RECENT ADVANCES IN THE CHEMISTRY OF NATURAL PRODUCTS

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ABSTRACT

In this lecture, an account is presented of the high points in the progress towards the synthesis of vitamin B₁₂ made during 1968–1970 in the collaborative programme carried out at the Eidgenössische Technische Hochschule in Zürich and in Cambridge at Harvard, under the leadership of Albert Eschenmoser and the lecturer. The point of furthest advance is represented by the obtention by total synthesis of heptamethyl bisnorcobyrinate (IX), which has been found to be identical with a sample of natural provenance.

It is my privilege this morning to act as spokesman for two groups of investigators, in Zürich and in Cambridge, associated with Professor Albert Eschenmoser and myself, one of whose aims it is to effect the synthesis of vitamin B₁₂. Of the results of this very wide-ranging collaborative investigation, only a portion can be presented here, and the choice I have made is to portray the present state of the work insofar as it relates directly to the establishment of a synthetic path to the vitamin.

The next previous International Symposium on the Chemistry of Natural Products, held in London in 1968, adopted as its symbol a device [cf. (I)] which
we could not but regard as exhortatory; as we may see we were able to return the compliment, perhaps in measure less than we might have desired, but certainly no less than we could have hoped. If now we examine the cyclic ether (II), divested of the London symbol, which represented our point of furthest advance in 1968, we see that the synthetic compound does indeed possess much in common with our ultimate objective, vitamin B\textsubscript{12} (III). Thus, the four nitrogen-containing five-membered rings A, D, C and B had been linearly connected in the necessary way, and the formidable stereochemical problem posed by the embedment within the macrocyclic nucleus of the vitamin of no less than nine centres of chirality [starred in (II) and (III)] had been solved completely. Finally, the groupings attached at these asymmetric centres were clearly in each case either identical with or closely related to those at the corresponding sites in the vitamin.

To commence a review of our progress since 1968, let us first examine the opportunities as they appeared to us at that time. Let us first recall that vitamin B\textsubscript{12} has been prepared by partial synthesis by Bernhauer and his colleagues at Stuttgart, from the simpler substance, cobyric acid (IV). That is to say, the free
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carboxyl group of cobyric acid has served as a reactive centre to which the
attachment of the isopropanolamine-phosphate-ribose-dimethylbenzimidazole
chain has already been achieved. Consequently, it is cobyric acid which is the
immediate objective of any who would essay the synthesis of vitamin B₁₂, and
the proper comparison of achievement and objective in 1968 is that between the
cyclic ether (II) and cobyric acid (IV). But this comparison too, impressive
though it be, is in some respects illusory, since it was already clear in the
summer of 1968 that the cyclic ether was essentially a synthetic dead end. It was
in fact a very stable substance which put up a very successful resistance toward
any attempts to modify it in the direction of cobyric acid. It had been prepared
inadvertently, through the changes depicted in (VI), by the action of trimethyl-
oxonium fluoborate on a cobalt derivative of corrigenolide (V), in an attempt to
prepare a pre-corrinoid intermediate of a type familiar to us from earlier model
studies. Thus, corrigenolide (V) represented our actual point of furthest

advance in 1968, and it was that substance which we must compare and
contrast with cobyric acid; of course the points of complementarity are scarcely
less striking than those to which I have already alluded. More pertinent to our
present analysis of the opportunities which lay before us in 1968 are the
differences between corrigenolide and cobyric acid, as emphasized in (VII) and
(VIII). Here we may direct attention in turn to the following points. First, where

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there are carbomethoxy groups at six points in corrigenolide, there are in cobyric acid five primary amide groups and one free carboxyl group. Although the conversion of carbomethoxy groups to primary amide groups is a process which might easily be envisaged, it seemed quite clear that there would be no way of distinguishing the carbomethoxy terminus of the propionic acid chain attached to ring D from the other carbomethoxy groups. Consequently, corrigenolide itself must be regarded in a sense only as a model compound, albeit an excellent one, which must at some time be replaced in the synthetic scheme of things by a very similar substance bearing a group other than carbomethoxy, and transformable into carboxyl, at the apposite site. Nevertheless, we made the decision to proceed with corrigenolide, confident that it would be an excellent model and that the experience we should gain with it would be applicable to the differentiated intermediate which we must ultimately prepare.

