THE SYNTHESIS OF PORPHINS AND RELATED MACROCYCLES

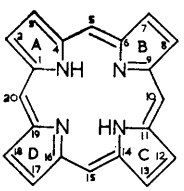
By R. L. N. HARRIS, A. W. JOHNSON, and I. T. KAY

(CHEMISTRY DEPARTMENT, UNIVERSITY OF NOTTINGHAM)

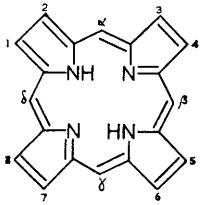
IN this Review it is intended to survey the main methods arising from the classic work of Hans Fischer[1] for the synthesis of porphins and related compounds. The more biochemical aspects of porphin chemistry, particularly the problems of biosynthesis,[2] have been reviewed elsewhere,[3] where some of the problems of chemical synthesis have also been outlined. The literature survey covers the period up to the end of September 1965.

Nomenclature

We propose to use the nomenclature (1) recommended by I.U.P.A.C.[4] for the porphin ring system although some authors prefer, and still use, the

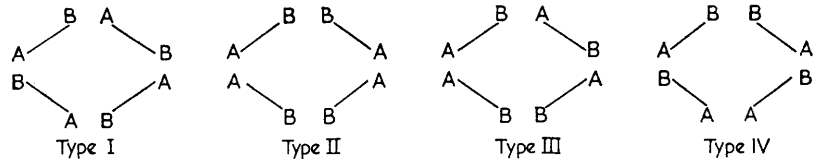


(1)



(2)

Fischer scheme (2). When each of the four pyrrole rings of a porphin bears two different substituents A and B in the β-positions, then four isomers exist:



For ætioporphyrins A = Me; B = Et
For coproporphyrins A = Me; B = $-CH_2 \cdot CH_2 \cdot CO_2H$ (P)
For uroporphyrins A = $-CH_2 \cdot CO_2H$ (A); B = $-CH_2 \cdot CH_2 \cdot CO_2H$

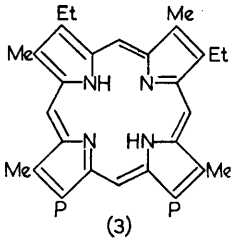
[1] H. Fischer and H. Orth, "Die Chemie des Pyrrols", vols. I, IIi, and IIii, Liepzig, 1934—1940.

[2] C. Rimington, *Rev. Pure Appl. Chem.*, 1958, **8**, 129; S. Granick and D. Mauzerall in "Metabolic Pathways", ed. D. M. Greenberg, Academic Press, New York and London, 1961, vol. II, p. 525; G. S. Marks, *Ann. Rep. Chem. Soc.*, 1962, **59**, 385; J. Lascelles, "Tetrapyrrole Biosynthesis and its Regulation", Benjamin, New York and Amsterdam, 1964.

[3] R. Lemberg and J. W. Legge, "Hæmatin Compounds and Bile Pigments", Interscience, New York, 1949; J. E. Falk, J. N. Phillips, R. Hill, and C. H. Gray in "Comprehensive Biochemistry", Elsevier, Amsterdam, London and New York, 1963, vol. IX, pp. 1—98; R. Lemberg, *Rev. Pure Appl. Chem.*, 1956, **6**, 1; J. E. Falk, "Porphyrins and Metalloporphyrins", Elsevier, 1964; T. S. Stevens in "Chemistry of Carbon Compounds", ed. E. H. Rodd, Elsevier, 1959, vol. IVB, p. 1104.

[4] I.U.P.A.C. rules for nomenclature, *J. Amer. Chem. Soc.*, 1960, **82**, 5582.

In the case of porphins containing two substituents A and B in rings A and B and two substituents A and C in rings C and D, fifteen isomers are possible. The naturally occurring porphins of this type possess the so-called IX-arrangement of substituents, *e.g.*, mesoporphyrin-IX (3; A = Me, B = Et, C = $-CH_2 \cdot CH_2 \cdot CO_2H$). Other porphins referred to in this Review include phylloporphyrin (*e.g.*, γ-phylloporphyrin-XV; 4) and rhodoporphyrin (*e.g.*, rhodoporphyrin-XV; 5).



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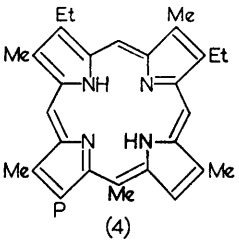

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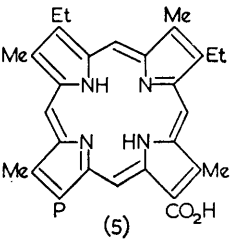
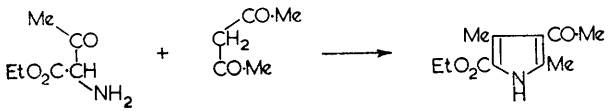


(5)

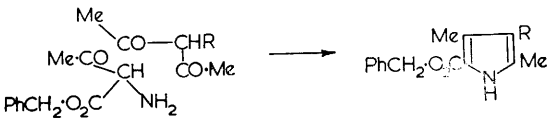
P = $-CH_2 \cdot CH_2 \cdot CO_2H$

Synthetic Intermediates

(i) **Pyrroles.**—The classical Knorr synthesis of pyrroles is exemplified by the preparation of ethyl 3-acetyl-2,4-dimethylpyrrole-5-carboxylate:

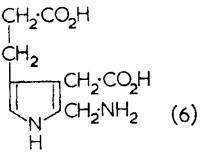


An important modification of the method was described by Fischer and Fink[5] in two papers. In this work, acetoacetaldehyde diethylacetal was condensed with oximino-acetoacetic ester under the usual reductive conditions but the condensation involved the loss of an acetyl group. Kleinspehn[6] modified the method by the use of oximino-malonic ester and, later,[7] 2-oximino-1,3-diketones, and Johnson, Markham, *et al.*[8] have recommended oximino-acetoacetic esters (particularly the benzyl and t-butyl esters to facilitate the easy removal of the ester group) and α-oximino-ketones in the condensation with 1,3-diketones.



[5] H. Fischer and E. Fink, *Z. physiol. Chem.*, 1944, **280**, 123; 1948, **283**, 152; see also G. H. Cookson, *J. Chem. Soc.*, 1953, 2789.
[6] G. G. Kleinspehn, *J. Amer. Chem. Soc.*, 1955, **77**, 1546.
[7] G. G. Kleinspehn and A. H. Corwin, *J. Org. Chem.*, 1960, **25**, 1048.
[8] A. W. Johnson, E. Markham, K. B. Shaw, *et al.*, *J. Chem. Soc.*, 1958, 1430, 4258; A. W. Johnson, E. Markham, and R. Price, *Org. Syntheses*, 1962, **42**, 92.

These modified Knorr syntheses have found wide application in the preparation of intermediates for the synthesis of porphins, *e.g.*, pyrroles containing β-diethylaminoethyl side-chains[9] which will yield β-vinyl groups[cf10] after Hofmann degradation. A review[11] has covered many other synthetical developments in pyrrole chemistry as well as physical properties and chemical reactions, but the more recent mass spectral studies on pyrroles[12] as well as certain specific syntheses might be mentioned. Thus glycine ester derivatives[13] have been used as pyrrolic intermediates, and special syntheses of pyrroles containing carboxymethyl and β-carboxyethyl substituents in the nuclear β-positions have been described.[14] Such pyrroles include the biologically important porphobilinogen[15] (6), a recent synthesis[16] of which utilises the fission of a 3,6-dihydro-2-pyridone ring for the formation of the aminomethyl- and carboxymethyl-side-chains.



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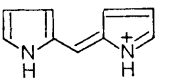


(7)

Of the substitution reactions of pyrroles, the application of the Vilsmeier reaction (phosphorus oxychloride–*NN*-dimethylformamide) for the introduction of α-formyl groups into pyrroles[17] might be stressed as having particular value for the preparation of useful porphin intermediates.

(ii) **Dipyrromethenes.**—The classical synthesis[18] of dipyrromethene salts (7) by the acid-catalysed condensation of an α-formylpyrrole with a pyrrole containing an α-unsubstituted position (or an α-grouping, *e.g.*, α-carboxy, which is easily removed) is still the main method of synthesis and the high yields obtained have not necessitated further developments. Dipyrromethenes can also be obtained by the controlled oxidation of dipyrromethanes.

[9] A. M. Fargali, R. P. Enstigneeva, and N. A. Preobrazhenskii, *Zhur. obshchei Khim.*, 1964, **34**, 898; *Chem. Abs.*, 1964, **60**, 15812.

[10] 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.

[11] E. Baltazzi and L. I. Krimen, *Chem. Reviews*, 1963, **63**, 511.

[12] H. Budzikiewicz, C. Djerassi, A. H. Jackson, G. W. Kenner, D. J. Newman, and J. M. Wilson, *J. Chem. Soc.*, 1964, 1949.

[13] H. Rapoport, C. D. Willson *et al.*, *J. Amer. Chem. Soc.*, 1962, **84**, 630; 1964, **86**, 5293; W. G. Terry, A. H. Jackson, G. W. Kenner, and G. Kornis, *J. Chem. Soc.*, 1965, 4389.

[14] S. F. MacDonald, *J. Chem. Soc.*, 1952, 4176, 4184.

[15] S. F. MacDonald *et al.*, *Canad. J. Chem.*, 1957, **35**, 715; 1961, **39**, 2043.

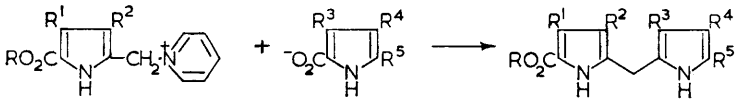
[16] B. Frydman, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, 1965, **87**, 3530.

[17] For a review see G. G. Kleinspehn and A. E. Briod, *J. Org. Chem.*, 1961, **26**, 1652.

[18] H. Fischer and H. Orth, "Die Chemie des Pyrrols", vol. IIi, Liepzig, 1937, p. 1.

A notable feature of recent studies on dipyrromethenes has been the demonstration of the easy addition of nucleophils at the *meso*-position to yield *meso*-substituted dipyrromethanes. Examples include the addition of hydroxyl and methoxyl anions,[19] bisulphite,[20] methyl carbanions (Grignard),[21] and the carbanions of cyanoacetic ester[22] and dicyanomethane.[23]

(iii) **Dipyrromethanes.**—These substances (*e.g.*, 8) have been used extensively in the post-Fischer period as intermediates[10,24–26] for the synthesis of porphins. Many of the methods used for the preparation of dipyrromethanes are those evolved by Fischer[27] but a variation in the method of pyrrolic coupling involving the condensation of (2-pyrrolylmethyl)pyridinium salts with pyrrole-2-carboxylate salts has been developed by Kenner:[28,29]

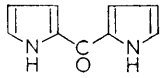


The reduction of dipyrromethenes, *e.g.*, by sodium borohydride, also finds occasional application.[10] The configuration of dipyrromethane- and dipyrromethene-5-esters is governed by internal hydrogen bonding,[30] and may have a profound effect on reactivity.

