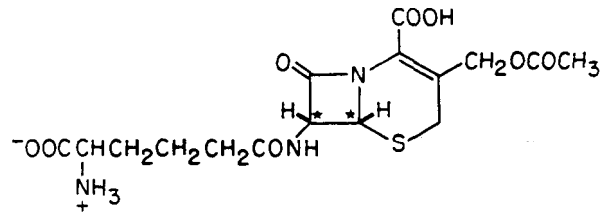
R.B. WOODWARD

Recent advances in the chemistry of natural products

Nobel Lecture, December 11, 1965

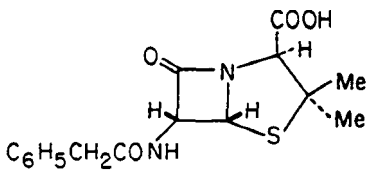
The Nobel Prize in Chemistry for 1965 has been awarded for contributions to the art of chemical synthesis. It gives me much pleasure to record here my gratification with the citation, which properly signalizes an exciting and significant aspect of synthetic activity. But that aspect is one which is more readily - and I dare say more effectively - exemplified and epitomized than it is articulated and summarized. Having here this morning the responsibility of delivering a lecture on a topic related to the work - for which the Prize was awarded, I have chosen to present an account of an entirely new and hitherto unreported investigation which, I hope, will illuminate many facets of the spirit of contemporary work in chemical synthesis.

Cephalosporin C, a product of the metabolism of *Cephalosporium acremonium,* was isolated in 1955 by Newton and Abraham[1] in an investigation notable for its perspicacity as well as its painstaking attention to detail. The investigation of the structure of the metabolite was successfully concluded in 1961 through studies in which both chemical[2] and X-ray crystallographic[3] techniques were employed. The molecular array (I) thus laid bare strikes one



I

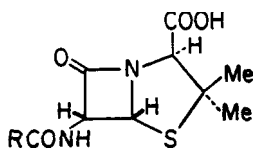
at once as having affinities with a hitherto well-known class of substances which has constituted one of the most challenging and recalcitrant synthetic objectives of our generation. I refer of course to the penicillins, of which penicillin G (II) - one of the earliest known and one which has been widely used in medicine - may serve as an example. There can be few organic chemists



II

who do not know the fascinating history of the penicillins[4]. How, following up an early observation of Alexander Fleming, Chain and Florey isolated the first penicillin shortly after the outbreak of the Second World War. How the powerful practical desiderata of those trying times led to the establishment of a mammoth British/American program which had as its objectives the determination of the structure and the synthesis of the penicillins. How the chemical investigations, and especially the X-ray crystallographic studies of Dorothy Hodgkin conquered the structural problem, and how despite the best efforts of probably the largest number of chemists ever concentrated upon a single objective the synthetic problem had not been solved when the program was brought to a close at the end of the War. Many chemists continued to be fascinated by the problem, and some were still willing to gamble their skill against its obstinacy. In 1959, after more than a decade of intensive investigation, John Sheehan[5] succeeded in the development of methods by which penicillins could be prepared by total synthesis. That these methods have not come into practical use does not detract from this major achievement, but only emphasizes that the challenge presented to the synthetic chemist by the penicillins has not been exhausted.

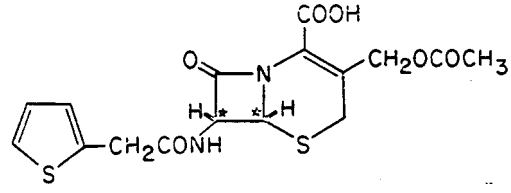
A parenthesis is probably desirable at this point in order to allay some concern among those who have not been initiated in these matters. I have used the plural term "penicillins" because Nature provides several closely related substances, differing only in the acyl group attached to the nitrogen atom which is itself situated a to the lactam carbonyl group of the general structure (III). Furthermore, chemists have found ways of removing these acyl groups from the natural representatives of the class, and attaching entirely new and



III

R	*Penicillin*	*R*	*Penicillin*
$C_6H_5CH_2$	G	$CH_3(CH_2)_6$	K
$CH_3CH_2CH{:}CHCH_2$	F	$C_6H_5OCH_2$	V
p-$HOC_6H_4CH_2$	X	$CH_2{:}CHCH_2SCH_2$	O

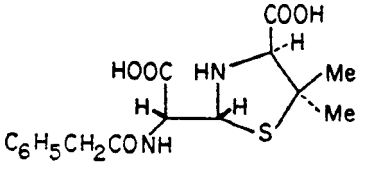
different groupings to the nitrogen atom thus freed. In this way, many hundreds of artificial penicillins have been prepared. The situation is similar in respect to cephalosporin C, in that a whole class of cephalosporins has been created by replacement of the ω-[D-(—)-α-aminoadipoyl] residue of the natural metabolite by numerous other acyl groups. In both classes - the penicillins and the cephalosporins - some of the derived substances possess properties which confer on them special utility in medicine. Thus, cephalosporin C itself possesses antimicrobial activity of a relatively low order of magnitude, which, however, early attracted special interest because it persisted against organisms which had become resistant to the penicillins. In some of the derived cephalosporins this especially interesting aspect of the antimicrobial activity is retained, while at the same time the level of activity is much heightened. Further, the activity extends over the range of Gram-negative and Gram-positive organisms. Consequently, some of these substances, of which cephalothin (IV) may serve as an example[6], have already achieved utility in medicine as broad-spectrum antibiotics of low toxicity, effective against penicillin-resistant organisms.



