# PEDLER LECTURE*

## Porphyrins and Related Ring Systems

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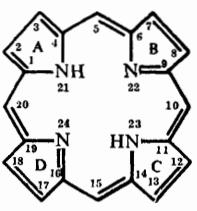
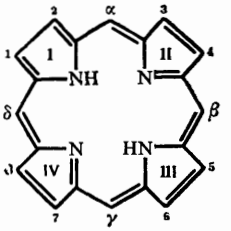
Studies on the porphyrin ring system have been a major preoccupation of our research group for nearly twenty years. In the present account, I.U.P.A.C. numbering recommendations (1) will be adopted[1] rather than the older German system (2). A versatile chemist can adopt any of several features of this remarkable molecule for study, for example, *ab initio* calculations, spectral studies, the relationship of structure and aromaticity, the effects on the physical and chemical properties of complexed metals, usually present as square-planar, pyramidal, or octahedral complexes, and structural, synthetic, and biochemical aspects of the naturally occurring porphyrins.




(1)



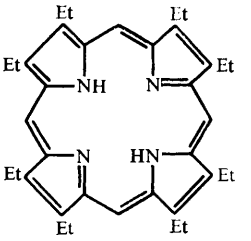

(2)

For many of the fundamental properties, two individual porphyrins have been studied in detail, octaethylporphyrin (3; OEP)† with free *meso*-positions and tetraphenylporphyrin (4; TPP) with free β-positions. Nature, however, does not adopt such simplifications of the substituent pattern, and in the ingenious porphyrin biosynthesis has contrived an unsymmetrical arrangement of substituents to be formed in nearly all cases, *e.g.* the key intermediate uroporphyrinogen III (5) from the single pyrrole porphobilinogen (6). The nature of this polymerization has been the subject of much speculation but, by application of

* Delivered at a Meeting of the Chemical Society on 10th October, 1974, at the Scientific Societies' Lecture Theatre, London, W.1.

† Many porphyrin chemists have reason to be grateful to Professor H. H. Inhoffen for generous gifts of octaethylporphyrin, which have facilitated many studies of the properties of this compound.

[1] *Biochemistry*, 1974, **13**, 1555.



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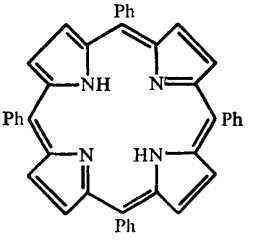

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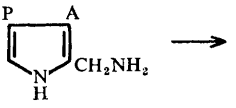
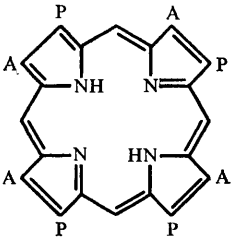


(5) A = $CH_2CO_2H$
P = $CH_2CH_2CO_2H$



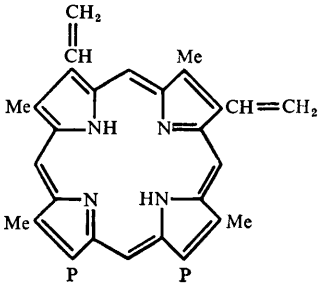
(6)

$^{13}$C-labelled intermediates, Battersby and others[2] have gone a long way towards an understanding of the route, which involves an intramolecular rearrangement of ring D alone, the other three units of porphobilinogen (rings A, B, and C) being incorporated intact.

The arrangement of the $\beta$-substituents in (5) undergoes modification and elaboration before dehydrogenation in other biologically important molecules such as protoporphyrin-IX (7), pemptoporphyrin (8),[3] chlorophyll a (9), and vitamin $B_{12}$ coenzyme (10) with its corrin chromophore, and the synthesis of these molecules has been achieved only by intensive effort by several research schools. In the most complex case, vitamin $B_{12}$, the nature of its substituent groups, their absolute stereochemistry, and the consequent problems of synthesis[4] may at times have tended to obscure its relationship with the porphyrins, but this was a small price to pay for the wealth of new synthetic methods, the conception of the Woodward–Hoffman rules, and the ultimate success of the synthesis.

The traditional and still useful [2 + 2] methods for porphyrin syntheses based on dipyrromethenes[5] or dipyrromethanes[6] may suffer severe limitations,

[2] A. R. Battersby, E. Hunt, and E. McDonald, *J.C.S. Chem. Comm.*, 1973, 442; *cf.* J. H. Mathewson and A. H. Corwin, *J. Amer. Chem. Soc.*, 1961, **83**, 135.
[3] S. Sano, T. Shinga, J. M. French, and E. Thonger, *Biochem. J.*, 1965, **97**, 250.
[4] R. B. Woodward, *Pure Appl. Chem.*, 1973, **33**, 145; A. Eschenmoser, *Quart. Rev.*, 1970, **24**, 366; 23rd I.U.P.A.C. papers, Boston, 1971, **2**, 69.
[5] H. Fischer and H. Orth, 'Die Chemie des Pyrrols', Vol IIi, Akademische Verlag, Leipzig, 1937, p. 158.
[6] G. B. Arsenault, E. Bullock, and S. F. MacDonald, *J. Amer. Chem. Soc.*, 1960, **82**, 4384.



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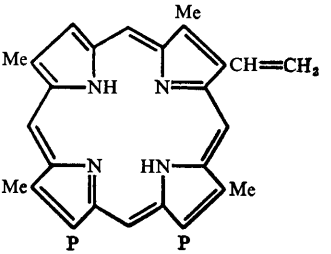

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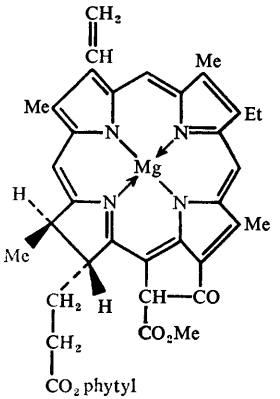

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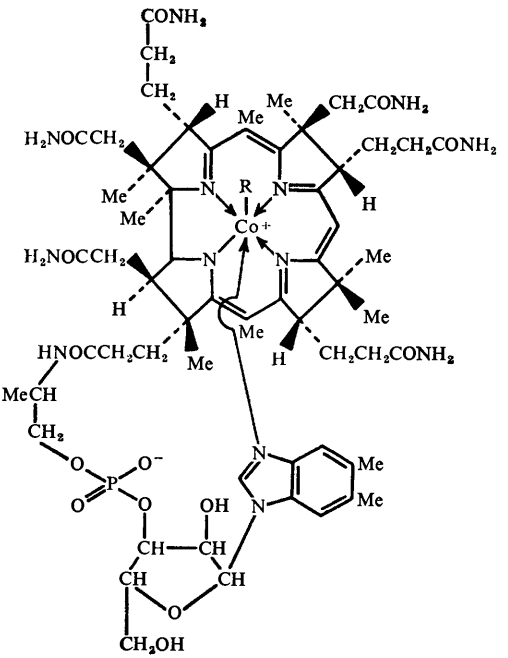
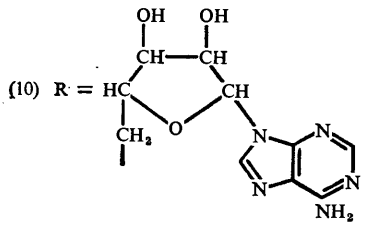
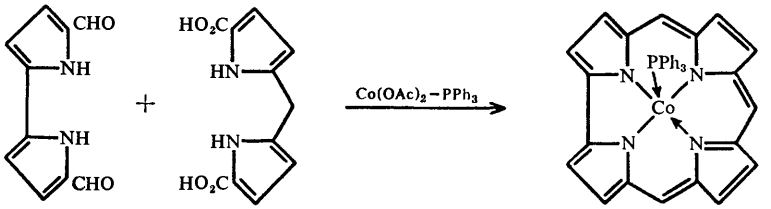


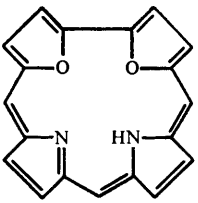
(10) R = 

low yields and undesirable by-products, when applied to the preparation of unsymmetrical porphyrins. Moreover, attempts to apply [2 + 2]-type syntheses




(12) (11)

to the preparation of the related ring system corrole (11), *i.e.* by reaction of 5,5′-diformyl-2,2-bipyrroles (12) with dipyrromethane-5,5′-dicarboxylic acids or 5,5′-diformyldipyrromethanes with 2,2′-bipyrrole-5,5′-dicarboxylic acids, have been generally unsuccessful except in the presence of triphenylphosphine and cobalt(II) ions.[7] The use of a metal ion as a template in the preparation of modified porphyrins clearly is not applicable if the macrocycle does not form metal complexes, *e.g.* the 21,22-dioxacorroles (13) in which two furan rings