The methylene bridge linking the two pyrrole rings is fairly easily broken and many examples have been quoted[*e.g.*,31] of exchange reactions occurring with dipyrromethanes particularly under acid conditions. Dipyrromethanes containing only alkyl substituents (including carboxymethyl and β-carboxyethyl) are usually very unstable and cannot be kept, but when used *in situ* they represent important intermediates in many porphin syntheses, *e.g.*, uroporphyrin preparations.[25,26] Dipyrromethanes, like pyrroles, are very susceptible to electrophilic substitution and in this series also the Vilsmeier method has been successfully used for the formation of 5,5-diformyl derivatives.[32]

[19] K. J. Brunings and A. H. Corwin, *J. Amer. Chem. Soc.*, 1942, **64**, 593.
[20] A. Treibs and R. Zimmer-Galler, *Annalen*, 1963, **664**, 140.
[21] H. Booth, A. W. Johnson, F. Johnson, and R. A. Langdale-Smith, *J. Chem. Soc.*, 1963, 650.
[22] A. C. Jain and G. W. Kenner, *J. Chem. Soc.*, 1959, 185.
[23] P. Bamfield, A. W. Johnson, and J. L. Leng, *J. Chem. Soc.*, 1965, 7001.
[24] S. F. MacDonald, *J. Amer. Chem. Soc.*, 1957, **79**, 2659.
[25] G. B. Arsenault, E. Bullock, and S. F. MacDonald, *J. Amer. Chem. Soc.*, 1960, **82**, 4384.
[26] E. J. Tarlton, S. F. MacDonald, and E. Baltazzi, *J. Amer. Chem. Soc.*, 1960, **82**, 4389.
[27] H. Fischer and H. Orth, "Die Chemie des Pyrrols", vol. I, Liepzig, 1934, p. 331.
[28] A. Hayes, G. W. Kenner, and N. R. Williams, *J. Chem. Soc.*, 1958, 3779.
[29] A. H. Jackson, G. W. Kenner, and D. Warburton, *J. Chem. Soc.*, 1965, 1328.
[30] L. P. Kuhn and G. G. Kleinspehn, *J. Org. Chem.*, 1963, **28**, 721.
[31] A. Treibs and H. G. Kolm, *Annalen*, 1958, **614**, 199.
[32] E. Bullock, R. Grigg, A. W. Johnson, and J. W. F. Wasley, *J. Chem. Soc.*, 1963, 2326.

(iv) **Dipyrryl Ketones.**—These substances (9), which are prepared either by the condensation of α-substituted pyrroles with phosgene (carbonyl chloride) or by oxidation of the corresponding dipyrromethane with lead tetra-acetate,[33] have found a limited application in the preparation of porphins.[34]



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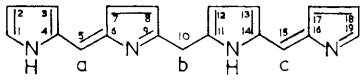
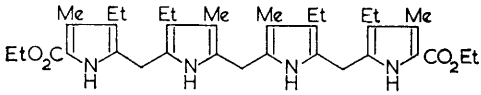


(10)

(v) **Tetrapyrrolic Intermediates.**—1,19-*Dideoxy-bilanes, -bilenes, and -biladienes.* The nomenclature used in this series[35] is based on that of the bile pigments suggested by Lemberg and Legge.[36] The revised numbering is in line with that recommended for the porphins and the removal of the terminal oxygen functions is indicated by the prefix, 1,19-dideoxy. The use of letters to indicate unsaturation between the rings is retained, *e.g.*, 1,19-dideoxybiladiene-*ac* (10). Corwin and Coolidge[37] prepared the 1,19-dideoxybilane (11) from the dipyrromethane-5,-5′-dicarboxylic ester (12; R = CO_2 Et) by removal of one ester group by hydrolysis and decarboxylation and then self-condensation of (12; R = H) in presence of formic and hydrobromic acids, and finally hydrogenation to give (11).



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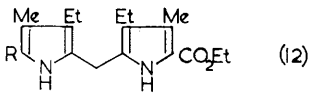


(12)

1,19-Dideoxybilane-1,19-dicarboxylic acids can also be prepared by reduction of the corresponding tetrapyrrolic monoketones with diborane in tetrahydrofuran–ethyl acetate and the products can be dehydrogenated to the corresponding 1,19-dideoxybilenes-*b* (*e.g.*, 13) by the action of t-butyl hypochlorite.[34]

Following the method of Fischer and Kurzinger,[38] whereby a 5,5′-dimethoxymethyldipyrromethene is condensed with two equivalents of a

[33] J. M. Osgerby and S. F. MacDonald, *Canad. J. Chem.*, 1962, **40**, 1585.

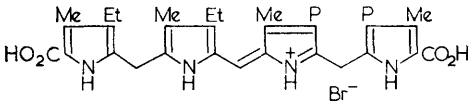
[34] A. H. Jackson, G. W. Kenner, G. McGillivray, and G. S. Sach, *J. Amer. Chem. Soc.*, 1965, **87**, 676; A recent paper by P. S. Clezy and A. W. Nichol (*Austral. J. Chem.*, 1965, **11**, 1835) also describes the synthesis of a *meso*-hydroxyporphin.

[35] A. W. Johnson and I. T. Kay, *J. Chem. Soc.*, 1961, 2418.

[36] R. Lemberg and J. W. Legge, "Hæmatin Compounds and Bile Pigments", Interscience, New York, 1949, p. 105.

[37] A. H. Corwin and E. C. Coolidge, *J. Amer. Chem. Soc.*, 1952, **74**, 5196.

[38] H. Fischer and A. Kurzinger, *Z. physiol. Chem.*, 1931, **196**, 213.



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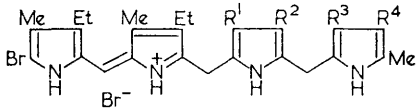
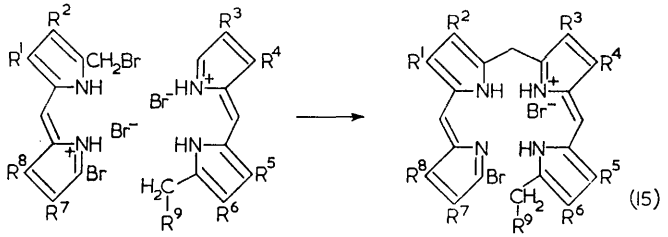


(14)

2-unsubstituted pyrrole, Johnson and Kay[35] have prepared several 1,19-dideoxybilenes-*b* containing terminal methyl groups. 1,19-Dideoxybilenes-*a* of type (14) have been prepared[39] by condensation of a 5-bromo-5′-bromomethyldipyrromethene with a dipyrromethane-5-carboxylic acid.

By far the most useful class of linear tetrapyrrolic intermediates from the point of view of porphin synthesis is the 1,19-dideoxybiladienes-*ac* (*e.g.*, 15). These were first prepared by Johnson and Kay,[35] by the acid-catalysed condensation of two equivalents of a 2-formylpyrrole with a dipyrromethane-5,5′-dicarboxylic acid (or two equivalents of a 2-unsubstituted pyrrole with a 5,5′-diformyldipyrromethane). Later[40] a method was evolved for the preparation of 1,19-dideoxybiladienes-*ac* containing unsymmetrically arranged substituents. This involved the condensation of a 5-bromo-5′-bromomethyldipyrromethene with a 5-unsubstituted 5′-alkyldipyrromethene to produce, after treatment with mineral acid, the 1-bromo-19-alkylbiladiene-*ac* salts (15) in 70—90% yield:



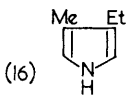
(15)

The use of these intermediates for the synthesis of porphins will be considered in the following section. Strictly speaking, the bile pigments should be considered along with the linear tetrapyrrolic compounds, but as these substances are degradation products of porphins rather than intermediates for porphin synthesis, they have been omitted from this Review.

Porphin Synthesis

(i) **From Pyrroles.**—The first synthesis of a porphin directly from the self-condensation of a pyrrole was the formation of ætioporphyrin by the action of formic acid on opsopyrrole (16).[41]

[39] J. Ellis, A. H. Jackson, A. C. Jain, and G. W. Kenner, *J. Chem. Soc.*, 1964, 1935.
[40] R. L. N. Harris, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.*, (*C*), 1966, 22.
[41] H. Fischer and A. Treibs, *Annalen*, 1926, **450**, 146.



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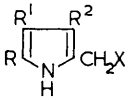


(17)

X = OH, OMe, OAc, Br, Cl, NH_2, NMe_2 etc.
R = H, CO_2H, CO_2CMe_3

This method obviously gives rise to mixtures of porphins when the pyrrole is unsymmetrically substituted, as in (16), and was not exploited to any extent by Fischer. In 1935, Rothemund[42] found that the reaction of pyrrole with aldehydes in the presence of pyridine under pressure and at elevated temperatures gave rise to small yields of *meso*-substituted porphins. Thus acetaldehyde gave rise to *meso*-tetramethylporphin and formaldehyde gave a small yield of the parent porphin itself.

In a later Paper[43] the reaction was extended to the preparation of *meso*-tetraphenylporphin the yield of which was later improved[44,45] by the addition of zinc acetate to the reaction mixture followed by demetallation of the resulting *meso*-tetraphenylporphin zinc complex with mineral acid. An earlier claim[46] to have isolated an "isoporphin" as a secondary product from this coupling reaction was later shown[47] to be in error when the compound was identified as a chlorin. The Rothemund reaction was investigated in detail by Arnott and Calvin[48] who isolated six porphyrin-like products from the reaction of pyrrole and benzaldehyde and postulated structures for them. The reaction has also been extended to the preparation of *meso*-tetra-(*o*- and *p*-substituted phenyl)porphins,[49,50] and the water soluble *meso*-tetra-(4-pyridyl)porphin.[51]

Another porphin synthesis utilising the self-condensation of pyrroles involves a pyrrole of type (17) which is polymerised, usually in the presence of acid or by heat, and the resulting porphyrinogen oxidised *in situ* to the porphin. The first example of a synthesis of this type was reported by Siedel and Winkler[52] who prepared ætioporphyrin in yields of up to 49% by heating (17; R′ = Me; R^2 = Et; R = CO_2H; X = OH, later[53] shown to be OAc) either in presence of copper bronze, zinc oxide, or in acidic methanolic solution. In the latter case ætioporphyrinogen was also isolated from the reaction mixture. Variants of this general reaction have been ap-

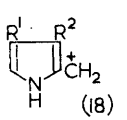
[42] P. Rothemund, *J. Amer. Chem. Soc.*, 1935, **57**, 2010.
[43] P. Rothemund and A. R. Menotti, *J. Amer. Chem. Soc.*, 1941, **63**, 267.
[44] R. H. Ball, G. D. Dorough, and M. Calvin, *J. Amer. Chem. Soc.*, 1946, **68**, 2278.
[45] J. H. Priesthoff and C. V. Banks, *J. Amer. Chem. Soc.*, 1954, **76**, 937.
[46] P. Rothemund, *J. Amer. Chem. Soc.*, 1939, **61**, 2912.
[47] M. Calvin, R. H. Ball, and S. Arnott, *J. Amer. Chem. Soc.*, 1943, **65**, 2259.
[48] S. Arnott and M. Calvin, *J. Org. Chem.*, 1943, **8**, 205.
[49] G. M. Badger, R. A. Jones, and R. L. Laslett, *Austral. J. Chem.*, 1964, **17**, 1028.
[50] D. W. Thomas and A. E. Martell, *J. Amer. Chem. Soc.*, 1956, **78**, 1335.
[51] E. B. Fleischer, *Inorg. Chem.*, 1962, **1**, 493.
[52] W. Siedel and F. Winkler, *Annalen*, 1943, **554**, 162.
[53] E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw. *J. Chem. Soc.*, 1958, 1430.

plied to the synthesis of porphin,[54] octamethylporphin,[55] ætioporphyrin,[56] octaethylporphin,[57] coproporphyrin,[53,58] tetramethyltetrapropylporphin,[59] uroporphyrin,[60] and octa-arylporphins.[61] The usefulness of this easy porphin synthesis is however restricted to porphins containing eight identical β-substituents derived from pyrroles (17; $R^1 = R^2$) as it has been shown recently that a random mixture of porphin isomers is obtained from the pyrroles (17; $R^1 \neq R^2$). Thus, earlier claims for a synthesis of specific coproporphyrin[53,62] and uroporphyrin[60] isomers by this method have been refuted.[58,63] The mechanism of the reaction presumably involves the polymerisation of the primary pyrrolecarbonium ion (18) which, in the presence of acid, can be considered equivalent to a mixture of the di-α-free pyrrole and formaldehyde, this then giving rise to the statistically predicted[63] porphin isomer distribution $\frac{1}{8}$I:$\frac{1}{8}$II:$\frac{1}{2}$III:$\frac{1}{4}$IV.

