

STUDIES ON THE SYNTHESIS OF CORRINS

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The corrin structure is perhaps the finest gift that X-ray analysis has so far bestowed on the organic chemistry of low molecular weight natural products. It is the most recent member of that biogenetically related group of ligand systems which includes the two porphyrinoid structures, porphin and chlorin, and through which nature fulfils some of its fundamental biochemical processes. In the form of a cobalt complex, the corrin system constitutes the structural nucleus of the B₁₂ vitamins and, very probably, the B₁₂ coenzymes. Research in the area of this group of natural products has been in a state of continuous and rapid development ever since vitamin B₁₂ was isolated in 1948¹.

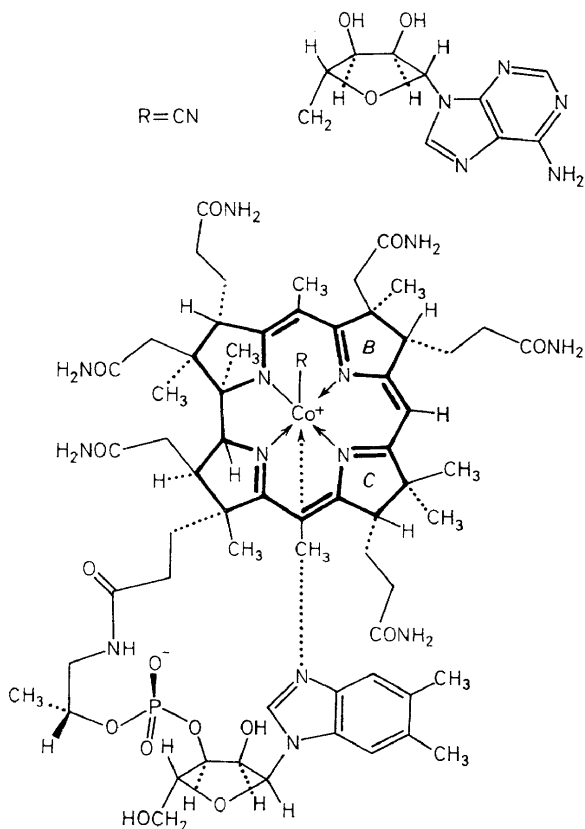


Figure 1

As far as structural chemistry is concerned, these studies culminated in the elucidation of the structure of vitamin B₁₂ (R=CN) in the middle of the fifties², and in Lenhart's and Hodgkin's³ recent discovery of a cobalt-carbon bond in the structure of one of Barker's⁴ B₁₂ coenzymes (*Figure 1*). X-ray analysis has thus enriched the chemistry of natural products with a class of structures containing two essentially non-classical features—the corrinoid ligand system and the cobalt-carbon bond. To a large extent knowledge of the specific chemistry of new structural types was formerly a by-product of the constitutional analysis by chemical degradation; in the present case, the subsequent acquisition of such knowledge remains as a task for natural product chemistry.

This task, even though it is to be tackled subsequently, is none the less a challenge which has been taken up in several laboratories, and one of the more striking expressions of growing knowledge in this field is the partial synthesis of coenzyme B₁₂ from vitamin B₁₂, recently achieved by the research groups of Johnson-Smith and Bernhauer⁵. Nonetheless, we seem to be only at the beginning of a new and fascinating chapter of organic chemistry, for the hidden potentialities within the corrinoid structure can only be hinted at by considering some of the enzymatic reactions that have recently been shown to be controlled by B₁₂-cofactors. For the organic chemist, their structural course seems to be almost a kind of provocation.

Figure 2 refers in particular to two reactions which are at the centre of

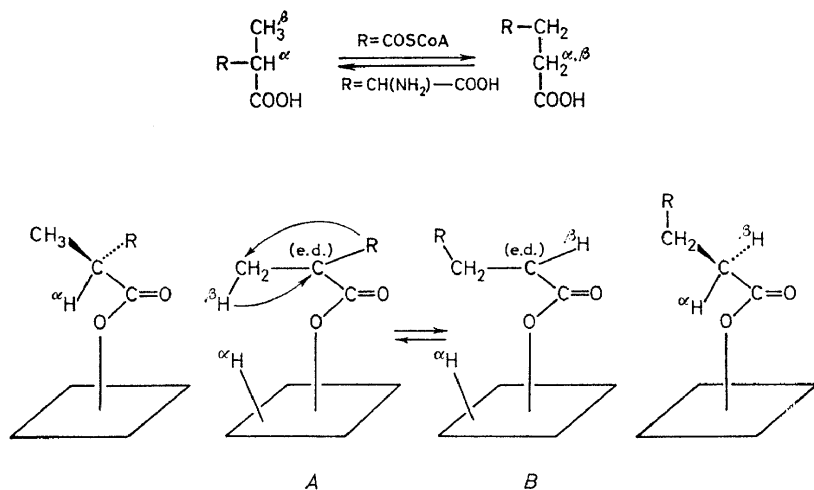


Figure 2

current interest, namely, the enzymatic rearrangement of the coenzyme A derivative of methylmalonic acid leading to the coenzyme A derivative of succinic acid⁶, and the structurally related rearrangement of L-glutamic acid to L-threo-β-methyl-aspartic acid⁷. The numerous experimental facts known about these two rearrangements might be incorporated within the body of organochemical experience if it is assumed that the B₁₂-enzymes are able to create an electron-deficient centre (e.d.) at the position α to the

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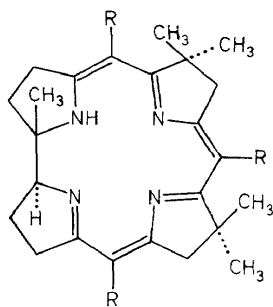
carboxyl group of the substrates, and that these then equilibrate by way of a ($\beta \rightarrow \alpha$, $\alpha \rightarrow \beta$)-double rearrangement.

One of the more striking experimental observations demands that, during these rearrangements, the α -hydrogen atom of the substrate does not exchange with protons from the environment^{6, 7}. Is it one of the functions of the double bond system of the corrin ligand to act as a temporary store for this hydrogen? And if so, is the hydrogen transferred to the corrin ring as a proton, leaving behind a substrate-carbanion which is oxidized by cobalt to an electron deficient entity *via* a carboxylate-cobalt ligand bond? These and further questions may be asked, and there is no lack of speculative answers. What is lacking, however, is even the prerequisite for such considerations, namely, knowledge of the general organic chemistry of the corrin system. To broaden the structural basis for the elaboration of such knowledge is one of the motivations for studies on the development of synthetic pathways toward the corrin structure. From a purely preparative point of view, investigations in this direction can hardly avoid involvement in new preparative aspects, as demonstrated by the pioneer work of the Cambridge⁸ and Nottingham⁹ groups. The results obtained by our own group in this field form the theme of my lecture.

