BIOORGANIC CHEMISTRY 9, 1–26 (1980)

meso-Methylporphyrins and -Chlorins[1]

KEVIN M. SMITH, GRAHAM M. F. BISSET, AND MICHAEL J. BUSHELL

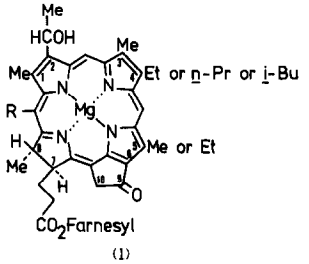
Department of Chemistry, University of California at Davis, Davis, California 95616

Received February 15, 1979

Two efficient synthetic routes to *meso*-methylporphyrins and -chlorins are described. In the first, *meso*-formylporphyrins and -chlorins are reduced to the corresponding *meso*-hydroxymethyl derivatives, and after zinc chelation and treatment with acetic anhydride in pyridine, the resulting *meso*-acetoxymethylporphyrins are reduced to *meso*-methyl with sodium borohydride or by catalytic hydrogenation. The second route is more efficient in that copper(II) *meso*-formylporphyrins and -chlorins can be reduced directly with tetra *n*-butylammonium borohydride in hot 1,2-dichloroethane to give the copper(II) *meso*-methyl analog. Using the procedures developed herein, a formal total synthesis of the *meso*-pheophorbide from *Chlorobium* chlorophyll "660" band 6 is decribed, and certain photooxidation and electrophilic deuteration problems in the *meso*-methylchlorin series are clarified.

INTRODUCTION

The *Chlorobacteriaceae* (green photosynthetic sulfur bacteria) produce large amounts of pigments called the *Chlorobium* chlorophylls (*1*). Two different series of chlorophylls have been identified, and have been designated bacteriochlorophylls *c* and *d* by Jensen (*2*), though the more classical names *Chlorobium* chlorophylls "660" and "650" appear still to be in popular use (the numbers refer to the wavelength of the major red absorption of the extracted pigments in ether). The structures of these compounds have been the subject of much controversy (*3*), since each series of chlorophylls appears to consist of at least six homologous fractions (or "bands") (*4*, *5*) of generic structure shown in (**1**). Brockmann has recently characterized bacteriochlorophyll *e* from brown *Chlorobacteriaceae* (*6*).



(1)

R = H ; CHLOROBIUM CHLOROPHYLLS '650'

R = Me; CHLOROBIUM CHLOROPHYLLS '660'

[1] Dedicated by the authors to the memory of Professor George W. Kenner, F.R.S.

0045-2068/80/010001-26$02.00/0

Three homologous fractions were obtained (*7, 8*) which have structures similar to the *Chlorobium* chlorophylls "660," differing only in having a formyl group at the 3-position.

Katz *et al.* (*9*), by means of a detailed mass spectrometric analysis of the chlorophylls, have confirmed that the esterifying alcohol is farnesol. Strouse and co-workers (*10–12*) have since shown that, although farnesol is the major esterifying alcohol, a portion of the chlorophyll mixture is esterified with minor amounts of five different alcohols: 4-undecyl-2-furan methanol, geranyl geraniol, *cis*-9-hexadecen-1-ol, tetrahydrogeranyl geraniol, and phytol. The amounts of these minor alcohols vary with the age of the culture.

The position of the *meso*-substituent in the "660" series has been a cause for controversy. Holt *et al.* (*13*) initially sited it at the δ-position, while Mathewson *et al.* (*14, 15*) placed the *meso*-alkyl group in either the α- or β-position. Loss of the high field *meso*-proton in the nmr spectrum, and failure to form a δ-chloro derivative, was considered good evidence that the δ-position is substituted. However, it is known that the γ- and δ-*meso*-protons (i.e., those on either side of the reduced ring) of a chlorin are more susceptible to electrophilic substitution (*16*) than are the α- or β-protons, or *meso*-protons on the corresponding porphyrins; moreover, Mathewson *et al.* observed that one of the two *meso*-protons in the 660 chlorophylls and in the pheophorbides was easily exchanged. This finding led them to suggest that the δ-position must be unsubstituted, and thus that the alkyl group must be at the α- or β-position.

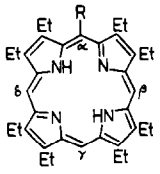
In addition to the convincing synthetic evidence provided by MacDonald's group (*17*) and Kenner's group (*18*), there now exists an overwhelming weight of evidence placing the *meso* substituent at the δ-position (*3*). We conducted (*3, 19*) an extensive investigation into the ^{13}C nmr spectra of chlorophyll derivatives and showed that the α- and β-*meso*-carbons were shifted in trifluoroacetic acid by about 10 ppm, while the γ- and δ were shifted only slightly. In this way it was possible to assign the pairs of resonances (α, β and γ, δ). Inspection of the undecoupled ^{13}C nmr spectrum of the methyl mesopheophorbides from *C. ethylicum* showed the γ- and δ-carbons to be singlets, hence quaternary. It was also possible to deduce that the α-position is the one which undergoes deuterium exchange. Presumably the β-position does not exchange due to the electron-withdrawing influence of the carbonyl group in ring E. The enhanced nucleophilicity of the α-position has been demonstrated by an interesting cyclization reaction (*3, 20*), and a novel photooxygenation reaction which affords an acetylbilitriene (*19–21*) has provided yet more evidence for the presence of the *meso*-alkyl group at the δ-position.

The stereochemistry of the three chiral centers of the *Chlorobium* chlorophylls has been established. Ring D was shown to have the same configuration, (7*S*, 8*S*), as chlorophyll *a* (*6*). The 2-hydroxyethyl group was determined to have the (*R*) configuration (*22*) by use of a modified Horeau analysis.

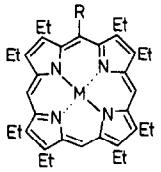
In this paper we describe efficient synthetic and chemical studies on model *meso*-methylchlorins, from which we are able to gain further insight into the electronic structure of the alkylated nucleus; this knowledge has enabled us to explain the regiospecificity of the electrophilic deuteration and photooxidative cleavage reactions observed in the natural series. The synthetic approach to these

models required a detailed investigation of metalloporphyrin methylation procedures, and from this we have also developed a formal total synthesis of the mesopheophorbide from *Chlorobium* chlorophyll 660, band 6.

meso-Methyl-substituted porphyrins can be obtained by total synthesis. Cox *et al.* (*18*) prepared two phylloporphyrins related to the *Chlorobium* chlorophylls from a *b*-bilene intermediate, and Johnson's 1′-bromo-8′methyl-*a*, *c*-biladiene method has been extended to prepare *meso*-alkylporphyrins (*23*). Treatment of *a*, *c*-biladiene-1′,8′-dicarboxylic acids with acetaldehyde produces *meso*-methylporphyrins (*24*). However, these routes cannot be extended to the preparation of chlorins, since there exists no convenient general method of chlorin synthesis from open-chain precursors, and it has been shown (*25*) that attempted reduction of the iron(III) complex of *meso*-methyloctaethylporphyrin leads only to octaethylchlorin; i.e., the *meso*-substituent is lost. Fischer (*26*) claimed that reduction of γ-phylloporphyrin-XV hemin gave specifically the 7,8-dihydroporphyrin, presumably because reduction in ring D relieves steric compression; probably the 6-unsubstituted position in Fischer's example is an important factor. Direct methylation of palladium octaethylporphyrin with methyl fluoro-sulfonate produced the palladium complex of *meso*-methyloctaethylporphyrin in 36% yield (*27*). This method is not suitable for our purposes owing to the difficulty of removing the metal, and this method is not applicable to other metalloporphyrins.



(2) R = Me
(3) R = CH_2OH
(13) R = CHO



(4) M = Zn; R = CHO
(8) M = Zn; R = CH_2OH
(9) M = Zn; R = CH_2OAc
(14) M = Cu; R = CHO
(15) M = Cu; R = Me
(16) M = Cu; R = CH_2OH

meso-Methyloctaethylporphyrin (**2**) had previously been prepared (*28*) in low yield by lithium aluminum hydride reduction of the mesylate from hydroxymethyloctaethylporphyrin (**3**). A 30% yield was obtained from reduction of zinc(II) *meso*-formyloctaethylporphyrin (**4**) with sodium borohydride. Finally, Arnold *et al.* (*29*) have reported the low yield formation of (**2**) by treatment of (**3**) with sulfuric acid.

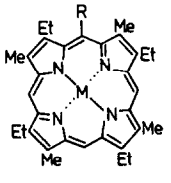
These results clearly suggested that the most promising approach to the required *meso*-methylchlorins involved the corresponding formyl compounds.

RESULTS AND DISCUSSION

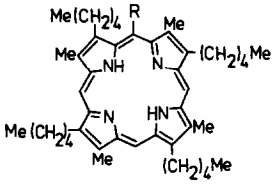
meso-Methylporphyrins

Our preliminary experiments revealed that lithium aluminum hydride reduction of nickel(II) *meso*-formyletioporphyrin-I (**5**) gave in good yield the nickel(II)

complex (**6**) of *meso*-methyletioporphyrin-I, which could be demetalated to give (**7**). However, these results were difficult to reproduce and were unsatisfactory for that reason. Another method employed sodium borohydride reduction of *meso*-formylporphyrins to their hydroxymethyl analogs; chelation[2] with zinc(II) gave the complex (**8**), which gave the acetoxymethyl derivative (**9**). Catalytic hydrogenation of this pseudo-benzyl ester gave, after demetalation, the required *meso*-methylporphyrin (**2**) in good, but sometimes erratic, yield.



(5) M = Ni; R = CHO
(6) M = Ni; R = Me
(7) M = 2H; R = Me



(10) R = CH_2OH
(11) R = CH_2OAc
(12) R = Me

In view of the irreproducibility of the foregoing routes, we decided to investigate other methods for achieving conversion of *meso*-formyl- into *meso*-methylporphyrins. Treatment of the hydroxymethylporphyrin (**10**) with acetic anhydride in pyridine gave the acetoxymethyl analog (**11**) (*30*), which was reduced successfully with sodium borohydride in *tert*-butyl alcohol, the desired *meso*-methylporphyrin (**12**) being obtained in 80% yield. We had previously observed (*25, 30*) that treatment of *meso*-acetoxymethylporphyrins with hot methanol in dichloromethane for a few minutes gave the corresponding methoxymethylporphyrins; this observation led us to seek another system for reduction of the acetoxymethylporphyrins, since we expected that, in the general sense, alcoholic solvents for the borohydride reduction would be unsatisfactory. A simple modification employed reduction of *meso*-acetoxymethylporphyrins with tetra-*n*-butylammonium borohydride (*31*), which is totally soluble in chlorohydrocarbons such as 1,2-dichloroethane. Complete reduction to *meso*-methylporphyrin (**12**) in 75–90% yield, using tetra-*n*-butylammonium borohydride in refluxing 1,2-dichloroethane, occurred during 1 hr.

