Translated from *Uspekhi Khimii*, **49**, 2132-2158 (1980) U.D.C. 547.324;547.402

Synthesis of Corroles and Octadehydrocorrins

N.S.Genokhova, T.A.Melent'eva, and V.M.Berezovskii

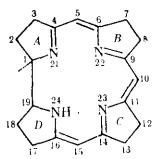
A survey has been made of methods for the synthesis of corroles and their complexes with various metals, and also methods for the synthesis of metal complexes of 1,19-disubstituted octadehydrocorrins from biladienes, bilenes, and bilatrienes and of nickel complexes of 1-substituted octadehydrocorrins by the oxidative and non-oxidative cyclisation of biladienes. Aspects of the structure of corroles and metal complexes of corroles and octadehydrocorrins are discussed. A list of 76 references is included.

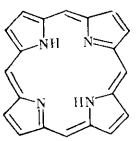
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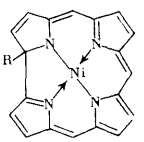
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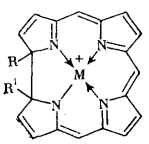
I. INTRODUCTION

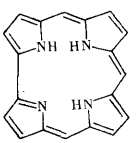
Corroles and octadehydrocorrins are tetrapyrrole macrorings related both to corrin (I)—a partly hydrogenated tetrapyrrole system present in biological catalysts, e.g.vitamin B_{12} and its coenzymes—and to porphyrin (II), which forms the framework of chlorophyll, haemin, and cytochromes.

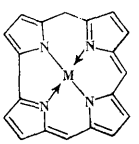

(I)


(II)


(III)


(IV)


(V)


(VI)

Octadehydrocorrins† are known as the neutral nickel complexes of 1-substituted derivatives (III) and in the cationic form of metal complexes of 1,19-disubstituted derivatives (IV). Corroles (V), like octadehydrocorrins, contain a direct $\alpha\alpha'$-bond between two pyrrole rings, but unlike them are aromatic compounds, thereby approaching the porphyrin system (II). Corroles are known also as metal complexes (VI).

Corroles and metal complexes of octadehydrocorrins differ from porphyrins and also corrins both in chemical and physicochemical properties and in methods of synthesis. Furthermore, the cobalt complexes of octadehydrocorrins catalyse the oxidation of reduced nicotinamide–adenine dinucleotide, one of the most important links in the electron-transport system of the living cell[2]. It is therefore of undoubted interest to examine routes and methods for the synthesis of corroles and octadehydrocorrins.

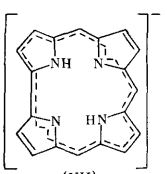
Foreign reviews[3-8] covering the synthesis of tetrapyrrole macrorings devote only individual chapters to corroles and octadehydrocorrins. The main advances in this field were surveyed[9] in 1969. The present Review covers all published information on methods for the synthesis of corroles and octadehydrocorrins, paying special attention to work appearing during the past decade.

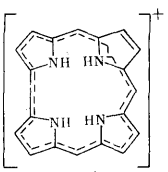
† The name *octadehydrocorrin* applies to the macroring in (III) and (IV); it has been recommended by the Commission for Biochemical Nomenclature of the International Union of Pure and Applied Chemistry and the International Union of Biochemistry[1].

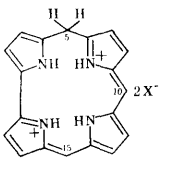
II. SYNTHESIS OF CORROLES

1. Structure and Properties of Corroles

The search for synthetic routes to corrin led to the synthesis of corroles (V), which forms red crystals. It contains an aromatic cyclic system with eighteen π-electrons, as indicated by an intense Soret band (~400 nm) in its electronic absorption spectrum, which contains also bands in the region of 540, 550, and 600 nm.[10]


(VII)


(VIII)

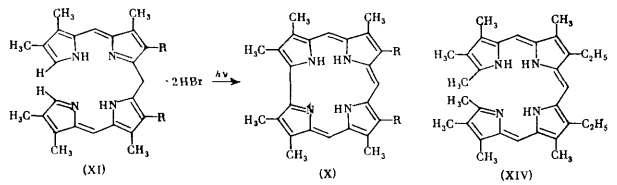

(IX)

Addition of dilute alkali to solutions of corroles readily converts them into stable aromatic anions (VII),[10-12], which distinguishes them in particular from porphyrins[13]. Corroles readily undergo monoprotonation when treated with a dilute solution of hydrobromic acid in acetone. This involves formation of crystalline monohydrobromides, existing as aromatic ambident cations (VIII).[12] The green solutions of corroles in concentrated sulphuric acid do not contain a Soret band in the electronic spectrum, which indicates the appearance of the "blocked" conjugated structure of the tautomeric non-aromatic dication (IX) with the additional protonation at carbon atom 5,[11] not at $C_{(10)}$ as assumed previously[10,11]. Addition of alkali to a solution of the dication (IX) converts the latter back into the original corrole (V).

2. Synthesis of Corroles from Biladienes-*ac*

The free bases of corroles (X) have been synthesised from 1,19-dideoxybiladienes-*ac* (XI) containing hydrogen atoms at positions 1 and 19, by the photocyclisation of their dilute methanolic solutions in the presence of a small excess of

ammonia or aqueous sodium acetate[11,14], and also by the photocyclisation of aqueous solutions in the presence of ammonia and potassium hexacyanoferrate(III):[15]

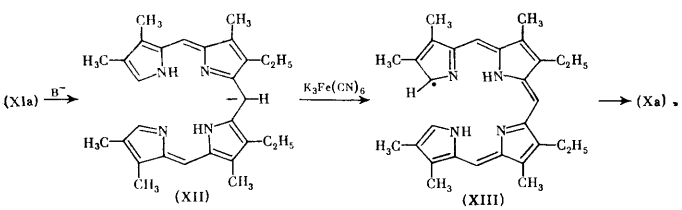


(XI) (X) (XIV)

a) R = C_2H_5, b) R = $CH_2CH_2COOH_3$

On the assumption that formation of corroles had a free-radical mechanism[16,17] an examination was made of the influence of various initiators (of free-radical processes) and one-electron oxidising agents on cyclisation of the 1,19-unsubstituted biladiene-*ac* (XIa). It was found that cyclisation occurred very rapidly in the presence of ammonia and potassium hexacyanoferrate(III), iron(III) chloride, cerium sulphate, and hydrogen, benzoyl, and t-butyl peroxides; in all cases the corresponding corrole (X) was isolated in 68 to 84% yield[16].

These reactions require the presence of a base, which indicates initial detachment of a proton from a 10-methylene group of biladiene during photocyclisation. This is confirmed by the fact that 10,10-dimethylbiladienes are not cyclised to a corrole[18]. Formation of corroles is appreciably accelerated by ultraviolet irradiation of solutions of biladienes; yet replacement of atmospheric oxygen by nitrogen has no appreciable effect on the course of the reaction. Cyclisation apparently involves successive formation of an anion (XII) and an intermediate radical (XIII):

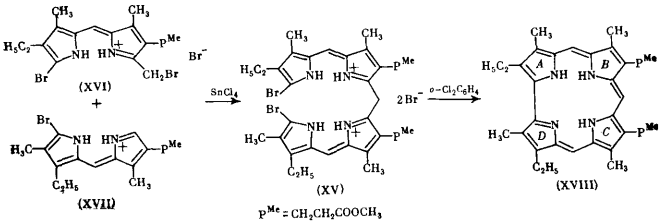


(XII) (XIII)

In an attempt to synthesise the corrole (X) from 1,19-dimethylbiladiene-*ac* ultraviolet irradiation of the methanolic solution yielded mainly the bilatriene (XIV) with some porphyrin[19].

The synthesis of corroles[10] by the photolysis of alkaline solutions of biladienes-*ac* in which positions 1 and 19 are unsubstituted is restricted by the methods for obtaining these intermediate compounds, in whose formation the degree of symmetry of the β-substituents plays an important part.