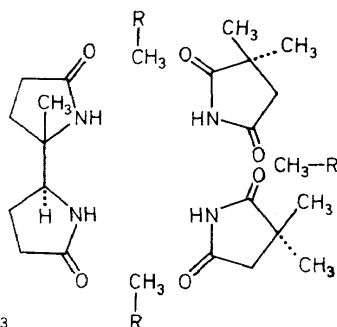
Right at the outset of our work, certain known features in the chemistry of vitamin B₁₂ had indicated that the choice of the specific corrinoid structure to be synthesized would have to be made with caution.

In vitamin B₁₂ (*Figure 1*) oxidative substitution reactions occur at the free β -position of ring B with remarkable ease¹⁰, suggesting that this centre is easily converted into a trigonal intermediate. Corresponding observations on the structurally similar α -positions of ring A and C do not seem to have been made. The reason may lie not so much in the corrin nucleus itself as in the presence of the methyl groups at the neighbouring *meso*-positions. The intermediate arrangement in which the methylene group of a corresponding propionic acid side chain has become coplanar with such a methyl group is obviously unfavourable because of steric strain. It is therefore difficult to predict the behaviour of such α -positions in an unsubstituted corrin. That is to say, the important question of the relative ease of tautomerization or dehydrogenation of such a system to pyrrolic derivatives must remain undecided. Such changes could represent one of the main dangers that a corrin synthesis might come to grief for unfair reasons. It is, of course, just the task of synthetic corrin chemistry to provide experimental answers to such questions, nevertheless, we have chosen as the first objective of our work, not the unsubstituted corrin itself, but rather a derivative of the pentamethyl-corrin (I). In this system, the distribution of the methyl groups is asymmetrical. The position of the peripheral quaternary centres and the anti-relationship of the ring-junction A-D correspond to the arrangement in the natural system. Any synthesis of such a structure will require the development of methods which allow a differentiation between the ring bridges in the "Northern" and "Southern" parts of the molecule.

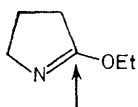
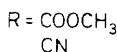
The underlying concept of our work starts from the transparent formalism that a corrin derivative of type (I) is at the same oxidation level as the assembly of structures (II). From this point of view, the problem of constructing the double bond system of the corrin nucleus emerges as a reversal



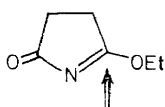
(I)



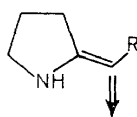
(II)



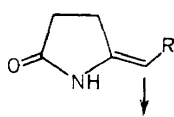
(III)



(IV)



(V)



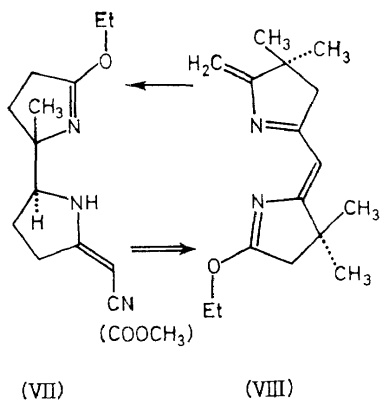
(VI)

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. Such an approach necessitates an appropriate activation of the electrophilic reactivity of the lactam and imide carbonyl systems. This brings us to the iminoesters, a class of compounds to which we have assigned a central rôle in our investigation. Since the early pioneering work of Pinner¹¹, the increased electrophilic reactivity of iminoester carbon compared with amide carbon has been well known¹². However, the possibility of using iminoesters as electrophilic condensation partners in the formation of carbon-carbon bonds seems to have attracted little attention, although some isolated cases have been recorded¹³. In the present context, however, one might consider that in a chemical synthesis of corrins the nucleophilic type of substitution at iminoester carbon could play a rôle analogous to that of the electrophilic substitution reactions at the α -positions of pyrrole derivatives in porphyrin synthesis. It was this hypothesis which led us at the outset of our work to investigate experimentally the properties of simple iminoesters of types (III) and (IV) with regard to their conversion into products of types (V) and (VI) respectively, as well as the further condensation of these products with their precursors to give the corresponding bicyclic systems. I do not propose to discuss these experiments in detail at this stage, as their essential features will appear later in the course of my account. At present, I only wish to emphasize that these experiments played a crucial part in helping us to conceive the structural details of the synthetic route to which we decided to adhere.

This route can best be illustrated in terms of the structures of two components which we shall refer to as the "Western" (VII) and the "Eastern" (VIII). Each of these structures possesses an electrophilic and nucleophilic centre, which are arranged in a specific manner with regard to their relative reactivity: The "Eastern" iminoester group, which we expect to be the

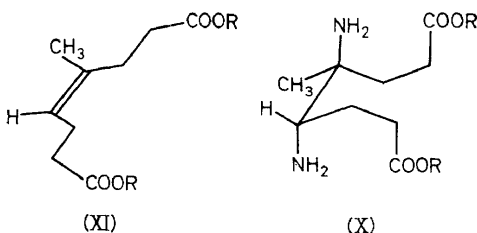
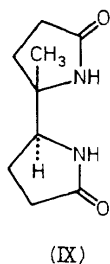
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more reactive one, lies opposite the "Western" nucleophilic carbon from which a structurally specific carbon-carbon condensation may be initiated by a deprotonation of the free NH-group.



We consider first the problem of a synthesis of the "Western" component (VII).

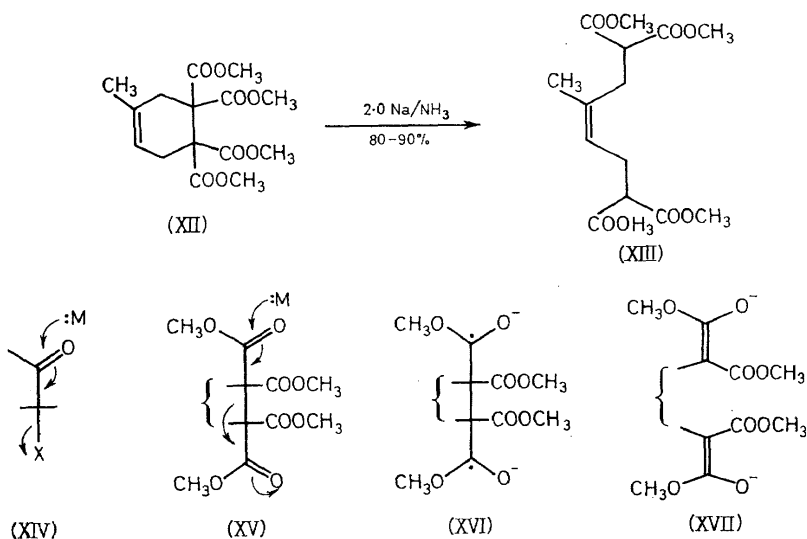
Within the framework of the iminoester concept, the simplest approach to this problem would involve the preparation of the dilactam (IX), with the assumption that subsequent differentiation between the two lactam carbonyls may prove possible. An obvious precursor of this dilactam is the



corresponding diamine (X) which, in turn, is seen to be the product of a *trans*-diamination of the double bond of the olefinic diester (XI). The first experimental step to be discussed here in detail deals with the preparation of this olefinic system.