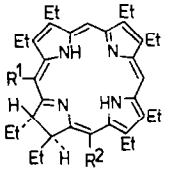
In order to further test the usefulness of tetra-*n*-butylammonium borohydride in the porphyrin series, the *meso*-formylporphyrin (**13**) was reduced in 1,2-dichloroethane to the hydroxymethyl analog (**3**) with relative ease. However, the copper(II) *meso*-formylporphyrin (**14**) (obtained directly from the Vilsmeier formylation) was unexpectedly reduced directly to copper(II) *meso*-methylporphyrin (**15**), in 87% yield, using the reagent. The reaction was complete in 1 hr and thin-layer chromatography indicated formation of the copper(II) hydroxymethylporphyrin (**16**) as a short-lived intermediate. Demetalation of (**15**) using 1 : 1 sulfuric and

[2] Chelation with zinc(II) at this stage was an important step because our subsequent strategy required catalytic hydrogenation. If the metal ion itself is stable to reduction, metalloporphyrins do not normally form porphyrinogens upon hydrogenation, but metal-free porphyrins do; we foresaw that hydrogenation of the metal-free *meso*-substituted porphyrin would produce porphyrinogen with the possibility of elimination of the bulky *meso*-substituent upon reoxidation to the porphyrin state.

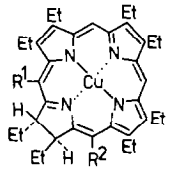
trifluoroacetic acids yielded the *meso*-methylporphyrin (**2**). Reduction of the copper(II) *meso*-hydroxymethylporphyrin (**16**) (obtained with sodium borohydride from the copper(II) *meso*-formylporphyrin (**14**),) with tetra-*n*-butylammonium borohydride in 1, 2-dichloroethane also gave the copper(II) *meso*-methylporphyrin (**15**) in 88% yield. The direct reduction of *meso*-formyl- to *meso*-methylporphyrin (**2**) could also be achieved with nickel(II) or zinc(II) as chelating metals using tetra-*n*-butylammonium borohydride in 1,2-dichloroethane.

meso-Methylchlorins

The formyl group was to be introduced into *trans*-octaethylchlorin (**17**) using the Vilsmeier procedure; and since formylation will not occur on metal-free porphyrins and chlorins, a suitable metal complex was required. The zinc complex of octaethylchlorin was demetalated under the reaction conditions, no formylation being observed, a result in agreement with those of other workers (*32*). The choice of metal appeared to rest between copper, nickel, and cobalt.

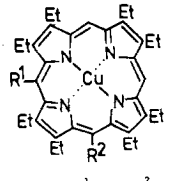


(17) $R^1 = R^2 = H$
(26) $R^1 = CH_2OH$; $R^2 = H$
(30) $R^1 = Me$; $R^2 = H$
(32) $R^1 = R^2 = Me$

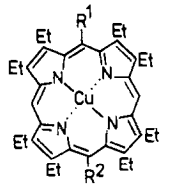


(18) $R^1 = R^2 = H$
(20) $R^1 = CHO$; $R^2 = H$
(22) $R^1 = R^2 = CHO$
(25) $R^1 = CH_2OH$; $R^2 = H$
(28) $R^1 = CH_2OAc$; $R^2 = H$
(29) $R^1 = Me$; $R^2 = H$
(31) $R^1 = R^2 = Me$
(33) $R^1 = R^2 = CH_2OH$

Copper was chosen as it is an easy complex to prepare, and is relatively easy to remove from the macrocyele when required. Copper(II) octaethylchlorin (**18**) was subjected to formylation under Vilsmeier conditions for 1.5 hr at 50°C, followed by hydrolysis, after which four major spots were observed by tlc. Preparative tlc was the most efficient way of separating these; and the bands were identified, in increasing order of polarity, as copper(II) *meso*-formyloctaethylporphyrin (**19**) (18%); copper(II) *meso*-formyloctaethylchlorin (**20**) (30%); copper(II) *meso*-diformyloctaethylporphyrin (**21**) (6%); and copper(II) diformyloctaethylchlorin (**22**) (9%). When the formylation was left for only 30 min before hydrolysis, 75–80% yields of copper monoformyloctaethylchlorin (**20**) were obtained after



(19) $R^1 = CHO$; $R^2 = H$
(21) $R^1 = R^2 = CHO$

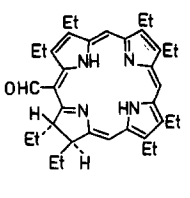


(23) $R^1 = R^2 = CHO$

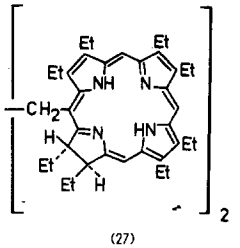
column chromatography. Longer reaction times or higher temperatures led to increased amounts of material being oxidized to undesired porphyrin, and performing the reaction under nitrogen made no difference to the amount of porphyrins obtained. Using a larger excess of Vilsmeier complex led to increased amounts of diformylated products being formed, but again more oxidation to the porphyrin was observed, the ratios of porphyrin to chlorin being typically about 1 : 1. On rechromatography of the copper(II) diformylporphyrin, a minor, slightly less polar compound was obtained. This substance had a visible absorption spectrum similar to that of, and the same molecular weight as, the diformylporphyrin (**21**), thus identifying it as the isomeric copper(II) α,γ-diformyloctaethylporphyrin (**23**). Electrophilic substitution on chlorins is much more facile at the γ- and δ-positions, adjacent to the reduced ring (*16*); hence the diformyl copper(II) chlorin is solely the γ,δ-isomer (**22**). Oxidation of chlorin **22** under the Vilsmeier reaction conditions leads to the α,β-diformyl copper(II) octaethylporphyrin (**21**); the majority of the diformyl porphyrin arises in this way. The α, γ-diformyl copper(II) octaethylporphyrin (**23**), the minor constituent, arises from diformylation of copper(II) octaethylporphyrin resulting from oxidation of the chlorin before formylation, and formylation of the monosubstituted porphyrin.

Treatment of copper(II) monoformyloctaethylchlorin (**20**) with 10% sulfuric in trifluoroacetic acid at room temperature did not completely remove the metal, even after three treatments. Extensive oxidation also occurred, leading to the free base formyloctaethylporphyrin (**13**). The desired γ-formyloctaethylchlorin (**24**) was obtained in only 58% yield. In order to improve the reaction, it was decided to attempt removal of the copper at a later stage in the synthesis. The free base γ-formyl chlorin (**24**) was fully characterized; and its nmr spectrum confirmed that the formyl group was at the γ-position (next to the reduced ring), since one of the high field *meso*-protons was missing. The formyl proton appears at -1.92 τ. Attempts to produce more copper(II) diformyloctaethylchlorin (**22**) by Vilsmeier formylation on the copper(II) monoformyloctaethylchlorin (**20**) were unsuccessful, extensive oxidation to porphyrin having occurred.

Sodium borohydride reduction of copper(II) formyloctaethylchlorin (**20**) gave the hydroxymethyl compound (**25**) in high yield. Demetalation was attempted using 10% sulfuric and trifluoroacetic acids. After two treatments at room temperature, the visible spectrum showed that most of the metal had been removed. However, instead of (**26**) the product was shown to be the chlorin dimer (**27**), with spectroscopic properties analogous to the porphyrin dimer of Arnold *et al.* (*29*). The unexpected formation of the dimer, together with the low yield on



(24)



(27)

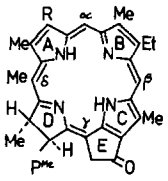
demetalation at the formyl stage, meant that demetalation should be the last stage in the synthesis.

The acetoxymethyl compound (**28**), obtained from (**25**), was found to be very reactive toward nucleophiles, and on attempted tlc decomposed to the alcohol; it was therefore used immediately after preparation. Two methods were attempted for reduction of the acetoxymethylchlorin to copper(II) *meso*-methyloctaethylchlorin. Hydrogenation over palladium on charcoal was the first method to be investigated. In a typical experiment, copper(II) hydroxymethyloctaethylchlorin (**25**) was converted into the acetate, then hydrogenated overnight. The resulting copper(II) *meso*-methyloctaethylchlorin (**29**) was chromatographed to remove some alcohol (**25**) (10%), then demetalated to give *meso*-methyloctaethylchlorin (**30**) (30%), *meso*-methyloctaethylporphyrin (**2**) (17%), together with copper(II) *meso*-methyloctaethylchlorin (**29**) (10%).

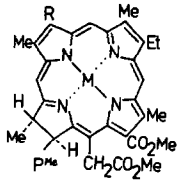
Since the acetoxymethyl compound was so labile toward nucleophiles, it was thought that $NaBH_4$ might prove a convenient reducing agent; but on account of solvent problems outlined earlier, we chose to use the tetra-*n*-butylammonium borohydride reagent discussed previously. Again, it seemed that the presence of a metal was important to the reaction, as were the precise conditions. Generally, the copper complex of the formyl chlorin, e.g. (**20**), was dissolved in 1,2-dichloroethane and gently refluxed (oil bath 95–100°C). An excess of tetra-*n*-butylammonium borohydride was then added and the reaction monitored by tlc. Typically, the green formyl compound was rapidly converted to a more polar blue compound, the hydroxymethyl compound (actually as the borate ester). A slower second step then ensued, which converted the polar tlc spot into a fast moving blue spot, copper(II) *meso*-methyloctaethylchlorin (**29**). Copper(II) γ,δ-diformyloctaethylchlorin (**22**) was converted into copper(II) γ,δ-dimethyloctaethylchlorin (**31**), which on demetalation led to γ,δ-dimethyloctaethylchlorin (**32**) in 46% yield, together with a small amount of the corresponding porphyrin. The hydroxymethyl compounds (**25**, **33**) were also substrates for the reagent. Copper(II) hydroxymethyloctaethylchlorin (**25**) in an analogous fashion led to *meso*-methyloctaethylchlorin and *meso*-methyloctaethylporphyrin in 59 and 24% yields, respectively. Oxidation during demetalation was again a problem, but the overall yields to *meso*-methylchlorins were much improved.

Synthesis of the Mesopheophorbide (**35**) *Corresponding to Chlorobium Chlorophyll 660 Band 6.*

Band 6 (Holt's assignment) (*33*) of the pheophorbides from the *Chlorobium* chlorophylls 660 has the structure (**35**). It is the only band postulated to have a 5-methyl group (although there is still controversy over the identity of the minor fractions), and the structure has been confirmed (*17*). Since synthetic routes to *meso*-methylchlorins had now been developed, a synthesis of the molecule (**35**) (the methyl pheophorbide) was possible. In addition to permitting a test of the generality of our *meso*-methylchlorin synthesis, the target molecule (**35**) would be invaluable for hplc and chemical studies of the chlorophylls. Band 6 is presently the only fraction from the 660 chlorophylls which can be synthesized using



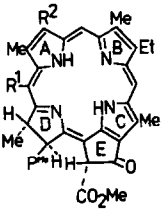
(34) R = Et
(35) R = CH(OH)Me



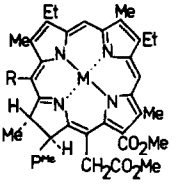
(36) M = Cu; R = CH=CH$_2$
(37) M = Cu; R = CH=CHCHO
(39) M = 2H; R = CH=CH$_2$
(40) M = 2H; R = Et
(41) M = Cu; R = Et

commercially available pheophytin *a*, since the 4- and 5- position side chains are the same (4-Et, 5-Me). Initial attempts to prepare the 2-vinylpheophorbide of **35** were unsuccessful owing to terminal formylation, under Vilsmeier conditions, of the 2-vinyl groups in copper(II) chlorin-e_6 trimethyl ester (**36**), to give (**37**). These difficulties can be overcome by protection of the troublesome vinyl function, and work on this modification is in progress. However, in order to test our approach to the natural pigment we settled on a synthesis of the "meso"-(2-ethyl) pheophorbide (**34**).

