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The Chemistry of Corrin Systems

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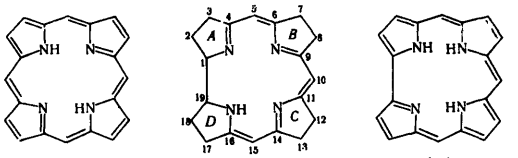
The review deals with the modern state of the chemistry of corrin compounds. The principal methods of the synthesis of corroles, metal complexes of tetradehydrocorrins and corrins are discussed together with the mechanisms of the cyclisation of tetrapyrrole systems on irradiation or in the presence of metal salts, which leads either to corroles or tetradehydrocorrin complexes. The limits of the applicability of the methods for the synthesis of corrins via imino-ethers and by the reduction of tetradehydrocorrins are estimated. The results of studies on the stereospecific synthesis of cobyrinic acid are presented. The available literature data on the properties of synthetic corrinoid systems are considered as well as the properties of the metal complexes, deuterium exchange, protonation and alkylation of corroles and corrins and the rearrangements of tetradehydrocorrins. Much attention has been devoted to the spectroscopic characteristics of tetrapyrrole macrocyclic compounds, in particular their ultraviolet, infrared, and NMR spectra, which are widely used to establish the structure of corrin systems. The bibliography includes 82 references.

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I. INTRODUCTION

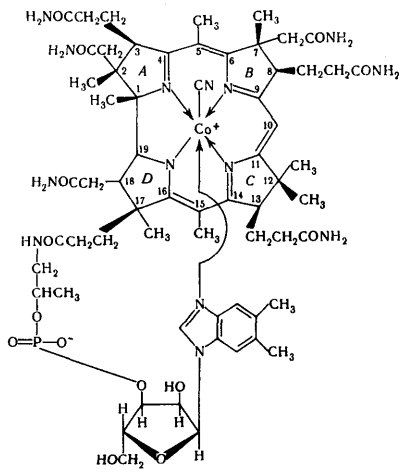
The attention of chemists is at present increasingly drawn to biologically active substances which play an important role in the living processes of organisms. Such substances are in particular the macrocyclic tetrapyrrole systems, two types of which are encountered in nature. The first type consists of porphyrins (I), for example haemin, which is the basis of the blood pigment (haemoglobin) and cytochrome coenzymes, and also dihydroporphyrins or chlorins, for example the pigment in plant leaves—chlorophyll. The second type consists of corrins (II)†, for example cobalamins, represented by vitamin B_{12} and its coenzyme:



(I) (II) (IV)

Both types include important natural compounds, characterised by a similar asymmetric distribution of β-substituents in the ring and the fact that they exist as metal complexes. The close relation between these two groups is demonstrated by the fact that the early stage of their biosyntheses includes porphobilinogen[2-4].

Vitamin B_{12} (cyanocobalamin) (III) counteracts pernicious anemia. As a coenzyme, vitamin B_{12} catalyses many enzymic reactions, in particular the conversion of glutamate into methylaspartate[5], succinyl-coenzyme A into methylmalonyl-coenzyme A,[6,7] and 1,2-diols into deoxyaldehydes[8-11] and the dissociation of lysine into aliphatic acids and ammonia[12]. The methyl analogue of the vitamin B_{12} coenzyme takes part in the synthesis of methionine[13] and the cobamide coenzyme serves also as a cofactor in the reduction of ribonucleosides[14] and in the synthesis of egg albumin[15].



(III)

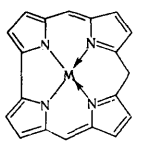
The chemical structure of vitamin B_{12} has been completely elucidated as a result of a brilliant application of X-ray diffraction analysis[16] and studies on chemical degradation[2]. The cobalamine molecule can be divided into two parts, known as the "planar" part and the "nucleotide"; the latter lies in a plane almost perpendicular to the planar component. In the planar part the central cobalt atom is linked to four reduced pyrrole rings, forming a macrocycle. Three of the four junctions are formed by the *meso*-carbon atoms and in the fourth position the junction is formed by a direct bond between two α-carbon atoms of the heterocyclic rings. The macrocycle contains six conjugated double bonds and nine asymmetric carbon atoms.

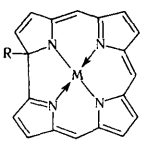
† The name "corrin" is given to the macrocyclic compound (II) which constitutes the basis of vitamin B_{12}; it was adopted in 1957 at the First International Symposium on Vitamin B_{12}.[1]

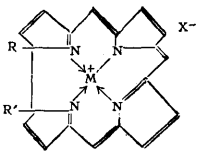
Several reviews have been written on the chemistry and biochemistry of vitamin B_{12} and its coenzyme[2,17-20].

The macrocyclic compound (IV), differing from corrin by four additional double bonds and constituting an 18π-electron aromatic system, was synthesised[21] in 1964. This compound was called "corrole"[22]. It is of independent interest as a new aromatic heterocyclic system.

At present three types of new heterocyclic compounds[23] with two directly linked pyrrole rings and containing ten double bonds are known: corroles (IV) and their metal complexes (V), neutral nickel and cobalt complexes of 1-substituted tetradehydrocorrins (VI) and salts of the nickel and cobalt complexes of 1,19-disubstituted tetradehydrocorrins (VII). The last two macrocyclic compounds are not aromatic, and therefore they are referred to as tetradehydrocorrins and not substituted corroles.


(V)


(VI)


(VII)

The structure of tetradehydrocorrins includes, like that of corroles, a direct α-carbon–α-carbon bond between two pyrrole rings but differs from corrins by a higher degree of unsaturation. Possibly pyrroles and tetradehydrocorrins are intermediates in the biosynthesis of vitamin B_{12}. In the study of the biosynthesis of cobalamin[3,24] it was established that porphobilinogen is a precursor of both corrin and porphyrins. It is believed[20,25-27] that porphobilinogen condenses to a linear tetrapyrrole system and the latter cyclises either into porphyrin or into corrin, possibly via corrole.

The complete chemical synthesis of vitamin B_{12} has not as yet been achieved. The most difficult problem is the stereospecific synthesis of the central heterocyclic part of the molecule with the required substituents.

II. METHODS FOR THE SYNTHESIS OF CORRIN SYSTEMS

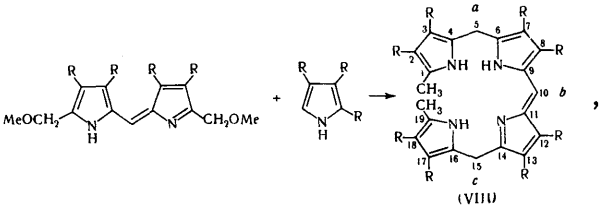
A. SYNTHESIS OF CORROLES AND TETRADEHYDROCORRINS

1. Synthesis of Corroles by Photocyclisation

Methods for the synthesis of corrole and tetradehydrocorrins were developed by Johnson and coworkers. Corroles are synthesised by the photocyclisation of linear tetrapyrrole systems, namely the dihydrobromides of 1,19-dideoxybiladienes-*ac*[28-31] and the hydrobromides of 1,19-dideoxybilenes *b*‡[28,32]. Special methods have been developed for the preparation of these tetrapyrrole systems.

‡ Since the bile pigments (bilirubin) are the most thoroughly investigated tetrapyrrole systems, the bile pigment nomenclature has been adopted for all the tetrapyrrole systems[33]. The prefix "deoxy" indicates the absence of two hydroxy-groups in positions 1 and 19.

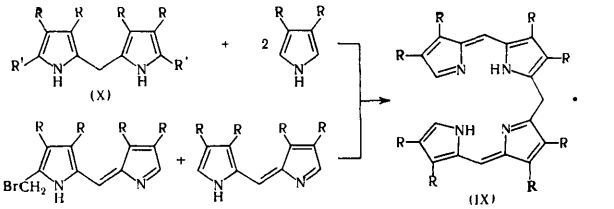
Bilenes-*b* (VIII) were synthesised by the condensation[28,32] of 5,5′-di(methoxymethyl)dipyrromethene with two equivalents of 2,3,4-trialkylpyrrole:


(VIII)

where R = H, CH_3, or C_2H_5.

Two methods have been developed for the synthesis of biladienes-*ac* (IX).

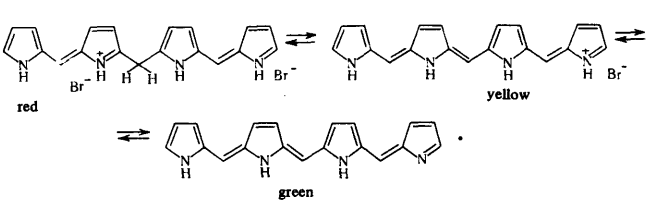
1. Condensation[28] of 5,5′-diformyldipyrromethane (X, R′ = CHO) with two equivalents of 3,4-dialkylpyrroles or condensation of dipyrromethane-5,5′-dicarboxylic acids (X, R′ = COOH) with two equivalents of 5-formyl- or 5-acetyl-pyrroles:


(IX)

2. Condensation[29-31] of 5-bromomethyldipyrromethene with dipyrromethene having a free α-position in the presence of tin chloride.

Corrole was obtained for the first time[34] by irradiating with the light from a tungsten lamp a suspension of a biladiene-*ac* in boiling methanol in the presence of a base. This results in the formation of a solution, the colour of which rapidly changes from yellow to green and then to red; from the last solution, crystals of corrole (IV) precipitate on cooling[35]. Relatively stable nickel and copper complexes of corrole[35], which may be obtained by the addition of metal cations either to solutions of corroles or to a suspension of 1,19-dideoxybiladienes-*ac* before irradiation, have been isolated.

The exact mechanism of the photocyclisation of biladienes-*ac* to corroles has still not been established[36,37], but it is most probable that the reaction has a free-radical mechanism[23,37]. Protons in the 10-position are definitely involved in the cyclisation. Solutions of the dihydrobromides of 1,19-dideoxybiladienes in benzene are red, while those in alcohol and in dimethyl sulphoxide are yellow, becoming green on addition of a base, for example piperidine. The colour change is caused by the abstraction of a proton in the 10-position by polar solvents and the formation of the monohydrobromide of 1,19-dideoxybilatriene-*abc*, which is converted into a free base under the action of piperidine.

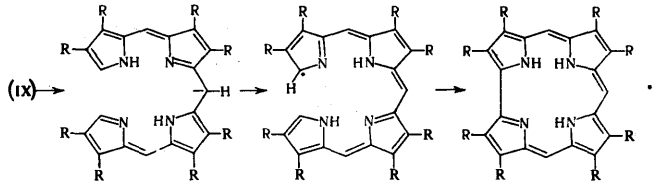


Photocyclisation of biladienes-*ac* is possible only in the presence of bases, which indicates the initial elimination of a proton from the central methylene group during the

photocyclisation process. This hypothesis is confirmed by the fact that 10,10-dimethylbiladienes are not cyclised to corroles[32].

Apart from the protons at the C_{10} atom, the photocyclisation is greatly affected by substituents in the 1- and 19-positions and also by the presence of metals. Corrole could not be obtained from 1,19-dimethylbiladiene by photocyclisation, while the cyclisation of biladienes unsubstituted in the 1- and 19-positions takes place readily. The reason for this is that the 1,19-dimethyl or 1,19-diethoxycarbonyl groups give rise to steric hindrance to cyclisation.

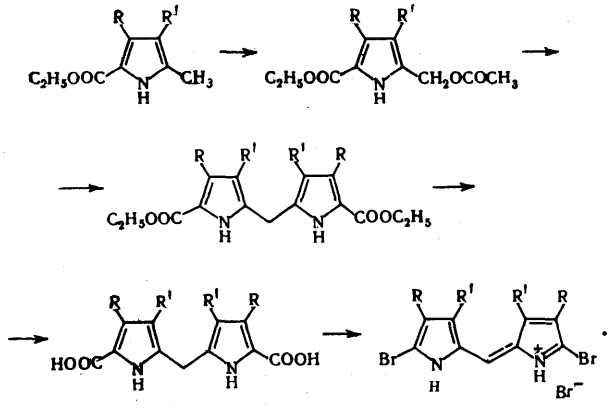
The mechanism proposed for the formation of corrole includes the formation of an intermediate radical:



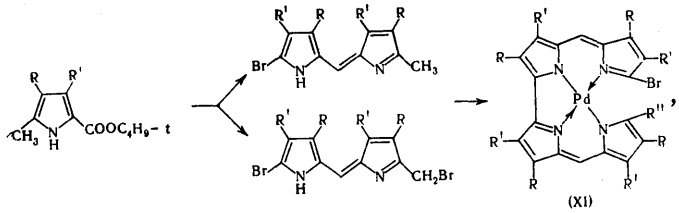
The effect of various free-radical initiators and one-electron oxidising agents on the cyclisation of 1,19-dideoxy-2,3,7,8,12,13,17,18-octa-alkylbiladienes-*ac* in the presence of ammonia has been examined[37]. When potassium hexacyanoferrate(III), ferric chloride, ceric sulphate, hydrogen peroxide, benzoyl peroxide, or t-butyl peroxide are added, cyclisation takes place readily and the replacement of atmospheric oxygen by nitrogen does not affect the rate of reaction and the yield of corroles; the corroles are formed in yields of 68–84%.

