Studies of Spiro-chlorin Formation Using Porphyrin Amides

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Syntheses of 7-(3-ethoxycarbonylpropyl)-2,3,5-triethyl-1,4,6,8-tetramethylporphyrin (**8**) (*via* the MacDonald dipyrrylmethane route) and 2-(2-chloroethyl)-4-ethyl-6-methoxycarbonyl-7-(3-methoxycarbonylpropyl)-1,3,5,8-tetramethylporphyrin (**22**) (*via* the tripyrrene route) are described. The corresponding pyrrolidides of these compounds were cyclized in high yield to furnish the spiro imines (**20** and **30** respectively), but attempts to hydrolyze these imines to the appropriate spiroketochlorins were largely unsuccessful. A small amount of the spiroketochlorin **9** (from **8**) was obtained, and this was successfully hydrogenated to give the dihydro derivative **21**. The major problem in imine hydrolysis was observed to be reversion to the parent porphyrin through simple bond migration and spiro ring cleavage. A successful transformation of protoporphyrin-IX dimethyl ester (**31**) into mesoporphyrin-IX dimethyl ester (**32**) using di-imide generated from di-potassium azodicarboxylate is described.

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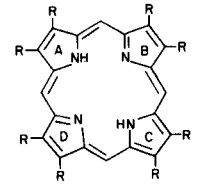
Methods for regioselective transformation of the porphyrin nucleus (**1**) into its chlorin (7,8-dihydroporphyrin) analog (**2**) are severely limited. With the exception of Fischer's sodium in alcohol reduction of γ-phylloporphyrin-XV (2) [which depends critically upon the substituents (3)], straightforward reduction of porphyrins to chlorins is non-specific with regard to the pyrrole sub-unit affected. On the other hand, several examples of controlled spiro-chlorin formation have been described (4-8); the most celebrated of these (**3**→**4**) is that used by Woodward (5) in his synthesis of chlorophyll-a. *Gem*-Disubstituted chlorins have again been cast into the limelight with the determination of the structure of sirohemes (9) from sulfite and nitrite reductases, and with the demonstration (10) that sirohydrochlorin (**5**) is an intermediate in the biosynthesis of vitamin B_{12}.



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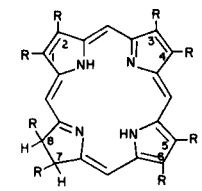

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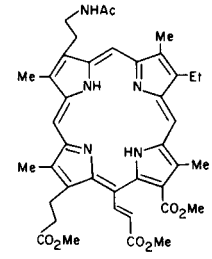

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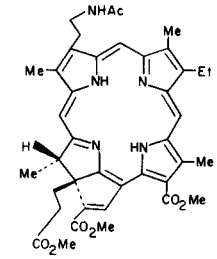

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In this paper we describe the development of a route to spiroketochlorins which is capable of further modification for sirohydrochlorin and normal (dihydro) chlorin synthesis. Our approach is based upon the phosphoryl chloride catalyzed cyclization (**6**→**7**) reported some years ago by Collier, *et al.*, (4). Unfortunately, as a result of an unexpected reversion back to porphyrin during the final hydrolysis stage of the spiro-chlorin formation, yields of the required product were disappointing.

Model Studies.

In order to investigate spirochlorin ring formation as a viable route to a synthesis of chlorophyll-a, we decided to initially employ a porphyrin which was substituted with alkyl groups, rather than the unsymmetrical array required in a chlorophyll-a precursor. For the present purposes, we also preferred to have a carbocyclic rather than heterocyclic [*Cf.* Collier, *et al.*, (4)] spiro ring. We reasoned that the porphyrin **8** with a butyric acid ester side chain might afford **9**, in which the spiroketo ring would be amenable to opening to give **10** (for sirohydrochlorin syntheses) or **11** (for normal chlorophyll-a synthesis) (Scheme 1). Our initial synthetic objective was therefore the model porphyrin **8** with a butyric acid ester side chain in which the remaining seven alkyl groups had been chosen for ease of synthesis using the 2 + 2 MacDonald method (11).

Attempts to react the bromoethylpyrrole **12** with *t*-butyl ethyl sodiomalonate were unsuccessful, so we turned to direct formation of the pyrrole ester **13**, (R = H) with a butyric acid ester side chain from diones. Accordingly, acetylacetone was alkylated with ethyl bromobutyrate in acetone/potassium carbonate to give the dione **14**. Under standard conditions with oximino benzyl acetoacetate, this

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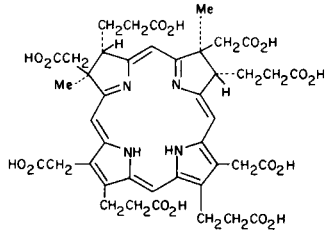
gave 46-51% yields of pyrrole **13** (R = H). With lead tetraacetate, **13** (R = H) gave a 98% yield of the acetoxymethylpyrrole **13** (R = OAc) which was treated with the known (12) 5-unsubstituted pyrrole **15** in acetic acid containing a catalytic quantity of toluene *p*-sulfonic acid (13) to give dipyrrylmethane (**16**), in good yield. Catalytic hydrogenolysis cleaved the benzyl ester in **16**, and treatment with trifluoroacetic acid then gave the 5,5'-diunsubstituted dipyrrylmethane, **17**, which was condensed in methanol and methylene chloride containing toluene *p*-sulfonic acid with the diformyldipyrrylmethane, **18**, to give the required porphyrin, **8**, with a butyric acid ester side chain in 37% yield from **16** and **18**.

In order to mimic the amide/phosphoryl chloride cyclization (4), we decided to synthesize the pyrrolidide **19**, and this was accomplished in 90% yield from **8** by treatment with pyrrolidine/hydrogen chloride in tetrahydrofuran. Treatment of **19** with phosphoryl chloride in pyridine at 60° during three hours led to a quantitative formation (spectrophotometry) of the chlorin **20**. Tlc showed most of the material to be very polar, as might be expected for the imine salt, **20**, but some hydrolysis had apparently occurred during the work-up, and a small amount of fast running material on preparative tlc was



