CENTENARY LECTURE

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Roads to Corrins

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The beautiful and intriguing structure of vitamin B_{12} stands among the finest contributions of British science to the chemistry of low molecular weight natural products.[1] This structure happened to have a rather fateful influence on our own research activity; it induced us a number of years ago to embark on a major endeavour in organic synthesis, the synthesis of corrinoids.[2] To expose and summarise results of these studies in a Chemical Society Centenary Lecture seems, therefore, not inappropriate.

At the time, the development of synthetic roads to corrins appeared as one of the prerequisites to a systematic study and exploration of corrin chemistry. Moreover, there always was, and there still is in the background of this work the alluring and exacting problem of a chemical total synthesis of vitamin B_{12} itself. In fact, the permanent confrontation with the numerous complex problems of a vitamin B_{12} synthesis did, in more than one instance, exert a most fruitful feed-back effect on the progress to be attained in the broader field of corrinoid and porphinoid synthesis. The deeply interwoven stories of corrin and vitamin B_{12} syntheses can actually be taken to illustrate a type of research mechanism by which involvement in a synthetic project towards a structurally novel and sufficiently complex natural product is bound to fertilise organic synthesis beyond the immediate structural boundaries of the specific synthetic problem.

In an account of the present state of our work on corrinoid synthesis, special reference must be made to the important accomplishments in this field of A. W. Johnson and his collaborators.[3] Furthermore, it seems appropriate to mention here the truly pioneering efforts and contributions made by the Cambridge school[4] to the corrin problem, and by J. W. Cornforth's[5] group to

[1] D. Crowfoot-Hodgkin, A. W. Johnson, and A. R. Todd, *Chem. Soc. Special Publ.* No. 3, 1955, 109; D. Crowfoot-Hodgkin, J. Kamper, J. Lindsey, M. Mackay, J. Pickworth, J. H. Robertson, C. B. Shoemaker, J. G. White, R. J. Prosen, and K. N. Trueblood, *Proc. Roy. Soc.*, 1957 *A*, **242**, 288; for a review see R. Bonnett, The Chemistry of the Vitamin B_{12} Group, *Chem. Revs.*, 1963, **63**, 573.

[2] A. Eschenmoser, *Pure and Appl. Chem.*, 1963, **7**, 297.

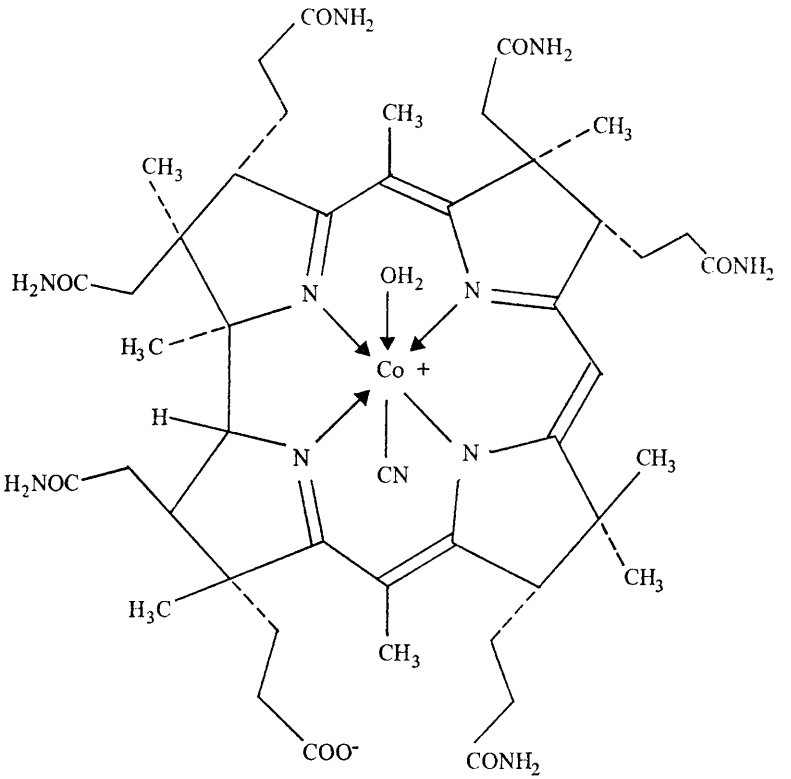
[3] A. W. Johnson, *Chem. in Brit.*, 1967, 253; *cf.* also H. H. Inhoffen, J. Ullrich, H. A. Hoffmann, and G. Klinzmann, *Tetrahedron Letters* 1969, 613.

[4] R. Bonnett, V. M. Clark, A. Giddey, and A. R. Todd, *J. Chem. Soc.*, 1959, 2087, and subsequent papers.

[5] J. W. Cornforth, reported by P. B. D. de la Mare, *Nature*, 1962, **195**, 441; J. W. Cornforth, Discussions on recent experiments on the chemistry of corrins, The Royal Society, London, June 4 (1964).

the one of vitamin B_{12} synthesis. The epochal impact on chemical theory of R. B. Woodward's involvement in the B_{12} problem is well recorded.[6] The specific synthetic achievements of the Harvard group have been the subject of a recently published lecture[7] and some aspects of this work are bound to be dealt with also in this report.

Formula (1) in Figure 1 introduces the structure of the simplest known corrinoid natural product, cobyric acid.[8] Since this compound has already



(1)

Figure 1

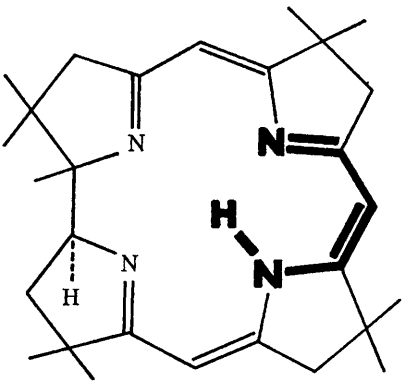
[6] R. B. Woodward "The Conservation of Orbital Symmetry", *Chem. Soc. Special Publ.* No. 21, 1967, 217.
[7] R. B. Woodward, *Pure and Appl. Chem.*, 1968, **17**, 519.
[8] K. Bernhauer, H. Dellweg, W. Friedrich, G. Gross, F. Wagner, and P. Zeller, *Helv. chim. Acta.*, 1960, **43**, 693; K. Bernhauer, F. Wagner, and P. Zeller, *ibid.*, p. 696; D. Dale, D. Crowfoot-Hodgkin, and K. Venkatesan, 'Crystallography and Crystal Perfection' 1963, p. 237, Academic Press, London; D. Crowfoot-Hodgkin, *Proc. Royal Soc.*, 1965, ***A***, **288**, 294.

served as the starting material for a partial synthesis of vitamin B_{12}[9] and since B_{12}-coenzymes can nowadays be made easily from the vitamin,[10] cobyric acid represents the immediate goal of all the work aiming at a total synthesis of vitamin B_{12} and the B_{12}-coenzymes. Its structure lacks the characteristic nucleotide parts of the vitamin and the coenzymes but contains all other essential elements of the vitamin's corrinoid nucleus. In particular, it contains the peripheral carboxy functions in their primary amide form *except* the one of the propionic acid chain attached to ring D; this free carboxy group has been crucial in the partial synthesis of the vitamin, and its synthetic differentiation from all other carboxy functions presents a particular hurdle in a total synthesis.

At the heart of any project for a synthesis of vitamin B_{12} must be a concept for the construction of the central corrin chromophore. In keeping with this—and with the historical development—the first section of this account deals with the earlier work on this problem.

1 'The Old Road': Synthesis of Corrin Complexes *via* A/B-Iminoester Cyclisations[11]

The corrin ligand system (2) (see Figure 2) is at the same oxidation level as the



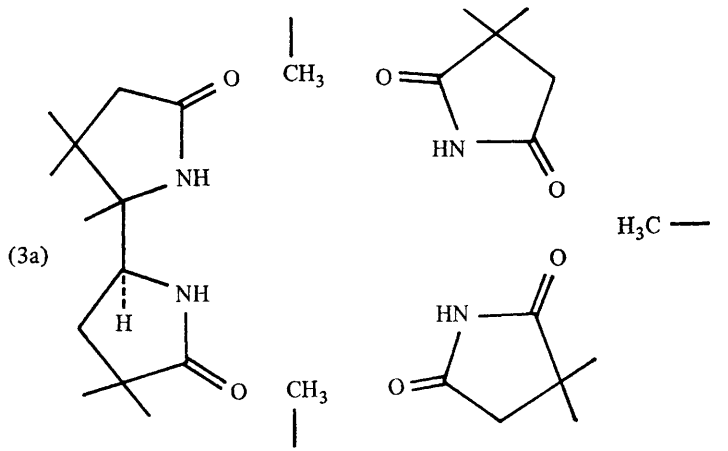
(2)

Figure 2

[9] W. Friedrich, G. Gross, K. Bernhauer, and P. Zeller, *Helv. chim. Acta*, 1960, **43**, 704.

[10] E. L. Smith, L. Merwyn, A. W. Johnson, and N. Shaw, *Nature*, 1962, **194**, 1175; K. Bernhauer, O. Müller, and G. Müller, *Biochem. Z.*, 1962, **336**, 102; O. Müller and G. Müller, *ibid.*, p. 229; A. W. Johnson, L. Merwyn, N. Shaw, and E. L. Smith, *J. Chem. Soc.*, 1963, 4146.

[11] (*a*) E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew Chem.*, 1964, **76**, 393; *Angew. Chem. Internat. Edn.*, 1964, **3**, 490; (*b*) A. Eschenmoser, R. Scheffold, E. Bertele, M. Pesaro, and H. Gschwend, *Proc. Royal Soc.*, 1965, *A*, **288**, 306; (*c*) M. Pesaro, I. Felner, and A. Eschenmoser, *Chimia*, 1965, **19**, 566; (*d*) I. Felner, A. Fischli, A. Wick, M. Pesaro, D. Bormann, E. L. Winnacker, and A. Eschenmoer, *Angew. Chem.*, 1967, **79**, 863; *Angew. Chem. Internat. Edn.*, 1967, **6**, 864.



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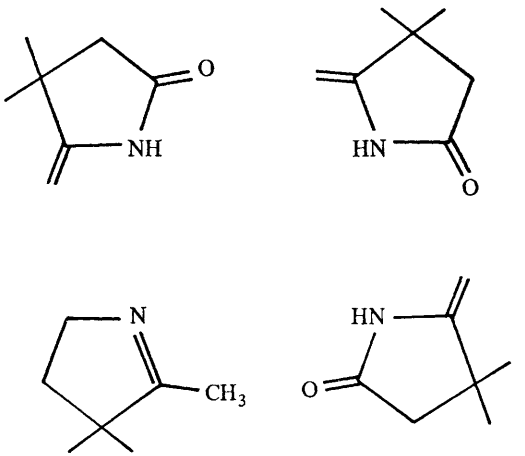


(4)

Figure 2—*continued*

assembly of structures (3); in other words, the latter can be considered to represent the products of a formal hydrolytic 'retrosynthesis' of the corrin chromophore. As simple and transparent as this formalism may appear, it had in fact served as an heuristic basis on which the strategy of the 'old' corrin synthesis was conceptually erected. From this way of looking at things the

problem of constructing the double-bond system of the corrin chromophore presented itself in principle as a reversal of formal hydrolytic processes, that is to say, as a series of stepwise carbon–carbon condensations between imide or lactam carbonyl groups and suitably activated carbon bridge components. The saturated structural district of rings A and D with their direct ring junction could, of course, not be covered by this type of formalism and, as a consequence, bicyclic dilactam derivatives of type (3a) were the obvious choice as starting materials containing these two rings. It was only recently that the formalistic concept of 'equality of oxidation level' could be boldly extended to include also the A/D-ring junction [see assembly of structures (4)] in order to serve once more as a retrosynthetic stimulant for the concept of still another (the 'new') type of corrin synthesis (see Section 4).

The concept of involving lactam and imide carbonyl groups in successive carbon–carbon condensations clearly required a method that would allow a smooth and dependable activation of the electrophilic reactivity of these systems.

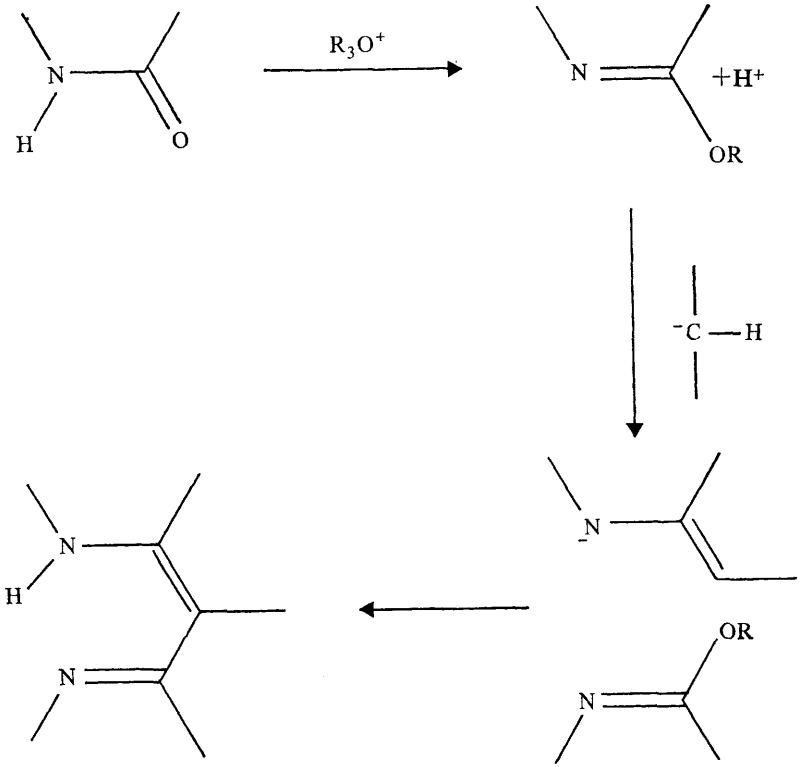


Figure 3

Alkylation at carbonyl oxygen with Meerwein's trialkyloxonium ions[12] proved to be such a method. Not in all, but in a great many instances iminoesters served satisfactorily as intermediates in the route which had to be developed for constructing derivatives of the vinylogous amidine system, which is [see formula (2)] the characteristic structural element of the corrin chromophore. Figure 3 gives an abstract of this condensation principle.

Figure 4 summarises the typifying final steps in the 'old' synthesis of corrin

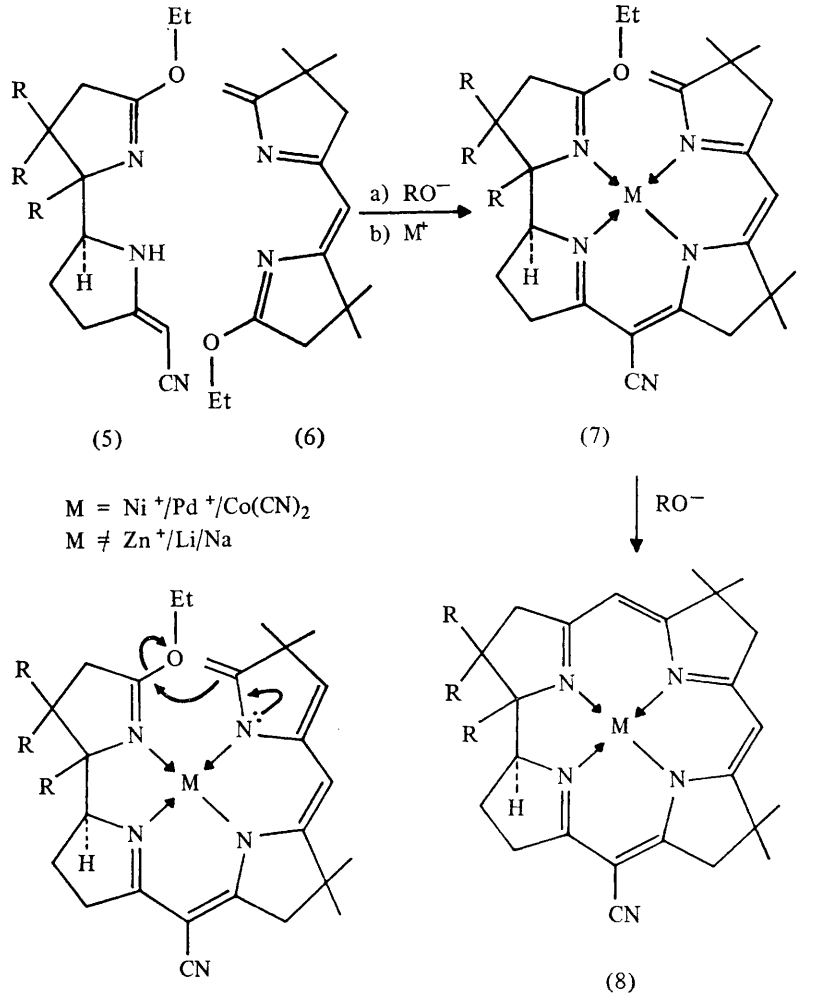


Figure 4

[12] H. Meerwein, H. Hinz, P. Hoffmann, E. Kroning, and E. Pfeil, *J. Prakt. Chem.*, 1937, **147**, 17; H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Wilfang, *J. Prakt. Chem.*, 1939, **154**, 83.

complexes. The approach demands the preparation of two components (5) and (6) containing rings A/D, and rings B/C respectively; the various ways which were developed for their preparation have been discussed elsewhere.[11] The two components are combined in a structurally specific way by two consecutive iminoester–enamine condensations. The first of them is induced by sodium ethoxide by NH-deprotonation of the enamine system of the A/D-component (5) leading to a specific intermolecular attack of the iminoester carbon of the B/C-component (6). Self-condensation of the A/D-component (5) is neither expected nor observed to occur since the conjugated iminoester system of the B/C-component is, for obvious reasons, more reactive towards C-nucleophiles than the isolated iminoester system in ring A. The labile precorrinoid ligand system is complexed with a transition metal ion [*e.g.* nickel(II), palladium(II) or cobalt(II→III)] in order to stabilise the system and, at the same time, to arrange the four nitrogens of the ligand in a common plane, bringing, thereby, the two remaining condensation centres of rings A and B into close proximity. The crystalline, diamagnetic metal complexes (7) do, in fact, cyclise smoothly under the influence of a strong base, *e.g.* potassium t-butoxide. The function of the base is to increase the nucleophilic reactivity of the exocyclic enaminoid methylidene carbon at ring B by deprotonation of the peripheral methylene group either at ring B [see intermediate (9)] or ring C.

