Syntheses of Chlorins from Unsymmetrically Substituted Iron Porphyrins

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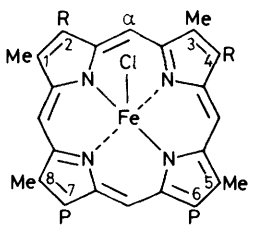
Mesohemin (**1**), deuterohemin (**2**), protohemin (**3**), 6,7-dipropylmesohemin (**22**), 1-(2-carboxyethyl)-*meso*-tetraphenylhemin (**30**), coprohemin-II (**23**), 2-acetyldeuterohemin (**40**), 2,4-diacetyldeuterohemin (**41**), and phyllohemin (**51**) were reduced to chlorins using sodium in isopentyl alcohol. Analytical and semi-preparative h.p.l.c. were used for separation, purification, and quantitation of isomers, which were then identified using ^{1}H n.m.r. and mass spectroscopy. In the case of the mesochlorins (**6**), (**8**), (**10**), and (**12**), the ring-D reduced product, (**10**), was identified by comparison with an authentic sample prepared from rhodochlorin dimethyl ester (**14**). The results cast doubt on some previous claims that reduction of unsymmetrical hemins gives only one, or at most two chlorin products, but they also elaborate the electronic and steric factors which control selectivity of reduction.

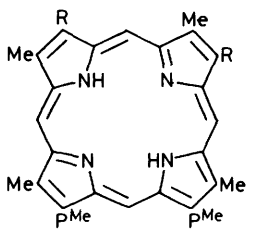
The hydroporphyrins comprise a large family of natural products, many of which are of central biological importance. Among the largest of its subgroups are the chlorins, the magnesium(II) complexes which include many of the known chlorophylls. Iron chlorins are also known as the prosthetic groups involved in a number of systems such as the heme in sulphemoglobin,[1] in myeloperoxidase,[2,3] in the catalase from *Neurospora crassa*,[4,5] as well as the heme-d from *Escherichia coli* and other bacteria.[6] To date, no synthetic method has been devised in which the chlorin (7,8-dihydroporphyrin) is built in the rational step-by-step fashion now commmonly employed in porphyrin synthesis, though various 'reduced' systems bearing geminally substituted (non-oxidizable) moieties have been synthesized.[7,8] Methods for preparation of *cis* reduced chlorins,[9,10] and isobacteriochlorins[11,12] have been described, but the only general method for synthesis of *trans* reduced chlorins involves dissolving metal reductions of hemins.[13–17]† In the past this method had been limited substantially to porphyrins that were symmetrically substituted to avoid the problems of structural isomers.

Sodium reduction of mesohemin (**1**) produces four isomers,[18] and separation was possible by high performance liquid chromatography (h.p.l.c.). It has been reported by others[19] that the sodium reductions of deuterohemin (**2**) and protohemin (**3**) produced only two isomers (ring-A and ring-B reduced isomer), and possibly even only one (ring-A reduced isomer).[20] These results were deduced from 60 MHz n.m.r. spectra, and without the benefit of h.p.l.c. Since the results seemed in conflict, and no study had ever been undertaken to examine the substituent effect upon the specificity of reduction,‡§ we set out to explore substituent effects which determine reduction selectivity,¶ and whether isomeric mixtures of chlorins could be separated by h.p.l.c.

We first developed an improved method for the h.p.l.c. separation of the four mesochlorin-IX dimethyl ester (DME) isomers (**6**), (**8**), (**10**), and (**12**). With silica gel, cyclohexane–ethyl acetate proved superior to our hexane–toluene–isopropyl alcohol (100:3:0.3) system.[18] Comparison of the two h.p.l.c. tracings in Figure 1 demonstrates that with the use of the latter solvent system partial separation of isomers was observed after 91 min. With a 95:5 cyclohexane–ethyl acetate mixture after 62 min one sees near base-line separation of the ring-A reduced isomer (**6**) from the ring-B reduced isomer (**8**), with base-line resolution from the combination of ring-D and ring-C reduced isomers (**12**) and (**10**), respectively, along with partial separation of ring-D from the ring-C reduced isomer. One recycle provided separation of the latter two mesochlorin isomers.

The ring-D reduced mesochlorin DME (**10**) was definitively identified by comparison with an authentic sample of the (7*S*,8*S*)-chlorin obtained by partial synthesis from rhodochlorin DME (**14**). Thus, rhodochlorin was transformed into the β-keto ester chlorin (**15**) using literature procedures.[21] As shown in Scheme 1, compound (**15**) was reduced with sodium borohydride to give the hydroxypropionate chlorin (**16**), which was transformed into the *trans*-acrylate (**17**) with phosphoryl chloride, and then hydrogenated over palladized charcoal to give the required chlorin (7*S*,8*S*)-(**10**), together with a small





(**1**) R = Et
(**2**) R = H
(**3**) R = CH=CH$_2$
(**4**) R = CH=CH$_2$
(**5**) R = Et

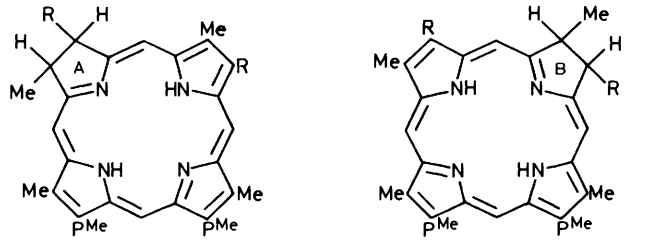
P = $CH_2CH_2CO_2H$
P^{Me} = $CH_2CH_2CO_2Me$

† Other methods of reduction, such as catalytic hydrogenation, di-imide reduction, and photoreduction yield exclusively *cis* chlorins (see refs. 9 and 10).

‡ The influence of the central metal upon sodium reduction of metalloporphyrins has been extensively studied; see ref. 9.

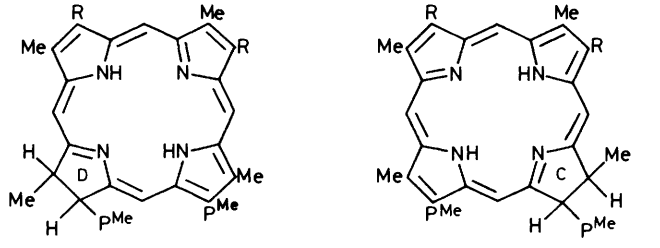
§ Although Fischer prepared chlorins from several unsymmetrically substituted porphyrins, no study of isomeric purity was undertaken except for the report that the reduction of γ-phylloporphyrin-XV yields only the ring-D reduced chlorin; (*a*) H. Fischer and A. Stern, 'Die Chemie des Pyrrols,' Akademische Verlag, Leipzig, 1940. vol. II, part 2, p. 144; (*b*) H. Fischer and F. Balaz, *Liebigs Ann. Chem.*, 1942, **553**, 166.

¶ Birch reductions are well known to be profoundly affected by the nature of the substituents attached to the aromatic ring: A. S. Birch, A. L. Hinde, and L. Radom, *J. Am. Chem. Soc.*, 1980, **102**, 3370, 6430; *ibid.*, 1981, **103**, 4074.



(6) R = Et
(7) R = H

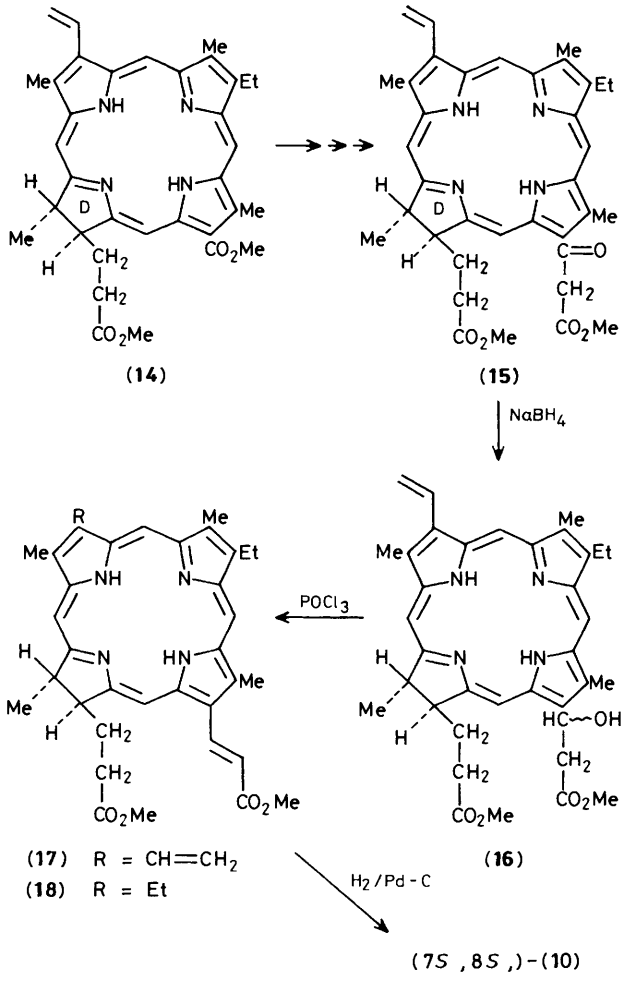
(8) R = Et
(9) R = H



(10) R = Et
(11) R = H

(12) R = Et
(13) R = H

$P^{Me} = CH_2CH_2CO_2Me$
All chlorins are *trans*-reduced



Scheme 1.

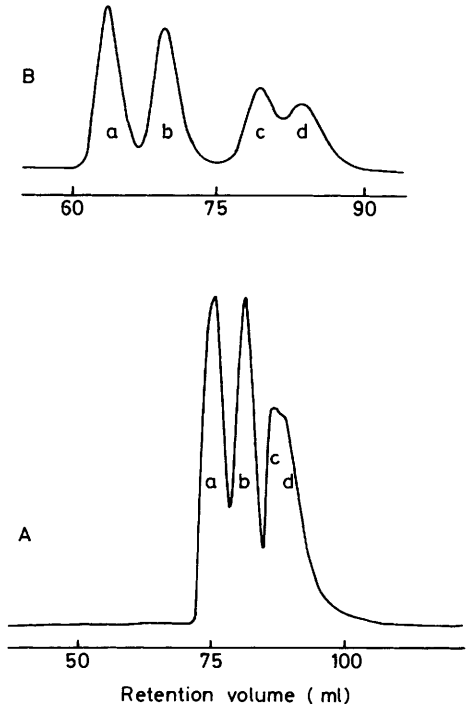


Figure 1. Normal phase h.p.l.c. traces of mesochlorin dimethyl esters (**6**), (**8**), (**10**), and (**12**), A. using hexane–toluene–isopropyl alcohol (100:3:0.3); B, using 5% ethyl acetate in cyclohexane. Column: μPorasil, 250 × 4.6 mm i.d. flow rate 1.3 ml/min, with detector set at 405 nm (A) or 1.5 ml/min, with detector set at 644 nm (B). Structural assignments: a, (**6**); b, (**8**); c, (**10**); d, (**12**)

amount of the corresponding 2-ethyl acrylate (**18**) as a by-product. Co-injection of the required product with the mixture of isomers obtained from sodium reduction (Figure 1) allowed unambiguous identification of the ring-D reduced chlorin.

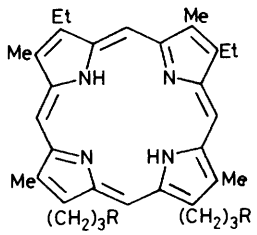
The establishment of an efficient method for the separation of mesochlorin isomers allowed us to re-examine the claim[19,20] that the sodium reduction of protohemin-IX (**3**) yielded only the ring-A and/or ring-B reduced mesochlorin isomers. Since we knew four isomers of mesochlorin-IX (**6**), (**8**), (**10**), and (**12**) were produced from the reduction of mesohemin-IX (**1**), we considered that the vinyl groups of protohemin might be responsible for the differing isomer ratios, acting either to stabilize the build-up of electron density in the ring being reduced, or perhaps acting as an 'electron sink' and feeding electrons into the attached ring.

