Current Aspects of Corrinoid Synthesis

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CHAPTER II

CURRENT ASPECTS OF CORRINOID SYNTHESIS*

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This lecture deals essentially with three current aspects of corrinoid synthesis: first, with the present state of the work towards a synthesis of vitamin B_{12}, as it is proceeding in the ETH laboratories in collaboration with Professor Woodward's group at Harvard; second, with the feed back this B_{12} work has been—and still is—exerting on the general field of corrin synthesis; and finally, with one of the main lessons synthetic corrin chemistry has taught us, namely, the powerful potentials of the concept of template controlled synthesis.

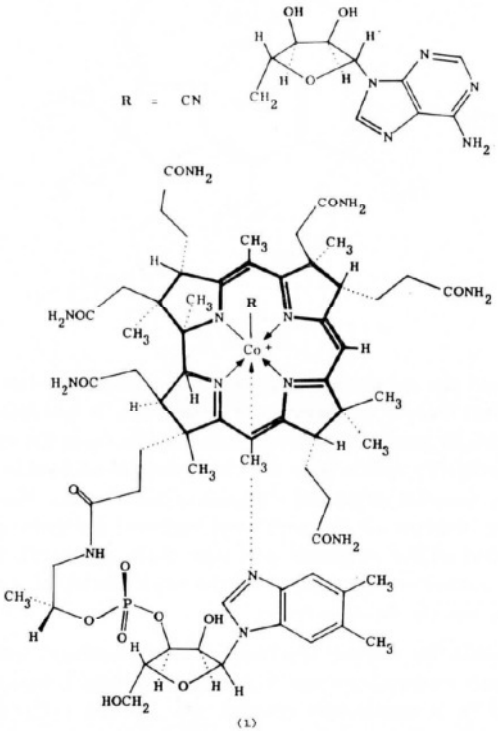
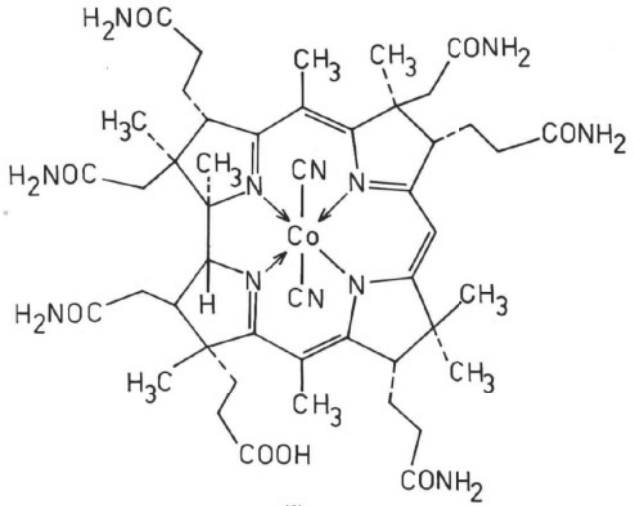


FIGURE 1

*An address presented before "The Robert A. Welch Foundation Conferences on Chemical Research. XII. Organic Synthesis," which was held in Houston, Texas, November 11-13, 1968.

Corrinoids are derivatives of the basic ligand system which forms the structural nucleus of the naturally occurring coenzymes B_{12} (fig. 1; e.g. R = 5′-adenosyl) and of vitamin B_{12} (R = CN). Important work from two laboratories[1] has shown that vitamin B_{12} can be converted to corresponding cobalt-alkyl derivatives, including the 5′-adenosyl-coenzyme B_{12} itself. The key processes of such conversions are the reduction of cobalt to the mono-



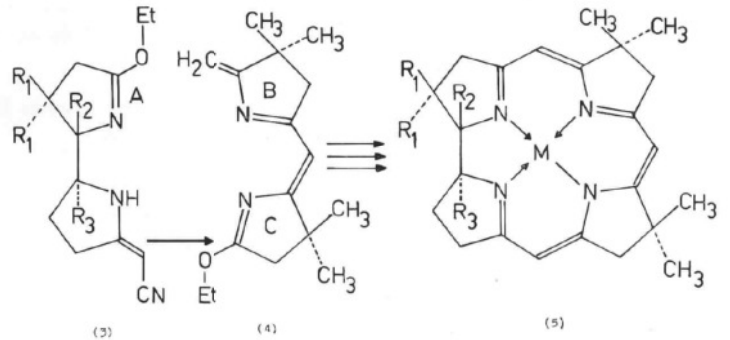
(2)

FIGURE 2

valent state and the subsequent alkylation of a cobalt(I)-lone pair by corresponding alkyl halides or tosylates. Furthermore, it had been shown[2] that vitamin B_{12} can be partially synthesized chemically from the naturally occurring cobyric acid (2) which lacks the characteristic nucleotide part, but contains all other essential structural elements of the vitamin. Most importantly, this derivative contains all the peripheral carboxyl functions in their amide form except that of the propionic acid side chain at ring D. It is this compound which represents the goal of all the work aiming at a total synthesis of vitamin B_{12} and the B_{12}-coenzymes.

Fig. 3 recalls the original approach[3] towards synthetic corrin complexes. Two components containing rings A and D, and rings B and C respectively, are combined in a structurally specific way by two consecutive enamine-iminoester condensations. Sodium ethoxide induces the first condensation between rings D and C by NH-deprotonation of the enamine system in ring D; then a metal ion, e.g. cobalt(II), nickel(II) or palladium(II), is introduced which tends to arrange the four nitrogens of the precorrinoid ligand

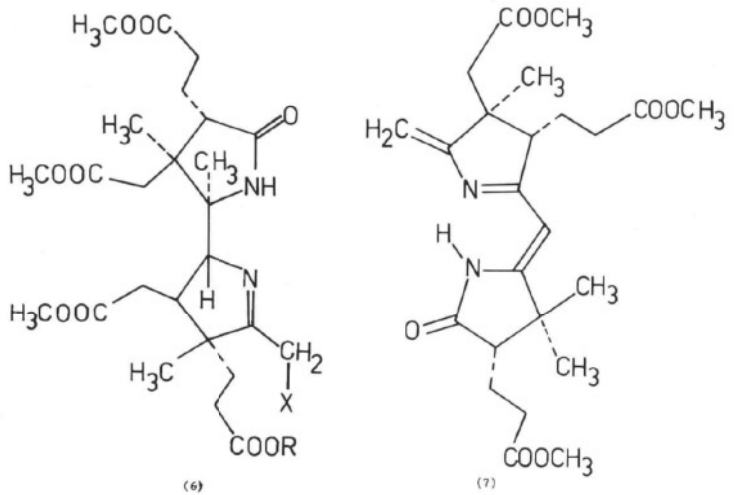
system in a common plane and brings thereby the two remaining condensation centers of rings A and B into close proximity; and finally, the corrin ring is closed by treatment of such a robust precorrinoid metal complex with a deprotonating base.



(3) (4) (5)

R_1	R_2	R_3
H	H	H
H	H	CH_3
CH_3	CH_3	H

FIGURE 3



(6) (7)

FIGURE 4

The translation of this concept into a synthesis of vitamin B_{12} itself requires the availability of two components, e.g. those depicted in fig. 4. The synthesis of the left-side component (6), containing rings A and D, has been achieved, brilliantly of course, by the Harvard group[4], whereas the contribution of the ETH group concerned the preparation of the B/C component (7). The background of, and the problems encountered in the accomplishment of this latter task is the first object of the present discussion.

A retrosynthetic analysis of the structural features of the vitamin B_{12} molecule reveals the following network of synthetic opportunities.

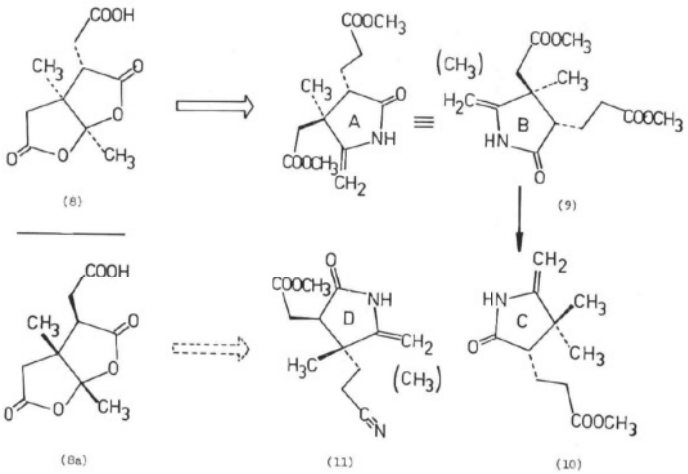


FIGURE 5

Take the optically active dilactone-monocarboxylic acid (8) as the starting material. An elongation of the free carboxyl chain by one methylene unit, a structurally specific replacement of one of the lactone ether oxygens by NH, and a conversion of the potential methyl ketone grouping into its enamide form leads to compound (9), the precursor designate of ring B.

The precursor of ring C in its enamide form (10) differs from the ring-B precursor (9) only by having the carbomethoxy group of the acetic acid side chain replaced by hydrogen. This formal relationship challenges a search for a process which would bring about such a demethoxycarbonylation, any such process making both rings B and C available from the single starting material (8).

It is tempting to push this kind of strategic analysis somewhat further:

the dilactone carboxylic acid (8) could in principle serve as the starting material not only for the precursors of rings B and C but also for that of ring A; the A and B precursors in their enamide form are constitutionally and configurationally identical. What is more striking, however: a reaction sequence analogous to the one which converts the dilactone acid (8) to the ring B precursor (9) would transform the *enantiomeric* dilactone acid (8a) to a potential precursor of ring D, (11), provided that not the free acetic acid side chain, but the lactonized (-CH_2-CO-O)-chain is lengthened by a methylene unit. This reflects a familiar, yet biogenetically still puzzling feature of the vitamin B_{12} structure, namely, that the structural periphery of ring D appears, in a sense, constitutionally rearranged and configurationally inverted. Remarkably enough, the racemic dilactone monocarboxylic acid (8/8a) could, in principle, serve as the starting material for the synthesis of all four ring precursors.

In fact, the three enamides (9), (10) and (11) have been synthesized in our laboratory in optically active form of known chirality, starting from the two enantiomeric dilactone monocarboxylic acids (8) and (8a). The ring B → ring C conversion, however, is of value only with respect to configurational correlations and in connection with biosynthetic work because in both Prof. Woodward's and Dr. Cornforth's[5] laboratories ring C compounds of type (10) have been prepared with relative ease from optically active camphor. Furthermore, the preparation of the potential ring D precursor (11) is, at least for the time being, a luxurious matter, since the Harvard synthesis of the complete A/D component makes its availability unnecessary.

The strategy delineated in fig. 5 ignores one specific aspect of the vitamin B_{12} structure, namely, the two extra methyl groups bound to the B_{12} chromophore at the meso carbons between rings A/B and C/D respectively. If one started from a dilactone monocarboxylic acid (8) which would already contain such a methyl group at the appropriate position, first of all, the aesthetics of the structural relationships depicted in fig. 5 would be lost; furthermore, and more important, experimental experience in the field of corrin synthesis has amply confirmed what had to be suspected at the very beginning, namely, that the final cyclization step in the corrin synthesis (3) + (4) → (5) (see fig. 3) is almost fatally hampered by the presence of an exocyclic ethylidene group at ring B. The two missing methyl groups must be introduced at a later stage of the synthesis.