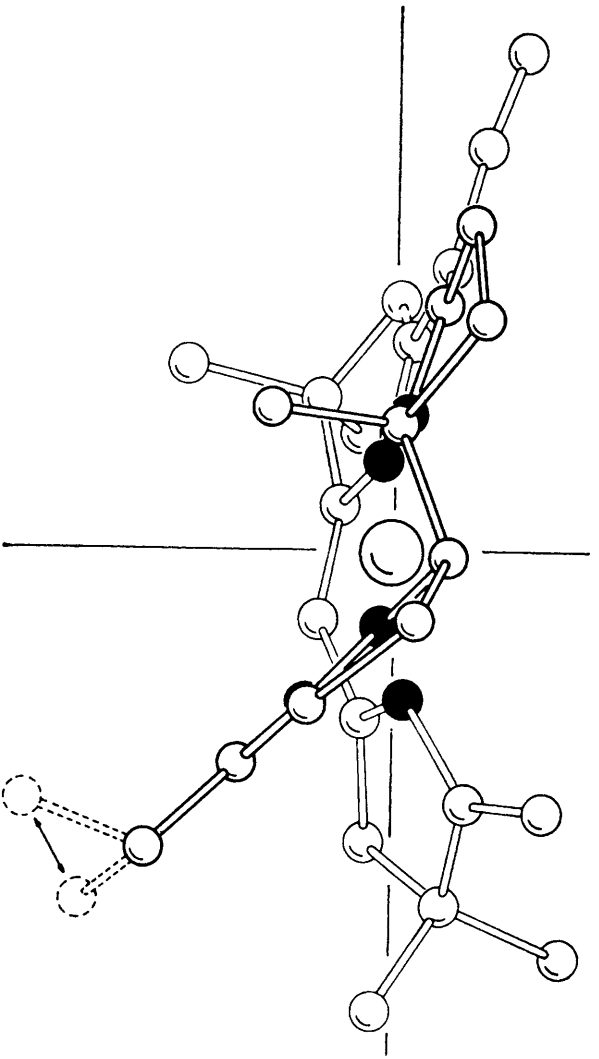
Two corrin complexes prepared in this way, namely nickel(II)-7,7,12,12,19-pentamethyl-15-cyano-corrin chloride and dicyanocobalt(III)-1,2,2,7,7,12,12-heptamethyl-15-cyano-corrin [(8), R = CH_3] have been subjected to *X*-ray crystallographic structure analysis in the laboratories of Professor J. D. Dunitz[13] and Professor P. Galen-Lenhert[14] respectively, so that full knowledge of the detailed structural properties of the ligand system in these complexes is available today. Thanks to a twofold contribution of Professor Dunitz's group[13,15] we are even in the rare possession of detailed insight into the structural reactant–product relationship in one of the precorrin→corrin transformations. Figure 5 presents side views of the structure of nickel(II) complexes in the above-mentioned pentamethyl series before [(10)[15]] and after [(11)[13]] cyclisation.[16] In the diamagnetic precorrinoid complex (10) the four nitrogen atoms and the nickel ion do in fact lie approximately in a common plane, and the two cyclisation centres in rings A and B are almost optimally juxtaposed for cyclisation, being separated by a distance of about 3·4 Å, which amounts to about twice the value of the van der Waals radius of a trigonal carbon.

What are the limitations of this type of corrin synthesis?

First of all, the method seems to be strictly confined to the preparation of corrin complexes of those transition metal ions which form robust complexes

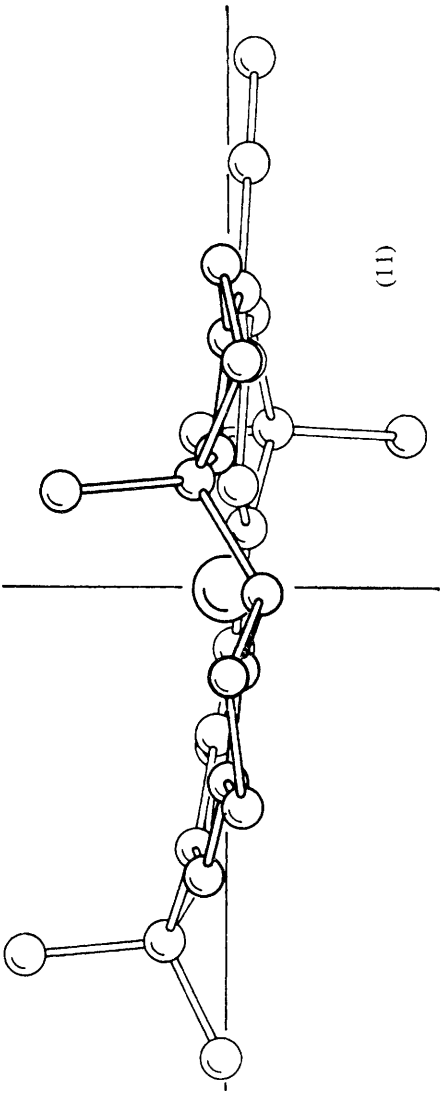
[13] J. D. Dunitz and E. F. Meyer, jun., *Proc. Royal Soc.*, 1965, *A*, **288**, 324.
[14] P. Galen-Lenhert and T. J. Shaffner (unpublished); *cf.* T. J. Shaffner, Thesis, Vanderbilt, 1969.
[15] M. Dobler and J. D. Dunitz, *Acta Cryst.*, 1966, **21**, A110.
[16] I thank Professor Dunitz, ETH, for kindly permitting the reproduction of Figure 5 before publication.

with the corresponding precorrinoid ligands. Experiments aiming at a cyclisation of the labile precorrinoid complexes of sodium, lithium or zinc have failed. This limitation precludes in particular the preparation of metal-free corrins since neither under acidolytic nor reductive conditions (cyanidation included) was it possible to remove metal ions, such as nickel, palladium or cobalt from their very stable corrin complexes without concomitant destruction of the ligand. The great stability of these complexes is, by the way, not due to an



(10)

Figure 5



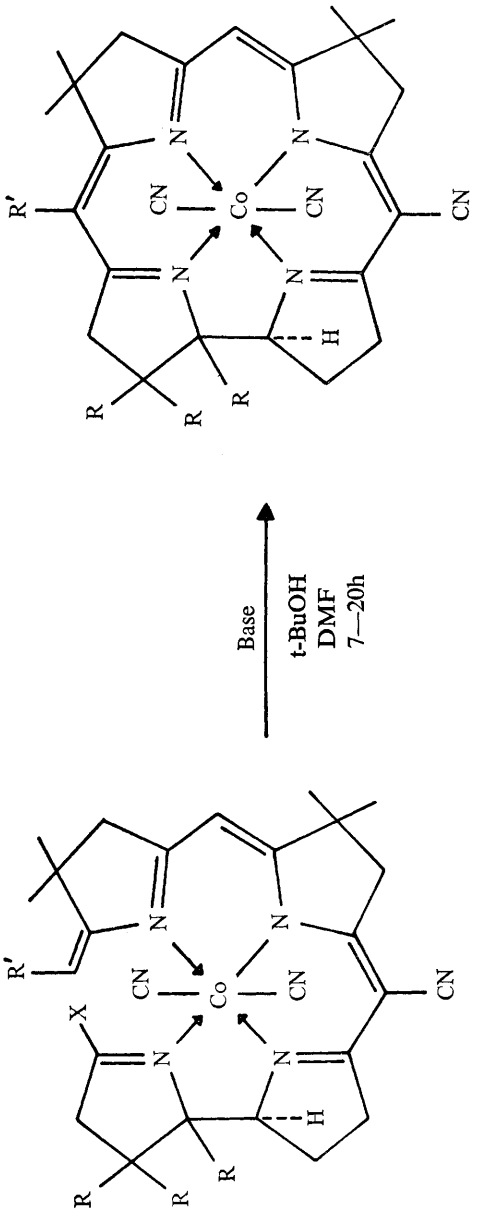
(11)

Figure 5—*continued*

inherently strong electronic metal–chromophore interaction, but is clearly a kinetic consequence of *macrocyclic chelation* (corresponding A/D-seco-corrinoid nickel complexes lose the nickel ion to cyanide ion with great ease; see later, Figure 24).

A further limitation of the method concerns the influence of the substitution pattern in the precorrinoid ligand on the ease of cyclisation of dicyano cobalt(III)-

complexes (12)→(13) (see Figure 6). Whereas in the least substituted series R=R¹=H (and likewise in the case of the corresponding 19-methyl derivative[11b]) the cyclisation proceeds smoothly at room temperature in over 90% yield, a



X	R	R'	
t-BuOK 20°	OC_2H_5	H	H	90%
t-BuOK 50°	OC_2H_5	$\underline{CH_3}$	H	65%
NaH(diglyme) 120°	OC_2H_5	$\overline{CH_3}$	$\underline{CH_3}$	10%
150°	OC_2H_5	CH_3	H	5%
150°	$\underline{SCH_3}$	CH_3	H	50%

Figure 6

vitamin B_{12}-like substitution by methyl groups in ring A [(12), $R=CH_3$, $R^1=H$] necessitates a somewhat higher reaction temperature and tends to have an adverse effect on the cyclisation yield. Not surprisingly, an additional methyl group at the critical methylidene reaction centre [(12), $R=CH_3$, $R^1=CH_3$][17a] hampers the cyclisation step to such an extent that the outcome may rather be called a 'mode of formation' of 5-methyl-corrin complexes [(13), $R^1=CH_3$] than a synthesis of them.

Ethyl di-isopropylamine, chosen as an example of a less aggressive base, hardly induces cyclisation of precorrinoid complexes of type (12) ($R=CH_3$, $R^1=H$, $X=OC_2H_5$) at all, even at high reaction temperatures. However, with a view to the problem of vitamin B_{12} synthesis, it was of interest to learn that the corresponding thioiminomethylester derivative [(12) $R=CH_3$, $R^1=H$, $X=SCH_3$] does cyclise at 150 °C in the presence of this base.[17b]

Irrespective of such limitations, this 'old' approach to corrins served its original purpose of bringing corrin complexes within the reach of organic synthesis, thereby making possible the initiation of studies contributing to an understanding of the chemical and physico-chemical properties inherent in this biologically important type of structure. Such studies have been done in our[18] and other[19] laboratories and some are still under way. Their results will not be discussed here with the exception of one which has an immediate bearing on a synthetic problem. It concerns the relative reactivity of the *meso* position of the corrin chromophore towards electrophilic substitutions.[18]

Figure 7 shows a reaction sequence by which methyl groups can be introduced with some degree of selectivity into the *meso* positions 5 and 15 of the corrin chromophore.[18b] Chloromethylphenylsulphide in the presence of silver tetrafluoroborate reacts at room temperature with the cobalt complex (14) to give the mono-substitution product (15). A subsequent treatment with Raney nickel produces the 15-methyl derivative (16). The observed specificity in this methylation is believed to be predominantly the result of steric control; however, a repetition of the process at a somewhat elevated reaction temperature (*ca.* 50 °C) starting from (16), produces the 5,15-dimethylated complex (17) and the isomeric 10,15-dimethyl derivative in a ratio of about 5:1. It seems therefore—and this is corroborated by deuteriation as well as cyanidation experiments[18a,b] and coincides, by the way, with calculated HMO-localisation energies[18c]—that the two 'natural' *meso* positions at the corrin chromophore are the somewhat more reactive ones in electrophilic substitution reactions. This fact merits attention with respect to vitamin B_{12} synthesis (and biosynthesis?) in the light of what has been said above about the A/B cyclisation to 5-methyl-corrin complexes.

[17] (*a*) D. Miljkovic and M. Roth; M. Roth, Thesis, ETH (to be published); (*b*) K. J. Schossig and M. Roth; M. Roth, Thesis, ETH.

[18] (*a*) D. Bormann, A. Fischli, R. Keese, and A. Eschenmoser, *Angew. Chem.*, 1967, **79**, 867; *Angew. Chem. Internat. Edn.*, 1967, **6**, 868. (*b*) E. L. Winnacker, Thesis, ETH, 1968; (*c*) R. Keese, *Tetrahedron Letters*, 1969, 149.

[19] H. Kuhn, K. H. Drexhage, and H. Martin, *Proc. Royal Soc.*, 1965, *A*, **288**, 384; P. Day, *Theor. chim. Acta*, 1967, **7**, 328; J. Seibl, *Org. Mass. Spectr.*, 1968, **1**, 216; B. Briat and C. Djerassi, *Nature*, 1968, **217**, 918, *Bull. Soc. chim. France*, 1969, 135.

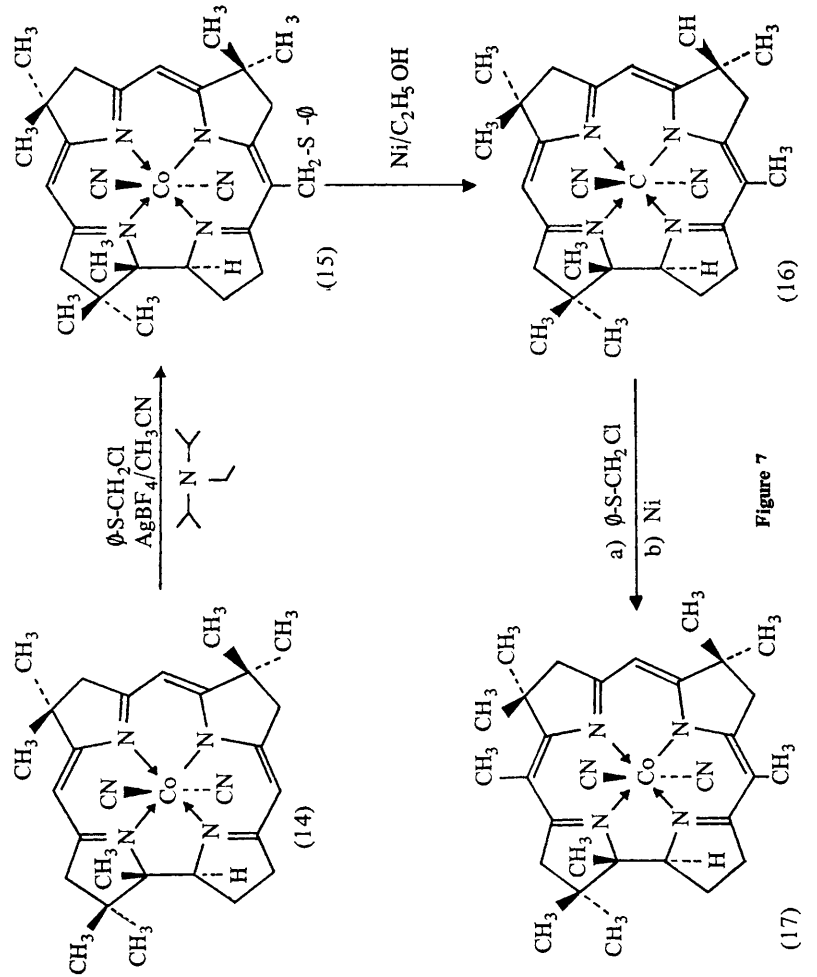


Figure 7

2 The Methods of Sulphide Contraction *via* Oxidative and Alkylative Coupling

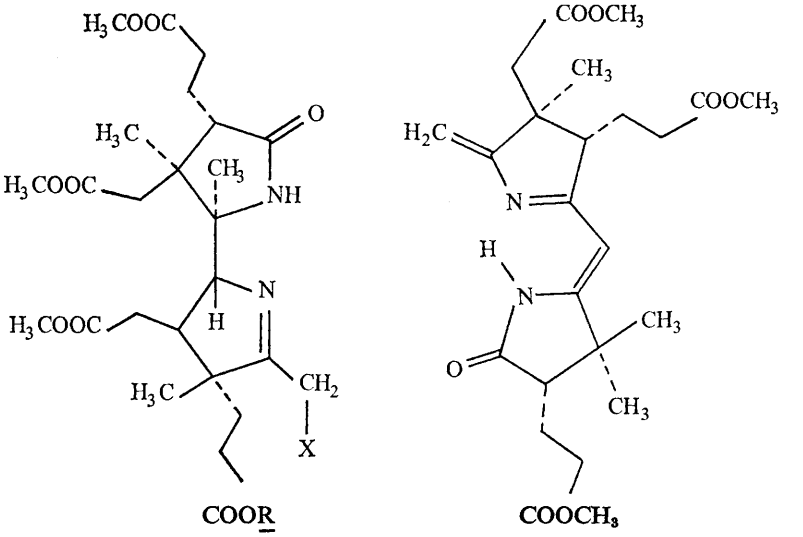
A fresh and lasting impetus to the field of corrin synthesis came from the work towards a synthesis of vitamin B_{12}. The relevant part of this development together with some of its consequences will now be discussed.

The translation of the concept of corrin synthesis

into a synthesis of vitamin B_{12} itself requires the construction of two bicyclic, optically active components of known chirality such as (18) and (19) (see Figure

8). In view of the complementary directions of the work that had, at the time, independently been started towards these goals in the Harvard and ETH laboratories, it was agreed with Professor R. B. Woodward to economise and channel the respective efforts towards a Harvard (A/D)- and an ETH (B/C)-

HARVARD ETH



(18) (19)

Figure 8

component and to merge eventually in the final problem of bringing the two components together. The present discussion remains confined to that crucial situation which built itself up in the central phase of the synthesis of the B/C-component (19), that is, in the coupling of the precursors of rings B and C (see Figure 9).[20]

[20] A discussion of the synthesis of the ring B precursor (20) and of its conversion to the ring C precursor (21) is given in A. Eschenmoser, Accademia Nazionale dei Lincei, Conferenze, X. Corso Estivo di Chimica, Roma 1968, 183; *cf.* theses, ETH, of J. Wild, 1964, U. Locher, 1964, A. Wick, 1964, R. Wiederkehr, 1968, and P. Dubs, 1969; exploratory work by J. Muchowski, J. Sims, D. Coffen, and T. Bogard; see also ref. 7.
The ring C material (21) used for the coupling experiments B+C→B—C has been prepared in the Harvard Laboratories[7] from (+)-camphor by a synthesis paralleling earlier investigations of J. W. Cornforth *et al.*[5]

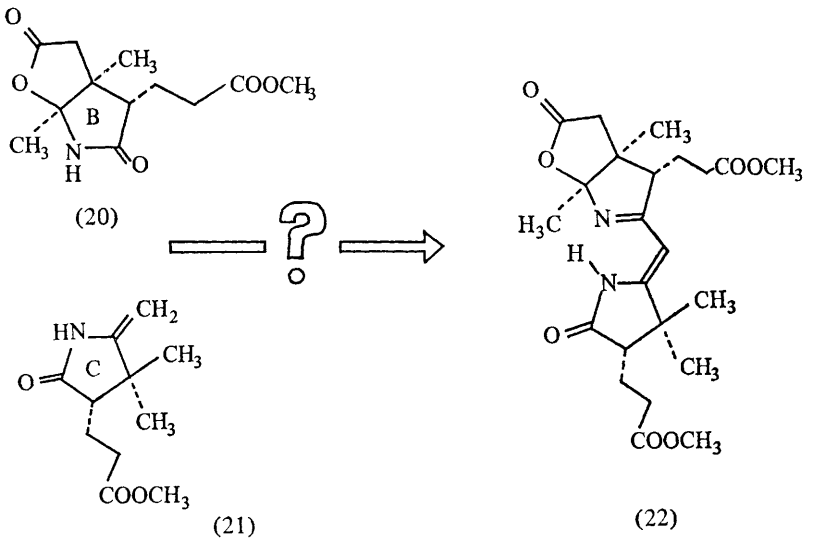


Figure 9

The problem of combining the ring B precursor in its lactone-lactam form (20) with the precursor of ring C in its enamide form (21) appears—remember the discussion on corrin retrosynthesis in Section 1—simply to be one of an intermolecular elimination of the elements of water to form the tricyclic structure (22); it implies, however, that central problem in corrin synthesis, namely, the construction of a ring-bridging vinylogous amidine system. Whereas the principle of iminoester-enamine condensation (see Figure 3) had served analogous purposes in a number of instances[11,21] in the synthesis of simpler corrins, it failed completely—and in a multitude of attempted structural versions and reaction conditions—to bring about a coupling of the ring precursors (20) and (21) in the desired direction. Combined experience out of these experiments and of investigations on related systems point at two main aspects of this failure. Firstly, the methylidene carbon of enamides of type (21), although quite reactive towards strong electrophiles,[22] appears not sufficiently nucleophilic for reacting with non-activated iminoesters in neutral or basic medium (attempts to induce condensation through acid catalysis were hampered by the instability of such enamides towards acids[2,22]) and secondly, iminoester derivatives of the bicyclic lactone-lactam (20) turned out to be much less prone to undergo condensations with carbanionoid partners than structurally analogous, but less substituted, iminoesters of the α-pyrrolidone family. While the first-mentioned property of enamides is clearly related to electrophilic deactivation of enamine reactivity

[21] W. Häusermann, Thesis, ETH, 1966.
[22] (*a*) R. Scheffold, Thesis, ETH, 1963; (*b*) W. Huber, Thesis, ETH, 1969.

by the acyl group, the latter reveals the iminoester condensation as a 'soft' process with a high susceptibility to steric hindrance.

