SOME ASPECTS OF THE CHEMISTRY OF PENICILLIN

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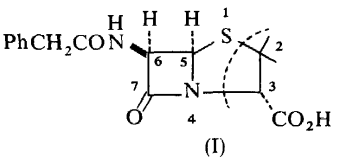
ABSTRACT

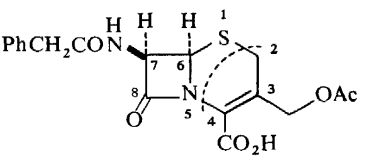
Some recent advances in the chemistry of penicillin are presented.

The group of antibiotics known as the penicillins have a unique position in chemistry. Not only were they the first type of antibiotic to be widely accepted in medical practice, but their chemistry proved to be of unusual interest and complexity. Modern fermentation plants have reduced the cost of the penicillins such that one should now regard these compounds as a potentially useful raw material, suitable as starting point for further transformations.

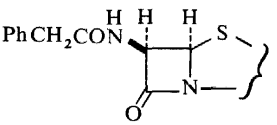
As an example one may quote the use of penicillins as precursors for the synthesis of the related, and important, antibiotics, the cephalosporins. The parent penam (I) and cephem (II) systems have similar chemical structures notably the identical β-lactam grouping (III) and the same C_5 isoprenoid-like unit to the right of the dotted lines in (I) and (II). The systems differ in that the cephalosporins have a higher oxidation level than the penicillins and a different substitution pattern on the C_5 unit.



(I)



(II)

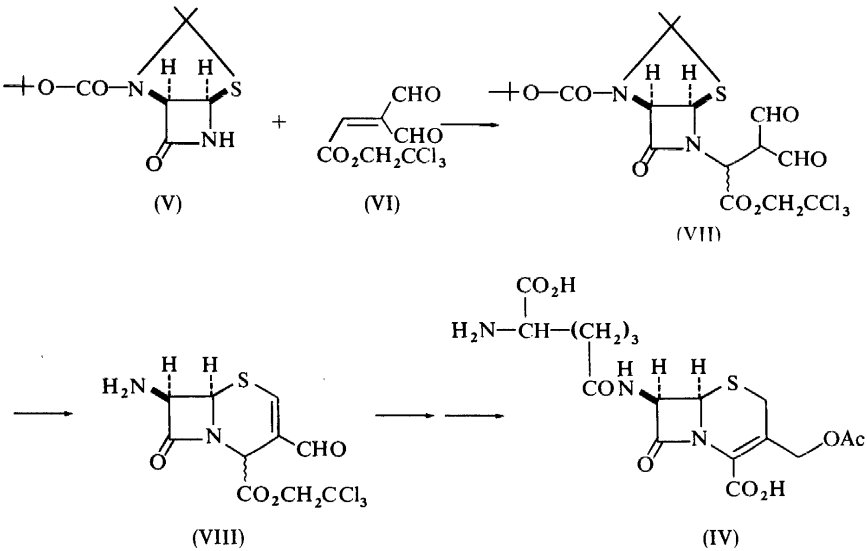


(III)

In order to convert chemically the penam into the cephem system two approaches can be conceived, both requiring modification of the thiazolidine ring without any concomitant change of the chemically sensitive β-lactam moiety. Firstly one could open the five-membered ring of the penam nucleus and cleave off the C_5 carbon chain from the β-lactam nitrogen, eventually replacing it with a new carbon framework of the desired substitution pattern.

P.A.C.— 33 —1, —B

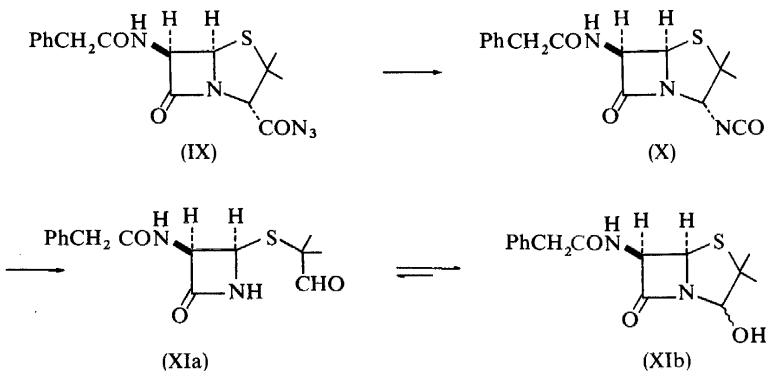
This approach has appeal in that it would permit considerable variation in the type of new grouping added. Woodward, Heusler *et al.*[1] have exemplified the second stage of this approach in a total synthesis of cephalosporin C (IV). Thus, the synthetic intermediate (V) was reacted with αβ-unsaturated dialdehyde ester (VI) to give the Michael addition product (VII). This, with trifluoroacetic acid, was transformed into the cephem derivative (VIII) and eventually into cephalosporin C (IV).



