# Transformations of Penicillins. Part V.[1] Reactions of Olefin and Acetylene Derivatives with the Sulphenic Acid Intermediates from Penicillin *S*-Oxides

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Norbornadiene, dimethyl acetylenedicarboxylate, and vinyl ethers react with the sulphenic acids produced by heating penicillin *S*-oxides. Norbornadiene, diketen (4-methyleneoxetan-2-one), and dimethyl acetylenedicarboxylate react by addition, whereas vinyl ethers, such as dihydropyran, react by substitution with loss of water. Methanolysis of the vinyl ether products can be achieved with dilute methanolic hydrochloric acid. Removal of the nitrogen-containing substituent of the β-lactam ring from the vinyl ether products has been effected *via* the pyrazoline route. A novel substitution reaction occurs on heating the 3-hydroxypenam (22) with acrylaldehyde: methacrylaldehyde is displaced and the 4-hydroxycepham (25) is formed. Some reactions of this cepham are reported.

SULPHENIC ACIDS are known to undergo electrocyclic addition to olefinic double bonds.[2] For example, 1,1-dimethylethanesulphenic acid, prepared by the thermolysis of di-t-butyl sulphoxide at 80°, readily adds to electrophilic olefins at room temperature. The latter addition reaction is itself reversible, since exchange of the electrophilic olefin is also possible.[3]

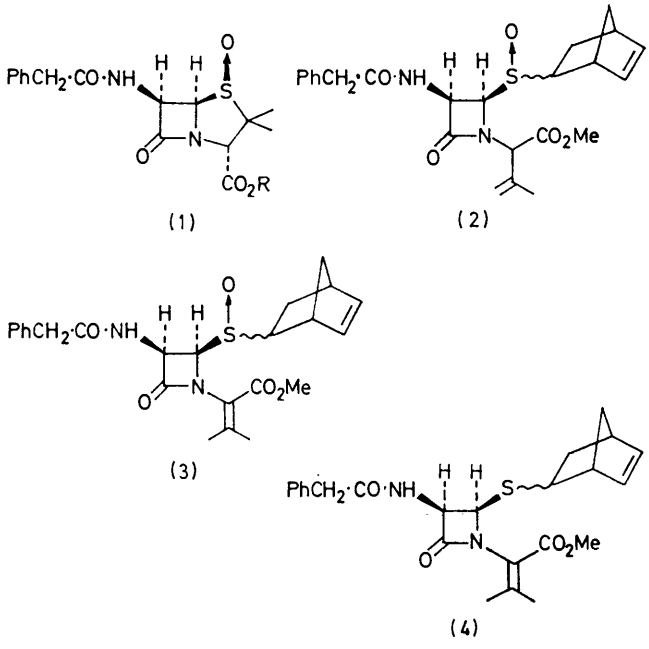
An intramolecular example of the combination between a sulphenic acid and an olefin is exemplified by

[1] Part IV, R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes, and M .V. Taylor, preceding paper.

[2] J. A. Shelton and K. E. Davis, *J. Amer. Chem. Soc.*, 1967, **89**, 718.

[3] *Cf.* C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, 1960, **92**, 1819; D. W. Emerson, and T. J. Kimiski *J. Org. Chem.*, 1969, **34**, 4115; C. R. Johnson, *Quart. Reports Sulphur Chem.*, 1969, **4**, 33; K. Tsujihara, K. Harada, N. Furukawa, and S. Oae, *Tetrahedron*, 1971, **27**, 6101.

the isomerisation of the (*R*)-*S*-oxides of (6*R*)-6-phenylacetamidopenicillanates into the corresponding (*S*)-isomers.[4] Since the evidence for the sulphenic acid intermediates, produced by heating the penicillin *S*-oxides, is unequivocal [4,5] it was considered reasonable to attempt intermolecular trapping reactions with external olefinic bonds. In order to be successful such trapping reactions must be able to compete efficiently with the intramolecular reaction. One method for ensuring this was to employ a large excess of a strained olefin. If successful, the reverse, elimination reaction would also be disfavoured. In order to test this proposal methyl (6*R*)-6-phenylacetamidopenicillanate (*S*)-*S*-oxide (1) was heated, under nitrogen, in norbornadiene. After 18 h the excess of norbornadiene was removed to produce an oily mixture. This consisted mainly of the βγ-unsaturated adducts (2), together




with the conjugated derivatives (3). By heating the mixture in benzene containing a few drops of pyridine, or triethylamine, formation of the conjugated isomers was completed. The product still appeared to be a mixture of the epimeric *S*-oxides bonded both *exo* and *endo* to the norbornene skeleton. Preparative t.l.c. afforded the major component as a crystalline solid, $C_{24}H_{28}N_2O_5S$. That this was the norbornadiene adduct was shown by its $^1H$ n.m.r. and mass spectra. In the latter spectrum one of the major fragmentations was loss of the norbornadiene unit and formation of the ion (a) at *m/e* 315. The n.m.r. spectrum showed signals at τ 4·85 (1H, d, *J* 4 Hz) and 4·18 (1H, dd, *J* 4 and 9 Hz) assigned to the substituent protons of the β-lactam group, which was also indicated by its characteristic i.r. absorption, $\nu_{max.}$ 1780 $cm^{-1}$.

Reduction of the isolated norbornadiene adduct (3) with phosphorous tribromide in *NN*-dimethylformamide at 0° for 10 min [6] gave the corresponding sulphide (4), which could also be obtained by reduction of the crude norbornadiene adducts followed by treatment with triethylamine.

