Preparation of Intermediates for Uroporphyrin Synthesis

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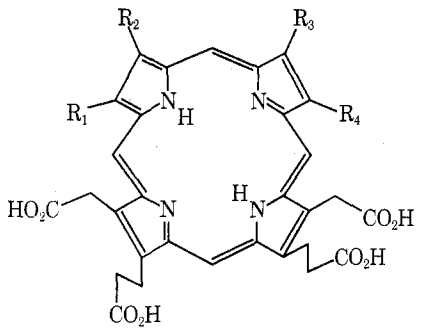
The obtention of dipyrrylmethanes necessary for the synthesis of uroporphyrins III, IV, and II (as octamethyl esters) is described. The necessary pyrroles were prepared by transesterification of the corresponding tribenzyl esters with methanol and sulfuric acid, which produced the transesterification of the side chain esters, but not of the nuclear benzyloxycarbonyl groups. The dimethyl esters of the 2-methyl-5-benzyloxycarbonylpyrroles thus obtained were converted into their 2-chloromethyl derivatives, which were condensed at 180 °C with the dimethyl esters of the 5-free 2-benzyloxycarbonylpyrroles. The tetramethyl esters of the 5,5′-dibenzyloxycarbonyldipyrrylmethanes thus prepared were converted by hydrogenolysis into the corresponding 5,5′-dicarboxydipyrrylmethanes, which were condensed with the tetramethyl ester of a 5,5′-diformyldipyrrylmethane to afford the above-mentioned uroporphyrin esters. The 5,5′-free dipyrrylmethane necessary for the synthesis of the 5,5′-diformyldipyrrylmethane was obtained by hydrogenolysis of a 5,5′-dibenzyloxycarbonyldipyrrylmethane, decarboxylation with iodine of the resulting 5,5′-diacid, and reduction of the 5,5′-diiododipyrrylmethane with hydrogen.

Uroporphyrins are valuable synthetic products since some of their reduced derivatives (e.g., uroporphyrinogens III and IV) are important biosynthetic intermediates of the porphyrin metabolism.[1] Uroporphyrin isomers are best prepared by MacDonald's procedure, which consists in an acid-catalyzed condensation of a 5,5′-diformyldipyrrylmethane and a 5,5′-free dipyrrylmethane.[2,3] By using the recently introduced refinements of this condensation technique,[4] it was possible to increase the simplicity of the reaction for the synthesis of uroporphyrins III **1**, IV **2**, and II **3** (see Experimental Section).

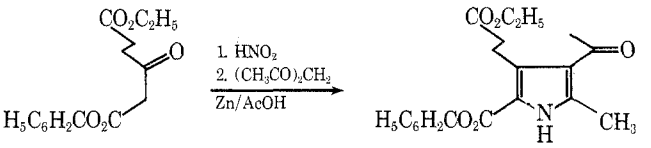


1, $R_1 = R_3 = CH_2CO_2H$; $R_2 = R_4 = CH_2CH_2CO_2H$
2, $R_1 = R_4 = CH_2CH_2CO_2H$; $R_2 = R_3 = CH_2CO_2H$
3, $R_1 = R_4 = CH_2CO_2H$; $R_2 = R_3 = CH_2CH_2CO_2H$

An efficient and versatile synthesis of the required pyrrylmethane intermediates is hence the main objective for a preparative synthesis of the three uroporphyrin isomers. It is also of interest for biosynthetic studies that each pyrrole unit of the uroporphyrin ring should be built into the structure independently of the other three rings, allowing in this way a differential labeling of the substituents of each ring. Hence, the synthesis of symmetrically substituted dipyrrylmethanes should be carried out following the pattern of an asymmetric dipyrrylmethane synthesis, avoiding the so-called dimerization reactions of 2-halomethylpyrroles to give symmetrical dipyrrylmethanes.[3]

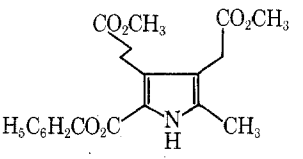
The outline of the method which we propose for the synthesis of the required dipyrrylmethanes (Scheme I) is based on the asymmetric condensation of 2-chloromethyl-5-benzyloxycarbonylpyrroles **4** with 2-benzyloxycarbonylpyrroles **5** to obtain the 5,5′-benzyloxycarbonyldipyrrylmethanes **6**. Hydrogenolysis of the benzyl groups then gave the 5,5′-carboxydipyrrylmethanes **7**, which were then directly condensed with a 5,5′-diformyldipyrrylmethane **8** (also derived from **7**) to obtain the desired uroporphyrins.