2. Attempts at Synthesis of Corrole by the Introduction from the Outside of a *meso*-Carbon Atom and Cyclisation of Tetrapyrrole Systems on Introduction of Hetero-Atoms

The cyclisation of various tetrapyrrole systems with introduction from the outside of a *meso*-carbon atom has been investigated as one of the possible ways of synthesising corrole[21,32,38]. The initial dipyrromethenes with symmetrical β-substituents were synthesised from substituted 5-ethoxycarbonyl-2-methylpyrroles[39], which, on oxidation with lead tetra-acetate, are converted into 2-acetoxymethylpyrroles and in an acid medium the latter are condensed into dipyrromethanes. After the hydrolysis of the ester groups, dipyrromethane-5,5′-dicarboxylic acid is treated with bromine in acetic acid and the hydrobromide of β-substituted 5,5′-dibromodipyrromethene is obtained[40]:



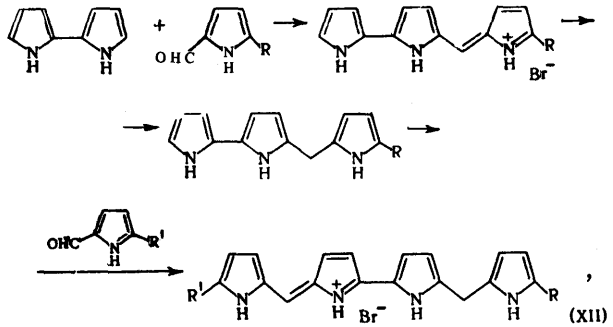
Dipyrromethenes with asymmetric β-substituents can be obtained by the action of bromine on the t-butyl ester of 5-methylpyrrole-2-carboxylic acid[41]; this results in the formation of a mixture of 5-bromo-5′-methyldipyrromethene and 5-bromo-5′-bromomethyldipyrromethene. The condensation of these pyrromethenes in the presence of palladium on strontium carbonate yields the chelate complex (XI, R″ = CH_3), which could not be cyclised. When two moles of 5,5′-dibromodipyrromethene were condensed in the presence of palladium on strontium carbonate or in the presence of copper and cobalt salts[22], the corresponding metal complexes (XI, R″ = Br) were obtained but these could not be cyclised either under the action of formaldehyde in an acid medium:



(XI)

where R = R′ = H, R = R′ = CH_3, or R = CH_3 and R′ = Br.

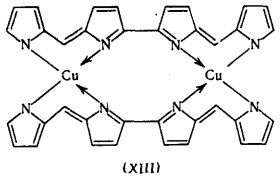
Tetrapyrrole systems (XII) containing a direct α-carbon–α-carbon bond between the two pyrrole rings have been used to synthesise corroles[38]. Two methods have been proposed for the preparation of compound (XII). When 2,2′-bipyrroles are condensed[28,42] with 2-formylpyrrole[43], one molecule of formylpyrrole adds on and 5-(pyrrol-2-yl)dipyrromethene is formed; hydrogenation of the latter yields pyrrolyldipyrromethane, the reaction of which with 2-formylpyrrole gives compound (XII):



(XII)

where R = R′ = H, R = R′ = CH_3, or R = CH_3 and R′ = Br.

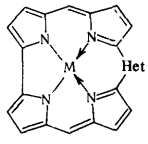
The second method of synthesising compound (XII) consists in the condensation[32] of 2-chloromethylpyrroles with 5-(pyrrol-2-yl)dipyrromethenes in the presence of tin chloride. In the cyclisation of the tetrapyrrole system (XII) in the presence of copper[32] or zinc[44] acetates, the corresponding chelate complexes of type (XI) and the copper complex (XIII) where isolated.



(XIII)

However, it it was not possible to introduce the *meso*-carbon atom into the tetrapyrrole system and cyclise the latter into corrole, a pseudocorrole system could be synthesised by the external introduction of a hetero-atom (O, N, or S).

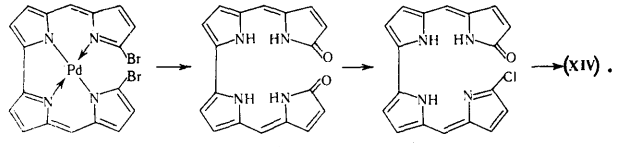
Oxa-, aza-, methylaza-, and thia-analogues of corrole (XIV) are planar compounds; each of the bridge atoms (Het = O, N, or S) contains at least one pair of free electrons which participate in the overall conjugated macrocyclic system:



(XIV)

In the condensation of two molecules of 5-bromodipyrromethenes in the presence of palladium on strontium carbonate a tetrapyrrole palladium complex (XV) [22] was obtained; when refluxed in the presence of hydrochloric acid it yielded a cyclic product to which the structure of a hydroxopalladium complex of corrole was initially ascribed [22]. Subsequent studies [45,46] showed that this compound is a derivative of the cyclic ether (XIV) (Het = O) in which the C_{10} carbon atom has been replaced by oxygen. Nickel and copper complexes of this ether have been synthesised.

The mechanism of the cyclisation of the free tetrapyrrole dibromide to the cyclic ether is probably as follows: in the course of the acid hydrolysis of the dibromide two products are formed—a dilactam (XVI) and a monolactam (XVII); the latter is produced as a result of the hydrolysis of one bromine atom and replacement of the second bromine atom by chlorine. Under the action of copper(II) acetate, nickel chloride, and palladium(II) chloride, the monolactam (XVII) is converted into complexes of the cyclic ether (XIV):



(XV) (XVI) (XVII)

Possibly the monolactam (XVII) isomerises initially to a lactim form, which in fact gives rise to the metal complexes.

The macrocyclic ether (XIV Het = O) can be obtained in a free form when copper is removed by treating the copper complex with concentrated sulphuric acid at 20°C. When the copper complex is treated with hot concentrated hydrochloric acid, the ring opens with formation of the monolactam (XVII). Under these conditions, nickel and palladium complexes are not converted into the dilactam (XVI), i.e. ring opening is facilitated by preliminary removal of the metal.

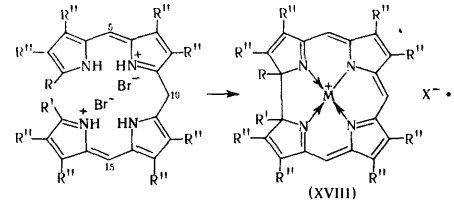
Treatment of the free cyclic ether with metal salts results in the formation of the corresponding metal complexes. The attempts to synthesise the macrocyclic ether (XIV) from the dibromides of the nickel and cobalt chelate complexes of type (XV) resulted in the formation of the dilactam (XVI) only.

The aza- and thia-derivatives (XIV, Het = NH, NCH_3, S) were synthesised by treating the palladium derivative (XV) in pyridine with ammonia, methylamine, or sodium sulphide respectively. The cyclic aza-derivatives were obtained in the form of both palladium and copper complexes as well as the free cyclic compounds.

3. Synthesis of Metal Complexes of Tetradehydrocorrins

Since in natural corrins the macro-ring has an angular 1-methyl group, the synthesis of various tetrahydrocorrins with angular substituents attracted much attention.

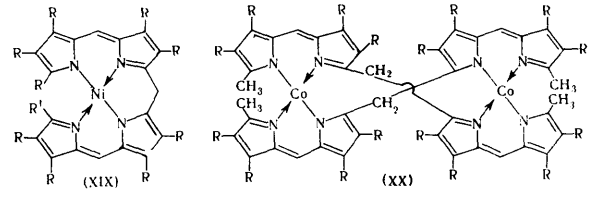
Aeration [47] of solutions of dihydrobromides of 1,19-dimethyl- or 1,19-diethoxycarbonyl-1,19-dideoxybiladienes-*ac* in the presence of bases and nickel or cobalt acetates yields salts of the nickel or cobalt complexes of 1,19-substituted tetradehydrocorrins (XVIII, M = Ni or Co, and R = R′ = CH_3 or $COOC_2H_5$): [48,49]



(XVIII)

Treatment of the methanol solutions of the dihydrobromides of 1,19-dimethyl-1,19-dideoxybiladienes-*ac* or the corresponding bilenes-*b* with copper salts results in the formation of porphyrin, the cyclisation of which takes place with the loss of one carbon atom [33].

When methanol solutions of 1,19-dimethyl-1,19-dideoxybiladiene-*ac* are heated with sodium and nickel acetates, a chelate nickel complex of biladiene (XIX) is formed initially and on further aeration and treatment with NO_3^-, Cl^-, or ClO_4^- ions cyclises into a complex of 1,19-dimethyltetradehydrocorrin (XVIII). In the reaction of 1,19-dimethyl-1,19-dideoxybiladienes-*ac* with cobalt acetate, the biladiene cobalt complex was not isolated; in this case the formation of the cobalt complex of 1,19-dimethyltetradehydrocorrin is accompanied by that of compound (XX), containing two tetrahedral cobalt atoms and two biladiene ligands [47]. Under the conditions of mass-spectrometric analysis, this dimer dissociates and cyclises with the elimination of hydrogen, being converted into the cobalt complex of 1,19-dimethyltetradehydrocorrin. The cyclisation of 1,19-disubstituted 1,19-dideoxybiladienes can be achieved only in the presence of a metal:

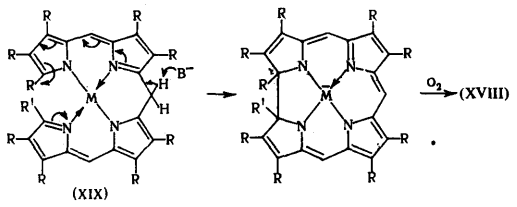


(XIX) (XX)

For a more detailed investigation of the cyclisation of biladienes, certain biladienes with substituents in the 5-, 10-, and 15-positions were synthesised [47]. It was found that the cyclisation of 10,10-dimethylbiladienes is impossible under any conditions. The cyclisation products of 5,10-dimethylbiladienes were not identified. The cyclisation of 5,15-dimethyl- and 10-methyl-biladienes yielded the salts of the nickel complexes of 5,15-dimethyl-10-methyl-tetradehydrocorrins, the cyclisation of 10-methylbiladienes being much slower than that of biladienes with a free 10-position.

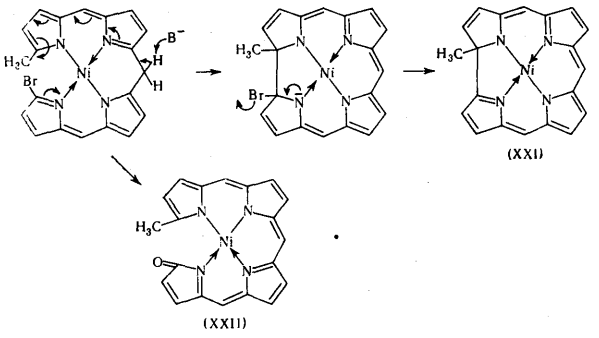
The following mechanism was proposed for the cyclisation of 1,19-disubstituted 1,19-dideoxybiladienes-*ac* on the basis of these observations [36,47]. Initially a metal complex (XIX) is formed, the metal having a coordinating effect on the 1- and 19-positions, bringing them closer together and thereby facilitating the cyclisation. In the presence of

a base, the proton is eliminated from the C_{10} atom and an anion is formed, which on oxidation with atmospheric oxygen is converted into a complex of 1,19-disubstituted tetradehydrocorrin (XVIII):



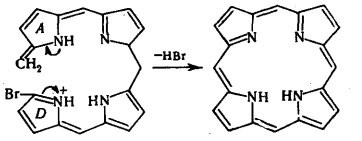
To synthesise tetradehydrocorrins with an angular 1-methyl group, the dihydrobromides of 19-bromo-1-methyl-1,19-dideoxybiladienes-*ac* were cyclised. When methanol solutions of these compounds are heated with bases in the presence of nickel ions[50], nickel complexes of 1-methyltetradehydrocorrin (XXI) are readily formed in the absence of atmospheric oxygen[51]. The presence of air causes the formation of the nickel complex of the lactam (XXII); ordinary heat treatment of 19-bromo-1-methyl-1,19-dideoxybiladienes results in the formation of porphyrins[51].