(V) (VI) (VII)

(VIII) (IV)

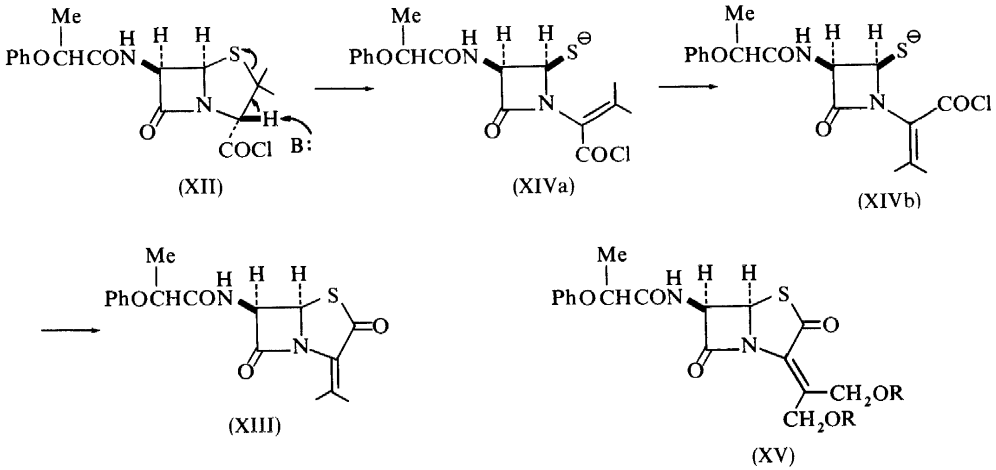
A simple method for opening the thiazolidine ring of the penam nucleus has been described by Sheehan and Brandt[2]. Curtius rearrangement of the penicillin acid azide (IX) afforded the isocyanate (X), which was readily hydrolysed to the corresponding aldehyde (XIa). The latter exists mainly in the closed form (XIb). All that is required is a method for breaking the remaining sulphur to carbon bond before adding a new carbon fragment.



(IX) (X)

(XIa) (XIb)

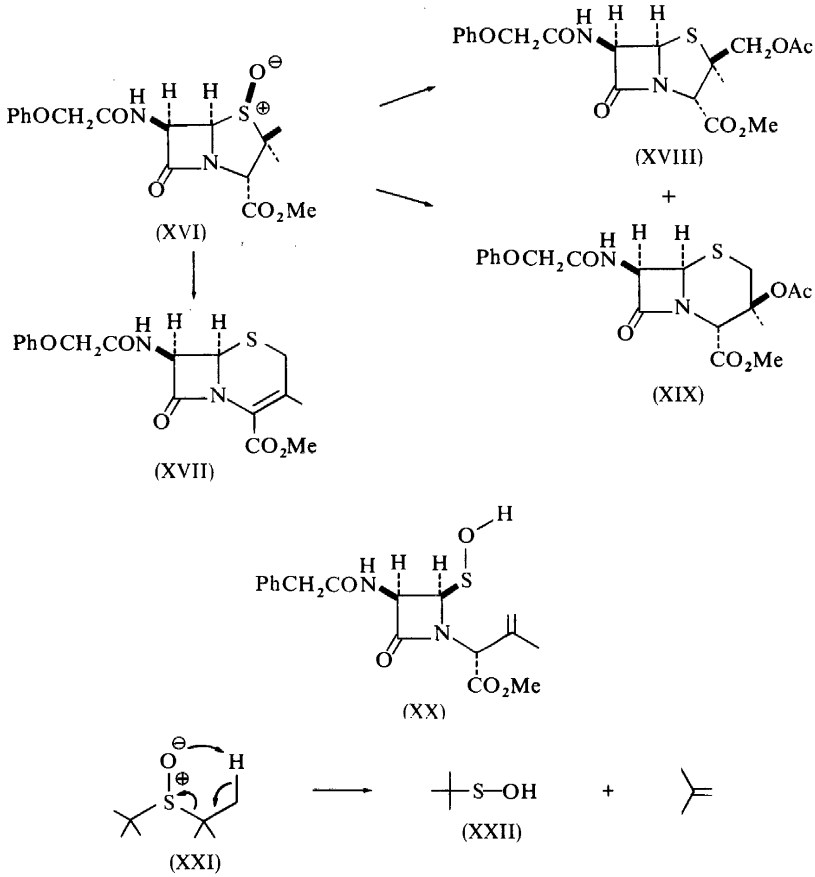
The second approach that could be adopted for the conversion of the penam nucleus into the cephem structure involves (formally) selective oxidation of the two methyl groups and ring expansion of the thiazolidine ring. To date two approaches have been investigated. Treatment of the acid chloride, or mixed anhydride, of a penicillanic acid (e.g. XII) with tertiary organic base induced a striking transformation into anhydropenicillin (XIII)[3]. This rearrangement proceeds via opening of the thiazolidine ring to the anion (XIVa), followed by rotation about the nitrogen–carbon bond to the conformer (XIVb) and recyclization to the thiolactone (XIII). Compared to penicillin, anhydro-compounds like (XIII) are remarkably stable.



However, under carefully controlled conditions the reaction has been reversed[4], the thiolactone ring being opened and recyclized to give back the penicillin. Oxidation of the allylic methyl groups of the anhydro-pencillin would modify the structure [e.g. to (XV)] and one could envisage opening of the thiolactone and recyclization to derivatives of the cephem type. Up to the present such transformations, although mechanistically feasible, have not been reported.

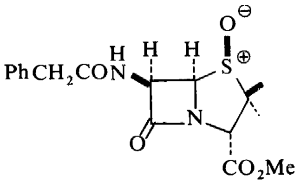
An alternative method for oxidizing the methyl groups employs a simple, yet elegant, approach. When a penam sulphoxide ester such as (XVI) was subjected to acid treatment a novel rearrangement reaction took place[5]. One of the products was desacetoxycephem derivative (XVII). Furthermore, with acetic anhydride the sulphoxide (XVI) afforded[6] two principal products, shown to be the substituted penicillin (XVIII) and the acetoxycepham (XIX).

