THE TOTAL SYNTHESIS OF VITAMIN B_{12}

R. B. WOODWARD

Department of Chemistry, Harvard University, Cambridge, Mass. 02138, USA

ABSTRACT

The final stages in the total synthesis of vitamin B_{12} are reported.

It was particularly appropriate, I think, and most pleasant for us this morning to see the splendid film provided by our Russian friends, in which the very successful Symposium at Riga was enshrined for posterity. Appropriate in the sense, from my own point of view, that I did report there at Riga, on the progress we had made up until that time, namely, the summer of 1970, in the joint programme, which had as one of its objectives the synthesis of vitamin B_{12}—a programme carried out collaboratively by myself and Professor Eschenmoser at the Eidgenössische Technische Hochschule in Zürich, with of course our colleagues in Cambridge and Zürich. We have worked very closely and intimately together in this project, and it is an achievement—such as it may be—of the two groups together. So, anything I say this afternoon—or what is left of the morning and this afternoon—I am saying for Professor Eschenmoser and his colleagues as well as for myself and my colleagues in Cambridge.

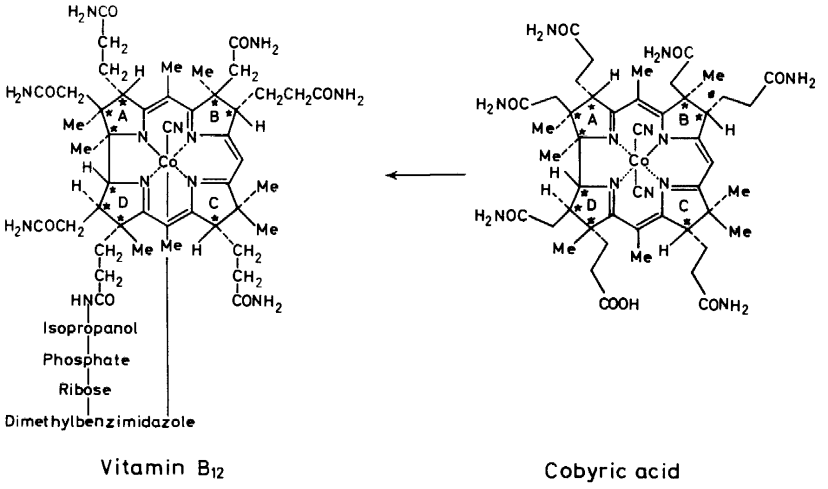


Figure 1

Figure 1 simply reviews again our objective, vitamin B_{12}, a rather familiar structure to those of you who have attended the various lectures that I have given as this programme has developed. You see that vitamin B_{12} is made up of a central macrocyclic nucleus in which are embedded four five-membered heterocyclic rings, with various sidechains, most of them similar to one another, with the exception of a particular one, which differs from the others in that where the others contain a primary amide grouping, in the unique one there is an amide derived from isopropanolamine; the hydroxyl group of the isopropanolamine is attached to phosphate, then to ribose and then to dimethylbenzimidazole. Then in the centre of this molecule is the very interesting feature of a cobalt atom which is coordinated in vitamin B_{12} to the dimethylbenzimidazole nucleus. Now, on the right you see the formula of another closely related substance—cobyric acid, otherwise known as factor V_{1A}. It is also a natural product, and it can be derived from vitamin B_{12} by cleaving the sidechain—the isopropanolamine/phosphate/ribose/dimethylbenzimidazole sidechain—to give a free carboxyl group; and so you see that cobyric acid is really identical with vitamin B_{12} insofar as the nuclear portion is concerned; it only lacks the special sidechain which is characteristic of vitamin B_{12}. I mentioned that cobyric acid is a natural product, that it can be prepared by the degradation of vitamin B_{12}, and from the point of view of the synthetic chemist, it is important to recognize that as early as 1960, cobyric acid was converted into vitamin B_{12}. In other words, to the carboxyl group of cobyric acid the special sidechain was attached by partial synthesis to give vitamin B_{12}. Thus, at the time that the work of Professor Eschenmoser and myself commenced, our objective was the synthesis of cobyric acid, since we knew that from cobyric acid to vitamin B_{12} itself, the path had already been laid down in 1960.

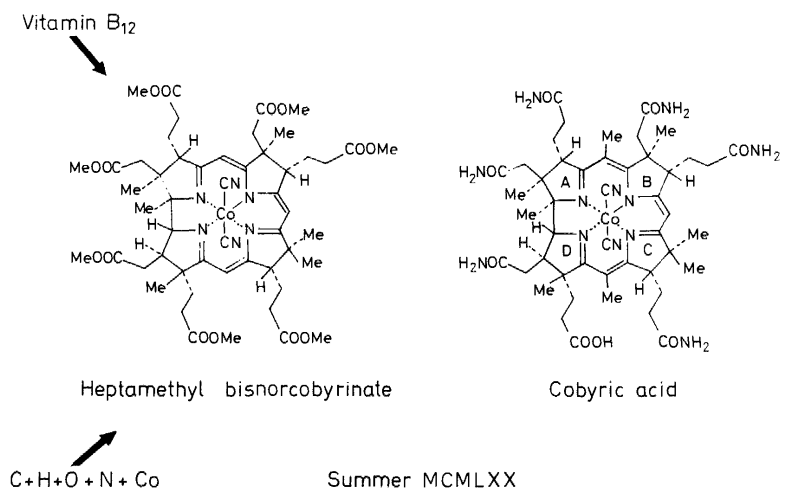


Figure 2

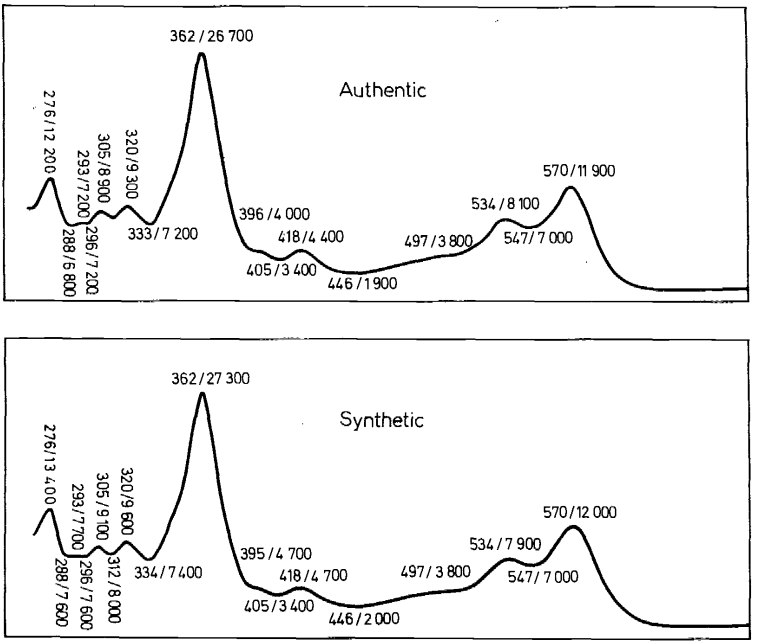


Figure 3

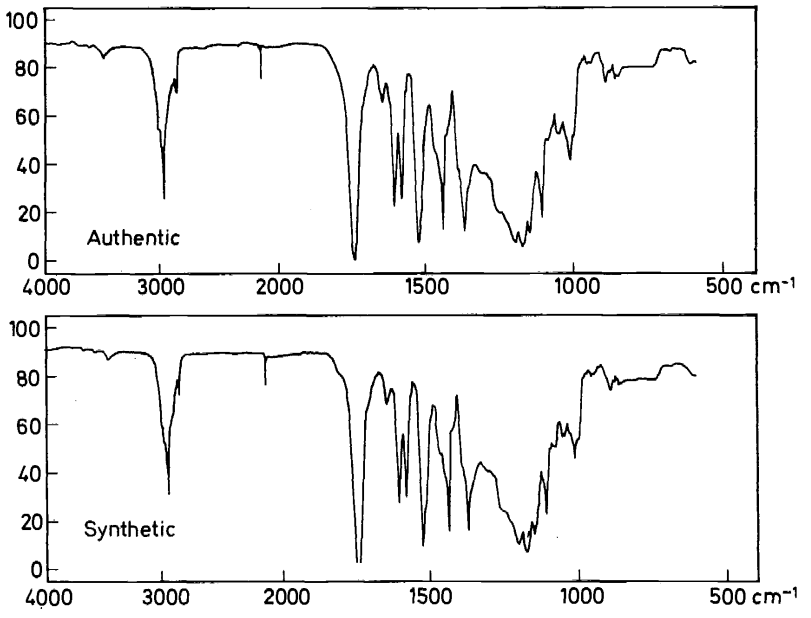


Figure 4

In *Figure 2* we see the position which we had reached in the summer of 1970, and it was in Riga at that time that I described the work leading up to the synthesis of heptamethylbisnorcobyrinate; you see it has a great many of the features of cobyric acid, our target. The nucleus is present just as required, the sidechain groupings are attached, and resemble closely those which are required in order to have cobyric acid; an important point was that we had gone to considerable trouble in the course of the some ninety-five steps which led to this heptamethylbisnorcobyrinate to introduce the various centres of chirality, of which there are nine in this nucleus, in the correct sense. So, at that time—the summer of 1970—we had synthesized heptamethylbisnorcobyrinate from carbon, hydrogen, oxygen, nitrogen and cobalt. We were able to compare the synthetic material with material that had been obtained by the degradation of vitamin B_{12}. In *Figure 3* you will see the comparison of the electronic spectra of the synthetic heptamethylbisnorcobyrinate and the authentic heptamethylbisnorcobyrinate. Now I do myself rather object to that term 'authentic'. I don't know what's more authentic about the material derived from natural sources than the synthetic material; so I attribute to Professor Eschenmoser the choice of this somewhat misleading word. We needn't examine the spectra in detail—there is a considerable similarity between the two! In *Figure 4* there are the infra-red spectra of the synthetic and the authentic heptamethylbisnorcobyrinates, and again you will see that the spectra may be regarded as very similar indeed.