Fig. 6 shows a reaction sequence by which methyl groups can be introduced into the meso positions between rings A/B and C/D respectively of synthetic dicyano-cobalt(III)-corrin-complexes.[6] Chloromethyl-phenyl-sulfide in the presence of silver tetrafluoroborate reacts at room temperature selectively

with the complex (12) to give the mono-substitution product (13). A subsequent Raney nickel treatment produces the methyl derivative (14). The observed selectivity in this first methylation is believed to be predominantly the result of steric control. However, a repetition of this process at a somewhat elevated reaction temperature (40-50°) produces the 5,15-dimethylated complex (15), beside the isomeric 10,15-dimethyl-derivative in a ratio of about 5:1. Fortunately, the two "natural" meso positions for the methyl groups

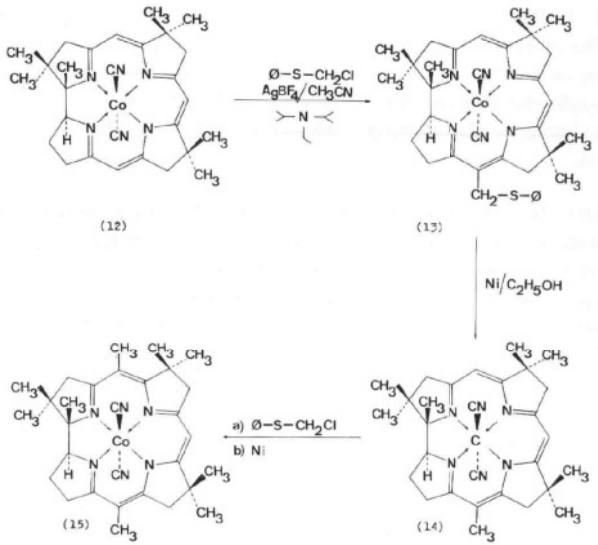


FIGURE 6

at the corrin chromophore appear to be the somewhat more reactive ones in electrophilic substitutions. This conclusion is corroborated by the results of deuteration and cyanidation experiments[7]. The finding provides the basis for some optimism with respect to the end phase of the B_{12} endeavour.

Let's return now to one of the major problems on the ETH side of the B_{12} synthesis, namely, to the condensation of the ring B precursor (16) in its lactone-lactam form with the ring C enamide (10) to form the potential B/C component (17). Formally, the problem appears simply to be one of an intermolecular elimination of the elements of water. However, it implies the most central problem of corrin synthesis, namely, the construction of the vinylogous amidine system which represents the characteristic structural element of the corrin chromophore. The preparative solution originally developed for this

purpose was the enamine-iminoester condensation; the essentials of this procedure are abstracted in fig. 8.

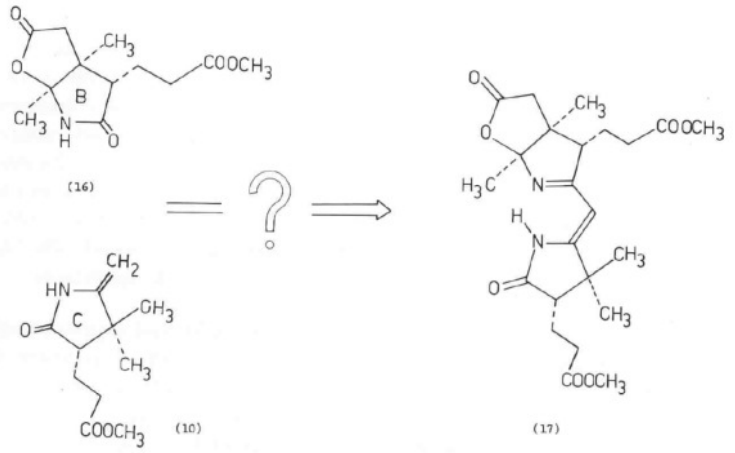


FIGURE 7

A lactam group is first activated by alkylation with triethyl-oxonium-tetrafluoroborate to form the corresponding iminoester. This electrophilic species is condensed with a carbanionoid component to form a product which, in one of the tautomeric forms, is an enamine derivative. Finally, condensation of the enamine with an iminoester leads to a vinylogous amidine.

Whereas this principle has most successfully served its purpose in the

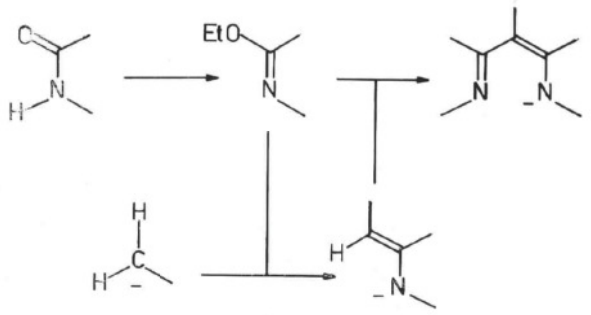


FIGURE 8

synthesis of simpler corrin complexes in a number of cases (see fig. 3 and [3]), it failed completely, and this in a multitude of attempted structural versions, to bring about a coupling of the precursors of ring B (16) and C (10) into the direction of structure (17). At least two reasons for this failure became apparent; first the methylidene carbon of the enamide (10), although quite reactive towards strong electrophiles, is not sufficiently nucleophilic to react with iminoesters in neutral or basic media; attempts to achieve a condensation by acid catalysis is hampered by the instability of the enamide towards acids. Second, iminoesters of the lactone-lactam (16) turned out to be much less prone to undergo condensations with carbanionoid partners than similar, but less substituted iminoesters of the α-pyrrolidone family; there is hardly a way out than to ascribe this difference in behaviour to a specifically high susceptibility of iminoester condensation processes to steric hindrance.

Fortunately, there was a way out both conceptually and experimentally. Whenever in organic synthesis one is confronted with a situation where the success of an *intermolecular* synthetic process is thwarted by a deficiency in reactivity or by steric hindrance, one can—or even one should—look out for any possibility of rearranging the structural stage of the problem in such a way that the critical synthetic step has not to proceed *intermolecularly*, but can proceed *intramolecularly*. The concept which led to a successful realization of this principle in the present problem is abstracted in fig. 9.

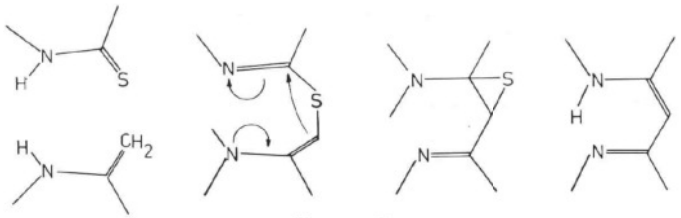


FIGURE 9

The lactam group is first converted to the corresponding thiolactam system. The sulfur atom, strongly nucleophilic and situated farther away from the bulky substituents than the original iminoester carbon, is then oxidatively linked to the methylidene carbon of the enamide partner. An intermediate is thereby formed which fulfills the structural prerequisites for an intramolecular enamide-(thio)-iminoester condensation. To be sure, such a process, formally leading to an episulfide intermediate, is hardly a downhill process. However, it is well known that sulfur departs quite often from episulfide systems with great ease, especially so in the presence of thiophiles like phosphines or phosphites, leaving behind the corresponding carbon-carbon double bond. In our

case, the formation of this double bond amounts to the generation of the desired vinylogous amidine system.

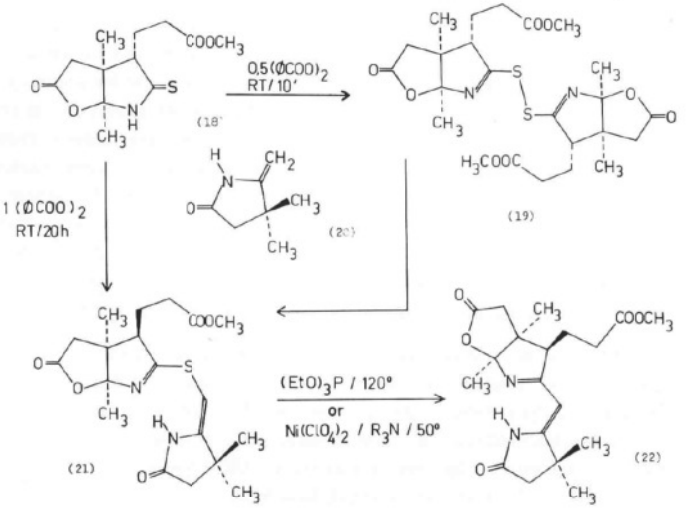


FIGURE 10

Admittedly, there was a rather long and hazardous way from this formalistic concept to its preparatively acceptable realization. Fig. 10 summarizes the state of experience eventually reached in the investigation of a semi-model system, namely, the coupling of the ring B-thiolactam (18) with the simple enamide (20). The oxidative coupling of the thiolactam (18) (prepared from

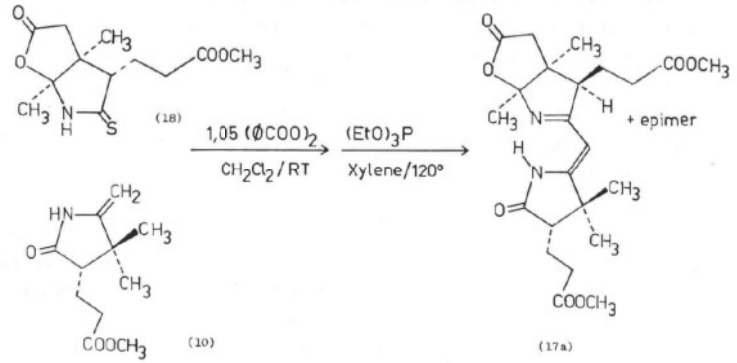


FIGURE 11

the lactam (16) via an iminoester with H_2S, or by reaction with P_2S_5 directly) with the enamide (20) to the intermediate (21) could be achieved by various methods, but oxidation with benzoylperoxide proved to be preparatively by far the most satisfactory. The identified intermediate in the coupling reaction is the readily formed bis-imidoyl-disulfide (19) which undergoes an acid (trace of HCl) catalyzed electrophilic substitution at the methylidene carbon of the enamide; thereby the liberated equivalent of thiolactam (18) is reconsumed by further oxidation. It was possible to isolate the rather unstable thiobridged intermediate (21) in crystalline form after chromatography on silicagel at 0° and to verify its structure both analytically and spectroscopically. Heating with triethylphosphite in xylene converts this intermediate to a mixture of two diastereomeric vinylogous amidine derivatives (22) in 80-90% yield. Other conditions and reagents bring about this sulfide contraction too, but the phosphite treatment is by far the most satisfactory method.

