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meso-Reactivity of Porphyrins and Related Compounds. Part 9.[1] Photo-oxygenation of Octaethyloxophlorin

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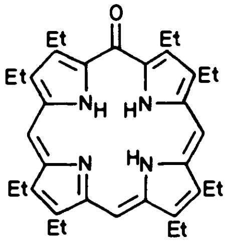
The photo-oxygenation of octaethyloxophlorin has been investigated under basic and under neutral conditions. In both cases unstable intermediate stages are observed spectroscopically. In methanolic sodium methoxide the solution becomes bleached and tetraethyl(methanol)propentdyopent is a significant product. In neutral solutions (*e.g.* benzene–methanol) the major products are octaethyl-5,15-dioxo-5,15-dihydroporphyrin (**4**) and octaethyl-19-formyl-21*H*,24*H*-bilin-1,15-dione (**7**), the formation of octaethyl-21*H*,24*H*-bilin-1,19-dione (**6**) being a minor pathway. A mechanistic rationalisation is proposed.

Although the solutions of the dication of octaethyloxophlorin (**1**) have been observed to be rather resistant to photochemical change, solutions of the monocation and, especially, the monoanion were rapidly bleached in air under similar conditions.[2] We were interested to determine if dipyrrolic compounds, especially propentdyopent adducts, were produced in this reaction, formally by cleavage at opposite *meso*-bridge positions. Fuhrhop and his colleagues[3,4] have described the photo-oxygenation of zinc and nickel complexes of (**1**), leading to oxygenated tetrapyrroles of various sorts.

Irradiation of the oxophlorin (**1**) with visible light in an aerated solution in methanol–tetrahydrofuran (or methanol–benzene) containing sodium methoxide caused the blue–green solution to become yellow ($\lambda_{max.}$ 454 nm) as shown in Figure 1. Irradiation in the absence of oxygen did not lead to the formation of the yellow pigment, and there was little change in the absorption spectrum within 2.5 h. The rate of formation of the yellow pigment was scarcely affected by the presence of Rose Bengal. Attempts to isolate the yellow intermediate were unsuccessful: on attempted purification at this stage a complex mixture of products was formed, which was not investigated further. Solutions of the yellow intermediate remained yellow when stored in the dark in the presence of air, but continued irradiation (45 h) of the aerated solution gave a near-colourless solution. Purification of the products from this second stage by preparative thin layer chromatography gave a mixture from which the major product, tetraethyl(methanol)propentdyopent (**2**)* and the corresponding water adduct (**3**) were isolated in yields of 20 and 6% respectively. Both compounds gave an intense Stokvis reaction. When the second stage of the photo-oxidation was carried out for a protracted period (72 h) the yield of the propentdyopent adducts was diminished, and some diethylmaleimide (10%) was isolated.



(**1**)

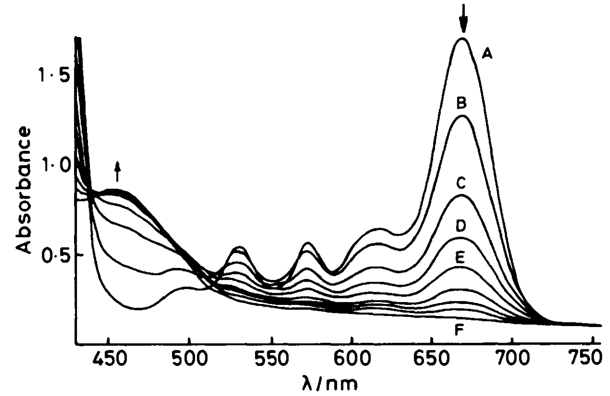


Figure 1. Effect of irradiation of octaethyloxophlorin in the presence of oxygen in 8.5 × 10^{-3}M sodium methoxide in 5% tetrahydrofuran–methanol: A = 0 min, B = 1 min, C = 3 min, D = 5 min, E = 8 min, F = 21 min

