# Stepwise Synthesis of Unsymmetrically Substituted Porphyrins: Isocoproporphyrin

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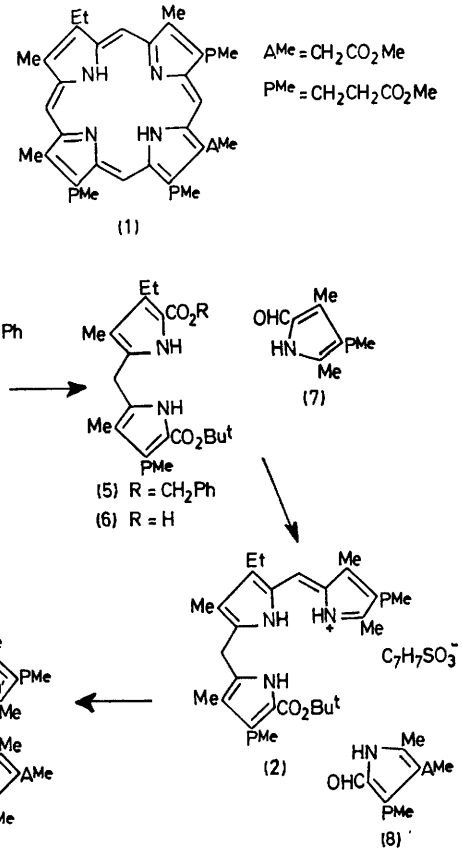
*Summary* A new, general, stepwise porphyrin synthesis in which tripyrrenes (**2**) and 1′,8′-dimethyl-*a*,*c*-biladienes (**9**) are crystalline and fully characterised intermediates is exemplified in the first total synthesis of isocoproporphyrin tetramethyl ester (**1**).

CONTEMPORARY methods for synthesis of porphyrins usually proceed either by direct condensation of two dipyrrolic intermediates or else by formation of an open-chain tetrapyrrole from two such units, followed by cyclisation.[1] These methods have served well, even from the early days of porphyrin synthesis, but it is often necessary to take advantage of symmetry elements within the target molecules in order to avoid the formation of porphyrin mixtures. Apart from a single, very limited example,[2] methods for porphyrin synthesis employing the truly stepwise progression through pyrrole, dipyrrole, tripyrrole, to tetrapyrrole have not been developed. We now report such an approach, exemplifying the method by the typical synthesis of isocoproporphyrin tetramethyl ester (**1**), an irregularly substituted porphyrin,[3] the free acid of which is found in the faeces of patients suffering from symptomatic cutaneous hepatic porphyria, and in rats with porphyria due to hexachlorobenzene poisoning.[4,5]

1′,8′-Dimethyl-*a*,*c*-biladiene salts can be cyclised[6,7] in good yields using an oxidative procedure with copper(II) salts. Hitherto, the *a*,*c*-biladienes have usually been prepared by condensation of 2 mol. of a 2-formyl-5-methylpyrrole with 1 mol. of a 5,5′-di-unsubstituted pyrromethane; symmetry restrictions imposed by this have resulted in the use of 1′,8′-dimethyl-*b*-bilenes for synthesis of unsymmetrically substituted porphyrins by the 'copper salt' method.[8]

Our modification employs tripyrrenes [*e.g.* (**2**)][9] as discrete intermediates. Thus, condensation of the 2-acetoxymethylpyrrole (**3**)† with the 2-unsubstituted pyrrole (**4**) in acetic acid containing a catalytic quantity of toluene-*p*-sulphonic acid[10] gave the pyrromethane (**5**) (72% yield) which was debenzylated by hydrogenation over palladised charcoal to furnish the half-acid (**6**)† (95%). Treatment with the 2-formyl-5-methylpyrrole (**7**) in the presence of toluene-*p*-sulphonic acid gave the key tripyrrene intermediate as its toluene-*p*-sulphonate (**2**)† (80%). Further




treatment with a second, *different*, 2-formyl-5-methylpyrrole (**8**)† in trifluoroacetic acid and hydrobromic acid afforded the unsymmetrically substituted 1′,8′-dimethyl-

† New compound which gave a satisfactory elemental analysis, and mass, visible (where appropriate), and n.m.r. spectra compatible with the formulation shown.

*a,c*-biladiene di-hydrobromide (**9**)† (89%). Cyclisation with copper(II) acetate in dimethylformamide furnished the copper(II) complex of (**1**) which was demetallated in trifluoroacetic acid containing 5% sulphuric acid to give isocoproporphyrin tetramethyl ester (**1**)† (30%), m.p. 182—183 °C (corr.).‡

The product (**1**) was satisfactorily identified by t.l.c., high-pressure liquid chromatography, m.p., and mixed m.p. with authentic isocoproporphyrin tetramethyl ester, and possessed a n.m.r. spectrum ($CDCl_3$) virtually identical with that published,[4] thereby confirming the proposed[5] structure.

Generality of the new approach has been tested by the syntheses of rhodoporphyrin-XV dimethyl ester and 2,4,7-triethyl-6-methoxycarbonyl-1,3,5,8-tetramethylporphin.

We thank Dr. G. H. Elder for supplying a sample of natural isocoproporphyrin tetramethyl ester, m.p. 180—182 °C (corr.),‡ and Professor A. H. Jackson for helpful discussions concerning the progress of his independent synthesis of (**1**).

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‡ Evacuated capillary; on a Kofler hot-stage only partial melting (*ca.* 175—177 °C) was observed with both the synthetic and natural samples.

[1] For a recent review see A. H. Jackson and K. M. Smith, in 'Total Synthesis of Natural Products', vol. 1, ed. J. W. ApSimon, Wiley, New York, 1973, p. 143.

[2] R. P. Evstigneeva, A. F. Mironov, and L. I. Fleiderman, *Doklady Akad. Nauk S.S.S.R.*, 1973, **210**, 1090; A. F. Mironov, M. A. Kulish, V. V. Kobak, B. V. Rozynov, and R. P. Evstigneeva, *Zhur. obshchei Khim.*, 1974, **44**, 1407.

[3] The structure originally proposed[4] for isocoproporphyrin has recently been revised.[5] For a synthesis of the incorrectly assigned compound see P. S. Clezy and V. Diakiw, *Austral. J. Chem.*, 1973, **26**, 2697.

[4] G. H. Elder, *Biochem. J.*, 1972, **126**, 877.

[5] M. S. Stoll, G. H. Elder, D. E. Games, P. O'Hanlon, D. S. Millington, and A. H. Jackson, *Biochem. J.*, 1973, **131**, 429.

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[7] P. S. Clezy and A. J. Liepa, *Austral. J. Chem.*, 1971, **24**, 1027.

[8] J. M. Conlon, J. A. Elix, G. I. Feutrill, A. W. Johnson, M. W. Roomi, and J. Whelan, *J.C.S. Perkin I*, 1974, 713; P. S. Clezy, A. J. Liepa, and N. W. Webb, *Austral. J. Chem.*, 1972, **25**, 1991; see also refs. 6 and 7.

[9] In another context we have already demonstrated that the sensitive 1′-t-butyl ester remains intact during the acid catalysed pyrromethene formation, A. H. Jackson, G. W. Kenner, and K. M. Smith, *J. Chem. Soc.* (*C*), 1971, 502.

[10] J. A. S. Cavaleiro, A. M. d'A. Rocha Gonsalves, G. W. Kenner, and K. M. Smith, *J.C.S. Perkin I*, 1973, 2471.