Protoporphyrin-IX DME (**4**) was prepared from commercial hemin (**3**)[22] and mesoporphyrin-IX DME (**5**) was prepared from protoporphyrin-IX DME *via* catalytic hydrogenation over 10% palladized charcoal. Addition of iron chloride and hydrolysis of the propionate esters (KOH–methanol) produced either hemin in >95% yield from starting porphyrin.[23] Reduction of protohemin IX (**3**) utilizing a modified procedure of Corwin[17] and Fischer,[14–16] removal of iron chloride and esterification produced four isomers of mesochlorin-IX DME (**6**), (**8**), (**10**), and (**12**) in a ratio of 85:15 of (rings) A + B:C + D where A = B and C = D. Reduction of mesohemin-IX (**1**), demetallation, and esterification yielded the same isomeric ratio as observed earlier,[18] where A + B:C + D was 2:1 and A = B and C = D. Repetition of the reduction of protohemin with a different equivalency of sodium yielded an isomeric ratio approximately the same as that found with the reduction of mesohemin. Because of these initial disparities in our own results, and with those of others,[19,20] we decided to examine in

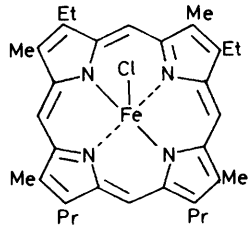
Table 1. Yields and isomeric composition of chlorins obtained by sodium reduction of mesohemin (**1**) and protohemin (**3**)

Hemin	Gram equiv. of Na per mmol hemin	No. of isomers	Yield[a] (%)	Relative proportions of isomers (%)[b]
Mesohemin (**1**)	10	4	56	A + B = 66 C + D = 34
Mesohemin (**1**)	13	4	54	A + B = 65 C + D = 35
Mesohemin (**1**)	15	4	88	A + B = 77 C + D = 23
Mesohemin (**1**)	20	4	71	A + B = 78 C + D = 22
Protohemin (**3**)	5	4	<1	A + B = 71 C + D = 29
Protohemin (**3**)	10	4	35	A + B = 65 C + D = 35
Protohemin (**3**)	15	4	56	A + B = 63 C + D = 37
Protohemin (**3**)	20	4	38	A + B = 61 C + D = 39
Protohemin (**3**)	24	4	67	A + B = 85 C + D = 15
Protohemin (**3**)	24	4	61	A + B = 62 C + D = 38

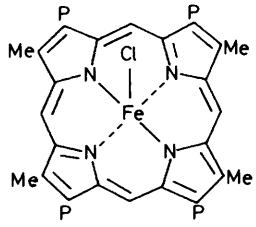
[a] Yields determined over three reaction sequence (hemin→iron chlorin→chlorin→chlorin DME). [b] Percentages of isomers determined by integration of h.p.l.c. peaks (Hewlett-Packard integrator model 3390A, detector set at 410 and 644 nm).



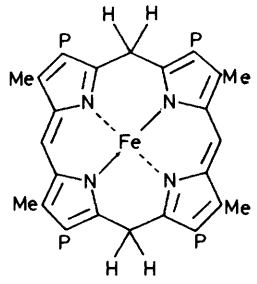
(**19**) R = OH
(**20**) R = OMes
(**21**) R = H



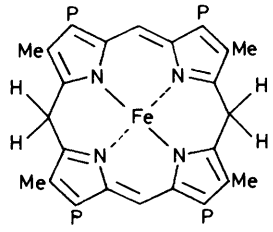
(**22**)



(**23**)



(**24**)



(**25**)

P = $CH_2CH_2CO_2H$

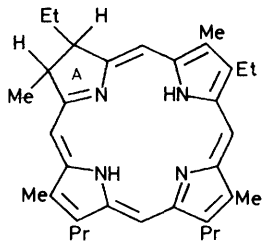
detail the reduction of both mesohemin (**1**) and protohemin (**3**). Before h.p.l.c. analysis, the products of the reduction were chromatographed on alumina to remove excess of porphyrin. At this stage a small sample was usually recrystallized for analysis. The isomer mixture was usually not oxidized with dichlorodicyanobenzoquinone (DDQ), ferric chloride, or any other oxidant to remove isobacteriochlorin formed in the reduction. Results of the reduction of mesohemin and protohemin are detailed in Table 1. Even though the amount of sodium used was varied by a factor of 5, the isomer ratios A + B:C + D altered only by 10%, averaging 72:28 in the reduction of mesohemin and 64:36 in the reduction of protohemin. Best yields were found when 15—20 g of sodium per mmol of hemin were used. Deuterohemin (**2**), the 6,7-propyl mesohemin analogue (**22**), and propenoate hemin (**30**) (see below, and Table 2) were prone to form tetrahydroporphyrin by-products and the reported yields of these chlorins are consequently lowered. Between 5 and 10 g of sodium/mmol heme was the cut-off point for formation of mesochlorin. When 5 g equiv. were used, no mesoporphyrin was formed, and the major product (>80%) was protoporphyrin. Two partially resolved peaks just preceding the h.p.l.c. peak of protoporphyrin-IX DME (**4**) appeared to be (spectrophotometry, rhodo-type)[24] a mixture of the monoethyl monovinyl derivatives.

We could not confirm the observation[19,20] of only one or (at most) two isomers from the reduction of protohemin even when conditions identical with those reported previously[19] were used. Yields were poor, generally in the range 20—30%, but the isomeric ratios were found to be in agreement with our own (Table 1), averaging 65:35 for A + B:C + D. However, the melting point determined for the isomeric mixture of mesochlorins was 126—131 °C, dramatically different from the melting point reported by Clezy[19] (190—191 °C) and Fischer[25] (190 °C). (The melting point of mesoporphyrin-IX DME lies somewhere in the range 210—216 °C).[26] Preferential reoxidation of the ring C and D chlorins to mesoporphyrin-IX may be the reason for earlier failure to detect any ring-C or ring-D reduced chlorin, but further work (*vide infra*) appears to rule out this hypothesis.

We could not explain why ring-A and ring-B reduced mesochlorins were produced in slightly greater than twice the amount as were the ring-C and ring-D reduced mesochlorins. Dreiding models demonstrated the ability of the propionic acid moiety to lie directly over its attached ring and adjacent *meso* periphery. It was possible that the carboxylate anion would discourage the build-up of charge on the attached peripheral and adjacent meso * positions and, thereby, slow down the rate of formation of ring-C and ring-D reduced chlorin. To test this hypothesis the all-alkyl analogue (**22**) of mesohemin was prepared. Thus, mesoporphyrin-IX DME (**5**) was reduced with lithium aluminium hydride (LAH) to afford (**19**) in 93% yield. Bis-mesylation of (**19**) gave (**20**) and further reduction with LAH yielded (**21**) in 37% yield over the two reaction sequence.† Insertion of iron chloride in 97% yield completed the sequence to (**22**).

* In aprotic solvents reductive alkylation shows addition to opposite *meso* positions. (*a*) J. W. Buchler and L. Puppe, *Liebigs Ann. Chem.*, 1970, **740**, 142; (*b*) M. Fontecave, J. P. Battioni, and D. Mansuy, *J. Am. Chem. Soc.*, 1984, **106**, 5217.

† When the free base was used in the reduction of the bis-mesylate, porphyrins metallated with aluminium were formed as a by-product. However, insertion of zinc before reduction with lithium aluminium hydride did not increase the yield of (**19**).



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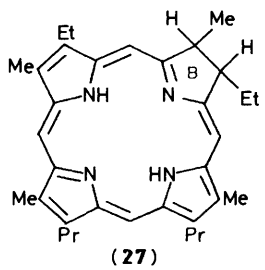

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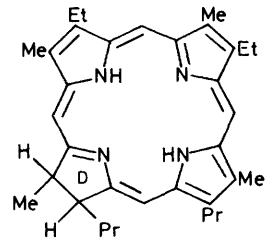

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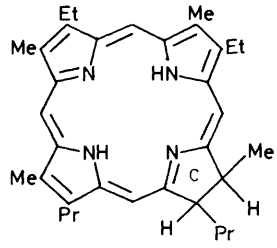


(29)

All chlorins are *trans*-reduced

Table 2. Yields and isomeric composition of chlorins obtained by sodium reduction of hemins

Hemin	Gram equiv. of Na per mmol hemin	No. of isomers	Yield [a] (%)	Relative proportions of isomers (%)[b]
Phyllohemin (**50**)	19	2	40[c]	D = 95 Other = 5
Phyllohemin (**50**)	10	2	45[c]	D = 95 Other = 5
Deuterohemin (**2**)	10	4	19	A + B = 75 C + D = 25
Deuterohemin (**2**)	14.5	4	71	A + B = 80 C + D = 20
Deuterohemin (**2**)	19	4	25	A + B = 77 C + D = 23
6,7-Dipropyl analogue (**22**) of mesohemin	15	4	35	A + B = 50 C + D = 50
6,7-Dipropyl analogue (**22**) of mesohemin	20	4	54	A + B = 50 C + D = 50
Coprohemin-II (**23**)	15—25		0	
Tetraphenylhemin acrylate (**30**)	<8		0	
Tetraphenylhemin acrylate (**30**)	12	3	51	*d*
Tetraphenylhemin acrylate (**30**)	>12	3	23	*d*

[a] Yields determined over three reaction sequence (hemin→iron chlorin→chlorin→chlorin ester). [b] Percentages of isomers determined by integration of h.p.l.c. peaks (Hewlett-Packard integrator model 3390A, detector set at 410 and 644 nm). [c] Yields are based on h.p.l.c. analysis. [d] Not determined.

Reduction of (**22**) and demetallation yielded four isomers (**26**)—(**29**) of the 6,7-propylmesochlorin, along with varying amounts of porphyrin and isobacteriochlorin depending on amounts of sodium used (Table 2). Three compounds were always detected. Porphyrin starting material could be removed by chromatography on alumina, while isobacteriochlorin could be separated on h.p.l.c. only, running just ahead of the chlorin band. The visible absorption spectrum of the isobacteriochlorin exhibited the usual split Soret band and three satellites [$\lambda_{max.}(CH_2Cl_2)$ (relative absorbance), 368 nm (100), 378 (87.1), 400 (68.5), 506 (10.1), 542 (14.9), 582 (24.9)]. Titration with DDQ gave a chlorin with its typical absorption band at 646 nm.

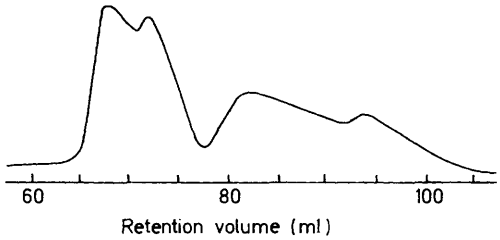
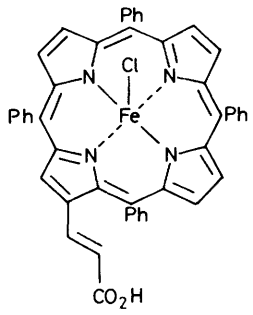


Figure 2. Normal phase h.p.l.c. trace (first recycle) of dipropylmesochlorins (**26**)—(**29**). Column: μPorasil, 0.25% ethyl acetate in cyclohexane, at 2 ml/min with detector set at 644 nm

The h.p.l.c. trace of the 6,7-dipropylmesochlorin isomer mixture (Figure 2) shows two peaks after one recycle, with peak 1 and peak 2 marginally resolved into two peaks. A solvent system of 0.25% ethyl acetate–cyclohexane allowed resolution of peak 1 into peak 1a and peak 1b, but peak 2 was not resolved. ^{1}H N.m.r. decoupling experiments showed that peak 1 contained the compounds (**26**) and (**27**). Structures of compounds from peak 1a and peak 1b were differentiated in a nuclear Overhauser enhancement (n.O.e.) study wherein the compound of peak 1a was identified as the ring-A reduced isomer (**26**). Similarly, peak 1b was shown to contain the ring-B reduced isomer (**27**). As with mesochlorins (**6**), (**8**), (**10**), and (**12**) the first two peaks off the column proved to be the ring-A and ring-B reduced isomers, respectively. N.m.r. spectroscopy likewise established that the ring-C and -D reduced isomers belong to peak 2 (see Experimental section).

Integration of h.p.l.c. peak 1 and peak 2 proved the ratio of A + B:C + D to be 1:1, strongly suggesting that the carboxylates are responsible for the difference in the amounts of isomers formed in the mesohemin reduction. When coprohemin-II (**23**) (Table 2) was subjected to sodium reduction no chlorin was formed when as much as 25 g per mmol of hemin were employed. Spectrophotometry of the reaction mixture revealed a major absorption at 490 nm, indicating a metallated porphodimethene[27] such as (**24**) and/or (**25**). With the addition of DDQ this band decreased in intensity with concomitant increase in the Soret band at 390 nm.

