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Synthesis of Corrins and Related Macrocycles Based on Pyrrolic Intermediates

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Synthesis of corrins and related macrocycles based on pyrrolic intermediates

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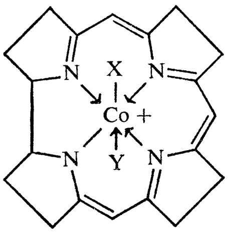
Intermediate in structure between porphyrins and corrins are the corroles and 1-methyltetradehydrocorrins. These ring systems, like the porphyrins, can be obtained by cyclization of linear tetrapyrrolic compounds, reactions which have been shown to proceed by orbital symmetry-allowed electrocyclic processes, and examples will be quoted. Thermolysis of nickel 1-methyltetradehydrocorrins causes a migration of the methyl group whereas similar treatment of nickel 1,19-dimethyltetradehydrocorrin salts yields porphyrin derivatives; the mechanisms of these transformations have been elucidated. Stepwise hydrogenation of metal tetradehydrocorrin salts (10 double bonds) yields a series of macrocycles containing 9, 8, 7, 6 and 5 double bonds and conditions necessary to obtain corrins have been established.

The elucidation of the structure of vitamin B_{12} by X-ray crystallography (Hodgkin *et al.* 1957; Hodgkin 1958) is one of the main achievements in the history of this remarkable substance. The recognition of the nature of the cobalt(III) corrin (**1**) chromophore inspired tremendous efforts in both synthesis (Woodward 1973; Eschenmoser 1970, 1971) and biosynthesis (Scott *et al.* 1974*a*, *b*), and in an attempt to link these approaches we have examined the possibility of producing corrins from pyrrolic intermediates. We found that linear tetrapyrroles of the bilene-b (**2**) or biladiene-ac (**3**) types bearing two, one or no terminal (positions 1 and 19 in **2**) methyl groups could be cyclized either to porphyrins or to tetradehydrocorrins containing two (**4**), one (**5**) or no (**6**, the corrole ring system) angular (positions 1 and 19) methyl groups (see scheme 1 for experimental conditions). Although these cyclizations involve large π-electron systems, they



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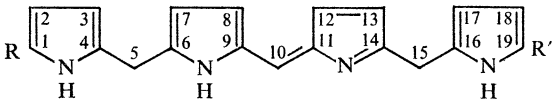

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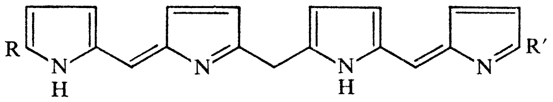

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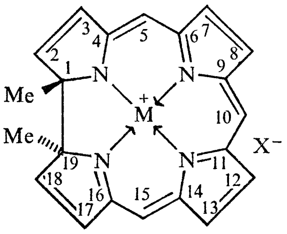
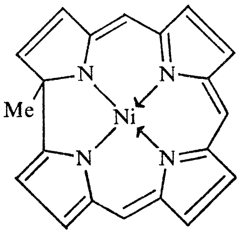
are controlled by orbital symmetry. The metal plays a key role when it is present by acting as a template in preventing undue distortions from the plane and ensuring that reactive centres are held in proximity. It has been found that a nickel 1,19-dimethyltetradehydrocorrin (**4**) can be resolved as its D-camphorsulphonate and thus the angular methyl substituents are in the trans configuration (Grigg, Johnson, Johnson & Smith 1971). In the formation of **4** from the biladiene-ac salt in presence of base, air and nickel ions, the initial stage is the formation of the nickel biladiene-ac complex which then forms the corresponding anion by loss of a proton from



4 M = Ni (II), Co(II)
X = Br, Cl, ClO_4



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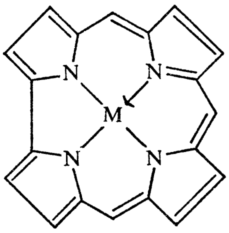
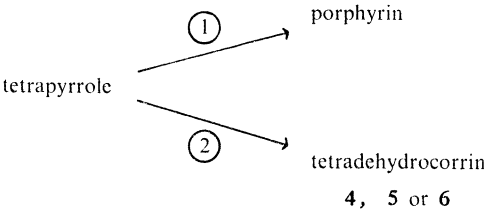