We were intrigued by the mechanistic intricacies of the reactions described by Morin and his colleagues. We have subsequently investigated these sulphoxide rearrangements in some detail. The most likely common intermediate in the reactions is the sulphenic acid (XX). Some precedent exists for the formation of this acid thermally, since it has been shown by n.m.r. measurements and by chemical reactions that di-*t*-butylsulphoxide (XXI) dissociates, on heating at 80°, into the sulphenic acid (XXII) and isobutene[7]. That such an intermediate is also formed from the penam sulphoxides was demonstrated by the experiments summarized in the sequel.

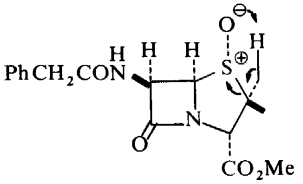


Oxidation of a penicillin ester normally affords the (*S*)-sulphoxide, for example benzylpenicillin methyl ester gives the sulphoxide (XXIIIa). In contrast, oxidation of this ester with iodobenzene dichloride in aqueous pyridine[8] gave the enantiomeric[9] (*R*)-sulphoxide (XXIIIb), also prepared independently by the Eli Lilly group[10]. We noted that the (*R*)-sulphoxide readily rearranged to the (*S*)-isomer simply on heating in benzene. It seemed to us that this reaction must be a thermal elimination by a six-electron sigmatropic transition state and involving the 2α-methyl group [see (XXIIIb)] to furnish the sulphenic acid (XXIVa). Recyclization of the sulphenic acid on to the ethylenic linkage to give the normal (*S*)- i.e. β-sulphoxide would require rotation about the C_2—C_3 bond [(XXIVa) → (XXIVb)] and delivery of the sulphenic acid proton to form the 2β-methyl group of the sulphoxide (XXV, X = H). We were able to confirm this mechanistic explanation by running the reaction in the presence of deuterated *t*-butanol, which exchanged the sulphenic acid proton for deuterium and thus gave, on recyclization, the 2β-monodeuteromethyl-derivative (XXV, X = D). The incorporation and configuration of the deuterium were shown by mass spectrometry and n.m.r. analysis[11]. These experiments not only demonstrate the existence

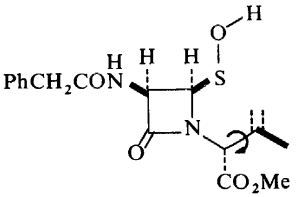
of the sulphenic acid (XX), but show also that it must have a relatively long life in order to allow for the rotation about the C_2—C_3 bond. Some comparable deuterium incorporation experiments have been independently reported by Cooper[12].



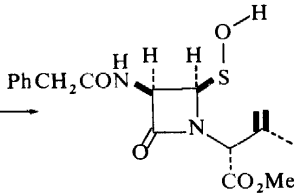
(XXIIIa)



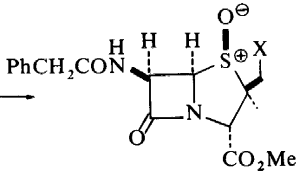
(XXIIIb)



(XXIVa)

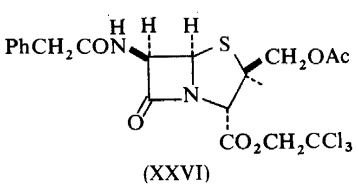


(XXIVb)

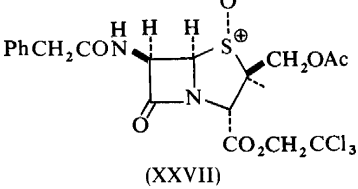


(XXV)

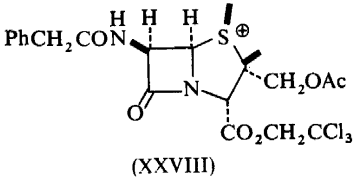
As mentioned above, the rotation about the C_2—C_3 bond [(XXIVa) → (XXIVb)] inverts the two methyl groups of a penicillin. We have been able to confirm this[13] by the following experiments. As noted earlier the acid-catalysed acetylation of a penicillin (*S*)-sulphoxide afforded *inter alia* the 2β-acetoxypenicillin. We were thus able to prepare the acetoxy-substituted penicillin (XXVI). Oxidation of this with iodobenzene dichloride in aqueous pyridine gave the (*R*)-sulphoxide (XXVII) which isomerized, on heating in refluxing toluene, into the isomer (XXVIII), shown by n.m.r. analysis, to bear the acetoxy substituent in the 2α-methyl group. Subsequent reduction of the sulphoxide, using phosphorus tribromide in dimethylformamide, gave the sulphide (XXIX), isomeric to the starting material (XXVI).