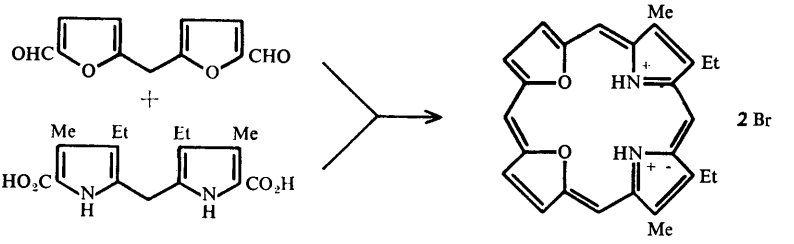

(13)

substitute two of the pyrroles. In the absence of metal ions the yields were low.[8]

A [2 + 2]-type condensation was used successfully for a synthesis of a 21,22-dioxaporphyrin (14),[9] but for 21-oxa- (15; X = O), 21-thia- (15; X = S), 21,23-dioxa- (16; X = Y = O), 21,23-dithia- (16; X = Y = S), and 21-oxa-23-thia-porphyrins (16; X = O, Y = S) a [3 + 1]-type condensation was more appropriate.[10]

The spectral properties of these rings reflect their aromatic character and their overall resemblance to the porphyrins. Unexpected properties were the unusual

[7] J. M. Conlon, A. W. Johnson, W. R. Overend, D. Rajapaksa, and C. M. Elson, *J.C.S. Perkin I*, 1973, 2281.
[8] M. J. Broadhurst, R. Grigg, and A. W. Johnson, *J.C.S. Perkin I*, 1972, 1124.
[9] Professor T. J. King, personal communication.
[10] M. J. Broadhurst, R. Grigg, and A. W. Johnson, *J. Chem. Soc.* (*C*), 1971, 3681.



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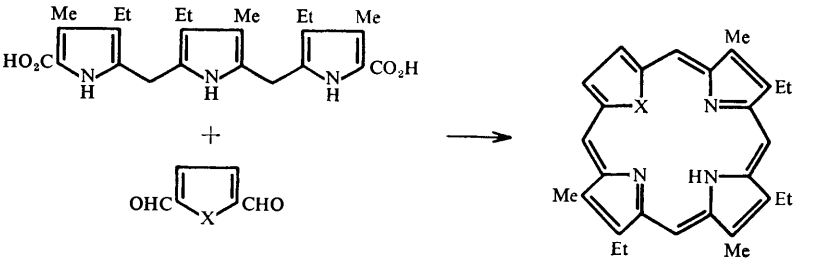

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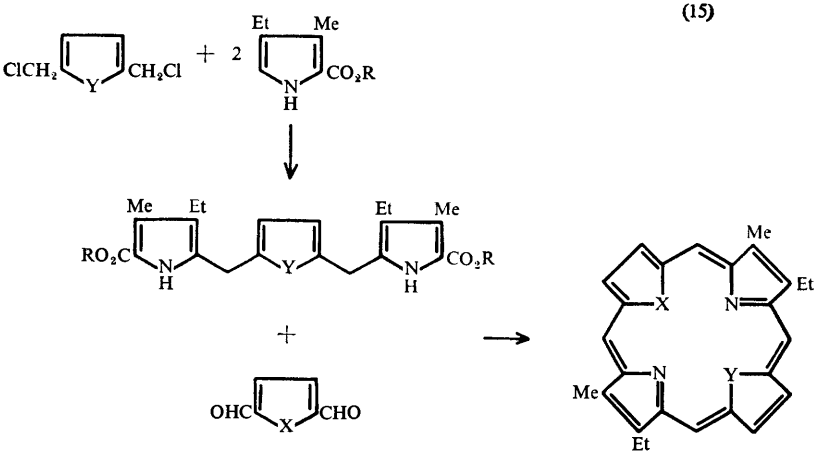
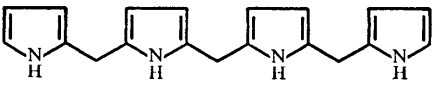


(16)

mass spectra of the oxa-derivatives, where intense $M + 2$ ions were observed, and the high basicities of the dioxa-compounds, which precluded the isolation of the free bases. Only the mono-oxaporphyrin formed a range of stable metal complexes. For the unsymmetrical porphyrins, the main developments in preparative methods have resulted from the operation of the [2 + 2]-type condensations in two stages, *i.e.* by isolation and manipulation of the intermediate tetrapyrrole. Bilanes (17), while retaining all of the high nucleophilic

character of the pyrroles, are normally too unstable to be useful because of the high probability of fission and recombination reactions. Some chemical reactivity must therefore be sacrificed for stability and ease of handling, and this is achieved by the introduction of electrophilic centres, usually by modifications of the linking groups. The tetrapyrrolic systems which have found most favour are the bilenes-*b* (18),[11] the biladienes-*ac* (19),[12] and the *b*-oxo-bilanes (20).[13]



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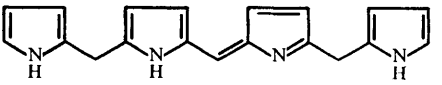

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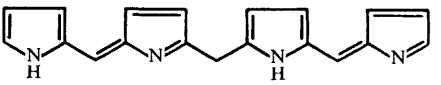

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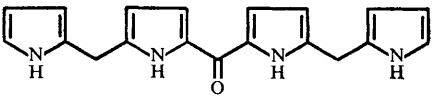


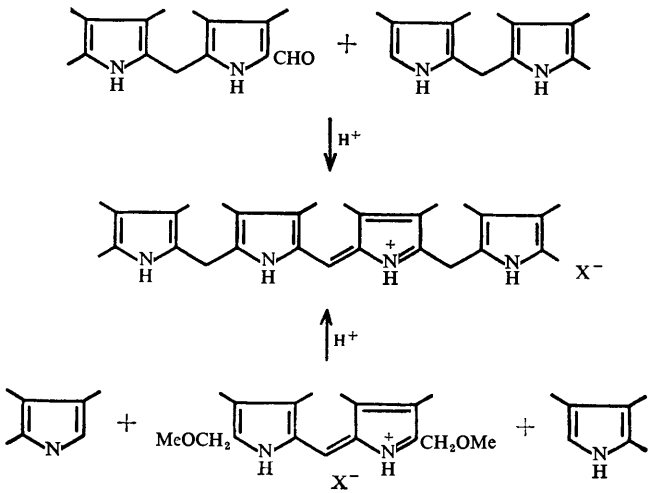
(20)

The choice is then one of availability of intermediates in the light of the nature of the eventual $\beta$-substitution pattern.

Methods of synthesis of these intermediates follow the conventional means of linking pyrrole rings, and can be summarized as follows:

*Bilenes*-b. The most versatile method is the condensation of a 5-formyldipyrromethane with a 5-unsubstituted (or 5-carboxy) dipyrromethane (Scheme 1)[14] although the lability of certain bilenes-*b* requires care in the choice of substituents.[15] Alternative methods include the condensation of a 5,5′-dimethoxy-

[11] H. Fischer and A. Kurzinger, *Z. physiol. Chem.*, 1931, **196**, 213.
[12] A. W. Johnson and I. T. Kay, *J. Chem. Soc.*, 1961, 2418.
[13] A. H. Jackson, G. W. Kenner, G. McGillivray, and K. M. Smith, *J. Chem. Soc.* (*C*), 1968, 294.
[14] A. F. Mironov, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Tetrahedron Letters*, 1965, 183; V. D. Rumyantseva, A. F. Mironov, and R. P. Evstigneeva, *Zhur. obshchei Khim.*, 1973, **43**, 1600 (*Chem. Abs.* 1974, **80**, 37 035); A. H. Jackson, G. W. Kenner, and K. M. Smith, *J. Chem. Soc.* (*C*), 1971, 502.
[15] J. M. Conlon, J. A. Elix, G. I. Feutrill, A. W. Johnson, M. W. Roomi, and J. Whelan, *J.C.S. Perkin I*, 1974, 713; P. S. Clezy and C. J. R. Fookes, *Austral. J. Chem.*, 1974, **27**, 371.



**Scheme 1**

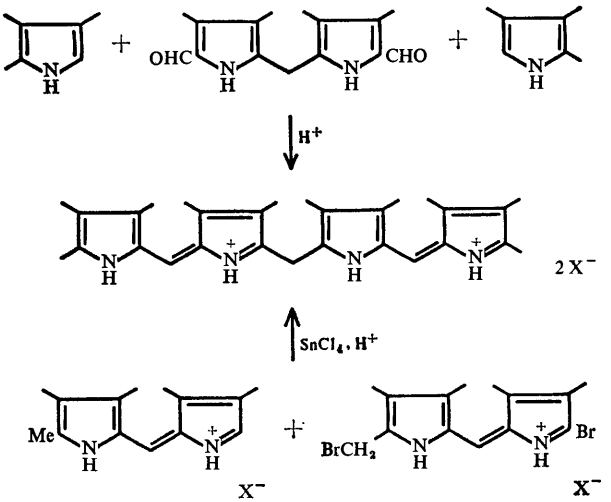
methyldipyrromethene with two equivalents of a 5-unsubstituted pyrrole,[12] which places limitations on the preparation of unsymmetrically substituted bilenes. Finally, the so-called α-oxobilane route[16] involves several stages and the more direct routes are usually preferable.

