

RECENT ADVANCES IN THE CHEMISTRY OF NATURAL PRODUCTS

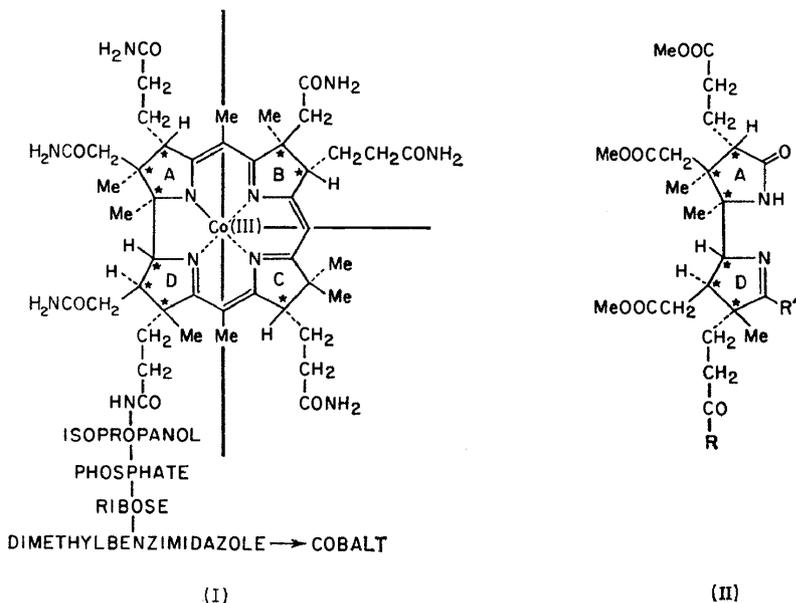
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It gives me great pleasure to exercise this opportunity to present to you some of the results of a collaborative investigation which has as one of its objectives the synthesis of vitamin B₁₂. These studies have been pursued in my laboratory at Cambridge and in that of Albert Eschenmoser at Zürich. They have been prosecuted on a very broad front, and in the limited time available here it will be possible to describe only a small portion of the work. I have chosen to present those results which seem to us at present most surely destined to constitute established stages in the achievement of the specific objective of synthesizing vitamin B₁₂. To make this choice is not to derogate the interest and fascination of other portions of the investigation. Indeed, before embarking on today's story, I permit myself a parenthesis. The history of organic chemistry provides in abundance instances of the major role played by the study of natural products in revealing, extending, and shaping the fundamental bases of the science. Time and again the penetration of a new sector of the vast, often surprising and always beautiful panorama of natural products has led to new insights which could hardly have been achieved by more self-conscious fundamental investigations. This role of natural product studies is in no way diminished in our day, and it will certainly continue in the future; the proposition cannot be better illustrated than by my alluding to the fact that the principle of orbital symmetry conservation arose directly from our studies on vitamin B₁₂ synthesis. But that story has been outlined in another place¹, and I shall have nothing further to say about it today.

Let us commence by scrutinizing the structure of the vitamin B₁₂ molecule (I). That intricate and fascinating array, revealed to us by the beautiful x-ray crystallographic studies of Dorothy Hodgkin, exhibits certain resemblances to other natural substances. Thus, like the blood pigment, haem, and the leaf pigment, chlorophyll, it contains a metal atom embedded within a macrocyclic nucleus containing four five-membered heterocyclic rings—A, B, C and D. But while in the blood and leaf pigments these five-membered rings are held together by single-carbon bridges, in the case of vitamin B₁₂ two of them, rings A and D, are directly linked. Above all, the most striking contrast between vitamin B₁₂ and its more simply constituted relatives, haem and chlorophyll, lies in the realm of stereochemistry. The porphyrin nucleus of the haem molecule is constituted entirely of trigonal carbon atoms and presents no points of stereochemical interest; the dihydroporphyrin, or chlorin, nucleus of chlorophyll presents only the relatively trivial stereochemical problem associated with the presence of two unsymmetrically substituted tetrahedral carbon atoms. In striking contrast, the periphery

of the nucleus of vitamin B₁₂ is adorned by no less than nine unsymmetrically substituted tetrahedral carbon atoms (starred in I). This situation clearly presented an unparalleled challenge and a magnificent opportunity for the testing of—and perhaps for the further development of—the principles of stereospecific synthesis.



Let us first examine the stereochemical problem associated with any projected synthesis of vitamin B₁₂ in the most general terms. The heavy vertical and horizontal lines shown in I divide the areas of chirality within the nucleus into three groups. The first and simplest of these is that containing the single asymmetric centre in ring C; the second includes the two adjacent centres in ring B, while the third contains the six contiguous unsymmetrically substituted tetrahedral carbon atoms of rings A and D. If now we consider any one of these groups in relation to the others, it seems clear that they are situated at such remove, each from the others, that it would be most difficult to generate a desired configuration within one group under the influence of chirality already present in one of the other sectors. The solution to the problem of generating the needed relative stereochemical relations among the three groups is relatively simple: we must use what may be called the principle of *absolute asymmetric synthesis*. That is to say, we must prepare building blocks representing, separately, each of the three chiral groupings. Each of these building blocks must be prepared in optically active form, and of the properly specified absolute configuration. Then, when such building blocks are combined, the *relative* configurations at the various centres of chirality must necessarily be the desired ones. This principle of absolute asymmetric synthesis, simple though it be, has been relatively little utilized—except in certain conspicuous instances—for example, in the synthesis of oligopeptides and oligonucleotides, where its use, though of

crucial importance, has tended to be rather inherent than explicitly recognized. This first stage of our general analysis may be summarized in the conclusion that we must prepare three optically active building blocks of specified absolute configuration, one of them representing the A/D portion of the vitamin B₁₂ molecule, one representing the ring B sector, and the third representing ring C.

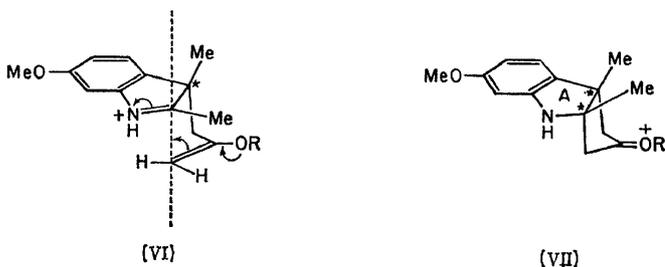
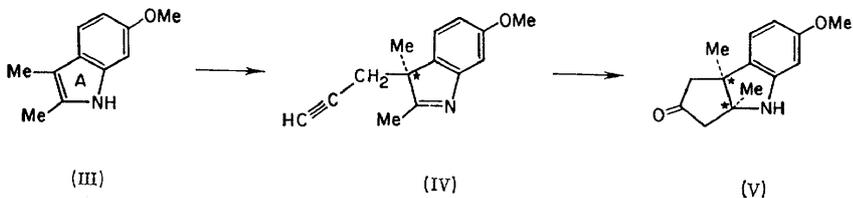
Now let us consider the stereochemical circumstances *within* each of the specified groups. The problem presented in the ring C sector is clearly a simple one, and that associated with the projected ring B building block only slightly more complicated. In sharp contrast, the crowded concatenation of six contiguous asymmetric centres embedded within the A/D moiety represents a formidable challenge. Here the close proximity of many centres invites the possibility of the utilization of *stereospecific synthesis by induction*—that is to say, the creation of new centres in a desired stereochemical sense under the directive influence of chiral factors present in prior intermediates. We shall see that in the event the problem was mastered through the use of a combination of induced and absolute asymmetric synthesis.

A further point of detail remains before our initial objective can be defined in full. Of the seven chains attached to the periphery of the vitamin B₁₂ nucleus, six terminate in simple amide groups. The seventh is emburdened by a sequence of biochemically familiar groupings, the last of whose members is coordinated to the central cobalt atom. The problem presented to the synthetic chemist by this isopropanolamine-phosphate-ribose-dimethylbenzimidazole chain has already been solved. Cobyric acid, the substance containing a simple carboxyl group at the end of the apposite chain, is, like vitamin B₁₂ itself, a naturally occurring substance, and the conversion of the acid into the vitamin has already been achieved by Bernhauer and his collaborators. Consequently, this aspect of the problem need concern us further only in that we must bear in mind the necessity of distinguishing one carboxyl group from all of the others in some way.

It is now possible to define our initial objective in terms of the structure II. This array represents a projected building block ultimately to be used in combination with others, representing rings B and C, for the construction of the entire nucleus of vitamin B₁₂. It contains the six contiguous asymmetric centres present in the corresponding part of the molecule of the vitamin, each of them appositely substituted with groupings identical with or clearly readily convertible to those required. It must be prepared in optically active form, and in the absolute configuration designated. The groups R and R' are not as yet specified in detail. Clearly the former must be differentiable from the methoxyl groups at the termini of the other chains, and R' should be of such nature as to possess reactive potentialities for the construction of the required bridge to the ring C sector.

We turn now from general analysis to specific synthetic detail. Our point of departure is the methoxydimethylindole (III), which is easily preparable by the acid-catalyzed cyclization of the Schiff base from *m*-anisidine and acetoin. Certainly the indole seems a far cry from vitamin B₁₂, but it may be observed that it does contain a five-membered nitrogen-containing ring to which two methyl groups are attached in adjacent positions; it is this ring which is destined to become ring A of the vitamin B₁₂ molecule. When the

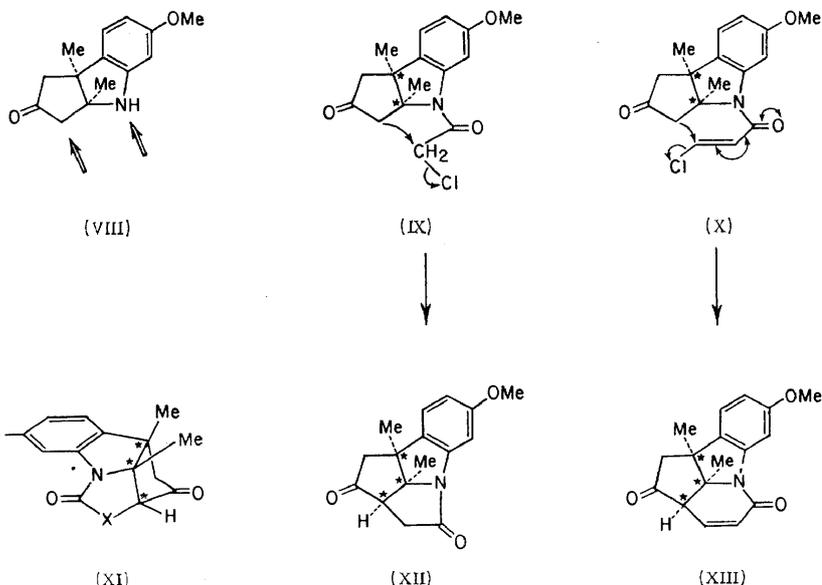
indole, in the form of the magnesium derivative prepared by its reaction with methylmagnesium iodide, is treated with propargyl bromide, the propargyl indolenine (IV) is smoothly produced. In this reaction chirality is generated for the first time, and of course since no asymmetric element has been employed in the preparation of the indolenine, the substance actually in hand at this stage of our work was a racemic mixture, comprised of IV and the corresponding enantiomer. When the indolenine is treated in methanol solution with boron trifluoride and mercuric oxide, it undergoes smooth cyclization to the tricyclic ketone (V). This reaction deserves comment in a number of directions. One is that the formation of an isomeric product of quite different gross structure was a distinct possibility; the skele-