Corroles having an unsymmetrical arrangement of β-substituents have been obtained by the thermal cyclisation of 1,19-dibromobiladienes-*ac*. Thus 1,19-dibromo-1,19-dideoxybiladiene-*ac* dihydrobromide (XV), obtained by condensation of the dipyrromethene (XVI) with the 5′-unsubstituted 5-bromodipyrromethene (XVII) in the presence of tin(IV) chloride, was converted into the corrole (XVIII) by boiling with *o*-dichlorobenzene[20]:

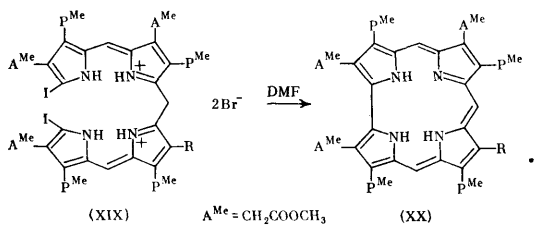


(XVI) (XVII) (XV) (XVIII)

P^{Me} = $CH_2CH_2COOCH_3$

Corroles having non-alkyl β-substituents in rings A and D were unknown until 1975,[21] perhaps because groups larger than methyl in positions 2 and 18 prevent the photocyclisation of 1,19-biladienes-*ac*.[10]

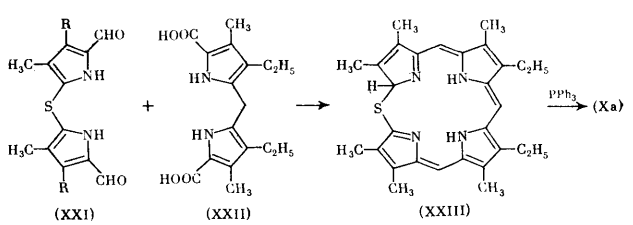
A more promising method for synthesising corroles having different substituents in rings A and D was thermal cyclisation of 1,19-dibromobiladienes-*ac* (XV) in *o*-dichlorobenzene[20] or of 1,19-di-iodobiladienes-*ac* (XIX: R = CH_3, A^{Me}) in dimethylformamide (DMF).[21] 1,19-Dideoxy-1,19-di-iodobiladienes-*ac* (XIX) with acetic and propionic residues in β-positions were more reactive than the corresponding 1,19-dibromo-derivatives[20], the former yielding corroles (XX: R = CH_3, A^{Me}) when heated in DMF:[21]



(XIX) A^{Me} = CH_2COOCH_3 (XX)

3. Synthesis of Corroles via Sulphur-containing Compounds

Corroles have been obtained by cyclising linear dipyrrole compounds containing sulphur. The condensation of bis-5-formylpyrrol-2-yl sulphide (XXIa) with methane-2,2′-dipyrrole-5,5′-dicarboxylic acid (XXII) at −10 °C in the presence of hydrogen chloride gives a 10–20% yield of a dark red product (XXIII), which when boiled with excess of triphenylphosphine in *o*-dichlorobenzene is converted into the corresponding corrole (Xa):[22]

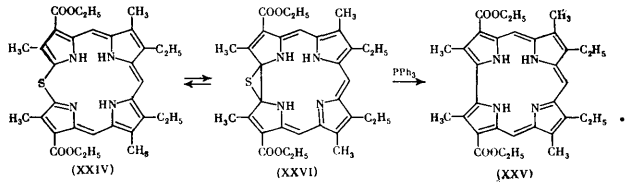


(XXI) (XXII) (XXIII)

a) R = CH_3, b) R = $COOC_2H_5$

However, when the sulphide (XXIb) is condensed with the dicarboxylic acid (XXII), the dark blue crystalline *meso*-thiaphlorin (XXIV) of non-aromatic character is obtained[22], whose desulphurisation in boiling *o*-dichlorobenzene leads to

formation of the corrole (XXV) in 35–40% yield, apparently with intermediate formation of a thi-iran derivative (XXVI):[8]



(XXIV) (XXVI) (XXV)

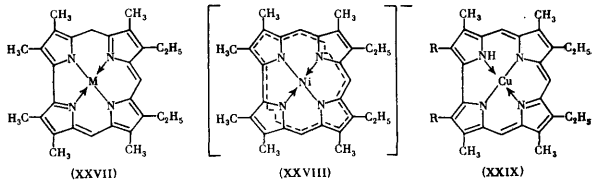
Conducting the reaction in the presence of triphenylphosphine increases the yield of the corrole (XXV) to 60%.

III. SYNTHESIS OF METAL COMPLEXES OF CORROLES

1. Structure of Complexes of Corrole with Bivalent Metals

In metal complexes of corrole a bivalent metal (zinc, nickel, palladium) replaces only two of the three imino-hydrogen atoms; the third hydrogen atom moves to another site in the chromophore. The aromatic conjugated system is disrupted in such complexes, as indicated by the absence of an intense Soret band from the electronic spectra of the above three metal complexes[10,15,23,24]. Such absence indicates that these complexes (XXVII: M = Ni, Pd) are derivatives of a tautomeric non-aromatic base corresponding to a dication of type (IX).[12]

For a long time the site of the "extra" hydrogen atom in the ligand could not be established, since the paramagnetic nature of nickel octa-alkylcorroles prevented the use of nuclear magnetic resonance spectroscopy for this purpose. The atom was arbitrarily located at $C_{(10)}$.[15] In order to solve this structural problem an examination was made of the protonation of corrole in fluorosulphuric acid, which established that in the formation of dications protonation is considerably more rapid at $C_{(5)}$ than at $C_{(10)}$.[12] On this basis the structure (XXVII) was ascribed to complexes of corroles with bivalent metals.



(XXVII) (XXVIII) (XXIX)

a) R = C_2H_5, b) R = CH_3.

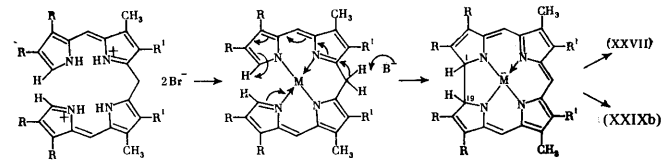
Addition of alkali to the green solutions of the nickel complex of corrole (XXVII: M = Ni) produces a Soret band in the electronic spectrum, apparently owing to formation of the stable ambident aromatic anion (XXVIII), whose solutions are red. This colour change is reversed on acidification.

Spectral data for the copper complexes of corroles indicate the presence of a continuous π-chromophore, and therefore the formula (XXIX) was suggested[15].

2. Synthesis of Nickel, Copper, Zinc, and Palladium Complexes of Corrole

Metal complexes of corroles can be obtained both by the cyclisation of 1,19-disubstituted 1,19-dideoxybiladienes-*ac* in the presence of metal acetates in hot methanol and by introduction of the metal into the free base of corrole[10].

Corrole complexes of nickel (XXVII: M = Ni) and copper (XXIXb) have been synthesised by the ultraviolet irradiation of methanolic solutions of biladienes-*ac* (XXX) containing terminal hydrogen atoms, in the presence of nickel or copper ions and a base[10,11]. Initially a metal–biladiene complex (XXXI) is apparently formed, in which the metal has a coordinating effect on positions 1 and 19, draws them together, and thereby facilitates cyclisation:

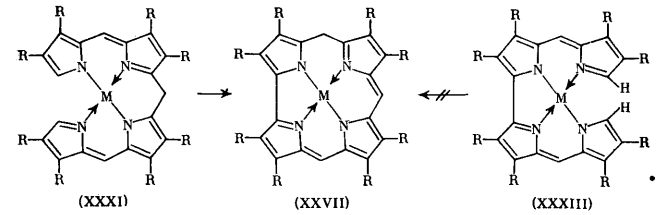


(XXX) (XXXI) (XXXII), M=Ni, Cu

a) R = CH_3, R' = C_2H_5; b) R = R' = CH_3; c) R = R' = C_2H_5.

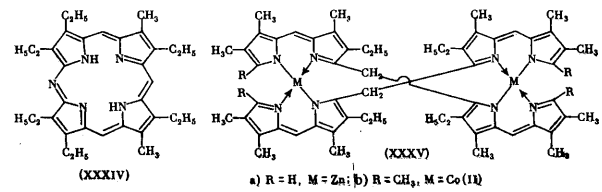
In the presence of a base a proton is detached from the $C_{(10)}$ atom in the metal complex (XXXI) and an anion (XXXII) is formed, which then passes into a neutral metal–corrole complex, (XXVII)[10,11] or (XXIX)[15] depending on the metal.

Whereas metal–corrole complexes (XXVII) are readily formed from metal–biladiene complexes (XXXI),[10] it has not proved possible to cyclise metal complexes of 5,5'-bisdipyrromethenes (XXXIII), which also contain terminal hydrogen atoms[18]:



(XXXI) (XXVII) (XXXIII)

Bulky β-substituents present at positions 2 and 18 in a biladiene-*ac* deactivate positions 1 and 19, and have an adverse influence on formation of a direct αα'-bond. Other reactions can then occur, e.g. formation of the azaporphyrin (XXXIV) by photocyclisation of an ammoniacal solution of the biladiene-*ac* (XXXc) containing ethyl groups at positions 2 and 18, whereas the corresponding 2,18-dimethylated compounds are converted under these conditions into a corrole[10].

