Recent Developments in the Chemistry of Pyrrolic Compounds

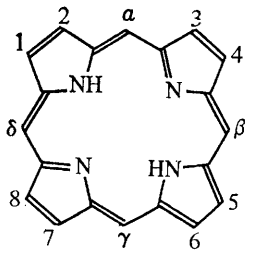
By K. M. Smith
ROBERT ROBINSON LABORATORIES, UNIVERSITY OF LIVERPOOL

1 Introduction

The previous Quarterly Review[1] in this general area of chemistry covered synthetic aspects of the literature up to October 1965. It is intended that this Review shall comment upon selected developments within the field since that time, in a way which will indicate the overall direction of current research in this branch of chemistry. Monopyrrolic substances will be discussed only briefly, so that more space can be given to developments in the chemistry of polypyrrolic compounds. The Review is designed to be more biologically inclined than a recent one[2] by members of the Braunschweig School. Literature received in England after the beginning of July 1970 has not been considered.

2 Nomenclature

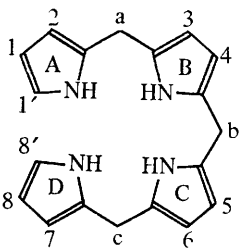
The advantages of various systems for numbering the porphyrin nucleus are at present under active discussion with a view to choosing a unified convention. For the purposes of this Review, the Fischer system (1) will be used for porphyrins, since it provides continuity with the classical literature[3] (to which much of



1 – 8 peripheral positions

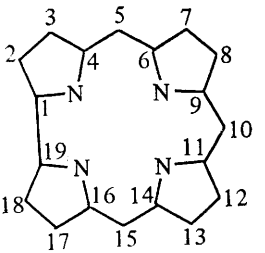
a, *β*, *γ*, *δ* *meso*-positions

(1)



'Bilane'

(2)



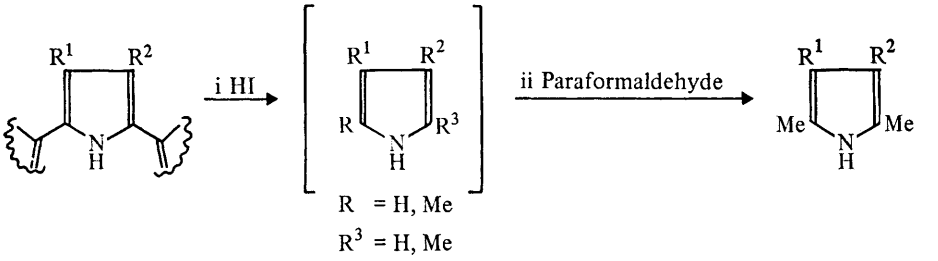
(3)

[1] R. L. N. Harris, A. W. Johnson, and I. T. Kay, *Quart. Rev.*, 1966, **20**, 211.
[2] H. H. Inhoffen, J. W. Buchler, and P. Jäger, *Fortschr. Chem. org. Naturstoffe*, 1968, **26**, 284.
[3] *E.g.* H. Fischer and H. Orth, 'Die Chemie des Pyrrols', Vols. I, IIi and IIii, Akad. Verlagsges., Leipzig, 1934—1940. An excellent reprint of these books is now available; Johnson Reprint Corp., New York and London, 1968.

current progress is directly related) and with the bile pigment nomenclature (2). The system (3) will be used for corrinoid compounds, as recommended by I.U.P.A.C.

3 Pyrroles

A viable route to some hitherto relatively inaccessible pyrroles is provided by 'reductive C-alkylation'[4] (Scheme 1) and it appears that the method may also be

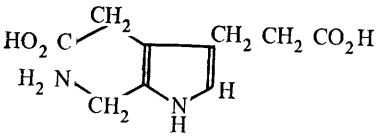


Scheme 1

applicable to the degradative structure determination of porphyrins. Existing procedures in the literature are not completely satisfactory; reduction of porphyrins with hydriodic acid usually gives homologous mixtures of unstable pyrroles, which are only poorly suited to separation and identification (*e.g.* by g.l.p.c.). The fact that this method furnishes up to four pyrroles from each monocyclic unit of the porphyrin nucleus has led to a greater reliance on oxidative degradation. Potassium permanganate in potassium carbonate solution[5] gives a mixture of pyrrole dicarboxylic acids, often in low yields, while room temperature oxidation of porphyrins with chromic acid yields a mixture of maleiimides. Monocyclic units of the macrocycle which bear labile side-chains (*e.g.* formyl, vinyl *etc.*) are not recovered intact. Reductive C-alkylation involves the reduction of the porphyrin with hydriodic acid followed by addition of paraformaldehyde to the reaction mixture. In this way, mixtures of tetrasubstituted pyrroles are obtained which are quite stable and can be efficiently identified and separated by g.l.p.c. An added bonus to the method is that porphyrins bearing *meso*-substituents are degraded to pyrroles in which the *meso*-function is retained in the corresponding pyrrole α-side-chain.[4a] Rüdiger[6] has recently reported a new oxidative structure determination method for bile pigments.

[4] (*a*) B. V. Gregorovitch, K. S. Y. Liang, D. M. Clugston, and S. F. MacDonald, *Canad. J. Chem.*, 1968, **46**, 3291; (*b*) M. W. Roomi and S. F. MacDonald, *ibid.*, 1970, **48**, 139.
[5] R. A. Nicolaus, L. Mangoni, and L. Caglioti, *Ann. Chim. (Italy)*, 1956, **46**, 793.
[6] W. Rüdiger in 'Porphyrins and Related Compounds', Biochemical Symposium No. 28, ed. T. W. Goodwin, Academic Press, London, 1968, p. 121.

Much interest has centred on porphobilinogen (PBG) (4) which, after its isolation[7] from the urine of patients suffering from acute porphyria, has been



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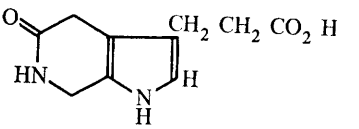

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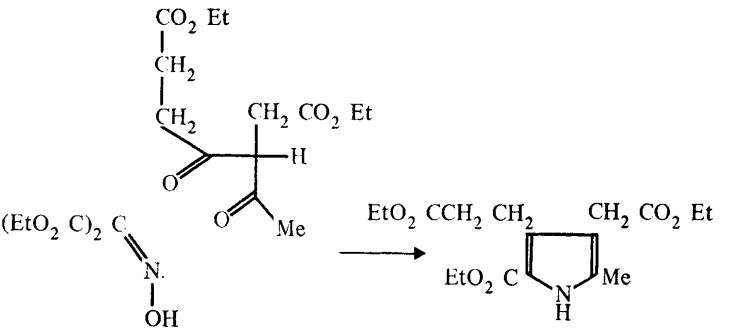

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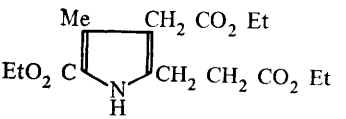
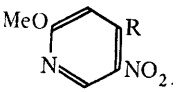


Scheme 2

[7] R. G. Westall, *Nature*, 1952, **170**, 614.

shown to be the direct biosynthetic precursor of the blood and plant pigments. Earlier syntheses[8] of PBG have been improved[9] by increased efficiency in the preparation of (6) (Scheme 2), which had earlier been converted to PBG in 29% yield.[8c] An ingenious synthesis of PBG by Rapoport and co-workers[10] takes into account the readily reversible transformation of PBG into its lactam (5). Thus, the trisubstituted pyridine derivative (7; R = Me) was elaborated to the azaindole (8) *via* (7; R = CH_2COCO_2Et). The required propionic acid side-chain was constructed by means of a Mannich reaction and diethylsodiomalonate, furnishing (9) after exhaustive hydrolysis. Catalytic reduction of the pyridone ring in (9) gave (10), which underwent ready decarboxylation to PBG lactam (5). The final



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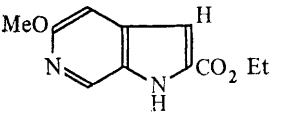

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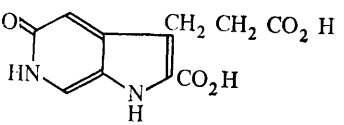

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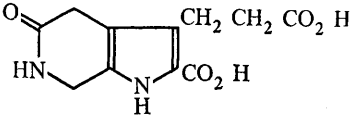


(10)

step to PBG was accomplished with dilute alkali, the overall yield of 19% from the pyridine (7; R = Me) representing a considerable improvement on existing synthetic routes.

4 Dipyrrolic Compounds

A. Pyrromethanes (Dipyrrylmethanes).—Until recently it was thought that pyrromethanes [*e.g.* (13)] were unsuitable intermediates for the synthesis of porphyrins, due to their acid lability unless substituted with electron-withdrawing groups. The success of the variations of the MacDonald synthesis (see Section 5) has now shown beyond any doubt that pyrromethanes are indeed of great utility. Considerable effort has been devoted to pyrromethane synthesis.[11] The

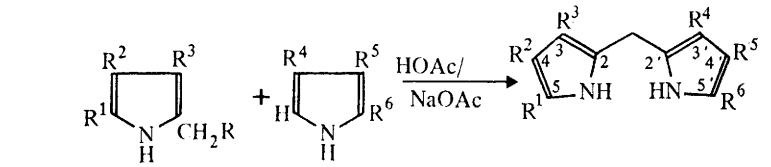
[8] (*a*) A. H. Jackson, D. M. MacDonald, and S. F. MacDonald, *J. Amer. Chem. Soc.*, 1956, **78**, 505; (*b*) A. H. Jackson and S. F. MacDonald, *Canad. J. Chem.*, 1957, **35**, 715; (*c*) G. P. Arsenault and S. F. MacDonald, *ibid.*, 1961, **39**, 2043.

[9] H. Plieninger, P. Hess, and J. Ruppert, *Chem. Ber.*, 1968, **101**, 240.

[10] B. Frydman, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, 1965, **87**, 3530; B. Frydman, S. Reil, M. E. Despuy, and H. Rapoport, *ibid.*, 1969, **91**, 2338.

[11] *E.g.* Ref. 3, Vol. I, p. 331; A. H. Jackson, G. W. Kenner, and D. Warburton, *J. Chem. Soc.*, 1965, 1328; E. J. Tarlton, S. F. MacDonald, and E. Baltazzi, *J. Amer. Chem. Soc.*, 1960, **82**, 4389.

most widely applicable of all approaches to unsymmetrical pyrromethanes is outlined in Scheme 3; condensation of an α-unsubstituted pyrrole (12) with a

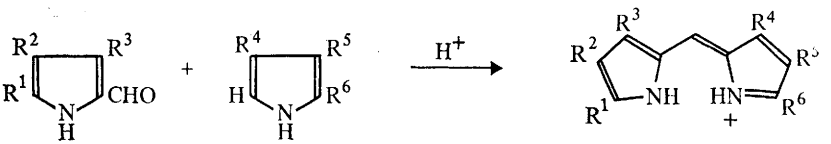


(11) (12) (13)

Scheme 3

pyrrole (11) bearing a potential carbonium ion, in acetic acid in presence of sodium acetate, gives good yields of pyrromethanes (13) in most cases. The advantage of this method is that α-unsubstituted pyrroles (12) having electron-withdrawing groups are still sufficiently nucleophilic, within limits, to condense under the reaction conditions; t-butyl esters are able to survive these acidic conditions. A thorough examination of the synthesis and stability of differentially protected unsymmetrical pyrromethanes has been carried out.[12]

B. Pyrromethenes (Dipyrrylmethenes).—These highly coloured compounds have been extensively used[13] as intermediates in the synthesis of porphyrins, and many more recent developments have utilised them in this respect (see Section 5 B, C). The method of choice for the synthesis of pyrromethenes [*e.g.* (15)] is the acid-catalysed condensation of an α-unsubstituted pyrrole (12) with an α-formyl-pyrrole (14). In the absence of complications, this is a very satisfactory method which often proceeds in quantitative yields. High yields are essential, however,

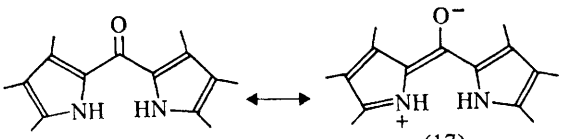


(14) (12) (15)

[12] P. J. Crook, A. H. Jackson, and G. W. Kenner, *J. Chem. Soc.* (*C*), in press; P. J. Crook, Ph.D. Thesis, Liverpool, 1968.
[13] Ref. 3, Vol. IIi, p. 158.

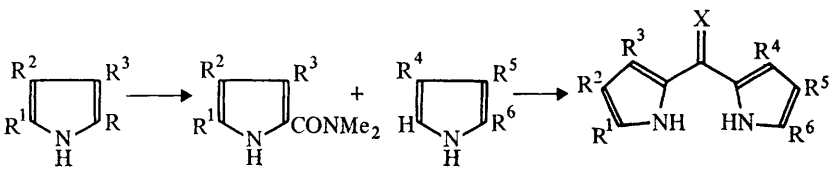
since pyrromethenes are particularly difficult to purify, either as their salts or free bases, by methods other than recrystallisation. Chromatography rarely produces any improvement in purity, due to the disposition of pyrromethenes to chromatograph in wide bands on columns and preparative thick layer plates.

C. Pyrroketones (Dipyrrylketones).—Pyrroketones [*e.g.* (16)] can be regarded as bis-vinylogues of amides, and therefore do not and would not be expected to react as normal ketones. Indeed, their i.r. spectra [ν_{max} (C=O), *ca.* 1580 cm^{-1}] indicate a large contribution from mesomeric forms such as (17). Reduction



(16) (17)

cannot be achieved with borohydride, but with diborane the electron-rich carbonyl group is reduced[14] to give the corresponding pyrromethane; this latter reaction has been of use in the conversion[15] of certain pyrroketones to porphyrins. Various synthetic routes[16] to these compounds are available, but for successful application to porphyrin synthesis a viable method for preparing unsymmetrical pyrroketones is essential. In this respect, the oxidation of pyrromethane-5,5′-dicarboxylic esters is useful,[17] and a very versatile synthesis *via* the Vilsmeier–Haack procedure has been exploited.[14] In the latter approach, an α-dimethylamidopyrrole (19) is activated with phosphoryl chloride and then condensed with an α-unsubstituted pyrrole (12) as nucleophile. The resultant imine salt (20;

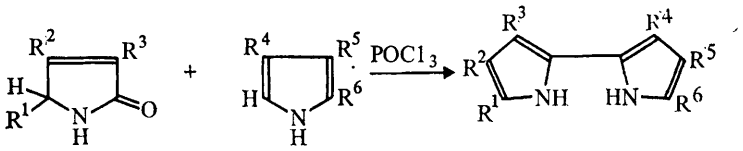


(18) (19) (12) (20)

[14] J. A. Ballantine, A. H. Jackson, G. W. Kenner, and G. McGillivray, *Tetrahedron*, 1966, Suppl. 7, 241.
[15] (*a*) A. H. Jackson, G. W. Kenner, G. McGillivray, and G. S. Sach, *J. Amer. Chem. Soc.*, 1965, **87**, 676; (*b*) A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc.* (*C*), 1967, 2045.
[16] Ref. 3, Vol. I, p. 361; A. Treibs and K. H. Michl, *Annalen*, 1952, **577**, 129.
[17] J. M. Osgerby and S. F. MacDonald, *Canad. J. Chem.*, 1962, **40**, 1585.

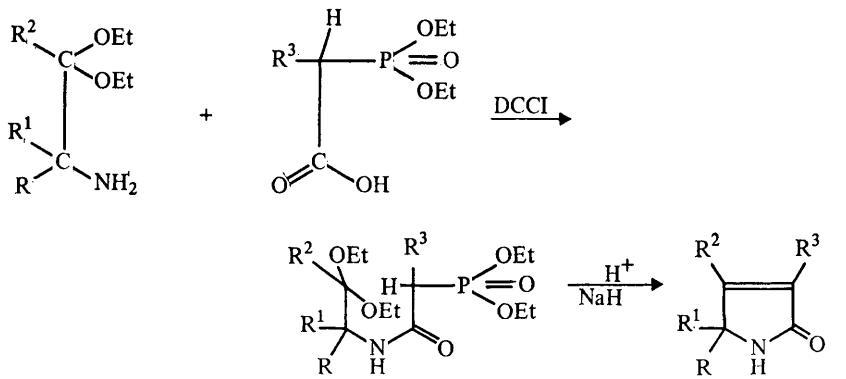
X = $^{+}NMe_2$ ^{-}Cl) is then hydrolysed to the pyrroketone (20; X = 0). Pyrrole amides are readily available from amines and pyrrole acid chlorides (18; R = COCl) or else by trichlorination of α-methylpyrroles (18; R = Me) to (18; R = CCl_3) followed by treatment of the crude reaction mixture with dimethylamine and hydrolysis. A new route to pyrroketones has been reported,[18] utilising 5,5′-diformylpyrromethanes (13; R_1 = R_6 = CHO) or pyrromethanes with 5- and 5′-ester functions. This involves treatment of the appropriate pyrromethane with bromine followed by sulphuryl chloride (or in cases with sulphuryl chloride alone) and represents a pathway to pyrroketones with particularly useful substituents.

D. 2,2′-Bipyrryls.—These compounds [*e.g.* (22)] are prepared either by the Ullmann reaction (*cf.* biphenyls) or more favourably[19] by the Vilsmeier–Haack condensation of α-unsubstituted pyrroles (12) and 3-pyrrolin-2-ones (21). It is



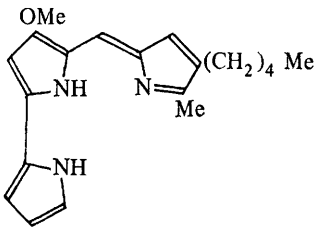
(21) (12) (22)

interesting to note that a wide variety of 3-pyrrolin-2-ones are now readily accessible in an overall yield of about 50%[20] through an internal Emmons reaction:



[18] P. S. Clezy, A. J. Liepa, A. W. Nichol, and G. A. Smythe, *Austral. J. Chem.*, 1970, **23**, 589.
[19] J. Bordner and H. Rapoport, *J. Org. Chem.*, 1965, **30**, 3824.
[20] G. Stork and R. Matthews, *Chem. Comm.*, 1970, 445.