For well known reasons, olefinic bonds, substituted with three alkyl

groups, are among those structural arrangements of which synthetic organic chemists are not particularly fond. For this very reason, however, such structural arrangements have their own special merit; they stimulate the search for new synthetic procedures. In the present case, the method that was developed may well be considered as a tailor-made solution for the problem of the stereospecific synthesis of such *cis*-substituted olefinic dicarboxylic acid derivatives. It is based on a principle which has had its place in synthetic natural product chemistry ever since the advent of the Harvard steroid synthesis¹⁴, namely, that in constructing a carbon chain it may be beneficial to insert one too many carbon-carbon linkages, if thereby one can make use of the synthetic power of the Diels-Alder reaction. The novel aspect of the present case is a ring opening by a reductive cleavage of a carbon-carbon single bond. This reaction arose from asking the question

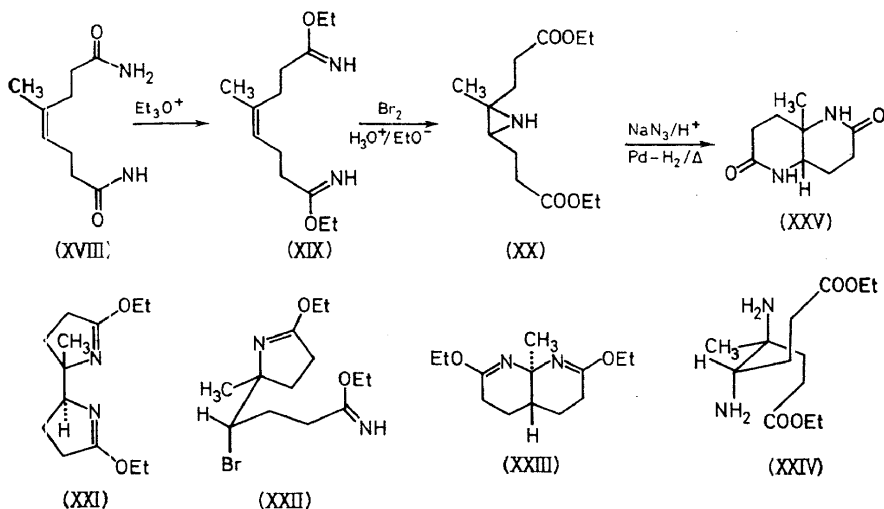


as to whether the rôle of the electrophilic leaving group X (X = Halogen, OAc *etc.*) in the well-known reductive process of type (XIV) can be assumed by a malonic ester group. Experiment impressively affirmed this possibility: the cyclic tetraester (XII), easily available in quantity by a Diels-Alder reaction between isoprene and tetramethyl-ethylenetetra-carboxylate, can be virtually titrated with sodium in liquid ammonia between -70 and -40° , whereby exactly two gram-atoms of sodium are consumed and the aliphatic tetraester (XIII) can be isolated in high yield. The smoothness of this reductive cleavage is undoubtedly related to the concomitant formation of the stable bis enolate (XVII); an accompanying steric decompression may exert a favourable effect. It remains undecided, however, which of the two representations of the process, (XV) or (XVI), is the more appropriate.

The possibility of easily producing unlimited amounts of the aliphatic tetraester encouraged us to persist with a synthetic route which proved to hold in store a series of surprises. The first of these was encountered in trying to develop a method for the *trans*-diamination of the double bond. The

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original intention of achieving this by suitable electrophilic addition reactions, with iodo-isocyanate¹⁵ for example, was thwarted by the discovery that, under varied conditions, both in the tetraester and the corresponding diester, such reactions proceed with internal participation of an ester carbonyl group leading to butyrolactone derivatives, that is, to blind alleys. It was this result, however, which was eventually put to work in the following way.

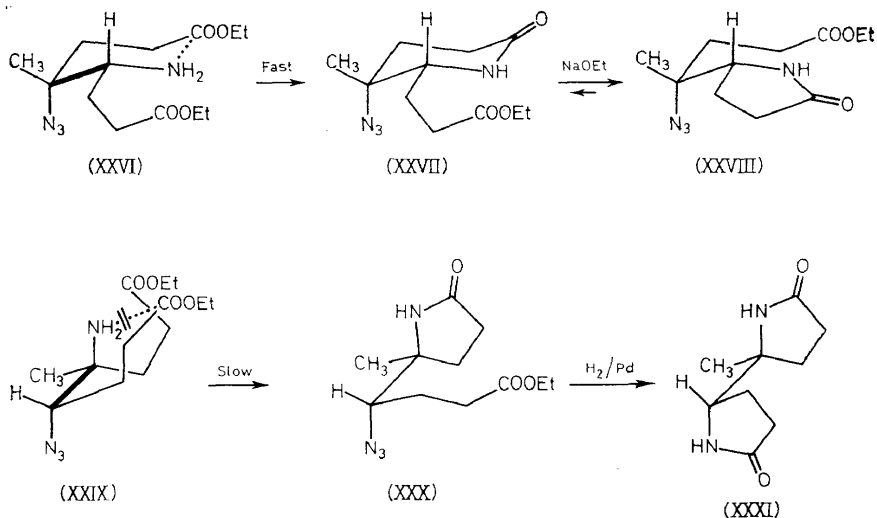


Carbonyl-oxygen is known to be the site of nucleophilic reactivity in an amide group. The method of choice for transferring this reactivity to the nitrogen is to convert the amide into a corresponding iminoester; this can be achieved under mild conditions and in high yield by using Meerwein's triethyloxonium-tetrafluoroborate¹⁶. While treatment of the diamide (XVIII) with bromine leads to a bromo-butylolactone, careful bromination of the diiminoester (XIX) in chloroform at 0°, subsequent mild hydrolysis with dilute hydrochloric acid, and final treatment with base, produces the aziridine derivative (XX). The main product formed in the bromination step is the monocyclic bromodiiminoester (XXII); the size of the ring and the secondary position of the bromine are deduced from the infrared ($\nu_{\text{C}=\text{N}} = 1640 \text{ cm}^{-1}$) and the n.m.r.-spectrum ($\delta_{\text{CHBr}} = 4.1$). The stereochemistry of the aziridine is derived on the basis of two assumptions that are well documented in related reactions, namely, that the bromination step is an assisted *trans*-addition, and that the base-induced cyclization of the intermediate α -bromo-amine ejects the bromide ion with inversion.