Now these data, and other information that we had, gave us confidence that we had in fact achieved the synthesis of this substance closely related to cobyric acid. However, the situation in fact was not quite as clear-cut as would be suggested by the results that I have presented to you so far. I should emphasize that both of these substances whose spectra I have shown you were beautifully crystalline materials; both the synthetic material and the material derived from natural sources were beautifully crystalline substances with identical electronic and infra-red spectra. However, when we examined the nuclear magnetic resonance spectra of the two materials in detail, we discovered that the situation was somewhat more complicated than we had supposed. In *Figure 5* you will see the nuclear magnetic resonance spectra of the authentic and the synthetic materials. There is a far-reaching similarity between the spectra of the samples from the two different sources. But in the region of the nuclear magnetic resonance spectrum in which the resonances attributable to the methyl groups of the carbomethoxyl groups of the periphery appear, you will notice that the resonances are similar but there is one striking difference, in this sense: the small arrow below the upper spectrum points to one of the bands in a fairly complicated assemblage. Correspondingly in the spectrum of the synthetic sample we see not one band, but rather two—one in the same place as the band to which the arrow already referred to points but of half the intensity; then there is a new band which does not appear at all in the upper spectrum. What is the explanation of this divergence in this important physical property of the two substances—the one derived from natural sources and the other, the synthetic sample? The solution of the problem is shown in *Figure 6*; in short, the beautifully crystalline synthetic sample was a mixture of two substances—equal parts of two substances—one of them indeed the heptamethylbisnorcobyrinate

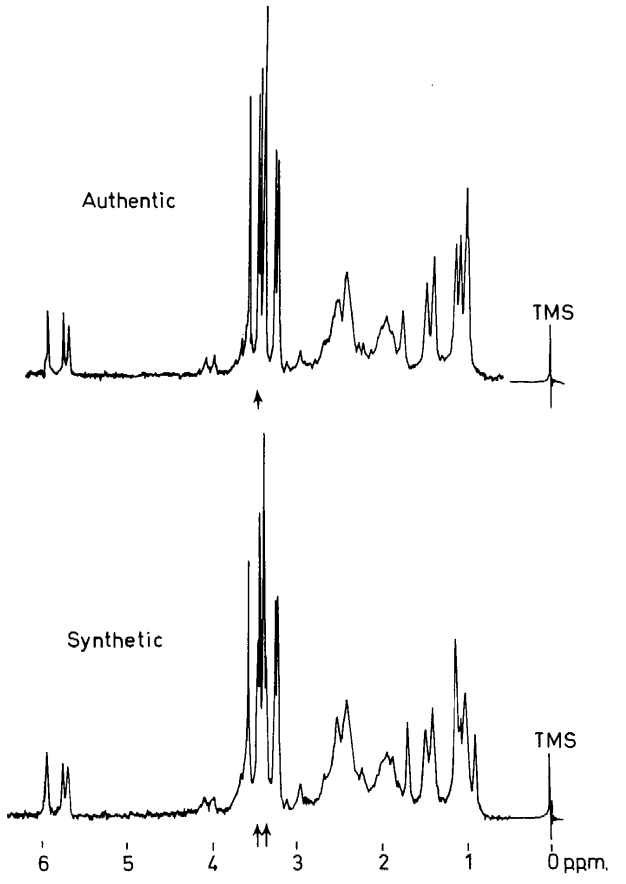
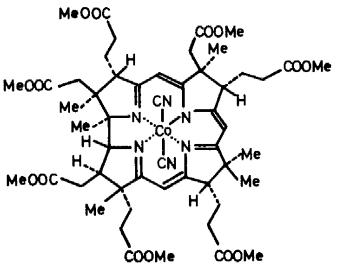
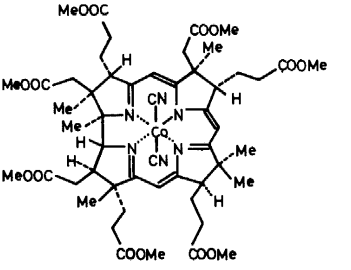


Figure 5



Heptamethyl bisnorcobyrinate

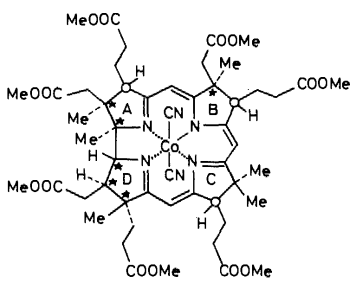


Heptamethyl bisnor*neo*cobyrinate

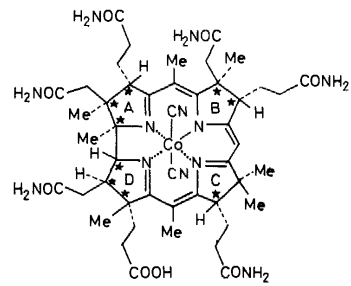
Figure 6

which we desired. Fifty per cent of that mixture, however, consisted of another substance, heptamethylbisnor*neo*cobyrinate, which differs from heptamethylbisnorcobyrinate in one point only, namely, while in the bisnorcobyrinate, the propionic chain at ring C is below the molecular plane, in the *neo* compound the propionic chain attached to ring C is above the molecular plane. In other words, these substances are simply stereoisomers, differing in configuration at one of the many centres of chirality within this large nucleus. I have gone into this matter at some length in order to indicate that one of the very large problems in the latter stages of the synthesis of vitamin B_{12} has been the stereochemical problem. Of course, throughout our work on the synthesis of vitamin B_{12} we have had to pay very serious attention to stereochemistry. As I have already mentioned earlier, we did attempt to place each asymmetric carbon atom—that is to say, the groups about the asymmetric carbon atom—in the desired orientation as it was introduced in the synthetic scheme. But towards the latter part of the synthesis we came across and had to deal with a very serious stereochemical problem of a somewhat different nature.

We have just seen that the first samples of synthetic heptamethylbisnorcobyrinate which we obtained were mixtures of two stereoisomeric materials, differing in that case at a centre in ring C. Now let us examine *Figure 7*. It



Heptamethyl bisnorcobyrinate(s)



Cobyric acid

1 Stereochemistry / separation
2 Nuclear methylation
3 Differentiation

Figure 7

is a fact that the substances of the vitamin B_{12} series are susceptible of ready isomerization at *three* of the centres in this macrocyclic array: at C.3, in ring A, inversion of the propionic chain can take place; likewise at C.8 in ring B, inversion can occur very readily; and finally, as already mentioned, at C.13 in ring C, ready inversion takes place under various conditions. So you see that the situation with which we were faced was one in which although we had in the course of our earlier synthetic operations taken pains to make

sure that the configurations were the desired ones—desired in the sense that they corresponded to the natural configurations—we were now faced with the problem that we could lose the stereochemical integrity of our substances at the three centres mentioned. And that created problems of separation. I might say parenthetically that this problem—this new stereochemical problem which has been so important in the latter stages of our work—is of varying degrees of importance, depending upon which centre one is considering. The natural configuration is the preferred one in rings A and B. In ring C the situation is otherwise; on the grounds of theoretical considerations, there was no reason to suppose that there should be very much preference for one or the other of the orientations of the propionic chain in ring C. As we shall see there is in fact somewhat of a preference for the unnatural configuration. So what then were the problems still facing us at the time when we had synthesized heptamethylbisnorcobyrinate? You will realize of course that the qualifying remarks that I have made do not change the situation in respect to the point that we had reached in the summer of 1970. We had in fact synthesized heptamethylbisnorcobyrinate—but we had isolated it as a beautifully crystalline mixed crystal with the *neo* isomer. If we look at the heptamethylbisnorcobyrinates, leaving stereochemistry undefined at the three centres which I have discussed, we then clearly faced problems of stereochemistry, and of course associated problems of the separation of very closely related molecules. Next, we must consider the structural differences, aside from stereoisomeric relationships, between the compounds we had reached and cobyric acid, which we must reach in order to complete the synthesis of vitamin B_{12}. The major structural changes were these: At the bridging positions 15 and 5 in heptamethylbisnorcobyrinate and its congeners there are no methyl groups, whereas in cobyric acid those bridge positions are occupied by methyl groups. So it was necessary to devise some way of introducing these still lacking methyl groups. Now furthermore, you will notice that cobyric acid contains chains terminating in six instances with primary amide groups, while a seventh chain terminates differently, i.e. in a free carboxyl group. Now these synthetic substances that we had in the summer of 1970 had in the place of the amide groupings around the periphery, carbomethoxyl groups—carbomethoxyl groupings at all seven positions. While we might reasonably hope to transform the carbomethoxyl groups into primary amide groups, clearly we had a problem here of differentiation. That is, we must in some way differentiate one chain terminus from all the others. So that was the third major problem which we faced in the summer of 1970.

In *Figure 8* there is a brief summary of what might be called the model experiments, describing the latter stages in the production of the left-hand portion—the A/D portion—of the vitamin B_{12} molecule, used in the experiments which led to the heptamethylbisnorbyrinates that I have described. These model experiments started with the key intermediate which we call β-corrnorsterone, and they involve attack on the corrnorsterone molecule by methanol in the presence of acid. Now in the reaction of acidic methanol with β-corrnorsterone two things occurred and can be discerned in the product, which we called hesperimine. One thing that happens is the simple cleavage of the six-membered lactam ring by a molecule of methanol,

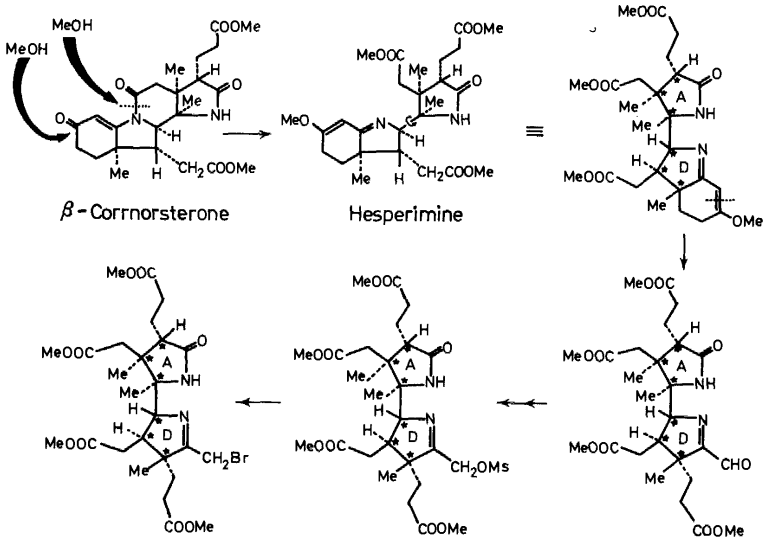


Figure 8

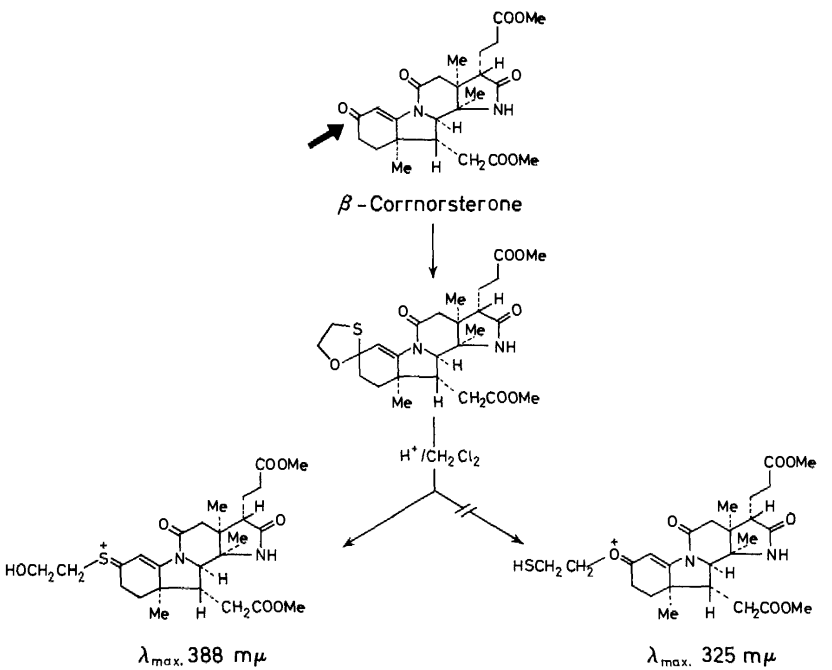


Figure 9

giving one of the array of carbomethoxyl groups. At the same time the system generated at the other side of the point of cleavage, which would ordinarily be a β-amino-α,β-unsaturated carbonyl system, is methylated, and appears as a β-methoxy-α,β-unsaturated imine system. Thus, you see that two methoxy groups are introduced in this methanolic hydrogen chloride treatment of β-corrnorsterone; it is an important fact that one of them is needed. We want that carbomethoxyl group; but you see that the other we do *not* want. If you follow the scheme through, you observe that this second methoxyl group becomes part of the carbomethoxyl group of the propionate chain attached to ring D. Clearly, we must have something different at that point, in order to differentiate that chain from the other six ester chains attached to the periphery of the molecule.