2,2′-Bipyrryls owe their importance to the presence of this structural feature in prodigiosin (23) and in the corroles (24). There have been no recent major advances in the chemistry of isolated 2,2′-bipyrryls, even though interest in the chemistry of the corroles and related macrocycles has flourished. Advances in the latter area have not depended on stimulation from bipyrryl chemistry because



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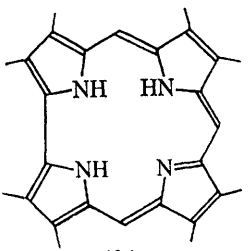

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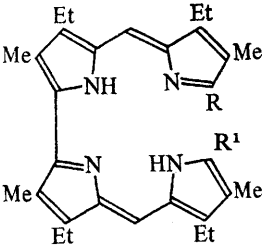


(25)

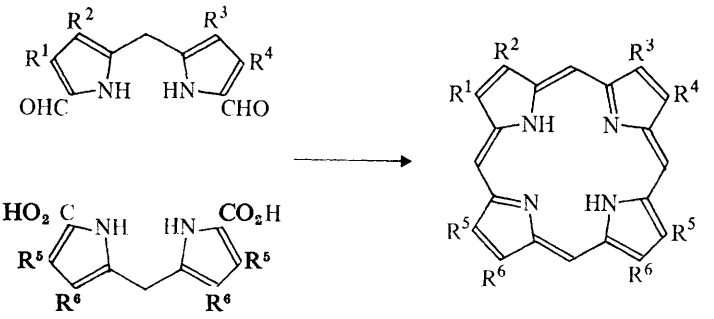
without exception the pyrrole–pyrrole link has been formed as the last stage in production of the macrocycle. Indeed, various attempts to prepare corroles by cyclisation of 5,5′-bipyrromethenyls (25) have so far been unsuccessful.[1]

5 'Linear' Tetrapyrrolic Compounds

In this context, the term 'linear' is applied to compounds [*e.g.* (2)] which have four pyrrole rings linked consecutively at the α-positions by means of carbon bridges. Molecular models show that such compounds are far from linear, being forced into coiled conformations by the repulsive interactions of neighbouring β-substituents. In this Review, they will be drawn in the coiled form to indicate the proximity of rings A and D, which is an important factor in the understanding of their reactivity.

Progress in this area of pyrrolic chemistry has been striking, mainly because of the increased effort expended on porphyrin synthesis through tetrapyrrolic intermediates. This aspect has in turn been facilitated by improvements in methods for the selective activation and differential protection of functional groups in the dipyrrolic compounds from which the tetrapyrroles have been synthesised. The major difficulties encountered in the synthesis of both symmetrical and unsymmetrical porphyrins are those of separation and identification of the products from reactions in which more than one porphyrin can be formed. These difficulties are avoided in the earlier MacDonald synthesis[21] (Scheme 4) by a careful choice of the dipyrrolic intermediates, which limits the generality of the synthesis to porphyrins with an element of symmetry. Almost all recent major developments in porphyrin synthesis[22] have utilised linear tetrapyrrolic compounds. The reason for this is obvious; synthesis of such compounds, followed by cyclisation

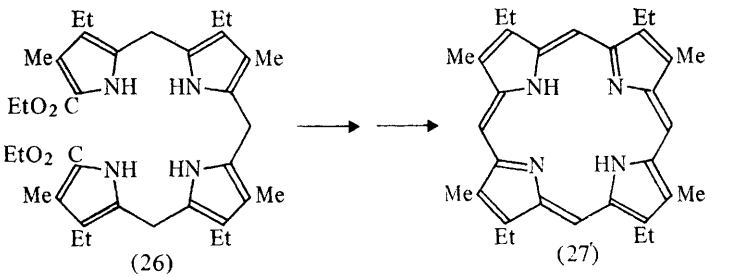
[21] G. P. Arsenault, E. Bullock, and S. F. MacDonald, *J. Amer. Chem. Soc.*, 1960, **82**, 4384.
[22] (*a*) A. H. Jackson and G. W. Kenner, *Nature*, 1967, **215**, 1126; (*b*) A. W. Johnson, *Chem. in Britain*, 1967, 253.



Scheme 4

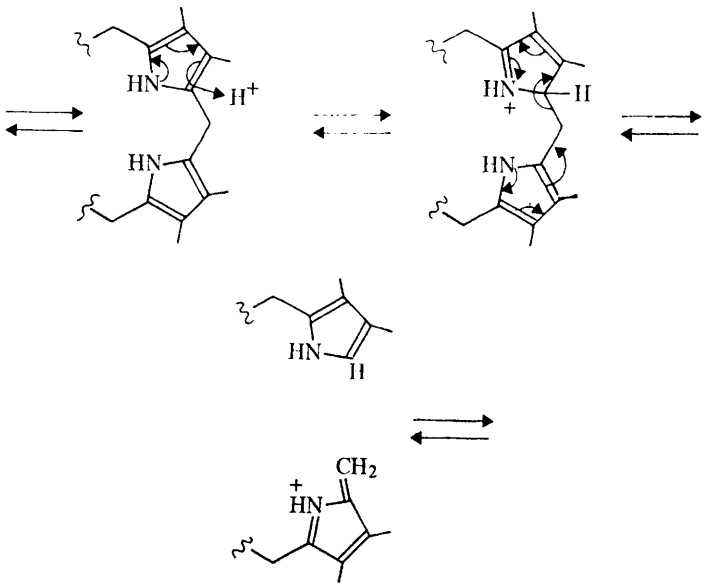
at rings A and D, dispenses with the symmetry requirements of the earlier methods (*e.g.* Scheme 4) which employed the direct formation of macrocycles by the one-step condensation of two dipyrrolic compounds. The chemist does still, however, need to ensure that the conditions used to couple rings A and D do not fragment the tetrapyrrole, which will result in the production of a mixture of porphyrins.

A. Bilanes.—An early attempt to synthesise a porphyrin *via* a linear tetrapyrrole has been described by Corwin and Coolidge,[23] who prepared a bilane (26) which



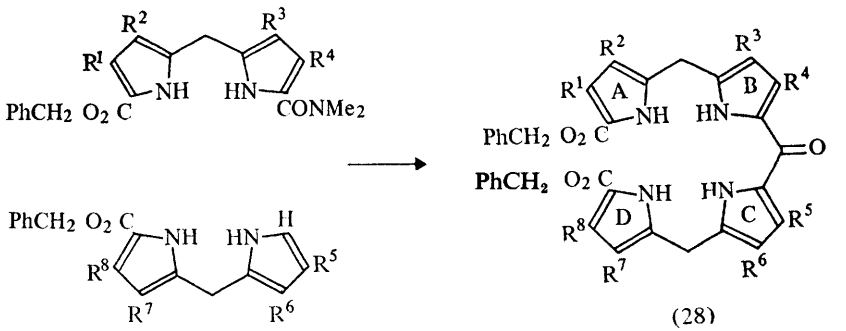
was reportedly cyclised under acidic conditions to aetioporphyrin-II (27). This type of cyclisation has since been shown[24] to give a mixture of porphyrins due to random redistribution of the pyrrole rings:

[23] A. H. Corwin and E. C. Coolidge, *J. Amer. Chem. Soc.*, 1952, **74**, 5196.
[24] D. Mauzerall, *J. Amer. Chem. Soc.*, 1960, **82**, 2601; G. S. Sach, Ph.D. Thesis, Liverpool, 1964.



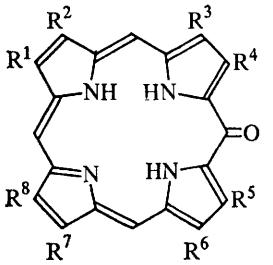
It is unfortunate that the earlier workers chose aetioporphyrin-II as their objective since it is only possible to distinguish aetioporphyrin-II from the other three 'type-' isomers[1] by *X*-ray crystallographic techniques. Clearly, the integrity of the tetrapyrrole must be maintained during the final cyclisation and this has been accomplished in recent developments by building stabilising structural features into the tetrapyrroles.

b-Oxobilanes (28) are pyrroketones which are stable to acid-catalysed redistribution of the pyrrole rings by virtue of the electron-withdrawing ester functions (rings A and D) and the oxo-function (rings B and C). Such compounds are readily available by means of the Vilsmeier–Haack reaction:



(28)

Catalytic debenzylation gives the 1′,8′-dicarboxylic acid (28; R = H) which can be cyclised with trimethylorthoformate (which supplies the carbon bridge atom) under acidic conditions to the isomerically pure oxophlorin (29). Acetylation to the *meso*-acetoxyporphyrin (30; R = OCOMe) followed by hydrogenation and



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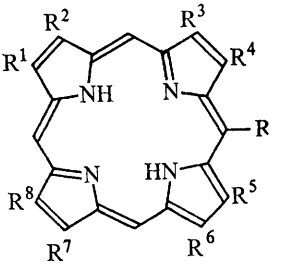
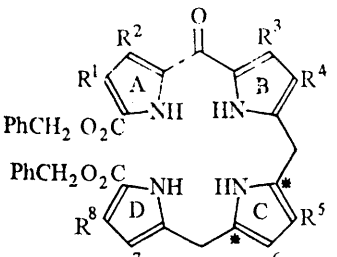


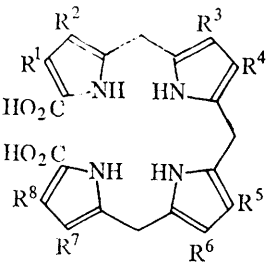
(30)

re-oxidation gives the porphyrin (30; R = H) in reasonable yield.[15a,25]

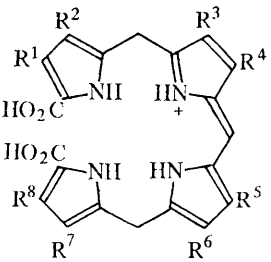
When the oxo-function is sited in the *a*-position, it is clear that the tetrapyrrole, an *a*-oxobilane (31), is vulnerable to attack by protons (at *) in ring C. This difficulty has been surmounted by diborane reduction of the oxo-function to give the bilane-1′,8′-dicarboxylic acid (32) after catalytic debenzylation. Oxidation with t-butyl hypochlorite furnishes the *b*-bilene (33) (plus certain amounts of the *a*-



(31)



(32)

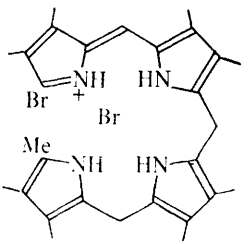


(33)

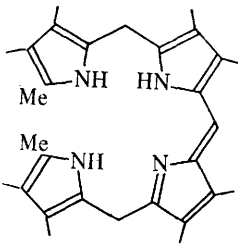
[25] A. H. Jackson, G. W. Kenner, G. McGillivray, and K. M. Smith, *J. Chem. Soc.* (*C*), 1968, 294.

and *c*-bilenes) which can be cyclised to porphyrin (30; R = H) through the agency of trimethylorthoformate and trichloroacetic acid, in 25% yield.[15] Only the *b*-bilene material in the bilene mixture can furnish porphyrinic material, which accounts for the low yield in the final step. Both the *a*- and *b*-oxobilane routes are reliable and versatile, having been used in the synthesis of a variety of demandingly complicated porphyrins (see Section 6). The major disadvantage of these approaches is the complexity of the reaction sequence. An earlier limitation[1] due to the enforced symmetry requirement of one of the pyrromethane intermediates has been overcome as a result of advances in the selective protection[12] of pyrromethane esters.

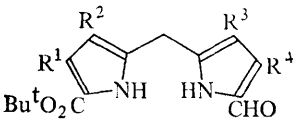
B. Bilenes.—Cyclisation of *a*-bilenes [*e.g.* (34)] gives mixtures of porphyrins[26] while oxidative cyclisation of 1′,8′-dimethyl-*b*-bilenes (35) to porphyrins can be achieved satisfactorily with cupric salts in pyridine.[27] The *a*-oxobilane synthesis[15] proceeds to porphyrins through a *b*-bilene (33), and this has led to the development of a synthesis *via* these compounds, prepared by more rational means.[28] Acid-catalysed condensation of a 5-formylpyrromethane (36) with a pyrromethane 5-carboxylic acid (37) furnishes the corresponding crystalline t-butyl



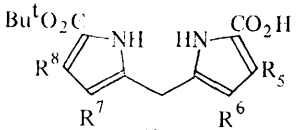
(34)



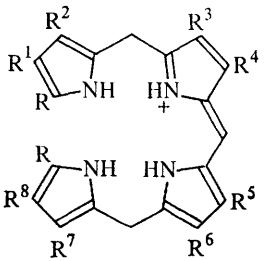
(35)



(36)



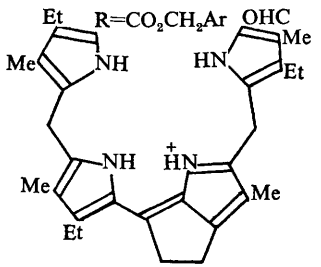
(37)



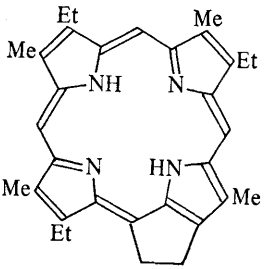
(38)

[26] J. Ellis, A. H. Jackson, A. C. Jain, and G. W. Kenner, *J. Chem. Soc.*, 1964, 1935.
[27] A. W. Johnson and I. T. Kay, *J. Chem. Soc.*, 1961, 2418; P. S. Clezy and A. J. Liepa, *Chem. Comm.*, 1969, 767.
[28] M. T. Cox, R. Fletcher, A. H. Jackson, G. W. Kenner, and K. M. Smith, *Chem. Comm.*, 1967, 1141; A. H. Jackson, G W. Kenner, and K. M. Smith, *J. Chem. Soc.* (*C*), in press.

b-bilene-1′,8′-dicarboxylate (38; R = CO_2Bu^t), usually in quantitative yield. Treatment with trifluoroacetic acid causes de-esterification with concomitant decarboxylation to the 1′,8′-unsubstituted *b*-bilene (38; R = H), which can be cyclised to porphyrin with trimethylorthoformate. Yields are good, but in certain complex cases (especially when electron-withdrawing groups are situated on the methene moiety) small amounts of other porphyrins are obtained. This is probably a result of redistribution or scrambling of the pyrrole rings due to intermolecular attack of the 1′- and 8′-positions of one *b*-bilene molecule at the activated *b*-position of another. Other work[29] has also disclosed the production of mixtures of porphyrins from cyclisations which presumably proceed through *b*-bilenes activated towards nucleophilic attack by electron-withdrawing substituents. Recently, Rapoport and Flaugh[30] published a synthesis of deoxophylloerythroaetioporphyrin (40) (which occurs in crude oil), by means of a *b*-bilene



(39)

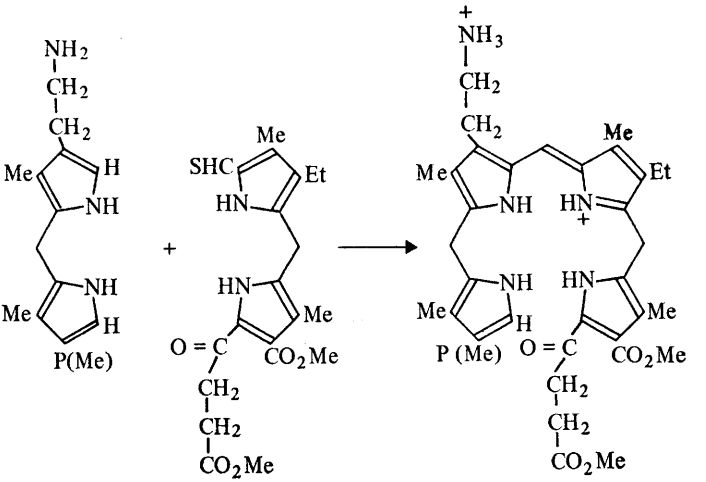


(40)

intermediate (39). All of the bilene syntheses described above, are strictly speaking, two-stage variants of the MacDonald synthesis[21] proceeding through *b*-bilenes to overcome the otherwise inherent symmetry limitations. Perhaps the most famous application of this approach was that used by Woodward in the preparation of the porphyrin (42) required for his elegant synthesis of chlorophyll-*a*.[31] A *b*-bilene (41) was a fleeting intermediate in this transformation.

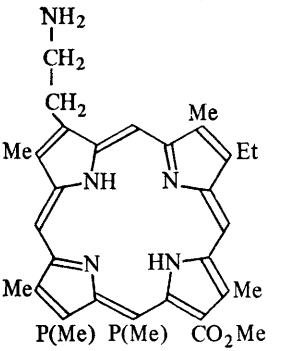
C. Biladienes.—The utility of the Fischer porphyrin synthesis[32] has been greatly extended by a modification[33] introduced by Johnson and the Nottingham School. Instead of the classical one-step condensation of two pyrromethenes (*e.g.* Scheme 5) to the porphyrin macrocycle, an *a,c*-biladiene (45) is first isolated from reaction between two suitably activated unsymmetrical pyrromethenes (43) and (44), using tin ions as a template. After removal of the metal with hydrobromic acid, the biladiene (45) is cyclised, often in high yield, by refluxing in *o*-dichloro-

[29] J. L. Davies, *J. Chem. Soc.* (*C*), 1968, 1392.
[30] M. E. Flaugh and H. Rapoport, *J. Amer. Chem. Soc.*, 1968, **90**, 6877.
[31] R. B. Woodward, *Angew. Chem.*, 1960, **72**, 651; *Pure Appl. Chem.*, 1961, **2**, 383.
[32] Ref. 3, Vol. IIi, p. 166.
[33] R. L. N. Harris, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.* (*C*), 1966, 22.