The monocyclic bromo-diiminoester (XXII) is structurally very close to the bicyclic diiminoester (XXI); a transformation of (XXII) into (XXI) would simply require a ring-closing substitution reaction, proceeding with intermediate participation of the cyclic imino nitrogen. However, experiments seem to confirm the anticipated stereoelectronic restriction on such

a participation. For instance, the reaction initiated by silver tetrafluoroborate in methylene chloride does indeed produce a bicyclic diiminoester in good yield, but its constitution proved to be not (XXI), but (XXIII), which results from a Wagner-Meerwein rearrangement of the ring methylene group.

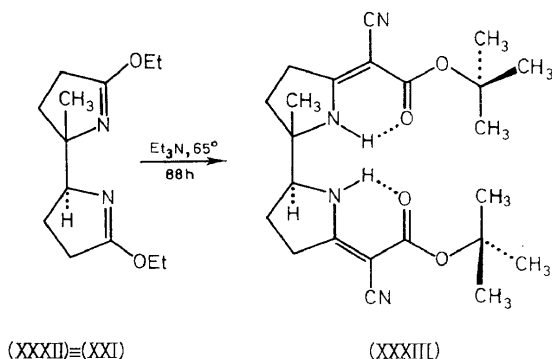
With the aziridine derivative (XX) in hand, the problem of the *trans*-diamination was at least settled in principle. The way to the required five-membered dilactam, however, was still not cleared. Contrary to our expectation that the diamine (XXIV) would ring-close to the *five*-membered dilactam, it was the *six*-membered dilactam (XXV) which was obtained exclusively when the aziridine ring was opened with an excess of azide ions in the presence of one mole of mineral acid, followed directly by catalytic hydrogenation and subsequent gentle heating to induce lactam formation. At this point, however, Dr Pesaro in our laboratory made an equally surprising, but at the same time both clarifying and useful, observation. When the



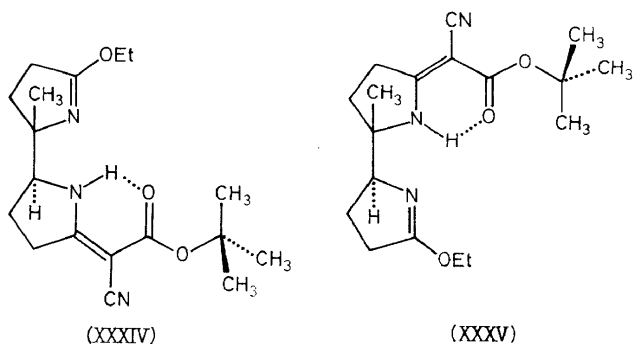
sequence of operations is interrupted before the hydrogenation step, a crystalline by-product separates within a few hours in about 10 per cent yield from an ethereal solution of the reaction mixture. It is the six-membered azido monolactam (XXVII). The major part of the amino-azide mixture (XXVI/XXIX) cyclizes much more slowly. After several days at room temperature an isomeric crystalline azido-lactam is obtained in up to 70 per cent yield and this proves to be the five-membered azido-lactam (XXX) and not an isomeric six-membered lactam. After catalytic hydrogenation and subsequent heating in anisole, the latter promptly yields the desired five-membered dilactam (XXXI = IX). The stereochemistry of this dilactam requires a *trans*-opening of the aziridine ring. This undoubtedly takes place, for in the five-membered azido monolactam (XXX), the azide group can be shown by n.m.r. spectroscopy to be secondary, as would be expected from an *S_N2* type of ring opening.

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The difference in behaviour of the two isomeric amino azides (XXVI) and (XXIX) merits comment. The ring closure of the amine (XXVI) to the six-membered monolactam (XXVII) represents the formation of the thermodynamically less stable isomer, for the equilibrium (XXVII) \rightleftharpoons (XXVIII) can be established in the presence of sodium ethoxide and is found to lie on the side of the five-membered azido monolactam (XXVIII). In the case of the isomeric amino azide (XXIX) with its amino group at the tertiary carbon, a kinetically controlled ring closure to a corresponding six-membered monolactam would be sterically retarded, for the conversion of the carbonyl carbon of the cyclizing ester group into a tetrahedral intermediate creates a 1,3-diaxial steric interaction with a side chain methylene group. The conformational differences between six- and five-membered rings would lead one to anticipate that this kind of steric retardation should be less in a five- than in a six-membered system.

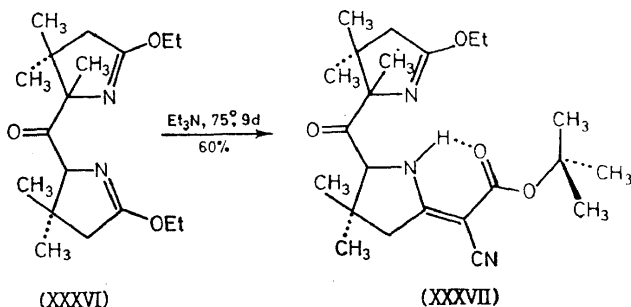


With the next step, we come to the first application of the previously discussed concept of carbon-carbon condensation by way of iminoesters. The efficiency of the method is illustrated by the observation that the diiminoester (XXXII \equiv XXI), obtained easily from the aforementioned dilactam with triethyloxonium-tetrafluoroborate, condenses with *t*-butylcyanoacetate in the presence of catalytic amounts of triethylamine (at 65° for 88 h) to give the crystalline bis-condensation product (XXXIII) in 95 per cent yield. The corresponding mono-condensation products can easily be obtained at room temperature using a shorter reaction time.



At this stage then, we are confronted with the earlier question as to the extent to which the two condensation centres of the bicyclic diiminoester can be differentiated. In other words, does the single methyl group exert any marked steric influence on the relative ease with which the two trigonal reaction centres can be converted into tetrahedral intermediates?