Whenever in the synthesis of complex organic molecules one is confronted with a situation where the success of an intermolecular synthetic process is thwarted by any type of kinetically controlled lack of reactivity, one should look out for opportunities of altering the structural stage in such a way that the critical synthetic step can proceed intramolecularly rather than intermolecularly.

Adherence to this pragmatic principle in the situation described above and setting priority for the development of a general instead of—in the structural sense—a 'local' solution of the problem, led to what turned out to be a conceptual and eventually also a preparative breakthrough. The basic concept is abstracted in Figure 10.

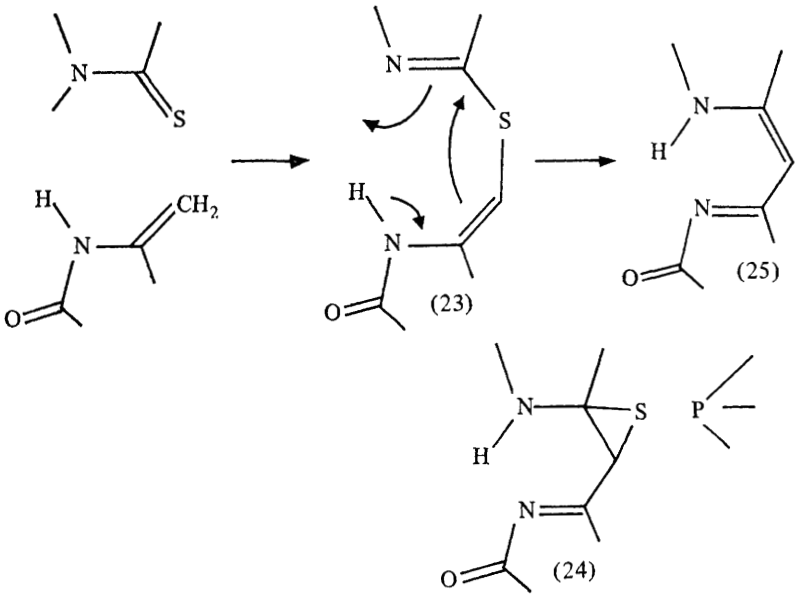


Figure 10

The lactam group of the one condensation partner is first converted to the corresponding thiolactam system. Its nucleophilic sulphur atom, sterically unhindered by being removed from any bulky substituents in the carbonyl environment by the long carbon–sulphur bond, is then linked to the methylidene carbon of the enamide partner to form a sulphur-bridged intermediate of type (23). Formally, such a system now fulfils the structural requirements for an *intramolecular* version of a (thio)iminoester–enamide condensation. The process [see 'arrowism' depicted in formula (23)] would result in an episulphide deriva-

tive of type (24) which, of course, could not be expected to appear as an actual product; it could, however, offer the chance of acting as a labile, reversibly formed intermediate in a reaction sequence leading either to a vinylogous *N*-acyl-amidine system (25) by loss of sulphur, or to a corresponding mercapto derivative by rearrangement. It is well known that the sulphur of episulphide systems departs quite often with great ease, especially to thiophiles like phosphines or phosphites, leaving behind a carbon–carbon double bond.[23] The overall result envisaged in this concept is, of course, reminiscent of a mechanistically loosely defined group of processes known in the chemical literature as 'sulphur extrusion reactions'.[24]

Extensive experimentation was required to clear the way from the concept to a preparatively acceptable synthetic process.[25] The most satisfactory coupling method turned out to be the oxidation of the thiolactam partner (20a) (Figure 11) with one equivalent of benzoylperoxide[26] in the presence of the enamide (21) and a trace of HCl. The identified intermediate in this process is the readily formed bis-imidoyldisulphide (26) which, in turn, induces an acid-catalysed electrophilic substitution at the methylidene carbon of the enamide; the liberated equivalent of thiolactam (20a) is recycled by further oxidation. The coupling product is subjected without isolation[27] to a thermal treatment with triethylphosphite to give a 1:2 mixture of the two epimeric B/C-components (22) and (22a) in 70% overall yield, whereby the β-epimer (22a) is easily obtained in crystalline form.

The configuration at the (CH)-position of ring B in vinylogous amidine derivatives of type (20)/(20a) has been found to be extremely labile: traces of HCl equilibrate the epimers (22)/(22a) in $CDCl_3$ at room temperature within a short time. The configuration of the crystalline main epimer (22a) is actually the 'unnatural' one; fortunately, this fact can be considered harmless because it has recently become known that in authentic vitamin B_{12} derivatives the corresponding position is likewise configurationally labile and that, luckily enough, the natural configuration is the more stable one.

According to the original concept, the structure of the final B/C-component had been envisaged to contain an enaminoid exocyclic methylidene group at ring B [see (19) in Figure 8]. In practice, however, this structure turned out to be unstable relative to its endocyclic tautomer (27) which was formed as the exclusive product when the tricyclic lactone derivative (22a) was subjected to the ring-opening conditions of methanolic sodium methoxide in the presence of an excess of diazomethane[28] (see Figure 12). On the other hand, extended

[23] N. P. Neureiter and F. G. Bordwell, *J. Amer. Chem. Soc.*, 1959, **81**, 578; D. D. Denney and M. J. Boskin, *ibid.*, 1960, **82**, 4736; M. Sander, *Chem. Revs.*, 1966, **66**, 326.
[24] J. D. Loudon, in 'Chemistry of Organic Sulphur Compounds' ed. N. Kharash, Pergamon, Oxford, 1961, vol. 1 p. 299.
[25] B. Golding, P. Löliger, and H. Gschwend; *cf.* P. Löliger, Thesis, ETH, 1968.
[26] *cf.* F. Hodosan, *Bull. Soc. chim. France*, 1957, 633.
[27] The structure of the sulphur-bridged coupling product has been fully characterised in a closely related model system derived from thiolactam (20a) and the enamide (39).[25]
[28] The corresponding equilibrium ratio between the tautomers with exocyclic and endocyclic double bonds is about 1:1 ($CHCl_3$; *ca.* 30°) in the case of the less substituted analogue (44).[11b]

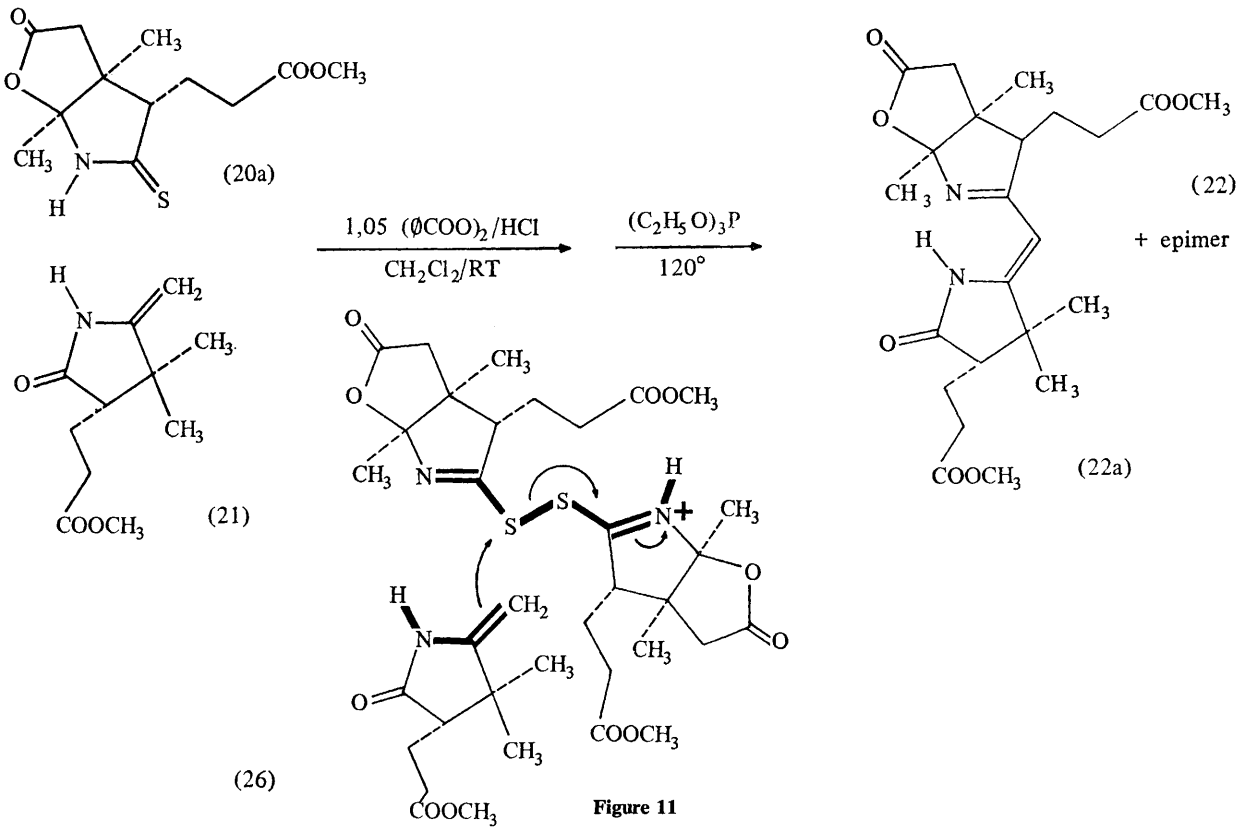


Figure 11

model studies on the problem of the D/C-coupling of the A/D- and B/C-components had eventually made it clear that very probably not an iminoester condensation, but a coupling *via* sulphide contraction would have to bring about this major synthetic step. Therefore, the thiolactam structure (29) came to be considered as the final form of the ETH component; the reaction scheme (22a)→(28)→(29) in Figure 12 summarises its preparation from the corresponding lactam derivative (22a). The intermediate conversion of the free lactam to the methylmercury complex (28) with methylmercury isopropoxide[29] served the purpose

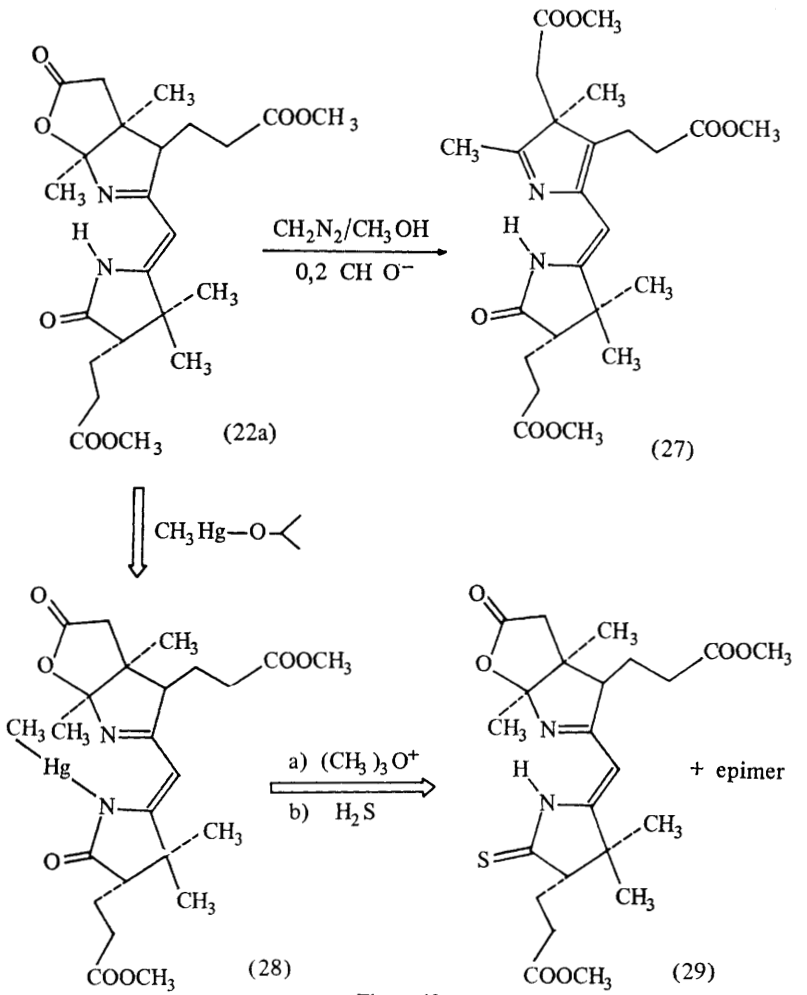


Figure 12

[29] R. Scheffold, *Helv. chim. Acta*, 1969, **52**, 56.

of achieving a smooth and specific *O*-alkylation with trimethyloxonium-tetrafluoroborate.

Vinylogous amidines are diaza-derivatives of β-dicarbonyl systems. It should, therefore, be possible to adapt the condensation principle of sulphide contraction to the synthesis of other potential β-dicarbonyl systems and also of β-dicarbonyl compounds themselves. This indeed proved to be the case by an alternative preparative version of the condensation principle, namely, by the method of sulphide contraction *via* alkylative (compared to oxidative) coupling (see Figure 13).

Sulphide contraction via alkylative coupling

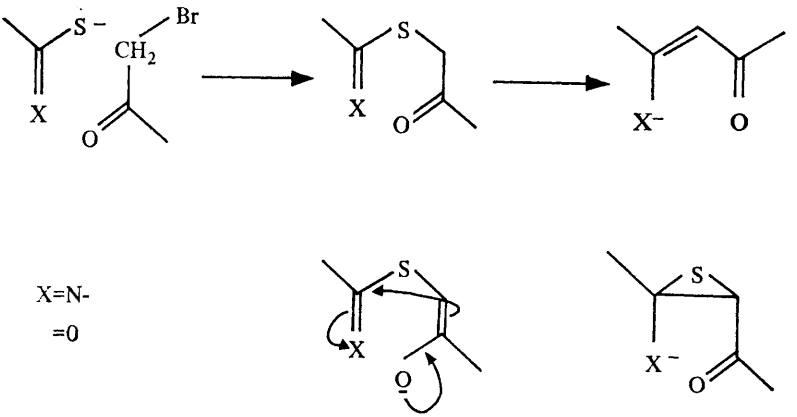
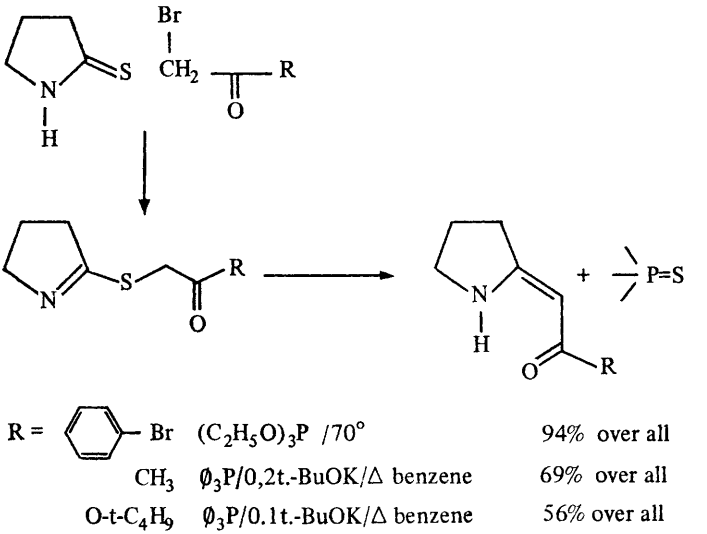


Figure 13

Thioamides and salts of thioacids are known to be *S*-alkylated by α-bromocarbonyl compounds with great ease to give the corresponding thioiminoesters and thioesters respectively. As indicated in Figure 13, these alkylation products in their adequately enolised form possess the complementarily arranged reactivity centres required for intramolecular 1,3-condensations and subsequent sulphur transfer, that is, for processes completely analogous to the one discussed above in connection with the formation of vinylogous amidines. The results of experiments carried out on simple systems do, in fact, amply illustrate the preparative feasibility and apparent generality of this method for the synthesis of vinylogous amides and β-dicarbonyl compounds.[30]

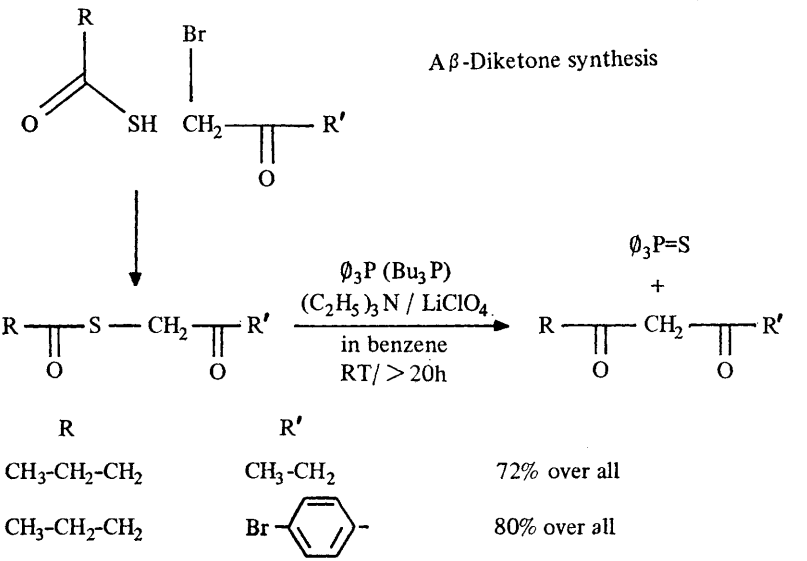
[30] (*a*) P. Dubs, Thesis, ETH, 1969; (*b*) M. Roth, Thesis, ETH (to be published), see also P. Dubs, E. Götschi, M. Roth, and A. Eschenmoser, *Chimia*, 1970, **24**, 34.