Second, it is obvious that cobalt must be introduced into the molecule; this facet of the work which lay before us might appear trivial, but in the event such was not to be the case.

Third, it must be mentioned now that in the preparation of corrigenolide our carefully constructed stereochemical relationships had been violated at the points of attachment of the propionic ester chains to rings B and C. These are very labile centres, and the corrigenolide available to us was in fact a mixture of diastereomers differing in configurations at the sites mentioned. Clearly, it would be necessary at some time to restore the stereochemical situation obtaining in cobyric acid and in vitamin B\textsubscript{12} itself. We had little concern on this point with respect to the propionic chain attached to ring B since it has been shown that the stable configuration is that which obtains in the natural substance. By contrast, little information is available about the similar stereochemical point in ring C; we had to face the prospect that we might ultimately obtain mixtures of substances differing in configuration in ring C, and of very similar properties.

The fourth, and perhaps most tantalizing, problem with which we were faced was the closure of the macrocyclic ring which forms the nucleus of vitamin B\textsubscript{12}; in some way the apposite methyl group attached to ring B must be transformed into the bridging carbon atom linking rings A and B, while at the same time of course the lactone ring of corrigenolide must be made into the acetamide chain attached to ring B.

The fifth and last requirement lay in the necessity of introducing methyl substituents at the bridges between rings A and B, and C and D.

These tasks which lay before us in 1968 are succinctly summarized in Figure 1. As I have indicated already, we chose to defer the important problem of ester differentiation. Further, we decided, at least tentatively, to deal with the

FIVE PROBLEMS
1. Introduction of cobalt
2. Closure of macrocyclic ring
3. Ester differentiation
4. Introduction of methyl groups at bridges
5. Restoration of lost stereochemistry
problem of the introduction of the extra methyl groups at a later stage in the investigation, and we felt that the restoration of lost stereochemistry might well take care of itself—in any event, there seemed no point in trying to cope explicitly with this problem at this stage of the investigation, since stereochemistry elaborately restored would very probably be lost yet again at one or another point along the path we should traverse.

In short, we decided in 1968 that our major task in the biennium which would elapse between London and Riga was the closure of the macrocyclic ring. This might have seemed a modest objective to those unfamiliar with the magnitude of the challenges which synthetic work with molecules of such complexity and variegated reactivity present, but the event has shown that Professor Eschenmoser and I judged our adversary well.

The task, then, which we set for ourselves in 1968 was to transform corrigenolide [(V)≡(VII)] into heptamethyl bisnorcobyrinate (IX); we regarded ourselves as especially fortunate in that this latter beautifully crystalline substance had been prepared by degradation from vitamin B₁₂ by Bernhauer, Wagner and their collaborators.

In the summer of 1968 corrigenolide had only just been prepared, and its appearance on the scene had represented the first success in a long and arduous campaign to effect the union of our hard-won components, representing respectively the A/D and B/C portions of the vitamin B₁₂ molecule. The methods which had led to the first appearance of the key intermediate were tentative and capricious, and in order to prepare a sound basis for further advance it was necessary to undertake the development of a thoroughly reliable and reproducible method for the preparation of corrigenolide in high yield. The preparation of the two key building blocks—the bromide (X) and the thiolactam (XI)—has been described elsewhere*. These substances combine in tetrahydrofuran—t-butanol solution in the presence of potassium tertiary butoxide to give the

extremely labile thioether/Type I (XII). Such is the sensitivity of the reactants, and particularly the product, that the successful execution of this operation requires rigorous adherence to the highest standards of experimental precision. All solvents and reagents must be purified afresh before use, rigorous stoichiometric relationships must be respected, and thoroughly effective methods for the exclusion of the slightest traces of air and moisture must be taken. When these conditions are met, the thioether/Type I can be prepared in essentially quantitative yield.

Our reasoning in undertaking the preparation of the thioether/Type I will be apparent upon study of (XIII) and (XIV). Numerous attempts to effect the direct formation of an appositely placed carbon–carbon bond between various A/D and B/C intermediates had been uniformly unsuccessful. In these circumstances we turned to the device of effecting a preliminary union of the two moieties of the desired product through a sulphur atom, as exemplified in the structure of the thioether/Type I. In this way the centres between which we desired that a bond be created had been forced into proximity, and we could expect that the desired carbon–carbon bond-forming reaction, which would now be an intramolecular process, would take place relatively readily, by contrast with bimolecular equivalents or analogues which had so often failed.
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The special process we envisaged in the case of the thioether/Type I is suggested by the arrows with which (XIII) is encumbered. The electronic processes thus depicted would lead to a kind of episulphide (XIV) from which there was reason to suppose that sulphur might be extruded or extracted.