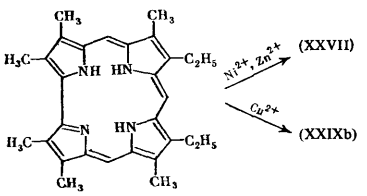


(XXXIV) (XXXV)

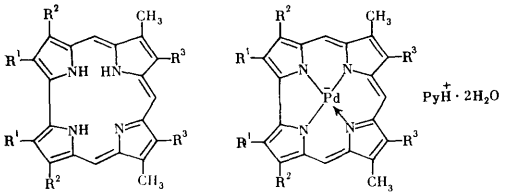
a) R = H, M = Zn; b) R = CH_3, M = Co(II).

Zinc–biladiene-*ac* complexes could not be converted into corroles[10], since they have a tetrahedral configuration (XXXVa),[25] with the terminal α-hydrogen atoms occupying positions unfavourable to formation of a direct αα'-bond.

Corrole complexes of bivalent zinc and nickel (XXVII: M = Ni, Zn) and also copper (XXIXb) were obtained[10] by adding the cations to a solution of the corrole (XXXVI) in either pyridine or aqueous ammonia:

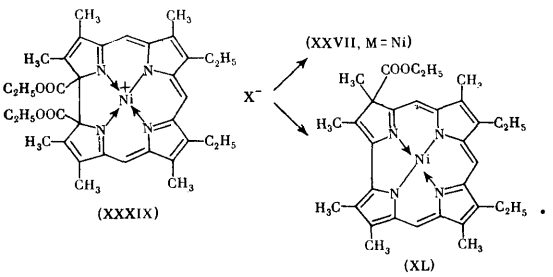


Treatment of the corrole (XXXVII) with palladium acetate in pyridine solution leads to the formation of crystalline pyridinium salts of palladium–corrole anions (XXXVIII) in 89–92% yield, isolated as the dihydrates[15], which are aromatic like the original corrole (XXXVII). On treatment with acids these salts pass into unstable, apparently neutral palladium complexes of the corroles, which could not be isolated.



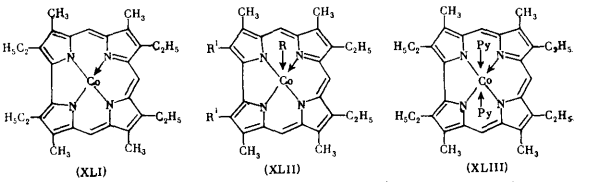
a) $R^1 = R^3 = CH_3$, $R^2 = C_2H_5$; b) $R^1 = R^3 = C_2H_5$, $R^2 = CH_3$

Nickel–corrole complexes can be obtained[26,27] from the corresponding complex of the octadehydrocorrin (XXXIX) containing angular ethoxycarbonyl substituents. Successive hydrolysis and decarboxylation of the angular groups in the complex (XXXIX: X = NO_3) gave the nickel–corrole complex (XXVII),[26] but heating the nitrate or chloride of octadehydro-1,19-diethoxycarbonylcorrin (XXXIX: X = NO_3, Cl) in chlorobenzene led to isolation of the nickel–corrole complex (XL):[27]



3. Structure and Properties of Cobalt Complexes of Corrole

Two types of cobalt–corrole complexes are known, the first of which do not contain axial ligands. Because of their paramagnetism they were originally regarded as cobalt(II) complexes[10], but are paramagnetic square–planar cobalt(III)–corrole complexes (XLI).[28–30] Complexes of the second type are formed in the presence of pyridine, triphenylphosphine, or *p*-tolyl isocyanate, and are five-coordinated cobalt(III)–corrole complexes (XLIIa–d) containing these compounds as axial ligands[31]. Addition of excess of pyridine to solutions of both types of complexes leads to the formation of octahedral dipyridine–cobalt(III)–corrole (XLIII), which is stable only in the presence of excess of pyridine[31].



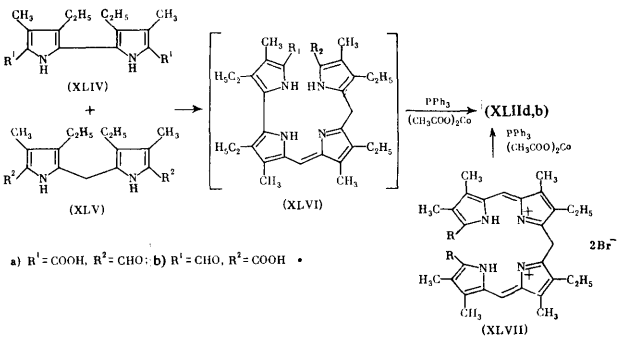
a) R = Py, $R^1 = C_2H_5$; b) R = PPh_3, $R^1 = CH_3$; c) R = *p*-$CN \cdot C_6H_4 \cdot CH_3$, $R^1 = C_2H_5$; d) R = PPh_3, $R^1 = C_2H_5$

Thus cobalt is tervalent in all its complexes with corroles: i.e. in these compounds all three imino-hydrogen atoms have been replaced. The complexes are either square–planar, pyramidal, or octahedral depending on the number of axial ligands[31]. In contrast, nickel[24], palladium, and copper[15] form only square–planar complexes of corroles in which these metals are bivalent.

4. Synthesis of Cobalt Complexes of Corrole

The synthesis of tetrapyrrole macrocycles such as corroles[10], octadehydro-1-methylcorrins[32], and 1,19-dialkyloctadehydrocorrin salts[33], which contain a direct bond between two pyrrole rings, involves the cyclisation of linear tetrapyrrole derivatives, e.g. 1,19-dideoxybiladienes-*ac*, bilenes-*b*, or bilatrienes. In 1973 the first [2 + 2] synthesis of corrole was accomplished that did not involve formation of a direct bond in the last stage of cyclisation[31].

Reaction between 3,3′-diethyl-4,4′-dimethyl-2,2′-bipyrrole-5,5′-dicarboxylic acid (XLIVa) [19] and 3,3′-diethyl-5,5′-diformyl-4,4′-dimethyldipyrromethane (XLVa) [10] in the presence of hydrobromic acid in methanol at 0 °C gives a red deposit, which when heated in methanol containing cobalt(II) acetate and triphenylphosphine is converted into the cobalt(III) complex (XLIId) having a triphenylphosphine group as an axial ligand:



a) R^1 = COOH, R^2 = CHO; b) R^1 = CHO, R^2 = COOH

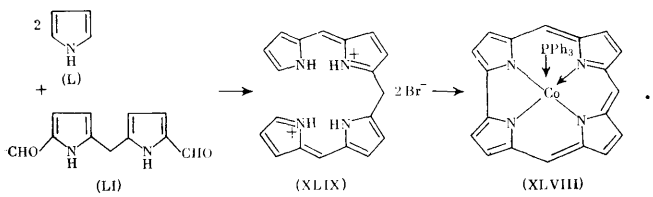
The same product (XLIId) can be obtained by condensing the bipyrrolyl (XLIVb) with the dipyrromethanedicarboxylic acid (XLVb).

These reactions may involve intermediate formation of *a*-norbilenes-*c* (XLVIa,b). The successful cyclisation of (XLIV) and (XLV) into a corrole emphasises the importance of cobalt both in stabilising the intermediate compound and in conferring a favourable configuration on it, since it had previously proved impossible to convert (XLIV) and (XLV) into a corrole in the absence of a complexing metal[31].