A Synthesis of Vinylogous Amides



R =	Br	$(C_2H_5O)_3P$ /70°	94% over all
	CH_3	ϕ_3P/0,2t.-BuOK/Δ benzene	69% over all
	O-t-C_4H_9	ϕ_3P/0.1t.-BuOK/Δ benzene	56% over all

Figure 14



R	R'	
CH_3-CH_2-CH_2	CH_3-CH_2	72% over all
CH_3-CH_2-CH_2	Br-C$_6$H$_4$-	80% over all

Figure 15

The examples chosen to illustrate the formation of vinylogous amides[31] (see Figure 14) reveal some plausible reactivity differences. In contrast to the case of the aromatic ketone derivative (R = *p*-BrC_6H_4), the examples with bromo-acetone and α-bromo-t-butylacetate require the presence of a catalytic amount of base in order to induce the enolisation considered to be necessary for the contraction process. The presence of a base is also compulsory for the contraction of the thioester derivatives of Figure 15 to the corresponding β-diketones. Not surprisingly, these conversions can easily be achieved in high yields *e.g.* by potassium t-pentoxide and triphenylphosphine (or tributylphosphine) in benzene at somewhat elevated temperatures; however, of greater preparative interest is the discovery that tertiary organic amines cleanly induce these contractions at room temperature in benzene, provided that anhydrous lithium perchlorate is present.[30b] This salt has been found to be the most effective catalyst among a number of metal salts tested in order to find an *S*- and/or *O*-complexing agent that would speed up either the enolisation step or the contraction process, or even both. Admittedly, there is hardly any dearth of methods available for the preparation of β-dicarbonyl compounds; however, mildness of reaction conditions, potential versatility,[32] and structural controllability are properties which may well hold out some prospect for the method as a new tool in organic synthesis. (*Note added in proof.* The potentially unsafe $LiClO_4$ can be replacedby LiBr.)

Things in the field of corrin synthesis started moving again, after the B/C-problem in vitamin B_{12} synthesis had, so to say, given birth to the sulphide contraction method. The next two sections deal with such developments.

3 Synthesis of Metal-free Corrins by A/B-Cyclisation *via* Suplhide Contraction[33]

As previously discussed, an important limitation of the synthesis *via* A/B-iminoester cyclisation is its restriction to the synthesis of corrin complexes with those metal ions which form robust square planar or octahedral complexes with the precorrinoid ligand, but which cannot, so far at least, be removed again after cyclisation. It was the method of A/B-cyclisation by sulphide contraction *via* oxidative coupling that was found to cure the situation. At the time, a major impetus to get metal-free corrin ligands accessible by synthesis had come from J. I. Toohey's[34] surprising and important discovery of cobalt-free corrinoid natural products occurring in certain photosynthetic bacteria. Peculiar chemical and spectroscopic observations on these products clearly made a study of structurally well-defined synthetic derivatives desirable. Furthermore,

[31] This type of formation of vinylogous amide systems has been adumbrated by observations described by E. B. Knott, *J. Chem. Soc.*, 1955, 916.

[32] It has been found more recently that the method is also applicable to the synthesis of enolizable β-diketones, β-formylketones, and β-keto-esters which are alkylated in the α-position.[30b]

[33] A. Fischli and A. Eschenmoser, *Angew. Chem.*, 1967, **79**, 865; *Angew. Chem. Internat. Edn.*, 1967, **6**, 866; *cf.* A. Fischli, Thesis, ETH, 1968; H. U. Blaser, Thesis, ETH, (to be published).

[34] J. I. Toohey, *Proc. Nat. Acad. Sci. USA*, 1965, **54**, 934; *Fed. Proc.* 1966, **25**, 1628.

an availability of synthetic metal-free corrin ligands could be expected to open the door to a colourful (and theoretically interesting) palette of new corrin complexes.

An A/B-cyclisation *via* sulphide contraction was originally planned to start from a precorrinoid ligand containing a thiolactam group in ring A and being loosely complexed with a metal ion like zinc(II) which could be removed again after cyclisation by acidolysis. However, the treatment of a precorrinoid sodium salt of type (7) (M = Na; R = CH_3, see Figure 4) with hydrogen sulphide in the presence of trifluoroacetic acid, followed by complexation with zinc(II) perchlorate, did not produce a thiolactam derivative, but the cyclic isomer (30) (see Figure 16). Notwithstanding, reaction conditions could be elaborated which make use of this product as a starting material for the sulphide contraction process. Reaction with benzoylperoxide in methylenechloride in the presence of trifluoroacetic acid brings about the desired oxidative coupling of the sulphur to the exocyclic methylidene carbon of ring B; the crystalline complex (31) can be isolated in as much as 72% yield after contact of the reaction mixture with methanol. Subsequent treatment with trifluoroacetic acid in dimethylformamide at elevated temperature leads to contraction and produces the corrin complexes (32) and (33), the former as the main product, in spectroscopic yields up to 80%.

The formulae (30a)—(31c) depict a tentative interpretation of the rather intricate series of processes involved. We assume that in the first step trifluoroacetic acid can establish the conversion of (30) to the thiolactam derivative (30a) [(30) does not react in the absence of acid], and that the latter is attacked by benzoylperoxide to form the *O*-benzoate of the thiolactam-*S*-oxide (30b) which then reacts—very probably assisted by the template effect of the zinc ion[35]—with the enaminoid methylidene carbon of ring B to give the sulphur-bridged intermediate (31a). Consideration of molecular models reveals the interesting feature that the ring B double bond of this intermediate is not expected to return easily to the exocyclic position, as long as the nitrogen atoms of rings A and B remain co-ordinated to the central zinc ion; the geometrical situation created by the sulphur bridge in a complex is such that the double bond in the exocyclic position is expected to be heavily strained. Yet, restoration of that double bond in the exocyclic position is clearly a prerequisite for the reaction to proceed further in the desired direction. The fact that sulphide contraction (31)→(32), (33) does occur with trifluoroacetic acid in dimethylformamide suggests that an acid induced decomplexation of the ligand system precedes the formation of an intermediate of type (31b) in which the system can now better accommodate the exocyclic double bond by virtue of the higher flexibility of the free ligand system compared to its zinc complex. Contraction to the hypothetical episulphide intermediate (31c) and a subsequent, not unexpected, rearrangement leads then to the 5-mercapto-corrin ligand which is isolated as its crystalline zinc complex (32). The following experimental fact strongly

[35] The same treatment on a decomplexed derivative of (30) produces only small amounts of corrinoid products.

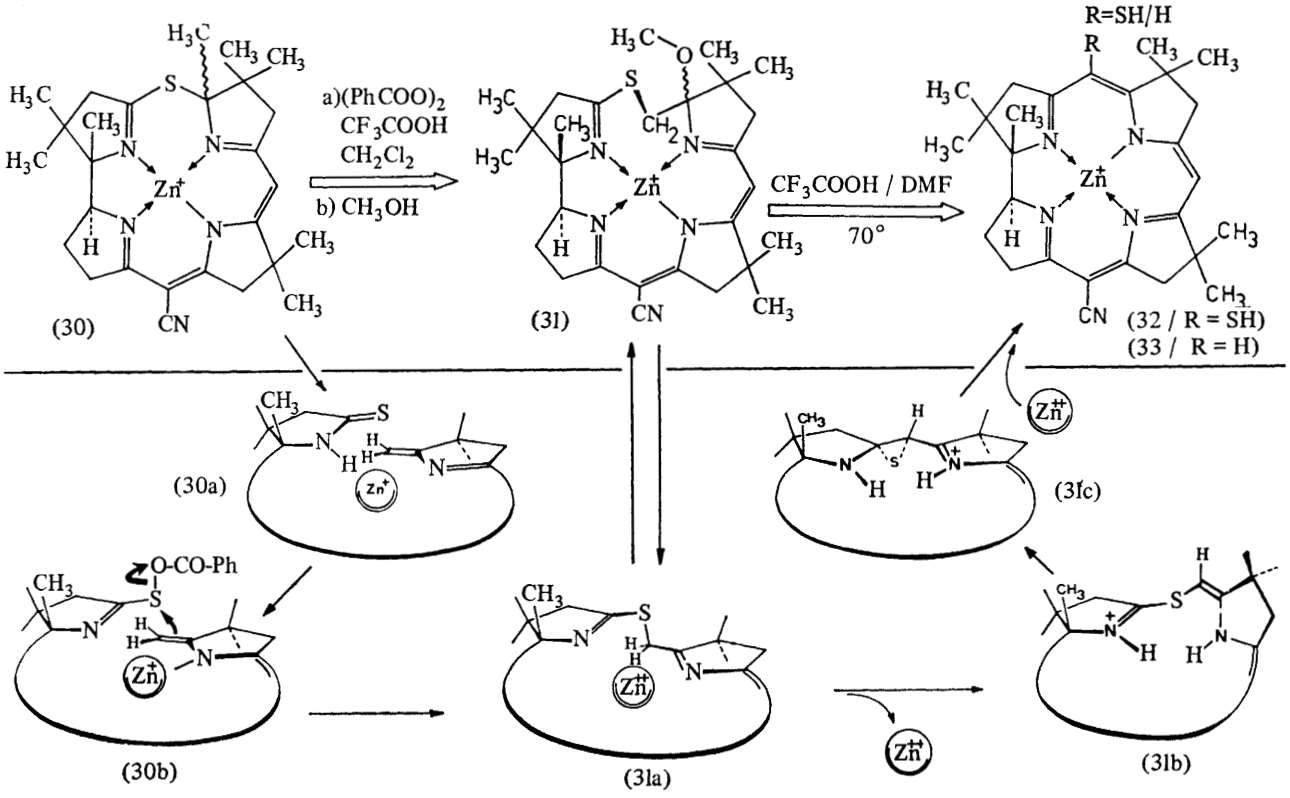

(30)
a)(PhCOO)2
CF3COOH
CH2Cl2
b) CH3OH
(31)
CF3COOH / DMF
70°
R=SH/H
(32 / R = SH)
(33 / R = H)
(30a)
(31c)
(30b)
(31a)
(31b)

Figure 16

supports the decomplexation hypothesis: treatment of the sulphur-bridged complex (31) with trifluoroacetic acid in dimethylformamide in the presence of 2 additional equivalents of zinc ions no longer produces appreciable amounts of the corrinoid products (32) and (33). It has been checked that these complexes would, in fact, survive these reaction conditions if they were formed.

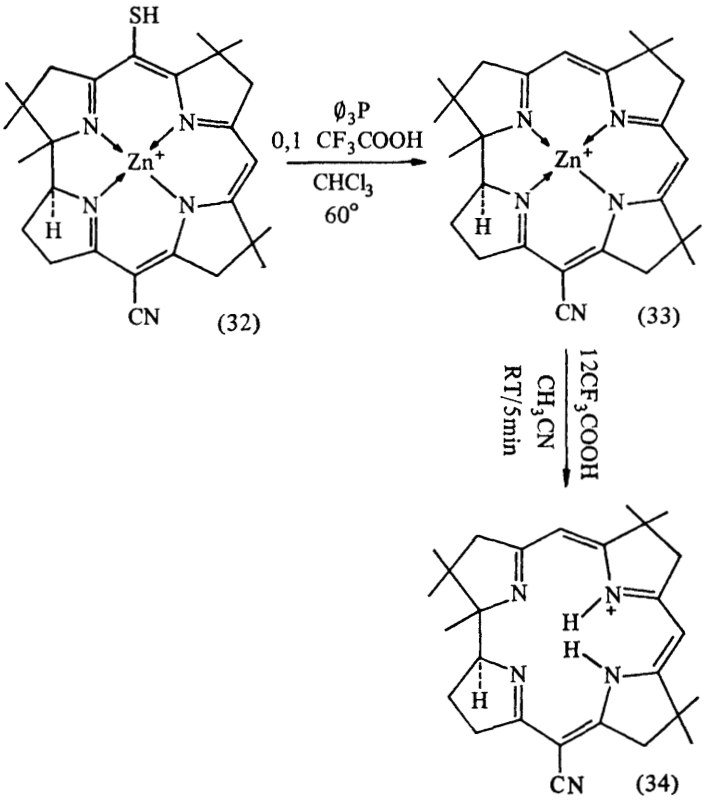
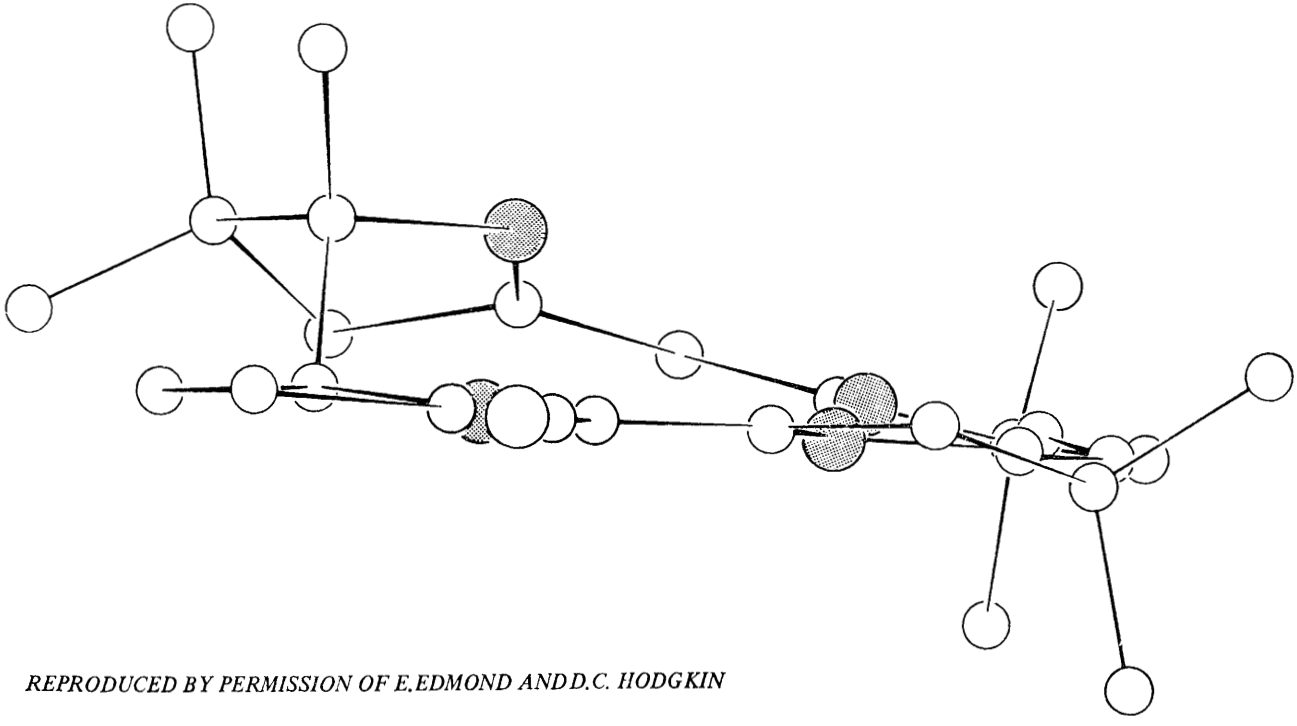


Figure 17

The 5-mercapto-corrin zinc complex (32) can be cleanly desulphurised by triphenylphosphine in the presence of trifluoroacetic acid in chloroform to give the corrin zinc complex (33) which, in sharp contrast to the behaviour of the corresponding robust complexes of nickel, cobalt, and palladium, loses the metal ion with delightful ease under the influence of trifluoroacetic acid in acetonitrile. Various corrinium salts, tentatively[36] formulated as (34), have been isolated in crystalline form.

[36] The tentativeness in this formulation refers to the position of the two NH-hydrogens only. The gross constitution has been chemically proved by conversion of (34) to the known dicyanocobalt(III) complex [8, R = CH_3; M = $Co(CN)_2$].

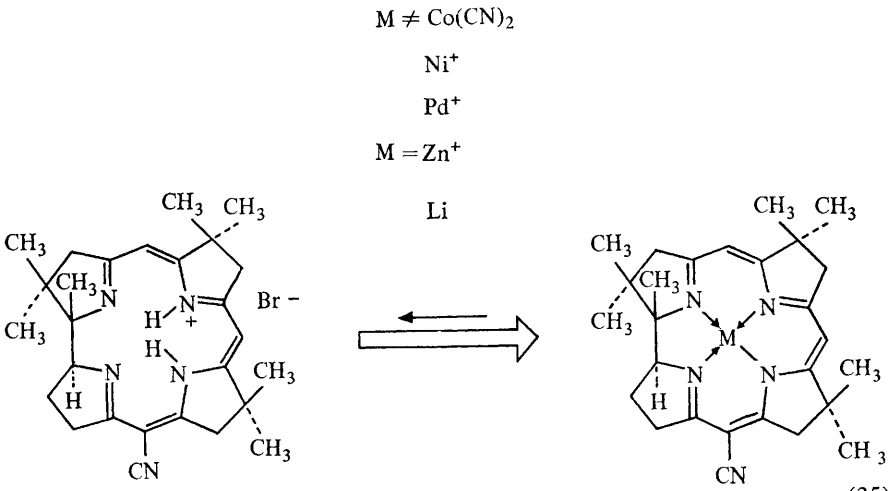


REPRODUCED BY PERMISSION OF E.EDMOND AND D.C. HODGKIN

Figure 18

Figure 18 reports a very recent contribution from Oxford, that is, the result of an *X*-ray structure analysis of the 1,2,2,7,7,12,12-heptamethyl-15-cyano-corrinium bromide (34; X = Br)[37]. While the analysis fully confirms the constitution and the configuration of the synthetic ligand system, it reveals surprising structural details about the substance in its solid state. Rings B, C, and D are almost perfectly placed in a common plane, whereas ring A dramatically sticks out of that plane, and its nitrogen—admittedly to our astonishment—appears bonded to one of the two immonium hydrogens which is also engaged in a hydrogen bridge to a molecule of ethanol, the solvent of crystallisation.