Having demonstrated the feasibility of intermolecular trapping reactions on the sulphenic acid intermediates we investigated the use of an electrophilic substrate. The reagent chosen was dimethyl acetylenedicarboxylate, since Shelton and Davis had demonstrated the ease of addition of 1,1-dimethylethanesulphenic acid to such acetylenic esters.[2] Heating the sulphoxide (1; R = Me) with the acetylene in dry benzene for 19 h again afforded a complex mixture of products containing both conjugated and unconjugated esters. After treatment with triethylamine followed by chromatography through alumina, one principal product was obtained as a crystalline solid. Its mass spectrum and elemental analysis showed this to be a 1 : 1 adduct. Its $^1H$ n.m.r. spectrum revealed unexpected features. Besides the phenylacetamido and β-lactam protons it showed three ester methyl groups, only one vinylic methyl group, and four remaining protons. These four protons were arranged as a geminal pair coupled to one of the remaining protons in an ABX manner, the latter proton being separately coupled to the fourth proton. Since the i.r. spectrum showed a shoulder at 1720 $cm^{-1}$ as well as peaks at 1785 (β-lactam), 1730 (saturated ester), and 1660 $cm^{-1}$ (amide), the isolated product was assigned structure (5). This must arise *via* the initially expected adduct (6) by further cyclisation during either the trapping reaction or the isolation. The configuration of the sulphoxide bond has been assigned both on the basis of analogy with the normal penam system,[7] in which the (*S*)-configuration is preferred, and on the basis of solvent shift studies in deuteriobenzene (see Experimental section).[8]

Although a categoric assignment of stereochemistry about the two methoxycarbonyl-bearing atoms [positions 2 and 3, see (5)] cannot be made, an examination of Dreiding models allows a tentative formulation of configuration about these positions. If we assume that the sulphoxide configuration is (*S*), there is only one conformation of the eight-membered ring which allows strong hydrogen bonding between this group and the phenylacetamide NH-bond. This is represented by structure (5a), and in this conformation transannular interactions are also minimised. In order to explain

[4] D. H. R. Barton, F. Comer, D. G. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1059.

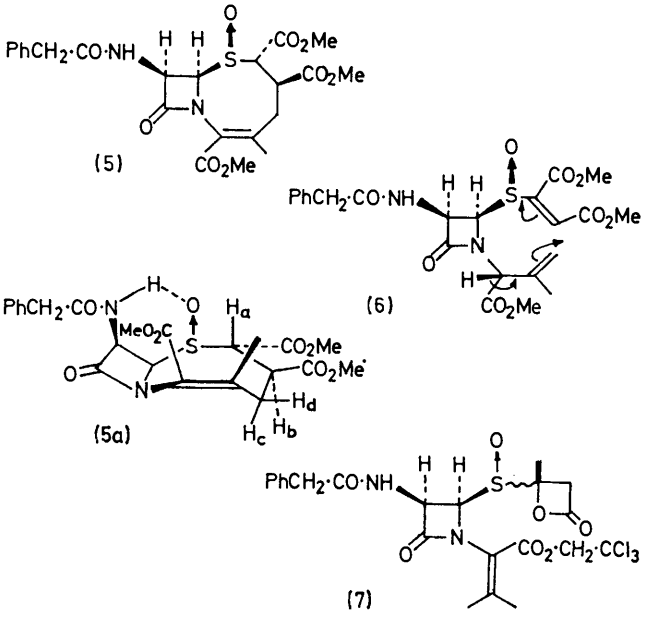
[5] D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540; R. D. G. Cooper, *J. Amer. Chem. Soc.*, 1970, **92**, 5010.

[6] *Cf.* G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. van Heyningen, *J. Org. Chem.*, 1970, **35**, 2430.

[7] R. D. G. Cooper, P. V. DeMarco, and D. O. Spry, *J. Amer. Chem. Soc.*, 1969, **91**, 1528; R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *ibid.*, p. 1408; D. H. R. Barton, F. Comer, and P. G. Sammes, *ibid.*, p. 1529.

[8] P. Lazlo, *Progr. N.M.R. Spectroscopy*, 1967, **3**, 348; T. Ledaal, *Tetrahedron Letters*, 1968, 1683.

the large coupling constant between $H_a$ and $H_b$ [see (5a)] these protons must be in an almost antiperiplanar conformation about the C(2)–C(3) bond; synperiplanar




conformations do not appear to be readily accessible about this bond. If this is so the two methoxycarbonyl groups at positions 2 and 3 must have a mutually *trans*-configuration, as depicted (5). The coupling constants between the geminal protons, $H_c$ and $H_d$, and $H_b$ (*viz.* 2·5 and 6 Hz) are consistent with this assignment. The adduct (5) could also be reduced by phosphorus tribromide in dimethylformamide to give the corresponding sulphide.

Attempts to extend this type of trapping reaction to other electrophilic olefinic systems, such as maleic anhydride, citraconic anhydride, and chloromaleic acid, failed; no β-lactam containing adducts were detected amongst the complex products. However, diketen (4-methyleneoxetan-2-one) did react, giving a 1 : 1 adduct. The presence of the new quaternary methyl group in its $^1$H n.m.r. allows assignment of the structure (7). Its i.r. spectrum showed the β-lactone carbonyl absorption band at 1776 cm$^{-1}$. Although this material ran as a single entity on t.l.c., its n.m.r. spectrum indicated that it was contaminated with traces of isomers.

One further type of olefinic bond was used to trap the sulphenic acid intermediates, namely that in the nucleophilic vinyl ethers and keten acetals. In an initial experiment, dihydropyran was treated with the trichloroethyl ester (1; R = $CH_2$·$CCl_3$). A slow reaction ensued, the rate of which was considerably enhanced by the addition of a trace of aluminium tribromide.[9] After all the starting material had reacted, the crude product was first treated with triethylamine, to isomerise any unconjugated olefins into the conjugated form, and then precipitated from ether with light petroleum. Analysis of the crystalline product showed it to be a 1 : 1 adduct having lost the elements of water. It was *not* a sulphoxide: mild oxidation with sodium periodate afforded two sulphoxides. The mass spectrum did not show the molecular ion but contained a peak at *m/e* 431, corresponding to the fragment (a; R = $CH_2$·$CCl_3$) formed by loss of the dihydropyranylthio-group. The $^1$H n.m.r. spectrum was consistent with its formulation as the vinyl sulphide (8). Initial attempts to hydrolyse the vinyl ether group proved abortive both in the presence of dilute aqueous acid and with aqueous mercury(II) chloride.[10] However, on heating the sulphide (8) in methanolic 0·05N-hydrogen chloride a mixture of all the four corresponding methoxyacetals (9) was formed. In contrast, oxidation of the vinyl sulphide (8) with *N*-bromosuccinimide in methanol [11] gave only one product, the dimethoxy-derivative (10).