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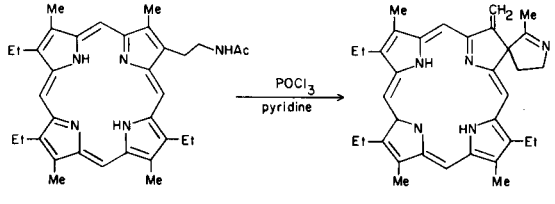
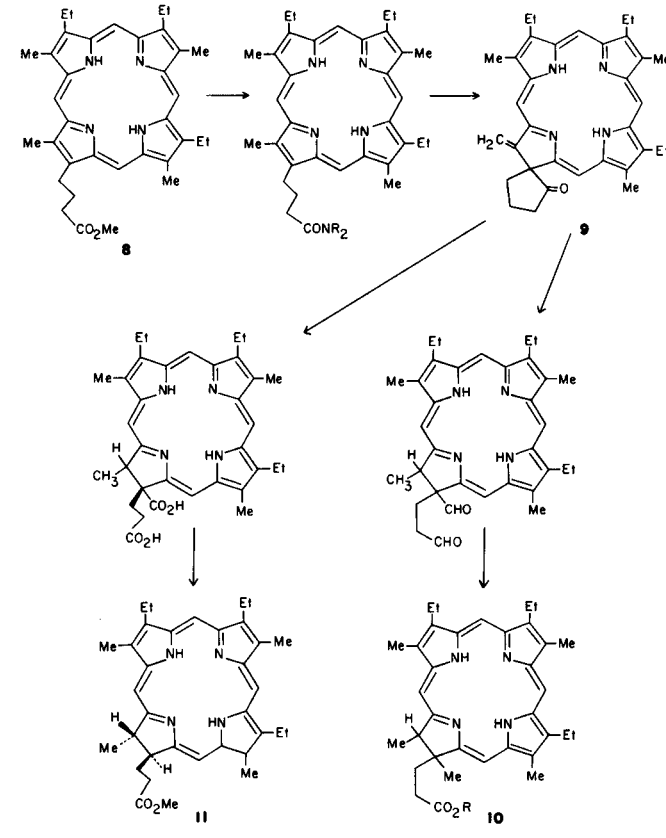


6 **7**

shown to be the spiroketochlorin **9**. Attempts to carry out a separate hydrolysis of the remaining imine salt, **20**, were uniformly unsuccessful, but we did not spend much time attempting to optimize conditions since we were anxious to move to a system with more relevant substituents, and away from our model. The major type of reaction observed was reversion to porphyrin, and if strong bases, or acids, or high temperatures were used, this reversion (Scheme 2) was often quantitative. This can be readily rationalized since the imine **20** is still at the oxidation level of a porphyrin, and the driving force for bond migration to return to the porphyrin chromophore must be high. If methanol

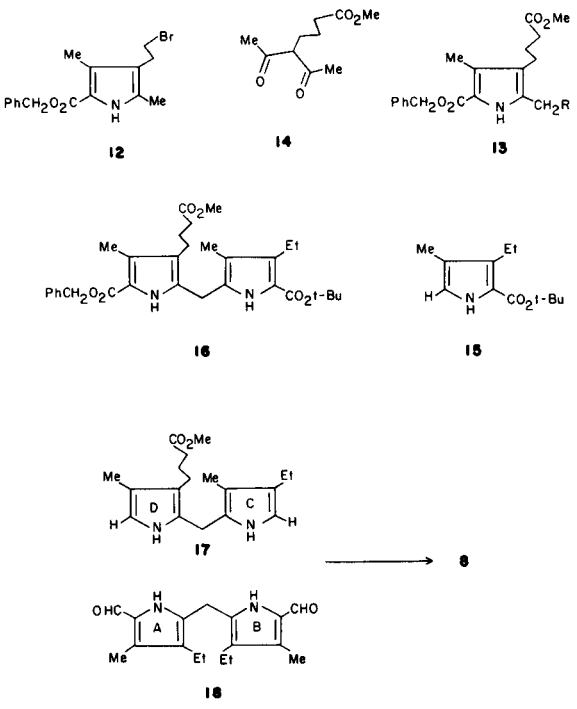


Scheme I

was used to destroy excess phosphoryl chloride then part of the recovered porphyrin was as the methyl ester. However, catalytic hydrogenation of the spiroketochlorin **9** was successful, and the dihydro derivative **21** was obtained in 83% yield. It was clear from nmr spectra at 220 MHz that only one stereoisomer had been produced, and comparison of the shifts for the 8-H and 8-CH_3 with those in methyl pheophorbide-a and other natural chlorins suggested that the stereochemistry was as shown in structure **21**, *i.e.*, the opposite to that nominally required for a synthesis of chlorophyll-a. We suspected that, nevertheless, during the opening and decarboxylation steps required later (Scheme 1), the most stable, *trans*, arrangement in ring D would prevail.

Studies Using a Possible Chlorophyll-a Synthetic Intermediate.

Our immediate synthetic objective for the non-model series was the compound, **22**, which is related to 2-vinylrhodoporphyrin-XV ester except that the propionic ester has been exchanged for at butyric ester at position 7 (14). Since the compound is completely unsymmetrical from the synthetic standpoint, we chose to use the tripyrrene route (15) to accomplish its synthesis. The dipyrrylmethane **23** (13) was hydrogenated to give the carboxylic acid, **24**, which was condensed in methylene chloride and methanol containing toluene *p*-sulfonic acid, with the formyl pyrrole



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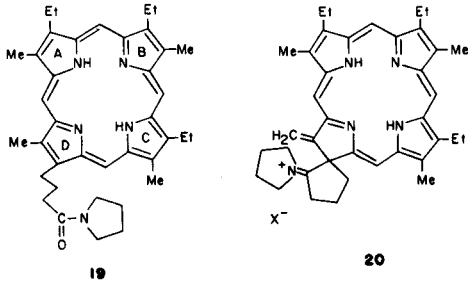
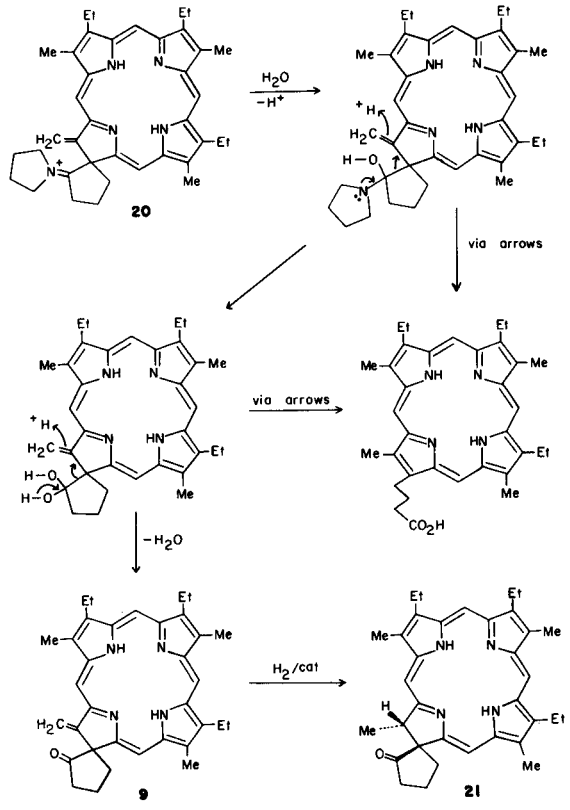


