mmol) of 6-carbamoyl-1-cyclohexyl-3-methyluracil (**1a**) in 1 mL of 70% perchloric acid was heated at 85–90 °C as specified in Table I. After cooling, the precipitate was collected by filtration, washed with water, and recrystallized from water to give **3** (see Tables I and II).

Hydrolysis of 1-Benzyl-6-carbamoyl-3-methyluracil (1g) in Hydrobromic Acid. A suspension of 520 mg (2 mmol) of **1g** in 10 mL of hydrobromic acid was refluxed as specified in Table I. After cooling, the separated irritating oil was extracted with ether and the extract was washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4), and evaporated under reduced pressure to give 300 mg (88%) of benzyl bromide, which was identified by comparison of its IR spectrum with that of a commercial product. The aqueous layer was evaporated under reduced pressure, and the residue was triturated with water. The insoluble solid was collected by filtration and recrystallized (see Tables I and II).

Registry No.—**1a,** 53293-13-3; **1b,** 55643-12-4; **1c,** 55643-13-5; **1d,** 2019-20-7; **1e,** 55643-15-7; **1f,** 55643-16-8; **1g,** 55643-14-6; **2,** 705-36-2; **3,** 55643-21-5; **4a,** 53293-09-7; **4b,** 55643-19-1; **4c,** 55643-20-4; **4d,** 49846-86-8; **5d,** 4116-38-5; **5e,** 55643-17-9; **5f,** 55643-18-0; **8,** 68843-56-1; **9,** 65-86-1; **10,** 68843-57-2; **11,** 68843-59-4; **12,** 68843-60-7; **13,** 68843-58-3.

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Preparation of Intermediates for Coproporphyrin Synthesis

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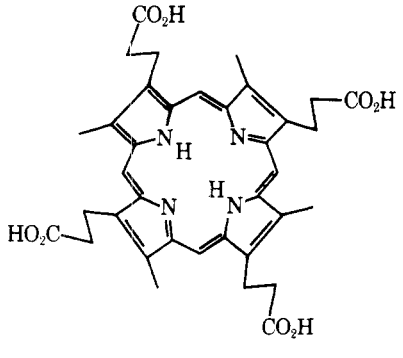
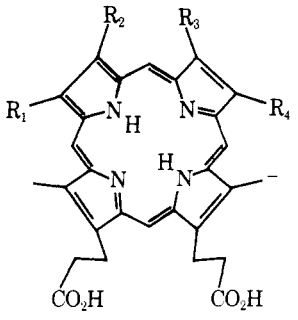
The synthesis of dipyrrylmethanes necessary for the obtention of coproporphyrins I–IV (**1–4**) is described. The synthesis of the former was designed so as to avoid isomeric mixtures in order to obtain pure samples of the latter. The asymmetric dibenzyl-3,4′-bis(β-ethoxycarbonylethyl)-4,3′-dimethyl-5,5′-dipyrrylmethane as well as the symmetric dibenzyl 3,3′-dimethyl-4,4′-bis(β-ethoxycarbonylethyl)-5,5′-dipyrrylmethanedicarboxylate were obtained. Hydrogenolysis of the dibenzyloxycarbonyl groups and condensation of the 5,5′-dicarboxydipyrrylmethanes with a 5,5′-diformyldipyrrylmethane gave **3** and **4**. Conversion of *tert*-butyl 3,4′-dimethyl-4,3′-bis(β-ethoxycarbonylethyl)-5′-(benzyloxycarbonyl)-5-dipyrrylmethanecarboxylate into a (*tert*-butyloxycarbonyl)-5′-formyldipyrrylmethane was followed by treatment of the latter with hydrogen bromide. By a self-condensation of the resulting product, **1** was obtained in good yield.

Coproporphyrins are important natural products since several of their reduced derivatives (coproporphyrinogens) are metabolic intermediates in protoporphyrin biosynthesis. The four coproporphyrin isomers I–IV, structures **1–4**, respectively, have been prepared by synthesis using different methods. All four coproporphyrin isomers were originally prepared by Fischer and co-workers following his method of fusion of dipyrrylmethenes.[1] They were also prepared by thermal decarboxylation of the corresponding uroporphyrins,[1] and **2** was prepared by condensation of a 5,5′-dipyrrylmethanedicarboxylic acid with formic acid.[1] Fischer's method was again used by Morsingh and MacDonald[2] to prepare **3** and **4**. The latter were also prepared by Kenner and co-workers[3] using the α-oxobilane route to porphyrins. They again described the synthesis of **1** following Fischer's method of fusion in succinic acid of a dipyrrylmethene which was in turn obtained by the self-condensation of a pyrrole acid.[3] We found that the simplest approach to obtain the four coproporphyrin isomers in a pure form is to use MacDonald's original approach[4] in its simplified form,[5] which consists in the condensation of a diformyldipyrrylmethane with a dicarboxydipyrrylmethane.