A similar reaction of the sulphoxide (1; R = $CH_2$·$CCl_3$) was effected with isobutyl vinyl ether. Chromatography of the products through alumina afforded one major, but unstable, product. This was the *trans*-vinyl ether (11), assigned the *trans*-configuration about the olefinic bond on the basis of its $^1$H n.m.r. spectrum (*J* 12 Hz). An n.m.r. spectroscopic examination of the crude product also showed the presence of small amounts of the corresponding *cis*-isomer, but this was not isolated. The *trans*-vinyl ether (11) was unstable to treatment with acid. On heating it in benzene, or toluene, containing a catalytic amount of toluene-*p*-sulphonic acid, isobutyl alcohol was eliminated with formation of a new product, $C_{20}H_{19}Cl_3N_2O_4S$. This showed *no* amide NH protons (i.r.) but it did contain a β-lactam carbonyl group ($\nu_{max.}$ 1780 cm$^{-1}$). The $^1$H n.m.r. spectrum confirmed the absence of the original acetamide NH proton in that the β-lactam protons appeared as two doublets at τ 3·66 and 4·27 (*J* 6 Hz). On this basis the product was assigned the dihydrothiazine structure (12). Its mass spectrum was fully consistent with this structure, having strong peaks at *m/e* 217 and 99 [ions (b) and (c)]. Hydrolysis of the isobutyl ether (11) with dilute methanolic hydrogen chloride again effected a smooth transformation to the acetal (13).

The sulphoxide (1; R = $CH_2$·$CCl_3$) was also treated with 1,1-diethoxyethene. In this case the corresponding vinyl ether was not produced. Instead *in situ* hydrolysis appeared to be the preferred course since the product, obtained in high yield after treatment with triethylamine, was the ethyl ester (14), $\nu_{max.}$ 1770, 1730, 1670, and 1540 cm$^{-1}$.

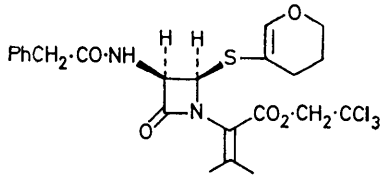
The products from the vinyl ether and keten acetal trapping reactions are of potential use in the preparation

[9] D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1683.

[10] P. L. Macdonald and H. G. Fletcher, *J. Amer. Chem. Soc.*, 1959, **81**, 3719.

[11] *Cf.* M. Gaydou, *Tetrahedron Letters*, 1972, 4055.

of penicillin analogues with a modified skeleton. In order to take synthetic advantage of such adducts removal of the nitrogen-containing substituent is essential. Oxidative methods [12] have the inherent disadvantage of possible oxidation of the sulphur atom or its substituents. Therefore the $C_5$ fragment attached to the β-lactam ring was removed by means of the pyrazoline route.[13]



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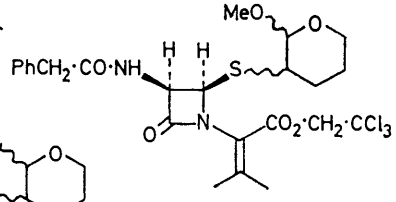

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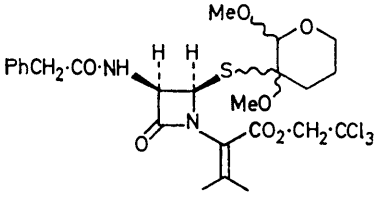

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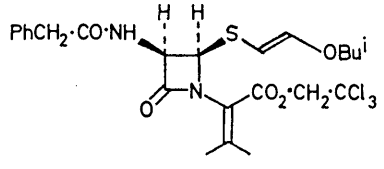

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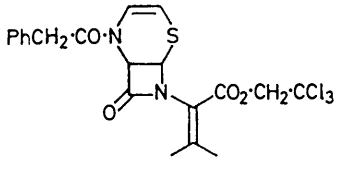

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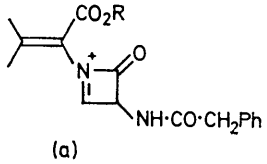
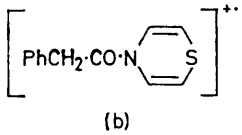


(a)



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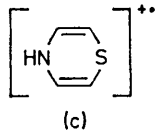
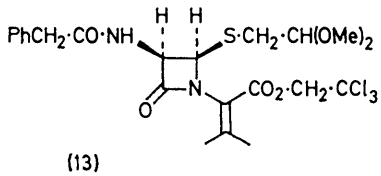


(c)

Addition of diazomethane to the dihydropyran derivative (3) occurred specifically across the double bond of the unsaturated ester group. The two pyrazoline isomers (15) were separated and treated either with potassium t-butoxide in t-butyl alcohol or with zinc dust in aqueous acetic acid. In all cases the corresponding β-lactam (16) was obtained. Of the two methods used for the removal of the pyrazoline ring the latter was more efficient, since prolonged treatment of the adducts with base caused decomposition of the product



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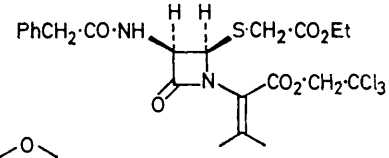

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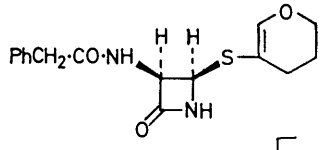

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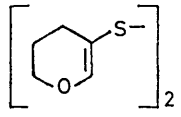

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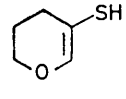

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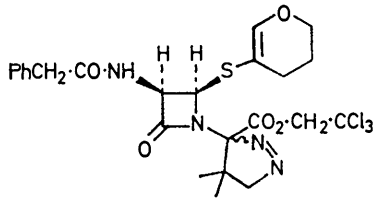
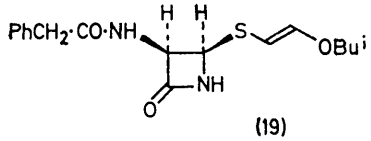


(15)

(16) with formation of the disulphide (17). The latter disulphide is presumably formed *via* elimination of the thiol (18), followed by its rapid oxidation under the reaction conditions. The structure of the disulphide (17) was confirmed by its synthesis from dihydropyran and sulphur monochloride.