IV

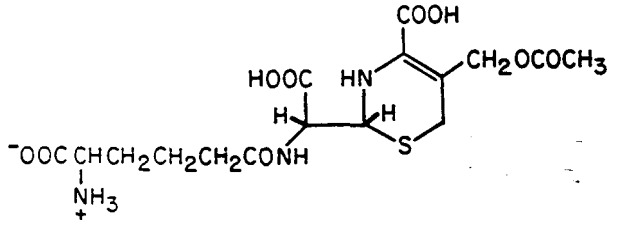
in considering the development of a plan for the synthesis of any complicated substance, it is always desirable to look at the problem from an entirely fresh point of view. Nevertheless, in the case at hand, it was pertinent to examine whether the experience gained and the results achieved in synthetic studies on the penicillins might be usefully applicable to the structurally related cephalosporins. We rejected this possibility at the outset for several reasons. I have already alluded to the fact that the known penicillin syntheses,

hard-won, brilliant achievements though they are, are lacking in practicality. Further, the problems which had had to be overcome in devising methods for penicillin synthesis had been quite difficult enough without adding to them the intricacies which would have been associated with the achievement of stereospecificity in the creation of asymmetric intermediates, and this aspect had been slighted. Finally, a special chemical point was of much importance. The β -lactam ring common to the penicillins and the cephalosporins is highly susceptible to hydrolytic cleavage. In the case, for example, of penicillin G (II), the product of this hydrolysis is penicilloic acid (V). The synthesis of



V

penicilloic acid and its analogs, at least by non-stereospecific methods, was a relatively simple problem, and by far the largest number of attempts to synthesize penicillins - and the only successful ones - involved the deceptively simple task of removing the elements of water from penicilloic acid analogs, with closure of the four-membered β-lactam ring. In the case of the cephalosporins the situation is strikingly different. Here the β-lactam ring is also easily cleaved, but the proximate product of the hydrolysis, which must have the structure (VI), is not a known substance. Its intricate and delicate con-

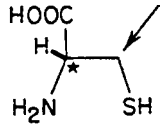


VI

stitution is such that it does not survive even the mild conditions of its generation from the corresponding lactam. Clearly then, it would be unwise to essay the synthesis of a cepahalosporin from such a hitherto unknown and obviously highly fugitive precursor.

Often in the course of synthetic work one or two key ideas set the style,

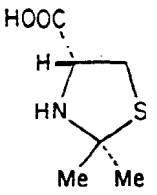
development, and outcome of the investigation, while providing the flexibility essential for any long journey through unknown territory, beset with perils which at best can be only dimly foreseen. In planning our synthesis of cephalosporin the first of these definitive concepts was our choice of L(+)-cysteine (VII) as our starting material. This readily available substance pos-



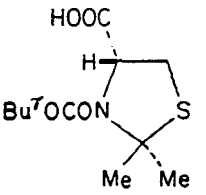
VII

sesses a two-carbon backbone to which are attached a carboxyl group, an α-nitrogen atom and a β-sulfur atom-in short, it presents in ready-made fashion a large portion of the crucial substituted β-lactam moiety of the cephalospot-ins. Furthermore, it is optically active, and the groups arranged about its one asymmetric carbon atom (starred in VII) are oriented in an absolute stereochemical sense precisely as are the similar groups in the objective; that is to say, as soon as the decision to use cysteine had been made, our stereochemical problem was in a sense already halfsolved, since the cephalosporin nucleus contains only one further asymmetric center (*cf.* stars in I and IV). On the other hand, advantageous as this choice obviously was in many ways, it was also clear that associated with it was a special problem which could by no means be viewed lightly. The cysteine molecule is a tightly assembled package of highly reactive groupings. The amino group, the sulfhydryl group, the carboxyl group, and the α-methine group each possess characteristic features of chemical reactivity, and represent points at which ready modification of the molecule might be expected. But the only remaining feature of the molecule, the simple saturated β-methylene group, represents a point at which there is little or no precedent for chemical attack. And yet, in the light of our plan we must in some way introduce a nitrogen atom at that point, preferably in a stereospecific manner (*cf.* arrow in VII). Further, even assuming that a method should be discovered for overcoming the defences of the molecule at that strong point, it was clear that we should be dealing with intermediates containing two electronegative atoms bound to the same carbon atom - a situation well known for its potentialities in conferring sensitivity and instability upon molecules so constituted. In sum, our initial decision placed us in the exhilarating position of having to make a discovery, and of being prepared to deal with substances of an especially precarious constitution.

Our first actual operations consisted quite naturally in so modifying the cysteine structure as to depress the reactivity of the amino, sulfhydryl, and carboxyl groups. Thus, the amino acid was first converted by reaction with acetone into the thiazolidine (VIII)', which in its turn reacted with *tert*-

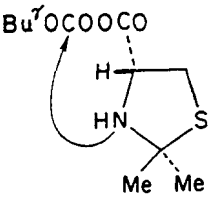


VIII

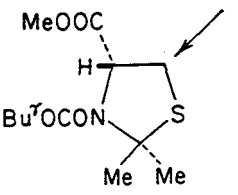


IX

butyloxycarbonyl chloride in the presence of pyridine to give the corresponding *N-tert*-butyloxycarbonyl compound (IX). Some special interest attaches to the fact that the acylation reaction undoubtedly takes place through internal delivery of the *N-tert*-butyloxycarbonyl group, which first becomes attached at the carboxyl site to give the mixed anhydride (X). The acylated thiazolidine was next converted into the methyl ester (XI) with diazomethane.