Since methyl pheophorbide-*a* (**38**) bears a highly negative β-keto-ester function we chose to begin our synthesis with chlorin-e_6 trimethyl ester (**39**), readily obtainable from commercial pheophytins (*34*). Mesochlorin-e_6 trimethyl ester (**40**) was prepared in 93% yield from chlorin-e_6 trimethyl ester (**39**) by hydrogenation of the zinc complex over palladium on charcoal, followed by removal of the metal. The *meso*-methyl group was incorporated as follows in an overall yield of



(38) R^1 = H; R^2 = CH=CH$_2$
(46) R^1 = Me; R^2 = Et



(42) M = Cu; R = CHO
(43) M = Cu; R = CH$_2$OH
(44) M = Cu; R = CH$_2$OAc
(45) M = 2H; R = Me

15% (the compounds in this series were less susceptible to oxidation to the corresponding porphyrins than were the chlorins in the octaethyl series, probably due to steric reasons associated with the increased bulk of the substituents). The copper(II) chelate (**41**) was formylated with the Vilsmeier complex to give (**42**), which was reduced with sodium borohydride to give the corresponding hydroxymethylchlorin (**43**) and then converted into the acetoxymethyl derivative (**44**) using acetic anhydride in pyridine. Catalytic hydrogenation and demetalation gave *meso*-methylmesochlorin-e_6 trimethyl ester (**45**).

The isocyclic ring was reformed by brief treatment with potassium *tert*-butoxide in *tert*-butyl alcohol and dry pyridine (*21*). After esterification using diazo-

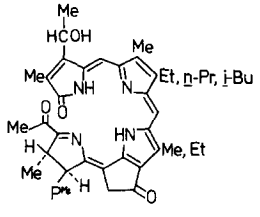
methane, δ-methylmesopheophorbide-*a* (**46**) was obtained in 78% yield. This compound was heated in collidine for 2 hr at 190°C to produce the required *meso*-analog of band 6 (**34**) in 84% yield. The identity of the synthetic material was established by the usual spectroscopic and analytical techniques, and by high performance liquid chromatographic comparison (using two Waters Associates reverse phase C-18 micropore columns, 10% H_2O in CH_3CN, 2 ml/min flow rate, 2000 psi)[3] with natural mesopheophorbides of the 660 series.

Properties of meso-Methylchlorins

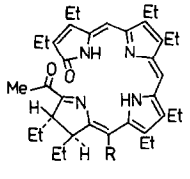
An interesting observation was made during the small-scale preliminary reactions to test the acetoxymethyl route to *meso*-methylchlorins. The copper complex and free base α,γ-dimethyloctethylchlorin (**32**) were very susceptible to photooxidative degradation. A visible spectrum of (**32**) was run, and the cell was allowed to stand in sunlight for 40 min. There was little sign of absorption due to the chlorin, but merely a broad low intensity bile pigment type absorption. This initial observation of very facile photocleavage was followed up with further experiments.

Photooxidation of meso-Methylchlorins

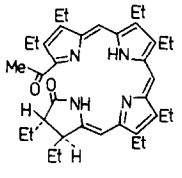
In earlier work (*19, 20*) we isolated a polar purple compound on tlc of the methyl pheophorbides from *C. ethylicum*, which was identified as the photooxidation product (**47**) by its visible absorption and nmr spectra. A detailed analysis of the mass spectral fragmentation pattern revealed that the compound was a single isomer, i.e., there was no evidence for the acetyl group being on ring A, and thus the photooxidation gave specifically the compound with the acetyl on ring D.



(47)



(48) R = Me
(49) R = H



(50)

[3] Full details of our efficient hplc 660 chlorophyll separations will be reported elsewhere.

Further evidence for the specificity of the ring opening was obtained (*21*) by photooxidation of the 2-vinyl and 2-methoxyethyl compounds. Mass spectral fragments corresonding to ring A containing an acetyl group, or ring D containing just a carbonyl group, were never observed.

Fuhrhop (*35*) has found that photooxidation of metalloporphyrins and metallochlorins leads to metalloformylbiliverdins, and the photooxidation has been shown to involve singlet oxygen. Zinc(II) octaethylchlorin was found to react very rapidly under irradiation to yield a complex mixture of products, but careful control of conditions allowed isolation of a zinc formylbiliverdin. The nmr spectrum showed that this compound was a mixture of two isomers, i.e., those with the formyl group on either terminal ring. The ratio of the two isomers appeared by nmr spectroscopy to be about 1 : 1 (the aldehyde proton singlet was split into two signals of equal intensity at τ, 0.38, 0.44, as was one of the methine proton singlets, τ, 4.23, 4.27).

A repeated scan photooxidation experiment on γ,δ-dimethyloctaethylchlorin (**32**) was performed. The compound was dissolved in toluene, and the visible spectrum run. The cell was then placed in direct sunlight for 5-min periods, and the spectrum run again. After the first few scans, there were five isosbestic points; but on continued exposure to light further degradation occurred (*25*). A minor polar compouind from preparative tlc of γ,δ-dimethyloctaethylchlorin (**32**) was shown by mass spectroscopy to be the acetylbilitriene (**48**) (*m/e* 596 (100%), 553 (57%)). The fragmentation pattern was not well defined enough to demonstrate whether the material was a mixture of isomers. Further degradation of the acetylbilitriene is possibly due to cleavage of ring D to give a tripyrrinone.

γ-Methyloctaethylchlorin (**30**) was found to be more stable to irradiation. Illumination with a 100-W bulb for 1 week led to a complex mixture, the major components of which were *meso*-methyloctaethylchlorin and *meso*-methyloctaethylporphyrin. The zinc complex of γ-methyloctaethylchlorin, however, was very susceptible to photooxidation (incorporation of zinc significantly lowers the oxidation potential (*36*)). The blue zinc complex was dissolved in CH_2Cl_2 and the solution purged with air for 48 hr in daylight. Preparative tlc revealed two main bands, starting material and a more polar yellow–brown band. The starting material was redissolved in CH_2Cl_2 and left for 4 days. After preparative tlc and further purification by column chromatography on alumina, the photooxidation product was obtained in about 50% yield, the remaining material being mostly on the baseline.

The nmr spectrum showed that both ring-opened isomers (**49**) and (**50**) had been formed, in approximately a 2 : 1 ratio. Two of the methine protons were split into a 2 : 1 doublet (τ 2.87, 2.89; 3.54, 3.67), and the CH_3 of the acetyl group was clearly split into a 1 : 2 doublet (7.59, 7.63). Thus the *meso*-methyl group does have some directing influence on the ring opening (since in zinc(II) octaethylchlorin a 1 : 1 mixture was produced). The two isomers could not be separated, even by hplc. The major product is probably the one with the acetyl on ring D (by analogy with the other photooxidations). Formation of both isomers is possibly due to the lower oxidation potential of the zinc complex, allowing the apparently less favorable mode of ring opening, and absence of the isocyclic ring carbonyl.

Deuteration Studies on meso-Methylchlorins

It is well known that the γ- and δ-positions adjacent to the reduced ring in chlorins are much more susceptible to electrophilic attack than are the α- or β-positions, or the *meso*-positions on the corresponding porphyrins (*16*). It seems, though, that when a δ-methyl group is present, as in the *Chlorobium* chlorophylls 660, the α-position is activated toward electrophilic substitution, as evidenced by its facile exchange in warm deuteroacetic acid (*3, 19*). The β-proton is presumably not exchanged owing to the local electron-withdrawing effect of the isocyclic ring carbonyl group.

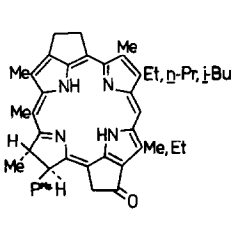
γ,δ-Dimethyloctaethylchlorin (**32**) shows one singlet in its nmr spectrum at 0.5 τ for the α- and β-protons, and a singlet for the *meso*-methyl groups at 6.21 τ. The compound was recovered unchanged (i.e., with no detectable deuteration) after treatment with 1 : 1 MeOD/1,2-dichloroethane at 60° for 5 hr. Heating at 100°C in deuteroacetic acid for 3.5 hr resulted in partial exchange of the *meso*-protons. After treating with DOAc at 100°C for 15 hr, the *meso*-protons integrated for approximately 0.25H. Thus, the half-life of the α- and β-*meso*-protons in γ,δ-dimethyloctaethylchlorin is about 5 hr, a substantial rate increase over the α- and β-protons in *trans*-octaethylchlorin, which are virtually unaffected in refluxing DOAc.

To discover whether the α- and β-*meso*-protons exchange at the same rate, a deuteration experiment was attempted using γ-methyloctaethylchlorin (**30**). An nmr spectrum, run after being heated for 6 hr in DOAc at 100°C, showed that the δ-proton at 1.17 τ had been completely exchanged, while the α- and β-protons were still present. Heating was continued for a further 24 hr, after which a significant amount of degradation had occurred; therefore the product was chromatographed before running the nmr spectrum. The nmr spectrum of the first band taken from the column, γ-methyloctaethylchlorin, showed that both the remaining *meso*-protons had been deuterated to some extent. The lower field singlet appeared to be smaller than the other *meso*-resonance, and the ratio of integration was about 28 : 33 (peak at 9.74: peak at 9.51 τ). The higher field *meso*-proton integrated for 0.75H. The usual order for the *meso*-resonances in mono-*meso*-substituted chlorins is (from low to high field) β, α, and δ. Thus this preliminary result suggests that the β-proton exchanges somewhat more readily than the α-proton, suggesting that the *meso*-methyl group activates the *meso*-position adjacent, rather than opposite, to it. If this is the case, then the activation of the α-position in the *Chlorobium* chlorophylls 660 is more easily understood.

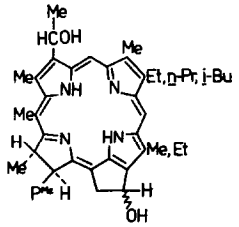
Mesochlorin-e_6 triethyl ester (**40**) has *meso*-proton singlets at τ 0.34, 0.64, and 1.35. Again these are assigned to the β-, α-, and δ-protons, respectively (*37*). Synthetic δ-methylmesochlorin-e_6 triethyl ester (**45**) has only two *meso*-protons. and the lack of high field resonance indicates δ-substitution. The remaining resonances at τ 0.46 and 0.59 are assigned to the β- and α-protons, respectively, and the β-proton is moved to higher field compared with the δ-unsubstituted chlorin (**40**), a typical effect of *meso*-substitution in porphyrins. δ-Methylmesochlorin-e_6 trimethyl ester was heated in DOAc/$CHCl_3$ (3 : 1) for 5 hrs. The nmr spectrum showed that the α-*meso*-proton had diminished greatly in intensity.