This then is the preparative solution of the B/C problem: the (+)-enantiomer of the ring B thiolactam (18) is oxidized with an equimolar amount of benzoylperoxide in the presence of the enamide (10) and a trace of HCl in methylene-chloride at room temperature and then, after removal of the acidic components of the reaction mixture (HCl, benzoic acid), the crude coupling product is heated with triethylphosphite in xylene. A 1:2 mixture of the two diastereomeric B/C components (17) and (17a) in about 70% yield is obtained, the socalled β-epimer (17a) in crystalline form in about 50% yield over all.

Is there anything wrong with the stereochemical outcome of this coupling reaction? Yes and no. It is found that the tertiary carbon of ring B in vinylogous amidine derivatives of type (17)/(17a) is configurationally extremely labile: traces of HCl equilibrate the epimers (17)/(17a) in a $CDCl_3$-NMR-probe solution at room temperature within less than an hour, the equilibrium lying at a ratio (17a):(17) of approximately 2:1. The configuration of the crystalline main epimer is in fact the "unnatural" one; fortunately, this fact is harmless because it has recently become known that in authentic vitamin B_{12} derivatives the very same position is also configuratively labile, and that, luckily enough, the natural configuration appears to be the more stable one.

The lactone-lactam (17a), although in essence structurally complete, was not quite ready yet to serve as the B/C component for the Harvard-ETH coupling operation. Extended model studies on this forthcoming problem had made it rather clear that, in all probability, not an iminoester condensation, but a coupling via a sulfide contraction, would have to provide the way for overcoming this major synthetic obstacle. Therefore, the lactone-lactam (17a) had to be converted to the corresponding thiolactam.

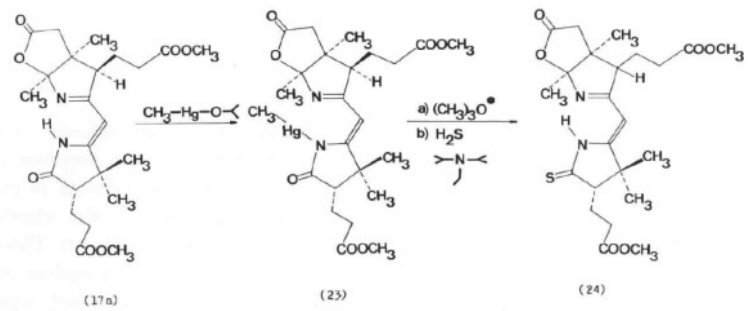


FIGURE 12

Here we became confronted with an instructive difficulty. The classical reagent P_2S_5 attacks not only the lactam function of (17a), but with comparable ease also the lactone group. The same proved to be true for the reaction with trimethyloxonium-tetrafluoroborate. However, the desired lactone-thiolactam can be made by converting (17a) first into the methyl-mercury derivative (23) with methyl-mercury-isopropoxide[8]. In this mercury complex the lactam oxygen is expected to be activated towards the attack of an alkylating agent, whereas the carbonyl oxygen of the lactone group is not. In fact, the methyl-mercury derivative (23) can cleanly be alkylated at the lactam-oxygen with trimethyloxonium-tetrafluoroborate, and subsequent thiolysis with H_2S in the presence of ethyl-diisopropyl amine produces the desired lactone-thiolactam (24). At this point now we seemed to be ready for what had for a long time been eagerly awaited at both sides of the Atlantic. However, ahead of us, there was serious trouble waiting.

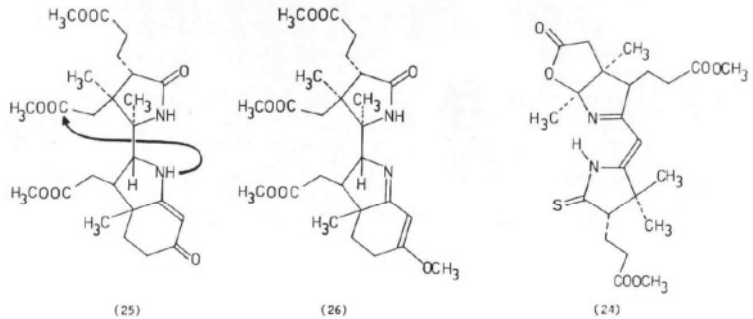


FIGURE 13

The candidate originally envisaged to serve as the A/D component for the A/D → B/C-coupling was the tricyclic enamino-ketone (25). This ex-

pectation soon proved to be illusionary, because the compound emerged from the Harvard laboratories as an extremely labile one, the reason for its lability being a ring closure between the enamine NH-group and one of the methyloxycarbonyl groups at ring A (see arrow in 25)) that most disturbingly takes place under almost any condition. This cyclization suppresses the systems enaminoid character, supposed to be a prerequisite for the coupling. A derivative which is stable towards this kind of cyclization was found in the O-methylether (26), but—alas—its nucleophilic reactivity at the vinylic carbon turned out to be far too low for coupling reactions of any sort. There is no need to describe here any of the numerous unsuccessful coupling attempts. It is sufficient to offer a glimpse at the cartoon[9] in fig. 14 which most accurately describes the situation which prevailed in the two laboratories for quite a while (each of the two gentlemen apparently thinking of the other: "May be you should start at your side all over again").

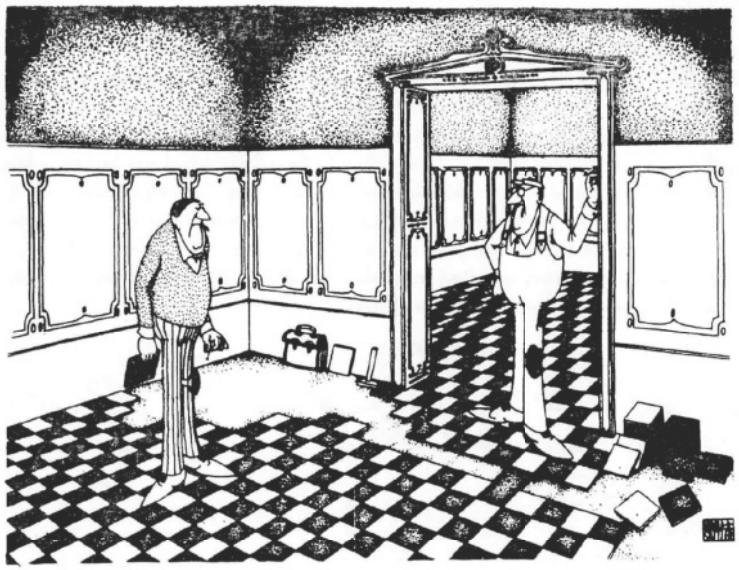


FIGURE 14

Things started moving again after two developments had emerged from the temporary crisis. The first, induced independently in both laboratories, led to an alternative to the oxidative version of the sulfide contraction method, namely, the *sulfide contraction via alkylative coupling.*

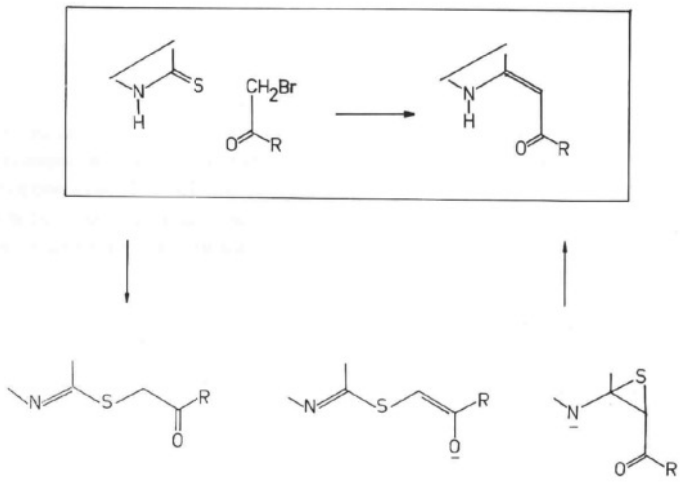


FIGURE 15

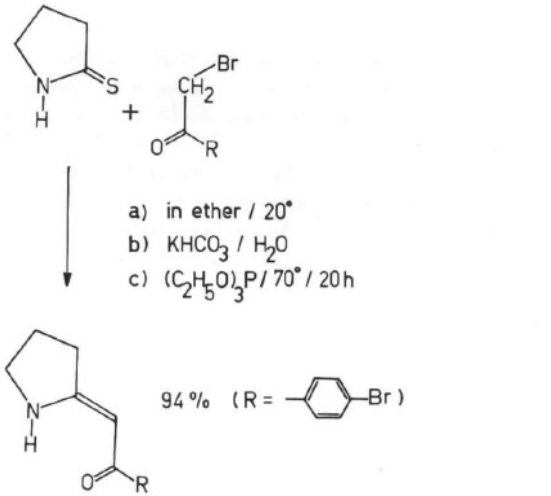


FIGURE 16

Bromomethyl-carbonyl compounds alkylate the sulfur of secondary thiolactams with great ease. Subsequent treatment of the S-alkylation product with a thiophile, in some cases in the presence of an enolizing base, removes the sulfur in a process essentially analogous to the one discussed earlier. The over all process produces the corresponding β-imino-enone derivatives; yields are generally quite high. A gala example, namely the one with thiopyrrolidone and p-bromo-phenacyl-bromide, is illustrated in fig. 16.[10] Bromo-acetone and α-bromo-tert.-butylacetate behave analogously, although in these cases catalytic amounts of tert.-butoxide are needed to induce the enolization which preceeds the sulfide contraction step.[10]

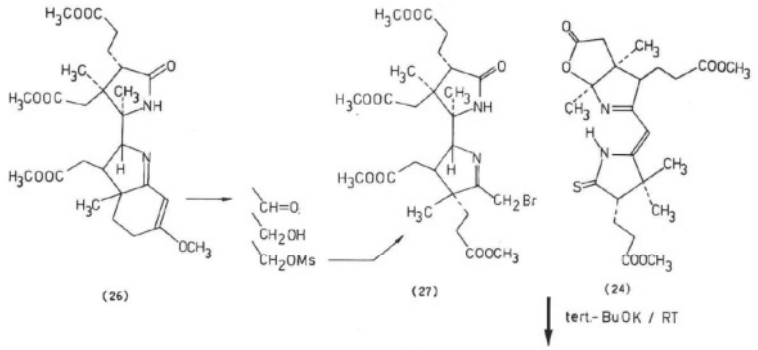


FIGURE 17

The other and most important development came from the Harvard group who showed that their A/D-enolether derivative (26) can be ozonolysed with high selectivity at the carbon-carbon double bond leading to the corresponding formylketimine which, in turn, can be converted to the bromo-methyl derivative (27). This type of structure represents the final and ideal solution to the problem of finding a suitable form of the A/D component for the A/D → B/C-coupling, the method to be used being the sulfide contraction via alkylative coupling. The present state of this critical phase of the project, onwards from which the experimental efforts of the two laboratories merged, is illustrated in fig. 18.