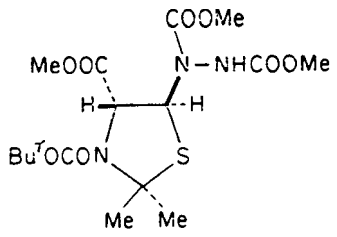
X



XI

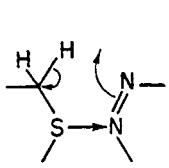
These three simple changes had sufficed to convert the cysteine molecule into one whose methylene group (arrow in XI) might now enjoy a far better relative position in respect to reactivity as compared with that same grouping in the original cysteine. But they also served another function: by incorporating the methylene group in a ring, and thereby rendering rotation about the α,β carbon-carbon bond impossible we had set the stage for bringing about transformations at the methylene group in a stereospecific manner.

I shall not detail here the many weapons which were brought into play against that still expectedly recalcitrant methylene grouping. Suffice it to say that the protected ester (XI) reacted with excess dimethyl azodicarboxylate at 105° during forty-five hours to give the hydrazo diester (XII) in almost quantitative yield. It is of special interest that we have been able to assemble

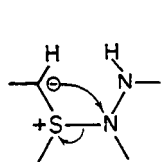


XII

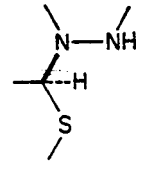
evidence which suggests that this novel reaction involves initial attack of the sulfur atom upon the azo grouping, and that the formation of this bond may be concerted with migration of hydrogen from the methylene group to the second nitrogen atom (*cf.* XIII+ XIV-+ XV). Thus, if substances containing



XIII

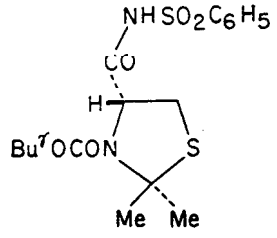


XIV



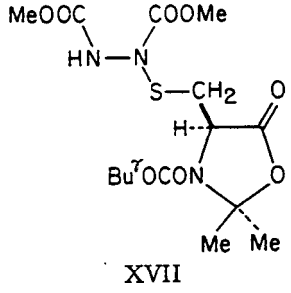
XV

free active hydrogen, such as the acid (IX), and the benzenesulfonyl amide (XVI) are brought into reaction with dimethyl azodicarboxylate, attack upon

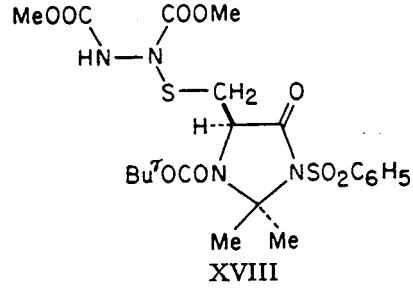


XVI

a methylene group is not observed, and the products (XVII and XVIII)

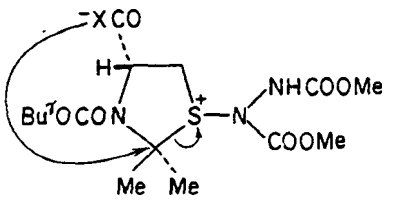


XVII

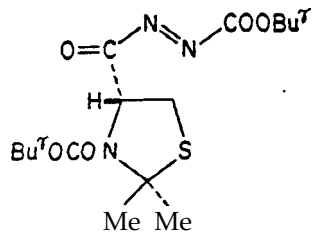


XVIII

contain an actual sulfur-nitrogen bond (*cf.* XIX). Further, we have been unable to observe an intramolecular version of the reaction - for example, with the compound (XX) - a circumstance which we connect with the very unfavourable geometry, in this case, of a transition state in which hydrogen moves as sulfur attacks nitrogen. Another special point of interest is that the

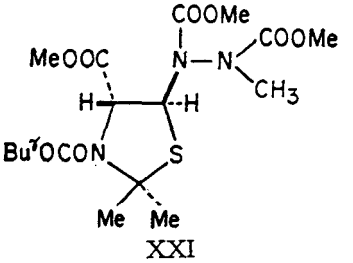


XIX



x x

conditions for the reaction, simple though they are, must be adhered to rigorously. At lower temperatures reaction is too slow to be useful, while if the temperature is raised only a small amount, the reaction is much less clean, and among the products is the *N*-methylated derivative (XXI) ! In any event,

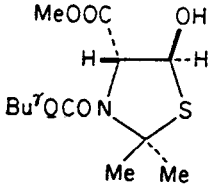


XXI

the new reaction was propitious in that we had achieved a substitution at the desired site, and in that the newly attached grouping was one which might be expected to exhibit selective reactivity. A very important point is that the reaction is stereospecific; the hydrazo diester grouping is introduced solely on one side of the ring. Clearly, this result is associated with the presence in (XI) of the carbomethoxyl grouping, whose bulk deprives the attacking moiety of the opportunity for attachment on the alternative side of the relatively rigid five-membered ring. Of course, the stereospecificity here exhibited was in a way of precisely the wrong kind, since what we required was the introduction of a nitrogen atom on the same side of the ring as the carbomethoxyl group. But this simply meant that we must now replace the newly introduced group with inversion of configuration at the β-carbon atom, a

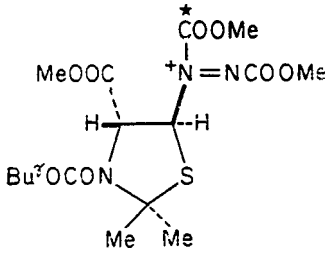
task which we might have taken in hand with little apprehension had it not been for the presence of the sulfur atom, whose attachment to the center at which inversion was required might render invertible intermediates non-existent or malefactory.

