

SYNTHESIS OF UROPORPHYRIN-III, AND RELATED HEPTA- AND PENTA-CARBOXYLIC PORPHYRINS
BY MODIFICATIONS OF THE MACDONALD METHOD

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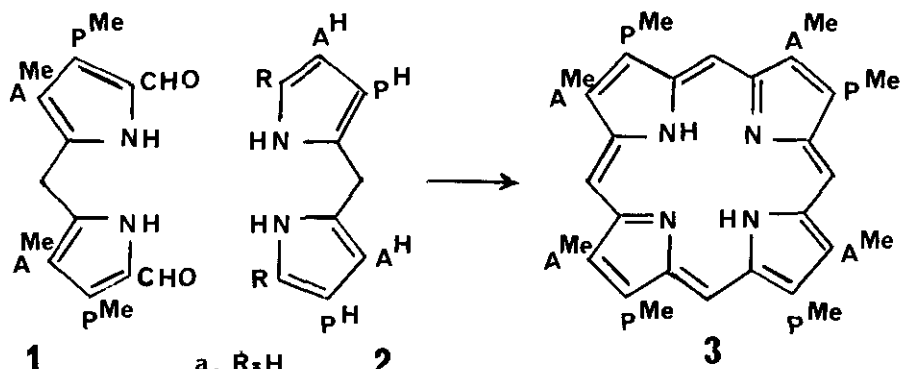
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Abstract - A modification of the MacDonald route has been developed in which all four pyrrole units of uroporphyrin-III have been derived from the same conveniently prepared starting pyrrole. Related henta- and penta-carboxylic porphyrins have also been synthesised by condensation of appropriate α -formyl pyrromethane- α' -carboxylic acids; in each case other porphyrins with different numbers of acidic side-chains were also produced but the desired products were easily separated (as their methyl esters) by h.p.l.c.

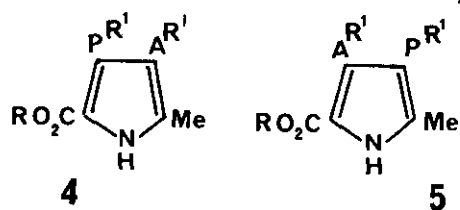
Although the MacDonald route for porphyrin synthesis was first developed over twenty years ago, it is still the most convenient method for preparing a wide range of porphyrins including uroporphyrin-III. In the original procedure the diformylpyrromethane (1) was condensed with the di- α -free pyrromethane (2a) in acetic acid containing a catalytic amount of hydriodic acid, and the intermediate porphodimethene was then autoxidised to uroporphyrin-III, isolated as the octamethyl ester(3). (Scheme 1)

The precursors of the two pyrromethanes were the two isomerically substituted pyrroles (4a) and (5a) but the preparation of pyrroles with the second type of substitution pattern (5) is somewhat more lengthy than that of pyrroles of type (4), and if α -benzyl ester (5b) is required, two extra trans-esterification steps are required at the end of the synthesis.² Furthermore, the route to the pyrroles (4b) has recently been considerably improved by Kenner and Smith.³

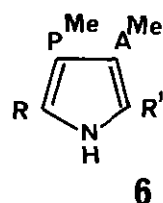
The relative accessibility of pyrrole (4b) (compared with pyrroles of type (5)), therefore, led us to develop a new synthesis of uroporphyrin-III (3) using it as the sole precursor of all four rings (Scheme 2). The pyrrole benzyl ester (4b) was trichlorinated with sulphuryl chloride and the intermediate trichloromethyl pyrrole hydrolysed by aqueous sodium acetate at 70° to the pyrrole-2-carboxylic acid (6a). Esterification of the latter with diazomethane, followed by hydrogenolysis over palladium-charcoal, then afforded the pyrrole-5-carboxylic acid (6b). Treatment of the sodium salt of the latter with iodine and potassium iodide, followed by hydrogenolysis over platinum oxide then afforded the desired