Reduction of the monoacrylate (**30**) (Table 2) produced unexpected results. The amount of sodium employed was critical. Varying within ±4 of 12 g per mmol of sodium resulted in sharp curtailment of the chlorin yield. Less than 8 g equiv. yielded only mixtures (after work-up) of the monoacrylate (**31**) and monopropionate (**32**). Greater than 16 g equiv. resulted in the majority of products being over-reduced beyond the chlorin stage. With 12 g equiv. the major product was chlorin. The visible absorption spectrum exhibited a strong chlorin band at 652 nm after demetallation, esterification, and work-up. N.m.r. data (Experimental section) indicated that no reduction occurred in the ring with the attached propionate. At least two of the four ring-reduced isomers were present, and taking into account the three types of nitrogen protons seen in the ^{1}H n.m.r. spectrum, it may be assumed that the three ring-reduced isomers (**33**)—(**35**) are present in the mixture. It is doubtful that the carboxylate is solely responsible for the selectivity seen in this case. Rather, a combination of factors, such as the destabilizing effect of the carboxylate anion plus a stabilizing



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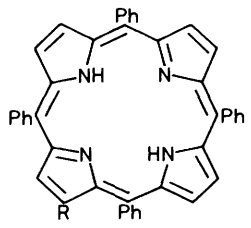
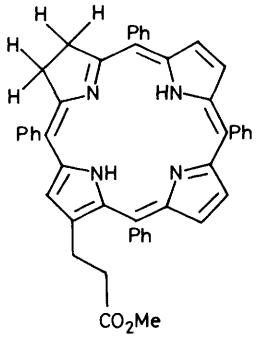
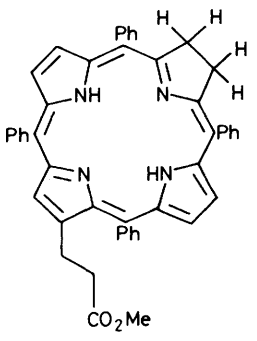


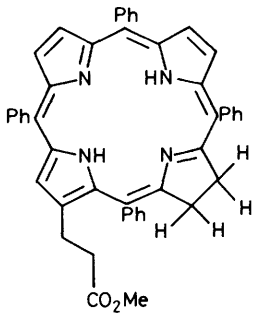
(31) R = $CH{=}CHCO_2Me$
(32) R = $CH_2CH_2CO_2Me$



(33)



(34)



(35)

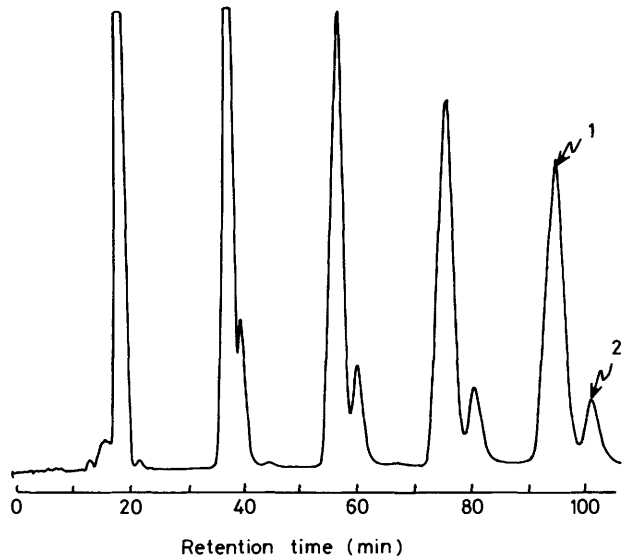
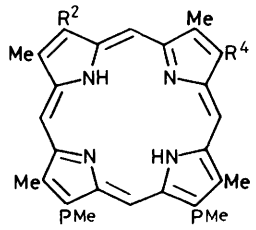
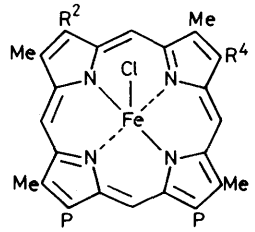


Figure 3. Normal phase h.p.l.c. trace of deuterochlorin isomers (**7**), (**9**), (**11**), and (**13**). Four recycles were necessary to obtain baseline separation between A + B (peak 1) and C + D (peak 2) pairs of isomers. Column: μPorasil, 11% ethyl acetate in cyclohexane, at 2 ml/min with detector set at 644 nm



(36) $R^2 = R^4 = H$
(37) $R^2 = R^4 = Ac$
(38) $R^2 = Ac$ $R^4 = H$
(39) $R^2 = H$, $R^4 = Ac$



(40) $R^2 = Ac$, $R^4 = H$
(41) $R^2 = R^4 = Ac$

(neutral) effect of the many β-unsubstituted positions are probably involved.

The results from the reduction of the tetraphenylhemin (**30**) suggested that besides the carboxylate the unsubstituted position also played a role in determining the selectivity of isomer production. Unlike alkyl groups, hydrogens are not electron-donating and, therefore, are better able to stabilize (or at least not deter) anion formation. As an example of this, it has been reported[19,20] that reduction of deuterohemin (**2**) (with its ring hydrogens at C-2 and C-4) produced only the ring-A and/or ring-B reduced chlorins. We decided to re-examine these claims.

Commercial hemin was subjected to resorcinol fusion[28] and Grinstein[22] conditions to provide deuteroporphyrin-IX DME (**36**) in 71% overall yield. Deuterohemin (**2**) was prepared as were previous hemins. Reduction, demetallation, and esterification afforded deuterochlorins (**7**), (**9**), (**11**), and (**13**) (Table 2) which were chromatographed using h.p.l.c. (Figure 3), which showed two peaks resolved on the fourth recycle (92 min). The larger first peak exhibited a chlorin band absorption at 648 nm, while the second showed a chlorin band at 642 nm. Both peaks showed correct high resolution mass spectra for 'deuterochlorin'. The ^1H n.m.r. spectrum of material from peak 1 indicated a mixture of ring-A and ring-B reduced deuterochlorin DME (**7**) and (**9**). The material from peak 2 was likewise shown to contain a mixture of ring-C and ring-D reduced deuterochlorins (**13**) and (**11**). We were usually unable to resolve peak 1 or peak 2 into their respective components except under unique circumstances (Figure 4) in which the chromatographed sample contained large amounts of over-reduced material (not picked up by the detector set at 644 nm).

Like the 6,7-dipropylmesohemin (**22**), deuterohemin (**2**) when reduced with sodium was prone to isobacteriochlorin formation. The visible absorption spectrum exhibited a typical isobacteriochlorin split Soret band at 389 and 397 nm, as well as three satellite bands appearing at 508, 544, and 584 nm (in a ratio of 1:1.7:2.6, respectively). Upon addition of DDQ the satellite bands disappeared with concomitant emergence of a chlorin band at 646 nm. The average isomer ratios of deuterochlorin were found to be 78:22 for A + B:C + D (Table 2). This is a *ca.* 30% drop in the amount of ring-C and ring-D reduced isomer obtained with the reduction of mesohemin and protohemin. In fact, when the isobacteriochlorin–chlorin mixture was oxidized with DDQ the ratio changed to 88:12 for A + B:C + D. This result is not surprising since ring-A and ring-B are most prone to reduction. By shaving of peak 1 in Figure 3, the two isomers were collected with a 70:30 enrichment of the slower-moving isomer, which allowed us to detail n.m.r. data for

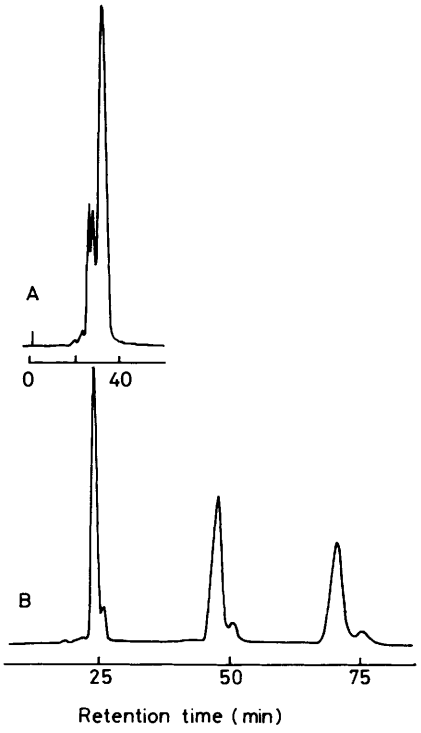


Figure 4. Normal phase h.p.l.c. trace of deuterochlorin isomers (**7**), (**9**), (**11**), and (**13**) showing: A, eluant reversal due to the presence of large quantities of (undetected at 644 nm) isobacteriochlorin produced by over reduction (solvent 13.6% ethyl acetate in cyclohexane). This reversal was observed with μPorasil, Dynamax, and Chromax columns; B, normal elution pattern after the mixture shown in A was subjected to controlled DDQ oxidation to eliminate isobacteriochlorin (solvent 11% ethyl acetate in cyclohexane). Column: μPorasil, flow rate 1.5 ml/min with detector set at 644 nm

that particular compound. Because of fortuitous results (*vide infra*) we deduce that the enriched cut contains, as the major isomer, ring-B reduced deuterochlorin DME (**9**).

Exchanging an electron-donating substituent (alkyl) with a neutral substituent (hydrogen) increased the chlorin isomer ratio in favour of those rings where the substituent exchange took place. The obvious next step was to introduce an electron-withdrawing group at a β-position. Owing to their facile synthesis from β-free metallated porphyrins, acetylporphyrins were chosen. Thus, copper(II) was inserted into deuteroporphyrin-IX DME (**36**) and the product was acetylated with a mixture of acetic anhydride and stannic chloride.[29] The diacetylated analogue was separated from the mono-acetylated mixture using a gravity column, and the mono-acetyl isomers were separated by preparative h.p.l.c. Removal of copper (TFA–H_2SO_4) yielded (**37**), (**38**), and (**39**) whose hemins were prepared as previously described.

Sodium reduction of 2-acetyldeuterohemin (**40**), removal of iron, esterification, and work-up yielded a product mixture which, when chromatographed by h.p.l.c., gave the surprisingly simple tracing seen in Figure 5. Peaks b and c contained 90% of the products in a relative ratio of 19:81 and overall yield of 13:57% respectively. The compound collected from peak b exhibited a chlorin absorption band at 646 nm. No peaks were observed in the range 6—7 p.p.m. in the ^{1}H n.m.r. spectrum where the C*H*(OH)Me normally appears.[30] N.m.r. spectroscopy also indicated that no reduction had occurred in either ring-C or ring-D of the starting hemin. A quartet and triplet observed at 3.88 p.p.m. and 1.74 p.p.m. respectively, describe an ethyl substituent attached to an aromatic ring. The absence of an