Experimentally, two isomeric products are formed (72 per cent yield in Et_3N at 20° for 69 h) in a ratio of about 2:1. The main product (XXXIV) can easily be separated from its isomer (XXXV) by chromatography on silica-gel. The structures of the two isomers follow unambiguously from their mass spectra, in which the most prominent peaks originate from a rupture of the intercyclc carbon-carbon bond.



An analogous mono-condensation can be cited which provides a further and illustrative answer to the sort of question just discussed. A diiminoester derivative of constitution (XXXVI), in which the two condensation centres are situated in positions β to one and two quaternary carbons respectively, undergoes a mono-condensation not only much more slowly, but also more specifically. The main product is crystalline and has constitution (XXXVII), as shown by its mass spectrum. In this more highly substituted system the influence of the one extra methyl group in one of the rings is reflected in a product ratio of about 10:1.

Decarboxylative fission of the two isomeric monocyno-*t*-butylesters (*e.g.* (XXXIV), brought about by treatment with anhydrous trifluoroacetic acid under strictly controlled conditions ($20^\circ/10$ min), completes the reaction sequence leading to the "Western" corrin components of type (VII). The decarboxylation products are obtained as liquids; the n.m.r.-spectra in the ethylenic proton range indicate the presence of both geometrical stereoisomers in approximately equal amounts. Their separation, possibly difficult, was fortunately not necessary for our purpose and was not attempted.

Before turning to a discussion of the "Eastern" component, I should like now to digress for a moment from the rather straight and narrow corrin theme.

Up till now, there have been two occasions in developing our synthetic pathway when we have made use of two quite different synthetic potentialities of the iminoester system: in an internal alkylation of the iminoester nitrogen, and a nucleophilic substitution at the trigonal iminoester carbon.

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A third type of reactivity is displayed in substitution reactions at the α -carbon of the alkoxy group by way of an alkyl-oxygen fission¹⁷. A novel a.d. for preparative purposes, promising variation of this third type of reactivity is a reaction which we have recently investigated in connection with some problems in the peptide field¹⁸, and which has also been observed in another connection by Vorbrüggen¹⁹ at Stanford: the esterification of carboxylic acids by means of Meerwein's²⁰ acetals of dimethylformamide (DMF). We have found benzoic acid, for example, to be converted into its *s*-butylester in about 95 per cent yield by 1.2 equivalents of the DMF-di-*s*-butylacetal within two hours at 80° in benzene solution (Figure 3). The

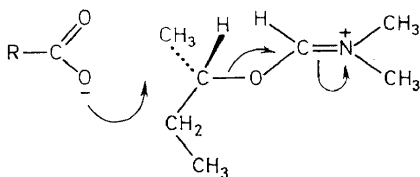
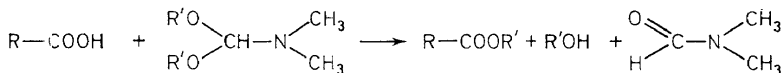
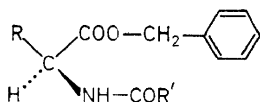


Figure 3

following experimental observations show that we are dealing here with an alkylation of the carboxylate oxygen. In the first place, the esterification of benzoic acid with the optically active DMF-acetal of *S*-2-butanol proceeds both in benzene at 80° and in acetonitrile at room temperature with practically complete inversion; secondly, 2,4,6-trimethyl-benzoic acid, a prototype of sterically highly hindered carboxylic acids, is esterified with DMF-diethyl-acetal at practically the same rate as is benzoic acid; and thirdly, under otherwise similar conditions, benzoic acid remains largely unesterified by the di-neopentylacetal of dimethylformamide.



<i>N</i> -DOBC-L-val	in benzene/80° / 1.5 h	96%
-L-phe	25° / 54 h	90%
-L-try	80° / 1.5 h	78%
gly-L-leu	80° / 1 h	73%

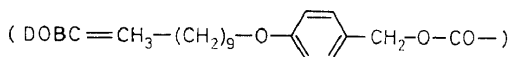


Figure 4

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In *Figure 4* a few examples are listed which illustrate the use of the esterification method for the preparation of benzylestere of amino-acid derivatives. As a process which does not depend on an activation of the carboxyl group, but consists of an alkylation of the carboxylate oxygen, the reaction has, *a priori*, a good chance of proceeding without racemization. So far, we have found in the cases of L-valine and L-phenylalanine that the corresponding optically pure crystalline benzylestere-hydrochlorides are obtained in yields of 95 and 89 per cent respectively after selective cleavage of the *N*-protecting group with trifluoroacetic acid.

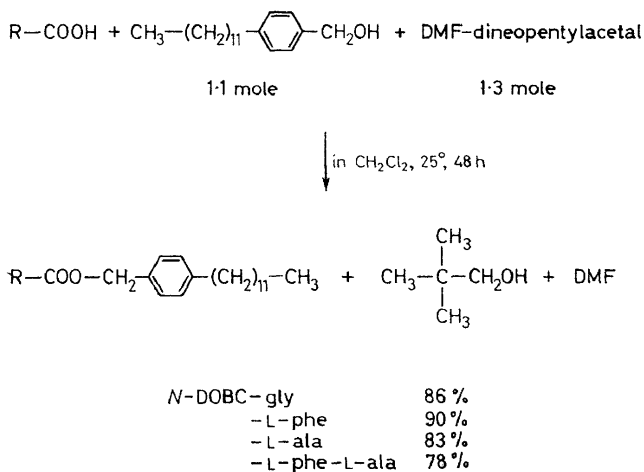
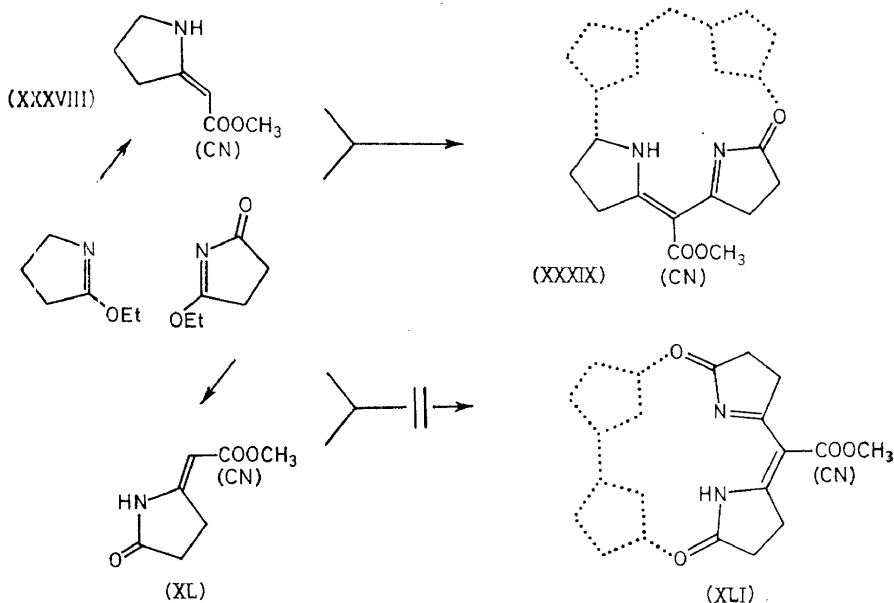