The potassium salt of the B/C component (24) is alkylated at sulfur by the A/D-bromide (27) in a smooth and clean reaction to form the labile pentacyclic thioiminoester derivative (28). The semimagic system methylmercuryisopropoxide-borontrifluoride-triphenylphosphine in benzene under rigorous exclusion of air converts this product at about 70° within less than one hour into a desulfurized product in an estimated 50-60% overall yield. Although this material has not been obtained yet in crystalline form, the as-

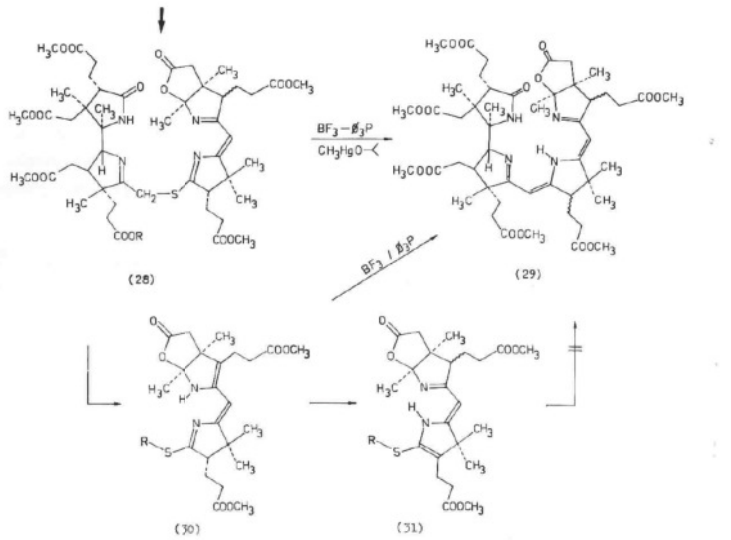


FIGURE 18

signment of constitution (29) to it is well documented spectroscopically. Formulas (30) and (31) describe tentative constitutions of two isomeric condensation products which are formed with greatest ease from (28) on chromotography. Although much remains to be learned about the intricacies of these structures and reactions, the investigators let themselves be pushed forward by the electrifying challenge of the forthcoming cyclization step. By doing this, they simply plunged into another nightmare.

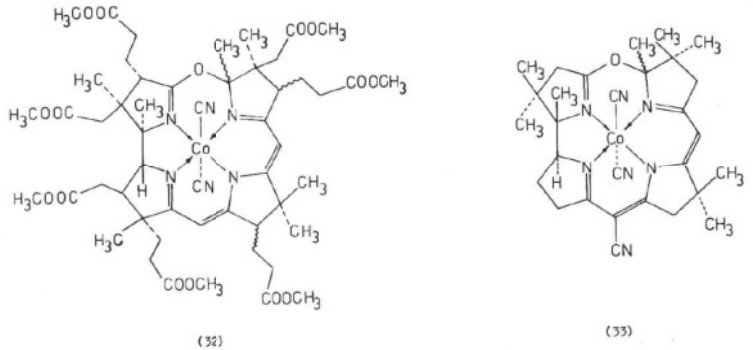
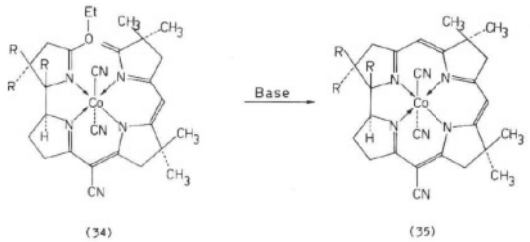


FIGURE 19

Formula (32) shows the structure of a non-corrinoid cobalt(III) complex which is formed in a sequence of operations including insertion of cobalt(II) into the ligand (29), alkylation with trimethyloxonium-tetrafluoroborate and, finally, treatment with excess cyanide ions in the presence of air. This is a dead end, as experiments with the structurally analogous complex (33) showed. In fact, a rather large number of preliminary experiments aiming at a cyclization of cobalt complexes derived from the pentacyclic condensation product (29) have ended, as yet, in vain.

How are precorrinoid ligand systems cyclized to corrins? Figs. 20-25 illustrate the present state of knowledge on this problem at the level of the structurally simpler synthetic corrinoids.



	R = H	R = CH_3
tert.-BuOK (H) / Py 7.5 h / 20°	> 90 %	
tert.-BuOK (H) / DMF 15 h / 50°		65 %
/ tert.-BuOH / DMF 18 h / 150°		ca. 5 %

FIGURE 20

The method developed originally[3] requires the preparation of precorrinoid iminoester complexes of type (34) and their cyclization to corrin complexes of type (35) by treatment with a strong base. The ease of cyclization is, not unexpectedly, found to be rather strongly dependent on the substitution pattern in ring A (see R = H and R = CH_3). The conditions required for the cyclization of the B_{12}-like substituted complex (34/R = CH_3) can hardly be expected to be applicable to a corresponding hepta-ester derivative in the B_{12} series (presumptions based on experiences of Drs. Claisen and Dieckmann!). Fortunately, alternative versions of the precorrin

→ corrin cyclization have been developed recently, and, remarkably enough, it was sulfur again, that paved the way.

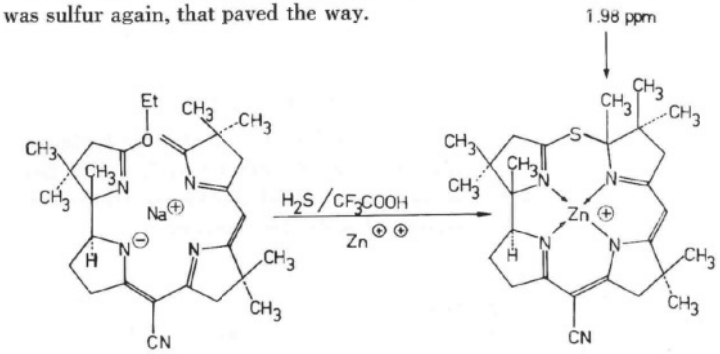


FIGURE 21

In trying to prepare the thiolactam derivative of the precorrinoid sodium salt (36) by acid catalyzed thiolysis, the crystalline zinc complex (37) was isolated. This compound served originally as a starting material for the synthesis of metal free corrin derivatives (see below); it recently has also been used for making the cobalt(III) thioiminoester complex (39) by the route (37) → (38) → (39) illustrated in fig. 22.

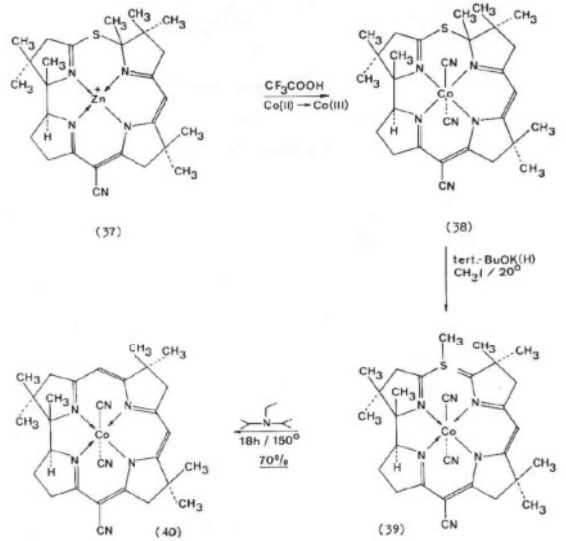


FIGURE 22

In sharp contrast to the O-iminoester complex (34/R = CH_3, see fig. 20) the corresponding thio-analogue (39) does cleanly cyclize to the cobalt(III) corrin complex (40) at elevated temperatures in ethyl-diisopropyl-amine. This thio-iminoester-pathway offers a potentially welcome alternative to the original potassium tert.-butoxide cyclization method.

The second and structurally more deviating alternative to the iminoester cyclization is based on the principle of sulfide contraction. It was in fact this approach which provided a solution to a central problem in synthetic corrin chemistry, namely, the preparation of metal free corrins.[11]

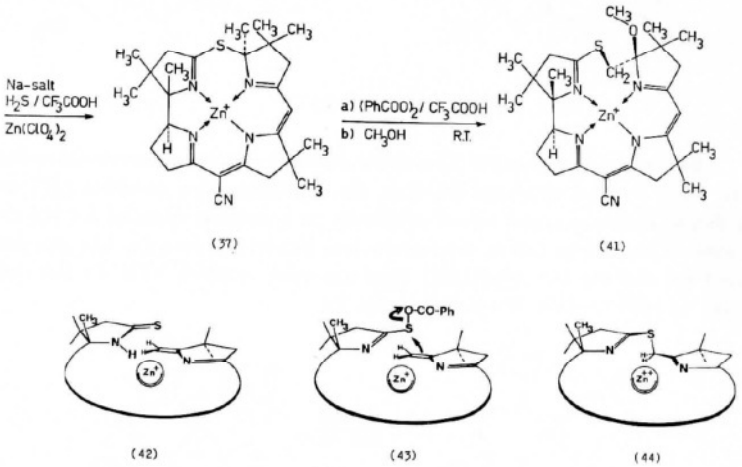


FIGURE 23

Treatment of the aforementioned zinc complex (37) with benzoyl peroxide in the presence of trifluoroacetic acid in CH_2Cl_2 at room temperature, followed by contact of the reaction product with methanol, produces the crystalline compound (41). This exotic conversion is assumed to be brought about by the following series of processes: trifluoroacetic acid establishes the equilibrium between the bridged complex (37) and its thiolactam isomer (42), the latter is then attacked by benzoylperoxide (this reagent does not react with (37) in the absence of the acid) to form the O-benzoate of the thiolactam-S-oxide (43) which—assisted by the template effect of the zinc ion—reacts with the enaminoid exocyclic methylidene carbon at ring B to produce an intermediate of type (44). Methanol is subsequently added in order to isolate and characterize a crystallizable reaction product of the oxidation step. Consideration of molecular models of structure (44) reveal the

interesting feature that the double bond in ring B is not supposed to return to the exocyclic position as long as the lone pairs of the trigonal nitrogens of rings A and B take part in coordination with the zinc ion; the geometrical situation created by the sulfide bridge in the zinc complex is such that the substituents of the exocyclic double bond could hardly be in a common plane. Yet, restoration of that exocyclic double bond is certainly a prerequisite for the reaction to proceed further in the desired direction of a sulfide contraction. Fig. 24 illustrates how this goal is attained.