19 20

25 (obtained by catalytic debenzylation of pyrrole **13** (R = H) followed by decarboxylation and Vilsmeier formylation) to give the crystalline and fully characterized tripyrrene salt **26**. With formylpyrrole **27** in trifluoroacetic and hydrobromic acids, the a,c-biladiene dihydrobromide **28** was obtained in 84% yield. Cyclization of the a,c-biladiene in refluxing dimethylformamide with copper(II) chloride gave the copper porphyrin which was directly demetalated using 50% sulfuric acid in trifluoroacetic acid, to give the required porphyrin **22** after re-esterification. The next step was to prepare the 7-substituent for spirochlorin formation; this was accomplished by treatment of the diester **22** with pyrrolidine/hydrogen chloride in tetrahydrofuran as previously. As expected, the nuclear ester was not sensitive to these conditions, and after recycling, a 95% yield of the monoamide **29** was obtained. Conversion of **29** into the spirochlorin imine was successful and a prominent peak at 672 nm was soon apparent. However, when handled, the spiro chlorin reverted almost entirely to the porphyrin

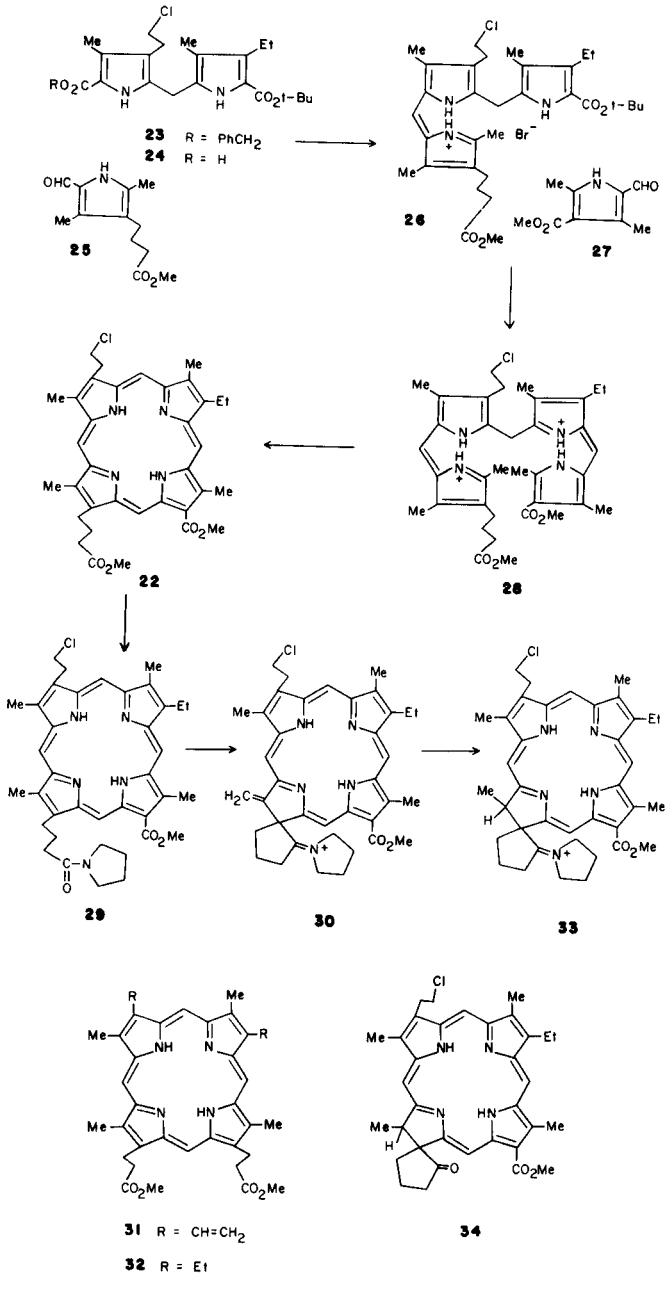


20 via arrows via arrows 9 21

Scheme 2

system, even more readily than in the model series. The same observations were made with the zinc(II) complex of **29**. Attempts to form the spirochlorin using *p*-toluenesulfonyl chloride, or thionyl chloride, were also unsuccessful.

We reasoned that the reversion to porphyrin during the hydrolysis stage (Scheme 2) could be avoided if the exocyclic double bond in the imine **30** could be reduced prior to hydrolysis, provided conditions could be found which would not also cause reduction of the imine function. Catalytic hydrogenation of the imine **30** yielded only very polar products which could not be characterized, even after hydrolysis. Model studies showed that protoporphyrin-IX dimethyl ester (**31**) could be readily transformed into mesoporphyrin-IX dimethyl ester (**32**) using di-imide generated from dipotassium azodicarboxylate, and this was applied to the spirochlorin system. A standard phosphoryl chloride/pyridine cyclization of **29** or its zinc(II) complex gave the corresponding imine which was treated with di-imide. The product obtained, presumably **33**, was stable but a satisfactory C,H,N analysis for it could not be obtained, possibly on account of mixed counterions being present. The Soret band in the visible spectrum showed a 10 nm hypsochromic shift indicating (see reference 4 and the λ max difference between compounds **9** and **21**) that the exocyclic double bond had been



reduced. However, attempts to hydrolyze the product to give the spirochlorin **34** were unsuccessful, and supplies of material were exhausted in attempts to accomplish this transformation.

Conclusions.

Satisfactory methods for high yield syntheses of spiroimines from porphyrin amides have been developed. However, attempts to obtain the corresponding spiroketochlorins were thwarted by the reversion of the chlorin to the parent porphyrin.

EXPERIMENTAL

Melting points were measured on a microscopic hot stage apparatus, and are uncorrected. Tlc monitoring of all reactions was performed on glass slides coated with Merck GF 254 silicagel. Column chromatography was carried out on Merck neutral alumina. Electronic absorption spectra were measured using a Unicam SP-800 spectrophotometer, usually on solutions in methylene chloride. ^{1}H Nmr spectra were measured on a Varian XL-100 or Perkin-Elmer PE-34 instrument, in deuteriochloroform solution with tetramethylsilane as the internal standard. Mass spectra (direct insertion probe, 70 eV, 50 μA, source temp ca. 200°) were measured using and AEI MS-9 or AEI MS-12 instrument.

