Pyrroles and Related Compounds. Part XXVIII.[1] β-Keto-esters in the Porphyrin Series

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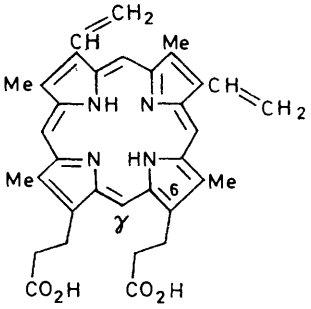
Porphyrin carboxylic acids are converted into the corresponding β-keto-esters by reaction between the acid chlorides and t-butyl methyl malonate, followed by treatment with trifluoroacetic acid. Iodine in methanol reacts with the magnesium chelate of the keto-ester anion derived from rhodoporphyrin-XV dimethyl ester, giving the chelate of 10-methoxyphaeoporphyrin-a_5 dimethyl ester. The significance of these results in relation to the biosynthesis of chlorophyll is discussed.

GRANICK'S classical investigations established that protoporphyrin-IX (1) is a biogenetic precursor of chlorophyll-*a* (2).[2] Perhaps the most intriguing question about the complicated transformation of (1) into (2) is how the carbocyclic (frequently termed isocyclic) ring is formed. In Part II,[3] a speculation about formation of a carbon–carbon bond by a Michael-type transfer of electrons from an enolate of a β-keto-carboxylic side-chain at position 6 to the γ-position of the macrocycle was advanced. A different, but not dissimilar speculation about intramolecular reaction between an enolised β-keto-ester side-chain and the nucleus, activated by diprotonation, was put forward by Woodward.[4] The



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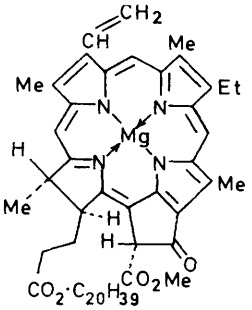

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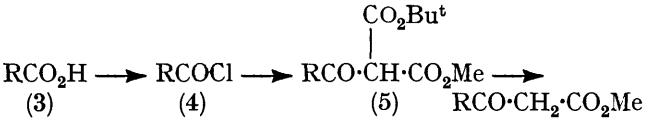
purpose of the present work was to prepare porphyrin β-keto-esters and to explore their behaviour under conditions supposedly favourable to cyclisation. This work paved the way for investigations more closely connected with the biosynthesis of the carbocyclic ring (see following paper).

Studies in the synthesis of monopyrrolic β-keto-esters [5] had shown that acylation of dialkyl malonates is a serviceable route in that series. It seemed likely to be suitable also in the porphyrin area because the requisite carboxylic acids are available. Looking forward to synthesis of compounds bearing easily reduced vinyl substituents, we chose t-butyl (rather than benzyl) as the temporary malonate substituent. Initially, the route was tested with a porphyrin having only one carboxy-group and an arbitrary array of methyl and ethyl groups at the other seven peripheral positions,[1] and our scheme was as follows:



R = 2,6,7-triethyl-1,3,5,8-tetramethylporphinyl

The carboxylic acid (3) was obtained from the methyl ester; its visible absorption spectrum showed the expected change from rhodo-type [6] (in pyridine) to aetio-type (in methanolic 0·1M-sodium methoxide), corresponding to destruction of the conjugation between the carbonyl group and the macrocyclic π-electrons; this diagnostic test was important in our later work. The acid chloride (4) was treated directly with a large excess of methyl t-butyl sodiomalonate, giving a 71% yield of the keto-malonate (5), without any diacylation being detected. The structure (5) was not in doubt, but the highest-mass peak in the mass spectrum corresponded to complete loss of the keto-malonate side-chain, except for one hydrogen atom. The keto-malonate (5) was considerably enolised (^{1}H n.m.r. spectrum in $CDCl_3$), unlike the monopyrrolic analogues.[5] Its visible spectrum was of the oxorhodo-type (in chloroform) rather than of the rhodo-type, but on ionisation it changed to the aetio-type (in methanolic sodium methoxide). The t-butyloxycarbonyl group was removed from (5) by cold trifluoroacetic acid, and the resulting keto-ester (6) (obtained in 77% yield) possessed the expected spectral properties, except that the highest-mass ion corresponded to acetylporphyrin rather than the molecular ion. Loss of 58 mass units proved to be the rule in the mass spectra of keto-esters throughout this series of investigations, but more recently, true molecular ions have been observed (MS12 or Varian CH 5D spectrometer instead of MS9).