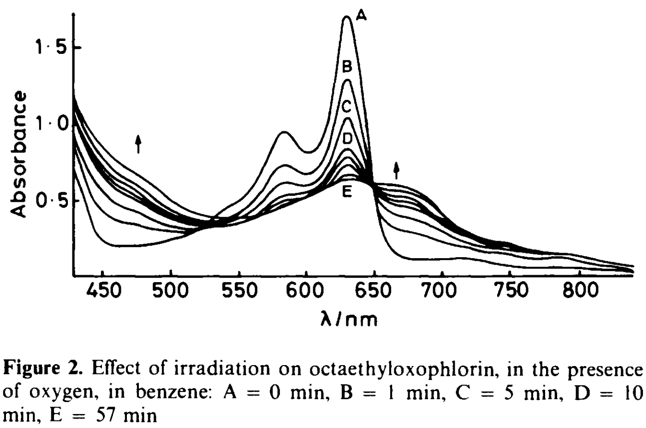
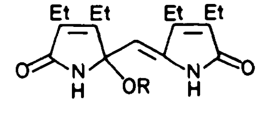


Figure 2. Effect of irradiation on octaethyloxophlorin, in the presence of oxygen, in benzene: A = 0 min, B = 1 min, C = 5 min, D = 10 min, E = 57 min



(**2**) R = Me
(**3**) R = H

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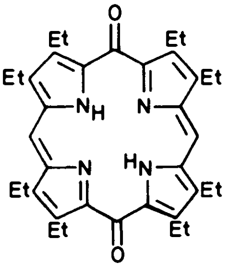
* Propentdyopent, the trivial name for 5-(2-oxo-2*H*-pyrrol-5-ylmethylene)pyrrol-2(5*H*)-ones.

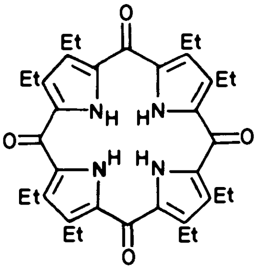
In order to help elucidate possible pathways in the reaction, the photo-oxidation was also investigated under less forcing conditions in neutral media. Visible irradiation of a dilute aerated solution in benzene resulted in the rapid decay of the absorption bands at $\lambda_{max.}$ 592 and 640 nm, and the appearance of a broad absorption in the visible at *ca.* 650 nm (Figure 2). A similar spectroscopic change was observed with tetrahydrofuran as solvent. Further irradiation of this solution had little effect but attempts to isolate this green product by removal of solvent by freeze drying led to decomposition (see below).

When a polar hydroxylic solvent (5% tetrahydrofuran in methanol) was employed there was initially a broadly similar spectroscopic change to that observed before, but after 2.5 h the solution had become red, with the appearance of a new absorption at *ca.* $\lambda_{max.}$ 525 nm, and the loss of the broad band at 650 nm. A fine red crystalline precipitate formed. There was no reaction in this solvent system in the dark, and only a very slow reaction was observed when the air flush was replaced by nitrogen, confirming that the process was indeed a photo-oxygenation.

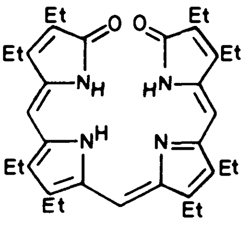
The red precipitate was shown by spectroscopic methods to be octaethyl-5,15-dioxo-5,15-dihydroporphyrin (**4**), isolated in a total yield of 18%. The n.m.r. spectrum clearly showed that the system was oxygenated at the opposite *meso*-position by the appearance of signals from two sets of equivalent ethyl groups. This was confirmed by comparison with an authentic sample prepared by reduction of octaethylxanthoporphyrinogen (**5**) with sodium borohydride.[5] Fuhrhop has reported the formation in almost quantitative yield of the zinc(II) complex of (**4**) by photo-oxygenation of zinc(II) octaethyloxophlorin in pyridine.[4] However, we find that in the photoreaction of the free base in tetrahydrofuran/methanol the 5,15-dioxo compound is not the only product. Chromatography of the mixture remaining after removal of crystalline (**4**) gave (in addition to a further quantity of that compound) three other components: octaethyl-21*H*,24*H*-bilin-1,19-dione (**6**) (2%), tetraethyl(methanol)propentdyopent (**2**) (0.3%), and octaethyl-19-formyl-21*H*,24*H*-bilin-1,15-dione (**7**) (19%). The last named compound was identified by spectroscopic considerations and by mass spectrometry. It was identical with a sample prepared by the photo-oxygenation of magnesium octaethylporphyrin.[6]



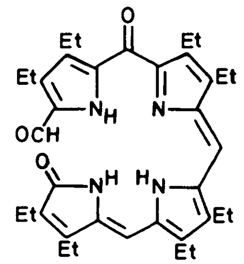
(**4**)



(**5**)



(**6**)