6 M = H_3, Co(II), Fe(II)
Ni (II), Cu(II), Pd(II)

SCHEME 1. CYCLIZATIONS OF TETRADEHYDROCORRINS



A: R = R′ = Me
B: R = H; R′ = Me
C: R = R′ = H

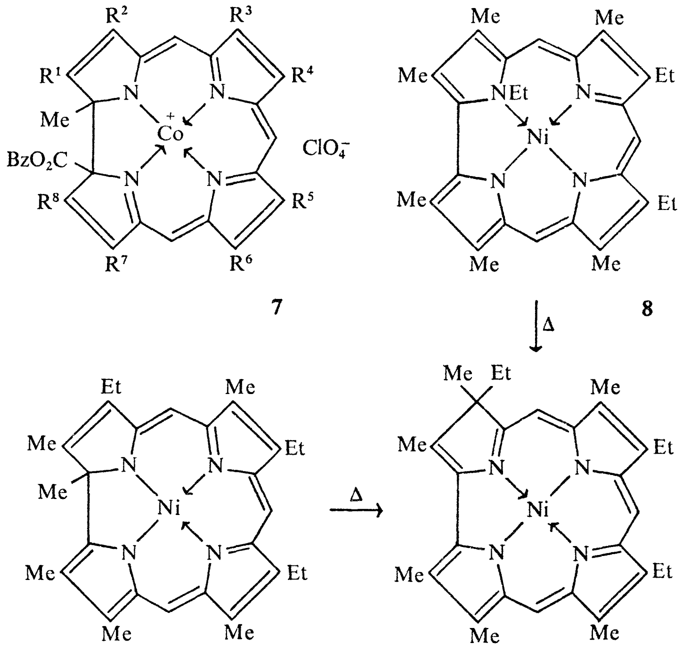
Series 1

Series A: Cu(II) in MeOH (Johnson & Kay 1961) or dimethylformamide (Clezy & Liepa 1971) (extrusion of C)
Series B: Heat in *o*-dichlorobenzene (Harris, Johnson & Kay 1966)
Series C: H.CHO (addition of C) (Johnson & Kay 1965)

Series 2

Series A: Ni(II) or Co(II); air, base (Dolphin, Johnson, Leng & van den Broek 1966)
Series B: Ni(II), base (Clarke *et al.* 1967)
Series C: Light, base (with or without metal) (Clezy & Liepa 1971)

C10 (Dolphin *et al.* 1966). The anion, as a $(4n+2)\pi$-electron system should cyclize in a disrotatory manner to yield a *cis*-orientation of the angular methyl groups which is contrary to the experimental observation. However, as the cyclization was carried out in presence of air, it is probable that the anion is first oxidized to the corresponding cation, a $4n$ π-electron system, which should be subject to conrotatory cyclization and yield a product with a trans arrangement of the angular methyl groups as observed. In support of this view of the reaction pathway, oxidation of the nickel biladiene-ac with triphenylmethyl perchlorate (hydride abstraction to give the cation) in absence of air gave a moderate yield of the nickel 1,19-dimethyltetradehydrocorrin salt.