*Biladienes*-ac. Two good methods are available for these intermediates. In the first, a 5,5′-diformyldipyrromethane is condensed with two equivalents of a 5-unsubstituted (or 5-carboxy) pyrrole, or alternatively a 5-formylpyrrole (two equivalents) is condensed with a dipyrromethane-5,5′-dicarboxylic acid.[12] In the second,[17] a 5-unsubstituted-5′-methyldipyrromethene is brominated to a 5-bromo-5′-bromomethyldipyrromethene and this is condensed with a 5-methyldipyrromethene in the presence of stannic chloride. The resulting tin complex of the 1-bromo-19-methylbiladiene-*ac* is then decomposed by acid. These methods are illustrated in Scheme 2.

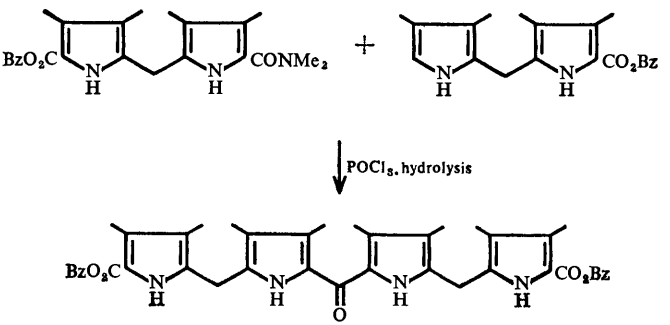
b-*Oxobilanes*. These are prepared[13] by condensation of the phosphoryl chloride complex of the monobenzyl ester mono(dimethylamide) of a dipyrromethane-5,5′-dicarboxylic acid with a benzyl 5-unsubstituted dipyrromethane-5′-carboxylic ester (Scheme 3). These intermediates have been used extensively by Kenner and his colleagues for porphyrin synthesis, the additional oxygen being removed eventually in an additional step by a sodium amalgam reduction of the corresponding *meso*-acetoxy-derivative.

[16] Reviews: A. H. Jackson and K. M. Smith, 'The Total Synthesis of Natural Products', Wiley-Interscience, New York, 1973, Vol. 1, p. 143, K. M. Smith, *Quart. Rev.*, 1971, **25**, 31.

[17] R. L. N. Harris, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.* (*C*), 1966, 22.



**Scheme 2**

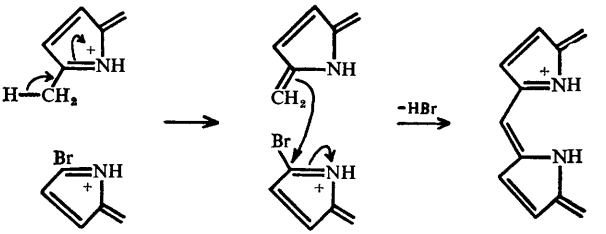


**Scheme 3**

The remaining features of the porphyrin syntheses are the introduction of the final *meso*-carbon atom and the method of cyclization to the macrocycle. Intermolecular condensation using orthoformic ester is favoured by Kenner and co-workers[16] but a range of intramolecular cyclizations is also available. The obvious use of a formyl group at C-1 has received limited attention,[18] largely because of the preparative difficulties, and although a carboxy-group can provide the requisite carbon for the linkage,[19] a methyl group at C-1 has been the most popular choice. In these cases, when hydrogen (bilene-*b*) or bromine

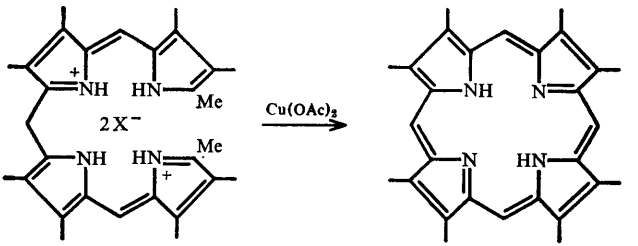
[18] *E.g.* M. E. Flaugh and H. Rapoport, *J. Amer. Chem. Soc.*, 1968, **90**, 6877.
[19] A. R. Battersby, G. L. Hodgson, M. Ihara, E. McDonald, and J. Saunders, *J.C.S. Perkin I*, 1973, 2973.

(biladiene-*ac*) is the substituent at C-19, cyclization occurs on heating[17,20] by the mechanism shown in Scheme 4.



**Scheme 4**

When a methyl, formyl, or carboxy-group is the C-19 substituent in the 1-methyl-biladiene-*ac* or -bilene-*b*, cyclization can be achieved by heating in the presence of copper(II) salts,[12] when one carbon substituent is expelled (Scheme 5). *NN*-Dimethylformamide,[21] pyridine,[22] or even methanol–acetic acid[23]



**Scheme 5**

represent improvements on the methanol advocated originally. Scores of porphyrins have been prepared by these methods, including nearly all of the naturally occurring compounds, these achievements representing a mammoth effort on the part of several research schools.[16,24]

In an important extension of porphyrin synthesis from bilenes-*b* and biladienes-*ac*, it has been shown that in the presence of nickel or cobalt salts (the presence of metal ions was not a prerequisite for the 1,19-unsubstituted bilenes-*b* or biladienes-*ac*, which required only brief irradiation), cyclizations occurred with

[20] I. D. Dicker, R. Grigg, A. W. Johnson, H. Pinnock, K. Richardson, and P. van den Brock, *J. Chem. Soc.* (*C*), 1971, 536.

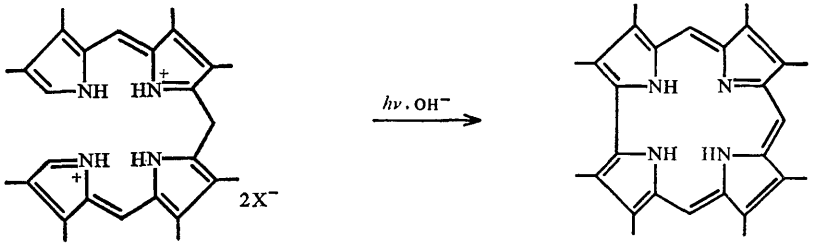
[21] R. Grigg, A. W. Johnson, R. Kenyon, V. B. Math, and K. Richardson, *J. Chem. Soc.* (*C*), 1969, 176.

[22] P. S. Clezy and A. J. Liepa, *Austral. J. Chem.*, 1971, **24**, 1027.

[23] A. F. Mironov, V. D. Rumyantseva, B. V. Rumyantseva, and R. P. Evstigneeva, *Zhur. org. Khim.*, 1971, **7**, 165 (*Chem. Abs.*, 1971, **74**, 112 026).

[24] R. L. N. Harris, A. W. Johnson, and I. T. Kay, *Quart. Rev.*, 1966, **20**, 211; A. W. Johnson, *Chem. in Britain*, 1967, **3**, 253.

the formation of a direct linkage between rings A and D as is found in vitamin $B_{12}$. Although terminal halogen substituents (*i.e.* at C-1 or C-19) were eliminated, ester and alkyl substituents were retained as angular substituents. The new ring systems so obtained were corrole (11)[25] and the 1-mono- (21)[26] and 1,19-di-substituted (22)[27] tetradehydrocorrins as their metal derivatives.

