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SYNTHESIS OF N-MONO-ALKYLPORPHYRINS

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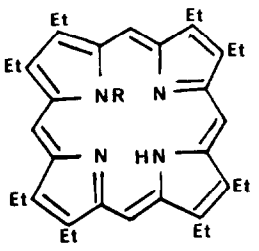
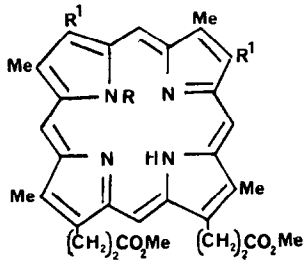
Abstract: Direct alkylation of porphyrins with alkyliodides in presence of acetic acid affords exclusively the N-mono-alkyl derivatives.

N-Substituted porphyrins are fascinating compounds from a chemical point of view, especially in the ways in which they differ from the parent porphyrins.[1] Interest in these compounds has recently been greatly stimulated by the discovery that the so-called "green pigments" occasionally found in liver are N-substituted derivatives of haem.[2] They are formed by suicide inactivation of the haem of cytochrome-P_{450} by a wide variety of drugs, and other substances. Their physiological role is so far uncertain, but the simple N-mono-alkyl derivatives of protoporphyrin-IX have been shown to be powerful inhibitors of ferrochelatase (the enzyme which inserts iron into protoporphyrin to make haem) both in mammalian[3] and plant systems.[4] The natural green pigments are, however, only formed in very small amounts and for this reason there is a considerable interest in their synthesis.

The direct N-alkylation of porphyrins has been achieved by a variety of alkylating agents, of which methyl fluorosulphonate is probably the most effective.[2] However, the yields are poor because all these methods result in the formation of N,N-dialkylated and N,N,N-trialkylated porphyrins, as well as the desired monoalkyl products, and these must be separated chromatographically. In order to obviate the formation of the unwanted di- and tri-N-alkylated porphyrins we took advantage of the high basicity[5] of N-alkylporphyrins (first pKa ~11) compared with N-unsubstituted porphyrins (first pKa ~7). We reasoned that in presence of a weak acid the N-alkylporphyrins would be converted to their monocations, thus protecting them from further alkylations, whilst the N-unsubstituted porphyrins would not be appreciably protonated. Acetic acid proved to be the most suitable acid for this purpose, and on heating octaethyl porphyrin (1a) with methyl iodide in chloroform containing 5% acetic acid for 5 hr N-methyloctaethylporphyrin (1b) was formed in ca. 60% yield (virtually quantitative allowing for octaethylporphyrin recovered after chromatography). The direct N-methylation of protoporphyrin-IX dimethylester (2a), mesoporphyrin-IX dimethylester (3a), and of coproporphyrin-III tetramethylester (4a) has also been achieved in a similar fashion; in each case the yield of N-methylporphyrins (2b), (3b) and (4b) was



1a) R=H 1b) R=Me
1c) R=Et 1d) R=CH_2CH_2OH



2) R^1=CH=CH_2 a) R=H
3) R^1=Et b) R=Me
4) R^1=CH_2CO_2Me c) R=CH_2CH_2OH

over 90%, although mixtures of isomers were, of course, formed (for convenience only one isomer is shown in structures (2b), (3b) and (4b)). Meso-Tetraphenyl porphyrin can be methylated in excellent yield in this manner, and octaethyl porphyrin has now also been converted to its N-ethyl (1c) and N-(2-hydroxyethyl) (1d) derivatives, showing that the method is not confined to N-methylporphyrins. The preparation of the N-hydroxyethyl-porphyrin is of special interest because the "green pigment" derived from ethylene is a mixture of N-(2-hydroxyethyl) protoporphyrins (2c).[6] N-Methyloctaethylchlorin has also been prepared by this method in ca. 60% yield but other by-products were also formed.

Further applications of this simple, direct, method of mono-N-alkylation of porphyrins are being investigated.

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