The corresponding cobalt(III) complex of corrole containing an axial triphenylphosphine ligand (XLIIb: R = $(C_6H_5)_3P$) has been obtained by cyclising 1,19-dideoxybiladiene-*ac*

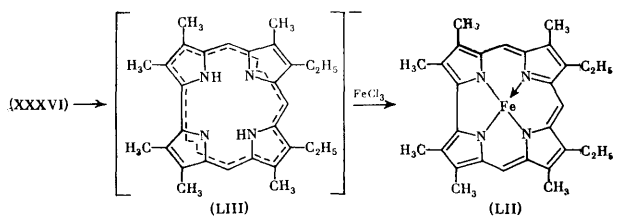
dihydrobromide (XLVII: R = H) in the presence of cobalt(II) acetate and triphenylphosphine in hot methanol. On the other hand, when a biladiene-*ac* containing methyl groups at the terminal positions 1 and 19 (XLVII: R = CH_3) is heated with cobalt(II) acetate and triphenylphosphine in methanol, a paramagnetic green product separates that proves to be a dimeric form of the cobalt complex of the biladiene (XXXVb).[25,31,33,34]

The stabilising effect of a coordinated triphenylphosphine ligand in the synthesis of cobalt corroles has been used in the synthesis of the triphenylphosphinecobalt(III) complex of corrole itself (containing no β-alkyl substitutents). This complex (XLVIII) has been obtained[31] by cyclising in the presence of cobalt(II) acetate and triphenylphosphine the dihydrobromide of 1,19-dideoxybiladiene-*ac* (XLIX), which is formed when pyrrole (L) is condensed with 5,5'-diformylmethane-2,2'-dipyrrole (LI) [35,36] and which, like its 1,19-disubstituted analogue[36], decomposes when an attempt is made at isolation or cyclisation in the absence of triphenylphosphine[37]:



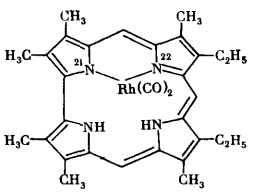
5. Synthesis of Iron Complex of Corrole

Besides the cobalt(III)—corrole complexes a paramagnetic crystalline complex of tervalent iron (LII) has been synthesised by treating with iron(III) chloride the corrole anion (LIII) obtained from 8,12-diethyl-2,3,7,13,17,18-hexamethylcorrole (XXXVI):[31]



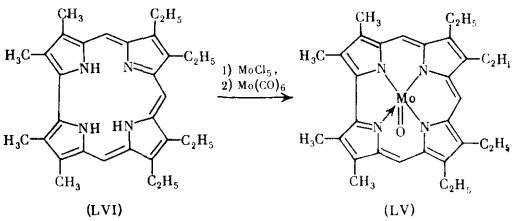
6. Synthesis of Rhodium and Molybdenum Complexes of Corroles

Rhodium[38,39] and molybdenum[40] complexes of corroles have been obtained quite recently. Reaction between the corroles (XXXVI) and di-μ-chlorobisdicarbonylrhodium $Rh_2(CO)_4Cl_2$ leads to formation of a monorhodium complex



as in the case of thiaphlorins, whereas dirhodium complexes are formed with porphyrins and azaporphyrins. The type of rhodium complex depends on the number of imino-hydrogen atoms present in the central portion of the tetrapyrrole macroring[38]. Each coordinated dicarbonylrhodium unit requires the presence of one imino-group and one nitrogen atom devoid of a hydrogen atom. Since corroles on alkylation form di-*N*-alkyl derivatives at the adjacent nitrogen atoms 21 and 22,[12] the structure (LIV) has been suggested for the monorhodium—corrole complex. The latter breaks down on crystallisation, and is less stable than the bisdicarbonylrhodium complex of porphyrin.

The discovery of superconducting materials[41] was followed by attempts to obtain conductors comprising planar metal complexes located one above the other and containing a metal—metal bond. These led to synthesis of the molybdenum—corrole complex (LV) [40] by the action of the corrole (LVI) either on molybdenum pentachloride or on hexacarbonylmolybdenum in decalin in an atmosphere of nitrogen:



However, the resulting oxomolybdenum(V) 7,8,12,13-tetraethyl-2,3,17,18-tetramethylcorrole (LV) proved to be a monomeric five-coordinated oxomolybdenum complex having an axial oxygen atom.

IV. SYNTHESIS OF METAL COMPLEXES OF 1,19-DISUBSTITUTED OCTADEHYDROCORRINS

1. Structure and Properties of Metal Complexes of 1,19-Disubstituted Octadehydrocorrins

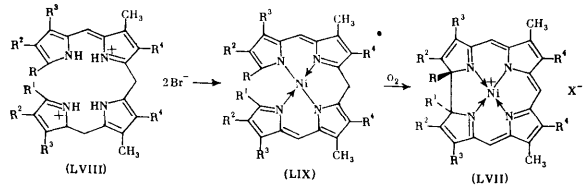
The metal complexes of 1,19-disubstituted octadehydrocorrins are macrocyclic tetrapyrrole compounds in which two pyrrole rings form a direct bond between the αα-carbon atoms at positions 1 and 19. They contain 1,19-angular substituents having a *trans* configuration. This series of compounds became known only in 1964.[26]

1,19-Disubstituted octadehydrocorrins form crystals of violet or dark cherry colour. Their electronic absorption spectra contain three principal bands in the ranges 280—300, 350—365, and 500—580 nm, and are devoid of the Soret band (at ~400 nm) characteristic of aromatic macrocycles such as corroles and porphyrins. The metal atom cannot be removed from an octadehydrocorrin complex without destruction of the organic macroring.

2. Synthesis of Nickel Complexes of 1,19-Disubstituted Octadehydrocorrins from Biladienes-*ac*

The traditional method for obtaining nickel complexes of 1,19-disubstituted octadehydrocorrins (LVII) is base-catalysed oxidative cyclisation of the 1,19-disubstituted 1,19-

dideoxybiladienes-*ac* (LVIII) [42] in alcoholic solution in the presence of excess of nickel acetate[33,43]:



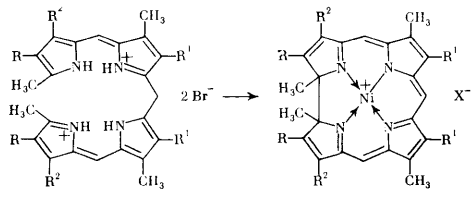
(LVIII) (LIX) (LVII)

(a) R=R¹=R²=R³=CH₃, R⁴=C₂H₅, X=NO₃, Cl;
(b) R=R¹=R³=R⁴=CH₃, X=ClO₄;
(c) R=R¹=R³=R⁴=CH₃, R²=OCH₂C₆H₅, X=Br;
(d) R=R¹=R³=R⁴=CH₃, R²=COOC₂H₅, X=ClO₄.
(e) R=R¹=R³=R⁴=CH₃, R²=CN, X=ClO₄;
(f) R=R¹=COOC₂H₅, R²=R³=CH₃, R⁴=C₂H₅;
(g) R=R¹=OCH₃, R²=R³=R⁴=CH₃;
(h) R=COOC₂H₅, R¹=R²=R³=CH₃, R⁴=C₂H₅;
(i) R=R¹=R³=R⁴=CH₃, R²=CH₂COOH, X=ClO₄;
(j) R=R¹=R²=R³=CH₃, R⁴=CH₂CH₂COOH, X=ClO₄;
(k) R=R¹=R³=CH₃, R²=CH₂COOH, R⁴=CH₂CH₂COOH, X=ClO₄.

Thus boiling 8,12-diethyl-1–3,7,13,17–19-octamethylbiladiene-*ac* (LVIIIa) with nickel and sodium acetates in methanol for a short time (30 s) gives the nickel–biladiene complex (LIXa), which on further aeration followed by treatment with nitrate ions is converted into the nitrate of the crystalline nickel–octadehydrocorrin complex (LVIIa), and into the corresponding crystalline chloride (LVIIa) when chloride ions are used. The decasubstituted octadehydrocorrin–nickel compex has been obtained as the perchlorate (LVIIb).[44,45] Similarly, cyclisation of the biladiene-*ac* (LVIIIc) gives the nickel complex (LVIIc) with benzyloxy-groups at positions 3 and 17,[46] and a nickel complex (LVIId) with ethoxycarbonyl substituents at positions 2 and 18 has been obtained from the biladiene (LVIIId).[47] A nickel complex of 2,18-dicyano-octadehydrocorrin (LVIIe) could not be synthesised in the usual way[47]: it has been obtained by aerating a chloroform solution of the biladiene (LVIIIe) containing hydrobromic acid, since in alcoholic solution or on addition of sodium acetate this biladiene is converted into a bilatriene, which under these conditions cannot be cyclised to the octadehydrocorrin.