Encouraged by these results, we turned to synthesis of the β-keto-ester (7d), which is closely related to the supposed intermediates in chlorophyll biosynthesis. The synthesis involved differentiation of the two ester functions in rhodoporphyrin-XV dimethyl ester (7a). This was achieved by alkaline total hydrolysis and acid-catalysed partial re-esterification. It was predicted that

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[1] Part XXVII, T. T. Howarth, A. H. Jackson, and G. W. Kenner, preceding paper.

[2] S. Granick, *J. Biol. Chem.*, 1948, **172**, 717; *The Harvey Lectures*, 1950, **44**, 220.

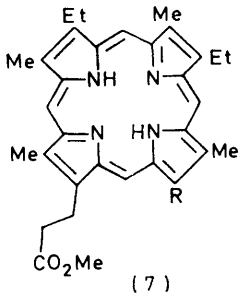
[3] A. C. Jain and G. W. Kenner, *J. Chem. Soc.*, 1959, 185.

[4] R. B. Woodward, *Ind. chim. belge*, 1962, **27**, 1293.

[5] T. T. Howarth, A. H. Jackson, J. Judge, G. W. Kenner, and D. J. Newman, *J.C.S. Perkin I*, 1974, 490.

[6] J. E. Falk, 'Porphyrins and Metalloporphyrins,' Elsevier, Amsterdam, 1964, p. 73.

protonation of the nuclear carboxy-group would be inhibited by the double positive charge on the macrocycle, whereas the side-chain carboxy-group would retain almost aliphatic disposition to esterification. A



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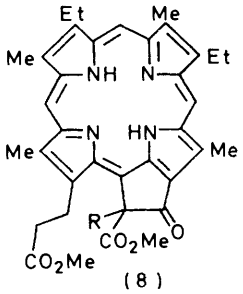
a; R = CO_2Me
b; R = CO_2H
c; R = CO_2Et
d; R = $CO \cdot CH_2 \cdot CO_2Me$



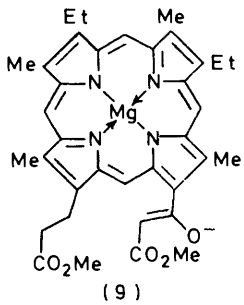
(8)

a; R = H
b; R = OMe

monoester was indeed obtained without difficulty, and its structure (7b) was confirmed by (i) the change in its visible absorption spectrum from rhodo-type (in chloroform) to aetio-type (in methanolic sodium methoxide), (ii) the lack of the low-field methoxy-resonance (ring current effect) in the ^1H n.m.r. spectrum (in trifluoroacetic acid) compared with that of the diester (7a),[7] and (iii) the conversion into the acid chloride and then ethanolysis, to give an ethyl methyl diester which still showed the loss of 73 mass units in the mass spectrum, corresponding to fragmentation of the propionate *methyl* ester side-chain.[8] The last criterion also afforded evidence for homogeneity of the acid chloride, which was treated with methyl t-butyl sodiomalonate as in the case of (4). In this instance, the keto-malonate could not be crystallised, but it yielded the crystalline keto-ester (7d) [in an overall yield of 50% from the carboxylic acid (7b)] having the expected spectral properties, including a rhodo-type visible absorption spectrum.

With the two porphyrin β-keto-esters (6) and (7d) in hand, we were able to attempt non-enzymic closure of the carbocyclic ring. Woodward[4] made the appealing proposal that discharge of a porphyrin dication by an enolised β-keto-ester system would lead to a phlorin salt containing the carbocyclic ring, and that the reaction could be carried forward essentially irreversibly in the biosynthetic direction through oxidation of the phlorin nucleus back to the porphyrin level. Both keto-esters are appreciably enolised in deuteriochloroform (n.m.r. spectroscopy) and they were readily converted into the green diprotonated species, but evidence for cyclisation was not obtained from experiments with addition of hydrogen chloride, sulphuric acid, or boron trifluoride–ether complex to solutions in methylene chloride, chloroform, methanol, benzene, ether, or tetrahydrofuran. Our own proposal[3] was less specific. Activation of the keto-ester, by either ionisation or enolisation, was envisaged, and it was considered that the electrons displaced from the γ-position during ring closure would have to be accepted by either an oxidising agent or a conjugated double bond in the magnesium chelate which was probably involved in the cyclisation. A magnesium chelate would be instantly decomposed by acids, and therefore base-catalysis was indicated. All attempts, however, to initiate cyclisation by simple base-catalysed reactions of the keto-esters or their metal chelates (zinc or magnesium) were unsuccessful. At this point, our thoughts were decisively influenced by a communication[9] which described the ready oxidation of porphyrin magnesium chelates to π-cation radicals. It stimulated us to explore the oxidative mechanism for acceptance of the electrons displaced from the γ-position.