ton present in IV could in principle—and does under certain conditions—suffer rearrangement to a hydroquinoline system. But in fact, under carefully defined conditions that dangerous bypath can be avoided completely. Of greater moment is the circumstance that in the course of the formation of the new carbon-carbon bond, which completes the construction of the new five-membered ring, a new asymmetric centre is generated. *A priori*, two isomeric substances might have been produced. In fact, only one was obtained. That is to say, the reaction proceeded in an entirely stereospecific manner. We felt that there was excellent reason to suppose that of the two substances which might be produced, the one which was actually formed must be that (V) in which the two methyl groups were on the same side of the tricyclic skeleton, as desired. The formulae (VI) and (VII) represent rather crudely the basis for our confidence that the reaction had followed the course outlined. It is clear that the reaction proceeds through the intermediacy of the methyl enol ether (VI)—the product of the addition of the elements of methanol to the acetylenic bond in the indolenine (IV). Now, when a bond is formed by the union of two trigonal centres, the

transition state for the bond-forming reaction will be lower in energy as it is easier to achieve that condition in which the perpendiculars to the planes of the combining trigonal atoms are co-linear. Now, in the case at issue, the short chain of atoms whose terminus is one of those atoms involved in the bond-forming reaction is already oriented in a particular sense, through attachment of the chain to the one asymmetric centre in the indolenine. In these circumstances the conditions just specified strongly favour bond formation to that face of the indolenine ring to which the chain is already attached in the precursor; as the new bond is formed in the sense described, it is clear that the methyl group at the newly formed centre is placed in the desired position, on the same side of the heterocyclic ring as that attached to the one asymmetric centre in IV. Another way of putting the matter is that if the short three-carbon chain is to be stretched from one side of the indolenine ring to the other, a transition state of relatively very high energy would of necessity be involved. Here we have a very simple example of what we have designated above as induced asymmetric synthesis, namely, creation of a new asymmetric centre stereospecifically in a desired sense, under the influence of asymmetry already present.

The tricyclic ketone (V \equiv VIII) has played the key role in all of our



studies of routes to a suitable A/D building block. In VIII the structure of the ketone has been adorned with two bold arrows which may be helpful in outlining the fundamental bases for our choice of the ketone for so important a role. Thus, the tricyclic ketone contains a nitrogen atom to which a replaceable hydrogen atom is attached. We felt that we should be able to effect the union of the tricyclic ketone with any one of a large number of possible arrays which might ultimately provide the material for elaboration of those sections of the desired A/D intermediate representing ring D of vitamin B₁₂. Further, after initial attachment of such arrays at nitrogen,

we envisaged the possibility of making a new bond, from the carbon atom of the methylene group adjacent to the carbonyl function in the five-membered carbocyclic ring, to the previously attached array, *in a stereospecific manner*. This basic plan may be illustrated by presenting two simple examples. Thus, the tricyclic ketone (VIII) is transformed readily into the chloroacetyl amide (IX), or the chloroacryloyl amide (X), when it is treated with the corresponding acid chloride in the presence of pyridine. When either of these amides is treated with potassium tertiary butoxide in tertiary butanol, cyclization to the corresponding tetracyclic substance—the five-membered lactam (XII), or the six-membered unsaturated lactam (XIII)—takes place. In the course of these cyclizations a third asymmetric centre is created; again, in each case, although two stereoisomeric substances might have been formed, in fact a single product is cleanly produced. And here also our reasons for supposing that these stereospecific reactions had taken the desired course were simple ones. The molecules of the tricyclic ketone (VIII) and the derived amides (IX and X) are far from the planar assemblages they may appear to be on casual inspection of their two-dimensional representations. They are in fact highly concave, as suggested in XI, which picture also suggests the serious difficulty which would be attendant upon the creation of a short bridge of atoms, originating at nitrogen and terminating in a bond to the opposite face of the five-membered carbocyclic ring. Here then is yet another example of the creation of asymmetry in a desired sense under the influence of prior molecular asymmetric factors.

It should be emphasized again at this point that although the structures which I have presented are those of specific enantiomers, the substances actually in hand at this stage of our investigation were racemic compounds. Clearly it was necessary at some point to effect resolution into optically active enantiomers, only one of which would have the absolute configuration corresponding to that of vitamin B₁₂ itself. In the event, this important step in our work was effected with the tricyclic ketone, in the manner summarized in *Figure 1*. The procedure is no more than a simple variant of the classical method of resolution by combination of the racemic material with an optically active substance, followed by separation of the resulting diastereomers, but it does present an element of novelty which may be of some general utility. Briefly, the diastereomeric ureas resulting from the combination of the racemic tricyclic ketone with optically active α -phenylethylisocyanate are very readily separable (one of them crystallizes beautifully, and the other not at all!), and are readily re-converted to the parent active tricyclic ketones when pyrolyzed. This procedure enabled us to obtain both optically active forms of the tricyclic ketone readily in a state of optical purity.

Of course, *Figure 1* is in one sense anticipatory, in that nothing that I have described so far permits the assignments of absolute configurations there shown. At this point in our investigation it was of crucial importance for us to know the absolute configurations of the resolved ketones. Only one of them of course might ultimately be transformable into vitamin B₁₂, while the other could only be converted into an enantiomer of the natural substance. None the less, as we shall see, the ready availability of both isomers was of much importance in our subsequent work.

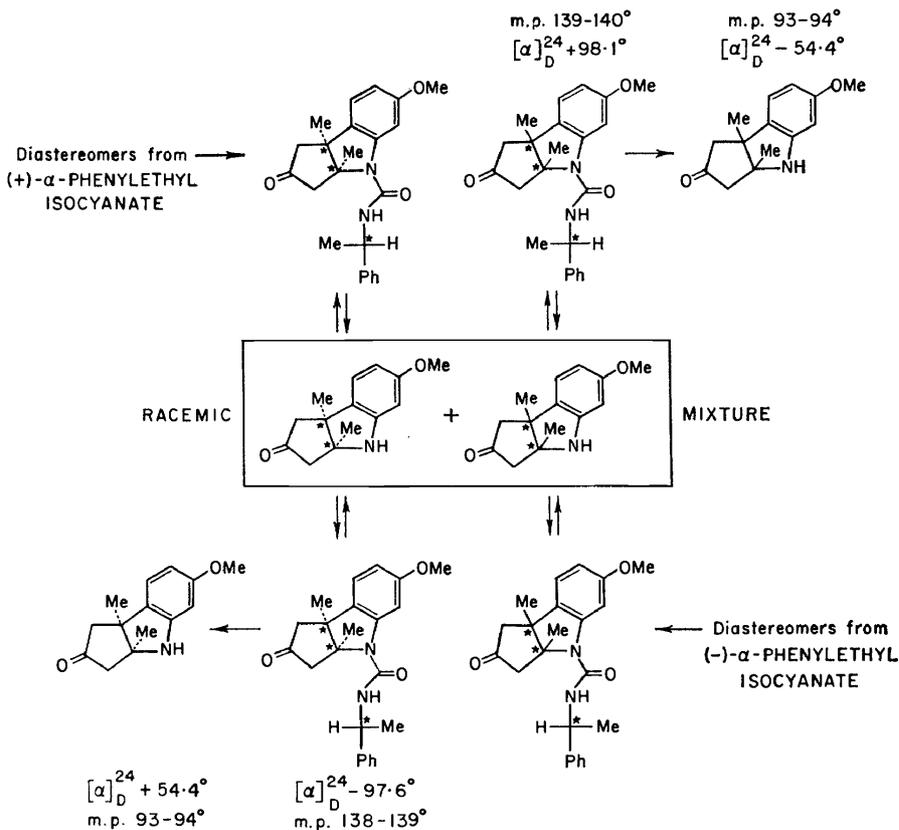
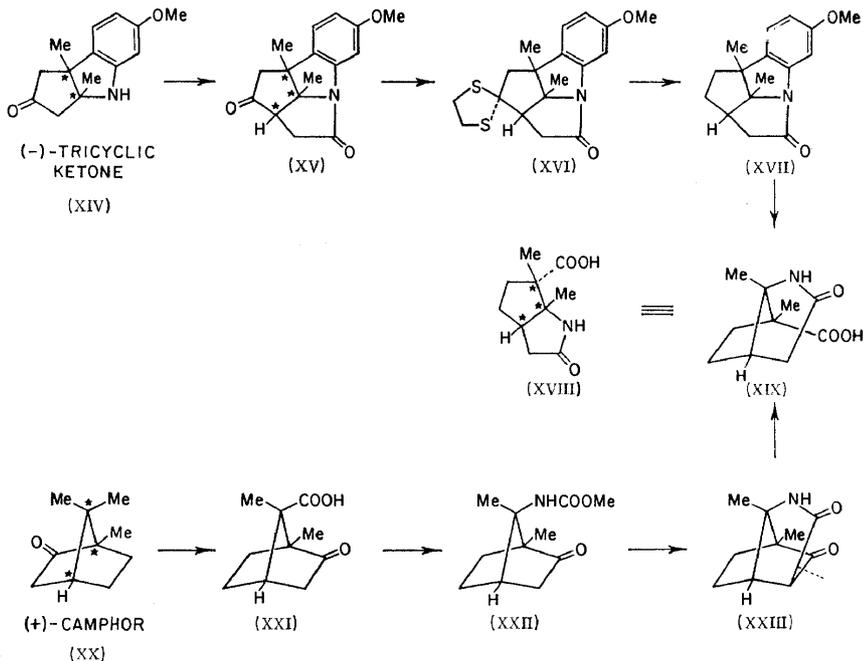


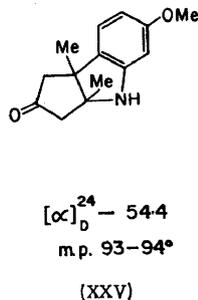
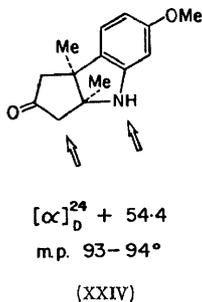
Figure 1

In order to establish the necessary relationships, the *laevo*-rotatory tricyclic ketone (XIV) was transformed into the optically active tetracyclic lactam (XV), following the path already described for the corresponding racemic compounds (VIII \rightarrow IX \rightarrow XII). The ketonic carbonyl group of XV was then removed through treatment of the corresponding thioketal (XVI) with Raney nickel, and the aromatic ring in the resulting lactam (XVII) was destroyed through ozonization, to give the bicyclic lactam acid (XVIII \equiv XIX). Now, in an independent series of transformations, the keto-acid (XXI)—a substance of known absolute configuration, readily available by a previously established route from *dextro*-rotatory camphor (XX)—was degraded through the chloride, azide, and isocyanate to the methyl urethane (XXII). When the latter was treated in tertiary butanol solution with potassium tertiary butoxide and potassium hydroxide, it was converted to precisely the same lactam (XVIII \equiv XIX) which had been obtained from the *laevo*-rotatory tricyclic ketone. No doubt the final stage in the sequence just described involves the intermediacy of the tricyclic ketolactam (XXIII), produced by base-catalyzed deprotonation at the methylene group adjacent to the ketonic carbonyl function in XXII, followed by attack of the resulting anionoid carbon upon the urethane carbonyl group. Clearly,