When the hydrazo diester (XII) was oxidized in boiling benzene for two hours, using somewhat more than two moles of lead tetraacetate, and the resulting reaction mixture was treated with excess anhydrous sodium acetate in boiling dry methanol for twenty-four hours, the *trans*-hydroxy ester (XXII) was produced. This sequence is not as simple as it might at first appear,

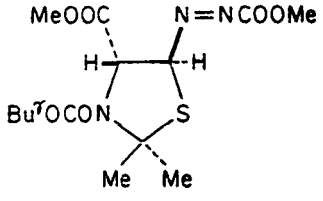


XXII

and we know some of the intermediary stages through which it proceeds. It is reasonable to suppose that the hydrazo compound, like all hydrazine derivatives, is susceptible to removal of two electrons by an oxidant. The resulting species (XXIII) must lose a carbomethoxyl group (starred) very readily to an

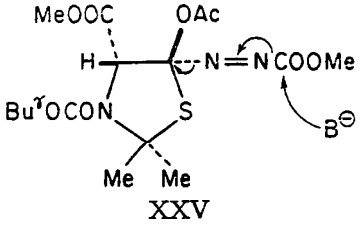


XXIII



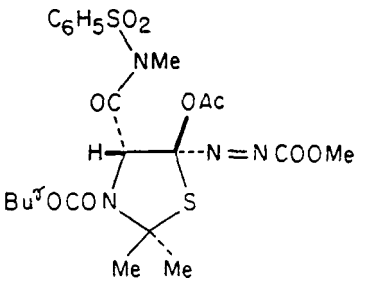
XXIV

available nucleophile. The product (XXIV) is of a type which would be expected to be transformed further by lead tetraacetate into an acetoxyazo compound (XXV); the spectroscopic evidence for the presence of such an

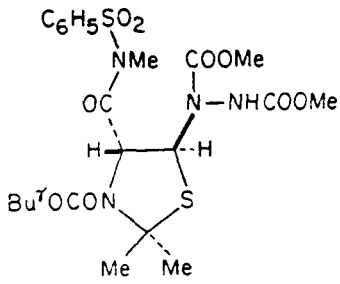


XXV

intermediate after the conclusion of the lead tetraacetate oxidation is convincing, when compared with the parallel characteristics of a similar compound (XXVI), isolated in the crystalline state and fully characterized, after

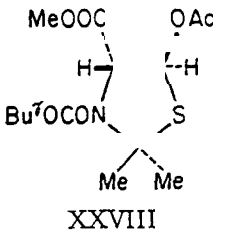


XXVI

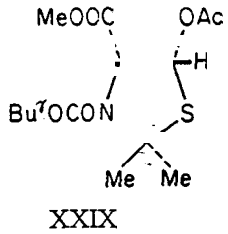


XXVII

oxidation of the sulfonamide (XXVII). The next change is the loss of a second carbomethoxyl group, again under nucleophilic attack (arrows in XXV), followed by loss of elementary nitrogen, and accession of a proton to the β-carbon atom. The final change is a simple base-catalyzed methanolysis of the acetoxy group. Special note should be made of the fact that these transformations involve a replacement at an asymmetric center. This replacement is stereoselective, in that by far the major product is the *trans*-acetoxy ester (XXVIII); no doubt the bulk of the adjacent carbomethoxyl group plays its role in forcing the acetoxy group into the more spacious location. None the less, a small amount of the *cis*-acetoxy ester (XXIX) is produced, but for reasons which will be developed shortly, this minor departure from stereospecificity is corrected almost at once.

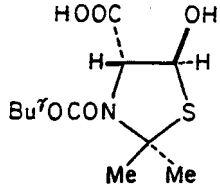


XXVIII

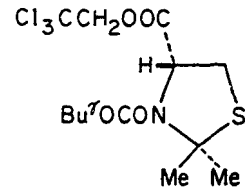


XXIX

The very existence of the *trans*-hydroxy ester (XXII) deserves special comment. It should first be noted that its structure was established with definitive rigor through its preparation by the action of diazomethane upon the corresponding acid (XXX). This acid was synthesized by a series of reactions similar to those outlined above, except that the carboxyl group of the thiazolidine (IX) was protected by the attachment of a β,β,β-trichloroethyl

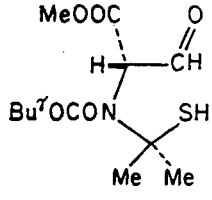


XXX

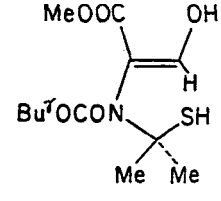


XXXI

grouping (*cf.* XXXI), which was removed reductively after introduction of the β-hydroxy group. The structure of the hydroxy acid was established beyond any question by a complete three-dimensional X-ray crystallographic study, brilliantly executed by Dr. Gougoutas in Cambridge. We have already alluded to the potentiality for instability inherent in the attachment of more than one electronegative atom to the same carbon atom, and it will be useful at this point to illustrate in some detail the factors which might have hurled us from the plateau on which we were-now standing. Thus, the hydroxy ester (XXII) is an obvious candidate for participation in ring-chain tautomerism with an open-chain isomer (XXXII), which in its turn, possessing as it does a β-dicarbonyl system, could readily undergo essentially irreversible tautomerization to a stable β-hydroxyacrylic ester (XXXIII).