(**7**)

Comparison with an old sample of octaethyloxophlorin showed that this was the red compound referred to by Bonnett, Dimsdale, and Sales[7] as being present in aged solutions of octaethyloxophlorin, and not (**4**) as suggested by Fuhrhop.[8]

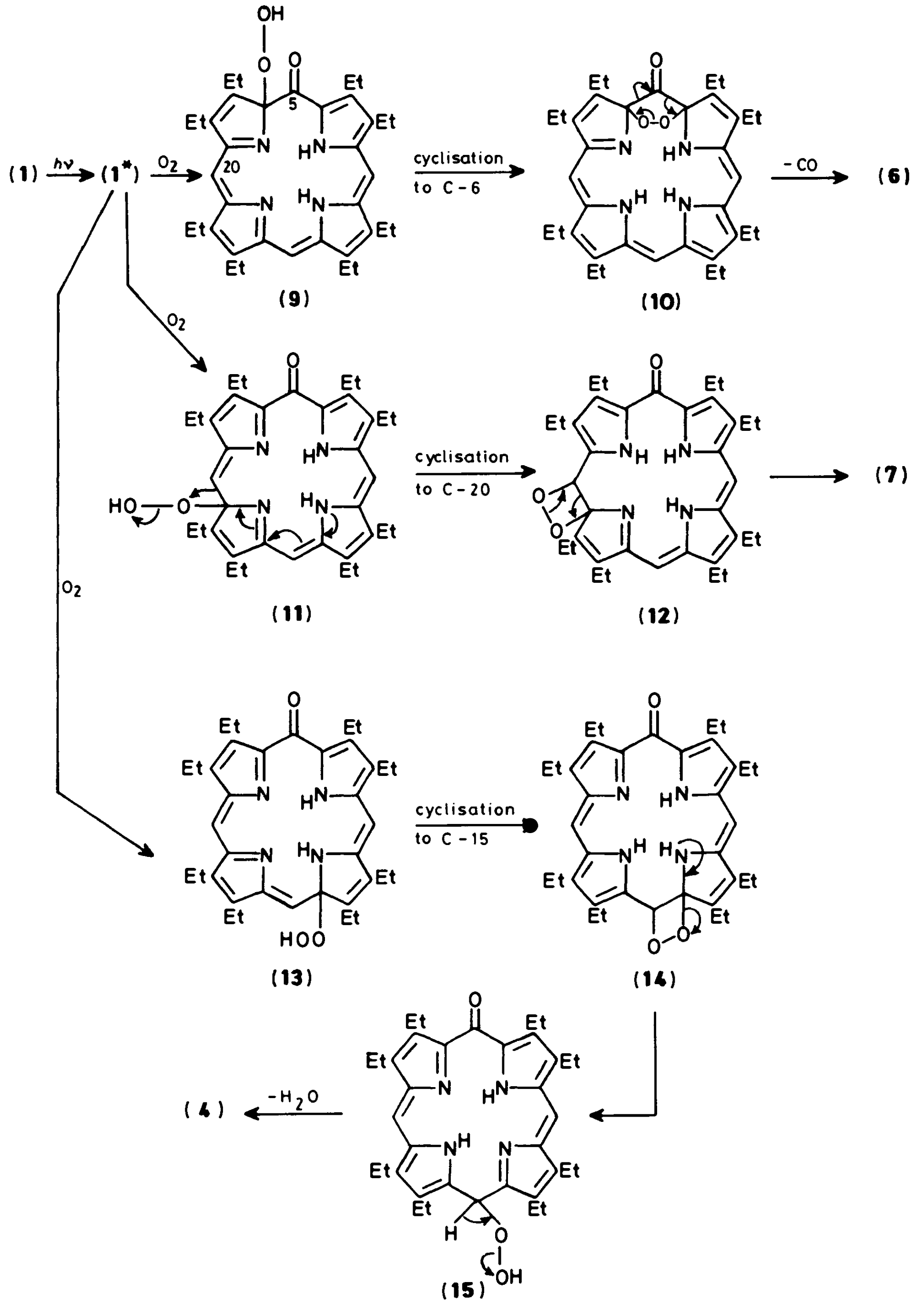
Long-term irradiation (70 h) led to a slight decrease in the yield of the dione (**4**), and a slight increase in the yield of the methanol propentdyopent (**2**). Diethylmaleimide was also detected in low yield. In benzene–methanol none of the dione (**4**) was detected, although the yield of the formyl derivative (**7**) was slightly increased. Both dione (**4**) and formyl derivative (**7**) were slowly photodegraded in both 50% tetrahydrofuran–methanol and 10% benzene–methanol in air, with the methanol propentdyopent (**2**) being detected as one of the products in both solvent systems.

