HETEROCYCLES, Vol. 7, No. 1, 1977

SYNTHESES AND PROPERTIES OF MESO-METHYL PORPHYRINS AND CHLORINS

Michael J. Bushell, Brian Evans, George W. Kenner,
and Kevin M. Smith†
The Robert Robinson Laboratories, University of Liverpool,
P.O. Box 147, Liverpool L69 3BX, England

Good overall yields of *meso*-methylporphyrins (**3**) or chlorins (**1**,**2**) are obtained by reduction of the appropriate formyl derivative, followed by acetylation with acetic anhydride in pyridine of the resulting hydroxymethyl compound and reduction with Pd-C/H_2 or $NaBH_4$.

In order to clarify certain problems arising from our studies on the *Chlorobium* chlorophylls,[1] and to facilitate the development of a formal total synthesis of one of these pigments,[2] we needed to develop an efficient route to model *meso*-methylchlorins (e.g. **1**,**2**). Such compounds could, in principle, be approached either by reduction of a *meso*-methylporphyrin (**3**) or by regioselective methylation of a chlorin (e.g. **4**). In this Communication we describe efficient routes to compounds of type (**1**), (**2**), and (**3**).

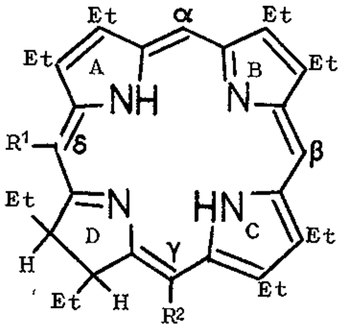
Available routes to simple *meso*-methylporphyrins (other than those through total synthesis[3]) are either limited in generality[4] or else give unacceptably low overall yields.[5] However, the

Dedicated to Professor R.B. Woodward on the anniversary of his 60th birthday.

earlier work[5a] had clearly shown that the most promising approach to *meso*-methylporphyrins (3) was that *via* the corresponding *meso*-formylporphyrin. Thus, reduction of nickel(II) *meso*-formylaetioporphyrin-I (5; R=Me)[6] at -78° with lithium aluminium hydride (LAH) gave a 75% yield of the nickel(II) *meso*-methylporphyrin (6; R=Me) which was demetallated to give the required product (3; R=Me) in excellent yield. This method, however, was not reproducible. Moreover, at temperatures above -78° the *meso*-substituent was lost altogether, and LAH reduction of the zinc(II) or copper(II) complexes of *meso*-formylaetioporphyrin-I at -78° gave the metal complex of the corresponding hydroxymethylporphyrin (7; R=Me). In the octaethylporphyrin series, LAH reduction of the *meso*-formyl nickel(II) complex (5; R=Et) gave the hydroxymethylporphyrin complex, and complete loss of the *meso* substituent was observed in many reactions, presumably owing to the increased steric congestion in this series.

The most efficient general route to *meso*-methylporphyrins (3) to be discovered was as follows. $NaBH_4$ reduction of the *meso*-formylporphyrins (8) gave 85-90% yields of the hydroxymethylporphyrins (7) which were chelated with zinc(II)[7] and then treated with acetic anhydride/pyridine. The resulting acetoxymethylporphyrins (9) were then hydrogenated over palladised charcoal to give, after demetallation, a 80% overall yield [from (7)] of the required *meso*-methylporphyrins (3).

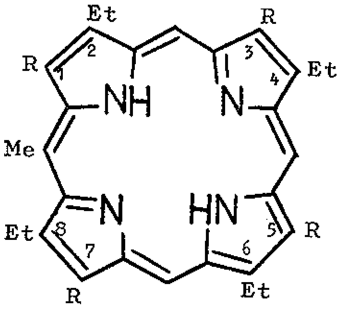
Unexpected lability in the acetoxymethylporphyrins (9) was observed. For example, if attempts were made to crystallise the compounds (9) from MeOH then the corresponding *meso*-methoxymethylporphyrins (10) were isolated in very high yield. The same compounds could be obtained from the *meso*-methylporphyrin zinc(II) complex by treatment with thallium(III) trifluoroacetate, followed