Fuhrhop and Mauzerall[9] showed that removal of one electron from the magnesium chelate of octaethylporphyrin was accompanied by a spectral change from $\lambda_{max.}$ 404, 542, and 578 to 398 and 683 nm. The magnesium chelate prepared from (7d) by the action of n-propoxymagnesium bromide and transesterification with methanol was, however, unaffected by iodine in methanol, a reagent which was effective with magnesium octaethylporphyrin. This result was not surprising, in view of the electron-withdrawing power of the group at position 6, whether in the keto or the enol form. Bromine or iron(III) chloride in methanol did produce the desired absorption at 680 nm, but there was no further spectral change indicative of cyclisation, during several hours. On the other hand, addition of a little aqueous 10% sodium carbonate to the magnesium chelate moved the absorption maxima from 418, 554, and 602 to 410, 544, and 580 nm, presumably by proton abstraction



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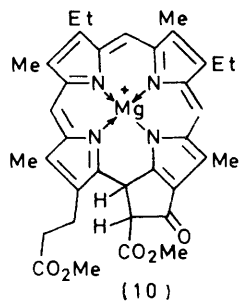

(10)

yielding the sodium enolate (9). Addition of iodine to this solution caused a rapid change to maxima at 550 and 620 nm (diffuse). Acidic removal of the magnesium and subsequent chromatography yielded two porphyrinic products. The major product (7% yield) was shown conclusively by mass spectroscopy and comparison with an authentic sample, prepared from methyl phaeophorbide-*a*, to be 10-methoxyphaeoporphyrin-a_5 dimethyl ester (8b). The minor component was apparently (mass spectrum) an oxophlorin derived from (8b). If transesterification with sodium methoxide in methanol was not performed after magnesium insertion, the 7-n-propyl ester, homologous to (8b), was produced (mass

[7] P. A. Burbidge, G. L. Collier, A. H. Jackson, and G. W. Kenner, *J. Chem. Soc.* (*B*), 1967, 930.

[8] A. H. Jackson, G. W. Kenner, K. M. Smith, R. T. Aplin, H. Budzikiewicz, and C. Djerassi, *Tetrahedron*, 1965, **21**, 2913.

[9] J.-H. Fuhrhop and D. Mauzerall, *J. Amer. Chem. Soc.*, 1968, **90**, 3875.

spectral molecular ion at 664 and loss of $C_2H_4O_2$ from the 10-position, instead of $C_4H_7O_2$ from a 10-propoxy-group). The 10-methoxyphaeoporphyrins gave, as expected, a negative reaction in the ' phase test ' for an enolisable hydrogen atom in the isocyclic ring.

The mechanism of this cyclisation deserves some comment, although any such considerations are necessarily speculative. Our preliminary announcement [10] stated that ' formation of the isocyclic ring may be envisaged as reaction between the radical cation derived from the magnesium–macrocycle complex and the radical derived from the enolate '. We had in mind, in addition to the work of Furhrhop and Mauzerall,[9,11] the oxidative coupling of enolates.[12] Dolphin and his co-workers [13] have specifically preferred to regard our cyclisation as addition of the unoxidised enolate to the magnesium porphyrin π-dication,[14] generated by removal of two electrons from the macrocycle. At first sight there seems little ground for such a supposition, because iodine is not sufficiently powerful an oxidising agent to convert magnesium octaethylporphyrin into the dication. In defence of Dolphin's suggestion, however, we point out that the enolate ion may be supposed to lower the oxidation potential of the macrocycle conjugated to it, so that double electron abstraction by very weak oxidising agents becomes feasible. Until physical methods are refined to the point where they can differentiate between [cation radical–enolate radical] and [dication–enolate anion] situations in conjugated systems, further discussion seems pointless. In any case, removal of two electrons from the enolate of the magnesium chelate (9) and formation of a carbon–carbon bond leads to a new chelate (10) of an isoporphyrin.[4,14] Loss of a proton, as expected, would then give the magnesium chelate of (8a).