The synthesis of **1** was achieved by the self-condensation



1



2, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH_2CH_2CO_2H$
3, $R_1 = R_3 = CH_3$; $R_2 = R_4 = CH_2CH_2CO_2H$
4, $R_1 = R_4 = CH_2CH_2CO_2H$; $R_2 = R_3 = CH_3$

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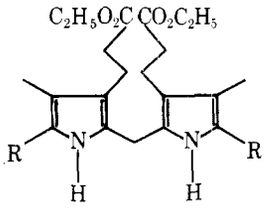
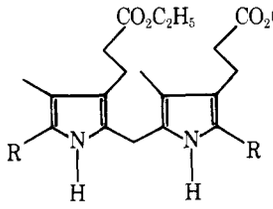
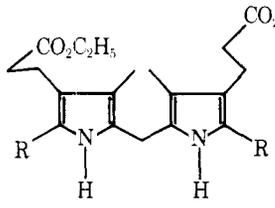
of a 5-formyl-5′-carboxydipyrrylmethane. The method has been used to obtain uroporphyrins III, IV, and II,[5] and also 2.[3] It allows a synthesis of coproporphyrins in which each pyrrole ring is built into the structure independently of the other three rings, allowing in this way a differential labeling of the substituents of each ring. It requires, however, that the asymmetrically substituted dipyrrylmethanes should not be contaminated with symmetrical dipyrrylmethanes, a requisite which is not easy to comply with in dipyrrylmethane synthesis. The diformyldipyrrylmethane 5[6] is the obvious choice for the



5, R = CHO
32, R = CO_2H



6, R = CO_2CH_2Ph
24, R = CO_2H



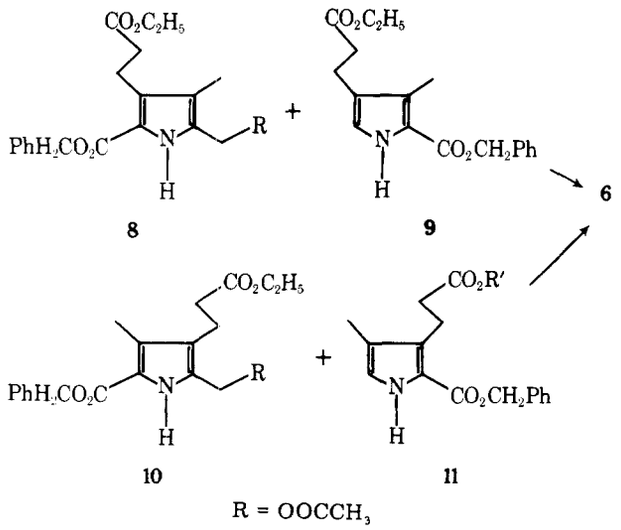
7, R = CO_2CH_2Ph
25, R = CO_2H

synthesis of 3 and 4. The corresponding dicarboxydipyrrylmethanes were obtained by hydrogenolysis of the 5,5′-bis(benzyloxycarbonyl)dipyrrylmethanes 6 and 7.

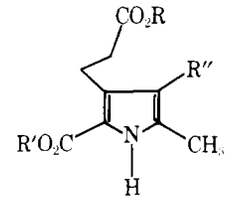
Dipyrrylmethane 6 can be obtained by condensing either the acetate 8 with the α-unsubstituted pyrrole 9 or the acetate 10 with the α-unsubstituted pyrrole 11 (Scheme I).

The condensation of the acetate 8 and 9 in acetic acid in the presence of *p*-toluenesulfonic acid[7] gave 6 contaminated with 7, formed by the self-condensation of 8. Both dipyrrylmethanes were identified by TLC on silica gel coated plates. The same happened when the 2-(chloromethyl)pyrrole 8 (R = Cl) was condensed with 9 in acetic acid at 180 °C.[5] Hence, this approach was not followed since it led to a mixture of 3 and 4. The condensation of 10 and 11 afforded only 6, and was then pursued. A possible undetected contamination with a dipyrrylmethane formed at the expense of 10 will result in the synthesis of 3 contaminated with 2, a situation which is easily detected by TLC analysis on cellulose-coated plates.[8] The synthesis of dipyrrylmethane 7 can be easily achieved by the self-dimerization of 8, or by condensation of 8 and 11.

Scheme I



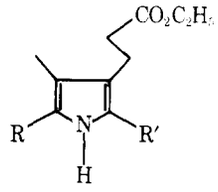
R = $OOCCH_3$



12, R = R′ = C_2H_5; R″ = H
13, R = R′ = C_2H_5; R″ = CHO
14, R = R′ = C_2H_5; R″ = CH_3
15, R = R′ = H; R″ = CH_3
16, R = R′ = CH_2Ph; R″ = CH_3
17, R = C_2H_5; R′ = CH_2Ph; R″ = CH_3

The acetate 8 was derived from the β-unsubstituted pyrrole 12.[9] Formylation with the Vilsmeier-Haak procedure gave 13, which was reduced with hydrogen to the 2,3-dimethylpyrrole 14. The hydrogenation was carried out over palladium on charcoal at low pressure as described for the lower homologous pyrrole.[10] The diethyl ester 14 was saponified to the diacid 15, and the latter was transformed into the dibenzyl ester 16 by treatment with benzyl chloride in the presence of triethylamine. Direct transesterification of 14 to 16 was also achieved by heating at 120 °C with sodium benzylate in benzyl alcohol during 72 h (compare also with ref 11). The dibenzyl ester 16 was transesterified to the ethyl benzyl ester 17 by treatment with ethanol-sulfuric acid,[5] and the latter was transformed into 8 with lead tetraacetate.