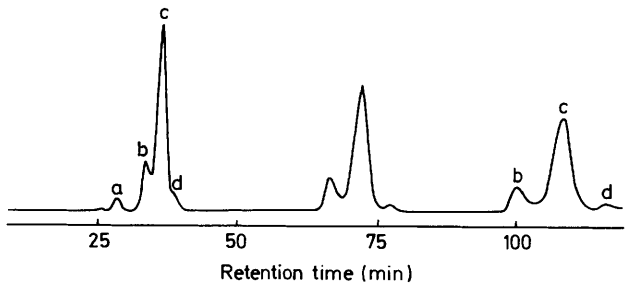


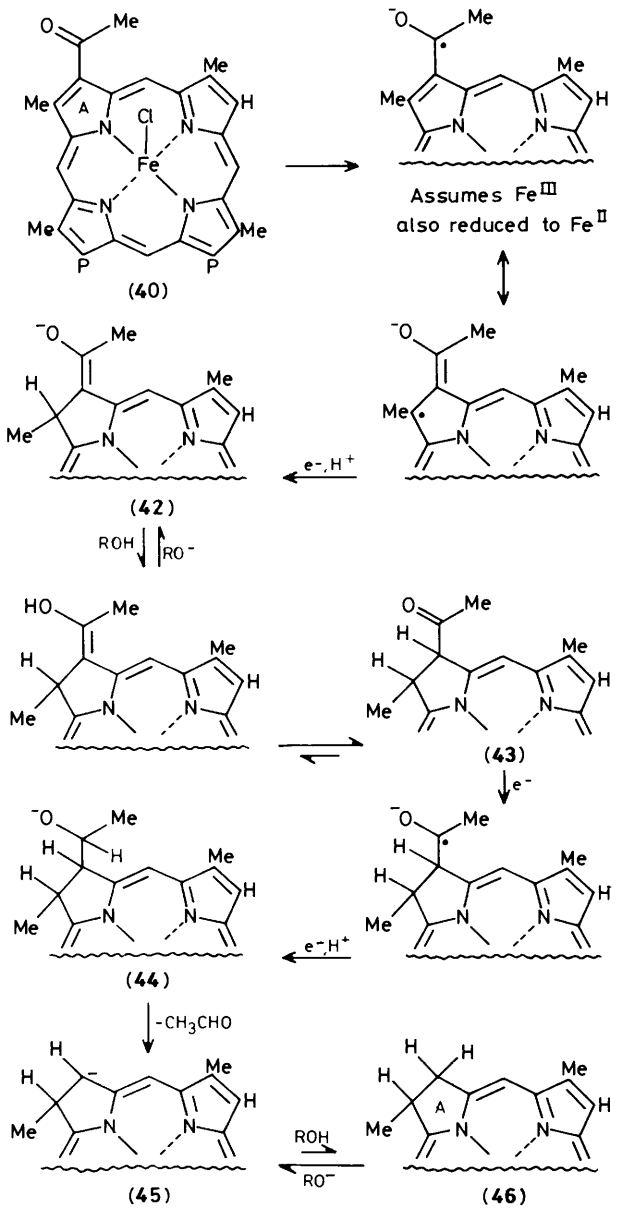
Figure 5. Normal phase h.p.l.c. trace of reduction products from 2-acetyldeuterohemin (**40**). Assignments: a, unidentified isobacteriochlorin; b 2-ethyldeuterochlorin DME (**49**); c, 86:14 ratio of deuterochlorins (**7**):(**9**); d, unidentified chlorin. Column: μPorasil, 10% ethyl acetate in cyclohexane, at 2 ml/min with detector set at 644 nm

aromatic β-hydrogen peak along with the observation that the protons attached to the reduced ring integrated to three, strongly suggested the structure to be 2-ethyldeuterochlorin DME, ring-B reduced (**49**). High resolution mass spectrometry corroborated the structure. The selectivity of this reduction is difficult to rationalize. Loss of the acetyl oxygen could occur if the alkoxide formed from the reduction of the acetyl group eliminated with the assistance of an iron of another hemin acting as a Lewis acid. Benzyl alkoxides are known to be eliminated when treated with aluminium trichloride.[31] The resulting vinyl group would then be reduced to ethyl under the reaction conditions. However, the reaction mixture is highly dilute and this seems unlikely. *E*2 Elimination from an α-hydroxyethylporphyrin under basic conditions does not normally occur, although an internal displacement of hydroxide ion by the electron added to the ring system may be possible. By either speculation, the selectivity seen in the reduction would then be attributed to the β-hydrogen having more stability towards anion formation than either the ethyl or propionate substituent. These results indicate that loss of the acetyl oxygen may somehow inhibit reduction in the ring that carries the acetyl (*vide infra*).

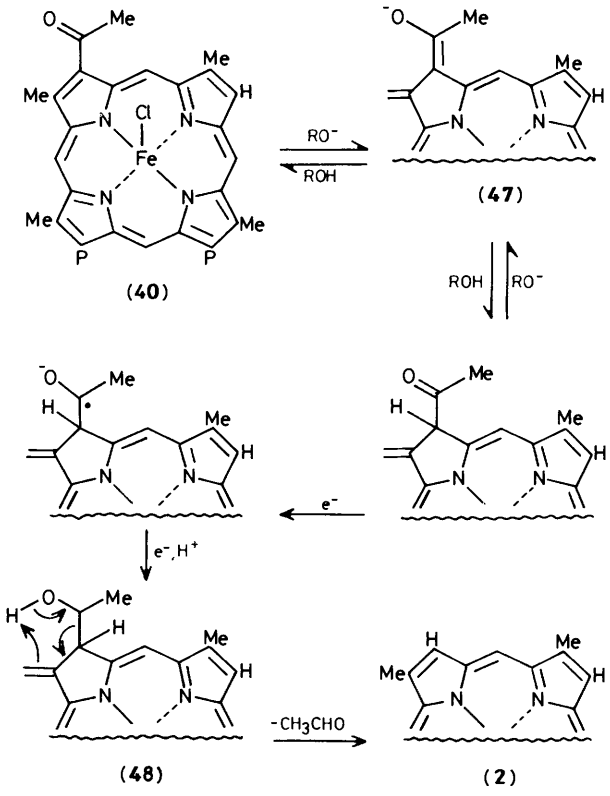
The visible absorption spectrum of material from peak c indicated a chlorin (648 nm). Like peak b, the n.m.r. spectrum of peak c material showed no hydroxyethyl methine resonance, but furthermore exhibited no resonances which could be ascribed to an ethyl group. The spectra exhibited no peaks to indicate reduction had occurred in either ring-C or ring-D. The meso proton resonances suggested the presence of two compounds in a ratio of 86:14. The spectrum was identical with that taken from the cuts of peak 1 of deuterochlorin except that this spectrum showed high enrichment of that isomer which would correspond to the faster-moving isomer of peak 1 in Figure 3. A n.O.e. study allowed identification of the major isomer as ring-A reduced deuterochlorin DME (**7**). The slower-moving isomer of peak a in Figure 5 must, therefore, be ring-B reduced deuterochlorin DME (**9**).

In this case not only the oxygen functionality, but the whole acetyl group was cleaved. A 1,4-reduction (Scheme 2) of the acetyl of (**40**) would form a compound protonated at position 1 with the acetyl enolate occupying the C-2 position, as depicted in (**42**). Protonation of the enolate and tautomerization would form the acetylchlorin (**43**). Reduction of the acetyl to the hydroxyethyl anion, seen in compound (**44**), and expulsion of acetaldehyde would form the stabilized carbanion analogue (**45**)* which, upon protonation, would yield the iron-containing

* In 1.0M potassium t-butoxide–t-butyl [^{2}H]alcohol, at room temperature, zinc(II) tetraphenylchlorin was deuteriated completely at the saturated carbons with an exchange half life of 2 h; H. W. Whitlock and M. Y. Oester, *J. Am. Chem. Soc.*, 1973, **95**, 5738.



Scheme 2.



Scheme 3.

chlorin (**46**). While this explains the selectivity of ring-A reduction coupled with the loss of acetaldehyde, it does not elucidate a pathway for the formation of ring-B reduced deuterochlorin DME (**9**). It is unlikely that under the reaction conditions isomerization from the anion (**45**) to the ring-B reduced chlorin occurs. If acetaldehyde was lost before reduction occurred, yielding deuterohemin, one would expect to see the three other isomers besides the ring-A reduced chlorin. Ring-C and ring-D reduced isomers were *not* detected in this case, but the formation of 14% of ring-B reduced deuterochlorin DME (**9**) indicated that only 3% of ring-C and ring-D reduced deuterochlorin would be formed, an amount that would make identification difficult. In this case acetaldehyde might be eliminated as illustrated in Scheme 3. The hydrogens on the methyl vicinal to the acetate are acidic. Indeed, complete deuteriation of the 1-CH_3 of 2-acetyldeuteroporphyrin is quite facile.[32,33] Under the basic conditions of reduction, the 1-CH_3 of (**40**) could be deprotonated, forming a vinyl group at C-1, and an enolate on C-2, as depicted by compound (**47**). Protonation would then yield a hydrogen and acetyl at the now saturated C-2 position. Pulling the compound out of the acid-base equilibrium with reduction of the acetyl would form the homoallylic alcohol (**48**). The latter could undergo a retro-ene reaction, re-establishing aromaticity with concomitant loss of acetaldehyde. Deuterohemin prepared in this manner could then be reduced in all four rings (see Table 2).

Reduction of 2,4-diacetyldeuterohemin (**41**) yielded the h.p.l.c. trace shown in Figure 6. N.m.r. and high resolution mass spectrometry identified the five major peaks as follows: (*a*) peaks a and b as ring-A and ring-B reduced mesochlorin DME, (**6**) and (**8**), respectively; (*b*) peak c as a mixture of ring-C and ring-D reduced mesochlorin DME, (**12**) and (**10**); (*c*) peak d as a mixture of ring-B reduced 2-ethyldeuterochlorin DME (**49**) and ring-A reduced 4-ethyldeuterochlorin DME (**50**) and what appears to be 5%, or less, of the opposite reduced ring monoethyldeuterochlorins; (*d*) peak e as an approximately 1:1 mixture of ring-A and ring-B reduced deuterochlorins, (**7**) and (**9**), respectively. Formation of these products was consistent with the results found with the reduction of 2-acetyldeuterohemin (**40**). All combinations of loss of the oxygen function to yield the ethyl group and/or loss of acetaldehyde are found in the above compounds. However, it was surprising to find that ring-C and ring-D reduced mesochlorin were formed in amounts that equalled the quantity formed of ring-A and ring-B reduced mesochlorins. This amounts to roughly a 55% increase from the normal isomer distribution of ring-C and ring-D reduced mesochlorin (see Table 1). Loss of the oxygen function has the opposite effect of loss of acetaldehyde on the selectivity of ring reduction; loss of acetaldehyde promotes reduction of the ring that contains the acetyl, whereas loss of the acetyl oxygen strongly inhibits reduction of the ring that contains the acetyl.

Fischer has reported that sodium reduction of phyllohemin

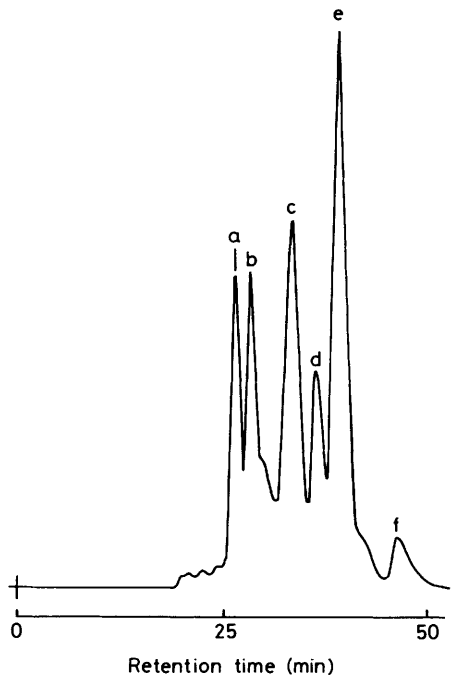
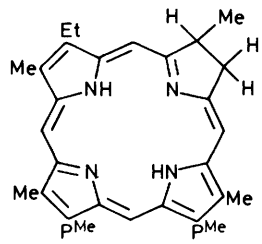
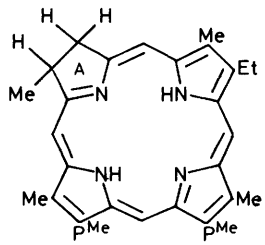


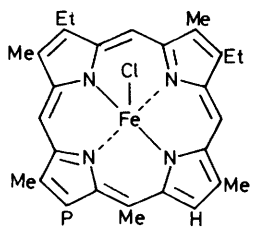
Figure 6. Normal phase h.p.l.c. trace of reduction products from 2,4-diacetyldeuterohemin (**41**). Assignments: a, mesochlorin (**6**); b, mesochlorin (**8**); c, mesochlorins (**10**) and (**12**); d, 2-ethyldeuterochlorin DME (**49**) and 4-ethyldeuterochlorin DME (**50**); e, deuterochlorins (**7**) and (**9**); f, unidentified compound (non-chlorin). Column: μPorasil, 7% ethyl acetate in cyclohexane, at 2 ml/min with detector set at 646 nm



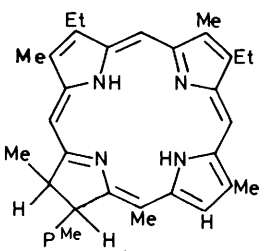
(**49**)



(**50**)



(**51**)



(**52**)

(**51**) yielded 100% of the ring-D reduced isomer (**52**).* Our results effectively corroborate his results as we found reduction of (**51**) yielded at least 2 isomers, but in a 95:5 ratio with the larger peak containing the ring-D reduced phyllochlorin methyl ester (**52**).