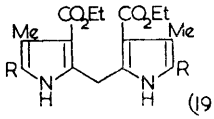
Earlier mechanisms suggested to rationalise the supposed preferential formation of III-type porphins *in vitro* may however have some bearing on the mechanism involved for the enzymically controlled polymerisation of porphobilinogen to uroporphyrinogens-I and -III (reviews[2]), where the random distribution of isomers is not observed. Many hypothetical mechanisms[e.g.53,64,65] have been suggested to account for the almost universal occurrence of III-type porphin isomers in Nature.

In summary, the laboratory synthesis of porphins from pyrroles, by either of the two general routes described, often gives acceptable yields, but is applicable mainly to porphins bearing eight identical β-substituents or to derivatives of these bearing also four identical *meso*-substituents.

(ii) **From Dipyrromethanes.**—One of the first porphin syntheses attempted was the condensation of the dipyrromethanes (19, R = CHO) and (19, R = H) in the presence of perchloric acid.[66] It is remarkable that no porphin was detected although the characteristic porphin spectrum



(18)



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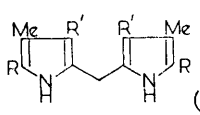


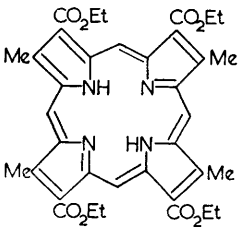
(20)

[54] U. Eisner and R. P. Linstead, *J. Chem. Soc.*, 1955, 3742; S. Krol, *J. Org. Chem.*, 1959, **24**, 2065.
[55] U. Eisner, R. P. Linstead, E. A. Parkes, and E. Stephen, *J. Chem. Soc.*, 1956, 1655.
[56] A. W. Johnson, I. T. Kay, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, 1959, 3416.
[57] U. Eisner, A. Lichtarowicz, and R. P. Linstead, *J. Chem. Soc.*, 1957, 733.
[58] I. T. Kay, *Proc. Acad. Nat. Sci.*, 1962, **48**, 901.
[59] A. H. Jackson, P. Johnston, and G. W. Kenner, *J. Chem. Soc.*, 1964, 2262.
[60] A. Treibs and W. Ott, *Annalen*, 1958, **615**, 137.
[61] M. Friedmann, *J. Org. Chem.*, 1965, **30**, 859.
[62] E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *Nature*, 1960, **185**, 607.
[63] D. Mauzerall, *J. Amer. Chem. Soc.*, 1960, **82**, 2601.
[64] J. H. Mathewson and A. H. Corwin, *J. Amer. Chem. Soc.*, 1961, **83**, 135.
[65] E. Bullock, *Nature*, 1965, **205**, 70.
[66] H. Fischer and P. Halbig, *Annalen*, 1926, **447**, 123.

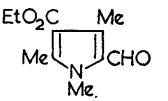
was observed when (19, R = CHO) alone was treated with hydrochloric acid. Historically this represents the first porphin synthesis and it has recently been repeated by Arsenault, Bullock, and MacDonald[25] who isolated the tetramethyltetraethoxycarbonylporphin and showed that the reported spectrum demonstrated its presence.

Shortly afterwards, Fischer and his co-workers[67,68] reported the successful synthesis of ætioporphrin-II by the action of formic acid and air at 40° on the dipyrromethanes (20; R = CO_2H or H; R′ = Et). Porphins were also obtained by heating (20; R = CO_2H; R′ = Et) *in vacuo* and from the corresponding diethyl ester by the action of hydrobromic acid and acetic acid under pressure. These porphin syntheses were not used extensively by Fischer since mixtures of porphyrin isomers were sometimes obtained,[69] depending on the nature of the β-substituents. This is because under the acidic conditions of the condensation, dipyrromethane bridge cleavage occurs[31,70,71] and random isomer formation occurs.

Formally analogous to these syntheses was the synthesis of the porphin (21)[72] in which the dipyrromethane (20; R = H; R^1 = CO_2Et) was condensed with the *N*-methylpyrrole (22) in acidic solution to give the porphin (21) in 40% overall yield.



(21)



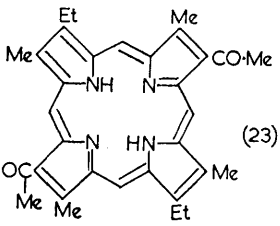
(22)

In this case the *N*-methylpyrrole supplied the necessary bridge carbons, probably through tripyrrylmethane intermediates. In Fischer's method the bridge carbons were supplied by the formic acid.

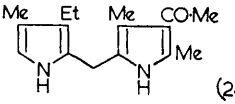
Kleinspehn and Corwin[73] obtained small yields of diacetylporphins (*e.g.*, 23, as its copper complex) by treatment of the 5-methyldipyrromethane (24) with cupric acetate in boiling naphthalene, although the presence of other porphins in the reaction mixture indicated probable cleavage of the dipyrromethane bridge.

Arsenault, Bullock, and MacDonald[25] have developed a very successful

[67] H. Fischer and P. Halbig, *Annalen*, 1926, **448**, 193.
[68] H. Fischer and G. Stangler, *Annalen*, 1927, **459**, 53.
[69] H. Fischer and J. Hiernis, *Z. physiol. Chem.*, 1931, **196**, 155.
[70] H. Fischer and H. J. Riedl, *Z. physiol. Chem.*, 1932, **207**, 193.
[71] A. Treibs and G. Fritz, *Annalen*, 1938, **611**, 162.
[72] J. S. Andrews, A. H. Corwin, and A. G. Sharp, *J. Amer. Chem. Soc.*, 1950, **72**, 491.
[73] G. G. Kleinspehn and A. H. Corwin, *J. Amer. Chem. Soc.*, 1960, **82**, 2750.

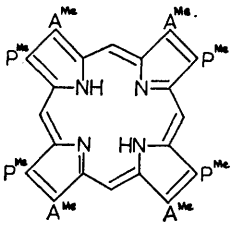


(23)

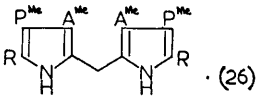


(24)

porphin synthesis based on the condensation of a 5,5′-diformyldipyrromethane with a 5,5′-unsubstituted dipyrromethane. The resulting porphomethene is oxidised by æration in buffered solution and the porphin isolated in yields of 55—65%. Thus uroporphyrin-II (25) was obtained in 65% yield from the condensation of (26; R = CHO) with (26; R = H) and similar reactions were used to prepare uroporphyrins-III[26] and -IV.[25]



(25)



· (26)

A^{Me} = $-CH_2\cdot CO_2Me$
P^{Me} = $-CH_2\cdot CH_2\cdot CO_2Me$

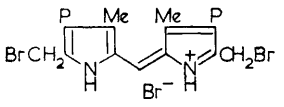
A^{Me} = $-CH_2\cdot CO_2Me$
P^{Me} = $-CH_2\cdot CH_2\cdot CO_2Me$

A thorough investigation of the conditions for the condensation of dipyrromethanes in this way showed the choice of acid catalyst to be critical, hydriodic acid in acetic acid proving by far the most effective. The yields of porphins seemed to be proportional to the nucleophilicity of the acid anion.

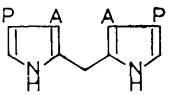
Arsenault, Bullock, and MacDonald[25] also showed that, with these experimental conditions, the integrity of the dipyrromethanes was maintained, and they demonstrated the usefulness of dipyrromethanes further by the condensation of the 5,5′-dibromomethyldipyrromethene (27) with the dipyrromethane (28) to give after oxidation and esterification a 33% yield of the porphin (29). There was no evidence that bridge cleavage of the dipyrromethane, with resultant isomer formation, had occurred.

The MacDonald synthesis has been employed by several schools recently and includes the preparation of a rhodoporphyrin[29] and a di-*meso*-methylporphin.[74] The method was also envisaged[75] for the synthesis of porphins related to porphyrin-*a*, which as its iron complex is the pros-

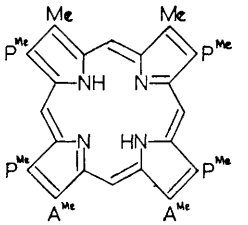
[74] G. M. Badger, R. A. Jones, and R. L. Laslett, *Austral. J. Chem.*, 1964, **17**, 1157.
[75] G. M. Badger, R. L. N. Harris, and R. A. Jones, *Austral. J. Chem.*, 1964, **17**, 987, 1002.



(27)



(28)

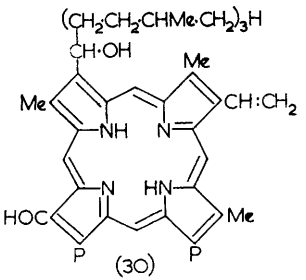


(29)

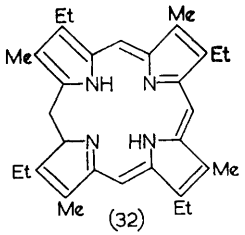
thetic group of cytochromes *a* and a_3. The structure of porphyrin-*a* has been shown recently[76] to be (30).

The limiting factor in the synthesis of porphins from dipyrromethanes is the ambiguity caused if one or both of the dipyrromethanes is unsymmetrically substituted, when condensation of the dipyrromethanes may occur in either or both of two ways. This drawback has been overcome in the elegant Harvard synthesis[10] of chlorophyll-*a* (below), in which a method similar to that of MacDonald was used to link up two dipyrromethanes. However as both dipyrromethanes were unsymmetrically substituted two isomeric porphins were possible. To overcome this difficulty, the dipyrromethanes were held in the required configuration as a Schiff's base before condensation to the required porphin, a method which, unfortunately, is not capable of easy generalisation.

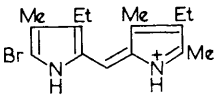
(iii) **From Dipyrromethenes.**—In their first attempt to prepare xanthobilirubinic acid, Fischer and Klarer[77] found that the action of sulphuric acid on the dipyrromethene (31) gave a small quantity of ætioporphyrin-I (32).



(30)



(32)

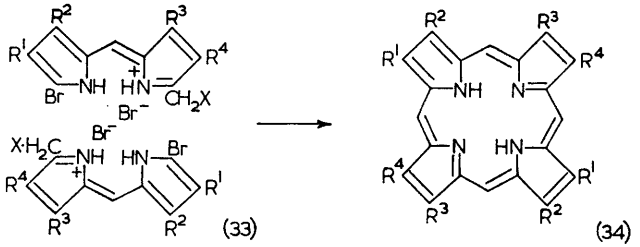


Br^- (31)

[76] M. Grassl, U. Coy, F. Lynen, *et al.*, *Biochem. Z.*, 1963, **337**, 35; **338**, 864.
[77] H. Fischer and J. Klarer, *Annalen*, 1926, **448**, 178.

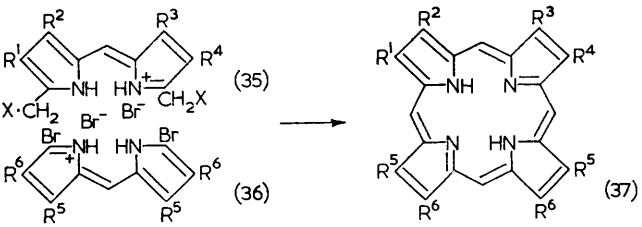
Subsequently,[78] the conditions were modified by the substitution of various organic acids for sulphuric acid, the best results being obtained when the methene was fused briefly with succinic acid or tartaric acid.

A further modification which occasionally led to improved yields was the use of 5-bromo-5′-bromomethylmethenes, when available. The general synthesis, therefore, is represented by (33; X = Br or H → 34).



In this type of synthesis each dipyrromethene supplies one of the bridge carbon atoms and a single porphyrin can be expected only if both dipyrromethenes are identical, *i.e.*, the self-condensation of a single dipyrromethene. When different dipyrromethenes are employed three porphyrins can be formed; one by cross-condensation and two by self–condensation. Nevertheless the cross-condensation of two dipyrromethenes of this type has been used with some success, especially when the physical properties of the three porphins so obtained facilitate their ready separation as, for example,[79] in the separation of mesoporphyrin-I from ætioporphyrin-I and coproporphyrin-I formed as by-products.