In order to prepare the α-unsubstituted pyrrole 11, the oxidation of the α-methyl group of 17 was attempted. Treatment with sulfuryl chloride under various conditions always led to some chlorination of the β-methyl group together with the α-methyl group. Since this side reaction could not be avoided, the synthesis of 11 was derived from the easily

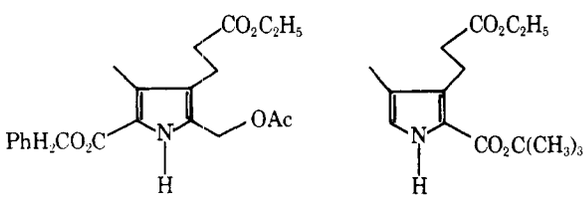


18, R = $CO_2C(CH_3)_3$; R′ = CH_3
19, R = $CO_2C(CH_3)_3$; R′ = CO_2H
20, R = $CO_2C(CH_3)_3$; R′ = CO_2CH_2Ph
21, R = CO_2H; R′ = CO_2CH_2Ph
22, R = I; R′ = CO_2CH_2Ph
23, R = H; R′ = CO_2CH_2Ph

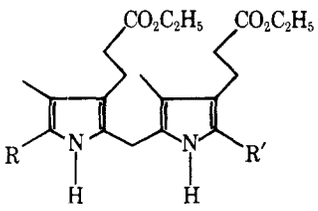
available pyrrole 18. Treatment of 18 with sulfuryl chloride in the presence of potassium carbonate spared the *tert*-butyloxy group and allowed the obtention of the acid 19 in reproducible yields. Esterification of 19 with benzyl chloride in the presence of triethylamine afforded pure 20, which was used as crude product and hydrolyzed with trifluoroacetic acid to 21. Iodination of 21 gave the 5-iodo-2-(benzyloxycarbonyl) ester 22, which was reduced with zinc in acetic acid to 23. This last procedure was found to be general for many α-iodopyrroles and allowed the synthesis of α-unsubstituted pyrroles in the presence of substituents carrying benzyl esters.

The hydrogenolysis of 6 and 7 gave the 5,5′-dicarboxydipyrrylmethanes 24 and 25, which were directly condensed with 5 to give 3 and 4. The coproporphyrins were isolated as their tetramethyl esters. The synthesis of 1 was achieved by first condensing the acetate 10 with the known pyrrole 26[12,13] (Scheme II). The condensation was carried out in methylene chloride in the presence of *p*-toluenesulfonic acid, and the resulting dipyrrylmethane 27 was transformed into the acid

Scheme II



10 26



27, R = CO_2CH_2Ph; R′ = $CO_2C(CH_3)_3$
28, R = CO_2H; R′ = $CO_2C(CH_3)_3$
29, R = H; R′ = $CO_2C(CH_3)_3$
30, R = CHO; R′ = $CO_2C(CH_3)_3$
31, R = CHO; R′ = CO_2H

28 by hydrogenolysis over Pd/C. Thermal decarboxylation of 28 gave the α-unsubstituted dipyrrylmethane 29, which was formylated to 30 by using dimethylformamide–benzoyl chloride.[14] The immonium chloride was extracted into water and hydrolyzed to 30 by adjusting the solution to pH 8. The 5-(*tert*-butyloxycarbonyl)-5′-formyldipyrrylmethane 30 was treated for a few minutes with 20% HBr in glacial acetic acid, which removed the *tert*-butyloxy ester group (as monitored by NMR), and the resulting formyl acid 31 was dissolved in methylene chloride and self-condensed to 1 by addition of *p*-toluenesulfonic acid. The condensation of 5 with the known acid 32 afforded 2. All four of the coproporphyrin isomers thus obtained were found to be the pure isomers when analyzed by the usual TLC methods.[8,15]

Experimental Section[16]

Ethyl 2-Methyl-4-(β-ethoxycarbonylethyl)-3-formyl-5-pyrrolecarboxylate (13). Phosphorus oxychloride (21.6 mL, 0.24 mol) was added dropwise to 39 mL of dimethylformamide at 5 °C, and the mixture was kept during 15 min at 20 °C. A solution of 9 g (0.036 mol) of pyrrole 12[9] in 60 mL of dimethylformamide was then slowly added to the former solution while the mixture was kept at 5 °C with continuous stirring under moisture exclusion conditions. The resulting solution was heated at 25 °C for 1 h and cooled, and a concentrated sodium hydroxide solution was added to adjust the mixture to pH 8. After a further heating at 75 °C during 15 min, the mixture was poured over 2 L of ice water and filtered, and the aldehyde 13 was recrystallized from ethanol–water: 6.5 g (65%); mp 123–124 °C (lit.[2] mp 121–122 °C). The aldehyde 13 was sublimed at 120 °C/0.05 torr for a final purification: NMR ($CDCl_3$) δ 1.3 (m, 6, $-CH_2CH_3$), 2.55 (s, 3, $-CH_3$), 3.1 (m, 4, $-CH_2CH_2CO_2R$), 4.2 (q, 4, $-CH_2CH_3$), 10.0 (s, 1, -CHO).

Anal. Calcd for $C_{14}H_{19}O_5N$: C, 59.8; H, 6.7; N, 5.0. Found: C, 59.7; H, 6.6; N, 5.1.

Ethyl 2,3-Dimethyl-4-(β-ethoxycarbonylethyl)-5-pyrrolecarboxylate (14). The sublimed aldehyde 13 (3.4 g) was dissolved in 150 mL of ethanol and was reduced with hydrogen at 50 psi during 15 h over 3 g of 10% palladium on charcoal. The catalyst was filtered, the solution was evaporated to dryness, and the residue was crystallized from methanol–water: 2.7 g (84%); mp 92–93 °C (lit. mp 88–89[2] and 94 °C[11]); NMR ($CDCl_3$) δ 1.3 (m, 6, $-CH_2CH_3$), 1.95 (s, 3, C_3-CH_3), 2.2 (s, 3, C_2-CH_3), 2.8 (m, 4, $-CH_2CH_2CO_2R$), 4.25 (q, 4, CH_2CH_3).

Anal. Calcd for $C_{14}H_{21}O_4N$: C, 62.9; H, 7.9; N, 5.2. Found: C, 63.1; H, 7.8; N, 5.1.