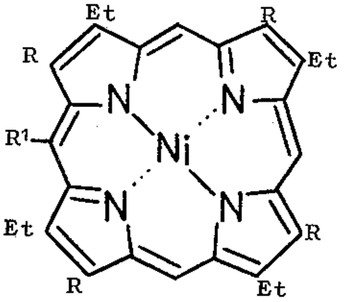
(1) R^1 =Me; R^2 =H

(2) R^1 = R^2 = Me

(4) R^1 = R^2 = H

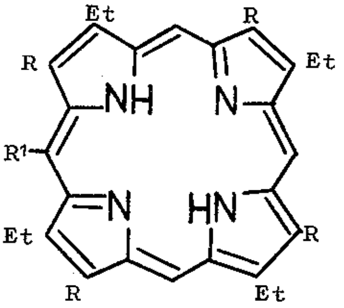


(3)



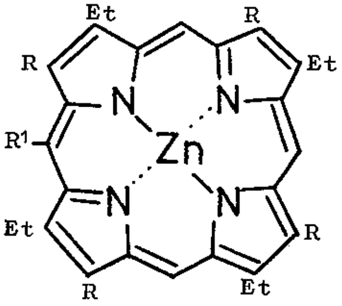
(5) R^1 = CHO

(6) R^1 = Me



(7) R^1 = CH_2OH

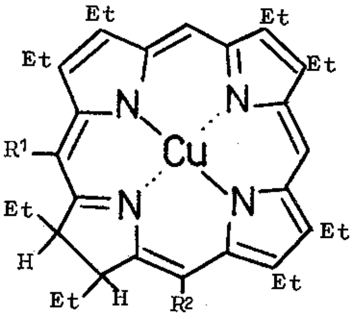
(8) R^1 = CHO



(9) R^1 = CH_2OAc

(10) R^1 = CH_2OMe

(R = Me and/or Et throughout)



(11) R^1 = R^2 = H

(12) R^1 = R^2 = CHO

(13) R^1 = CHO; R^2 = H

(14) R^1 = CH_2OH; R^2 = H

(15) R^1 = CH_2OAc; R^2 = H

(16) R^1 = Me; R^2 = H

by an aqueous work-up (furnishing the hydroxymethyl compound) and then treatment first with acetic anhydride/pyridine, and then MeOH.

Fischer has claimed[8] that reduction of γ-phylloporphyrin-XV haemin (using Na/amyl alcohol) gives specifically the 7,8-dihydro analogue, presumably because reduction in ring D relieves steric compression between the γ-methyl group and the 7-propionate. Na/amyl alcohol reduction[9] of the haemin from meso-methylporphyrin (3; R=Et) gave only trans-octaethylchlorin (4) after demetallation, showing not only that the methyl group in a more sterically hindered environment is liable to cleavage, but also that the 6-unsubstituted position in Fischer's example is an important factor.

Owing to our failure to reduce the porphyrin (3; R=Et) to the required chlorin (1), we next investigated the indirect methylation of the copper(II) complex (11) of trans-octaethylchlorin.[9] Prolonged treatment of (11) with $POCl_3$/DMF under Vilsmeier conditions gave, after hydrolysis, a separable mixture (preparative TLC) of the copper(II) complexes of the $\gamma\delta$-diformylchlorin (12), the δ-monoformylchlorin (13) and their corresponding porphyrins. Briefer treatment with $POCl_3$/DMF gave a good yield of the mono-formylchlorin copper(II) complex (13). Reduction with $NaBH_4$ gave the hydroxymethylchlorin (14) which was acetylated with acetic anhydride/pyridine to furnish the acetoxymethylchlorin (15); catalytic hydrogenation (palladised charcoal) or reduction with $NaBH_4$ (less efficient) gave the δ-methylchlorin complex (16) which was demetallated with H_2SO_4/CF_3CO_2H to give the required chlorin (1). The NMR spectrum of (1) showed a sharp singlet for the δ-methyl at τ 6.0. The free-base (1) was only slightly susceptible to photo-oxidation (see Refs. 1 and 10), but the zinc(II) complex was smoothly cleaved to give acetylbilinone zinc(II) complex.

The γδ-dimethylchlorin (2) was prepared by submitting the γδ-diformyl copper(II) complex (12) to a similar series of transformations as described for the mono-substituted series. The γδ-dimethylchlorin was shown (Figure 1) to be extremely susceptible to photooxidation, even as the free base. The absence of isosbestic points in Figure 1 after the first few scans indicates that the ring-opened product suffers further degradation to give as yet undefined products.