* See footnote § on p. 3119

Conclusions

The reduction of protohemin (**3**), mesohemin (**1**), deuterohemin (**2**), and the 6,7-propyl mesohemin analogue (**22**) always produced four ring reduced isomers in varying yields and proportions. This selection of compounds demonstrates that the chlorin isomer distribution is dependent on the ability of a substituent to stabilize or destabilize anionic charge and not dependent on the number of equivalencies of sodium used. The acetyl substituent was able to direct ring reduction but was lost during the reaction. Reduction of phyllohemin (**51**) demonstrated that release of steric congestion [9] between neighbouring *meso* and adjacent β-substituents overrides substituent electronic effects. Based upon our collected data, using the all alkyl substituent analogue for comparison, an ordering of the ability of a substituent to promote (inhibit) attached ring reduced isomer formation is as follows: vinyl < alkyl < H ≤ carboxylate (destabilizing) ≪ carbonyl (stabilizing and destabilizing) ≤ *meso* substituent that causes steric compression between itself and an adjacent β-substituent. In each case ring-A reduced isomer was eluted faster than ring-B reduced isomer which, in turn, was eluted faster than ring-C and ring-D reduced isomers on a silica gel column when using h.p.l.c. Resolution of chlorin isomers was not always possible.

Experimental

General.—M.p.s are uncorrected and were measured on a Thomas–Bristoline hot stage. Electronic absorption spectra were measured on a Hewlett-Packard 8450A spectrophotometer using solutions in dichloromethane. Mass spectra were obtained on a VG Analytical ZAB-HS instrument (70 eV, EI, mass reference perfluorokerosene). ^{1}H N.m.r. spectra were obtained in $CDCl_3$ either at 90 MHz (Varian EM390), 360 MHz (Nicolet NT-360) or 500 MHz (Nicolet NT-500), with chemical shifts reported in p.p.m. relative to internal standards of tetramethylsilane (0 p.p.m., 90 MHz spectra) or chloroform (7.258 p.p.m., 360 and 500 MHz). Elemental analyses were performed at the Microchemical Analysis Laboratory, U.C. Berkeley.

Wherever possible, reactions and work-up were performed under an atmosphere of nitrogen and in the dark (aluminium foil). Reactions were monitored using thin-layer chromatography (t.l.c.) using commercially available Eastman-Kodak 13181 (100 micrometer thick) silica gel sheets. Gravity and flash column chromatography employed either Merck neutral alumina (70—230 mesh) or Merck silica gel 60. The alumina was deactivated with either 6% water (Brockman Grade III) or 15% water (Brockman Grade V) before use. Analytical high performance liquid chromatography (h.p.l.c.) was performed on a Waters Associates HPLC instrument equipped with a Model 6000A solvent delivery system, a Valco model C60 injector and either a Perkin-Elmer LC55B or LDC/Milton Roy Spectro-Monitor D variable wavelength detector. A Waters RCM-100 module system equipped with a Radial Pak LC cartridge (5 μm. 8 mm i.d., silica gel normal phase) was used. Semi-preparative HPLC utilized the above instrumentation except for the column, which was either a Chromax silica gel column (10 μm particle size, 10 mm i.d.) or a Rainin Dynamax Macro HPLC silica gel column (8 μm particle size, 21.4 mm i.d. × 25 cm). Preparative h.p.l.c. was performed on a Waters Associates Prep 500A chromatograph using a PrepPak-Silica/500 column. An ISCO Model 1840 variable wavelength absorbance monitor was used for detection.

Hemins.—Unless otherwise noted, all hemes were prepared in the following typical manner. Acetonitrile (150 ml) was refluxed under nitrogen for 1.5 h. The solution was then cooled to 70 °C and $FeCl_2 \cdot xH_2O$ was added. When the ferrous chloride was

dissolved a solution of mesoporphyrin-IX DME (**5**) (0.5 g, 0.84 mmol) in degassed chloroform (70 ml) was added dropwise to the reaction mixture over the course of 1 h. After addition was complete the reaction mixture was stirred for 30 min at 70 °C, then cooled to room temperature, exposed to the atmosphere, and stirred for an additional 30 min. The solution was then diluted with dichloromethane (100 ml), washed with 0.2M HCl (2 × 200 ml), water (2 × 100 ml), and the solvent removed under reduced pressure. The residue was redissolved in methanol (200 ml) and to this solution was added water (9 ml) and potassium hydroxide (2.1 g). The reaction mixture was stirred at room temperature under nitrogen in the dark and the reaction was complete after 24 h as indicated by t.l.c. The solution was diluted with water (100 ml) and brought to pH 2 by addition of concentrated HCl. This solution was extracted with dichloromethane (3 × 100 ml) and the combined organic layers were washed with water (100 ml) and dried (Na_2SO_4). Dilution of the dichloromethane–hemin solution with tetrahydrofuran (THF) (100 ml) and concentration to a volume of 25 ml, generally led to precipitation of the hemin. The solution was filtered, and the filtrate washed with light petroleum. The solid was dried *in vacuo* in a toluene pistol to yield pure mesohemin (**1**) (0.545 g, 0.82 mmol, 96%), m.p. >300 °C; $\lambda_{max.}$(relative absorbance) 380 (100), 510 (18.7), 534 (16.9), 592 (9.6), and 636 nm (10.1). The following hemins were prepared in the same way. γ-Phylloporphyrin-XV (0.063 g, 0.12 mmol) yielded phyllohemin (**51**) (0.069 g, 0.1 mmol, 96%), m.p. >300 °C; $\lambda_{max.}$(relative absorbance) 406 (100), 504 (14.1), 536 (8.3), 574 (6.8), and 628 nm (3.4). Deuteroporphyrin-IX DME (**36**) (0.3 g, 0.56 mmol) yielded deuterohemin (**2**) (0.33 g, 0.5 mmol, 94%), m.p. >300 °C. 2-Acetyldeuteroporphyrin IX DME (**38**) (0.2 g, 0.4 mmol) yielded 2-acetyldeuterohemin (**40**) (0.23 g, 0.4 mmol, 97%), m.p. >300 °C; $\lambda_{max.}$ (relative absorbance) 383 (97), 404 (100), 508 (11.1), 542 (20), and 638 nm (13.3). 2,4-Diacetyldeuteroporphyrin-IX DME (**37**) (0.3 g, 0.5 mmol) yielded 2,4-diacetyldeuterohemin (**41**) (0.32 g, 0.5 mmol, 93%), m.p. >300 °C; $\lambda_{max.}$ (relative absorbance) 418 (100), 512 (10.7), 548 (6.6), 586 (5.3), and 638 nm (3.5). 6,7-Dipropylmesoporphyrin-X DME (**21**) (0.12 g, 0.22 mmol) yielded 6,7-dipropylmesohemin (**22**) (0.134 g, 0.21 mmol, 97%), m.p. >300 °C; $\lambda_{max.}$ (relative absorbance) 378 (100), 508 (8.0), 534 (8.0), and 638 nm (4.0); *m/z* (relative intensities) 595.2292 [Calc. for $C_{34}H_{40}ClFeN_4$: M^+, 595.2294 (45)], 561 (30), 560 (M − Cl; 100), 317 (18), and 217 (32). 1-(2-Methoxycarbonylvinyl)-*meso*-tetraphenylporphyrin (**31**) (0.135 g, 0.19 mmol) yielded 1-(2-carboxyvinyl)-*meso*-tetraphenylhemin (**30**) (0.15 g, 0.19 mmol, 99%), m.p. 212—214 °C; $\lambda_{max.}$ (relative absorbance) 426 (100), 512 (10.0), 584 (2.2), and 658 nm (0.2). Protohemin was supplied by Mid-Century, Posen, IL, and used without further purification.

Typical Sodium/Isopentyl Alcohol Reduction of a Hemin.—Unless otherwise noted, and except for equivalencies, all chlorins were prepared in the following typical manner. Mesohemin (**1**) (48 mg, 0.08 mmol) was suspended in dry isopentyl alcohol (25 ml) and the mixture was refluxed under nitrogen for 0.5 h. Sodium metal (1.2 g) was added to the refluxing solution over a 5 min period, and the reaction mixture was heated (oil-bath at 165 °C) for 0.5 h after the solution turned green. At this time, the reaction was cooled to 80 °C and water (30 ml) was added. The mixture was acidified to pH 2 by addition of concentrated hydrochloric acid and then extracted with dichloromethane (60 ml). The organic layer was washed with water (30 ml) and the solvent removed under reduced pressure. The crude mesochlorin iron(III) chloride was dissolved in glacial acetic acid (75 ml) and to this reaction mixture was added a saturated solution of ferrous sulphate in concentrated hydrochloric acid (15 ml). The mixture was stirred under nitrogen at room temperature for 40 min at which time the mixture was diluted with water (80 ml) and extracted with dichloromethane (2 × 60 ml). The combined extracts were washed with water (2 × 30 ml), dried (Na_2SO_4), and evaporated under reduced pressure to yield crude mesochlorins as a dark green solid. The solid was redissolved in dry, degassed methanol (30 ml) and sulphuric acid (2 ml) and the solution was stirred overnight under nitrogen at ambient temperature. The mixture was then diluted with water (50 ml) and extracted with dichloromethane (2 × 50 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (30 ml) and water (30 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on neutral alumina (Brockmann Grade III) eluting with dichloromethane and recrystallized from ethanol to yield pure mesochlorins (33.2 mg, 0.056 mmol, 76%). See Tables 1 and 2 for yields of the following chlorins.

2,4-*Diethyl*-6,7-*bis*(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethyldihydroporphyrins* (**6**), (**8**), (**10**), *and* (**12**).—*Mesochlorin DME* (*all four ring reduced isomers*), m.p. 126—131 °C (lit.,[19] m.p. 190—191 °C, lit.,[24] 190 °C) (Found: C, 72.3; H, 7.4; N, 9.35. $C_{36}H_{44}N_4O_4$ requires C, 72.46; H, 7.43; N, 9.39%); $\lambda_{max.}$ 390 (ε 166 000), 488 (11 600), 494 (11 800), 520 (2 300), 544 (500), 594 (3 100), 616 (3 000), and 646 nm (60 700); δ(360 MHz, $CDCl_3$) 10.12, 10.06, 9.75, 9.73, 9.71, 9.20, 9.18, 9.10, 9.07, 8.88, 8.85, and 8.81 (s, 16 H, *meso*-H), 4.42—4.10 m, 32 H, protons attached to reduced rings, 6,7-CH_2CH_2CO and 2,4-CH_2CH_3). 3.80—3.33 (m, 60 H, 6,7-OCH_3, 1,3,5,8-CH_3), 3.31—3.07 (m, 12 H, 6,7-CH_2CH_2CO), 2.96—2.20 (m, 12 H, CH_2CH_3 attached to reduced rings, 6,7-CH_2CH_2CO attached to reduced rings), 2.07—1.80 (m, 12 H, CH_3 attached to reduced rings), 1.78—1.60 (m, 6 H, 2,4-CH_2CH_3), 1.18—0.67 (m, 6 H, 2,4-CH_2CH_3 attached to reduced rings); *m/z*(relative intensities) 596.3381 [M^+; Calc. for $C_{36}H_{44}N_4O_4$: 596,3365 (100)], 598 (6, M + 2), 597 (37, M + 1), 595 (31, M − 1), 594 (70, M − 2), 528 (10), 521 (7, M − $CH_2CO_2CH_3$ + 2 H), 505 (11), 478 (6), 456 (7), 455 (10), 444 (6), 436 (7), 379 (12), 369 (17), 317 (28), 286 (16), 255 (60), 235 (22), 224 (16), 227 (22), and 212 (38).