In a similar manner the vinyl ether (11), the dihydrothiazine (12), and the ester (14) were converted into the corresponding β-lactams (19)—(21).



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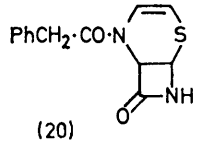

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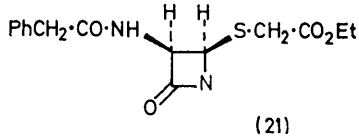


(21)

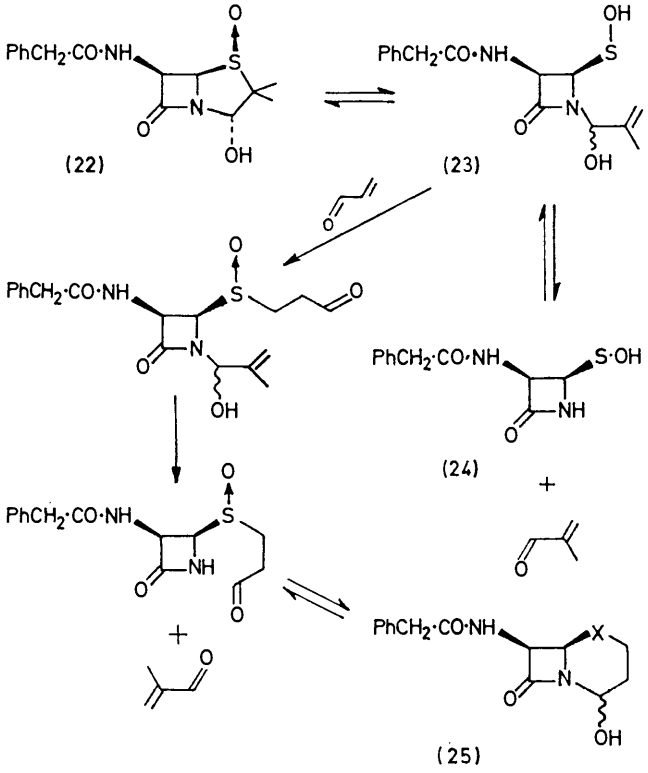
One further trapping reaction is of interest. In associated work [14] it has been found that the 3-hydroxy-

[12] *Cf.* E. G. Brain, A. J. Eglington, J. H. C. Naylor, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1972, 229.

[13] D. H. R. Barton, D. G. T. Greig, P. G. Sammes, and M. V. Taylor, *Chem. Comm.*, 1971, 845.

[14] W. G. E. Underwood *et al.*, unpublished work.

penam *S*-oxides [15] such as (22) can undergo trapping reactions under suitable conditions. In this case, however, the intermediate sulphenic acid (23) can collapse further by decomposition of the carbinol, liberating methacrylaldehyde. Since the intermediate sulphenic acid (24) produced in this process is extremely unstable, such trapping reactions often proceed only in low yield. Thus, attempted trapping of the alcohol (22) with dimethyl acetylenedicarboxylate proved abortive. An exception proved to be acrylaldehyde, which reacted with the alcohol (22) to give the hydroxycepham (25; X = SO), isolated as a mixture of isomers.




SCHEME

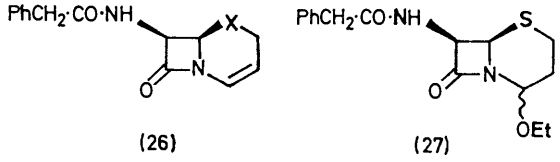
Although no evidence for the order of bond cleavage and bond formation was obtained a possible Scheme is outlined. The formation of this compound represents a new example of the simultaneous *N*- and *S*-alkylation of the β-lactam nucleus of a penicillin derivative. That the sulphur atom added to the terminal end of acrylaldehyde is consistent with the results observed by Shelton and Davis for the addition of sulphenic acids to conjugated systems.[2]

$^1$H N.m.r. analysis of the product (25; X = SO) showed that the 4-hydroxy-groups equilibrated slowly in solution to give mainly the (4*S*)-isomer. Recrystallisation from ethanol also caused equilibration to the (4*S*)-isomer, the (1*S*)-oxide crystallising out initially, followed by crops containing a mixture with the (1*R*)-oxide.

The assignment of configuration to the isomers was based on consideration of the n.m.r. coupling constants. If we assume a chair conformation in the six-membered tetrahydrothiazine ring, and that there is no internal hydrogen bonding of the hydroxy-group to the 1-oxide, the coupling constants show that the 4-hydroxycepham formed by equilibration must be the (4*S*)-isomer. That there is no internal hydrogen bonding between the hydroxy-group and the sulphoxide group is substantiated by the evidence for hydrogen bonding between the NH-group and the 1-oxide,[16] the NH signal appearing at τ *ca.* 2 in [$^2H_6$]dimethyl sulphoxide. The presence of the 4-hydroxy-group appears to make no difference to the hydrogen bonding between the NH group and the 1-oxide and it is therefore unlikely that the hydroxy-group is also bonded to the sulphoxide.*

Dehydration of the principal alcohol sulphoxide (25; X = SO) [(1*S*, 4*S*)-isomer] with thionyl chloride afforded the corresponding cephem (26; X = SO). Attempted reduction of the alcohol with phosphorus tribromide in dimethylformamide [6] was accompanied by dehydration, to give the sulphide (26; X = S). Both the sulphoxide (26; X = SO) and the sulphide (26; X = S) had u.v. spectra typical of the ceph-3-em system.[18] The sulphoxide (26; X = SO) could also be reduced with the phosphorus tribromide reagent to give the sulphide (26; X = S), whilst peracetic acid oxidation of the latter regenerated the (1*S*)-sulphoxide (26; X = SO). Further oxidation of the sulphoxide (26; X = SO), with an excess of the peracetic acid, gave the corresponding sulphone (26; X = $SO_2$). A reduction of the sulphoxide (25; X = SO), without the accompanying dehydration, was effected with a mixture of acetyl chloride and potassium iodide in dimethylformamide to give the hydroxy-sulphide (25; X = S).