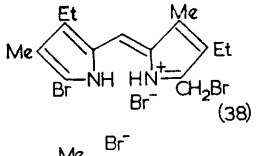
A logical variation of this method was developed[68] to overcome this shortcoming. A 5,5′-dimethyl- or 5,5′-dibromomethyl-dipyrromethene (35; X = H or Br) was condensed under similar conditions with a 5,5′-dibromodipyrromethene (36) to give the porphin (37). In this variation, one dipyrromethene component supplies both bridge carbon atoms. Unfortunately, this method is also limited in that a single porphin can be obtained only if both of the dipyrromethenes (35 and 36) are symmetrically substituted.



[78] H. Fischer, H. Friedrich, W. Lamatsch, and K. Morgenroth, *Annalen*, 1928, **466**, 147.

[79] H. Fischer and A. Kirrmann, *Compt. rend.*, 1929, **189**, 467.

A third variation has been applied to the synthesis of pyrroporphyrin-XVIII[80] (40) by the condensation of the dipyrromethenes (38) and (39), to give the two porphins (40) and (41) which were readily separated since (40) carries a carboxylic acid grouping. In this case, formally analogous to the first method, the self-condensation of (39) is avoided by using a non-brominated dipyrromethene.



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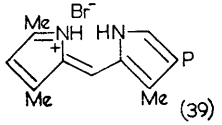
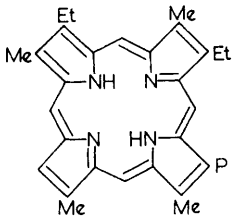
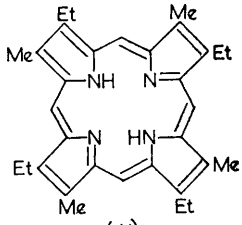


(39)



(40)



(41)

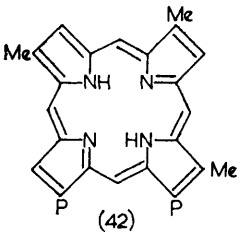
These classical syntheses of porphins by the fusion of dipyrromethenes suffer from other limitations. First, the rather severe experimental conditions do not permit the full retention of labile (electronegative and unsaturated) substituents. Thus the yield of rhodoporphyrin-XV by condensation of the appropriate dipyrromethenes was $<0{\cdot}1\%$.[81] Secondly, *meso*-substituents are partly or completely eliminated; for example, the yield of γ-phylloporphyrin-XV by this method was also low, and a mixture of eight different porphins was obtained.[82]

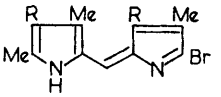
Despite all of these limitations the synthesis of porphins from dipyrromethenes by the classical Fischer method has remained a standard synthetical approach to porphins and a vast number of them has been prepared by these methods.[83] As a consequence of these syntheses, Fischer and his school deduced the structures of hæmin, chlorophylls-*a* and -*b* and achieved the classical synthesis of hæmin in 1929.[84] A more recent outstanding example of the application of this method was the synthesis of cytodeuteroporphyrin, a degradation product (42) of hæmin-*a* by MacDonald and his colleagues.[85]

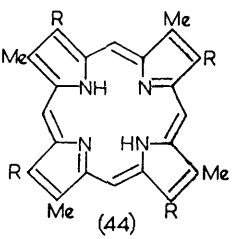
Other methods have been developed for the synthesis of porphins from dipyrromethenes. Thus Corwin and Sydow[86] prepared ætioporphyrin-I copper complex by treatment of the dipyrromethene (43; R = Et) with boiling t-butylamine, and the tetraethoxycarbonylporphin copper complex (44; R = CO_2 Et) was similarly obtained by the action of cuprous chloride in boiling naphthalene on (43; R = CO_2Et). The free porphyrin was also

[80] H. Fischer and A. Schormuller, *Annalen*, 1929, **473**, 211.
[81] H. Fischer, H. Berg, and A. Schormuller, *Annalen*, 1930, **480**, 113.
[82] H. Fischer and H. Helberger, *Annalen*, 1930, **480**, 235.
[83] Ref. 18, p. 158, *et seq.*
[84] H. Fischer, *Naturwiss.*, 1929, **17**, 611.
[85] G. S. Marks, D. K. Dougall, E. Bullock, and S. F. MacDonald, *J. Amer. Chem. Soc.*, 1960, **82**, 3183.
[86] A. H. Corwin and V. L. Sydow, *J. Amer. Chem. Soc.*, 1953, **75**, 4484.

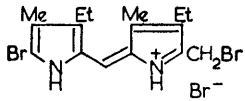
obtained in 2% yield from the hydrobromide of (43; R = CO_2 Et) and metallic silver in molten terphenyl.[87]

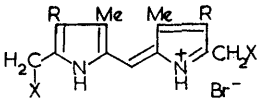

(42)


(43)


(44)

Small yields of ætioporphyrin-I–palladium complex have been obtained[88] from an ethanolic solution of the dipyrromethene (45) by the action of palladium oxide on calcium carbonate.


(45)


(46)

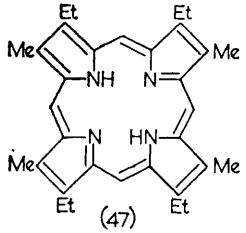
Yields of up to 21% of ætioporphyrin-II, as its copper complex, have been obtained from the dipyrromethene (46; X = OH or OMe, R = Et) under mild conditions by the action of cupric acetate in methanol.[35] Other metal salts were ineffective and the reaction with cupric salts is attributed to their ability to form square planar intermediates, necessary for porphin formation. This reaction has also been used[58] to prepare coproporphyrin-II from (46; X = OMe, R = $CH_2 \cdot CH_2 \cdot CO_2Me$).

However if porphin mixtures are to be avoided, the usefulness of these methods is again limited to the self-condensation of one dipyrromethene.

(iv) **From Linear Tetrapyrroles.**—Redistribution reactions during coupling reactions of dipyrromethenes and dipyrromethanes in porphin syntheses, as well as limitations with regard to symmetry, led to the development of alternatives, particularly designed for the preparations of porphins containing unsymmetrically arranged β-substituents. Ideally these syntheses should involve the coupling of pyrroles individually in a specific way utilising stable intermediates with the penultimate formation of a linear tetrapyrrolic compound which is subsequently cyclised to the porphin. Several studies on this so-called "stepwise" porphin syntheses have been reported recently, the first by Corwin and Coolidge,[87] who hydrolysed the 1,19-dideoxybilane ester (11) (p. 214) and treated the

[87] A. H. Corwin, W. S. Caughey, and R. Singh, *J. Org. Chem.*, 1960, **25**, 290.
[88] A. W. Johnson, I. T. Kay, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, 1959, 3416.

product with formic acid to give a porphin claimed to be ætioporphyrin-II (47). It should be noted however that the conditions employed for the final ring closure have been known to cause methane bridge cleavage with the resultant production of more than one porphin isomer.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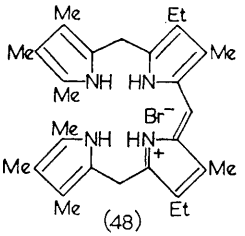
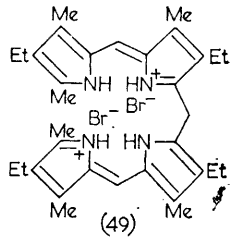
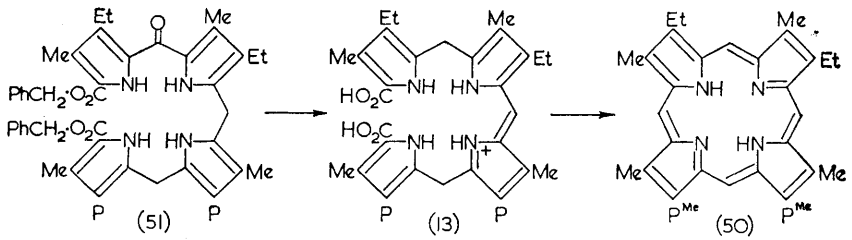

(48)


(49)

Johnson and Kay[85] found that both the 1,19-dideoxybilene-*b* (48) and the 1,19-dideoxybiladiene-*ac* (49) underwent an easy oxidative cyclisation to the corresponding porphin–copper complex in the presence of cupric salts and yields of 20—30% were recorded. As in the case of the oxidative condensations of dipyrromethenes by cupric salts, the cyclisation is probably facilitated by the intermediate formation of a planar cupric complex where the reactive terminal positions are held in juxtaposition. This easy cyclisation of linear tetrapyrroles cannot be regarded as a stepwise porphin synthesis however, since the method of preparation of the linear tetrapyrroles necessitated that the terminal rings were identical. Furthermore, in an evaluation of this method of porphin synthesis it was found[89] that although β-acetyl groups in the terminal rings survived the mild cyclisation conditions, the yield of porphin was lowered to prohibitive levels. Presumably the acetyl groups deactivate the terminal methyl groups.[90]

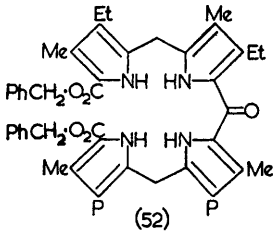
Two new related porphin syntheses have recently been reported by Jackson, Kenner, McGillivray, and Sach.[34] In one method the 1,19-dideoxybilene-*b*-1,19-dicarboxylic acid (13) (p. 214) was cyclised by treatment with methyl orthoformate–trichloroacetic acid and the resulting product on æration gave mesoporphyrin-IX (50) in 25% overall yield from the *a*-oxobilane (51).


(51) (13) (50)

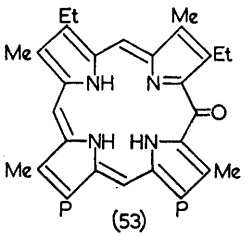
[89] G. M. Badger, R. L. N. Harris, and R. A. Jones, *Austral. J. Chem.*, 1964, **17**, 1013.
[90] A. F. Mironov, R. P. Evstigneeva, and N. A. Preobrazhensky, *Tetrahedron Letters*, 1965, 183.

Two other porphins were also prepared by this route and the yields were shown to be of the same order.

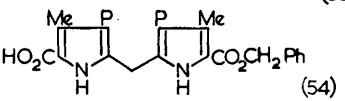
The second method involved the synthesis of the 1,19-dideoxy-*b*-oxobilane (52) followed by hydrogenolysis and decarboxylation to the corresponding 1,19-dideoxy-*b*-oxobilane with free terminal (1,19) positions. This was then cyclised by the use of methyl orthoformate–boron trifluoride ether complex to the "β-hydroxyporphyrin" (53), sodium amalgam reduction of which gave the porphin (50) in 24% overall yield from (52).



(52)



(53)



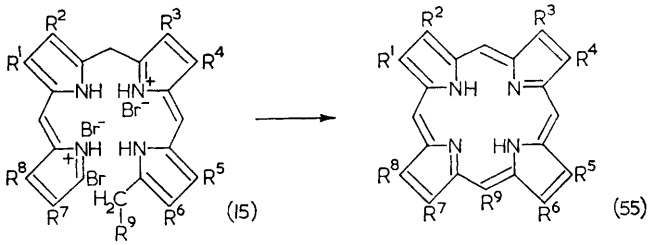
(54)

Clearly, these methods are limited to the synthesis of porphins bearing substituents which are capable of withstanding the conditions of the intermediate steps; in particular, reductions involving either diborane or sodium amalgam. Furthermore, the intermediate dipyrromethane monocarboxylic esters (*e.g.*, 54) were prepared by partial hydrogenation of the dibenzyl esters and the direction of this partial hydrogenation may be difficult to control in the case of an unsymmetrically substituted dipyrromethane. The relatively large number of steps in the syntheses is also a major drawback.

Attempts have also been made[39] to develop a porphin synthesis by the cyclisation of 1,19-dideoxybilenes-*a* of type (14) (p. 215) but nuclear magnetic resonance (n.m.r.) examination of the porphins so obtained clearly demonstrated that the products were mixtures and the authors concluded that the synthesis was not synthetically useful.