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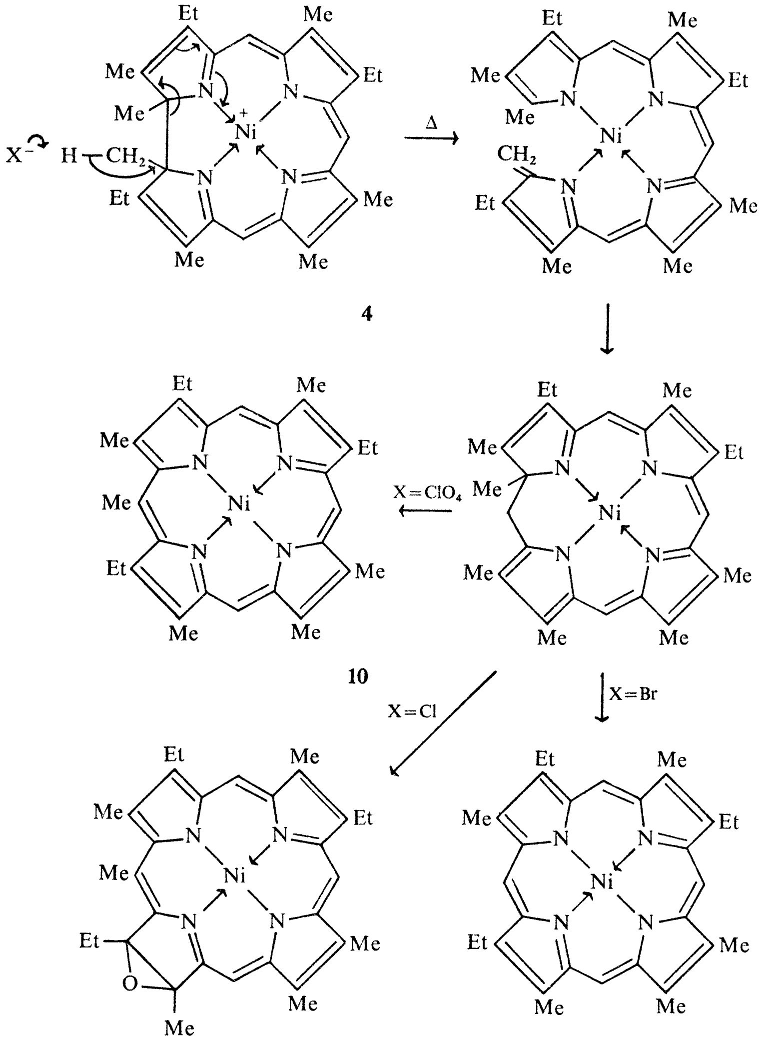
The formation of 1-methylcorrins from the three types of tetradehydrocorrin (**4**, **5** and **6**) would involve not only additions to the ββ-double bonds, but also removal of one angular substituent from the 1,19-disubstituted tetradehydrocorrin salts (**4**) or the addition of one methyl group at C1 of a corrole (**6**). The latter reaction has not been achieved, but angular ester substituents, especially benzyl esters, can be readily removed so that cobalt(II) 1-benzyloxycarbonyl-19-methyltetradehydrocorrin salts (**7**) can be visualized as stabilized derivatives of cobalt(II) 1-methyltetradehydrocorrins (Conlon *et al.* 1974).

The introduction of β-gem dialkyl substituents into the corrin nucleus might be achieved by rearrangement reactions or by additions to the ββ-double bonds of tetradehydrocorrins. Two rearrangement reactions which yield the same product, a nickel 3,3-dialkyltetradehydrocorrin (**9**), are the thermal rearrangements of nickel *N*-alkylcorroles (**8**), and nickel 1-alkyltetradehydrocorrins (**5**). The structure of the product was established by use of ethyl marker groups and interpretation of n.m.r. spectra. However, at the present time these reactions have been reported only for single pyrrolic rings.

In contrast to the thermal rearrangement of the nickel 1-alkyltetradehydrocorrins, the nickel 1,19-dialkyltetradehydrocorrin salts (**6**) give porphyrins when they are heated (Grigg *et al.* 1969). Of the two angular aklyl groups, one, usually methyl, is the source of the porphyrin fourth meso carbon and, depending on the nature of the anion, the other alkyl tends to be either retained as a meso substituent (e.g. **10**) (perchlorate anion) or expelled (bromide anion). In the case of the chlorides, oxidation accompanies the rearrangement and it is mainly the meso-substituted chlorin oxide (**11**) which is obtained (Hamilton & Johnson 1971) although, as with the other anions, mixtures of porphyrin derivatives were obtained. The current view of the mechanism of this rearrangement is summarized in scheme 2.

Scheme 2. Thermolytic conversion of tetradehydrocorrin salts to porphyrins



Another rearrangement reaction of the metal tetradehydrocorrin salts, which leads to gem-β-dialkyl substituted compounds, is the pinacol rearrangement of the hydroxylation products. As with hydrogenation (see below), hydroxylation of the salts involves rings B and C in the