The mechanism of the formation of 1-methyltetrahydrocorrins can be represented as follows:



In contrast to cyclisation which leads to complexes of 1,19-disubstituted tetradehydrocorrins, the formation of 1-methyltetradehydrocorrins includes the elimination of hydrogen bromide without an oxidation stage. The cyclisation is very rapid and the nickel complex of the biladiene was not isolated. In contrast to the alkaline cyclisation of 19-bromo-1-methyl-1,19-dideoxybiladienes, the formation of porphyrins[30,52] includes a stage involving the formation of an intermediate with an enamine structure of ring *A* followed by the attack of the enamine on the α-carbon atom of ring *D*.

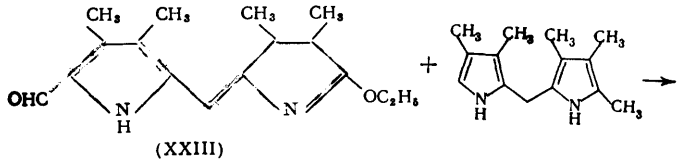
The cyclisation of 19-bromo-1-methyl-1,19-dideoxybiladienes was extended to 1-ethyl and 1-isopropyl-1,19-dideoxybiladienes, which were converted into the nickel complexes of the corresponding 1-alkyltetradehydrocorrins.

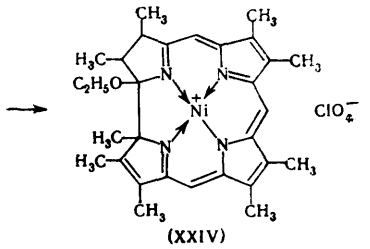


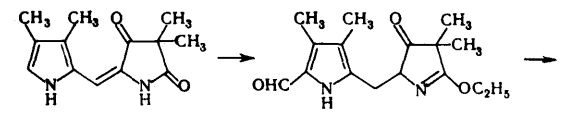
Attempts were made to activate the cyclisation of 19-bromo-1-methyl-1,19-dideoxybiladienes using copper acetate instead of nickel acetate, but the sole reaction product was then the copper complex of porphyrin. The cyclisation of 19-bromo-1-methyl-1,19-dideoxybiladienes in the presence of cobalt acetate in various solvents yielded a mixture of products. These results are inconsistent with the ease of isolation of the cobalt complexes of 1,19-disubstituted tetradehydrocorrins[47] and can be accounted for by the high reactivity of the cobalt complex of 1-methyltetradehydrocorrin. Hydrogenation of solutions obtained after treating 19-bromo-1-methyl-1,19-dideoxybiladienes with cobalt acetate over Raney nickel at 100°C under a pressure of 100 atm yields the cobalt complex of 1-methylcorrin[23].

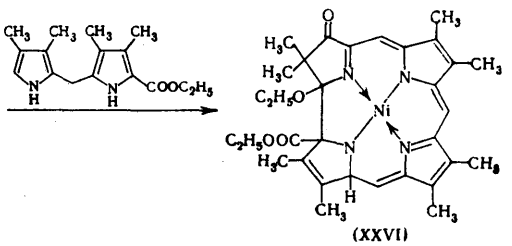
The cyclisation of biladienes[53] containing the 19-alkoxy- instead of the 19-bromo-group has been described, but the use of such compounds proved to be less convenient. The cyclisation of the dihydrobromides of 19-ethoxycarbonyl-1-methyl-1,19-dideoxybiladienes-*ac*[47] yields the nickel complexes of 19-ethoxycarbonyl-1-methyltetradehydrocorrins; the ester group may be removed by hydrolysis followed by decarboxylation.

The cyclisation of certain reduced pyrrole derivatives constitutes a modification of the biladiene synthesis[53]. Condensation of the imino-ether (XXIII), obtained by the action of the Meerwein reagent[54,55] on the corresponding pyrrolidone, with 5-methyldipyrromethane yields a linear tetrapyrrole derivative, which is cyclised, without isolation, by aeration in the presence of nickel acetate into the complex (XXIV) containing 9 double bonds. The condensation of 3,3-dimethylpyrrole-2,4-dione with 2-formyl-3,4-dimethylpyrrole yields the dipyrromethene (XXV), which is hydrogenated, formylated, and converted into an imino-ether. The condensation of the latter with 5-ethoxycarbonyl-3,3′,4,4′-tetramethyldipyrromethane in the presence of nickel acetate yields the complex (XXVI) containing 8 double bonds:









B. SYNTHESIS OF CORRINS

There exist three approaches to the synthesis of the corrin ring—the central component of vitamin B_{12}. On the basis of the biosynthetic mechanism of the formation of corrin, Johnson[23] carried out the ring-closure of linear tetrapyrrole systems with subsequent reduction of the resulting macrocyclic compounds—metal complexes of tetrehydrocorrins.

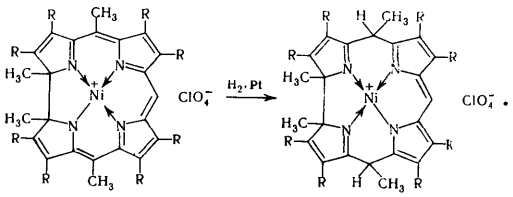
Eschenmoser and coworkers[56] achieved the synthesis of corrin from compounds oxidised to the same extent as the natural corrin compounds, using imino-ethers as the electrophilic components in the condensation reaction involving the formation of C–C bonds.

Neither of these methods permits the synthesis of corrins with a definite steric disposition of the β-substituents, analogous to their disposition in the corrin ring of vitamin B_{12}, where there are nine asymmetric centres. Woodward[57] is close to achieving the stereospecific synthesis of the corrin ring.

1. Synthesis of Corrins and Mono- and Di-dehydrocorrins by the Reduction of Tetradehydrocorrins

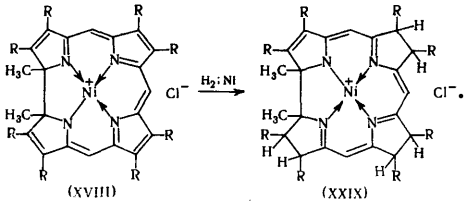
One of the methods for the synthesis of corrins is reduction of 1-methyltetradehydrocorrins. In the course of studies on the conditions governing the formation of corrins, a number of macrocyclic compounds intermediate between corrins and tetradehydrocorrins as regards degree of oxidation have been synthesised.

In the hydrogenation of corrole solutions[35] in the presence of platinum an extremely unstable unidentified product was isolated, which was rapidly oxidised in air and converted into the initial corrole. In the hydrogenation of the nickel complex of 1,5,15,19-tetramethyltetradehydrocorrin (XXVII)[47] in the presence of platinum the compound combines with one mole of the hydrogen and an amorphous very unstable orange perchlorate is formed, the ultraviolet spectrum of which resembles that of the nickel complex of dipyrromethene; the possible structure of the hydrogenated compound is represented by formula (XXVIII).



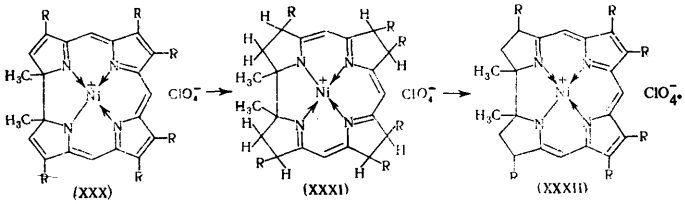
(XXVII) (XXVIII)

The salts of the nickel and cobalt complexes of 1,19-dimethyltetradehydrocorrins could not be reduced with zinc in acetic acid or sodium borohydride in methanol nor could they be hydrogenated over platinum[47]. The hydrogenation of the chloride and perchlorate of the nickel complex of 1,19-dimethyltetradehydrocorrin (XVIII) in the presence of Raney nickel at 100°C and a pressure of 100 atm proved to be more successful. Under these conditions, the product is the orange-yellow salt of the nickel complex of monodehydrocorrin (XXIX) containing seven double bonds. It is stable to oxidation and does not break down under the action of acids and alkalis:



(XVIII) (XXIX)

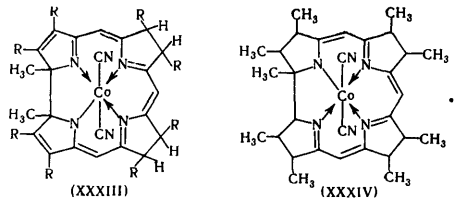
In all the corrins known at the present time[56] the directly linked pyrrole rings do not contain a ββ-double bond. Since the ββ-double bond of ring *A* in compound (XXIX) is sterically protected, a study was made of the hydrogenation of the perchlorate of the nickel complex of 1,19-dimethyltetradehydrocorrin (XXX) with free 2- and 18-positions[23], which results in the formation of the salt of the nickel complex of 1,19-dimethylcorrin (XXXI):



(XXX) (XXXI) (XXXII)

When compound (XXXI) is heated with alcoholic potassium hydroxide in air, a purple substance is rapidly formed, the ultraviolet and visible spectra of which are analogous to those of the tetradehydrocorrin complex but with an overall hypsochromic shift; the NMR spectrum corresponds to 7,12-didehydrocorrin (XXXII).[58] Similar dehydrogenation by bases in the presence of oxygen was observed previously[59].

The hydrogenation of the perchlorate of the cobalt complex of 1,19-dimethyltetradehydrocorrin (XVIII)[47] in the presence of Raney nickel at 100°C and a pressure of 100 atm leads to didehydrocorrin (XXXIII) after treatment with sodium cyanide, while hydrogenation of the cobalt complex of 1-methyltetradehydrocorrin of type (XXI)[23] under the same conditions gives 1-methylcorrin (XXXIV), isolated in the form of the cyanide. It is an amorphous product (probably a mixture of stereoisomers), its visible spectrum coincides with that of dicyanocobalamin, and the NMR spectrum indicates the presence of three *meso*-protons and the absence of olefinic substituents:



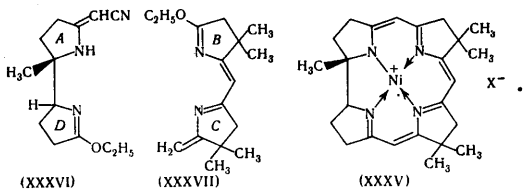
(XXXIII) (XXXIV)

Partial hydrogenation of substituted corrins and tetradehydrocorrins gives rise to asymmetric carbon atoms and the reaction products are mixtures of stereoisomers. Thus the reduction of tetradehydrocorrins cannot be used as a method for synthesising corrin systems analogous to natural corrins and by this method one cannot obtain compounds with a specified steric disposition of β-substituents.

2. Synthesis of Corrins via Imino-ethers

Corrins containing certain β-methyl substituents were synthesised for the first time by Eschenmoser and coworkers in 1964.[56] Imino-ethers[60] were used in this synthesis as the electrophilic components of the condensation in the formation of the nitrogen–carbon conjugated chain of the corrin chromophore[61,62]. These reactions were possible owing to the Meerwein reagent—triethyloxonium tetrafluoroborate[55].

