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THE meso-HYDROXYLATION AND meso-BENZOXYLATION OF PYRIDINE OCTAETHYLHAEMOCHROME

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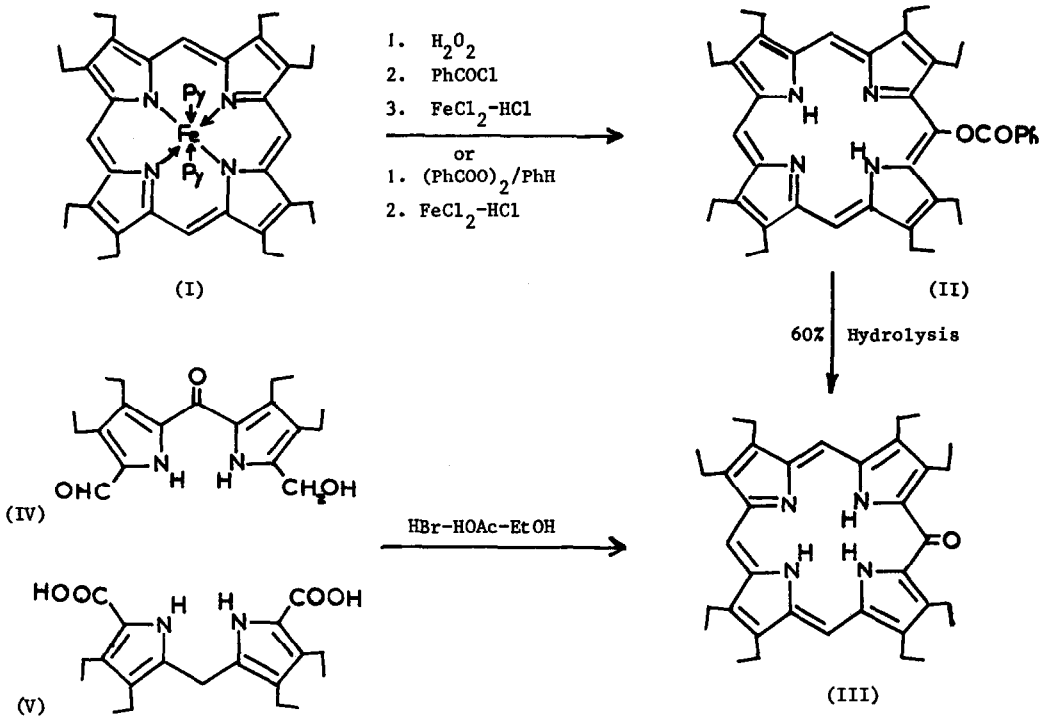
Our studies on the meso-substitution of porphyrins and related compounds[1] have been extended to the biologically significant example of hydroxylation. Earlier workers[2] examined the direct hydroxylation of pyridine haemochromes, a route thought to be analogous to that followed in porphyrin catabolism[3], but the structures assigned to the products were difficult to confirm by the methods then available (~1940). Recently oxophlorins have been prepared by ring-synthesis[4,5]: the spectra of these compounds resemble those of the oxyporphyrins made earlier by direct substitution, although important differences in detail have been noted[5]. A proper comparison has not been possible because the same system has not been approached by both routes: such an example is now provided.

Treatment of pyridine octaethylhaemochrome (I) with hydrogen peroxide (1 mol.) in pyridine (50°, 15 mins., N_2) gave an olive-green solution which, on addition of benzoylchloride, slowly became red again. Demetallation and chromatography gave 5-benzoxyoctaethylporphyrin (II, 75%), dark purple prisms m.p. 267 - 268° from methanol-chloroform. The same compound was obtained when (I) was treated with benzoyl peroxide in benzene, followed by demetallation. The visible spectrum was marginally of the aetio type[6], but the N.M.R. spectrum confirmed that meso-substitution had occurred ($CDCl_3$, τ -0.17 (2 protons), 0.01 (1 proton)). Alkaline hydrolysis (N_2) gave dark blue crystals of octaethyloxophlorin (III), m.p. 255° (decomp.) when rapidly heated.[7] The N.M.R. spectrum in trifluoroacetic acid had τ -0.36 (singlet, 2 protons); -0.09 (singlet, 1 proton); 5.93, 6.00 (overlapping quartets, 16 protons); 8.20, 8.40 (overlapping triplets, 24 protons); and 12.20, 13.03 (broad singlets, 2 protons each) consistent with the diprotonated form of structure (III). The visible spectrum in chloroform showed three bands and an inflection (λ_{max} 404.5, 547 (infl.), 586.5, 632.5 mμ ε 144,000, 4,800, 9,200 and 16,300 respectively).

The oxophlorin (III) was synthesised using a slightly modified MacDonald synthesis. 5,5'-Dimethyl-3,3',4,4'-tetraethyldipyrrylketone was treated at 2-3° in ethereal tetrahydrofuran with

ethereal t-butylhypochlorite (4.4 mol.) to give, after hydrolysis in situ, 5-formyl-5'-hydroxymethyl-3,3',4,4'-tetraethyldipyrrylketone (IV, 50%) m.p. 171 - 172° (decomp.) which, on acid-catalysed condensation with 3,3',4,4'-tetraethyldipyrrylmethane 5,5'-dicarboxylic acid[8] (V, 1 mol.) under nitrogen gave octaethyloxophlorin (30%) identical with that obtained by direct attack on the pyridine haemochrome.



All new compounds reported here gave satisfactory elemental analyses. The oxophlorin (III) was analysed both by combustion analysis and by precision mass measurement of the molecular ion.

This is the first example in which the meso-substituted formulation of the product of direct substitution of an octaalkylporphyrin (which previously rested heavily on N.M.R. evidence)[1] has been confirmed by its ring synthesis. We regard the initial step in the direct substitution as a free radical process involving the hydroxyl radical, which is known to possess marked electrophilic character.[9] The reaction is thus rather analogous to aromatic hydroxylation using Fenton's reagent,[10] but here the Fe(II) → Fe(III) change occurs within the heteroaromatic system.

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