Pyrroles and Related Compounds. Part XXXI.[1] Porphyrin Ketones [2]

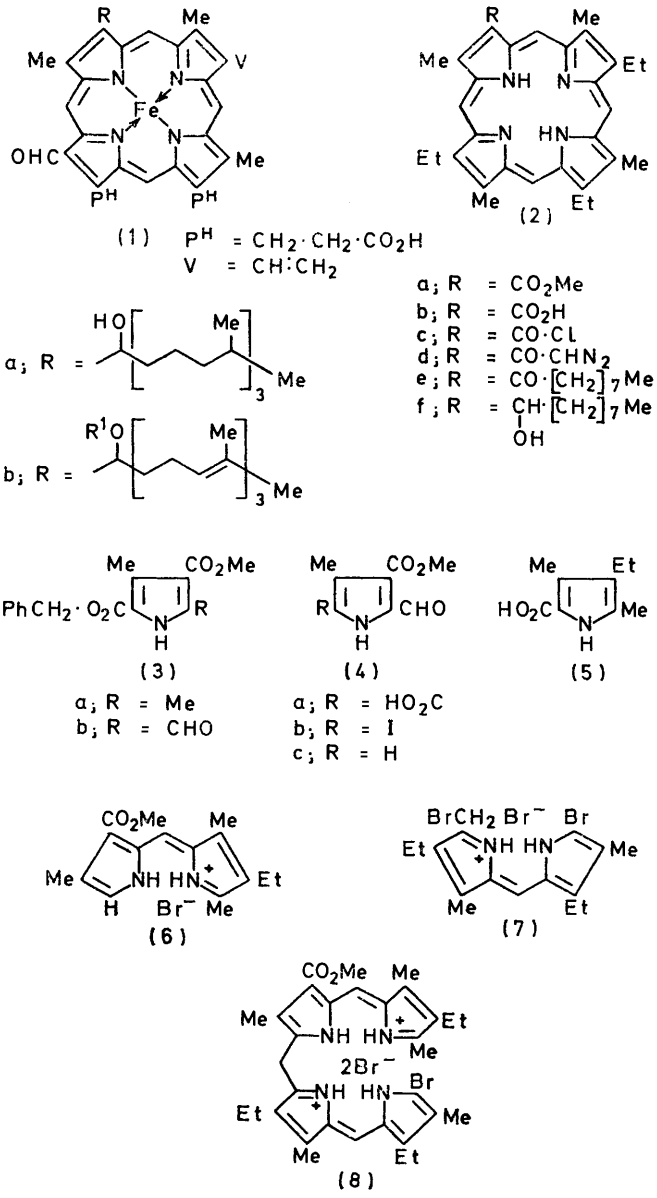
By Raymond V. H. Jones, George W. Kenner,* and Kevin M. Smith, The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

The synthesis of 4,6,8-triethyl-2-methoxycarbonyl-1,3,5,7-tetramethylporphin (2a) *via* the *a,c*-biladiene route is reported. Treatment of the corresponding acid chloride (2c) with diazomethane afforded the diazo-ketone (2d) which furnished the porphyrin ketone (2e) when treated with triheptylborane. With sodium borohydride, the alcohol (2f) was obtained, thereby opening up a definitive route to the hydroxyalkyl type of substituent which is favoured in some proposals for the structure of haem-*a*.

EARLIER parts of this series have described syntheses of porphyrins bearing methoxycarbonyl substituents [3,4] and certain manipulations of this substituent.[4,5] This paper reports further reactions of porphyrin nuclear carboxy-groups aimed at elaboration to give porphyrin ketones; such compounds are potentially important intermediates in the synthesis of haem-*a*, the prosthetic group of cytochrome oxidase. At the time that this work began the structure (1a), with the saturated hydroxyalkyl side-chain at the 2-position,[6] was generally accepted, but since that time, convincing evidence for a *trans,trans*-farnesylethyl substituent with a labile 1'-function [*i.e.* structure (1b)] has been presented.[7]

We decided upon the model methoxycarbonylporphyrin (2) for our experiments, and chose to synthesise it by the *a,c*-biladiene route,[8] since no substantial problems in pyrromethene synthesis were posed by this substituent orientation, and this approach is well suited to the preparation of fairly large quantities of material.