As expected, the alcohol sulphide (25; X = S) reacted with ethanol in the presence of acid, to give the




corresponding ethyl ether (27), probably *via* the corresponding open-chain aldehyde-amine form. The sulphoxide alcohol (25; X = SO) gave the same ether by concomitant reduction of the sulphoxide bond. Surprisingly, the olefin sulphide (26; X = S) also reacted

* An independent preparation of (25; X = S) has recently been reported.[17]

[15] D. H. R. Barton, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, B. E. Looker, and W. G. E. Underwood, *Chem. Comm.*, 1971, 1137; D. H. R. Barton, I. H. Coates, and P. G. Sammes, *J.C.S. Perkin I*, 1973, 599; for the preparation of the corresponding sulphide see J. C. Sheehan and K. G. Brandt, *J. Amer. Chem. Soc.*, 1965, **87**, 5468.

[16] See ref. 6 and R. D. G. Cooper, P. V. DeMarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc.* (*C*), 1970, 340.

[17] R. Scartazzini, J. Gosteli, H. Bickel, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 2567.

[18] R. Nagarajan and D. O. Spry, *J. Amer. Chem. Soc.*, 1971, **93**, 2310.

with acidified ethanol to give the ether (27). The latter ethanolysis must reflect the enamide character of the double bond. In contrast the sulphoxide (26; X = SO), which is more electron-withdrawing than the sulphide, did not add ethanol under these conditions, and none of the ether (27) was obtained from this precursor in comparable reaction times. It appears that any reduction of the sulphoxide (26; X = SO) is proceeding much more slowly in this reaction than in the case of the corresponding alcohol (25; X = SO).

## EXPERIMENTAL [19]

I.r. spectra were recorded with a Unicam SP 200 spectrometer for Nujol mulls, unless otherwise stated, and u.v. spectra with a Unicam SP 800 spectrometer for ethanolic solutions. Mass spectra were determined with an A.E.I. MS9 machine, important peaks being assigned by accurate mass measurements. $^1$H N.m.r. spectra were recorded with either a Varian A 60 or HA100 instrument for solutions in deuteriochloroform containing tetramethylsilane as internal reference. Reactions were monitored by t.l.c. on Merck silica gel $GF_{254}$ with acetone–benzene and ethyl acetate–benzene as solvents. Light petroleum refers to the fraction of boiling range 60—80°. M.p.s were determined with a Kofler hot-stage apparatus. Solutions were dried over anhydrous sodium sulphate.

*Reaction of the Sulphoxide* (1; R = Me) *with Norbornadiene.*—The sulphoxide (0·34 g) in norbornadiene (freshly distilled; 5·5 ml) was heated to reflux for 18 h. The excess of norbornadiene was removed under reduced pressure to give an oil (0·47 g). T.l.c. showed that the product consisted of two major components. The mixture in benzene (10 ml) and pyridine (0·5 ml) was heated for 3 h, cooled, washed with dilute phosphoric acid and water, and then dried and evaporated. The residue was separated by preparative t.l.c. (diethyl ether; 3 elutions) to give *methyl α-isopropylidene-α-[(2R,3R)-2-(norborn-5-en-2-ylsulphinyl)-4-oxo-3-phenylacetamidoazetidin-1-yl]acetate* (3) (0·17 g, 40%), m.p. 145—147° (ethyl acetate), $[\alpha]_D^{25}$ +89·5° (*c* 1·0 in EtOAc), $\nu_{max.}$ 3300 (NH), 1780 (β-lactam), 1740 (ester), 1680 (amide), and 1540 cm$^{-1}$ (amide), τ 2·77br (5H, Ph), 3·20 (1H, d, *J* 9 Hz, NH), 4·18 (1H, dd, *J* 4 and 9 Hz, H-3), 4·85 (1H, d, *J* 4 Hz, H-2), 6·28 (3H, s, MeO), 6·46 (2H, s, C*H*$_2$Ph), 7·80 (3H, s), and 7·83 (3H, s), with norbornadienyl protons at 3·9 (1H, m), 4·2 (1H, m), 7·1br (1H, s), and 7·5—8·8 (6H, m) (Found: C, 63·1; H, 6·2; N, 6·1; S, 6·9. $C_{24}H_{28}N_2O_5S$ requires C, 63·1; H, 6·2; N, 6·1; S, 7·0%).

*Reduction of the Norbornadiene Adduct* (3).—The adduct (3) (0·14 g) in dry *NN*-dimethylformamide (6 ml) was treated at 0° with phosphorus tribromide (0·85 g). After 10 min the solution was poured into ice–water and extracted with dichloromethane. The extract was washed with water, dried, and evaporated to give, as a non-crystalline solid, the *sulphide* (4) (0·105 g, 80%), $\nu_{max.}$ (film) 3300 (NH), 1765 (β-lactam), 1720 (ester), 1670 (amide), and 1540 cm$^{-1}$ (amide) (Found: C, 65·3; H, 6·4; N, 6·2; S, 7·3. $C_{24}H_{28}N_2O_4S$ requires C, 65·4; H, 6·4; N, 6·4; S, 7·3%). The same sulphide was obtained as a major product by treatment of a mixture of the crude norbornadiene-trapped products with phosphorus tribromide, followed by treatment with triethylamine in benzene and, finally, isolation by preparative t.l.c.