Again the β-proton does not exchange because of the nuclear ester at the 6-position, and this is an added piece of evidence for δ-substitution in the *Chlorobium* chlorophylls. Since the synthetic chlorin (**45**) must be substituted at the δ-position, there cannot any longer be any doubt that the *Chlorobium* chlorophylls 660 possess a δ-alkyl group, and that the α-*meso*-proton is readily exchangeable.

Deuteration was attempted on two *Chlorobium* chlorophyll degradation products, the 2,α-ethylene pheophorbides (**51**) and the 9-hydroxy-9-desoxo-pheophorbides (**52**). The 2,α-ethylene pheophorbides (**51**) were prepared by refluxing the methyl pheophorbides in benzene containing *p*-toluenesulfonic acid.



(51)



(52)

The 2,α-ethylene pheophorbides showed a great propensity to aggregate in solution. Assignment of the spectra, followed by analysis of the aggregation shifts, revealed that the aggregation is specific, and probably involves a face–face type of dimer. This very strong π–π interaction could be due to the increased planarity of the ring and the electron density differences within the macrocyle (*38–41*), both consequences of the introduction of the ethylene bridge between C-2 and the α-position. The deuteration experiment on this compound was not successful; the β-proton still did not exchange readily, again probably due to the isocyclic ring carbonyl group.

Reduction of the isocyclic ring carbonyl group produced the diol (**52**), a compound which was very insoluble and easy to crystallize, even as the homologous mixture (in contrast to the methylpheophorbides). The nmr spectrum showed that the β-*meso*-proton was strongly deshielded, resonating at −0.03 τ, with the α-proton at 0.52 τ. Treatment with DOAc : $CHCl_3$ (1 : 1) for 5 hr completely removed the α-*meso*-resonance and left the β-proton resonance diminished. It seems that removal of the isocyclic ring carbonyl group causes an increase in the ring current (hence the deshielding of the β-proton), and also makes the β-proton more labile, though not to the same extent as the α-*meso*-proton.

EXPERIMENTAL

General conditions were as described in a previous paper (*42*). High performance liquid chromatography was performed on a Waters Associates ALC/GPC-201 with a 405-nm ultraviolet detector.

Nickel(II) meso-Methyletioporphyrin-I (6)

A solution of nickel(II) *meso*-formyletioporphyrin-I(5) (200 mg) in THF (100 ml) was added to a suspension of lithium aluminum hydride (200 mg) in THF (50 ml) at −78°C. After 5 min, the green solution had turned red in color and aqueous THF was cautiously added. The mixture was poured into $CHCl_3$ (250 ml), washed with dilute sulfuric acid (250 ml), water (300 ml), dried (Na_2SO_4), and evaporated. Chromatography of the resulting solid on alumina (grade III) using CH_2Cl_2 as eluant gave a pink forerun (nickel(II) etioporphyrin-I) followed by purple red eluates which were evaporated and the solid crystallized from CH_2Cl_2–methanol as purple prisms (146 mg, 75%), mp > 300°C.

Anal. Calcd for $C_{33}H_{38}N_4Ni$: C, 72.15; H, 6.97; N, 10.20. Found: C, 72.43; H, 7.14; N, 10.29%.

Visible spectrum λ_{max} 404 (ϵ 160,500), 529 (8900), and 565 nm (12,700).

Mass spectrum *m/e:* ^{58}Ni, 548 (100%) and 533 (20%).

meso-Methyletioporphyrin-I (7)

Nickel(II) *meso*-methyletioporphyrin-I (30 mg) was stirred overnight in concentrated sulfuric acid (25 ml). The mixture was carefully poured into ice water (200 ml) and extracted with CH_2Cl_2 (2 × 100 ml). The combined CH_2Cl_2 extracts were washed with water (200 ml), dried (Na_2SO_4), and evaporated. Chromatography of the resulting solid on grade III alumina using CH_2Cl_2 as eluant gave a red band which was collected and the eluates were evaporated. Crystallization of the solid from CH_2Cl_2–methanol gave the product as purple prisms (30 mg, 86%), mp > 310°C.

Anal. Calcd for $C_{33}H_{40}N_4$: C, 80.44; H, 8.18; N, 11.37. Found: C, 80.41; H, 8.25; N, 11.40%.

Visible spectrum λ_{max} 406 (ϵ 169,400), 505.5 (13,800), 538.5 (5600), 576 (5700), and 627 nm (1300).

Mass spectrum *m/e:* 492 (100%) and 478 (20).

^1H nmr spectrum: τ, 0.01 (2H, s, 2x *meso*-H); 0.21 (1H, s, *meso*-H); 5.60 (3H, s, *meso*-CH_3); 5.90–6.20 (8H, m, CH_2CH_3); 6.48 (6H, s, 2x, CH_3); 6.52 (3H, s, CH_3); 6.56 (3H, s, CH_3); and 8.05–8.40 (12H, m, CH_2CH_3).

Zinc(II) *Complex of* 7

A solution of the porphyrin (140 mg) in CH_2Cl_2 (50 ml) was treated with a solution of zinc(II) acetate (150 mg) in methanol (40 ml) and the volume was reduced by distillation to about 40 ml, whereupon the product crystallized as fluffy red needles (144 mg, 92%), mp > 300°C.

Anal. Calcd for $C_{33}H_{38}N_4Zn$: C, 71.28; H, 6.89; N, 10.08; Zn, 11.76. Found: C, 71.15; H, 6.77; N, 10.35; Zn, 11.49%.

Visible spectrum λ_{max} 407 (ϵ 211,000), 537 (114,800), and 570 nm (11,000).

Zinc(II) meso-Hydroxymethyloctaethylporphyrin (8)

meso-Formyloctaethylporphyrin (650 mg) was dissolved in dry THF (300 ml) containing methanol (30 ml) and sodium borohydride (3 g) was added to the stirred

solution. After 2 hr, water (25 ml) was added followed by CH_2Cl_2 (250 ml) and the mixture was washed with water (3 × 400 ml). The dried (Na_2SO_4) extracts were evaporated and the solid obtained was chromatographed on alumina (grade III) using CH_2Cl_2 as eluant. A red forerun was discarded and upon elution of the column with CH_2Cl_2–2% methanol, a red band was obtained. The eluates were treated with a solution of zinc(II) acetate (1 g) in methanol (50 ml) and the volume was reduced by distillation. Water was periodically added and the product crystallized as red prisms (639 mg, 88%), mp > 300°C.

Anal. Calcd for $C_{37}H_{46}N_4OZn.1/2H_2O$; C, 69.74; H, 7.43; N, 8.79; Zn, 10.24. Found: C, 69.84, 70.01; H, 7.39, 7.40; N, 8.96; Zn, 9.91, 10.16.

Visible spectrum λ_{max} 407 (ϵ 151,800), 537.5 (7900), and 579 nm (8900)

Infrared 3180 cm^{-1}(OH).

^1H nmr spectrum: The compound was not sufficiently soluble for a satisfactory spectrum to be obtained.

meso-Hydroxymethyletioporphyrin-I

This compound was similarly prepared in 89% yield by reduction of *meso*-formyletioporphyrin-I. Crystallization from CH_2Cl_2–petroleum ether(bp 60–80°C) gave rust-red fluffy needles, mp > 300°C.

Anal. Calcd for $C_{33}H_{40}N_4O$: C, 77.92; H, 7.93; N, 11.01. Found: C, 77.75; H, 7.95; N, 11.06%.

Visible spectrum λ_{max} 404 (ϵ 110,500), 504 (12,100), 538 (8400), 573 (5800), and 624 nm (4000).

meso-Methoxymethyloctaethylporphyrin

Zinc(II) *meso*-methyloctaethylporphyrin (200 mg) was dissolved in dry THF (25 ml) containing $CHCl_3$ (75 ml) and the solution was flushed with nitrogen for 5 min. A solution of thallium(III) trifluoroacetate (195 mg) in THF was added and the mixture was stirred for 5 min. SO_2 gas was bubbled through the mixture for 30 sec followed by the addition of hydrochloric acid (2 ml) in THF (10 ml). $CHCl_3$ (200 ml) was added and the mixture washed with water (3 × 300 ml) and the organic phase was evaporated using toluene to azeotropically remove the water. Acetic anhydride (10 ml) and pyridine (10 ml) were added and the mixture was heated at 70°C for 10 min. The solution was evaporated to dryness and the solid obtained was chromatographed on silica plates using CH_2Cl_2 as eluant. A reddish purple band was extracted into CH_2Cl_2–5% methanol and the methoxymethylporphyrin produced was crystallized from CH_2Cl_2–*n*-hexane as purple prisms (31 mg), mp 193–194°C.

Anal. Calcd for $C_{38}H_{50}N_4O$: C, 78.85; H, 8.71; N, 9.68. Found: C, 78.45, H, 8.61; N, 9.67%.

Visible spectrum: λ_{max} 405 (ϵ 143,400), 506 (12,000), 540 (8500), 575.5 (5500), and 627 nm (4100).

^1H nmr spectrum: τ −0.10 (2H, s, 2x *meso*-H); 0.09 (1H, s, *meso*-H) 3.58 (2H, s, CH_2OCH_3); 5.80–6.00 (16H, m, CH_2OCH_3); 6.08 (3H, s, CH_2CH_3); and 8.00–8.20 (24H, m, CH_2CH_3).

Zinc (II) meso-Methoxymethyletioporphyrin-I

A solution of *meso*-acetoxymethyletioporphyrin-I (240 mg) in CH_2Cl_2 (50 ml) was treated with a solution of zinc(II) acetate in methanol (25 ml) and upon reduction of the volume by distillation, the product crystallized as a bright red fluff (245 mg, 95%), mp > 300°C.

Anal. Calcd for $C_{36}H_{40}N_4OZn$: C, 69.68; H, 6.88; N, 9.56; Zn, 11.15. Found: C, 69.56; H, 6.76; N, 9.80; Zn, 11.20%.

Visible spectrum λ_{max} 405.5 (ϵ 195,100), 535.5 (14,500), and 577 nm (17,800).

Mass spectrum *m/e*: ^{64}Zn, 584 (100%), 554 (65%), and 540 (17%).

^1H nmr spectrum: τ, −0.91, −0.82, −0.78 (each 1H, s, 3x *meso*-H); 3.91 (2H, s, CH_2OCH_3); 5.82–6.26 (8H, m, CH_2CH_3); 6.04 (3H, s, OCH_3); 6.41, 6.59 (12H, 2s, 4x CH_3); and 8.06–8.33 (12H, m, CH_2CH_3).

meso-Acetoxymethyloctaethylporphyrin

meso-Hydroxymethyloctaethylporphyrin (150 mg) was heated at 90°C in acetic anhydride (10 ml) and pyridine (10 ml) for 3 hr. The solution was evaporated and the solid was chromatographed on alumina (grade III) using CH_2Cl_2 as eluant. Evaporation of the red eluates gave a solid which crystallized from CH_2Cl_2–petroleum ether(bp60–80°C) as purple platelets (108 mg, 67%), mp 169–170°C.