Figure 5

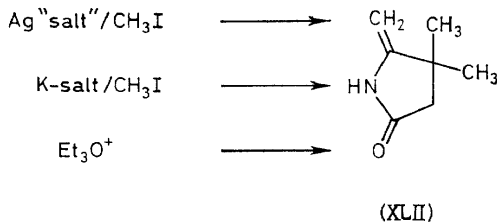
The most recent development²¹ in the exploration of this esterification method is indicated in *Figure 5*. By virtue of its relative inertness in the S_N2 alkylation step of the esterification process, the di-neopentylacetal of dimethylformamide has proved to be a useful mediator in esterifications with substituted benzylalcohols, *e.g.* *p*-dodecyl-benzylalcohol and *p*-methoxybenzyl alcohol. At least in the examples tested so far, the procedure turns out to be exceptionally mild and simple; its potential advantage is that essentially only one mole of alcohol is required, and only volatile by-products, neopentylalcohol and dimethylformamide, are produced. The limitations of the method, especially with regard to the range of alcohols that can be used, remain to be determined.

Returning now to the problem of synthesizing the "Eastern" corrin component, formulae (XXXVIII) to (XLI) illustrate the outcome of experimental tests concerning the usefulness of the iminoester concept in going from the monocyclic to the bicyclic level. It was gratifying to find that condensations to compounds of the type (XXXIX) proceed smoothly at room temperature in the presence of sodium ethoxide; they represent a model for the final task of combining the "Western" and "Eastern" corrin component. An analogous condensation to the bicyclic system (XLI) would constitute the corresponding device for a construction of the "Eastern"

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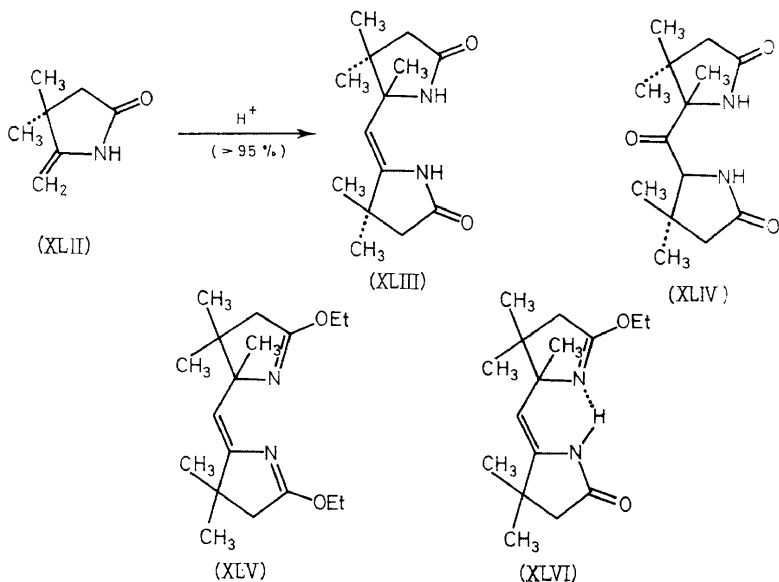


component. While the structural difference between the enamine reactants (XXXVIII) and (XL) consists only in that the latter contains an additional carbonyl group, the effect on reactivity is incisive. Such condensations to give compounds of type (XLI) have so far proved unsuccessful. It is, of course, plausible that the nucleophilic reactivity at carbon in a *C,N*-diacylated enamine compared to a corresponding *C*-monoacylated system should be lower. As one of the possible consequences to be drawn from this observation, we were led to a study of the *N*-monoacylated system (XLII) which

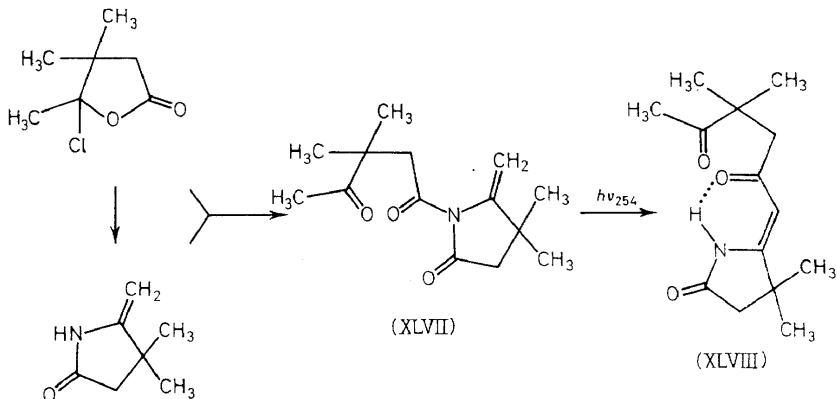


turned out to be the source of much valuable information. This may be illustrated by the finding that it was possible to alkylate this enamide at will either on oxygen, nitrogen or carbon by simply varying the alkylating reagent. The most interesting and valuable result is the course of the methylation of the "silver salt"—that is to say, of the material formed by the reaction of the sodium salt with silver tetrafluoroborate. Nucleophilic reactivity at carbon is demonstrated even more impressively by the discovery that under the influence of catalytic amounts of acids the enamide (XLII) can undergo a smooth dimerization in practically quantitative yield. Apart from the fit of the spectral and analytical data, the structure (XLIII) of the dimer is supported by the presence of an internal hydrogen bond in

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the mono-iminoester derivative (XLVI). Such bonding can be deduced from the infrared and n.m.r. spectrum, and may explain the considerable difference in basicity between the mono- (XLVI) and the di-iminoester (XLV) ($pK^*_{MCS} = \sim 3$ and 6.40 respectively). The most remarkable feature of this dimerization is the facility with which the diquaternary substitution pattern in one of the two rings of the dimer is formed. It is this kind of heavy accumulation of alkyl groups that is found in ring A of natural corrinoids. In passing, I may mention that the dimer (XLIII) constitutes the starting material for the preparation of a keto-dilactam of constitution (XLIV), the diiminoester derivative (XXXXVI) of which has been mentioned previously.