In *Figure 9* I summarize the observations which led to a simple and elegant solution of this differentiation problem. At the top we see again our corrnorsterone and a heavy arrow points to its rather reactive carbonyl group. This carbonyl group is part of a somewhat unusual system—a β-acylamino-α,β-unsaturated carbonyl system—and as such the carbonyl group possesses fairly high reactivity; it is possible, for example, to make from β-corrnorsterone the hemithioketal in which the carbonyl group of the original corrnorsterone is transformed into a cyclic ketal, with one sulphur and one oxygen atom. Now, spectroscopic studies with this hemithioketal were very interesting, in this sense, i.e. when methylene chloride solutions of this substance were treated with traces of trifluoroacetic acid, a very strikingly intense long wavelength absorption at 388 mμ appeared; through extensive model studies with related compounds, we could recognize that very long wavelength absorption as being associated with the unusual acylamino-α,β-unsaturated thioketone -onium salt system. The sulphur here is positively charged—or to be quite precise, the charge is in fact distributed over the whole unsaturated system. The especially interesting thing is that the acidic treatment of the hemithioketal resulted exclusively in the cleavage of the carbon–oxygen bond to give the *sulphonium* compound. Spectroscopic studies revealed that there was absolutely no cleavage whatsoever of the carbon–sulphur bond, which would have led to the analogous substance with an *oxonium* rather than a sulphonium system. We were very familiar with compounds of this type also through model studies; we knew that they would absorb at 325 mμ, and in the spectra obtained by the treatment of the hemithioketal with acids there was no trace of absorption at 325 mμ. Thus, we could be sure that the attack of acid upon this hemithioketal system involved the entirely selective cleavage of the carbon–oxygen bond. The clear implication of that observation was that we might well be able to keep a carbon–sulphur bond at that position while introducing a carbon–oxygen bond somewhere else. That was in fact the solution to the differentiation problem.

As shown in *Figure 10*, β-corrnorsterone was treated under acidic conditions with a mixture of methanol, on the one hand, and a mercaptan on the other. Under acidic conditions, reaction took place; very obligingly the methanol attacked the lactam ring giving the required carbomethoxyl group while the mercaptan attacked the α,β-unsaturated carbonyl system introducing an *RS* group. So, all in one reaction the two requisite molecules

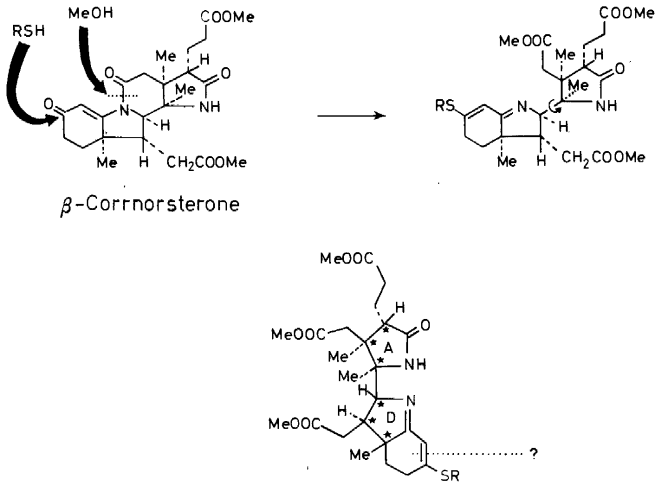
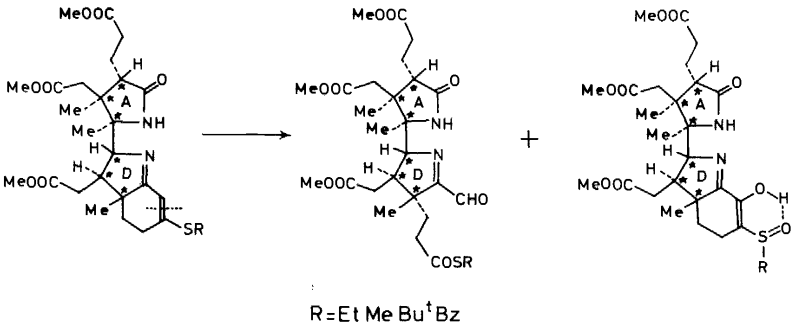


Figure 10

each did their proper duty, there was no crossing over; they behaved themselves in a way which we found most gratifying. The extent to which that is the case is quite remarkable. Even with very, very small proportions of methanol, the methanol cleaves the lactam ring, while the mercaptan becomes part of the unsaturated system. At the bottom of *Figure 10* you will see the product of this combined action of a mercaptan and methanol on β-corrnorsterone, just rewritten in another way. We have simply redrawn the molecule in order to bring out the relationship of the intermediate to the left-hand part of the vitamin B_{12} molecule. This molecule contains the desired new carbomethoxyl group, and a newly introduced thioalkyl group attached to a carbon–carbon bond. In the model studies we had simply ozonized the corresponding carbon–carbon double bond, and obtained a substance which has an aldehyde group at one side of the cleavage, and in that case, a carbomethoxyl group at the other. Now when we had obtained these alkylmercapto analogues, of course there was a question in our minds. We were somewhat apprehensive of whether we should in fact be able to carry out simply an ozonization of the unsaturated sulphur compound, as we had in the oxygen case. Why were we apprehensive about this point? Well, of course because unlike oxygen, sulphur is itself an easily oxidizable atom, and we were concerned lest the sulphur might itself become oxidized and the ozonization take quite a different course. So, even though we had effected by this somewhat remarkable reaction a solution to the problem of differentiating the requisite site, we were still not sure whether we could use this very simple solution.

If we now examine *Figure 11*, you will see that to some extent our apprehensions had been not without basis. In all cases so far, I believe, I have used *SR* in the discussion, and I have not identified *R*. In fact that reaction—the combined action of mercaptans and methanol on β-corrnorsterone—is



R=Et Me Bu^{t}Bz

Figure 11

very general, and can be carried out with almost any mercaptan. In particular, here is a series—ethyl, methyl, *t*-butyl and benzyl. We made all of these analogues by the action of the proper mercaptan, methanol and acid on β-corrnorsterone, and then we subjected them to ozonization—the ozonization being carried out in methanol at $-90°$. In every case all of these substances underwent cleavage in part to give the aldehydo thioester which is the product of the direct cleavage of the carbon–carbon bond, putting oxygen on either side of the cleavage point. But, in all of these cases there was formed a secondary product of rather unusual structure, a β-hydroxy-α,β-unsaturated sulphoxide; you see that in this secondary product indeed the sulphur had itself become oxidized. Now there are many interesting points about that secondary product and its formation; for example, it is clear that the sulphur is not oxidized first, because we were able to prepare from these alkyl mercapto compounds the corresponding sulphoxides, and those are inert to ozone. So the formation of these secondary products is a complicated process. We cannot specify in detail how they are formed but of course we do not really want to have them formed at all. In the series I have shown, reading from left to right, starting with ethyl going to methyl, then *t*-butyl and benzyl, the amount of the desired product, the aldehydo thioester, is higher as one goes from left to right, and the amount of the secondary product, the hydroxysulphoxide, decreases. That is to say, in

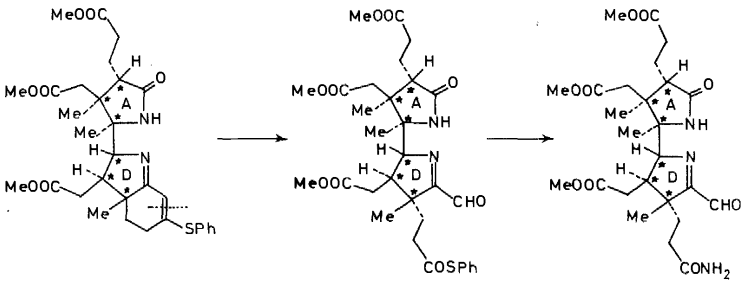


Figure 12

the case of the ethylmercapto derivative, the yields of the aldehydo thioester and the hydroxysulphoxide are almost the same; in the case of the benzylmercapto compound, the aldehydo thioester is produced in about 65 per cent yield and the hydroxysulphoxide in only 15 per cent yield, so it is already getting to be very nearly a practical proposition. However, this series, or the behaviour of this series, suggested an even better solution to the problem by the choice of yet a different group.

In *Figure 12*, we see the case, namely, the phenyl case, that is produced by the reaction of thiophenol and methanol on cornorsterone in the presence of hydrogen chloride. Needless to say, we could deduce in advance that the phenylthio compound would be much more difficult to prepare than any of the alkyl compounds, but a systematic study overcame all the difficulties and ultimately we were able to make the phenylthio compound in very high yield. On ozonization of the phenylthio compound, the aldehydo thioester was essentially the exclusive product. There was none of the corresponding hydroxy sulphoxide produced in the ozonization. There were other products produced if the ozonization was not carried out under very carefully defined conditions, but I need not bore you with such details this afternoon. It was in fact possible to bring about a very smooth ozonization of the thiophenyl compound to the aldehydo thioester.

Now about the time that we had the thioester in hand, we thought perhaps we should do some of this reading that I am so famous for, and find out about the properties of thioesters. Certainly the idea is current in the minds of most chemists, I think, that thioesters are very much more reactive than the corresponding oxygen analogues. In fact it turns out on examination of the literature that the statement must be severely qualified. With respect to the hydrolytic action of oxygen-bases on thioesters, the reactivity of thioesters and their oxygen analogues is almost the same. With respect to acidic hydrolysis, in fact the thioesters are more resistant to hydrolysis than are their oxygen analogues. However, there is a very interesting problem for future study, in the fact that the situation is quite different with nitrogen bases; although the facts are not really very well documented, it does appear that the attack of nitrogen bases on thioesters is very much more ready than the corresponding attack upon the analogous oxygen esters. In any event, in this case, the case at hand, the action of liquid ammonia on the phenyl thioester proceeds to the formation of the primary amide in a reaction which is *the* one in my experience which is most nearly quantitative; very, very smooth replacement of the thiophenol grouping by ammonia takes place to give the aldehydo amide shown on the right.

Now we may go on to *Figure 13*. We see the remaining few steps for the completion of the synthesis of the differentiated A/D building block for vitamin B_{12} synthesis. Here again is the aldehydo amide, which is reduced by sodium borohydride—the aldehyde group is simply reduced to the corresponding primary carbinol grouping. Then the carbinol grouping is transformed into the mesylate by treatment with—and this is a special point I think worthy of mention—treatment with methanesulphonic anhydride in the presence of pyridine at about 0°. The special point of interest here which might be useful to some of you in the future is this use of methanesulphonic anhydride rather than the more usual methanesulphonyl chloride or bromide.