*Reaction of the Sulphoxide* (1; R = Me) *with Dimethyl Acetylenedicarboxylate.*—The sulphoxide (0·73 g) in benzene (35 ml) containing the acetylenic ester (2·85 g) was heated to reflux for 19 h under oxygen-free nitrogen. The solvent and the excess of reagent were removed under reduced pressure, and the residue (1·6 g) was dissolved in dichloromethane and filtered through silica gel (50 g). Elution with 1 : 1 dichloromethane–acetone afforded a partly purified product (1·06 g), which was further purified by column chromatography through alumina (grade V; 30 g) (eluant benzene–ether, then acetone) and preparative t.l.c. (silica gel G) to give one major product (0·20 g), which eventually crystallised as needles of *trimethyl 3-methyl-10-oxo-9-phenylacetamido-7-thia-1-azabicyclo*[6.2.0]*dec-2-ene-2,5,6-tricarboxylate S-oxide* (5), m.p. 137—139° (from ether), $[\alpha]_D^{25}$ −4·2° (*c* 2·8 in $CHCl_3$), $\nu_{max.}$ 3300 (NH), 1785 (β-lactam), 1725 (ester), 1710 (unsaturated ester), 1655 (amide), and 1510 cm$^{-1}$ (amide), τ 2·75br (5H, s, Ph), 3·26 (1H, d, *J* 9 Hz, NH), 4·10 (1H, dd, *J* 5 and 9 Hz, β-lactam CH), 5·28 (1H, d, *J* 5 Hz, β-lactam CH), 6·30 (6H, s, 2 × MeO) 6·34 (3H, s, MeO), 6·46 (2H, s, C*H*$_2$Ph), and 7·94 (3H, s); superimposed on these signals was a double AB quartet at τ 6·13 (*J* 13 and 6 Hz) and 7·50 (*J* 13 and 2·5 Hz), besides signals at 6·50 (1H, ddd, *J* 2·5, 6, and 12 Hz) and 6·00 (1H, d, *J* 12 Hz); τ ($C_6D_6$) 2·90 (5H, s, Ph), 3·00 (1H, d, *J* 9 Hz, NH), 4·05 (1H, dd, *J* 9·5 Hz, β-lactam CH), 5·96 (1H, d, *J* 5 Hz, β-lactam CH), 6·06 (1H, d, *J* 12 Hz), 6·06 (1H, dd, *J* 6 and 13 Hz), 6·25 (1H, ddd, *J* 2·5, 6, and 12 Hz), 6·77 (9H, s, 3 × MeO), 6·90 (2H, s, C*H*$_2$Ph), 7·78 (1H, dd, *J* 2·5 and 13 Hz), and 8·12 (3H, s) (Found: C, 54·5; H, 5·2; N, 5·3; S, 6·3. $C_{23}H_{26}N_2O_9S$ requires C, 54·5; H, 5·2; N, 5·5; S, 6·3%).

*Reduction of the Adduct* (5).—A portion of the sulphoxide (5) (20 mg) was treated with phosphorus tribromide (0·05 g) in dimethylformamide at 0° for 15 min. The product was worked up in the normal way to yield, as an amorphous solid, a new, less polar compound. This product was not characterised but was immediately oxidised with sodium periodate in aqueous tetrahydrofuran to give back the starting sulphoxide.

*Trapping with Diketen.*—The trichloroethyl sulphoxide (1; R = $CH_2{\cdot}CCl_3$) (3·0 g) in dioxan (10 ml) and diketen (freshly distilled; 10 ml) was heated under reflux for 6 h. The excess of solvent was removed under reduced pressure and the resulting oil chromatographed on silica gel (35 g) with 5 : 1 benzene–ethyl acetate as solvent. The major product, obtained as a mixture of isomers, was *2,2,2-trichloroethyl α-isopropylidene-α-[(2R,3R)-2-(2-methyl-4-oxo-oxetan-2-ylsulphinyl)-4-oxo-3-phenylacetamidoazetidin-1-yl]acetate* (7; R = $CH_2{\cdot}CCl_3$) (2·4 g, 68%), $\nu_{max.}$ ($CHBr_3$) 3380 (NH), 1776 (β-lactone), 1750 (β-lactam), 1740 (ester), 1674 (amide), 1510 (amide), and 1030 cm$^{-1}$ (sulphoxide), τ 2·69 (5H, s, Ph), 3·12 (1H, d, *J* 10 Hz, NH), 4·29 (1H, dd, *J* 4 and 10 Hz, 3-H), 5·05 (1H, d, *J* 4 Hz, 2-H), 5·24 (2H, s, C*H*$_2{\cdot}CCl_3$), 5·77 and 6·06 (2H, ABq, *J* 12 Hz, C*H*·CO), 6·36 (2H, s, C*H*$_2$Ph), 7·74 (3H, s), 7·84 (3H, s), and 8·48 (3H, s) (Found: C, 47·1; H, 4·2; Cl, 19·2; N, 5·1; S, 5·9. $C_{22}H_{23}Cl_3N_2O_7S$ requires C, 46·8; H, 4·1; Cl, 18·7; N, 4·9; S, 5·7%).

*Trapping with Dihydropyran.*—The sulphoxide (1; R = $CH_2{\cdot}CCl_3$) (25 g) in freshly distilled dihydropyran (200 ml) containing a small quantity of aluminium tribromide

[19] Some of this work has been published in preliminary form: I. Ager, D. H. R. Barton, G. Lucente, and P. G. Sammes, *J.C.S. Chem. Comm.*, 1972, 601.

