqueous solution was extracted with methylene chloride (2 × 50 mL), and the extracts were washed with a sodium bicarbonate solution followed by water, then dried (Na_2SO_4) and evaporated. The residue was crystallized from cyclohexane: 1.0 g (90%); mp 95 °C; NMR ($CDCl_3$) 1.98, 2.0 (s, 6, CH_3 and CH_3CO), 3.1 (m, 2, CHCl), 3.6 (m, 2, pyrr-CH_2), 5.0 (s, 2, $CH_2O.Ac$), 5.3 (s, 2, CH_2Ph), 7.4 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{18}H_{20}O_4NCl$: C, 61.8; H, 5.7; N, 4.0. Found: C, 62.0; H, 5.7; N, 4.0.

Benzyl 3-(β-Benzyloxycarbonylethyl)-4-methyl-2-pyrrolecarboxylate (25). *tert*-Butyl 3-(β-ethoxycarbonylethyl)-4-methyl-2-pyrrolecarboxylate (**17**, 2 g) was dissolved in 25 mL of ethanol and 25 mL of a 10% sodium hydroxide solution and saponified as described for **5**. The obtained acid **24** (0.91 g, 65%) was esterified with distilled α-diazotoluene as described for **8**. The product was filtered through a TLC silica gel column using the usual technique and 0.6% methanol in benzene as eluent. On evaporation of the eluates, the dibenzyl ester was obtained: 0.93 g (60%) (cyclohexane); mp 63–64 °C; NMR ($CDCl_3$) 2.0 (s, 3, CH_3), 2.8 (m, 4, CH_2CH_2), 5.1 (s, 2, CH_2Ph side chain), 5.25 (s, 2, CH_2Ph nucleus), 6.6 (b, 1, CH), 7.3 ppm (b, 10, C_6H_5).

Anal. Calcd for $C_{23}H_{23}O_4N$: C, 73.2; H, 6.1; N, 3.7. Found: C, 73.3; H, 6.2; N, 3.8.

Benzyl 3-(β-Methoxycarbonylethyl)-4-methyl-2-pyrrolecarboxylate (26). The dibenzyl ester **25** (2 g) was dissolved in a mixture of 500 mL of anhydrous methanol and 100 mL of concentrated sulfuric acid, and the solution was kept during 3 h at 20 °C. It was then poured over 2 L of ice–water, the aqueous solution was extracted with methylene chloride (3 × 200 mL), and the organic layer was washed with a saturated sodium bicarbonate solution, followed by a water wash, dried (Na_2SO_4), and evaporated to dryness. The residue was filtered through a TLC silica gel column using 0.6 methanol in benzene as eluent. The pooled eluates were evaporated, and the residue crystallized from cyclohexane: 1.2 g (75%); mp 62–63 °C; NMR ($CDCl_3$) 2.0 (s, 3, CH_3), 2.75 (m, 4, CH_2CH_2), 3.55 (s, 3, OCH_3), 5.2 (s, 2, CH_2Ph), 6.55 (b, 1, H), 7.3 ppm (b, 5, C_6H_5).

Anal. Calcd for $C_{17}H_{19}O_4N$: C, 67.8; H, 6.3; N, 4.6. Found: C, 68.0; H, 6.3; N, 4.6.

Dibenzyl 3,3′-Dimethyl-4-(β-chloroethyl)-4′-(β-methoxycarbonylethyl)-5,5′-dipyrrylmethanedicarboxylate (22). The acetate **14** (210 mg, 0.6 mequiv) and the pyrrole **26** (1.80 mg, 0.6 mequiv) were dissolved in 10 mL of glacial acetic acid containing 2.2% of *p*-toluenesulfonic acid. The mixture was heated under nitrogen at

43 °C for 3.5 h; it was then poured over 100 mL of ice water, and the precipitate was filtered, dried, and crystallized from methanol: 250 mg (70%); mp 121 °C (methanol); NMR ($CDCl_3$) 1.94, 1.96 (s, 6, CH_3), 2.7 (m, 8, CH_2CH_2), 3.57 (s, 3, OCH_3), 3.66 (s, 2, $-CH_2-$), 5.2 (s, 4, CH_2Ph), 7.2 ppm (b, 10, C_6H_5).