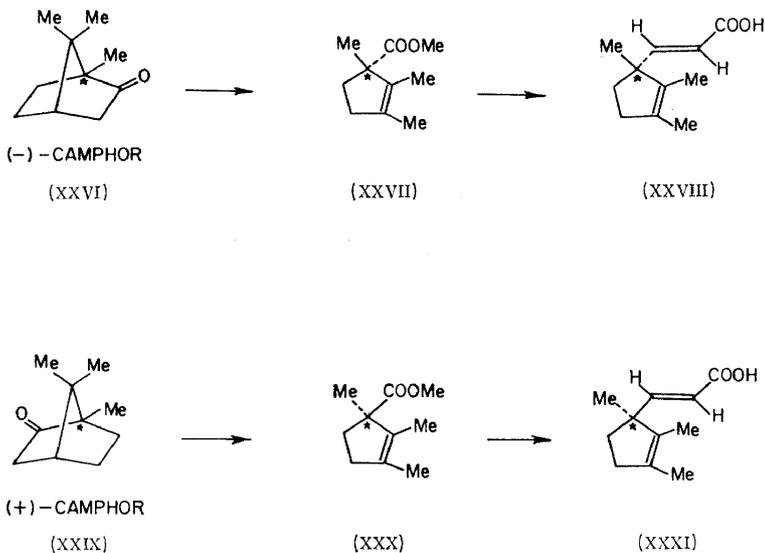


the β -ketoamide system present in XXIII is then cleaved in the expected sense by hydroxide ion. In any event, the correlation of the tricyclic ketone with camphor establishes rigorously the absolute configurations of our key intermediates. But it does more than that. It confirms also the gross structure of the tricyclic ketone—it will perhaps be recalled that I alluded briefly earlier to a certain ambiguity in that connection—and more important, it demonstrates rigorously that our anticipations in respect to the senses of the stereospecific reactions leading to tetracyclic materials, for example, XV, according to the plan which I have described, were correct.

In sum, we were now able to build further upon the secure foundation of our knowledge that our key tricyclic ketone possessed the desired structure (cf. XXIV and XXV), and with a basis for confidence that its utilization in accordance with our general plan would be feasible. It should now be recalled that the plan envisaged a prior attachment, at the basic nitrogen atom of the tricyclic ketone, of a grouping of atoms which might be tailored



to represent ring D of our goal. In fact we have attached many different groupings of atoms to the tricyclic ketone, and each of the resulting products has been found to undergo reactions of much interest and fascination. Here we shall be concerned only with that one of the attached groupings which has shown itself to be of greatest utility in bringing us most effectively and directly forward in our search for a route to the synthesis of vitamin B₁₂. That grouping is contained within the molecule of the trimethylcyclopentenylacrylic acid (XXVIII). This acid is readily available from methyl laurolenate (XXVII), through reduction by lithium aluminium hydride



to the corresponding alcohol, oxidation by chromic acid to the aldehyde, condensation with carbomethoxymethylenetriphenylphosphorane, and hydrolysis. Methods for the preparation, from readily available *laevo*-rotatory camphor (XXVI), of the methyl laurolenate which serves as the starting point for this simple sequence, have long been known, but none of them were satisfactory from the preparative point of view, and at the time of our initial work there was a certain ambiguity in respect of the stereochemistry of the product. Consequently, a number of new routes were investigated, of which that portrayed in *Figure 2* was found to be practical and efficacious. It will be noted that the acid (XXVIII) contains one asymmetric carbon atom, and that its absolute configuration is known with certainty. A further stereochemical point of much importance is that the large groups are disposed about the double bond in the *trans* relationship—a fact which was readily established through nuclear magnetic resonance studies. Finally, mention should be made of the fact that the enantiomeric acid is readily available through a parallel sequence from *dextro*-rotatory camphor (XXIX → XXX → XXXI). Combination of the *laevo*-rotatory acid, through its acid chloride, with the *dextro*-rotatory tricyclic ketone (cf. XXXII) leads smoothly to the amide (XXXIII), which in its turn, when treated with potassium tertiary butoxide in tertiary butanol affords the pentacyclic lactam (XXXIV). An

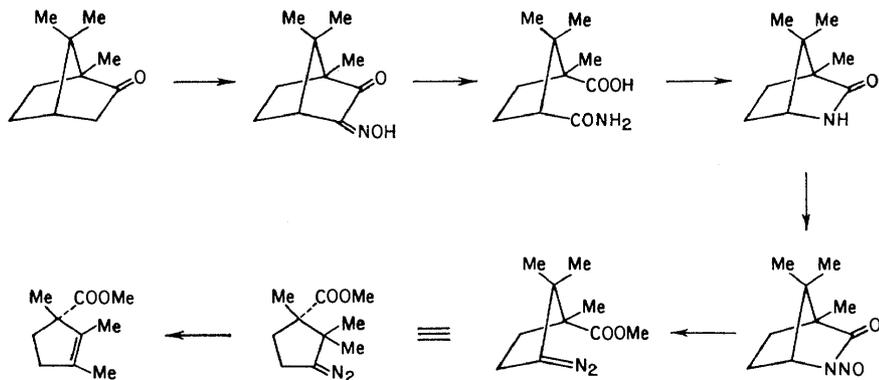
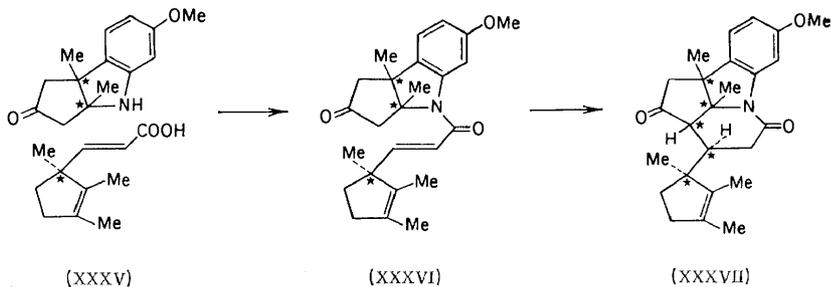
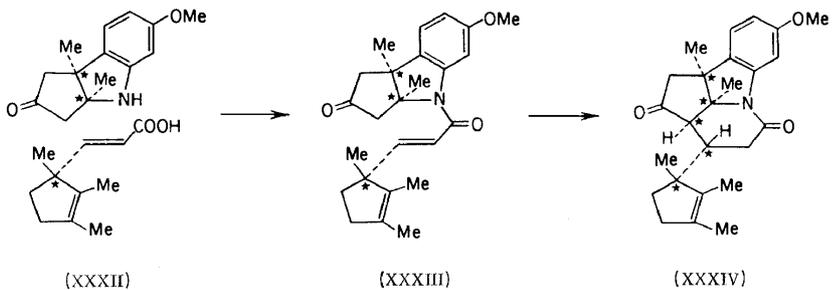


Figure 2

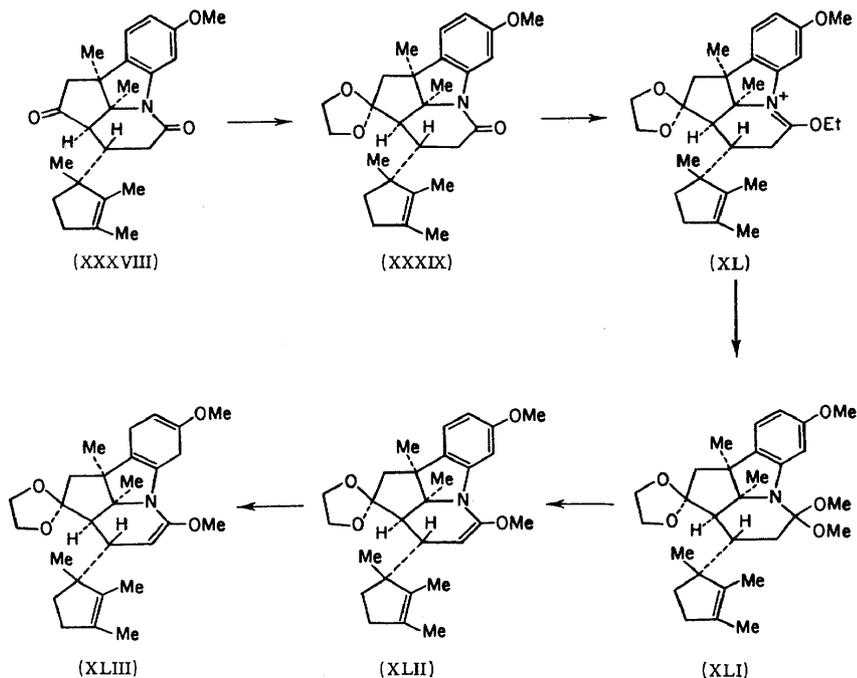
entirely analogous series (XXXV \rightarrow XXXVI \rightarrow XXXVII), starting with the *dextro*-rotatory acrylic acid and the *laevo*-rotatory tricyclic ketone, leads to the enantiomeric lactam. Three stereochemical aspects of these changes deserve special comment. First, the choice of optically active components of known and specified absolute configurations insures that in the amide (XXXIII) and the lactam (XXXIV), the relative chiralities in the pertinent areas of the product molecules must necessarily have the desired character. Indeed, we observe here an example of what I have called absolute asymmetric synthesis in my introductory remarks. Second, it should be noted that in the cyclization (XXXIII \rightarrow XXXIV) two new asymmetric centres are created, one at each terminus of the newly formed carbon-carbon bond.



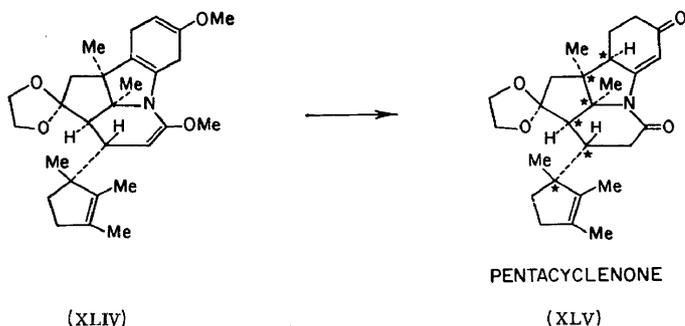
The considerations already advanced earlier provide a basis for assurance that the hydrogen atom at the upper terminus of the newly formed bond in XXXIV must appear on the same side of the molecule as the methyl groups already present in XXXIII and in the tricyclic ketone. Finally, the situation at the other terminus is only scarcely less clear, though it is not easy to portray with the planar representations available here; but inspection of models reveals clearly that if the large groups are *trans* disposed about the double bond in XXXIII, the transition state for the bond-forming reaction leading to that product with the hydrogen atom above the molecular plane should be much lower in energy than the alternative which would lead to the other *a priori* possible product. Had the double bond in XXXIII been *cis*, the opposite stereochemical result would have been anticipated, and we have here, so to speak, a case of translation of defined geometrical isomerism into desired orientation at a tetrahedral site. A special parenthesis is perhaps not out of place at this time. It will be noted that XXXIV and XXXVII are optically active, enantiomeric substances, each of which contains five contiguous asymmetric centres, created stereospecifically—each exhibiting the desired orientation of its attached substituents. It says a good deal for the facility of the synthetic processes I have described so far, and for the skill of my collaborators, that we have prepared upwards of two hundred grams of each of these substances in the pure state.