Anal. Calcd for $C_{39}H_{50}N_4O_2$: C, 77.19; H, 8.31; N, 9.23. Found: C, 77.27; H, 8.38; N, 9.35%.

Visible spectrum λ_{max} 404 (ϵ 156,200), 506 (12,400), 540 (8900), 575 (5700), and 625 nm (4700).

Infrared 1725 cm^{-1} ($COCH_3$).

Mass spectrum *m/e*: 606 (11%), 548 (100%), and 534 (40%).

^1H nmr spectrum: τ, −0.10 (2H, s, 2x *meso*-H); 0.09 (1H, s, *meso*-H); 2.67 (2H, s, CH_2OAc); 5.80–6.10 (16H, m, CH_2CH_3); 7.71 (3H, s, $OCOCH_3$); and 8.00–8.25 (24H, m, CH_2CH_3).

α-Methyl-1,3,5,7-tetramethyl-2,4,6,8-tetra-(n-pentyl)porphyrin (**12**)

(*a*) *Sodium borohydride/tert-butanol method.* Sodium borohydride (60 mg) in dry *tert*-butanol (10 ml) was added to a solution of α-acetoxymethyl-1,3,5,7-tetramethyl-2,4,6,8-tetra-(*n*-pentyl)porphyrin (30 mg) (**10**) (*30*) in dry dichloromethane (30 ml) and the mixture was refluxed for 24 hr. The solution was then diluted with dichloromethane (50 ml), washed with water (3 × 50 ml), dried over anhydous sodium sulfate, and evaporated to dryness *in vacuo*. Purification by column chromatography (grade III alumina, dichloromethane elution) and recrystallization from dichloromethane/methanol afforded purple crystals of (**12**) (23 mg; 80%), mp 169°C.

Anal. Calcd for $C_{45}H_{64}N_4$: C, 81.76; H, 9.76; N, 8.48. Found: C, 81.28; H, 9.57; N, 8.77%.

$CDCl_3$ nmr spectrum: τ 9.18–8.93 (m, 12H, 5′-CH_3); 8.58–8.36 (m, 8H, 4′-CH_2); 8.34–8.17 (m, 8H, 3′-CH_2); 7.91–7.63 (m, 8H, 2′-CH_2); 6.48, 6.47, 6.44, 6.43 (each

s, 3H, 1,3,5,7-C*H*$_3$); 5.51 (s, 3H, *α-meso*-C*H*$_3$); 0.22 (s, 1H, *γ-meso*-H); 0.04 (s, 2H, *β*, *α-meso-H*).

Mass spectrum *m/e*: (rel intensity): 660 (M^+, 100%), 647 (47%), 589 (13%), 532 (4%), 475 (4%), 417 (4%), 330 (24%).

Visible spectrum λ_{max} 409 (ϵ 177,000), 508 (14,000), 542 (6000), 578 (600), and 628 nm (1400).

(*b*) *Tetra-n-butylammonium borohydride method.* Tetra-*n*-butylammonium borohydride (200 mg) (*31*) in dry 1,2-dichloroethane (10 ml) was added to a solution of α-acetoxymethyl-1,3,5,7-tetramethyl-2,4,6,8-tetra-(*n*-pentyl)porphyrin (50 mg) in dry 1,2-dichloroethane (10 ml) and the mixture refluxed for 0.5 hr. The solution was then diluted with dichloromethane (20 ml), washed with water (3 × 5 ml), dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. Purification by column chromatography and recrystallization as in method *a* afforded purple crystals (40 mg, 87%) with physical and spectroscopic properties identical to that of method *a* above.

α-Hydroxymethyloctaethylporphyrin (3)

Tetra-*n*-butylammonium borohydride (200 mg) in dry 1,2-dichloroethane (10 ml) was added to a solution of α-formyloctaethylporphyrin (100 mg) (*28*) in dry 1,2-dichloroethane (20 ml) and the mixture was refluxed for 5 min. To this was then added a 3% aqueous solution of hydrogen peroxide (5 ml) and a 40% aqueous solution of sodium hydroxide (5 ml) and the reaction was refluxed a further 15 min. The organic layer was separated, washed with water (2 × 50 ml), dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. Purification by column chromatography (grade III alumina, dichloromethane elution) and recrystallization from dichloromethane/methanol afforded (3) (91 mg, 90%), the properties of which were identical to those found in the literature (*28*).

meso-Methyloctaethylporphyrin (2)

(*a*) *From Zinc(II) meso-Hydroxymethyloctaethylporphyrin* (8) Zinc(II) *meso*-hydroxymethyloctaethylporphyrin (639 mg) was heated at 80°C in acetic anhydride (10 ml) and pyridine (20 ml) for 4 hr. The mixture was evaporated, dissolved in THF (100 ml) containing triethylamine (0.1 ml), and stirred under an atmosphere of hydrogen with 10% palladized charcoal (50 mg) for 12 hr. Filtration of the mixture through Celite and evaporation of the filtrate gave a purple solid which was stirred in trifluoroacetic acid (20 ml) for 10 min. CH_2Cl_2 (200 ml) was added and the mixture washed with water (3 × 200 ml) and dried (Na_2SO_4). The solid obtained on evaporation of the extracts was chromatographed on alumina (grade III) using CH_2Cl_2 as eluant and the purple eluates were evaporated. Crystallization of the solid obtained from CH_2Cl_2–methanol gave purple microneedles (440 mg, 79%), mp 262–264°C.

Anal. Calcd for $C_{37}H_{48}N_4 \cdot H_2O$: C, 78.40; H, 8.89; N, 9.88. Found: C, 78.52; H, 8.66; N, 10.00%.

Visible spectrum λ_{max} 408 (ϵ 140,600), 507 (11,500), 540 (4600), 578 (4700), and 629 nm (1100).

^{1}H nmr spectrum: τ, 0.00 (2H, s, 2x *meso*-H); 0.20 (1H, s, *meso*-H); 5.40 (3H, s, *meso*-CH_3); 5.80–6.03 (16H, m, CH_2CH_3); and 7.98–8.22 (24H, m, CH_2CH_3).

(*b*) *From Copper(II) meso-Formyloctaethylporphyrin* (**14**). Tetra-*n*-butylammonium borohydride (300 mg) in dry 1,2-dichloroethane (20 ml) was added to a solution of copper(II) *meso*-formyloctaethylporphyrin (644 mg) in dry 1,2-dichloroethane (50 ml) and the solution was refluxed for 1 hr. The solution was cooled and washed with a 3% aqueous solution of hydrogen peroxide (50 ml), then a 10% aqueous solution of sodium hydroxide (50 ml), and finally with water (50 ml). Drying over anhydrous sodium sulfate and evaporation to dryness *in vacuo* afforded a solid which was purified by column chromatography (grade III aluminia, dichloromethane elution) and recrystallization from methanol/dichloromethane to give (**15**), copper(II) *meso*-methyloctaethylporphyrin (547 mg, 87%) mp 278°C.

Anal. Calcd for $C_{37}H_{46}N_4Cu$; C, 72.81; H, 7.60; N, 9.18. Found: C, 72.61; H, 7.45; N, 9.20%.

Mass spectrum (relative intensity): 609 (M^+, 100%), 608 (96%), 594 (40%), 304.5 (62%).

Visible spectrum (CH_2Cl_2), λ_{max} 406 (ϵ 232,000), 533 (10,900), and 564 nm (11,600).

The copper chelate (**15**) (100 mg) was treated with a 1 : 1 mixture of concentrated sulfuric acid and trifluoroacetic acid (10 ml) for 2 hr at room temperature, and then poured over ice water (100 ml). The aqueous solution was extracted with dichloromethane (3 × 50 ml), and the combined extracts were washed with a saturated solution of sodium bicarbonate, water, and then dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. Purification was achieved by column chromatography (grade III alumina, dichloromethane elution) and recrystallization from dichloromethane/methanol to yield purple crystals (71 mg, 79%) of (**2**), identical in every respect to that obtained by method *a* above.

Nickel(II) or zinc(II) *meso*-formyloctaethylporphyrin could both be reduced to their corresponding *meso*-methyl analogs by this method, the latter being particularly useful because of the ease of removal of the zinc after reduction.

(*c*) *From copper(II) α-hydroxymethyloctaethylporphyrin* (**16**). Copper(II) α-hydroxymethyloctaethylporphyrin (*43*) was reduced by method *b* described above to give copper(II) *meso*-methyloctaethylporphyrin (**15**) in 88% yield. Demetalation proceeded as described above to give the *meso*-methyl porphyrin (**2**) in 80% yield.

Vilsmeier Formylation of Copper(II) trans-Octaethylchlorin (**18**)

(a) Copper(II) *trans*-octaethylchlorin (80 mg) was dissolved in dry 1,2-dichloroethane (70 ml) and added over 20 min to a stirred solution of the Vilsmeier complex prepared from $POCl_3$ (3 ml) and DMF (3 ml) at 50°C. The blue color changed to bright green as soon as it was added. After stirring at 50°C for 10 min, the temperature of the oil bath was raised to 70°C for 1 hr. A saturated solution of sodium acetate (200 ml) was added and the reaction stirred at 80°C for 2 hr. The layers were separated and the aqueous layer was washed with CH_2Cl_2, then the

combined organic layers were washed with water, dried (Na_2SO_4), and evaporated. Preparative tlc in 30% toluene/CH_2Cl_2 was the most efficient way of separating the mixture, which contained four main bands. These were identified as: copper(II) *meso*-formyloctaethylporphyrin (**19**) (15 mg, 18%), *m/e* 623,625,(100%); copper(II) δ-formyloctaethylchlorin (**20**), (25 mg, 30%), mp 189.5–191°C (from CH_2Cl_2/methanol) [*Anal.* Calcd for $C_{37}H_{46}CuN_4O$: C, 70.95; H, 7.45; N, 8.95. Found: C, 70.92; H, 7.40; N, 9.10%; *m/e:* 627,625 (100%); λ_{max} 391 (ε 61, 600), 409.5 (114, 500), 463 (2750), 499 (5200), 537 (2900), 605 (inf) (9390), and 648 nm (28,300)]; copper(II) diformyloctaethylporphyrin (**21**) (5 mg, 6%), *m/e* 653, 651 (100%), this material was mainly the α,β-isomer, but on rechromatography a minor band, slightly less polar, was obtained with the same molecular weight, and visible spectrum, 404, shoulder at 415, 539, 575, 646 nm, which was the α,γ-isomer (**23**); copper(II) γ,δ-diformyloctaethylchlorin (**22**) (7 mg, 9%), mp 207.5–210°C (from CH_2Cl_2/methanol).

Anal. Calcd for $C_{38}H_{46}CuN_4O_2$: C, 69.75; H, 7.09; N, 8.56. Found, C, 69.50; H, 7.23; N, 8.46%.