Anal. Calcd for $C_{33}H_{35}O_6N_2Cl$: C, 67.1; H, 5.9; N, 4.7. Found: C, 66.9; H, 6.0; N, 4.6.

Benzyl 3,3'-Dimethyl-4-(β-chloroethyl)-4'-(β-ethoxycarbonylethyl)-5'-*tert*-butyloxycarbonyl-5-dipyrrylmethanecarboxylate (18). A solution of the acetate **14** (170 mg, 0.5 mequiv) and the pyrrole **17** (160 mg, 0.5 mequiv plus 15%) were dissolved in 2.5 mL of glacial acetic acid containing 2.2% of *p*-toluenesulfonic acid and condensed as described for **22.** The reaction product was purified by filtration through a TLC silica gel column following the usual procedure and using 1% methanol in benzene as eluent. On evaporation of eluates, 136 mg (47%) of the dipyrrylmethane **18** was obtained: mp 113 °C (methanol–water); NMR ($CDCl_3$) 1.3 (t, J = 7 Hz, 3, CH_3CH_2), 1.6 [s, 9, $C(CH_3)_3$], 2.1 (b, 6, CH_3), 2.9 (m, 4, CH_2CH_2CO), 3.78 (m, 4, CH_2CH_2Cl), 4.0 (s, 2, pyrr-CH_2-pyrr), 4.3 (q, J = 7 Hz, 2, CH_2CH_3), 5.5 (s, 2, CH_2Ph), 7.7 (b, 5, C_6H_5).

Anal. Calcd for $C_{31}H_{39}O_6N_2Cl$: C, 65.3; H, 6.8; N, 4.9. Found: C, 65.2; H, 6.9; N, 5.0.

1-(β-Chloroethyl)-4,6,7-(β-methoxycarbonylethyl)-2,3,5,8-tetramethylporphyrin (19). A solution of 270 mg of the dibenzyl ester **22** in 100 mL of glacial acetic acid was reduced over 200 mg of 10% palladium on charcoal at 50 psi during 2 h. The catalyst was filtered and the solution evaporated to dryness in vacuo, affording 112 mg (0.27 nmol, 60%) of the diacid **23.** It was dissolved in a mixture of 80 mL of dry methylene chloride and 8 mL of methanol, 91 mg (0.27 nmol) of the dialdehyde **20** was added followed by 212 mg of *p*-toluenesulfonic acid, and the mixture was kept in the dark during 24 h at 20 °C. Methanol (8 mL) saturated with zinc acetate dihydrate was then added, and the mixture was kept for an additional 48 h; it was then evaporated to dryness at 40 °C, and the residue was dissolved in 60 mL of a 5% sulfuric acid in methanol solution. The solution was kept during 16 h at 20 °C in the dark; it was then diluted with 200 mL of chloroform and washed with water (80 mL), then with a 5% sodium carbonate solution (80 mL), and again with water (80 mL), dried (Na_2SO_4), and evaporated to dryness at 40 °C. The residue was dissolved in 1% methanol in benzene and filtered through a column (2 × 30 cm) of TLC silica gel, packed and prewashed with the same solvent. The eluates containing the main porphyrin fraction (as monitored by fluorescence) were collected and evaporated to dryness, and the residue dissolved in the above-mentioned solvent was adsorbed on a silica gel 60 prepacked column for liquid chromatography (Merck, Darmstadt, size B). Applying enough pressure to obtain a 0.6 mL/min flux of eluent, the porphyrin **19** was eluted separately from two satellite porphyrin bands. On evaporation of the eluent, porphyrin **19** was obtained in crystalline form and was crystallized from benzene–cyclohexane: 22 mg (23%); mp 193 °C; NMR (0.05 M $CDCl_3$) 3.27 (m, 6, $CH_2CO_2CH_3$), 3.50, 3.57 (b, 12, CH_3), 3.68 (s, 9, OCH_3), 4.27 (m, 10, pyrr-CH_2, CH_2CH_2Cl), 9.87, 9.92, 9.97, 10.07 ppm (s, 4, =CH); MS *m/e* 686.5 (M^+, 80%).

