

THE SYNTHESIS OF PORPHYRINS VIA DIPYRRROMETHENES

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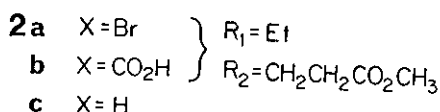
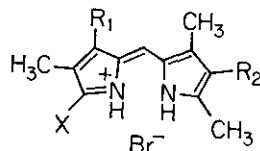
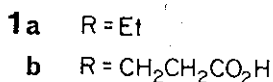
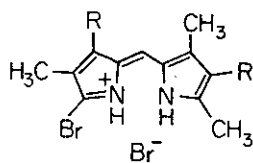
Dedicated to Professor R. B. Woodward on the occasion of his
sixtieth birthday

The Fischer porphyrin synthesis from dipyrromethene precursors has been improved. The same conditions (bromine in refluxing anhydrous formic acid) which give enhanced yields of centrosymmetric porphyrins from 5-bromo-5'-methyl-2,2'-dipyrromethenes also give substantially higher yields of porphyrins derived from readily available 5,5'-dimethyl and 5,5'-dibromo dipyrromethenes.

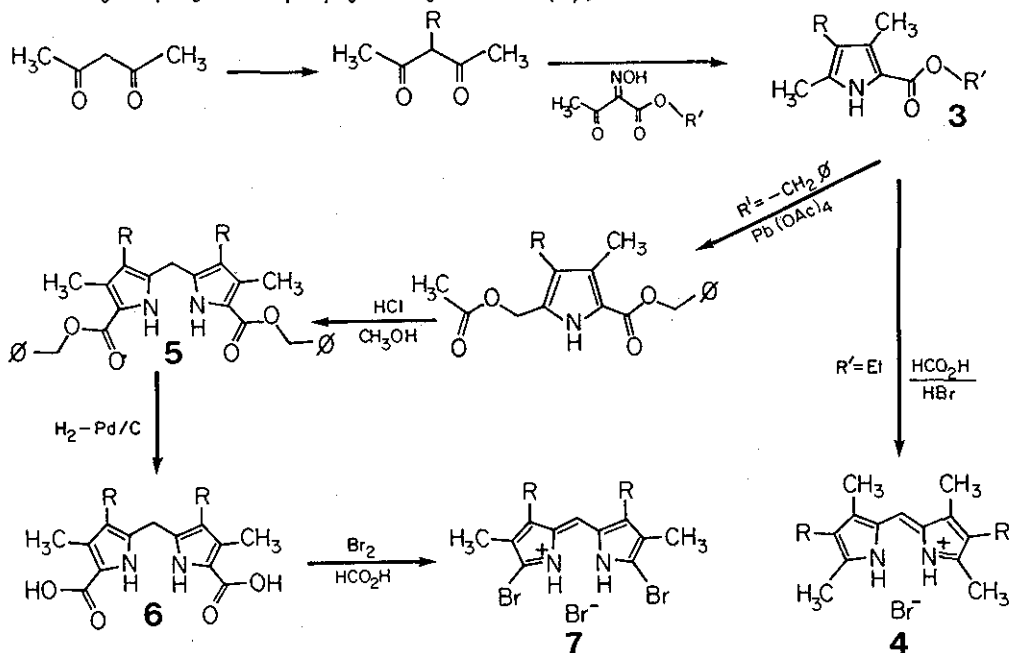
Dipyrromethenes have been employed as intermediates in porphyrin synthesis since the pioneering and epic work of Hans Fischer in the 1920's. In general the yields of porphyrins obtained by such methods are usually low (1), but Smith (2) recently reported that 5-methyl-5'-bromodipyrromethenium perbromides (**1**) gave high yields (40-60%) of type I porphyrins¹ when refluxed in anhydrous formic acid, and further noted that small amounts of water partially diverted the reaction to biliverdins of head-to-head symmetry.

This synthesis can be generalised for the synthesis of porphyrins with C_{2h} symmetry, and for example it was found (3) that the carboxydipyrromethene (**2b**), which is more conveniently prepared than the unsubstituted analog (**2c**), was brominatively decarboxylated and cyclised, without isolation, to porphyrin. We have found that in our hands such reactions proceed with yields of about 40%.

¹Assuming equivalent nitrogen atoms and a planar porphyrin then the four porphyrins which contain two different substituents, one on each pyrrole ring, have the following point group symmetries. Type I, C_{4h} ; II, D_{2h} ; III, C_s ; IV, C_{2v} . See R. Bonnett, *Nomenclature, The Porphyrins*, ed. D. Dolphin, Academic Press, in press, Volume I - Structure and Synthesis - Part A, Chapter 1.