The oxidative cyclisation of biladienes enables us to obtain metal complexes of octadehydrocorrins containing angular ethoxycarbonyl (LVIIf) [33] and methoxyl (LVIIg) [48] substituents. The 1,19-diethoxycarbonyl derivative (LVIIf) could be obtained in higher yield (85%) than the compounds (LVIIa, b). Nickel complexes of octadehydrocorrins having two different angular substituents have also been synthesised by oxidative cyclisation, e.g. the nickel complex (LVIIh) from 1,19-dideoxy-1-ethoxycarbonyl-19-methylbiladiene-*ac* (LVIIIh).[33]

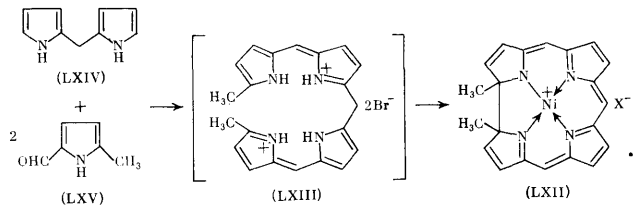
Oxidative cyclisation of biladienes[43,49] has been used also to obtain nickel complexes of 1,19-disubstituted oxydehydrocorrins having partly vacant β-positions[43,50,51]. Nickel complexes with unsubstituted positions 2 and 18 (LXa,b),[43,51,52] 8 and 12 (LXc),[50] and also 2, 3, 17, and 18 (LXd) [43] are obtained in the usual way[33] from the corresponding biladienes-*ac* (LXIa–d):[42]



(LXI) (LX)

(a) R=H, R¹=C₂H₅, R²=CH₃, X=ClO₄;
(b) R=H, R¹=R²=CH₃, X=ClO₄;
(c) R=R²=CH₃, R¹=H, X=ClO₄;
(d) R=R²=H, R¹=CH₃.

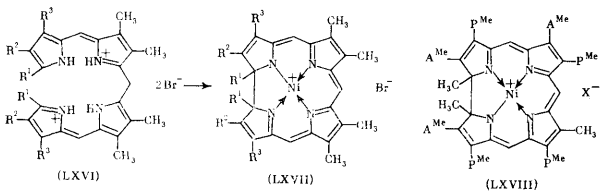
However, several difficulties were encountered in synthesis of the nickel complex (LXII) of octadehydro-1,19-dimethylcorrin with completely unsubstituted β-positions[36,53]. The initial 1,19-dideoxy-1,19-dimethylbiladiene-*ac* (LXIII), formed by the condensation of 2,2′-dipyrrolylmethane (LXIV)[35] with excess of 2-formyl-5-methylpyrrole (LXV) in chloroform solution in the presence of hydrogen bromide, was subjected to cyclisation without being isolated, owing to its extreme instability:



(LXIV) (LXV) (LXIII) (LXII)

The reaction was conducted in methanol in the presence of nickel and sodium acetates at room temperature for 3 h, and gave 2–22% yields of the nickel–octadehydrocorrin complex (LXII). If DMF is used as solvent, cyclisation goes more smoothly for 15 min even without the addition of sodium acetate, and the yield rises to 26%.[36,53]

The interest in the synthesis of octadehydrocorrins containing residues of acetic and propionic acids as β-substituents arises understandably from the presence of such substituents in naturally occurring corrin and porphyrin macrocycles. As early as 1969 perchlorates were obtained of several nickel complexes of octadehydrocorrins containing propionic ester groups in various positions in the pyrrole rings[54]. It then proved possible by the cyclisation of biladienes-*ac* (LXVI) to prepare nickel complexes of octadehydrocorrins (LXVII) [55] containing acetic and propionic ester groups at positions 2, 3, 17, and 18 in rings A and D:



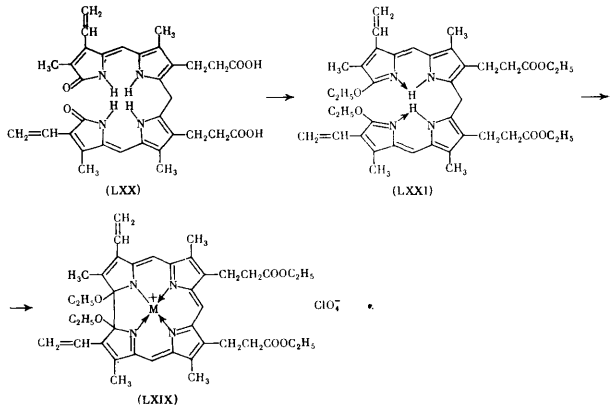
(LXVI) (LXVII) (LXVIII)

R¹=CH₃, COOC₂H₅, COOCH₂C₆H₅; R² и R³=CH₃, CH₂COOCH₃, CH₂COOC₂H₅, CH₂CH₂COOCH₃, CH₂CH₂COOC₂H₅
A^Me=CH₂COOCH₃, P^Me=CH₂CH₂COOCH₃.

Finally, a nickel–octadehydrocorrin complex (LXVIII) containing propionic and acetic ester groups at all β-positions in the macroring was obtained[56] in 1975. Cyclisation of the corresponding biladiene was accomplished in the presence of nickel acetate. It is noteworthy that this biladiene is an intermediate compound in the synthesis of porphyrins[54] and corroles[10]. Other nickel–octadehydrocorrin complexes contain acetic ester residues at positions 2 and 18 (LVIIi) [50] and propionic ester groups at positions 8 and 12 (LVIIj) [47] have also been obtained; in the complex (LVIIk) all four positions are occupied by ester substituents[47].

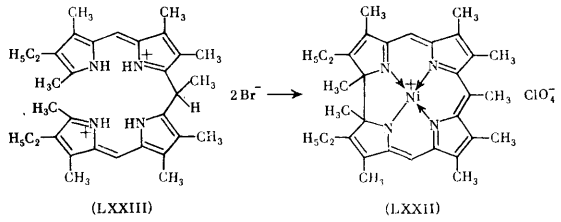
A nickel–octadehydrocorrin complex has been prepared also from the natural yellow pigment bilirubin (LXX),[57] which on treatment with triethyloxonium tetrafluoroborate in di-isopropylethylamine and dichloromethane was converted into the biladiene-*ac* (LXXI),[58] cyclisation of which in the presence of

nickel acetate and sodium perchlorate with heating in air led to formation of the complex (LXIX: M = Ni):[57]



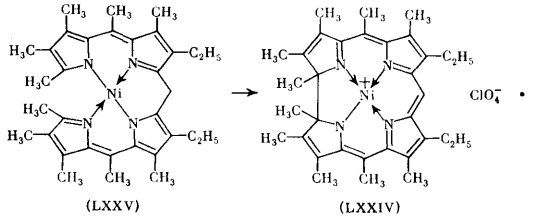
(LXX) (LXXI) (LXIX)

An interesting extension of the cyclisation of 1,19-disubstituted biladienes-*ac* is its application to biladienes containing *meso*-methyl groups. The nickel complex of octadehydro-2,18-diethyl-1,3,7,8,10,12,13,17,19-nonamethylcorrin (LXXII) was obtained by cyclising the corresponding 10-methylbiladiene (LXXIII):[33]



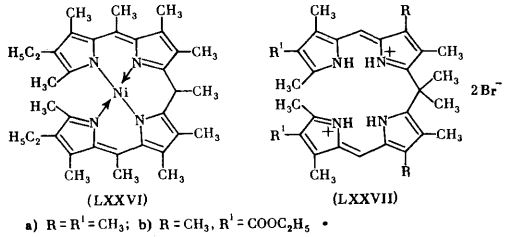
(LXXIII) (LXXII)

The nickel–octadehydrocorrin complex (LXXIV) containing methyl groups at the *meso*-positions 5 and 15 was obtained by aerating the 1,19-dideoxybiladiene-*ac* complex (LXXV):[33]



(LXXV) (LXXIV)

The nickel complex (LXXVI) of completely *meso*-substituted biladiene-*ac*,[33] like the 10,10-dimethylbiladiene (LXXVII),[18] could not be converted into the octadehydrocorrin complex.



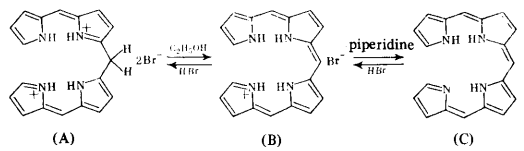
(LXXVI) (LXXVII)

a) R = R' = CH_3; b) R = CH_3, R' = $COOC_2H_5$.

An important condition for the cyclisation of biladienes-*ac* into octadehydrocorrins is the formation of metal complexes of 1,19-dideoxybiladienes (LIX). The first stage in the cyclisation[33] of the biladiene-*ac* dihydrobromide (LVIII) into the 1,19-disubstituted octadehydrocorrin consists in formation of the nickel–biladiene complex (LIX), which was isolated under controlled conditions, and in the presence of sodium acetate and air converted into the cyclic nickel–octadehydrocorrin complex (LVII).