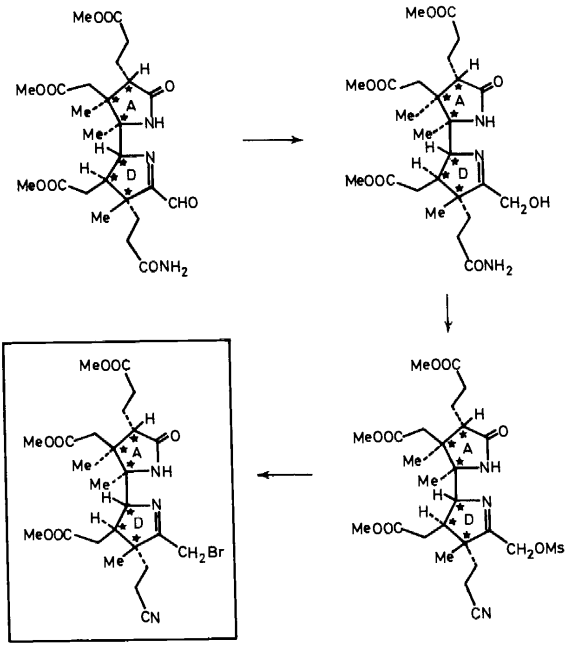


Figure 13

We have had, in our model experiments—that is, in the undifferentiated series—considerable trouble using methanesulphonyl chloride for the mesylation, in that the product mesylate tended to undergo displacement by chloride ion to give chloride, rather than mesylate, as product. I am sure many of you have had similar experiences in the attempted preparation of mesylates, namely, to get a secondary product which can be very annoying, as it had been for us in this series. Of course, when one uses methanesulphonic anhydride, there is no such alternative, no complicating reaction, and the desired reaction takes place very smoothly. Further, methanesulphonic anhydride is a beautifully crystalline reagent. In the case at hand the mesylation of the primary hydroxyl group was accompanied by another expected reaction, namely, the primary amide group was at the same time dehydrated to give a nitrile group. The final step in the sequence was simply the displacement of the mesyl group by bromide using lithium bromide in dimethylformamide. With the bromonitrile, a beautifully crystalline material, we had completed the problem of preparing an A/D building block for incorporation into a vitamin B_{12} synthesis with requisite groupings, stereochemistry defined in the desired sense, at each of the six asymmetric centres, and with the all-important differentiation of the terminus of the chain attached to ring D, where there is a nitrile grouping as contrasted with the ester groupings at the other three chain termini.

Now we could use the bromide in condensations analogous to those

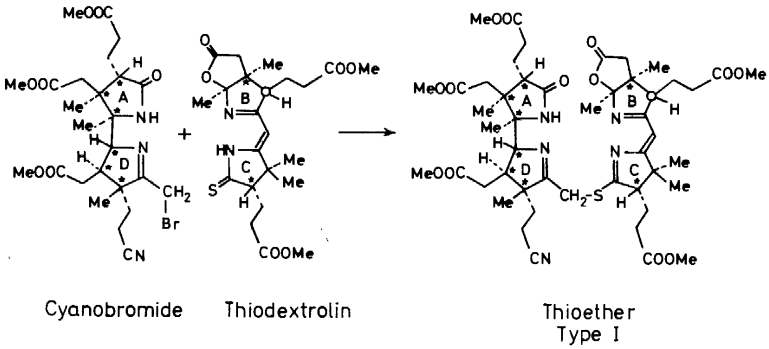


Figure 14

studied in the model series. We see in *Figure 14* the first step in the sequence of reactions which leads to the combination of the completed left-hand portion of the B_{12} molecule with the right-hand or B/C building block, which is called thiodextrolin. Thiodextrolin incorporates the atoms required for rings B and C. The differentiated cyanobromide has the stuff of which rings A and D and the attached groupings may be made. Thiodextrolin—and I shall make a special point here particularly in view of the emphasis which I have placed upon stereochemical considerations in my opening remarks—thiodextrolin as actually used by us is itself not a single individual compound; it is a beautifully crystalline substance, but it is a mixture of compounds differing in configuration at the ring B asymmetric centre, i.e. the thiodextrolin which we actually used in the condensation I am going to describe is a mixture of two substances, one of which has the propionic acid ester chain above the plane of the molecule, and the other has that chain below. We have been able to separate the two isomeric substances, but there is no use in separating them, because in the subsequent steps the group becomes equilibrated very readily, and one is just wasting one's time in separating the pure substances—

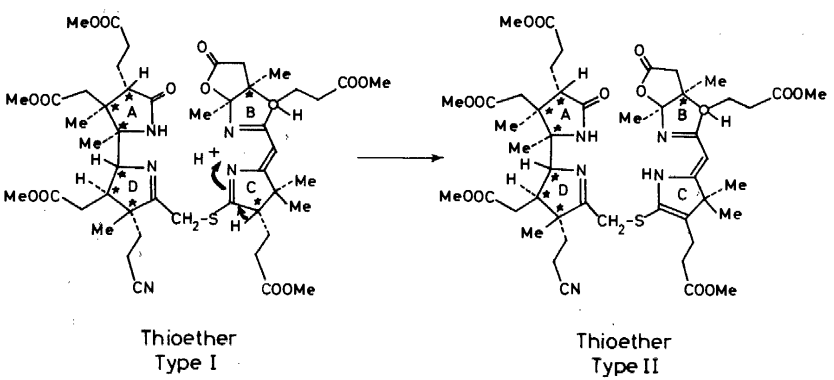


Figure 15

another example of the special stereochemical situation which confronted us in these terminal stages of our work. Well, the condensation of thiodextrolin with the cyanobromide takes place in quantitative yield in the presence of potassium *t*-butoxide. One can see that the thioamide grouping is ionized, and the highly nucleophilic sulphide atom then attacks the CH_2Br grouping with displacement of bromide to give a carbon–sulphur link to give the thioether Type I—Type I because we found early in working with these substances that they were very labile, and undergo quite a plethora of changes. In particular, thioether Type I is prone, as you can see in *Figure 15*, to an isomerization in which the carbon–nitrogen double bond is transformed into a carbon–carbon double bond to give thioether Type II. I should say parenthetically at this point that this very ready change of the thioether Type I to thioether Type II constituted in our work a stumbling block occupying almost a year's very concentrated effort. Thus, it took a great deal of work to find out how to proceed further from thioether Type II, which was rather regarded for some time as a dead end. That is history, and I shall not go into its details; as shown in *Figure 16*, thioether Type II was ultimately found to be

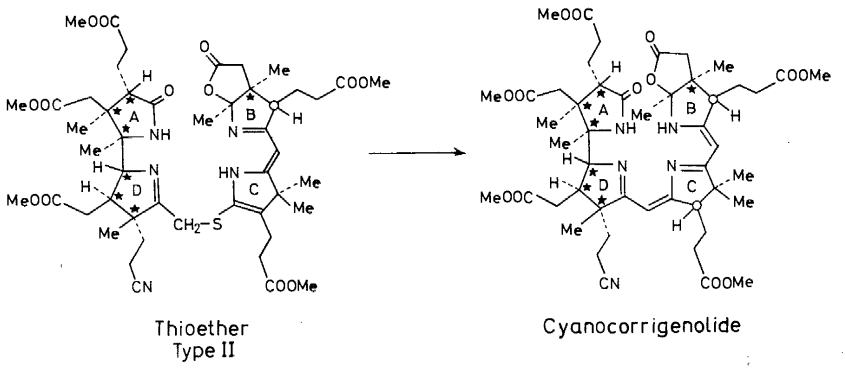


Figure 16

readily transformable in a forward direction. What is required of course is the removal of the sulphur, and the formation of a carbon–carbon bond from ring C to the bridging carbon atom. You see what we were doing here was bringing the two halves of the molecule together through the sulphur atom, and then taking the sulphur out and leaving the two halves attached by carbon. We had to do that because all our efforts to effect a direct union between the two molecules to give a carbon–carbon bond by bimolecular processes had been fruitless. This transformation is carried out with tris β-cyanoethyl phosphine and trifluoroacetic acid in sulpholane, or more recently in nitromethane. It takes place very smoothly, and gives us the two halves of the molecule—the A/D half and the B/C half—joined together through a carbon–carbon bond, in this substance named here cyanocorrigenolide; the corrigenolide was a kind of hopeful name, given since we had aspirations that the compound might someday be turned into a corrin.

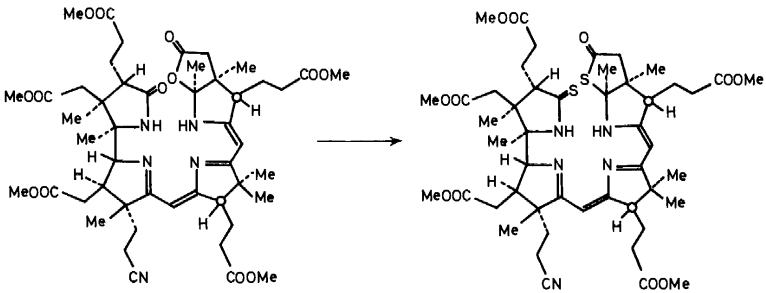


Figure 17

In *Figure 17* we see the key transformation for all the further stages in the work, namely, the transformation of the lactam lactone into a corresponding dithio compound. The lactam grouping is transformed into a thiolactam grouping and the lactone grouping is transformed into a thiolactone grouping. Both these changes are brought about by the action of phosphorus pentasulphide on cyanocorrigenolide in toluene solution in the presence of γ-picoline. Under the right conditions, the formation of the dithio compound takes place very smoothly. From the dithio compound it was possible to develop two alternative ways of proceeding further. In *Figure 18* we see the very simple first stage in the first of these methods, namely, the transformation of the thiolactam on the left into the corresponding *S*-methyl derivative; that was brought about very easily using trimethyloxonium fluoborate for a very short time; that methylates the thiolactam grouping, and does not cause any damage elsewhere in this rather complicated molecule.