The 10-methoxy-substituent in (8b) is an unwelcome excrescence. It is easy to see how it arises from the anion of the chelate of (8a), a reaction which is well known with the magnesium-free porphyrin.[15] In principle, it should be possible to achieve closure of the carboxylic ring without this unwelcome subsequent reaction. We made some experiments along these lines with the magnesium chelate of (7d) without any success, but this work was suspended when we discovered a very efficient cyclisation of (7d) and its 2-vinyl congener to the thallium(III) chelates of (8a) and the corresponding vinyl phaeoporphyrin respectively.[16] Nevertheless, the present work is, in our opinion, biogenetically significant in indicating the probable viability of a biological pathway from the series of magnesium chelates of porphyrins derived from protoporphyrin-IX (1) to the chlorophyll series through electron abstraction from enolates of magnesium chelates of porphyrin β-keto-esters.

[10] M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J. Amer. Chem. Soc.*, 1969, **91**, 1232.
[11] J.-H. Fuhrhop and D. Mauzerall, *J. Amer. Chem. Soc.*, 1969, **91**, 4174.
[12] O. H. Matteson and C. A. Wachtmeister, *Tetrahedron Letters*, 1967, 1855.
[13] D. Dolphin, R. H. Felton, D. C. Borg, and J. Fajer, *J. Amer. Chem. Soc.*, 1970, **92**, 743.

EXPERIMENTAL

M.p.s were measured on a microscope hot-stage apparatus. Neutral alumina (Woelm; Brockmann grade V) was used for chromatographic separations. Visible absorption spectra were measured with a Unicam SP 800 spectrophotometer, ^{1}H n.m.r. spectra with a Varian A-60 or HA-100 spectrometer, and mass spectra with an A.E.I. MS9 instrument (at 50 μA and 70 eV, with direct inlet and source temperature between 200 and 220°).

2,6,7-Triethyl-1,3,5,8-tetramethylporphin-4-carboxylic Acid (3).— 2,6,7-Triethyl-4-methoxycarbonyl-1,3,5,8-tetramethylporphin [1] (150 mg) in pyridine (150 ml) and 10% w/v potassium hydroxide–methanol (150 ml) was heated under reflux during 3 h, during which time the initial rhodo-type visible absorption spectrum ($\lambda_{max.}$ 510, 548, 575, and 633 nm) changed to the aetio-type ($\lambda_{max.}$ 500, 535, 568, and 620 nm). The solution was poured into water (500 ml) and neutralised with 2N-hydrochloric acid. The precipitated porphyrin was extracted with methylene chloride–pyridine (*ca.* 10 : 1), the extract was washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated to leave the *porphyrin*, which crystallised from pyridine–methanol as purple needles (125 mg, 86%), m.p. >320° (Found: C, 75·3; H, 7·1; N, 11·3. $C_{31}H_{34}N_4O_2$ requires C, 75·3; H, 6·9: N, 11·3%), τ (CF_3·CO_2H) −1·80, −1·13, −0·92, and −0·86 (4 *meso*-H), 5·81 (q) and 8·19 (t) (3Et), 5·89 (3-Me), 6·28 (3Me), and 13·8br (NH), $\lambda_{max.}$ (pyridine) 4·07 (ε 186,000), 507 (11,000), 544 (13,800), 571 (8000), and 628 nm (1890), $\lambda_{max.}$ ($CHCl_3$–HCl) 423 (ε 212,000), 559 (13,700), and 607 nm (10,500), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 396 (ε 173,000), 498 (13,100), 534 (10,200), 568 (6360), and 620 nm (3540).

2,6,7-Triethyl-1,3,5,8-tetramethylporphin-4-carbonyl Chloride (4).—The foregoing porphyrincarboxylic acid (50 mg) was dissolved in thionyl chloride (1 ml) and kept at room temperature for 1 h. Evaporation *in vacuo* gave a green residue which was used immediately, without purification, in subsequent reactions. A portion of the acid chloride was treated with methanol; t.l.c. showed almost quantitative formation of the methyl ester.