In the absence of a metal it has proved impossible to achieve the cyclisation of biladienes into octadehydrocorrins [16,33], in contrast to the formation of corroles[10,16]. The initiating reaction is probably detachment of a proton from the central methylene group in the metal–biladiene complex (LIX). Involvement of the methylene group of 1,19-dideoxybiladienes is indicated by the absence of cyclisation when the two 10-hydrogen atoms have been replaced by two methyl groups[18], whereas the 10-methyl derivative (LXXIII) cyclises only slightly more slowly than does the unsubstituted compound. Yet the rate of cyclisation of the 5,15-dimethyl derivative (LXXV) is of the same order as that of the *meso*-unsubstituted compound.

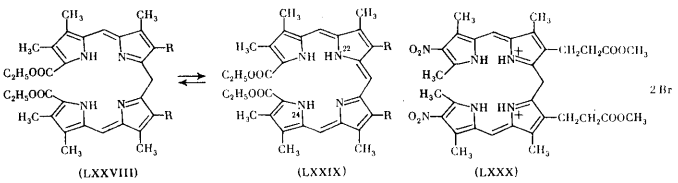
Data on the acidic properties of protons attached to carbon atom 10 in 1,19-dideoxybiladienes-*ac* have been obtained from a study of the visible absorption spectra[16]. Biladiene dihydrobromides (A) form red solutions in chloroform, benzene, and dichloromethane, but yellow solutions in methanol, ethanol, and dimethyl sulphoxide (DMSO); the solutions become green on addition of an organic base, e.g. piperidine. These colour changes are consistent with abstraction of a proton by polar solvents with formation of 1,19-dideoxybilatriene-*abc* monohydrobromides (B), which are converted by excess of piperidine into the corresponding free bilatriene bases (C):[6,19]



(A) (B) (C)

The monohydrobromides (B) are characterised by intense absorption at 420–450 and 750–800 nm, whereas the corresponding bases (C) have absorption bands at 400 and 650 to 750 nm. If a biladiene contains a 10-methyl group, its ethanolic solution does not absorb in the range 650–750 nm when piperidine is present, but the spectrum of a 10,10-dimethylbiladiene in fact remains unchanged with variation in the type of solvent[16].

Detachment of a 10-proton is faciliated by the presence of electron-accepting substituents in the biladiene-*ac*.[16,47,59–61] Yet biladienes containing alkyl, hydrogen, or iodine at positions 1 and 19 exist only as salts like the dihydrobromide (A),[59] and 1,19-diethoxycarbonylbiladienes are equilibrium mixtures of a biladiene salt of type (A) and bilatrienes of types (B) and (C).[59] For example, biladiene-*ac* (LXXVIIIa) is present in chloroform solution partly as a bilatriene salt of type (B),[16] but (LXXVIIIb) exists in dichloromethane solution partly as the tautomeric 22,24-dihydrobilatriene (LXXIX):[60]

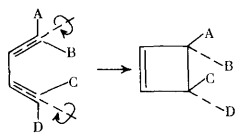


(LXXVIII) (LXXIX) (LXXX)

a) R = C_2H_5; b) R = CH_3.

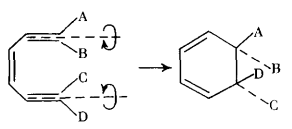
Dinitrobiladiene (LXXX) [61] is present in chloroform solution as a mixture of a neutral bilatriene of type (C) and a monocation of type (B), but the 2,18-dicyanobiladiene dihydrobromide (LVIIIe),[47] when dissolved in chloroform, passes into a 2,18-dicyanobilatriene hydrobromide of type (B), which is converted in methanol into the free 2,18-dicyanobilatriene base of type (C).

The action of a base on the intermediate nickel–biladiene complex (LIX) yields the anion (LXXXI), which is a 22-π-electron system (or an 18-π-electron system if the two cross-conjugated double bonds are neglected). Two further stages—electrocyclic formation of a direct 1,19-bond and an oxidation stage—are required to convert this anion into the nickel complex of octadehydro-1,19-dimethylcorrin (LVII). The sequence of these stages has been established from a determination of the stereochemistry of (LVII), which has a *trans*-configuration of the angular 1- and 19-alkyl substituents[5,62]. In electrocyclic processes[63] conjugated acyclic 4*n*-π-electron systems undergo cyclisation in a conrotatory manner, e.g.



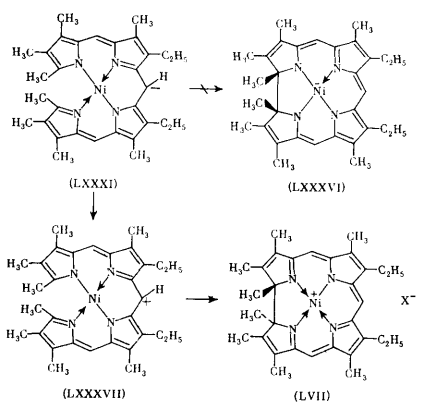
(LXXXII) (LXXXIII)

whereas (4*n* + 2)-π-electron systems cyclise in a disrotatory manner, e.g.



LXXXIV) (LXXXV)

The cyclisation of (LXXXI), which is of the second type, should also involve rotation of terminal groups in opposite sense with formation of the *cis*-isomer (LXXXV), which on oxidation may be converted into the *cis*-octadehydrocorrin–nickel complex. Since, however, the 1,19-disubstituted octadehydrocorrin (LVII) exists in the *trans*-form, the anion (LXXXI) probably undergoes initial two-electron oxidation to the cation (LXXXVII), which is a 4*n*-π-electron system, and on cyclisation is converted into the *trans*-compound (LVII):[8]



(LXXXI) (LXXXVI)

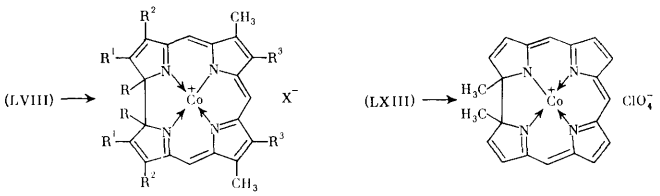
(LXXXVII) (LVII)

The action of several one-electron oxidants in DMSO was examined[54] in the search for milder methods of cyclising 1,19-disubstituted biladiene salts into octadehydrocorrin macrorings containing labile side-chains. Cyclisation of the nickel–biladiene-*ac* complex (LXXV) in the presence of ammonium cerium nitrate in DMSO yields the nickel–octadehydro-1,19-dimethylcorrin complex (LXXIV), which was isolated as the perchlorate in 39% yield.

Cyclisation of 1,19-dideoxybiladienes-*ac* into octadehydrocorrins in the presence of one-electron oxidants apparently occurs also by a free-radical mechanism with intermediate formation of bilatrienes-*abc*.

3. Synthesis of Cobalt and Palladium Complexes of 1,19-Disubstituted Octadehydrocorrins from Biladienes-*ac*

Cyclisation of the 1,19-disubstituted biladiene-*ac* (LVIIIa) is far more rapid in the presence of cobalt acetate than of nickel acetate. Aeration of a methanolic solution at room temperature gives the perchlorate (LXXXVIIIa) of the cobalt–octadehydrocorrin complex in 71% yield[33]:



(LVIII) (LXXXVIII) (LXIII) (LXXXIX)

LXXXVIII: a) R=R¹=R²=CH₃, R³=C₂H₅, X=ClO₄; b) R=R¹=R²=R³=CH₃, X=ClO₄;
c) R=COOC₂H₅, R¹=R²=CH₃, R³=C₂H₅, X=ClO₄;
d) R=R¹=R³=CH₃, R²=OCH₂C₆H₅, X=Br;
e) R=R¹=R³=CH₃, R²=(CH₂)₂COOH, X=ClO₄;
f) R=R²=CH₃, R¹=CH₂COOH, R³=(CH₂)₂COOH, X=ClO₄.

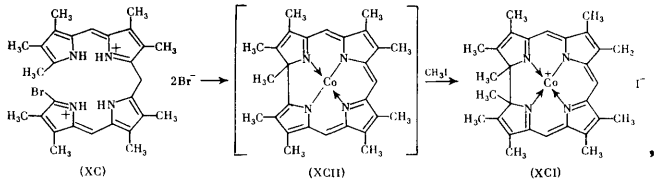
The decamethylated complex (LXXXVIIIb) has also been obtained as the perchlorate[44,45]. The 1,19-diethoxycarbonylbiladiene (LVIIIf) cyclises more rapidly in the presence of cobalt acetate than does the 1,19-dimethyl derivative (LVIIIa), and forms the complex (LXXXVIIIc) in 80% yield[33].