The building blocks for the synthesis of the required dipyrrylmethanes were the dimethyl esters of the 5-benzyloxycarbonylpyrroles. Benzyl δ-ethyl-β-oxoadipate (**9**), readily obtained by transesterification of diethyl β-ketoadipate,[5] was oximinated with sodium nitrite and then condensed with 2,4-pentanedione to give the β-acetylpyrrole **10**.



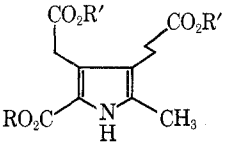
9 **10**

Oxidation of **10** with thallium(III) nitrate in methanol[6] gave the dimethylbenzylpyrrole **11** in 61% yield.



11

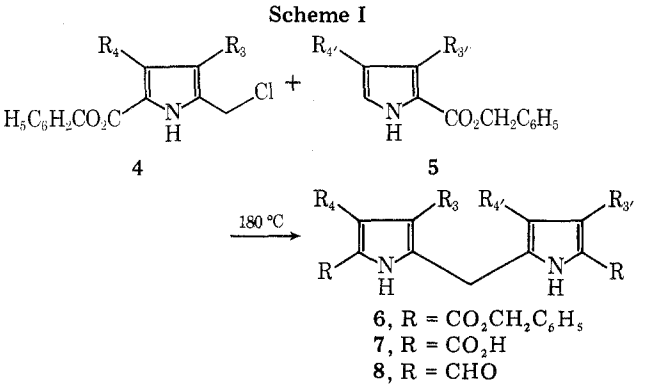
The isomeric dimethylbenzylpyrrole **12** was obtained by an acid-catalyzed transesterification with methanol of the tribenzyl ester **13**[7]. While the base-catalyzed transesterification



12, $R = CH_2C_6H_5$; $R' = CH_3$
13, $R = R' = CH_2C_6H_5$

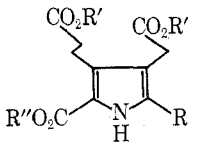
of **13** with methanol met with considerable difficulties (see ref 7 and discussion therein), the acid-catalyzed transesterification afforded **12** in 84% yield. Moreover, the procedure was

Scheme I



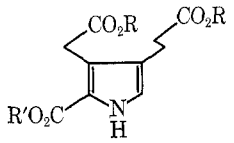
found to be a general one for all the analogous tribenzyl esters (see below).

Dimethyl benzyl esters of the α-free pyrroles were prepared by a similar pattern. The readily available[6] dimethylethylpyrrole **14** was oxidized to the acid **15**, the latter was decarboxylated by iodination, and the 2-iodopyrrole **16** was reduced to the α-free triester **17**. Saponification of the ester groups, followed by treatment of the triacid **18** with α-diazotoluene, afforded the tribenzyl ester **19** in 68% yield. Acid-catalyzed transesterification of **19** with methanol gave the dimethylbenzyl ester **20** in 70% yield.



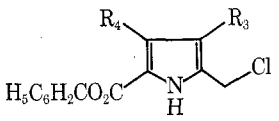
14, R = CH_3; R′ = CH_3; R″ = C_2H_5
15, R = CO_2H; R′ = CH_3; R″ = C_2H_5
16, R = I; R′ = CH_3; R″ = C_2H_5
17, R = H; R′ = CH_3; R″ = C_2H_5
18, R = R′ = R″ = H
19, R = H; R′ = R″ = $CH_2C_6H_5$
20, R = H; R′ = CH_3; R″ = $CH_2C_6H_5$

Analogously, by saponification of the isomeric triethyl ester **21**, followed by treatment of the triacid **22** with α-diazotoluene, the tribenzyl ester **23** was obtained. Acid-catalyzed transesterification of **23** gave the dimethylbenzyl ester **24** in 69% yield.



21, R = R′ = C_2H_5
22, R = R′ = H
23, R = R′ = $CH_2C_6H_5$
24, R = CH_3; R′ = $CH_2C_6H_5$

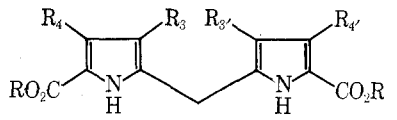
The 2-methylpyrroles **11** and **12** were transformed into their 2-chloromethylpyrroles **25** and **26** by using sulfuryl chloride, and the latter were condensed with the α-free pyrroles **20** and **24**.