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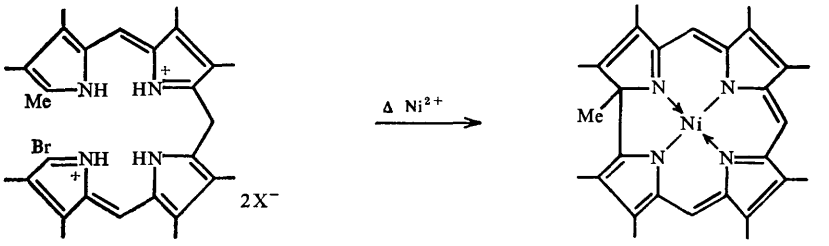


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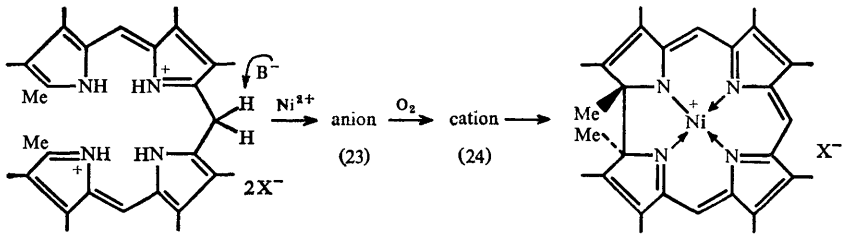
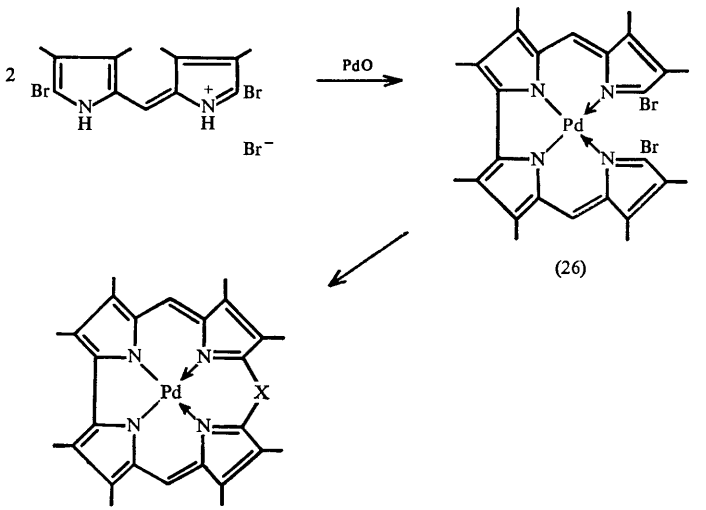



(22)

Consideration of the mechanism of these cyclizations suggests that they are orbital-symmetry-allowed conrotatory electrocyclic processes, on evidence

[25] A. W. Johnson and I. T. Kay, *J. Chem. Soc.*, 1965, 1620.
[26] D. A. Clarke, R. Grigg, R. L. N. Harris, I. T. Kay, and K. W. Shelton, *J. Chem. Soc.* (*C*), 1967, 1648.
[27] D. Dolphin, R. L. N. Harris, J. L. Huppatz, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.* (*C*), 1966, 30.

largely taken from considerations of the mode of formation of (22).[28] Resolution of the product as its (+)-D-camphorsulphonate provides conclusive evidence for the *trans* arrangement of the angular 1- and 19-methyl groups. The initial step was the formation of the metal–biladiene-*ac* complex, and also the production of a conjugated chromophore by deprotonation at C-10 was implied by the demonstration of the lability of the C-10 protons.[29] Action of the base on the nickel–biladiene-*ac* intermediate produces the anion (23) which is a $22\pi$-electron system (or an $18\pi$-electron system if the two cross-conjugated bonds are discounted) and which should cyclize in a disrotatory manner to give the *cis*-isomer. However, an oxidation step is also involved, and if the oxidation precedes cyclization to yield the cation (24), cyclization should proceed in a conrotatory manner to yield the *trans*-product (22) as observed. This view of the mechanism received support from the oxidation (hydride abstraction) of the nickel–biladiene-*ac* complex in degassed dimethyl sulphoxide with trityl perchlorate at room temperature, when the corresponding *trans*-1,19-dimethyltetradehydrocorrin perchlorate was obtained in good yield.[28] The demonstration of the operation of orbital-symmetry requirements in such a large $\pi$-electron array owes much to the template effect of the central metal atom which ensures close proximity of the interacting centres and prevents severe distortions of the $\pi$-electron system. The formation of the neutral 1-methyltetradehydrocorrin–nickel(II) complex involves an elimination of hydrogen bromide rather than an oxidation.

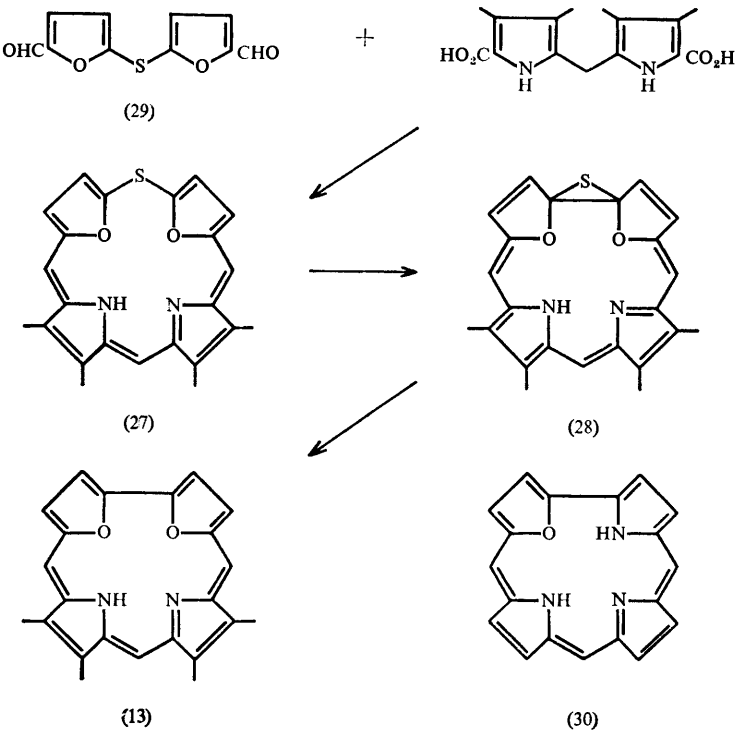



(25) X = O, S, NH, or NMe
but *not* $CH_2$

[28] R. Grigg, A. P. Johnson, A. W. Johnson, and M. J. Smith, *J. Chem. Soc.* (*C*), 1971, 2457.
[29] D. Dolphin, A. W. Johnson, J. Leng, and P. van den Broek, *J. Chem. Soc.* (*C*), 1966, 880.

Structural variations on the corrole nucleus include palladium complexes of the ring systems (25; X = O, S, NMe, NH, or tautomer) prepared by cyclization of the metal derivatives of bis-(5-bromo-2,2′-dipyrromethenyls) (26) in the presence of hydrochloric acid, sodium sulphide, methylamine, or ammonia respectively.[30] The macrocycle (25; X = O) was the first, historically, to be prepared containing the direct linkage between two pyrrole rings.[31]

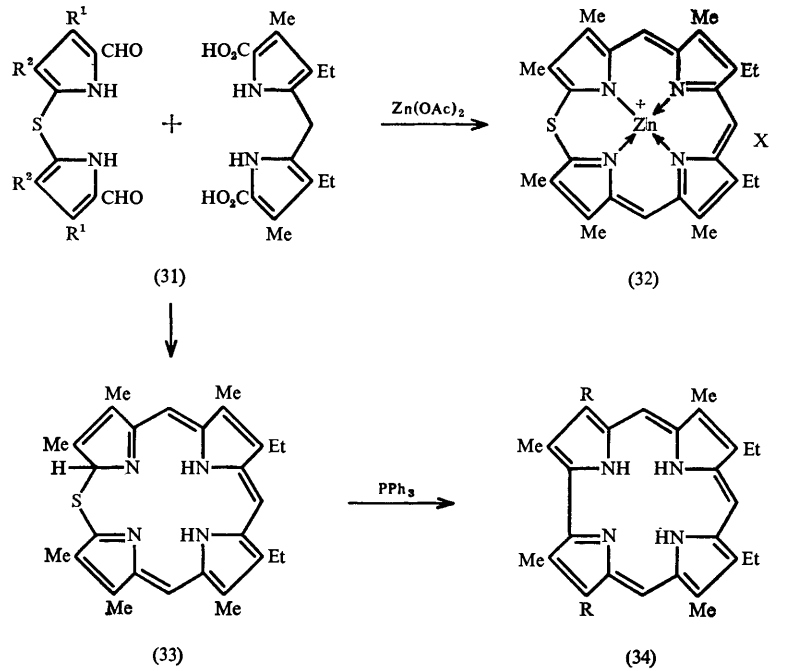
In a search for a more efficient synthesis of dioxacorroles (see above) recourse was made to electrocyclic cyclizations but with the incorporation into the molecule of an extrudable atom or fragment, of which sulphur seemed a possibility, *i.e.* a combined disrotatory $(4n + 2)\pi$-electron electrocyclic cyclization followed by chelotropic loss of sulphur was sought. The compounds required were thus the *meso*-thia-macrocycles (27) in which a disrotatory cyclization of the $18\pi$-electron system would yield the thiiran intermediate (28), which would then lose sulphur to form the dioxacorrole derivative (13).[8]




[30] A. W. Johnson, I. T. Kay, and R. Rodrigo, *J. Chem. Soc.*, 1963, 2336.
[31] A. W. Johnson and R. Price, *J. Chem. Soc.*, 1960, 1649; A. W. Johnson and I. T. Kay, *Proc. Chem. Soc.*, 1961, 168.