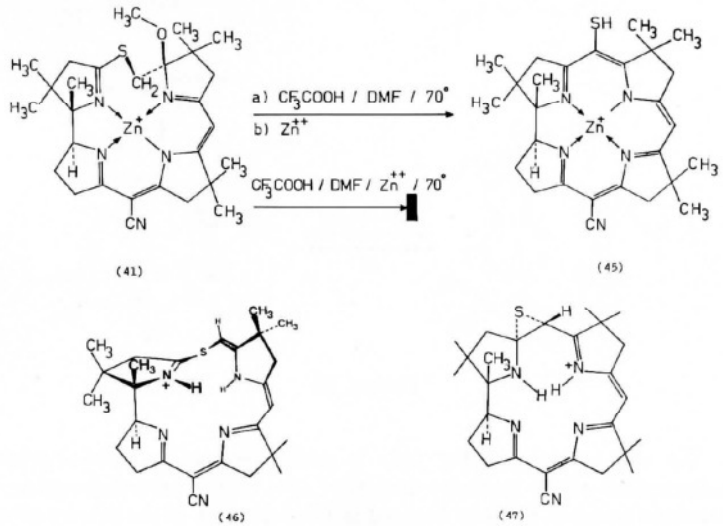


FIGURE 24

Trifluoroacetic acid in dimethylformamide at 70° converts the complex (41)—after work up in the presence of zinc ions—to the mercapto-corrin complex (45). A smaller amount of the corresponding desulfurized complex (see (48) in fig. 25) is also obtained. It is assumed that in the nucleophilic solvent DMF an acid induced decomplexation precedes the formation of an intermediate of type (46) in which the system can now accommodate the exocyclic double bond at ring B due to the much higher flexibility of the free ligand compared with its zinc complex. An intramolecular rearrangement via the hypothetical episulfide intermediate (47) would then lead to the mercapto-corrin chomophore. There is one piece of experimental evidence available which strongly supports the decomplexation hypothesis; treatment a) of complex (41) *in the presence of excessive zinc ions* did not produce any detectable

amounts of corrinoid products (45) or (48); to be sure, it has been checked that complex (45) would indeed survive such reaction conditions.

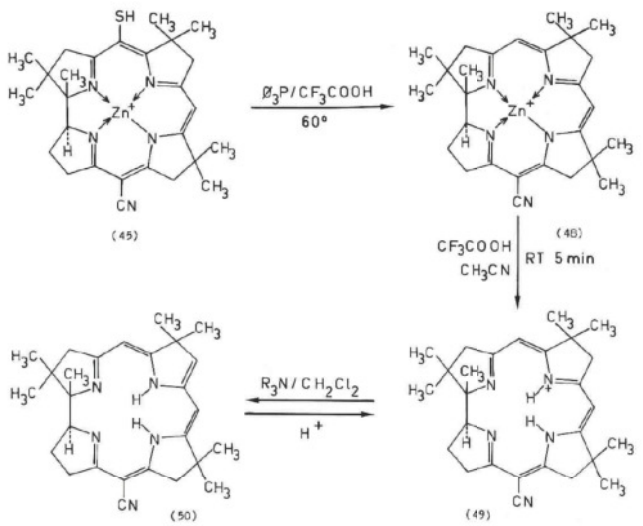


FIGURE 25

The zinc corrin complex (48) is easily obtained by acid catalyzed desulfurization of the mercapto derivative (45) with triphenylphosphine in chloroform solution. In sharp contrast to the behaviour of the corresponding robust complexes of nickel, cobalt and palladium, this zinc complex (48) loses now the metal ion with delightful ease in acetonitrile solution in the presence of trifluoro-acetic acid to give the corresponding metal free corrin in the form of crystalline immonium salts (49). In view of the high stability of corrin cobalt and nickel complexes it was most interesting to find that the metal free corrin base is a very labile molecule which surprisingly prefers to exist in the tautomeric form (50). Ironically, this metal free corrin likes to be a non-corrin. Excellent conditions have been found by which cobalt can be cleanly introduced into the ligand system (49) to form the identical cobalt corrin complex (40) discussed earlier.

To sum up at this point: three different types of processes have been developed so far to achieve the cyclization between rings A and D of precorrinoid metal complexes to corrin complexes of the general type (5). The formula (51) (see fig. 26) indicates the general direction of experimental efforts

towards a cyclization in the "slightly" more intricate B_{12} series. There must be—and there certainly is—hope.

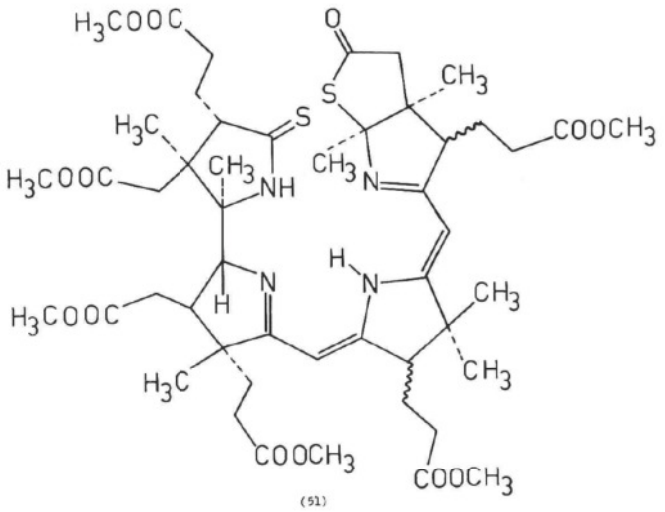
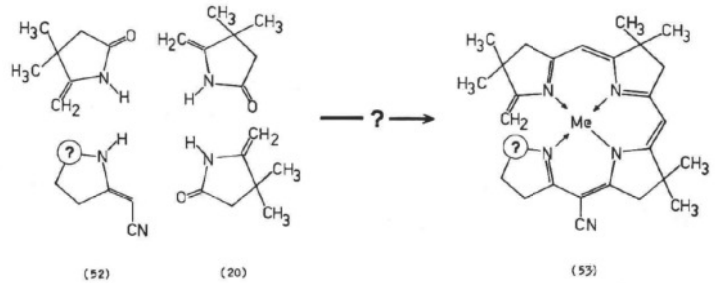


FIGURE 26

The typifying feature of the general approach to corrins discussed so far is the final metal template controlled cyclization between rings A and B. Inevitably, the concept requires the construction of a precursor component containing rings A and D and thereby the solution of the stereochemical problem of joining these two rings together stereospecifically in a trans fashion. To impose stereospecificity on a ring-joining reaction would certainly be a worthy task for a metal template. Let us therefore consider a completely different type of a potential corrin synthesis: to construct first the corrin chromophore system by joining rings A, B, C and D together in a row, to introduce then a metal ion, and to achieve a final cyclization between rings A and D under both the constitutional and configurational control of the metal template. Such an approach, beside being reminiscent to A. W. Johnson's[3] corrinoid synthesis, has been inspired by the structural regularities in the vitamin B_{12} molecule, regularities which are reflected in the fact that potential enamide precursors of all four rings of vitamin B_{12} can chemically be synthesized from the two enantiomers of one single chiral starting material (see earlier discussion referring to fig. 5). Fig. 27 formulates at the structural

level of the simplest enamide ring precursors (20) the synthetic problems posed by this alternative type of corrin synthesis.



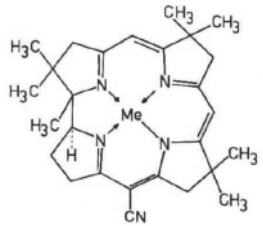
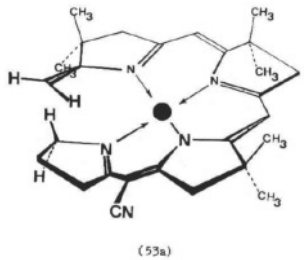
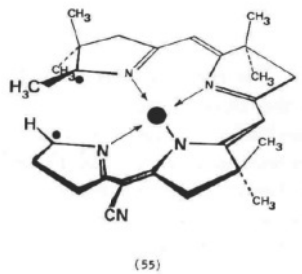


FIGURE 27





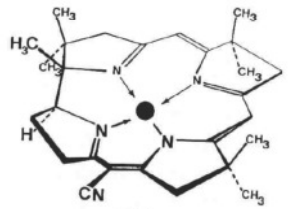


FIGURE 28

What type of reaction could possibly be envisaged to accomplish a stereospecific ring closure between rings A and D in an A/D-seco-corrinoid intermediate of type (53) to form the corrin complex (54)? What kind of functional group should be introduced at the question mark position of the ring D precursor (52)? A radical and daring answer to the latter question was: no functional group at all. This answer is simply inspired by the fact that a seco-corrinoid complex of structure (53), in which a (CH_2)-group stands for the question mark, is plainly isomeric with the corrin complex (54). The two systems differ only by the position of a hydrogen atom and of a carbon-carbon bond. A cyclization would simply require a corresponding transfer of a hydrogen atom and a rearrangement of a carbon-carbon bond. This kind of uninhibited formalism immediately rises to a scientifically realistic and exciting problem as soon as one considers the geometry imposed on the ligand system by the central metal ion.

Models of metal complexes (53a) display the ligand system coiling around the metal ion and one of the ring D methylene hydrogens lying directly underneath the exocyclic methylidene group of ring A; this is the case the more one tries to hold all four ligand nitrogen atoms in a common plane with the coordination center. The models do in fact suggest that such planoid complexes might optimally fulfill the geometrical prerequisites for an antarafacial sigmatropic 1,16-hydrogen transfer between the aforemen-

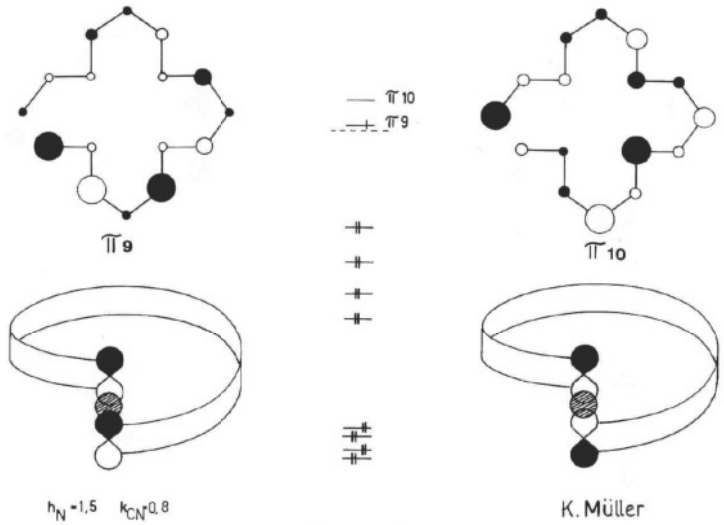


FIGURE 29

tioned positions of rings D and A. The formal primary product of such an obviously endothermic process would be the 15-center 16-electron π-system (55). This new π-system would contain two formally non-bonding π-electrons —in fact, it cannot be represented by a classical formula if one neglects 1,3-σ-bonds—and could gain the stabilization energy of a new carbon-carbon single bond by a necessarily antarafacial, electrocyclic 15-$(\pi \rightarrow \sigma)$-isomerization to the trans-corrin complex (54a).

What are the predications to be drawn from the Woodward-Hoffmann rules[12] on the conservation of orbital symmetry with respect to these two hypothetical processes?

Fig. 29 illustrates the symmetry of the frontier HMO-orbital π_9 of the 16-center-(16 + 1)-π-electron system which is relevant in the sense of a Woodward-Hoffman frontier orbital analysis to the 1,16-hydrogen jump in the electronic ground state. The analysis refers to the ligand π-system ignoring the metal orbitals. On its way from the position 1 on the π-system's top side to the position 16 on the π-system bottom side the hydrogen would run from a bonding into an antibonding frontier orbital interaction. The prognosis therefore is: if this hydrogen transfer can be induced at all, it would have to be tried photochemically. Notably, an analogous frontier orbital consideration for the second of the two formal processes predicts that the antarafacial 1,15-$(\pi \rightarrow \sigma)$-cycloisomerization should be thermally allowed in the electronic ground state (see fig. 30).