In *Figure 19* you will see a very important stage. Actually, two stages are shown here; the first of them consists in the opening of the thiolactone

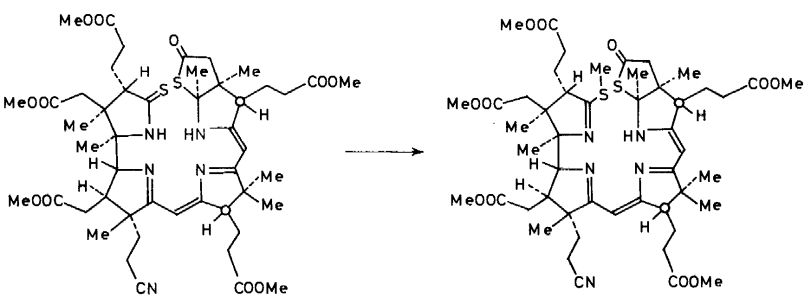
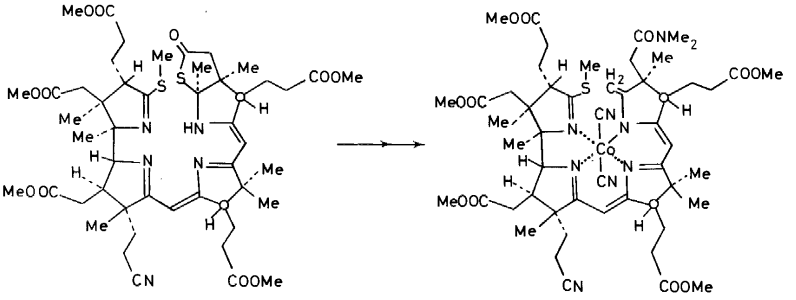


Figure 18

grouping by dimethylamine. Now this is a very remarkable reaction; dimethylamine in methanol at room temperature effects the cleavage of the thiolactone grouping to give a product in which we have a dimethylamide grouping—from the dimethylamine of course—and then, at the other side of the point of cleavage, the sulphur has vanished and a methyl group has become converted into an exocyclic methylene group. This really looks like



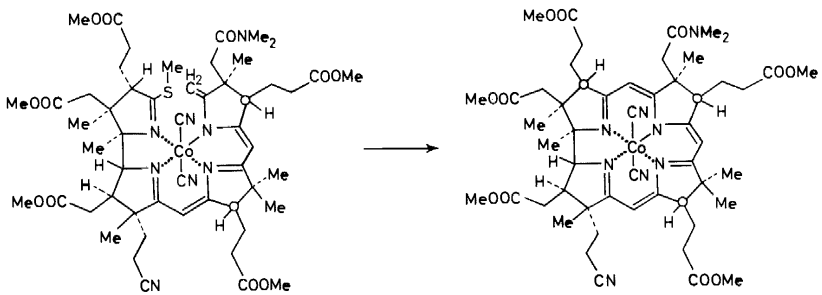
S-Methyldithiocyanocorrigenolide

Figure 19

a very simple process, but it took a long time to find it, and it was critical for the success of our efforts. The lactone or thiolactone groupings in this series are very stable; opening up the systems with oxygen bases, for example, requires large excesses of base, and it is not possible to isolate the products—to get them away from the large excess of bases required for the opening reaction. Dimethylamine is unique, in that it effects the opening very smoothly, giving a stable dimethylamide as product, with its all-important exocyclic methylene group. One of the problems which came up in the efforts to get this far was this: namely, that the exocyclic position of the double bond is not the stable position of the double bond in cleavage products; any equilibrium conditions lead to endocyclic compounds which simply have a methyl group attached to ring B, and which are useless for further experiments. But the dimethylamine does the job very nicely, and after the thiolactone ring has been opened and the other changes have taken place, the resulting exocyclic methylene compound is directly cobaltated—converted into the corresponding cobalt compound. Here again this is a problem where we hadn't anticipated any difficulty, but in fact the cobaltation of these substances turned out to represent a major problem. In many hundreds of experiments in cobaltating this and other materials, we found to our dismay that cobalt was an extremely effective catalyst for the destruction of our compounds. That was the most frequent result we observed over a period of almost a year; but it turns out that specifically the anhydrous cobalt halides—cobalt chloride or iodide in tetrahydrofuran—rather uniquely effect smooth cobaltation of this and other related compounds. That provided a very practical solution to the problem of getting cobalt into the middle of these substances.

I'll tell parenthetically here a story about making cobalt complexes. The inorganic literature is rife with mention of the fact that charcoal—animal charcoal—is a good catalyst for making complexes of cobalt, and it would appear that the typical inorganic chemist faced with the prospect of making a cobalt complex throws in some form of cobalt, and then a spoonful of charcoal in order to bring about the desired cobaltation. We suspect ourselves that what is behind that is that the charcoal—at least in the old days—used to have a lot of chloride ion on it and that probably it is the halide ion which is a very important catalyst for the cobaltation, both in this ancient method, and in our method using the cobalt halides in tetrahydrofuran.

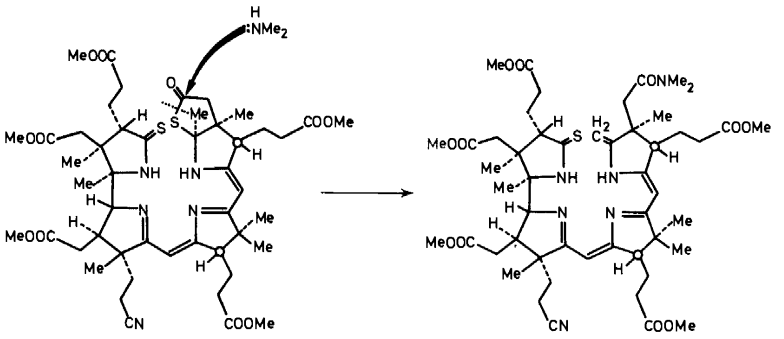
In the cobalt complex, prepared as described, everything was ready for the crucial cyclization—the preparation of the macrocyclic system which we required. If you examine *Figure 20* you see that what we have to do now



Bisnorcobyrinic acid
a b d e g Pentamethyl ester
c Dimethylamide f Nitrile (s)

Figure 20

is make a bond between the terminal carbon atom of the exocyclic methylene group and the appropriate carbon atom of ring A, by displacement of the methylthio group. Of course, the cobalt plays a very useful function, apart from the fact that we need to have the cobalt in our compound anyway; it also holds the nucleus together, in a way which clearly will facilitate the cyclization reaction. And in fact the cyclization of the complex takes place in high yield under various basic conditions. Among the best are the use of diazabicyclononane in dimethylacetamide as solvent at 60° for a few hours. That leads to a smooth cyclization of the kind that I described with displacement of the methylthio grouping, with the formation of the desired new carbon–carbon bond. We now have the entire macrocyclic system of the corrins, and indeed at this point we can give our compound a name related to vitamin B_{12}: bisnorcobyrinic acid abdeg pentamethyl ester c dimethylamide f nitrile. We have now one way in which we were able to effect the cyclization leading to the macrocyclic ring. This essentially was the method developed in Cambridge, while in Zürich our colleagues devised an alternative method based upon their model studies in the preparation of simple metal-free corrins.



Dithiocyanocorrigenolide

Figure 21

In *Figure 21* we see that the first stage in this alternative method again involves the modification of the thiolactone ring using dimethylamine, and in this as in the previous case the action of dimethylamine leads to the formation of dimethylamide containing an exocyclic methylene group. Again that reaction takes place smoothly in this case. The next stage here, shown on *Figure 22*, consists in the preparation from the exocyclic methylene compound of a zinc derivative—a zinc derivative which has not been structurally

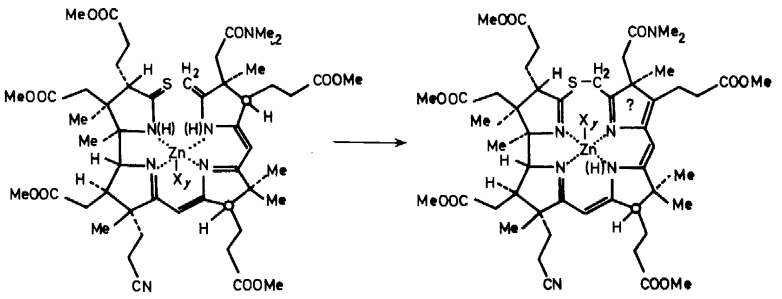


Figure 22

defined completely. We cannot say precisely what the structure of that zinc compound is; but we do know that there is zinc in the middle of the non-macrocyclic array, and no doubt the zinc plays a role, as does cobalt in the previous method, of holding the long linear molecule together in a configuration or conformation favourable to cyclization. In this case the next step after the formation of the zinc derivative is an oxidative step; oxidation with iodine in methanol leads to the formation of a sulphur–carbon bond to give a thioether. Again, we can't specify the order of steps which is involved in this oxidative carbon–sulphur bond formation. One of the rather attractive

possibilities is that the first step is halogenation of the exocyclic methylene group followed by displacement of the iodine from the resulting CH_2I group by the nucleophilic sulphur to give the thioether grouping. That process leads in any event to a system very reminiscent of that which we had in the experiments leading to the union of the A/D and B/C portions of the vitamin B_{12} molecule at the bottom, that is, when we were joining ring D to ring C. Now here in joining ring B to ring A, we have created a similar situation. We have effected the bridging between rings A and B, first by making a carbon–sulphur bond, and as we seen in *Figure 23*, the next stage is very similar to that

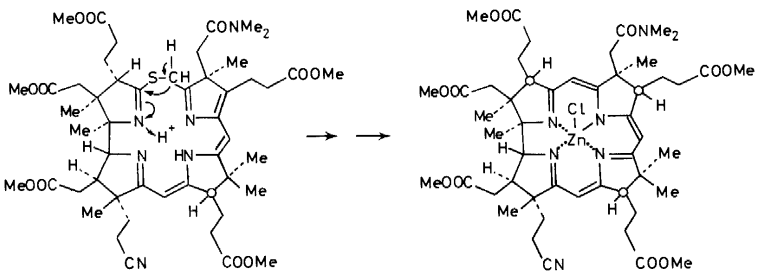
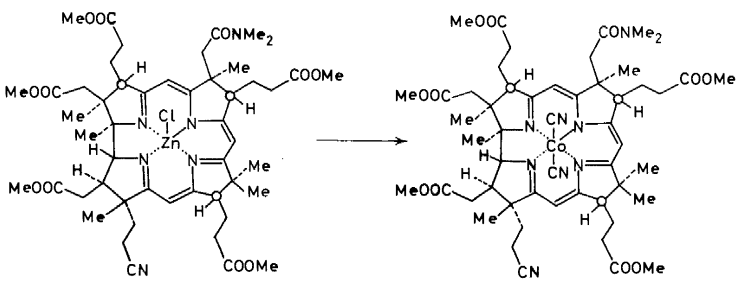


Figure 23

discussed earlier; after removal of the zinc, treatment with, in this case, triphenyl phosphine or tris-β-cyanoethyl phosphine in the presence of trifluoroacetic acid in dimethylformamide, leads again to the extrusion of sulphur, and a carbon–carbon bond is formed. A corrin system is produced, and in this sequence, in practice at this point, zinc is introduced simply as a means of facilitating purification of the product. In the next step, the zinc (*Figure 24*) is simply removed—the zinc can be removed from these compounds on acid treatment very readily—and replaced by cobalt, using cobalt chloride in tetrahydrofuran as before. The product of the whole sequence is the same



Bisnorcobyrinic acid
abdeg Pentamethyl ester
c Dimethylamide f Nitrile (s)

Figure 24

product as that obtained by the base-catalysed cyclization method, viz. the bisnorcobyrinic acid abdeg pentamethyl ester c dimethylamide f nitrile—exactly the same substance obtained by the other method. Two things might be mentioned at this point. Notice first that I am being very careful *not* to specify the stereochemistry of the three centres which I discussed earlier, since we know that in any of these reactions we may have inversion to a greater or lesser extent at one or more of these centres. We know that the nitriles prepared by these cyclization sequences, either the eliminative method or the oxidative method, are mixtures of substances—mixtures of diastereomers differing in configuration at those centres marked by open circles. Second, it may be noted that the two processes for the preparation of the corrin system give approximately the same overall yields; in practice, the oxidative method is somewhat superior, in that it is relatively easier to reproduce, even though it is a very complicated sequence indeed.