P(Me) = $CH_2CH_2CO_2Me$

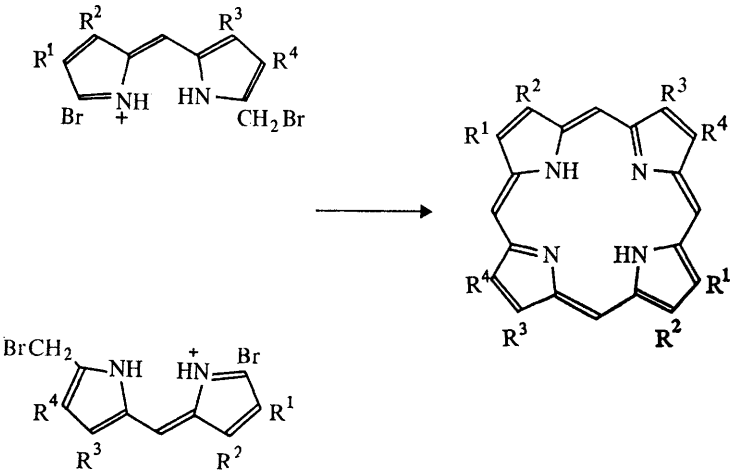
(41)



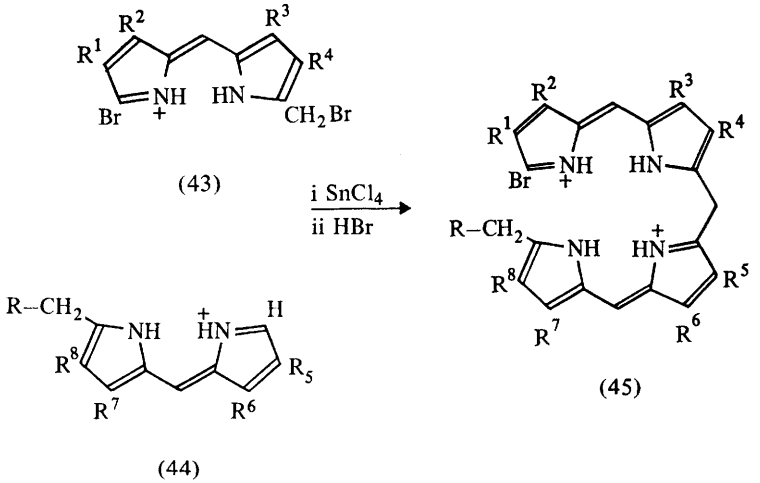
(42)

benzene. Even more recently, room temperature cyclisation during two days in dimethylsulphoxide and pyridine has been used.[34] This provides a good, simple

[34] P. Bamfield, R. L. N. Harris, A. W. Johnson, I. T. Kay, and K. W. Shelton, *J. Chem. Soc.* (*C*), 1966, 1436.



Scheme 5



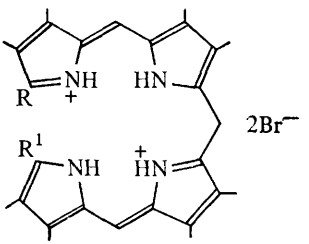
(43)

(44)

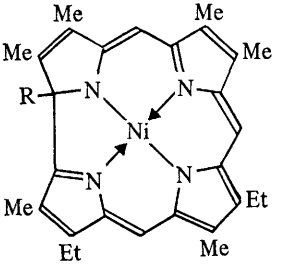
(45)

general porphyrin synthesis when the pyrromethenes (43) and (44) are accessible, and it is particularly amenable to large scale preparations. Treatment of 8′-bromo-1′-methyl-*a*,*c*-biladiene hydrobromides (46; R = Me, R^1 = Br) with

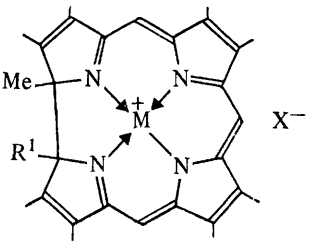
cupric salts (and other one-electron oxidising agents) also produces porphyrins,[35] as does the heating of 1′-methyl-*a*,*c*-biladienes (46; R = Me, R^1 = H). More



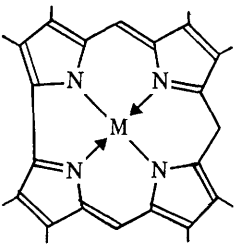
(46)



(47)



(48)

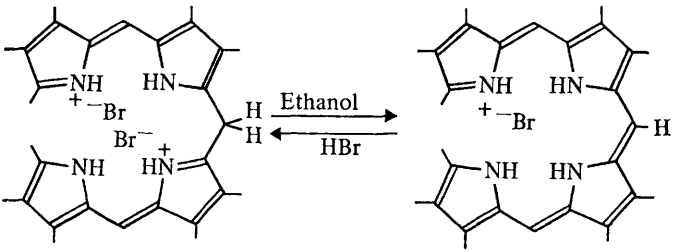


(49)

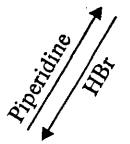
interestingly, when these biladienes are heated in presence of nickel salts and a base (*e.g.* piperidine) a high yield of the 1-methyltetradehydrocorrin nickel salt (45; R = Me) is obtained.[36] When solutions of 1′,8′-dimethyl-*a*,*c*-biladiene salts (46; R = R^1 = Me) are aerated in the presence of base and nickel or cobalt salts, the corresponding metal complexes (48; R^1 = Me) are produced.[37] Irradiation of 1′,8′-unsubstituted *a*,*c*-biladienes (46; R = R^1 = H) in the presence of base and nickel or cobalt ions leads to the theoretically interesting corrole metal complexes (49). Metal-free corroles (24) are accessible by a similar procedure, in the absence of metal salts,[38] or alternatively by heating solutions of 1′,8′-dibromo-*a*,*c*-biladienes [*e.g.* (46; R = R^1 = Br)] in *NN*-dimethylformamide.[33] The spectroscopic properties of *a*,*c*-biladienes and their metal salts have been closely examined.[38,39]

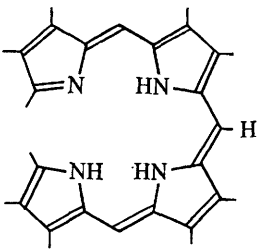
[35] R. Grigg, A. W. Johnson, R. Kenyon, V. B. Math, and K. Richardson, *J. Chem. Soc.* (*C*), 1969, 176.
[36] D. A. Clarke, R. Grigg, R. L. N. Harris, A. W. Johnson, I. T. Kay, and K. W. Shelton, *J. Chem. Soc.* (*C*), 1967, 1648; R. L. N. Harris, A. W. Johnson, and I. T. Kay, *Chem. Comm.*, 1965, 355.
[37] D. Dolphin, R. L. N. Harris, J. Huppatz, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.* (*C*), 1966, 30. See also Ref. 35.
[38] D. Dolphin, A. W. Johnson, J. Leng, and P. v.d. Broek, *J. Chem. Soc.* (*C*), 1966, 880; A. W. Johnson and I. T. Kay, *J. Chem. Soc.*, 1965, 1620.
[39] Y. Murakami, Y. Kohno, and Y. Matsuda, *Inorg. Chim. Acta*, 1969, **3**, 671.

D. Bilatrienes.—*a,b,c*-Bilatriene free bases [*e.g.* (52)] are green tetrapyrrolic compounds which occur importantly in natural systems as the 1′,8′-dioxo-compounds, such as biliverdin (see Sections 6 and 11). Johnson and co-workers[38] have shown that bilatrienes can be produced by dissolution of an *a,c*-biladiene hydrobromide (50) in ethanol. The polar solvent presumably abstracts a proton



(50) (51)





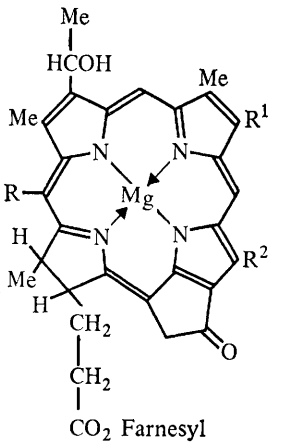
(52)

from the acidic *b*-methylene group to yield the yellow hydrobromide (51) of a bilatriene. Conversion of this material to the green free-base (52) is achieved with an excess of piperidine. The acidity of the *b*-methylene of *a,c*-biladienes is an important factor in the base-catalysed cyclisation of their cobalt or nickel salts to various macrocycles.[38] The visible absorption spectra of *a,b,c*-bilatriene free-bases are similar to those of phlorins[40] and oxophlorins[41] (see Section 8).

6 Porphyrins

New developments in the construction of porphyrins, the mechanics of which have been discussed in Section 5, have led to reports of the syntheses of porphyrins of increased complexity. The synthesis of coproporphyrin [*e.g.* (53; $R^1 = R_2 = P$)] and uroporphyrin isomers by MacDonald and his co-workers[21] was the

Table 1 *Proposed*[43] *structures for Chlorobium Chlorophylls (650) and (660)*

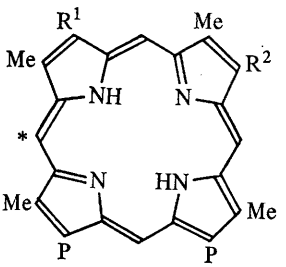


	(650) Series			(660) Series		
Fraction	R^1	R^2	R	R^1	R^2	R
1	Bu^i	Et	H	Bu^i	Et	Et
2	Pr^n	Et	H	Bu^i	Et	Me
3	Bu^i	Me	H	Pr^n	Et	Et
4	Et	Et	H	Pr^n	Et	Me
5	Pr^n	Me	H	Et	Et	Me
6	Et	Me	H	Et	Me	Me

[40] R. B. Woodward, *Ind. chim. belge*, 1962, **27**, 1293.
[41] A. H. Jackson, G. W. Kenner, and K. M. Smith, *J. Chem. Soc.* (*C*), 1968, 302; *J. Amer. Chem. Soc.*, 1966, **88**, 4539.
[42] J. L. Archibald, D. M. Walker, K. B. Shaw, A. Markovac, and S. F. MacDonald, *Canad. J. Chem.*, 1966, **44**, 345.

advance that heralded a new era in porphyrin synthesis. This is all the more important, since the power of total synthesis for structural confirmation was never greater than in this field; porphyrins derived from the *Chlorobium* chlorophylls (Table 1) are a case in point. The structures of the compounds corresponding to fractions 1—6 of the (650) series and 5 and 6 of the (660) series have been synthesised[42] and identified with the natural compounds. However, when the structure proposed[43] for (660) fraction 4 was synthesised by the *b*-bilene method,[28] it was found, not least by *X*-ray powder photographs, to be identical with the natural material from fraction 3. Even more mysteriously, the synthetic compound corresponding to the proposed structure[43] for fraction 3 could not be identified with any of the (660) series. These results cast considerable doubt on the existence of *meso*-ethyl groups in any of the (660) compounds.[44]

The ubiquitous protoporphyrin-IX (53; $R^1 = R^2 = V$) is a desirable objective for synthesis (on account of its involvement in the biosynthesis of haem and chlorophyll), and this has been achieved on different occasions.[45] Special mention should be made of the Russian School, which has carried out a thorough investigation in this area, using analogues of the MacDonald procedure,[21] and culminating in the synthesis of protoporphyrin-IX.[45c] The more versatile *b*-oxobilane approach[45b] has the added advantage that it allows for the specific labelling of the product with tritium (53; at *) due to a property of the intermediate oxophlorin (see Section 8). This labelled protoporphyrin-IX has been incorporated[46] into chlorophyll by an isolated chloroplast system,[47] confirming



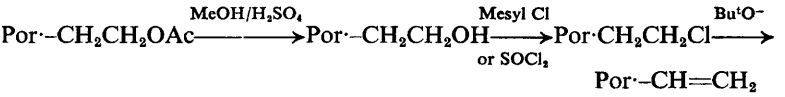
P = $CH_2CH_2CO_2H$

V = $CH{=}CH_2$

(53)

[43] A. S. Holt, J. W. Purdie, and J. W. F. Wasley, *Canad. J. Chem.*, 1966, **44**, 88.
[44] A. H. Jackson and G. W. Kenner in Ref. 6, p. 3.
[45] (*a*) H. Fischer and K. Zeile, *Annalen*, 1929, **468**, 114; Ref. 3, Vol. IIi, p. 396; (*b*) R. P. Carr, P. J. Crook, A. H. Jackson, and G. W. Kenner, *Chem. Comm.*, 1967, 1025; (*c*) R. P. Evstigneeva, V. N. Guryshev, A. F. Mironov, and G. Y. Volodarskaya, *Zhur. obshchei Khim.*, 1969, **39**, 2558.
[46] See Footnote 1 in M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J. Amer. Chem. Soc.*, 1969, **91**, 1232.
[47] J. M. Charlton, K. J. Treharne, and T. W. Goodwin, *Biochem. J.*, 1967, **105**, 205.

deductions from work with algal mutants. The classical method for introduction of vinyl groups into porphyrins is the Hofmann degradation of peripheral (2-aminoethyl) side-chains. A new, efficient access to this substituent has been reported:[45b]



The acetoxyethyl side-chain is introduced at the pyrrole stage by means of diborane reduction of a (methoxycarbonylmethyl)pyrrole, followed by acetylation of the resultant (2-hydroxyethyl)pyrrole.

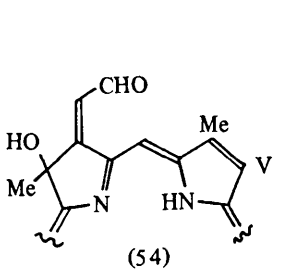
Pemptoporphyrin[48] is a faecal metabolite which, on the basis of physical evidence, can be allocated two possible isomeric structures, (53; R^1 = V, R^2 = H) or (53; R^1 = H, R^2 = V). Both of these isomers have been synthesised[49] by the *b*-oxobilane route, and the structure of pemptoporphyrin defined as (53; R^1 = H, R^2 = V). The Nottingham group simultaneously synthesised[50] (53; R^1 = H, R^2 = V), which was identified with the isomer defined as pemptoporphyrin by Kenner and co-workers.[49]

Spirographis spallanzanii, a species of polychaete worm, has the ferrous complex of chlorocruoroporphyrin (*Spirographis* porphyrin) (53; R^1 = CHO, R^2 = V) as the prosthetic group of its oxygen transport pigment. The porphyrin has been synthesised earlier,[51] but these approaches have utilised deuteroporphyrin-IX (53; R^1 = R^2 = H) or protoporphyrin-IX (53; R^1 = R^2 = V), which necessitates the production and separation of both possible isomers (53; R^1 = CHO, R^2 = V) and (53; R^1 = V, R^2 = CHO); it is not easy to assign an absolute structure to each isomer. The most ingenious of these syntheses was reported by Inhoffen and co-workers,[51b] and involved the photo-oxidation of protoporphyrin-IX (53; R^1 = R^2 = V) dimethyl ester to photoprotoporphyrin-IX (54) and isophotoprotoporphyrin-IX (55). These isomers were then separated, treated independently with sodium borohydride, and the resultant allylic diols [*e.g.* (56)] rearranged with acid to the glycols [*e.g.* (57)]. Periodic acid cleavage gave spirographis porphyrin (53; R^1 = CHO, R^2 = V) or isospirographis porphyrin (53; R^1 = V, R^2 = CHO), depending on the particular isomer. Absolute proof of the isomeric structure of spirographis porphyrin has recently been furnished by its total synthesis.[49,52]

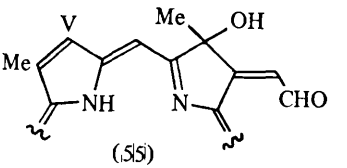
[48] J. M. French, M. T. England, J. Lines, and E. Thonger, *Arch. Biochem. Biophys.*, 1964, **107**, 404; S. Sano, T. Shingu, J. M. French, and E. Thonger, *Biochem. J.*, 1965, **97**, 250.
[49] A. H. Jackson, G. W. Kenner, and J. Wass, *Chem. Comm.*, 1967, 1027.
[50] P. Bamfield, R. Grigg, R. W. Kenyon, and A. W. Johnson, *Chem. Comm.*, 1967, 1029; *J. Chem. Soc.* (*C*), 1968, 1259.
[51] (*a*) H. Fischer and G. Wecker, *Z. physiol. Chem.*, 1942, **272**, 1; R. Lemberg and J. Parker, *Austral. J. Exptl. Biol.*, 1952, **30**, 163; (*b*) H. H. Inhoffen, K. M. Bliesener, and H. Brockmann, *Tetrahedron Letters*, 1966, 3779; *Annalen*, 1969, **730**, 173.
[52] P. Bamfield, R. Grigg, A. W. Johnson, and R. W. Kenyon, *J. Chem. Soc.* (*C*), 1968, 1259.

The Harderian gland is situated behind the eyeball of the rat, and produces a secretion which functions as a lubricant for the eyelids. The gland also produces and stores certain porphyrins, notably protoporphyrin-IX (53; $R^1 = R^2 = V$), with smaller amounts of coproporphyrin-III (53; $R^1 = R^2 = P$) and a tricarboxylic porphyrin. The latter has been named harderoporphyrin.[53] The two possible isomeric structures for the tricarboxylic porphyrin (53; $R^1 = V$, $R^2 = P$) and (53; $R^1 = P$, $R^2 = V$) have been synthesised by the *b*-oxobilane

Protoporphyrin–IX
(53; $R^1 = R^2 = V$)



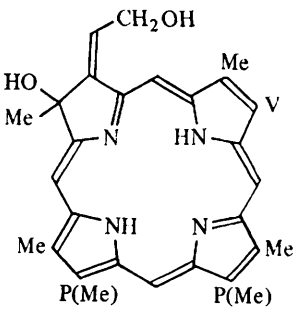
(54)



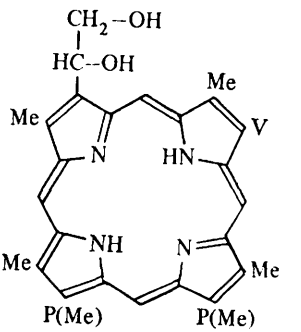
(55)

Spirographis porphyrin
(53; R^1 = CHO, R^2 = V)

Isospirographis porphyrin
(53; R^1 = V, R^2 = CHO)



(56)

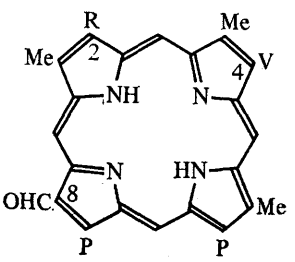


(57)

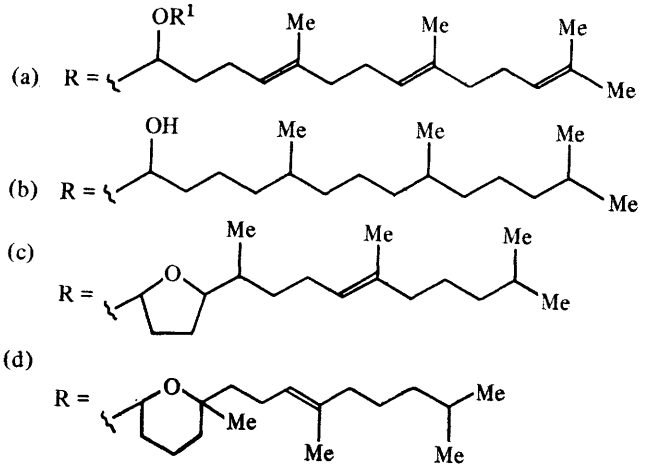
[53] G. Y. Kennedy, A. H. Jackson, G. W. Kenner, and C. J. Suckling, *FEBS Letters*, 1970, **6**, 9; 1970, **7**, 205.

route, and the structure of harderoporphyrin shown to be (53; R^1 = V, R^2 = P).[53] The Harderian gland is biosynthetically important from two points of view. It is unusual for animals to store metal-free porphyrins, and this is probably due to the absence, in the gland, of an iron-chelating enzyme. The 2-vinyl-4-propionic acid structure defined for harderoporphyrin makes it seem likely that the biogenesis of protoporphyrinogen-IX from coproporphyrinogen-III proceeds by modification of the 2-propionic side-chain before the 4-propionic acid.