The introduction of various metal ions into the synthetic corrin ligand (34) has not, as yet, presented major difficulties; specific reaction conditions for different metal ions had to and could be found in order to produce the respective (crystalline and diamagnetic) metal complexes (35) in good yields [*e.g.* over 90% for M = $Co(CN)_2$]. Figure 19 summarises the experience hitherto available.



M = $Co(CN)_2$	$Co^{II}(ClO_4)_2$	/CH_3CN	/RT→O_2/CN^-
Ni^+	$Ni^{II}(CH_3COO)_2$	/CH_3CN	/70°
Pd^+	$Pd^{II}(CH_3COO)_2$	/C_2H_5OH	/70°
$Rh(CN)_2$	$[Rh^I(CO)_2Cl]_2$	/CH_3COOH(Na)	/100°→O_2/CN^-
Zn^+	$Zn^{II}(ClO_4)_2$	/CH_3CN/R_3N	/RT
Li	LiOH	/$CHCl_3$	/RT

Figure 19

[37] E. Edmond and D. Crowfoot-Hodgkin, unpublished results; I thank these authors for kind permission to report these results before publication.

The situation with respect to the reversal of these complexations has been discussed already (see above).

There is one feature among the chemical properties of synthetic metal-free corrinium salts of type (34) deserving here a special comment: ironically, the neutral metal-free species in this series prefers to exist as a non-corrin. Monodeprotonation of the corrinium ion (34) by tertiary amines in nonpolar solvents or by sodium hydroxide in ethanolic solution leads to an 'enaminised' form of the neutral ligand (pK^*_{MCS} 8·6 in titration by 0·1 N-HCl in dimethyl-cellosolve–water 1:1). The structure (36) is based on the distinct presence of *three* different vinyl protons in the n.m.r. spectrum, the position of the enaminoid double bond being inferred from the experimentally established fact[18a] that in synthetic nickel(II) and cobalt (III)complexes the methylene group in ring B is the preferred site of peripheral CH-deprotonation. Figure 20 reflects the course of deprotonation by the electronic spectrum which cleanly (and reversibly) decays to a non-corrinoid spectrum which is highly reminiscent of the one observed by J. I. Toohey[34] for natural metal-free corrinoids in strongly alkaline solution.

4 'The New Road': Synthesis of Corrins *via* Photochemical A/D-Cycloisomerisation[38]

A characteristic feature of the corrin syntheses discussed so far is a final metal-template-assisted cyclisation between rings A and B. Inevitably, this type of approach requires the construction of bicyclic precursors containing rings A and D and implies the solution of the major configurational problem of connecting these two rings together stereospecifically in a *trans* fashion. To impose stereospecificity on such a ring-connecting process would truly be a worthy task for a metal template, and this, in fact, is a central feature of the following alternative concept of corrin synthesis: To construct first the corrin chromophore by joining rings A, B, C, and D together, to introduce then a metal ion, and to achieve finally a cyclisation between rings A and D under both the constitutional and configurational control of the metal template. Such an approach, beside being reminiscent of A. W. Johnson's[3] syntheses of corrole and tetradehydrocorrin systems, has been inspired and forcibly promoted by the specific structural regularities present in the natural corrinoids. These regularities reflect themselves in a remarkable network of synthetic opportunities emerging from a retrosynthetic analysis of the cobyric acid structure (see Figure 21).

Take the chiral dilactone-monocarboxylic acid (37) as the starting material. An elongation of the free carboxylic acid chain by one methylene unit, followed by a structurally specific replacement of one of the endocyclic lactone oxygens by NH and, finally, conversion of the potential methyl ketone system into its enamide form, leads to a compound which can serve as the precursor not only of ring B, but potentially also of ring A. The precursor of ring C in its enamide form differs from the ring A/B precursor by nothing more than the

[38] Yasuji Yamada, D. Miljkovic, P. Wehrli, B. Golding, P. Löliger, R. Keese, K. Müller, and A. Eschenmoser, *Angew. Chem.*, 1969, **81**, 301; *Angew. Chem. Internat. Edn.*, 1969, **8**, 343.

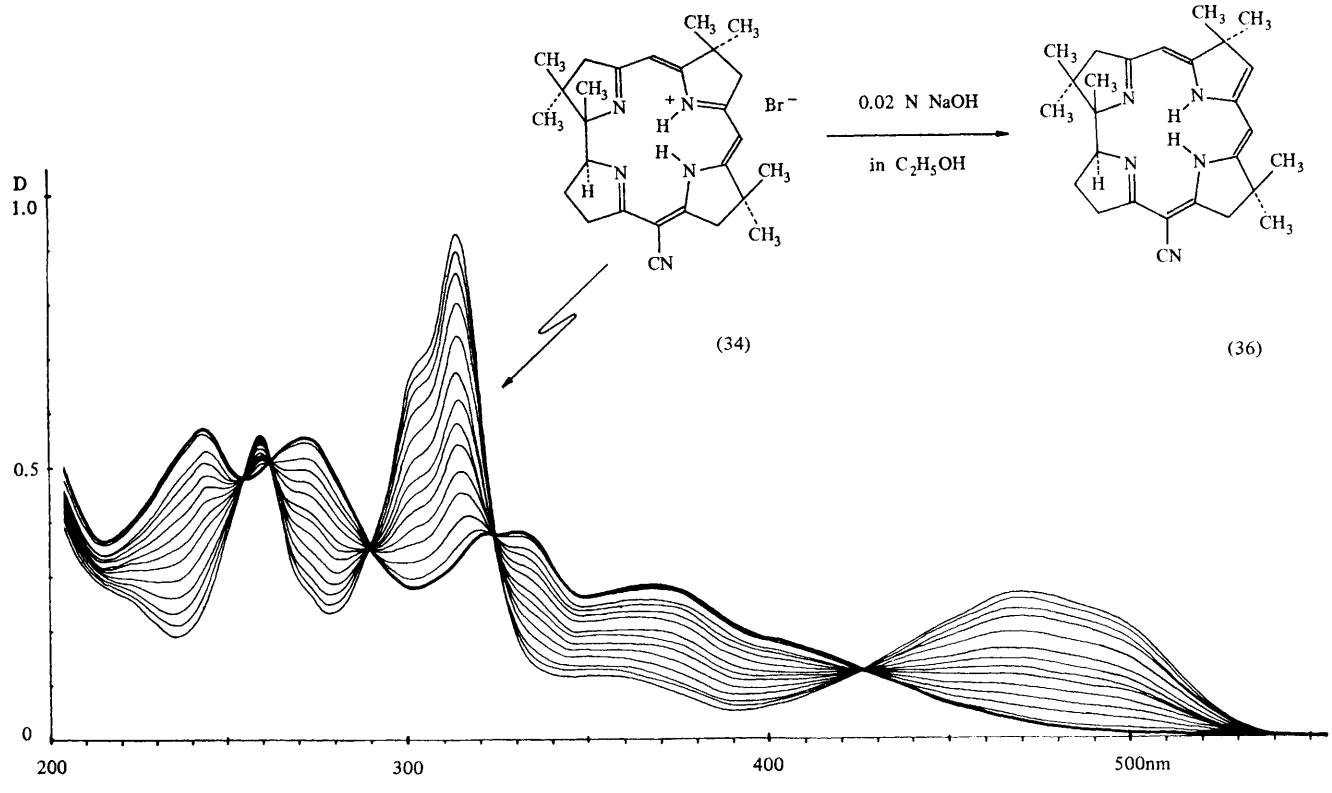
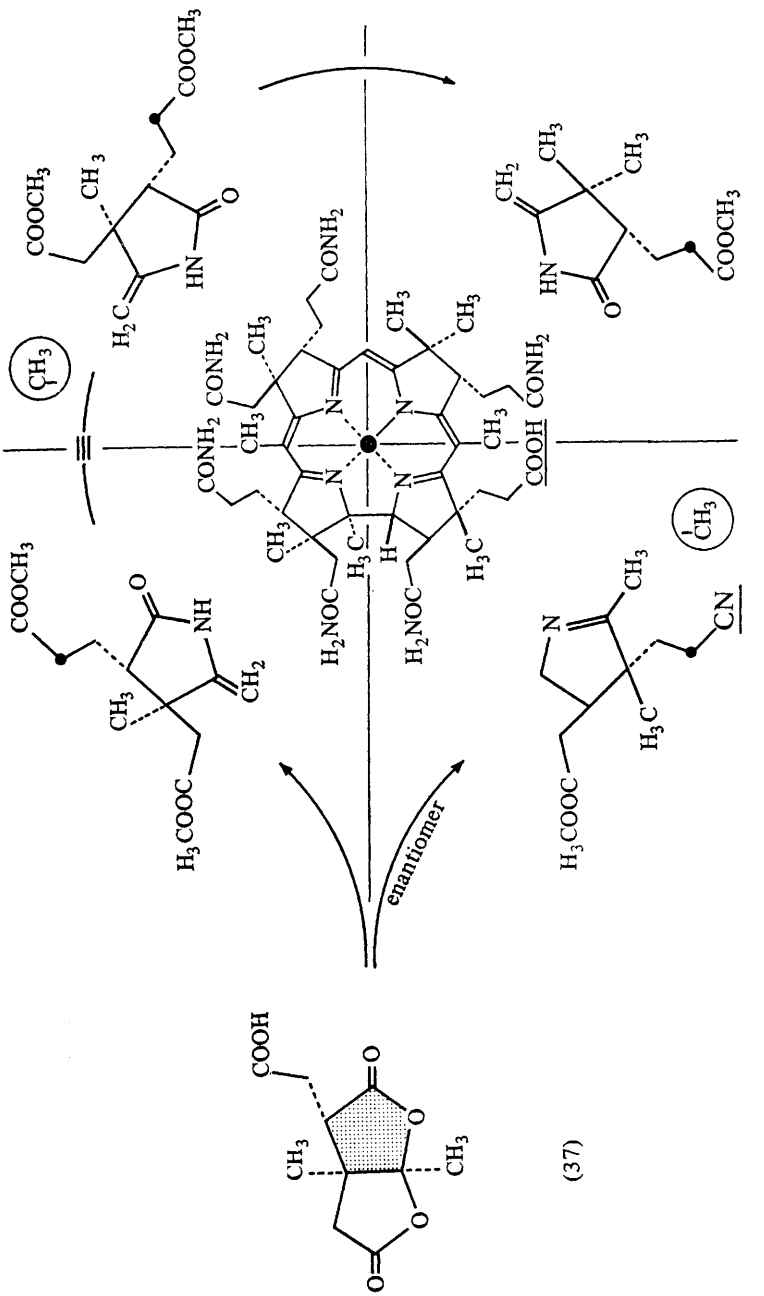


Figure 20



(37)

Figure 21

carbomethoxy group of the acetic acid side chain being replaced by hydrogen. A chemical realisation of this relationship makes the ring C precursor available from the A/B-intermediate. A reaction sequence essentially analogous to the one which leads from the dilactone-monocarboxylic acid (37) to the A/B-precursor can transform the enantiomeric form of the same starting material into a potential precursor of ring D, provided that not the free acetic acid side chain, but rather the lactonised (CH_2-CO-O)-chain is lengthened by a methylene unit. In doing that, an important requirement must be taken care of, namely, that the propionic carboxy function of ring D must eventually be chemically differentiable from all other carboxy functions. Finally, the specific ring D concept illustrated in the Figure implies a reductive replacement of the lactam carbonyl group by a methylene group.[39]

This strategy ignores one special feature of the cobyric acid structure, namely, the two extra methyl groups bound to the corrin chromophore at the meso carbons between rings A/B and C/D. Placing a corresponding methyl group in the starting material (37) seems easily possible, but would destroy at once the synthetic relationship between the four ring precursors. These methyl groups are to be introduced *post festum* (compare Figure 7).

To sum up at this point: clearly as a reflection of underlying regularities in the biosynthesis of the natural corrinoids, we find ourselves confronted with the striking opportunity that the two enantiomers of one single starting material appear convertible to three optically active, chirally correct intermediates which could serve as precursors of all four rings in a potential synthesis of cobyric acid—provided that methods are, or could be made, available for putting them together.

A tailor-made method for the construction of the chromophore part had in the meantime come to hand, the method of sulphide contraction *via* oxidative coupling. The extraordinary challenge to provide a potential solution for the other and most crucial problem, the final A/D-cyclisation, gave the impetus to recent investigations which led to a new and, as we now know, rather broad road to corrins. Figure 22 formulates the concept at the structural level of simple enamide enamine ring precursors.

As delineated earlier, the assembly (4) of the four simple ring precursors is on the same oxidation level as the ligand system of a corrin complex (35). Furthermore, an A/D-seco-corrinoid metal complex of type (38) is isomeric with the corrin complex (35), the two systems differing only in the position of one hydrogen atom and of one carbon–carbon bond. Models of such seco-corrinoid metal complexes display the ligand system coiling around the metal ion and having a ring D methylene hydrogen atom lying directly underneath the exocyclic methylidene double bond of ring A; this is true the more one tries to hold all four ligand nitrogen atoms in a common plane with the co-ordination centre. A jump of this hydrogen atom to the methylidene carbon would formally create a new conjugated 15-centre-16-electrons π-system of admittedly higher energy

[39] The synthesis of the ring D precursor formulated in Figure 21 from the enantiomer of (37) has actually been accomplished (R. Wiederkehr, P. Dubs, and W. Fuhrer).

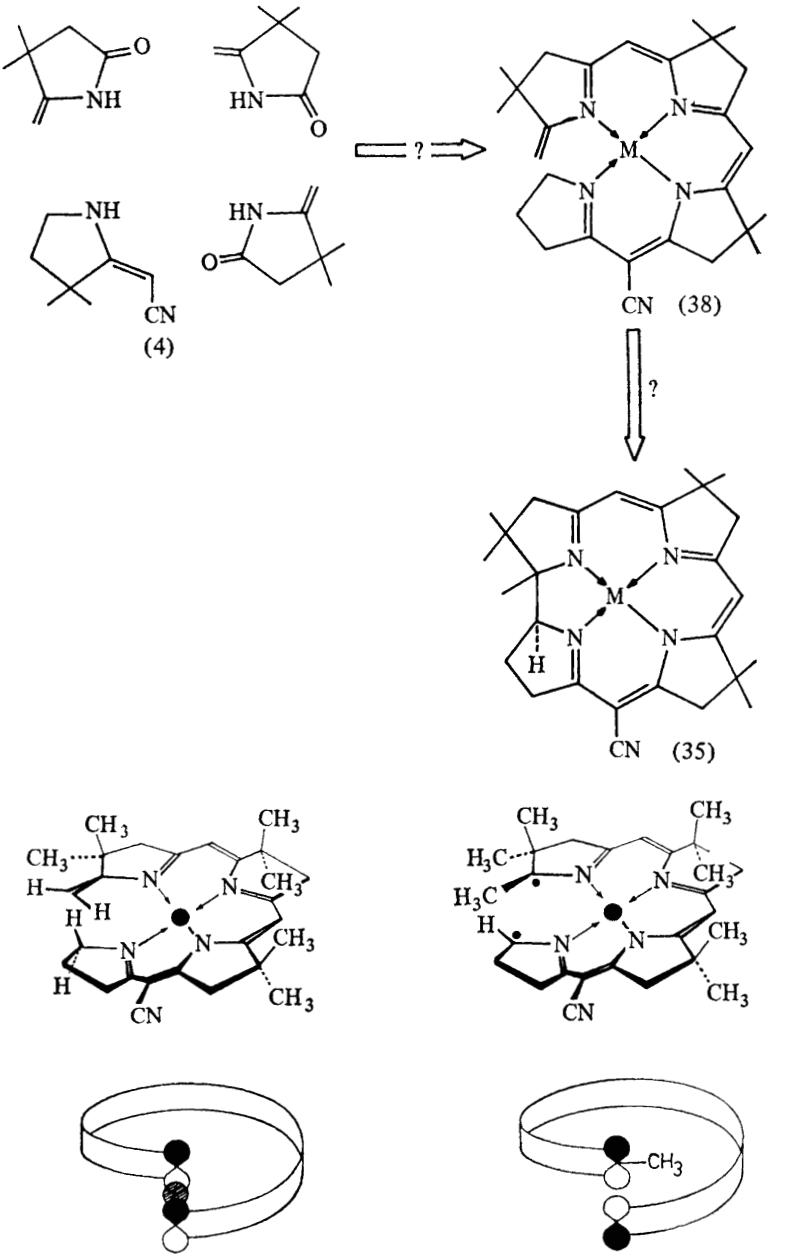

NH
O
HN
O
NH
CN
(4)
HN
O
?
N
N
M
N
N
CN
(38)
?
N
N
M
N
N
H
CN
(35)
CH3
CH3
CH3
H
N
N
CH3
H
H
N
N
CH3
H
CN
CH3
CH3
CH3
H3C
N
N
CH3
H3C
H
N
N
CH3
CN
CH3
CH3
CH3

Figure 22

(it cannot be presented by a classical formula if one neglects 1,3 σ-bonds), but which in turn could gain the stabilisation of a carbon–carbon σ-bond by simple collapse to the corrin complex (35). Stereochemically, such a collapse within a helically deformed planoid metal complex could hardly avoid leading to the *trans* configuration of the A/D ring junction.