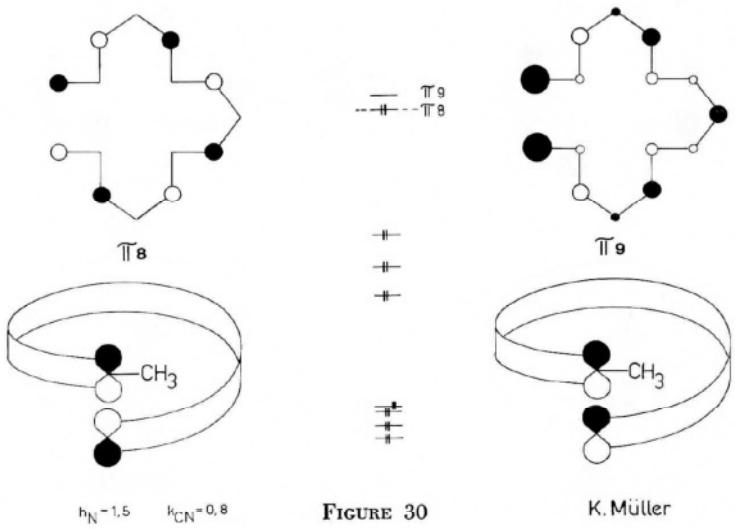


FIGURE 30

So much about wishful formalisms, model considerations and orbital symmetry prognoses—let us turn then to experimental facts.[13] First of all, seco-corrinoid metal complexes of type (53a) had to be constructed. This was achieved by condensation of three molecules of the enamide ring precursor (20) by the now familiar method of sulfide contraction via oxidative coupling and by subsequent addition of the fourth ring by an enamine-iminoester condensation.

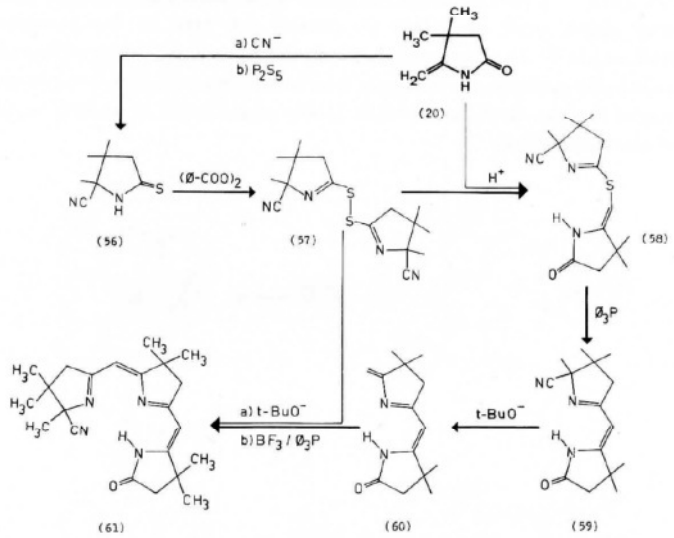


FIGURE 31

The first coupling of two enamide precursors (20) requires protection of the highly nucleophilic enamide double bond of the potential thioamide partner. This protection is best provided by the cyanide group[14] which can easily be introduced in alkaline medium and which survives the conditions of the subsequent reactions; eventually it can be cleanly expelled from vinylogous amidines by strong base. In contrast to the enamide (20) itself, the corresponding cyanolactam can be converted without difficulty into the corresponding thiolactam (56) by the classical P_2S_5-method. In a sequence of operations completely analogous to the B/C-coupling in the vitamin B_{12} series (see fig. 9-11), oxidation of the cyano-thiolactam (56) with benzoylperoxide in the presence of the enamide (20) leads to the bicyclic thiobridged intermediate (58) in high yield. Heating in triphenylphosphine brings about the sulfide

contraction to the vinylogous amidine derivative (59), and subsequent treatment with potassium tert.-butoxide eliminates the protecting group to form the bicyclic lactam (60). This compound had been used in our earlier work and had been prepared by different methods at the time.[3] The repetition of the process adds another vinylogous amidine unit to the bicyclic intermediate (60) producing the tricyclic analogue (61). In this more complicated case, a base induced version of the oxidative enamide-thiolactam coupling had to be used (NH-deprotonation of the lactam (60) and reaction with the isolated disulfide (57)). A further deviation refers to the subsequent sulfide contraction step which most profitably is carried out here in the presence of borontrifluoride.[15] The very efficient catalytic role of borontrifluoride is mechanistically ambiguous, it simply had been presumed that a coordinative bridging of the two flanking nitrogen atoms would result in a steric acceleration of the contraction.

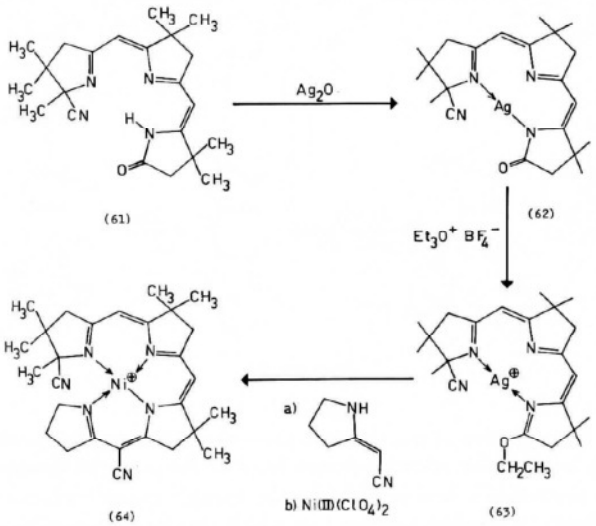


FIGURE 32

The experiments towards the addition of the fourth ring via an enamine-iminoester condensation led, once again, to an instructive experience. In contrast to the case of the bicyclic analogue (60)[3], the direct O-alkylation of the tricyclic lactam (61) with triethyloxonium-tetrafluoroborate proved to be preparatively useless, because presumably indiscriminate O- and N-alkylation occurred. This difficulty is overcome in the corresponding silver complex

(62), in which the sp^2-electron pairs of at least two of the three nitrogen atoms are blocked towards alkylation by the presumably diagonal coordination of the silver ion. Alkylation of the silver complex (62) to (63) and subsequent reaction with the ring D component in its free enamine form produce the tetracyclic condensation product which is conveniently isolated from the reaction mixture in the form of its magnificently crystalline diamagnetic nickel(II) complex (64). Cyanide ions remove the nickel(II) ion with great ease, thus allowing the preparation of complexes with other metal ions.

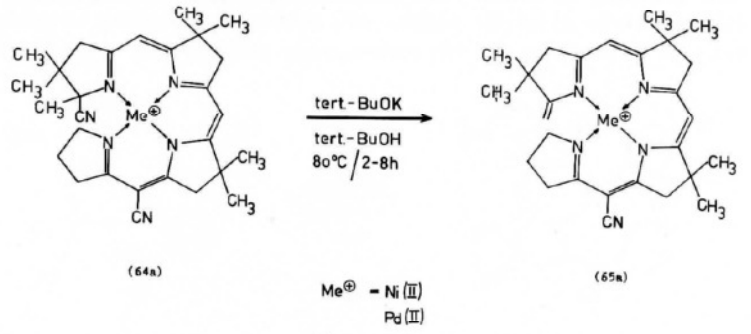


FIGURE 33

The cyanide protecting group in complexes of type (64a/Me = Ni(II) and Pd(II)) is removed by deprotonation with potassium tert.-butoxide to yield the seco-corrinoid complexes of type (65a). The constitution of the crystalline nickel and palladium complex (65a/Me = Ni(II) and Pd(II) is

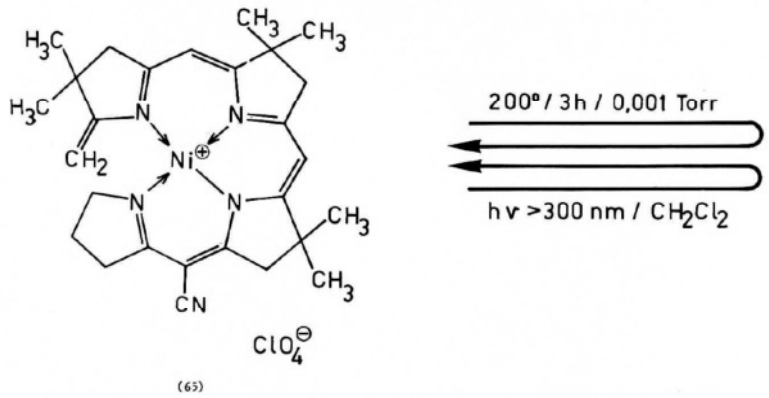


FIGURE 34

convincingly verified by their analytical and spectroscopic data, particularly by their transparently interpretable proton resonance spectra. Both complexes show a close similarity in the spectral properties, both are diamagnetic in chloroform solution and therefore of square-planoid structure.

At this stage then, we are back to the crucial question: does that macrocyclic hydrogen jump occur?

The experiment's verdict had humbly to be accepted: neither thermally (that is heating up to 200°) nor photochemically under various conditions did—as yet—the nickel(II) complex (65) disclosed any tendency to undergo this type of reactivity. But the corresponding palladium(II) complex (66)

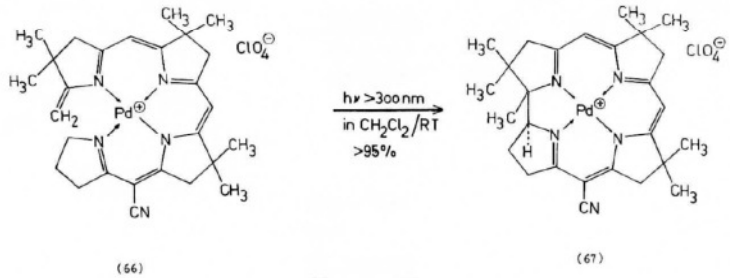


FIGURE 35

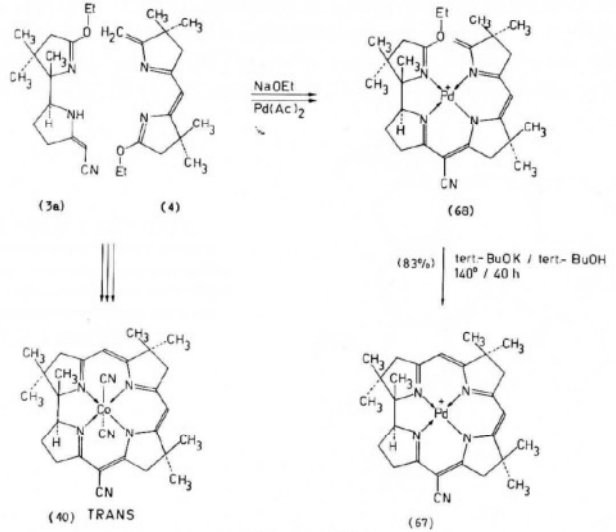


FIGURE 36

does undergo the cyclization with fabulous ease—photochemically. UV-light from a mercury high pressure lamp, or simply sunlight, transform oxygen-free solutions of this complex in pyrex vessels at room temperature into the palladium(II)-corrin complex (67) without detectable by-products. This process, in fact, turned out to be by far the cleanest and smoothest step we ever encountered in synthetic corrin chemistry. On the other hand, no UV-spectroscopic indication for the occurrence of a thermally induced cycloisomerization of the palladium(II) complex has been obtained so far.