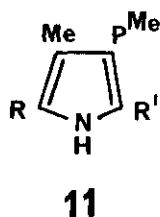
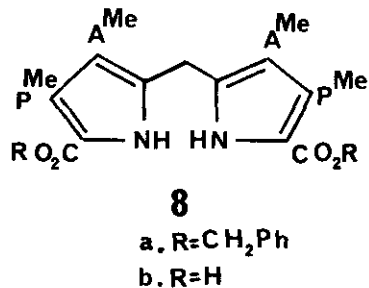
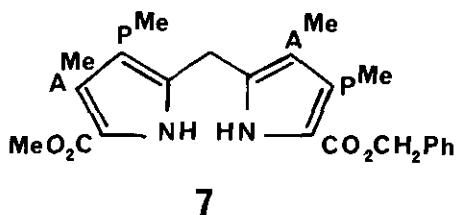
Scheme 1



a. $R=R'=Et$
 b. $R=CH_2Ph$ $R'=Me$



a. $R=CO_2CH_2Ph$, $R'=CO_2H$
 b. $R=CO_2H$, $R'=CO_2Me$
 c. $R=H$, $R'=CO_2Me$
 d. $R=CO_2CH_2Ph$, $R'=CH_2OAc$
 e. $R=CO_2CH_2Ph$, $R'=CHO$
 f. $R=H$, $R'=CHO$
 g. $R=H$, $R'=CH=NNHCOCH_2 + NMe_3$



a. $R=CO_2CH_2Ph$, $R'=CH_2Br$
 b. $R=CO_2CH_2Ph$, $R'=CHO$
 c. $R=H$, $R'=CHO$
 d. $R=H$, $R'=CH=NNHCOCH_2 + NMe_3$
 e. $R=CO_2CH_2Ph$, $R'=CH_2OAc$

$R = CH_2CO_2R$
 $P = CH_2CH_2CO_2R$

α -free pyrrole (6c).

The original pyrrole (4b) was also converted by treatment with lead tetra-acetate into the acetoxymethyl derivative (6d) and the latter was coupled with the α -free pyrrole (6c) in dichloromethane in presence of stannic chloride⁴ at -20° to give the desired unsymmetrical pyrromethane monobenzyl, pentamethyl ester (7) in good yield. This was hydrolysed to the hexacarboxylic acid (2b) by heating with 10% aqueous sodium hydroxide followed by acidification.

Self condensation of the acetoxymethylpyrrole (6d) afforded the symmetrical pyrromethane dibenzyl ester (8a) which was then hydrogenolysed to the corresponding di-acid (8b) over palladium-charcoal. Decarboxylation of the latter in dimethylformamide at 180° followed by cooling and addition of benzoyl chloride enabled the required diformyl pyrromethane (1) to be prepared in good yield.

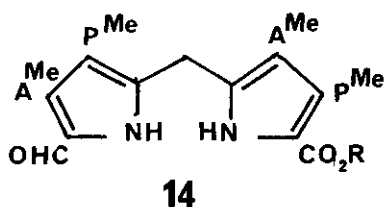
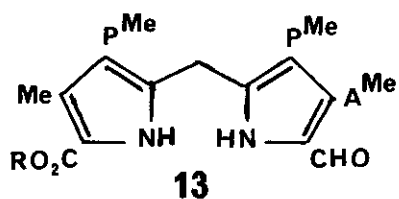
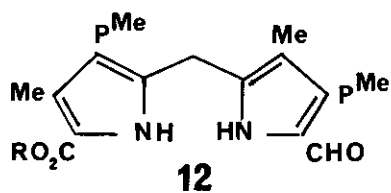
Uroporphyrin-III was then prepared by condensing the pyrromethane hexa-acid (2b) with the dialdehyde (1) in dichloromethane-methanol in presence of *n*-toluene sulphonic acid at 20° for one day. Methanolic zinc acetate was then added and after a further two days the product was worked up and esterified with 5% sulphuric acid in methanol to afford uroporphyrin-III octamethyl ester in good yield m.p. $261-262^{\circ}$ (lit.¹ $255-260^{\circ}$).