Benzyl 2,3-Dimethyl-4-(benzyloxycarbonylethyl)-5-pyrrolecarboxylate (16). Procedure A. The diethyl ester 14 (13 g) was dissolved in 12 mL of 10% sodium hydroxide and 6 mL of ethanol, and the mixture was evaporated to dryness at 110 °C. The residue was dissolved in 20 mL of water, the solution was adjusted to pH 2 with concentrated hydrochloric acid, and the precipitated acid 15 was filtered (2.0 g, 74%), dried, and dissolved in a mixture of 50 mL of dimethylformamide, 28 mL of triethylamine, and 30 mL of benzyl chloride. The mixture was kept at 20 °C during 48 h; it was then evaporated to dryness in vacuo (100 °C), and the residue dissolved in 200 mL of methylene chloride was washed with water (3 × 50 mL), 5% sodium bicarbonate (2 × 50 mL), and water again (2 × 50 mL) and then dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized from methanol: 3.2 g (74%); mp 127–129 °C (lit.[11] mp 130 °C); NMR ($CDCl_3$) δ 1.9 (s, 3, C_3-CH_3), 2.15 (s, 3, C_2-CH_3), 2.8 (m, 4, $CH_2CH_2CO_2R$), 5.1, 5.2 (s, 4, $CH_2C_6H_5$), 7.35 (br, 10, $-C_6H_5$).

Anal. Calcd for $C_{24}H_{25}O_4N$: C, 73.6; H, 6.4; N, 3.6. Found: C, 73.5; H, 6.4; N, 3.5.

Procedure B. The diethyl ester 14 (2 g) was dissolved in 800 mL of benzyl alcohol containing 0.1 g of sodium, and the mixture was heated during 72 h at 150 °C. The benzyl alcohol was distilled off in vacuo, and the residue was crystallized from methanol: 1.4 g (47%) of 16 was obtained; mp 127–129 °C.

Benzyl 2,3-Dimethyl-4-(β-ethoxycarbonylethyl)-5-pyrrolecarboxylate (17). Dibenzyl ester 16 (2 g) was added at 5 °C to a mixture of 24 mL of sulfuric acid and 480 mL of anhydrous ethanol. The mixture was kept with continuous stirring at 20 °C during 15 h. It was then poured over 600 mL of ice water, and the precipitate was filtered, dried, and crystallized from methanol–water: 1.5 g (83%); mp 81–83 °C; NMR ($CDCl_3$) δ 1.3 (t, 3, CH_2CH_3), 2.0 (s, 3, C_3-CH_3), 2.2 (s, 3, C_2-CH_3), 2.8 (m, 4, $-CH_2CH_2CO_2R$), 4.15 (q, 2, CH_2CH_3), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 (br, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{23}O_4N$: C, 69.3; H, 7.0; N, 4.2. Found: C, 69.9; H, 6.9; N, 4.1.

Benzyl 2-(Acetoxymethyl)-3-methyl-4-(β-ethoxycarbonylethyl)-5-pyrrolecarboxylate (8). Lead tetraacetate (6 g) was added in small portions during 1 h to a stirred solution of 3 g of 17 in 30 mL of glacial acetic acid. The solution was kept at 20 °C with constant stirring during a further 15 h. It was then poured into 500 mL of ice water, and the precipitate was filtered and crystallized from methanol–water: 2.2 g (75%); mp 80–82 °C; NMR ($CDCl_3$) δ 1.2 (t, 3, CH_2CH_3), 2.05 (br, 6, C_3-CH_3, $OCOCH_3$), 2.75 (m, 4, CH_2CH_2CO), 4.1 (q, 2, CH_2CH_3), 5.0 (s, 2, CH_2OCOCH_3), 5.3 (s, 2, $-CH_2C_6H_5$), 7.35 (br, 5, C_6H_5).

Anal. Calcd for $C_{21}H_{25}O_6N$: C, 65.1; H, 6.5; N, 3.6. Found: C, 65.1; H, 6.6; N, 3.5.

***tert*-Butyl 2,4-Dimethyl-3-(β-ethoxycarbonylethyl)-5-pyrrolecarboxylate (18).** A solution of 20 g of sodium nitrite in 70 mL of water was slowly added to a stirred solution of 50 g of *tert*-butyl acetoacetate and 87 mL of glacial acetic acid, and the temperature was kept below 5 °C until the addition was completed. The mixture was kept overnight at 5 °C and was then added to a stirred mixture of 53 g of ethyl 4-acetyl-5-oxohexanoate, 54 g of zinc, and 54 g of sodium acetate in 58 mL of acetic acid. Supplemental 54 g of zinc was simultaneously added to the mixture, which warmed up spontaneously. After the additions were completed, the mixture was further heated at 65 °C during 1 h and then was cooled and poured over 1 L of ice water. The precipitate was filtered and crystallized from methanol–water: 2.8 g (30%); mp 66–68 °C; NMR ($CDCl_3$) δ 1.25 (t, 3, CH_2CH_3), 1.55 (s, 9, $-C(CH_3)_3$), 2.2, 2.25 (s, 6, $-CH_3$), 2.55 (m, 4, CH_2CH_2CO), 4.15 (q, 2, CH_2CH_3).

Anal. Calcd for $C_{16}H_{25}O_4N$: C, 65.1; H, 8.5; N, 4.7. Found: C, 65.3; H, 8.6; N, 4.8.