Benzyl 4-(3-Ethoxycarbonylpropyl)-3,5-dimethylpyrrole-2-carboxylate (**13**, R = H).

A solution of 82.2 g. of sodium nitrite in 140 ml. of water was added dropwise to a well stirred solution of 152 g. of benzyl acetoacetate in 67.5 ml. of glacial acetic acid, the temperature being kept below 10°. Stirring was maintained for a further 1 hour. Water and ether were added and the organic phase was dried over sodium sulfate before evaporation of the solvent under *vacuo*. The oxime obtained was dissolved in 60 ml. of glacial acetic acid and added to a solution of 170 g. ethyl 5-acetyl-6-oxoheptanoate (15) in 500 ml. of glacial acetic acid, at such a rate that the temperature was kept at 65°. At the same time an intimate mixture of 170 g. of zinc dust and 170 g. of anhydrous sodium acetate was added portionwise. Stirring was continued for a further 2.5 hours keeping the temperature at 65° and then the reaction mixture was slowly poured into ice-water. Recrystallization from aqueous methanol (three times) yielded colorless needles of the desired pyrrole (125 g., 46%; 51% on a 69 g. scale), m.p. 82-83°; nmr: δ 8.92 (1H, br) NH, 7.32 (5H, m) C_6H_5, 5.24 (2H, s) $C_6H_5CH_2$, 4.16 (2H, q) CH_2CH_3, 2.48-2.08 (4H, m), 1.77 (2H, q) $CH_2CH_2CH_2CO_2Et$, 2.26 (3H, s), 2.14 (3H, s) 2x Me, 1.24 (3H, t) CH_2CH_3.

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.82; H, 7.32; N, 4.32.

Benzyl 5-Acetoxymethyl-4-(3-ethoxycarbonylpropyl)-3-methylpyrrole-2-carboxylate (**13**, R = OAc).

Lead tetraacetate (14.4 g.) was added in portions over 2 hours to a stirred solution of 10.6 g. of the foregoing pyrrole in 170 ml. of glacial acetic acid and 3.4 ml. of acetic anhydride. After stirring overnight at room temperature, 200 ml. of water was added dropwise. The precipitated pyrrole was filtered, washed well with water, dried and recrystallized from ether-hexane to give colorless needles (10.5 g., 85%), m.p. 90.5-91.5°; nmr: δ 9.16 (1H, br) NH, 7.33 (5H, m) C_6H_5, 5.26 (2H, s) $C_6H_5CH_2$, 4.97 (2H, s) CH_2, 4.08 (2H, q) CH_2CH_3, 2.58-2.16 (4H, m), 1.92-1.62 (2H, m) $CH_2CH_2CH_2CO_2Et$, 2.27 (3H, s) Me, 2.02 (3H, s) $COCH_3$, 1.23 (3H, t) CH_2CH_3.

Anal. Calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.64; H, 6.75; N, 3.50.

2-Formyl-3,5-dimethyl-4-(3-ethoxycarbonylpropyl)pyrrole (**25**).

Benzyl 4-(3-ethoxycarbonylpropyl)-3,5-dimethylpyrrole-2-carboxylate **13** (R = H) (20 g.) in 600 ml. of freshly distilled tetrahydrofuran and 0.2 ml. of triethylamine was hydrogenated at room temperature and atmospheric pressure over palladized charcoal (10%, 2 g.) until uptake of hydrogen was complete (about 2 hours). The catalyst was filtered on Celite and the filtrate was evaporated to dryness to give a pink oil which was crystallized from tetrahydrofuran-hexane to give 4-(3-ethoxycarbonylpropyl)-3,5-dimethylpyrrole-2-carboxylic acid (16 g., 97%), as a pale pink sticky solid; nmr: δ 9.19 (1H, br) NH, 4.19 (2H, q) CH_2CH_3, 2.51-2.12 (4H, m), 1.80 (2H, q) $CH_2CH_2CH_2CO_2Et$, 2.31 (3H, s), 2.17 (3H, s) 2 × CH_3, 1.29 (3H, t) CH_2CH_3. The foregoing pyrrole-2-carboxylic acid (16 g.) was decarboxylated by heating in an oil bath at 160° for 30 minutes with a slow stream of nitrogen passing over it. The red oil so obtained was dissolved in 100 ml. of methylene chloride and added dropwise to 100 ml. of dry methylene chloride containing the complex formed by allowing 32 ml. of phosphoryl chloride to stir with 34 ml. of dimethyl-

formamide while cooling in ice for 20 minutes. The reaction was allowed to stir for 20 minutes and was then heated at reflux for 1 hour. A saturated solution of sodium acetate in water (500 ml.) was then cautiously added and the mixture was stirred overnight. The organic layer was separated and the aqueous layer washed with 2 × 100 ml. of methylene chloride. All of the organic layer was then washed with 3 × 250 ml. of water, dried over anhydrous sodium sulfate, filtered, boiled with decolourizing charcoal, filtered through Celite and evaporated. The pale yellow oil obtained was crystallized from dichloromethane-hexane as off-white needles (6.6 g., 59%), m.p. 67-69°; nmr: δ 9.44 (1H, s) CHO, 4.13 (2H, q) C*H*$_2$CH$_3$, 2.46-2.26 (4H, m), 1.80 (2H, q) CH$_2$CH$_2$CH$_2$CO$_2$Et, 2.98 (3H, s), 2.27 (3H, s) 2 × CH$_3$, 1.25 (3H, t) CH$_2$C*H*$_3$; ms: m/e 237 (100%), 192 (53), 164 (38), 149 (49), 136 (70).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.06; H, 8.18; N, 5.93.