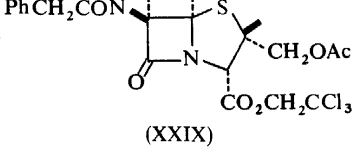
(XXVI)



(XXVII)

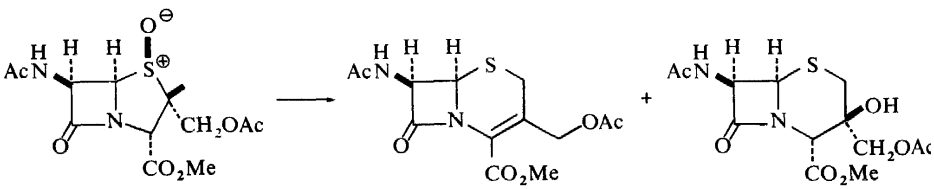


(XXVIII)



(XXIX)

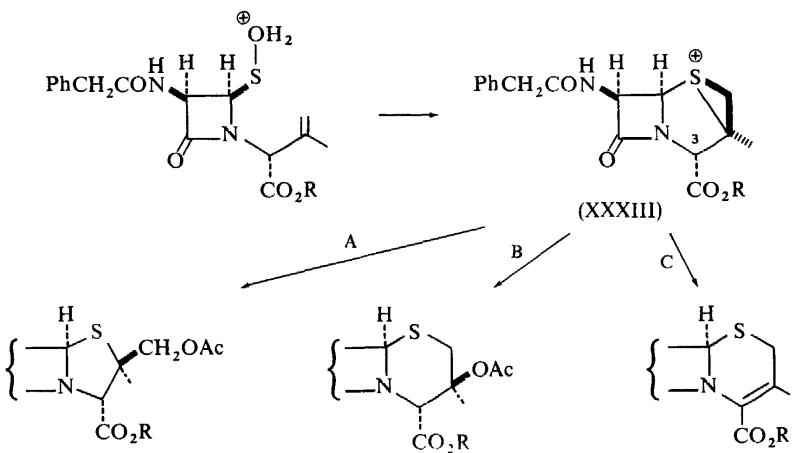
Comparable results have been obtained by Spry[14] who has shown, as expected, that further rearrangement of the sulphoxide (XXX) under acidic conditions leads to the cephalosporin derivatives (XXXI) and (XXXII), thus accomplishing the desired oxidation of both methyl groups from penicillin and the required ring expansion. However, the overall yield was very poor.



(XXX) (XXXI) (XXXII)

The mechanism of the ring expansion and substitution reactions can now be summarized (cf. refs. 6, 15, 16). The initial sulphenic acid must, under the acidic conditions of the reaction, be protonated and undergo intramolecular nucleophilic attack by the olefinic linkage to form a sulphonium ion intermediate (XXXIII) (*Scheme 1*). Attack by nucleophiles, such as acetate ions, can either open the sulphonium ion ring of (XXXIII) to give the appropriate acetoxy substituted systems, or remove a proton from position 3 to form the ring-expanded cephalosporin.

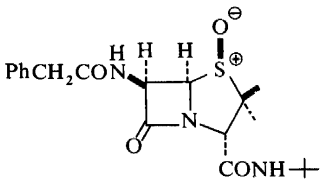
Scheme 1.



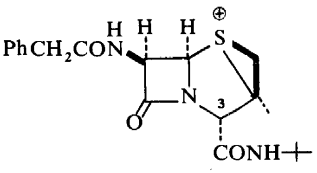
(XXXIII)

In our own work we have investigated the effect of the *t*-butylamide function upon the nucleophilic cleavage reactions of the corresponding sulphonium ion. The (*S*)-sulphoxide (XXXIV) should furnish the corresponding ion (XXXV). Being an amide we anticipated that the enolizability of the 3β-proton should be reduced thus decreasing or eliminating the role of path C (see *Scheme 1*). In the event, treatment of the (*S*)-sulphoxide (XXXIV) with acetic anhydride afforded, as minor product, the 2β-acetoxy-penicillin

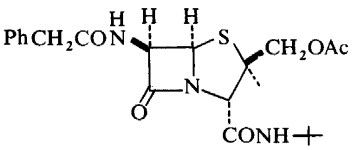
derivative (XXXVI) and, as major product, the cepham derivative (XXXVII). An authentic specimen of (XXXVI) was prepared from the corresponding acid. The constitution and stereochemistry of the cepham product (XXXVII) were determined by spectroscopic, especially n.m.r., methods. The same reaction sequence was then repeated in the *p*-bromobenzyl series to obtain, after oxidation, the (*R*)-sulphoxide of the *p*-bromo-derivative of (XXXVII). An x-ray crystallographic analysis of this compound, kindly carried out by Professor D. Rogers and Dr M. L. Smart, confirmed its assigned constitution and stereochemistry[17]. In the *t*-butyl-amide series no cephalosporin derivative (path C of *Scheme 1*) was formed, in accordance with our initial concept.



(XXXIV)

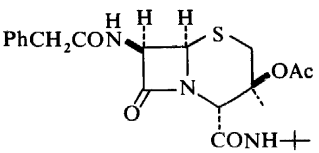


(XXXV)



(XXXVI)

+



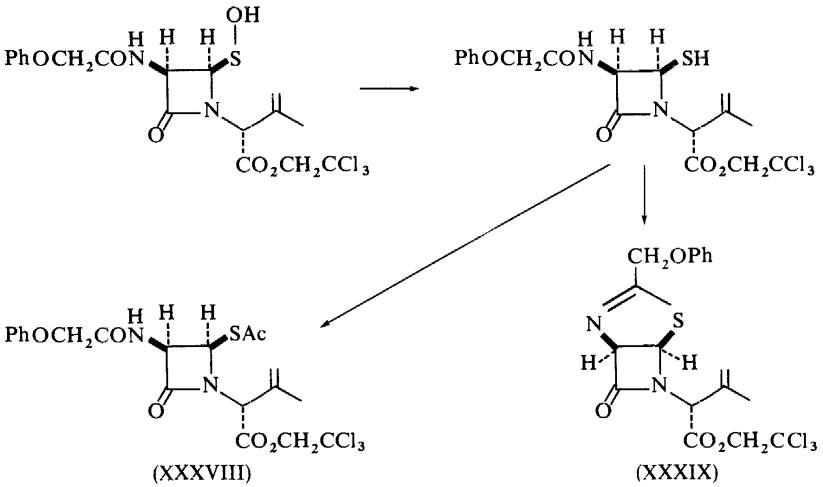
(XXXVII)

