A Stepwise Synthesis of Porphyrins and Related Macrocycles from 1,19-Dideoxybiladienes-ac*

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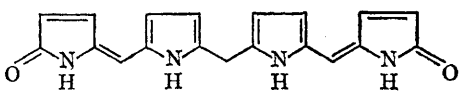
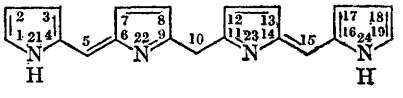
THE classical Fischer condensation of dipyrromethenes[4a] applied to the synthesis of unsymmetrically substituted porphyrins invariably gives rise to a mixture of products, and when applied to porphyrins containing electronegative or meso-substituents may cause the loss of these groups. Thus the synthesis of rhodoporphyrins[4b] and phylloporphyrins[4c] by this method gave mixtures from which, after an arduous separation, the required porphyrin was isolated in yields rarely exceeding 3%. The main alternative porphyrin synthesis, based on dipyrromethanes,[5] was used as the basis of a recent synthesis of chlorophyll a,[6] but the method employed to ensure that the required orientation was maintained during the coupling of the dipyrromethanes cannot be readily generalised.

We now report a porphyrin synthesis which is essentially a two-stage Fischer dipyrromethene



(a)



(b)

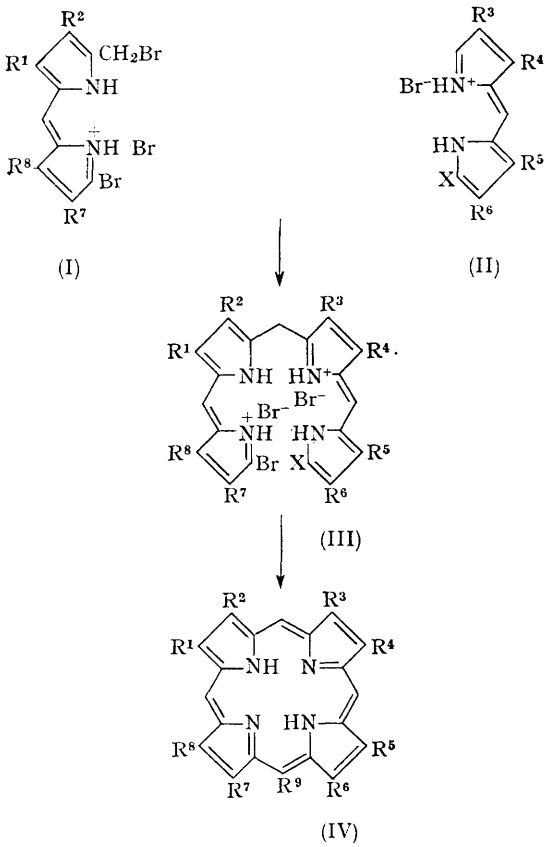
* The term biladiene had been used[1] to represent the bile pigment derivative (a) and the corresponding tetrapyrrolic system (b) has been referred to as 1',8'-dideoxybiladiene-ac.[2] It would be more logical, however, to use the numbering system (b) corresponding to that recommended for the porphyrins,[3] and this we have done in this Communication.

[1] R. Lemberg and J. W. Legge, "Haematin Compounds and Bile Pigments", Interscience, New York and London, 1949, p. 105.
[2] A. W. Johnson and I. T. Kay, *J. Chem. Soc.*, 1961, 2418.
[3] I.U.P.A.C. rules for porphyrin nomenclature; *J. Amer. Chem. Soc.*, 1960, **82**, 5582.
[4] H. Fischer and H. Orth, "Die Chemie des Pyrrols", Akad. Verlag., Leipzig, Vol. II, i, 1937, (a) pp. 160—173, (b) pp. 532—533, (c) pp. 345—360, (d) p. 447, (e) p. 359.
[5] G. P. Arsenault, E. Bullock, and S. F. MacDonald, *J. Amer. Chem. Soc.*, 1960, **82**, 4384; S. F. MacDonald, *ibid.*, 1957, **79**, 2659.
[6] R. B. Woodward, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Closs, H. Dutler, J. Hannah, F. P. Hauck, S. Itô, A. Langemann, E. le Goff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta, and H. Volz, *J. Amer. Chem. Soc.*, 1960, **82**, 3800.