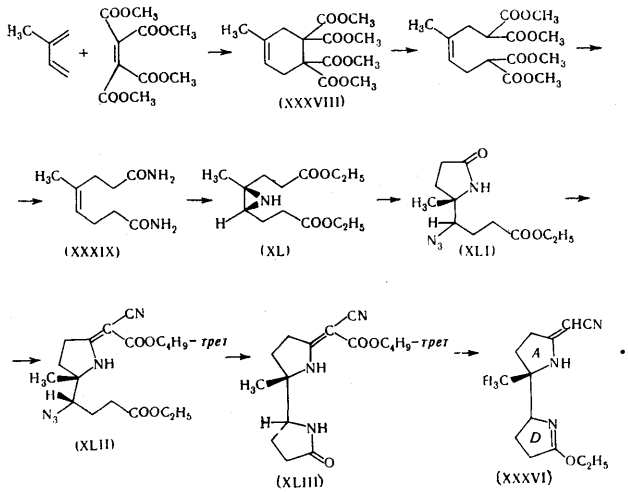
The synthesis of the corrin macrocyle (XXXV) consists of three principal stages: the formation of the *A*–*D* ring system (XXXVI), the formation of the *B*–*C* ring system (XXXVII), and finally the condensation of both systems with closure of the macroring (XXXV):[62]



(XXXVI) (XXXVII) (XXXV)

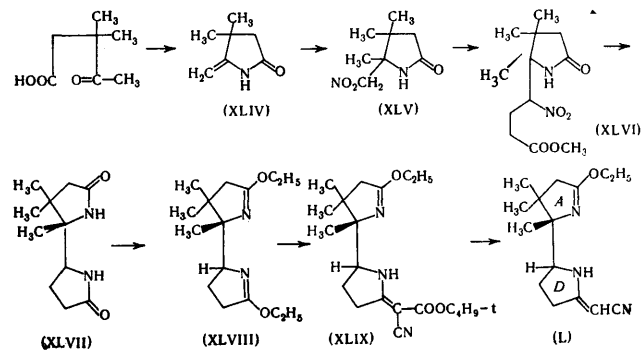
In the synthesis of the *A*–*D* ring system (XXXVI) the starting material is the tetraester (XXXVIII), which is obtained by the Diels–Alder reaction (see Scheme I).

Scheme 1



(XXXVIII) (XXXIX) (XL) (XLI) (XLII) (XLIII) (XXXVI)

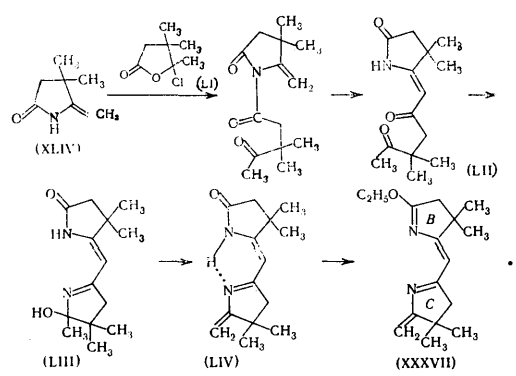
The opening of the ring (XXXVIII) leads to an aliphatic tetraester, which is converted under the action of sodium in liquid ammonia into the crystalline diamide (XXXIX). Stereospecific imination of the double bond in compound (XXXIX) followed by hydrolysis yields an aziridine derivative with the *cis*-configuration (XL). Under the action of the azide ion, a second nitrogen atom is introduced into the molecule with the opening of the aziridine ring and the formation of the butyrolactam ring (XLI). Condensation of the latter with butyl cyanoacetate leads to the ester (XLII). Selective catalytic hydrogenation of the azido-group in compound (XLII) results in the formation of the bicyclic monolactam (XLIII). Elimination of the butyl ester group by treatment with anhydrous trifluoroacetic acid and alkylation of the lactam group with an excess of triethyloxonium tetrafluoroborate yields the *A*–*D* ring system (XXXVI).



(XLIV) (XLV) (XLVI) (XLVII) (XLVIII) (XLIX) (L)

The cyclic enamide (XLIV) was used as the starting material in the synthesis of the *A*–*D* ring system. On nucleophilic addition of nitroethane to compound (XLIV) in the presence of potassium t-butoxide, the nitro-derivative (XLV) is formed. The Michael condensation of methyl acrylate with compound (XLV) yields a mixture of diastereoisomers (XLVI) which on reduction in the presence of Raney nickel is converted into a mixture of the diastereoisomeric dilactams (XLVII); the latter are readily separated by virtue of their different solubilities. The dilactam (XLVII) is converted[54,61] into the di-imino-ether (XLVIII), the treatment of which with butyl cyanoacetate gives compound (XLIX); the conversion of only one imino-group in compound (XLIX) is due to steric factors; compound (XLIX) is converted into compound (L).

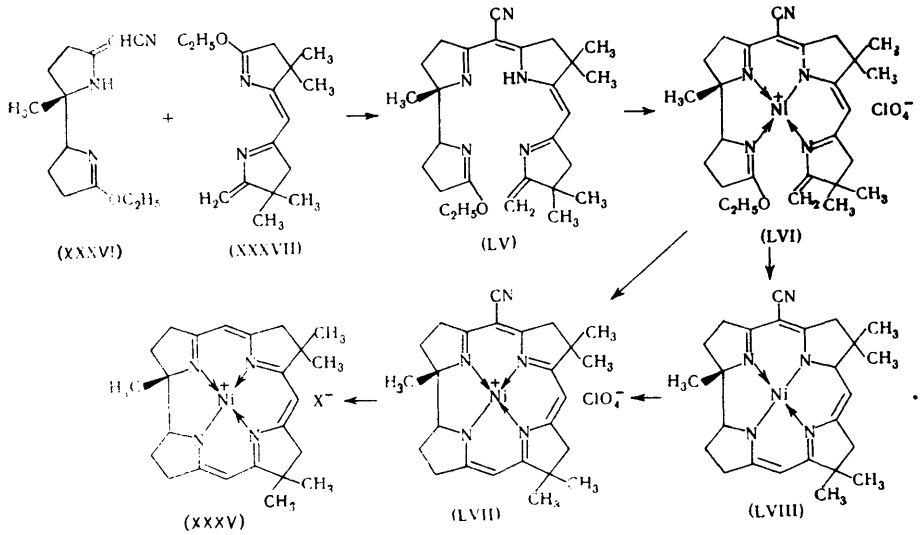
In the synthesis of the *B*–*C* ring system the starting material was also compound (XLIV). *N*-Acylation of the potassium salt of this enamide with a pseudo-acid chloride (LI) followed by photochemical rearrangement leads to compound (LII). The replacement of the carbonyl oxygen atom in compound (LII) by a nitrogen atom is achieved by the action of ammonia in methanol, which results in compound (LIII), the tertiary hydroxy-group of which is readily eliminated with formation of compound (LIV). Because of the intermolecular hydrogen bond in compound (LIV), when the latter is acted upon by triethyloxonium tetrafluoroborate, only *O*-alkylation takes place with formation of compound (XXXVII):



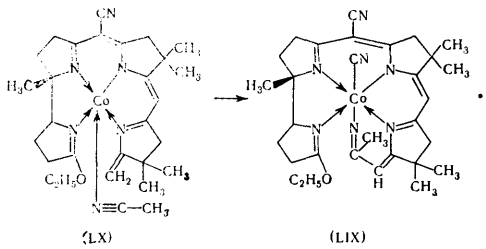
(XLIV) (LI) (LII) (LIII) (LIV) (XXXVII)

The main synthetic problem is the combination of both corrin components: the *A*–*D* (XXXVI) and *B*–*C* (XXXVII) ring systems[56]. It was solved using the specific C → C condensation of the β-iminocrotononitrile group of compound (XXXVI) with the imino-ether group of compound

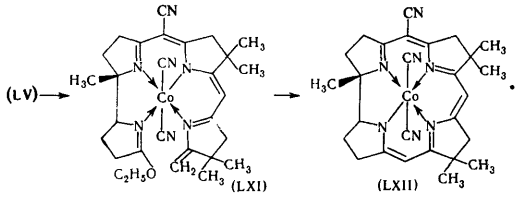
(XXXVII), leading to compound (LV), isolated as the sodium salt. The interaction of this salt with nickel perchlorate in acetonitrile yields the planar complex (LVI), where the imino-ether group and the exocyclic methylene group are sterically fixed, i.e. the geometrical conditions for the closure of the macroring have been created. When compound (LVI) is acted upon by potassium t-butoxide and then treated with perchloric or hydrochloric acid, compound (LVII) is formed. If an acid medium is avoided in the cyclisation reaction, the neutral deprotonated corrin complex (LVIII) is isolated, the protonation of which by acids leads to compound (LVII). When compound (LVII) is hydrolysed in an acid medium, the nitrile group is eliminated and compound (XXXV) is formed:



In the synthesis of the cobalt complex of corrin in the presence of acetonitrile, compound (LIX), called "pseudocorrin", was formed[63]. Initially a complex with acetonitrile attached to the cobalt atom (LX) is probably formed, whereby acetonitrile is activated and fulfils the role of the imino-ether group of ring *A*, which attacks the exocyclic methylene group:



In the absence of acetonitrile the reaction of the sodium salt (LV) with cobalt perchlorate leads, after treatment with cyanide ions and aeration, to the neutral complex (LXI), which cyclises to the dicyanide (LXII) under the action of potassium t-butoxide[64]:

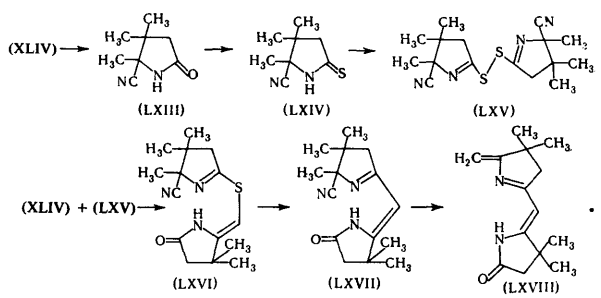


Analogous condensation of compound (L) with compound (XXXVII) results in the formation of the dicyanide of the cobalt complex of 1,2,2,7,7,12,12-heptamethylcorrin[65].

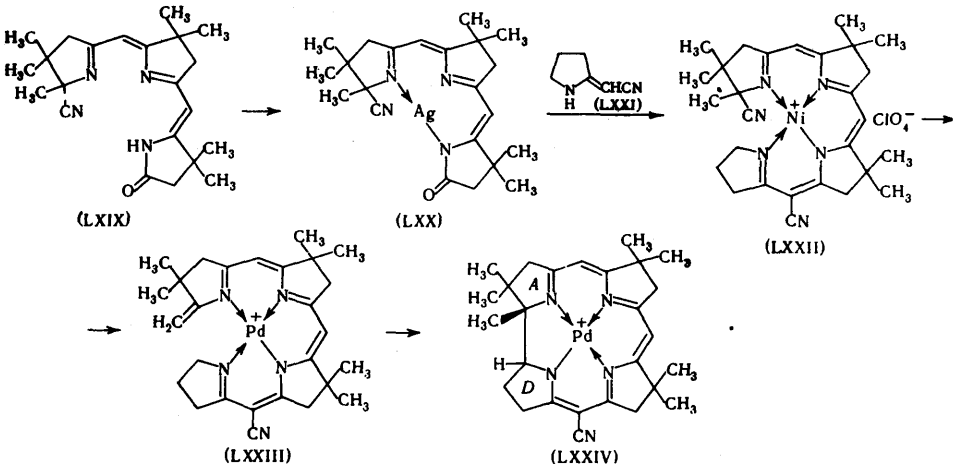
3. Synthesis of Corrins by the Introduction of a Sulphur Bridge Atom

Eschenmoser and coworkers[66] synthesised corrin also by another procedure, based on the formation of the corrin ring from monocyclic enamines and enamides by introducing a sulphur bridge atom; the final stage in this process is the photo-induced cycloisomerisation of the metal complexes of the tetracyclic system, proposed earlier by Johnson[37], and the formation of a bond between rings *A* and *D*.

Before introducing the enamide (XLIV) into the condensation reaction, the active C=C bond is protected by converting compound (LXIII) into the cyano-lactam (XLIV), the reaction of which with P_2S_5 yields the thiolactam (LXIV). The final oxidative formation of the sulphide bridge between the thiolactam (LXIV) and the enamide (XLIV) takes place under the action of benzoyl peroxide; this involves the intermediate formation of the di-imidazolinyl disulphide (LXV), which, under the action of an acid catalyst, undergoes an electrophilic substitution reaction with the CH_2 group of the enamide (XLIV) leading to the formation of compound (LXVI). Since the enamide (XLIV) is inert with respect to benzoyl peroxide, the formation of compound (LXVI) can be achieved in a single stage:



Scheme 2



When compound (LXVI) is heated with triphenylphosphine, compound (LXVII) is formed, which, after elimination of the CN group, is converted into the bicyclic lactam (LXVIII). Repetition of the process makes it possible to add to the lactam (LXVIII) a further molecule of compound (LXIV) and obtain the tricyclic lactam (LXIX). To introduce the fourth ring, the silver complex (LXX) is synthesised, in which the two nitrogen atoms are protected by being linked to silver. The reaction of the complex (LXX) with triethyloxonium tetrafluoroborate and subsequent condensation with pyrrolidine (LXXI) yields a tetracyclic compound, which is isolated as the perchlorate of the nickel complex (LXXII); under the action of palladium acetate in the presence of potassium cyanide, this compound is converted into the palladium complex and, after the elimination of the protective CN group, compound (LXXIII) is obtained, which cyclises quantitatively under the action of ultraviolet radiation or sunlight with formation of the palladium complex of 15-cyano-1,2,2,7,7,12,12-heptamethylcorrin (LXXIV) (see Scheme 2).