The mechanisms of these photo-oxygenations are of considerable interest. While the later stages, leading to propentdyopent adducts and maleimides presumably follow the pathways observed for linear tetrapyrrole photo-oxygenation,[9] the nature of the first stage is by no means clear. The similarity of the visible spectrum of the green intermediate (Figure 2) to that reported[9] for the octaethyloxophlorin radical initially led to the plausible view that the green intermediate was that radical. However, four pieces of evidence had to be set against this conclusion, thus: (i) the radical has a Soret band[8] whereas the green intermediate does not; (ii) earlier workers had found it possible to purify the octaethyloxophlorin radical by chromatography,[8,10] whereas the green intermediate could not be handled in this way without extensive decomposition; (iii) the photo-oxygenation of (**1**) in benzene was not attended by an increase in the e.s.r. signal (over that found generally in oxophlorin samples due to the adventitious presence of a radical as an impurity);[7,8] and (iv) when the octaethyloxophlorin radical was subjected to photo-oxygenation under the neutral conditions described here, it was essentially unchanged.

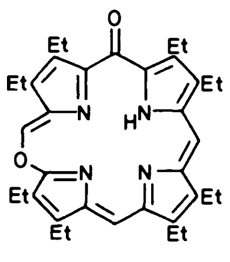
In view of the multiplicity of products, the green intermediate stage may well itself be a mixture. We suggest that, possibly *via* electron transfer process intermediates (leading to radical ion-superoxide pairs), the oxophlorin excited state reacts with ground state oxygen to give a mixture of valley hydroperoxides (**9**), (**11**), and (**13**) which then, respectively, lead to the macrocyclic oxygenated compounds (**6**), (**7**), and (**4**) as shown (Scheme). The pathway to (**6**) resembles that postulated for haem catabolism (although recent evidence[11] indicates that two molecules of dioxygen are involved in the cleavage of the oxyhaem) but, in the absence of co-ordinated iron, this is a very minor pathway. The other two pathways are rationalised in terms of dioxetane rings, which could alternatively arise by addition of singlet oxygen to (**1**). An attractive alternative for the formation of (**7**) is the Hock rearrangement of (**11**, arrows) leading to (**16**), hydrolysis of which would generate the formylbilindione (**7**). We thus suppose that the green intermediate contains a mixture of (**9**), (**11**), and (**13**), and that the electronic spectrum (Figure 2) is markedly influenced by the most extensive bilin chromophore (**9**). The view that the macrocyclic skeleton is retained intact in the green intermediate is supported by the observation that, on catalytic hydrogenation of the green intermediate in benzene, a yellow solution was obtained which on aeration and preparative t.l.c. gave the starting oxophlorin (**1**) in 50% isolated yield. It is interesting to note that Barratt[12] formulated the unstable initial product which he obtained on the photo-oxygenation of magnesium protoporphyrin dimethyl ester as (**17**), *i.e.* the hydroxy analogue of the skeleton of (**9**). The problem is being studied further to test these and other interpretations of oxophlorin photo-oxygenation.

Experimental

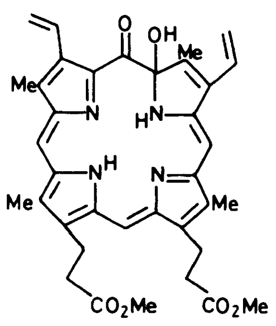
General experimental procedures have been described.[1,2]



Scheme. Arrows on (11) refer to generation of (16)—see text.