Having clearly established the existence of the sulphenic acid intermediate as a relatively long-lived species, further methods for trapping it were investigated. Since the chemistry of sulphenic acids is not well established new methods had to be examined. A possible approach is by reduction to the thiol. Elegant work by the Lilly group has achieved this reduction by using trivalent phosphorus. On heating the sulphoxide with acetic anhydride and trimethylphosphite[18] the thiol was produced and acylated to the *S*-acetyl derivative (XXXVIII).

In the absence of the acylating agent the thiol group added to the sidechain amide group to form a thiazoline (XXXIX)[19].

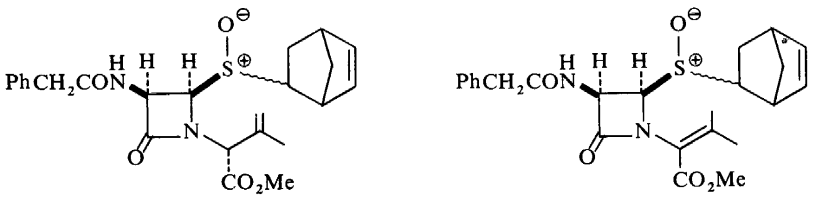
Another possibility was to make use of the observation that the sulphenic acid intermediate could reform a sulphoxide by addition to an external ethylenic linkage in a *cis*-type sigmatropic manner as in the sulphoxide inversion already described above. Suitable, reactive olefins must be chosen so as to compete with the intramolecular process. Heating the (*S*)-sulphoxide (XXV, X = H) in norbornadiene, which is noted for its reactivity, indeed gave one major adduct which was readily isomerized by trimethylamine into a crystalline αβ-unsaturated ester. The latter was shown by analytical and spectroscopic data as well as by further degradation to be the desired adduct

(XL) and its non-crystalline precursor to be the corresponding βγ-unsaturated derivative (XLI).



(XXXVIII) (XXXIX)

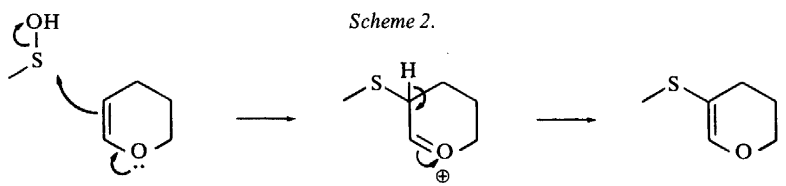
Yet another type of reaction might be anticipated for the sulphenic acid intermediate. In the ring expansion of the penicillin sulphoxides into desacetoxycephalosporin the nucleophilic attack of the olefin on to the protonated sulphenic acid to form a sulphonium ion was proposed (*Scheme 1*).



(XL) (XLI)

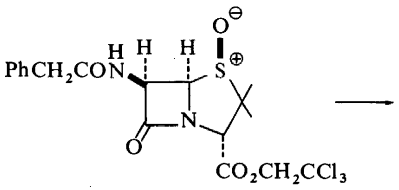
Therefore, other, more nucleophilic, double bonds might also compete successfully with the intramolecular process for displacement of OH_2 from the sulphur. Such a result was achieved with dihydropyran (*Scheme 2*) and is common to vinyl ethers in general. On treatment of the (*S*)-sulphoxide (XLII) with dihydropyran in benzene solution in the presence of a trace of aluminium bromide, followed by conjugation of the initially formed βγ-unsaturated isomer by triethylamine at room temperature, a nicely crystalline

Scheme 2.

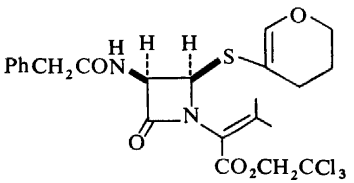


derivative was formed. Analytical and spectroscopic data showed that this was the conjugated ester (XLIII).

This compound makes an attractive precursor for the synthesis of modified β-lactam antibiotics. The first problem, which we have now solved[20], is to remove the unsaturated C_5 unit under mild conditions that do not destroy the β-lactam ring. Addition of diazomethane to the ester (XLIII) gave in a

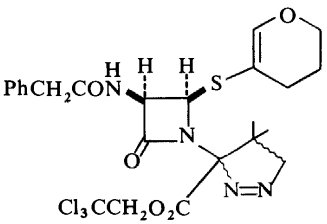


(XLII)

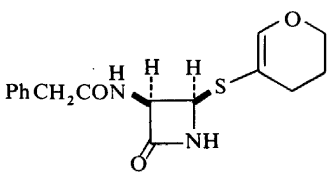


(XLIII)

slow, but quantitative, reaction a mixture of stereoisomeric major and minor adducts (XLIV). We conceived two simple procedures for the removal of the whole sidechain (*Scheme 3*). Firstly, formation of the anion [see (XLV)] should lead to the azine (XLIV) and the desired β-lactam residue. Secondly, reduction of the azo-linkage to the hydrazine (XLVI) should at once permit elimination of the β-lactam residue [see arrows in (XLVII) and formation of the hydrazone (XLVIII)]. Both of these methods work. Treatment of the adduct (XLIV), either as a stereoisomeric mixture or as individual components, with potassium *t*-butoxide afforded the crystalline β-lactam (XLIX).