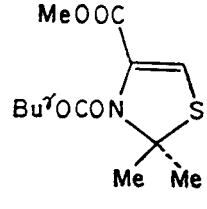


XXXII



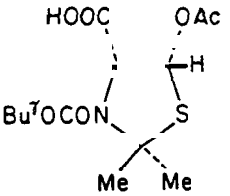
XXXIII

This same substance might alternatively be reached directly through a ready β-elimination of the sulfur atom. Either of these sulfhydryl tautomers might well lose thioacetone to give the corresponding *N*-monosubstituted urethane. Finally, it would not have been surprising if the newly introduced hydroxyl group, or indeed any of the newly introduced β-disposed group-

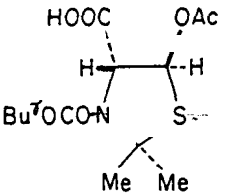


XXXIV

ings along the way, had been susceptible of ready elimination with the formation of the thiazoline (XXXIV). That the hydroxy ester is in the event a stable manipulable compound-that it does not too readily succumb to these potentialities for its self-destruction - was a major new result of our investigation so far. We can in fact say something more about these potentialities at this time. It was mentioned above that at one stage in the replacement of the hydrazo diester grouping by the hydroxyl group, a certain amount of *cis*-acetoxy ester (XXIX) is produced at an intermediary stage. Yet the sole product of the whole sequence is the *trans*-hydroxy ester (XXII). From our work with the trichloroethyl ester (XXXI), the *cis*- and *trans*-acetoxy acids (XXXV) and (XXVI) have been isolated in the pure, crystalline state. Each

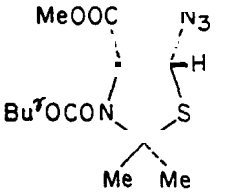


XXXV

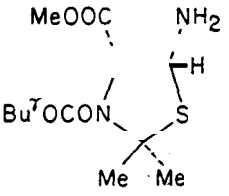


XXXVI

of these stereoisomeric substances is transformed on hydrolysis into the same *trans*-hydroxy compound (XXX)*. Thus, it is clear that the hydroxy compounds do participate in ring-chain tautomerism, but that reclosure of the open-chain aldehyde (*cf.* XXXII) is so much favored over enolization of the aldehyde group, or loss of thioacetone, that these latter changes, which would have been fatal to our prospects, do not obtrude.



XXXVII

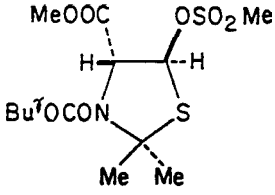


XXXVIII

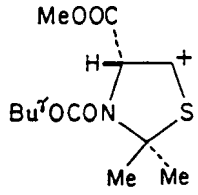
The hydroxy ester (XXII) was now transformed by treatment in dimethylformamide with excess diisopropylethylamine and methanesulfonyl chloride, followed by concentrated aqueous sodium azide, to the *cis*-azido ester (XXXVII), which was in its turn reduced in methanol solution by aluminum

* Subsequent to the delivery of this lecture, we have demonstrated explicitly that the pure *cis*-acetoxy ester (XXIX) is converted in high yield to the *trans*-hydroxy ester (XXII) under our methanolysis conditions.

amalgam at -15° during twenty-four hours to the *cis*-amino ester (XXXVIII). The structure of the latter was again confirmed by a complete X-ray crystallographic study carried out by Dr. Gougoutas. It is clear that this sequence of changes involves the intermediacy of the methanesulfonyl derivative (XXXIX), which does in the event undergo normal bimolecular nucleo-

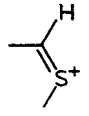


XXXIX



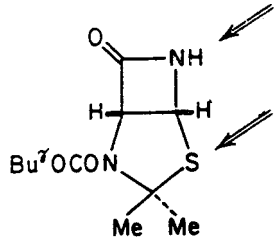
XL

philic displacement with inversion, in the classic mold, when attacked by azide ion. The dread possibility that the intermediary sulfonate might be too readily susceptible of ionization to a cation (XL), which would have led on to the thiazoline (XXXIV), or to stereochemically indiscriminate or undesired substitution at the β-carbon atom, was fortunately not manifest. No doubt avoidance of this danger is associated with the predictable relatively high energy of the electronic configuration (XII).