Haem-*a*[54] is the prosthetic group of cytochrome oxidase, the mitochondrial haemoprotein of vital biological significance. The exact nature of the 2-side-chain [in (58)] has been the main point of disagreement in reports of structural investigations;[54] suggestions have ranged from a 2-(*trans,trans*-farnesylethyl) chain with a labile group in the 1′-position[55a] (58*a*) to a side-chain with no double bond[55b] (58b) or with a 5- or 6-membered heterocycle[55c] (58c, d). The



(58)



syntheticist is indeed faced with a formidable problem in attempting to conquer this molecule,[56] due to the presence of three different labile side-chains [at 2, 4,

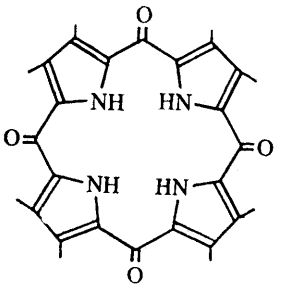
[54] A good source for information up to 1966 is 'Hemes and Hemoproteins', eds. B. Chance, R. W. Estabrook, and T. Yonetani, Academic Press, New York and London, 1966.
[55] (*a*) G. A. Smythe and W. S. Caughey, *Chem. Comm.*, 1970, 809; (*b*) M. Grassl, U. Coy, R. Seyffert, and F. Lynen, *Biochem. Z.*, 1963, **338**, 771; (*c*) R. Lemberg, *Rev. Pure Appl. Chem. (Australia)*, 1965, **15**, 125; M. R. Lemberg, *Physiol. Rev.*, 1969, **49**, 48.
[56] For an indication of the difficulties involved in such a project, see G. M. Badger, R. L. N. Harris, and R. A. Jones, *Austral. J. Chem.*, 1964, **17**, 987, 1002.

and 8 in (58)]. Present porphyrin syntheses are only adequate to cope with two such substituents.

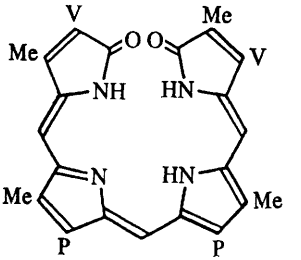
The wealth of information on the electrophilic substitution of porphyrins has been reviewed thoroughly by Inhoffen, Buchler, and Jäger,[2] and further comment is therefore unnecessary.

Oxidation of free porphyrins with lead tetra-acetate furnishes xanthoporphyrinogens [*i.e. meso*-tetraoxoporphyrins (59)],[57] while oxidation with hydrogen peroxide in the presence of acid gives 'geminiketones' (see Section 7).

The intricately balanced redox properties of metal complexes of porphyrins play a critical rôle in the processes of photosynthesis and respiration. The reductive features of porphyrin chemistry are discussed in this Review under the separate headings of their products, but the nature and properties of their oxidation products are, in the main, far less clearly defined. Iron complexes of



(59)



(60)

porphyrins can be converted *in vitro* to bile pigments [*e.g.* biliverdin-IXα[58] (60)], and oxophlorin iron complexes (see Section 8) are intermediates in this transformation.[59] The process involves the loss of one *meso*-carbon atom (as carbon monoxide[60]) and would, unlike the *in vivo* catabolism, be expected to be random with respect to the particular carbon atom (α, β, γ, or δ) removed. Fischer[59b] was careful to use a symmetrical (type-1) porphyrin, but Stier[61] claimed the production of mixtures of isomeric bile pigments by the coupled oxidation of unsymmetrical porphyrins. On the other hand, Lemberg[59a] used haemin [the iron(III) complex of protoporphyrin-IX (53; $R^1 = R^2 = V$)] and claimed the coupled oxidation with

[57] H. Fischer and A. Treibs, *Annalen*, 1927, **457**, 209; H. H. Inhoffen, J.-H. Fuhrhop, and F. v.d. Haar, *ibid.*, 1966, **700**, 92.

[58] The '-IXα' nomenclature indicates that the bile pigment is related to a Type-IX porphyrin by oxidative removal of the α-*meso*-carbon atom.

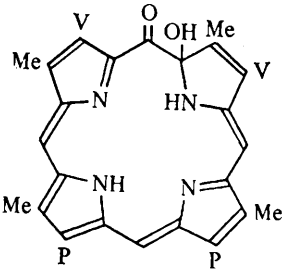
[59] (*a*) R. Lemberg, B. Cortis-Jones, and M. Norrie, *Biochem. J.*, 1938, **32**, 171; R. Lemberg, *ibid.*, 1935, **29**, 1322; (*b*) H. Fischer and H. Libowitzsky, *Z. physiol. Chem.*, 1938, **255**, 209; 1938, **251**, 198.

[60] T. Sjoestrand, *Acta physiol. Scand.*, 1952, **26**, 328, 334, 338.

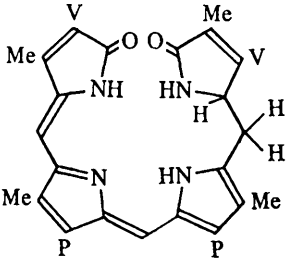
[61] E. Stier, *Z. physiol. Chem.*, 1942, **272**, 239; 1942, **275**, 155.

hydrogen peroxide to be specific, biliverdin-IXα (60) being the only isomer isolated. As a result, haemin was thought for many years to be a special case due to its biological rôle. However, several groups of workers have recently shown[62] that the bile pigment obtained by the coupled oxidation of haemin is a mixture of approximately equal amounts of the four possible isomeric verdins (– IXα, – IXβ, – IXγ, and – IXδ).[62b–d] In contradistinction, on the basis of mass spectrometric results, a further group of workers has suggested[63] that the product from the oxidation is solely the – IXβ (or δ) isomer. It is most interesting to note, however, that the coupled oxidation of myoglobin and haemoglobin is largely specific to the α-position, suggesting the presence of some directional influence on the part of the protein environment around the haem molecule.[63,64]

Photo-oxidation of the magnesium complex of protoporphyrin-IX (53; $R^1 = R^2 = V$) gives a green pigment, lacking magnesium, and formulated[65] as the hydroxyoxophlorin [*e.g.* (61)]. This material can easily be transformed into



(61)

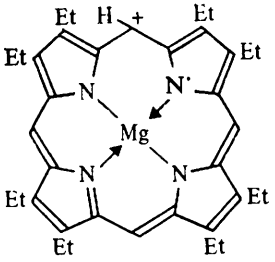


(62)

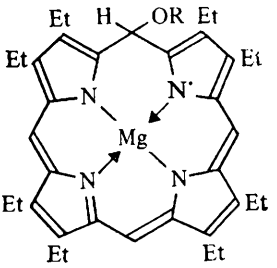
bili*violins* [*e.g.* (62)], which should be compared with the *verdins* obtained by the coupled oxidation of the corresponding iron complex.

Fuhrhop and Mauzerall[66] have reported the reversible oxidation of magnesium octaethylporphyrin (and other metal complexes[66b]) with iodine in methanol, the spectroscopic data of the product resembling that of a phlorin (see Section 8). E.s.r. measurements showed it clearly to be a free radical resulting from one-electron oxidation; the phlorin formulation (64), obtained from the cation-radical (63) was preferred[66a] on account of its spectra and stability (several hours) in alcoholic solvents, though no further evidence has been obtained.[66b] Other oxidants (dichlorodicyanobenzoquinone, bromine, *N*-bromosuccinimide, ferric chloride, and ferric perchlorate) also accomplish this oxidation in methanol. The

[62] (*a*) Z. Petryka, D. C. Nicholson, and C. H. Gray, *Nature*, 1962, **194**, 1047; (*b*) Ref. 6, p. 129; (*c*) P. Ó. Carra and E. Colleran, *FEBS Letters*, 1969, **5**, 295; (*d*) R. Bonnett, and A. F. McDonagh, *Chem. Comm.*, 1970, 237.
[63] A. W. Nichol and D. B. Morell, *Biochim. Biophys. Acta.*, 1969, **184**, 173.
[64] P. Ó. Carra and E. Colleran, *Biochem. J.*, 1969, **115**, 13P; See also Ref. 62c.
[65] J. Barrett, *Nature*, 1967, **215**, 733.
[66] (*a*) J.-H. Fuhrhop and D. Mauzerall, *J. Amer. Chem. Soc.*, 1968, **90**, 3875; (*b*) J.-H. Fuhrhop and D. Mauzerall, *ibid.*, 1969, **91**, 4174.



(63)



(64)

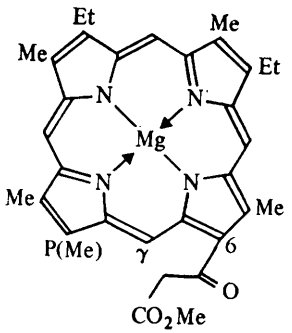
facility of the oxidation of the magnesium complex, compared with, for example, the corresponding zinc chelate, is regarded as a possible rationalisation of Nature's choice of magnesium complexes for the photosynthetic pigments. Electrolysis of magnesium octaethylporphyrin in dichloromethane also leads[67] to a one-electron oxidation product, identical with that from iodine in methanol. Mauzerall's formulation[66a] of the product as a phlorin (64) is criticised due to the similarity of the electronic spectra of the product with those calculated for a cation-radical. Continued electrolytic oxidation[67] of the cation-radical leads to the reversible production of a dication, by a further one-electron abstraction:

$$\text{(Metalloporphyrin)} \underset{-e}{\overset{+e}{\rightleftharpoons}} \text{(Metalloporphyrin)}^{+\cdot} \underset{-e}{\overset{+e}{\rightleftharpoons}} \text{(Metalloporphyrin)}^{2+}.$$

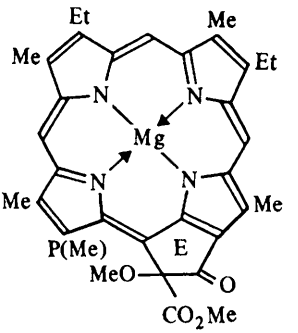
These oxidations have been extended to transition-metal complexes of porphyrins and to the magnesium and zinc complexes of $\alpha\beta\gamma\delta$-*meso*-tetraphenylporphyrin. The iron, cobalt, and nickel chelates of the tetraphenylporphyrin show three successive one-electron abstractions on electrochemical oxidation;[68] the first involves oxidation at the metal atom and is followed by two further abstractions from the porphyrin ligand. All three one-electron oxidations are reversible. $\alpha\beta\gamma\delta$-*meso*-Tetraphenylporphyrin is a popular substrate for physical measurements which is not particularly analogous, either electronically or sterically, to the compounds of the natural systems. However, chlorophyll-*a*, ethyl chlorophyllide-*a* and bacteriochlorophyll have been examined in these oxidations.[66b,67] In earlier work, Stanienda has reported the polarographic oxidation potentials of porphyrins, their metal complexes and of chlorophylls.[69] It has been postulated[70] that the isocyclic ring (ring E) of chlorophyll (see Section

[67] R. H. Felton, D. Dolphin, D. C. Borg, and J. Fajer, *J. Amer. Chem. Soc.*, 1969, **91**, 196; J. Fajer, D. C. Borg, A. Forman, D. Dolphin, and R. H. Felton, *ibid.*, 1970, **92**, 3451.
[68] A. Wolberg and J. Manassen, *J. Amer. Chem. Soc.*, 1970, **92**, 2982.
[69] A. Stanienda and G. Biebl, *Z. phys. Chem.* (*Frankfurt*), 1967, **52**, 254; A. Stanienda, *Z. phys. Chem.* (*Leipzig*), 1965, **229**, 257.
[70] Ref. 3, Vol. IIii, p. 37; A. C. Jain and G. W. Kenner, *J. Chem. Soc.*, 1959, 185; See also Ref. 40.

7) might arise by cyclisation of a 6-(β-ketoester) substituent to the γ-position of a suitable porphyrin precursor [*e.g.* (65)]. An analogue of this change has been



(65)



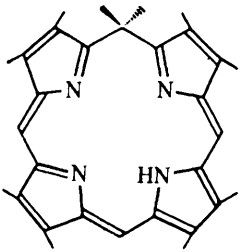
(66)

accomplished[71] *in vitro*, by the oxidation of the magnesium complex (65) with iodine in methanolic potassium carbonate to the chelate (66). The 10-methoxy-group is an unfortunate consequence of the reaction medium, and there is ample precedent for its incorporation. The authors envisage[71] the cyclisation to (66) as involving reaction of the cation-radical of the macrocycle with the radical obtained by oxidation of the β-ketoester enolate-anion. Another interpretation[72] (cyclisation of the magnesium porphyrin dication with the enolate-anion) has been suggested; it is probably a matter of semantics in a conjugated system such as this.

Isoporphyrins [*e.g.* (67)] are isomeric structures of porphyrins, having a saturated bridging (*meso*-) carbon atom. Until recently, no evidence for their existence had been uncovered. Electrolytic oxidation of zinc αβγδ-*meso*-tetraphenylporphyrin to its dication, (68), followed by treatment of this powerful electrophile with methanol gives a green compound which was isolated and allocated the isoporphyrin structure (69).[72]

N-Methylporphyrins have been known for some considerable time; *NN'*-dimethylporphyrins have now been isolated and characterised,[73] as have similar derivatives of related macrocycles.[73b] The n.m.r. spectra indicate that the two methyl groups are sited on adjacent [*cf.* (70)] rather than opposite [*cf.* (71)] nitrogen atoms. As expected, the methyl groups are in a *trans*- configuration above and below the plane of the porphyrin ring. When octaethylporphyrin

[71] M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J. Amer. Chem. Soc.*, 1969, **91**, 1232.
[72] D. Dolphin, R. H. Felton, D. C. Borg, and J. Fajer, *J. Amer. Chem. Soc.*, 1970, **92**, 743.
[73] (*a*) G. R. Dearden and A. H. Jackson, *Chem. Comm.*, 1970, 205;
(*b*) M. J. Broadhurst, R. Grigg, G. Shelton, and A. W. Johnson, *Chem. Comm.*, 1970, 231.



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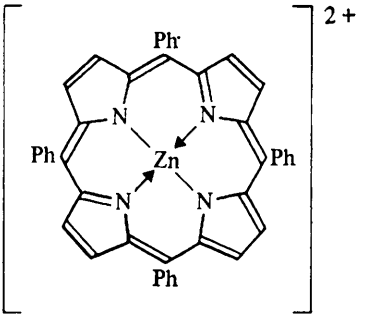
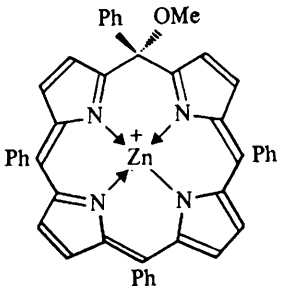


(68)

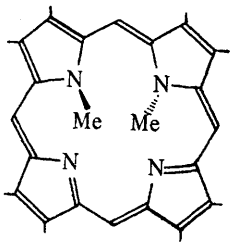


X^-

(69)

is heated in methyl fluorosulphonate in a sealed tube at 100 °C, an *NN'N''*-trimethylporphyrin (72) is produced,[74] with the methyl groups presumably in the '*trans-trans*' configuration. This material decomposes on keeping to the *NN'*-dimethylporphyrin with the methyl groups on opposite nitrogen atoms but in

[74] R. Grigg, A. Sweeney, G. R. Dearden, A. H. Jackson, and A. W. Johnson, *Chem. Comm.*, 1970, 1273.



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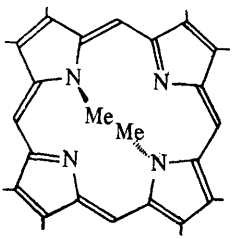

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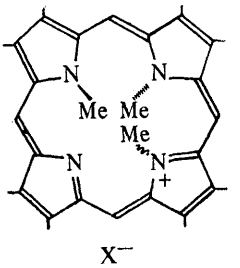
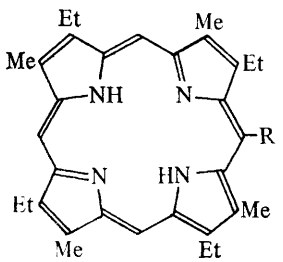


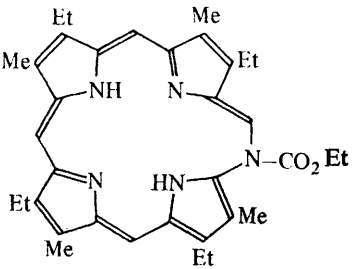
(72)

the *cis* orientation; this compound could also be made by carrying out the methylation in boiling chloroform as solvent.[74]

An interesting expansion reaction of the porphyrin nucleus has been reported.[75] Treatment of aetioporphyrin-I (73; R = H) with ethoxycarbonylnitrene leads to



(73)



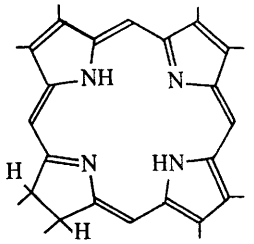
(74)

the ring-enlarged derivative (74), which can be converted to the *meso*-substituted porphyrin (73; R = $NHCO_2Et$) by heating.