A novel stepwise synthesis of porphins and related macrocycles has recently been reported by Harris, Johnson, and Kay.[40] This is essentially a two-stage Fischer dipyrromethene condensation in which orientation difficulties of the coupling have been overcome by the isolation of the intermediate 1,19-dideoxybiladiene-*ac* salts (15) (p. 215). These were then cyclised to the corresponding porphins (55) in yields of up to 81% by heating their solutions in *o*-dichlorobenzene. Using this method, nine porphins were synthesised and were shown to be homogeneous and logically derived from the corresponding 1,19-dideoxybiladiene-*ac*. Furthermore the method also permits the retention of electronegative and

meso-groups, as evidenced by the synthesis of rhodoporphyrins and γ-phylloporphyrin-XV. Recently, the final cyclisation has been achieved at room temperature by employing dimethyl sulphoxide and pyridine as solvent. Yields of porphins when this modified cyclisation method was used have been as high as 87%.[91]



Synthesis of Reduced Porphins

(i) **Chlorins.**—The chlorin or 18,19-dihydroporphin ring system is the chromophore of chlorophyll and has therefore been studied extensively. Chlorins were prepared by Fischer[92] either by reduction of porphins, usually with sodium and alcohols, or by degradation of chlorophyll. A useful method for the synthesis of simple chlorins is the self-condensation of 2-dimethylaminomethylpyrroles in presence of one equivalent of ethylmagnesium bromide in boiling xylene[93,94] and the easy quantitative dehydrogenation of the products to the corresponding porphins using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was also recorded.[95] Eisner[94] has also described the preparation of some tetrahydro- (cf. bacteriochlorophyll),[96,97] hexahydro-, and octahydro-porphins. Several naturally occurring chlorophylls other than the well-known chlorophylls-*a* and -*b* are known, and some of the structural variations have been determined. The new additions, found in species of algae and green sulphur bacteria include chlorophylls-*c*, -*d*, and -*e* and the so-called *Chlorobium* chlorophylls 650 and 660.[97] Thus chlorophyll-*d* is probably 3-formyl-3-devinylchlorophyll-*a*[98] and the *Chlorobium* chlorophylls appear to contain *trans-trans*-farnesol in place of phytol[99] and to contain a 3-α-hydroxyethyl substi-

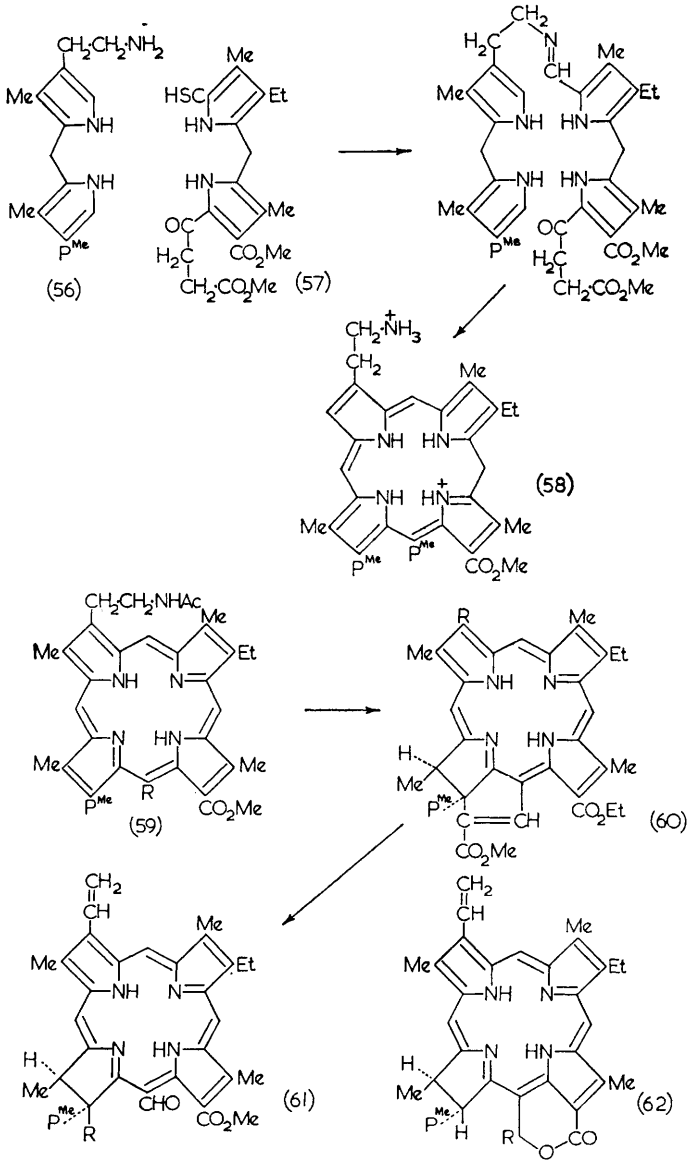
[91] P. Bamfield, R. L. N. Harris, A. W. Johnson, I. T. Kay and K. W. Shelton, *J. Chem. Soc.* (*C*), 1966, in the press.
[92] H. Fischer and A. Stern, "Die Chemie des Pyrrols", vol. IIii, Liepzig, 1940, p. 144.
[93] R. P. Linstead, *Chem. Soc. Spec. Publ. No. 3*, 1955, 83; U. Eisner, R. P. Linstead, *et al.*, *J. Chem. Soc.*, 1955, 3742; 1956, 1655; 1957, 733.
[94] U. Eisner, *J. Chem. Soc.*, 1957, 854.
[95] M. Whalley, *Chem. Soc. Spec. Publ. No. 3*, 1955, 98; U. Eisner and R. P. Linstead, *J. Chem. Soc.*, 1955, 3749.
[96] Ref. 92, p. 305 *et seq.*; J. Lascelles, ref. 2.
[97] J. H. C. Smith and C. S. French, *Ann. Rev. Plant Physiol.*, 1963, **14**, 181.
[98] A. S. Holt and H. V. Morley, *Canad. J. Chem.*, 1959, **37**, 507; J. W. Purdie and A. S. Holt, *Canad. J. Chem.*, 1965, **43**, 3347.
[99] H. Rapoport and H. P. Hamlow, *Biochem. Biophys. Res. Comm.*, 1961, **6**, 134.

tuent[100] (nomenclature, p. 210). Some synthetical studies have been reported.[101]

Perhaps the most important contribution to porphin chemistry in recent years has been the total synthesis of chlorophyll-*a* by Woodward and his colleagues.[10,102] The goal of the synthesis was chlorin-e_6, which had previously[103] been converted back into chlorophyll. The synthesis of chlorin-e_6 involved firstly the preparation of a totally unsymmetrical porphin and then the conversion of the porphin into the chlorin in such a way that the extra hydrogen atoms were introduced into ring D in a controlled manner.

As stated above the porphin was obtained by condensation of two dipyrromethanes, one of which (56) was very unstable and was allowed to react at once with the other (57) to form a Schiff's base bridging group which served to hold the molecules in position while the formation of the macrocycle was effected by the action of strong methanolic hydrogen chloride. The product (58) was the dication of a stable dihydroporphin of a novel type, the first example of a phlorin (see below) and it was oxidised to the porphin by treatment with iodine. After protection of the primary amino-group by acetylation (*i.e.*, 59; R = $-CH_2{\cdot}CH_2{\cdot}CO_2Me$), a solution of the product in warm acetic acid was oxidised by air to (59; R = $-CH{:}CH{\cdot}CO_2Me$) with an acrylic ester side-chain. The overall yield of porphin from the dipyrromethanes was *ca.* 50%. It was then found that, because of the molecular crowding around the acrylic ester grouping, the porphin (59; R = $-CH{:}CH{\cdot}CO_2Me$) could be equilibrated with the purpurin (60; R = $-CH_2{\cdot}CH_2{\cdot}NHAc$). Hydrolysis with N-methanolic hydrogen chloride and treatment with dimethyl sulphate and methanolic sodium hydroxide (Hofmann degradation) introduced the vinyl group into ring A (60; R = $-CH{:}CH_2$). Oxidation with air in presence of light caused a fission of the isocyclic ring with the formation of the purpurin (61; R = $-CO{\cdot}CO_2Me$) and dilute methanolic potassium hydroxide brought about a reverse aldol reaction in removing the oxaloyl group, with the simultaneous cyclisation of the γ-formyl group and the 13-ethoxycarbonyl group yielding a pseudo-ester (62; R = OMe, R′ = Me). Mild alkaline hydrolysis of this derivative gave racemic chlorin-5 (61; R = H), which was resolved through its quinine salts, when the (+)-chlorin-5 proved to be identical with a product obtained by degradation of chlorophyll. The remaining stages of the conversion of (+)-chlorin-5 to optically active chlorin-e_6, identical once again with a sample obtained from chlorophyll, involved the chain-lengthening of the γ-formyl group to a γ-methoxycarbonylmethyl group by standard reactions.

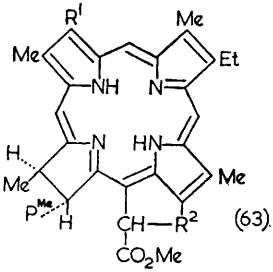
[100] A. S. Holt, D. W. Hughes, *et al.*, *J. Amer. Chem. Soc.*, 1961, **83**, 499; 1962, **84**, 2835.
[101] J. L. Archibald, S. F. MacDonald, K. B. Shaw, *et. al.*, *J. Amer. Chem. Soc.*, 1963, **85**, 644; *Canad. J. Chem.*, 1966, **44**, 345.
[102] R. B. Woodward, *Rev. Pure Appl. Chem.*, 1961, **2**, 383.
[103] A. Stoll and E. Wiedemann, *Fortschr. chem. Forsch.*, 1952, **2**, 538.



The German synthesis of phæphorbide-*a* (63; R′ = CH:CH$_2$, R^2 = CO; free acid)[104,105] relied a great deal on the earlier work from the Munich school, particularly the partial reduction of porphins to chlorins using sodium in pentyl alcohol. It will be apparent that in an unsymmetrical

[104] M. Strell, A. Kalojanoff, and H. Koller, *Angew. Chem.*, 1960, **72**, 169.
[105] M. Strell and A. Kalojanoff, *Annalen*, 1962, **652**, 218.

porphin, the addition of hydrogen can occur in any of the four rings but in this case reductions were claimed to involve only ring D, reactions which might well be re-examined using more modern physical methods for proof of identity. The starting point of the synthesis was the 3-deethylphylloporphyrin (64), itself obtained in poor yield (0·5%) by condensation of the appropriate dipyrromethenes.[106] This had been reduced to the corresponding chlorin[107] and a series of standard manipulations then used to convert the 15-methyl group into a 15-methoxycarbonylmethyl.[108] The product, 3-devinylisochlorin-e_4 (65; R′ = H, R² = $-CH_2{\cdot}CO_2Me$) as its copper derivative was diacetylated (3,13-positions) and then partly deacetylated to the 3-monoacetyl compound (65; R′ = $-CO{\cdot}CH_3$; R² = $-CH_2{\cdot}CO_2Me$).[109] The results of these acetylation studies have been questioned by Inhoffen,[110] although he was able to prepare the 3-monoacetyl compound by a modified procedure. The same product, as an optically active isomer, had been obtained by a degradation[111] of chlorophyll-*a* and thus formed a useful relay. It was reduced with sodium borohydride to the alcohol (65; R′ = $-CHOH{\cdot}CH_3$; R² = $-CH_2{\cdot}CO_2Me$) and the corresponding iron complex treated with dichloromethyl ethyl ether[cf.112] to form the isocyclic ring, although side reactions involving the 3-(α-hydroxyethyl) group also occurred. The product was therefore hydrolysed with alkali and re-methylated with diazomethane whereupon a compound (63; R′ = $-CHOH{\cdot}Me$, R² = CHOH) was obtained which was converted into phæphorbide-*a* (63; R′ = $CH{:}CH_2$,



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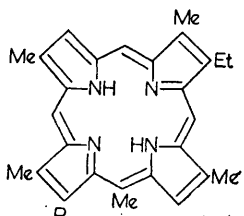

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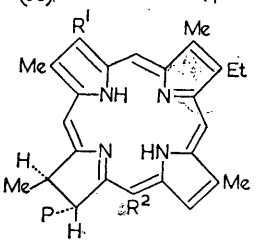


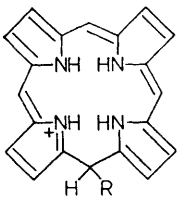
(65)

[106] A. Treibs and R. Schmidt, *Annalen*, 1952, **577**, 105.
[107] H. Fischer and F. Baláž, *Annalen*, 1942, **553**, 166.
[108] M. Strell and A. Kalojanoff, *Annalen*, 1952, **577**, 97; *Angew. Chem.*, 1954, **66**, 445.
[109] H. Fischer, F. Gerner, W. Schmetz, and F. Baláž, *Annalen*, 1944, **557**, 134.
[110] H. H. Inhoffen, *Angew. Chem., Internat. Edn.*, 1964, **3**, 322.
[111] H. Fischer and J. M. Ortis-Valez, *Annalen*, 1939, **540**, 224.
[112] H. Fischer and F. Gerner, *Annalen*, 1947, **559**, 47.