Those familiar with the earlier history of our programme will recall that the same principle was used successfully in joining the B and C building blocks of our B/C intermediate, thiodextrolin (XI), after a similar lack of success in effecting direct union. In that case treatment of the sulphur-bridged B/C intermediate with triethylphosphite under mild conditions had led to the desired result. In the case at hand, no such facile achievement of our objective rewarded our efforts. Initial attempts to effect the desulphurisation of thioether/Type I under a wide variety of conditions were almost uniformly unsuccessful. The cause of these initial failures lay in the circumstance that a ready alternative demeanour is available to the thioether/Type I under the influence of the cationoid reagents which might have brought about the desired change. This possibility is outlined in (XV). The protonation of the nitrogen atom of ring C is very readily followed by the loss of a proton from carbon to give thioether/Type II (XVI), a relatively stable substance, in which it will be recognized that the structural preconditions for the desired carbon–carbon bond-forming reaction are absent. It may be noted also that the stability of the thioether/Type II is very probably associated with the presence within its structure of a relatively stable vinylogous amidine system. Furthermore, it may be expected that this same system will undergo preferential combination with protons or other cationoid species—a circumstance likely to frustrate, or at least render very difficult, a reprotonation at carbon in ring C. The situation at this point may be summarized by depicting the thioether/Type I as a substance precariously balanced on a precipice, off of which all of our efforts pushed it into the valley represented by the dormant thioether/Type II. Needless to say, innumerable early efforts to effect the desulphurization of the latter were made—alas, with anything but encouraging results.

The first resolution of these difficulties came purely from the experimental side, as a byproduct of experiments on the purification of the thioether/Type I. We observed that when that substance was chromatographed on basic alumina, it was, not surprisingly, partly transformed into thioether/Type II. More
important, however, was the observation that yet a third, relatively polar and slow-moving, substance was also apparent in the chromatograms. This new material—thioether/Type III (XVIII)—turned out to be yet another tautomer of thioether/Type I, formed no doubt by the processes outlined in (XVII). It will be noted that like the thioether/Type I—and unlike thioether/Type II—it retains the structural pre-requisites (cf. arrows in XVIII) for the desired carbon–carbon bond-forming reaction; furthermore, the distribution of its unsaturated centres is such that the ready constitution of the vinylogous amidine system which so stabilizes the thioether/Type II cannot be a simple one-step process. These circumstances are very probably responsible for the gratifying observation that the thioether/Type III (XIX) could be desulphurized, to give corrigenolide (XX), by treatment with boron trifluoride and triphenylphosphine in hot benzene solution, in yields approaching 90 per cent.

This first preparation of corrigenolide afforded striking testimony of the experimental skill of its discoverer, Dr Yoshito Kishi. All of the operations had to be conducted with every conceivable precaution in respect to purity of reagents, exclusion of oxygen and moisture, and with the greatest possible speed. It will easily be imagined that it would be a difficult, if not impossible, task to develop so intricate and complicated a procedure into a reproducible method for the relatively large-scale preparation of the desired key intermediate.
The precise circumstances leading to the transformation of thioether/Type I into thioether/Type III were mysterious. Further, the thioether/Type III was only scarcely less susceptible than its fragile progenitor in respect to conversion to the stable and apparently useless thioether/Type II. And finally, even in the best, very small-scale, experiments the overall yield of corrigenolide from the bicyclic intermediates (X) and (XI) approximated only 40 per cent. Clearly an alternative procedure was necessary if we were to have a firm base upon which to build our explorations beyond corrigenolide.

Consequently, it represented a very great advance when our collaborators in Zürich discovered that if the thioether/Type I were converted to its methyl mercury derivative (XXI), the latter was directly convertible to corrigenolide (XX) by the boron trifluoride/triphenylphosphine/benzene procedure. The theoretical basis for its relative degree of success is not at all clear, but in any event this greatly simplified method served the valuable purpose of permitting us to prepare corrigenolide in sufficient quantity to begin our forward explorations. But the method still was far from satisfactory.