Dichlorination of the pyrrole (3a) with sulphuryl chloride, followed by hydrolysis with aqueous sodium acetate gave an 87% yield of the formylpyrrole (3b), which was hydrogenated over palladised charcoal to furnish the carboxylic acid (4a). Iodinative decarboxylation and catalytic hydrogenation gave the 2-unsubstituted pyrrole (4c) by way of the iodopyrrole (4b). Treatment with kryptopyrrole-2-carboxylic acid (5) in the presence of 48% hydrobromic acid gave an 86% yield of the pyrromethene hydrobromide (6). Alkylation with 5-bromo-5'-bromomethyl-3,4'-diethyl-3',4-dimethylpyrromethene hydrobromide (7) and tin(IV) chloride gave a 90% yield of the required *a,c*-biladiene dihydrobromide (8) after demetallation with hydrobromic acid. After heating the biladiene briefly in refluxing *o*-dichlorobenzene, a 63% yield of the required methoxycarbonylporphyrin was obtained. This compound (2a) was hydrolysed to the corresponding carboxylic acid (2b) with potassium hydroxide in methanol and pyridine, and treatment of (2b) with oxalyl chloride in methylene chloride afforded a high yield of the corresponding acid chloride (2c).



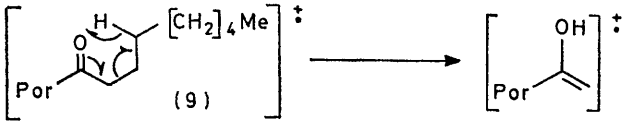
In another porphyrin series, we had carried out preliminary experiments involving reaction of acid chlorides with dialkylcadmium reagents. However,

[1] Part XXX, G. W. Kenner, S. W. McCombie, and K. M. Smith, preceding paper.
[2] Preliminary publication, R. V. H. Jones, G. W. Kenner, T. Lewis, and K. M. Smith, *Chem. and Ind.*, 1971, 129.
[3] T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J.C.S. Perkin I*, 1974, 502.
[4] M. T. Cox, A. H. Jackson, G. W. Kenner, S. W. McCombie, and K. M. Smith, *J.C.S. Perkin I*, 1974, 516.
[5] M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J.C.S. Perkin I*, 1974, 512.
[6] M. Grassl, U. Coy, R. Seyffert, and F. Lynen, *Biochem. Z.*, 1963, **338**, 771.
[7] G. A. Smythe and W. S. Caughey, *Chem. Comm.*, 1970, 809.
[8] R. L. N. Harris, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.* (*C*), 1966, 22; P. Bamfield, R. L. N. Harris, A. W. Johnson, I. T. Kay, and K. W. Shelton, *ibid.*, p. 1436.

this method required [9] rigorous exclusion of oxygen, and even then, on account of the necessarily small scale on which these reactions were performed, small quantities of the esters (produced by oxidation of the reagent) as well as the required alkyl porphyrinyl ketones were obtained. These difficulties were not impossible to overcome, but we were also conscious of the need to use homologues of the natural terpenoid skeleton when preparing the dialkylcadmium reagent, in order to accomplish the synthesis of compounds related to haem-*a* (1). We therefore turned our attention to an approach which could utilise directly the terpenoid skeleton, namely the reaction of diazo-ketones with alkylboranes.[10]

Porphyrin diazo-ketones had not been reported in the literature, but treatment of the acid chloride (2c) with diazomethane (excess) gave a 28% yield of the diazo-ketone (2d); the mass balance for the reaction was made up very largely of the methoxycarbonyl-porphyrin (2a) which could be recycled. The diazo-ketone (2d) was stable in alcoholic solvents and its separation from (2a) was facilitated by its high stability during chromatography on alumina.

A model borane was prepared by hydroboration of hept-1-ene with diborane [11] and the resulting triheptylborane, in excess, was treated with the diazo-ketone (2d) under nitrogen. Exposure of the reaction mixture to oxygen resulted in almost instantaneous bleaching, but if the mixture was treated with aqueous potassium hydroxide before being opened to the atmosphere, a 52% yield * of the n-octyl porphyrinyl ketone (2e) was obtained. The mass spectrum of the ketone was very similar to others that we have recorded,[12] and it showed in addition, fragmentations due to McLafferty rearrangement (9) as well as direct loss of the C_8H_{17} side-chain by α-cleavage.



m/e 590 (100%) *m/e* 492 (20%)

Reduction of the ketone function in (2e) was readily accomplished with sodium borohydride in tetrahydrofuran–t-butyl alcohol, and the formation of the required alcohol (2f) was readily monitored by the change in the visible absorption spectrum from rhodo-type [13] to aetio-type; a 73% yield of the required hydroxyalkyl-porphyrin was obtained in this way.