Mass spectrum *m/e*: 665,653 (100%).

Visible spectrum λ_{max} 390 (ε 83,500), 415 (65,900), 504 (5200), 540 (2700), 615 (9700), 662 nm (36,900).

(b) The Vilsmeier complex was made from $POCl_3$ (2 ml) and DMF (2 ml). To a solution of this was added copper(II) *trans*-octaethylchlorin (650 mg) in 1,2-dichloroethane over about 15 min, while the complex was warmed up to 50°C, and the green solution was heated at this temperature for 15 min. Then a solution of sodium acetate (250 ml) was added and heating and stirring were continued for a further 2 hr. After the same workup as previously, copper(II) δ-formyloctaethylchlorin (**20**) was recrystallized from CH_2Cl_2 as glistening green platelets (510 mg, 75%). An alternative to thick layer chromatography of the compound was to chromatograph on alumina (grade III) in toluene.

δ-*Formyl-trans-octaethylchlorin* (**24**)

Copper(II) δ-formyloctaethylchlorin (**20**) (171 mg) was stirred in 10% H_2SO_4 in TFA (33 ml) for 25 min at room temperature. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ solution, water, dried (Na_2SO_4), and evaporated. All the copper was not removed by this treatment, so the process was repeated two times more. After chromatography on alumina (grade III, elution with toluene) the formyl chlorin-free base was crystallized from CH_2Cl_2/methanol as glistening purple plates (87 mg, 58%), mp 212–214°C.

Anal. Calcd for $C_{37}H_{48}N_4O$: C, 78.68; H, 8.57; N, 9.92. Found: C, 78.94; H, 8.64; N, 10.01%.

Mass spectrum *m/e*: 564 (100%).

nmr spectrum: τ, −1.92 (1H, s, CHO); 0.41, 0.64, 1.36 (each 1H, s, β,α,δ-*meso*-protons); 4.86, 5.70 (m, each 1H, 7,8-H); 6.0–6.35 (12H, q, 6 × CH_2); 7.65–8.05 (4H, m, 7,8-CH_2); 8.15–8.4 (18H, t, 6 × CH_3); 8.95, 8.96 (6H, t, 7,8-CH_3).

A minor band eluted next was identified as the free base formyloctaethylporphyrin (**13**), (30 mg 20%).

nmr spectrum: τ, −2.2 (1H, s, CHO); −0.04 (2H, s, *meso*-H); 0.07 (1H, s, *meso*-H); 5.85–6.05 (12H) and 6.13 (4H, q 8 × CH_2); 8.05–8.2 (18H, t, 6 × CH_3); 8.28 (6H, t, 2 × CH_3).

Copper(II) Hydroxymethyl-trans-octaethylchlorin (**25**)

The copper(II) formyloctaethylchlorin (267 mg) was dissolved in $CHCl_3$ (50 ml) and stirred at room temperature. A solution of $NaBH_4$ (200 mg) in methanol (50 ml) was added. The reaction was stirred for 2 hr and the mixture was poured into water, extracted with CH_2Cl_2, the organic layers washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on alumina [grade III elution with $CHCl_3$/toluene (1/1)]. A forerun contained copper(II) octaethylchlorin (20 mg) and copper δ-formyloctaethylchlorin (10 mg). The major blue band was the required copper(II) hydroxymethyloctaethylchlorin, which would not crystallize, and was therefore obtained as a glass (220 mg). λ_{max} 403 (shoulder at 390), 495, 531, 580, 621 nm.

The "Chlorin Dimer" (**27**)

The copper(II) δ-hydroxymethyloctaethylchlorin (200 mg) was stirred in 10% H_2SO_4/TFA at room temperature for 20 min before the solution was poured into water, extracted with $CHCl_3$, and the organic layer was washed with water, NaOAc aq, water, dried (Na_2SO_4), and evaporated. The visible absorption spectrum showed that the copper had been removed from about 60% of the mixture so the process was repeated. Chromatography on grade III alumina gave two bands, and the faster running chlorin band was crystallized from CH_2Cl_2/methanol as purple plates (125 mg). Thin layer chromatography revealed the presence of a blue impurity, probably the metal complex. Separation of these was very difficult but was achieved by repeated chromatography on preparative tlc plates. The compound was obtained pure (40 mg) and crystallized from CH_2Cl_2/methanol as shining purple plates, mp 265–267°C.

Anal. Calcd for $C_{74}H_{98}N_8$: C, 80.82; H, 8.98; N, 10.19. Found: C, 80.56; H, 8.86; N, 10.42%.

The mass spectrum was impossible to count above 650, but the molecular weight was estimated to be 1100 ± 10 amu (3%), the most prominent peaks were around the half-mass region 550 (100%), 549 (74%).

Visible spectrum λ_{max} 386 (ϵ 190,000), 401 (301,400), 499 (30,100), 525 (4800), 549 (3600), 594 (10,000), 644 (84,300), 652 nm (53,800).

meso-Methyl-trans-octaethylchlorin (**30**)

(a) Copper(II) δ-hydroxymethyloctaethylchlorin (150 mg) was dissolved in acetic anhydride (13 ml) and pyridine (10 ml), and stirred at 90°C for 3 hr. Toluene was added and evaporated; this was repeated until all the pyridine had been removed. The residue was dissolved in THF (50 ml) with triethylamine (0.2 ml) and 10% Pd/C (100 mg). The mixture was stirred under hydrogen overnight. After

filtration through Celite to remove the catalyst and evaporation, the residue was chromatographed on alumina (grade III, elution with CH_2Cl_2) to remove some starting alcohol (15 mg). The major fast running band [copper(II) *meso*-methyloctaethylchlorin] was demetalated by stirring in 15% H_2SO_4/TFA at room temperature for 30 min (two treatments). The residue was chromatographed on alumina (Grade III); the forerunning blue metal complex (10.5%) was separated, and the other two bands were collected and crystallized from CH_2Cl_2/methanol. The major fraction was identified as the desired δ-*meso*-methyloctaethylchlorin (40 mg, 30.4%), mp 185–187°C.

Anal. Calcd for $C_{37}H_{50}N_4$: C, 80.68; H, 9.15; N, 10.17. Found: C, 80.78; H, 8.87; N, 10.28%.

nmr spectrum: τ, 0.29, 0.51, 1.20 (each 1H, s, *meso* H); 5.5, 5.6 (each 1H, m, 7,8-H); 6.0 (3H, s, *meso*-methyl); 5.94–6.23 (12H, 6 × CH_2); 7.65–8.0 (4H, m, 7,8-CH_2); 8.1–8.35 (18H, t, 6 × CH_3,); 8.96, 8.98 (each 3H, t, 7,8-CH_3).

Mass spectrum, *m/e*: 550 (100%), 521 (24%).

Visible spectrum λ_{max} 399 (ϵ 185,700), 499 (15,100), 574 (2100), 546 (2100), 592 (5000), 646 nm (52,500).

The next band eluted was shown to be the corresponding *meso*-methyloctaethylporphyrin (2), (23 mg, 17%), mp 254–256°C (lit 262–264°C (*44*)).

Anal. Calcd for $C_{37}H_{48}N_4$: C, 80.96; H, 8.82; N, 10.21. Found: C, 81.21; H, 9.38, N, 10.16%.

nmr spectrum: τ, −0.01 (2H, s) and 0.20 (1H, s, *meso*-H); 5.39 (3H, s, *meso*-methyl; 5.8–6.05 (16H, q, 8 × CH_2); 8.0–8.25 (24H, t, 8 × CH_3).

Mass spectrum, *m/e*: 548 (100%).

(b) The copper(II) δ-hydroxymethyloctaethylchlorin (250 mg) was dissolved in 1,2-dichloroethane (15 ml) and heated to gentle reflux on an oil bath at 100°C. Solid tetrabutylammonium borohydride was added (four portions of 100 mg at 5-min intervals) and the reaction was monitored by tlc. When the reaction appeared to be complete, the solution was allowed to cool, and water was added. The layers were separated and the organic layer was washed with water, dried (Na_2SO_4), and evaporated. The metal was removed by two treatments with 20% H_2SO_4/TFA for 30 min and the residue was chromatographed on alumina [grade III elution with toluene/hexane (3/1)], and the small amount of copper complex taken off and treated with H_2SO_4/TFA. After rechromatography of the two main bands, they were recrystallized from CH_2Cl_2/methanol and identified as δ-methyloctaethylchlorin (129 mg; 59%) and *meso*-methyloctaethylporphyrin (2) (53 mg; 24%) by comparison with authentic samples.

γ,δ-*Dimethyl-trans-octaethylchlorin* (32)

Copper(II) γ,δ-diformyloctaethylchlorin (21), (100 mg) was dissolved in 1,2-dichloroethane (20 ml) and heated to gentle reflux on an oil bath at 100°C. Tetrabutylammonium borohydride (four portions of 100 mg) was added periodically, and the reaction was monitored by tlc. There was a rapid reaction, complete in 2–3 min which caused a color change to blue, and on tlc there was a very polar spot, and no starting material. A slower second step then followed which

produced a very fast moving spot. The reaction was complete after 25 min. The solution was allowed to cool, then water was added and the layers were separated. The aqueous layer was washed with CH_2Cl_2, and the combined organic layers were washed with water, then evaporated with toluene to remove any residual water. The product was demetalated by stirring in H_2SO_4/TFA, (4/1); two treatments were necessary to remove most of the copper. The residue was chromatographed on alumina [grade III, elution with toluene/hexane (3/1)]. The small amount of metal complex was separated, and retreated with H_2SO_4/TFA. The major product, γ,δ-dimethyloctaethylchlorin was recrystallized from CH_2Cl_2/methanol (40 mg, 46.3%), mp 172–173.5°C.

Anal. Calcd for $C_{38}H_{52}N_4$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.97; H, 8.99; N, 9.70%.

nmr spectrum: τ, 0.5 (2H, s, *meso*-H); 5.45–5.6 and 5.6–5.75 (each 1H, m, 7,8-H); 6.2 (6H, s, *meso*-CH_3); 5.8–6.4 (12H, 6 × CH_2 q); 8.0–8.5 (22H, t, 6 × CH_3, and m, 7,8-CH_2); 8.9 (6H, t, 7,8-CH_3).

Mass spectrum, *m/e*: 564 (100%), 535 (30%).

Visible spectrum, λ_{max} 407 (ε 169,000), 510 (12,600), 538 (4500), 608 (4200), and 663 nm (45,200).

Chlorin-e_6 Trimethyl Ester (**39**)

Methyl pheophorbide-*a* (**38**) (1.0 g) was dissolved in dry THF (50 ml) and stirred under nitrogen for 10 min. Sodium metal (200 mg) was dissolved in methanol (40 ml) and the mixture was added. The reaction was allowed to stir at room temperature for 1 hr, was poured into water, and then extracted with CH_2Cl_2, and the organic layer washed with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in $CHCl_3$ and treated with excess diazomethane in ether. The solid obtained was chromatographed on alumina [grade III elution with toluene/CH_2Cl_2 (1/1)]. The major band, chlorin-e_6 trimethyl ester, was recrystallized from CH_2Cl/methanol (700 mg, 67%). The remaining material was mainly starting material, which was recovered and used again. In this way an overall yield of 88.7% was obtained in preparation 6 g of chlorin-e_6 trimethyl ester. mp 205–207°C (lit 211°C (*45*)).