This is no place to describe in detail the plethora of mysterious factors which seemed to affect the outcome of the reaction. As an example, it may be mentioned that freshly prepared triphenylphosphine/boron trifluoride reagents did not seem to be as effective as aged ones; but were the ageing allowed to proceed too long, the results were also unsatisfactory. So variable in fact were our experiences that the occasionally successful practitioner was regarded by his frustrated colleagues as quite as much a wizard as a scientist. And in any event, after innumerable studies there seemed no reason to suppose that even if a wholly reproducible procedure could be developed, the yield of pure corrigenolide would exceed 40 per cent. Quite clearly the development of a superior alternative was still an important pre-requisite for further progress.

We therefore undertook an exhaustive study of the relationships between the various isomeric thioethers, mainly in the hope that we might develop a reproducible method of producing the type III species in good yield. The results of this long and arduous study are succinctly summarized in Figure 2. The thioether/Type I (XII), which, as has already been mentioned, can be prepared from the appropriate components in quantitative yield, is a participant in a
readily established equilibrium with the thioether/Type III (XIX). Either of these isomers is therefore all too prone to transformation to the stable thioether/Type II (XVI), which can in fact easily be prepared in quantitative yield, for example, by the action of a trace of trifluoroacetic acid on the Type I isomer in methylene chloride solution. Every attempt to modify reaction conditions with the aim of augmenting Type III had the invariable result of driving the reaction system inexorably to the stable product. These circumstances at least defined the problem very clearly. The obvious solution must lie in the discovery of a method for the transformation of the Type II isomer into corrigenolide, and even though an enormous amount of labour already had been unsuccessfully expended in the attempt to bring about that much-desired change to no avail, re-doubled efforts in that direction were taken in hand.

Ultimately these efforts were crowned with success. The choice of solvent was crucial. When the thioether/Type II (XXII), which has already been described as preparable in quantitative yield, was heated in sulpholane with 5.3 equivalents of trifluoroacetic acid and 4.5 equivalents of tris-(ß-cyanoethyl)-phosphine at 60° for twenty hours, corrigenolide (XXIII) was produced in 85 per cent yield. It remains only to mention that the isolation and purification of corrigenolide presented obstacles only less formidable than those attendant upon the discovery of a satisfactory method for its preparation. The key intermediate is, like its progenitors, a participant in equilibria among a number of tautomeric species — equilibria all too easily mobilized in most chromatographic systems used for purification and isolation. It may be mentioned further that all chromatographic purifications had to be carried out in the complete absence of oxygen. But these problems too were in the end surmounted, and the battle for corrigenolide was won.

The audience will perhaps share my relief that we may now turn to a description of some of the explorations which we were able to build on the solid base of an excellent method for the preparation of corrigenolide. The first of
these involves the acid-catalysed cleavage of the lactone ring of corrigenolide [cf. arrows in (XXIV)]. When the latter was allowed to stand for sixteen hours in 3N methanolic hydrogen chloride, it was smoothly transformed into a mixture of two stereoisomeric methyl incorrigenates (XXV). These isomers are of much interest in a number of directions.

First, it will be noticed that the conversion of a tetrahedral centre in ring B to the trigonal condition simplifies the stereochemical situation, and indeed it was possible to obtain one of the methyl incorrigenates as a beautifully crystalline substance, whose physical properties could be determined accurately and quantitatively. These measurements confirmed the assigned structure in every detail, and thus indirectly gave us confidence that our formulation of the corrigenolides was correct. Furthermore, it was found that both the crystalline and the oily isomers were converted by acidic catalysts to the same equilibrium mixture—that is, not surprisingly, the propionic ester chain attached to ring C is readily invertible. Finally, it will be noticed [cf. heavy arrow in (XXV)] that the methyl incorrigenates are tantalizingly closely related to our immediate objective, methyl bisnorcobyrinate (IX); in formal terms all that is required to effect the desired transformation is the elimination of the elements of a molecule of water, utilizing the lactam oxygen atom and two hydrogen atoms of the activated methyl group attached to ring B.

Regrettably, this hopeful augury was never translated into anything more substantial. In methyl O-methylincorrigenate (XXVI), a substance readily preparable from the corresponding lactam through treatment successively with methylmercury isopropoxide and trimethyloxonium fluoborate, the stage would appear to be admirably set for macrorcyclic ring closure. But all attempts to bring about the desired transformation were of no avail. The substances of the incorrigenate series turned out to possess a startlingly variegated and fascinating chemistry. They undergo very readily a wide spectrum of transformations under the influence of heat, acid, light and oxygen, or combinations of those agents. But none of these transformations led in the desired direction, and all had to be regarded as bypaths which, however interesting they might be in themselves, led us no nearer to our objective.