2,6,7-Triethyl-4-[(methoxycarbonyl)-t-butoxycarbonylacetyl]-1,3,5,8-tetramethylporphin (5).—Methyl t-butyl malonate (0·5 g, 22 mol. equiv.) in dry tetrahydrofuran (40 ml) was treated with sodium hydride (63 mg, 20 mol. equiv.). After the initial brisk effervescence had subsided, the suspension was left at room temperature during 30 min, then added to the foregoing acid chloride (from 70 mg of carboxylic acid) and the mixture was shaken vigorously until all the porphyrinic material had dissolved. After a further 15 min at room temperature, the solvent was evaporated off and the residue was partitioned between methylene chloride and 2N-hydrochloric acid (150 ml; 2 : 1). The organic layer was washed with water (3 × 50 ml), dried ($MgSO_4$), and evaporated to dryness; the residue was treated with an excess of diazomethane in ether. After 30 min at 0° the solution was washed with dilute acetic acid, aqueous 10% sodium hydrogen carbonate (50 ml), and water, dried ($MgSO_4$), and evaporated. The oily residue was chromatographed on grade V neutral alumina (elution with methylene chloride and then chloroform) to give an amorphous red solid from the chloroform eluates. Re-

[14] J. Fajer, D. C. Borg, A. Forman, D. Dolphin, and R. H. Felton, *J. Amer. Chem. Soc.*, 1970, **92**, 3451.
[15] H. Fischer and A. Stern, ' Die Chemie des Pyrrols,' Akademische Verlag, Leipzig, 1940, p. 176.
[16] G. W. Kenner, S. W. McCombie, and K. M. Smith, *J.C.S. Chem. Comm.*, 1972, 844; *J.C.S. Perkin I*, 1974, 527.

crystallisation from chloroform–methanol gave the *product* (65 mg, 71%) as minute purple needles. An accurate m.p. could not be determined owing to thermal decomposition, but an estimate, based on observation when the sample was placed on the preheated hot plate, is 210—215° (Found: C, 71·8; H, 7·1; N, 8·8. $C_{39}H_{46}N_4O_5$ requires C, 72·0; H, 7·1; N, 8·6%). The n.m.r. spectrum ($CDCl_3$) was extremely complex, owing to a high level of enolisation. Resonances conclusively assigned were: τ 5·90 (3-Me), 8·55 (Bu^t), and 8·26 (t, $3CH_2{\cdot}CH_3$); $\nu_{max.}$ ($CHCl_3$) 1625 and 1715 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 407 (ε 173,000), 507 (8870), 543 (11,700), 568 (9400), and 620 nm (1770), $\lambda_{max.}$ ($CHCl_3$–HCl) 429 (ε 218,000), 570 (11,000), and 618 nm (7100), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 396 (ε 173,000), 497 (13,200), 534 (10,600), 566 (6340), and 619 nm (4150).

2,6,7-*Triethyl*-4-*methoxycarbonylacetyl*-1,3,5,8-*tetramethylporphin* (6).—The foregoing porphyrin (25 mg) in trifluoroacetic acid (0·63 ml) was kept at room temperature during 10 min. The solvent was evaporated off and a solution of the residue in methylene chloride (30 ml) was washed with aqueous 10% sodium hydrogen carbonate (20 ml) and water (2 × 20 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed on grade V alumina, with methylene chloride as eluant, to give a red solid which crystallised from ether. Recrystallisation from methylene chloride–methanol gave the *product* (16·5 mg 77%) as minute purple prisms, which decomposed above 260° (Found: C, 74·3; H, 7·1; OMe, 5·7. $C_{34}H_{38}N_4O_3$ requires C, 74·2: H, 7·0; OMe, 5·6%), τ ($CDCl_3$) −0·45, 0·43, 0·65, and 0·81 (4 *meso*-H), 5·55 (2H) and 6·48 (3H) ($CO{\cdot}CH_2{\cdot}CO_2Me$), 6·13 (3-Me), 6·65, 6·71 and 6·83 (3Me), and 8·33 (m, $3CH_2{\cdot}CH_3$), $\nu_{max.}$ ($CHCl_3$) 1645 and 1725 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 410 (ε 163,000), 510 (8680), 547 (12,400), 571 (8260), and 628 nm (1450), $\lambda_{max.}$ ($CHCl_3$–HCl) 423 (ε 178,000), 560 (12,000), and 605 nm (8260), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 397 (ε 155,000), 499 (11,600), 534 (8990), 568 (5870), and 619 nm (3040), *m/e* 492 (63%) and 450 (100%).