Yields of dideoxybiladienes-ac and derived porphyrins

Porphyrin (IV)	Yield of dideoxy-biladiene-ac (III)	Yield of porphyrin (IV)	M.p. (uncorr.)
$R^1 = R^3 = R^4 = R^5 = R^7 R^8 = Me$; $R^2 = R^6 = Et$; $R^9 = H$	90	81	>300°
$R^1 = R^2 = R^4 = R^6 = R^8 = Me$; $R^3 = R^5 = R^7 = Et$; $R^9 = H$	86	75	>300
$R^1 = R^5 = R^7 = R^8 = Me$; $R^2 = R^3 = R^4 = R^6 = Et$; $R^9 = H$	92	72	>300
$R^1 = R^4 = R^5 = R^7 = R^8 = Me$; $R^2 = R^6 = Et$; $R^3 = P^{Me}$; $R^9 = H$	84	65	283—284
$R^1 = R^3 = R^5 = R^8 = Me$; $R^2 = R^6 = Et$; $R^4 = CO_2Et$; $R^7 = P^{Et}$; $R^9 = H$	77	55	208—209
Rhodoporphyrin XII diethyl ester $R^1 = R^3 = R^5 = R^7 = Me$; $R^2 = R^8 = Et$; $R^4 = CO_2Et$; $R^6 = P^{Et}$; $R^9 = H$	93	50	193—194
Rhodoporphyrin I diethyl ester $R^1 = R^3 = R^5 = R^8 = Me$; $R^2 = R^4 = Et$; $R^6 = R^7 = P^{Me}$; $R^9 = H$	81	63	210—212 (lit.[4d] 212)
Mesoporphyrin IX dimethyl ester $R^1 = R^4 = R^5 = R^8 = R^9 = Me$; $R^2 = R^3 = Et$; $R^7 = P^{Me}$; $R^6 = H$	70	27	280—281
γ-Phylloporphyrin IV methyl ester $R^1 = R^3 = R^5 = R^8 = R^9 = Me$; $R^2 = R^4 = Et$; $R^7 = P^{Me}$; $R^6 = H$	73	29	233—234 (lit.[4e] 235)
γ-Phylloporphyrin XV methyl ester			

$P^{Me} = CH_2{\cdot}CH_2{\cdot}CO_2Me$; $P^{Et} = CH_2{\cdot}CH_2{\cdot}CO_2Et$

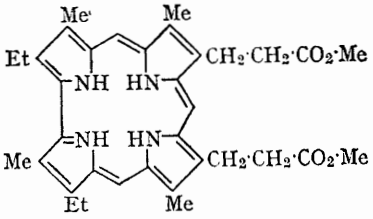


condensation in which the orientation difficulties have been overcome by the isolation of the intermediate dideoxybiladienes-ac. This method, which permits the retention of electronegative and meso-substituents, is also capable of variation to yield other tetrapyrrolic macrocyclic systems. In the initial reaction, a 5-bromo-5′-bromomethyldipyrromethene hydrobromide (I) is condensed with a dipyrromethene hydrobromide with an unsubstituted 5-position (II) in methylene dichloride in presence of stannic chloride, to produce dideoxybiladiene-ac stannic complexes which are not isolated but treated with hydrobromic acid to give the dihydrobromides (III) in overall yields of 70—90%. In this manner we have prepared unsymmetrically substituted 1-bromo-dideoxybiladienes-ac of two types containing either terminal alkyl (III; X = CH_2R^9) or bromo- (III; X = Br) groups.

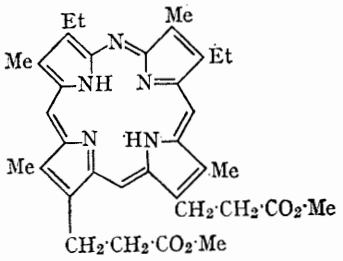
In previous communications, we have described other methods for the synthesis of symmetrically substituted dideoxybiladienes-ac containing terminal methyl, hydrogen, or ester groups and also their ready cyclisation to porphyrins,[2] corroles,[7] and 1,19-disubstituted tetradehydrocorrins.[8] When the dideoxybiladienes-ac (III; X = CH_2R^9) were heated under reflux for *ca.* 15 minutes in *o*-dichlorobenzene, they cyclised to the corresponding porphyrins (IV) in high yield (Table) and with retention of β-ester or meso-substituents.

By this method, nine porphyrins have been prepared so far and the purity of the products has

[7] A. W. Johnson and I. T. Kay, *Proc. Chem. Soc.*, **1964**, 89.
[8] D. Dolphin, R. L. N. Harris, A. W. Johnson, and I. T. Kay, *Proc. Chem. Soc.*, 1964, 359.



(V)



(VI)

been demonstrated by thin-layer-chromatographic examination or, in the cases of mesoporphyrin IX and phylloporphyrin XV, by the m.p.s. of the methyl esters and copper complexes. When the dideoxybiladienes-ac (III; X = Br) were heated in *o*-dichlorobenzene, they readily cyclised to the corresponding corrole, and when treated with methanolic sodium azide they gave the corresponding monoazaporphyrin. Thus the corrole (V; 26%; m.p. 168—170°) and the azaporphyrin (VI; 45%; m.p. 219—220°), having substitution patterns similar to that of mesoporphyrin IX, have been prepared.

The cyclisation of the 1-alkyl-19-bromodeoxybiladienes-ac provides a novel and general method for the preparation of unsymmetrically substituted porphyrins and the yields obtained represent a substantial improvement on existing methods. The related syntheses of corroles and monoazaporphyrins provides a novel route to the unsymmetrically substituted members of these series.

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