XLI

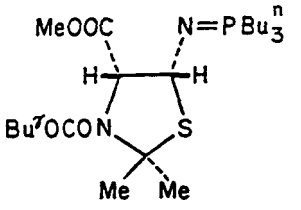
At this point we had succeeded in the major objective of introducing a properly oriented nitrogen atom into the β-position of the cysteine moiety. In short, the entire stereochemical problem presented by the cephalosporins had now been solved. It is appropriate here to introduce the second of the key ideas upon which our general plan was based. It was that we should attempt the preparation of the β - lactam (XLII), having it in mind that this substance,



XLII

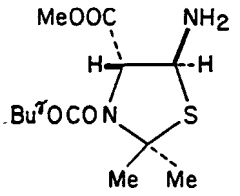
if procurable, would contain the basic structural elements common to the cephalosporins and the penicillins, and that it might serve as the source of a wide variety of known - and new - substances through the fusion of new rings at the presumably reactive nitrogen and sulfur atoms (arrows in XIII). The *cis*- amino ester (XXXVIII) now in hand differed from the desired lactam only by the elements of a molecule ofmethanol. The attachment of the amino and carbomethoxyl groups in (XXXVIII) to a relatively rigid ring system might be expected to favor formation of a new ring, and it was an interesting feature of the X-ray crystallographic study that the distance between the amino nitrogen atom and the carbonyl carbon atom was unusually low (2.82 A). In all these circumstances, we felt that the stage had been well set, and we were gratified to find that when the *cis*-amino ester was treated with triisobutylaluminum in toluene it was in fact converted into the desired β-lactam (XIII). Again, the very existence of this substance, containing as it does potentialities for annihilation parallel to those discussed above in some detail for the hydroxy ester (XXII), further compounded by the considerable strain within the β-lactam ring, represents a major result of our investigation. In view of the importance of the intermediate its structure was established in detail and with complete rigor through yet a further three-dimensional X-ray crystallographic investigation by Dr. Gougoutas.

Our success with the remarkable series of substances I have described must tend to obscure the venturous spirit without which their investigation could not have been taken in hand. Lest it still be felt that our concern with the lability and versatility of our intermediates had been chimerical, it may be mentioned that the phosphinimine (XLIII), prepared from the azido ester (XXXVII) and tri-*n*-butylphosphine, gave on hydrolysis even under the mildest conditions, in addition to the *cis*-amino ester (XXXVIII), appreci-

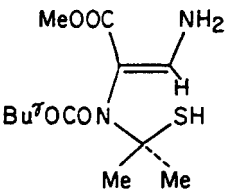


XLIII

able quantities of the *trans*- amino ester (XLIV) and the stable, non-cyclizable open-chain isomer (XIV)! Clearly, the formation of these substances involves subtly determined tautomeric changes closely parallel to those discussed in detail above in respect of the hydroxy ester (XXII).

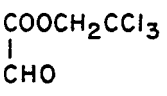


XLIV

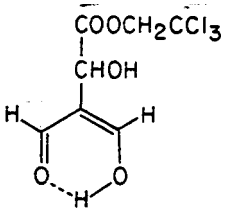


XLV

We were now ready to reduce to practice our presumption that the β-lactam (XIII) would be a versatile intermediate, capable of further development through fusion of further atomic groupings at the reactive nitrogen and sulfur atoms. In order to procure a suitable component for combination with the β-lactam, *d*- tartaric acid was converted into its di-β,β,β-trichloroethyl ester and the latter was oxidized, using sodium metaperiodate in aqueous methanol, to β,β,β -trichlorethyl glyoxylate (XLVI), isolated as the cor-

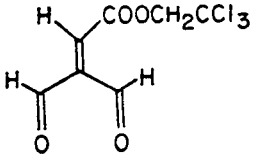


XLVI

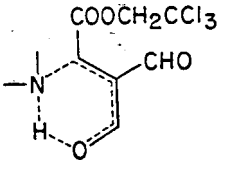


XLVII

responding hydrate. This substance was condensed in aqueous solution with the sodium salt of malondialdehyde to give an aldol of the structure (XL,VII). The aldol-condensation product in its turn lost a molecule of water when it was heated in normal octane, and the novel, highly reactive dialdehyde (XLVIII) was produced. This powerful electrophile was chosen in the hope



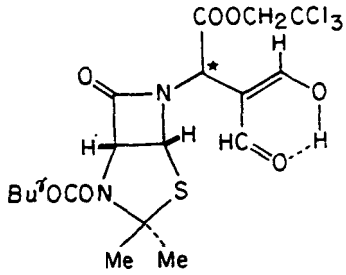
XLVIII



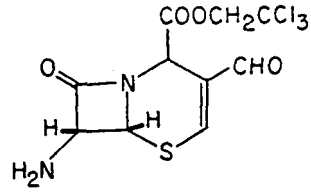
XLIX

that it might combine directly with a substance containing active hydrogen in a concerted cycloaddition process requiring no catalysis (*cf.* XLIX). The desire to avoid catalysts in reactions involving the β-lactam was of course a

consequence of our apprehension that such substances might well mobilize one or more of the capacities for self-destruction inherent in the intricate construction of our key intermediate.

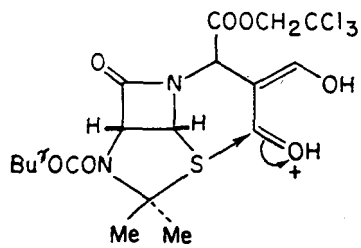


L



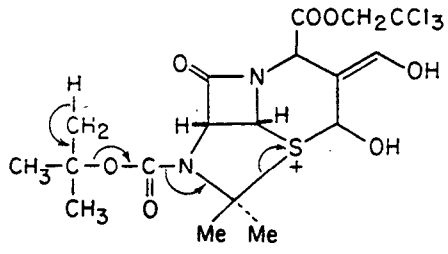
LI

In the event, when the β-lactam was heated with the dialdehyde in normal octane at 80° during sixteen hours, combination took place in the desired fashion, and the adduct (L) was produced. The latter in its turn, when allowed to stand in trifluoroacetic acid at room temperature during two and one- half hours, was transformed to the amino aldehyde (LI). The general nature of the processes involved in this latter change is clear. In particular, the crucial closure of the new six-membered ring is a consequence of the attack of the strongly electrophilic carbon atom of a protonated carbonyl group upon the nucleophilic sulfur atom (arrows in LII). The course of the ancillary changes