2,4-*Diethyl*-7-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin*-6-*carboxylic Acid* (7b).—2,4-Diethyl-6-methoxycarbonyl-7-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin (165 mg) in pyridine (30 ml) was treated with potassium hydroxide (3 g) in methanol (30 ml). The solution was heated under reflux during 30 min, then left overnight at room temperature, poured into 2N-hydrochloric acid, and neutralised with dilute ammonium hydroxide. The solid was extracted into methylene chloride–pyridine (*ca.* 5 : 1) and the organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was dissolved in 5% w/v sulphuric acid–methanol (250 ml) and set aside in the dark for 16 h. The solution was poured into dilute ammonium hydroxide and neutralised with 2N-hydrochloric acid. The insoluble solid was extracted into methylene chloride (300 ml); the extract was washed with water, dried ($MgSO_4$), and evaporated. The resulting solid crystallised from tetrahydrofuran–benzene to give the *product* (110 mg, 68%) as purple needles, m.p. >310° (Found: C, 71·6; H, 6·7; N, 10·3. $C_{33}H_{36}N_4O_4$ requires C, 71·7; H, 6·6; N, 10·1%), τ ($CF_3{\cdot}CO_2H$) −1·84, −1·14, −0·94, and −0·88 (4 *meso*-H), 5·80 (q) and 8·18 (t) (2Et), 5·88 (5-Me), 5·41 (t), 6·63 (t), and 6·23 (s) ($CH_2{\cdot}CH_2{\cdot}CO_2Me$), and 6·26 (3H) and 6·28 (6H) (3Me), $\lambda_{max.}$ ($CHCl_3$) 406 (ε 187,000), 509 (10,200), 548 (13,600), 575 (8000), and 631 nm (1970), $\lambda_{max.}$ ($CHCl_3$–HCl) 425 (ε 222,000), 563 (13,600), and 610 nm (9550), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 397 (ε 219,000), 497 (17,000), 533 (12,100), 569 (8110), and 621 nm (4910).

2,4-*Diethyl*-7-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin*-6-*carbonyl Chloride*.—The foregoing acid (110 mg) in thionyl chloride (6 ml) was kept at room temperature during 1 h, then evaporated to give the acid chloride as a green residue which was used immediately, without purification.

Treatment of this acid chloride (from 5 mg of the corresponding acid) with dry ethanol gave a solid which was recrystallised from chloroform–methanol to give lustrous purple prisms (3·7 mg, 73%) of 6-ethoxycarbonyl-2,4-diethyl-7-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin (7c), identified by its mass spectrum [*m/e* 580 (M^+)].

2,4-*Diethyl*-6-(*methoxycarbonylacetyl*)-7-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (7d).—To methyl t-butyl malonate (3·8 g) in dry tetrahydrofuran was added sodium hydride (0·52 g), and after the brisk effervescence had subsided the suspension was left at room temperature during 30 min. The foregoing acid chloride (from 110 mg of the carboxylic acid) in methylene chloride (10 ml) was added and the stoppered flask was shaken during 30 min at room temp. The solvent was evaporated off and the residue was partitioned between methylene chloride (100 ml) and 2N-hydrochloric acid (50 ml). The organic layer was washed well with water, dried ($MgSO_4$), and evaporated to dryness, and the residue was chromatographed on grade V alumina (elution first with methylene chloride and then with chloroform). Concentration of the chloroform fraction gave a red gum (the keto-diester) which could not be crystallised and was therefore taken into trifluoroacetic acid (3 ml) and left at room temperature during 20 min. Methylene chloride (50 ml) was added and the solution was washed with aqueous 10% sodium hydrogen carbonate (2 × 50 ml) and water (2 × 50 ml), and then dried ($MgSO_4$). Evaporation gave minute purple prisms which were purified by chromatography on grade V alumina (elution with methylene chloride). The resulting purple solid crystallised from chloroform–petroleum (b.p. 60—80°) to give the *product* (55 mg, 46% based on porphyrin acid) as purple needles, m.p. 282—284° (decomp.). Further recrystallisation gave crystals with m.p. 292—294° (decomp.). These m.p.s were determined by placing the sample on the hot-stage at *ca.* 250° with subsequent rapid heating. If the sample was placed on the block at *ca.* 215° and heated rapidly, it did not melt below 310°. If the sample was placed on the block at 260° it melted immediately (Found: C, 71·0; H, 6·6; N, 9·3. $C_{36}H_{40}N_4O_5$ requires: C, 71·0; H, 6·6; N, 9·2%), τ (0·05M in $CDCl_3$) * −0·46, 0·35, 0·40, and 0·43 (4 *meso*-H), 5·43 (s, disappeared on shaking with NaOD, $CO{\cdot}CH_2{\cdot}CO_2Me$), 5·76 (t), 6·83 (t), and 6·41 (s) ($CH_2{\cdot}CH_2{\cdot}CO_2Me$), *ca.* 6·2 (m), 8·28 (t), and 8·30 (t) (2Et), 6·12 (5-Me), 6·39 ($CO{\cdot}CH_2{\cdot}CO_2Me$), 6·60 (6H) and 6·69 (3H) (3Me), and 14·26br (2NH), $\lambda_{max.}$ ($CHCl_3$) 410 (ε 222,000), 509 (12,100), 544 (15,900), 573 (10,700), and 630 nm (2070), $\lambda_{max.}$ ($CHCl_3$–HCl) 423 (ε 267,000), 560 (18,000), and 606 nm (10,900), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 396 (ε 172,000), 497 (12,900), 533 (9650), 568 (6350), and 620 nm (3770), $\nu_{max.}$ ($CHCl_3$) 1620, 1645, and 1745 cm^{-1}, *m/e* 550 (23%) and 508 (100%).