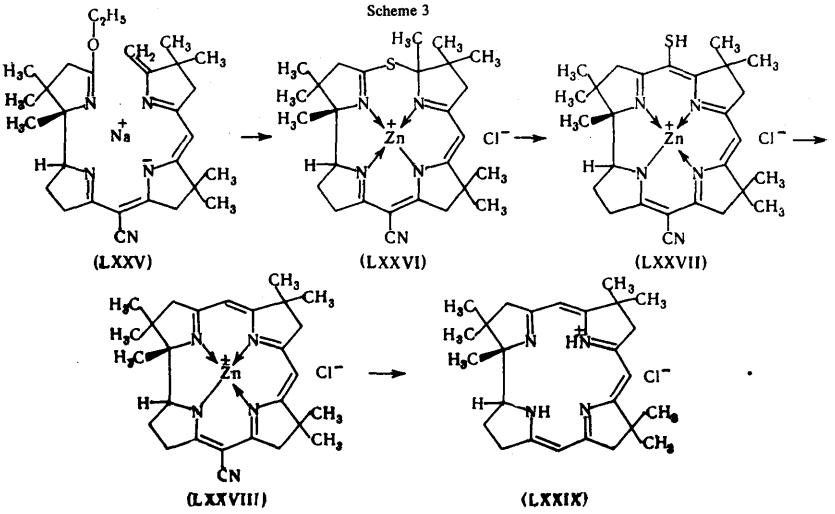
The structure of compound (LXXIV) was established on the basis of infrared, ultraviolet, NMR, and mass spectra and also by synthesis from compound (L) (*A*–*D* ring system) and compound (LXVIII) (*B*–*C* ring system). The nickel complex of compound (LXXII) could not be cyclised—probably the palladium(II) ion has a high tendency towards planar coordination.

A corrin system without cobalt was isolated[67] from the photosynthesing bacterium *Chromatium* strain D; this led to the syntheses of similar compounds. The synthesis is based on the formation of an amidine system with the intermediate introduction of a sulphur bridge atom[68].

In contrast to the imino-ether method for the synthesis of the corrin system, in the presence of a sulphur bridge atom it is not necessary to fix the ligand system into a rigid metal complex and it is possible to employ the labile zinc complex, from which the zinc ion can be readily removed in an acid medium.

Under the action of hydrogen sulphide in an acid medium, the tetracyclic compound (LXXV)[65] is converted into a thiolactam derivative, which is isolated as the zinc complex (LXXVI); without isolation of the intermediates, the latter is converted into the complex (LXXVII) by means of the following reactions: (a) oxidation with benzoyl peroxide in the presence of trifluoroacetic acid; (b) heating with trifluoroacetic acid in the presence of ethylenediaminetetra-acetic acid; (c) treatment with zinc perchlorate.

Scheme 3



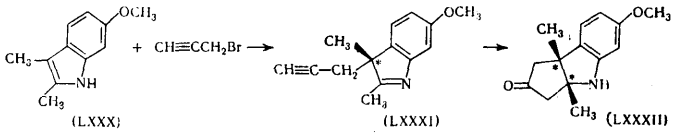
Probably trifluoroacetic acid converts compound (LXXVI) into an open-chain thiolactam which is oxidised by benzoyl peroxide, the sulphur atom being transferred to the methylene group of ring *B*; heating in the presence of ethylenediaminetetra-acetic acid results in the formation of the corrin chromophore; at the beginning of this process the intermediate breakdown of the complex ligand system probably takes place (Scheme 3).

Under the action of triphenylphosphine, the complex (LXXVII) is smoothly converted into compound (LXXVIII), the treatment of which with trifluoroacetic acid leads to the hydrochloride of the corrin base (LXXIX). [68]

4. Studies on the Stereospecific Synthesis of the Corrin Ring in Cobyrinic Acid

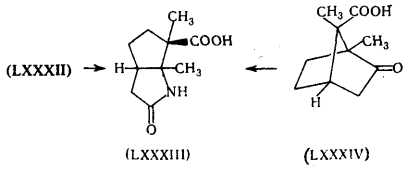
The corrin ring of vitamin B_{12} contains nine asymmetric centres, six of which are in the *A* –*D* ring system. To synthesise the corrin ring of vitamin B_{12} in which eight substituents have the correct absolute orientation, Woodward and Eschenmoser and coworkers obtained compounds which consist of rings *B* and *C* and the *A* –*D* ring system in an optically active form with the corresponding absolute specific configuration [57].

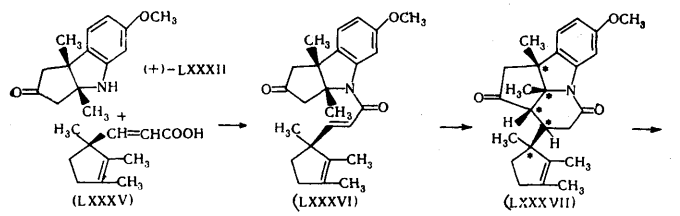
Rings *A* –*D* were obtained from methoxydimethylindole (LXXX). [69] The first asymmetric centre was produced by the reaction of the magnesium derivative of indole (LXXX) with propargyl bromide. Under the action of boron trifluoride and mercury(II) oxide in methanol, propargylindolenine (LXXXI) cyclises stereospecifically, yielding a tricyclic ketone (LXXXII) and forming the second asymmetric centre:

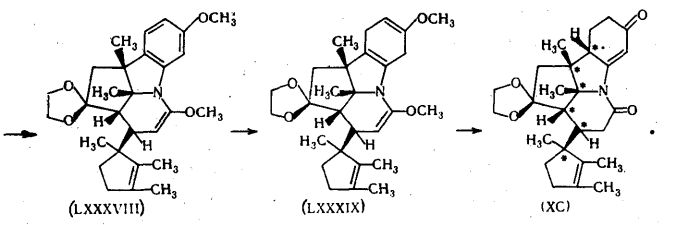


The tricyclic ketone (LXXXII) was separated into optical isomers by crystallising the diastereoisomeric ureas formed by the reaction of the racemic compound (LXXXII) with optically active α-phenylethyl isocyanate.

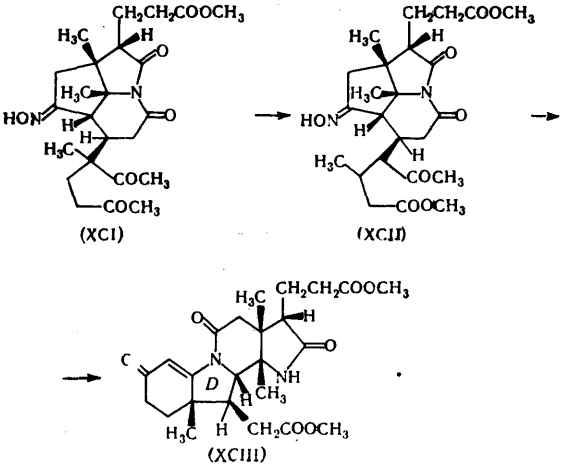
The absolute configurations [57] of the tricyclic ketones (LXXXII) were established by converting the laevorotatory isomer of compound (LXXXII) into the acid (LXXXIII) derived from the tricyclic lactam, which had been obtained from the keto-acid (LXXXIV) with known absolute configuration:



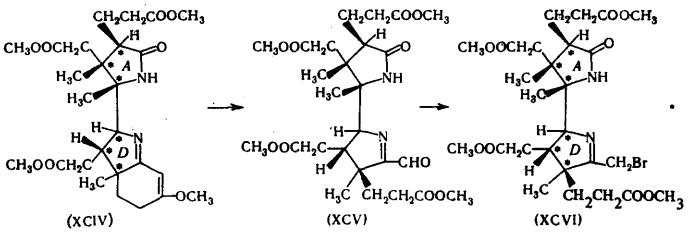




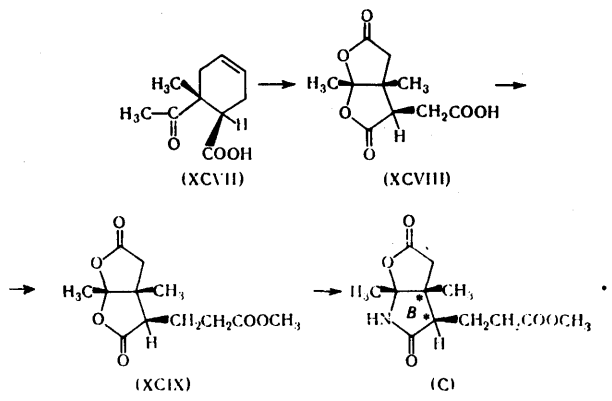
When the dextrorotatory tricyclic ketone (LXXXII) was condensed with the laevorotatory acid (LXXXV), the amide (LXXXVI) was formed, which, on treatment with potassium t-butoxide, gave the pentacyclic lactam (LXXXVII) containing two new asymmetric centres. To protect the active oxo- and carbamoyl groups, compound (LXXXVII) was converted into the ketal of the methoxyenamine (LXXXVIII), which was converted by treatment with lithium in liquid ammonia into the dihydro-derivative (LXXXIX). Acid treatment of compound (LXXXIX) yields the pentacyclenone (XC) with formation of the sixth and last asymmetric centre necessary for the synthesis of the *A* –*D* ring. To introduce a second nitrogen atom into the pentacyclenone (XC) molecule, the protecting ketal group is removed with formation of an oxime, the treatment of which with ozone and then iodic (HIO_3) acid and diazomethane converts it into compound (XCI). This substance is then converted into the keto-ester (XCII), the Beckmann rearrangement of which yields compound (XCIII) with two five-membered nitrogen-containing rings *A* and *D*:



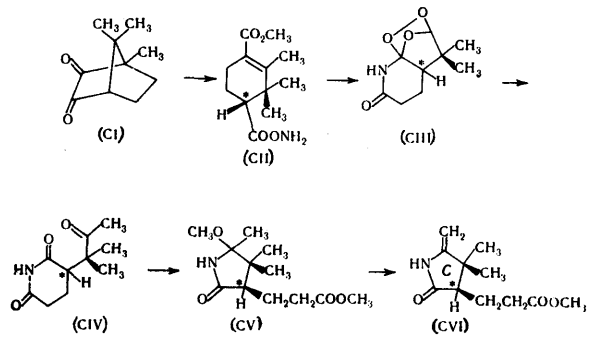
By heating compound (XCIII) with an excess of a base, acidifying, and treating with diazomethane, an isomer differing from compound (XCIII) by the orientation of the propionic acid chain was obtained. Its treatment with a methanol solution of hydrogen chloride leads to compound (XCIV), which, on reaction with ozone, subsequent acidification, and treatment with dimethyl sulphide gives rise to the aldehyde (XCV). The latter is converted into the bromide (XCVI), which constitutes the left-hand half of the vitamin B_{12} molecule:



The synthesis of ring *B* was begun with the condensation of β-acetyl-β-methylacrylic acid with butadiene leading to the cyclohexenecarboxylic acid (XCVII), which was separated into optical isomers by crystallising its salts with optically active α-phenylethylamine. Oxidation of the dextrorotatory acid (XCVII) gave the dilactone acid (XCVIII). By lengthening the acetate chain, the acid (XCIX) was obtained, which, after treatment with ammonia, was converted into the lactam (C), i.e. ring *B*. The absolute configuration of compound (C) was established by converting it into succinimide, the product of the ozonolysis of heptamethyl cobyrinate:

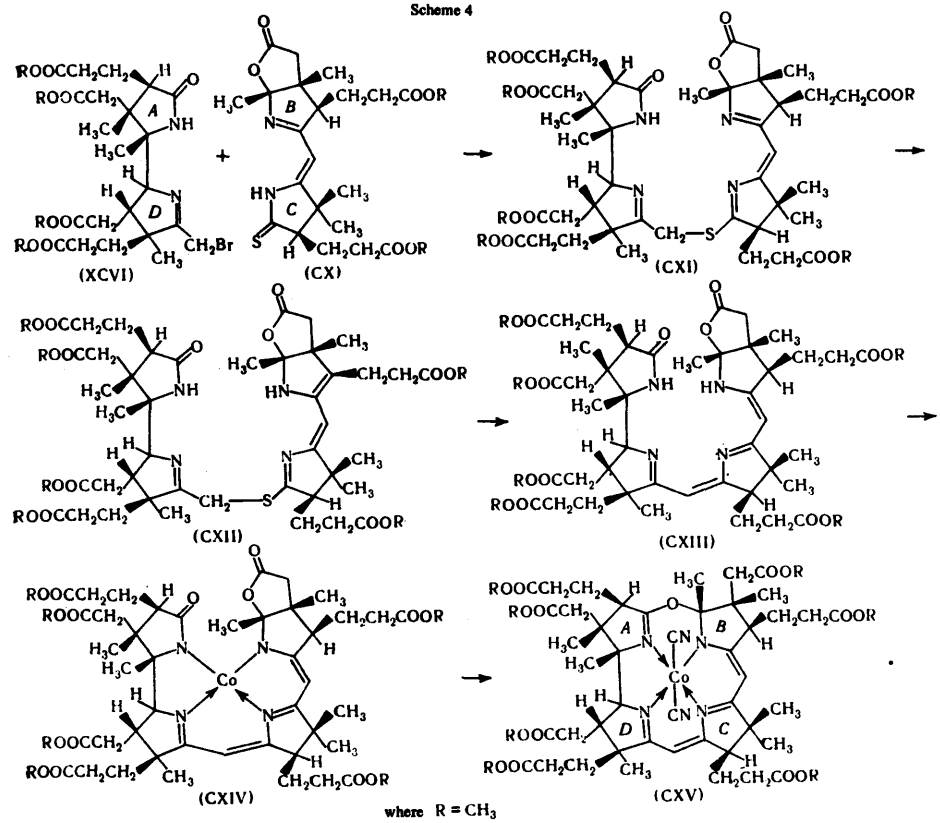


Ring *C* was synthesised from the dextrorotatory camphorquinone (CI), which was converted by a number of reactions into the amide (CII) with formation of the asymmetric centre of the required absolute configuration. Treatment of this amide with ozone leads after a number of reactions to the ozonide (CIII), the reduction of which yields compound (CIV) and the latter is converted in an acid medium into compound (CV). Finally pyrolysis of compound (CV) gives rise to the lactam (CVI), which constitutes ring *C*:

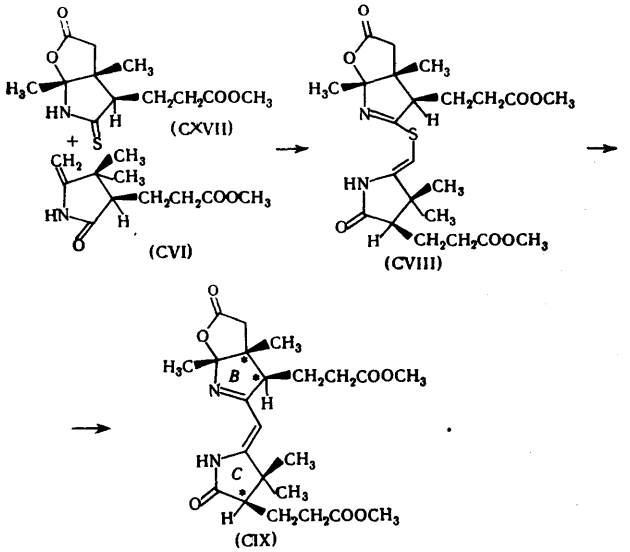


Rings *B* and *C* are joined by the introduced of a sulphur bridge atom [66] (see p. 933). The lactam (C) (ring *B*) is first converted into the thiolactam (CVII). Treatment of compound (CVII) and the enamide (CVI) (ring *C*) with benzoyl peroxide results in the formation of the S-bridge derivative (CVIII), which, on heating with $(C_2H_5O)_3P$, is converted into compound (CIX), constituting the *B*–*C* ring

Scheme 4



system with all the substituents having the correct absolute configuration:



For condensation into corrin, compound (CIX) was converted into the thiolactam (CX), which combines with the bromide (XCVI) in the presence of potassium t-butoxide with formation of the very labile sulphide (CXI). Under the action of aluminium oxide, compound (CXI) is converted into the isomer (CXII), which is desulphurated by treatment with diphenylphosphine, yielding compound (CXIII). The reaction of compound (CXIII) with cobalt perchlorate in acetonitrile in the presence of di-isopropylethylamine yields the cobalt derivative (CXIV). However, treatment of compound (CXIV) with triethyloxonium tetrafluoroborate gave the cyclic ether (CXV) instead of the expected corrin (see Scheme 4).

There is no doubt that cobyrinic acid will be synthesised in the near future.

III. PROPERTIES OF CORRIN SYSTEMS

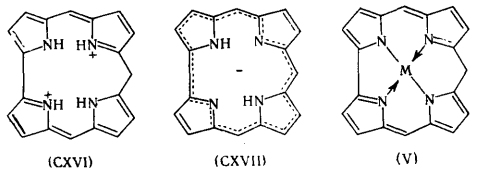
The chemical and physical properties of synthetic corrins, tetradehydrocorrins, and corroles have been little investigated§. Corrin compounds, both as free bases and metal complexes, are crystalline, intensely coloured, high-melting substances. They are sparingly soluble in water and organic solvents and readily soluble in chloroform.

The corrin ring without a metal is a base of moderate strength[68] with a pK of 8.6 (in the 4 : 1 dimethylcellosolve–water solvent).

A. CHEMICAL PROPERTIES

1. Formation and Properties of Metal Complexes

Free corrin systems (corroles and corrins) readily form metal complexes. Under the action of concentrated sulphuric or trifluoroacetic acid, the corrole (IV) [35] is converted into the non-aromatic dication (CXVI), from which the initial corrole is regenerated by treatment with alkali. The addition of dilute alkali to corrole solutions leads to the formation of the stable aromatic anion (CXVII). When corrole is treated with solutions of nickel or cobalt salts in the presence of ammonia, the corresponding metal complexes (V) are formed, the principal structural unit of which is a non-aromatic base corresponding to the dication (CXVI):



The reaction of corrin hydrochloride (LXXIX) with an excess of $Co[(CH_3)_2NCHO]_6[ClO_4]_2$ in acetonitrile yields, after oxidation with air and treatment with cyanide ions, the dicyanide of the cobalt complex 15-cyano-1,2,2,7,7,12,12-heptamethylcorrin[68].

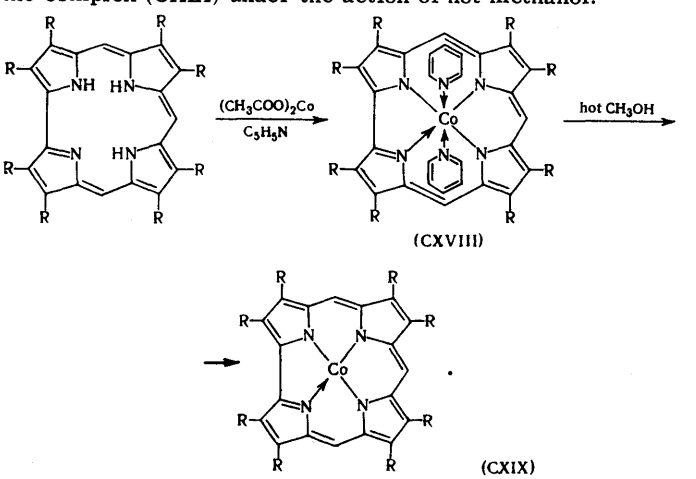
The cobalt and nickel complexes of corrins and 1,19-dimethyltetradehydrocorrins are extremely stable; the metal atom cannot be removed by treatment with strong acids and alkalis[21,47,56]. In this respect the complexes resemble natural cyanocobalamin[2].

Corrin systems are stable. Only two cases of the rupture of the tetracyclic macroring are known: the conversion of 1,19-dialkyltetradehydrocorrins on heating in *o*-dichlorobenzene into porphyrins[23,51] and the oxidation of the nickel complex of 1-methyltetradehydrocorrin to the lactam (XXII) by chromatography on alumina[51]. The mechanism of the oxidation was not established—possibly the 19-hydroxy-1-methyl derivative is formed initially and then converted into the lactam.

In contrast to the cobalt and nickel complexes, the zinc complex of corrin[68] is fairly labile, liberating the metal in an acid medium at room temperature and yielding the hydrochloride of the free base.

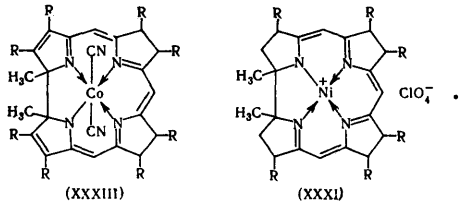
The nickel, cobalt, and copper complexes of corrole are relatively stable[35]. Their solutions are green, becoming red on treatment with alkali with the appearance of a Soret band in the ultraviolet spectra, which indicates the formation of an aromatic system.

The capacity of the cobalt atom to form octahedral complexes is responsible for the high reactivity of the cobalt complexes of corrin systems. The treatment of corrole with cobalt acetate in pyridine[36] results in the formation of the dipyridine complex (CXVIII), which is converted into the complex (CXIX) under the action of hot methanol:



§ The properties of synthetic corrin systems only are considered in the present review. The chemical and physical properties of cobalamins are deal with in other reviews[2,17].

When cobalt complexes of corrin[64] and 1,19-dimethyltetradehydrocorrins[47] are treated with cyanide ions, the corresponding dicyano-compounds are formed. The reduction of the dicyanide (XXXIII) with sodium borohydride followed by treatment with methyl iodide gives rise to spectroscopic changes corresponding to the formation of a derivative with a cobalt–methyl bond. This compound is readily photolysed and after treatment with sodium cyanide is reconverted into the initial complex (XXXIII):



(XXXIII) (XXXII)

The nickel complex (XXXI) is known to react with methyl iodide in an alkaline medium[63], but the structure of the product formed has not been established.

2. Deuterium Exchange

Deuteration of all types of corrinoid systems has been investigated—corrole[35], the nickel complex of 1-methyltetradehydrocorrin[51], and also the nickel and cobalt complexes of corrin[70].

All three *meso*-protons of corroles are rapidly exchanged for deuterium in deuterotrifluoroacetic acid[35], in contrast to porphyrins[71] where there is no exchange in the *meso*-positions under analogous conditions.

The *meso*-protons of the nickel complex of 1-methyltetradehydrocorrin are also exchanged in an acid medium. It was found that in a 0.25 M solution of the complex in deuterotrifluoroacetic acid at 35°C the period required for 50% exchange of the proton in the 10-position is 15 min and that for the protons in the 5- and 15-positions is 11 min[51].

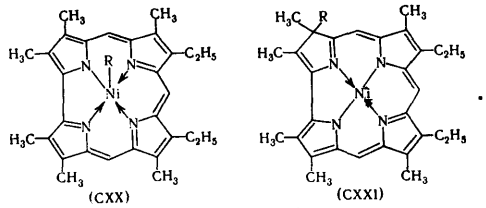
When the dicyanide of the cobalt complex of corrin is deuterated in an acid medium (pD 2, 5 days),[70] all three vinyl *meso*-protons are also exchanged but the allyl protons are not. When the duration of the deuteration process is reduced to 24 h, partial deuterium exchange takes place, preferentially in the 15-position.

The base-catalysed deuteration of the cobalt and nickel complexes of corrins[70] takes place selectively in the 8-position, i.e. the exchange takes place only in the allyl methylene group of ring *B*. The deuteration of the dicyanide of the cobalt complex of corrin under the action of the (1 : 1 t-C_4H_9OD–D_2O)–NaOD–KCN system (concentration of complex 0.071 M, pD 12, duration 7 h, temperature 31°C) is a first-order reaction with respect to corrin, the time required for 50% exchange being 99 ± 5 min. The exchange of protons in the 8-position of the nickel complex of corrin takes place even in the presence of a weak base (1 : 1 pyridine–D_2O, 15 h).