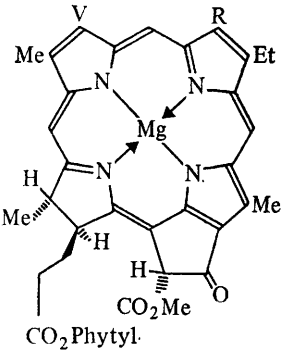
7 Chlorins

Chlorins are 7,8-dihydroporphyrins which are important because of the presence of the chromophore (75) in many of the macrocyclic photosynthetic pigments known as the chlorophylls. These pigments have been the focus of much recent research, reviewed elsewhere.[76] The designation 'chlorophyll' was originally given to the two photosynthetic pigments (76) of higher plants, but has since been expanded to include the corresponding agents of other organisms, with the exception of the biliproteinoids (*e.g.* phycocyanin and phycoerythrin) which will be discussed in Section 11.

[75] R. Grigg, *Chem. Comm.*, 1967, 1238.
[76] 'The Chlorophylls', eds. L. P. Vernon and G. R. Seely, Academic Press, New York, 1966.



(75)



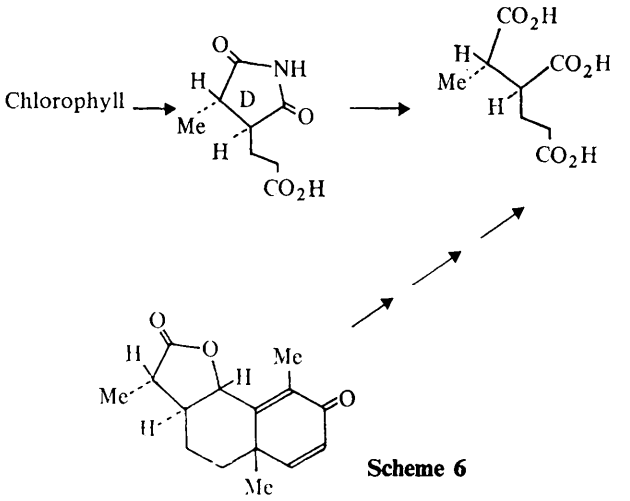
a) R = Me
b) R = CHO

(76)

Chlorophyll chemistry has not recently experienced a singular melioration of the magnitude of Woodward's synthesis[31] of chlorophyll-*a* (76a), but progress on a variety of fronts has been impressive. The *trans*- disposition of the 7- and 8- (ring D) hydrogen atoms of chlorophylls -*a* and -*b* has long been recognised. Inhoffen and co-workers[77] have now shown that the 7-propionate side-chain and the 10-carbomethoxy-group are in the *trans*- configuration. The only remaining structural problem, the absolute stereochemistry, has been defined by Fleming[78a,b] and Brockmann[78c] using degradative comparison with (−)-α-santonin (see Scheme 6 for a gross simplification of the evidence). Chlorophylls -*a'* and -*b'* have been shown,[79] by consideration of n.m.r. spectra, to be C-10 epimers of the natural compounds; the absolute configuration of these compounds follows from the other work.[78] The absolute stereochemistry of bacteriochlorophyll, a tetrahydroporphyrin which is the photosynthetic pigment of purple bacteria, has been given as (77).[78b,80] It is interesting to note that C-10 epimers of bacteriochlorophyll also exist,[79] though chromatographic systems have not yet been optimised to separate these. The power of n.m.r. and mass spectrometry in structural determination has been indicated by publication of work on the characterisation of the chlorophylls-*c* (78),[81] which are *porphyrins* featuring an acrylic side-chain of considerable biosynthetic interest.

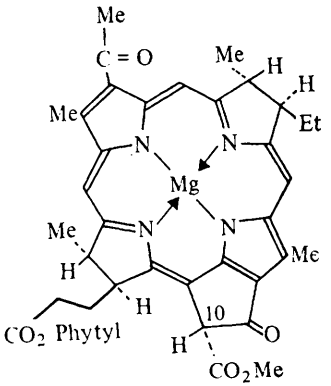
Strains of green sulphur bacteria, such as *Chlorobium thiosulfatophilum*

[77] H. Wolf, H. Brockmann, H. Biere, and H. H. Inhoffen, *Annalen*, 1967, **704**, 208.
[78] (*a*) I. Fleming, *Nature*, 1967, **216**, 151; I. Fleming, *J. Chem. Soc.* (*C*), 1968, 2765. (*c*) H. Brockman, *Angew. Chem.*, 1968, **80**, 233 (*Internat. Edn.*, 1968, **7**, 221).
[79] J. J. Katz, G. D. Norman, W. A. Svec, and H. H. Strain, *J. Amer. Chem. Soc.*, 1968, **90**, 6841; H. H. Strain and W. M. Manning, *J. Biol. Chem.*, 1942, **146**, 275.
[80] H. Brockmann and I. Kleber, *Angew. Chem.*, 1969, **81**, 626 (*Internat. Edn.*, 1969, **8**, 610). H. Brockmann, *Angew. Chem.*, 1968, **80**, 234, (*Internat. Edn.*, 1968, **7**, 222).
[81] R. C. Dougherty, H. H. Strain, W. A. Svec, R. A. Uphaus, and J. J. Katz, *J. Amer. Chem. Soc.*, 1966, **88**, 5037; 1970, **92**, 2826.

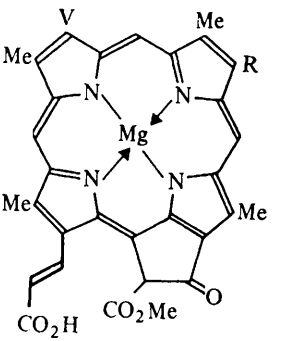


Scheme 6

(-)-α-Santonin



(77)



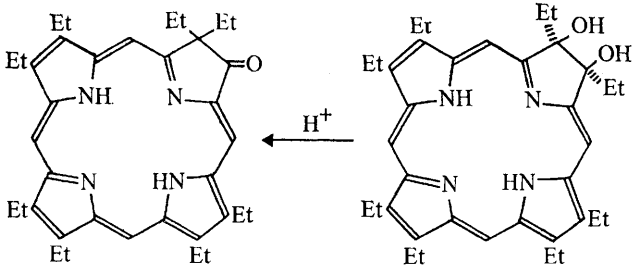
R = V or Et

(78)

produce *Chlorobium* chlorophylls (650) and (660) (see Section 6). The figures correspond to the wavelength, in nanometers, of their absorption maxima in the red, and there are thought to be six homologous fractions in each group (see Table 1). The *meso*-substituents in the (660) series are of particular interest, as is the intriguing problem of the biosynthetic derivation of the chlorophylls themselves.

No rational, stepwise ring synthesis of chlorins exists to date; most have been prepared from porphyrins, usually by reduction with sodium in alcohols. The reduction of porphyrins to chlorins is a fascinating aspect of the chemistry of the macrocycle, especially since the biosynthesis of chlorophyll proceeds through the magnesium complex of a porphyrin. Inhoffen and his colleagues[82] have shown that reduction of octaethylporphyrin with diborane in tetrahydrofuran gives a 5:1 mixture of *cis*- and *trans*-octaethylchlorin. *X*-ray crystallographers have suggested[83] that porphyrins have mutually distinct regions of π-localisation and aromaticity, and the ease of reduction of porphyrins to chlorins is evidence for this point of view. Diimide in β-picoline or pyridine converts octaethylporphyrin to *cis*-octaethylchlorin with a high degree of stereoselectivity;[84] this should be compared with the reduction of the iron complex of octaethylporphyrin to *trans*-octaethylchlorin with the traditional sodium in alcohol reagent. The sequential reduction of α, β, γ, δ-*meso*-tetraphenylporphyrin and its zinc complex to the corresponding chlorins and bacteriochlorins has also been examined.[84]

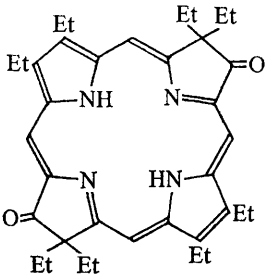
Reactions which achieve reduction of a peripheral double bond with the concomitant introduction of a geminal substituent are of interest because both geminal substitution, and the reduced feature, are characteristics of the corrinoid macrocycle of vitamin B_{12} (see Section 10). Several reactions of this general type have been reported.[85] The most promising of these has been examined by several groups, but exploited most successfully by the Braunschweig School.[85d] Oxidation of octaethylporphyrin with hydrogen peroxide in sulphuric acid gives an oxo-



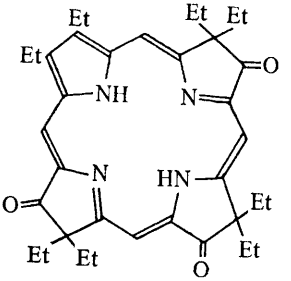
(79) (80)

[82] H. H. Inhoffen, J. W. Buchler, and R. Thomas, *Tetrahedron Letters*, 1969, 1145.
[83] *E.g.* L. E. Webb and E. B. Fleischer, *J. Amer. Chem. Soc.*, 1965, **87**, 667; S. J. Silvers and A. Tulinsky, *ibid.*, 1967, **89**, 3331; J. L. Hoard, M. J. Hamor, T. A. Hamor, and W. S. Caughey, *ibid.*, 1965, **87**, 2312.
[84] H. W. Whitlock, R. Hanauer, M. Y. Oester, and B. K. Bower, *J. Amer. Chem. Soc.*, 1969, **91**, 7485.
[85] (*a*) G. L. Collier, A. H. Jackson, and G. W. Kenner, *Chem. Comm.*, 1966, 299; *J. Chem. Soc.* (*C*), 1967, 66; (*b*) R. Grigg, A. W. Johnson, and A. Sweeney, *Chem. Comm.*, 1968, 697; (*c*) Y. Chang, P. S. Clezy, and D. B. Morell, *Austral. J. Chem.*, 1967, **20**, 959; (*d*) H. H. Inhoffen, *Pure Appl. Chem.*, 1968, **17**, 443; See also Ref. 2; (*e*) R. Bonnett, D. Dolphin, A. W. Johnson, D. Oldfield, and G. F. Stephenson, *Proc. Chem. Soc.*, 1964, 371; R. Bonnett, M. J. Dimsdale, and G. F. Stephenson, *J. Chem. Soc.* (*C*), 1969, 564.

chlorin (79), recently renamed[85d] as a 'geminiketone'. Such compounds can also be efficiently obtained by treatment of octaethylporphyrin with osmium tetroxide, the resultant diol (80) being transformed to the geminiketone (79) with acid, presumably by a process analogous to the pinacolone rearrangement of diols. Further treatment of geminiketones with hydrogen peroxide or osmium tetroxide and sulphuric acid results in the production of diketones [*e.g.* (81)] and even a triketone [*e.g.* (82)]. Corphins [*e.g.* (83)] (see Section 10) are both biosynthetically and theoretically interesting and have been synthesised in most elegant

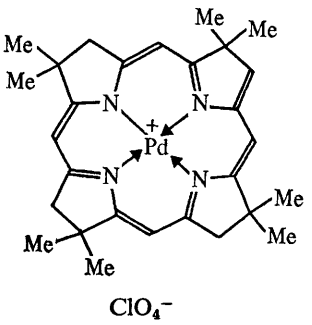


(81)

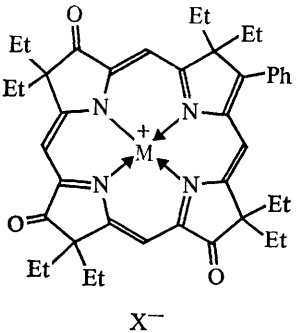


(82)

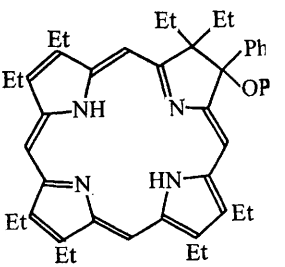
fashion by Eschenmoser's group.[86] Sequential treatment of octaethylporphyrin through the triketone to an analogue of the corphins is, unfortunately, not possible, but a clever modification[87] of the sequence allows the synthesis of a corphin-tetrageminaltriketone (84); treatment of the mono-geminiketone (79)



(83)



(84)



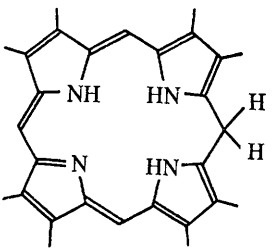
(85)

[86] A. Eschenmoser, A. P. Johnson, P. Wehrli, and R. Fletcher, *Angew. Chem.*, 1968, **80**, 622 (*Internat. Edn.*, 1968, **7**, 623); H. Gschwend, R. Scheffold, E. Bertele, M. Pesaro, and A. Eschenmoser, *Chimia* (*Switz.*), 1964, **18**, 181; *Proc. Roy. Soc.*, 1965, **A288**, 306.
[87] H. H. Inhoffen and N. Müller, *Tetrahedron Letters*, 1969, 3209.

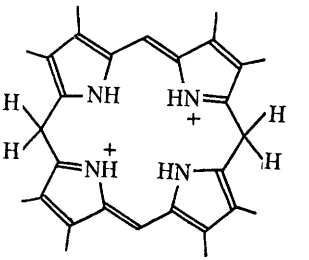
with phenyl-lithium furnishes the alcohol (85) which can be carried through to (84) by treatment of various metal complexes (*e.g.* Zn, Pd, Cu, Ni) with osmium tetroxide and acid.

8 Phlorins and Oxophlorins

Woodward's total syntheses often produce an added chemical bonus, along with the elegantly constructed target molecule; the most recent example of this characteristic is the uncovering of the mysteries of orbital symmetry[88] as a result of a chance observation in the vitamin B_{12} synthesis. In a similar way, the phlorins [*e.g.* (86)] were discovered and their fundamental chemistry elucidated[40] due to their intermediacy in the chlorophyll-*a* synthesis.[31] Phlorins are dihydro-



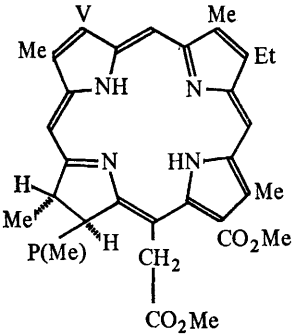
(86)



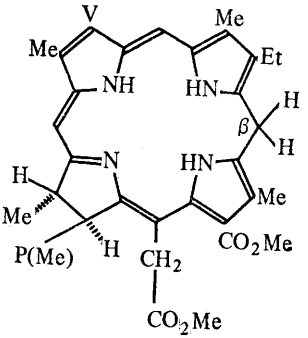
(87)

porphyrins, isomeric with chlorins, having one extra hydrogen on nitrogen and the other on a *meso* carbon atom. They are the normal product of photoreduction of porphyrins and can be prepared by one-electron reduction.[89] Phlorin free-bases are blue (λ_{max} 620 nm); the monocation is olive green (λ_{max} 725 nm) and results from protonation at the remaining free nitrogen. The dication (87), produced in strong acid, has a bisporphomethene structure, resulting from protonation at a *meso* carbon atom. Further reduction of phlorins furnishes porphomethenes and porphyrinogens, and they are easily oxidised to porphyrins with mild oxidising agents such as air or iodine. Electrolysis of chlorins [*e.g.* (88)] gives a *chlorin-β-phlorin* (89)[90] which can be photolysed in the presence of oxygen and methanol to compounds (90; R = Me) of the bacteriochlorin type. If the latter reaction is performed in dioxan–water, the product is a *trans*-dihydroxy-compound (90; R = H), which can be transformed into rhodin g_7 trimethyl ester

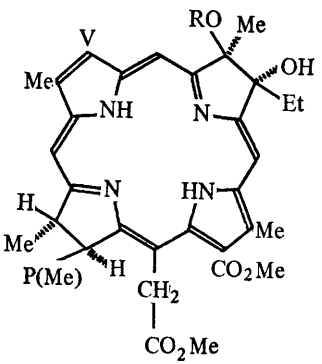
[88] R. B. Woodward and R. Hoffman, *Angew. Chem.*, 1969, **81**, 797 (*Internat. Edn.*, 1969, **8**, 781).
[89] *E.g.* D. Mauzerall, *J. Amer. Chem. Soc.*, 1962, **84**, 2437; H. H. Inhoffen, P. Jäger, R. Mählhop, and C.-D. Mengler, *Annalen*, 1967, **704**, 188; H. H. Inhoffen and P. Jäger, *Tetrahedron Letters*, 1964, 1317; 1965, 3387; G. L. Closs and L. E. Closs, *J. Amer. Chem Soc.*, 1963, **85**, 818.
[90] Ref. 85d, p. 445.



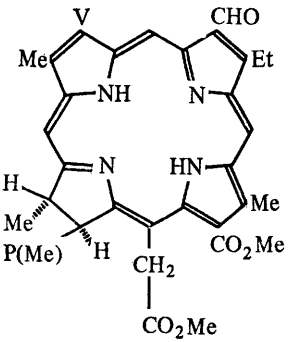
(88)



(89)



(90)

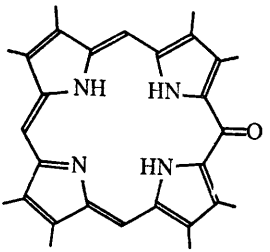


(91)

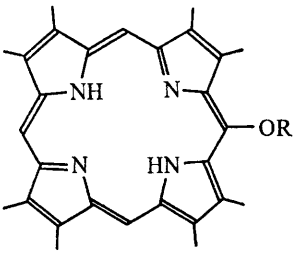
(91) from which chlorophyll-*b* (76b) is accessible. This constitutes a formal total synthesis of chlorophyll-*b*, based on Woodward's conquest[31] of chlorin e_6 trimethyl ester (88).

The blue oxophlorins (earlier known as hydroxyporphyrins or oxyporphyrins) (92) have been postulated as intermediates in the catabolism of porphyrins leading to bile pigments, and derive their new name by analogy with the phlorins. Their electronic absorption spectra are very similar, and this was one piece of evidence used to assign the *oxo-* (92) rather than the tautomeric *hydroxy-* structure (93; R = H) to these compounds.[41] A thorough investigation[41,91] into the nature of oxophlorins has been stimulated by the intermediacy of these

[91] (*a*) P. S. Clezy and A. W. Nichol, *Austral. J. Chem.*, 1965, **18**, 1835; (*b*) P. S. Clezy, F. D. Looney, A. W. Nichol, and G. A. Smythe, *ibid.*, 1966, **19**, 1481; (*c*) P. S. Clezy, A. J. Liepa, and G. A. Smythe, *ibid.*, 1970, **23**, 603.