10-*Methoxyphaeoporphyrin*-a_5 *Dimethyl Ester* (8b).—(a) *Magnesium* 2,4-*diethyl*-6-(2-*methoxycarbonylacetyl*)-7-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin*. The foregoing porphyrin β-keto-ester (27 mg) was treated with an excess of a suspension of n-propoxymagnesium bromide in n-propanol at 75—78° (oil-bath) during 4 h under nitrogen.

* This spectrum was complex owing to the presence of both keto and enol forms.

The solution was evaporated *in vacuo* and the residue was partitioned between ether (30 ml) and water (30 ml). The organic layer was washed with a solution of disodium hydrogen phosphate (2·5 g) and ammonium acetate (2·5 g) in water (25 ml), then with water (2 × 20 ml), dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in methanol (100 ml) and a 0·1M-solution of sodium in methanol (15 ml) was added. After stirring during 21 h in the dark, the solution was poured into methylene chloride (100 ml) and water (100 ml) and the organic phase was washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated to dryness. The residue crystallised from ether–light petroleum (b.p. 60—80°) as a greenish purple powder (20 mg, 71%).

(b) *Side-chain cyclisation.* The foregoing magnesium complex (20 mg) was dissolved in methanol (100 ml) ($\lambda_{max.}$ 418, 554, and 602 nm) and aqueous 10% sodium carbonate (1·6 ml) was added (spectrum changed to 410, 544, and 580 nm), followed by a solution of iodine (50 mg) in methanol (10 ml). After 30 min at room temperature (there was no change in the visible absorption spectrum, $\lambda_{max.}$ 550 and 620 nm, after 5 min) the mixture was poured into methylene chloride (100 ml) and water (100 ml). The organic layer was washed successively with 2N-hydrochloric acid (100 ml), aqueous 4% sodium thiosulphate (100 ml), aqueous 7% sodium hydrogen carbonate (50 ml), and finally water (50 ml), dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on alumina (grade III) (10 g) [elution with methylene chloride–benzene (1 : 1 and then 7 : 3) and finally methylene chloride alone]. The band which was pale green on the column and red-brown in solution was collected initially, and this was shown to be an oxophlorin with an isocyclic ring and a 10-methoxy-group (*m/e* 652) [$\lambda_{max.}$ (CH_2Cl_2) 418, 507, 544, 573, and 640 nm]. The major fraction appeared dark green on the column and red-green in solution. Crystallisation from methylene chloride–methanol gave purple needles (1·4 mg, 7%), m.p. 255—258°, mixed m.p. with authentic 10-methoxyphaeoporphyrin-a_5 dimethyl ester 254—257°; mass spectra of (a) authentic material: *m/e* 637 (10%), 636 (22), 579 (11), 578 (42), 577 (100), 504 (3), 503 (7), 502 (6), 318 (2), and 288·5 (2); (b) synthetic material: *m/e* 637 (17%), 636 (26), 579 (19), 578 (31), 577 (100), 504 (6), 503 (13), 502 (10), 318 (4), and 288·5 (5) (Found: M^+, 636·295; $M^+ - 59$, 577·281. Required: M^+, 636·295; $M^+ - 59$, 577·281).

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