Mesochlorin DME (*ring-*A *reduced*) (**6**), m.p. 118—120 °C; $\lambda_{max.}$ 388 (ε 147 000), 486 (11 500), 494 (12 000), 520 (3 300), 590 (3 330), 614 (3 200), and 644 (61 100); δ(360 MHz, $CDCl_3$), 9.71 (s, 2 H, β-H, γ-H), 8.87 and 8.86 (s, 2 H, α-H, δ-H), 4.64 and 4.46 (m, 2 H, 1- and 2-H), 4.33 and 4.20 (t, 4 H, 6,5-CH_2CH_2CO), 3.99 (q, 2 H, 4-CH_2CH_3), 3.67 and 3.66 (s, 6 H, 6,7-OCH_3), 3.52, 3.46, and 3.43 (s, 9 H, 3,5,8-CH_3), 3.21 and 3.19 (br t, 4 H, 6,7-CH_2CH_2CO), 2.6—2.0 (m, 2 H, 2-CH_2CH_3), 1.92 (d, 3 H, 1-CH_3), 1.75 (t, 3 H, 4-CH_2CH_3), 1.08 (t, 3 H, 2-CH_2CH_3), and −2.5 (br s, 2 H, NH); *m/z* 596.3377 (M^+; Calc. for $C_{36}H_{44}N_4O_4$: M^+, 596.3365). Optical spectrum of iron(III) chloride complex, in CH_2Cl_2 (typical of all four mesochlorin isomers); $\lambda_{max.}$ 378 (ε 88 000), 472 (8 100), 598 (24 900), and 754 (2 300).

Mesochlorin DME (*ring-*B *reduced*) (**8**), m.p. 133—136 °C; $\lambda_{max.}$ 387 (ε 174 000), 486 (12 400), 494 (12 900), 520 (3 500), 592 (3 330), 616 (3 100), and 644 (65 100); δ(360 MHz, $CDCl_3$) 9.70, 9.69 (s, 2 H, γ-H, δ-H), 8.87 and 8.86 (s, 2 H, α-H, β-H), 4.65 and 4.47 (m, 2 H, 3-and 4-H), 4.34 and 4.21 (t, 4 H, 6,7-CH_2CH_2CO), 3.90 (q, 2 H, 2-CH_2CH_3), 3.68 and 3.67 (s, 6 H, 6,7-OCH_3), 3.46, 3.44, and 3.43 (s, 9 H, 1,5,8-CH_3), 3.20 and 3.17 (br t, 4 H, 6,7-CH_2CH_2CO), 2.6—2.0 (m, 2 H, 4-CH_2CH_3), 1.92 (d, 3 H, 3-CH_3), 1.78 (t, 3 H, 2-CH_2CH_3), 1.07 (t, 3 H, 4-CH_2CH_3), and −2.5 (br s, 2 H, NH); *m/z* 596.3350 (M^+; Calc. for $C_{36}H_{44}N_4O_4$: 596.3365).

Mesochlorin DME (*ring-*C *reduced*) (**12**), m.p. 122—124 °C; $\lambda_{max.}$ 387 (ε 160 000), 486 (10 000), 492 (10 100), 518 (1 400), 592 (2 100), 616 (2 400), and 644 nm (62 200); δ(360 MHz, $CDCl_3$) 9.74 and 9.68 (s, 2 H, α-H, δ-H), 8.85 and 8.84 (s, 2 H, β-H, γ-H), 4.56 (m, 2 H, 5-and 6-H), 4.24 (t, 2 H, 7-CH_2CH_2CO), 3.89 and

3.87 (br q, 4 H, 2,4-CH_2CH$_3$), 3.70 and 3.62 (s, 6 H, 6,7-OCH$_3$), 3.55, 3.53, and 3.40 (s, 9 H, 1,3,8-CH$_3$), 3.17 (t, 2 H, 7-CH_2CO), 2.75, 2.60, 2.50 and 2.40 (m, 4 H, 6-CH_2CH_2CO), 1.90 (d, 3 H, 5-CH$_3$), 1.77 and 1.76 (br t, 6 H, 2,4-CH$_2$CH_3), −2.53 (br s, 2 H, NH); *m/z* 596.3345 (M^+; Calc. for $C_{36}H_{44}N_4O_4$: 596.3365).

Mesochlorin DME (*ring*-D *reduced*) (**10**), m.p. 124—127 °C; $\lambda_{max.}$ 387 (ε 162 000), 486 (11 000), 492 (11 100), 518 (2 000), 592 (2 700), 612 (3 000), and 644 nm (64 600); δ(360 MHz, $CDCl_3$) 9.72 and 9.71 (s, 2 H, α-H, β-H), 8.86 and 8.84 (s, 2 H, γ-H, δ-H), 4.56 (m, 2 H, 7- and 8-H), 4.24 (t, 2 H, 7-CH_2CH$_2$CO), 3.99 and 3.86 (q, 4 H, 2,4-CH_2CH$_3$), 3.71 and 3.61 (s, 6 H, 6,7-OCH$_3$), 3.56, 3.43, and 3.41 (s, 9 H, 1,3,5-CH$_3$), 3.17 (t, 2 H, 5-CH$_2$CH_2CO), 2.60, 2.40, 2.30 and 2.15 (m, 4 H, 7-CH_2-CH_2CO), 1.90 (d, 3 H, 8-CH$_3$), 1.78 and 1.75 (t, 6 H, 2,4-CH$_2$CH_3), −2.53 (br s, 2 H NH); *m/z* 596.3391 (M^+; Calc. for $C_{36}H_{44}N_4O_4$: 596.3365).

6-(1-*Hydroxy*-2-*methoxycarbonylethyl*)*rhodochlorin Methyl Ester* (**16**).—The chlorin β-keto ester (**15**)[21] (70 mg; 0.115 mmol) in dichloromethane (30 ml) and methanol (18 ml) was stirred at 0 °C (ice bath) and treated with sodium borohydride (400 mg) for 10 min. The solution was neutralized with 10% sulphuric acid in methanol (60 ml), poured into a separatory funnel containing dichloromethane (100 ml), washed with water (3 × 200 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was purified on an alumina column (Brockman Grade V), eluting with dichloromethane, and the green eluates were evaporated to give a residue which was crystallized from ether–hexane to give the title compound (46 mg, 65%), m.p. >300 °C (Found: C, 70.5; H, 6.8; N, 9.0. $C_{36}H_{42}N_4O_5$ requires C, 70.80; H, 6.93; N, 9.17%); $\lambda_{max.}$ 398 (ε 131 000), 496 (11 000), 524 (2 100), 552 (1 400), 602 (3 400), and 656 nm (42 100); δ(360 MHz, $CDCl_3$) (diastereoisomeric mixture) 9.95, 9.71 and 8.91 (each s, 2 H, *meso*-H), 9.28 and 9.22 (each s, 1 H, *meso*-H), 8.33—8.00, 6.45—6.05 (each m, 2 H, 4 H, CH=CH_2), 6.86—6.50 and 3.70—3.75 [each m, 2 H, 4 H, C*H*(OH) CH_2CO], 4.70—4.40 (m, 4 H, 7-H, 8-H), 3.90—3.70 (m, 4 H, CH_2CH$_3$), 3.80, 3.76, 3.60, and 3.56 (each s, 3 H, CH$_3$), 3.54, 3.50, and 3.38 (each s, 6 H, CH$_3$), 2.90—2.20 (m, 8 H, CH$_2$CH$_2$CO), 1.92 (d, 6 H, 8-CH$_3$), and 1.74 (t 6 H, CH$_2$CH_3); NH not observed; *m/z* (relative intensities), 610 (100), 592 (87), 536 (67), 505 (32), 449 (28), and 421 (34).

6-(trans-2-*Methoxycarbonylvinyl*)*rhodochlorin Methyl Ester* (**17**).—The foregoing hydroxypropionate chlorin (**16**) (45 mg, 0.074 mmol) in dry pyridine (4 ml) was stirred at 60 °C and treated with phosphoryl chloride (0.6 ml) for 20 min, after which methanol (10 ml) was added dropwise. The mixture was diluted with chloroform (50 ml), washed with water (3 × 100 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by thick layer chromatography (silica gel) eluting with 2% methanol in dichloromethane. Crystallization from dichloromethane–methanol gave the title compound (39 mg, 90%), m.p. 195—196 °C; $\lambda_{max.}$ 408 (ε 45 300), 504 (4 600), 528 (2 200), 534 (2 000), and 674 nm (21 000); δ(360 MHz, $CDCl_3$) 9.72, 9.69, 9.04, and 8.83 (each s, 1 H, *meso*-H), 9.26 and 7.06 (each d, *J* 16 Hz, 1 H, CH=CHCO), 8.27—7.94, 6.45—6.08 (each m, 1 H and 2 H, CH=CH_2), 4.80—4.16 (m, 2 H, 7- and 8-H), 4.06, 3.67, 3.66, 3.50, and 3.33 (each s, 3 H, CH$_3$), 3.80 (m, 2 H, CH_2CH$_3$), 2.96—2.16 (m, 4 H, CH$_2$CH$_2$CO), 1.91 (d, 3 H, 8-CH$_3$), and 1.75 (t, 3 H, CH$_2$CH_3); NH not observed; *m/z* (relative intensities), 592 (100), 577 (7), 505 (31), 475 (5), and 431 (7).

(7S,8S)-*Mesochlorin-IX Dimethyl Ester* (7*S*,8*S*)-(**10**).—The foregoing acrylate (**17**) (35 mg, 0.059 mmol) in tetrahydrofuran (20 ml) was stirred at room temperature with 10% palladized charcoal (10 mg) under an atmosphere of hydrogen for 31 h. The resulting solution was poured through a bed of Celite and the filtrate was evaporated to dryness to give a residue which was purified on thick layer plates (silica gel), eluting with 2% methanol in dichloromethane. The fastest moving band was identified as 2-*ethyl*-6-(2-*methoxycarbonylvinyl*)*rhodochlorin methyl ester* (**18**) (5 mg, 14%), m.p. 117—118 °C; δ(360 MHz, $CDCl_3$) 9.77, 9.57, 9.04, and 8.75 (each s, 1 H, *meso*-H), 9.27 and 7.06 (each d, *J* 16 Hz, 1 H, CH=CHCO), 4.72—4.22 (m, 2 H, 7- and 8-H), 4.05, 3.71, 3.63, 3.37, and 3.34 (each s, 3 H, CH$_3$), 3.92 and 3.83 (each q, 2 H, CH_2CH$_3$), 3.05—2.12 (m, 4 H, CH$_2$CH$_2$CO), 1.88 (d, 3 H, 8-Me), 1.77 and 1.72 (each m, 3 H, CH$_2$CH_3); NH not observed. The second most mobile band afforded the title compound (7*S*,8*S*)-(**10**) (25 mg, 71% ex. dichloromethane–methanol), m.p. 124 °C (Found: C, 72.65; H, 7.5; N, 9.2. $C_{36}H_{44}N_4O$ requires C, 72.46; H, 7.43; N, 9.39%); $\lambda_{max.}$ 378 (ε 173 000), 484 (13 400), 492 (13 500), 518 (2 500), 544 (700), 592 (3 500), 616 (3 900), and 644 nm (67 600); δ(360 MHz, $CDCl_3$) 9.75, 9.74, 8.90, and 8.86 (each s, 1 H, *meso*-H), 4.67—4.54 (m, 2 H, 7- and 8-H), 4.26 (t, 2 H, 7-CH_2CH$_2$CO), 4.01 and 3.89 (q, 4 H, 2,4-CH_2CH$_3$), 3.74 and 3.64 (s, 6 H, 6,7-OCH$_3$), 3.59, 3.47, and 3.44 (s, 9 H, 1,3,5-CH$_3$), 3.20 (t, 2 H, 5-CH$_2$CH_2CO), 2.60 and 2.84—2.30 (m, 4 H, 7-CH_2CH$_2$CO), 1.90 (d, 3 H, 8-CH$_3$), and 1.80 and 1.78 (t 6 H, 2,4-CH$_2$CH_3); NH not observed; *m/z* 596 (100), 581 (7), 523 (11), 509 (27), and 449 (3). The iron(III) chloride complex was prepared as described above (80%); $\lambda_{max.}$(ether) 376 (ε 92 000), 472 (8 400), 598 (25 800), and 754 (2 700).