Perhaps also this is the point at which I should emphasize explicitly the importance of the availability of the “unnatural” enantiomer (XXXVII). Much as had been our progress at this point, we were not unaware that we still had far to go, and that it might be either necessary or desirable—as indeed it turned out to be—to investigate a considerable number of alternatives for further advance. In these explorations we were able to utilize XXXVII, confident that whatever new route we might establish through its study would be applicable to its counterpart (XXXIV) of the natural series; our experience has been such that this is just about the only kind of model study which we regard as wholly reliable! And in fact, although the reactions I shall describe in the sequel will be presented for compounds in the natural series, almost all of them were first discovered using the enantiomeric substances.

The aromatic ring present in the lactam (XXXIV \equiv XXXVIII) has served as a stable platform upon which a highly asymmetric assemblage has been established and aggrandized. Clearly that ring has no counterpart in the structure of vitamin B₁₂, and it is now time to modify that part of the structure of the lactam. In synthetic design, it is desirable, when such supporting structural features have served their purpose, rather to modify them in the sense of transforming them into some needed grouping than simply to destroy or remove them. In the case at hand, we felt that progress in that direction could be made should we be able to bring about the reduction of the aromatic ring—in particular, reduction by metal/liquid ammonia combinations to the dihydro level—that is to say, Birch reduction. But before such a change could be contemplated, it was clear that other groupings present in XXXVIII must be protected in some way. The first of these necessary protections was very simply accomplished through conversion of XXXVIII to the corresponding ketal (XXXIX) in the usual way. The



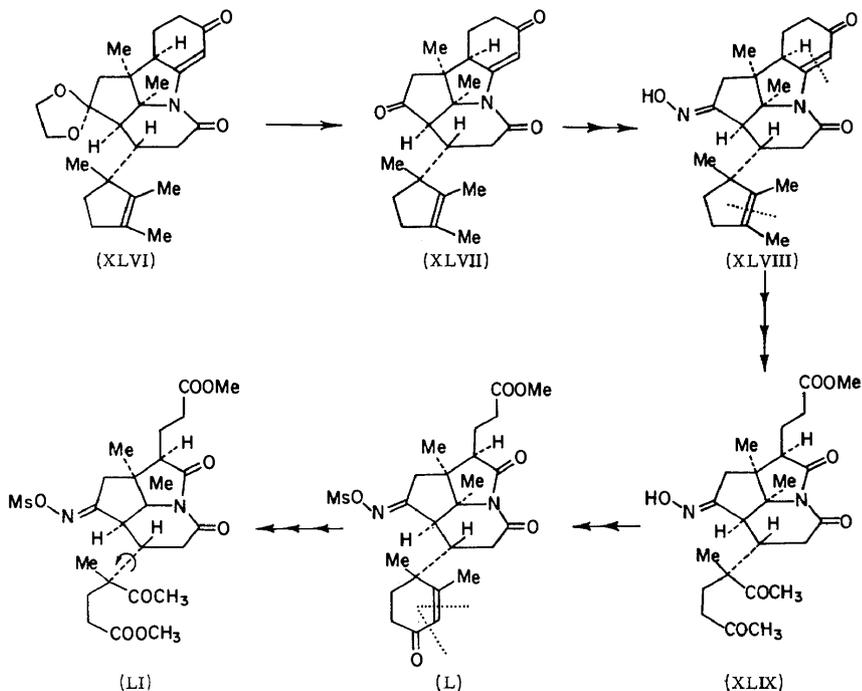
remaining problem of protecting the lactam grouping, which would be expected to—and does—suffer ready reduction under the contemplated conditions, turned out to be a far more formidable problem. But the solution finally achieved is an interesting and elegant one. The lactam (XXXIX) reacts readily with triethyloxonium fluoborate to give the immonium salt (XL), and the latter, in its turn, is converted by sodium methoxide in scrupulously dried methanol to the orthoamide derivative (XLI). When this dimethoxy compound is heated in toluene it loses the elements of methanol and affords the methoxy enamine (XLII). The methoxy enamine system is impervious to the powerful reducing conditions needed for the attack upon the aromatic ring, and when XLII is treated with a large excess of lithium in a properly constituted mixture of liquid ammonia, tertiary butanol, and tetrahydrofuran, it is smoothly transformed into the dihydro aromatic compound (XLIII \equiv XLIV). The molecule of the reduction



product contains several acid-sensitive groupings. When subjected to acid treatment under carefully controlled conditions, XLIV is converted to a substance (XLV) for which we have adopted the trivial name pentacyclenone; in this transformation the vinyl ether function is hydrolyzed, the lactam grouping is reconstituted, and the carbon-carbon double bond originally situated in the β,γ relationship to the newly generated carbonyl group migrates into the conjugated position. Of special interest is the fact that the last of these changes is coincident with the generation of the sixth and last of the contiguous chiral centres needed in our projected A/D building block (II). In this instance, as in all previous generations of chirality in our sequence, the reaction occurred stereospecifically. Only a single substance was produced, but when we first had pentacyclenone in hand, we possessed no means of ascertaining which of the two *a priori* possible orientations might be present. Nor in this instance did we have any particularly convincing argument as to which assignment should be made. As we shall see in the sequel the newly placed hydrogen atom appears on the same side of the molecule as the methyl group at the adjacent chiral centre, that is to say, in the *undesired* orientation. After the fact, we can present a reasonable defence of Nature's action in this respect, but I should hardly feel justified in taking some of the limited time available here today to put forward arguments which we did not regard as convincing before we knew the result. How does it happen that we were so little concerned with the orientation at the centre at issue, by contrast with the very great care we had exercised in the establishment of the desired configuration at each of the other centres? Essentially because we were cognizant of the fact that this centre, in XLV, and in the projected intermediates we had in mind, is so situated in relation to a carbonyl or similar group as to be susceptible of inversion. Consequently, we felt that should it be generated in the unwanted sense—as indeed it turns out to have been—it should at least in principle, not be too difficult a problem to effect the necessary inversion. It should be added that although the necessity of protecting the lactam grouping through the use of a series of very highly sensitive intermediates makes the reduction sequence one which calls forth the utmost in care and experimental skill, the lactam (XXXIX) can in practice be converted to pure crystalline pentacyclenone (XLV) reproducibly in an overall yield approaching 90 per cent.

When pentacyclenone (XLV \equiv XLVI) is further treated with acid, it is converted into the corresponding ketone (XLVII). At this point it will be desirable to unveil a further basic feature of our synthetic plan. All of you will have noted that the intermediates discussed so far contain but a single nitrogen atom, and will be aware of the necessity of introducing a second if our proximate objective is to be reached. In a general sense, every variant of our plan involved the element of introducing the needed second nitrogen atom through Beckmann rearrangement of a properly constituted oxime. We have demonstrated the feasibility of this method in many instances; the time is now at hand to describe the most useful of them. It is not possible to convert the ketone (XLVII) directly into the desired monoxime (XLVIII). The carbonyl grouping which must be oximated is a very hindered one, while that which forms part of the acylated vinylogous amide system is both unhindered and reactive. Consequently, the first product of the oximation

of (XLVII) is a dioxime. Fortunately however, the unwanted oximino group is very readily removed, selectively, by treatment with nitrous acid in acetic acid under very mild conditions; these circumstances permit the essentially quantitative transformation of XLVII into the desired monoxime (XLVIII) in a very simple sequence of operations. A stereochemical point deserves comment here. The successful realization of our general plan for embedding our second nitrogen atom properly in the carbon skeleton requires that the oxime have its hydroxyl group oriented in the sense shown, since only in that case will migration of the desired carbon-carbon bond be concomitant with Beckmann rearrangement. It will be noted that the space on one side of the nitrogen atom in XLVIII is quite free, while the other side is quite extraordinarily hindered. This circumstance left us in little doubt that the compound in hand was oriented in the desired sense.

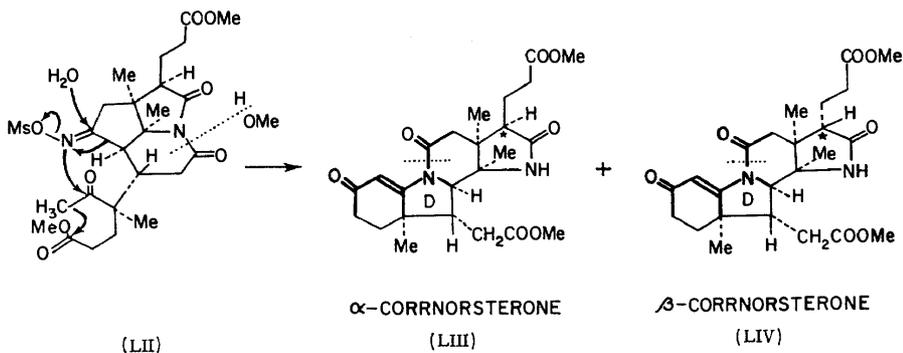


With the obtention of the monoxime we were in a position to effect the final re-fashioning of what had been our aromatic ring, and at the same time to begin the process of shaping our trimethylcyclopentenyl grouping into something more nearly resembling the ring D portion of the vitamin B₁₂ molecule. Thus, when the oxime was successively subjected, first to treatment in methanol solution with ozone at -80° , then with periodic acid, and finally with diazomethane, the intermediate (XLIX) was smoothly produced. Clearly, two expected changes are involved in this transformation. The cyclohexenone ring is cleaved; at one terminus of the broken double bond a desired lactam function is generated, and the carbon atom at the other terminus is extruded—the periodate oxidation is included to insure