Anal. Calcd for $C_{37}H_{42}N_4O_6$: C, 69.57; H, 6.63; N, 8.77. Found: C, 69.77; H, 6.70; N, 8.85%.

nmr spectrum: τ, 0.35, 0.48, 1.27 (each 1H, s, *meso*-H); 1.98 (1H, m) and 3.65–3.93 (2H, m, CH=CH_2); 4.70 (2H, ABq, γ-CH_2); 5.6 (2H, m, 7,8-H); 5.74 (3H, s, 6-CO_2CH_3); 6.23 (3H, s, γ-CO_2CH_3); 6.37 (3H, s, 7-CO_2CH_3); 6.44, 6.56, 6.74 (each 3H, s, 1,3,5-methyls); 7.4, 7.8 (4H, m, CH_2CH_2); 6.25 (2H, q) and 8.31 (3H, t, CH_2CH_3); 8.25 (3H, d, 8-CH_3).

Mass spectrum, *m/e*: 638 (100%) 606 (5%), 579 (17%), 566 (9%), 565 (8%), 553 (7%), 491 (7%), 479 (12%).

Copper(II) Chlorin-e_6 Trimethyl Ester (**36**)

Chlorin-e_6 trimethyl ester (**39**) was dissolved in $CHCl_3$ and warmed on a water bath. A solution of cupric acetate in methanol was added and the incorporation of

copper was followed by the change in the visible spectrum, chiefly by the shift from 664 to 627 nm of the long-wavelength absorption maximum. The solution was poured into a separatory funnel and washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on alumina (grade V, elution with CH_2Cl_2). In this way quantitative yields of the copper complex were obtained. The compound was crystallized from CH_2Cl_2/methanol, mp 211–214°C (lit 218–220°C (*45*)).

Anal. Calcd for $C_{37}H_{40}N_4O_6Cu$: 63.46; H, 5.76; N, 8.00. Found: C, 63.57; H, 5.70; N, 8.00%.

Mass spectrum, *m/e*: 701, 699 (100%).

Visible spectrum λ_{max} 396 (ϵ 80,000), 412 (108,000), 500(4900), 537 (3000), 587 (10,000), 627 nm (46,000).

Copper(II) 2-(2-Formylvinyl)-2-desvinyl-chlorin-e_6 Trimethyl Ester (**37**)

Copper(II) chlorin-e_6 trimethyl ester (905 mg) was dissolved in dry 1,2-dichloroethane (100 ml) and added to solution of the Vilsmeier complex made from $POCl_3$ (4.5 ml) and DMF (4 ml) in 1,2-dichloroethane at 50°C, over about 15 min. The reaction mixture was left at 50°C under nitrogen for 1.5 hr. The initial deep blue color of the starting material changed to a green color on addition to the complex, then the reaction mixture turned a brownish-yellow color. Saturated sodium acetate solution was added and the mixture was refluxed for 2 hr. The layers were separated, the aqueous phase was washed with $CHCl_3$, and the combined organic layers were washed with water, dried (Na_2SO_4), and evaporated. After treatment with etheral diazomethane (a process which led to higher yields) the mixture was chromatographed on alumina (grade III, elution with CH_2Cl_2). The main fraction was collected and rechromatographed on Grade V alumina. The diformylated compound was crystallized from CH_2Cl_2 to yield 672 mg (67%), mp 241–244°C.

Anal. Calcd. for $C_{38}H_{40}N_4O_7Cu$: C, 61.93; H, 5.33; N, 7.41. Found: C, 61.72; H, 5.45; N, 7.40%.

Mass spectrum, *m/e*: 755 (100%), 740 (9%), 727 (22%), 715 (16%), 682 (12%), 608 (28%).

Mesochlorin-e_6 Trimethyl Ester (**40**)

Chlorin-e_6 trimethylester was converted into the zinc complex by treatment with zinc acetate in $CHCl_3$ and methanol, the reaction being followed by the change in the visible spectrum, especially the shift of the long-wavelength absorption band to 636 nm. The resulting zinc complex was dissolved in THF (150 ml) with triethylamine (0.2 ml) and 10% Pd/C (200 mg). The mixture was stirred under hydrogen for 1.5 hr and was then filtered through Celite and the solvent evaporated. A visible spectrum showed a hypsochromic shift of the 636 band to 624 nm, and the solid was dissolved in $CHCl_3$ and shaken with 20% HCl in a separatory funnel for 1 min. The organic layer was separated, washed with sodium bicarbonate, water, dried (Na_2SO_4), and evaporated. Crystallization from

CH_2Cl_2/hexane gave the desired mesochlorin-e_6 trimethyl ester, (1.494 g, 93%), mp 146°C (lit 150°C (*46*)).

nmr spectrum: τ, 0.34, 0.64, 1.35 (each 1H, s, *meso*-H); 4.72 (2H, ABq, γ-CH_2); 5.6 (2H, m, 7,8-H); 5.75 (6-CO_2CH_3); 6.05–6.3 (4H, q, 2 × CH_2); 6.24 (3H, s, γ-CO_2CH_3); 6.38 (3H, s, 7-CO_2CH_3); 6.44, 6.67, 6.71 (each 3H, s, 1,3,5-CH_3); 7.4–7.55 and 7.7–7.95 (4H, m, CH_2CH_2); 8.15–8.35 (9H, 8-CH_3, and 2,4-CH_3).

2-(2-Formylvinyl)-2-desvinylchlorin-e_6 Trimethyl Ester (*47*)

The copper complex (**37**) of the diformylated chlorin-e_6 trimethyl ester (40 mg) was stirred in concd H_2SO_4 (20 ml) for 1.5 hr, then was poured onto ice and extracted into CH_2Cl_2; the organic layer was washed with sodium bicarbonate solution, water, dried (Na_2SO_4), and evaporated. After chromatography on alumina (grade V, elution with CH_2Cl_2) the major product was collected and recrystallized from CH_2Cl_2/methanol to yield the demetalated product (22 mg, 60%), with a long-wavelength absorption band at 717 nm. This material was not further characterized.

nmr spectrum: τ, −1.56 (1H, s, CHO); −0.07 (1H, d, 2-CHO): 0.67, 0.75 (each 1H, s, *meso*-H); 1.2–1.6 (1H, m); 2.6–3.1 (1H, m, CH=CH_2); 4.9 (2H, bs, γ-CH_2); 5.76 (3H, s, CO_2CH_3); 6.16 (3H, s, γ-CH_3); 6.3 (3H, s, 7-CO_2CH_3); 6.63, 6.73, 6.9 (each 3H, s, 1,3,5-CH_3); 6.4 (2H, m) and 8.6 (3H, t, CH_3CH_2); 7.2–7.8 (4H, m, CH_2CH_2); 8.4 (3H, d, 8-Ch_3).

δ-meso-Methylmesochlorin-e_6 Trimethyl Ester (**45**)

Mesochlorin-e_6 trimethyl ester (**40**), (397 mg) was converted into the copper complex (**41**) by refluxing in CH_2Cl_2 and adding small portions of a solution of cupric acetate in methanol. The reaction was monitored by the changes in visible absorption, mainly by the shift of the major red absorption from 653 to 626 nm. The solvents were removed and the residue was chromatographed on grade V alumina (elution with $CHCl_3$). The royal blue copper complex was not crystallized, [*m/e* 703, 701 (100%)], but was dissolved in dry 1,2-dichloroethane (100 ml) and added to the Vilsmeier complex made from $POCl_3$ (1.2 ml) and DMF (1 ml) at 50°C. The reaction mixture was refluxed for 1 hr and then saturated sodium acetate solution (250 ml) was added and the reaction mixture was refluxed for a further 2 hr. After the usual workup, the reaction mixture was chromatographed on grade V alumina (elution with toluene). This removed a small amount of starting material, but tlc revealed the presence of a minor light green band contaminating the major dark green formylchlorin band. The copper(II) formylchlorin (**42**) could not be crystallized. (In another experiment it was obtained as a glass, in 85% yield, but about 5% impure.) It was therefore reduced directly with $NaBH_4$ (300 mg) in methanol (30 ml) and CH_2Cl_2 (50 ml). After 1 hr, a visible absorption spectrum indicated that the major red absorption band had moved from 660 to 633 nm, showing that the formyl group had been reduced. The reaction mixture was poured into water, extracted with CH_2Cl_2, and the organic layer was washed with water, dried, and evaporated. After chromatography on

alumina (grade V, elution first with toluene, then CH_2Cl_2), the blue copper hydroxymethylmesochlorin-e_6 trimethyl ester (**43**) was obtained as a foam which did not crystallize. The hydroxymethyl compound was converted to the acetoxymethyl analog (**44**) by heating at 90°C for 4 hr in pyridine (30 ml) and acetic anhydride (20 ml). The solvents were removed, then toluene was added and removed on the rotary evaporator four times until all pyridine had been removed. Thin layer chromatography on an alumina plate showed that the acetate had been produced, while on silica it decomposed to give largely a spot corresonding to the hydroxymethyl compound. The acetate (**44**) was dissolved in THF (100 ml) with triethylamine (0.2 ml) and 10% Pd/C (200 mg). This mixture was stirred under hydrogen overnight, and after column chromatography (grade III alumina, elution with CH_2Cl_2) to remove some copper(II) hydroxymethylmesochlorin-e_6 trimethyl ester, the main band was demetalated in 22% H_2SO_4/TFA (two treatments of 30 min each). Preparative tlc of the residue on silica (elution with 3% methanol in CH_2Cl_2) followed by column chromatography on alumina (grade V, elution with CH_2Cl_2) produced *meso*-methylmesochlorin-e_6 trimethyl ester (**45**) (45 mg, 15%),[4] mp 95–96°C.

Anal. Calcd for $C_{38}H_{46}N_4O_6$: C, 69.92; H, 6.80; N, 8.58. Found: C, 69.74; H, 6.58; N, 8.60%.

nmr spectrum: τ, 0.46, 0.60 (each 1H, s, β, α-*meso*-H); 4.66, 4.75, 4.96, 5.05 (2H, ABq, γ-CH_2); 5.44, 5.7 (each 1H, m, 7,8-H); 5.75 (3H, s, 6-CO_2CH_3); 6.16 (6H, s, γ-CO_2CH_3, δ-CH_3); 6.12, 6.24 (each 2H, q) and 8.31 (6H, t, 2 × CH_3CH_2); 6.39, 6.46, 6.60, 6.70 (each 3H, s, 7-CO_2CH_3), 1,3,5-CH_3); 7.4–7.6, 7.7–7.9, 8.0–8.2 (4H, m, CH_2CH_2); 8.43 (3H, d, 8-CH_3).

Mass spectrum, *m/e*: 654 (100%), 593 (13%), 495 (11%).