At an earlier time, such consideration might have remained untested by being relegated into the realm of wishful formalism, but not so nowadays after the advent of R. B. Woodward and R. Hoffman's[40] generalisations on orbital symmetry control of concerted organic reactions. The two above mentioned

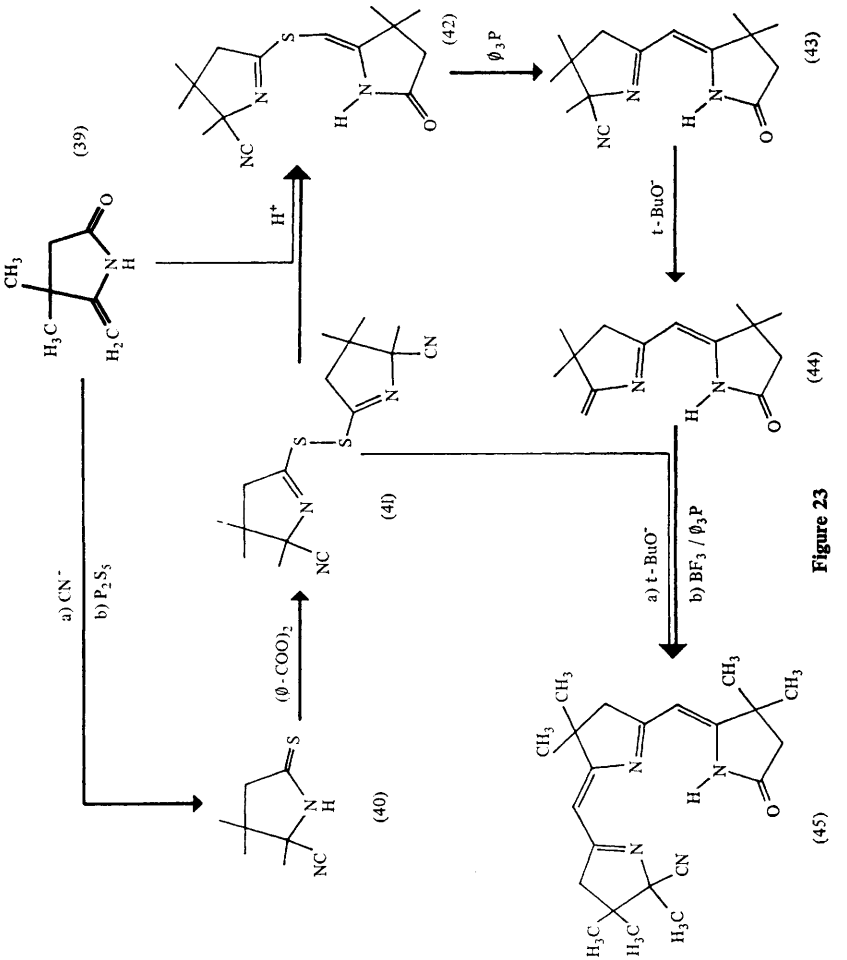


Figure 23

[40] R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, 1965, **87**, 395, 2511; R. Hoffmann and R. B. Woodward, *ibid.*, p. 2046, 4388, 4389; R. B. Woodward and R. Hoffmann, *Angew. Chem.*, 1969, **81**, 797.

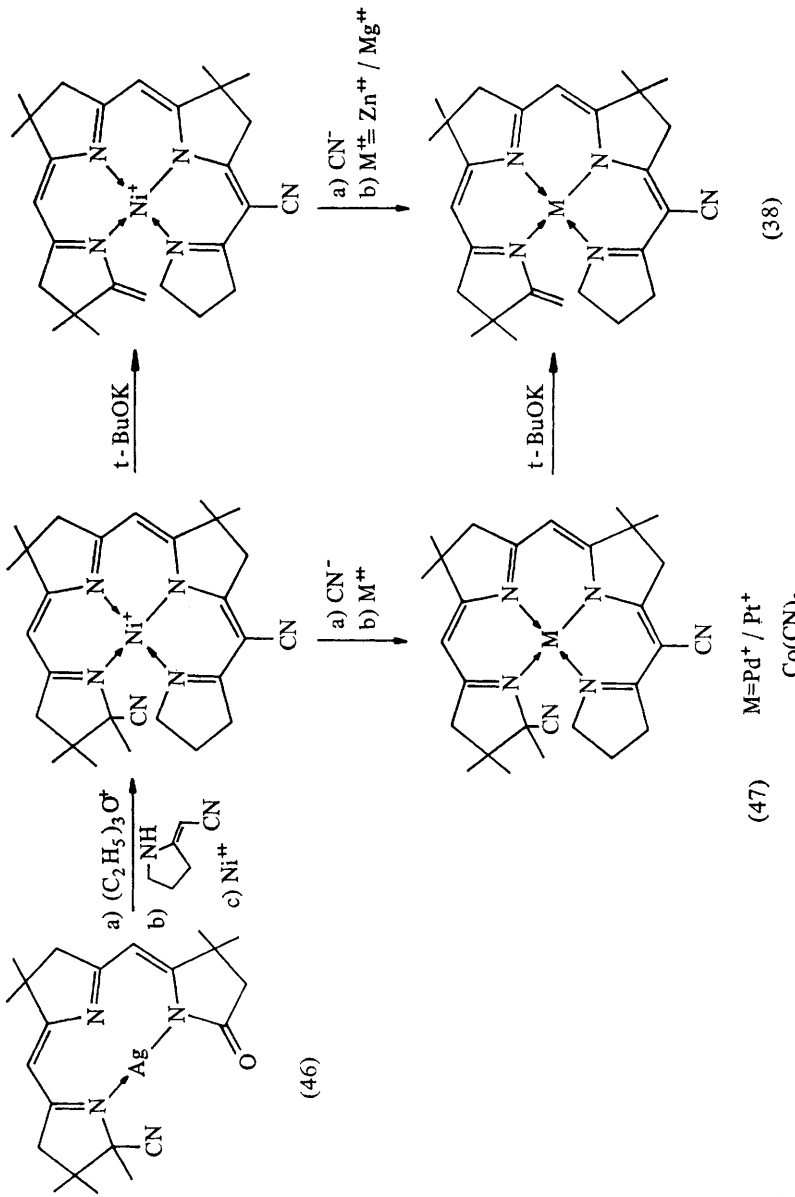

a) $(C_2H_5)_3O^+$
b)
c) Ni^{++}
a) CN^-
b) M^{++}
t-BuOK
a) CN^-
b) $M^{++} \equiv Zn^{++} / Mg^{++}$
t-BuOK
(46)
(47) M=Pd^+ / Pt^+
$Co(CN)_2$
(38)

Figure 24

processes formally classify as an antarafacial sigmatropic 1,16-hydrogen transfer and an antarafacial electrocyclic 1,15-$\pi \rightarrow \sigma$-isomerisation. In a simple frontier orbital analysis the hydrogen transfer emerges as a 'thermally forbidden' process whereas the antarafacial 1,15-cycloisomerisation appears symmetry allowed in the electronic ground state (symmetries of frontier orbitals π_9 and π_8 respectively at reaction centres; see Figure 22).

Figures 23 and 24 illustrate the reaction sequence by which A/D-seco-corrinoid complexes of type (38) can be prepared in a straightforward way by connecting three molecules of the enamide ring precursor (39) by the method of sulphide contraction *via* oxidative coupling and by subsequent addition of a fourth ring by an enamine–iminoester condensation.

The first enamide coupling requires protection of the strongly nucleophilic enamide double bond of the potential thioamide partner. This protection proved to be best provided by the cyanide group which is introduced with KCN in aqueous solution.[41] It survives the conditions of the subsequent steps and can, eventually, be cleanly expelled from vinylogous amidine derivatives by strong base. In contrast to the enamide (39) itself, the corresponding cyanolactam can easily be converted to the thiolactam (40) by reaction with P_2S_5. In a sequence of events completely analogous to those of the B/C-coupling in the B_{12}-series (see Section 2, Figures 10 and 11), oxidation of the cyanothiolactam (40) with benzoylperoxide in the presence of the enamide (39) leads to the bicyclic thio-bridged intermediate (42) in high yield. Heating in triphenylphosphine brings about sulphide contraction to the vinylogous amidine derivative (43) and subsequent treatment with potassium t-butoxide eliminates the protecting group to form the bicyclic lactam (44). This compound had already served as a central intermediate in the earlier corrin approach[11] (see Figure 4), but had to be prepared at the time by less straightforward methods.

Repetition of the ring-connecting process adds another vinylogous amidine unit to the bicyclic intermediate (44) producing the bicyclic analogue (45). In this more complex case, a preparative version of the oxidative enamide–thiolactam coupling procedure has to be used, involving base induced NH-deprotonation of the enamide partner (44), followed by reaction with the isolated disulphide intermediate (41). A further deviation refers to the subsequent contraction step which responds strongly to catalysis by boron trifluoride.

The incorporation of the fourth ring by an enamine–iminoester condensation requires the transformation of the lactam group of the tricyclic intermediate (45) into its iminoester. In contrast to the experience with the tricyclic analogue (44),[11] the direct *O*-alkylation of (45) with triethyloxonium-tetrafluoroborate proved preparatively useless because rather indiscriminate *O*- and *N*-alkylations occur. This difficulty is effectively overcome in the corresponding silver complex (46) (see Figure 24) in which the (presumably digonal) co-ordination with the

[41] The addition of CN^- is expected to proceed only after tautomerisation to the *N*-acyl-ketimine isomer [compare with the addition of nitromethane to (39)[11d]]. The method of masking an enamide double bond by cyanide was first used in another connection by R. B. Woodward and A. Wick (unpublished).

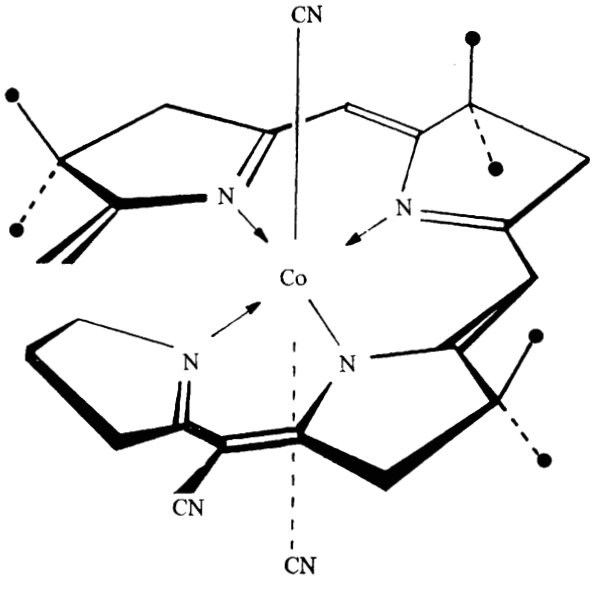
silver ion protects the sp^2-electron pairs of at least two nitrogen atoms against *N*-alkylation. Reaction of this silver complex with triethyloxonium-tetrafluoroborate, directly followed by condensation with the ring D component in its free enamine form, produces the desired tetracyclic system which is isolated in high yield as the beautifully crystalline Ni^{II}-complex (47, M = Ni^+). Fortunately, cyanide ions remove the nickel(II) with great ease, thus allowing the preparation of complexes with other metal ions, *e.g.* Pd^{II}, Pt^{II}, or Co^{III}. The cyanide protecting group in complexes (47) is expelled under the influence of potassium t-butoxide to yield A/D-seco-corrinoid systems of type [38, M = Ni^+, Pd^+, Pt^+, $Co(CN)_2$]. The very labile complexes with Zn^{II} and Mg^{II} can be prepared by carefully controlled cyanide induced metal exchange on the corresponding nickel(II) complexes (38, M = Ni^+).[42]

All these seco-corrinoid complexes have been obtained in pure and crystalline form and the assignment of their structures is fully supported by analytical and spectral data. A somewhat problematic situation has been encountered in the cobalt series. The removal of the cyanide protecting group with t-butoxide from the dicyanocobalt(III) complex [47, M = $Co(CN)_2$] resulted in the isolation of not one, but two different crystalline dicyanocobalt(III) complexes in about equal amounts, both having the molecular weight corresponding to structural formula [38, M = $Co(CN)_2$] and both showing n.m.r. signals compatible with this constitution. On the basis of differences in their u.v. and i.r. spectra, diastereomeric structures of type (48) and (48a) (see Figure 25) are tentatively assigned to these two compounds. The one believed to represent the *trans*-dicyano complex (48) appears thermodynamically less stable; it can be quite cleanly converted into the isomeric complex, *e.g.* by heating in t-butanol.

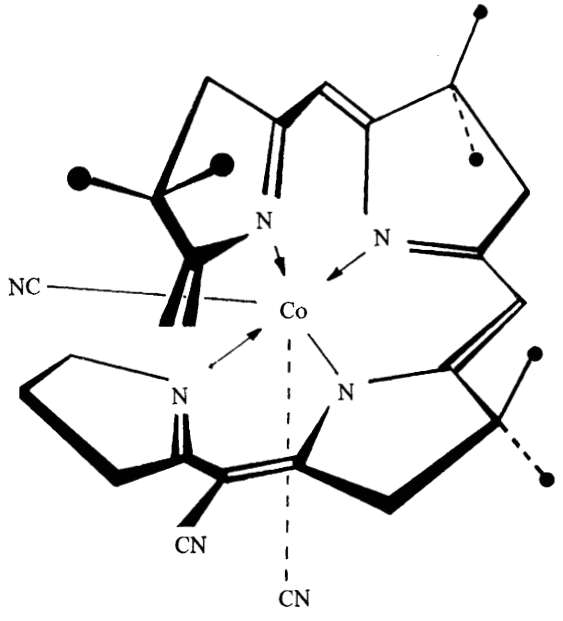
A summary of the expanding and continuingly exciting experience of the photochemical cycloisomerisation of A/D-seco-corrinoid metal complexes to corresponding corrin complexes is given in Figure 26. The reaction revealed itself as an all-or-none process, its success most remarkably depending on the nature of the central metal ion. Whereas the seco-corrinoid complexes of palladium(II), platinium(II), zinc(II), and magnesium(II) [38, M = Pd^+, Pt^+, Zn(Cl), and Mg(Cl)] in degassed solutions cyclise at ambient temperature in essentially quantitative yield to the corresponding *trans*-corrin complexes (35) on irradiation with light in the range of *ca.* 300–530 nm[38,42] (pyrex-filtered u.v. light, sunlight or just artificial visible light[43]), no cyclisation whatsoever has been detected under similar and other conditions in the cases of the nickel(II) and both dicyanocobalt(III) complexes [38, M = Ni^+ and $Co(CN)_2$, compare (48) and (48a)]. The successful cycloisomerisations are by far the cleanest and most delightful steps we have ever encountered in synthetic corrin chemistry. On the other hand, preliminary experiments have given no u.v.-spectroscopic in-

[42] Work by H. Wild (Pt, Zn, Mg) and L. Ellis (Co).

[43] The electronic absorption spectra of these seco-corrinoid metal complexes have intense absorption bands in the region 300—350 nm and 450—530 nm; *e.g.* M = Zn(Cl): λ_{max} = 268 nm (log ϵ = 4·41), 293 (4·18), 328 (4·58), 377 (3·85), 405 (3·66), 511 (4·15) nm (in C_2H_5OH).



(48)



(48a)

Figure 25

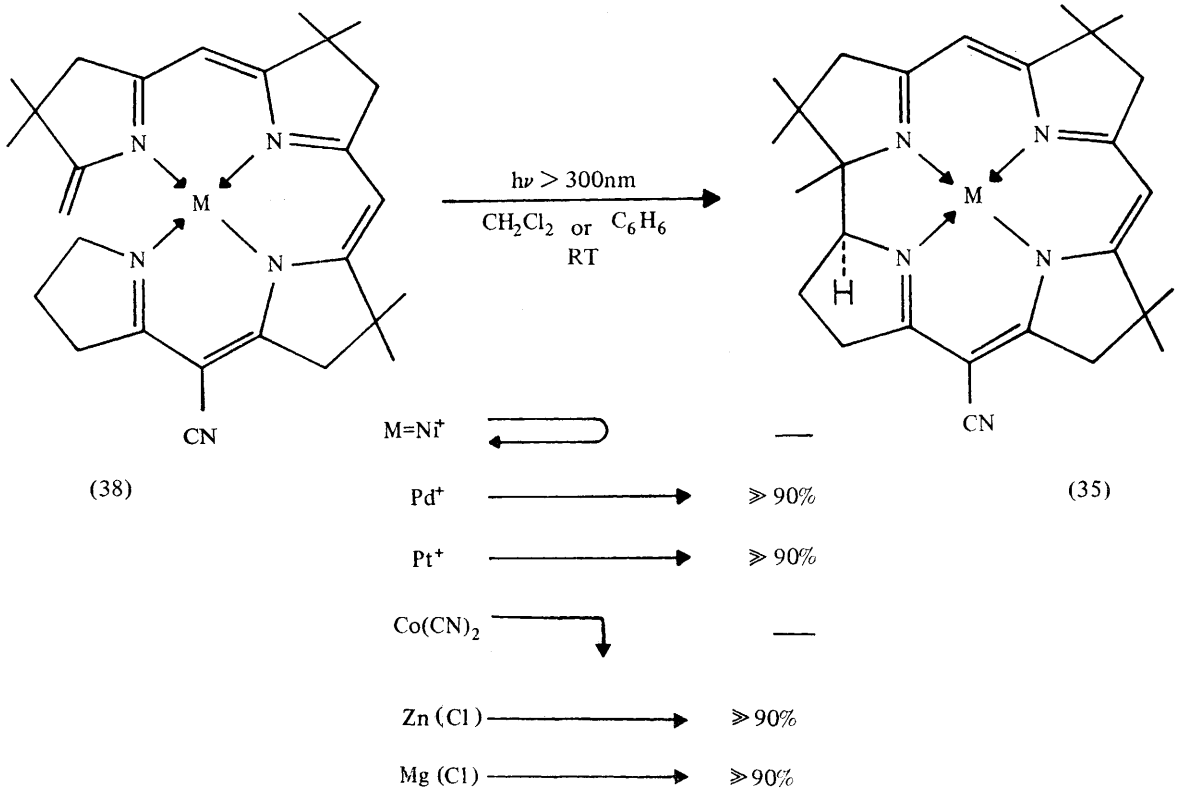

hν > 300nm
CH2Cl2 or C6H6
RT
M
N
CN
H
(38)
(35)
M=Ni+
Pd+
Pt+
Co(CN)2
Zn (Cl)
Mg (Cl)
⩾ 90%
⩾ 90%
⩾ 90%
⩾ 90%

Figure 26

dication of the occurrence of a thermally induced cycloisomerisation of either the palladium(II) or the nickel(II) and dicyanocobalt(III) complexes (38).

Both constitution and configuration of the photochemical cycloisomerisation products [35, M = Pd^+, Pt^+, Zn(Cl), and Mg(Cl)] are beyond any doubt: u.v., i.r., n.m.r., and mass spectra of the Pd- and Zn-complexes are identical with the spectra of the corresponding 1,2,2,7,7,12,12-heptamethyl-15-cyano-*trans*-corrin complexes prepared by the classical routes described in Sections 1 and 3 (see Figures 4 and 19), whereas the structure of the magnesium complex has been proved by conversion into the metal-free derivative. The structural assignments in this synthetic series rest solidly on two *X*-ray analyses contributed by P. Galen-Lenhert and T. J. Shaffner [35, M = $Co(CN)_2$][14], and E. Edmond and D. Crowfoot-Hodgkin (34) (see Figure 18).[37]

The plain and, in a way, still surprising fact that certain A/D-seco-corrinoid complexes are found to cycloisomerise so smoothly to corrin complexes does, in a sense, lend substance to the reaction formalism envisaged in the planning stage of the work; but much more importantly, it confronts us now with a number of incisive and provocative mechanistic questions. An important lead to these problems is the apparent yes-or-no dependence of the cycloisomerisation on the nature of the metal ion.