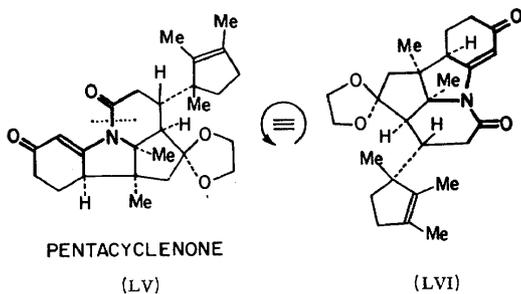
the completeness of this process, and the diazomethane treatment to effect esterification of the resulting carboxyl group. The overall change generates a propionic ester side chain attached in the desired position to the required five-membered lactam ring which represents ring A in our objective. At the same time, the double bond of the trimethylcyclopentenyl grouping is cleaved simply, a carbonyl group appearing at each terminus. Quite as important as these changes which do occur is one that does not. Remarkably, the oxime grouping survives the ozone treatment. Oximes in general are relatively susceptible to attack by electrophilic agents, and ozone is by no means the least powerful of the latter. Perhaps this useful imperturbability of our oxime grouping is in part attributable to steric hindrance; perhaps also the mildness of the conditions plays a role, and it is not excluded that the solvent intervenes between the relatively facile carbon-carbon double bond cleavages and attack upon the oximino grouping. In any event, the survival of the oxime grouping has enabled us to traverse a relatively simple path among a plethora of more complicated possibilities—some of which were in fact reduced to practice before the transformation of XLVIII into XLIX was realized. Our next conversion involves the further modification of the newly generated 1,5 dicarbonyl system in XLIX, and in that connection a special point deserves comment. *A priori* the cyclization of such an unsymmetrically substituted diketone might occur in either of two alternative directions. If a proton be abstracted by a basic reagent from the more hindered of the two acetyl groupings, the attack of the resulting anionoid carbon atom upon the relatively unhindered carbonyl group would lead to one type of cyclohexenone. We have found in several instances, closely related to XLIX, that the course of reaction just specified is that observed when cyclization is brought about by hydroxide ions. However, in sharp contrast, when cyclization is catalyzed by pyrrolidine acetate in methanol, the cyclization cleanly follows the alternative course. Clearly in these cases reaction is initiated, and its ultimate course determined, by enamine formation at the less hindered of the two carbonyl groups. Thus, when XLIX is cyclized by the pyrrolidine acetate/methanol procedure, and the resulting cyclohexenone is mesylated in the usual way, L is obtained. Now, before proceeding to the crucial Beckmann change some further moulding of the array of carbons destined to constitute ring D was desirable. When the cyclohexenone (L) is subjected to the action of ozone in wet methyl acetate, followed first by periodic acid and then by diazomethane, the cyclohexenone ring is modified in the expected way, and the keto ester (LI) is obtained.

At this point a few general remarks about the Beckmann rearrangement are in order. Cyclopentanone oximes usually undergo the process with considerably more difficulty than cyclohexanone or open-chain oximes, for steric reasons which are clear in a general way and need not be explicated here. In the case at hand, it might well be expected that the change would be more than ordinarily difficult, since the transition state for the rearrangement involves electron deficiency in the carbon framework, and the relevant atoms involved in LI are not far distant from a number of strongly electron-attracting groups. Beyond that, the steric factors which render the change difficult for simple cyclopentanones are probably exacerbated within the tricyclic framework of LI. In the light of these considerations we were not

surprised to find that our mesylate was indeed quite extraordinarily loath to undergo the desired transformation. Nevertheless, when **LI** \equiv **LII** is heated in methanol for two hours at 170° in the presence of polystyrene sulphonic acid, the desired Beckmann change takes place smoothly, with formation of a new six-membered lactam ring, and placement of the second nitrogen atom in its proper relation to the first. But that is not all that occurs. The diacylamine system of **LII** is cleaved by methanol, giving on the one hand a simple lactam ring and on the other an acetic ester side-chain.



compare:



Further, the newly placed nucleophilic nitrogen atom is five atoms removed from an electrophilic carbonyl group, to the carbon atom of which a new bond is made. Beyond that, there is yet another potentiality for bond formation within **LII**, consequent upon the presence of an activated methyl group six atoms removed from an ester carbonyl group—and this possibility too is realized. In sum, the product obtained when the mesylate (**LII**) is subjected to the specified conditions is the compound **LIII**, which we have more-or-less jocularly dubbed " α -cornorsterone". The 'corr' in this appellation represents our hope that the substance is destined one day to be transformed into a corrin; the 'norsterone' devolves from the fact that **LIII** is a ketone whose skeleton is that of a norsteroid if the nitrogens be ignored; and finally, if the name be pronounced in Slurvian, it becomes "cornerstone"! Of rather more consequence are the specific structural features present in α -cornorsterone, perhaps the most important of which is the newly formed five-membered nitrogen-containing ring, which may be seen to be the actual required ring D of our projected A/D intermediate. We observe that the

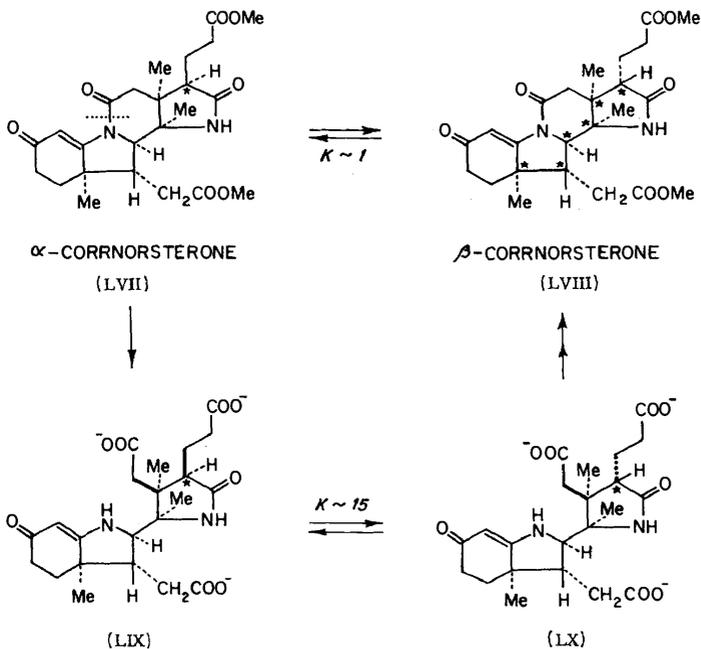
ring bears, as needed, an acetic ester chain and a methyl group, properly situated and oriented. It should be noted, at least briefly, that the formation of ring D in this way provides an elegant solution to a subtle and potentially very formidable problem of differentiation within polyfunctional intermediates such as those at hand. The dimensions of the problem may be intimated by alluding to the predicament we should have been in had the newly placed nitrogen atom interacted with the carbomethoxyl group of the just mentioned acetic ester chain to produce a five-membered lactam system. Two further points about α -cortnorsterone deserve special mention. First, the relatively simple method of producing this important intermediate, which I have just described, was not that by which we made it for the first time. It was in fact first produced by an alternative, experimentally very elegant, but far longer and less practical route, and subsequently several other paths were laid down before the one outlined here was discovered. Second, it is of no little interest that the β -acylamino- α,β -unsaturated carbonyl system embedded within the tricyclic skeleton in α -cortnorsterone (heavy lines in LIII) was one with whose highly characteristic physical—especially spectroscopic—properties we had already become familiar at a much earlier stage in our work, since an identical system is present in our earlier intermediate pentacyclenone (cf. LV \equiv LVI \equiv XLVI). This fortunate coincidence permitted us to recognize and sequester α -cortnorsterone relatively easily from reaction mixtures in which it was first, rather inefficiently, produced.

Our studies of the chemical properties of pentacyclenone had also been of some importance in that they had suggested that the first stages in the necessary further modification of α -cortnorsterone might not present a special occasion for difficulty. Thus, it is clear that the newly formed six-membered lactam ring in α -cortnorsterone has no place in our projected A/D building block, and that it must be cleaved (dotted line in LIII), to free the ring D nitrogen atom, and at the same time generate the requisite acetic acid chain, appositely attached to ring A. Now, we had found that the similar six-membered lactam ring in pentacyclenone was relatively easily cleaved by alkaline reagents (dotted line in LV). The opening of the ring by hydroxide ion could easily be followed spectroscopically. It was also possible to show that solutions containing the cleaved material, when acidified, gave a fugitive imino acid, which spontaneously reverted to pentacyclenone in a short time. It was therefore a most sinister development when we discovered that the six-membered lactam ring of α -cortnorsterone was quite unaffected by the treatment which had sufficed for the ready cleavage of the very similar structural unit in pentacyclenone. Indeed, although the ring in α -cortnorsterone could be cleaved by alkaline reagents, the process required extreme conditions and a large excess of alkali. The cleaved product produced in these circumstances was present in so overwhelming an admixture of inert or harmful concomitants as to be useless for further synthetic work. Furthermore, when such solutions containing cleaved material were acidified, in this case the corresponding free acid was so fugitive that its presence could not even be detected spectroscopically. Nor could the resistance of the lactam ring to opening be overcome through the use of acidic reagents. Many ingenious schemes were devised in attempts

to coax the recalcitrant ring to behave properly; their ingenuity was exceeded only by the uniformity with which they turned out to be unsuccessful. The temptation at this stage of our work to feel that we had been hoist with the petard of a subtle and inherent flaw in our plan was strong, but fortunately a most remarkable observation came to our rescue. α -Corticosterone is by far the major product of the acid-catalyzed transformation of the oxime mesylate (LII). However, we had isolated in the pure crystalline form, and characterized fully, a tiny amount of a very minor concomitant product. The properties of this second substance were strikingly similar to those of α -corticosterone; its ultraviolet spectrum, its infrared spectrum, its nuclear magnetic resonance spectrum and its mass spectrum—each of them rich in detail—differed only in minor respects from those of the major product. We could only conclude that the two substances must be stereoisomers, and should that be the case they could differ only in the orientation of the propionic ester chain attached to the five-membered lactam ring of each molecule. It will be recalled that at this stage we had no way of knowing the absolute configuration, at the pertinent centre, in the precursors of α -corticosterone, and in that substance itself. Now, with both diastereomers in hand, we could be confident that one of them represented the desired natural configuration. But which was which? Comparison of certain features in the nuclear magnetic resonance spectra of the corticosterones and some rather similarly constituted monocyclic analogues, very liberally interpreted, had suggested a very highly tentative assignment of the unnatural configuration (LIII) to α -corticosterone. But the danger of such far-flung extrapolations is all too clear, and essentially we regarded the matter as *sub judice*. Now, when our fortunes in our battle with the lactam ring of α -corticosterone were at their lowest ebb, we became mindful of a most remarkable fact. *The lactam ring in the isomer, β -corticosterone, is exceptionally easily cleaved by alkaline reagents.* Indeed, in this case the cleavage is far readier than that observed for pentacyclenone. At first sight this spectacular contrast between the α - and β -corticosterones seemed so astonishing as perhaps to call in question our identification of the relationship between the two substances. However, further reflection not only permitted the rationalization of the remarkable observations in terms of the accepted hypothesis, but provided an insight which was of very great consequence for our further progress, both in understanding and in practice.