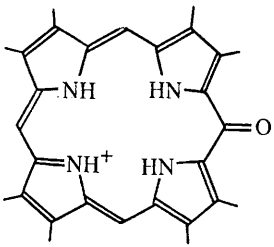


(92)

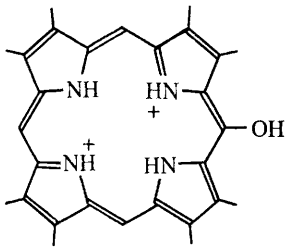


(93)

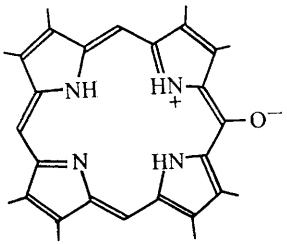
compounds in the route to porphyrins expounded by Kenner and co-workers.[22a] The discarded hydroxy-form (93; R = H) has the full macrocyclic conjugation of normal porphyrins, and would be expected to be red [and indeed, the corresponding methyl and ethyl ethers (93; R = Me or Et) are red], whereas the oxo-form (92) has the interrupted conjugation exhibited in the phlorins and *a,b,c*-bilatrienes (see Section 5D), the free-bases of which are characteristically blue. The n.m.r. investigation of oxophlorin structure was complicated by the paramagnetism associated with a little biradical character[41,91] in these compounds. Oxophlorin



(94)



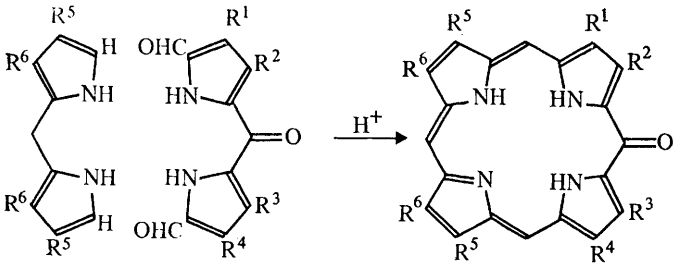
(95)



(96)

monocations (94) are olive green (*cf.* phlorins) and result from protonation on nitrogen. The dication (95) is similar to those of normal porphyrins, and has the hydroxy-structure, as have the metal complexes of oxophlorins.[41] By analogy with pyrroketones (see Section 4C), one would expect considerable contribution from mesomeric dipolar forms [*e.g.* (96)] and the i.r. spectra of oxophlorin free-bases and monocations [ν_{max}(C=O) 1560 cm^{-1}] indicate this is so. The bisvinylogous amide nature of oxophlorins is exemplified by their reaction with Meerwein's reagent, triethyloxoniumtetrafluoroborate, yielding the corresponding ethyl ether (93; R = Et) of the hydroxy-form. An alternative proposal[91a,b] for the structure of oxophlorins has recently been withdrawn.[91c]

Oxophlorins were first prepared by the Fischer and Lemberg Schools in the 1930's, as intermediates in the chemical transformation of porphyrins to bile pigments by coupled oxidation with hydrogen peroxide. Fischer also succeeded in preparing oxophlorins by the mysterious reduction of xanthoporphyrinogens (59) with hydrogen bromide in acetic acid,[92] an approach which has been exploited by Inhoffen's group.[57] There are two major routes to oxophlorins from pyrrolic compounds. The more versatile is that through *b*-oxobilanes (see Section 5A), developed by the Liverpool School.[22a,44] The second approach, used by Bonnett,[93] Clezy,[91] and their respective co-workers, is a modification of the MacDonald porphyrin synthesis (Scheme 4), and therefore one of the two dipyrrolic halves



(97) (98)

must be symmetrical. The best version of this approach[91c] is the condensation of the pyrromethane (97) with the 5,5′-diformylpyrroketone (98) in trifluoroacetic acid or in nitromethane in the presence of hydrogen bromide, and achieves yields of 70%. This route is now even more amenable in view of advances in the preparation of 5,5′-diformyl pyrromethanes[94] and -pyrroketones.[18]

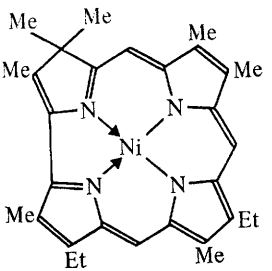
[92] H. Fischer and K. Gangl, *Z. physiol. Chem.*, 1942, **272**, 259.
[93] R. Bonnett and M. J. Dimsdale, *Tetrahedron Letters*, 1968, 731.
[94] R. Chong, P. S. Clezy, A. J. Liepa, and A. W. Nichol, *Austral. J. Chem.*, 1969, **22**, 229.

A sulphur analogue of oxophlorins has been synthesised,[95] but the assignment of its exact structure presently appears confused. Hydroxyoxophlorins [*e.g.* (61)] have been prepared by the photo-oxidation of porphyrin magnesium complexes in benzene.[65]

9 Corroles and Tetradehydrocorrins

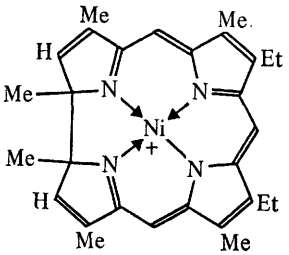
Avenues to corroles (24) and tetradehydrocorrins [*e.g.* (47) and (48)] have been mentioned earlier in this Review. Corroles have an 18π-electron aromatic system, and exhibit an intense Soret band in their electronic absorption spectra as a result of this chromophore (see Section 15A). Their aromaticity is also manifest in n.m.r. spectra; the 5-, 10-, and 15-protons are strongly deshielded by the induced ring current.[96] Alkylation of corrole metal complexes had been reported[97] to occur on the metal atom, but *X*-ray results have now shown that methylation with methyl iodide in the presence of base causes alkylation of the nitrogen atom of ring A.[98] Initial interest in corroles has waned in recent times, mainly in favour of the tetradehydrocorrins, which like corroles are obtained from *a,c*-biladienes, but with different terminal (1′,8′) substituents.

Thermolysis of neutral nickel 1-methyltetradehydrocorrins [*e.g.* (47; R = Me)] has been shown to give the corresponding 3,3′-*gem*-dialkylcorrole [*e.g.* (99)] due to a migration of a methyl group;[99b] these compounds were earlier thought to be the isomeric 2,2′-*gem*-dialkyl compounds.[99a] In contrast, heating of nickel 19-alkyl-1-methyltetradehydrocorrin *perchlorates* (48; R^1 = Alkyl, X = ClO_4) yields *meso*-substituted porphyrins by ring-expansion and migration of the 19-group.[99b] The yields and nature of the products of these thermolyses appear to depend upon the anion, if any, present in the tetradehydrocorrin. A most notable use of tetradehydrocorrins is their expeditious, albeit vigorous, reduction to



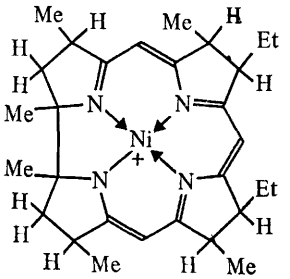
(99)

[95] P. S. Clezy and G. A. Smythe, *Chem. Comm.*, 1968, 127. See also *Austral. J. Chem.*, 1969, **22**, 239.
[96] A. W. Johnson and I. T. Kay, *J. Chem. Soc.*, 1965, 1620.
[97] R. Grigg, A. W. Johnson, and G. Shelton, *Chem. Comm.*, 1968, 1151.
[98] R. Grigg, T. J. King, and G. Shelton, *Chem. Comm.*, 1970, 56.
[99] (*a*) R. Grigg, A. W. Johnson, K. Richardson, and K. W. Shelton, *Chem. Comm.*, 1967, 1192; 1968, 897; *J. Chem. Soc.* (*C*), 1968, 1291; (*b*) R. Grigg, A. W. Johnson, K. Richardson, and K. W. Shelton, *J. Chem. Soc.* (*C*), 1969, 655.



ClO_4

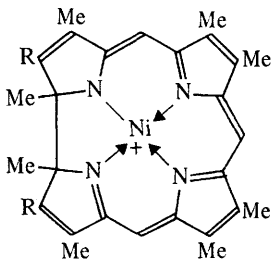
(100)



ClO_4

(101)

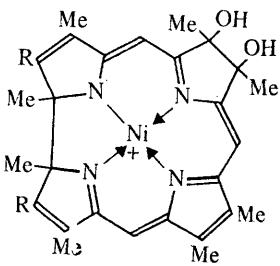
corrins (see Section 10). Thus, hydrogenation of the tetradehydrocorrin salt (100) at 160 °C and 100 atmospheres in the presence of Raney nickel produces a mixture of corrin epimers, isolated as their perchlorates (101)[100]. A similar reaction was performed on a cobalt tetradehydrocorrin salt, and the product isolated as the dicyanide.[22b] The present limitation to the generality of this route is the steric hindrance to reduction of some double bonds caused by 2- and 18-alkyl substituents. A further approach to corrins *via* tetradehydrocorrins has been examined by Inhoffen and his co-workers.[101] Treatment of tetradehydrocorrin metal chelates [*e.g.* (102)] with osmium tetroxide gives a mixture of diols [*e.g.* (103)] and tetraols [*e.g.* (104)]. Further hydroxylation of the nickel complexes gives hexaols [*e.g.* (105)] and octaols [*e.g.* (106)]. The latter have the



Br^- or ClO_4^-

R = H or Me

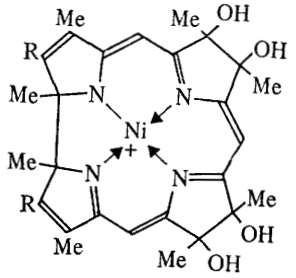
(102)



(103)

[100] R. Grigg, A. W. Johnson, and P. v.d. Broek, *Chem. Comm.*, 1967, 502. See also D. Dolphin, R. L. N. Harris, J. L. Huppatz, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.* (*C*), 1966, 30.

[101] H. H. Inhoffen, J. Ullrich, H. A. Hoffmann, and G. Klinzmann, *Tetrahedron Letters*, 1969, 613; H. H. Inhoffen, J. Ullrich, H. A. Hoffmann, G. Klinzmann, and R. Scheu, *Annalen*, 1970, **738**, 1.



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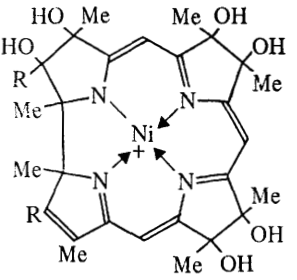
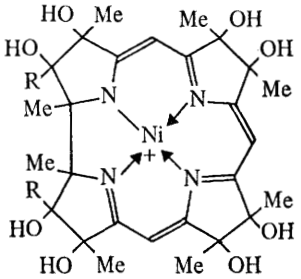


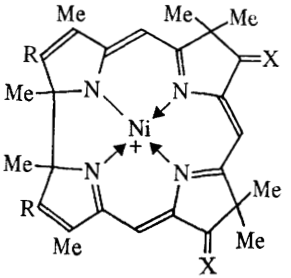
OH^-

(105)



OH^-

(106)



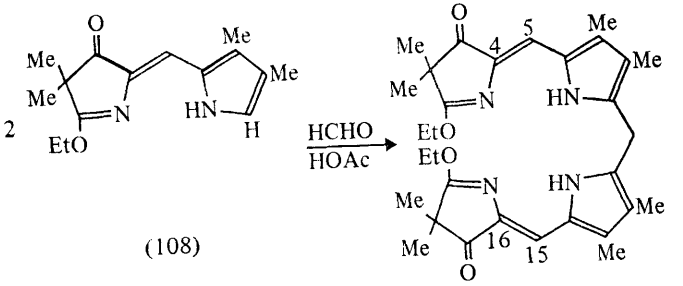
OH^-

(107)

chromophore which is characteristic of the corrins. Some of these hydroxy-derivatives have been converted[101] to the corresponding geminiketones with sulphuric acid, and the diketones [*e.g.* (107; X = O)] obtained from the tetraols, reduced under pressure over Raney nickel to didehydrocorrins [*e.g.* (107; X = H_2)]. Low reactivity due to steric factors at the 2- and 18-positions influences the course of the hydroxylation, as might be expected from Johnson's results.[100] For example, only the octaol (106; R = H) can be prepared directly from the corresponding tetradehydrocorrin. In other cases, octaols are obtained by retreatment of the appropriate tetraols with osmium tetroxide. As a result of this limitation, a more general approach has been examined,[102] utilising the self-condensation of compounds such as (108) through the agency of formaldehyde and acetic acid. This furnishes *a,c*-biladiene-3,17-diketones (109), which are potential sources of the corresponding tetradehydrocorrins [*e.g.* (110)]. A major complication of this approach is geometrical isomerism about the 4,5- and 15,16-double bonds, but these unwanted configurations can be converted to the

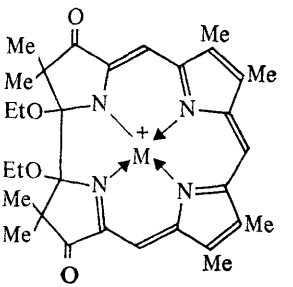
[101] A. Gossauer and H. H. Inhoffen, *Annalen*, 1970, **738**, 18; A. Gossauer, D. Miehe, and H. H. Inhoffen, *ibid.*, 1970, **738**, 31.

required stereoisomers (109). Certain reactions of nickel tetrahydrocorrins salts have been reported;[103] nickel 1-methyltetradehydrocorrins [*e.g.* (48; R^1 = H, M = Ni)] readily exchange the 5-, 10-, and 15-protons for deuterium in deuterio-



(108)

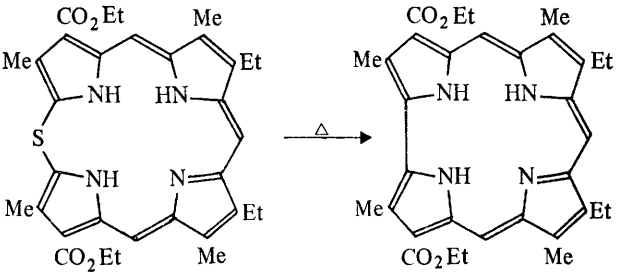
(109)



(110)

trifluoroacetic acid. This has led to a study of electrophilic substitution (bromination, chlorination, nitration, and methylation) and the products have been established as the 5-substituted derivatives. Corroles have been prepared[104] by the

[103] R. Grigg, A. W. Johnson and K. Richardson, *Chem. Comm.*, 1968, 896. See also Ref. 36.
[104] M. J. Broadhurst, R Grigg, and A. W. Johnson, *Chem. Comm.*, 1970, 807.

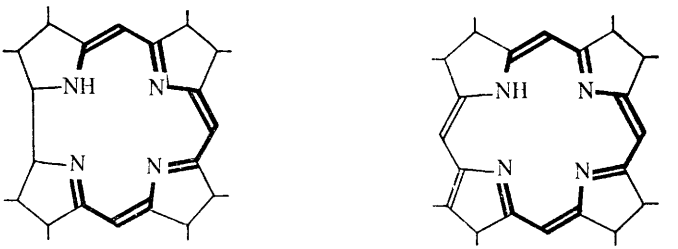


(111) (112)

symmetry-allowed extrusion of sulphur from a *meso*-thiaphlorin (111). Thus, heating of (111) in *o*-dichlorobenzene during 2 hours gave the corrole (112) in 40% yield; addition of triphenylphosphine to the reaction increased the yield to 60%.[104]

10 Corrins and Corphins

Neither corrins (113) nor corphins (114) are, strictly speaking, pyrrolic compounds, and hence their chemistry will not be reviewed in detail here. Some



(113) (114)

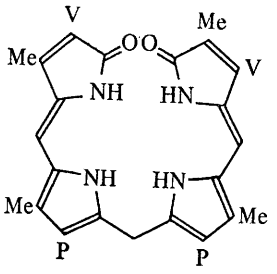
mention is pertinent, however, since both types of compound have been approached synthetically from pyrroles. The corrin skeleton is present in the ligand of vitamin B_{12}, the total synthesis of which is drawing towards its conclusion.[105] The Zurich School, led by Eschenmoser, is responsible for all of the

[105] R. B. Woodward, *Pure Appl. Chem.*, 1968, **17**, 519; A. Eschenmoser, Chem Soc. Centenary Lecture, 1969; *Quart. Rev.*, 1970, **24**, 366.

reported syntheses of corrins from non-pyrrolic starting materials.[106] One of these syntheses,[106b] involving formation of the corrin macrocycle by a magnificently conceived 'Woodward–Hoffmann'-type cyclisation, is a tribute to the stature of modern aspects of synthetic organic chemistry. Corphins are the corrinoid analogues of porphyrins, and have been constructed from both pyrrolic[87] and non-pyrrolic[86] compounds. It is known that vitamin B_{12} and porphyrins are biosynthesised from the same monopyrrolic precursor, PBG (4). However, little more than this is known about the derivation of the corrin skeleton, and it is not beyond the bounds of possibility that a corphin is involved in the *in vivo* skeletal rearrangement of porphinoid to corrinoid systems.[86] Such a chemical conversion has not been achieved.