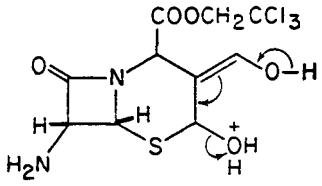


LII

need not be specified in detail. A number of more-or-less equivalent schemes may be considered, among which those portrayed in (LIII) and (LTV) should be included; a special point is that the amino group which is ultimately freed very probably appears at some time during reaction as the corresponding Schiff base (LV) - and we have found that Schiff bases are readily cleaved in trifluoroacetic acid solution. In any event, from the practical point of view it was most gratifying that the protecting groups - that is, the *N-tert*-butyl-

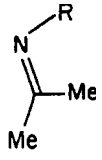


LIII



LIV

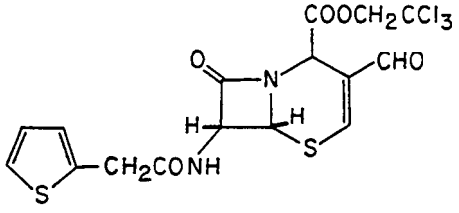
oxycarbonyl group and the bridging isopropylidene group which had so well served their several purposes and were now no longer wanted - were removed concomitantly with the crucial formation of the new six-membered ring.



LV

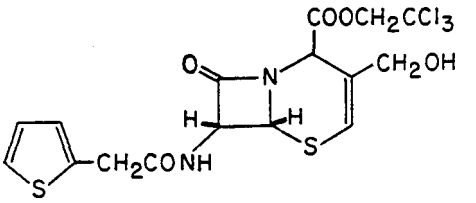
Mention should be made at this point of a special stereochemical detail. The adduct (L) contains one asymmetric carbon atom (starred in L) in addition to those present in the β-lactam. The combination reaction gives both of the *a priori* possible products, which have been separated and carefully characterized. Although the matter is under active study, we cannot as yet make rigorous stereochemical assignments for the two isomers. In any event, the point is not an important one from the practical point of view, since as we shall see shortly, asymmetry at the center under discussion is expunged in subsequent operations.

The amino aldehyde (LI) was next acylated in benzene solution with thiophene-2-acetyl chloride in the presence of pyridine, and the resulting amide (LVI) was reduced, using diborane in tetrahydrofiuane solution, to the



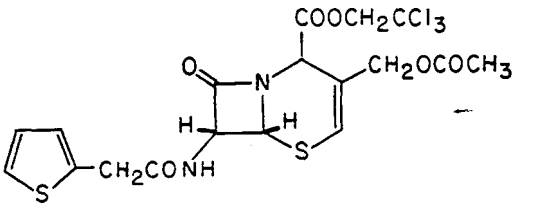
LVI

alcohol (LVII). The latter was acetylated in the normal way with acetic anhydride and pyridine to give isocephalothin β,β,β -trichloroethyl ester



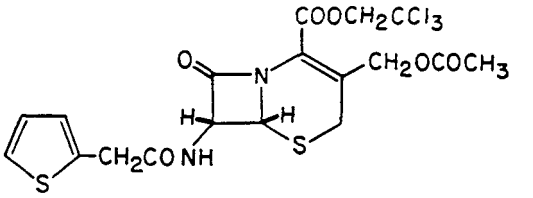
LVII

(LVIII). In its turn this β,γ -unsaturated ester was smoothly equilibrated with the corresponding α,β -unsaturated isomer - cephalothin β,β,β -trichloro



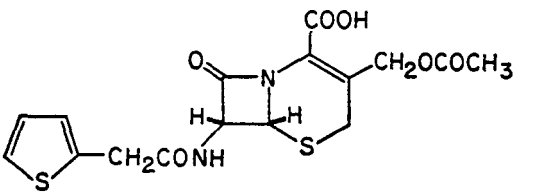
LVIII

ethyl ester (LIX) - when it was allowed to stand in anhydrous pyridine solution at room temperature for three days. Although the β,γ-unsaturated isomer is favored in this equilibrium ($K_{\text{normal/iso}} = 1/3$), the two isomers were



LIX

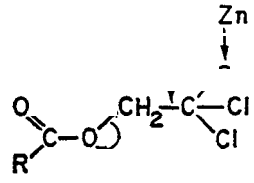
found to be readily separable by chromatography on silica gel. The conjugated ester was now reduced by zinc dust in 90% aqueous acetic acid at room temperature, and cephalothin (IV ≡ LX) was obtained. The properties of the



LX

synthetic substance were identical in all respects with those of material prepared from natural cephalosporin C[6].