In *Figure 25* you will see again the structure of the diastereomeric corrins prepared by various methods, and at the bottom, there are the traces of

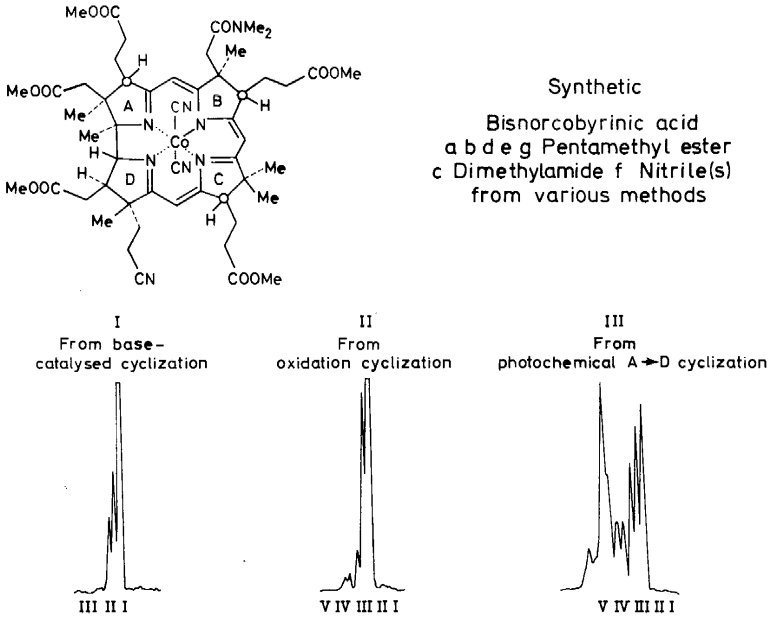


Figure 25

chromatograms—in this case liquid–liquid chromatograms. Here I should say that of absolutely crucial importance to all of our further work has been our taking up the use of high pressure liquid or liquid–liquid chromatography to effect the very difficult separations with which we were faced from this point onwards. The power of these high pressure liquid chromatographic methods hardly can be imagined by the chemist who has not had experience

with them; they represent relatively simple instrumentation and I am certain that they will be indispensable in the laboratory of every organic chemist in the very near future. In *Figure 25* we see three chromatographic traces. What one does in high pressure chromatography is use some sort of monitoring device to ascertain what is coming out of the columns. In the case of the corrins of course it is very easy to use spectroscopic detection since the light absorption of these substances is very strong. In a typical mixture of corrins from the base-catalysed cyclization method you can see three components; from the oxidative method one can see those three and two more. On the right one sees the chromatographic trace obtained from a mixture of substances, again of the same gross structure, obtained by quite a different sequence developed by Professor Eschenmoser and his colleagues, involving a photochemical cyclization to establish the ring A/D bond. Now at the time that this trace was produced, the photocyclization of an intermediate containing no bond between rings A and D was carried out on a zinc derivative; the formation of the A/D bond was non-stereospecific, and led to a complicated mixture of substances separated by liquid–liquid chromatography. Five of them were the same as the five produced in the oxidative cyclization; then there were several more which represent substances differing in stereochemistry at the A/D ring juncture. So the photochemical method in its early stages was non-stereospecific but it has not been found that using a corresponding cadmium derivative in the photoreaction, a stereospecific cyclization takes place almost exclusively to give materials of the natural series.

Now we can proceed with the further elaboration of these corrins. In *Figure 26* we see the dimethylamide group which appeared in our molecules

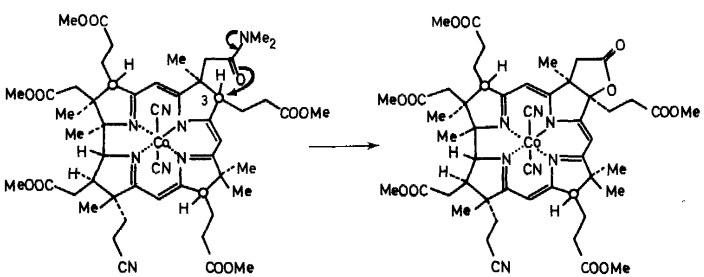


Figure 26

as a consequence of the fact that dimethylamine could perform the unique function of opening up the thiolactone ring of earlier intermediates to give an exocyclic methylene compound; the dimethylamide group produced in that way turns out to be very usefully placed in respect to the next reaction desired, which is an oxidation, using iodine in acetic acid, of the dimethylamide to a lactone. The oxidative process involves the participation of the amide grouping in the formation of a new carbon–oxygen bond and the amide, with the electron-releasing nitrogen atom, is uniquely constructed to facilitate this reaction—which does not take place with the corresponding ester.

Thus, the iodine–acetic acid oxidation of the dimethylamide gives the lactone and in *Figure 27* you see why we wanted to have a lactone group; we are now coming to grips with the problem of introducing substituents—methyl groups—into positions 5 and 15. The lactone that we just prepared is a substance in which the 10 position is surrounded by very heavily substituted positions. You see that at C.12 there are two methyl groups; thus, C.12 is a fully substituted carbon atom. Now, having made the lactone ring, C.8 also is a fully substituted position. We felt that we had created a situation in which C.10 was virtually inaccessible—just simply so crowded by groups whose sheer bulk was protecting it that it would be very difficult indeed to get any reagent to attack the C.10 position; of course that was very important, because we wished to introduce substituents selectively into C.5 and C.15. In *Figure 27* you see also the actual solution to that problem. When the lactone is treated with chloromethyl benzyl ether in sulpholane at 75° to 80° for several hours, the reagent attacks the 5 and 10 positions. The initial

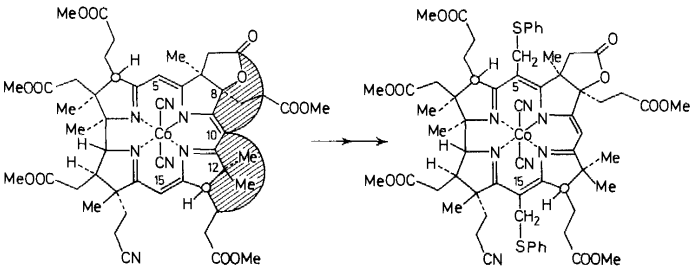


Figure 27

substituent at either position or both is very probably of course a benzyloxymethyl group, but the acid generated in the reaction cleaves that grouping to give a chloromethyl group. That's not isolated. In the same reaction sequence, thiophenol is introduced in order to transform the CH_2Cl group into a CH_2S phenyl group and therefore I show here the actual product of the sequence, which is carried out without isolation of any intermediary stages. The product is the bisphenylthiomethyl substituted derivative—substituted with phenylthiomethyl at C.15 and at C.5; no attack at C.10.

Now the production of the phenylthiomethyl compound was particularly important in the early stages of our work because the introduction of the large phenylthio grouping permitted the easy separation of the reaction product—in particular the *bis* substituted reaction product—from the starting material and less highly alkylated materials, by plate chromatography; the large phenylthio grouping made these compounds run very much faster in plate chromatograms than the unwanted substances, and permitted an easy separation of the desired *bis*-substituted phenylthiomethyl compound.

Furthermore, the presence of the thiophenyl groupings permits an easy transformation to the desired final groups—methyl groups—by Raney nickel

desulphurization, as shown in *Figure 28*. Raney nickel cleaves the carbon–sulphur bonds and transforms the phenylthiomethyl groupings into the methyl groupings as desired. At the same time, the Raney nickel reduces the carbon–oxygen bond of the lactone to give a free carboxyl group. Esterification of the resulting free carboxyl group with diazomethane leads to an ester

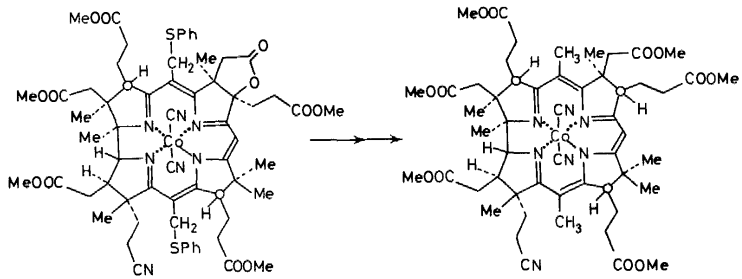


Figure 28

group. Thus, at this stage we have cobyrinic acid abcdeg hexamethyl ester f nitrile. We had in this sequence effected the introduction of the desired methyl groups at the bridge positions, and the product is a mixture of stereoisomeric nitriles, now properly substituted. I have told elsewhere the somewhat hilarious story of our special difficulties with this sequence; the use of chloromethyl benzyl ether, though it does bring about the changes that I have just described, is not efficient. The yields are regrettably rather low and in Cambridge and in Zürich we developed a method which was appearing to give very much superior results using chloromethyl methyl ether. Some of you may have heard that the scheme crashed in ruins when it was found that the cyano group at the same time was converted into a carbomethoxyl group.

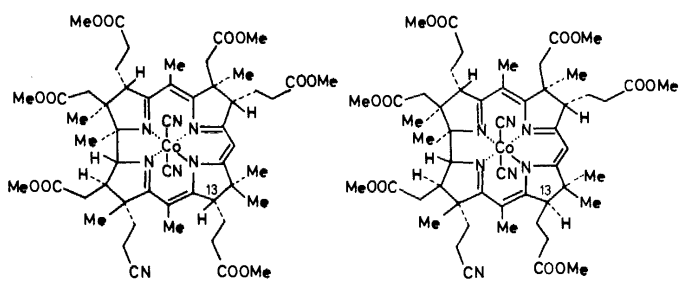


Figure 29

That of course was not very useful, so we had to return to the use of the chloromethyl benzyl ether in a process which I have to state is not yet one which we really regard as satisfactory, though the result is not in doubt; the yield is definitely poor and needs improvement. This is what we regard still as a weak area in the synthesis where more work must be done.