Benzyl 5′-*t*-Butoxycarbonyl-3-(3-ethoxycarbonylpropyl)-4′-ethyl-3′,4-dimethyldipyrrylmethane-5-carboxylate (**16**).

t-Butyl 3-Ethyl-4-methylpyrrole-2-carboxylate (12) (1.7 g.) in 30 ml. of glacial acetic acid was treated with 3.0 g. of benzyl 5-acetoxymethyl-4-(3-ethoxycarbonylpropyl)-3-methylpyrrole-2-carboxylate (**13**, R = OAc) and then 107 mg. of toluene *p*-sulfonic acid hydrate before being stirred under nitrogen at 40° during 4 hours. The mixture was then poured into 100 ml. of water, extracted with 3 × 100 ml. of methylene chloride, washed with aqueous sodium bicarbonate, water, and then dried over sodium sulfate. Evaporation gave an oil which was chromatographed on alumina (Brockmann Grade III; elution with ethyl acetate/toluene, 1:1). The appropriate eluates were evaporated and the resulting oil was dried under vacuum to a brittle foam (3.1 g., 75%); nmr: δ 8.96 (1H, br), 8.86 (1H, br) 2 × NH, 7.28 (5H, m) C$_6$H$_5$, 5.20 (2H, s) C$_6$H$_5$C*H*$_2$, 4.04 (2H, q) OC*H*$_2$CH$_3$, 3.78 (2H, s) CH$_2$ bridge; 2.66 (2H, q) C*H*$_2$CH$_3$, 2.50-2.14 (4H, m), 1.89-1.59 (2H, m) CH$_2$CH$_2$CH$_2$CO$_2$Et, 2.24 (3H, s) 1.92 (3H, s) 2 x Me, 1.50 (9H, s) Bu′, 1.30-0.96 (6H, m) CH$_2$C*H*$_3$ and OCH$_2$C*H*$_3$.

Benzyl 5′-(*t*-Butyloxycarbonyl)-3-(2-chloroethyl)-4′-ethyl-3′,4-dimethyldipyrrylmethane-5-carboxylate (**23**).

Toluene *p*-sulfonic acid hydrate (200 mg.) was added to a mixture of 5 g. of benzyl 5-acetoxymethyl-4-(2-chloroethyl)-3-methylpyrrole-2-carboxylate (13) and 3 g. of *t*-butyl 4-ethyl-3-methylpyrrole-2-carboxylate (12) in 180 ml. of glacial acetic acid at 40° and under an atmosphere of nitrogen. Heating was continued for 5 hours when the solution was diluted with 500 ml. of methylene chloride and the solution washed with successive portions of saturated aqueous sodium hydrogen carbonate until the aqueous phase remained slightly basic. The organic phase was then washed with water, dried over anhydrous sodium sulfate and the solvent removed under vacuum. The residual red oil was chromatographed on alumina eluting with *n*-hexane and the eluates were evaporated to leave a red glass (6.7 g., 96%) which could not be induced to crystallize; nmr δ 9.57 (1H, br), 8.98 (1H, br) 2 × NH, 7.20 (5H, m) C$_6$H$_5$, 5.24 (2H, s) C*H*$_2$C$_6$H$_5$, 3.84 (2H, s)-CH$_2$ 3.38 (2H, t) CH$_2$-C*H*$_2$-Cl, 2.81 (2H, t) C*H*$_2$-CH$_2$-Cl, 2.76 (2H, q) C*H*$_2$-CH$_3$, 2.26 (3H, s) CH$_3$, 1.96 (3H, s) CH$_3$, 1.50 (9H, s) OC(CH$_3$)$_3$, 1.10 (3H, t) CH$_2$-C*H*$_3$.

5′-(*t*-Butoxycarbonyl)-3-(2-chloroethyl)-4′ethyl-3′,4-dimethyldipyrrylmethane-5-carboxylic Acid.

The foregoing dipyrrylmethane diester (6.7 g.) was dissolved in 600 ml. of freshly distilled tetrahydrofuran and 0.1 ml. of triethylamine and hydrogenated at room temperature and atmospheric pressure over palladized charcoal (10%, 0.7 g.) until uptake of hydrogen was complete. The solution was filtered through Celite and filtrates were evaporated to give the required dipyrrylmethane acid as a pale red glass (5.2 g., 97%) which could not be induced to crystallize. This compound was used directly without further purification.

t-Butyl-3-(2-chloroethyl)-6-(3-ethoxycarbonylpropyl)-1-ethyl-2,4,5,6′-tetramethyltripyrrene-b-1′-carboxylate Hydrobromide (**26**).

5′-(*t*-Butoxycarbonyl)-3-(2-chloroethyl)-4′-ethyl-3′4-dimethyldipyrrylmethane-5-carboxylic acid (10.2 g.) and 5.91 g. of 2-formyl-3,5-dimethyl-4-(3-ethoxycarbonylpropyl)pyrrole in 600 ml. of dry methylene chloride were treated with 14.0 g. of toluene *p*-sulfonic acid hydrate in 100 ml. of dry methanol and stirred at room temperature for 1 hour. [An immediate red coloration (λ max 488 nm) developed on addition of the toluene *p*-sulfonic acid hydrate.] The reaction mixture was poured into 100 ml. of water and the organic layer was washed with 100 ml. of a 3% aqueous solution of sodium carbonate, then water, and dried over anhydrous sodium sulfate. The organic phase was evaporated to about 100 ml. and hydrogen bromide gas was bubbled into it for about 5 seconds. Dry benzene (100 ml.) was immediately evaporated, another 100 ml. of dry benzene was again added (to azeotrope all traces of free hydrogen bromide) and the mixture was evaporated. The residue was dissolved in the mininum volume of dry methylene chloride, then dry diethyl ether was added slowly with scratching until the tripyrrene began to crystallize as a bright red powder. After standing in the refrigerator overnight the crystals were filtered and washed thoroughly with dry diethyl ether to give 6.5 g. (40%) m.p. 212-215°; nmr: δ 13.32 (1H, br), 13.24 (1H, br), 10.00 (1H, br) 3 × NH, 7.12 (1H, s) = CH-, 4.37 (2H, s) -CH$_2$-, 4.16 (2H, q) OC*H*$_2$CH$_3$, 3.33 (2H, t), 2.50 (2H, t) CH$_2$-CH$_2$-Cl, 2.87 (2H, q) CH$_2$CH$_3$, 2.72 (3H, s), 2.31 (3H, s), 2.28 (3H, s), 2.07 (3H, s) 4 × CH$_3$, 2.44-2.36 (4H, m), 1.80 (2H, q) C*H*$_2$-C*H*$_2$-C*H*$_2$-CO$_2$Et, 1.56 (9H, s) OC(CH$_3$)$_3$, 1.27 (3H, t) OCH$_2$ C*H*$_3$, 1.08 (3H, t) CH$_2$C*H*$_3$; vis: λ max 488 nm (ε 92,000).

Anal. Calcd. for $C_{32}H_{45}BrClN_3O_4$: 59.04; H, 6.97; N, 6.45. Found: C, 59.33; H, 7.16; H, 6.19.