25, R_3 = $CH_2CO_2CH_3$; R_4 = $CH_2CH_2CO_2CH_3$
26, R_3 = $CH_2CH_2CO_2CH_3$; R_4 = $CH_2CO_2CH_3$

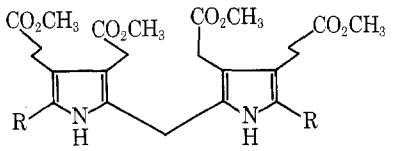
The condensation reaction was carried out in glacial acetic acid containing 1% of sodium acetate. To overcome the deactivation produced by the 2-benzyloxycarbonyl substituents in **20** and **24** it was necessary to carry out the reaction at 180 °C in a closed vessel. Under those conditions, no randomization of the reaction products took place, no "irrational" dipyrrylmethanes were obtained,[3] and the desired dipyrrylmethanes were isolated in approximately 70% yield. By condensation of **25** and **24**, the dipyrrylmethane **27** was obtained; by condensation of **25** and **20** the dipyrrylmethane **28** was obtained; and by condensation of **26** and **24** the dipyrrylmethane **29** was obtained.

For the synthesis of uroporphyrins III, IV, and II, it was necessary to prepare the 5,5′-diformyldipyrrylmethane **30**. This was achieved by using dipyrrylmethane **28** as a starting material. Hydrogenolysis of the benzyl esters, followed by treatment of the resulting diacid **31** with iodine, afforded the 5,5′-diiododipyrrylmethane **32** in good yield. Hydrogenolysis of **32** gave the 5,5′-free dipyrrylmethane **33**, which was



27, R_3 = $R_{4'}$ = $CH_2CO_2CH_3$; R_4 = $R_{3'}$ = $CH_2CH_2CO_2CH_3$; R = $CH_2C_6H_5$
28, R_3 = $R_{3'}$ = $CH_2CO_2CH_3$; R_4 = $R_{4'}$ = $CH_2CH_2CO_2CH_3$; R = $CH_2C_6H_5$
29, R_3 = $R_{3'}$ = $CH_2CH_2CO_2CH_3$; R_4 = $R_{4'}$ = $CH_2CO_2CH_3$; R = $CH_2C_6H_5$
31, R_3 = $R_{3'}$ = $CH_2CO_2CH_3$; R_4 = $R_{4'}$ = $CH_2CH_2CO_2CH_3$; R = H
34, R_3 = $R_{4'}$ = $CH_2CO_2CH_3$; R_4 = $R_{3'}$ = $CH_2CH_2CO_2CH_3$; R = H
35, R_3 = $R_{3'}$ = $CH_2CH_2CO_2CH_3$; R_4 = $R_{4'}$ = $CH_2CO_2CH_3$; R = H

transformed into the 5,5′-diformyldipyrrylmethane **30** by using the Vilsmaier–Haack procedure[8]. The attempted thermal decarboxylation of the diacid **31** to **33** gave very poor yields, while attempts made by using trifluoroacetic acid lead to extensive decomposition of the dipyrrylmethanes.



30, R = CHO
32, R = I
33, R = H

Uroporphyrins III **1**, IV **2**, and II **3** (as octamethyl esters) were obtained by condensing the diformyldipyrrylmethane **30** with the diacids **31**, **34**, and **35** obtained "in situ" after hydrogenolysis of the benzyl esters of **27**, **28**, and **29**. The *p*-toluenesulfonic acid catalyzed condensations were performed in methylene chloride[4] and there was no need to carry out a previous decarboxylation of the diacids **31**, **34**, and **35**, since analogous yields (approximately 30–50%) were obtained when the reactions were carried out with the 5,5′-free dipyrrylmethanes. Decarboxylation of the uroporphyrins to coproporphyrins and TLC analysis of the latter[9,10] indicated that the obtained uroporphyrins were the pure isomers.

Experimental Section[11]

Benzyl 2-Methyl-3-acetyl-4-(β-ethoxycarbonylethyl)-5-pyrrolecarboxylate (10). A solution of 18 g of sodium nitrite in 60 ml of water was slowly added to a stirred mixture of 67 g (0.24 mol) of α-benzyl δ-ethyl-β-ketoadipate (**9**) and 100 ml of glacial acetic acid, while the temperature was kept at 10 °C. After the addition was completed, the mixture was kept overnight at 5 °C, and then added to a constantly stirred mixture of 24.5 g (0.24 mol) of 2,4-pentanedione, 44 g of zinc, and 44 g of sodium acetate in 100 ml of acetic acid. A supplemental amount of 44 g of zinc was added in small portions during the addition of the isonitroso derivative. The resulting mixture was kept at 65 °C during 60 min with constant stirring, and was then poured into 1 l. of ice water. The precipitate was filtered and crystallized from methanol–water: 57.5 g (65%); mp 100–101 °C; NMR ($CDCl_3$) 1.2 (t, *J* = 7 Hz, 3, CH_2CH_3), 2.4, 2.5 (s, 3, 3, $COCH_3$, CH_3), 2.5, 3.4 (m, 2, 2, $-CH_2CH_2-$), 4.15 (q, 2, CH_2CH_3), 5.3 (s, 2, CH_2Ph), 7.3 ppm (b, 5, Ph).