Consider that when the lactam ring of α -corticosterone is cleaved, the resulting acetate chain must occupy considerably more space than is needed for the accommodation of the atoms of its precursor, and that in the highly cluttered molecular circumstances space is very much at a premium. Looking at the problem in these terms one must conclude that less space is available for the newly formed acetate chain in the case of the α -corticosterone cleavage than in the corresponding instance of β -corticosterone. How can this be? *Only if the propionic ester side-chain of α -corticosterone is attached to the five-membered lactam ring on the same side as the acetate chain generated when the lactam ring is cleaved.* In the case of β -corticosterone, then, the propionic ester chain must be on the opposite side of the lactam ring, and consequently, far less well placed to compete for space with the acetate chain. Thus, this interpretation of the dramatic contrast in the behaviour of the two corticoste-

sterones provided our first rather solid basis for the assignment of the structures LIII to α -cornnorsterone and LIV to β -cornnorsterone. But it did more than that: the clear implication of the analysis just presented was that if we should be able to effect equilibration between the cleaved forms of the two series, the material of the desired natural orientation should be heavily predominant. And indeed, such turned out to be the case. When α -cornnorsterone (LIII \equiv LVII) is heated for some time in a large excess of concentrated base, and the resulting solution is acidified and then



treated with diazomethane, pure crystalline β -cornnorsterone (LIV \equiv LVIII) can be isolated in almost 90 per cent yield, and about 6 per cent of α -cornnorsterone can be recovered. Clearly under these conditions the hydrolyzed forms (LIX and LX) are equilibrated, and as expected, the substance having the acetate and propionate chains out of one another's way predominates; it is of some interest that direct equilibration of the cornnorsterones, which may be brought about by the action of methoxide ion in scrupulously dried methanol solution, leads to a mixture comprised of about equal parts of the two isomers. We now had a simple and practical method in hand for the preparation of β -cornnorsterone, and had reason to believe that in that substance the stereochemical problem presented by the six contiguous asymmetric centres of the A/D portion of the vitamin B₁₂ molecule had been solved in its entirety. But while some of the configurational assignments in β -cornnorsterone were absolute, others were based upon argument, however cogent, and we deemed it desirable to be able to build our further work upon a completely assured basis. Consequently, a single crystal of brominated β -cornnorsterone was subjected to three dimensional

x-ray crystallographic analysis, with the result shown in *Figure 3*. It was most gratifying to observe that the gross structure, and every stereochemical detail which we felt we had built into our construction, were rigorously confirmed. It may be noticed that the determination was carried out on a crystal of bromo- β -cornorsterone of the unnatural absolute configuration; a rather special instance, perhaps, of our advantage in not having to waste material of the natural series in exploratory, developmental and confirmatory experiments!

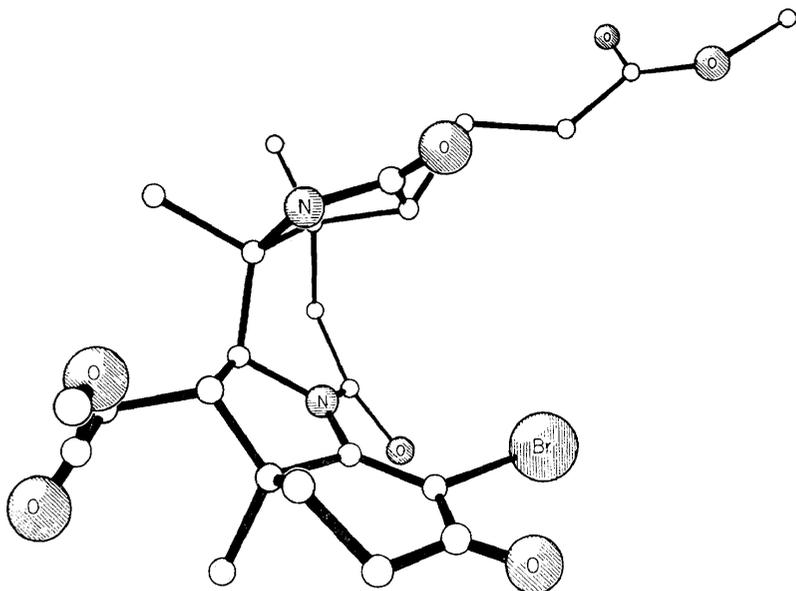
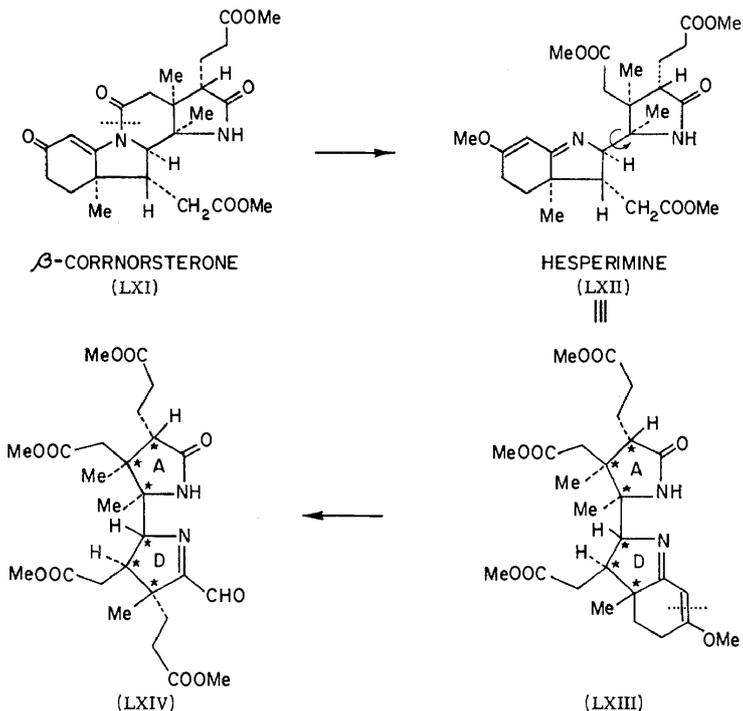


Figure 3

The lability of the six-membered lactam ring of β -cornorsterone to alkali is also exhibited in the presence of acidic reagents. When β -cornorsterone (LXI) is treated with methanolic hydrogen chloride, the ring is cleaved and hesperimine (LXII \equiv LXIII) is produced. On one side of the point of cleavage (cf. dotted line in LXI), a needed acetic ester chain, attached to ring A, is generated. It is of much importance that at the other terminus the initially formed vinylogous amide system is further modified, with the production of the novel vinylogous iminoether grouping present in hesperimine; for our experience leaves no doubt that the simple product of the addition of the elements of methanol to the lactam bond would be highly unstable relative to its precursor—that is to say, the *O*-methylation of the vinylogous amide system, and the consequent deprival of the second nitrogen atom of its hydrogen atom is crucial in permitting the open system to survive. Beyond that, as we shall see shortly, the appearance in hesperimine of that same vinylogous iminoether system opened novel possibilities for further developments which would otherwise not have been accessible.

I may perhaps interject a few comments upon our adoption of the name "hesperimine" for the intermediate (LXII). It has been a loose but fairly consistent practice of the Zürich group to refer to the B/C moiety of the

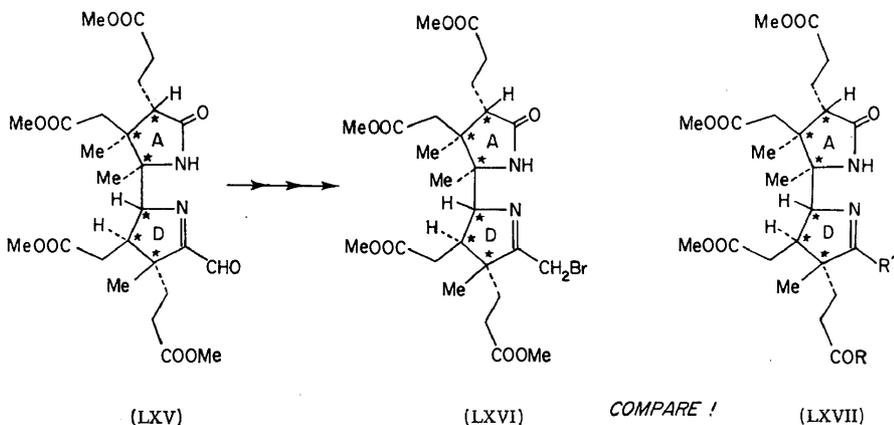
vitamin B₁₂ molecule as the 'eastern' half, and the A/D area as the 'western' part. By contrast, Cambridge custom has tended to utilize the terms 'right' and 'left'. In such trivial affairs consistency is hardly a matter of moment, and we need not cavil at the action of the Zürich group in adopting the name "dextrolin" for a B/C building block which they first succeeded in constructing. When in Cambridge, more tardily, the A/D intermediate (LXII \equiv LXIII) became available, the prior onomastic action of the Zürich group suggested some such designation as "sinistraline" for the new



intermediate. But reference to the Oxford English Dictionary gave reason for pause; listed under 'sinister' and 'sinistral' was a most formidable array of ominous correlatives: prejudicial, unfavourable, evil, bad, base, pertaining to misfortune or disaster, adverse, unlucky, unsound, and many others. Some bolder spirits would not have hesitated to attach a name with such inauspicious connotations to our precious and hard-won substance, upon which much in the way of hope still needed to be placed, but more superstitious counsel prevailed and the designation "hesperimine" was adopted. So in a way each of the groups paid a subtle compliment to the other.

I have alluded already to the special opportunities for further progress inherent in the newly constituted vinylous iminoether system of hesperimine (LXIII). When that substance is ozonized in methanol solution at -80° , and the reaction mixture is then treated with dimethylsulphide, an exceptionally smooth cleavage occurs (cf. dotted line in LXIII), and the aldehyde (LXIV) is produced. It is most remarkable that the powerful electrophilic

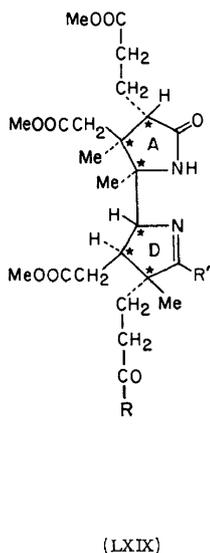
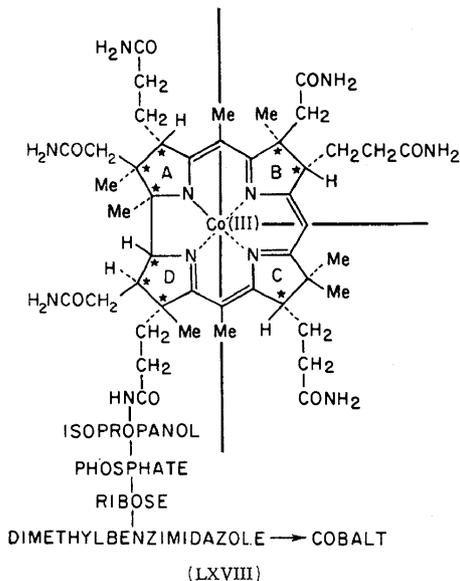
reagent ozone is utterly without effect upon the carbon–nitrogen double bond of hesperimine or that of the product aldehyde (LXIV). Very probably we observe here an example of the protection of a reactive grouping in the simplest of ways: the carbon–nitrogen double bond is so completely immersed in the sea of proximate substituents that the ozone is simply denied access to the grouping which it would otherwise destroy. Indeed, this same factor undoubtedly permits the existence of the aldehyde (LXIV) as a relatively stable and manipulable substance. To our knowledge no other α -iminoaldehydes are known, and in any but exceptional circumstances comparable with those obtaining in LXIV compounds of that class would be expected to be highly reactive and unstable. And beyond that, the same circumstances play a role in the next step in the final fashioning of our A/D intermediate. Thus, the aldehyde (LXIV \equiv LXV) is reduced by excess sodium boro-