The product was analysed for isomeric purity both by direct h.p.l.c. and by decarboxylation to coproporphyrin followed by paper chromatography in lutidine-ammonia. This showed that a small amount of the type-II isomer had been formed, presumably by self-condensation of the diformyl pyrromethane (1) in accord with our earlier experiences⁵ of using pyrromethane di-acids as intermediates in MacDonald type syntheses.

As the original procedure¹ utilising di- α -free pyrromethanes had given products of high isomeric purity, we therefore, decarboxylated the pyrromethane (2b) by heating with alkali in a sealed tube, in presence of hydrazine (as in the original MacDonald procedure¹), and coupled the resulting di- α -free pyrromethane with the diformyl pyrromethane (1) by the same method as described above. Uroporphyrin-III was obtained in good yield, essentially uncontaminated with isomers, as shown by h.p.l.c., and by paper chromatographic analysis of the derived coproporphyrin-III. These results clearly show all four pyrrole rings of uroporphyrin-III can be obtained from the one readily accessible pyrrole (4b).

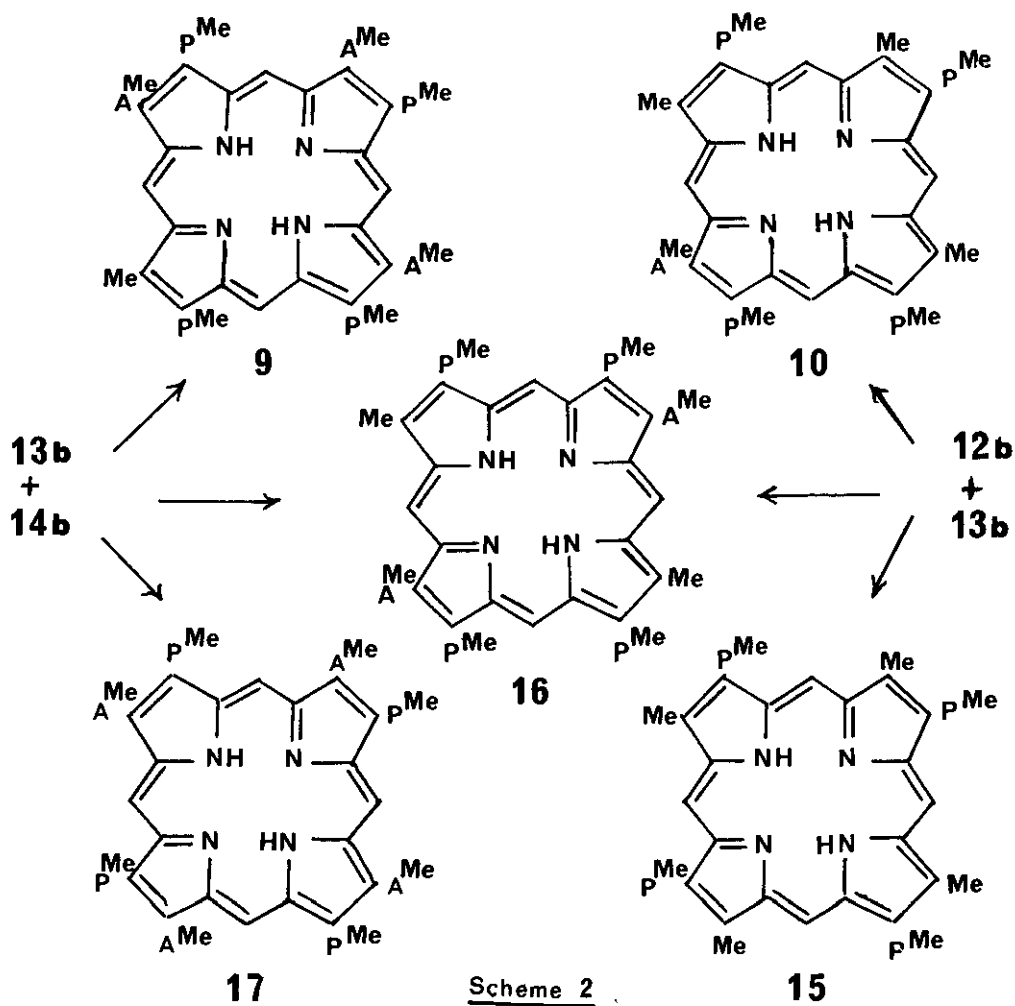
This approach should also be valid for other similarly substituted porphyrins such as coproporphyrin-III, but the synthesis of completely unsymmetrical porphyrins such as the type-III hentacarboxylic porphyrin (9) and the related pentacarboxylic porphyrin (10) cannot be carried out by the original MacDonald method because none of the possible dipyrrolic units from which they might be constructed is symmetrical.