Anal. Calcd for $C_{20}H_{23}O_5N$: C, 67.2; H, 6.4; N, 4.0. Found: C, 67.3; H, 6.5; N, 4.0.

Benzyl 2-Methyl-3-(methoxycarbonylmethyl)-4-(β-methoxycarbonylethyl)-5-pyrrolecarboxylate (11). Thalium(III) nitrate (12 g, 30 mmol) was added to a solution of 5.75 g (16 mmol) of the β-acetylpyrrole **10** in 200 ml of anhydrous methanol and 40 ml of 70% perchloric acid. The mixture was kept at 20 °C during 5 h, then poured over 500 ml of water, and the aqueous solution was extracted with chloroform (3 × 50 ml). The chloroform solution was washed with a sodium bicarbonate solution, then with water, dried (Na_2SO_4), and evaporated to dryness in vacuo. The residue was dissolved in a small volume of 10% methanol in benzene, and was filtered through a column (3.5 × 40 cm) of TLC silica gel, packed and prewashed with the

same solvent. The pyrrole 11 was eluted by applying a small pressure, the eluate was evaporated to dryness in vacuo, and the residue was crystallized from cyclohexane: 3.7 g (61%); mp 78 °C (lit.[7] 78 °C, mmp 78 °C); NMR ($CDCl_3$) 2.2 (s, 3, CH_3), 2.7 (m, 4, CH_2CH_2), 3.4 (s, 2, CH_2CO), 3.55, 3.6 (s, 3, 3, OCH_3), 5.2 (s, 2, $CH_2C_6H_5$), 7.3 ppm (s, 5, C_6H_5).

Benzyl 2-Methyl-3-(methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-5-pyrrolecarboxylate (12). Concentrated sulfuric acid (30 ml) was added to a solution of 6.2 g of the tribenzyl ester 13 in 600 ml of anhydrous methanol, while it was kept at 5 °C with constant stirring. The mixture was further kept at 20 °C during 8 h, then poured over 2 l. of ice–water. The precipitate was filtered, dried, and crystallized from cyclohexane: 3.7 g (84%); mp 111 °C (lit[7] mp 111 °C, mmp 111 °C); NMR ($CDCl_3$) 2.2 (s, 3, CH_3), 3.5, 3.6 (s, 3, 3, OCH_3), 5.2 (s, 2, $CH_2C_6H_5$), 7.2 ppm (s, 5, C_6H_5).

Ethyl 2-Carboxy-3-(methoxycarbonylmethyl)-4-(methoxycarbonylethyl)-5-pyrrolecarboxylate (15). Freshly distilled sulfuryl chloride (4 ml, 192 mmol) was added to 20 g (64 mmol) of the dimethyl ethyl ester 14 dissolved in 200 ml of anhydrous methylene chloride, while keeping the solution at 5 °C with constant stirring. The mixture was further kept at 20 °C during 30 min, the solvent was then evaporated to dryness in vacuo, 60 g of sodium acetate dissolved in 1 l. of warm water was added, and the mixture was boiled during 5 min. Sodium bicarbonate was added to the cooled suspension, the alkaline solution was extracted with ether (3 × 100 ml), and the aqueous phase was adjusted to pH 2 with concentrated hydrochloric acid. The precipitated acid was filtered, dried, and crystallized from ethanol–water, 14 g (63%), mp 186–187 °C.

Anal. Calcd for $C_{15}H_{19}NO_8$: C, 52.8; H, 5.6; N, 4.1. Found: C, 52.8; H, 5.5; N, 4.0.

Ethyl 2-Iodo-3-(methoxycarbonylmethyl)-4-(methoxycarbonylethyl)-5-pyrrolecarboxylate (16). A solution of 17.5 g of the acid 15 and 33 g of sodium bicarbonate in 260 ml of water was added to a stirred solution of 41 g of potassium iodide and 16.4 g of iodine in 26 ml of water. The mixture was stirred and heated at 75 °C during 1 h. After that period it was cooled at 5 °C during several hours, and the precipitate was filtered and crystallized from ethanol, 18.6 g (85%), mp 133 °C.