It had originally been suspected that the first observed, remarkable difference in the behaviour of the two (diamagnetic) square-planoid seco-corrinoid complexes of nickel(II) and palladium(II) might be simply caused by corresponding differences in their respective molecular geometry, remembering[44] that the palladium ion can be expected to enforce square-planarity of a ligand system more tightly than the more tolerant nickel ion.[45] However, the smooth cycloisomerisation of the supposedly stereochemically non-ideal chloro-zinc(II) and chloro-magnesium(II) complexes provide support for the idea that factors others than purely geometrical ones play a (or the) decisive role in the process. The lifetime of the reacting photoexcited state (or states?) of the chromophore might depend on the specific electronic structure of the metal ion in such a way that this dependence is critical for the occurrence or non-occurrence of the cyclisation process. It has been found in G. Quinkert's[46] laboratory that the quantum yield of the cyclisation of the palladium complex at room temperature is very low and that it vanishes at low temperature. Another important piece of information comes from A. J. Thompson's[47] recent work on the fluorescence of

[44] See, for example, the synthesis of the corphin system, A. P. Johnson, P. Wehrli, R. Fletcher, and A. Eschenmoser, *Angew. Chem.*, 1968, **80**, 622; *Angew. Chem. Internat. Edn.*, 1968, **7**, 623.

[45] Since the time that this lecture was given, the results of *X*-ray structure determinations of the seco-corrinoid complexes of nickel(II) and palladium(II) (38, M = Ni^+ and Pd^+, as perchlorates) have become available. The crystals of the two complexes are isomorphous and the square-planoid, tetrahedrally-distorted conformation of the ligand system in *both* complexes appears ideally suited for the hydrogen transfer process. The critical ($>CH_2 \ldots CH_2=$)-distances are 3·46Å (nickel) and 3·33 Å (palladium); private communication by Dr. M. Currie and Professor J. D. Dunitz, ETH.

[46] Private communication from Professor G. Quinkert and G. Prescher.

[47] A. I. Thompson, *J. Amer. Chem. Soc.*, 1969, **91**, 2780.

naturally occurring corrinoids, according to which cobalt(III)-corrinoids do not fluoresce, whereas corresponding metal-free derivatives do, the reason for this striking difference being that the open-shell transition metal ion would quench the fluorescing excited state of the corrin chromophore.[48] At present, these facts, together with the behaviour of the seco-corrinoid closed-shell metal ion complexes of zinc(II) and magnesium(II), hint at the possibility that occurrence of the photocycloisomerisation might be the result of its successful competition with intersystem crossing and/or internal conversion processes mediated by the metal ion in the lowest singlet excited state of the seco-corrinoid chromophore. Emission studies on a whole series of synthetic corrin complexes currently under way in Dr. A. J. Thompson's laboratory, extended quantum yield measurements and spectroscopic studies by Professor G. Quinkert's group, *X*-ray structure determinations by Professor J. D. Dunitz and his collaborators and, finally, systematic chemical investigations in our laboratory, are expected to provide the basis for an understanding of what we suspect to be a pregnant problem in the field of porphinoid metal complex photochemistry.

It has been mentioned earlier (see Figure 19) that zinc(II)-corrins can serve as starting materials for a whole series of other corrin complexes, including those of cobalt. Therefore, the photochemical cycloisomerisation of A/D-seco-corrinoid zinc(II) complexes, quite apart from its inherent mechanistic interest, promises to be a general synthetic approach to corrinoids containing a vitamin B_{12}-like substitution pattern in ring A. Quite specifically, the earlier discussion referring to cobyric acid (see Figure 21) now appears to describe a realistic synthetic opportunity.

In the laboratory, however, another problem has recently been more acute namely, to join the A/D with the B/C-component in the Harvard–ETH approach to cobyric acid.

5 Recent[49] Steps in the Harvard–ETH Approach to Cobyric Acid

It was during 1967 that both the Harvard and ETH groups had finally reached their respective goals by having accomplished syntheses of compounds which seemed structurally apt to serve as A/D- and B/C-components in a construction of the cobyric acid molecule. It soon became clear in both laboratories that earlier expectations were too optimistic in assuming that this condensation problem could be solved by merely following the conceptual and experimental paths paved in the earlier work on the synthesis of corrins. For instance, one of the candidates originally envisaged to serve as the A/D-component for an A/D–C/B coupling was the tricyclic enamino-ketone (49) (see Figure 27).

This assignment soon proved illusory because the compound surprisingly emerged from the work in the Harvard laboratories as an extremely labile one,

[48] According to preliminary experiments of Dr. A. J. Thompson, the synthetic chloro-zinc(II) complex (33) also shows fluorescence (private communication); compare also the luminescence properties of porphyrin complexes, R. S. Becker, Theory and Interpretation of Fluorescence and Phosphorescence, Wiley-Interscience, N.Y., 1969, p. 190.

[49] Refers to the time of delivering the lecture, November 1969; for later developments see footnote 58. For previous progress reports see R. B. Woodward;[7] A. Eschenmoser.[20]

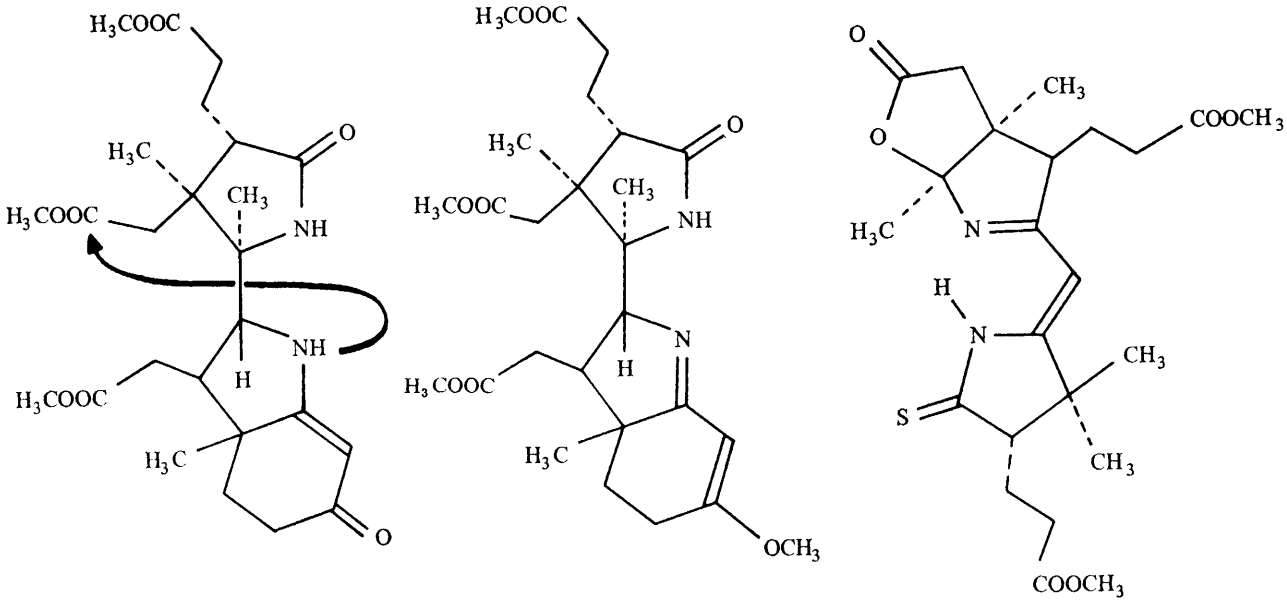

H3COOC
H3C
CH3
O
NH
H3COOC
NH
H
H3COOC
H3C
O
(49)
H3COOC
H3C
CH3
O
NH
H3COOC
N
H
H3C
OCH3
(50)
O
CH3
COOCH3
O
H3C
N
H
N
CH3
S
CH3
COOCH3
(29)

Figure 27

the reason for its lability being a ring closure between the enamine NH-group and one of the methoxy-carbonyl groups at ring A (see arrow) that most disturbingly takes place under almost any conditions. This cyclisation suppresses the system's enaminoid character required for all types of coupling processes under consideration. A derivative stable towards this sort of cyclisation was found in the enolether (50) but, unfortunately, its nucleophilic reactivity at the vinylic carbon appeared insufficient as judged from the completed failures of various coupling attempts. There is no need to describe here any of the other numerous unsuccessful experiments; it is equally informative to enjoy a glimpse of the cartoon[50] of Figure 28 which describes the situation as it prevailed in the two laboratories for quite a while.

Fortunately, the cartoon grossly exaggerates in one important respect: things started moving again after the Harvard group had tried, and succeeded, to ozonolyse with high selectivity the carbon–carbon double bond of the enolether system in their compound (50) (see Figure 29) to form the corresponding formyl-ketimine derivative which, in turn, could be reduced to the hydroxy compound and converted, *via* the mesylate, to the crystalline bromomethyl derivative (51). This type of structure represents an ideal solution to the problem of finding a suitable form of the A/D-component for the coupling with the B/C-component (29), the condensation method to be used being the sulphide contraction *via* alkylative coupling (see Section 2; Figure 13 and 14).

The potassium salt of the B/C-component (29) is alkylated specifically and smoothly at sulphur by the A/D-bromide (51) to form the labile pentacyclic thioiminoester derivative (52) (see Figure 30). The system boron trifluoride–triphenylphosphine–methylmercury-isopropoxide in benzene[51], converts this labile condensation product at about 70 °C within less than one hour into a desulphurised material in estimated overall yields of up to 50–60%. Although this material can be purified by chromatography, it has, as yet, never been obtained in crystalline form (it presumably contains components with epimerised centres at rings B and C); however, the assignment of structure (53) to it is well documented spectroscopically and fully supported by further transformations. Formulae (52a) and (52b) describe tentatively assigned structures of two isomeric condensation products which are formed with great ease from the thioiminoester (52) by chromatography on silicagel or in contact with traces of acids. The novel structures and reactions in this ADCB-series turned out to be full of intricacies, and a major research effort, invested mainly by the Harvard group, was needed for defining experimental conditions under which these systems behave interpretably and reproducibly and, above all, under which the condensation product isomers (52) and (52a, b) contract reliably in synthetically acceptable yields.[52]

[50] Cartoon by Sattler, published in '*Nebelspalter*', Nebelspalter-Verlag, Rorschach (Schweiz) and spotted by Dr. L. Werthemann, ETH.

[51] It is possible that methylmercury-isopropoxide prevents the formation of the isomer (52b) which is known not to contract under these conditions.

[52] A very recent and important result of these studies by the Harvard group is a reliable, high yield procedure for the acid-catalysed contraction of the thermodynamically most stable condensation product isomer (52b).

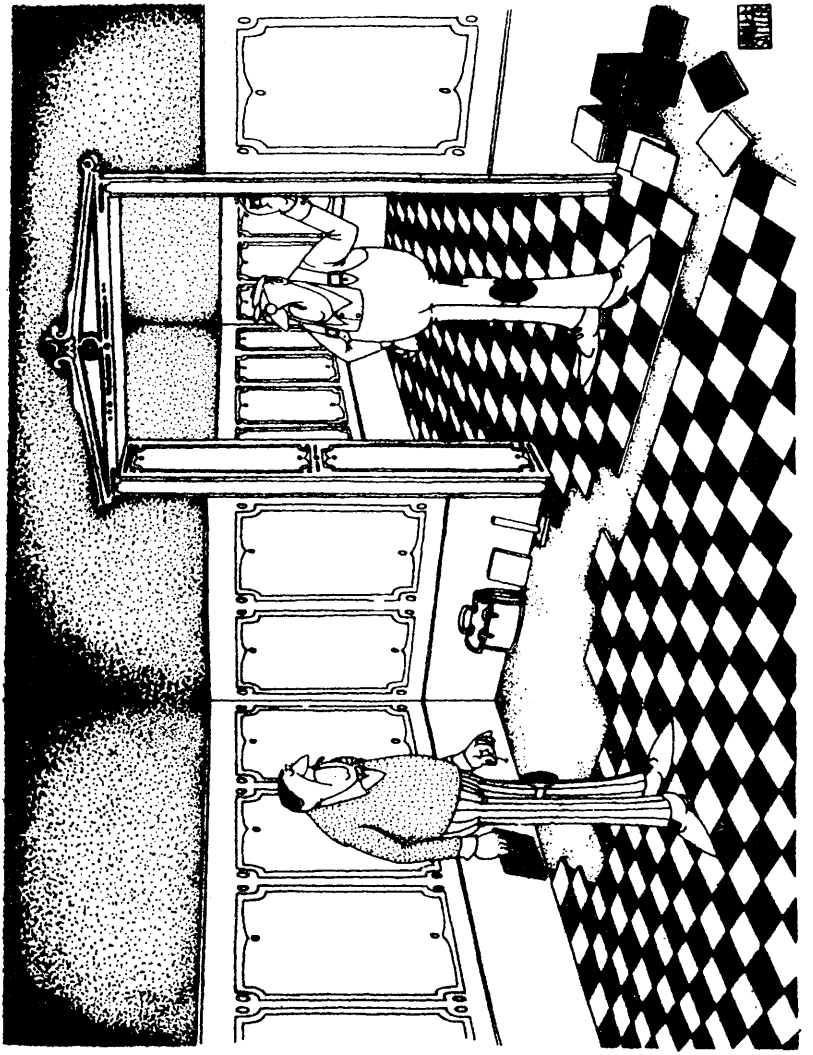


Figure 28

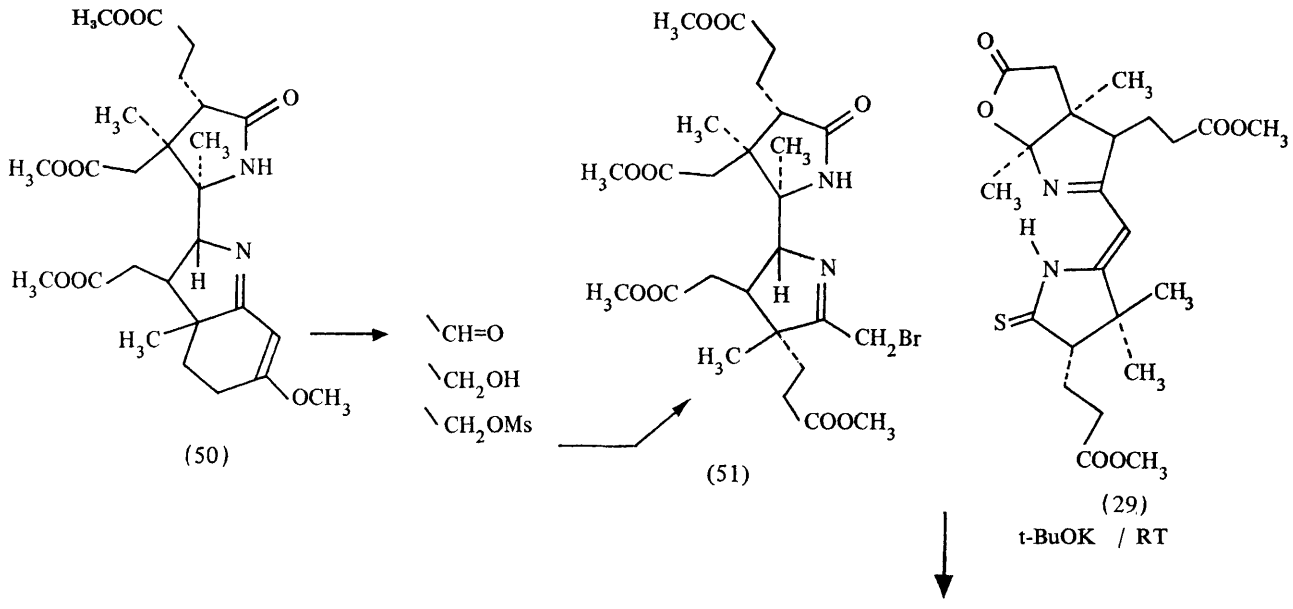

H3COOC
H3C
CH3
O
NH
H3COOC
N
H
H3COOC
H3C
OCH3
(50)
CH=O
CH2OH
CH2OMs
H3COOC
H3C
CH3
O
NH
H3COOC
N
H
CH2Br
H3C
COOCH3
(51)
O
O
CH3
COOCH3
CH3
N
H
N
S
CH3
CH3
COOCH3
(29)
t-BuOK / RT

Figure 29

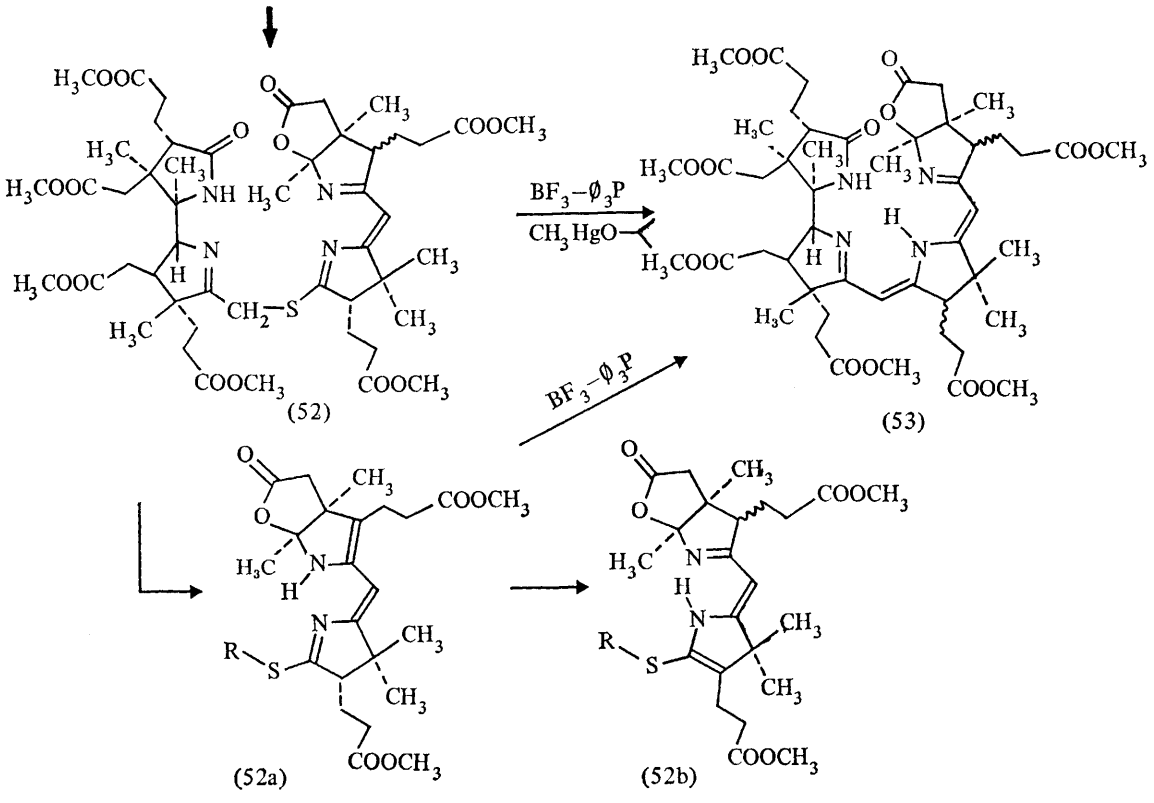


Figure 30

It did not come as too much of a surprise when the next important step, the A/B-cyclisation to the corrinoid system, revealed itself again as a major synthetic obstacle. Initial exploratory experiments on an introduction of cobalt into a ring A iminoester derivative of the ADCB-condensation product (53) to be followed by base catalysed or thermal iminoester cyclisation—a sequence of processes well under control in the case of simpler precorrinoid systems—showed little promise of success. Therefore, a major attack was launched towards the goal of achieving this cyclisation by making use of, for the third time in the whole project, the principle of sulphide contraction. In fact, it was in such experiments that the corrinoid chromophore finally appeared on the scene. The present state of these still incomplete cyclisation studies is summarised in Figure 31.[53]