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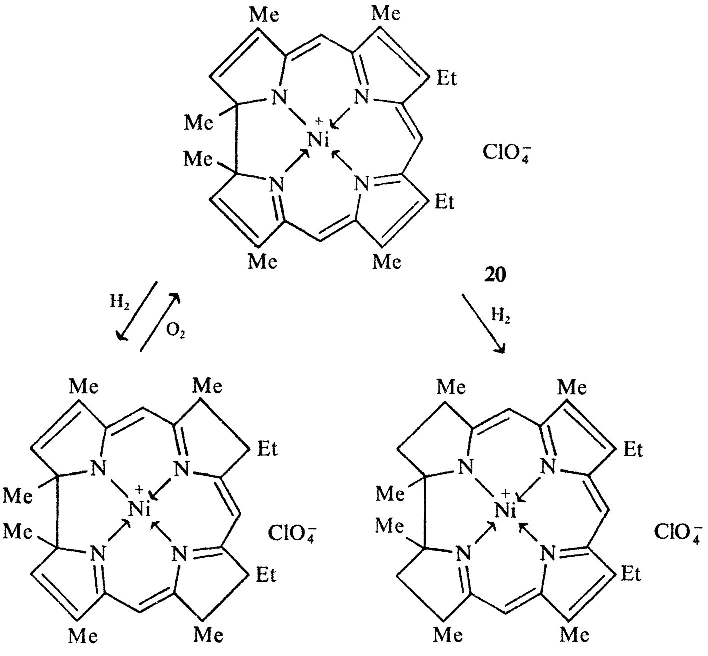
first place to yield a diol (e.g. **12**) and tetraol (**13**) but further reaction can give both hexaols and octaols (Inhoffen *et al.* 1970). Acid rearrangement of the 1,2-diol gave a mixture of two monoketones (part formulae **14** and **15**) and the tetraol gave two diketones (**16** and **17**) which were separated. Hydrogenolysis of **16** and **17** gave the didehydrocorrins (**18** and **19**).



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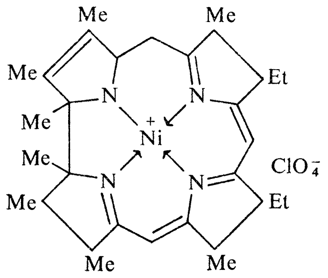
The course of hydrogenation of the nickel and cobalt tetradehydrocorrin salts also involves the ββ-double bonds but the course of the reaction is profoundly affected by the number and position of the β-alkyl substituents. In the absence of alkyl substituents at C2 and C18 (i.e. nickel 1, 3, 7, 8, 12, 13, 17, 19-octaalkyl tetradehydrocorrin salts, e.g. **20**), the hydrogenation products vary according to the experimental conditions. At room temperature rings A and D are hydrogenated with the formation of the nickel BC-didehydrocorrin salt (**21**) whereas at 100 °C the isomeric nickel AD-didehydrocorrin salt (**22**) is obtained (Dicker *et al.* 1971). Base-catalysed dehydrogenations of rings B and C (but not A and D) occurred very easily in presence of atmospheric oxygen, and the same pattern of dehydrogenation was observed in the mass spectrometer. Further hydrogenation of these products gave the amorphous nickel corrin salts often accompanied by the corresponding nickel dihydrocorrin salts, some of which were obtained crystalline.

Hydrogenation of nickel decaalkyl-tetradehydrocorrin salts (**4**) bearing alkyl groups at positions 1, 2, 3, 7, 8, 12, 13, 17, 18 and 19 also involves the ββ-double bonds of rings B and C in the first instance (Hamilton & Johnson 1971), but vigorous hydrogenation yields either the crystalline nickel isocorrin perchlorate (**23**) or the monodehydro-isocorrin derivative (**24**) and their formation is a consequence of the steric crowding of the alkyl substituents around the 1,19-linkage (Johnson, Overend & Hamilton 1973). However the presence of methyl substituents at the meso positions C5 and C15 may also have an effect so that the conversion of the fully substituted nickel tetradehydrocorrin salts to the corresponding corrins remains a possibility.

When the nickel AD-didehydrocorrin perchlorate (**22**) was treated with base and methyl iodide in an atmosphere of nitrogen the colour of the solution changed from orange to deep green and the methylation product (**25**) was obtained in which methylation of the enamine ring B has occurred and dehydrogenation of ring C (Dicker *et al.* 1971). The salt of the product was formulated as **26** on the basis of its n.m.r. and mass spectrum. Such structures are of interest



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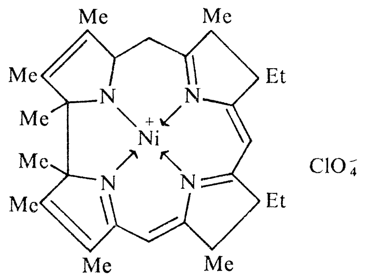