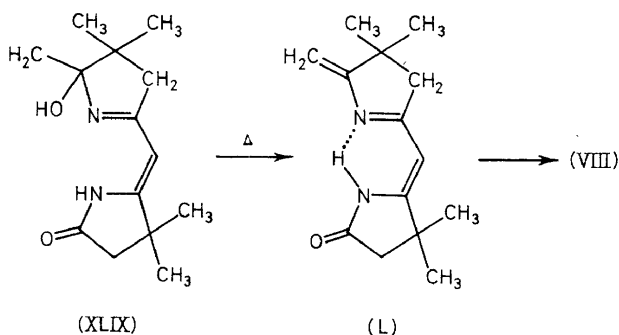


At the outset of the eventual synthesis of the "Eastern" corrin component we have an experiment initiated in our laboratory by Dr Scheffold on the acylation of the potassium salt of the enamide with the pseudochloride

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of mesitonic acid. He has observed almost exclusive *N*-acylation, the product (XLVII) (λ_{\max} . 242 $m\mu$), however, is partially rearranged to the *C*-acylated isomer (XLVIII) (λ_{\max} . 283 $m\mu$) during distillation. In order to use this product as an intermediate, introducing the missing nitrogen function was necessary.

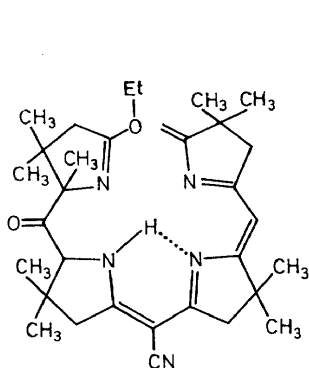
At first, preparative experiments on the pyrolytic nitrogen-to-carbon isomerization afforded us little encouragement. While heating at 290° for 15 minutes was found to be the best reaction conditions, even then the molecule was mostly cleaved and the yield of rearrangement product did not exceed 30 per cent. At this point, we dipped into the treasury of photochemistry—and were amply rewarded. The photochemically induced nitrogen-to-carbon rearrangement, brought about by irradiation of a 0.025 *M* cyclohexane solution with a mercury low pressure lamp, is a very rapid and essentially uniform reaction. It is masked, however, by a subsequent photochemical destruction of the *C*-acylated product, occurring at approximately half the rate of the rearrangement. In a strictly controlled flow process, with exposure times of less than ten minutes, the *C*-acylated enamide can be obtained in about 50 per cent yield with a conversion of approximately 70 per cent. The isomeric nitrogen-to-carbon migration of the ring-acyl-group occurs concomitantly only to a slight extent; in one of the experiments, the corresponding product has been isolated in a yield of about 1 per cent.



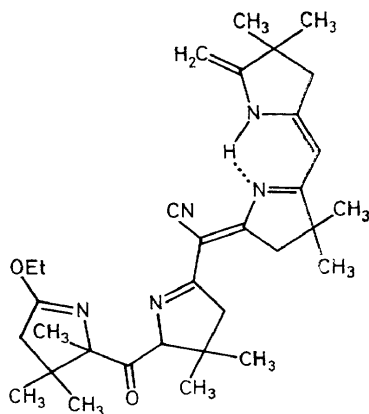
The introduction of nitrogen by treatment of the *C*-acylated enamide with methanolic ammonia leads first to the intermediate (XLIX); and then the tertiary hydroxyl group is eliminated by heating in toluene. These structural changes manifest themselves in characteristic and transparent spectral changes, and we need not go into the details of their structural correlation here, except perhaps to draw attention to a relevant change in the n.m.r. spectrum which accompanies the trigonalization of the quaternary carbon in the water elimination step (XLIX)→(L). This is evidenced by a coalescence of a typical methylene quadruplet ($J = 16$) into a methylene singlet. The crystalline compound (L) can be shown spectroscopically to contain an internal hydrogen bridge. This structural element must be regarded as a very welcome feature, for it is suspected of being largely responsible for the successful outcome of the subsequent step. In spite of its nature as a vinylogous amidine derivative, compound (L) is alkylated with triethyloxonium-tetrafluoroborate on oxygen, and affords a highly sensitive

but distillable liquid, the ethoxyl group of which is easily recognized in the n.m.r. spectrum. By this result the synthesis of the "Eastern" corrin component (VIII) is complete.

With the task of linking together the "Western" and the "Eastern" component in a structurally specific way we entered the final phase of our investigation. Let me remind you of the previously delineated strategy which we intended to follow: The first condensation step would have to be initiated in the "South-Western" corner by deprotonation of the NH-group, whereupon the adjacent carbon centre should react preferentially with the conjugated "South-Eastern" iminoester group. This group is expected to be more susceptible to nucleophilic attack than the isolated iminoester system in the "North-West" corner. Experimentally, this first condensation step proceeds smoothly in the presence of sodium ethoxide in diglyme solution at room temperature and affords a highly unstable material of the expected type to an estimated extent of about 70 per cent. It was possible to make this estimate because of the particularly fortunate fact that in a parallel series of experiments, starting from the previously mentioned keto-dilactam, one of the possible stereoisomeric condensation products was



(LI)



(LII)

obtained in crystalline form. This provided us with the opportunity of checking rigorously the analytical and spectral data of at least one member of this highly sensitive group of precorrinoid structures. These data, including the result of the molecular weight determination, are in accordance with the type of tetracyclic systems shown. For the time being, the very delicate questions concerning the stereochemistry are left undecided; however, we are inclined to believe that the two structural formulas (LI) and (LII) ought to be given preferential consideration.