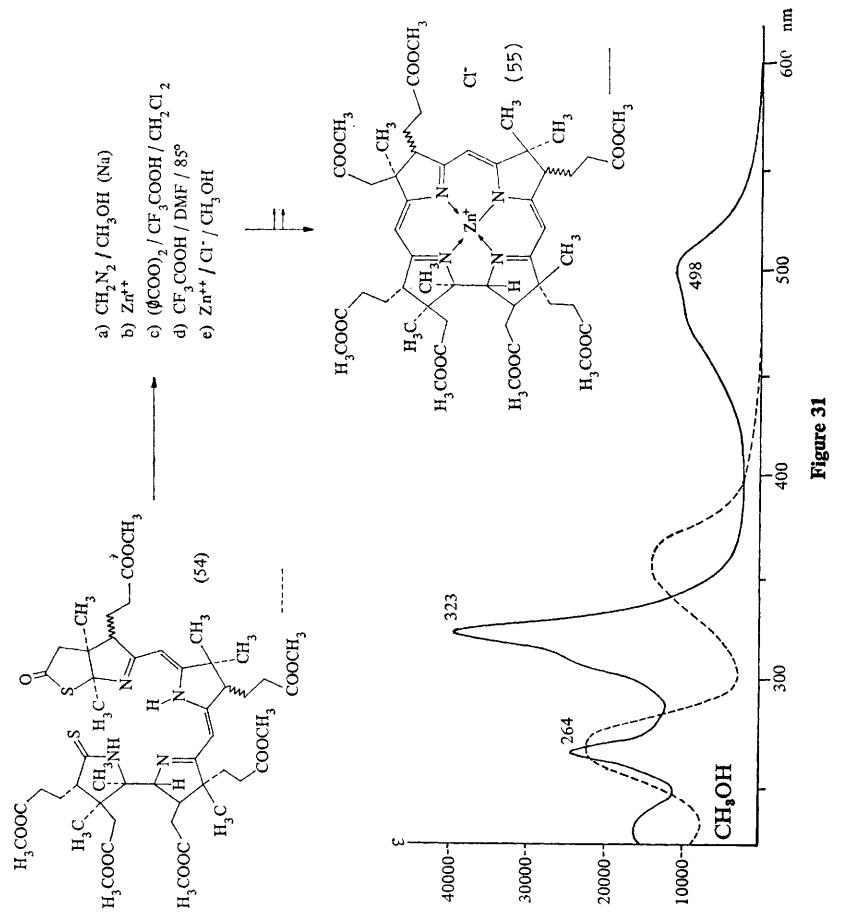


Figure 31

[53] Work by P. Schneider, F. Karrer, D. Becker, and W. Huber.

An A/B-cyclisation *via* sulphide contraction requires first of all the conversion of the ring A lactam group into the corresponding thiolactam system. Phosphorus pentasulphide under carefully controlled conditions brings about this transformation in high yield, but not without concomitant replacement of the ring B lactone oxygen by sulphur, to give the ADCB-thiolactam-thiolactone derivative (54). A sequence of operations, so far carried out without characterisation of the intermediates, but performed very closely to the reaction conditions extensively studied earlier in the synthesis of metal-free corrins (see Section 3; Figure 16), leads to a mixture of corrinoid cyclisation products, clearly recognised as such by the very characteristic electronic spectrum. This series of operations includes (*a*) the methoxide-induced eliminative opening of the thiolactone system in the presence of diazomethane in methanol (see the analogous process in Figure 12), (*b*) complexation in the same solvent with zinc(II) perchlorate, (*c*) oxidative coupling with benzoylperoxide in dichloromethane in the presence of trifluoroacetic acid, (*d*) acid-catalysed contraction in dimethylformamide and, finally, (*e*) recomplexation with zinc(II) chloride in methanolic solution. So far, only one of the corrinoid components produced in this process has been isolated in chromatographically homogeneous form; we believe that the structure of this component is that of the corrinoid zinc(II) complex (55). This assignment rests, for the time being, on the following three pieces of evidence: First, the highly characteristic electronic spectrum (reproduced in full line in Figure 31) corresponds convincingly to what one has to expect for the spectrum of a zinc(II) corrin complex;[54] second, the highest peak of significant intensity in the mass spectrum appears at the mass number 1013 which corresponds to the molecular weight of the complex-ion (55) and third, although the exploratory experiments on the acidolytic decomplexation and subsequent introduction of cobalt with cobalt(II) perchlorate cannot be said to have been successful already in a preparative sense, such experiments have resulted in the isolation of a chromatographically homogeneous but still not quite pure[55] material which clearly is a dicyanocobalt(III)–corrin complex: the structure and position of all the absorption bands in its electronic spectrum are highly characteristic and virtually identical to those observed in the spectrum of authentic dicyano-5,15-bis-desmethylcobyrinic acid heptamethylester (56), a crystalline compound available by degradation of vitamin B_{12}.[56]

Neither the cyclisation, nor the metal exchange procedure in the state of development indicated above represent what we can call a solution to the synthetic problem involved, yields are too low and products and intermediates have not been crystallised and not fully characterised so far; however, these

[54] This expectation relies on the known spectrum of the synthetic zinc(II) corrin complex (33) (see Figure 17).

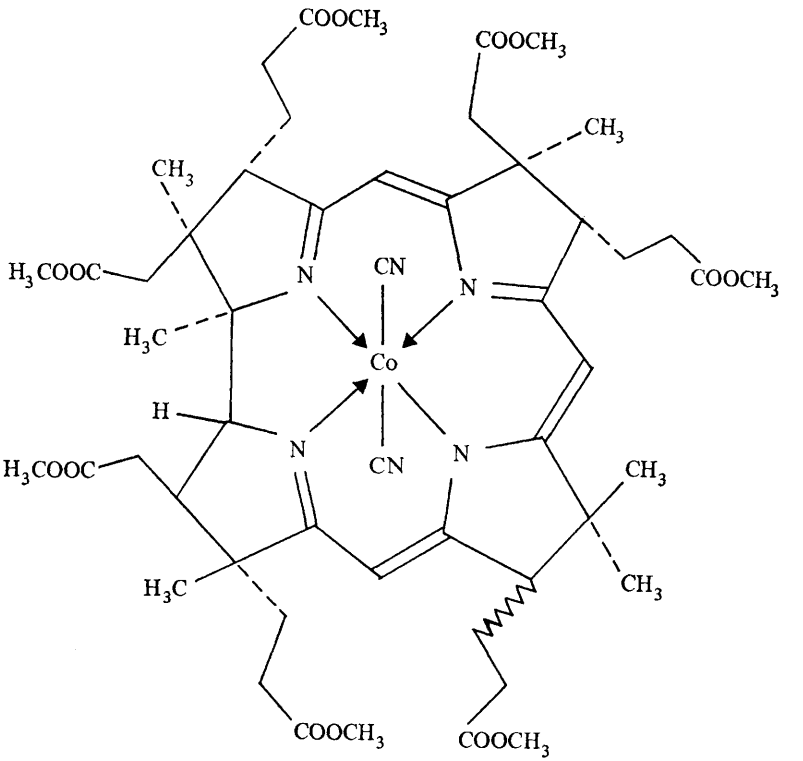
[55] The presence of impurities is indicated by the intensity of the absorption bands in the u.v. relative to those in the visible region.

[56] Prepared[57] by acid-catalysed methanolysis of material obtained from vitamin B_{12} by oxidation with $KMnO_4$ (unpublished work of K. Bernhauer and F. Wagner). I thank Professor Bernhauer and Dr. Wagner, Technische Hochschule Stuttgart, for generously supplying us with this material.

[57] Work by L. Werthemann and H. Maag.

results clearly mark the direction in which a thorough study must and will uncover further insights and eventual success.

Since the time that this lecture was given (November 1969), significant progress has been made by deviating from the above mentioned cyclisation procedure in the following way:[58] The ADCB-thiolactam-thiolactone derivative (54) reacts very smoothly with dimethylamine in methanol at room temperature to form a labile intermediate assigned the structure (57). Complexation with zinc perchlorate, followed by internal A/B-coupling through oxidation with iodine in methanol containing potassium iodide [see hypothetical intermediate (57a)], acidolytic decomplexation and concomitant sulphide contraction with trifluoroacetic acid in dimethylformamide in the presence of triphenylphosphine



(56)

Figure 32

[58] Work by P. Schneider, N. Hashimoto, and H. Maag.

and, finally, recomplexation with zinc perchlorate leads to the corrinoid zinc complex (58) (characterised by u.v.-vis., i.r., n.m.r., and m.s.) in a spectroscopically estimated overall yield [from (54)] of 60—70%.

After acidolytic removal of zinc by treatment with trifluoroacetic acid in acetonitrile, cobalt can be introduced very smoothly in high yield by reaction of the metal-free corrinium salt with cobalt(II) chloride[59] in tetrahydrofuran in the absence of base, followed by short treatment with aqueous potassium cyanide in air. The electronic spectrum of the chromotagraphically homogeneous (so far not crystallised) synthetic dicyanocobalt(III) complex (59) is reproduced in Figure 34 together with the spectrum of authentic dicyano-5,15-bis-desmethyl-cobyrinic acid heptamethyl ester (56)*.

There are three features in formula (56) which should not escape the readers' attention: the non-differentiable form of the propionic acid carboxy function at ring D, the absence of methyl groups in positions 5 and 15 of the corrin chromophore and, finally, the configurational uncertainty with respect to the (CH)-position in ring C. These are problems still to be solved before the journey to synthetic vitamin B_{12} can come to an end.

The nature of the work described in this lecture is such that very little would have been accomplished without the excellence, skill and enthusiasm of my doctoral students and postdoctoral collaborators who have devoted themselves to this endeavour. Their names appear in the list of references; those who have produced the results discussed here, are: R. Scheffold, E. Bertele, M. Pesaro, E. L. Winnacker, and K. J. Schossig (Section 1); B. Golding, P. Löliger, W. Huber, P. Dubs, and M. Roth (Section 2); A. Fischli and H. U. Blaser (Section 3); Yasuji Yamada, P. Wehrli, D. Miljkovic, L. Ellis, and H. Wild (Section 4); P. Schneider, F. Karrer, D. Becker, N. Hashimoto, L. Werthemann, and H. Maag (Section 5). I express here my deep appreciation to all of them.

I acknowledge Dr. R. Huff's and Dr. B. Place's efforts to correct the English manuscript; it is the author who is to be blamed for the remaining linguistic Germanisms.

The investigation has been supported by the Swiss National Foundation for the Promotion of Scientific Research.

* *Note added in proof.* In the meantime it has been possible to convert the dimethylamide group of the synthetic dicyano-cobalt(III) corrin complex (59) into the methoxycarbonyl function by alkylation of (59) with trimethyloxonium tetrafluoroborate, followed by treatment with aqueous potassium bicarbonate. The product has been obtained in beautifully crystalline form and is believed to be synthetic dicyano-5,15-bis-desmethyl-cobyrinic acid heptamethyl-ester (56); the chromatographic behaviour, the u.v.-vis. and i.r.-spectra, as well as the o.r.d.-curve of the synthetic material are identical with the corresponding data of the authentic compound (56).[58]

The complex (59) has now also been obtained by the Harvard group using the method of base catalysed thioiminoester cyclisation of the corresponding precorrinoid dicyanocobalt(III) complex.

[59] Cobalt(II) chloride is, according to recent findings of the Harvard group in the precorrinoid series, much superior to cobalt(II) perchlorate as complexation agent.

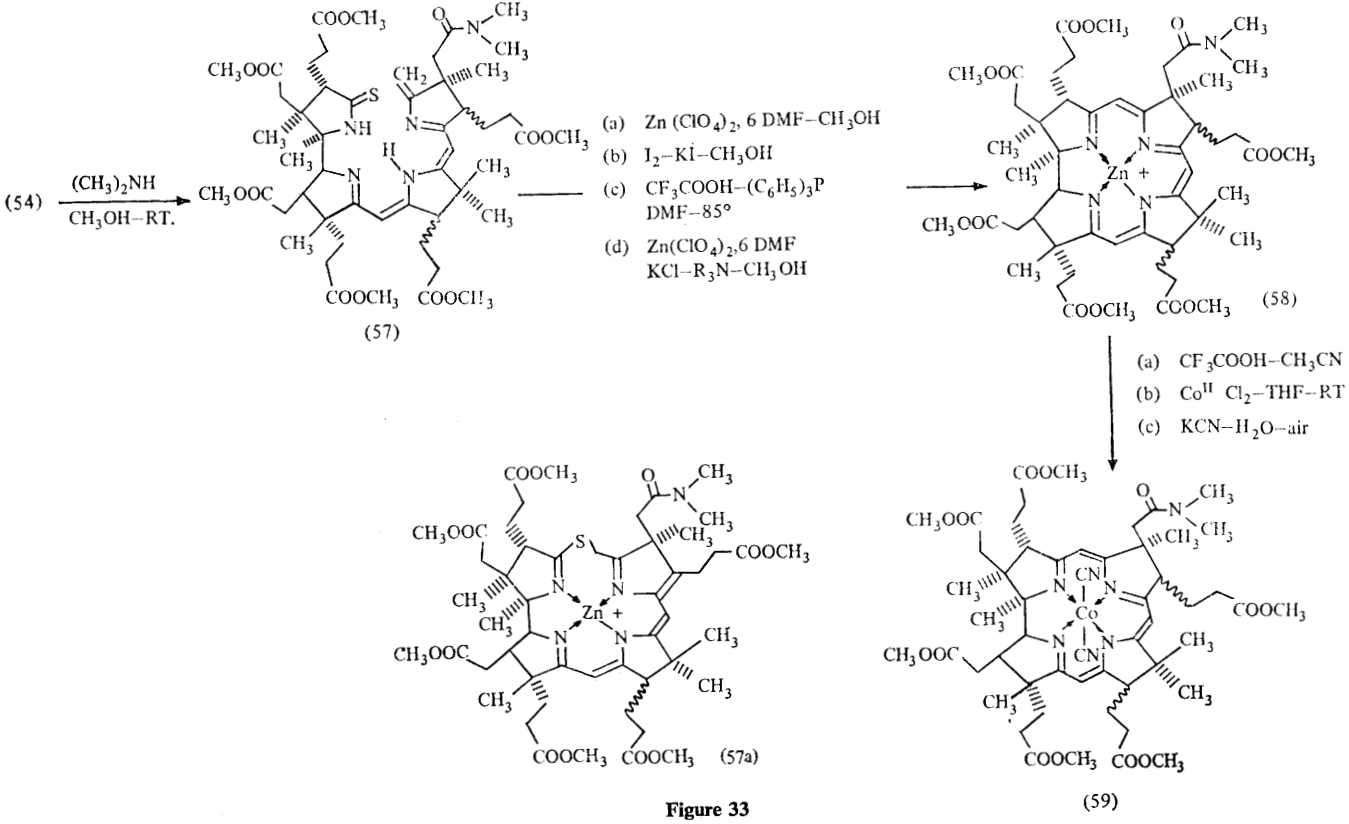

(54)
(CH3)2NH
CH3OH–RT.
(57)
(a) Zn (ClO4)2, 6 DMF–CH3OH
(b) I2–KI–CH3OH
(c) CF3COOH–(C6H5)3P
DMF–85°
(d) Zn(ClO4)2,6 DMF
KCl–R3N–CH3OH
(58)
(a) CF3COOH–CH3CN
(b) CoII Cl2–THF–RT
(c) KCN–H2O–air
(57a)
(59)

Figure 33

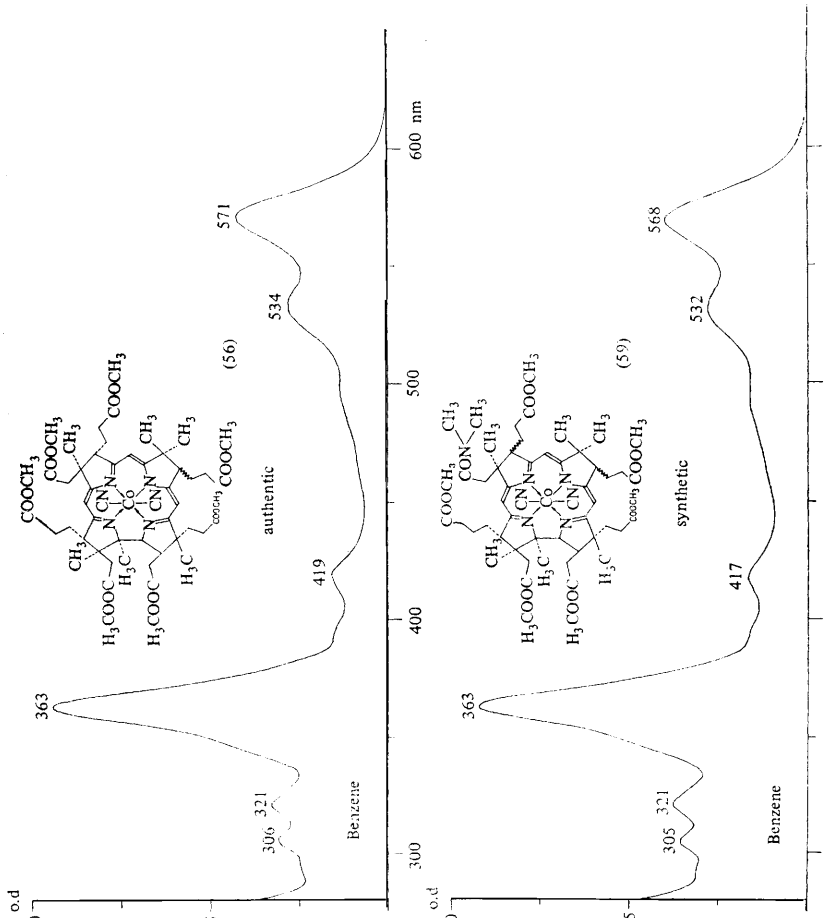

o.d
1,0
0,5
363
306
321
419
534
571
Benzene
authentic
(56)
300
400
500
600 nm
o.d
1.0
0.5
363
305
321
417
532
568
Benzene
synthetic
(59)

Figure 34