Both constitution and configuration of the photochemical cyclization product (67) are beyond any doubt: the UV-, IR-, NMR- and mass-spectra are identical with those of a complex which was prepared specifically for the purpose of direct comparison via the classical synthetic route (3a) + (4) → (68) → (67) (see fig. 36). The trans-configuration of the ring junction in the A/D-component (3a) has recently been verified by Prof. Galen-Lenhert's[16] X-ray analysis of the dicyano-cobalt(III) complex (40) which had been synthesized previously[3] from the same bicyclic component (3a).

Although the fact of the cycloisomerization (66) → (67) does—in a sense—lend substance to the reaction formalism envisaged in the planning of the work, the mechanism of the reaction remains as yet largely unknown. A series of incisive questions referring to the nature of the photoreactive species[17] and to the specific role of the metal ion remain to be answered. X-ray analysis of the precorrinoid nickel(II)- and palladium(II) complexes (65) and (66) may help to answer the question whether or not it is justified to correlate the drastic difference in the behaviour of these two complexes towards light with a corresponding difference in the geometry of these complexes. It is well known in coordination chemistry that the palladium(II) ion has much stronger tendency towards square-planar coordination than the nickel (II) ion. This difference in capacity of imposing square-planoid geometry on quadridentate organic ligand systems can indeed have major consequences in organic synthesis. The final part of this lecture

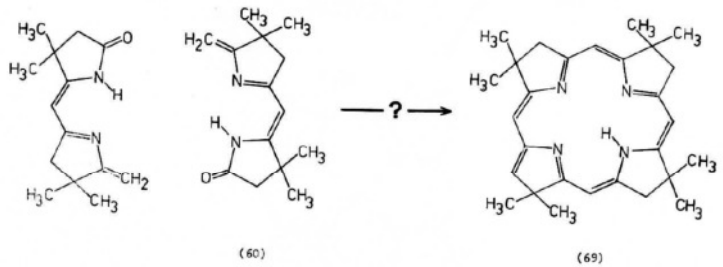
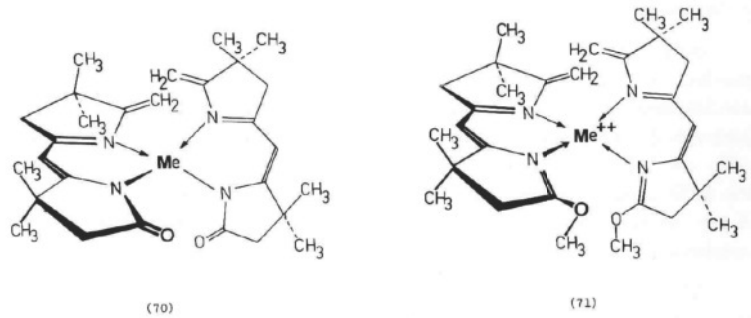


FIGURE 37

is intended to illustrate this statement with an example investigated some time ago in our laboratory, namely, the synthesis of what we call the corphin ligand system.[18]

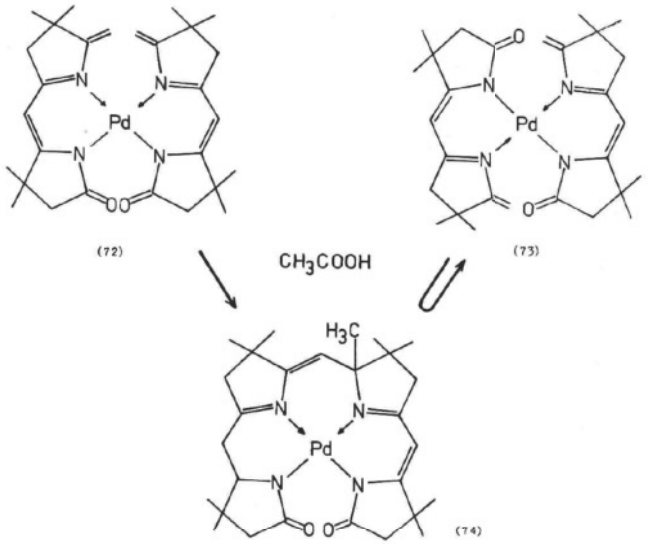
The porphinoid-corrinoid ligand (69) is formally a cyclic condensation product of the previously (see fig. 31) discussed bicyclic lactam (60). Exploratory experiments revealed no indication whatsoever that such a con-



(70) (71)

Me = Ni(II)
Co(II)

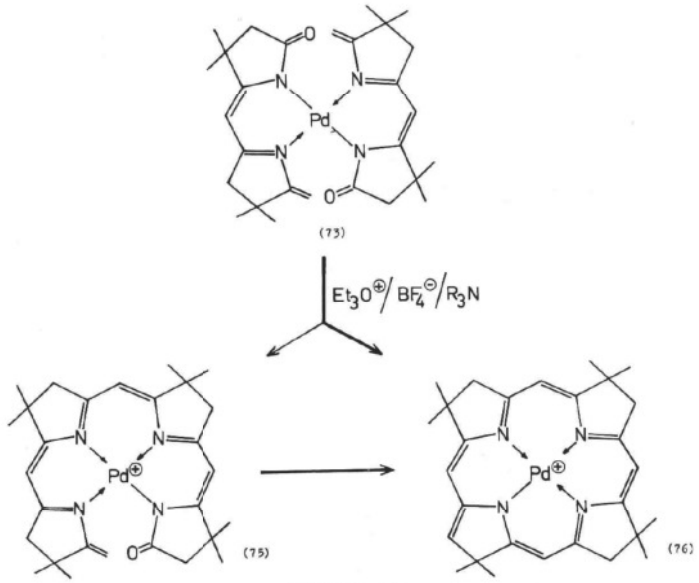
FIGURES 38 AND 39



(72) (73) (74)

densation might be experimentally realized without recourse to the template effect of metal ions. This expectation in mind, nickel(II) and cobalt(II) complexes of the lactam (60) and of corresponding O-iminoesters have been prepared. These complexes are obtained in high yields without showing any indication of stereoisomerism, they all are paramagnetic and therefore presumably not of the square-planoid, but of the tetrahedroid type (70) and (71) (see fig. 38). Under no conditions was it possible to achieve any condensation reaction between the two ligand moieties.

However, complexation of the potassium salt of lactam (60) with palladium(II) acetate did not produce one complex, but two of them. They are diastereomeric, diamagnetic and have therefore clearly the square-planoid structures (72) and (73). The cis-configuration of one member follows simply from the fact that under the influence of acetic acid at room temperature the compound is cleanly converted into a condensation product of structure (74), whereas the isomeric member remains unchanged under these conditions.



(73) (75) (76)

FIGURE 40

The latter isomer, that is the trans isomer (73), is transformed to the palladium(II)-corphin complex (76) very smoothly on treatment with triethyloxonium-tetrafluoroborate in methylenechloride at room temperature in

the presence of ethyl-diisopropylamine. The mono-condensed complex (75) which is isolated as a by-product of the reaction, can in turn be cyclized readily to (76) by alkylation under basic conditions. The intramolecular iminoester condensations involved in these processes occur so rapidly that iminoester intermediates could not be observed. What a contrast to the behaviour of the corresponding nickel(II) complex!

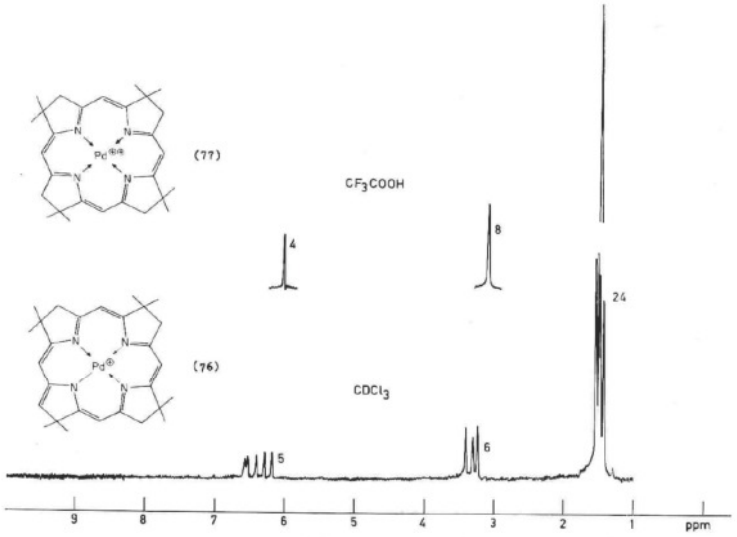


FIGURE 41

This short story of the corphin synthesis should not be closed without giving at least one piece of experimental evidence for the final cyclization products structure. This is the NMR-spectrum on fig. 41; it speaks in essence for itself.

The work presented in this lecture has been carried out by a group of excellent young chemists, to whom I express here my warmest appreciation. Their names appear in the list of references; the names of those, whose contributions to the B_{12}-project have been discussed here, but have not been published yet, are: Dr. Bernard Golding, Dr. Fritz Karrer, Dr. Karl Jürgen Schossig, Dr. Dan Becker, Dr. Heinz Gschwend, Dr. Alexander Wick, Dr. James Sims, Jost Wild, Urs Locher, Peter Löliger, Willi Huber, Peter Schneider, Paul Dubs, René Wiederkehr and Martin Roth.

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[17] Relevant photochemical studies on the reaction have been started in the laboratory of Prof. G. Quinkert, Technische Hochschule, Braunschweig.
[18] A. P. Johnson, P. Wehrli, R. Fletcher and A. Eschenmoser, Angew. Chem. **80**, 622 (1968), Angew. Chem. Int. Ed. **7**, 623 (1968).

INTRODUCTION AND DISCUSSION

[The following discussion took place after Dr. Eschenmoser's address.]

Dr. James A. Marshall (Discussion Leader) *Northwestern University:* I would like to thank Dr. Eschenmoser for a beautiful lecture. This paper is now open for questions.

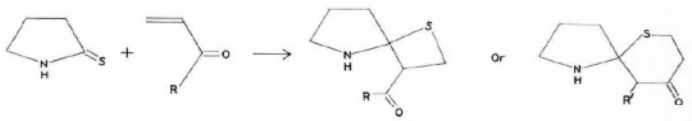
The reaction of thiolactams with electrophilic reagents is quite interesting. Have you looked at systems other than alpha halo carbonyl compounds?