Anal. Calcd for $C_{14}H_{18}NO_6I$: C, 40.0; H, 4.2; N, 3.3. Found: C, 39.9; H, 4.1; N, 3.3.

Ethyl 3-(Methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-2-pyrrolecarboxylate (17). Anhydrous sodium acetate (18 g) was added to a solution of 18 g of 16 in 150 ml of ethanol, and the mixture was reduced with hydrogen at 30 psi during 2 h over 3.6 g of 10% palladium on charcoal. The catalyst was filtered, the solution was evaporated to dryness in vacuo, the residue was dissolved in 250 ml of water, and the aqueous solution was extracted with chloroform (3 × 100 ml). The chloroform extracts were washed first with 10% thiosulfate, then with water, dried (Na_2SO_4), and evaporated to dryness. The oily residue crystallized from cyclohexane: 10 g (78%); mp 47–48 °C (benzene–petroleum ether); NMR ($CDCl_3$) 1.3 (t, J = 7 Hz, 3, CH_2CH_3), 2.7 (m, 4, CH_2CH_2), 3.5 (s, 2, CH_2CO), 3.6, 3.65 (s, 3, 3, OCH_3), 4.2 (q, J = 7 Hz, 2, CH_2CH_3), 6.8 ppm (b, 1, H_5).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.1; N, 4.9. Found: C, 56.5; H, 6.0; N, 4.8.

Benzyl 3-(Benzyloxycarbonylethyl)-4-(benzyloxycarbonylmethyl)-2-pyrrolecarboxylate (19). The triester 17 (6.8 g) was dissolved in a mixture of 80 ml of ethanol and 80 ml of 10% sodium hydroxide, and the solution was evaporated to dryness at 110 °C in an open flask. The residue was dissolved in 60 ml of water, the solution was adjusted to pH 2 with concentrated hydrochloric acid, and the precipitated triacid 18 was filtered and dried. Without further purification it was dissolved in methanol and distilled (60 °C, 0.2 mm). α-Diazotoluene[12] was added dropwise until Ehrlich's reaction was negative in the cold. The excess of α-diazotoluene was destroyed with acetic acid, the solution was evaporated to dryness in vacuo, and the residue was crystallized from cyclohexane: 8 g (68%); mp 81–82 °C (from methanol); NMR ($CDCl_3$) 2.9 (m, 4, CH_2CH_2), 3.6 (s, 2, CH_2CO), 5.2, 5.3 (s, 4, CH_2Ph), 5.45 (s, 2, nuclear CO_2CH_2Ph), 7.55 (b, 15, Ph) 6.8 ppm (b, 1, H_5).

Anal. Calcd for $C_{31}H_{29}NO_6$: C, 72.8; H, 5.7; N, 2.7. Found: C, 72.7; H, 5.6; N, 2.8.

Benzyl 3-(Methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-2-pyrrolecarboxylate (20). The tribenzyl ester 19 (10 g) was transesterified by using 1 l. of anhydrous methanol and 200 ml of concentrated sulfuric acid, as desribed in the preparation of 12. The obtained product was dissolved in a small volume of 3% methanol in benzene, and was filtered through a silica gel column (3 × 40 cm) packed and eluted with the same solvent under slight pressure. The fractions containing the pyrrole 20 were collected and evaporated to dryness in vacuo, and the residue was crystallized from benzene–cyclohexane: 4.9 g (70%); mp 61–63 °C (lit.[13] mp 60–63 or 49–52 °C); NMR ($CDCl_3$) 2.8 (m, 4, CH_2CH_2), 3.5 (s, 2, CH_2CO), 3.6, 3.65 (s, 6, OCH_3), 5.3 (s, 2, CH_2Ph), 6.8 (b, 1, H_5), 7.4 ppm (b, 5, Ph).

Anal. Calcd for $C_{19}H_{21}O_6N$: C, 63.5; H, 5.9; N, 3.9. Found: C, 63.4; H, 5.7; N, 3.8.