(16)



(17)

Photo-oxygenation of Octaethyloxophlorin in Basic Media.— (*a*) Octaethyloxophlorin (30 mg) was dissolved in tetrahydrofuran (33 ml) and treated with sodium methoxide (300 mg) in methanol (630 ml). The blue-green solution ($\lambda_{max.}$ 532, 573, 618, and 668 nm) was irradiated in a water-cooled Pyrex cell (10 °C, 500 W tungsten lamp at a distance of 20 cm) with slow air flush (dry, acid-free). After 15 min the solution had become yellow ($\lambda_{max.}$ 454 nm), and irradiation was continued for 45 h. The pale yellow solution ($\lambda_{max.}$ 284 nm) was poured into water (650 ml) and extracted vigorously with chloroform (2 × 500 ml). The organic layer was washed with water (250 ml), dried ($MgSO_4$), and subjected to preparative t.l.c. (silica gel HF, 40 × 40 × 0.1 cm, 1% MeOH–$CHCl_3$) to reveal a complex mixture from which was isolated (i) tetraethyl(methanol)propentdyopent (7.1 mg, 20.5%), identical with an authentic sample,[13] and (ii) tetraethyl(water)propentdyopent (2.1 mg, 6.3%), $\lambda_{max.}(CHCl_3)$ 280 nm, positive Stokvis reaction, identical (t.l.c.) with an authentic sample.

(*b*) An analogous reaction using benzene (66 ml) instead of tetrahydrofuran (33 ml) gave tetraethyl(methanol)propentdyopent (18%) as the major isolated product.

(*c*) Octaethyloxophlorin (5 ml) in benzene (11 ml) was treated with sodium methoxide (50 mg) in methanol (99 ml) and irradiated under the standard conditions (above) for 72 h. The solution was poured into chloroform (100 ml), washed with water (3 × 100 ml), dried (Na_2SO_4), and taken to dryness. Preparative t.l.c. (silica gel HF, 20 × 20 × 0.1 cm, 3% MeOH–$CHCl_3$) gave a complex mixture from which was isolated the following substances (spectroscopic yields given): (i) R_F 0.57, diethylmaleimide (4.9%), (ii) R_F 0.46, tetraethyl(methanol)propentdyopent (5.5%), and (iii) R_F 0.15, tetraethyl(water)propentdyopent (2.2%). Acidification and continuous extraction ($CHCl_3$, 24 h) of the initial aqueous extract, followed by t.l.c. separation (silica gel HF, light petroleum–ethyl acetate–isopropyl alcohol, 88:10:2) gave a further quantity (5%) of diethylmaleimide.

Experiments on the Yellow Intermediate.—Attempts to isolate the yellow intermediate ($\lambda_{max.}$ 454 nm) formed after *ca.* 15 min. were unsuccessful since decomposition occurred to give a complex mixture on work-up at this stage.

The subsequent reaction was shown to be photochemical. A sample of the yellow solution remained yellow and retained 75% of the absorbance at $\lambda_{max.}$ 454 nm on being kept in the dark in the presence of air for 72 h, whereas for a sample similarly treated but irradiated with visible light the absorbance at 454 nm had fallen to 5% of the original value, and the solution was virtually colourless.

Photo-oxygenation of Octaethyloxophlorin in Neutral Media.—(*a*) Octaethyloxophlorin (30 mg) in tetrahydrofuran (33 ml) was diluted with methanol (630 ml). The blue solution was irradiated under the standard conditions (above) for 4.5 h. The solution initially became green ($\lambda_{max.}$ *ca.* 660 nm, broad) but after 2.5 h had become red ($\lambda_{max.}$ *ca.* 530 nm, broad). A red precipitate was removed by filtration. Crystallisation from chloroform–methanol gave dark red needles (4.6 mg 15%) of 2,3,7,8,12,13,17,18-octaethyl-5,15-dioxo-5,15-dihydroporphyrin, m.p. 268—270 °C (lit.,[4] m.p. 270.5 °C). (Found: M^+, 564.345. $C_{36}H_{44}N_4O_2$ requires *M*, 564.346); $\lambda_{max.}(CHCl_3)$ 310 (44 100), 316 (45 460), 408 (96 700), and 499 nm (23 100); $\lambda_{max.}(CHCl_3–CF_3CO_2H)$ 316 (48 115), 415 (60 810), 456 (104 920), 520 (25 390), and 544 nm (44 100); ν(KBr) 3 306, 2 968, 1 605, 1 212, 1 012, 892, 873, 786, 710, and 640 cm^{-1}; $\delta(CDCl_3)$ 6.67 (s, 2 × *meso*-H), 2.72, 2.50 (q, q, 8 × CH_2), 1.59 (s, 2 NH, exchangeable D_2O), 1.14, and 1.10 (tt, 8 × CH_3).