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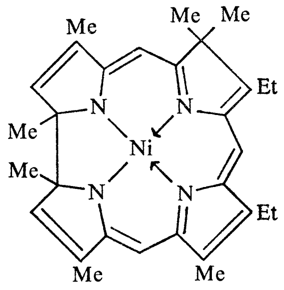

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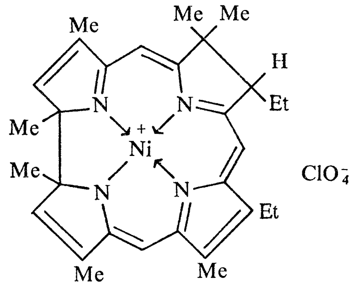

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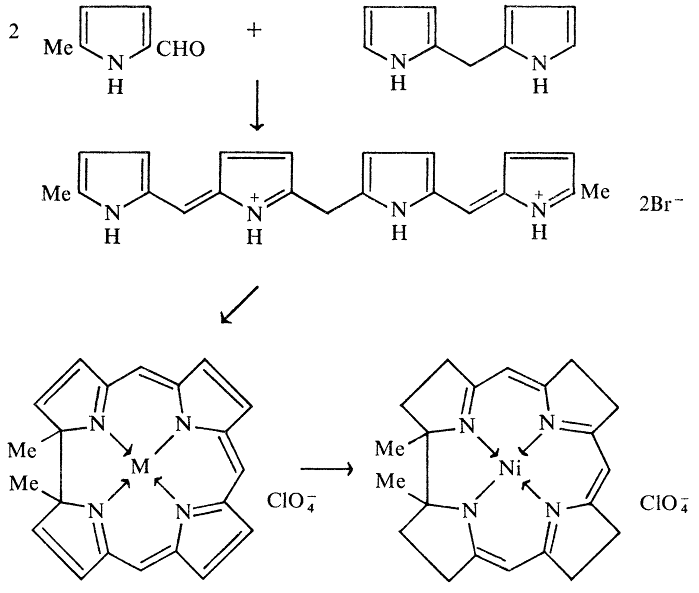
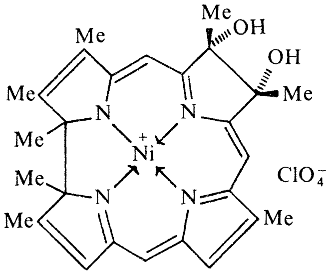


27 **28**

because of the presence of the gem-β-dialkyl substitution. In the absence of β-substituents the hydrogenation of the parent nickel(II) and cobalt(II) 1,19-dimethyltetradehydrocorrin salts (**27**) gave the corresponding crystalline metal corrin salts at room temperature and pressure, and in fact the complexed metal could act as catalyst for the reaction (Johnson & Overend 1972). The nickel corrin perchlorate (**28**) showed an n.m.r. spectrum containing singlets at τ 3.68 (1 H) and 4.0 (2 H) corresponding to the meso-protons indicating an absence of aromatic character. A crystalline by-product from the hydrogenation was also obtained and proved to be a nickel dihydrocorrin salt although the position of the double bonds was not established with certainty. Hydrogenation of the cobalt tetradehydrocorrin perchlorate at room temperature and 25 atm (2.5 MPa) of hydrogen also gave the corresponding corrin derivative isolated either as the cobalt(II) perchlorate or as the neutral dicyanocobalt(III) corrin. A smaller amount of the dicyanocobalt(III) dihydrocorrin was also identified. It was shown that under acid conditions



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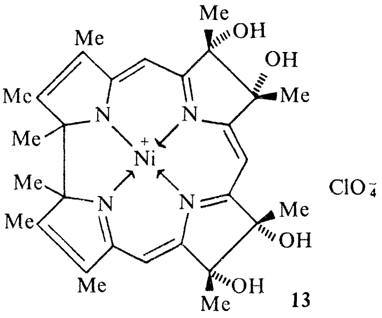

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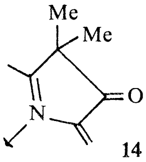

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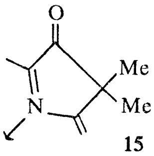

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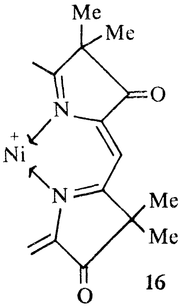