Benzyl 3-(Benzyloxycarbonylmethyl)-4-(benzyloxycarbonylethyl)-2-pyrrolecarboxylate (23). The triethyl ester 21[8] (4 g) was saponified to the acid 22 and esterified with α-diazotoluene as described for the preparation of the isomer 19. The product was dissolved in 1% methanol in benzene and was filtered through a silica gel column (4 × 40 cm) packed and eluted with the same solvent under slight pressure. The eluates containing the tribenzyl ester were pooled and evaporated to dryness, and the oily residue was crystallized from benzene–cyclohexane: 3.3 g (52%); mp 59–61 °C; NMR ($CDCl_3$) 2.7 (m, 4, CH_2CH_2), 3.9 (s, 2, CH_2CO), 5.05, 5.07 (s, 4, CH_2Ph), 5.25 (s, 2, nuclear CO_2CH_2Ph), 6.65 (b, 1, H_5), 7.3 ppm (b, 15, Ph).

Anal. Calcd for $C_{31}H_{29}NO_6$: C, 72.8; H, 5.7; N, 2.7. Found: C, 72.8; H, 5.6; N, 2.6.

Benzyl 3-(Methoxycarbonylmethyl)-4-(methoxycarbonylethyl)-2-pyrrolecarboxylate (24). The tribenzyl ester 23 (3.1 g) was transesterified with a mixture of 320 ml of anhydrous methanol and 64 ml of concentrated sulfuric acid by following the procedure described for 12. The product was crystallized from benzene–cyclohexane: 1.52 g (69%); mp 63–65 °C (lit.[13] mp 63.5–66 °C); NMR ($CDCl_3$) 2.6 (m, 4, CH_2CH_2), 3.6, 3.65 (s, 6, OCH_3), 3.75 (s, 2, CH_2CO), 5.3 (s, 2, CH_2Ph), 6.7 (b, 1, H_5), 7.3 ppm (b, 5, Ph).

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.5; H, 5.9; N, 3.9. Found: C, 63.4; H, 5.8; N, 3.9.

2-Chloromethyl-3-(methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-5-benzyloxycarbonylpyrrole (26). Sulfuryl chloride (0.28 ml, 3.5 mmol) was added to a solution of 13 (1.34 g, 3.5 mmol) in 13 ml of anhydrous methylene chloride, while the solution was kept at 5 °C with constant stirring. The mixture was further stirred at 20 °C during 30 min, then evaporated to dryness in vacuo, and the residue was crystallized from benzene–hexane or from methylene chloride–petroleum ether: 1.2 g (82%); mp 89–91 °C; NMR ($CDCl_3$) 2.7 (m, 4, CH_2CH_2), 3.6, 3.65 (s, 6, OCH_3), 3.8 (s, 2, CH_2CO), 4.6 (s, 2, CH_2Cl), 5.3 (s, 2, CH_2Ph), 7.4 ppm (b, 5, Ph).

Anal. Calcd for $C_{20}H_{22}NO_6Cl$: C, 58.9; H, 5.4; N, 3.4; Cl, 8.7. Found: C, 58.9; H, 5.5; N, 3.5; Cl, 8.5.

Dibenzyl 3,4′-(Methoxycarbonylmethyl)-4,3′-(methoxycarbonylethyl)-5,5′-pyrrylmethanedicarboxylate (27). 2-Chloromethylpyrrole 25[7] (500 mg, 1.22 mmol) and 450 mg (1.22 mmol) of dimethylbenzylpyrrole 24 were dissolved in 16 ml of glacial acetic acid containing 1% of sodium acetate, the solution was placed in a glass vessel, and the vessel was thoroughly deaerated while the solution was kept frozen (−10 °C). The vessel was closed (or sealed) under vacuum (0.1–0.2 mm), and heated at 180 °C during 90 min. After cooling the vessel it was opened, the solution was evaporated to dryness, and the residue was crystallized from methanol–water: 590 mg (65%); mp 96–97 °C; NMR ($CDCl_3$) 2.7 (m, 8, CH_2CH_2), 3.55, 3.64, 3.66 (s, 14, OCH_3, C_3CH_2CO), 3.8 (s, 2, C_4, CH_2CO), 3.95 (s, 2, $-CH_2-$), 5.3 (s, 4, CH_2Ph), 7.3 ppm (b, 10, Ph).

Anal. Calcd for $C_{39}H_{42}N_2O_{12}$: C, 64.1; H, 5.8; N, 3.8. Found: C, 64.0; H, 5.7; N, 3.7.

TLC analysis using 3% methanol in benzene indicated that 27 (R_f 0.60) was pure, and not contaminated with either 28 (R_f 0.80) or 29 (R_f 0.50).