It is the purpose of this communication to demonstrate that these reactions can be extended to use other classes of dipyrromethenes commonly used by Fischer (1), namely the reaction between 5,5'-dibromodipyrromethenes (**7**) with 5,5'-dimethyldipyrromethenes (**4**), to give porphyrins of type II, III, or IV symmetry. It should be noted that only one of the two components need be symmetric to ensure a unique product. This approach to porphyrin synthesis is especially useful in that both precursors are readily available from the 5-methylpyrrole-2-carboxylate esters (**3**), commonly employed in porphyrin syntheses (4), as outlined in Scheme 1.



SCHEME 1

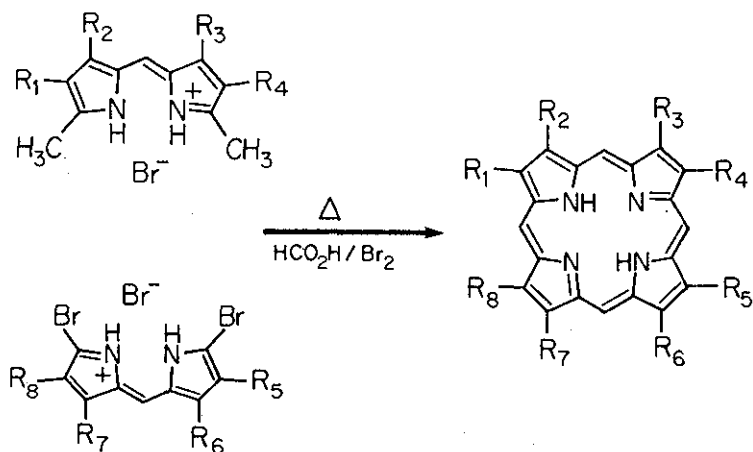
When symmetric, the 5,5'-dimethyldipyrromethenes are readily available from the corresponding 2-ethoxycarbonyl-5-methylpyrroles by refluxing in a mixture of formic and hydrobromic acids for several hours (5). This hydrolyzes the ester, and after decarboxylation the α -free pyrrole is formylated in a rate-limiting step, after which the formylpyrrole is consumed, as fast as it is formed, to give the dipyrromethene.

The dibromodipyrromethenes (7) require several steps in their synthesis and are best prepared via the benzyl esters of the dipyrromethane (5) which upon catalytic hydrogenolysis provides the sensitive 5,5'-dicarboxydipyrromethane 6 in a relatively stable form. Addition of this diacid to an excess of bromine in formic acid ensures rapid oxidation before acid-catalysed rearrangement or decomposition (6) can occur. The products (which may separate as perbromide salts) can be converted to the bromide salt by treatment with cyclohexene in dichloromethane.

The condensation step is carried out in a manner similar to that reported above (2) except that only *one* equivalent of bromine in formic acid is used. After two hours reflux only a small amount of porphyrin is observed, but when the mixture is boiled down to dryness porphyrin is formed (from a presumed porphodimethene precursor) in yields from 25-40%.

The porphyrins listed in Table 1 have been prepared by the above methods and the yields are quoted for the crystalline products. All the porphyrins gave satisfactory elemental analyses and they were shown to be isomerically pure by ^1H and ^{13}C NMR spectroscopy. Detailed experimental data are given for the synthesis of coproporphyrin IV which is typical of the syntheses required for the other porphyrins.

Table 1



<u>R₁</u>	<u>R₂</u>	<u>R₃</u>	<u>R₄</u>	<u>R₅</u>	<u>R₆</u>	<u>R₇</u>	<u>R₈</u>	<u>%</u>	<u>Trivial Name</u>
Me	Me	Me	Me	Me	pMe	pMe	Me	29.6%	Dimethyl Deutero IX
Et	Me	Me	Et	Me	pMe	pMe	Me	39.3%	Mesoporphyrin XIII
p ^H	Me	Me	p ^H	Me	pMe	pMe	Me	39.5%	Coproporphyrin IV
n-C ₁₂ H ₂₅	Me	Me	n-C ₁₂ H ₂₅	Me	pMe	pMe	Me	28%	
Et	Et	Et	Et	Me	pMe	pMe	Me	38.2%	
Et	Me	Me	Et	Me	Et	Et	Me	38.8%*	Aetioporphyrin IV
Me	Et	Et	Me	Me	Et	Et	Me	32.7%	Aetioporphyrin II
p ^H	Me	Me	p ^H	Me	Et	Et	Me	33.7%	Mesoporphyrin XII
Me	Me	Me	Me	Me	Et	Et	Me	30.4%	

* ex perbromide

Experimental4,4'-Di-(2-carboxylethyl)-3,3',5,5'-tetramethyl-2,2'-dipyrromethenium bromide (7) (4, R=CH₂CH₂CO₂H)

Ethyl 3-(2-methoxycarbonylethyl)-2,4-dimethylpyrrole-5-carboxylate (8) (3, R= -CH₂CH₂CO₂Me; R'=Et) (50.7 g, 0.20 mole) was warmed on a steambath in formic acid (105 ml, 98-100%). Concentrated HBr (27 ml, 48%) was added in one portion to the hot solution and heating was continued for 80 minutes until gas evolution (carbon dioxide and formate esters) ceased. On standing at room temperature overnight dense chunky solid, resembling sodium dichromate in appearance, crystallised. The product was collected by filtration, washed with methanol and air dried to give as a first crop 33.5 g (79%).