(*ca.* 100 mg) was heated to reflux for 40 h. The solution was evaporated and the residue dissolved in ethyl acetate. Triethylamine (10 ml) was added and the solution was stirred at room temperature for 10 min, washed with 4N-phosphoric acid (2 × 100 ml), saturated aqueous sodium hydrogen carbonate (2 × 100 ml), and water (100 ml), dried, and evaporated. The residue was dissolved in ether (250 ml); addition of light petroleum afforded a crystalline precipitate of 2,2,2-*trichloroethyl* α-[(2R,3R)-2-(3,4-*dihydro*-2H-*pyran*-5-*ylthio*)-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]-α-*isopropylideneacetate* (8) (13·3 g, 55%), m.p. 116—117° (from ether–hexane), $[\alpha]_D^{25}$ +60° (*c* 1·4 in $CHCl_3$), $\nu_{max.}$ 3350 (NH), 1770 (β-lactam), 1740 (unsaturated ester), 1665 (amide), 1625 (C=C), and 1540 $cm^{-1}$ (amide), τ 2·75br (5H, s, Ph), 3·55 (1H, s, vinylic proton), 3·88 (1H, d, *J* 8 Hz, NH), 4·68 (1H, dd, *J* 4 and 8 Hz, 3-H), 4·85 (1H, d, *J* 4 Hz, 2-H), 4·9 and 5·4 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·42 (2H, s, $CH_2Ph$), 7·76 (3H, s), 8·00 (3H, s); dihydropyran protons at 6·2 (2H, m) and 8·2 (4H, m) (Found: C, 50·0; H, 4·8; N, 4·9. $C_{23}H_{25}Cl_3N_2O_5S$ requires C, 50·3; H, 4·6; N, 4·6%).

Oxidation of the sulphide (8) (336 mg) with sodium periodate (0·5 g) in 1 : 1 water–dioxan at room temperature for 18 h followed by a standard work-up and preparative t.l.c. afforded starting material (48 mg) and two non-crystalline sulphoxides. The *more polar isomer* (130 mg) had $\nu_{max.}$ (film) 3300 (NH), 1770 (β-lactam), 1730 (unsaturated ester), 1680 (amide), 1620 (C=C), and 1540 $cm^{-1}$ (amide), 2·76 (5H, s, Ph), 2·50 (1H, d, *J* 10 Hz, NH), 4·30 (1H, dd, *J* 5 and 10 Hz, 3-H), 5·20 (1H, d, *J* 5 Hz, 2-H), 5·10 and 5·48 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·46 (2H, s, $CH_2Ph$), 7·72 (3H, s), 7·83 (3H, s); dihydropyran protons at 3·08 (1H, s, vinylic), 6·1 (2H, m), and 8·2 (4H, m) (Found: C, 49·0; H, 4·8; N, 4·8. $C_{23}H_{27}Cl_3N_2O_6S$ requires C, 48·8; H, 4·8; N, 4·95%). The *less polar sulphoxide* (58 mg) had a similar i.r. spectrum and τ 2·75br (5H, s, Ph), 3·30 (1H, d, *J* 10 Hz, NH), 4·23 (1H, dd, *J* 5 and 10 Hz, 3-H), 4·92 (1H, d, *J* 4 Hz, 2-H), 5·10 and 5·49 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·46 (2H, s, $CH_2Ph$), 7·78 (3H, s), 7·82 (3H, s); dihydropyran protons at 3·26 (1H, s, vinylic), 6·2 (2H, m), and 8·1 (4H, m). This isomer eventually crystallised; m.p. 157—159° (Found: C, 48·8; H, 4·5; N, 4·8. $C_{23}H_{27}Cl_3N_2O_6S$ requires C, 48·8; H, 4·8; N, 4·95%).

*Treatment of the Dihydropyran Adduct* (8) *with* N-*Bromosuccinimide*.—The adduct (2·0 g), *N*-bromosuccinimide (0·66 g), propylene oxide (0·48 ml), and sodium acetate were stirred in methanol (30 ml) at room temperature for 25 min. The mixture was then poured into ice-cold water (200 ml) and extracted into ethyl acetate (2 × 200 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate (2 × 200 ml), dried, and evaporated to give 2,2,2-*trichloroethyl* α-[(2R,3R)-2-(3,4-*dihydro*-5,6-*dimethoxy*-2H-*pyran*-5-*ylthio*)-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]-α-*isopropylideneacetate* (10) (2·20 g, 98%), m.p. 81—82° (ether), $[\alpha]_D^{22}$ −17° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ 3320 (NH), 1770 (β-lactam), 1740 (unsaturated ester), 1660 (amide), and 1540 $cm^{-1}$ (amide), τ 2·74 (5H, s, Ph), 3·90 (1H, d, *J* 8 Hz, NH), 4·63 (2H, m, 3-H and 2-H), 5·25 and 5·48 (2H, ABq, $CH_2CCl_3$), 5·72 (1H, s, MeO·C*H*·O), 6·40 (2H, s, $CH_2Ph$), 6·52 (2H, m, $O{\cdot}CH_2{\cdot}CH_2$), 6·78 (3H, s, MeO), 6·92 (3H, s, MeO), 7·72 (3H, s), 7·94 (3H, s), and 8·3 (4H, m) (Found: C, 48·7; H, 5·1; Cl, 17·3; N, 4·5; S, 5·4. $C_{23}H_{32}Cl_3N_2O_4S$ requires C, 49·2; H, 5·3; Cl, 17·4; N, 4·6; S, 5·3%).

*Methanolysis of the Dihydropyran Adduct*.—The adduct (75 mg) was heated in methanolic 0·05N-hydrogen chloride to reflux for 16 h. The solvent was removed *in vacuo* and the residue dissolved in benzene was washed with water (2×), dried ($MgSO_4$), filtered, and evaporated to give an oil (55 mg, 30%). T.l.c. showed one broad band which could not be separated by multiple elution. The product gave an $^1H$ n.m.r. spectrum which was consistent with its being a mixture of four isomers of the tetrahydropyranyl ether (9) (4 OMe signals, ratio *ca.* 1 : 1 : 1 : 1), $\nu_{max.}$ (film) 3300 (NH), 1765 (β-lactam), 1740 (unsaturated ester), 1670 (amide), and 1540 $cm^{-1}$ (amide). This mixture was not purified further.