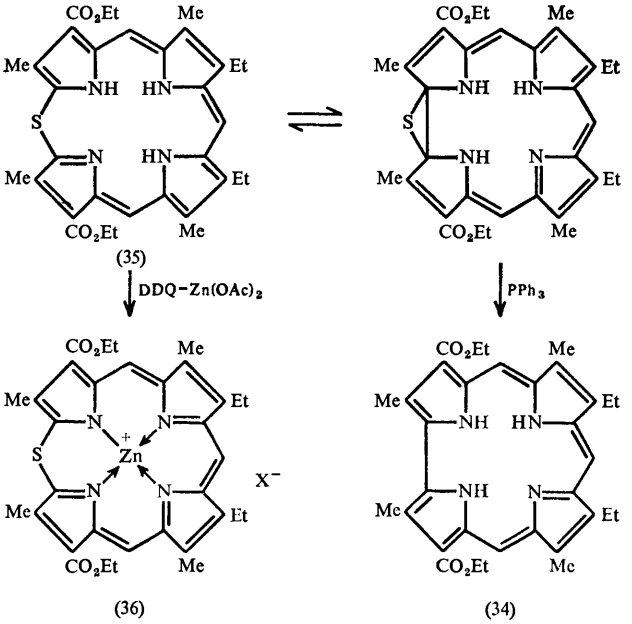
The sequence of reactions was investigated by the condensation of bis-(5-formylfuryl) sulphide (29) and the dipyrromethane-5,5′-dicarboxylic acid in presence of hydrogen bromide, when a non-sulphur-containing macrocycle was obtained and shown to be the required dioxacorrole (13) in some 27—30% yield, along with a small quantity of the mono-oxacorrole (30). None of the sulphur-containing intermediates was detected. The method has also been applied to the all-pyrrole series, where the bis-(5-formylpyrryl) sulphide (31; $R^1 = R^2 = Me$) was condensed with a dipyrromethane-5,5′-dicarboxylic acid at $-10$ °C in the presence of hydrogen chloride. A purple–red product (10—20%) was obtained together with an unstable green compound, isolated as a stable charged zinc complex and formulated as a zinc *meso*-thiaporphyrin (32). The n.m.r. spectrum of (32) suggested that the complex was aromatic with $\pi$-electron delocalization through the sulphur atom. The structure of the purple–red compounds has not been defined completely but (33) is consistent with the observed n.m.r. spectrum.

Treatment of the purple–red compound (33) with zinc acetate slowly gave the zinc thiaporphyrin (32), and when (33) was heated with an excess of triphenylphosphine in boiling *o*-dichlorobenzene it gave the corresponding corrole (34; R = Me; 15%). In another series, the bis-(5-formylpyrryl) sulphide (31; $R^1 = CO_2Et$, $R^2 = Me$) was condensed with a dipyrromethane-5,5′-dicarboxylic acid as before; a blue, air-stable crystalline product (52%) was obtained




(31) (32) (33) (34)

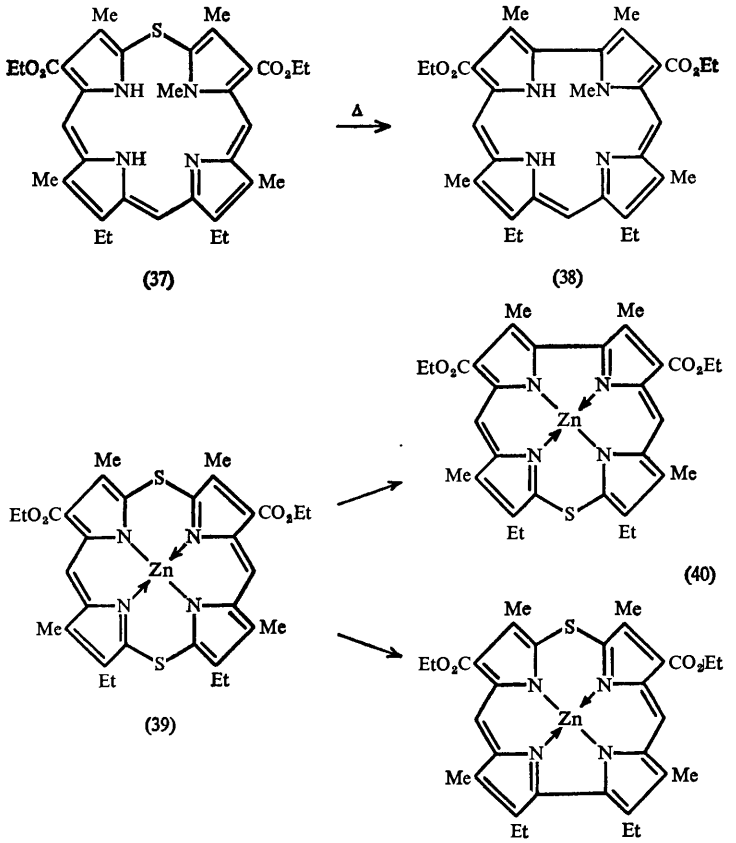
and formulated as the non-aromatic *meso*-thiaphlorin (35) on the basis of spectral and chemical evidence. Oxidation of (35) with 2,3-dichloro-5,6-dicyanobenzoquinone gave the unstable *meso*-thiaporphyrin, which was, however, readily isolated as the zinc complex (36). In this series also sulphur was extruded from the *meso*-thiaphlorin in boiling *o*-dichlorobenzene to give the corrole (34;




R = $CO_2Et$; 35—40%) but when the same reaction was carried out in the presence of triphenylphosphine the yield was increased to 60%. No noticeable effect on the yield was observed when the extrusion was effected in the presence of radical-trapping reagents, thus eliminating the possibility of a radical cleavage mechanism.

Extensions of the sulphur extrusion reaction for the synthesis of corroles included an examination of the *N*-methylthiaphlorin (37), which in a facile reaction gave the *N*-methylcorrole (38) in 85% yield when heated in trichlorobenzene. Also, when (37) was heated in acetic acid in the presence of palladium acetate, the palladium complex of (38) (27%) was obtained after only 2 min. Desulphurization of the dithia-macrocycle (39) in the presence of triphenylphosphine gave a 1:1 mixture (42%) of the two possible *meso*-thiacorroles (40) [*cf.* (25)] in a slow reaction, although with the corresponding zinc compounds it was faster and more efficient (66%).[8] Removal of the second sulphur atom did not occur.

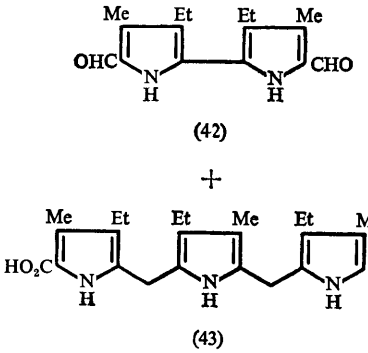
Thus far all the aromatic rings described have been of the $18\pi$-electron type



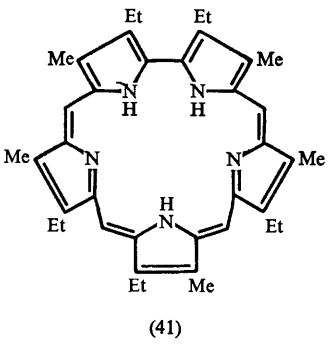

and it has been of special interest that representatives of the $22\pi$-electron type, the sapphyrins (41),[32] may be obtained by application of a [3 + 2]-type condensation.[33] Thus condensation of a 5,5′-diformylbipyrrole (42) with a tripyrranedicarboxylic acid (43) gave the sapphyrin (46%) which, on n.m.r. evidence, was aromatic [$\tau$(*meso*-H) −0.3 to −0.5; $\tau$(*N*-H) 13.9] and which showed a Soret band at 450 nm ($\epsilon$ 530 200). Related syntheses were used for preparations of a dioxasapphyrin (44), where a sulphur-extrusion-type synthesis was also employed successfully, a thiasapphyrin (45), a norsapphyrin (46), and a dioxanorsapphyrin (47). The dioxasapphyrin had been recognized earlier as a by-product in low yield from the [2 + 2]-type synthesis of dioxacorrole.

Turning now to reactions, the porphyrins have been studied in detail, especially with regard to electrophilic substitutions, where certain general trends are discernible. Substitution can occur at nitrogen, at *meso*-positions, or at a vacant

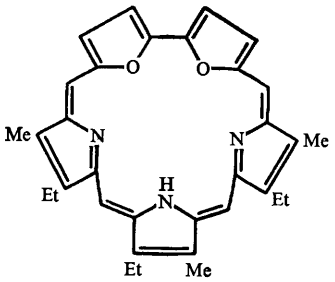
[32] Reported by Professor R. B. Woodward, Aromaticity Conference, Sheffield, 1966.
[33] M. J. Broadhurst, R. Grigg, and A. W. Johnson, *J.C.S. Perkin I*, 1972, 2111.