Methyl 8-(3-Ethoxycarbonylpropyl)-5-(2-chloroethyl)-3-ethyl-1′,2,4,6,7,8′-hexamethylbiladiene-a,c-1-carboxylate Dihydrobromide (**28**).

t-Butyl 6-(3-ethoxycarbonylpropyl)-3-(2-chloroethyl)-1-ethyl-2,4,5,6′-tetramethyltripyrrene-*b*-1′-carboxylate hydrobromide (**26**) (3.26 g.) was dissolved in 40 ml. of trifluoroacetic acid. To this solution was added 980 mg. of methyl 5-formyl-2,4-dimethylpyrrole-3-carboxylate (15) (**27**) dissolved in the minimum volume of methanol, followed immediately by 46 ml. of hydrogen bromide in acetic acid (45% w/w). The reaction mixture became hot and was stirred for 30 minutes when dry diethyl ether was added, causing precipitation of the required biladiene-*a,c* dihydrobromide salt, which was filtered and washed thoroughly with diethyl ether. Recrystallization from dichloromethane-hexane gave the biladiene-*a,c* salt (3.34 g., 84%) as red microprisms m.p. > 300°; nmr: δ 13.94 (1H, br), 13.90 (1H, br), 13.45 (1H, br), 13.34 (1H, br) 4 × NH, 7.31 (1H, s), 7.17 (1H, s) 2 × = CH-, 5.33 (2H, s)-CH$_2$-, 3.93 (3H, s) CO$_2$CH$_3$, 2.70 (2H, t) CO$_2$C*H*$_2$CH$_3$, 3.00 (2H, q) C*H*$_2$CH$_3$, 2.97 (3H, s), 2.75 (3H, s), 2.69 (3H, s), 2.65 (3H, s), 2.35 (3H, s), 2.03 (3H, s) 6 × CH$_3$, 3.19 (2H, t), 2.53 (2H, t) CH$_2$-CH$_2$-Cl, 2.46-2.30 (4H, m), 1.83 (2H, q) CH$_2$-CH$_2$-CH$_2$-CO$_2$, 1.28 (3H, t) -OCH$_2$C*H*$_3$, 1.17 (3H, t) CH$_2$C*H*$_3$; vis: λ max, 446 nm (64,900) and 519 (126,900).

Anal. Calcd. for $C_{36}H_{49}Br2ClN_4O_4$: C, 54.25; H, 6.20; N, 7.03. Found: C, 53.99; H, 5.91; N, 7.17.

2,3,5-Triethyl-7-(3-methoxycarbonylpropyl)-1,4,6,8-tetramethylporphyrin (**8**).

Benzyl 5′-*t*-butoxycarbonyl-3-(3-ethoxycarbonylpropyl)-4′-ethyl-2′,4-dimethyldipyrrylmethane-5-carboxylate (3.1 g.) in 65 ml. of tetrahydrofuran and 0.6 ml. of triethylamine was hydrogenated at room temperature and atmospheric pressure over 310 mg. of 10% palladized charcoal until uptake of hydrogen was complete (*ca.* 1.5 hours). The catalysts were filtered on Celite and the filtrate was evaporated to dryness to give a solid which was recrystallized from tetrahydrofuran-hexane to give 2.44 g. of the pyrromethane acid. This was dissolved in 35 ml. of trifluoroacetic acid and stirred for 30 minutes while a slow stream of nitrogen was passed through the solution. The solvent was removed *in vacuo* and the residual oil was dissolved in 100 ml. of methylene chloride, washed with 100 ml. of water, aqueous sodium bicarbonate, and then water. The dipyrrylmethane solution was taken with 1.31 g. of 3,3′-diethyl-5,5′-diformyl-4,4′-dimethylpyrromethane (16) and the volume was made up to 1.9 l. with methylene chloride. The solution was stirred vigorously and 6.55 g. of *p*-toluenesulfonic acid in 70 ml. of methanol was added. Stirring was continued for a further 12 hours. The solution was then washed with 3 × 100 ml. of water, aqueous sodium bicarbonate,

water, and then dried over sodium sulfate before evaporation of the solvent. The residue obtained was taken up in 100 ml. of 5% w/v sulfuric acid-methanol and then stirred overnight. This solution was then poured into 250 ml. of water, extracted with methylene chloride, washed with aqueous sodium bicarbonate, water, and then dried over sodium sulfate before removal of the solvent by evaporation. The residue obtained was chromatographed on alumina (Brockmann Grade II, elution with methylene chloride). The solid obtained after evaporation of the eluates was recrystallized from methylene chloride-methanol to yield the required porphyrin (935 mg., 37%), m.p. 240-241°; nmr: δ (~0.4M) 10.04 (4H, s) 4 × meso-H, 4.05 (8H, m) 3 × C*H*$_2$CH$_3$ and C*H*$_2$CH$_2$CH$_2$CO$_2$Me, 3.66 (3H, s) OMe, 3.62 (3H, s), 3.58 (6H, s), 3.65 (3H, s) 4x Me, 2.82-2.48 (4H, m CH$_2$C*H*$_2$C*H*$_2$CO$_2$Me), 1.84 (9H, m) 3 × CH$_2$C*H*$_3$; vis: λ max, 3.99 nm (ε 156,800), 495 (12,900), 528 (9,200), 561 (5,900) and 610 (5000); λ max in dichloromethane + 1% TFA, 402 nm (ε 429,900), 542 (16,800), and 583 (7,000).

Anal. Calcd. for $C_{35}H_{42}N_4O_2$: C, 76.33; H, 7.69; N, 10.17. Found: C, 76.33; H, 7.86; N, 10.27.

2,3,5-Triethyl-1,4,6,8-tetramethyl-7-(3-pyrrolidinylcarbonylpropyl)porphyrin (**19**).