Dibenzyl 3,3′-(Methoxycarbonylmethyl)-4,4′-(methoxycarbonylethyl)-5,5′-pyrrylmethanedicarboxylate (28). 2-Chloromethylpyrrole 25 (338 mg, 0.83 mmol) was condensed with the dimethylbenzylpyrrole 20 (300 mg, 0.83 mmol) in 18 ml of glacial acetic acid containing 1% of sodium acetate, following the technique described for 27. Crystallization of 28 from methanol gave 490 mg (80%): mp 144–147 °C; NMR ($CDCl_3$) 2.7 (m, 8, CH_2CH_2), 3.55 (b, 16, OCH_3, CH_2CO), 3.8 (s, 2, $-CH_2-$), 5.2 (s, 4, CH_2Ph), 7.3 ppm (b, 10, Ph).

Anal. Calcd for $C_{39}H_{42}N_2O_{12}$: C, 64.1; H, 5.8; N, 3.8. Found: C, 63.9; H, 5.8; N, 3.9.

It was pure by TLC analysis (3% methanol in benzene).

Dibenzyl 3,3′-(Methoxycarbonylethyl)-4,4′-(methoxycarbonylmethyl)-5,5′-pyrrylmethanedicarboxylate (29) was prepared following the method described for 27 and 28. From 330 mg of 2-chloromethylpyrrole 26 and 253 mg of pyrrole 24 was obtained 400 mg (78%) of 29: mp 133–135 °C (from methanol); NMR ($CDCl_3$) 2.6 (m, 8, CH_2CH_2), 3.5 (b, 12, OCH_3), 3.7 (b, 4, CH_2CO), 3.95 (b, 2, $-CH_2-$), 5.2 (s, 4, CH_2Ph), 7.3 ppm (b, 10, Ph).

Anal. Calcd for $C_{39}H_{42}N_2O_{12}$: C, 64.1; H, 5.8; N, 3.8. Found: C, 64.4; H, 5.8; N, 3.9.

It was pure by TLC analysis (3% methanol in benzene).

3,3'-Bis(methoxycarbonylmethyl)-4,4'-(methoxycarbonylethyl)-5,5'-diiodopyrrylmethane (32). Dibenzyl ester **28** (700 mg) dissolved in 150 ml of glacial acetic acid was reduced with hydrogen over 500 mg of 10% palladium on charcoal at 50 psi during 2 h. The catalyst was filtered, the solvent was evaporated in vacuo at 40 °C, and the obtained diacid **31** was suspended in methanol and filtered (420 mg, 80%). The crude diacid **31** was dissolved in a mixture of 20 ml of ethanol, 16 ml of water, and 400 mg of sodium bicarbonate. A solution of 400 mg of iodine in 16 ml of ethanol was then dropwise added to the aforementioned solution with constant stirring, the precipitate formed after completion of the addition was redissolved with gentle heating, and the mixture was cooled at 5 °C. The precipitate of crude **32** was filtered and used in the next step, 490 mg (94%). For analysis it was crystallized from methanol–water, mp 135–136 °C.

Anal. Calcd for $C_{23}H_{28}N_2O_8I_2$: C, 38.6; H, 3.9; N, 3.9. Found: C, 38.6; H, 3.8; N, 4.0.

3,3'-Bis(methoxycarbonylmethyl)-4,4'-(methoxycarbonylethyl)dipyrrylmethane (33). A solution of the diiodopyrrylmethane **32** (490 mg) and 500 mg of sodium acetate in 100 ml of ethanol was reduced with hydrogen over 250 mg of 10% palladium on charcoal at 30 psi during 2 h. The catalyst was filtered, the solution was evaporated to dryness in vacuo, and the residue was crystallized from ethanol–water: 200 mg (63%); mp 102–104 °C (from hexane, lit.[2] 103.5–105 °C); NMR ($CDCl_3$) 2.7 (m, 8, CH_2CH_2), 3.5 (b, 4, CH_2CO), 3.65, 3.75 (s, 14, OCH_3, $-CH_2-$), 6.5 ppm (b, 2, H_5 and $H_{5'}$).

Anal. Calcd for $C_{23}H_{30}N_2O_8$: C, 59.7; H, 6.5; N, 6.1. Found: C, 59.6; H, 6.4; N, 6.1.