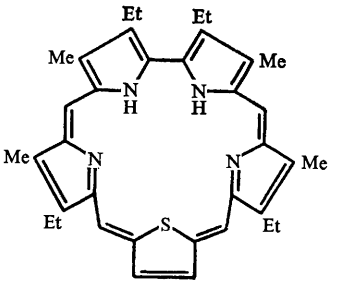
(42) + (43)



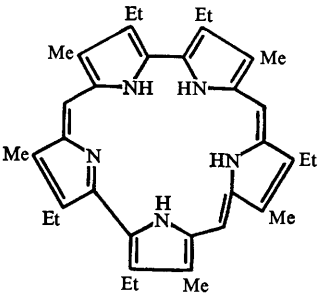
(41)



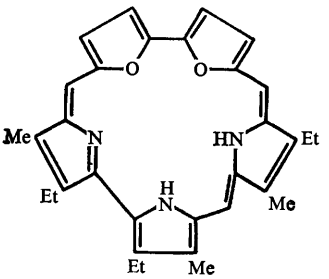
(44)



(45)



(46)

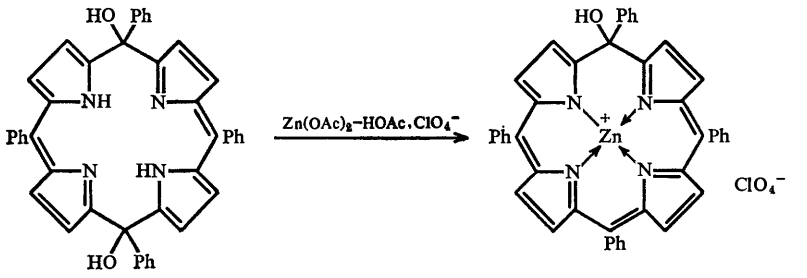


(47)

β-position, and, as expected, the reactions are slow in media where the macrocycle is protonated. Unexpected reactions are still encountered; thus bromination of *meso*-tetraphenylporphyrin (TPP) causes β-substitution[34] whereas nitration with nitric–sulphuric acids yields the isomers of the *ipso*-substitution product

[34] H. J. Callot, *Tetrahedron Letters*, 1973, 4987.

(48), the initially formed nitro-derivative being hydrolysed during isolation.[35] The hydroxy-groups can be removed successively to re-form the porphyrin *via* the hydroxyisoporphyrin (49).



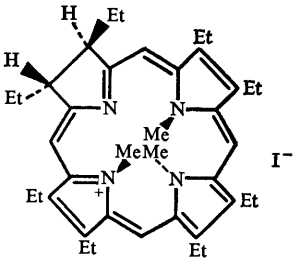

(48) (49)

The introduction of metals into the macrocycles can cause striking variations in reactivity, owing to reduction of the basicity of the nitrogens and hence reduction in the proportion of N-protonated species. Thus when copper(II) or iron(III) OEP was treated with deuteriotrifluoroacetic acid at room temperature for 20 min complete deuteriation of the *meso*-positions was observed, whereas $t_{\frac{1}{2}}$ for free OEP at 90 °C is 16 500 min.[36] The complexing metals may differ markedly in their effects. Thus, whereas the manganese(III) and iron(III) derivatives of aetioporphyrin I failed to react under Vilsmeier conditions, the copper(II) and nickel(II) complexes were converted smoothly into *meso*-monoformyl products after 30 min at 50 °C, and the cobalt(II) complex was very much more reactive and gave *meso*-diformyl derivatives after only 3 min at 50 °C.[37]

A striking feature of the porphyrin ring is its ability to retain aromaticity even when severely distorted by structural variations such as the removal of a carbon atom as in corrole (11) or the introduction of heteroatoms as described above. The aromatic properties can also be maintained after the introduction of bulky groups into the centre of the macrocycle, as is found with many heavy-metal complexes and with *N*-alkylation, where mono-, di-, and tri-*N*-methyl derivatives of porphyrins and chlorins have been described.[37,38] *N*-Methyl groups on adjacent rings occupy the *trans* configuration and the *N*-methyl groups, being highly shielded, are characterized by high-field signals in the n.m.r. spectrum. The *N*-trimethylchlorin salt (50) is noteworthy as it is the three non-reduced rings which are *N*-methylated; presumably *N*-methylation of the reduced ring seriously impairs the cyclic delocalization of electrons with consequent loss of aromaticity.[37] Methylation of any of the remaining three nitro-

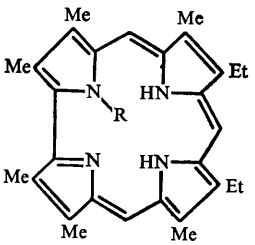
[35] M. Winter, unpublished observation.
[36] R. Bonnett, I. A. D. Gale, and G. F. Stephenson, *J. Chem. Soc.* (*C*), 1967, 1168.
[37] R. Grigg, G. Shelton, A. Sweeney, and A. W. Johnson, *J.C.S. Perkin I*, 1972, 1789.
[38] A. H. Jackson and G. R. Dearden, *Ann. New York Acad. Sci.*, 1973, **206**, 151.

gens is more favoured as an alternative pathway for conjugation through the β-positions is still available.

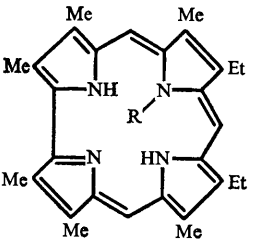


(50)

In corrole (11) the stable aromatic anion is readily formed and bears a structural relation to porphyrin equivalent to that of the cyclopentadienyl anion to benzene. Reaction of the anion with alkyl halides is facile and yields a mixture of N-21 (51) and N-22 (52) substitution products. When the *N*-22-allyl derivative



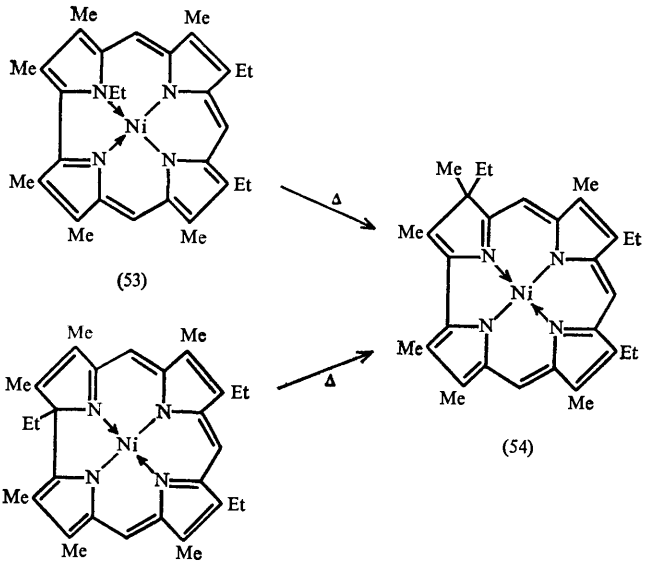
(51)



(52)

(52; R = $CH_2CH{=}CH_2$) was heated it reverted to the original corrole (29%) together with the N-21 isomer (24%), but further examination of the reaction mechanism showed that it was intermolecular and probably free-radical in nature.[39] However, intramolecular rearrangements of N-substituted corroles have been discovered, for example, when the nickel complex of the *N*-21-ethylcorrole (53) was heated in boiling chlorobenzene it rearranged to an isomeric product (54) with the *gem*-dialkyl group at C-3, the structure of which was proved by use of ethyl marker groups and n.m.r. studies.[40] Use of the palladium corrole anion[41] or bulky alkyl halides[40] caused direct substitution at C-3. This rearrangement is visualized as a double 1,5-sigmatropic shift of the

[39] M. J. Broadhurst, R. Grigg, G. Shelton, and A. W. Johnson, *J.C.S. Perkin I*, 1972, 143.
[40] R. Grigg, A. W. Johnson, and G. Shelton, *Annalen*, 1971, **746**, 32.
[41] R. Grigg, A. W. Johnson, and G. Shelton, *J. Chem. Soc.* (*C*), 1971, 2287.