Evaporation of the filtrates and addition of methanol gave second and third crops (4.5 and 2.5 g) which were largely the methyl esters. These were dissolved in hot methanol (200 ml) and treated with HBr (3.0 ml, 48%) and methyl orthoformate (30 ml). After standing for 48 hours the pure dimethyl ester (3.8 g) was collected along with a second crop (1.4 g) from the filtrates.

5,5'-Dibromo-3,3'-di-(2-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrromethenium bromide (7, R= -CH₂CH₂CO₂Me)

The dipyrromethane dibenzyl ester (5, R= -CH₂CH₂CO₂Me) (5) (30.85 g, 0.05 mole) and 10% Pd/c (1.54 g) were stirred under hydrogen (1 atm, room temperature) in tetrahydrofuran (500 ml) containing triethylamine (20 drops). The reaction was stopped when hydrogen uptake ceased by which time the dicarboxylic acid 6 (R= -CH₂CH₂CO₂Me) had crystallised out. The solids were collected by filtration, washed with a little tetrahydrofuran and dried on the Büchner. The filtrates were evaporated to dryness.

A solution of bromine (35.2 g) in formic acid (300 ml, 98-100%) was prepared. 100 ml of this solution was added in one portion to the evaporated residues and the mixture swirled until solution was complete. The solution was added to the original bromine/formic acid solution and the combined mixture was efficiently stirred magnetically at room temperature, while the filter cake from the hydrogenation was added in several portions. The reaction mixture was stirred briefly and filtered to remove the hydrogenation catalyst which was rinsed with formic acid (100 ml).

The combined filtrates were evaporated *in vacuo* until the product crystallised out. The mixture was then diluted with methanol in ether (1:7, 100 ml). The product was collected by filtration to give the pure product (16.3 g). The filtered catalyst entrained considerable product, which was dissolved in methylene dichloride (150 ml), filtered, concentrated and isolated as above to give a second crop of pure material (7.9 g). Concentration of the combined filtrates gave a third crop of 2.9 g. Total yield 27.1 g (92.6%). $^1\text{H NMR}_{\text{CDCl}_3}$ 2.07 (s, 6H), 2.64 (t, J=7Hz, 4H), 3.20 (t, J=7Hz, 4H), 3.63 (s, 6H), 7.68 (s, 1H), 14.09 (br, 2H). $^{13}\text{C NMR}_{\text{CDCl}_3}$ 172.89, 146.59, 132.48, 127.86, 127.07, 122.56, 52.04, 34.11, 20.53, 9.90. An analytical sample was recrystallised from dichloromethane-ethyl acetate. Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{Br}_3\text{N}_2\text{O}_4$: C, 39.14; H, 3.98; N, 4.80; Br, 41.11. Found: C, 39.10; H, 3.88; N, 4.60; Br, 41.33. On heating, the sample began darkening above 180° and was black by 190°, and tarred at ~ 195°.

Coproporphyrin IV tetramethyl ester (9)

4,4'-Di-(2-carboxyethyl)-3,3',5,5'-tetramethyl-2,2'-dipyrrromethenium bromide (431.7 mg, 1.02 mmole) and 5,5'-dibromo-3,3'-di-(2-methoxycarbonyl-ethyl)-4,4'-dimethyl-2,2'-dipyrrromethenium bromide (581.7 mg, 1.00 mmole)

were suspended in formic acid (5.0 ml, 98-100%) and treated with bromine (51.5 μ l). The mixture was refluxed in an oil bath for 2.5 hours. The solvent was then allowed to boil off over a period of 30 minutes during which time the porphyrin was formed.

To the residue was added methanol (25 ml) and concentrated sulfuric acid (2 ml), followed after ten minutes by trimethyl orthoformate (10 ml). After standing overnight, protected from moisture, the reaction mixture was diluted with dichloromethane, and then water. The organic phase was separated, basified with an excess of triethylamine and taken down to dryness *in vacuo*.

The crude product was chromatographed over silica gel (Woelm, activity I, 30 g) using 2% (v/v) methyl acetate in dichloromethane and then 5% methanol plus 2% methyl acetate in dichloromethane. A dark non-fluorescent forerun was discarded. The porphyrin-containing fractions were diluted with methanol (50 ml) and evaporated *in vacuo* until the product crystallised as sparkling purple blades, 281 mg (39.5%). Mp. sintered at 174° and melted at 178°. lit. 173° (9).

Acknowledgements

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