* We consider that this yield could be improved by more rigorous exclusion of oxygen (note the mention of irreversible bleaching).

[9] T. Lewis, Research Report, Liverpool, 1969.
[10] J. Hooz and S. Linke, *J. Amer. Chem. Soc.*, 1968, **90**, 5936.
[11] H. C. Brown, ' Hydroboration,' Benjamin, New York, 1962; H. C. Brown, ' Boranes in Organic Chemistry,' Cornell University Press, Ithaca, New York, 1972. The diborane was generated externally from sodium borohydride and boron trifluoride–ether complex.
[12] A. H. Jackson, G. W. Kenner, K. M. Smith, R. T. Aplin, H. Budzikiewicz, and C. Djerassi, *Tetrahedron*, 1965, **21**, 2913.

Few porphyrin ketones have heretofore been prepared, and those which have been reported [14] were usually obtained from Friedel–Crafts type acylations of peripherally substituted porphyrins. Earlier work in these laboratories has, however, indicated [15] that such unsubstituted compounds with diverse substituents (which characterise the porphyrins of biological significance) are more difficult to synthesise than those with a corresponding nuclear carboxy-group. We therefore consider that the work reported herein opens up a definitive route to a variety of porphyrin ketones.

EXPERIMENTAL

M.p.s were measured on a Kofler hot-stage apparatus. Neutral alumina (Merck; Brockmann grade III) was used for all chromatographic separations, and reactions were followed by t.l.c. and spectrophotometry as described in earlier parts of this series. Electronic absorption spectra were determined (solutions in methylene chloride) with a Unicam SP 800 spectrophotometer, ^{1}H n.m.r. spectra (in deuteriochloroform with tetramethylsilane as internal standard) with a Varian HA-100 instrument, and mass spectra with either an A.E.I. MS 902 or an A.E.I. MS 12 spectrometer (at 50 μA and 70 eV; direct inlet with source temperature 200—220°).

Pyrroles

Benzyl 5-Formyl-4-methoxycarbonyl-3-methylpyrrole-2-carboxylate (3b).—To a stirred solution of benzyl 4-methoxycarbonyl-3,5-dimethylpyrrole-2-carboxylate (3a) [3] (86·1 g) in acetic acid (600 ml) at 60° was added sulphuryl chloride (80 g, 2·2 equiv.) in glacial acetic acid (150 ml) during 15 min. The mixture was kept at 60° for a further 15 min then left at room temperature for 15 h before being poured into water (3 l). The precipitated dichloromethylpyrrole was filtered off and taken into methylene chloride (600 ml); the solution was washed with aqueous 5% sodium hydrogen carbonate (600 ml), dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in dioxan (400 ml) and added to aqueous sodium acetate trihydrate (5%; 400 ml). The mixture was refluxed during 3 h, left overnight at room temperature, and then extracted with methylene chloride. The extract was washed with water, aqueous 5% sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallised from methylene chloride–petroleum (b.p. 60—80°) to give the *formylpyrrole* (78·6 g, 87%), m.p. 143—145° (Found: C, 63·4; H, 5·0; N, 4·4. $C_{16}H_{15}NO_5$ requires C, 63·7; H, 5·0; N, 4·65%), τ −0·25 (CHO), 2·62 and 4·65 ($PhCH_2$), 6·10 (OMe), and 7·40 (Me).

5-Formyl-4-methoxycarbonyl-3-methylpyrrole-2-carboxylic Acid (4a).—The foregoing pyrrole (60 g) in tetrahydrofuran (400 ml) containing triethylamine (0·5 ml) and 10% palladised charcoal (3 g) was hydrogenated at room temperature and atmospheric pressure until uptake had ceased. Filtration and evaporation gave the *pyrrolecarboxylic acid*

[13] J. E. Falk, ' Porphyrins and Metalloporphyrins,' Elsevier, Amsterdam, 1964, p. 73.
[14] H. Fischer and H. Orth, ' Die Chemie des Pyrrols,' Akademische Verlag, Leipzig, vol. IIi, 1937, p. 293. However, such compounds have recently been obtained directly by ring fabrication using the copper salt cyclisation method: *e.g.* P. S. Clezy and A. J. Liepa, *Austral. J. Chem.*, 1971, **24**, 1027; 1970, **23**, 2477.
[15] M. T. Cox, Ph.D. Thesis, Liverpool, 1969.