***tert*-Butyl 2-Carboxy-3-(β-ethoxycarbonylethyl)-4-methyl-5-pyrrolecarboxylate (19).** To a mixture of pyrrole 18 (9 g) and 11 g of anhydrous potassium carbonate in 200 mL of carbon tetrachloride was slowly added 9 mL of sulfuryl chloride in 200 mL of carbon tetrachloride over a period of 30 min. The stirred mixture was heated during 4 h at 50 °C under a stream of nitrogen and then cooled, the potassium carbonate was filtered, and the solution was evaporated to dryness. The residue was dissolved in a mixture of 20 g of sodium acetate in 200 mL of 50% dioxane. The solution was heated at 110 °C for 2 h, cooled, diluted with 200 mL of water, adjusted to pH 2 with concentrated hydrochloric acid, and extracted (3 × 50 mL) with ethyl ether. The pooled ethereal extracts were extracted with a saturated sodium carbonate solution, which was then adjusted to pH 2 with concentrated hydrochloric acid. The precipitate was filtered, dried, and crystallized from methanol–water: 1.5 g (30%); mp 120–121 °C; NMR ($CDCl_3$) δ 1.25 (t, 3, CH_2CH_3), 1.60 (s, 9, $C(CH_3)_3$), 2.30 (s, 3, $-CH_3$), 2.8 (m, 4, $-CH_2CH_2CO$), 4.15 (q, 2, CH_2CH_3).

Anal. Calcd for $C_{16}H_{23}O_6N$: C, 59.1; H, 7.1; N, 4.3. Found: C, 59.2; H, 7.2; N, 4.3.

Benzyl 3-(β-Ethoxycarbonylethyl)-4-methyl-5-carboxy-2-pyrrolecarboxylate (21). The acid 19 (1.8 g) was dissolved in a mixture of 45 mL of dimethylformamide, 25 mL of triethylamine, and

30 mL of benzyl chloride, and the mixture was kept during 48 h at 20 °C under moisture exclusion conditions. The solution was then evaporated to dryness in vacuo (100 °C). The residue dissolved in 100 mL of methylene chloride was washed with a sodium carbonate saturated solution followed by a water wash, dried (Na_2SO_4), and evaporated to dryness. The residual **20** was an oily substance [NMR ($CDCl_3$) δ 1.55 (br, 9, $C(CH_3)_3$), 5.3 (s, 2, CH_2Ph), 7.4 (br, 5, Ph)] which was directly dissolved in trifluoroacetic acid (10 mL), and the solution was kept at 5 °C during 15 h. It was then poured over ice water (50 mL) and filtered. The residue was crystallized from methanol: 1.75 g (88%); mp 200–202 °C; NMR (TFA) δ 1.2 (t, 3, CH_2CH_3), 2.25 (s, 3, $-CH_3$), 2.8 (m, 4, $-CH_2CH_2CO$), 4.1 (q, 2, $-CH_2CH_3$), 5.3 (s, 2, $-CH_2C_6H_5$), 7.4 (br, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{21}O_6N$: C, 63.5; H, 5.8; N, 3.9. Found: C, 63.5; H, 5.9; N, 3.8.

Benzyl 3-(β-Ethoxycarbonylethyl)-4-methyl-5-iodo-2-pyrrolecarboxylate (22). The acid **21** (1.75 g) was dissolved in 30 mL of water containing 5.3 g of sodium carbonate, and the solution was added to a stirred mixture of 1.8 g of iodine and 5.3 g of potassium iodide in 30 mL of water. The final mixture was heated at 90 °C during 1 h, cooled, and filtered. The precipitate was crystallized from ethanol–water: 1.8 g (85%); mp 103–105 °C; NMR ($CDCl_3$) δ 1.2 (t, 3, $-CH_2CH_3$), 2.0 (s, 3, $-CH_3$), 2.75 (m, 4, $-CH_2CH_2CO$), 4.05 (q, 2, $-CH_2CH_3$), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 (br, 5, C_6H_5).

Anal. Calcd for $C_{18}H_{20}O_4NI$: C, 49.0; H, 4.5; N, 3.1. Found: C, 48.9; H, 4.6; N, 3.1.

Benzyl 3-(β-Ethoxycarbonylethyl)-4-methyl-2-pyrrolecarboxylate (23). The iodopyrrole **22** (1.5 g) was added to a suspension of 1.5 g of zinc in 75 mL of glacial acetic acid, and the mixture was heated at 130 °C during 3 h. Additional zinc (1.5 g) was added in portions during the heating. The mixture was then cooled, 0.2 mL of concentrated hydrochloric acid was added, the zinc was filtered off, the filtrate was diluted with 250 mL of ice water, and the precipitate was filtered, dried, and crystallized from cyclohexane: 1 g (92%); mp 56–57 °C; NMR ($CDCl_3$) δ 1.2 (t, 3, CH_2CH_3), 2.05 (s, 3, $-CH_3$), 2.8 (m, 4, CH_2CH_2CO), 4.15 (q, 2, $-CH_2CH_3$), 5.35 (s, 2, $-CH_2C_6H_5$), 6.7 (br, 1, H_5), 7.45 (br, 5, C_6H_5).

Anal. Calcd for $C_{18}H_{21}O_4N$: C, 68.6; H, 6.6; N, 4.4. Found: C, 68.6; H, 6.7; N, 4.6.