2,3,5-Triethyl-7-(3-methoxycarbonylpropyl)-1,4,6,8-tetramethylporphyrin (**8**) (213 mg.) in 110 ml. of tetrahydrofuran was stirred with 40 ml. of pyrrolidine and 8 ml. of 6*M* hydrochloric acid for 4 hours at room temperature. The solvent was then removed by evaporation *in vacuo*. The residue was dissolved in 100 ml. of chloroform, washed with hydrochloric acid (2*N*), water, aqueous sodium bicarbonate, water, and then dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed (Brockmann Grade III, alumina, elution with methylene chloride). The fastest running porphyrin was recrystallized from methylene chloride-methanol, yielding starting material (10 mg.). The second band was recrystallized from methylene chloride-methanol yielding the required porphyrin (201 mg., 88%), m.p. 268-269°; nmr: δ (~0.4M), 10.00 (4H, s) 4 × meso-H; 3.55 (9H, s), 3.57 (3H, s) 4 × Me; 4.15-3.90 (m), 3.77-3.33 (m), 2.75-2.27 (m) (20H) CH$_2$, 1.83 (9H, t) 2 × CH$_2$C*H*$_3$; vis: λ max, 398 nm (ε 189,200), 494 (12,600), 527 (9,500), 560 (6,700) and 609 (4,700); λ max in dichloromethane + 1% TFA, 403 nm (ε 433,700), 542 (16,900), and 583 (7,900).

Anal. Calcd. for $C_{36}H_{47}N_5O$: C, 77.38; H, 8.03; N, 11.88. Found: C, 77.09; H, 7.92; N, 11.94.

2-(2-Chloroethyl)-4-ethyl-6-methoxycarbonyl-7-(3-methoxycarbonylpropyl)-1,3,5,8-tetramethylporphyrin (**22**).

The a,c-biladiene dihydrobromide (**28**) (1.26 g.) was added to an already hot solution of 13.5 g. of copper(II) chloride in 240 ml. of dry dimethylformamide at 160°. The mixture was stirred for 4 minutes and immediately poured into 1 l. of water; the copper complex was extracted into dichloromethane until no color remained in the aqueous phase. The organic phase was washed with 3 × 500 ml. of water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was treated with 200 ml. of a 50% concentrated sulfuric acid/trifluoroacetic mixture with vigorous stirring for two and a half hours before being poured into 1 l. of water and extracted into 250 ml. of chloroform. The organic phase was washed with 500 ml. of water, 500 ml. of saturated aqueous sodium hydrogen carbonate solution, 2 × 500 ml. of water and then dried and evaporated to dryness. The residue was dissolved in 500 ml. of a 3% solution of concentrated sulfuric acid in methanol and allowed to stand in the refrigerator overnight before being poured into 500 ml. of a saturated aqueous solution of sodium acetate and extracted into methylene chloride until no more color remained in the aqueous phase. The organic phase was washed with 500 ml. of water, 500 ml. of saturated aqueous sodium bicarbonate solution, and 2 × 500 ml. of water, then dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on alumina (Brockmann Grade V, elution with methylene chloride) and then recrystallized from methylene chloride-methanol as purple micro prisms (0.47 g., 48%) m.p. 238-240°; nmr: δ 10.97 (1H, s), 10.06 (1H, s), 9.84 (1H, s), 9.76 (1H, s) 4 × meso- H, 4.45 (3H, s), 3.92 (3H, s), 3.66 (3H, s), 3.61 (3H, s), 3.59 (3H, s), 3.52 (3H, s) 6 × C*H*$_3$, 4.15 (2H, m), 3.82 (2H, m) CH$_2$-CH$_2$-Cl, 4.05 (2H, m) C*H*$_2$-CH$_3$, 2.70-2.58 (4H, m), 1.85 (2H, q) CH$_2$-CH$_2$-CH$_2$-CO$_2$Me, 1.52 (3H, t) CH$_2$C*H*$_3$; ms: m/e, 617 (34%), 615 (100), 580 (47), 565 (40), 527 (34), 478 (20); vis: λ max, 404 nm (ε 241,000), 508 (10,800), 545 (17,100), 571 (9,500), 628 (1,900).

Anal. Calcd. for $C_{35}H_{39}ClN_4O_4$: C, 68.34; H, 6.39; N, 9.11. Found: C, 68.57; H, 6.16; N, 9.14.

2-(2-Chloroethyl)-4-ethyl-6-methoxycarbonyl-7-(3-pyrrolidinylcarbonylpropyl)-1,3,5,8-tetramethylporphyrin (**29**).

The foregoing porphyrin dimethyl ester (0.24 g.) was dissolved in 200 ml. of warm freshly distilled tetrahydrofuran and treated with 15 ml. of concentrated hydrochloric acid. The solution was stirred for 5 minutes before adding 20 ml. of freshly distilled pyrrolidine. The reaction mixture was then stirred in the dark for 3 days keeping the temperature at 60° throughout. The solvent was removed by evaporation *in vacuo* and the residue was dissolved in 200 ml. of chloroform. The solution was washed with 200 ml. of 2*M* hydrochloric acid, 100 ml. of saturated aqueous sodium bicarbonate solution, and 2 × 200 ml. of water before being dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on alumina (Brockmann Grade III; elution with methylene chloride) which eluted some pure starting material. Chloroform eluted the required product which was recrystallized from dichloromethane-hexane as purple micro-prisms (0.156 g., 61%), m.p. 252-254°. Recycling of recovered starting material gave a 95% yield overall; nmr: δ 10.92 (1H, s), 9.94 (1H, s), 9.72 (1H, s), 9.63 (H, s) 4 × meso-H, 4.45 (3H, s), 3.87 (3H, s), 3.55 (6H, s), 3.44 (3H, s) 5 × CH$_3$, 4.15 (2H, m), 3.97 (2H, m) CH$_2$-CH$_2$-Cl, 4.04 (2H, m) C*H*$_2$-CH$_3$, 3.40 (4H, m), 3.10-2.96 (4H, m) pyrrolidide CH$_2$'s, 2.70-2.45 (4H, m), 1.81 (2H, q) CH$_2$-CH$_2$-CH$_2$-CO, 1.66 (3H, t) CH$_2$-C*H*$_3$; ms: m/e 656 (34%), 654 (100), 619 (67), 584 (44), 556 (67), 541 (89), 528 (89); vis: λ max 404 nm (ε 141,400) 508 (6,900), 545 (10,100), 571 (6,500), and 626 (1,600).

Anal. Calcd. for $C_{38}H_{44}ClN_5O_3$: C, 69.76; H, 6.78; N, 10.70. Found: C, 69.81; H, 6.62; N, 10.79.

2,3,5-Triethyl-1,4,6-trimethyl-8-methylene-7-(spirocyclopentanone-2'-yl)-chlorin (**9**).