(40 g, 95%), m.p. 170—200° (decomp.) (from methylene chloride–n-hexane) (Found: C, 51·0; H, 4·3; N, 6·9. $C_9H_9NO_5$ requires C, 51·2; H, 4·3; N, 6·6%), τ ($CF_3{\cdot}CO_2H$) −0·40 (CHO), 5·83 (OMe), and 7·25 (Me).

Methyl 2-Formyl-5-iodo-4-methylpyrrole-3-carboxylate (4b).—The foregoing pyrrole (17·62 g) in boiling methanol (150 ml) was treated in portions with sodium hydrogen carbonate (22·5 g). The resultant slurry was boiled for 15 min before addition of iodine (21 g). The mixture was refluxed during 10 min, then poured into iced water (1·5 l), and potassium iodide (7·5 g) was added. After warming on the water-bath during 45 min the solution was cooled and the crude product was filtered off. It was stirred with 1% sodium hydroxide solution (1600 ml) and undissolved solid was filtered off. The filtrate was brought to pH 5 with aqueous 10% acetic acid, whereupon the *iodopyrrole* separated as a pale cream solid (12·8 g, 53%), which was used without further purification in subsequent reactions. A sample recrystallised from methylene chloride–n-hexane had m.p. 162—164° (Found: C, 32·5; H, 2·9; N, 4·6. $C_8H_8INO_3$ requires C, 32·7; H, 2·7; N, 4·8%), τ 0·20 (CHO), 6·11 (OMe), and 7·73 (Me).

Methyl 2-Formyl-4-methylpyrrole-3-carboxylate (4c).—The foregoing iodopyrrole (10 g) in methanol (100 ml) containing anhydrous sodium acetate (7·7 g) and Adams platinum oxide (200 mg) was hydrogenated at room temperature and atmospheric pressure until uptake ceased. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in methylene chloride and water, and the organic phase was washed with more water before being dried ($MgSO_4$) and evaporated to dryness. The residue (4·7 g, 83%) was recrystallised from methylene chloride–n-hexane to give the *5-unsubstituted pyrrole*, m.p. 147—149° (Found: C, 57·8; H, 5·5; N, 8·1. $C_8H_9NO_3$ requires C, 57·5; H, 5·4; N, 8·4%), τ −0·16 (CHO), 3·15 (d, *J* 3 Hz, α-H), 6·16 (OMe), and 7·70 (Me).

Pyrromethene

4′-Ethyl-3-methoxycarbonyl-3′,4,5′-trimethylpyrromethene Hydrobromide (6).—To a stirred solution of 4-ethyl-3,5-dimethylpyrrole-2-carboxylic acid (13·2 g) (obtained by hydrogenation of the corresponding benzyl 2-carboxylate over palladised charcoal) and methyl 2-formyl-4-methylpyrrole-3-carboxylate (13·2 g) at 0° in dry methanol (500 ml) was added aqueous 48% hydrobromic acid (33 ml). The mixture was kept at 0° with stirring for 30 min, after which the *pyrromethene* hydrobromide (13·3 g, 48%) was filtered off and dried. In experiments on a smaller scale (1 g of each pyrrole) yields of pyrromethene between 83 and 86% were obtained. Material recrystallised from methylene chloride–n-hexane had m.p. 163—165° (Found: C, 54·1; H, 6·0; N, 7·6. $C_{16}H_{21}BrN_2O_2$ requires C, 54·4; H, 5·9; N, 7·9%), τ 1·55 (methine), 2·65 (d, *J* 3 Hz, 5-H), 6·07 (OMe), 7·21 (5′-Me), 7·52 (q) and 8·89 (t) (Et), and 7·62 and 7·66 (3′- and 4-Me).

