Coproporphyrin-III from Protoporphyrin-IX

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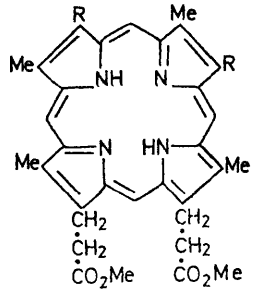
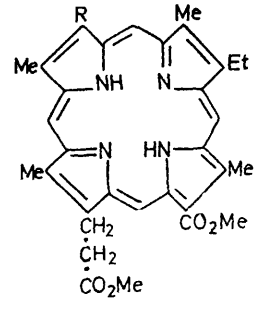
Summary Manipulation of the vinyl side-chains of the readily available protoporphyrin-IX dimethyl ester (**2**) allows the synthesis of coproporphyrin-III tetramethyl ester (**1**) in an overall yield of 37%.

WE have recently reported[1] new syntheses of coproporphyrin-III, a macrocycle of great biological significance, since its porphyrinogen is one of the biosynthetic precursors of protoporphyrin-IX. These syntheses from monopyrrolic precursors were necessarily complex, and we now report an efficient route to coproporphyrin-III tetramethyl ester (**1**) using protoporphyrin-IX dimethyl ester (**2**) as the starting material. In view of the ready accessibility of protoporphyrin-IX either from haemin[2] or haematoporphyrin[3] (both of which are commercially available), this work provides an efficient route to large quantities of coproporphyrin-III.

In the course of studies designed to accomplish the chemical modification and protection of the sensitive vinyl substituents of porphyrins from natural sources, we found that treatment of protoporphyrin-IX dimethyl ester (**2**) with 3 equiv.† of thallium(III) nitrate in methanol afforded[4] the bis-acetal (**3**),‡ m.p. 230° (decomp.), in 92% yield. Hydrolysis with aqueous acid, followed by borohydride reduction gave the known[3] bis-(2-hydroxyethyl)porphyrin (**4**)§ in an overall yield of 70% from protoporphyrin-IX dimethyl ester (**2**). This sequence of reactions was further exemplified by the transformation of 2-vinylrhodoporphyrin-XV dimethyl ester (**5**) (obtained[5] by the degradation of phaeophytin-*a*) into the corresponding 2-hydroxyethyl derivative (**6**) in 77% yield. This anti-Markownikoff hydration of vinyl substituents had thus achieved our original aim of vinyl protection, because we had earlier shown[3] that treatment of the bis-(2-hydroxyethyl)porphyrin (**4**) with thionyl chloride and dimethylformamide affords the bis-(2-chloroethyl)porphyrin (**7**), the zinc chelate of which was converted efficiently into protoporphyrin-IX with t-butoxide in t-butyl alcohol.





(**1**) R = $CH_2 \cdot CH_2 \cdot CO_2Me$
(**2**) R = $CH{:}CH_2$
(**3**) R = $CH_2 \cdot CH(OMe)_2$
(**4**) R = $CH_2 \cdot CH_2 \cdot OH$
(**7**) R = $CH_2 \cdot CH_2Cl$
(**8**) R = $CH_2 \cdot CH_2Br$
(**9**) R = $CH_2 \cdot CH_2 \cdot CN$
(**10**) R = $CH{:}CH \cdot CO_2H$
(**11**) R = CHO

(**5**) R = $CH{:}CH_2$
(**6**) R = $CH_2 \cdot CH_2 \cdot OH$

† We have established that the first equiv. of the reagent chelates with the macrocycle; results of experiments with protoporphyrin-IX dimethyl ester and 2 equiv. of the reagent will be described in the full paper.

‡ New compound which gave a satisfactory elemental analysis, and electronic absorption, mass, and n.m.r. spectra compatible with the structure shown.

§ The identity of this substance was established by comparison of t.l.c. and spectroscopic properties with an authentic sample, and by mixed m.p.

We extended our investigations to other substituents which might undergo elimination to give vinyl groups, and found that treatment of the bis-(2-hydroxyethyl)porphyrin (**4**) with thionyl bromide gave a 76% yield of the corresponding bis-(2-bromoethyl)porphyrin (**8**), ‡ m.p. 216—217°; elimination of hydrogen bromide from the zinc chelate of this compound could offer no great advantage over the bis-(2-chloroethyl) substance, but with sodium cyanide in *N*-methyl-2-pyrrolidone, (**8**) gave a 78% yield of the bis-(2-cyanoethyl)porphyrin (**9**),‡ m.p. 202—205° (with rapid heating). Treatment with saturated methanolic hydrogen chloride gave coproporphyrin-III tetramethyl ester (**1**)§ in 88% yield, and in an overall yield of 37% from protoporphyrin-IX dimethyl ester (**2**).

The transformations described above have the merit that they would allow the preparation of radiochemically labelled coproporphyrin-III from protoporphyrin-IX. The latter compound is readily available from enzymic incubations of labelled δ-aminolaevulinic acid or porphobilinogen, but it is not possible to obtain large quantities of coproporphyrin-III because the pool of this intermediate (as the porphyrinogen) in the biosynthetic system is normally small; however, protoporphyrin-IX and haemin are the end-points of porphyrin biosynthesis in many organisms and cell-free preparations (*e.g. Euglena gracilis*,[6] chicken erythrocytes[7]).

The bis-(acrylic acid)porphyrin (**10**) was synthesised[8] in 1960 by the Knoevenagel condensation of the bis-(formyl)-porphyrin (**11**) with malonic acid; the yields in this series of transformations from protoporphyrin-IX were, however, prohibitively low for it to be used generally as an avenue to coproporphyrin-III [which is accessible simply by reduction of the acrylic residues in (**10**)]. This approach was, however, used recently by Battersby and his co-workers[9] in the synthesis of specifically labelled material required for their biosynthetic studies.

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