A further point deserves special mention. The endocyclic array of double
bonds present in the incorrigenates was found to represent the stable array in this series. Virtually no evidence of any substantial conversion to the isomeric exocyclic structure (XXVII) was found in our studies. This experience at least put us on guard that should we succeed in preparing, by other methods, exocyclic substances containing the ring B array of (XXVII), we must take every precaution to avoid transformation of such materials to their stable endocyclic relatives.

Particularly disappointing was the refusal of the incorrigenates to cooperate in the formation of metal derivatives. Cobalt in particular, which was of course the metal of most interest to us, seemed to serve only as an effective catalyst for the destruction of the incorrigenates, and at long last we had to abandon our hopes for what had seemed to be a very promising series.

Greater success was attendant upon studies of another characteristic mode of opening of the lactone ring of the corrigenolides. As shown for the particular case of O-methylcorrigenolide (XXVIII)—preparable in the usual way by the action of trimethyloxonium fluoborate on the methylmercury derivative of corrigenolide—the lactone ring can be opened under the influence of basic substances by an eliminative process. Under basic conditions the initially
formed intermediate undergoes tautomerization to give the exocyclic species (XXIX). These reactions are all reversible, and it presented a source of much practical difficulty that the equilibrium lay very heavily on the side of the lactone species. Thus, in order to complete the conversion of O-methylcorrigenolide into the open form, a considerable excess of strong base is required. If the basicity of the media in which the transformation is taking place is lowered, re-lactonization occurs, even while the medium is still relatively strongly basic. These circumstances made it difficult to bring about the desired capture of the carboxylate ion, for example, by transformation into a methyl ester grouping, to give exocyclic methylene intermediates which might be expected to be stable, at least under basic conditions.

Nevertheless, we were able to make use of an observation we had made many years ago—namely, that carboxylate ions can be transformed into methyl esters by the action of diazomethane, even in basic media. Thus, working with very small quantities of material, and using a huge excess of diazomethane, we were able to convert O-methylcorrigenolide (XXVIII) to methyl O-methylcorrigenate (XXX). The latter in its turn was readily converted into the octahedral cobalt complex (XXXI), using cobalt chloride or cobalt iodide in tetrahydrofuran. This smooth cobaltation reaction stood in sharp contrast to a long series of disasters which we had experienced in attempts to make cobalt derivatives of various of our intermediates. Our experience has demonstrated in this and other cases that the cobalt halides are especially effective cobaltation reagents; their superiority to other forms of cobalt is so striking that the matter is certainly deserving of further study. The point is perhaps most forcefully made through mention of our observation that O-methylcorrigenolide itself, when treated with cobalt chloride or iodide in tetrahydrofuran, followed by air and cyanide ion, is converted to an acid which, when treated with diazomethane, smoothly gave the same complex (XXXI) which had hitherto
been preparable only with difficulty and in very small-scale experiments from methyl O-methylcorrigenate. In this case complexation is so favoured that it forces concomitant opening of the lactone ring. Finally, it may be mentioned that these same cobaltation conditions, applied in the case of methyl O-methylincorrigenate, also gave the complex (XXXI)—in this case, however, in very low yield, on the order of one to three per cent; this rather less than satisfactory conversion represents the only instance in which a substance of the incorrigenate series has been brought into the major sphere of action.

It is now appropriate to point out that the complex (XXXI), found ultimately to be readily available from O-methylcorrigenolide, is of a type possessing complementary reactive sites which had been most effectively utilized for the construction of model corrinoid substances by the Zürich group. Thus, the cyclization of the similar but simpler complex (XXXII) to the model heptamethylcorrin (XXXIII) can be brought about in essentially quantitative yield by the action of potassium tertiary butoxide under precisely specified conditions.