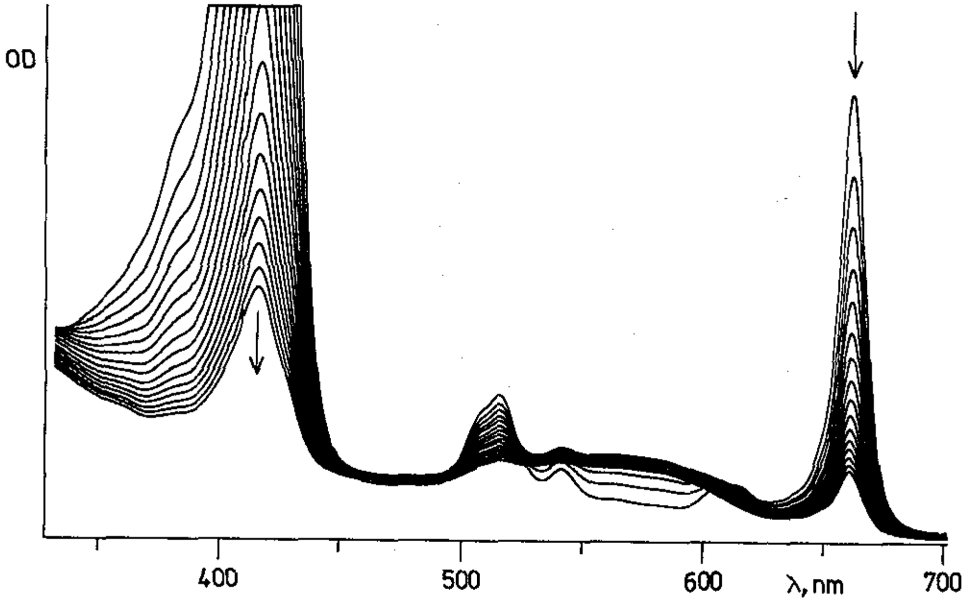


Figure 1: Repeated-scan visible absorption spectra showing the photo-oxidative cleavage (in daylight) of the dimethyl chlorin (2) in benzene solution.

REFERENCES AND NOTES

1 G.W. Kenner, J. Rimmer, K.M. Smith, and J.F. Unsworth, Phil. Trans. Roy. Soc., London, 273B, 255 (1976).

2 M.J. Bushell, work in progress.

3 E.g. A.H. Jackson and K.M. Smith, in "Total Synthesis of Natural Products", Vol. 1, ed. J.W. ApSimon, Wiley, New York, 1973, p. 181, 197.

4 R. Grigg, G. Shelton, A. Sweeney, and A.W. Johnson, *J. Chem. Soc.*, *Perkin Trans. I*, 1789 (1972).

5 a) O. Somaya, Dissertation, Braunschweig, 1967. b) D.P. Arnold, A.W. Johnson, and M. Winter, *J. Chem. Soc.*, *Chem. Comm.*, 797 (1976).

6 H.H. Inhoffen, J.-H. Fuhrhop, H. Voigt, and H. Brockmann Jr., *Annalen*, **695**, 133 (1966); A.W. Johnson and D. Oldfield, *J. Chem. Soc. C*, 794 (1966).

7 The zinc, which was inserted at this stage owing to the lability of the acetoxymethylporphyrin, is required in order to prevent porphyrinogen formation during the subsequent catalytic hydrogenation; we have found that most metalloporphyrins do not form porphyrinogens when subjected to catalytic hydrogenation.

8 H. Fischer and G.A. von Kemnitz, *Z. Physiol. Chem.*, **96**, 309 (1915); A. Treibs and E. Wiedemann, *Annalen*, **471**, 146 (1929); H. Fischer and F. Balaz, *Ibid.*, **553**, 166 (1942); H. Fisher and A. Stern, "Die Chemie des Pyrrols", Vol. IIii, Akademische Verlag., Leipzig, 1940.

9 H.W. Whitlock, R. Hanauer, M.Y. Oester, and B.K. Bower, *J. Amer. Chem. Soc.*, **91**, 7485 (1969); U. Eisner, A. Lichtarowicz, and R.P. Linstead, *J. Chem. Soc.*, 733 (1957).

10 J.-H. Fuhrhop, P.K.W. Wasser, J. Subramanian, and U. Schrader, *Annalen*, 1450 (1974).

Received, 26th March, 1977