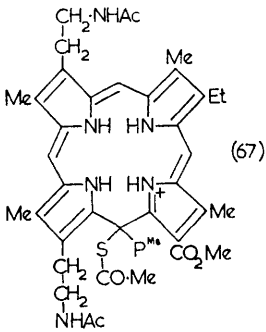
R^2 = CO; free acid rather than ester) by known reactions.[cf.113] The complexity of this synthesis, the very low yields reported for several of the stages, the omission of a resolution of the racemic compounds, and the failures to repeat some of the stages which have been reported, call for further work on this general approach.

(ii) **Phlorins.** These salts were first recognised by Woodward *et al.*[10] as intermediates in their chlorophyll synthesis (p. 227). In a more recent review, Woodward[114] has given more information on the preparation and properties of phlorin salts (66). Evidence was quoted for the existence of more than one isomeric phlorin from an unsymmetrical porphin and it was shown that, as a dihydroporphin system, the phlorins could be re-oxidised to the porphins with weak oxidising agents, *e.g.*, iodine, air, or chloranil, the blue phlorin free bases being more easily oxidised than the olive-green salts. The phlorins can also be produced by the photochemical reduction of porphins in presence of mild reducing agents, *e.g.*, ascorbic acid or tertiary amines,[115] by electrochemical reduction of porphins[116] and by the incomplete oxidation of porphyrinogens. The dihydorphlorin salts from chlorins have also been prepared.[116] It was found that thiols would add to some *meso*-substituted porphins to yield phlorins (67) by addition of the thiol at the substituted *meso*-position (cf. dipyrromethenes, p. 213).

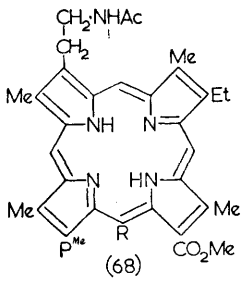
Another interesting observation was the equilibrium which exists between a porphin with crowded substituents (68; R = $CH_2 \cdot CH_2 \cdot CO_2Me$)



(66)



(67)



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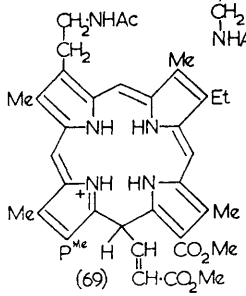

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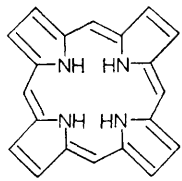
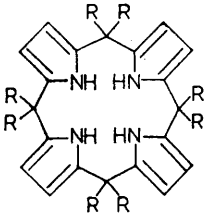


(70)

[113] H. Fischer, H. Mittenzwei, and D. B. Hevér, *Annalen*, 1940, **545**, 154.
[114] R. B. Woodward, *Ind. chim. belg.*, 1962, **27**, 1293.
[115] D. Mauzerall, *J. Amer. Chem. Soc.*, 1962, **84**, 2437.
[116] H. H. Inhoffen and P. Jäger, *Tetrahedron Letters*, 1964, 1317; 1965, 3387.

and the isomeric phlorin salt (69) in presence of acid. The structure of the latter was proved by quantitative oxidation to the corresponding porphin (68; R = $-CH{:}CH{\cdot}CO_2Me$). It was concluded that the two differently constituted electronic systems of porphins and phlorins must possess comparable energy. Interconversion of the two dihydroporphin systems, chlorins and phlorins, has not been achieved; nor has the cyclic conjugated tautomer (70; containing a 20-π-electron system) of the phlorins been observed experimentally.

(iii) **Porphyrinogens.**—These porphin reduction products are of two types: those (71; R = H) which are formally derived from the addition of six hydrogen atoms to the porphins and which readily undergo oxidation to porphins, and those which are derived by the condensation of ketones with 2,5-unsubstituted pyrroles (*e.g.*, 71; R = Me) and which do not oxidise to give porphins.



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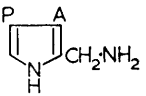


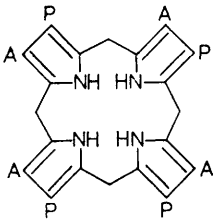
(72)

"Acetonepyrrole" was first prepared by von Baeyer[117] by the acid-catalysed condensation of acetone and pyrrole, and was later assigned the structure (71; R = Me).[118] This structure was in part confirmed by vigorous reduction studies to give mixtures of alkylpyrroles,[119] but it has received final confirmation by use of n.m.r. spectroscopy.[120] As expected, the yields of porphyrinogens formed by the condensation of ketones with pyrroles falls progressively as the size of the ketone increases.[121] Thus, the yields decrease from acetone (93·5%) through ethyl methyl ketone (54%) to benzophenone (3%).

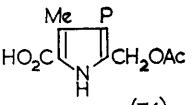
Porphyrinogens of type (71; R = H), the colourless hexahydro-derivatives of porphins, are readily prepared by the reduction of porphins using a variety of reducing agents, *e.g.*, phosphonium iodide,[122] sodium amalgam,[122] zinc dust and alkali,[122] and hydrogenation (platinum catalyst[123]). A review of the hydrogenation of porphins and tetra-azaporphins[95] is available. Porphyrinogens are also obtained by the polymerisation of porphobilinogen (72)[124] and related compounds. Thus uroporphyrinogen-

[117] A. von Baeyer, *Ber.*, 1886, **19**, 2184.
[118] V. V. Chelintzev and B. V. Tronov, *J. Russ. Phys. Chem. Soc.*, 1916, **48**, 105.
[119] P. Rothemund and C. L. Gage, *J. Amer. Chem. Soc.*, 1955, **77**, 3340.
[120] A. H. Corwin, A. B. Chivvis, and C. B. Storm, *J. Org. Chem.*, 1964, **29**, 3702.
[121] Ref. 18, p. 395.
[122] H. Fischer, H. Bartholomäus, and H. Roese, *Z. physiol. Chem.*, 1913, **84**, 262.
[123] H. Fischer and W. Zerweck, *Z. physiol. Chem.*, 1924, **137**, 242; J. B. Conant and J. F. Hyde, *J. Amer. Chem. Soc.*, 1930, **52**, 1233.
[124] D. Mauzerall, *J. Amer. Chem. Soc.*, 1960, **82**, 2605.

III (73)[125] which is formed by the enzymic polymerisation of porphobilinogen (72),[2] is an important intermediate in the biosynthetic pathway to the protoporphyrin and chlorophyll pigments.



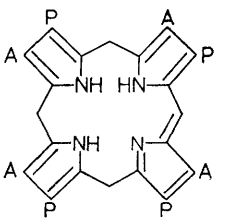
(73)



(74)

A feature of the chemistry of porphyrinogens is their thermodynamic and acid lability which in the past has often caused confusion as to the nature of the porphins derived from them. Fischer and Rotthaas[126] thus noted that reoxidation of the porphyrinogen obtained from the reduction of mesoporphyrin-IX (containing two carboxyl groups) with zinc and hot acetic acid gave a mixture of porphins having from one to three carboxyl groups per molecule.

More recently Mauzerall[115] has shown that uroporphyrinogen-III in hot acid incorporates [^{14}C]formaldehyde and is rapidly isomerised to a random mixture of isomers, and that the distribution of isomers is in agreement with the theoretically derived ratio $\frac{1}{8}$I:$\frac{1}{8}$II:$\frac{1}{2}$III:$\frac{1}{4}$IV. A similar ratio was also obtained for the polymerisation of porphobilinogen in acidic solution (cf. p. 217), and also for the distribution of coproporphyrins formed[58] by polymerisation of (74) in acidic solutions, although recently Bullock[65] has pointed out that the composition of a "random mixture" should vary with the relative nucleophilic reactivities of the 2,5-positions of the pyrrole depending upon the electronic effects of the adjacent 3,4-groups.



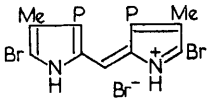
(75)

The autoxidation of uroporphyrinogen-III has been shown[125] to be photocatalytic and sensitised by the product, uroporphyrin-III. An intermediate stage in the oxidation was thought to be a porphomethene (75) possessing a dipyrromethene chromophore.

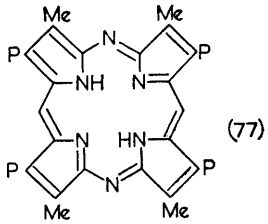
[125] D. Mauzerall and S. Granick, *J. Biol. Chem.*, 1958, **232**, 1141; S. Sano and S. Granick, *ibid.*, 1961, **236**, 1173.
[126] H. Fischer and A. Rotthaas, *Annalen*, 1930, **484**, 85.

Azaporphins (Imidoporphyrins)

These are aromatic macrocycles in which one or more of the porphin methine bridges has been replaced by imino-groups. The first synthesis[127] of a member of this group involved the prolonged action of ammonium hydroxide on the 5,5′-dibromodipyrromethene (76) and gave a small yield of the 5,15-diazacoproporphyrin-II (77). A similar reaction was used[128] to prepare 5,15-diazaoctaethylporphin.



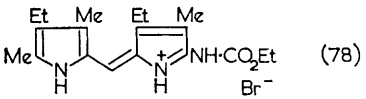
(76)



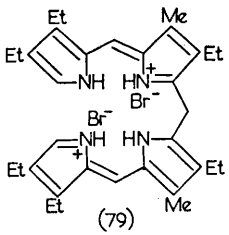
(77)

Extremely small yields of mono-azaporphins (in the ætio- and copro-series) were obtained[129] by heating the corresponding 5,5′-dibromodipyrromethenes in pyridine with aqueous alkali for 8 days at 130°, a reaction that does not appear to follow any logical course. The products from this reaction also included traces of diazaporphins and porphins. Light-absorption measurements[130] on the azaporphins prepared by these methods showed them to have spectra similar to those of the porphins.

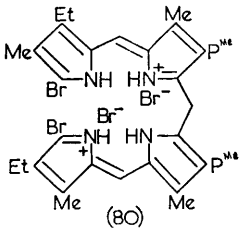
Better yields of monazaporphins were obtained[131] by treatment of the urethane (78) with bromine in acetic acid and more recently[132] as a by-product in the formation of a corrole by irradiation of the 1,19-dideoxybiladiene-*ac* (79) in the presence of ammonia.



(78)



(79)

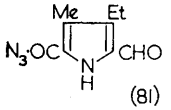


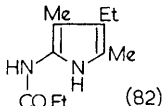
(80)

[127] H. Fischer, H. Haberland, and A. Müller, *Annalen*, 1935, **521**, 122.
[128] H. Fischer, H. Guggemos, and A. Schäfer, *Annalen*, 1939, **540**, 30.
[129] H. Fischer and W. Friedrich, *Annlaen*, 1936, **523**, 154.
[130] A. Stern, H. Wenderlein, and H. Molvig, *Z. physik. Chem.*, 1936, *A*, **177**, 40.
[131] F. Endermann and H. Fischer, *Annalen*, 1939, **538**, 172.
[132] A. W. Johnson and I. T. Kay, *J. Chem. Soc.*, 1965, 1620.