The mixture of nitriles obtained as just described was separated into a number of fractions by liquid–liquid chromatography under high pressure. One of the fractions obtained consisted of just the two substances shown in *Figure 29*—the cobyrinic acid abcdeg hexamethyl ester f nitrile, and the corresponding *neo* compound, that is, the two substances differing only in configuration of the propionic chain at C.13—in the natural series with the propionic acid chain below the molecular plane, in the other above. Actually, subsequently we have found even more powerful high pressure chromatographic methods which serve for the separation of these two substances cleanly. But as we shall see shortly there was no need—in fact it was not desirable—to separate the two at this stage. In *Figure 30* we see why it is not

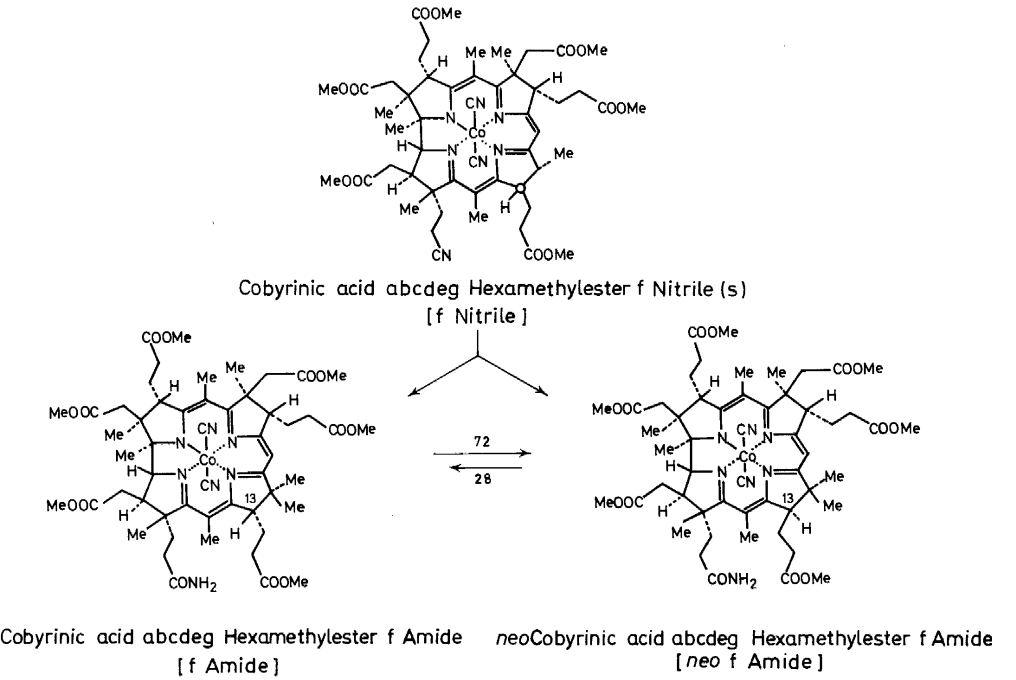


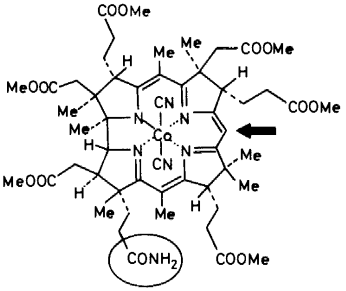
Figure 30

desirable or necessary to effect the separation of the normal and *neo* nitriles. The f nitriles are converted to the corresponding primary amides by treatment for about an hour with concentrated sulphuric acid. Concentrated sulphuric acid rather cleanly brings about the transformation of the nitrile grouping to the corresponding primary amide grouping. There is very little destruction of the corrin nucleus under what might be regarded as rather severe conditions.

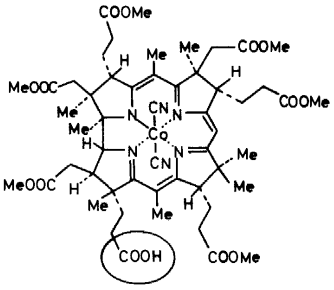
But there does accompany the conversion of nitrile to primary amide an equilibration of the propionic chain at C.13. Thus, even if one starts with the pure normal compound or the pure *neo* compound, in this sulphuric acid hydration of the nitrile group, the product is an equilibrium mixture of the two primary amides, that is, the cobyrinic acid abcdeg hexamethyl ester f amide, or for short, the f amide, and its corresponding *neo* isomer, differing in configuration at C.13 but otherwise exactly the same. Here also you see the numbers that I alluded to very briefly earlier in my lecture; notice that the unnatural series is actually preferred—these numbers were very carefully determined: 72 to 28 represents the ratio in favour of the *neo* compound. These amides are again very easily separable by high pressure chromatography and one can obtain the pure substances—the f amide and the *neo* f amide. The f amide is a beautifully crystalline well-characterized substance, and I may say here that we could at this stage take advantage of the fact that it was possible to prepare the f amide from heptamethylcobyrinate, namely, the substance containing carbomethoxyl groups at all seven chain termini. Heptamethylcobyrinate in its turn is readily preparable from vitamin B_{12} itself by vigorous methanolysis, and to describe the situation very briefly, when heptamethylcobyrinate—which contains four propionic chains—is ammonolysed under very mild conditions, a mixture of all four propionic monoamides is produced. Again, using high pressure chromatography, it is very easy to separate these four monoamides, and among them of course is the f amide. *The f amide obtained in that way from vitamin B_{12} by degradation is the same f amide which is prepared by the synthetic path that I have just described.* There is complete identity in the properties of the synthetic and authentic samples in respect to chromatographic behaviour, ultra-violet spectra, and the circular dichroism spectra†. They form crystals which are identical in appearance. Unfortunately, I can't say that a mixture melting point was taken, because neither of them melts—but they show identical non-melting behaviour!

Now let us examine *Figure 31*. What we had to do next was transform the f amide into the corresponding carboxylic acid—for short, the f acid. Now of course the conversion of an amide into a carboxylic acid is a reaction which has been carried out innumerable times in many cases. But we had here a very special problem, because we had to effect the conversion of the f amide to the f acid—left to right—without hydrolysis of the ester groupings, of which there are no less than six. One thinks at once, faced with this problem, of the possibility of deamination of the amide using nitrous acid or a nitrous ester or some other nitrous derivative. This is a reaction that has frequently been used for the conversion of amides to acids. However, both in Cambridge and Zürich the initial experiments—model experiments as it happened—on the deamination of various corrin amides with nitrous acid and nitrous esters were extremely disappointing, in that it was found that the corrin nucleus was exceptionally extraordinarily readily nitrosated at the position shown by the dark arrow, the 10 position. This extremely ready nitrosation of the

† Shortly after this lecture was presented, identical proton magnetic resonance spectra were found for the synthetic and authentic f amides, through the courtesy of Dr Englert [Roche, Basel].



Cobyrinic acid abcdeg Hexamethylester f Amide
[f Amide]



Cobyrinic acid abcdeg Hexamethylester
[f Acid]

Figure 31

10 position frustrated a very large number of efforts to effect the nitrous acid or ester deamination of the f amide with the intention of obtaining the f acid.

In these circumstances, in Zürich Professor Eschenmoser and his colleagues developed an extremely elegant method for the selective transformation of the f amide into the f acid. The details of that method are shown in *Figure 32*. Here I show only a portion of the molecule of the f amide—the relevant portion—containing ring D, the propionic chain and the f amide grouping.

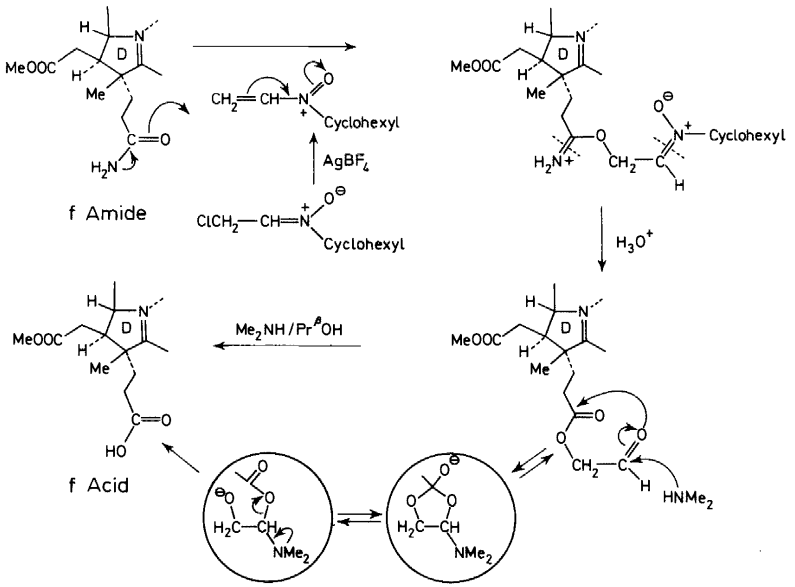


Figure 32

In the method which Professor Eschenmoser developed, he generated in the presence of the f amide the extremely highly reactive electrophilic species shown; that species is generated from the cyclohexylnitrone derived from chloroacetaldehyde. When that α-chloronitrone is treated with silver fluoborate, chloride ion is lost; the resulting extremely powerful electrophilic substance attacks the f amide in the expected position, namely, at oxygen. Now, very weak acid effects the hydrolysis of both the nitrogen–carbon multiple bonds in the resulting intermediate; that is, the iminoester nitrogen is cleaved to give a simple ester grouping, while at the same time the nitrone grouping is cleaved to give the corresponding aldehyde. Thus, the product of the action of very dilute acid on the initial reaction product is an aldehydo ester. When the aldehydo ester is treated with dimethylamine in isopropanol, the f acid is smoothly produced. You can see what a diabolically clever scheme this is. I didn't invent it, so I can give it that accolade. The dimethylamine attacks the aldehyde group by preference, *not* the ester group, and then very probably what is involved is a transfer—probably an equilibrium transfer—of the acyl group from one oxygen to the other. In the new ester, a situation has been created in which there can be an irreversible elimination of carboxylate ion. All of this takes place very cleanly; there is no involvement of the many ester groups elsewhere on the periphery of the molecule.

Thus, we had one method of making the f amide into the f acid, and it is as I said a very interesting and elegant one. You will note that it is very probably general, and although its generality has not yet been investigated, it really should be applicable in the case of other amides—not only, you will notice, primary amides, but also secondary and tertiary amides. Meanwhile, in Cambridge we had on paper other elegant schemes for effecting the selective conversion of the f amide to the f acid. We also had a very determined investigator, Elmar Konz, who just wouldn't take any nonsense about not being able to deaminate with nitrous acid or some derivative thereof. In *Figure 33* we see again the f amide; Dr Konz showed that if you just tried hard enough

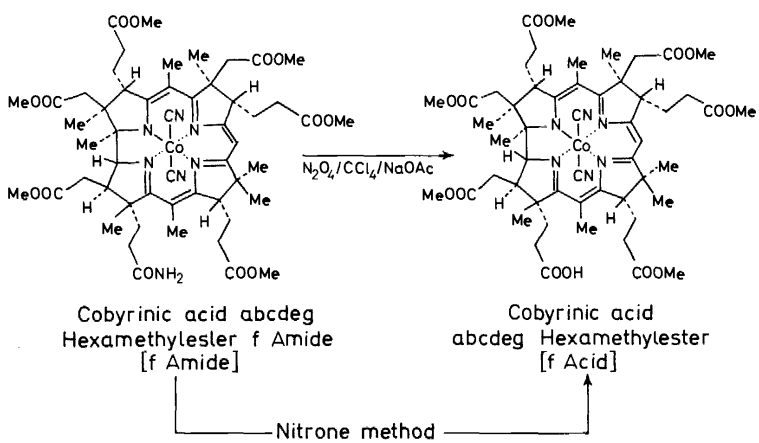


Figure 33

you could effect the transformation of the amide into the acid in very high yield, using a nitrous derivative. In this particular instance we used nitrogen tetroxide (N_2O_4) in carbon tetrachloride in the presence of sodium acetate at 0° for about an hour; under properly defined conditions the f amide is transformed into the f acid in 70 to 80 per cent yield with no nitrosation whatsoever taking place at the 10 position. So in these two methods we have essentially very beautiful examples of two facets of synthetic chemistry. It is usually possible, faced with a difficult stage, to develop an entirely new and intriguing method for surmounting the problem. It is also usually possible if one experiments long enough to make use of an older and initially unpromising method. In any event, we found two excellent methods for converting the f amide to the f acid. As it turns out in practice, the nitrogen tetroxide method is the simpler and easier one, and though it lacks the chemical elegance of the other method, it is by far the easier way to prepare the f acid.