Dibenzyl 3,4′-Bis(β-ethoxycarbonylethyl)-4,3′-dimethyl-5,5′-dipyrrylmethanedicarboxylate (6). The acetate **10**[17] (600 mg, 1.55 mmol) and the pyrrole **23** (488 mg, 1.55 mmol) were dissolved in 10 mL of glacial acetic acid, 10 mg of *p*-toluenesulfonic acid was added, and the mixture was heated at 45 °C during 3 h, cooled, and poured over 50 mL of water. The suspension was extracted with methylene chloride (3 × 20 mL). The extracts were washed with a saturated sodium bicarbonate solution and then with water, dried (Na_2SO_4), and evaporated in vacuo, and the residue crystallized from *n*-propyl alcohol–water: 740 mg (74%); mp 73–75 °C; NMR ($CDCl_3$) δ 1.2 (m, 6, $-CH_2CH_3$), 2.0 (s, 3, C_3-CH_3), 2.3 (s, 3, C_4-CH_3), 2.7 (m, 8, CH_2CH_2CO), 3.8 (s, 2, $-CH_2-$), 4.0 (q, 4, $-CH_2CH_3$), 5.2 (s, 4, $-CH_2C_6H_5$), 7.3 (br, 10, C_6H_5). It was homogeneous when checked by TLC on silica gel (3% methanol in benzene).

Anal. Calcd for $C_{37}H_{42}O_8N_2$: C, 69.2; H, 6.5; N, 4.4. Found: C, 69.1; H, 6.5; N, 4.5.

Dibenzyl 3,3′-Dimethyl-4,4′-bis(β-ethoxycarbonylethyl)-5,5′-dipyrrylmethanedicarboxylate (7). Procedure A. The acetate **8** (600 mg) was dissolved in a mixture of 14 mL of ethanol and 1 mL of hydrochloric acid, and the solution was heated at 100 °C during 6 h. The solution was cooled and diluted with water. The precipitated **7** was filtered, dried, and crystallized from methanol: 290 mg (60%); mp 77–79 °C; NMR ($CDCl_3$) δ 1.2 (t, 6, $-CH_2CH_3$), 2.0 (s, 6, $-CH_3$), 2.7 (m, 8, $-CH_2CH_2CO$), 3.7 (s, 2, $-CH_2-$), 4.0 (q, 4, $-CH_2CH_3$), 5.1 (s, 4, $CH_2C_6H_5$), 7.3 (br, 10, C_6H_5). It was homogeneous when checked by TLC on silica gel (2% methanol in benzene).

Anal. Calcd for $C_{37}H_{42}O_8N_2$: C, 69.2; H, 6.5; N, 4.4. Found: C, 69.1; H, 6.5; N, 4.5.

Procedure B. The acetate **8** (387 mg, 1 mmol) was condensed with the pyrrole **23** (315 mg) following the procedure described for the synthesis of **6**. Dipyrrylmethane **7** (320 mg, 50%) was obtained following the procedure described for **6**.

***tert*-Butyl 3,4′-Dimethyl-4,3′-bis(β-ethoxycarbonylethyl)-5′-(benzyloxycarbonyl)-5-dipyrrylmethanecarboxylate (27).** A solution of 720 mg (1.8 mmol) of the acetate **10**,[17] 650 mg (2.3 mmol) of the pyrrole **26**,[12,13] and 50 mg of *p*-toluenesulfonic acid in 50 mL of dry methylene chloride was heated at 35 °C during 6 h. The solution was cooled, washed with a saturated solution of sodium acetate and then with water, dried (Na_2SO_4), and evaporated to dryness. The oily residue was purified by PLC (layer thickness, 2 mm) on silica gel using 2% methanol in benzene: 500 mg (44%) of **27** was obtained; NMR ($CDCl_3$) δ 1.2 (m, 6, $-CH_2CH_3$), 1.5 (s, 9, $C(CH_3)_3$), 2.0 (s, 3, C_3-CH_3), 2.25 (s, 3, C_4-CH_3), 2.6 (m, 8, $-CH_2CH_2CO$), 3.85 (s, 2, $-CH_2-$), 4.1 (m, 4, $-CH_2CH_3$), 5.25 (s, 2, $CH_2C_6H_5$), 7.35 (br, 5, C_6H_5); MS *m/e* 608 (M^+, 5), 551 ($M^+ - C(CH_3)_3$, 12), 461 (551 − $CH_2Ph + H^+$, 14), 149 (100).

***tert*-Butyl 3,4′-Dimethyl-4,3′-bis(β-ethoxycarbonylethyl)-5-dipyrrylmethanecarboxylate (29).** A solution of 500 mg of **27** in 20 mL of methanol was reduced at 50 psi during 2 h over 250 mg of 10% palladium on charcoal. The solution was evaporated to dryness in vacuo, and the residual acid **28** was crystallized from benzene–hexane (280 mg, 66%; mp 128–130 °C) and heated at 160–165 °C at 0.05 torr during 3 min. The residue was dissolved in 2% methanol in benzene and was purified by filtration through a TLC silica gel packed column (20 × 2 cm) using the same solvent as eluant: 185 mg (92%); NMR ($CDCl_3$) δ 1.2 (m, 6, $-CH_2CH_3$), 1.5 (s, 9, $C(CH_3)_3$), 2.0 (br, 6, $-CH_3$), 2.7 (m, 8, $CH_2CH_2CO_2R$), 3.85 (s, 2, $-CH_2-$), 4.15 (m, 4, $-CH_2CH_3$), 6.4 (br, 1); it was homogeneous when submitted to TLC analysis; MS *m/e* 474 (M^+, 62), 418 (M^+ − isobutylene, 100).