The non-crystalline condensation products obtained from the two available isomeric "Western" components can be purified efficiently by chromatography on calcium hydroxide and—at least in the series leading to (LIII)—*via* the preparation and subsequent cleavage with EDTA of a crystalline zinc complex. The particularly relevant n.m.r. spectrum (*Figure 6*) of

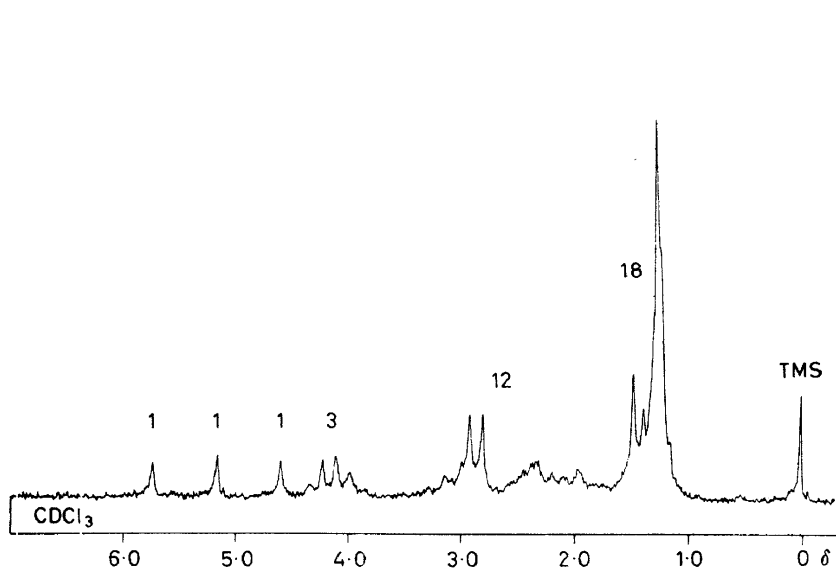


Figure 6

this material is in accordance with the type of constitution represented by formula (LIII). We find singlets of three ethylenic protons, the methylene quadruplet of one ethoxyl group, covering the signal of the one tertiary proton, and finally, signals corresponding to altogether 12 and 18 protons respectively in the methylene and methyl region. In alcohol solution, (LIII) exhibits ultraviolet light absorption maxima at 270, 280, 288 and 390 $m\mu$, $\log \epsilon = 4.40, 4.42, 4.36$ and 4.35 respectively.

What finally remains then, is the problem of closing the ring. It appeared clear from the very beginning that this step might possibly have the best chance of taking place within an appropriate square-planar or octahedral metal complex. In such complex formation the metal ion would be expected to have three effects which would favour this ring closure. First, to replace the imino hydrogen; secondly, to engage the iminoester nitrogen in complex bonding, thereby enhancing the electrophilic reactivity of the trigonal iminoester carbon; thirdly, and probably most important, to fix the two condensation centres at positions which may be near to bonding distance. The extent to which this last expectation will be realized will clearly depend both on the nature and valency state of the metal.

A beautifully crystallized nickel complex is formed in good yield when molar amounts of the aforementioned tetracyclic product (LIII), nickel perchlorate and sodium ethoxide are allowed to interact in acetonitrile at room temperature. The complex behaves as a monomolecular compound in methanol solution, it is orange in colour, cleanly diamagnetic in chloroform and, therefore, very probably of the square planar type—but the ring is not closed. This is unambiguously shown by the n.m.r. spectrum (Figure 7) which indicates the presence of three (and not two) ethylenic protons, as well as of one ethoxyl group. In methylene chloride solution it exhibits

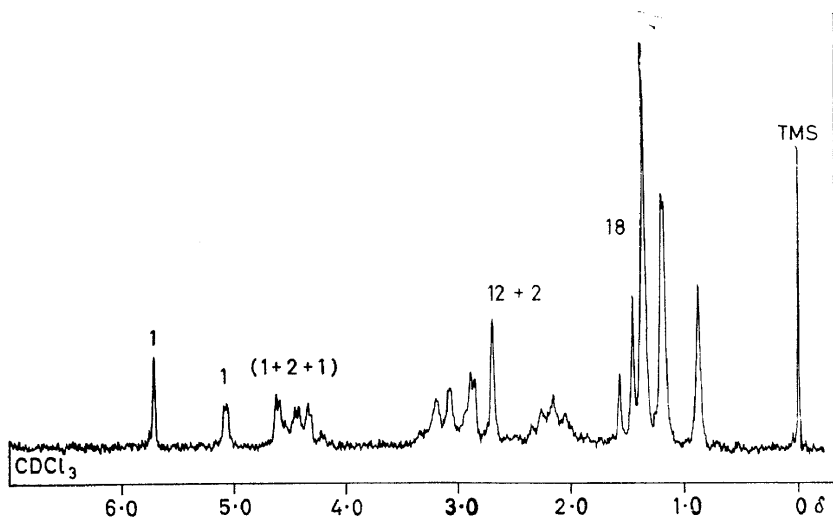
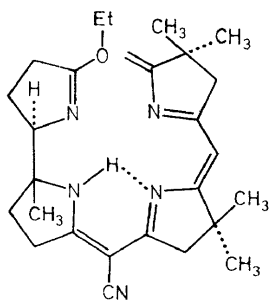
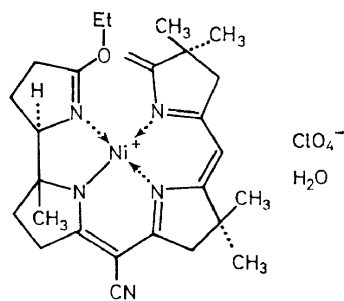


Figure 7

light absorption maxima at 251, 263, 306 and 430 $m\mu$, $\log \epsilon = 4.25, 4.20, 4.09$, and 4.09 respectively. The analytical and spectral data lead to the constitution represented in formula (LIV).



(LIII)



(LIV)

By using zinc perchlorate under otherwise identical conditions, the corresponding crystalline zinc complex is formed; its n.m.r. spectrum shows again the same structural features. Cobalt-(II)-perchlorate, on the other hand, behaves differently after subsequent oxidation of the complex with air, as we have found in parallel experiments in the isomeric series. With three different crystalline cyano-cobalt-(III)-complexes in hand, we are at the moment confronted with the fact that their N.M.R. spectra all show the presence of not three, but two vinyl protons, although the compounds still contain the ethoxyl group. The relevant experiments which are intended to support or disprove possible structures are under way and detailed discussion at this point would be premature.

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I conclude then with the statement that the work described in this lecture has not yet arrived at the stage of including a synthesis of the corrin structure. However, we believe that, as regards the chemical behaviour of the precorrinoid metal complexes, we have so far hardly scratched the surface of the subject.

I had the fortune to be associated with a group of highly able and dedicated young colleagues, to whom the work described in this lecture is due. Dr Fritz Elsinger, Heinz Cschwend, Hanspeter Gribi and Helmut Boos have made important contributions in various phases of the investigation. The main part of the work, however, has been done by Dr Mario Pesaro, Dr Rolf Scheffold and Dr Ehrhard Bertele and I take the opportunity to thank them and their colleagues for their wonderful co-operation. All of us acknowledge the highly valuable contribution of Mr Hans Grossmann, who has prepared large amounts of starting materials.

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