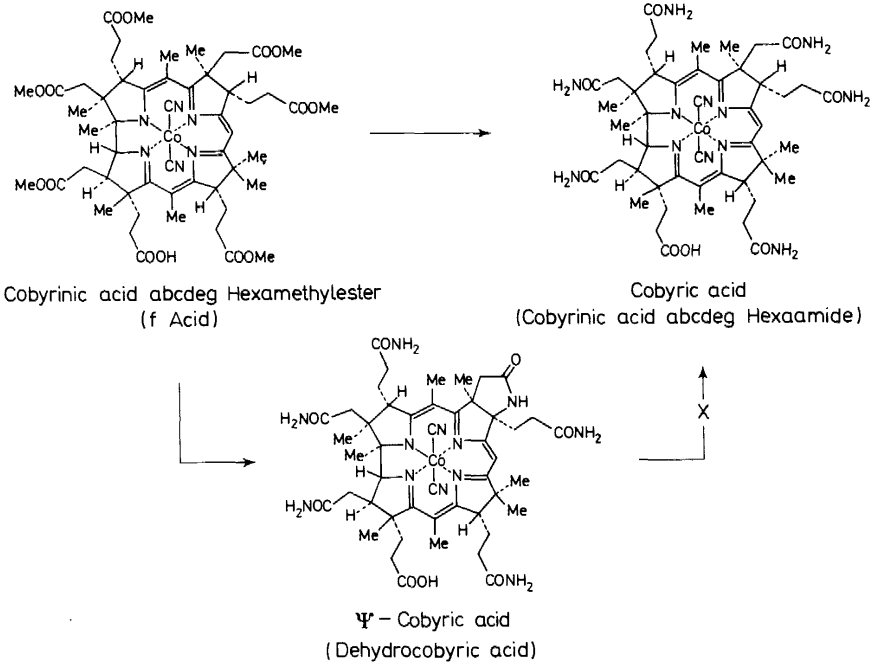


Figure 34

Now we thought we must really be getting close to the end. In *Figure 34* we have again the f acid, or to give it its whole name and dignity, cobyrinic acid abcdeg hexamethyl ester. Our problem is the one shown along the top of the figure, namely, to convert the carbomethoxyl groups, six of them, into primary amide groups. When first considering this problem we were not by any means free of apprehensions about it. The conversion of an ester into an

amide is frequently quite a difficult process, even in somewhat simpler cases than these. We know that in these molecules, three of the ester groupings, the acetic ester groupings, have very highly hindered carbonyl groups, and so we were not by any means sure that it would be a very easy matter to effect the ammonolysis of all six of the carbomethoxyl groups. Needless to say, we did some model experiments with heptamethylcobyrinate before the f acid was available. Those model experiments had already progressed fairly far last summer, and seemed quite promising. In fact, when we had treated heptamethylcobyrinate with ammonia—in detail, an approximately equal mixture of liquid ammonia and ethylene glycol—at 75° for periods of approximately 30 hours, we appeared to obtain fairly considerable quantities of cobyramide. Cobyramide is simply the amide of cobyric acid having seven primary amide groupings about the periphery, and that seemed a very promising result. In more recent studies, more careful studies, of this ammonolysis, we found that the vitamin B_{12} molecule was fighting right up until the last moment, because the cobyramide or the supposed cobyramide which we had obtained by the vigorous ammonolysis of heptamethylcobyrinate had the same electronic spectrum as cobyramide obtained from cobyric acid; it had essentially the same infra-red spectrum; its behaviour in all paper chromatographic systems that we investigated, and on all plate chromatographic systems that we investigated, was the same as that of authentic cobyramide. But on invesitigation with high pressure liquid chromatography, *we found that the material was not cobyramide at all*! It was an entirely different substance. Furthermore, when the f acid became available, and we applied the ammonolysis conditions, that is, treatment with ammonia and ethylene glycol at 75° for 30 hours to the f acid, the substance that was obtained was not cobyric acid, but rather an entirely different substance, which we called *pseudo*cobyric acid.

Again the product behaved identically with cobyric acid in its spectroscopic properties and in its behaviour in paper and plate chromatographic systems. But in high pressure liquid chromatographic systems, it was easily separable, and it was obvious that the product was not cobyric acid. It was in fact a well defined substance; we know now what it is, and I show it here: it is dehydrocobyric acid—a substance which has a new lactam grouping. You see that one of the sidechains has become converted not just simply to a primary amide grouping, but a further change has taken place with the formation of a new ring. That may seem a remarkable change, and indeed it is. I have not made a point of it this afternoon, but it is a fact that we carried out all reactions and in particular those involving basic conditions in this series taking extreme precautions to exclude oxygen. All solvents must be deoxygenated by freezing and thawing several times before use, immediately before use, and the one thing we could be sure of is that in these ammonolyses there was absolutely no oxygen present whatsoever. Now the formation of pseudocobyric acid or dehydrocobyric acid is an oxidation reaction. I just indicated that we certainly kept out any oxygen. Ammonia isn't a very good oxidant, nor is ethylene glycol, so what does go on here? Well, here we have, I think, an example of the fact that these compounds aren't as simple as they seem and that we're not really just dealing with substances in which we have ester groups. We have a complicated corrin nucleus with cobalt in the middle of it; I am sure that what is involved here is that the cobalt^{III}—the cobalt in

these corrins is in the valence state three—is in the course of these operations reduced to cobalt^{I} at the expense of the formation of the new bond. That of course would be where the oxidation reaction comes in; cobalt oxidizes the molecule, probably intramolecularly, to give the new carbon–nitrogen bond in pseudocobyric acid. Now what happens to the cobalt further? Cobalt^{I} is very easily oxidized, and we feel that the other product from the reaction is hydrogen; thus, an active hydrogen compound present in the reaction mixture reacts with the cobalt^{I} to give molecular hydrogen, so that the terminal stage in the reaction is rather analogous, if you wish, to the reaction of sodium and water to give hydrogen. It might be mentioned parenthetically that formation of a lactam or lactone ring in that area of the vitamin B_{12} molecule is a change which has been frequently observed before. I don't think in previous cases that there has been as much attention paid to the rigorous exclusion of any oxygen or of any other oxidizing agents as in our experiments: we can be very sure that there is no oxygen present other than in the molecule itself.

In any event, we had an ammonolysis which proceeded very smoothly to give amide groupings at five places. Unfortunately, there was a serious complication, that is, the lactam formation. A favourable thing was that the carboxyl group was untouched. *A priori* there were two possible ways of solving the new problem. Either we might convert pseudocobyric acid into cobyric acid, that is, by destroying the unwanted lactam ring. We did make a number of attempts to do that; that of course would be a reductive process, and we tried numerous reducing agents, all to no avail; we have been unable to convert pseudocobyric acid into cobyric acid. That seemed to be a dead end. The other alternative is to suppress the formation of the pseudocobyric acid by some means, and we tried various ways, ultimately finding an exceedingly simple one. If to the mixture of liquid ammonia and ethylene glycol, which I described earlier, one simply adds a few milligrammes of ammonium chloride, then the desired reaction—the conversion of the f acid into cobyric acid—takes place in essentially quantitative yield. No pseudocobyric acid is produced at all, no chromophore is destroyed. So this simple little device, that is, the addition of ammonium chloride, permits one to transform f acid into cobyric acid, as I say in virtually quantitative yield. Why does the ammonium chloride have this striking effect? By the way, the time for reaction is much less; it is over in 10 hours or so. We think that two things are involved here—first, a catalysis of the ammonolysis; it is not unreasonable to expect that the ammonium ion would catalyse the ammonolysis of esters, although no certified physical organic chemist would say that it would; they won't say anything about reactions in a 50/50 mixture of liquid ammonia and ethylene glycol; but they would be willing to admit—at least those to whom I have divulged these results—that it is perhaps not surprising that ammonium chloride catalyses the ammonolysis. But in addition, we think the ammonium chloride must also suppress the lactam formation; indeed it was put in there specifically to discourage the presence of $CONH^{\ominus}$ groupings, which we felt might be necessary as a stage in the formation of the pseudo compound. That was the reasoning that led to the putting in of the ammonium chloride, and I cannot judge whether the reasoning was correct, but the result was admirable. The cobyric acid was crystalline, and *it was identical in all*

respects, most particularly in liquid chromatographic behaviour, with cobyric acid derived from natural sources.

In *Figure 35* you see again cobyric acid, the material whose synthesis I have just described, and then you see on the left vitamin B_{12}, and I remind you that in 1960 cobyric acid was transformed into vitamin B_{12} by Friedrich, Gross, Bernhauer and Zeller. You will now realize that the synthesis of vitamin B_{12} is complete.

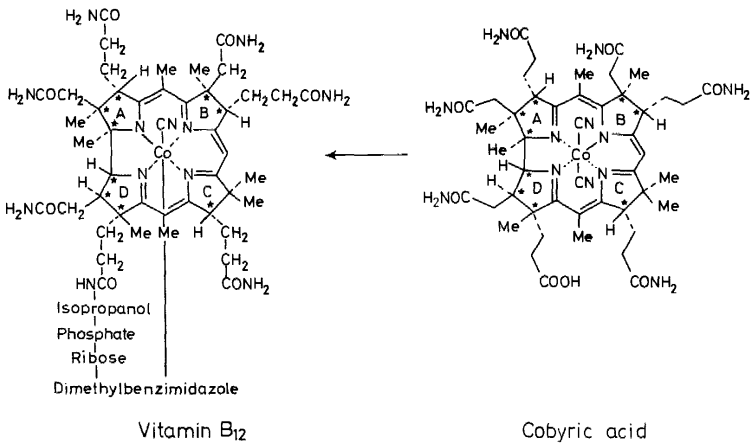


Figure 35

In *Figure 36*, we see the names of the men whose very beautiful and devoted work in the last year and a half brought about this very gratifying conclusion. In Zürich you see quite a group and in Cambridge quite a group from all nations, and it is to these gentlemen in Zürich and Cambridge to whom I am most happy to give my thanks for the privilege of having been able to collaborate with them. It is to them that you owe any pleasure that you may have received from my remarks here today.

Zürich	Cambridge	
Walter Fuhrer	Kaspar Burri	Yang-i Lin
Naoto Hashimoto	Pasquale Confalone	John McCall
Hans Maag	Graham Crawley	Hiroyuki Nohira
Naruyoshi Obata	Fernando Durán	Romeo Paioni
Walter Schilling	Helmut Hamberger	Dinanath Rane
Peter Schneider	Volker Jäger	Stanley Roberts
Jacob Schreiber	Philip Keehn	Geoffrey Shelton
	Dennis Keith	Wolfgang Trommer
	Elmar Konz	

Figure 36

ACKNOWLEDGEMENT

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