Dr. Eschenmoser: Apart from α-bromo-ketones, α-bromo-esters and methyl-α-bromo-malonate (which, by the way, works beautifully too), we have not investigated any other case.

Dr. Marshall: One might visualize an interesting result from a vinyl ketone, for example. This may involve a four-membered sulfide intermediate.

Dr. Eschenmoser: Then you enter a completely different system. The sulfide contraction proceeds, if it is so simple as we think, via an episulfide as an intermediate, although it is conceivable that the thiophile might complex with the sulfur before the contraction step. I think, a four membered ring intermediate is not expected to behave the same.

Dr. Marshall: That's right, but one still has the possibility of carbon-carbon bond formation in the following manner: [Drawing on the board.]



A

Dr. Eschenmoser: Yes, I see. We have not done anything in this direction at all.

Dr. Andrew Streitwieser (Discussion Leader) *University of California, Berkeley:* There are some rather complex aspects of your synthesis that you explained most completely. I understand very well on the basis of your explanation why a palladium template is satisfactory whereas a nickel complex is not. The use of the sulfur was also explained very beautifully, but there was one elementary aspect of a practical synthetic nature that recurred in your synthetic work that I couldn't fully appreciate.

At several points in the work, you used ethyl-diisopropyl-amine as a weak base. And I wondered why this particular amine out of all of those that could have been chosen was actually used repeatedly?

Dr. Eschenmoser: The diisopropyl-ethyl-amine is sometimes called the "Huenig base" and it has been proposed by Huenig as an amine of about normal basicity (normal compared to other tertiary amines), but with the quality of not being alkylated by alkyl halides, or only very slowly so. We use this diisopropyl ethyl amine in all those cases where we expect the base to function only as a proton acceptor and not to do anything else, e.g. to add to electrophilic centers or to become alkylated by alkyl halides. Furthermore, it should not complex with metal ions. This has actually never been subjected to a severe test, but we expect that the diisopropyl-ethyl-amine, due to steric hindrance in its tetrahedrally coordinated state, should behave as a weak ligand of a metal ion, or as no ligand at all. That means diisopropyl-ethyl-amine is used as a base in complexation experiments, e.g. with cobalt (II)-

perchlorate or palladium(II)-salts, then we expect it not to interfere with the desired reaction by complexing—that is "neutralizing"—our metal ion.

Dr. Robert E. Ireland (Discussion Leader) *California Institute of Technology:* Isn't it possible, in the vinyl sulfide to have two geometrical isomers, only one of which could form the necessary episulfide intermediate?

Dr. Eschenmoser: You refer to the model series?

Dr. Ireland: Yes.

Dr. Eschenmoser: We have no evidence that two isomers are formed, but it is possible that they are.

In the series which I discussed in the first part of the lecture, the thio-bridged intermediate is a rather labile material. The crystalline isomer which served for the characterization was obtained by chromatography on silica gel at zero degrees; it was isolated in about fifty per cent yield and was a single compound according to n.m.r. It is perfectly possible that the other isomer was also present, but not isolated. Our experience with analogous compounds of this series indicate that the geminal dimethyl group in one of the rings seems to direct the substituents at the exocyclic double bond into the position trans to the methyl groups. However, this point has not been investigated in the present case.

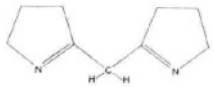
Dr. Nelson J. Leonard (Discussion Leader) *University of Illinois:* You have generated so many beautiful methods during this study that it seems mundane to ask questions about individual ones. But, in talking about the thiophiles, you mentioned that one could use ethyl phosphite or that one could use nickel perchlorate and base.

In the use of nickel perchlorate and base what happens to the sulfur? How does that work?

Dr. Eschenmoser: The one experiment in which we observed desulfurization by nickel perchlorate-diisopropyl ethyl amine gave us the desulfurized, contracted product in only about thirty per cent yield. We do not know any details of that reaction. We have not investigated it any further because we concentrated on the more transparent and preparatively more promising reaction with the common thiophiles. However, we learned from the experiment with nickel perchlorate that complexation could exert a pronounced influence on the ease of the desulfurization process.

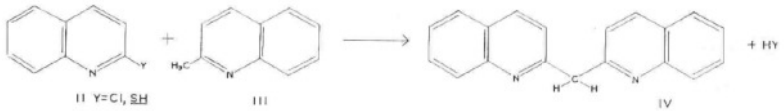
Dr. Ingo H. Leubner, Texas Christian University: I have a question to your reaction where you have formulated a sulfur dimer. May I go to the blackboard?

You have mentioned that you have used an oxidising reagent to make I, and I would like to ask you about this.



B

If you have two compounds, II and III, the reaction to the

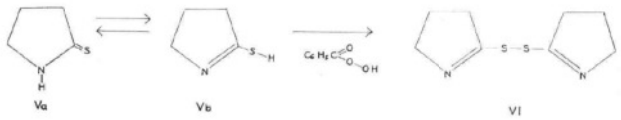


C

di-quinolyl-2-methane IV is acid catalysed. My question is now if it is necessary for you to use an oxidising reagent? The reaction to IV is acid catalysed and you mentioned that your reaction to yield I was also acid catalysed.

Dr. Eschenmoser: Now, is your question—

Dr. Leubner: Excuse me. You have formulated the reaction to I via a S-S-dimer, starting from Va, which is a tautomeric form of Vb.



D

Reaction II + III → IV reacts just with HCl as catalyst. So I wonder, if you need an oxidising reagent for your reactions? If you do not have the intermediate IV, that you propose, then you would have to propose an intermediate which is a carbonium-ion,—I think. An acid catalysed reaction without an oxidising reagent would then exclude a dimer formation, or would make it improbable.

Dr. P. de Mayo (Discussion Leader) *The University of Western Ontario:* This question is supposed to be a provocation to induce you to tell us something about the photochemistry. The low quantum yield and the temperature effect might just be interpreted as if this were a triplet reaction, the low quantum yield being because of the low rate of intersystem crossing.

The temperature effect that you describe sounds as though it is a process

with a very low activation energy and could be the kind of low activation energy that has occasionally been associated with intersystem crossings.

Now, I am not suggesting this too seriously, I am just trying to provoke you.

Dr. Eschenmoser: Paul, you made a statement, you did not ask a question, no?

Dr. de Mayo: The question is: — what is your opinion?

Dr. Eschenmoser: I think you are right in pointing out that the reaction has a good chance to be a triplet reaction. However, nothing has been done as yet in our laboratory to approach this problem experimentally. We know that the presence of oxygen is preparatively detrimental for the reaction, but this observation cannot be used as evidence in favor of the triplet hypothesis; oxygen *per se* oxidizes the peripheral methylene positions of such complexes with great ease.

Dr. de Mayo: Thank you.

Dr. Reginald H. Mitchell, University of Oregon: Having achieved your very cute synthesis of the system with the palladium in the center, could you describe some of your attempts to remove the palladium and replace it with a cobalt atom?

Dr. Eschenmoser: First of all, we are trying to prepare the dicyano cobalt (III) complex of the seco-corrinoid ligand to check if we can cyclize it to the cobalt corrin complex. As yet, we have no significant results in this direction.

Now, with regard to your question: If one starts with the metal free corrin ligand, it's a joy to put cobalt in. However, it has not been possible, neither with nickel corrin complexes nor with cobalt complexes of synthetic or natural origin, to remove the metal ion, either hydrolytically or reductively, without destroying the ligand. Preliminary experiments from our laboratory show that the same seems to be true with palladium.

Dr. Mitchell: Thank you.

Dr. Harry H. Wasserman (Discussion Leader) *Yale University:* I wonder, Professor Eschenmoser, if you would comment on the possible biogenesis of the linkage between rings A and D, and any pertinence that this may have to a method of synthesis.

Dr. Eschenmoser: Professor Wasserman's question [Referring to Figure 42] strikes at an important problem. As far as I am informed, the details of how the characteristic structural elements of the corrin ligand system are formed in nature are still unknown. Apart from Shemin's important findings

—that porphobilinogen is a precursor of vitamin B_{12} and that the extra methyl groups stem from methionine, nothing is really known about the problem how the corrin structure is formed. There is, however, no dearth of speculation about the problem, and it was in fact such a speculation which led us to become engaged in the synthesis of the novel porphinoid-corrinoid ligand system (80), the corphin system (*cf.* fig. 42).

The ligand (80) is on the same oxidation level as the porphinogen (78). One can easily imagine a chemically plausible sequence of reactions by which the four pyrrol rings of porphinogen become alkylated and by which the alkylation product then tautomerizes to the corphin structure (80). The latter structure differs from the corrin structure (79) by a reductive four electron-four proton-ring contraction. To find out if such a reductive corphin → corrin conversion can chemically be achieved is the aim of experiments with the model system (80) under way in our laboratory.

Dr. Leubner: I would like to ask you about photo ring closure, about the nickel and palladium complex.

Can it be that the nickel complex has a lower lying electronic state that is quenching your reaction? I always have nickel as a very colored ion in my mind. In other words, nickel could have a lower lying state and this state is quenching your reaction while palladium does not have such an electronic state.

Dr. Eschenmoser: You mean quenching the triplet state that Professor de Mayo mentioned?

Dr. Leubner: Any state, yes.

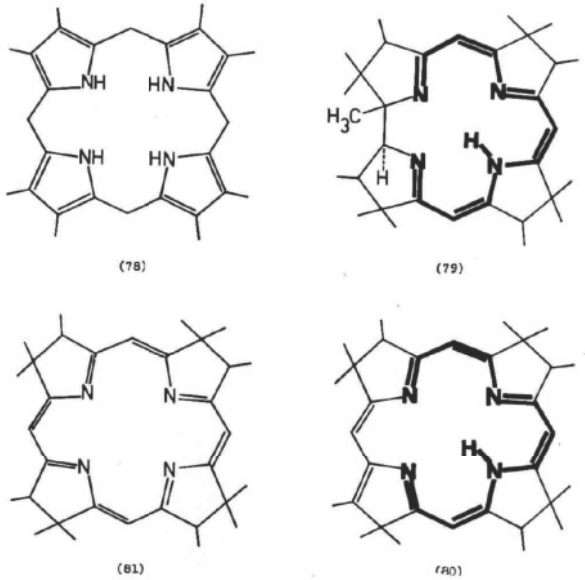
Dr. Eschenmoser: I don't know.

Dr. Leubner: Thank you.

Dr. John E. Baldwin (Discussion Leader) *University of Oregon:* A nickel complex was heated to 200 or 300 degrees and gave no reaction. With the palladium complex, however, the reaction occurred facilely at room temperature when the complex was exposed to light. Were you able to isolate this palladium complex before the closure between rings A and D and then heat it in the absence of light?

Dr. Eschenmoser: Yes, apparently I made myself not quite clear. Dr. Y. Yamada who has done this work was able to isolate this palladium complex in pure form by working in the dark. It is a crystalline compound, fully characterized by analytical and spectral data. We did try to cyclize the pal-

ladium complex thermally by heating it to about 200°, as we did with the corresponding nickel complex. In both cases, no spectral indication for the occurrence of a thermal cyclization was obtained.



E