3. Some Reactions of the Corrin Ring

Of the electrophilic substitution reactions in corrin systems, only the cyanation of the nickel and cobalt complexes of corrins[70] and the alkylation of the nickel complexes of corroles[72] and 1-methyltetradehydrocorrins[73] have been investigated. The reaction of the dicyanide of the cobalt complex of corrin with three equivalents of chlorosulphonyl isocyanate followed by treatment with dimethylformamide leads to the 15-cyano-derivative. The cyanation of nickel complexes of corrin and 8,8-dideuteriocorrin[70] also takes place in the 15-position.

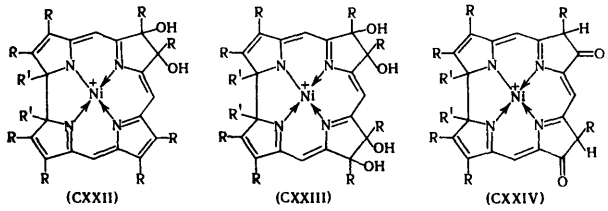
The alkylation of the nickel and cobalt complexes of 1-methyltetradehydrocorrins[73] with alkyl halides involves the 19-position, which results in the formation of salts of the complexes of 1,19-dialkyltetradehydrocorrins[23,51,73]. Methyl, ethyl, n-propyl, allyl, and benzyl groups were introduced in this way into the 19-position. The methylation of corrole[35] under the action of methyl iodide leads to the formation of a mixture of two *N*-methyl derivatives. The alkylation of the nickel complexes of corrole[72] involves the nickel atom with formation of an Ni–C bond, which yields Ni-alkyl derivatives (CXX). When compound (CXX) is heated in chlorobenzene in an atmosphere of nitrogen, a mixture of products is formed, containing the nickel complex of 3,3-dialkylcorrole (CXXI):



(CXX) (CXXI)

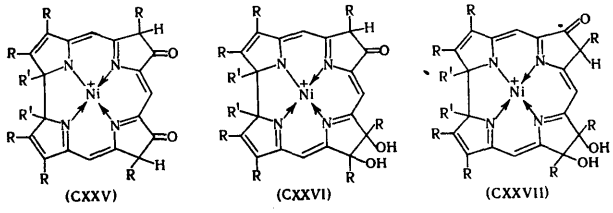
When allyl bromide is used as the alkylating agent[72], the nickel complex of *gem*-allylmethylcorrole (CXXI, R = $CH_2CH=CH_2$), which may be a product of the rearrangement of the Ni-allyl derivative, is isolated immediately.

The oxidation of the nickel complexes of tetradehydrocorrins with osmium tetroxide, leading to a mixture of 7,8-dihydroxytridehydrocorrins (CXXII) and 7,8,12,13-tetrahydroxydidehydrocorrins (CXXIII), has been investigated[74,75]:



(CXXII) (CXXIII) (CXXIV)

In the case of tetradehydrocorrins with free 2- and 18-positions, 2,3,7,8,12,13-hexahydroxydehydrocorrin and 2,3,7,8,12,13,17,18-octahydroxycorrin are formed in addition to compounds (CXXII) and (CXXIII). The pinacol rearrangement of compound (CXXIII) yields a mixture of diketones (CXXIV) and (CXXV):



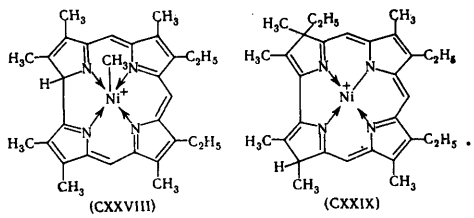
(CXXV) (CXXVI) (CXXVII)

The pinacol rearrangement of compound (CXXII) results in the formation of a mixture of monoketones, which, after treatment with OsO_4, are converted into dihydroxy-ketones (CXXVI) and (CXXVII), compound (CXXVI) being formed in

a greater amount. The structures of compounds (CXXVI) and (CXXVII) were confirmed by the products resulting from the pinacol rearrangement: compound (CXXVI) gives a mixture of compound (CXXIV) and compound (CXXV), while in the case of compound (CXXVII) only compound (CXXIV) is isolated.

Acids have different effects on the free bases of corroles and corrins and their metal complexes. The treatment of corrole with a dilute solution of hydrogen bromide in acetone leads to the formation of a monohydrobromide[34,35], in contrast to porphyrins which give rise to dihydrobromides under similar conditions. Similarly free corrin is isolated as the monohydrochloride[68].

The treatment of the nickel complex of 1-methyltetradehydrocorrin with strong acids, for example perchloric, results in the addition of a proton in the 19-position and the formation of a salt of the nickel complex[23,51]. The deprotonated complex of corrin (LVIII) is converted into the usual corrin complex under the action of hydrochloric or perchloric acid[65]. The nickel complex of the methyl derivative of corrole (CXX) is protonated by trifluoroacetic acid in the 19-position with formation of the complex (CXXVIII), which is converted by bases into the initial complex (CXX). When the nickel complex of *gem*-dialkylcorrole (CXXI) is treated with trifluoroacetic acid, a proton adds in the 17-position with formation of the complex (CXXIX):[72]



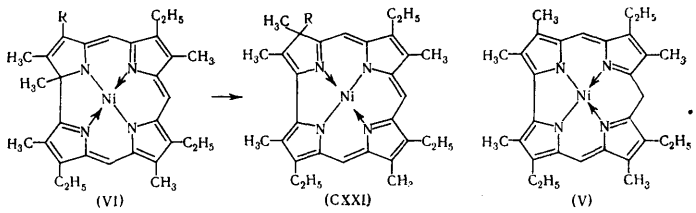
(CXXVIII) (CXXIX)

While alkylation of 1-methyltetradehydrocorrins leads to 1,19-dialkyl derivatives, there are reactions whereby 1,19-disubstituted tetradehydrocorrins are converted into corroles and 1-methyltetradehydrocorrins. The treatment of the perchlorate of the cobalt complex of 1,19-diethoxycarbonyltetradehydrocorrin with a methanol solution of sodium hydroxide at 20°C results in the hydrolysis and decarboxylation of both ethoxycarbonyl groups with formation of the cobalt complex of corrole. Similarly the nitrate of the nickel complex of 19-ethoxycarbonyl-1-methyltetradehydrocorrin is readily converted into the nickel complex of 1-methyltetradehydrocorrin[51].

In contrast to the ease of hydrolysis and decarboxylation of the 1- and 19-ethoxycarbonyl groups of tetradehydrocorrins, the hydrolysis of the 5-cyano-group of corrin complexes[56,64] with subsequent decarboxylation of the carboxylic acid formed takes place only after heating for many hours in an acid medium.

4. Rearrangements of Metal Complexes of Tetradehydrocorrins

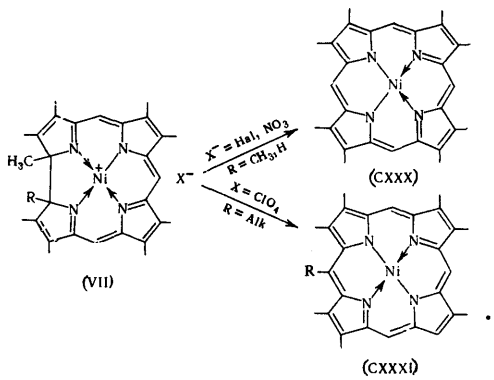
An interesting reaction of the nickel complexes of tetradehydrocorrins is their thermal rearrangement without expansion of the macroring. The nickel complexes of 1-methyltetradehydrocorrins (VI), which have a conjugated system of double bonds locked in the 1-position by an angular methyl group, are converted by refluxing in *o*-dichlorobenzene into nickel complexes of 3,3-dialkylcorrole (CXXI).[73,76] The migration of the angular methyl group from the 1- to the 3-position may be regarded as a sigmatropic shift[77]:



(VI) (CXXII) (V)

The thermal rearrangement of compound (VI) with R = H leads to the nickel complex of corrole of type (V) with formation of the acyclic lactam (XXII) as a side product. Another example of this kind of rearrangement is the formation of compound (CXXI, R = $COOC_2H_5$)[76] by heating the chloride of the nickel complex of 1,19-diethoxycarbonyltetradehydrocorrin in chlorobenzene with elimination of one ethoxycarbonyl group.

The salts of the nickel complexes of 19-alkyl-1-methyltetradehydrocorrins of type (VII) undergo the thermal corrin–porphyrin rearrangement[78] with expansion of the macroring, which leads to the formation of the nickel complexes of unsubstituted porphyrins (CXXX) or *meso*-substituted porphyrins (CXXXI):



(VII) (CXXX) (CXXXI)

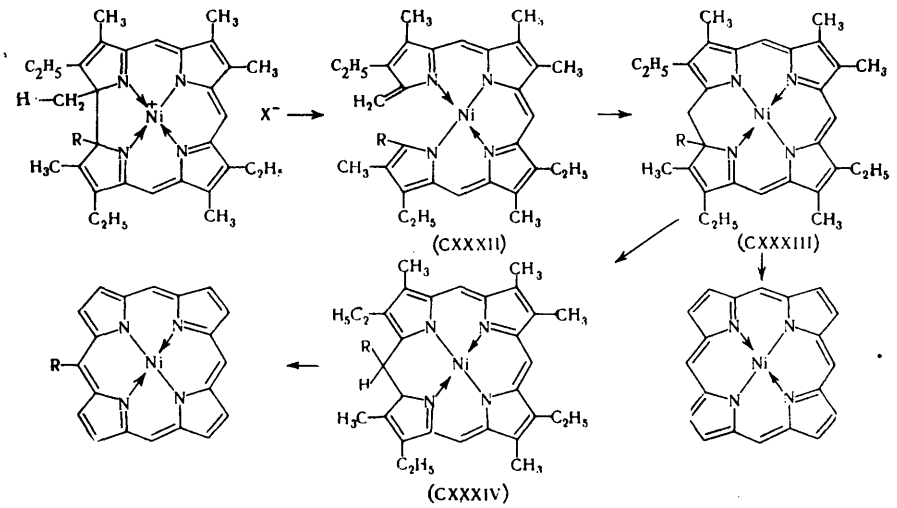
The formation of the nickel complexes of unsubstituted porphyrins takes place with elimination of an alkyl group in the rearrangement of the halides or nitrates of the nickel complexes of 19-alkyl-1-methyltetradehydrocorrins. The salts of the nickel complexes of 1,19-dimethyl- and 1-methyltetradehydrocorrins, containing any anion, give rise to the nickel complexes of substituted porphyrins, while the neutral nickel complex of 1-methyltetradehydrocorrin rearranges to 3,3-dialkylcorrole. This difference in thermal rearrangement is due to the presence of a positive charge in the macroring of salts of type (VII).

Perchlorates give rise mainly to *meso*-alkylporphyrins, formed by the migration of the alkyl group without isomerisation of its carbon framework; an exception is the 19-allyl derivative which is converted into *meso*-propenylporphyrin[78].

The first stage in the corrin–porphyrin rearrangement is the formation of an intermediate bilatriene complex (CXXXII) with elimination of a proton from the angular methyl group, the anion behaving as a base. The complex (CXXXII), containing a benzylidene instead of a methylene group, was isolated after the rearrangement of the bromide of the nickel complex of 19-benzyl-1-methyltetradehydrocorrin (see Scheme 5).

The cyclisation of compound (CXXXII)[78] leads to the complex (CXXXIII), which, after the migration or elimination of the alkyl group, is converted into a substituted or

Scheme 5



unsubstituted porphyrin. The type of porphyrin formed depends on the anion. The perchlorate ion, in the presence of which *meso*-substituted porphyrins are formed, has oxidising properties and the corrin–porphyrin rearrangement of perchlorates takes place via the cation (CXXIV).

The study of the rearrangement of the perchlorates of the nickel complexes of 1,19-dialkyltetradehydrocorrins with unsubstituted 2- and 18-positions showed that in this case the products are only *meso*-alkylporphyrins, i.e. there is no migration of the alkyl group to the adjacent free β-position.

The thermal corrin–porphyrin rearrangement of the chloride of the nickel complex of decamethyltetradehydrocorrin takes place anomalously, the product being the unsubstituted porphyrin and porphyrin oxide.

B. SPECTROSCOPIC PROPERTIES

One of the most important characteristics of tetrapyrrole macrocyclic systems is their absorption in the visible and ultraviolet regions. The electronic absorption spectra of the solutions of all corroles in chloroform have an intense absorption band at about 400 nm [30,34,35] (the Soret band) which indicates the aromaticity of the corrole ring. In concentrated sulphuric acid the Soret band disappears, i.e. corrole is converted into the non-aromatic dication (CXVI) (p. 937). The addition of dilute alkali to corrole solutions alters the spectrum, but the Soret band persists, which indicates that the anion (CXVII) is aromatic [35,36] (p. 937).