2,4-*Diethyl*-6,7-*bis*(3-*hydroxypropyl*)-1,3,5,8-*tetramethylporphyrin* (**19**).—To a suspension of lithium aluminium hydride (0.085 g, 2.24 mmol) in dry tetrahydrofuran (15 ml) cooled to 0 °C was added dropwise a solution of mesoporphyrin-IX DME (**5**) (0.5 g, 0.84 mmol) in dry tetrahydrofuran (75 ml). After 1 h, the addition was complete, and the mixture was stirred for an additional 4 h at 0 °C and then 1 h at room temperature. At this time the reaction was quenched with successive additions of water (1 ml), 10% aqueous sodium hydroxide (1 ml), and water (3 ml). The solution was filtered through a Celite pad, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on neutral alumina (Brockmann Grade V) eluting first with dichloromethane to remove starting material and then with dichloromethane–2% methanol. The major fraction was collected and recrystallized in dichloromethane–light petroleum to yield the title compound (0.421 g, 93%, 0.78 mmol) as red crystals, m.p. 278—280 °C (Found: C, 74.4; H, 7.7; N, 10.1. $C_{34}H_{42}N_4O_2$·0.5H_2O requires C, 74.56; H, 7.91; N, 10.23%); $\lambda_{max.}$ 399 nm (ε 149 500), 498 (11 800), 532 (8 300), 566 (5 400), and 620 (3 500); δ(360 MHz, $CDCl_3$) 10.08 (s, 4 H, α,β,γ,δ-H), 4.19 (br t, 4 H, 6,7-CH_2CH$_2$CH$_2$OH), 4.09 (q, *J* 7.65 Hz, 4 H, 2,4-CH_2CH$_3$), 3.96 (br t, 4 H 6,7-CH$_2$CH$_2$CH_2OH), 3.64 and 3.63 (s, 12 H, 1,3,5,8-CH$_3$), 2.50 (br t, 4 H, 6,7-CH$_2$CH_2CH$_2$OH), 1.87 (t, *J* 7.65 Hz, 6 H, 2,4-CH$_2$CH_3), and −3.76 (br s, 2 H, NH); *m/z* (relative intensities) 538.3291(14) (M^+; calc. for $C_{34}H_{42}N_4O_2$: 538.3311) 493 (6) (−CH$_2$CH$_2$OH), 430 (13), 393 (6), 341 (7), 281 (27), 248 (18), 207 (76), 180 (17), 137 (72), 73 (74), and 55 (100).

2,4-*Diethyl*-1,3,5,8-*tetramethyl*-6,7-*bis*(3-*methylsulphonylpropyl*)*porphyrin* (**20**).—Dihydroxypropylmesoporphyrin (**19**) (0.47 g, 0.83 mmol) was dissolved in dry dichloromethane (60 ml) and dry triethylamine (0.58 ml) and the solution cooled to 0 °C. Methanesulphonyl chloride (0.26 ml) was added dropwise, the reaction mixture stirred at 0 °C for 4 h and then warmed to room temperature and stirred for an additional 1 h. The reaction was then quenched with ice–water (30 ml), and the mixture washed with cold 10% aqueous hydrogen chloride (30 ml) and saturated aqueous sodium hydrogen carbonate (30 ml), and then evaporated under reduced pressure. The crude solid was chromatographed on neutral alumina (Brockmann Grade

III) eluting with dichloromethane to yield the title compound (0.357 g, 79%, 0.66 mmol). The solid was pure enough for the next reaction, but for analytical purposes was recrystallized from dichloromethane–light petroleum; it had m.p. 216—217.5 °C (Found: C, 62.55; H, 6.45; N, 8.15. $C_{36}H_{46}N_4O_6S_2$ requires C, 62.22; H, 6.67; N, 8.06%); $\lambda_{max.}$ 398 (ε 155 800), 498 (12 600), 532 (8 700), 568 (5 400), and 620 nm (3 600); δ(360 MHz, $CDCl_3$) 10.12, 10.10, and 10.05 (s, 4 H, α,β,γ,δ-H), 4.54 (m, 4 H, 6,7-$CH_2CH_2CH_2OSO_2$), 4.26 (br t, 4 H, 6,7-$CH_2CH_2CH_2OSO_2$), 4.10 (m, 4 H, 2,4-CH_2CH_3), 3.66, 3.65, 3.64, and 3.63 (s, 12 H, 1,3,5,8-CH_3), 2.94 and 2.93 (s, 6 H, 6,7-OSO_2CH_3), 2.75 (m, 4 H, 6,7-$CH_2CH_2CH_2OSO_2$), 1.87 (br t, 6 H, 2,4-CH_2CH_3), and −3.75 (br s, 2 H, NH).

2,4-*Diethyl*-1,3,5,8-*tetramethyl*-6,7-*dipropylporphyrin* (**21**).—Preparation of the title compound was accomplished by reduction of both (free base) (**20**) and zinc(II)-(**20**) in the following manner. To a suspension of lithium aluminium hydride (0.186 g) in dry tetrahydrofuran (10 ml) cooled to 0 °C was added dropwise a solution of bis-mesylate (**20**) (0.355 g, 0.51 mmol) in dry tetrahydrofuran (100 ml) [the same equivalencies held for reduction of Zn-(**20**)]. After 1 h, addition was complete and the solution then allowed to warm to room temperature at which temperature it was stirred for an additional 3 h. The reaction was quenched with successive additions of water (1 ml), 10% aqueous sodium hydroxide (1 ml), and water (3 ml). The solution was filtered through a Celite pad, dried (Na_2SO_4), and evaporated under reduced pressure. The crude solid was chromatographed on neutral alumina (Brockmann Grade III) eluting with dichloromethane–toluene (1:1). The major fraction was collected and recrystallized from dichloromethane–methanol to yield pure crystalline (**21**) (120 mg) (47%, 0.24 mmol). The yield of product upon reduction of Zn-(**20**) and removal of zinc was 49%; the overall yield of (**21**) from mesoporphyrin-IX DME was 28%, m.p. 266—268 °C(decomp.) (Found: C, 80.45; H, 8.1; N, 10.9. $C_{34}H_{42}N_4$ requires C, 80.59; H, 8.35; N, 11.06%); $\lambda_{max.}$ 398 (ε 160 400), 498 (22 000), 532 (18 500), 566 (15 170), and 620 nm (13 300); δ(360 MHz, $CDCl_3$) 10.10, 10.09, and 10.08 (s, 4 H, α,β,γ,δ-H), 4.08 (m, 8 H, 2,4-CH_2CH_3 and 6,7-$CH_2CH_2CH_3$), 3.65 and 3.64 (s, 12 H, 1,3,5,8-CH_3), 2.34 (m, 4 H, 6,7-$CH_2CH_2CH_3$), 1.88 (br t, 6 H, 2,4-CH_2CH_3), 1.29 (m, 6 H, 7,6-$CH_2CH_2CH_3$), and −3.74 (s, 2 H, NH); *m/z* (relative intensities) 506.3400(45) (M^+; Calc. for $C_{34}H_{42}N_4$: M^+, 506.3409), 507 (18) (M + 2), 478 (12) (−CH_2CH_3), 266 (5), 243 (10), 136 (6), 100 (23), and 91 (49).

2,4-*Diethyl*-1,3,5,8-*tetramethyl*-6,7-*dipropyldihydroporphyrins* (**26**)—(**29**).—6,7-*Dipropylmesochlorin* (*all four ring reduced isomers*), m.p. 151—156 °C; $\lambda_{max.}$ (relative absorbances), 391 (100), 494 (19.7), 526 (15.0), 592 (12.7), and 644 nm (26.0); δ(360 MHz, $CDCl_3$) 9.72 and 9.70 (s, 8 H, *meso*-H not adjacent to reduced ring), 8.60 (br s, 8 H, *meso*-H adjacent to reduced ring), 4.64 and 4.46 (m, 8 H, H on reduced ring), 4.15, 3.96, and 3.84 (m, 24 H, 2,4-CH_2CH_3, 6,7-$CH_2CH_2CH_3$), 3.53, 3.44, and 3.42 (s, 36 H, 1,3,5,8-CH_3), 2.55 and 2.35 (m, 8 H, 2,4-CH_2CH_3 and 6,7-$CH_2CH_2CH_3$ attached to reduced ring), 2.33—2.20 (m, 16 H, 6,7-$CH_2CH_2CH_3$, 6,7-$CH_2CH_2CH_3$ attached to reduced ring), 1.92 (m, 12 H, 1,3,5,8-CH_3 attached to reduced ring), 1.77 (m, 18 H, 2,4-CH_2CH_3), 1.25 (m, 18 H, 6,7-$CH_2CH_2CH_3$), 1.10 (m, 12 H, 2,4-CH_2CH_3 attached to reduced ring; 6,7-$CH_2CH_2CH_3$ attached to reduced ring), −2.52 (s, 8 H, NH); *m/z* (relative intensities) 508.3556 (30) (M^+; Calc. for $C_{34}H_{44}N_4$: M^+, 508.3569), 508 (8, M + 1), 507 (31, M − 1), 506 (78, M − 2), 477 (11), 316 (13), 236 (8), 217 (13), and 212 (18).

6,7-*Dipropylmesochlorin* (*ring*-A *reduced*) (**26**). Compound could not be crystallized; $\lambda_{max.}$(relative absorbances) 389 (100), 488 (6.8), 494 (7.3), 520 (2.3), 568 (1.2), 592 (2.1), 616 (2.3), and 646 nm (33.8); δ(360 MHz, $CDCl_3$) 9.71 and 9.68 (s, 2 H, β-H, γ-H), 8.85 and 8.84 (s, 2 H, α-H, δ-H), 4.63 and 4.44 (m, 2 H, 1- and 2-H), 4.03—3.94 (m, 4 H, 4-CH_2CH_3, 6- or 7-CH_2-CH_2CH_3), 3.83 (t, *J* 7.2 Hz, 3 H, 6- or 7-$CH_2CH_2CH_3$), 3.43 and 3.41 (s, 9 H, 3,5,8-CH_3), 2.22 (m, 6 H, 2-CH_2CH_3, 6,7-CH_2-CH_2CH_3), 1.92 (d, *J* 7.3 Hz, 3 H, 1-CH_3), 1.77 (t, *J* 7.7 Hz, 3 H, 4-CH_2CH_3), 1.23 (m, 6 H, 6,7-$CH_2CH_2CH_3$), 1.09 (t, *J* 7.3 Hz, 2-CH_2CH_3), and −2.5 (br s, 2 H, NH); *m/z* 508.3583 (M^+; Calc. for $C_{34}H_{44}N_4$: 508.3566).

6,7-*Dipropylmesochlorin* (*ring*-B *reduced*) (**27**). Compound could not be crystallized; ^{1}H n.m.r. spectrum identical with ring-A reduced isomer; *m/z* 508.3565 (M^+; Calc. for M^+, 508.3566).

6,7-*Dipropylmesochlorin* (*ring*-C *and ring*-D *reduced*) (**28**) and (**29**). Compound could not be crystallized; $\lambda_{max.}$ (relative absorbances), 390 (100), 496 (7.0), 526 (4.0), 570 (3.4), 626 (3.4), and 646 nm (32.0); δ(360 MHz, $CDCl_3$) 9.70 and 9.67 (s, 4 H, *meso* H not adjacent to reduced ring), 8.85, 8.84, and 8.83 (s, 4 H, *meso* H adjacent to reduced ring), 4.68—4.59 and 4.52—4.40 (m, 4 H, H attached to reduced ring), 4.0—3.8 (m, 12 H, 2,4-CH_2CH_3, 6,7-$CH_2CH_2CH_3$), 3.53, 3.43, and 3.41 (s, 18 H, 1,3,5,8-CH_3), 2.6—2.35 (m, 4 H, 6,7-$CH_2CH_2CH_3$ attached to reduced ring), 2.3—2.15 (m, 8 H, 6,7-$CH_2CH_2CH_3$, 6,7-$CH_2CH_2CH_3$ attached to reduced ring), 1.93 (overlapping d, *J* 7.2 Hz, 6 H, 5,8-CH_3 attached to reduced ring), 1.76 (br t, 12 H, 2,4-CH_2CH_3), 1.23—1.20 (m, 6 H, 6,7-$CH_2CH_2CH_3$), 1.13 and 1.04 (t, *J* 7.3 Hz, 6 H, 6,7-$CH_2CH_2CH_3$ attached to reduced ring), and −2.50 (br s, 4 H, NH); *m/z* 508.3575 (M^+; Calc. for $C_{34}H_{44}N_4$: 508.3566).

