Total Synthesis of an *N*-Methylporphyrin

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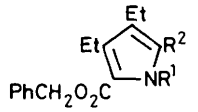
The first ring synthesis of an *N*-methylporphyrin starting from an *N*-methylpyrrole, and using the MacDonald route has been achieved.

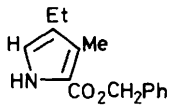
In recent years a number of *N*-substituted protoporphyrins have been isolated from mammalian liver where they arise by suicide inactivation of cytochrome P_{450}, caused by olefinic or acetylenic drugs, and other materials.[1,2] *N*-Methyl derivatives of protoporphyrin-IX have also been isolated and these are of particular pharmacological interest because they are strong inhibitors of the enzyme ferrochelatase.[1,2] *N*-Methylated porphyrins can be synthesised from the parent porphyrins by direct alkylation with methyl iodide, or better, methyl fluorosulphonate,[3] and poly-*N*-alkylation can be prevented by carrying out the alkylations in the presence of acetic acid.[4] However, in the case of unsymmetrical porphyrins like protoporphyrin-IX mixtures of all four *N*-monomethyl isomers are obtained. These can be separated by careful h.p.l.c.[5] but the separation of substantial amounts of material is tedious and time-consuming. For these reasons, we sought an alternative route to isomerically pure *N*-alkylporphyrins by total synthesis from *N*-substituted pyrroles. Earlier workers had little success with this approach,[6] although we have shown that copolymerisation of an acetoxymethylpyrrole and its *N*-methyl analogue afforded moderate yields of the *N*-substituted porphyrin.[7] Attempts to synthesise an *N*-methylporphyrin by the *a,c*-biladiene route were unsuccessful owing to expulsion of the methyl group in the final ring-closure step; this was not unexpected, bearing in mind the relatively high temperatures (145—150 °C in dimethylformamide) required for the cyclisation in the presence of copper salts.

Application of the MacDonald method has now led to the successful synthesis of the model *N*-methylporphyrin (**5**) from pyrrolic intermediates.[8] Thus the pyrrole (**1a**) was methylated by treatment with methyl iodide in dimethyl sulphoxide in the presence of base, and then treatment of the *N*-methylpyrrole (**1b**) with lead tetra-acetate afforded the acetoxymethylpyrrole (**1c**) in excellent overall yield. Toluene-*p*-sulphonic

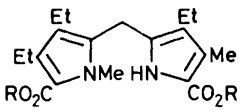


(1)

a; R^1 = H, R^2 = Me
b; R^1 = R^2 = Me
c; R^1 = Me, R^2 = CH_2OAc

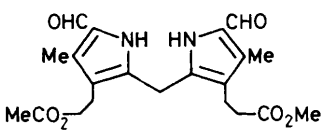


(2)

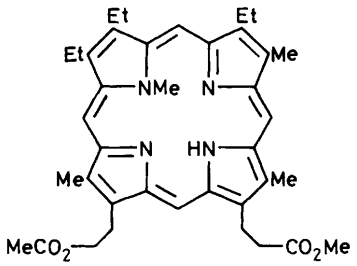


(3)

a; R = CH_2Ph
b; R = H



(4)



(5)

acid, or clay,[9] catalysed the condensation with the α-free pyrrole (**2**) to give the pyrromethane (**3a**) which was hydrogenolysed to afford the corresponding di-acid (**3b**). Condensation of the latter with the diformylpyrromethane[10] (**4**) in the presence of toluene-*p*-sulphonic acid in dichloromethane[11] followed by aeration in the presence of zinc acetate and re-esterification then afforded the desired *N*-methylporphyrin (**5**) in 25% yield. (A small amount of coproporphyrin-II tetramethylester was also found as a by-product, owing to self-condensation of the diformylpyrromethane.) The structure of the *N*-methylporphyrin (**5**) was confirmed by its spectroscopic behaviour[3b] *e.g.* the formation of mono- and di-cationic species on treatment with acid was shown by n.m.r. spectrometry (*N*-methyl resonance at δ −4.9) and by mass spectrometry and elemental analysis.

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