***tert*-Butyl 3,4′-Dimethyl-4,3′-bis(β-ethoxycarbonylethyl)-5′-formyl-5-dipyrrylmethanecarboxylate (30).** A solution of 165 mg of the dipyrrylmethane **29** in 0.4 mL of dimethylformamide was cooled at 5 °C, and 0.2 mL of benzoyl chloride was added in one portion. The mixture was kept under moisture exclusion conditions during 1 h at 20 °C and was then diluted with 5 mL of ethyl ether. The solution was extracted with water (3 × 2 mL). The aqueous extract was washed with ethyl ether (2 mL), diluted with 2 mL of methanol, and adjusted to pH 8 with a 5% sodium carbonate solution. The mixture was kept at 20 °C during 2 h and then was cooled at 5 °C, filtered, dried, and crystallized from methanol: 130 mg (74%); mp 122–123 °C; NMR ($CDCl_3$) δ 1.2 (m, 6, $-CH_2CH_3$), 1.5 (s, 9, $C(CH_3)_3$), 2.0, 2.1 (s, s, 6, $-CH_3$), 2.6 (m, 8, $-CH_2CH_2CO$), 3.8 (s, 2, $-CH_2-$), 4.1 (q, 4, $-CH_2CH_3$), 9.5 (s, 1, CHO).

Anal. Calcd for $C_{27}H_{38}O_7N_2$: C, 64.5; H, 7.6; N, 5.6. Found: C, 64.3; H, 7.6; N, 5.5.

Coproporphyrin III (3) (Tetramethyl Ester). A solution of 300 mg of the dibenzyl ester **6** in 20 mL of dry tetrahydrofuran and 0.3 mL of triethylamine was reduced over 300 mg of 10% palladium on charcoal at 50 psi during 4 h. The catalyst was filtered, the solution was evaporated to dryness in vacuo, the residue was dissolved in 5 mL of a diluted ammonium hydroxyde solution, and the diacid **24** was precipitated with glacial acetic acid, filtered, and dried. The diacid **24** (184 mg, 85%) was dissolved in a mixture of 185 mL of dry methylene chloride and 185 mL of anhydrous methanol. Diformyldipyrrylmethane **5**[14] (185 mg) was added. The solution was halved, 225 mg of *p*-toluenesulfonic acid was added to each half, and the mixtures were left during 24 h at 20 °C in the dark. Methanol (20 mL) saturated with zinc acetate dihydrate was added to each solution. The mixtures were kept in the dark for a further 48 h at 20 °C, and they were then pooled and evaporated to dryness in vacuo. The residue was dissolved in 200 mL of a 5% sulfuric acid solution in methanol and kept at 20 °C during 16 h. The solution was then diluted with 600 mL of chloroform, washed with 200 mL of ice water, then with 250 mL of a 5% sodium carbonate solution, and again with water (200 mL), dried (Na_2SO_4), and evaporated to dryness in vacuo at 40 °C. The residue was dissolved in a small volume of 3% methanol in benzene and filtered through a column (3 × 30 cm) of TLC silica gel, packed and prewashed with the same solvent. The main porphyrin band was eluted by applying a small pressure. The eluate was evaporated to dryness, and the tetramethyl ester of **3** was crystallized from benzene–cyclohexane: 74 mg (40%); mp 164–166 °C (lit.[3] mp 179–182 °C; lit.[2] mp softening 153–155 °C, melting 178–182 °C); NMR (0.05 M $CDCl_3$) δ 3.25 (m, 8, CH_2CO_2R), 3.6 (br, 12, $-CH_3$), 3.7 (br, 12, $-OCH_3$), 4.4 (m, 8, $-CH_2CH_2CO_2R$), 9.9 (br, 4, $-CH=$); MS *m/e* 710 (M^+, 85).

Anal. Calcd for $C_{40}H_{46}O_8N_4$: C, 67.6; H, 6.5; N, 7.9. Found: C, 67.5; H, 6.4; N, 7.9.

A sample of the tetramethyl ester was hydrolyzed to **3**, whose isomeric purity was established by TLC on cellulose-coated plates.[8,15]

Coproporphyrin IV (4) (Tetramethyl Ester). Dibenzyl ester **7** (300 mg) was reduced following the procedure described in the synthesis of **3**. The diacid (206 mg, 95%) was condensed with 200 mg of the diformylpyrrylmethane **5** as described for the synthesis of **3**. Esterification with methanol–sulfuric acid and purification by chromatography on a TLC silica gel column as described for **3** afforded **4** as its tetramethyl ester: 80 mg (40%); mp 181–183 °C (lit. mp 183–185[3] and 183–184 °C[2]); NMR (0.05 M $CDCl_3$) δ 3.25 (m, 8, $-CH_2CO_2R$), 3.5, 3.6 (s, s, 12, $-CH_3$), 3.7 (s, 12, $-OCH_3$), 4.35 (m, 8, $-CH_2CH_2CO_2R$), 9.9, 10.0, 10.1 (s, s, s, 1, 2, 1, $-CH=$); MS *m/e* 710 (M^+, 45).

Anal. Calcd for $C_{40}H_{46}O_8N_4$: C, 67.6; H, 6.5; N, 7.9. Found: C, 67.5;

H, 6.5; N, 7.8.

The isomeric purity of the tetramethyl ester of **4** was checked by hydrolysis of the ester to **4** and TLC analysis of the latter.[15]

Coproporphyrin I (1) (Tetramethyl Ester). The formyldipyrrylmethane **30** (100 mg) was dissolved in a mixture of 2 mL of glacial acetic acid and 0.4 mL of 40% hydrobromic acid in glacial acetic acid. The solution was kept at 5 °C during 15 min. It was then freeze-dried, the residue was dissolved in 60 mL of anhydrous methanol, and 100 mg of *p*-toluenesulfonic acid was added. The mixture was kept during 24 h at 20 °C in the dark. Methanol (10 mL) saturated with zinc acetate dihydrate was added to the solution, and the procedure described for the synthesis of **3** was followed to obtain **1** as its tetramethyl ester: 30 mg (43%); mp 245–247 °C (from methylene chloride–cyclohexane) (lit. mp 248–252[1] and 252–255 °C[3]); NMR (0.05 M $CDCl_3$) δ 3.25 (m, 8, CH_2CO_2R), 3.65, 3.7 (br, br, 24, OCH_3, CH_3), 4.4 (m, 8, $CH_2CH_2CO_2R$), 9.9 (br, 4, -CH=); MS *m/e* 710 (M^+, 35).

