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ON THE MODIFYING INFLUENCE OF SIX-MEMBERED CARBOCYCLIC RINGS IN PORPHYRIN CYCLIZATIONS: SYNTHESIS OF MESO, β -PROPANOPORPHYRINS

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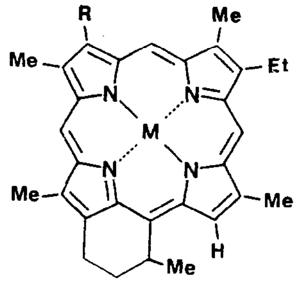
Abstract: Porphyrins with six-membered exocyclic rings have been synthesised by the MacDonald condensation and the a,c-biladiene route.

Although the presence of metalloporphyrins in oil shales was recognized more than fifty years ago[1], it has only been recently that individual porphyrins have been isolated and characterized[2]. A rich diversity of petroporphyrin structures have now been identified by proton NMR spectroscopy[2] and mass spectrometry. However, precise structural assignments cannot always be made and there is a need for synthetic samples[3] to provide unambiguous confirmation of proposed structures. Many of these geoporphyrins bear five-membered exocyclic rings. In 1984, Maxwell and coworkers reported the characterization of two vanadyl porphyrins, <u>1a</u> and <u>1b</u> (M = VO), with six-membered exocyclic rings from Serpiano oil shale((Triassic, Switzerland). The origin of these compounds is unknown, although it seems likely that they are related to the 15,17-butanoporphyrins also present in this oil shale[5]. A third porphyrin, isolated from Gilsonite bitumen as a nickel complex, was tentatively assigned[5b] as the meso, β -propanoporphyrin <u>2a</u> or <u>2b</u>. However, later studies[2b] demonstrated that this assignment was in error.

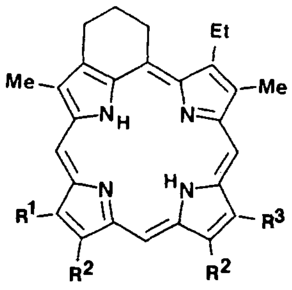
We have developed a new approach to the synthesis of porphyrins with six-membered exocyclic rings. Recently we reported[6] that 7-hydroxy-4,5,6,7-tetrahydroindoles <u>4a</u> and <u>4b</u> cyclotetramerize under acidic conditions to give the novel tetrapropanoporphyrins <u>3a</u> and <u>3b</u>. An earlier study by Flaugh and Rapoport[7] had demonstrated that five-membered carbocyclic rings severely inhibit porphyrin formation. This does not appear to be a problem with six-membered carbocyclic rings but we should note that the efficiency of these porphyrin cyclizations is likely to be modified by a variety of additional factors. Porphyrins <u>3a</u> and <u>3b</u> were probably formed via porphyrinogen (hexahydroporphyrin) intermediates and the earler study[6] only demonstrated that the six-membered exocyclic rings do not interfere with the formation of nonplanar porphyrinogen structures. All stepwise porphyrin syntheses involve intermediary structures (either isolated tetrapyrroles or putative intermediates) at a higher oxidation level and this may modify the influence of the carbocyclic ring.[8]



M = 2H

1 a. R = Et

b. R = Me

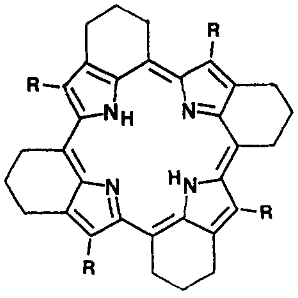


2 a. R^1 = Et R^2 = R^3 = Me

b. R^1 = R^2 = Me R^3 = Et

c. R^1 = R^3 = Me R^2 = P

d. R^1 = R^3 = Me R^2 = Et

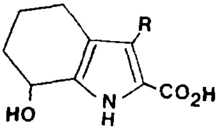


3 a. R = Me

b. R = Et

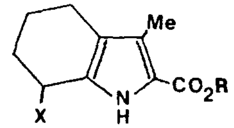
P = $CH_2CH_2CO_2Me$

Bz = CH_2Ph



4 a. R = Me

b. R = Et



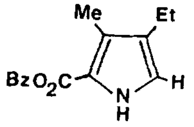
5 R = Bz

a. X = H b. X = OAc

c. X = OEt d. X = OMe

9 R = ^{t}Bu

a. X = H b. X = OH



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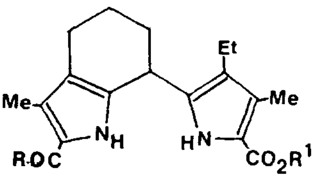