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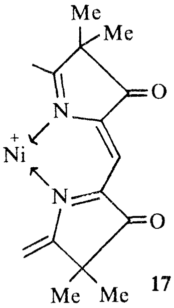

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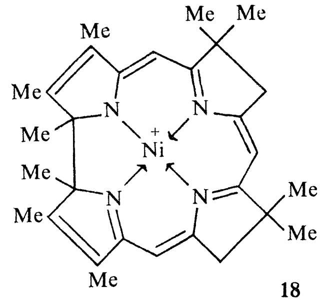

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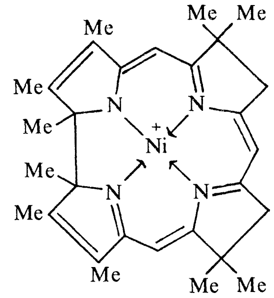

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all of these products exchanged the meso-protons very rapidly for deuterium. This total synthesis of the corrin ring system involves only three stages.

It gives me much pleasure in acknowledging the debt I owe to my many collaborators at the Universities of Nottingham and Sussex who provided the experimental results I have described in this paper.

References (Johnson)

Clarke, D. A., Grigg, R., Harris, R. L. N. Johnson, A. W., Kay, I. T. & Shelton, K. W. 1967 *J. chem. Soc.* (*C*), p. 1648.

Clezy, P. J. & Liepa, A. J. 1971 *Austral. J. Chem.* **24**, 1027.

Conlon, J. M., Elix, J. A., Feutrill, G. I., Johnson, A. W., Roomi, M. D. & Whelan, J. 1974 *J. chem. Soc., Perkin Trans. I*, p. 713.

Dicker, I. D., Grigg, R., Johnson, A. W., Pinnock, H., Richardson, K. & van den Broek, P. 1971 *J. chem. Soc.* (*C*), p. 536.

Dolphin, D., Harris, R. L. N., Huppatz, J. L., Johnson, A. W. & Kay, I. T. 1966 *J. chem. Soc.* (*C*), p. 30.

Dolphin, D., Johnson, A. W., Leng, J. & van den Broek, P. 1966 *J. chem. Soc.* (*C*), p. 880.

Eschenmoser, A. 1970 *Q. Rev.* **24**, 366.

Eschenmoser, A. 1971 *I.U.P.A.C. 23rd Congres Spec. Lect.* (Boston), **2**, 69. London: Butterworths.

Grigg, R., Johnson, A. P., Johnson, A. W. & Smith, M. J. 1971 *J. chem. Soc.* (*C*), p. 2457.

Grigg, R., Johnson, A. W., Richardson, K. & Shelton, K. W. 1969 *J. chem. Soc.* (*C*), p. 655.

Hamilton, A. L. & Johnson, A. W. 1971 *J. chem. Soc.* (*C*), p. 3879.

Harris, R. L. N., Johnson, A. W. & Kay, I. T. 1966 *J. chem. Soc.* (*C*), p. 22.

Hodgkin, D. C. 1958 *Fortschr. Chem. org. Naturstoffe* **15**, 167.

Hodgkin, D. C., Kamper, J., Lindsey, J., MacKay, M., Pickworth, J., Robertson, J. H., Shoemaker, C. B., White, J. G., Prosen, R. J. & Trueblood, K. N. 1957 *Proc. R. Soc. Lond.* A **242**, 228.

Inhoffen, H. H., Ullrich, J., Hoffmann, H. A., Klinzman, G. & Scheu, R. 1970 *Annalen* **738**, 1.

Johnson, A. W. & Kay, I. T. 1961 *J. chem. Soc.* 2418.

Johnson, A. W. & Kay, I. T. 1965 *J. chem. Soc.* 1620.

Johnson, A. W. & Overend, W. R. 1972 *J. chem. Soc., Perkin Trans. I*, p. 2681.

Johnson, A. W., Overend, W. R. & Hamilton, A. L. 1973 *J. chem. Soc., Perkin Trans. I*, p. 991.

Scott, A. I., Townsend, C. A., Okada, K., Cushley, R. J. & Whitman, P. J. 1974*a* *J. Am. chem. Soc.* **96**, 8069.

Scott, A. I., Townsend, C. A., Okada, K. & Kajiwara, M. 1974*b* *J. Am. chem. Soc.* **96**, 8054.

Woodward, R. B. 1973 *Pure appl. Chem.* **33**, 145.