Anal. Calcd for $C_{40}H_{46}O_8N_4$: C, 67.6; H, 6.5; N, 7.9. Found: C, 67.4; H, 6.2; N, 7.8.

Hydrolysis of the ester (6 M hydrochloric acid) gave **1**, which was pure by TLC analysis.[8]

Coproporphyrin II (2) (tetramethyl ester) was obtained following the procedure described for **3** and **4**. Condensation of 200 mg of the diacid **32**[14] and 200 mg of the diformyldipyrrylmethane **5** afforded 68 mg (30%) of **2** (tetramethyl ester): mp 285–287 °C (lit.[3] mp 286–289 °C); NMR (0.05 M $CDCl_3$) δ 3.25 (m, 8, CH_2CO_2R), 3.55, 3.6 (br, br, 24, CH_3, OCH_3), 4.35 (m, 8, $CH_2CH_2CO_2R$), 10.0 (br, 4, CH=); MS *m/e* 710 (M^+, 100).

Anal. Calcd for $C_{40}H_{46}O_8N_4$: C, 67.6; H, 6.5; N, 7.9. Found: C, 67.5; H, 6.3; N, 7.8.

Hydrolysis of the ester (6 M hydrochloric acid) gave **2**, which was pure by TLC analysis.[8]

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Registry No.—**1** (tetramethyl ester), 25767-20-8; **2** (tetramethyl ester), 865-16-7; **3** (tetramethyl ester), 5522-63-4; **4** (tetramethyl ester), 13306-30-4; **5**, 21211-64-3; **6**, 68781-31-7; **7**, 60204-96-8; **8**, 58684-20-1; **10**, 51741-18-5; **12**, 53700-88-2; **13**, 6122-77-6; **14**, 54278-18-1; **15**, 54278-16-9; **16**, 62562-72-5; **17**, 68781-32-8; **18**, 68781-33-9; **19**, 68781-34-0; **20**, 68781-35-1; **21**, 68781-36-2; **22**, 68781-37-3; **23**, 68781-38-4; **24**, 68813-11-6; **26**, 62562-80-5; **27**, 68781-39-5; **28**, 68781-40-8; **29**, 68813-12-7; **30**, 68781-41-9; **32**, 52091-10-8; *tert*-butyl acetoacetate, 1694-31-1; ethyl 4-acetyl-5-oxohexanoate, 2832-10-2.

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1,3-Diphenyldibenzo[*g,i*]thieno[3′,4′:3,4]pyrrolo[1,2-*a*]pyridine-2-S^{IV}, a New "Nonclassical" Thiophene System

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1,2-Dibenzoyldibenzo[*e,g*]pyrrolo[1,2-*a*]pyridine and P_4S_{10} at 140 °C in dry xylene gave 1,3-diphenyldibenzo[*g,i*]-thieno[3′,4′:3,4]pyrrolo[1,2-*a*]pyridine-2-S^{IV}, a "nonclassical" thiophene containing only three aromatic substituents attached to the thienopyrrole nucleus. Unstable to oxygen and light, it did not undergo cycloaddition with electron-deficient dipolarophiles. The analogous 1,3-diphenylbenzo[*g*]thieno[3′,4′:3,4]pyrrolo[1,2-*a*]pyridine-2-S^{IV} was prepared in a similar manner from 1,2-dibenzoylbenzo[*e*]pyrrolo[1,2-*a*]pyridine but was so unstable that it only had a transient existence. Other derivatives of the benzo- and dibenzopyrrolo[1,2-*a*]pyridine systems were prepared by cycloaddition reactions involving dimethyl acetylenedicarboxylate and intermediate anhydro-2-hydroxyoxazolium hydroxides derived from the corresponding 5-o..ophenanthridine and 2-oxoquinoline- and 1-oxoisoquinoline-*N*-acetic acids.

The "nonclassical" thiophenes, the thieno[3,4-*c*]thiophene (**1**), and the thieno[3,4-*c*]pyrrole (**2**) systems have only been isolated with aromatic substituents in the 1, 3, 4, and 6 positions.[2] It has been suggested that these aromatic substituents stabilize the system by electron delocalization or by a steric effect or by some combination of both, and in an effort to obtain experimental understanding of the role of these groups, we have attempted to synthesize representatives of the thieno[3,4-*c*]pyrrole system with fewer aromatic substituents. In an earlier study[3] attempted ring closure of 3,4-dibenzoyl-2-phenyl-1-methyl(or 1-phenyl)pyrrole to the corresponding thienopyrrole system was unsuccessful, the corresponding 3,4-bis(thiobenzoyl) derivatives of the pyrroles being obtained. In this present study our aim was to introduce additional conjugation involving one of the aromatic substituents to see whether this more extensive delocalization would allow the isolation of the fused-ring system with essentially three aromatic substituents. Suitable ring systems meeting these requirements would be those based on phenanthridine, quinoline, and isoquinoline and this publication describes our results in this area.

The most direc⁺ route to the desired system **7** involves ring

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