A cobalt–biladiene complex analogous to the nickel complex (LIX) could not be isolated[33]. Aeration of a suspension of the biladiene (LVIIIa) in methanol in the presence of cobalt acetate caused immediate separation of a small quantity of a green crystalline compound (XXXVb) containing two tetrahedral cobalt atoms and two quadridentate 1,19-dideoxybiladiene ligands[25,33]. Cyclisation of the biladiene-*ac* (LVIIIc) yields the cobalt–octadehydrocorrin bromide (LXXXVIIId) having benzyloxy-groups at positions 3 and 17.[46]

The cobalt–octadehydrocorrin complex (LXXXIX) with completely unsubstituted β-positions[36,53] was obtained from the biladiene-*ac* (LXIII) in 26% yield by the use of cobalt acetate in DMSO.[53] Cobalt complexes containing residues of acetic and propionic acids at β-positions are, like the nickel complexes, difficultly accessible because of the lability of the side-chains. However, octadehydrocorrins have been prepared containing residues of propionic esters in all the pyrrole rings[54] and residues of acetic and propionic esters at positions 2, 18 and 3, 17,[55] as well as those containing both acetic and propionic ester groups in all the pyrrole rings[56]. The cobalt complex (LXXXVIIIe) with propionic groups at positions 8 and 12, and (LXXXVIIIf) with acetic and propionic acid residues together at positions 2, 8, 12, and 18, are formed in lower yields than are the corresponding nickel complexes[47]. The cobalt complex (LXIX: M = Co) is obtained[57] similarly to the nickel complex (LXIX: M = Ni) from bilirubin (LXX).

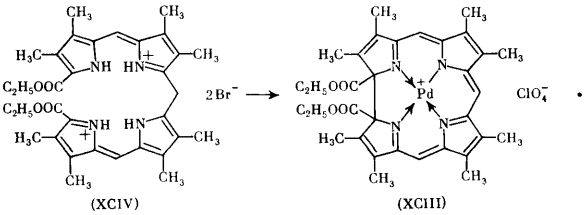
When 1-bromo-19-methylbiladiene-*ac* (XC) undergoes cyclisation in the presence of cobalt acetate in a degassed solvent, addition of iodomethane in the absence of oxygen leads to isolation of a crystalline iodide of the cobalt–octadehydro-1,19-dimethylcorrin complex (XCI), apparently an

alkylation product of the intermediate cobalt–octadehydro-1-methylcorrin complex (XCII):[64]



(XC) (XCII) (XCI)

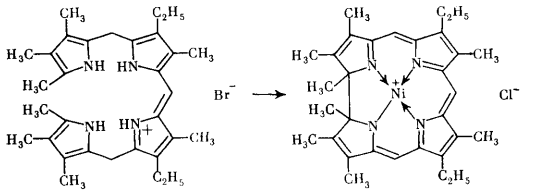
The palladium–octadehydrocorrin complex (XCIII) containing angular 1,19-ethoxycarbonyl substituents has been obtained by aeration of an alcoholic solution of the biladiene-*ac* (XCIV) (yield 35%):[65]



(XCIV) (XCIII)

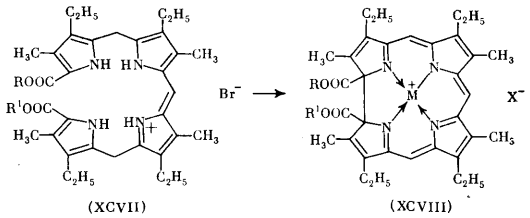
4. Synthesis of Nickel and Cobalt Complexes of 1,19-Disubstituted Octadehydrocorrrins from Bilenes-*b*

Johnson's oxidative cyclisation[33] can be applied not only to 1,19-dideoxybiladienes-*ac* but also to bilenes-*b* (XCV) to give metal complexes of octadehydrocorrins[43,66]. The cyclisation of 1,19-dimethylbilenes-*b* to nickel complexes of octadehydro-1,19-dimethylcorrins is accomplished under the same conditions as that of the corresponding salts of 1,19-dideoxy-1,19-dimethylbiladienes-*ac*.[43,66] For example, aeration of the bilene-*b* (XCV) in the presence of nickel and sodium acetates in boiling methanol followed by treatment with dilute hydrochloric acid gives the nickel–octadehydro-1,19-dimethylcorrin chloride (XCVI):[43]



(XCV) (XCVI)

Nickel and cobalt complexes of octadehydrocorrins with various substituents at positions 1 and 19 (XCVIII) have been obtained[66] from bilenes-*b* (XCVII):



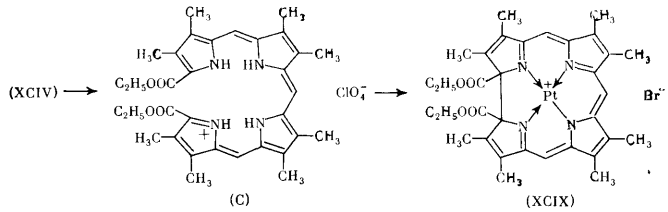
(XCVII) (XCVIII)

a) R = R^1 = C_2H_5; b) R = R^1 = $CH_2C_6H_5$; c) R = C_2H_5, R^1 = $CH_2C_6H_5$.

Far more severe conditions (DMF as solvent aerated at 70 °C for 4 h) are required[66] to obtain the cobalt–octadehydrocorrin complex (XCVIIIa: X = ClO_4) from bilene-*b* than to obtain a similar compound from the biladiene-*ac*.[33]

5. Synthesis of Platinum, Nickel, Cobalt, and Palladium Complexes of 1,19-Disubstituted Octadehydrocorrins from Bilatrienes-*abc*

Until 1977 octadehydrocorrins had been obtained only in the form of nickel[33,43], cobalt[33,67], and palladium complexes. Discovery of the antitumour activity of platinum complexes coordinated with nitrogen[68] led to the synthesis[69] of a platinum–octadehydrocorrin complex (XCIX), which was obtained only in insignificant quantities[69] by oxidative cyclisation[33,43] from the biladiene-*ac* dihydrobromide (XCIV). This complex was prepared in higher yields (15%) from the 1,19-dideoxybilatriene-*abc* hydroperchlorate (C),[16] which is formed when a methanolic solution of the biladiene-*ac* (XCIV) is heated with zinc perchlorate[69]. Boiling a suspension of platinum chloride, sodium acetate, and the bilatriene (C) in acetonitrile yields the platinum–octadehydrocorrin complex (XCIX):

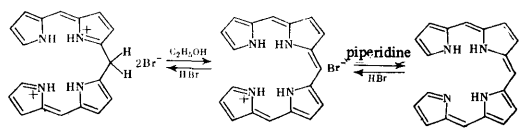


(XCIV) (C) (XCIX)

The synthesis of metal complexes of 1,19-diethoxycarbonyl derivatives of octadehydrocorrin from the bilatriene salt (C) gives better yields[69] of nickel, cobalt, and palladium complexes analogous to (XCIX) than those obtained from the biladiene-*ac* (XCIV). This applies especially to the palladium complex (yield 66%), previously obtained from the biladiene in 35% yield[65].

6. Nickel and Cobalt Complexes of 1,19-Disubstituted Octadehydrocorrins by Metal Exchange

A novel approach to the preparation of cobalt complexes of octadehydrocorrins, by the replacement of nickel using reductive fission of the macroring, was suggested[60] in 1974. When a metal–octadehydrocorrin complex, e.g. (CI: M = Ni), is treated with a reducing agent (hydrogen sulphide, sodium dithionite), it adds two electrons and passes into a negatively charged complex B, which after rupture of the $C_{(1)}$–$C_{(19)}$ bond is converted into the metal compiex of 22,24-dihydrobilatriene (CII: M = Ni); protonation of the latter at $C_{(10)}$ converted it into the neutral biladiene complex (CIII):



(A) (B) (C)

At this stage nickel is easily replaced by cobalt. Thus the nickel complex (CIII) is readily demetallised by the action of such acids as trifluoroacetic and hydrochloric, and the resulting biladiene (LXXVIIIb) can be recyclised in the presence of atmospheric oxygen and nickel or cobalt acetate to form the corresponding metal complex, e.g. (CI).[60]

Cobalt complexes occupy a special position, since they undergo ring cleavage even under very mild conditions (hydrogen sulphide at room temperature)[60].