Porphyrins

4,6,8-Triethyl-2-methoxycarbonyl-1,3,5,7-tetramethylporphin (2a).—To a solution of 4′-ethyl-3-methoxycarbonyl-3′,4,5′-trimethylpyrromethene hydrobromide (4·81 g) and 5-bromo-5′-bromomethyl-3,4′-diethyl-3′,4-dimethylpyrromethene hydrobromide[16] (6·56 g) in methylene chloride (630 ml) was added tin(IV) chloride (12 ml). The mixture was stirred at room temperature during 2 h and the solvent was then evaporated off. A mixture of 20% hydrobromic acid (650 ml; 48% aqueous) and methanol was added to the residue, which was then left at room temperature for 15 min. The *a,c*-biladiene dihydrobromide was filtered off, washed with a little methanol and dry ether, and dried under vacuum (yield 9·2 g, 90%); τ ($CDCl_3$) −3·8br (4NH), 1·50 and 2·86 (*a,c*-H), 4·79 (CH_2), 6·13 (OMe), 7·21 (1′-Me), 7·1—7·8 and 8·5—9·3 (3Et), and 7·67, 7·75, 7·79, and 7·94 (4Me). This hydrobromide (4·45 g) was ground into a fine powder and added to refluxing *o*-dichlorobenzene (800 ml). The mixture was refluxed during 15 min, cooled, and then evaporated under vacuum. The residue was chromatographed on alumina. Elution with methylene chloride followed by crystallisation from methylene chloride–methanol gave the *porphyrin* (1·9 g, 63%), m.p. >300° (Found: C, 75·4; H, 7·2; N, 11·1. $C_{32}H_{36}N_4O_2$ requires C, 75·6; H, 7·1; N, 11·0%), τ ($CF_3{\cdot}CO_2H$) (*meso*-proton signals obscured by solvent) 5·41 (OMe), 5·93 (1-Me), 5·77 (q) and 8·19 (t) (3Et), and 6·30 (3-, 5-, and 7-Me), $\lambda_{max.}$ (CH_2Cl_2) 405 (ε 192,000), 510 (9900), 550 (15,000), 576 (8500), and 635 nm (1600), $\lambda_{max.}$ (CH_2Cl_2–$CF_3{\cdot}CO_2H$) 424 (ε 210,000), 564 (12,800), and 613 nm (11,000), *m/e* 508 (100%).

4,6,8-Triethyl-1,3,5,7-tetramethylporphin-2-carboxylic Acid (2b).—The foregoing porphyrin (1·31 g) in pyridine (650 ml) and 10% w/v potassium hydroxide in methanol (650 ml) were heated under reflux during 3·5 h (visible spectrum rhodo ⟶ aetio). The mixture was diluted with water (4 l), neutralised with 2N-hydrochloric acid, and then extracted with methylene chloride–pyridine (10 : 1). The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness, and the residue was crystallised from pyridine–methanol to give the *porphyrincarboxylic acid* (1·22 g, 95%), m.p. >300° (Found: C, 75·1; H, 7·3; N, 11·5. $C_{31}H_{34}N_4O_2$ requires C, 75·3; H, 6·9; N, 11·3%), $\lambda_{max.}$ (pyridine) 408 (ε 189,000), 509 (12,000), 547 (13,900), 573 (8400), and 631 nm (1900), $\lambda_{max.}$ (CH_2Cl_2–$CF_3{\cdot}CO_2H$) 425 (ε 217,000), 559 (13,800), and 609 nm (10,900), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 396 (ε 175,000), 500 (13,000), 536 (10,000), 569 (7000), and 621 nm (3300), *m/e* 494 (95%), 450 (100).