Treatment of the 1,19-dibromo-1,19-dideoxybiladiene-*ac* (80) with sodium azide[40] gave 5-azamesoporphyrin-IX (45%), a method which is probably the only truly unambiguous monoazaporphin synthesis to date.

5,15-Diazaporphins have also been obtained by heating the acid azide (81)[131] or by the action of phenylhydrazine at 160—200° on the urethane (82).[131] Prolonged treatment of the dipyrromethene-bisurethane (83) with sodium carbonate and ethanol at elevated temperatures also gave small yields of 5,15-diaza-ætioporphyrin.[133]


(81)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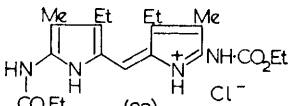
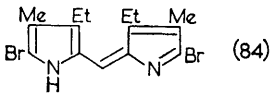

(83)

Several metal complexes of the 5,15-diazaporphins have been described[134] including the iron and magnesium complexes in the diaza-coproporphyrin series. 5,15-Diaza-ætioporphin-II copper complex has recently been prepared in high yield[135] by treating the copper complex of 5,5'-dibromodipyrromethene (84) with sodium azide in dimethylformamide.

Tetra-azaporphins (85) occupy a structurally intermediate position between phthalocyanins and porphins. The more successful syntheses of tetra-azaporphins resemble those used for phthalocyanins, *e.g.*, by heating unsaturated 1,2-dinitriles.[136]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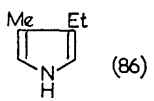
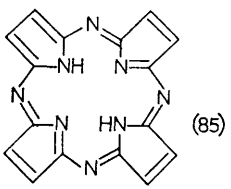

(86)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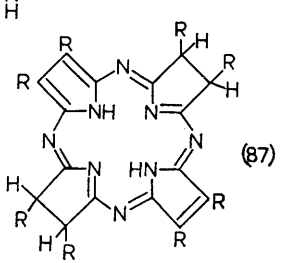

(87)

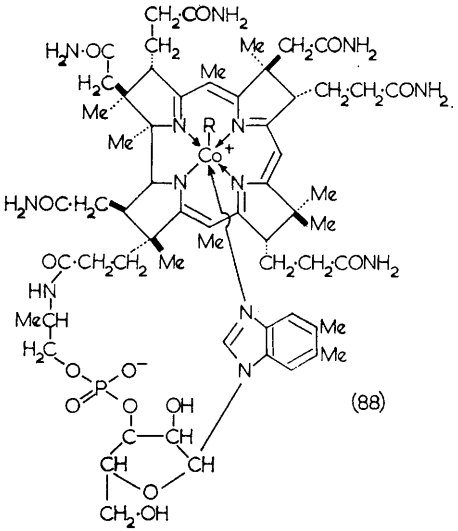
Fischer and Endermann[137] obtained a low yield of tetra-aza-ætioporphyrin (probably a mixture of isomers) by treatment of opsopyrrole (86) with bromine and ammonia in chloroform. A better synthesis was developed by Cook and Linstead,[136] who obtained fair yields of octa-

[133] W. Metzger and H. Fischer, *Annalen*, 1936, **527**, 1.
[134] H. Fischer and A. Müller, *Annalen*, 1937, **528**, 1.
[135] R. L. N. Harris, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.* (*C*), 1966, 22.
[136] A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 1937, 911, 929.
[137] H. Fischer and F. Endermann, *Annalen*, 1937, **531**, 245.

phenyltetra-azaporphin (85; R = Ph) metal complexes by heating dicyanostilbene in the presence of metals or metal salts. The latter synthesis was subsequently improved and extended (review[138]) and has been used to prepare tetramethyltetra-azaporphin,[139] the octamethyl derivative,[140] and the parent unsubstituted tetra-azaporphin.[141] Hydrogenation of tetra-azaporphin and three of its alkyl derivatives using a palladium-black catalyst gave coloured tetrahydro-derivatives[142] (*e.g.*, 87, or an isomer).

Macrocyclic Tetrapyrrolic Systems based on 2,2-Bipyrrole

The interest in these ring systems comes from their relationship to vitamin B_{12} (88; R = CN) and its coenzyme (88; R = 5′-deoxyadenosyl) (reviews[143]). The parent compound of the series has been named corrole (89)[132] and its octahydro-derivative, the basic ring system of vitamin B_{12}, is corrin (90).[4]



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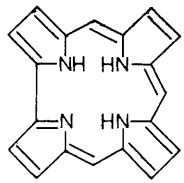

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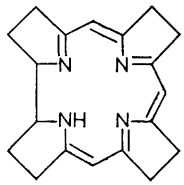
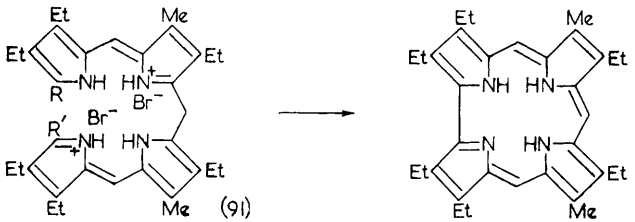


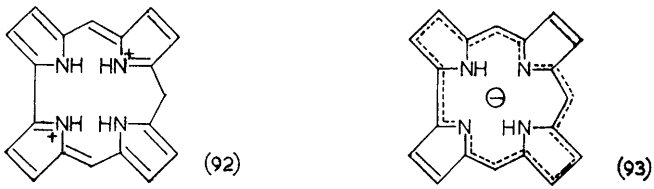
(90)

Corroles.—These compounds have been synthesised[132] by the action of light on a 1,19-diunsubstituted-1,19-dideoxybiladiene-*ac* dihydrobromide (*e.g.*, 91; R = R′ = H) in presence of base or, alternatively, by heating a solution of a 1,19-dibromo-1,19-dideoxybiladiene-*ac* (*e.g.*, 91; R = R′ = Br) in *NN*-dimethylformamide.[40] The aromatic (18-π-electron) nature of

[138] R. P. Linstead, *J. Chem. Soc.*, 1953, 2873.
[139] R. M. Brown, D. B. Spiers, and M. Whalley, *J. Chem. Soc.*, 1957, 2882.
[140] M. E. Baguley, H. France, and R. P. Linstead, *J. Chem. Soc.*, 1955, 3521.
[141] R. P. Linstead and M. Whalley, *J. Chem. Soc.*, 1952, 4839.
[142] G. E. Ficken, R. P. Linstead, E. Stephen, and M. Whalley, *J. Chem. Soc.*, 1958, 3879.
[143] R. Bonnett, *Chem. Reviews*, 1963, **63**, 573; K. Bernhauer, O. Müller, and F. Wagner, *Angew. Chem., Internat. Edn.*, 1964, **3**, 200.

the macrocycle was readily deduced from its n.m.r. spectrum in which the methine protons, deshielded at the periphery of the ring current, have a τ value of *ca.* +1, whereas the NH protons shielded at the centre of the ring current have a τ value of *ca.* 13·5. The visible spectrum of the corrole ring system also has features in common with porphins, in particular an intense Soret band at about 400 mμ.





From spectroscopic evidence it was concluded that corrole in strongly acidic solutions exists as the non-aromatic dication (92), and in alkaline solution as the aromatic anion (93). Methylation of the anion (93) occurred readily to give two isomeric *N*-methylcorroles.

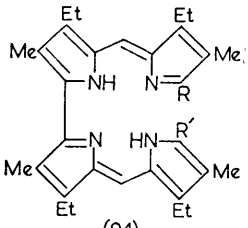
Corrole complexes of bivalent metals are derived from the non-aromatic structure (92), but on treatment with alkali, they form the complexes of the aromatic anion (93) and these, unlike (92), now contain a Soret band in the visible spectrum. It thus appears that in one of its tautomeric forms (92), corrole bears the same relation to porphin as does cyclopentadiene to benzene.

Numerous attempts[144,145] have been made to prepare corroles by the ring closure of 5,5-bis(dipyrromethenyls) (94) containing a variety of terminal substituents (R, R′) but all have been unsuccessful.

Corroles containing Heterocyclic Atoms at the 10-Position.—These aromatic (18-π-electron) macrocycles (95; X = O, NH, NMe, S) may be regarded[132] as the furan, pyrrole, *N*-methylpyrrole, and thiophen analogues of the porphins, and are prepared by the action of aqueous acid, ammonia, methylamine, and sodium sulphide respectively on the 5,5-bis-(5′-bromodipyrromethenyl) (94; R = R′ = Br) metal complexes, followed by removal of the metal with acid. The metallic derivatives of the macrocycles

[144] A. W. Johnson and R. Price, *J. Chem. Soc.*, 1960, 1649.
[145] A. W. Johnson, I. T. Kay, and R. Rodrigo, *J. Chem. Soc.*, 1963, 2336.

(95) have visible spectra similar to those of porphin–metal complexes. The formation of the cyclic ether (95; X = O) has been shown to proceed through the chloro-lactam (96) which rapidly cyclises to derivatives of (95; X = O) in the presence of metal salts.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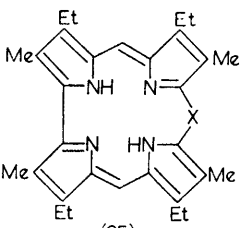
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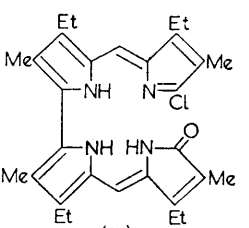
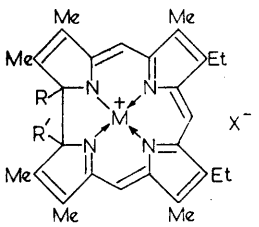
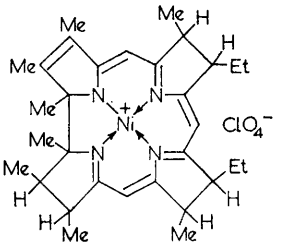

(96)

Tetradehydrocorrins.—Two types of non-aromatic tetradehydrocorrins, as their metal complexes, have recently been synthesised from 1,19-dideoxybiladienes-*ac*, containing a variety of terminal groups.


(97)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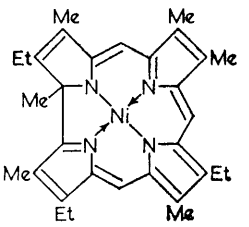

(99)

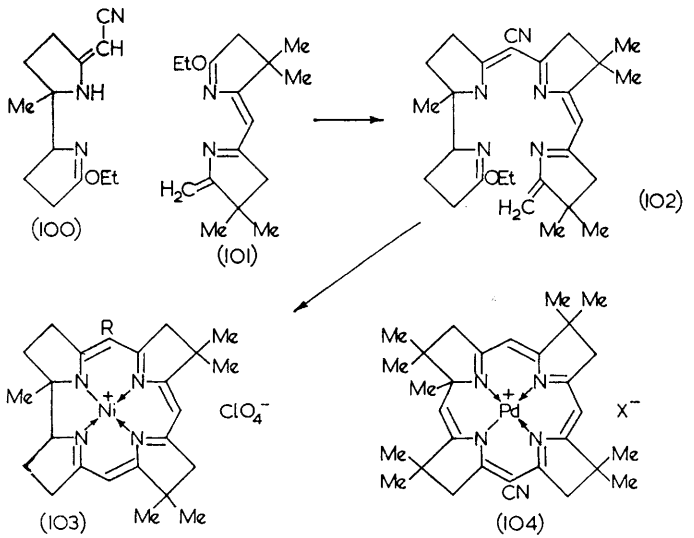
Treatment of the 1,19-dideoxybiladiene-*ac* salts (91; R = R′ = Me or CO_2Et; R = Me, R′ = CO_2Et) with nickel or cobalt ions in the presence of a base and with æration gives the cationic tetradehydrocorrin complexes of type (97; M = Co^{II} or Ni^{II}, X = Cl, NO_3, or ClO_4).[146,147] Proof of this structure is furnished by the n.m.r. spectrum of (97; R = R′ = Me, M = Ni^{II}, X = NO_3^-) in which the 1,19-dimethyl groups appear at τ 9·34. Several derivatives of (97) have been described including *meso*-methyl and hydrogenated derivatives. Thus hydrogenation under pressure of (97; R = R′ = Me; X^- = ClO_4^-) in presence of Raney nickel at 100° gave a product which is provisionally formulated as the monodehydrocorrin (98). An inter-relation between the tetradehydrocorrin and corrole series has been afforded by the conversion of (97; R = R′ = CO_2Et; X = ClO_4 M = Co) to the corresponding cobaltous corrole by removal of the ester groups by hydrolysis and decarboxylation.[146]

[146] D. Dolphin, R. L. N. Harris, J. L. Huppatz, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.* (*C*), 1966, 30.
[147] D. Dolphin, R. L. N. Harris, A. W. Johnson, and I. T. Kay, *Proc. Chem. Soc.*, 1964, 359.