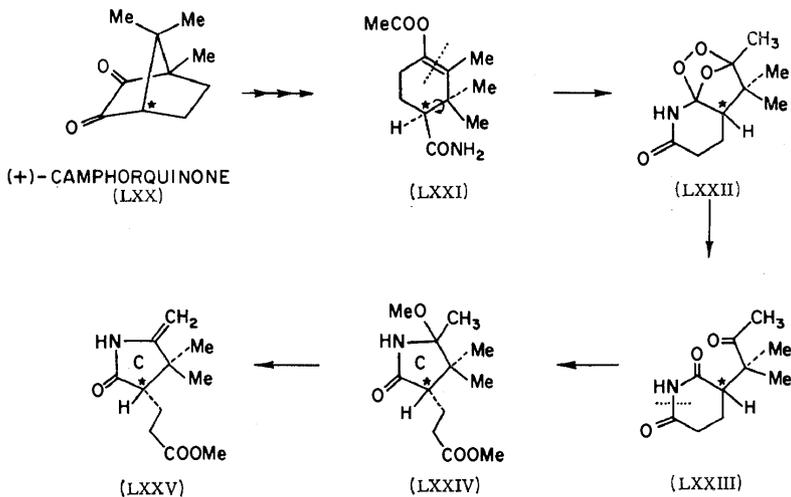
hydride in methanol to the corresponding alcohol. Again, no attack upon the carbon–nitrogen double bond takes place. When now the resulting primary alcohol is treated with methane sulphonyl chloride and pyridine, a mesylate is obtained which, with lithium bromide in dimethylformamide, affords the bromide (LXVI). Comparison of the structure of the bromide (LXVI) with LXVII (\equiv II \equiv LXIX) will reveal that with these few final stages, our initial objective has been reached, subject only to a single qualification: clearly an analogue of LXVI must be prepared, in which the propionic ester chain attached to ring D may be distinguished from the other side chains terminating in carbomethoxyl groups.

Let us now examine once again the full structure (LXVIII \equiv I) of our ultimate objective, vitamin B₁₂. I have completed the description of the preparation of a building block (LXIX) which represents the left-hand portion of the vitamin B₁₂ molecule. Now let us see how the story of the construction of a corresponding B/C intermediate unfolds.

I shall commence with the relatively simple problem of preparing an intermediate which represents ring C. Manasse and Samuel showed long ago that camphorquinone is converted under the influence of acidic reagents into a trimethylcyclohexanone carboxylic acid, whose structure was elucidated in subsequent studies by Simonsen and by Chakravarti. Cornforth

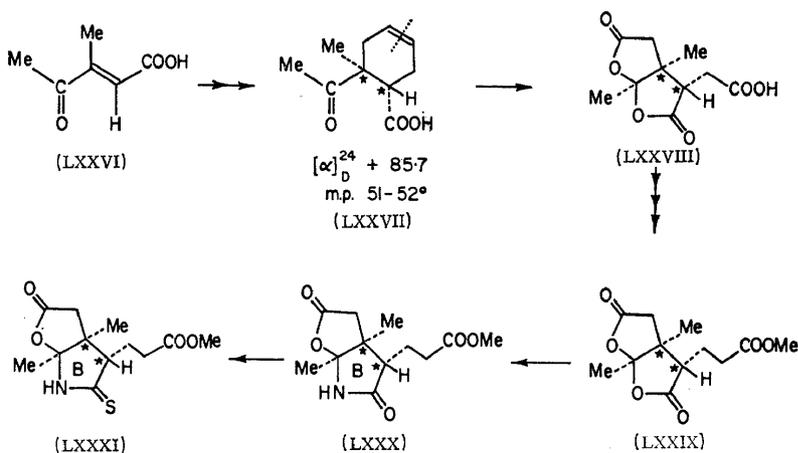


was the first to recognize that this keto-acid possesses structural elements very similar to those present in ring C of vitamin B₁₂. In the particular use to which we put these circumstances, *dextro*-rotatory camphorquinone (LXX) is converted by boron fluoride and acetic anhydride to an acetoxy-trimethylcyclohexene carboxylic acid, which is converted, through the chloride, to the corresponding amide (LXXI). Provided that the initial reaction be carried out under sufficiently mild conditions, optical purity is retained, and it will be noted that the choice of *dextro*-rotatory camphorquinone leads directly to the desired absolute configuration of the single asymmetric carbon atom needed in the intermediate (LXXI). Now, when LXXI is treated with ozone, a rather amusing sequence of changes occurs



which results in the 'false' ozonide (LXXII)—false in that it appears to be the product of ozonization of quite another substance than its actual precursor. Cleavage of the double bond (cf. dotted line in LXXI) leads at one terminus to a mixed anhydride grouping and at the other to a ketone oxide grouping. Reaction of the mixed anhydride function with the amide group leads to a succinimide, one of whose reactive carbonyl groups participates in cycloaddition with the ketone oxide grouping to afford the observed product (LXXII). When the latter is reduced, using zinc and methanol, the ketosuccinimide (LXXIII) is obtained. This intermediate in its turn is transformed by methanolic hydrogen chloride into the methoxylactam (LXXIV), which, when pyrolyzed, loses the elements of methanol and affords the unsaturated lactam (LXXV); the latter represents a complete solution to the problem presented by ring C.

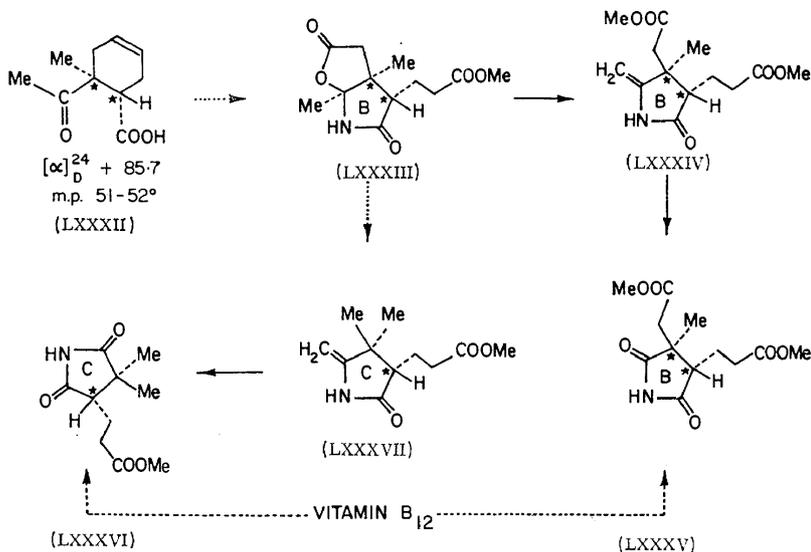
We may now turn our attention to ring B. Here our starting point is the β -methyl- β -acetylacrylic acid (LXXVI); it is important to note that the



stereochemical stage is set by the *trans* arrangement of the acetyl and carboxyl groups in this ethylenic intermediate. The unsaturated acid, in benzene solution, combines with butadiene in the presence of stannic chloride to give the cyclohexene acid (LXXVII), which is readily resolved by fractional crystallization of the diastereomeric salts which it forms with optically active α -phenylethylamine. Since the Diels-Alder reaction takes place in a stereospecific way, the methyl and carboxyl groups of the acid are situated on the same side of the newly formed cyclohexene ring, as desired. I shall anticipate a bit by pointing out that it is the *dextro*-rotatory acid which possesses the required absolute configuration shown. When this *dextro*-rotatory acid is oxidized with chromic acid, the dilactone acid (LXXVIII) is produced. It is clear that initially, cleavage of the double bond (dotted line in LXXVII) gives a new carboxyl group on either side of the point of cleavage; one of the new carboxyl groups, and that already present in LXXVII, cooperate with the ketonic carbonyl group in the construction of the dilactone system of LXXVIII. Next, the acetic acid chain in the dilactone is lengthened by the Arndt-Eistert method. The acid is converted into

its chloride, thence by reaction with diazomethane into a diazoketone, which with methanol in the presence of silver ion gives, through the intermediacy of a ketene, the expected dilactone propionic ester (LXXIX). This substance when treated with ammonia in methanol gives the lactam (LXXX), which represents essentially a complete solution of the ring B problem, though in detail, for reasons which will appear shortly, the lactam is further transformed by the action of phosphorus pentasulphide into the thiolactam (LXXXI). The replacement of the desired, rather than the alternative, oxygen atom by nitrogen when ammonia acts upon the dilactone (LXXIX) perhaps deserves a brief further comment. The desired lactam (LXXX) was in fact first prepared by a more elaborate method designed to insure the correct placement of the nitrogen atom. Only later was it discovered that the simple, direct reaction gave the desired product; later still it was found that both possible modes of attack of ammonia upon the dilactone (LXXIX) do occur and that the products can be equilibrated. It was then possible so to arrange the experimental conditions as to provide a simple direct route for the preparation of the desired lactam (LXXX).

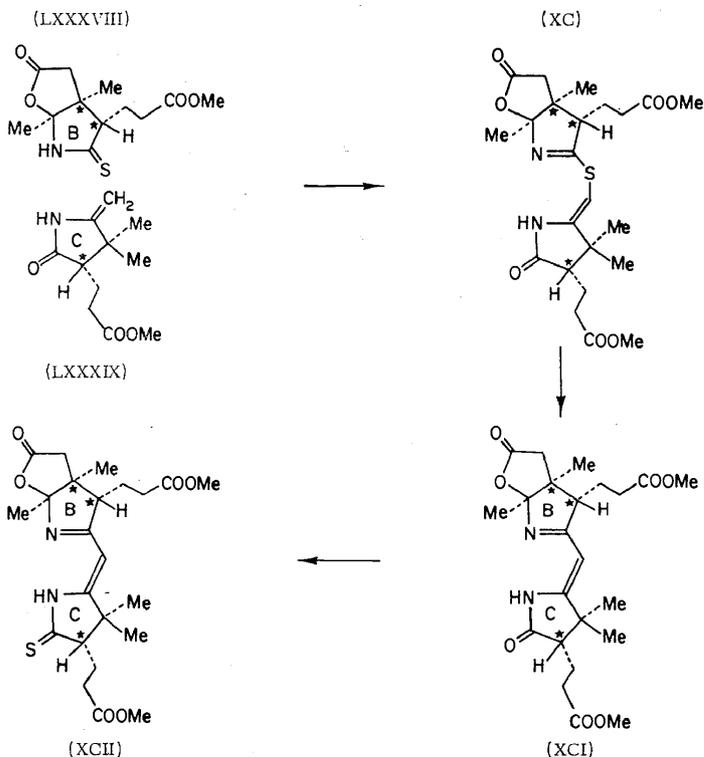
I have already alluded to the fact that I have anticipated in assigning the absolute configuration shown in LXXVII to the *dextro*-rotatory cyclohexene acid. The manner in which this assignment was in fact made presents several points of interest. When the lactam (LXXX \equiv LXXXIII) from the *dextro*-rotatory acid (LXXVI \equiv LXXXII) is treated with diazomethane



in methanol in the presence of a catalytic amount of sodium methoxide, the enamide ester (LXXXIV) is produced, and when the latter is ozonized, a succinimide (LXXXV) is obtained. This same succinimide is obtained when heptamethyl cobyrinate—the product of methanolysis of vitamin B₁₂ itself—is ozonized. Another product of this latter ozonization is the succinimide (LXXXVI). This substance was correlated with our ring C intermediate (LXXV \equiv LXXXVII) from which it was also produced by

ozonization. Finally, separate methods were developed in Zürich and Cambridge for the correlation of ring B with ring C, through conversion of LXXXIII into LXXXVII. These interrelationships left no doubt of the correctness of our assignments of absolute configuration, and, in that they correlate vitamin B₁₂ with *dextro*-rotatory camphor, they may be regarded as affording chemical confirmation of the assignment of the absolute configuration of the vitamin—as if that were needed!