2-Diazoacetyl-4,6,8-triethyl-1,3,5,7-tetramethylporphin (2d).—The foregoing porphyrin (0·41 g) in oxalyl chloride (5 ml) and methylene chloride (10 ml) was stirred at room temperature during 4 h. The solvents were evaporated off and dry benzene (5 ml) was added and removed; this procedure was repeated several times to remove residual oxalyl chloride. The residue was taken up in methylene chloride and added dropwise, during 30 min, to a stirred solution of diazomethane in ether [prepared by distilling a mixture of *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (7·0 g), ether (100 ml), potassium hydroxide (2·0 g), water (4 ml), and bis-(2-methoxyethyl) ether (12 ml) from a bath at 60°]. The red solution was then stirred at room temperature during 1 h, kept at 0° for 6 h, and evaporated to dryness. The residue was chromatographed on alumina (elution with methylene chloride). The major fraction (250 mg) was the methyl ester of the starting material, but a second band gave the *diazo-ketone* (122 mg, 28%), m.p. >315° (Found: C, 74·0; H, 6·9; N, 16·0. $C_{32}H_{34}N_6O$ requires C, 74·1; H, 6·6; N, 16·2%), insufficiently soluble for its n.m.r. spectrum to be measured satisfactorily; $\lambda_{max.}$ (CH_2Cl_2) 407 (ε 166,000), 507 (9800), 545 (11,500), 572 (9100), and 619sh nm (1200), $\nu_{max.}$ (CH_2Cl_2) 2100 cm^{-1} ($C{:}\overset{+}{N}{:}\overset{-}{N}$).

[16] K. M. Smith, *J.C.S. Perkin I*, 1972, 1471.

4,6,8-*Triethyl*-1,3,5,7-*tetramethyl*-2-*nonanoylporphin* (2e).—Triheptylborane was prepared in distilled tetrahydrofuran (14·0 ml) under nitrogen, from hept-1-ene (1·1 ml) and diborane generated externally from sodium borohydride (33 mg) in dry bis-(2-methoxyethyl) ether (0·5 ml) and boron trifluoride–ether complex (3·5 ml; excess) and carried through the olefin solution in a stream of dry nitrogen. The borane solution was then added in one portion to a solution of the foregoing porphyrin (48 mg) in dry chloroform (10 ml) under nitrogen. After stirring during 3 h, under nitrogen, 2N-potassium hydroxide (5 ml) was added and the stirring was continued for 10 min before removal of the organic phase from the apparatus. It was washed with water (100 ml), dried ($MgSO_4$), and evaporated, and the red residue was chromatographed on alumina [elution initially with petroleum (b.p. 60—80°), then with benzene, and finally with methylene chloride]. The last eluates contained the porphyrin; crystallisation from methylene chloride–methanol to give the *porphyrin ketone* (29 mg, 52%), m.p. 232—233° (Found: C, 79·0; H, 8·8; N, 9·3. $C_{39}H_{50}N_4O$ requires C, 79·3; H, 8·5; N, 9·5%), τ −0·50 and 0·21 (3H) (4 *meso*-H), 5·8—6·3 and 8·25 (3Et), 6·37, 6·46, 6·57, and 6·63 (4Me), *ca.* 8·0 ($CO{\cdot}CH_2$), 8·5—9·2 ($[CH_2]_6Me$), and 13·8br (2NH), $\lambda_{max.}$ (CH_2Cl_2) 405 (ε 170,000), 506 (9300), 544 (12,600), 574 (8300), and 621sh nm (1300), $\nu_{max.}$ (CH_2Cl_2) 1655 cm^{-1} (C:O), *m/e* 590 (100%), 492 (20), and 477 (25).

4,6,8-*Triethyl*-2-(1-*hydroxynonyl*)-1,3,5,7-*tetramethylporphin* (2f).—The foregoing porphyrin (27 mg) in tetrahydrofuran (3 ml) and dry t-butyl alcohol (20 ml) was treated with sodium borohydride (50 mg) and the mixture was heated under reflux for 2 h, during which time the visible absorption spectrum changed from rhodo- to aetiotype. The solvents were evaporated off, methylene chloride (50 ml) was added, and the mixture was poured into water (100 ml). The porphyrin was extracted with methylene chloride; the extract was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on alumina. Elution with methylene chloride gave a small amount of the starting ketone, but elution with chloroform containing 2% ethanol gave the *porphyrin* (21·1 mg, 73%), m.p. 217—218° (from methylene chloride–methanol) (Found: C, 79·3; H, 9·0; N, 9·3. $C_{39}H_{52}N_4O$ requires C, 79·0; H, 8·8; N, 9·45%), $\lambda_{max.}$ (CH_2Cl_2) 397 (ε 170,000), 497 (13,000), 531 (9300), 567 (6300), and 621 nm (3550), *m/e* 592 (34%) and 574 (100).

We thank Drs. R. Haley and T. Lewis for exploratory experiments, and Dr. P. A. Gunn for experimental assistance.

[3/1973 *Received*, 25*th October*, 1973]