Anal. Calcd for $C_{38}H_{43}O_6N_4Cl$: C, 66.4; H, 6.3; N, 8.2. Found: C, 66.3; H, 6.2; N, 8.1.

1-Vinyl-4,6,7-(β-methoxycarbonylethyl)-2,3,5,8-tetramethylporphyrin (3) (Trimethyl Ester). Methanol saturated with zinc acetate dihydrate (4 mL) was added to a solution of the β-chloroethylporphyrin **19** (22 mg) in 10 mL of dry methylene chloride. The mixture was warmed to 35 °C for a while, and then poured over 50 mL of water. The organic layer was separated, washed with aqueous sodium acetate, then with water, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 3.5 mL of dry tetrahydrofuran, and 11 mL of 1 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol was added. The mixture was kept in a sealed vessel under vacuum (50 μ) during 96 h at 20 °C. The vessel was then opened, the mixture was poured into water (100 mL), and the solution was adjusted to pH 6 with glacial acetic acid, then extracted with 1% pyridine in methylene chloride (3 × 30 mL). The organic extracts were dried (Na_2SO_4) and evaporated to dryness, and the residue was dissolved in 30 mL of 5% sulfuric acid in methanol. After keeping overnight at 20 °C in the dark, chloroform (150 mL) was added and the mixture was washed with aqueous sodium acetate, then with a sodium bicarbonate solution, and finally with water. The organic layer was dried (Na_2SO_4), evaporated to dryness, and purified by chromatography through a TLC silica gel column using 1% methanol in benzene as eluent. The eluates were evaporated to dryness and the residue was crystallized from benzene–cyclohexane: 14 mg (65%); mp 197–199 °C (the trimethyl ester of the porphyrin isolated by incubation of I had mp 197–198 °C; mmp 197–198 °C); R_f 0.40 (TLC, benzene–1% methanol); visible max spectrum ($CDCl_3$) 403 nm (ε 125 000), 502 (12 500), 536 (10 000), 573 (6670), 625 (4600) (see ref 1 for visible max of incubation product); NMR (0.05 M $CDCl_3$) 3.23 (m, 6, $CH_2CO_2CH_3$), 3.40 (s, 3, C_3 CH_3), 3.50 (s, 6, C_5 CH_3, C_8 CH_3), 3.60 (s, 3, C_2 CH_3), 3.7 (s, 9, OCH_3), 4.28 (m, 6, pyrr-CH_2), 6.26 (m, 2, $=CH_2$), 8.20 (m, 1, =CH), 9.77, 9.86, 9.92, 9.98 (s, 4, meso-CH); MS *m/e* 650 (M^+, 80%).

Anal. Calcd for $C_{38}H_{42}O_6N_4$: C, 70.1; H, 6.5; N, 8.6. Found: C, 70.0; H, 6.4; N, 8.5.

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Registry No.—**3** trimethyl ester, 60297-35-0; **4,** 62562-72-5; **5,** 53700-88-2; **6,** 54278-18-1; **7,** 62562-73-6; **8,** 62562-74-7; **9,** 62562-75-8; **10,** 62587-53-5; **11,** 54278-16-9; **12,** 62562-76-9; **13,** 62562-77-0; **14,** 62562-78-1; **16,** 62562-79-2; **17,** 62562-80-5; **18,** 62562-81-6; **19,** 62562-82-7; **20,** 4792-10-3; **22,** 62562-83-8; **23,** 62562-84-9; **24,** 62562-85-0; **25,** 51742-43-9; **26,** 51671-83-1; α-diazotoluene, 27457-43-8.

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