2,3,5-Triethyl-1,4,6,8-tetramethyl-7-(3-pyrrolidinylcarbonylpropyl)porphyrin (**8**) (300 mg.) was dissolved in 112 ml. of dry pyridine. Six ml. of phosphoryl chloride was added and the solution was stirred for 4 hours at 60°. The solution was cooled to 0° and 28 ml. of water was added dropwise. The solvent was evaporated *in vacuo* and the residue was dissolved in methylene chloride and washed twice with water. The solvent was removed *in vacuo* and the residue dissolved in 250 ml. of tetrahydrofuran. Sodium acetate (30 g.) in 90 ml. of water was added and the two phase system was stirred efficiently and heated under reflux for 1.5 hours. The solution was then allowed to return to room temperature, the water layer was extracted twice with methylene chloride and the combined organic extracts were evaporated *in vacuo*. The residue was dissolved in methylene chloride, washed with water, dried over sodium sulfate, before being evaporated to dryness. The residue obtained was chromatographed (Alumina, Brockmann Grade V, elution with benzene) and recrystallized from methylene chloride-hexane to give 50 mg., (19%) of the required product; nmr: δ (~0.4M) 9.77 (1H, s), 9.75 (1H, s), 9.38 (1H, s), 8.64 (1H, s) 4 × meso-H, 6.78 (1H, m), 5.78 (1H, m) =CH$_2$, 4.20-3.80 (6H, m) 3 × C*H*$_2$CH$_3$, 3.46 (3H, s), 3.41 (6H, s) 3 × Me, 3.16-2.60 (6H, m) CH$_2$CH$_2$CH$_2$, 1.79 (9H, t) 3 × CH$_2$C*H*$_3$; vis: λ max 399 nm (ε 211,000), 496 (14,000), 504 (13,000), 532 (15,000), 596 (3,700), and 655 (48,700).

Anal. Calcd. for $C_{34}H_{42}N_4O$: C, 78.12; H, 8.10; N, 10.72. Found: C, 77.81; H, 8.02; N, 10.77.

2,3,5-Triethyl-1,4,6,8-tetramethyl-7-(spirocyclopentanone-2'-yl)-7,8-chlorin (**21**).

The foregoing chlorin (24 mg.) in 24 ml. of tetrahydrofuran containing 1.2 ml. of triethylamine was hydrogenated, at room temperature and atmospheric pressure, over 24 mg. of 10% palladized charcoal for 1.5 hours. After filtration through Celite, the filtrate was evaporated to dryness and the product chromatographed on alumina (Brockmann

Grade V, elution with benzene). The eluates were evaporated *in vacuo* and the residue recrystallized from methylene chloride-hexane to yield the required product (20 mg., 83%), m.p. 259-260°; nmr: δ (~0.4M), 9.71 (1H, s), 9.68 (1H, s), 8.78 (1H, s), 8.53 (1H, s) 4 × meso-H, 4.93 (1H, q) 8-H, 4.10-3.80 (6H, m) 3 × CH_2CH_3, 3.43 (3H, s), 3.42 (3H, s), 3.40 (3H, s) 3 × Me, 3.10-2.45 (6H, m) $CH_2CH_2CH_2$, 1.89 (3H, d), 8-Me, 1.85-1.70 (9H, m) 3 × CH_2CH_3; ms: m/e 520 (100%), 505 (10), 492 (29), 477 (16), 464 (100), 449 (67), 260 (36), m* 434.5 (464 → 449), and 414.0 (520 → 464); vis: λ max, 391 nm (ε 186,800), 491 (12,300), 516 (3,700), 602 (3,700), and 630 (48,600); λ max in dichloromethane + 1% TFA, 394 nm (ε 227,800), 405 (186,700), 518 (5200), and 622 (25,400).

Anal. Calcd. for $C_{34}H_{40}N_4O$: C, 78.42; H, 7.74; N, 10.76. Found: C, 78.14; H, 7.65; N, 10.92.

2-(2-Chloroethyl)-4-ethyl-6-methoxycarbonyl-1,3,5,8-tetramethyl-7,7-[(α-pyrrolidinium)-tetramethylene]-7,8-chlorin (**33**).

2-(2-Chloroethyl)-4-ethyl-6-methoxycarbonyl-7-(3-pyrrolidinylcarbonyl-propyl)-1,3,5,8-tetramethylporphyrin (0.100 g.) was dissolved in 30 ml. of freshly distilled dry pyridine. Freshly distilled phosphoryl chloride (1 g.) was added and the solution was stirred at 60° under atmosphere of nitrogen for 4 hours. The solution was poured into 500 ml. of water and extracted into methylene chloride, dried over anhydrous sodium sulfate and evaporated to dryness. The dark green sticky solid obtained was dissolved in 20 ml. of freshly dry pyridine, then 2 g. of powdered dipotassium azodicarboxylate was added and the slurry was stirred under an atmosphere of nitrogen while allowing a solution of 10 ml. of glacial acetic acid in 15 ml. of dry pyridine to drip in slowly over a period of about 2 hours. The reaction mixture was allowed to stir in darkness for 12 hours when 2 ml. of glacial acetic acid in 5 ml. of pyridine was added before the reaction mixture was poured into 500 ml. of water and the product was extracted into methylene chloride. The organic phase was washed with 200 ml. of water, dried over anhydrous sodium sulfate and evaporated. The residue was recrystallized from dichloromethane-hexane to give dark green crystals (0.084 g., 84%), m.p. > 300°; vis: λ max, 404 nm (ε 70,200), 502 (4,500), 546 (4,600), 575 (3,400), 597 (2,400), and 655 (13,200). (Extinction coefficients are calculated on the assumption of a Cl^- counterion. A satisfactory C, H, N analysis for this material could not be obtained.)

Mesoporphyrin-IX Dimethyl Ester (**32**).

Protoporphyrin-IX dimethyl ester (17) (**31**) (100 mg.) was dissolved in 30 ml. of freshly distilled pyridine. To this solution was added 1 g. of freshly prepared dipotassium azodicarboxylate and the slurry was stirred under an atmosphere of nitrogen. A solution of 5 ml. of glacial acetic acid in 10 ml. of pyridine was added over a period of 1 hour and the reaction mixture was allowed to stir for another 1 hour. More glacial acetic acid (2 ml.) in 5 ml. of pyridine was added before the reaction mixture was poured into 500 ml. of water and the product was extracted into methylene chloride. The organic phase was washed with 200 ml. of water, 100 ml. of saturated aqueous sodium bicarbonate solution, and 2 × 200 ml. of water, then dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed on alumina (Brockmann Grade III, elution with methylene chloride), then recrystallized from dichloromethane-methanol, (98 mg., 97%) m.p. 212-214° [lit. (18) 212°]. This material was identical by mixed m.p., tlc and nmr spectroscopy with an authentic sample.

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