Our detailed studies of this model conversion, which followed upon the innovative development of this method by our Zürich colleagues, led to the discovery that the solvent used as reaction medium is of much importance. When the reactions were carried out in pure tertiary butanol, simple removal of the cobalt was the result. But if mixtures of dimethylformamide and tertiary butanol containing from 20 to 50 per cent of dimethylformamide were used, the desired cyclization reaction proceeded rapidly and smoothly, and dimethylsulfoxide—tertiary butanol mixtures were found to be even more efficacious. It may be mentioned that in these cyclization reactions it is absolutely essential to practise the utmost rigour in the exclusion of oxygen from the reaction mixtures, since both the corrins and their progenitors are destroyed with lightning rapidity by oxygen in the presence of basic reagents.

Having gained sufficient expertise in the model cyclization, our next step was to attempt to apply our experience to the corrigenate complex (XXXI). Time and again in the course of studies on the synthesis of vitamin B₁₂ we have found that models are something less than realistic—often strikingly so. In the case at hand, similar circumstances were found to obtain. It was not possible to effect the practical conversion of the precorrinoid complex (XXXI) to the desired heptamethyl bisnorcobyrinate (IX). None the less, the results were encouraging, in that reaction conditions were found under which the formation of the desired product in low yield could be detected by spectroscopic measurements. Attempts to force the reaction to follow the desired path to a greater extent unfortunately were not successful, the most frequent alternative result being the formation of the cyclic ether (II) from which this lecture took its departure.
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None the less, as we shall see, the indications of success obtained in these studies pointed the way to more satisfactory developments. In particular, our colleagues in Zürich had demonstrated in a number of instances that thioimino ethers are very much more reactive than the corresponding oxygen analogues, and there was consequently good reason to suppose that success might well attend attempts at the cyclization of a thio analogue of (XXXI).

At this point it is appropriate to mention the conversion of corrigenolide (XX) to dithiocorrigenolide (XXXIV). The dithio compound was early

prepared independently both in Cambridge and Zürich by the action of phosphorus pentasulphide on corrigenolide, and subsequent very careful studies in Zürich led to the development of a method by which the change could be effected smoothly and reproducibly in high yield. In Zürich, the plan was laid to utilize dithiocorrigenolide as the starting point for a series of reactions modelled upon the methods which had served so brilliantly for the preparation of simple metal-free corrins. Thus, dithiocorrigenolide (XXXIV) undergoes eliminative cleavage under the influence of potassium tertiary butoxide in methanol solution, and as in the case of the oxygen analogue, esterification of the resulting anion with excess diazomethane leads to an ester (XXXV). No

doubt in this particular instance an initially produced thioester is methanolized under the conditions of the reaction. Here as in the previously discussed elimination esterification sequence, it is difficult to bring about clean-cut and complete transformation in the desired direction except when working with very small quantities of material.
None the less, the methyl thiocorrigenate (XXXV) was converted to a zinc derivative (XXXVI), whose nature has not been clearly defined, but in which the zinc undoubtedly, by holding rings A and B in proximity, facilitates the next reaction, namely the oxidative conversion of the zinc complex by benzoyl peroxide to a cyclic thioether [(XXXVII), or an equivalent]. Again, the precise structure of this intermediate cannot be specified, but if we examine (XXXVIII), we may observe that the newly constituted thioether system is one in which the stage is properly set for carbon–carbon bond formation with elimination of sulphur. And indeed, when the zinc-free thio-bridged product (XXXVIII) is treated with trifluoroacetic acid and triphenylphosphine in dimethylformamide, the desired reaction occurs, and the product, after re-introduction of zinc, may be isolated as the chlorozinc complex (XXXIX), which, though not crystalline, has been fully characterized by ultraviolet/visible, infra-red, mass, and nuclear magnetic resonance spectroscopic studies.

These very gratifying results were marred only by the difficulties attendant upon obtention of a clean opening of the thiolactone system in the early stages. Consequently, the discovery in Zürich that the thiolactone ring could be very smoothly opened by a cleavage, rather than an eliminative, process was of very great importance. Thus, the action of dimethylamine in methanol solution upon dithiocorrigenolide (XL) leads very cleanly to the octamethyl thiocorrigenamide (XLI). Now, when (XLI) was converted to a zinc complex, oxidized, in this instance by means of iodine in methanol, treated with trifluoroacetic acid and triphenylphosphine, and re-complexed with zinc, the zinc complex (XLII)
was produced; the overall yield in this beautiful sequence exceeds 50 per cent. Further, it was a relatively easy matter to remove the zinc from (XLII) by treatment with acid, and to introduce cobalt to give octamethyl bisnorcorbinamide (XLIII), using the magic reagent cobalt chloride; it may be noted parenthetically that the introduction of cobalt even into the macrocyclic corrin using other cobaltation procedures had been a matter of much difficulty.