All corroles absorb at 396–399 nm (Soret band) and at 536–545, 550–553, and 592–594 nm. The Soret band persists in the spectrum of corrole hydrobromide [35] but there is additional absorption at 577 nm.

The spectra of the neutral complexes of corroles (V) (p. 937) do not contain the Soret band [35]; nickel complexes show a characteristic absorption at 360 and 659 nm, cobalt complexes absorb at 389, 499, and 528 nm, and finally copper complexes absorb at 397 and 548 nm. The salts of the nickel and cobalt complexes of 1,19-disubstituted tetradehydrocorrins (VII) (p. 927) have three characteristic absorption regions [47]: 273–278, 352–360, and 557–572 nm. The replacement of angular methyl groups by ethoxycarbonyl groups does not alter the spectrum [appreciably], the 557 nm band undergoing a bathochromic shift by 15 nm only, probably due to steric factors.

The presence of *meso*-methyl groups [47] has a considerable influence on the absorption of tetradehydrocorrins; when a *meso*-methyl group is introduced, the 557 nm band undergoes a bathochromic shift. The spectral shifts caused by the methyl group in the 10-position are equivalent to the overall effect of the methyl groups in the 5- and 15-positions; in both cases the 557 nm band is displaced by 45 nm and is located at 600 nm.

When the nickel complexes of 1-methyltetradehydrocorrins (XXI) (p. 930) are protonated by strong acids [23,47], the products are salts, the visible spectra of which are similar to those of the salts of the nickel complexes of 1,19-dimethyltetradehydrocorrins (XVIII) (p. 929). The spectra of the nickel and cobalt complexes of synthetic corrin [56,64] are typical for vitamin B_{12}. The visible spectrum of the dicyanide of the cobalt complex of 1-methylcorrin obtained by the reduction of the corresponding tetradehydrocorrin [23] coincides fully with the spectrum of cyanocobalamin [2].

Infrared spectroscopy has not been used quite as widely to characterise corrin systems. In the spectra of the nickel [56], cobalt [64], and zinc complexes of corrin and also in the spectrum of corrin hydrochloride [68] there are two intense bands in the region of the C=C and C=N absorption at 1592 and 1508 cm^{-1}, which are characteristic of the corrin chromophore and are present in the same region in the spectrum of cobyrinic acid [79].

The infrared spectra of the nitrates and perchlorates of the nickel and cobalt complexes of 1,19-disubstituted tetradehydrocorrins and also of the dicyanide of the cobalt complex of 1,19-dimethyltetradehydrocorrin [47] have been recorded; the spectra of the salts show absorption characteristic of the nitrate and perchlorate ions. In the spectra of compounds with angular ethoxycarbonyl groups there are bands at 1730–1740 cm^{-1} due to the ester carbonyl group, which is consistent with the presence in the tetradehydrocorrins of an ethoxycarbonyl group attached to an aliphatic carbon atom, while the ester carbonyl groups of biladienes, linked to unsaturated carbon atoms, absorb at 1695–1710 cm^{-1}.

Nuclear (proton) magnetic resonance spectra have been most widely used to establish the structures of tetrapyrrole macrocyclic compounds.

The NMR spectrum of 2,3,8,12,17,18-hexaethyl-7,13-dimethylcorrole[35], recorded in deuterochloroform using tetramethylsilane as standard contains a 0.88 τ singlet (5- and 15-*meso*-protons), a 1.18 τ singlet (10-*meso*-proton) a broad 13.48 τ singlet (the three protons of the NH groups), three partially overlapping quartets with the centre at 6.18 τ (the twelve protons of the methylene groups in the ethyl substituents), a 6.72 τ singlet (the six protons of the methyl groups), and three partially overlapping triplets with the centre at 8.30 τ (the 18 protons of the methyl groups in the ethyl substituents).

The NMR spectra of the chloride[36] and nitrate[47] of the nickel complex of 1,19-dimethyltetradehydrocorrin showed the following signals: a 9.34 τ singlet (the two angular methyl groups), a 2.41 τ singlet (the three *meso*-protons), a 7.30 τ singlet (the six methyl groups), and 8.54 τ triplet (the two methyl groups in the ethyl substituents), and a 6.83 τ quartet (the two methylene groups in the ethyl substituents).

The abnormally high signal due to the angular methyl groups (9.34 τ) is caused by the closeness of the $\beta\beta$-double bonds of the adjacent *A* and *D* rings, although it may be the result of the increasing drawing together of the cyclic system in consequence of the sp^3 hybridisation of both the 1- and 19-carbon atoms. The positive charge of the metal in the salts of 1,19-dimethyltetradehydrocorrins can lead to the de-screening of the protons of the 1- and 19-methyl groups, but this effect should be slight. In support of this hypothesis, one may say that neither vitamin B_{12} [80] nor synthetic corrin[56], which do not have a $\beta\beta$-double bond in rings *A* and *D*, give rise to signals in excess of 9 τ.

According to steric considerations the 1- and 19-substituents should be located on the opposite sides of the macroring.

The planar salts of the cobalt complexes of 1,19-dimethyltetradehydrocorrins are paramagnetic but the dicyanide octahedral complex[47] has a spectrum in which the angular methyl groups give rise to a signal of 9.26 τ.

The introduction of a 10-*meso*-methyl group results in a 6.83 τ singlet characterising this group, and reduces the intensity of the 2.55 τ singlet (two *meso*-protons), the remaining signals being unchanged. The spectrum of the nickel complex of 1,5,15,19-tetramethyltetradehydrocorrin reveals the presence of only one *meso*-proton (2.50 τ singlet), the 5- and 15-methyl groups giving rise to a 6.82 τ singlet and the two angular methyl groups to a 9.42 τ singlet[47].

The spectra of all the neutral nickel complexes of 1-methyltetradehydrocorrins[23,50,51] have an 8.5 τ singlet due to the three protons of the angular methyl group. The angular groups of the nickel complexes of 1-ethyl- and 1-isopropyl-tetradehydrocorrins[51] are characterised by 9.59 τ (ethyl) and 9.58 τ and 9.55 τ (isopropyl) singlets. The shielding of the angular alkyl groups can be accounted for by their closeness to the π-electron system of ring *A*, the degree of shielding depending strongly on the dimensions of the angular groups.

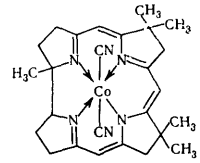
The protonation of the nickel complexes of 1-methyltetradehydrocorrins by strong acids results in the formation of salts the angular methyl groups of which are characterised by a 9.38 τ singlet[50] and the proton in the 19-position by a 6.73 τ singlet[51]; as for the metal complexes of 1,19-dimethyltetradehydrocorrins, the high signal due to the angular methyl group is caused by its interaction with the $\beta\beta$-double bond of the adjacent ring.

In the spectra of the nickel complexes of 1-methyltetradehydrocorrins[51] with several β-methyl substituents, the signal of one of them is at 8 τ, while those of the remaining methyl groups are at 7.6–7.8 τ. The study of the NMR spectra of many metal complexes of 1-methyltetradehydrocorrins with β-methyl substituents in various positions led to the conclusion that the shift of the signal to 8 τ is caused by the methyl group in the 3-position. Molecular models show that the substituents cluster together near the 1-, 2-, 18-, and 19-positions, i.e. the direct bond between rings *A* and *D* is protected.

The signals due to the *meso*-protons of the neutral nickel complexes of 1-methyltetradehydrocorrins[51] are at 2.8, 3.0, and 4.0 τ, while the analogous signals of the salts are at 2.4–2.5 τ (C_{10}) and 2.65–2.8 τ (C_5 and C_{15}). The lower chemical shift of the signals due to the *meso*-protons shows that the deshielding effect of the nickel cation is directed to the *meso*-positions. For example, the three *meso*-protons of the salts of the nickel complexes of 1,19-dimethyltetradehydrocorrins give rise to one or two singlets at 2.5 τ,[47] in contrast to porphyrin salts[81].

The signal due to the *meso*-proton of the nickel complex of 1-isopropyltetradehydrocorrin at 2.88 τ has the form of a sharp singlet, while the other two *meso*-protons give rise to very broad signals at 3.3 and 4.13 τ; the *meso*-protons of the nickel complex of 1-methyltetradehydrocorrin are characterised by three sharp singlets. Possibly in 1-isopropyltetradehydrocorrin the conformation equilibrium is established slowly along the axis passing through C_{10} and the C_1-C_{19} bond, similarly to the analogous effect in annulenes[82].

In the NMR spectra of the nickel and cobalt complexes of corrin[56,65] the positions, structures, and intensities of all the signals correspond to the following hypothetical molecular structure:



In the NMR spectrum of the dicyanide of the cobalt complex of corrin[70] in $CDCl_3$ there are signals due to five methyl groups, two non-allylic methylene groups, four allylic methylene groups, and three vinyl *meso*-protons, which are characterised by singlets at 4.60, 4.56, and 4.44 τ; the last refers to the proton in the 15-position and is very broad due to the spin–spin interaction with the protons of the allyl group of ring *C*, the signal of which is also a diffuse singlet at 7.16 τ. The methylene group in the 8-position is characterised by a singlet at 7.09–7.07 τ and the methylene groups in the 3- and 17-positions are characterised by a multiplet at 6.9 τ.

In the NMR spectrum of the nickel complex of corrin the *meso*-proton in the 15-position gives rise to a weak triplet; it has been established by the double resonance method that the triplet is due to the spin–spin interaction of the *meso*-proton with the methylene group of ring *C*.

The NMR spectra of the corrins (XXXI) and (XXXIV) [23] (p. 931), obtained by the hydrogenation of tetradehydrocorrins, show that none of the β-methyl groups is [part of] an olefinic substituent: the three *meso*-protons of corrin (XXXI) give rise to singlets at 3.93 and 4.04 τ and the *meso*-protons of compound (XXXIV) are characterised by a broad singlet at 4.5 τ.

As already noted, NMR spectroscopy is the principal method for the establishment of structures of tetrapyrrole macrocyclic compounds. This is particularly true as regards the determination of the structures of the reduction products of tetradehydrocorrins.

In the studies on the synthesis of corrins a number of tetrapyrrole macrocyclic compounds with different degrees of unsaturation were isolated. The metal complex (XXIV)[53] (p. 930), which has nine double bonds, is characterised by three singlets between 7.45 and 7.69 τ (aromatic methyl group), two doublets at 8.38 and 8.62 τ (aliphatic methyl group), and a singlet at 8.8 τ (angular methyl group).

The chelate complexes (XXVI),[53] (XXXII),[63] and (XXXIII)[47] (pp. 930 and 931) each contain eight eight double bonds. In the NMR spectra of these compounds there are signals due to the three *meso*-protons (singlets at 2.41–3.13 τ) [in the case of compound (XXVI) one *meso*-proton gives rise to a doublet] and signals arising from the methyl groups attached to the unsaturated carbon atoms (singlets at 7.55–7.75 τ). In the spectrum of compound (XXVI) there are singlets at 8.31 and 8.43 τ produced by the *gem*-methyl groups.

Compound (XXIX) contains seven double bonds[47] (p. 931). The spectrum of this compound is very complex, but certain assignments have been made: the *meso*-protons are characterised by three singlets near 4.4 τ, which coincide with the signals from the synthetic nickel complex of corrin[56]; the intensity ratios are not 1 : 1 : 1, probably because of the presence of several stereoisomers. The 7.97 τ singlet is due to the protons of the two olefinic methyl groups, which indicate the retention of the $\beta\beta$-double bond in ring *A* or *D*. The 9.22 τ singlet, corresponding to three protons, suggests the screening of one angular methyl group by the $\beta\beta$-double bond of an adjacent ring. Finally a complex series of peaks at 8.6–9.1 τ characterise the β-methyl groups attached to the aliphatic carbon atoms and the signals at 6.7–7.4 τ characterise the β-protons of the reduced rings.

In conclusion it should be noted that the development of the chemistry of corrin systems is still in the initial stage. Future studies will undoubtedly reveal many interesting and important facts in this field as well as theoretical generalisations, which will make it possible to synthesise natural biocatalytic systems and biologically active structures similar to them.

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