6,7-*Bis*(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethyldihydroporphyrins* (**7**), (**9**), (**11**), *and* (**13**).—*Deuterochlorin DME* (*all four ring reduced isomers*), m.p. 178—183 °C (lit.,[19] 210—212 °C, lit.,[34] 215 °C) (Found: C, 71.35; H, 6.8; N, 10.1. $C_{32}H_{36}N_4O_4$ requires C, 71.07; H, 6.71; N, 10.36%); $\lambda_{max.}$ 390 nm (ε 143 300), 496 (9 900), 524 (2 500), 566 (600), 592 (1 500), 618 (1 800), and 646 (34 600); δ(360 MHz, $CDCl_3$) 9.76—9.64 (m, 8 H, *meso* H adjacent to aromatic centre), 8.99—8.68 (m, 14 H, *meso* H adjacent to reduced ring and 2,4-H), 5.04—4.80 (m, 10 H, protons on reduced ring), 4.38—4.23 and 4.22—4.18 (m, 12 H, 6,7-CH_2CH_2CO), 3.68—3.52 (m, 60 H, 6,7-OCH_3 and 1,3,5,8-CH_3), 3.26—3.16 (m, 12 H, 6,7-CH_2CH_2CO), 2.81—2.20 (m, 8 H, 6,7-CH_2CH_2CO attached to reduced ring), 2.08—1.93 (m, 12 H, 1,3,5,8-CH_3 attached to reduced ring), and −2.48 (br s, 8 H, NH).

Deuterochlorin DME (A + B *reduced ring isomers*) (**7**) *and* (**9**); $\lambda_{max.}$(relative absorbances) 390 (100), 486 (4.5), 494 (4.7), 518 (1.0), 548 (0.4), 594 (1.4), 618 (1.3), and 648 (23.8); δ(500 MHz, $CDCl_3$) 9.73, 9.69, 9.66, and 9.65 (s, 4 H, *meso* H next to non-reduced centres), 8.93, 8.89, 8.88, and 8.87 (s, 4 H, *meso* H next to reduced centres), 8.80 and 8.61 (s, 2 H, 2- and 4-H), 4.96 (m, 4 H, 1,2,3,4-H), 4.33 (t, *J* 7.94 Hz, 4 H, 6,7-CH_2CH_2CO), 4.19 (t, *J* 7.87 Hz, 4 H, 6,7-CH_2CH_2CO), 3.68, 3.67, 3.66, 3.65, 3.61, 3.51, 3.46, 3.42, and 3.40 (s, 30 H, 6,7-OCH_3, and methyls attached to non-reduced centres), 3.19 (m, 8 H, 6,7-CH_2CH_2CO), 2.0 (m, 6 H, 1,3-CH_3 attached to reduced centre), and −2.4 (br s, 4 H, NH); *m/z* 540.2737 (M^+; Calc. for $C_{32}H_{36}N_4O_4$: 540.2737).

Deuterochlorin DME (C + D *ring reduced isomer*) (**11**) *and* (**13**); $\lambda_{max.}$(relative absorbances) 386 (100), 486 (5.1), 494 (5.5), 522 (1.4), 544 (0.8), 588 (1.8), 614 (1.6), and 642 nm (23.4); δ(360 MHz, $CDCl_3$) 9.78, 9.77, 9.66, and 9.64 (s, 4 H, *meso* H adjacent to nonreduced centres), 8.94, 8.90, 8.88, and 8.82 (s, 4 H, *meso* H adjacent to reduced centres), 8.70 and 8.63 (s, 4 H, 2- and 4-H), 4.60 (m, 4 H, 5,6,7,8-H), 4.24 (t, *J* 7.95 Hz, 4 H, 6,7-CH_2CH_2CO), 3.70 and 3.68 (s, 12 H, OCH_3), 3.62, 3.61, 3.56, 3.55, 3.54, and 3.52 (s, 18 H, methyls attached to non-reduced centres), 3.16 (m, 4 H, 6,7-CH_2CH_2CO), 2.81—2.21 (m, 8 H, 6,7-CH_2CH_2CO attached to reduced centres), 1.99 (dd, 6 H, CH_3-5,8 attached to reduced ring), and −2.47 (br s, 4 H, NH); *m/z* 540.2727 (M^+; Calc. for $C_{32}H_{36}N_4O_4$: 540.2737).

1-(2-*Methoxycarbonylethyl*)*tetraphenylchlorin* (**33**)—(**35**).—These compounds were prepared from the corresponding acrylate tetraphenylporphyrin (**31**)[35] by iron insertion and de-esterification to give (**30**) and followed by sodium reduction and the usual work-up. (Three ring reduced isomers); m.p. 132—136 °C; $\lambda_{max.}$(relative absorbances), 414 (100), 516 (5.7), 546 (3.2), 598 (2.3), and 652 nm (13); δ(360 MHz, $CDCl_3$) 8.54—7.39 (m, 25 H, Ph and protons attached to aromatic rings), 4.14 and 4.12 (s, 4 H, protons attached to reduced ring), 3.06, 2.91 (t, *J* 8 Hz, 2 H, 1-CH_2CH$_2$CO attached to aromatic ring), 2.76—2.66 (m, 2 H, 1-CH$_2$CH_2CO attached to aromatic ring), and −1.28 (d, NH), −1.45 (d, NH), and −1.69 (s, NH) (2 H); *m/z* (relative absorbances) 702.2965 (100) (M^+; Calc. for $C_{48}H_{38}N_4O_2$: 702.2995), 704 (22, *M* + 2), 703 (54, *M* + 1), 701 (10, *M* − 1), 700 (19, *M* − 2), 369 (10), 317 (18), 314 (16), 286 (11), 244 (8), 236 (18), 224 (11), 217 (19), and 212 (28).

Reduction Products of 2-*Acetyldeuterohemin* (**40**).—(a) *Deuterochlorin DME* (**7**) (ring-A reduced—86% of mixture); δ(360 MHz, $CDCl_3$) 9.69 and 9.66 (s, 2 H, β-H, γ-H), 8.93, 8.89, and 8.87 (s, 3 H, α-H, δ-H, 4-H), 4.96 (m, 3 H, 1-H, 2α-H, 2β-H), 4.33 (t, *J* 7.54 Hz, 2 H, 6- or 7-CH_2CH$_2$CO), 4.19 (t, *J* 7.88 Hz, 2 H, 6- or 7-CH_2CH$_2$CO), 3.68 and 3.66 (s, 6 H, 6,7-OCH$_3$), 3.51, 3.46, and 3.40 (s, 9 H, 3,5,8-CH$_3$), 3.18 (m, 4 H, 6,7-CH$_2$CH_2CO), 2.00 (d, *J* 6.6 Hz, 3 H, 1-CH$_3$), and −2.40 (br s, 2 H, NH).

(b) *Deuterochlorin DME* (**9**) (ring-B reduced—14% of mixture); $\lambda_{max.}$(relative absorbances), 388 (100), 486 (5.9), 494 (6.3), 520 (0.4), 548 (0.2), 596 (0.6), 618 (0.9), 648 nm (37.2); δ(360 MHz, $CDCl_3$) 9.73 and 9.66 (s, 2 H, H-8, δ-H), 8.88 8.80, and 8.61 (s, 3 H, α-H, β-H, 2-H), 4.95 (m, 3 H, 3-H, 4α-H, 4β-H), 4.32 (t, *J* 7.70 Hz, 2 H, 6- or 7-CH_2CH$_2$CO), 4.19 (t, *J* 7.84 Hz, 2 H, 6- or 7-CH_2CH$_2$CO), 3.68 and 3.65 (s, 6 H, 6,7-OCH_3), 3.62 and 3.43 (s, 9 H, 1,5,8-CH$_3$), 3.18 (m, 4 H, 6,7-CH$_2$CH_2CO), 1.99 (d, *J* 6.5 Hz, 3 H, 3-CH$_3$), and −2.38 (br s, 2 H, NH); *m/z* 540.2755 (M^+; Calc. for $C_{32}N_{36}N_4O_4$: M^+, 540.2737).

(c) 2-*Ethyl*-6,7-*bis*(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethyl*-3,4-*dihydroporphyrin* (**49**). 2-*Ethyldeuterochlorin DME* (*ring-B reduced*), m.p. 176—178 °C; $\lambda_{max.}$(relative absorbances) 392 (100), 496 (7.7), 524 (3.3), 592 (2.35), 618 (3.0), and 646 (26); δ(360 MHz, $CDCl_3$) 9.70 and 9.66 (s, 2 H, γ-H, δ-H), 8.89 and 8.83 (s, 2 H, α-H, β-H), 5.01—4.91 (m, 3 H, 3-H, 4α-H, 4β-H), 4.32 (t, *J* 7.69 Hz, 2 H, 6- or 7-CH_2CH$_2$CO), 4.19 (t, *J* 7.8 Hz, 2 H, 6- or 7-CH_2CH$_2$CO), 3.88 (q, *J* 7.62 Hz, 2 H, 2-CH_2CH$_3$), 3.68, 3.66 (s, 6 H, 6,7-OCH$_3$), 3.51 and 3.42 (s, 9 H, 1,5,8-CH$_3$), 3.18 (m, 4 H, 6,7-CH$_2$CH_2CO), 1.98 (d, *J* 6.30 Hz, 3 H, 3-CH$_3$), 1.74 (t, *J* 7.6 Hz, 3 H, 2-CH$_2$CH$_3$), and −2.40 (br s, 2 H, NH); *m/z* 568.3032 (M^+; Calc. for $C_{34}H_{40}N_4O_4$: *M*, 568.3050).

Reduction Products of 2,4-*Diacetyldeuterhemin* (**41**).—For n.m.r. and spectrophotometric data see previous experimental details.

(a) *Compounds* (**6**) *and* (**8**). For peaks a and b on h.p.l.c. (Figure 6), molecular ion calculated for *mesochlorin DME*; *m/z* 596.3369 (Calc. for $C_{36}H_{44}N_4O_4$: 596.3365).

(b) *Compounds* (**10**) *and* (**12**). For peak c on h.p.l.c. (Figure 6), molecular ion calculated for *mesochlorin DME*; *m/z* 596.3350 (Calc. for $C_{36}H_{44}N_4O_4$: 596.3365).

(c) *Compounds* (**49**) *and* (**50**). For peak d on h.p.l.c. (Figure 6), molecular ion calculated for 2- *and* 4-*ethyldeuterochlorin DME*; *m/z* 568.3065 (Calc. for $C_{34}H_{40}N_4O_4$: 568.3052) (100), 540(43), 495(26)(*M*-CH$_2$CO$_2$CH$_3$), 421(27), and 368(18).

(d) *Compounds* (**7**) *and* (**9**). For peak e on h.p.l.c. (Figure 6), molecular ion calculated for *deuterochlorin DME*; *m/z* 540.2732 (Calc. for $C_{32}H_{36}N_4O_4$: 540.2737).

2,4-*Diethyl*-7-(2-*methoxycarbonylethyl*)-1,3,5,γ,8-*pentamethyl*-7,8-*dihydroporphyrin* (**52**): *Phyllochlorin Methyl Ester* (*ring-D reduced*).—M.p. 149—151 °C (lit.,[16] m.p. 147 °C); $\lambda_{max.}$ (relative absorbances), 402 (100), 502 (10.0), 538 (5.3), 592 (4.8), and 644 nm (16.0); δ(360 MHz, $CDCl_3$) 9.70 and 9.52 (s, 2 H, α-H, β-H), 8.80 (s, 1 H, 6-H), 8.74 (s, 1 H, δ-H), 4.50 (m, 2 H, 7- and 8-H), 3.96 (s, 3 H, 7-OCH$_3$), 3.94 and 3.84 (q, *J* 7.8 and 7.6 Hz, 4 H, 2,4-CH_2CH$_3$), 3.63, 3.56, 3.40, and 3.37 (s, 12 H, 1,3,5,γ-CH$_3$), 2.62—2.42 and 2.38—2.20 (m, 4 H, 7-CH_2CH_2CO), 1.83—1.65 (m, 9 H, 2,4-CH$_2$CH_3, 8-CH$_3$), and −2.18 (br s, 2 H, NH); *m/z* 524.3139 (100) (M^+; Calc. for $C_{33}H_{40}N_4O_2$: 524.3154), 525 (48, *M* + 1), 510 (10), 509 (5) (−CH$_3$), 493 (6) (−OCH$_3$), 454 (13), 443 (13), 437 (30), (−CH$_2$CH$_2$CO$_2$CH$_3$), 316 (15), 268 (18), and 225 (15).

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