Dithiocorrigenolide obviously represented a possible source of the thioimino
ether complex (XLV) which our earlier experiments with the oxygen analogue (XXXI) had suggested might be a suitable corrinoid precursor, and indeed in Cambridge we found that 5-methyldithiocorrigenolide (XLIV), preparable from dithiocorrigenolide, by treatment with methylmercury isopropoxide, followed by trimethyloxonium fluoborate, was readily cleaved by dimethylamine; the resulting corrigenate was transformed, using cobalt chloride in tetrahydrofuran, into the desired complex (XLV). Further, after considerable experimentation, conditions have been found which permit the base-catalysed cyclization of (XLV) to octamethyl bisnorcobyrinamide in yields exceeding 70 per cent (cf. Figure 3). The octamethyl bisnorcobyrinamide (XLIII) obtained in Cambridge by the base-catalysed cyclization of the thiomethyl ether has been shown by chromatographic and spectroscopic techniques to be identical with that obtained in Zürich by the oxidative ring closure method.

![Figure 3](image-url)

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We were now very close to the objective set in 1968 for the London–Riga biennium. It remained only to effect the methanolation of the dimethylamide grouping of octamethyl bisnorcobyrinamide (XLIII=XLVI), to obtain heptamethyl bisnorcobyrinate (IX=XLVII). How nearly we had achieved our objective will perhaps best be illustrated through Figure 4, in which the spectra of the synthetic amide and the ester from natural sources are portrayed. The very close correspondence of these richly detailed spectra left us in little doubt that the synthetic substance possesses the structure we have assigned to it.

Only a few days ago, the conversion of octamethyl bisnorcobyrinamide into heptamethyl bisnorcobyrinate has been achieved. It was found in Zürich that treatment of the dimethylamide (XLVI) with trimethyloxonium fluoborate gave an iminium salt which was decomposed by concentrated aqueous sodium bicarbonate to yield, in part starting material, and in part the desired ester (XLVII). Though the process is not an efficient one in the synthetic sense, it permitted our Zürich colleagues to prepare several milligrammes of beautifully crystalline totally synthetic octamethyl bisnorcobyrinate. The spectroscopic
comparisons shown in Figures 5 and 6 leave no doubt of the identity of this synthetic material with the ester prepared from natural sources, and provide conclusive evidence that the problem of bringing about the construction of the corrinoid system of the vitamin $B_{12}$ molecule has been successfully solved.

Figure 5
What of the future? Comparison of the structures of heptamethyl bisnor-cobyrinate (XLVII=XLVIII) and cobyric acid (XLIX) reveals that two major problems must be solved in order to complete the synthesis of vitamin B$_{12}$. First, there is the matter of ester differentiation: clearly the intermediates described in this lecture must be replaced by close analogues in which the carboxethoxy terminus of the propionic residue attached to ring D is replaced by another grouping, to permit differential conversion of the six carboxethoxy groups of the other side chains to primary amide groups. Second, a way must be found to introduce the methyl substituents at the bridges linking rings A and B, and C and D. We do not underestimate the magnitude of these challenges still to be met, but we can now take up our work again, confident that we have built a solid basis for an ultimate solution of the problem of the synthesis of vitamin B$_{12}$. 

Figure 6
It is a pleasure to conclude these remarks with a richly deserved tribute to the men in Zürich and Cambridge whose skill and spirit have enabled us to come so far on an often difficult and perilous road (*Figure 7*). One need only recall that the materials available for the studies of the two years just past were prepared by

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<th>Zürich</th>
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<td>Dan Becker</td>
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<td>Naoto Hashimoto</td>
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<td>Willi Huber</td>
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*Figure 7*

sequences comprising some sixty-five to seventy steps to realize that these hard won materials could scarcely be used profligately. In consequence, the many hundreds of experiments which laid the basis for the advances I have described here were most often carried out on a very small scale—frequently using amounts on the order of ten to a hundred microgrammes. Any who contemplate for a moment the problems associated with carrying out reactions on sensitive substances at that level, with complete exclusion of oxygen and moisture, and establishment of strictly prescribed molar equivalents of various reagents, will apprehend at once the depth of the appreciation which Professor Eschenmoser and I have for our good fortune in having such collaborators.