Visible spectrum, λ_{max} 404 (ϵ 152,000), 508 (11,800), 537 (7500), 608 (4400), and 662 nm (42,700).

Methyl δ-Methylmesopheophorbide-a (46)

δ-Methylmesochlorin-e_6 trimethyl ester (76 mg) was dissolved in refluxing dry pyridine (8 ml). A solution of potassium *tert*-butoxide in *tert*-butyl alcohol was added (1 ml of a mixture of 100 mg potassium metal in 5 ml *tert*-butyl alcohol) and the reaction mixture was stirred for 1 min (now an orange color). Acetic acid (1 ml) was added and the mixture poured into water and CH_2Cl_2 in a separatory funnel; the layers were separated and the organic layer was washed with water, then evaporated with toluene. Thin layer chromatography showed some material on the baseline, so the mixture was treated with excess ethereal diazomethane. Chromatography on alumina (grade V elution with toluene/CH_2Cl_2) and crystallization from CH_2Cl_2/methanol produced **46** (54 mg, 78%).

nmr spectrum: τ, 0.55 (1H, s β-H); 0.7 (1H, s, α-H); 3.76 (1H, s, 10-H); 5.43, 5.63 (each 1H, m, 7,8-H); 6.16, 6.19, 6.35, 6.48, 6.68, 6.8 (each 3H, s, γ-CO_2CH_3, δ-CH_3, 7-CO_2CH_3, 1,3,5-CH_3); 7.3–8.0 (4H, m, CH_2CH_2); 6.1–6.5 (2 × CH_2 q) and

[4] *Note added in proof.* Much higher yields have been obtained by direct reduction of the copper(II) formylchlorin using sodium borohydride in acetic acid, followed by demetallation.

8.32 (6H, t, 2 × CH_3CH_2); 8.5 (3H, d, 8-CH_3). This material was used directly for conversion to the pyro compound.

Methyl δ-Methylmesopyropheophorbide-a (**34**)

Methyl δ-methylmesopheophorbide-*a* (31 mg) was heated in collidine on an oil bath at 190°C for 2 hr. The collidine was evaporated and the residue chromatographed on alumina (grade V, elution with CH_2Cl_2). The product (25 mg; 84%) was crystallized from CH_2Cl_2/methanol, and had mp 158–165°C.

Anal. Calcd for $C_{35}H_{40}N_4O_3$: C, 74.44; H, 7.14; N, 9.92. Found: C, 74.26; H, 7.40; N, 9.84%.

nmr spectrum: τ, 0.56, 0.68 (each 1H, s, *meso*-H); 4.75 (2H, s, 10-CH_2); 5.4, 5.5 (each 1H, m, 7,8-H); 4.0–4.5 (2 × CH_2, q) and 8.32 (6H, t, 2 × CH_3CH_2); 4.14, 4.35, 4.42, 4.62, 4.75 (each 3H, s, δ-CH_3, 7-CO_2CH_3, 1,3,5-CH_3); 7.7–8.0 (4H, m, CH_2CH_2); 8.5 (3H, d, CH_3).

Mass spectrum, *m/e*: 564 (100%), 549 (12%).

Visible spectrum, λ_{max} 412 (ε 114,000), 514 (9400), 547 (13,700) 607 (7700), 665 nm (48,600).

ACKNOWLEDGMENTS

We thank the National Institutes of Health (HL 22252) and Research Corporation for partial financial support of this work. Preliminary experiments by Dr. B. Evans are gratefully acknowledged. We are also grateful to the U.K. Science Research Council for award (to G.M.F.B. and M.J.B.) of a Foreign Travel Award.

REFERENCES

1. H. Larsen, *Kgl. Nor. Selskabs. Skrifter.* **1**, (1953); "The Chlorophylls" (L. P. Vernon and G. R. Seely, Eds.). Academic Press, London/New York, 1966.
2. A. Jensen, O. Aasmundrud, and K. E. Eimhjellen, *Biochim. Biophys. Acta* **88**, 466 (1964).
3. G. W. Kenner, J. Rimmer, K. M. Smith, and J. F. Unsworth, *Phil. Trans. Roy. Soc. London Ser. B* **273**, 255 (1976).
4. J. W. Purdie and A. S. Holt, *Canad. J. Chem.* **43**, 3347 (1965).
5. A. S. Holt, J. W. Purdie, and J. W. F. Wasley, *Canad. J. Chem.* **44**, 88 (1966).
6. H. Brockmann, Jr., *Phil. Trans. Roy. Soc. London Ser. B* **273**, 277 (1976).
7. A. Gloe, N. Pfennig, H. Brockmann, Jr., and W. Trowitzch, *Arch. Microbiol.* **102**, 103 (1975).
8. H. Brockmann, Jr., A. Gloe, N. Risch, and W. Trowitzch, *Ann. Chem.*, 566 (1976).
9. J. J. Katz, H. H. Strain, A. L. Harkness, M. H. Studier, W. A. Svec, T. R. Janson, and B. T. Cope, *J. Amer. Chem. Soc.* **94**, 7938 (1972).
10. M. Caple, H. C. Chow, R. M. Burns, and C. E. Strouse, *Brookhaven Symp. Biol.* **28**, 56 (1976).
11. H. C. Chow, M. B. Caple, and C. E. Strouse, *J. Chromatogr.*, **151**, 357 (1978).
12. M. B. Caple, H-C. Chow, and C. E. Strouse, personal communication.
13. A. S. Holt, D. W. Hughes, H. J. Kende, and J. W. Purdie, *J. Amer. Chem. Soc.* **84**, 2835 (1962).

14. J. H. MATHEWSON, W. R. RICHARDS, AND H. RAPOPORT, *Biochem. Biophys. Res. Commun.* **13,** 1 (1963).
15. J. H. MATHEWSON, W. R. RICHARDS, AND H. RAPOPORT, *J. Amer. Chem. Soc.* **85,** 364 (1963).
16. R. B. WOODWARD AND V. ŠKARIĆ, *J. Amer. Chem. Soc.* **83,** 4676 (1961).
17. J. L. ARCHIBALD, S. F. MACDONALD, AND K. B. SHAW, *J. Amer. Chem. Soc.* **85,** 644 (1963); J. L. ARCHBALD, D. M. WALKER, K. B. SHAW, A. MARKOVAC, AND S. F. MACDONALD, *Canad. J. Chem.* **44,** 345 (1966).
18. M. T. COX, A. H. JACKSON, AND G. W. KENNER, *J. Chem. Soc. C,* 1974 (1971).
19. K. M. SMITH AND J. F. UNSWORTH, *Tetrahedron* **31,** 367 (1975).
20. G. W. KENNER, J. RIMMER, K. M. SMITH, AND J. F. UNSWORTH, *J. Chem. Soc. Perkin Trans. I,* 845 (1978).
21. J. RIMMER, Ph.D Thesis, University of Liverpool, 1977.
22. N. RISCH AND H. BROCKMANN, JR., *Ann. Chem.,* 578 (1976).
23. P. BAMFIELD, R. L. N. HARRIS, A. W. JOHNSON, I. T. KAY, AND K. W. SHELTON, *J. Chem. Soc. C,* 1436 (1966).
24. D. HARRIS AND A. W. JOHNSON, *J. Chem. Soc. Chem. Commun.,* 771 (1977).
25. M. J. BUSHELL, B. EVANS, G. W. KENNER, AND K. M. SMITH, *Heterocycles* 7, 67 (1977).
26. H. FISCHER AND G. A. VON KEMNITZ, *Z. Physiol. Chem.* **96,** 309 (1915); A. TREIBS AND E. WIEDEMANN, *Annalen* **471,** 146 (1929); H. FISCHER AND F. BALAZ, *Annalen* **553,** 166 (1942).
27. R. GRIGG, G. SHELTON, A. SWEENEY, AND A. W. JOHNSON, *J. Chem. Soc. Perkin Trans. I,* 1789 (1972).
28. O. SOMAYA, Dissertation, Braunschweig, 1967.
29. D. P. ARNOLD, A. W. JOHNSON, AND M. WINTER, *J. Chem. Soc. Chem. Commun.,* 797 (1976); *J. Chem. Soc. Perkin Trans. I,* 1643 (1977).
30. K. M. SMITH AND G. M. F. BISSET, *J. Org. Chem.,* **44,** 2077 (1979).
31. A. BRÄNDSTRÖM, U. JUNGGREN, AND B. LAMM, *Tetrahedr. Lett.,* 3173 (1972); D. J. RABER AND W. C. GUIDA, *J. Org. Chem.* **41,** 690 (1976).
32. R. GRIGG, A. SWEENEY, AND A. W. JOHNSON, *J. Chem. Soc. Chem. Commun.,* 1237 (1970).
33. A. S. HOLT AND D. W. HUGHES, *J. Amer. Chem. Soc.* **83,** 499 (1961); H. V. MORLEY AND A. S. HOLT, *Canad. J. Chem.* **39,** 755 (1961).
34. G. W. KENNER, S. W. MCCOMBIE, AND K. M. SMITH, *J. Chem. Soc. Perkin Trans. I,* 2517 (1973).
35. P. K. W. WASSER AND J. -H. FUHRHOP, *Ann. N.Y. Acad. Sci.* **206,** 533 (1973).
36. J.-H. FUHRHOP *in* "Porphyrins and Metalloporphyrins", K. M. Smith, Ed., Elsevier, Amsterdam, 1975, p. 593.
37. H. SCHEER AND J. J. KATZ *in* "Porphyrins and Metalloporphyrins", K. M. Smith, Ed., Elsevier, Amsterdam, 1975, p. 399.
38. R. J. ABRAHAM, G. H. BARNETT, G. E. HAWKES, AND K. M. SMITH, *Tetrahedron* **32,** 2949 (1976).
39. R. J. ABRAHAM, B. EVANS, AND K. M. SMITH, *Tetrahedron* **34,** 1213 (1978).
40. R. J. ABRAHAM, F. EIVAZI, R. NAYYIR-MAZHIR, H. PEARSON, AND K. M. SMITH, *Org. Mag. Res.* **1,** 52 (1978).
41. B. EVANS, K. M. SMITH, G. N. LA MAR, AND D. B. VISCIO, *J. Amer. Chem. Soc.* **99,** 7070 (1977).
42. K. M. SMITH, F. EIVAZI, K. C. LANGRY, J. A. P. BAPTISTA DE ALMEIDA, AND G. W. KENNER, *Bioorg. Chem.* **8,** 485–496 (1979).
43. H. H. INHOFFEN, J. -H. FUHRHOP, H. VOIGT, AND H. BROCKMANN, JR., *Ann. Chem.* **695,** 133 (1966).
44. B. EVANS, Ph.D. Thesis, University of Liverpool, 1977.
45. H. FISCHER AND H. ORTH, "Die Chemie des Pyrrols," Vol. II (2), p. 98. Akademische Verlag, Liepzig, 1937.
46. H. FISCHER AND H. ORTH, "Die Chemie des Pyrrols," Vol. II (2), p. 102. Academische Verlag, Liepzig, 1937.
47. A. W. NICHOL, *J. Chem. Soc. C,* 903 (1970).