Uroporphyrin III Octamethyl Ester (1). A solution of 480 mg of the dibenzyl ester **27** in 150 ml of glacial acetic acid was reduced with hydrogen over 400 mg of 10% palladium on charcoal at 50 psi during 2 h. The catalyst was filtered, the solution was evaporated to dryness in vacuo, and the obtained diacid **34** was suspended in methanol and filtered (282 mg, 0.48 mmol, 77%). It was dissolved in a mixture of 240 ml of dry methylene chloride and 30 ml of methanol, 270 mg (0.48 mmol) of dialdehyde **30** (obtained from **33** as described elsewhere[8]) was added followed by 700 mg of *p*-toluenesulfonic acid, and the mixture was kept in the dark during 24 h at 20 °C. Methanol (30 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 150 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 400 ml of chloroform and washed with water (200 ml), then with a 5% sodium carbonate solution (200 ml), again with water (200 ml), dried (Na_2SO_4), and evaporated to dryness at 40 °C. The residue was dissolved in a small volume of a 1% methanol–chloroform solution and was filtered through a column (2 × 30 cm) of silica gel, packed and prewashed with the same solvent. The porphyrin containing eluates were crystallized from chloroform–methanol: 240 mg (50%); mp 264–266 °C (lit.[3] mp 258–260 °C); NMR (0.05 M in $CDCl_3$) 3.3 (m, 8, CH_2CH_2CO), 3.7, 3.8 (b, 24, OCH_3), 4.3 (m, 8, CH_2CH_2CO), 5.05 (b, 8, CH_2CO), 10.2 ppm (b, 4, CH).

Anal. Calcd for: $C_{48}H_{54}N_4O_{16}$: C, 61.1; H, 5.7; N, 5.9. Found: C, 61.3; H, 5.8; N, 6.1.

When a sample of **1** was decarboxylated to coproporphyrin III, the latter was found to be the pure isomer by TLC analysis.[10]

Uroporphyrin IV octamethyl ester (2) was obtained following the procedure described for **1**. Hydrogenolysis of 640 mg of the dibenzyl ester **29** afforded 300 mg (62%) of the diacid **35**. The latter was condensed with 250 mg of the dialdehyde **30** as described above, and 135 mg (30%) of uroporphyrin IV octamethyl ester (**2**) was obtained: mp 257–258 °C (benzene–cyclohexane) (lit.[2] mp 254–257 °C); NMR ($CDCl_3$) 3.3 (m, 8, CH_2CH_2CO), 3.68, 3.70, 3.77, 3.8 (s, 24, OCH_3), 4.3 (m, 8, CH_2CH_2CO), 4.9, 5.0 (b, 8, CH_2CO), 10.0 ppm (b, 4, CH).

Anal. Calcd for $C_{48}H_{54}N_4O_{16}$: C, 61.1; H, 5.7; N, 5.9. Found: C, 61.0; H, 5.6; N, 5.8.

When a sample of **2** was decarboxylated to coproporphyrin IV, the latter was found to be pure by TLC analysis.[10]

Uroporphyrin II octamethyl ester (3) was obtained following the procedure described for **1** and **2**. By condensation of 360 mg of the diacid **31** and 300 mg of the dialdehyde **30** was obtained 201.6 mg (37%) of uroporphyrin II octamethyl ester (**3**): mp 310–312 °C (from chloroform–acetone) (lit.[2] 307–312 °C); NMR ($CDCl_3$) 3.3 (m, 8, CH_2CH_2CO), 3.7, 3.9 (s, 24, OCH_3), 4.4 (m, 8, CH_2CH_2CO), 5.1 (b, 8, CH_2CO), 10.2 ppm (b, 4, CH).

Anal. Calcd for $C_{48}H_{54}N_4O_{16}$: C, 61.1; H, 5.7; N, 5.9. Found: C, 61.3; H, 5.9; N, 6.0.

By decarboxylation to coproporphyrin II and analysis of the latter by TLC[9] it was found to be the pure isomer.

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Registry No.—**1**, 553-18-4; **2**, 613-02-5; **3**, 531-42-0; **9**, 59562-70-8; **10**, 59562-71-9; **11**, 50622-64-5; **12**, 50622-78-1; **13**, 38252-61-8; **14**, 40515-71-7; **15**, 59562-72-0; **16**, 59562-73-1; **17**, 59562-74-2; **18**, 59562-75-3; **19**, 59562-76-4; **20**, 50622-60-1; **21**, 53700-90-6; **22**, 59562-77-5; **23**, 59562-78-6; **24**, 50622-82-7; **25**, 50622-68-9; **26**, 51912-03-9; **27**, 57907-57-0; **28**, 55305-15-2; **29**, 55305-18-5; **30**, 55258-98-5; **31**, 58950-41-7; **32**, 59562-79-7; **33**, 55374-15-7; **34**, 58950-42-8; **35**, 59562-80-0; sodium nitrite, 7632-00-0; 2,4-pentanedione, 123-54-6; α-diazotoluene, 766-91-6.

References and Notes

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