The porphyrinogen hentacarboxylic acid corresponding to the porphyrin (9) is the first



a R = CH₂Ph

b R = H



Scheme 2

intermediate in the biosynthetic conversion of uroporphyrinogen-III to coproporphyrinogen-III. Its structure was elucidated by ourselves^{5,7} and by other workers,^{8,9} by total syntheses of the porphyrin (9) via rationally constructed open-chain tetrapyrroles. The methods used were, however, relatively lengthy, and the overall yields were low, so that we sought another simpler route to such unsymmetrical porphyrins.

The advent of h.p.l.c. and especially the possibility of adapting it to preparative scale separations has now led us to develop a new variant of the MacDonald synthesis involving the condensation of two α -formyl-pyrromethane- α' -carboxylic acids with each other.¹⁰ Our strategy required the two original pyrromethanes to have different numbers of acidic (or ester side-chains) so that the three products formed (Scheme 2) would also have different numbers of carboxylic side-chains, and hence would be readily separable from one another by h.p.l.c.¹¹

Two of the pyrromethanes required for this work i.e. (12b) and (13b) were synthesised initially by condensation of the bromomethylpyrrole (11a) with the α -free- α' -formylpyrrole Girard derivatives (11d) and (6g) in acetic acid in presence of sodium acetate.¹² Dilute acid hydrolysis of the initially formed pyrromethane Girard derivatives then gave the formylpyrromethanes (12a) and (13a) and hydrogenolysis of the latter over palladium-charcoal afforded the desired α -formylpyrromethane- α' -carboxylic acids (12b) and (13b). Later we found that the formyl pyrromethane benzyl esters (12a) and (13a) could be prepared directly by tin (IV) chloride catalysed⁴ condensation of the acetoxymethylpyrrole (11e) with the formylpyrroles (11c) and (6f). The pyrromethane (14a) was also prepared in a similar manner from the acetoxymethylpyrrole (6d) and the formyl pyrrole (6f).

Condensation of the formylpyrromethane carboxylic acids (12b) and (13b), catalysed by toluene-*p*-sulphonic acid in methanol, then afforded a mixture of the three porphyrins (10), (15) and (16) (Scheme 2). These were readily separated by small-scale preparative h.p.l.c.¹¹ by reason of their differing polarities (because of the different side-chains) and the desired pentacarboxylic porphyrin penta-methyl ester (10), m.p. 217-219° (lit. m.p. 218-219°⁸, 211-212°⁷) was obtained in 8% yield from the two pyrromethanes, as well as coproporphyrin-I tetramethyl ester (15) and a type-II porphyrin hexamethyl ester (16). Similarly the heptacarboxylic ester (9) m.p. 223-224° (lit. m.p. 225-226°⁰⁻⁷, 225-226°⁸, 223-225°⁹) was obtained in 9% yield from the formyl pyrromethane carboxylic acids (13b) and (14b), and separated from the other two porphyrins, uroporphyrin I octamethyl ester (17) and the hexacarboxylic porphyrin (16).

Although the yields of each porphyrin in the final step of these syntheses are low, the overall yields compare well with those in previous multi-stage syntheses^{7,8,9} and the approach is very much more rapid. Further work is in progress to improve the yields in the final condensations, and other developments of this new approach include the synthesis of

unsymmetrical type-I porphyrins, which will be described later in a full publication.

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Dedication

This paper is dedicated to Prof. T. Kametani, "grand-master" of Heterocyclic Chemistry on the occasion of his retirement.

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