The filtrate was taken to dryness, and subjected to preparative layer chromatography (silica gel HF, 40 × 40 × 0.1 cm, acetone–light petroleum, 1:4) to give a complex mixture including a further quantity (2.3%) of the above 5,15-dioxodihydroporphyrin, R_F 0.88, together with the following: (i) R_F 0.37, 2,3,7,8,12,13,17,18-octaethyl-21*H*,24*H*-bilin-1,19-dione, (0.7 mg, 2.3%) identical (t.l.c., e.s., m.s.) with an authentic sample;[14] (ii) R_F 0.27, 2,3,7,8,12,13,17,18-octaethyl-19-formyl-21*H*,24*H*-bilin-1,15-dione, microcrystals (6.3 mg, 19%) from dimethyl sulphoxide–water, m.p. 211—213 °C (lit.,[6] m.p. 214—218 °C) (Found: M^+, 582.358. $C_{36}H_{46}N_4O_3$ requires *M*, 582.357), *m/z* (178°) 582 (*M*, 100%), 553 ($M - C_2H_5$, 13), 525.5 (m^*, 582→553), 433 (8), 432.265 (5, $C_{27}H_{34}N_3O_2$ requires 432.265), 272 (39), and 178.087 (6, $C_{10}H_{12}NO_2$ requires 178.087). $\lambda_{max.}(CHCl_3)$ 324.5 (32 500), 497 (9 900), 526 (15 200), 557 (16 700), and 644 nm (2 500); $\lambda_{max.}(CHCl_3–CF_3CO_2H)$ 332 (44 200), 600 (34 000), and 618 nm (36 500); ν(KBr) 3 225, 3 290, 1 685, 1 660, 1 628, and 1 598 cm^{-1}; $\delta(CDCl_3)$ 9.60 (s, CHO), 6.72, 5.82 (s, s, 2 × *meso*-H), 2.52 (m, 8 × CH_2), and 1.16 (m, 8 × CH_3); (iii) R_F 0.09, tetraethyl(methanol)propentdyopent (0.1 mg, 0.3%) after further purification by t.l.c.; $\lambda_{max.}$(EtOH) 277.5 nm, positive Stokvis reaction; identical (t.l.c.) with previous sample.

(*b*) A similar experiment, but continued for 70 h, gave the following product distribution: octaethyl-5,15-dioxo-5,15-dihydroporphyrin (18%), octaethyl-19-formyl-21*H*,24*H*-bilin-1,15-dione (23%), octaethyl-21*H*,24*H*-bilin-1,19-dione (0.4%), tetraethyl(methanol)propentdyopent (1.6%), and diethylmaleimide (0.9%).

(*c*) An irradiation experiment (72 h) using 25% benzene–methanol as solvent produced no red crystalline precipitate. T.l.c. fractionation as before gave the following product distribution: octaethyl-5,15-dioxo-5,15-dihydroporphyrin (0.03%), octaethyl-19-formyl-21*H*,24*H*-bilin-1,15-dione (28%), octaethyl-21*H*,24*H*-bilin-1,19-dione (0.05%), tetraethyl(methanol)propentdyopent (1.7%), and tetraethyl(water)propentdyopent (1%).

Experiments on the Green Intermediate.—(*a*) Attempts to isolate the green intermediate, $\lambda_{max.}$(benzene) 362 (33 900, based on equimolarity with starting oxophlorin), 394, (27 200), 644 (7 860), and 664 (7 620), were unsuccessful. Thus lyophilisation of the benzene solution gave a green solid which rapidly turned red. T.l.c. showed it to contain a complex mixture of pigments similar to that observed before, together with some unchanged oxophlorin.

(*b*) A solution of the green intermediate (10^{-4}M) in 50% tetrahydrofuran–methanol was treated with a trace of dilute sodium hydroxide to give a yellow solution with no pronounced absorption bands in the visible.

(*c*) Octaethyloxophlorin (5 mg) in thiophene-free benzene (110 ml) was irradiated as before for 3 h to give the green intermediate. The solution was then hydrogenated at atmospheric pressure over Adam's catalyst (6 mg) in the dark for 17 h. The pale yellow solution ($\lambda_{max.}$ 300, 342 nm) was filtered, and aerated in the dark for 7 days. The deep blue solution was concentrated and subjected to t.l.c. separation to give octaethyl-5,15-dioxo-5,15-dihydroporphyrin (0.017 mg, spectroscopic, 0.33%), octaethylporphyrin (0.04 mg, spectroscopic, 0.9%), and octaethyloxophlorin (2.5 mg, isolated, 50%).

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