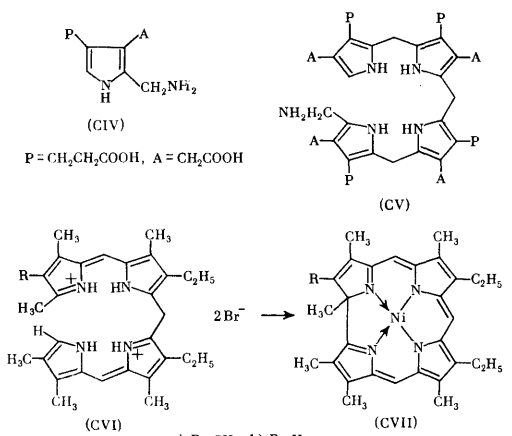
V. SYNTHESIS OF NICKEL COMPLEXES OF 1-SUBSTITUTED OCTADEHYDROCORRINS

1-Alkyloctadehydrocorrins are neutral complexes of bivalent nickel. The tetrapyrrole macroring contains only one angular substituent. Only nickel complexes of 1-alkyloctadehydrocorrins are known.

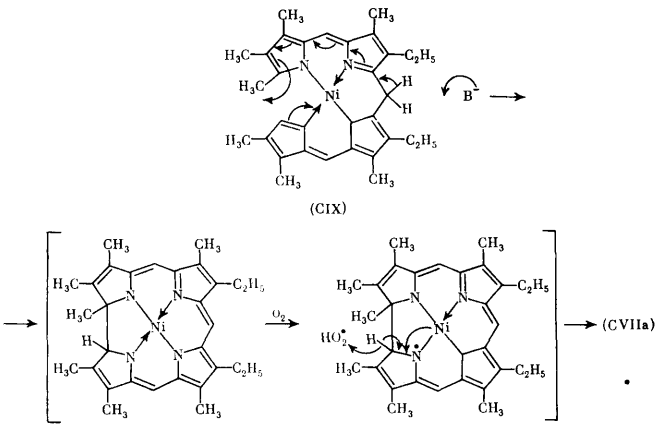
1. Synthesis of Nickel Complexes of 1-Substituted Octadehydrocorrins by the Oxidative Cyclisation of Biladienes-*ac*

Nickel complexes of octadehydro-1-methylcorrin are formed[7] by the cyclisation of 1-methylbiladienes-*ac*[76] when alkaline solutions are aerated in the presence of nickel ions.

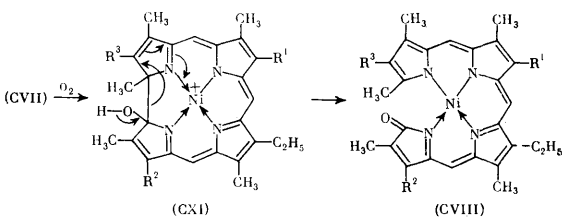
The biosynthesis of the corrin chromophore of vitamin B_{12} involves porphobilinogen (CIV), which is probably converted into a bilane derivative of the type (CV).[70–73] The cyclisation of 1,19-dideoxybiladienes containing an unsubstituted α-position (CVI) was examined[72] to ascertain whether a similarity exists in the mechanisms of the cyclisation of the bilane (CV) and biladienes-*ac*. Such cyclisation was effected[43,70] by heating the biladienes (CVIa,b) in methanol containing nickel acetate and piperidine, which in the presence of oxygen gave the octadehydro-1-methylcorrin–nickel complexes (CVIIa,b) in the respective yields 56% and 59%:



Although cyclisation of α-unsubstituted biladienes (CVI) is caused by aeration with oxygen[43], conversion of (CVIa) into the complex (CVIIa) requires partial degasification of the methanolic solution of biladiene and nickel acetate containing piperidine (in contrast to the cylisation of metal complexes of 1,19-disubstituted octadehydrocorrins, which occurs in the presence of excess of atmospheric oxygen), but in such a way that the quantity of oxygen remaining is sufficient for cyclisation and insufficient to oxidise (CVIIa) to the lactam (CVIII).[32] Formation of octadehydro-1-methylcorrin apparently involves free-radical intermediate compounds resulting from the action of oxygen on a carbanion obtained by detachment of a proton from the metal–biladiene complex (CIX) under the influence of a base[43]:



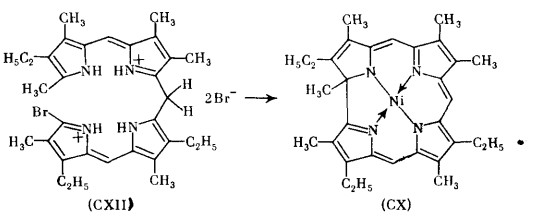
The mechanism of oxidation of the nickel complex (CVII) and (CX) to the lactam (CVIII) has not been established, although intermediate formation of octadehydro-1-hydroxy-19-methylcorrin (CXI) has been postulated[32,43]:



a) $R^1 = C_2H_5$, $R^2 = R^3 = CH_3$; b) $R^1 = CH_3$, $R^2 = R^3 = C_2H_5$.

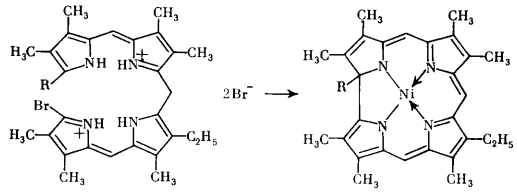
2. Synthesis of Nickel Complexes of 1-Substituted Octadehydrocorrins from Biladienes-*ac* by Non-oxidative Cyclisation

Nickel complexes of octadehydro-1-methylcorrins (CX) are formed by the cyclisation of dihydrobromides not only of 1-substituted biladienes-*ac* but also of 1-bromo-19-methylbiladienes-*ac* (CXII) in the presence of nickel ions and a base[5,32,33,74]:



This probably takes place in the absence of oxygen[32], which distinguishes it significantly from the cyclisation of dihydrobromides of 1,19-dimethyl- and 1-methyl-biladienes-*ac*, requiring an oxidation stage. When the reaction was conducted in the presence of oxygen, the lactam (CVIIIb) was isolated[32]. The cyclisation of (CXII) was extended to the

dihydrobromides of 1-bromo-19-ethyl(and isopropyl)biladienes-*ac* (CXIIIa,b), which gave the corresponding nickel octadehydro-1-alkylcorrins (CXIVa,b) in high yields[32]:



(CXIII) a) R = C_2H_5, b) R = $(CH_3)_2CH$ (CXIV)

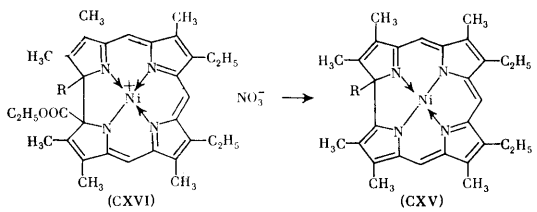
Nickel complexes of 1-alkyloctadehydrocorrins have been synthesised from 1-alkylbiladienes-*ac* containing various 19-substituents, e.g. alkoxy[75] and iodo[21], which are removed during the reaction, but the use of such initial compounds is less convenient than that of 19-bromobiladienes-*ac*.

Attempts to obtain cobalt complexes of octadehydro-1-methylcorrins by cyclisation of the corresponding biladienes in the presence of cobalt acetate in various solvents proved unsuccessful[32,64]. Such behaviour contrasts sharply with the ease of formation of cobalt complexes of 1,19-disubstituted octadehydrocorrins[33].

The attempted cyclisation of 1-bromo-19-methylbiladiene to the corresponding octadehydro-1-methylcorrin in the presence of copper acetate proved unsuccessful[32]. The reaction gives a low yield (8–25%) of a copper–porphyrin complex[42].

3. Synthesis of Nickel Complexes of 1-Substituted Octadehydrocorrins from 1,19-Disubstituted Octadehydrocorrins

Nickel complexes of 1-substituted octadehydrocorrins (CXVa, b) have been obtained from those of 1,19-disubstituted octadehydrocorrins (CXVIa,b) containing a 19-ethoxycarbonyl group[27,32]:



(CXVI) a) R = CH_3, b) R = $COOC_2H_5$ (CXV)

Hydrolysis and decarboxylation of the ethoxycarbonyl group in (CXVIa) gave a nickel complex of octadehydro-1-methylcorrin (CXVa) [32] identical with the compound obtained from the corresponding 19-bromo-1-methylbiladiene-*ac*. Rapid treatment of the octadehydro-1,19-diethoxycarbonylcorrin (CXVIb) [33] with aqueous caustic soda and rapid separation gives a good yield of the nickel complex of octadehydro-1-ethoxycarbonylcorrin (CXVb).[27]

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Thus a great deal of experimental information has accumulated during the past decade on the synthesis of metal complexes of octadehydrocorrins and corroles. This opens up the possibility of a broad study of these interesting and complicated compounds, akin to porphyrins and corrins, and possessing biological activity.

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