11 Bile Pigments

These open-chain tetrapyrroles [*e.g.* biliverdin-IXα (60)] are formed in mammals by the catabolism of the prosthetic group of haemoproteins.[107] All known natural bile pigments have the -IXα[58] configuration, with one exception; the tegumental pigment of the caterpillars of the cabbage butterfly is biliverdin-IXγ.[6] Biliverdin-IXα is the immediate product of rupture of the haem macrocycle in mammals, but it is reduced in most cases to compounds such as bilirubin (115) and stercobilin (116) before excretion in the faeces. The exact mechanism of bile pigment formation has mystified chemists for several decades. It is known that the α-*meso* carbon atom is lost as carbon monoxide in both the *in vivo* and



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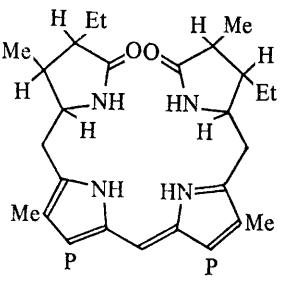
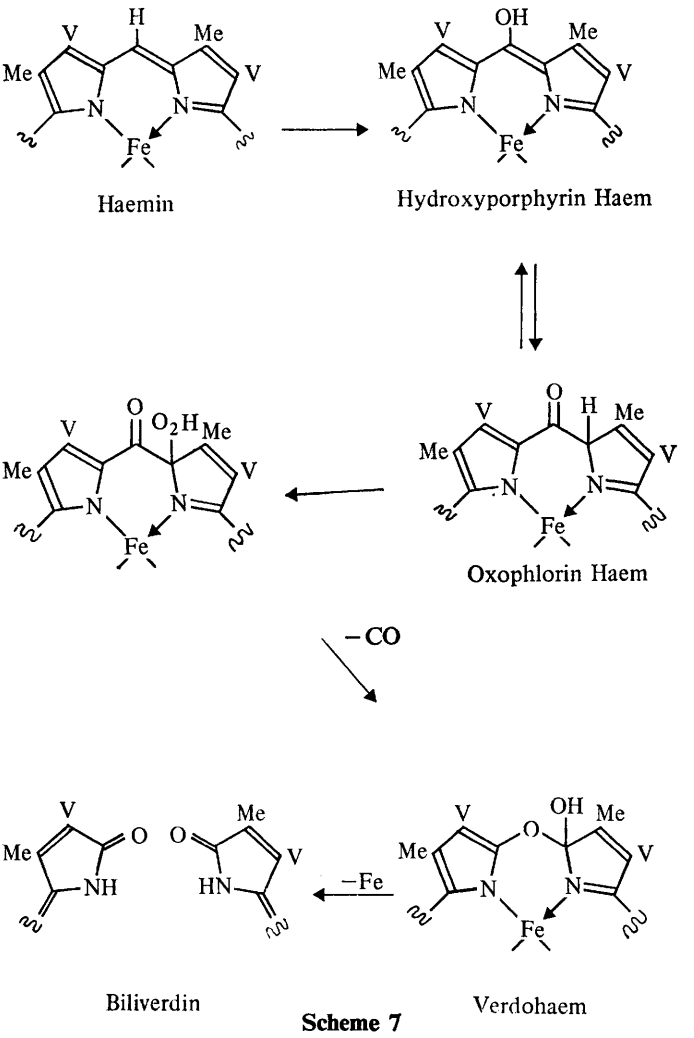


(116)

[106] (*a*) A. Eschenmoser, *Pure Appl. Chem.*, 1969, **20**, 1; E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem.*, 1964, **76**, 393 (*Internat. Edn.*, 1964, **3**, 490); I. Felner, A. Fischli, A. Wick, M. Pesaro, D. Bormann, E. L. Winnacker, and A. Eschenmoser, *Angew. Chem.*, 1967, **79**, 863 (*Internat. Edn.*, 1967, **6**, 864); A. Fischli and A. Eschenmoser, *Angew. Chem.*, 1967, **79**, 865 (*Internat. Edn.*, 1967, **6**, 866); (*b*) Y. Yamada, D. Miljkovic, P. Wehrli, B. Golding, P. Loeliger, R. Keese, K. Müller, and A. Eschenmoser, *Angew. Chem.*, 1969, **81**, 301 (*Internat. Edn.*, 1969, **8**, 343).

[107] For a review of the literature see R. Lemberg and J. W. Legge, 'Haematin Compounds and Bile Pigments', Interscience Publishers Inc., New York, 1949; C. H. Gray, 'The Bile Pigments', Methuen, London, 1953; R. Lemberg, *Rev. Pure. Appl. Chem.* (*Australia*), 1956, **6**, 1; T. With, 'Bile Pigments', Academic Press, New York and London, 1968; see also W. Rüdiger, *Angew. Chem.*, 1970, **82**, 527 (*Internat. Edn.*, 1970, **9**, 473).

chemical formation of bile pigments from porphyrins;[60] there have been many proposals for the mechanism,[44,108] and possibly the most attractive is that due largely to Lemberg, shown in Scheme 7. This suggests the intermediacy of

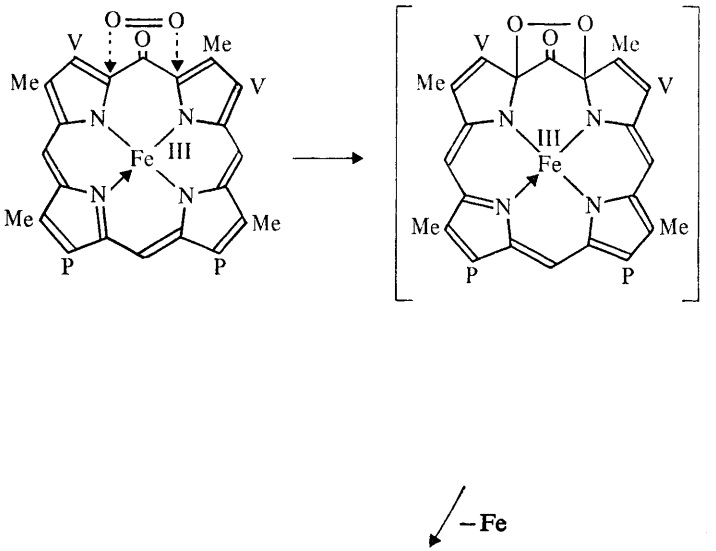


Scheme 7

oxophlorins and verdohaems, and both of these types of compound have been isolated and characterised in the chemical conversion. An attractive modification[44] to this Scheme is the addition of oxygen directly across the oxophlorin link (of the

[108] See *e.g.* C. Ó hEocha in Ref. 6, p. 91.

haemin anion[41]); the biliverdin is obtained from the oxygen adduct by loss of iron, carbon monoxide, and fission of the oxygen–oxygen bond:



Biliverdin–IX*α*

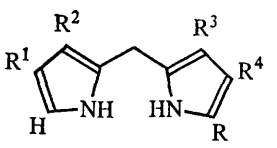
(60)

+

CO

There are, however, drawbacks to the ready acceptance of Scheme 7 and its modifications, not the least of which is the apparently enzymic nature of the transformation implicated by the *in vivo* catabolism, which gives only the -IXα isomer. The coupled oxidation of haemin gives all four possible isomeric bile pigments, but evidence in favour of Scheme 7 has recently been supplied by proof that the similar oxidation of myoglobin and haemoglobin is very largely specific to the α-position.[63,64]

Totally synthetic approaches to bile pigments[109] (excluding those from oxophlorins[41]) usually utilise the coupling of an unsubstituted (117; R = H) and a formylpyrrolylmethylpyrrolinone (117; R = CHO), or the corresponding unsaturated compounds (118). From this point of view, the synthetic problem is



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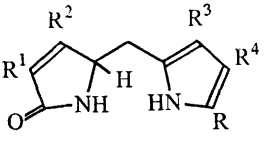

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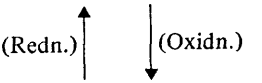

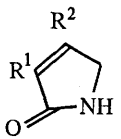

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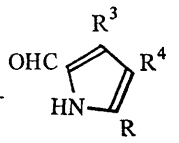

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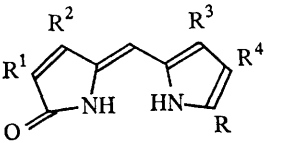
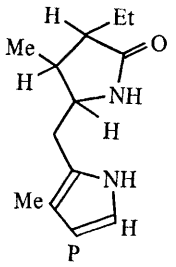


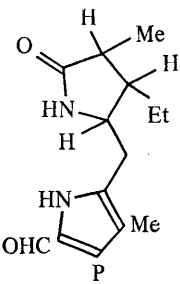
(118)

[109] (*a*) *E.g.* Ref. 3, Vol. IIi, p. 621; H. Fischer and H. Plieninger, *Z. physiol. Chem.*, 1942, **274**, 231; W. Siedel, *ibid.*, 1935, **237**, 8; (*b*) H. Plieninger and U. Lerch, *Annalen*, 1966, **698**, 196. (*c*) H. Plieninger and R. Steinsträsser, *ibid.*, 1969, **723**, 149; (*d*) H. Plieninger and J. Ruppert, *ibid.*, 1970, **736**, 43; H. Plieninger, K. Ehl, and A. Tapia, *ibid.*, 1970, **736**, 62.

simplified to the preparation of compounds such as (117), and a particularly favourable access is the hydrogen peroxide oxidation of the corresponding 5-unsubstituted pyrromethane (119).[110] An alternative approach[109b] is the condensation of pyrrol-3-en-2-ones [*e.g.* (120)] with formylpyrroles (121), and recent improvements[20] in the preparation of the former type of compound has boosted the merits of this already versatile route. Plieninger and Lerch[109b] have accomplished the total synthesis of racemic stercobilin-IXα (116), by condensation of (122) and (123). These latter compounds were obtained from the



(122)



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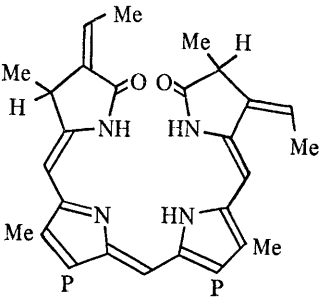
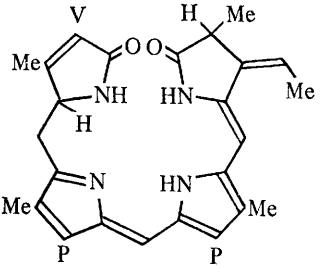


(124)

corresponding unsaturated intermediates [*e.g.* (117)] by reduction with either sodium in liquid ammonia (to give the *trans* epimers) or catalytically (to give the *cis* isomers). The syntheses of natural stercobilin-IXα (establishing the relative configurations of the asymmetric centres) and other optically-active urobilins have recently been reported.[109d]

Phytochrome is the photoreceptor for the photoregulation of growth in plants; it is also found in red and green algae. The exact structure of the bile pigment of phytochrome is not yet known with certainty, though a tentative structure (124) has been suggested.[111] Biliproteins are photosynthetically active algal bile pigments which still have a protein unit attached to the tetrapyrrole (phycobilin) portion; porphyrin precursors have been implicated in the formation of these compounds[112] and it has been shown that PBG (4) is incorporated into them. Structures have recently been proposed[111,113] for the red and blue algal pigments phycoerythrobilin (125) and phycocyanobilin (126) largely on the basis of n.m.r. and mass spectrometry.

[110] J. H. Atkinson, R. S. Atkinson, and A. W. Johnson, *J. Chem. Soc.*, 1964, 5999.
[111] H. W. Siegelman, D. J. Chapman, and W. J. Cole in Ref. 6, p. 107.
[112] R. F. Troxler, A. Brown, R. Lester, and P. White, *Science*, 1970, **167**, 192.
[113] H. W. Siegelman, D. J. Chapman, and W. J. Cole, *J. Amer. Chem. Soc.*, 1967, **89**, 3643; W. Rüdiger, P. Ó Carra, and C. Ó hEocha, *Nature*, 1967, **215**, 1477; H. L. Crespi, U. Smith, and J. J. Katz, *Biochemistry*, 1968, **7**, 2232.



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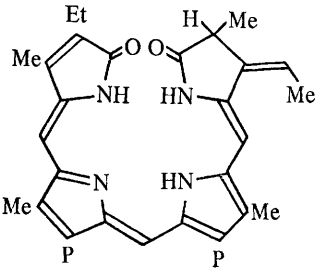
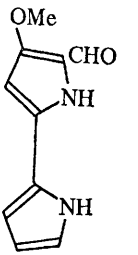


(126)

12 Prodigiosin

The 2,2′-bipyrrole derivative, prodigiosin (23), is a red pigment from *Serratia marcescens* which has attracted attention in recent years because its structure suggested that it might be derived by a similar biogenetic pathway to the porphyrins and corrins. However, it is now known that the amino-acid proline is a more efficient precursor than glycine [which supplies both nitrogen atoms of PBG (4)] and hence prodigiosin is derived by an entirely separate route. The total synthesis[114] of prodigiosin, accomplished by the final acid-catalysed condensation of the formylbipyrrole (127) with the monopyrrole (128), served also as the ultimate structural proof of this compound for which several structures had been proposed. More recently, the structure and total syntheses of undecylprodigiosin (129)[115] and metacycloprodigiosin (130)[116], two C-25 analogues of prodigiosin, have been published. In addition, a cyclic nonylprodigiosin derivative (131) has been reported.[117]



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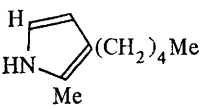

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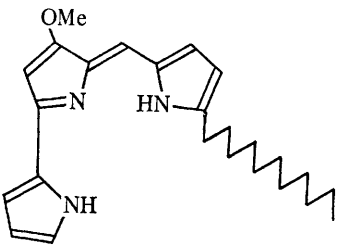
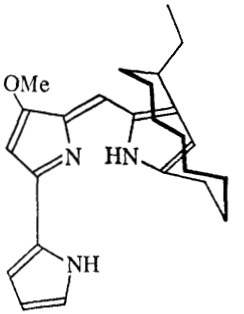


(129)

[114] H. Rapoport and K. G. Holden, *J. Amer. Chem. Soc.*, 1960, **82**, 5510; 1962, **84**, 635.
[115] H. H. Wasserman, G. C. Rodgers, and D. D. Keith, *Chem. Comm.*, 1966, 825; See also K. Harashima, N. Tsuchida, and J. Nagatsu, *Agric. and Biol. Chem. (Japan)*, 1966, **30**, 309; K. Harashima, N. Tsuchida, T. Tanaka, and J. Nagatsu, *ibid.*, 1967, **31**, 481.
[116] H. H. Wasserman, G. C. Rodgers, and D. D. Keith, *J. Amer. Chem. Soc.*, 1969, **91**, 1263; H. H. Wasserman, D. D. Keith, and J. Nadelson, *ibid.*, 1969, **91**, 1264.
[117] N. N. Gerber, *Tetrahedron Letters*, 1970, 809. See also N. N. Gerber, *Appl. Microbiology*, 1969, **18**, 1, for details of nonylprodigiosin.



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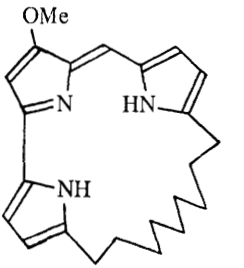
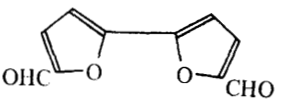


(131)

13 Newer Heterocycles Related to Porphyrins

The porphyrin macrocycle provides a good model for testing the validity of Hückel's rule for 18π-electron systems. (Porphyrins nominally have 11 double bonds and therefore 22π-electrons, but two of the peripheral double bonds do not enter into the delocalised system, resulting in an 18π-chromophore). The n.m.r. spectra of porphyrins show profound effects due to induction of a ring current; the NH protons appear at *ca.* 12—14τ due to shielding, while the *meso*-protons, being deshielded, resonate at *ca.* $-$ 1—+ 1τ. Analogues of porphyrin have been constructed to test Hückel's rule further, and a notable success has been corrole (24), which also has an 18π-electron system. In addition, macrocycles having different types of hetero-atom have been examined.[104,118] Compounds with one[118a] and two thiophen rings[104] have been shown to be aromatic, largely by application of n.m.r. spectrometry. Macrocycles incorporating furan rings[118b,c] have also been synthesised and investigated. Thus, condensation of 5,5′-diformyl-2,2′-bifuran (132) with the pyrromethane (133) gave a small yield (which could be



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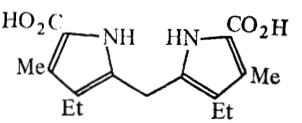

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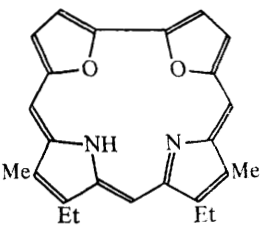
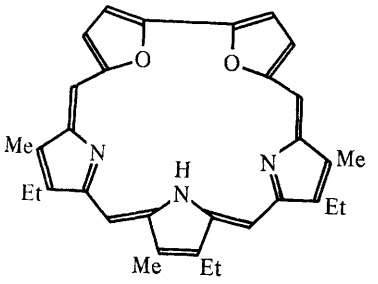


(134)

[118] (*a*) M. J. Broadhurst, R. Grigg, and A. W. Johnson, *Chem. Comm.*, 1969, 1480; (*b*) T. J. King and J. M. Gourley (Nottingham), unpublished results; (*c*) M. J. Broadhurst, R. Grigg, and A. W. Johnson, *Chem. Comm.*, 1969, 23.

improved by an alternative route) of the compound (134) possessing an aromatic 18π-system.[118c] Together with (134) there was also isolated a small amount of the non-rational 5-unit macrocycle (135), the structure of which was proved by its



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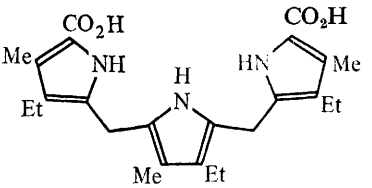
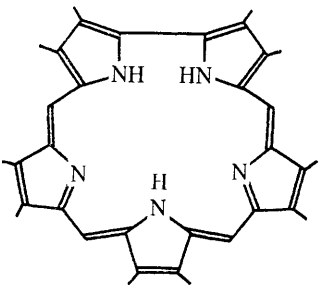


(136)

synthesis from the obvious intermediates (132) and (136). The compound (135) has a 22π-system, its aromaticity being exemplified by the resonances of the NH protons in the n.m.r. of the monoprotonated species at 15·5 and 16·8τ. Details of 'Sapphyrins'[119] have not yet been published, but it is known that these all-nitrogen 5-unit macrocycles (137) show evidence of π-delocalisation and aromaticity associated with its 22π-electron system.