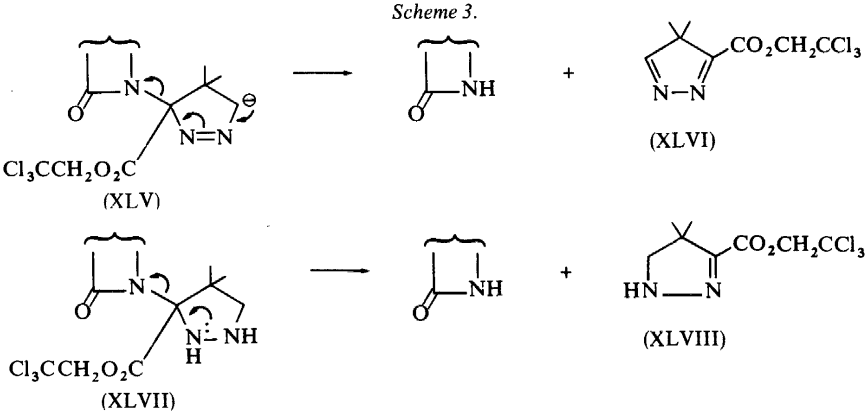


(XLIV)



(XLIX)

Scheme 3.



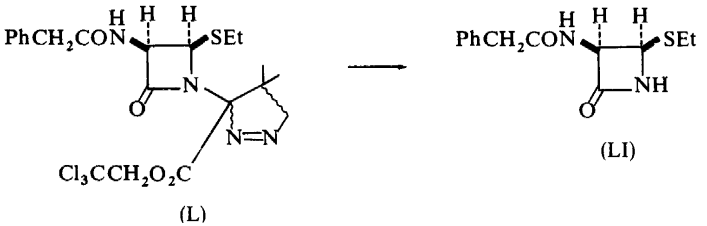
(XLV)

(XLVI)

(XLVII)

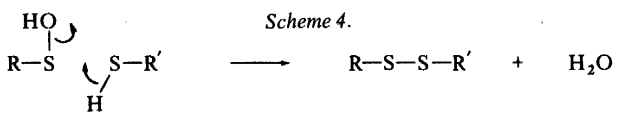
(XLVIII)

On reduction with zinc dust, as for normal cleavage of the trichloromethyl ester grouping[1], the adduct (XLIV) gave a quantitative yield of the β-lactam (XLIX). A similar result was also obtained for the *S*-ethyl derivative (L), whose preparation is described below. Addition of diazomethane gave, in quantitative yield, a stereoisomeric mixture of adducts (L) which was rapidly reduced by zinc dust in aqueous acetic acid to the free β-lactam (LI).



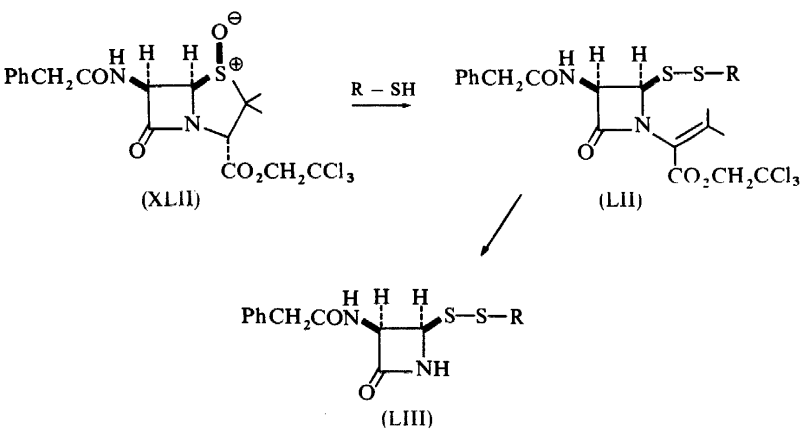
(L) (LI)

Recent work[21] on the trapping of penicillin sulphenic acids has considerably amplified our knowledge of this subject. We conceive that a sulphenic acid could also function as an electrophile towards a thiol (*Scheme 4*) thereby affording a disulphide. In the event, warming of the β-sulphoxide (XLII) with either isobutyl or *n*-butyl thiol gave in good yield the nicely crystalline disulphides (LII, R = Bu^i) and (LII, R = Bu). The isomerization of the initially formed isopropenyl compounds to the isopropylidene derivatives (LII) must presumably occur by addition followed by β-elimination of thiol.