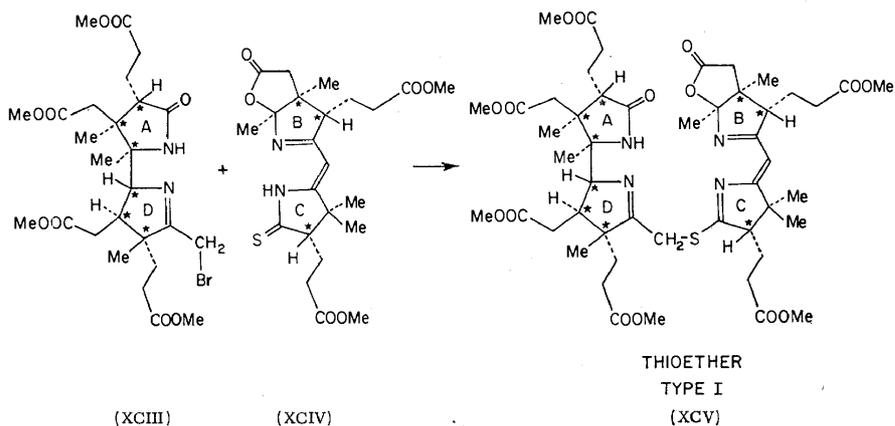
With intermediates representing rings B and C in hand, each optically active and of the required absolute configuration, it was possible to come to grips with the problem of combining the two. It will be noted that the construction of a new carbon-carbon bond is required, joining the nucleophilic terminal methylene carbon atom of the ring C component (LXXXV \equiv LXXXIX), and the electrophilic carbon atom of the thiocarbonyl group



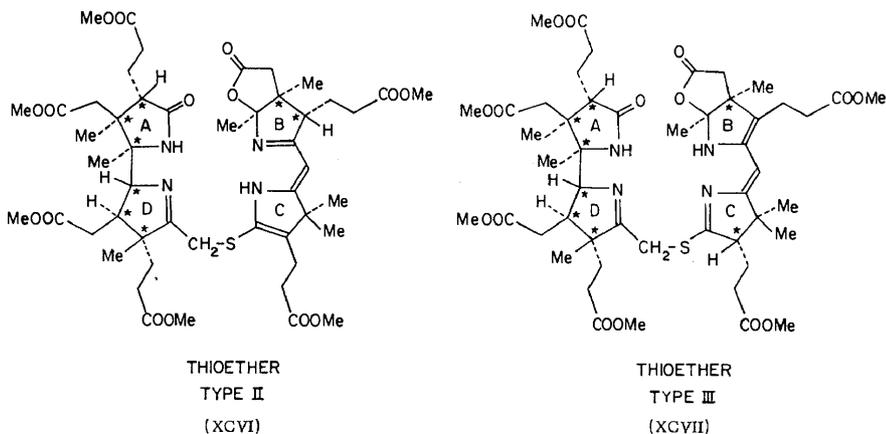
of the ring B component (LXXXI \equiv LXXXVIII). It is possible to envisage various ways of bringing about direct union in that fashion, and indeed in simple model cases such combinations could be realized. However, in the actual case at hand, all attempts at direct carbon-carbon bond formation were fruitless. The unsuccessful outcome of such experiments is not surprising when one contemplates the extraordinarily high steric demand consequent upon the heavy accumulation of substituents in each of the intermediates which must be brought together. Moreover, recognition of these circumstances provided the key to the discovery of a powerful indirect method for

effecting the desired union. We all know that enforced propinquity often leads on to greater intimacy, and we were able to provide a new illustration of that maxim. When the thiolactam (LXXXVIII) and the enamide (LXXXIX) are treated with benzoyl peroxide in methylene chloride solution, in the presence of a catalytic amount of hydrogen chloride, the sulphur-bridged intermediate (XC) is produced. It is clear that this reaction involves prior oxidation of the thiolactam to a disulphide, which in turn is attacked by the enamide, with cleavage of the newly formed weak sulphur-sulphur bond. Since the second stage releases a molecule of the original thiolactam, it is only necessary to adjust the concentration of the reactants properly to bring about smooth formation of the sulphur-bridged intermediate. Now, in the latter, rings A and B are forcibly confined in proximate portions of space, and the formation of the needed carbon-carbon bond would be an intramolecular process—and, it may be added, a process for which the stage is further favourably set in XC by the complementary electrical characters of the carbon atoms whose union is desired. In fact, when XC is heated with triethylphosphite in xylene solution, the sulphur atom is torn from the molecule, the desired carbon-carbon linkage is formed, and the B/C intermediate (XCI) is produced. Although we cannot specify the mechanism of the reaction in detail, it is not unlikely that something resembling an episulphide is involved. With the construction of XCI the problem of preparing a B/C building block, fully adorned with apposite substituents, correctly oriented in an absolute sense, has been completed. But in order to set the stage for the next chapter, the lactam (XCI) is converted into the thiolactam (XCII). In this case the conversion is rather more difficult than it had been in the instance of our ring B intermediates (cf. LXXX → LXXXI); here it is necessary to treat the iminoether derived from XCI by the action of trimethylxonium fluoborate with hydrogen sulphide.

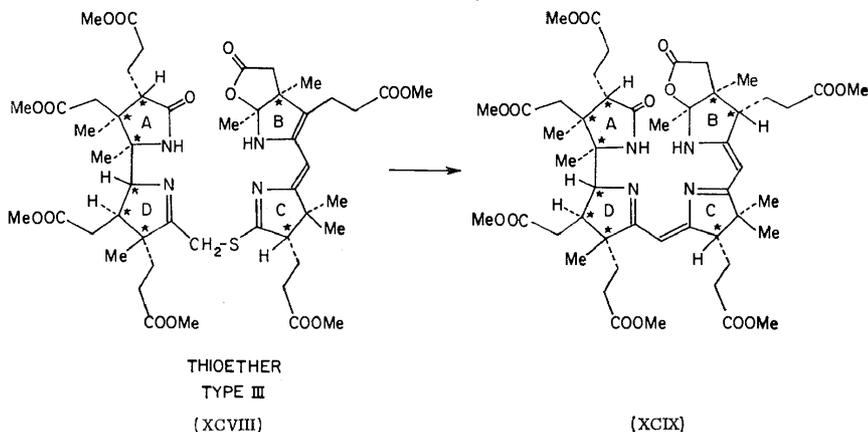
Now two intermediates were available, representing together all four rings—A, B, C, and D—of vitamin B₁₂, containing all of the asymmetric elements correctly oriented, and so laden with groups of complementary reactivity as to permit us to envisage a realistic possibility of forging a link between them. And indeed, the bromide (LXVI ≡ XCIII) and the thiolactam (XCII ≡ XCIV), in tertiary butanol solution in the presence of



a mole of potassium tertiary butoxide, combine smoothly to give the thioether (XCV), which we have designated thioether Type I. This initial product of combination is a highly labile substance. When attempts are made to isolate it in the pure form by chromatography on neutral alumina, it is transformed into two closely related isomers (XCVI and XCVII), designated thioether Type II and thioether Type III, respectively, of which the latter,

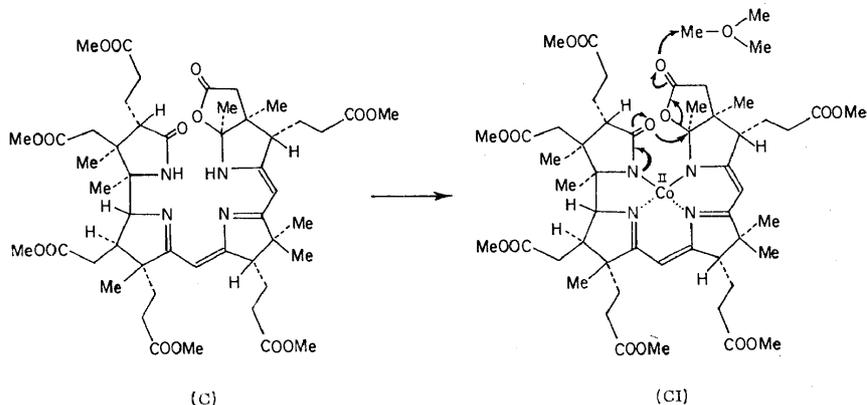


fortunately, predominates. While attempts to effect desulphurization of the former have not been attended by success, the thioether Type III (XCVII \equiv XCVIII) is smoothly desulphurized, when it is treated in benzene solution with triphenylphosphine and boron trifluoride, to give the intermediate XCIX, which contains the desired new direct carbon-carbon link. Now at last all four rings have been assembled in the same intermediate!

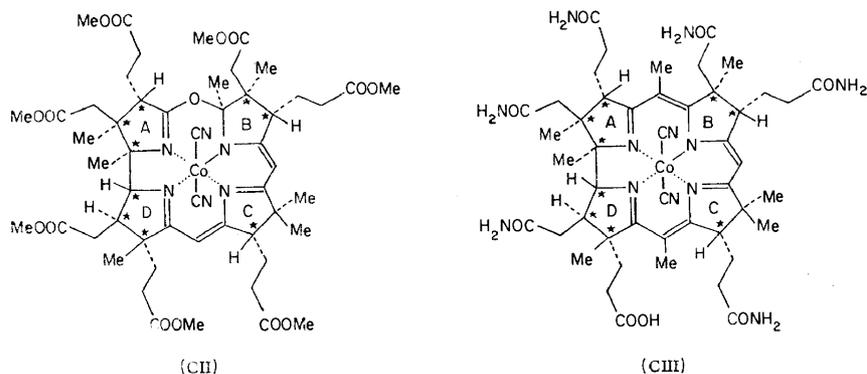


Our attempts so far to proceed further have followed lines discovered in model studies, and it need present no occasion for surprise that the real case has exhibited substantial differences in behaviour from the simple analogues. It is no problem to introduce divalent cobalt into XCIX (\equiv C), through treatment with cobalt perchlorate in acetonitrile in the presence of

diisopropylethylamine. But when the resulting cobalt compound (CI) was treated with trimethyloxonium fluoborate, with the object of converting the ring A lactam grouping into an iminoester system, we found that Nature had other things in mind. The reaction course followed is that



suggested by the arrows in CI, and leads, after appropriate ancillary operations, to the cyclic ether (CII). I think it is fair to say that this substance, which represents our present furthestmost point of advance, bears an encouraging resemblance to our final objective, cobyrinic acid (CIII), and



that although considerable work remains to be done in detail—some of which may present no little difficulty—the main outlines of a path which will lead to the completion of the synthesis of vitamin B₁₂ are now apparent.

Reference

- 1 R. B. Woodward. *Aromaticity*, Special Publication No. 21, The Chemical Society, London, 1967, p. 217.