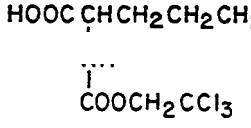
The final step in our synthesis of cephalothin, namely, the reductive removal of the β,β,β-trichloroethyl grouping is worthy of special comment. In planning our work it had been clear that the group destined to become the free carboxyl function of the final cephalosporin must appear in some protected form during the intermediary stages. Further, the protection must be such that it could be removed without doing violence to the highly sensitive β-lactam ring, which is especially prone to hydrolytic attack. Some years before, in Cambridge, Mr. Robert Kohler, faced with a not dissimilar problem, at my instigation investigated in a preliminary way the action of reductants upon β,β,β-trichloroethyl derivatives, with very encouraging results. The idea had been that an electron source could bring about a concerted elimination process (arrows in LXI) which might be highly favored on statistical grounds, and as well through the capacity of the chlorine atoms not directly



LXI

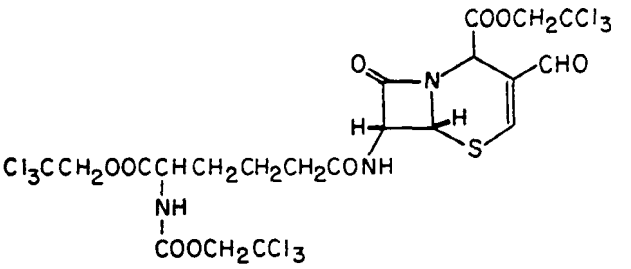
involved in the elimination process to facilitate electron accession in the transition state. As we have seen, and as further examples in the sequel will show, the grouping served the desired function admirably in our work in the cephalosporin field, and we suggest that it may well find some general utility; indeed, Dr. Fritz Eckstein, encouraged by his knowledge of our early studies, has very recently shown how it can be put to very good effect in work with the nucleotides[8].

We turn now to the completion of the synthesis of cephalosprin C itself. The amino aldehyde (LI) was in this case condensed in tetrahydrofurane solution with N-β,β,β-trichloroethyloxycarbonyl-D-(-)-α-aminoadipic acid (LXII) in the presence of dicyclohexylcarbodiimide. The resulting crude



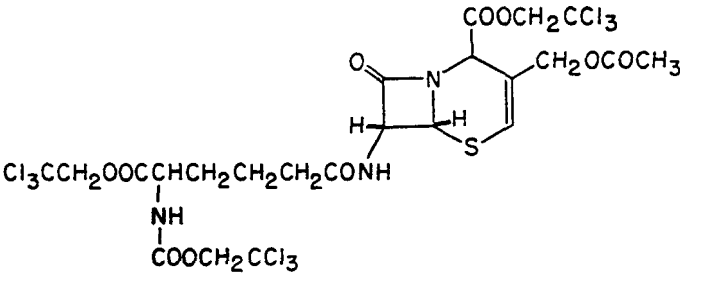
LXII

reaction mixture was then esterified directly, using β,β,β-trichloroethanol in methylene chloride in the presence of dicyclohexylcarbodiirnide and pyridine. This sequence of reactions gave two main products, which were readily separated by chromatography on silica gel using benzene/ethyl acetate (3/1) as eluant. The more polar of the two products was (LXIII), since it was



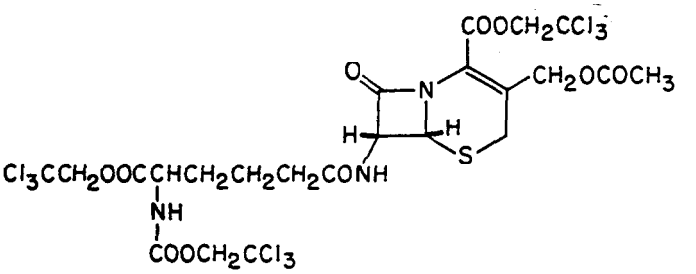
LXIII

converted by reduction in tetrahydrofurane with diborane, followed by acetylation with acetic anhydride/pyridine to the β,γ-unsaturated ester (LXIV).



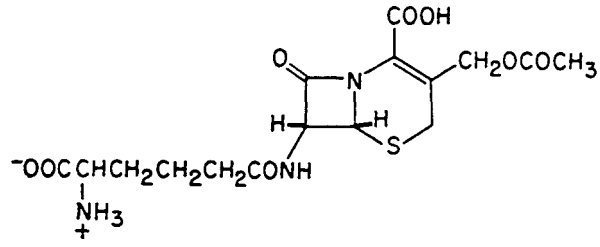
LXIV

As in the cephalothin series, this unconjugated ester was smoothly equilibrated with the conjugated isomer (LXV) when it was allowed to stand in pyridine



LXV

at room temperature for three days ($K_{normal/iso}$ = 1/4). Again, the two isomeric esters were readily separated, and the conjugated isomer was reduced by zinc dust and 90% aqueous acetic acid at 0° during two and one-half hours to synthetic cephalosporin C (LXVI = I). The identity of the synthetic material



LXVI

was in this case established through examination of its paper chromatographic behavior in several systems as well as through observation of its antibacterial activity against *Neisseria catarrhalis, Alcaligenes faecalis, Staphylococcus aureus* and *Bacillus subtilis.* Further the synthetic crystalline barium salt was identical in optical and spectroscopic properties with the salt of natural cephalosporin C.

It remains to express my very warm appreciation of the privilege of having been associated in the work which I have described with an outstanding group of colleagues at the Woodward Research Institute in Basel. Drs. Karl Heusler, Jacques Gosteli, Peter Naegeh, Wolfgang Oppolzer, Robert Ramage, Subramania Ranganathan, and Helmut Vorbrüggen are those whose high experimental skill and unflagging spirit brought this investigation to its successful conclusion, and I am glad to have this opportunity to express my admiration for their achievement.

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