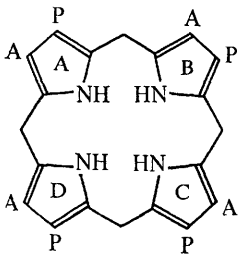
(137)

14 Biosynthesis

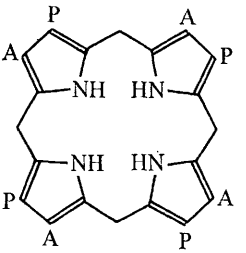
The biogenetic implications of developments within the pyrrolic field have been

[119] Disclosed by R. B. Woodward (Harvard) during discussions at the Symposium on Aromaticity, Sheffield, England, 1966.

discussed in a fragmentary way throughout this Review. However, one of the most fascinating problems in the whole of natural product chemistry has not been mentioned in the text, namely the mechanism by which Nature chooses to polymerise its building block, PBG (4), to uroporphyrinogen-III (138) and on occasions uroporphyrinogen-I (139). Types -II and -IV are never produced *in vivo*, and two enzymes are involved in the polymerisation, uroporphyrinogen-I synthetase and uroporphyrinogen-III co-synthetase; uroporphyrinogen-III is produced exclusively when the latter is in excess, and uroporphyrinogen-I in its absence. At intermediate concentrations a mixture is obtained. The really intriguing aspect is the way in which the fourth pyrrole ring (ring D) is switched around to produce the unsymmetrical uroporphyrinogen-III, which is the precursor of the haemoproteins in animals and of the chlorophylls of the plant



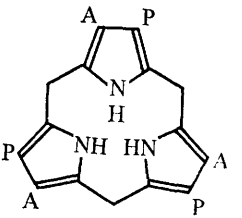
(138)



A = CH_2CO_2H

P = $CH_2CH_2CO_2H$

(139)

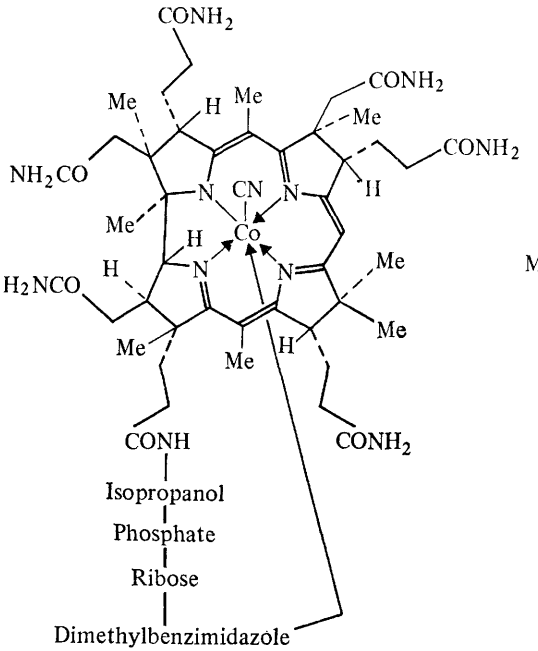


(140)

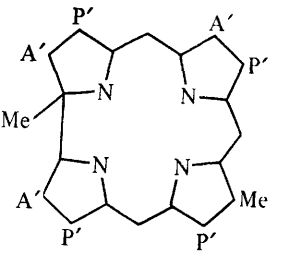
kingdom. Uroporphyrinogen-I can be obtained by the straightforward cyclisation of a symmetrical, rationally produced linear (A·P–A·P–A·P–A·P) tetrapyrrole. The considerable number of attempts to establish[120] the polymerisation pathway have rarely been able to make positive use of all of the available facts.[121] Suggestions have ranged from the hypothesis that the polymerisation is random but the co-synthetase binds only the type-III product, discarding the others, to molecular rearrangement of tetra-, penta-, and even octa-pyrrolic intermediates. A very recent proposal,[122] claiming to explain all of the facts, suggests that porphobilinogen is polymerised through the agency of uroporphyrinogen-I synthetase to cyclo-PBG_3 (140), which might be expanded to uroporphyrinogen-I by addition of PBG in the absence of co-synthetase, or else to uroporphyrinogen-

[120] For a survey of the proposals see G. S. Marks, *Ann. Reports*, 1962, **59**, 385 and L. Bogorad in 'Comparative Biochemistry of Photoreactive Systems', ed. M. B. Allen, Academic Press, Inc., New York, 1960, p. 227.
[121] *E.g.* L. Bogorad in Ref. 76, p. 481; G. S. Marks, *Bot. Rev.*, 1966, **32**, 56; E. Y. Levin, *Biochemistry*, 1968, **7**, 3781.
[122] J. Dalton and R. C. Dougherty, *Nature*, 1969, **223**, 1151.

III in the presence of the co-enzyme. As with some earlier hypotheses, this very plausible proposal can be modified to rationalise the biosynthesis of the corrinoid ligand of vitamin B_{12}, known to be derived from PBG (4). A simplification (142)



(141)



$A' = CH_2CONH_2$

$P' = CH_2CH_2CONH_2$

(142)

of the awe-inspiring structure (141) of the vitamin shows clearly its relationship to uroporphyrinogen-III, (138). The six extra methyl groups [omitted in (142)] are known to be methionine derived. The isolation and characterisation of vitamin B_{12} compounds lacking cobalt[123] has cast doubts upon an earlier proposal, based on *in vitro* transformations, that the porphyrin and corrin biosynthetic pathways might diverge at the linear tetrapyrrole stage, the corrinoid skeleton being produced as a result of the intervention of heavy metal ions.[124] It now seems likely that cobalt appears on the biogenetic horizon at a much later stage. The possibility that corrins might be biosynthesised from corphins (see Section 10) has been mentioned earlier.

[123] J. I. Toohey, *Proc. Nat. Acad. Sci. U.S.A.*, 1965, **54**, 934; *Fed. Proc.*, 1966, **25**, 1628; K. Sato, S. Shimzu, and S. Fukui, *Biochem. Biophys. Res. Comm.*, 1970, **39**, 170.
[124] I. D. Dicker, D. Dolphin, R. Grigg, and A. W. Johnson, *Chem. Comm.*, 1967, 560.

15 Application of Physical Methods

Electronic absorption spectroscopy proved to be a major diagnostic tool in early porphyrin chemistry,[3] without which progress might easily have been minimal. The recent introduction of more diverse physical techniques (*e.g.* n.m.r., e.s.r., *X*-rays, and mass spectrometry) has been important, not only as methods in their own right, but also because they are applicable to the often minute quantities of porphyrins which are naturally and synthetically available. Even n.m.r., which had been thought to be limited to investigations requiring tens of milligrams of material, has been revolutionised by the introduction of time-averaging computers, which also permit examination of marginally soluble substances. The use of modern physical techniques for structural determination has been augmented by their use also as probes into the fundamental facets of the chemistry of the macrocycle itself.

A. Electronic Absorption Spectroscopy.—The colour and graphical beauty of the visible spectra of porphyrins and related compounds are an aesthetic attraction for workers in this field. The main application of visible spectroscopy is for obtaining information on the gross structure of the compound (*i.e.* whether it is a porphyrin, chlorin, bacteriochlorin, phlorin *etc.*).[125] The 'Soret' band in these spectra is characteristic of the macrocyclic conjugation present in the compound, appearing at *ca.* 400 nm (ϵ_{max} 100—300,000). However, the satellite peaks at wavelengths longer than 450 nm can furnish information about the substituents sited on the nucleus. For example, metal-free porphyrins having all alkyl-type peripheral substituents exhibit an 'aetio-' type absorption spectrum (Figure 1a) while a 'rhodo-' type spectrum (Figure 1b) is shown by porphyrins bearing a strongly electron-withdrawing functionality (*e.g.* $-CO_2R$). Two such 'rhodifying' groups on adjacent pyrrole rings of the macrocycle cancel each other out, resulting in an 'aetio-' spectrum, but on diagonally opposite rings they reinforce each other and result in an 'oxo-rhodo-' spectrum (Figure 1c). *meso*-Substituents (*e.g.* alkyl, –OCOMe, –OAlkyl *etc.*) produce a 'phyllo-' type spectrum (Figure 1d) This is an extremely simplified version of the facts; complications arise with combinations of substituents, and massive changes occur when the visible spectra of metal complexes are measured.[125] A discussion of the data and interpretation of the spectra of porphyrins and metalloporphyrins has recently appeared,[126] underlining the important theoretical aspects of the chemistry of the macrocycle.[127]

B. Nuclear Magnetic Resonance Spectroscopy.—Information on the precise nature of porphyrin side-chains is available by application of this technique.

[125] For a comprehensive account of general methods within this field consult the major reference book: J. E. Falk, 'Porphyrins and Metalloporphyrins', Elsevier Publishing Company, Amsterdam, London and New York, 1964.
[126] A. H. Corwin, A. B. Chivvis, R. W. Poor, D. G. Whitten, and E. W. Baker, *J. Amer. Chem. Soc.*, 1968, **90**, 6577; 1969, **91**, 4016.
[127] *E.g.* M. Gouterman, *J. Mol. Spectroscopy*, 1961, **6**, 138; N. S. Hush, *Theor. Chim. Acta*, 1966, **4**, 108; I. Chen, *J. Mol. Spectroscopy*, 1967, **23**, 131, 144.

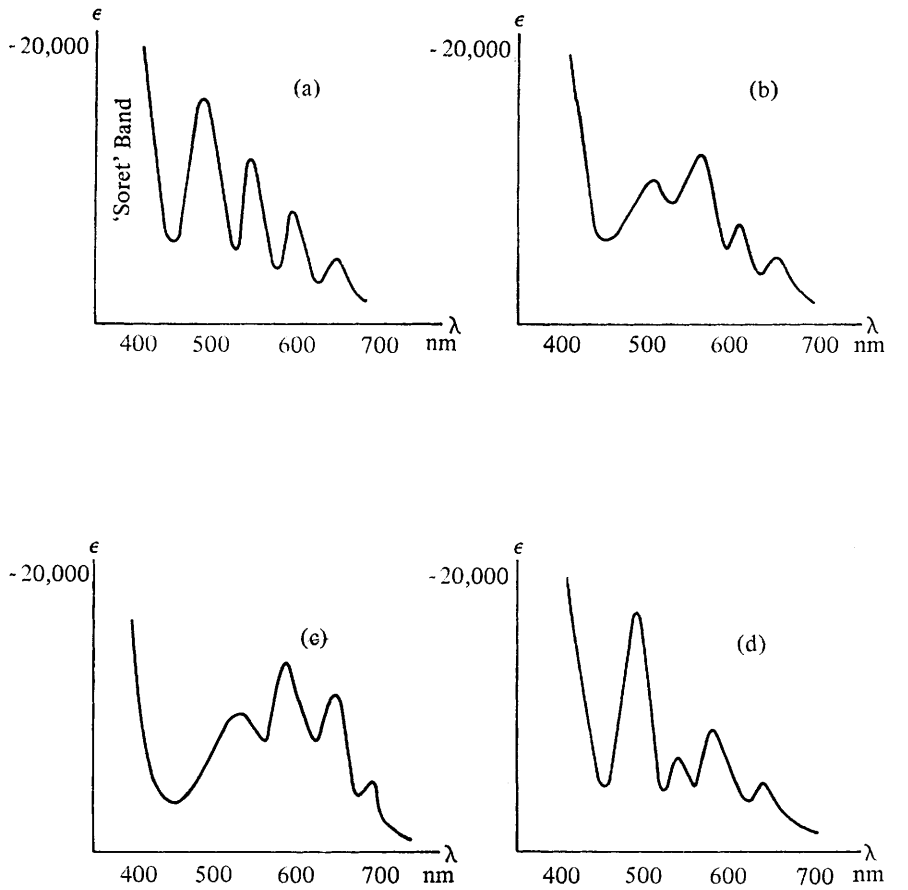


Figure 1

Indeed, in certain cases, even 'type-isomers'[1] can be distinguished.[128] The aromaticity of porphyrins is evidenced, in the now fashionable way, by consideration of induced ring currents. Thus, the *meso*-protons, being deshielded, resonate *ca.* − 1—+ 1τ (*cf.* benzene at 2·8τ) while the shielded N–*H* resonances appear at *ca.* 12—14τ. Experimental work on the n.m.r. spectra of porphyrins has been

[128] R. J. Abraham, A. H. Jackson, and G. W. Kenner, *J. Chem. Soc.*, 1961, 3468; R. J. Abraham, P. A. Burbidge, A. H. Jackson, and G. W. Kenner, *Proc. Chem. Soc.*, 1963, 134.

reported by several groups[128,129] and has been extended to an interesting theoretical interpretation of these results.[129b] The measurements are complicated by the solvent and concentration dependence of the chemical shifts, due largely to aggregation of the molecules into layers in solution. This aspect has also been examined from the point of view of the nature and thermodynamic stability of these aggregates.[128,129c] A most exciting extension of n.m.r. spectroscopy into the area of haemoproteins is now in progress and appears to be supplying an insight into the nature and functioning of myoglobin and haemoglobin in their natural environment.[130] Briefly, the spectra of the paramagnetic haemoproteins show the protons of the prosthetic group to be shifted by hyperfine interactions with the unpaired electrons delocalised from the iron. In many cases the resonances are well clear of the signals due to the protein portion of the molecule and are well resolved, even in myoglobin and haemoglobin. This permits, with a good degree of certainty, the allocation of resonances to particular protons on the porphyrin macrocycle. The important fact is that the resonances (spread out between *ca.* -15 and $+18\tau$) can be directly related to spin densities on the porphyrin ring and hence are sensitive to minute changes in the electron distribution of the haem group. In particular, this technique is furnishing information of the nature of the 'co-operative effect' of haemoglobin, by which the rate of uptake of oxygen is accelerated by the oxygenation of other sub-units within the haemoglobin molecule.

C. Mass Spectrometry.—Mass spectrometry of porphyrins and related compounds has flourished, not only because the great stability of the macrocycle provides for the easy derivation of molecular weights of unknown porphyrins, but also because the nucleus acts as an inert support for the side-chains, which it is therefore possible to study in detail, without the complication of fragmentation of the porphyrin nucleus. The introduction of 'direct-inlet' systems to the mass spectrometer was the single advance in instrumentation which allowed several different studies of the mass spectra of porphyrins and chlorins.[131] The mass spectra of porphyrins are strikingly characteristic; the molecular-ion is usually the base

[129] (*a*) W. S. Caughey and W. S. Koski, *Biochemistry*, 1962, **1**, 923; G. L. Closs, J. J. Katz, F. C Pennington, M. R. Thomas, and H. H. Strain, *J. Amer. Chem. Soc.*, 1963, **85**, 3809; R. J. Abraham, A. H. Jackson, G. W. Kenner, and D. Warburton, *J. Chem. Soc.*, 1963, 853; D. Doughty and C. W. Diggins, *J. Phys. Chem.*, 1969, **73**, 423. (*b*) R. J. Abraham, *Mol. Phys.*, 1961, **4**, 145. (*c*) E. Becker, R. Bradley, and C. J. Watson, *J. Amer. Chem. Soc.*, 1961, **83**, 3743; R. J. Abraham, P. A. Burbridge, A. H. Jackson, and D. B. Macdonald, *J. Chem. Soc.* (*B*), 1966, 620; R. J. Abraham and P. F. Swinton, *J. Chem. Soc.* (*B*), 1969, 903.

[130] K. Wuthrich, R. G. Shulman, and J. Peisach, *Proc. Nat. Acad. Sci. U.S.A.*, 1968, **60**, 373; A. Kowalsky, *Biochemistry*, 1965, **4**, 2382; R. J. Kurland, D. G. Davis, and C. Ho, *J. Amer. Chem. Soc.*, 1968, **90**, 2700; C. C. McDonald and W. D. Phillips, *ibid.*, 1967, **89**, 6332; S. Ogawa, R. G. Shulman, P. A. M. Kynoch, and H. Lehmann, *Nature*, 1970, **225**, 1042.

[131] (*a*) A. H. Jackson, G. W. Kenner, K. M. Smith, R. T. Aplin, H. Budzikiewicz, and C. Djerassi, *Tetrahedron*, 1965, **21**, 2913; (*b*) E. W. Baker, *J. Amer. Chem. Soc.*, 1966, **88**, 2311; D. G. Whitten, K. E. Bentley, and D. Kuwada, *J. Org. Chem.*, 1966, **31**, 322; D. R. Hoffman, *ibid.*, 1965, **30**, 3512; F. v.d. Haar, Dissertation, Braunschweig, 1966; E. W. Baker, T. F. Yen, J. P. Dickie, R. E. Rhodes, and L. F. Clark, *J. Amer. Chem. Soc.*, 1967, **89**, 3631; (*c*) H. Budzikiewicz, F. v.d. Haar, and H. H. Inhoffen, *Annalen*, 1967, **701**, 23.

(100%) peak, in the absence of very labile side-chains. Fragmentation of the side-chains provides a series of peaks, tapering off to zero intensity at about *m/e* 400. After a bare region, a series of doubly charged ions is found, which likewise tapers off to very low relative intensity at about *m/e* 200. The doubly-charged region is very highly populated as befits the highly aromatic character of the macrocycle; some peaks here can be found which are in the region of 20% of the base peak. A particularly important feature of one of the studies[131a] was possibly the earliest realisation that the production of metastable peaks is not dependent on one-step decompositions alone. It was found that a metastable peak was observed for a fragmentation which must logically have involved two or more separate groups cleaving individually, but simultaneously. This observation has been investigated further both inside [131c] and outside [132] the porphyrin field. The mass spectrometric behaviour of simple pyrroles[133a] and the more complicated di-, tri-, and tetra-pyrrolic compounds[133b] have been reported. As might be expected, bile pigments have received great attention in this context.[133b,134]

D. *X*-Ray Studies.—The importance of absolute structure determination is obvious in all fields of chemistry. It is doubly so in the porphyrin field because the determinations are able to reveal parameters of fundamental theoretical importance of both porphyrins and metalloporphyrins. A thorough review of *X*-ray applications to this field has recently appeared.[135]

I wish to thank Professors A. H. Jackson and G. W. Kenner F.R.S. for helpful discussions.

[132] J. Seibl, *Helv. Chim. Acta*, 1967, **50**, 263; E. Caspi, J. Wicha, and A. Mandelbaum, *Chem. Comm.*, 1967, 1161.
[133] (*a*) H. Budzikiewicz, C. Djerassi, A. H. Jackson, G. W. Kenner, D. J. Newman, and J. M. Wilson, *J. Chem. Soc.*, 1964, 1949; (*b*) A. H Jackson, G. W. Kenner, H. Budzikiewicz, C. Djerassi, and J. M. Wilson, *Tetrahedron*, 1967, **23**, 603.
[134] A. H. Jackson, K. M. Smith, C. H. Gray, and D. C. Nicholson, *Nature*, 1966, **209**, 581; D. J. Chapman, W. J. Cole, and H. W. Siegelman, *Biochemistry*, 1968, **7**, 2929; See also Ref. 63.
[135] E. B. Fleischer, *Accounts Chem. Res.*, 1970, **3**, 105. See also Ref. 83.