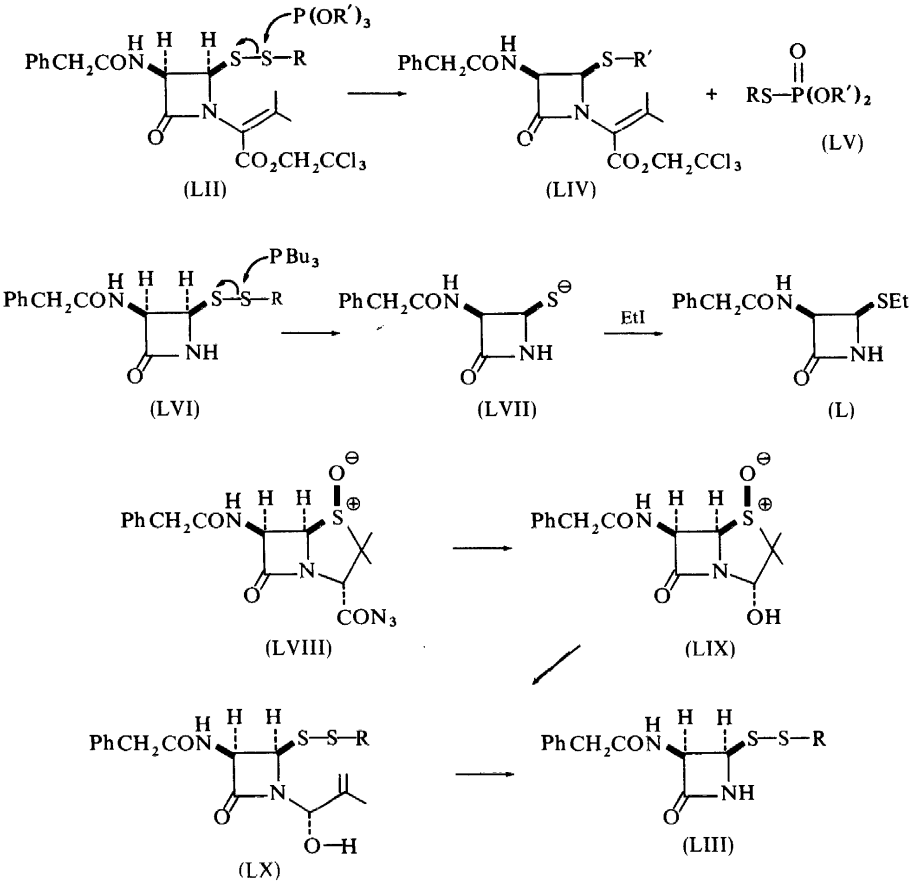


Scheme 4.

Application of the diazomethane degradation route[20] (see above) to (LII, R = Bu^i or R = Bu) gave without difficulty the des-C_5-unit disulphides (LII, R = Bu^i or R = Bu). In practice the zinc dust reduction of the intermediate pyrazolines proved more convenient than the *t*-butoxide elimination process.



(XLII) (LII) (LIII)



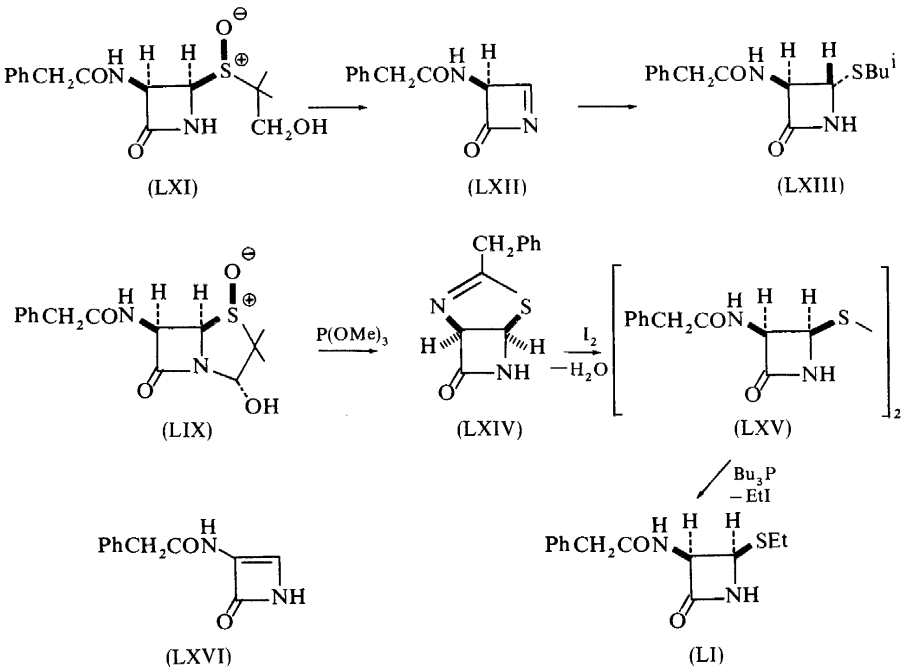
The disulphide function in compounds like (LII) and (LIII) lends itself very conveniently to the attachment of other functional groups to sulphur whilst keeping the sensitive β-lactam group unchanged. We conceived that the action of a phosphite upon for example (LII, R = Bu) would afford, by nucleophilic attack, sulphide anion and a positive phosphorus species $RS—\overset{\oplus}{P}(OR')_3$. An Arbusov-type reaction of the sulphide ion upon this phosphonium ion would then furnish alkylated sulphide and $RS—\overset{O}{\overset{\|}{P}}(OR')_2$ (LV). This conception was reduced to execution in the following way. The disulphide (LII, R = Bu) was treated with trimethyl and triethyl phosphites. It gave smoothly the alkyl sulphides (LIV, R^1 = Me) and (LIV, R^1 = Et). The latter compound has already been mentioned above without specification as to its mode of preparation.

An alternative procedure for the cleavage of the disulphide bond involves the use of trialkyl or triaryl phosphines. Thus the disulphide (LVI, R = Bu^i) was smoothly cleaved by tributylphosphine in dimethylformamide to give

the anion (LVII). Immediate addition of ethyl iodide afforded the now familar *S*-ethyl derivative (L).