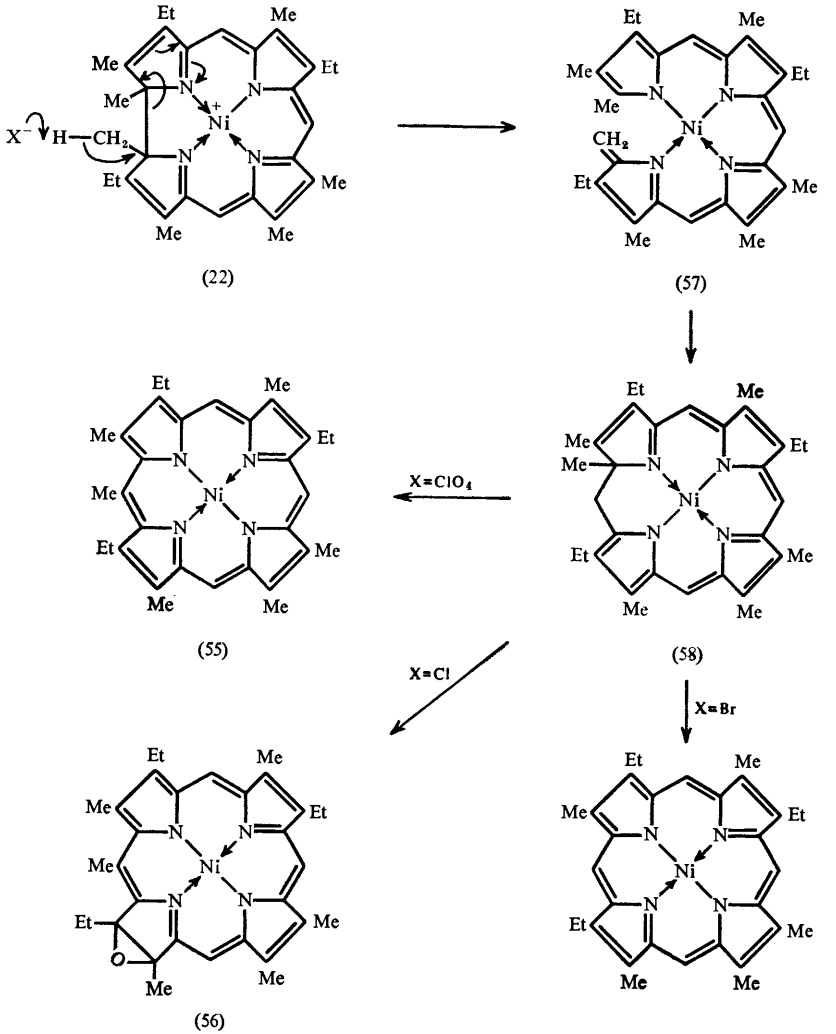



alkyl group across the face of the molecule, and the absence of 'crossed' products in the thermolysis of mixture supported our view of the intramolecular nature of the reaction. Related to this reaction was the rearrangement of the nickel 1-methyltetradehydrocorrins (21) which also produced (54).[42]

In the light of these rearrangements it seemed possible that only one of the angular methyl groups of the nickel or cobalt 1,19-dimethyltetradehydrocorrin salts (22) might be induced to migrate in a similar manner and thereby produce an intermediate of obvious value in a synthetic approach to the vitamin $B_{12}$ chromophore. However, the products from these reactions are porphyrins, and of the two angular groups one, usually methyl, is the source of the porphyrin *meso*-carbon and the other alkyl group is either retained as a *meso*-substituent [*e.g.* (55) (anion = perchlorate)[43] or the corresponding oxide (56) (anion = chloride)[44]] or the second alkyl is expelled (other anions).[43] The course of this interesting rearrangement has been elucidated [(22) → (57) → (58) → (55)] and it may well relate to certain aspects of the rearrangement of uroporphyrinogen III to the 1-methylcorrin chromophore of vitamin $B_{12}$.

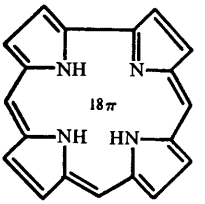
With the synthesis of corrole, an obvious extension of the porphyrin structural variations has been the homoporphyrin (59) and its aromatic dehydro-counterpart (60) to complete the trio along with corrole and porphyrin. One approach to such structures was the ring expansion with an aliphatic diazo-compound as

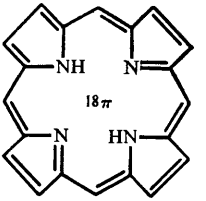
[42] R. Grigg, A. W. Johnson, K. Richardson, and M. J. Smith, *J. Chem. Soc.* (*C*), 1970, 1289.
[43] R. Grigg, A. W. Johnson, K. Richardson, and K. W. Shelton, *J. Chem. Soc.* (*C*), 1969, 655.
[44] A. Hamilton and A. W. Johnson, *J. Chem. Soc.* (*C*), 1971, 3879.

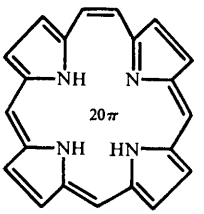



had been used successfully in the tropylium series.[45] An analogous ring expansion of octaethylporphyrin to (61) using azidoformic ester had been reported by Grigg,[46] but no reaction of the porphyrin was observed with diazoacetic ester. However, with the porphyrin–copper complex we observed addition of the carbene to the cross-conjugated $\beta$-double bonds to form isomers of the chlorin

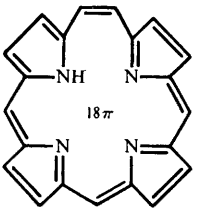
[45] A. W. Johnson, *J. Chem. Soc.*, 1954, 1331.
[46] R. Grigg, *J. Chem. Soc.* (*C*), 1971, 3664.


NH
N
18π
NH
HN

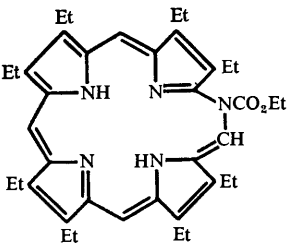

NH
N
18π
N
HN


NH
N
20π
NH
HN

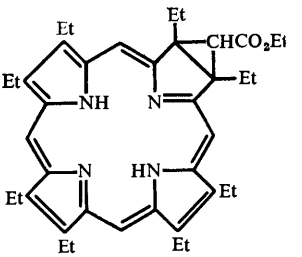
(59)


NH
N
18π
N
N

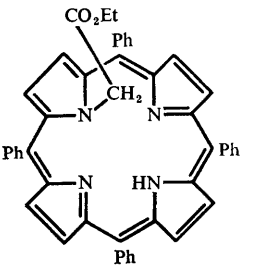
(60)


Et
Et
Et
Et
NH
N
NCO2Et
CH
N
HN
Et
Et
Et
Et
Et

(61)


Et
Et
CHCO2Et
Et
Et
NH
N
N
HN
Et
Et
Et
Et

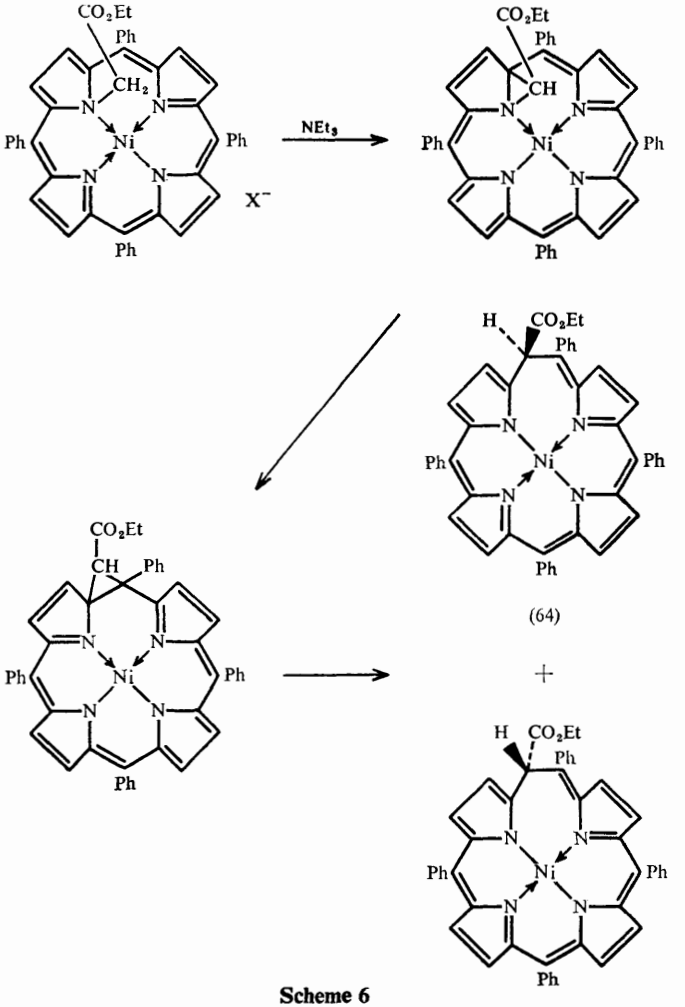
(62)


CO2Et
Ph
CH2
N
N
Ph
Ph
N
HN
Ph

(63)

(62) together with a little *meso*-substitution.[47] On the other hand zinc tetraphenylporphyrin was shown to cause reaction at nitrogen to give (63) together with $\beta$-addition.[48]

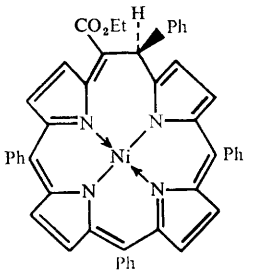
Zinc was readily removed from (63) by acid treatment, and an attempt to reintroduce nickel using nickel acetylacetonate in the presence of base caused a spectacular series of rearrangements, finally yielding the nickel derivatives of the homoporphyrin isomers (64) and (65) by the sequence shown in Scheme 6.[49]



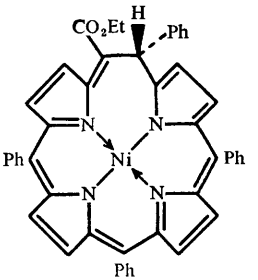

**Scheme 6**

[47] H. J. Callot, A. W. Johnson, and A. Sweeney, *J.C.S. Perkin I*, 1973, 1424.
[48] H. J. Callot, *Bull. Soc. chim. France*, 1972, 4387; H. J. Callot and T. Tschamber, *ibid.*, 1973, 3192.
[49] H. J. Callot and T. Tschamber, *Tetrahedron Letters*, 1974, 3155.