A second type of tetradehydrocorrin (99) has been obtained[148] by the cyclisation of the corresponding 19-bromo-1-methyl-1,19-dideoxybiladienes-*ac* in the presence of nickel ions. These neutral complexes readily undergo protonation at C(19) in the presence of strong acids to give cationic tetradehydrocorrins believed to be of type (97; R = Me, R′ = H, M = Ni^{II}).

Thus, by cyclisation under different experimental conditions, the 19-bromo-1-methyl-1,19-dideoxybiladienes-*ac* may give rise either to porphins (p. 225) or to tetradehydrocorrins of type (99) and it is tempting to suggest that the latter type of cyclisation or a closely related reaction is involved in the biogenesis of cobalamins. Biosynthetic experiments have shown that porphobilinogen (72) is intermediate both in the *in vivo* synthesis of porphins[2] and of cobalamins[149] and a linear tetrapyrrole could well be the point of divergence in the biosyntheses of these two important groups.

Corrins.—In a notable paper,[150] Eschenmoser and his colleagues have described the total synthesis of a corrin (103; R = H). In the synthesis extensive use was made of the Meerwein reagents, trialkyloxonium salts, for the conversion of an amide into the corresponding imino-ether, and the ability of these imino-ethers derived from cyclic amides to react with nucleophils, particularly carbanions, to link the various rings. The two components required for the final cyclisation were (100) and (101), and elaborate syntheses were evolved for each of these. The products were



[148] R. L. N. Harris, A. W. Johnson, and I. T. Kay, *Chem. Comm.*, 1965, 355.
[149] D. Shemin and R. C. Bray, *Ann. New York Acad. Sci.*, 1964, **122**, 615.
[150] A. Eschenmoser, *Pure Appl. Chem.*, 1963, **7**, 297; E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. J. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem., Internat. Edn.*, 1964, **3**, 490.

condensed together in presence of sodium ethoxide to yield (102) which was converted to its nickel complex by the action of nickel perchlorate in acetonitrile. Cyclisation to the macrocycle (103; R = CN) was then achieved by the action of potassium t-butoxide in t-butyl alcohol, and as a final step, the cyano-group was removed by hydrolysis and decarboxylation with dilute hydrochloric acid at 220°. The structure of the corrin nickel complex so produced (103; R = H) was confirmed by measurements of its n.m.r. spectrum and the *X*-ray diffraction pattern. A variation of these syntheses gives rise to a 1-substituted octahydroporphin derivative[151] (104).

Details are not yet published of the work initiated by Woodward and Cornforth in their respective schools on the total synthesis of vitamin B_{12}, which has been described in various public lectures, but it is clear that many other exciting developments can be expected in this field.

Physical Properties of Porphins and Chlorins

Many of the physical properties, particularly the characteristic ultraviolet and visible spectra of porphins, have been reviewed at length earlier,[3] and it is intended to make only brief reference to certain more recent work. *X*-Ray diffraction studies have been outstanding. A detailed study of the porphin–protein complexes myoglobin and hæmoglobin by Perutz, Kendrew, and their collaborators (reviews[152]) have led to remarkably detailed structures of these complex molecules. Coupled with the results of extensive chemical studies, the amino-acid sequences in the protein chains are now known, as is also the case for cytochrome-*c*.[153] Equally distinguished has been the *X*-ray crystallographic studies by Dorothy Crowfoot-Hodgkin and her associates on vitamin B_{12}[154] and its co-enzyme,[155] which culminated in the elucidation of the complete structures.

As regards the porphins themselves, several *X*-ray studies have been reported, *e.g.*, porphin itself,[156] *meso*-tetraphenylporphin and derivatives,[157] the nickel complexes of ætioporphyrin-I[158] and 3,8-diacetyldeuteropor-

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phyrin-IX dimethyl ester,[159] and the methoxyiron(III) complex of meso-porphyrin-IX dimethyl ester.[160] Some of these molecules were found to show appreciable deviations from the planar form.

Many studies have been made recently of the highly distinctive nuclear magnetic resonance (n.m.r.) spectra of porphins (review[161]). The spectra are characterised by signals at very low field (*ca.* -1 to $+1\tau$) associated with the *meso*-protons and at very high field (*ca.* 13—16τ) associated with the imino-protons. This wide spread is explained by the large induced ring current which deshields the substituents on the periphery of the ring and shields those on the inside of the ring. Deuteriochloroform is commonly used as solvent for these measurements but the concentration should be stated as the position and splitting of the signals may vary with dilution.[162] Porphins are usually soluble in trifluoroacetic acid when they are present as the corresponding dications, but the carboxylic proton absorbs in the same region as the *meso*-protons. Use of deuteriotrifluoroacetic acid overcomes this drawback, but in this case no signals from the imino-protons are observed owing to exchange. Detailed studies of the resonances due to β-alkyl substituents,[163] and the general effects of electron-withdrawing β-substituents,[164] *N*-alkyl substituents,[165] and *meso*-substituents[166,167] have been made. N.m.r. spectra of chlorins reflect the overall decrease in aromatic character in that the resonances of the *meso*-protons are shifted upfield and those of the imino-protons shifted downfield relative to porphin spectra. The lack of symmetry in the chlorin molecule caused by the extra hydrogens on ring D leads to a generally more complex spectrum. Calculations of the electron densities for porphin and chlorin molecules have been made.[168]

Studies of the mass spectra of porphins and chlorins have been reported recently[169] and details of fragmentation patterns have been given. As expected the large aromatic system is very stable and the substituents of the reduced ring in the chlorins are more labile than the porphin substituents.

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Substitution Reactions of Porphins and Chlorins

(i) **Deuteration.**—It has been suggested[170] that in the electronic system of porphins, the π-electrons tend to segregate into sextets in the pyrrole rings leaving the methene bridge positions electron-deficient. In support of this no change in the n.m.r. spectrum of rhodoporphyrin-XV dimethyl ester was observed after treatment with deuterioacetic acid at 90° for 5 hours. However, exchange of porphin *meso*-protons for deuterium has been observed[170] if the reaction conditions are sufficiently vigorous, *e.g.*, octaethylporphin with deuteriotrifluoroacetic acid at 100° for one month or 90% deuteriosulphuric acid in deuterium oxide at 20° overnight. The presence of an electron-donating *meso*-substituent, *e.g.*, as in *meso*-aminoætioporphyrin-I[167] permits mono-*meso*-deuteration to occur readily at room temperature with deuteriotrifluoroacetic acid and after one hour at 100°, the remaining *meso*-protons were exchanged. Chlorins, on the other hand, are susceptible to deuteration at the *meso*-positions (15 and 20) at either side of the reduced ring D.[170,171] At 100°, treatment of octaethylchlorin with deuterioacetic acid caused exchange also at the remaining *meso*-positions (5 and 10) and this occurred faster than the exchange reactions of the corresponding porphin in contrast to the theoretical predictions of Pullman.[168] The presence of the two labile *meso*-protons in chlorins gave rise to a little confusion in the case of chlorophyll, but it was eventually shown that the rate of exchange of the C(26) proton (of the isocyclic β-keto-ester) was at least two orders of magnitude more rapid than that of the C(20) *meso*-proton.[172]

(ii) **Other Electrophilic Substitution Reactions.**—Electron-density calculations suggest that an unsubstituted β-position in a porphin is more susceptible to electrophilic attack than a *meso*-position, and for example, bromination has been recommended[173] as a method which will permit the recognition of a free β-position. However prophins which are substituted in all eight β-positions are also subject to electrophilic substitution and Hans Fischer and his co-workers have described the preparation of a number of halogeno-,[174] nitroso-,[175] nitro-,[175] and sulphonic acid[176] substitution products from such compounds. It is possible that some nitrosoporphyrins may have physiological significance.[177] The orientation of the substituents in these compounds was not, however, always established with certainty. Although Fischer regarded certain of the halogeno- and sul-

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[171] R. Bonnett and G. Stephenson, *Proc. Chem. Soc.*, 1964, 296.
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[173] A. Treibs, *et al.*, *Annalen*, 1928, **466**, 188, 264.
[174] Ref. 18, p. 230.
[175] Ref. 18, p. 263.
[176] Ref. 18, p. 554.
[177] J. B. Fox and J. S. Thomson, *Biochemistry*, 1964, **3**, 1323.

phonic acid derivatives as *meso*-substitution products, the structure of the nitro-porphyrins has been variously formulated as containing side-chain nitro-substituents[178] and *meso*-nitro substituents.[179] An examination of the nitration products of ætioporphyrin-I[167] and octaethylporphin,[180] largely on the basis of the n.m.r. spectra, has shown that the nitro-groups are *meso*-substituted. Reduction of mono-nitroætioporphyrin-I gave the corresponding amino-compound which yielded a mononitro-monoamino-derivative on treatment with nitrous acid.[167]

(iii) **Oxidation of Porphins.**—The 10-*meso*-hydroxy-derivative of meso-porphyrin-IX has been obtained by a ring synthetic method[34] although the keto-structure (87) was favoured for the product. Similar *meso*-hydroxy-porphins appear to be formed by direct oxidation of the porphin by hydrogen peroxide or peroxy-radicals.[181] Reactions of porphins with osmium tetroxide, usually in pyridine solution, led to the formation of 17,18-dihydroxychlorins by direct hydroxylation.[182,183] When the hydroxylation of porphins was effected with hydrogen peroxide in presence of sulphuric acid[184] or when the 17,18-dihydroxychlorins were treated with sulphuric acid or oleum,[183] the so-called anhydrides of the 17,18-dihydroxychlorins were formed. It is possible that the product obtained from meso-porphyrin-IX by irradiation of a pyridine solution in presence of air[185] also belonged to this type. A reinvestigation[167,186] has shown that the main products formed by oxidation of ætioporphyrin-I or octaethylporphin with hydrogen peroxide in presence of sulphuric acid[184] are ketones *e.g.*, (88) formed in *ca.* 20% yield and produced by a pinacol rearrangement of the intermediate diols. The so-called "dioxychlorins" which were obtained by oxidation of chlorins (V; R = R′ = H), *e.g.*, by silver oxide and oxygen, and which were believed by Fischer[187] to be 17,18-dihydroxychlorins, have been shown[170] to be 20-chloro-chlorins formed by the action of the nascent chlorine liberated during the "purification".

(iv) **Reduction of Porphins.**—The well-defined reduction products of porphins, chlorins, porphyrinogens, and phlorins, are treated elsewhere in this Review but attention might also be drawn to the spectral evidence for

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[181] H. Libowitsky and H. Fischer, *Z. physiol. Chem.*, 1938, **255**, 209; H. Fischer and K. Herrle, *ibid.*, **251**, 85; R. Lemberg, B. Cortis-Jones, and M. Norrie, *Biochem. J.*, 1938, **32**, 149; K. Anan and H. S. Mason, *J. Biochem.* (*Tokyo*), 1961, **49**, 765.
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the existence of metalloporphin negative ions[188] formed by reduction with alkali metal derivatives. Photochemical oxidation–reduction studies of some porphins and their metal complexes have also been reported.[115,189]

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