We have also adapted the degradation procedure of Sheehan and Brandt[2] to the preparation of disulphides of type (LVI). The azide (LVIII) was transformed in the usual way[2] into the carbinolamine (LIX). This compound on warming with isobutyl or butyl thiol gave cleanly the disulphides (LIII, R = Bu^i) and (LIII, R = Bu).

Reduction of the carbinolamine (LIX) with sodium borohydride gave the crystalline alcohol (LXI). We anticipated that this alcohol would also afford disulphides of type (LIII) on heating with an alkyl thiol. In fact, treatment of the alcohol (LXI) with isobutyl thiol afforded an isobutyl sulphide (LXIII) with the unexpected *trans*-fusion of the two hydrogens attached to the β-lactam ring. We consider that this compound must be formed by an elimination process to afford (LXII) which then adds isobutyl thiol. Since compound (LXIII) is optically active it cannot be derived from the alternative elimination process, giving (LXVI), followed by thiol addition.



(LXI) (LXII) (LXIII)

(LIX) (LXIV) (LXV)

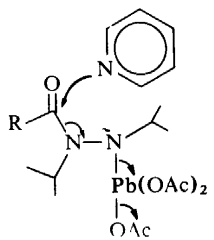
(LXVI) (LI)

Some further interesting transformations based on the carbinolamine (LIX) have also been effected. On treatment with trimethyl phosphite the masked aldehyde (LIX) gave, with loss of four carbon atoms, the β-lactam (LXIV). On treatment with iodine in the presence of water (LXIV) gave the disulphide (LXV). Cleavage of the latter with tributylphosphine in dimethylformamide followed by alkylation with ethyl iodide provided a further route to the ethyl sulphide (L).

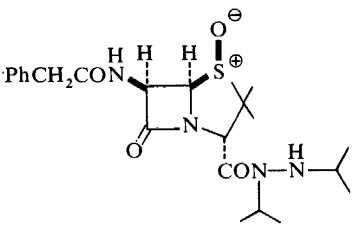
We conclude this account of recent progress in penicillin chemistry with the description of a new protecting group for carboxylic acids which can be

removed under very mild conditions[22]. It has been reported that *N*-benzoylhydrazobenzene is readily oxidized by lead tetraacetate to give a mixture of *cis*- and *trans*-azobenzene and benzoic acetic anhydride[23]. We conceived that a suitable 1,2-di-alkylhydrazine would have the alkyl groups sufficiently bulky so that only a mono-acyl derivative would be formed. On the other hand the hydrazine N—H would still be available for oxidation[24]. 1,2-Diisopropylhydrazine, which is readily available from the reduction of acetone azine, proved to possess just the right combination of properties. It gave, in very high yield, mono-acylated derivatives with benzoyl chloride and with palmitoyl chloride. These derivatives were quantitatively oxidized by lead tetraacetate in dry benzene containing a little pyridine to give back the parent acid. The hydrazine residue disappeared as gaseous products. The fission process may be represented as in *Scheme 5*. The small amount of pyridine added significantly improves the cleanness of the reaction.

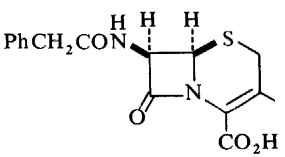
Scheme 5.



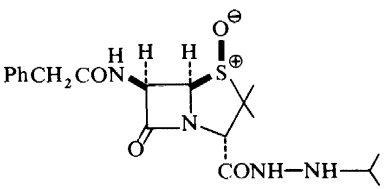
The corresponding penicillin sulphoxide derivative (LXVII) was readily prepared by the mixed anhydride procedure. Heating this hydrazide with pyridine phosphate, followed by removal of the hydrazide residue as described above, afforded the desacetoxycephalosporin (LXVIII) in 55 per cent overall yield.



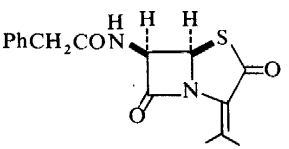
(LXVII)



(LXVIII)

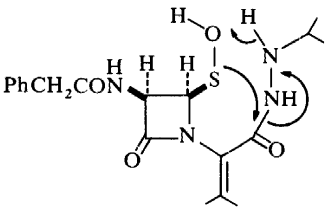


(LXIX)



(LXX)

In related experiments the monoisopropylhydrazide of penicillin G sulphoxide (LXIX) was prepared. Heating this hydrazide under the dehydrating conditions used above gave, unexpectedly, the anhydropenicillin[3,4] (LXX). This must be formed by an internal redox reaction between the hydrazide function and the sulphenic acid intermediate formed on heating the sulphoxide [see (LXXI)]. The formation of this compound is another example of the fascinating and diverse behaviour of sulphenic acids.



(LXXI)

It is clear that there remains much interesting work to be done on the reactions of the penicillin molecule.

It is a pleasure to acknowledge the contribution to this work, in conception, execution and in the writing up, made by my respected colleague Dr P. G. Sammes. Our accomplishments were made possible by the skilful collaboration of the following: Drs F. Comer, M. Girijavallabhan, D. G. T. Greig, G. Lucente and M. V. Taylor. Our account records also a small part of the excellent work carried out by Glaxo Research Ltd [(Mrs) C. M. Cooper and Drs G. Hewitt, B. E. Looker and W. G. E. Underwood]. We also thank Glaxo Research Ltd for generous financial support and the gift of starting materials.

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