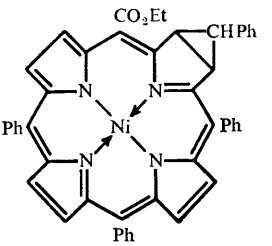
Details of an *X*-ray examination of (64) are not yet available (*cf.* ref. 49). At *ca.* 110 °C (64) equilibrated with its isomer (65), and at higher temperatures also with the isomers (66) and (67), formed by migration of the methine hydrogen. Finally, above 200 °C rearrangement to isomers of the chlorin (68) was observed.[50]




(66)




(67)

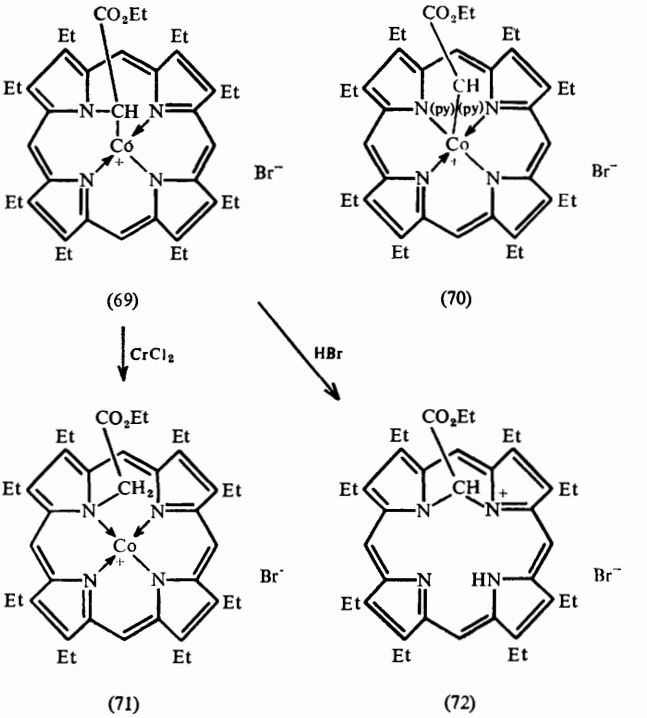



(68)

In a superb example of the effect of the complexed metal on the course of a given porphyrin reaction, *i.e.* reaction with aliphatic diazo-compounds, we have also examined the reaction of cobalt(II) and cobalt(III) octaethylporphyrins with diazoacetic ester, where a very rapid reaction occurred and yielded a rather unstable 1:1 adduct, a cobalt(III) salt which has been deduced to have structure (69), *i.e.* the carbene fragment inserts into one of the metal–nitrogen bonds.[51] In this salt the methine proton signal was not apparent in the n.m.r. spectrum until the deuteriochloroform solution was cooled to −35 °C, which may well indicate a degree of mobility of the carbene fragment within the molecule, *e.g.* between N-21 and N-22, which is retarded at low temperature. Furthermore, in deuteriochloroform the *meso*-proton signals were well separated as expected but in deuteriopyridine they were observed as one sharp singlet and the methine proton

[50] H. J. Callot and T. Tschamber, *Tetrahedron Letters*, 1974, 3159.
[51] P. Batten, A. Hamilton, A. W. Johnson, G. Shelton, and D. Ward, *J.C.S. Chem. Comm.*, 1974, 550.

signal was also clearly observable at room temperature, indicative of the presence of a symmetrical species, such as the metal carbene complex (70). Chromium(II) chloride reduction of (69) gave the cobalt(II) complex of *N*-ethoxycarbonylmethyl octaethylporphyrin (71) by fission of the metal–carbon bond, while ethanolic hydrogen chloride caused rearrangement, with loss of the metal, to the *cis*-N-21, 22-bridged derivative (72; R = $CO_2Et$). A related structure (72; R = H) has

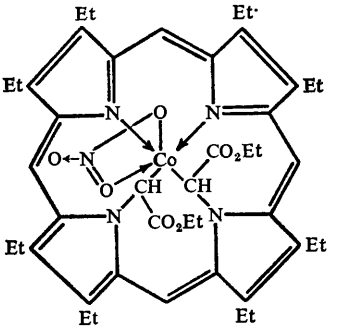



since been prepared by the action of methylene iodide on the porphyrin. Intermediate between structures (69) and (72) is a cobalt(II) compound obtained from (69) by the action of bromine, hydrobromic acid in presence of oxygen, or, most efficiently, by the action of diazoacetic ester on the cation radical derived from cobalt(II) octaethylporphyrin and bromine.[52] The new product could be converted into (72; R = $CO_2Et$) with more acid or into (69) with methanol.

In the presence of excess diazoacetic ester, the cobalt porphyrin has given a series of neutral cobalt(III) derivatives which are 2:1 adducts. The structure of

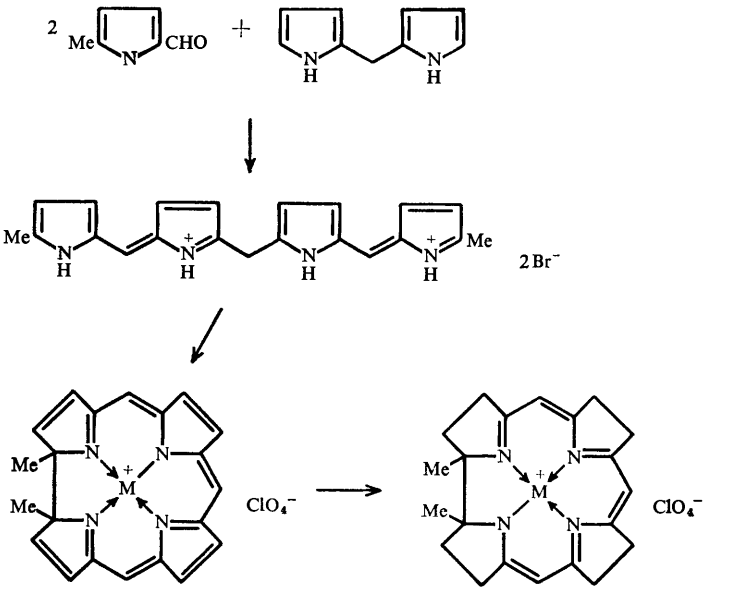
[52] D. Dolphin and R. H. Felton, *Accounts Chem. Res.*, 1974, **7**, 26; D. Dolphin, Z. Muljiani, K. Rousseau, and D. C. Borg, *Ann. New York Acad. Sci.*, 1973, **206**, 177.

one of these (73) has been established by *X*-ray crystallography,[9] the origin of the nitrate group being residual nitrite used in the preparation of the reagent.



(73)

Substitution reactions of nickel and cobalt 1,19-dimethyltetradehydrocorrin salts have been discussed elsewhere.[44,53] Among the addition reactions of these salts, the facile hydrogenation of the $\beta$-unsubstituted derivatives to yield the corresponding corrin salts (74) represents a short and efficient synthesis of this ring system.[54]



(74) M = $Ni^{I}$, $Co^{II}$, or $Co^{III}$

[53] C. M. Elson, A. Hamilton, and A. W. Johnson, *J.C.S. Perkin I*, 1973, 775.
[54] A. W. Johnson and W. R. Overend, *J.C.S. Perkin I*, 1972, 2681.

There remains much to be accomplished. The effect of co-ordinated metals on the course of many of the reactions of macrocycles is still at a preliminary stage of investigation and the underlying mechanisms are still largely obscure. This is particularly so in certain biological systems, for example the rearrangement reactions catalysed by vitamin $B_{12}$, where the cobalt undoubtedly plays a major role. The biosynthesis of vitamin $B_{12}$ is also a topic of much speculation and intensive research effort, and the involvement of porphyrinogens and the nature of subsequent rearrangements are still to be established. With the wealth of knowledge of pyrrole condensation reactions it might yet be possible to devise a scheme for $B_{12}$ synthesis which parallels the natural route, *i.e.* based on porphobilinogen (6) as a starting point. It is my hope that the reactions I have described will make some contribution to the solution of these much larger projects, and to all my colleagues at the Universities of Nottingham and Sussex who have worked so efficiently and conscientiously to achieve the results I have summarized, I accord my sincere gratitude.