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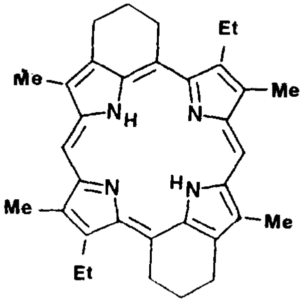
a. R = OBz R^1 = Bz

b. R = OH R^1 = H

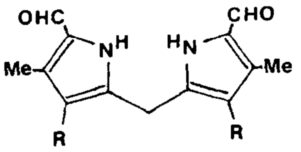
c. R = O^{t}Bu R = Bz

d. R = H R^1 = Bz

e. R = R^1 = H



10



8 a. R = P b. R = Et

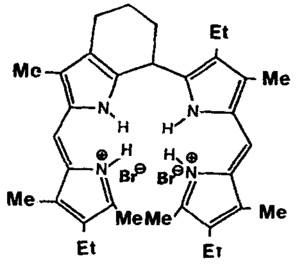


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Figure 1: Partial 360 MHz Proton NMR Spectrum of 7a in $CDCl_3$

Our first concern was to develop a synthesis of the hitherto unknown 7-pyrrolyltetrahydroindole system (see structure 7). Reaction of the tetrahydroindole benzyl ester 5a with lead tetraacetate in acetic acid afforded the 7-acetoxy derivative 5b in 86% yield, after crystallization from petroleum ether. Tetrahydroindole 5b readily underwent solvolysis in hot ethanol or methanol to give the corresponding ethers 5c and 5d, respectively. The acetoxy compound 5b condensed with the α-free pyrrole 6[9] in the presence of p-toluenesulfonic acid to give the required pyrrolyltetrahydroindole 7a in 73% yield. The proton NMR spectrum for 7a showed a multiplet at 4.07 ppm corresponding to the methine unit bridging the two pyrrole rings. The signals corresponding to the $-C\underline{H}_2-$ protons of the two benzyl esters varied greatly in appearance, depending on concentration and solvent. In dilute $CDCl_3$ solution (figure 1), one of the $-CH_2-$ units resolved into an AB quartet, while the other appeared as a singlet.

The dipyrrole 7a was used to investigate the efficiency of porphyrin cyclization by the MacDonald route[10]. Hydrogenolysis of 7a over palladium-charcoal gave the corresponding diacid 7b and subsequent condensation with the diformyldipyrrylmethane 8a[11] in the presence of p-toluenesulfonic acid gave the meso, β -propanoporphyrin 2c in 28% yield: m.p. 246-246.5°C; UV (CH_2Cl_2) λ_{max} nm ($\log_{10}\varepsilon$) 404(5.22, 503(4.17), 537(3.65), 572(3.77), 625(3.31); FAB-MS m/e 607 ($[M+H]^+$). Similarly, condensation of 7b with dipyrrylmethane 8b afforded the related porphyrin 2d in 21% yield.

The presence of the six-membered carbocyclic ring does not appear to significantly inhibit porphyrin condensation under these conditions. The study was therefore extended to the synthesis of a centrosymmetric porphyrin 10 with two six-membered exocyclic rings. The tert-butyl ester 9a reacted with lead tetraacetate to give an unstable acetoxy derivative which readily underwent hydrolysis to form the 7-hydroxytetrahydroindole 9b. Condensation of 9b with 6 under acidic conditions gave the mixed ester dipyrrole 7c. Treatment with trifluoroacetic acid, followed by extraction and formylation with p-nitrobenzoyl chloride-dimethylformamide, yielded the dipyrrole aldehyde 7d. Subsequent hydrogenolysis over palladium-charcoal gave the carboxylic acid 7e. Dipyrrole 7e underwent selfcondensation in the presence of p-toluenesulfonic acid to give porphyrin 10 in 25% yield. UV (CH_2Cl_2) λ_{max} nm ($\log_{10}\varepsilon$) 408(5.33), 508 (4.17), 574(3.75), 627(3.17).

One of the most widely used approaches to porphyrin synthesis involves the oxidative cyclization of a,c-biladienes[12] (e.g. 11). The dicarboxylic acid 7b was treated with two equivalents of 4-ethyl-3,5-dimethylpyrrole-2-carboxaldehyde in the presence of hydrobromic acid, and the required a,c-biladiene dihydrobromide 11 was isolated in 83% yield. Cyclization of 11 with copper (II) chloride in dimethylformamide gave very poor yields ($< 2\%$) of impure porphyrin. When the cyclization was carried out with copper (II) acetate in pyridine, pure porphyrin 2d was isolated in 3% yield, after demetallation with 5% sulfuric acid-trifluoroacetic acid. Zinc acetate-silver iodate[13] mediated cyclization gave superior results and 2d was obtained in 12% yield. None-the-less, typical yields for a,c-biladiene cyclizations are in the range of 25-35% and the carbocyclic ring clearly exerts a deleterious effect.

The conformation of the tetrapyrrolic intermediates presumably determines the efficiency of porphyrin cyclizations. When the six-membered ring links two pyrrole units via an sp^3 hybridized carbon, good yields of porphyrins result. (e.g. the MacDonald condensation). a,c-Biladienes are believed to undergo cyclization via fully conjugated bilatriene intermediates[9]. In this case, where the pyrrole units are fully conjugated, the six-membered ring appears to exert a malign influence on porphyrin formation.[14]

Acknowledgements

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