*Trapping with Isobutyl Vinyl Ether*.—The sulphoxide (1; R = $CH_2{\cdot}CCl_3$) (3 g) was heated in isobutyl vinyl ether (50 ml) and dioxan (10 ml) at reflux under oxygen-free nitrogen for 44 h. The excess of the solvent was removed *in vacuo* to give a brown gum. After treatment with triethylamine, chromatography through alumina (100 g; grade V) (eluant ethyl acetate–benzene mixtures) afforded an amorphous solid (1·69 g) shown, by t.l.c., to consist of one major and one minor product. Preparative t.l.c. (6 : 1 benzene–ethyl acetate; 3 elutions) afforded the major isomer (1·23 g, 35%), which was unstable at room temperature. The freshly isolated material showed $\nu_{max.}$ (film) 3320 (NH), 1765 (β-lactam), 1735 (ester), 1665 (amide), 1640 (C=C), and 1540 $cm^{-1}$ (amide), τ 2·76br (5H, s, Ph), 3·05 (1H, d, *J* 9 Hz, NH), 3·55 (1H, d, *J* 12 Hz, O·C*H*=CH), 4·65 (1H, dd, *J* 5 and 9 Hz, 3-H), 4·87 (1H, d, *J* 5 Hz, 2-H), 5·12 (1H, d, *J* 12 Hz, S·C*H*=CH), 5·12 and 5·45 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·50 (2H, s, $CH_2Ph$), 6·72 (2H, d, *J* 6 Hz, $O{\cdot}CH_2$), 7·74 (3H, s), 7·98 (3H, s), 8·2 (1H, m), 9·12 (6H, d, *J* 6 Hz).

Methanolysis of the isobutyl vinyl ether adduct (3·5 g) obtained directly from a trapping reaction, with methanolic 0·06N-hydrogen chloride at reflux for 1 h, afforded, after work-up and chromatography through alumina (100 g, grade V) (eluant 10 : 1 benzene–ethyl acetate) 2,2,2-*trichloroethyl* α-[(2*R*,3R)-2-(2,2-*dimethoxyethylthio*)-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]-α-*isopropylideneacetate* (13) (1·5 g, 44%), m.p. 90·5—91·5° (benzene–light petroleum), $[\alpha]_D^{23}$ −15° (*c* 0·9 in $CHCl_3$), $\nu_{max.}$ (film) 3320 (NH), 1770 (β-lactam), 1730 (unsaturated ester), 1680 (amide), and 1540 $cm^{-1}$ (amide), τ 2·74 (5H, s, Ph), 3·86 (1H, d, *J* 8 Hz, NH), 4·64—4·78 (2H, m, β-lactam protons), 5·10 and 5·45 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·40 (2H, s, $PhCH_2$), 5·80 [1H, t, *J* 5·5 Hz, $CH(OMe)_2$], 6·80 (3H, s, MeO), 6·83 (3H, s, MeO), 7·51 (2H, d, *J* 5·5 Hz, $CH_2{\cdot}S$), 7·72 (3H, s), and 7·99 (3H, s) (Found: C, 47·7; H, 5·0; Cl, 19·2; N, 5·0; S, 5·8. $C_{22}H_{27}N_2O_6S$ requires C, 47·7; H, 4·9; Cl, 19·2; N, 5·05; S, 5·8%).

*Reaction of the Vinyl Ether* (11) *with Anhydrous Acid*.—The vinyl ether (11) (0·90 g) in benzene (15 ml) was heated to reflux in the presence of toluene-*p*-sulphonic acid (0·05 g) for 1 h with gentle stirring; during this time benzene was distilled off and replaced with fresh, anhydrous solvent (20 ml). The remaining solvent was then removed *in vacuo* and the residue immediately purified by preparative t.l.c. (1 : 5 ethyl acetate–benzene) to give 2,2,2-*trichloroethyl* (1R,6R)-α-*isopropylidene*-α-(8-*oxo*-2-*phenylacetamido*-2,7-*diaza*-4-*thiabicyclo*[4.2.0]*oct*-3-*en*-7-*yl*)*acetate* (12) (0·50 g, 64%), m.p. 115—116° (ethyl acetate–light petroleum), $[\alpha]_D^{23}$ −454° (*c* 0·93 in $CHCl_3$), $\nu_{max.}$ 1770 (β-lactam), 1740 (unsaturated ester), 1680 (amide), and 1620 $cm^{-1}$ (C=C), τ 2·79br (5H, s, Ph), 4·30 (2H, m, β-lactam), 3·04 (1H, d,

*J* 6 Hz, N·C*H*=), 3·69 (1H, d, *J* 6 Hz, S·C*H*=), 5·05 and 5·45 (2H, ABq, *J* 12 Hz, $CH_2$·$CCl_3$), 6·78 (2H, s, $CH_2Ph$), 7·70 (3H, s), and 7·98 (3H, s), *m/e* 488 ($M^+$), 446, 370, 341, 298, 217 (strong), 99 (base peak), and 91 (Found: C, 48·8; H, 3·9; Cl, 21·6; N, 5·4; S, 6·9. $C_{20}H_{19}Cl_3N_2O_4S$ requires C, 49·0; H, 3·9; Cl, 21·7; N, 5·7; S, 6·5%).

*Trapping with* 1,1-*Diethoxyethene*.—The sulphoxide (1; R = $CH_2$·$CCl_3$) (0·50 g) in benzene (4 ml.) was heated to reflux with 1,1-diethoxyethene (2·0 g) for 42 h. The solvent and excess of reagent were removed *in vacuo* and the residue was chromatographed on a silica gel column (10 : 1 benzene–ethyl acetate) to give the ester (14) as a light yellow oil (0·4 g). Treatment with triethylamine followed by extraction afforded a light brown gum (0·23 g, 40%). A portion was further purified to give 2,2,2-*trichloroethyl* α-[(2R,3R)-2-*ethoxycarbonylmethylthio*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]-α-*isopropylideneacetate* (14), $[\alpha]_D^{21}$ −4·1° (*c* 0·6 in $CHCl_3$), $\nu_{max.}$ 3320 (NH), 1770 (β-lactam), 1730 (esters), 1670 (amide), and 1540 $cm^{-1}$ (amide), τ 2·7br (5H, s, Ph), 2·90 (1H, d, *J* 8 Hz, NH), 4·50 (1H, d, *J* 5 Hz, 4-H), 4·73 (1H, dd, *J* 4 and 8 Hz, 3-H), 5·23 (2H, ABq, *J* 12 Hz, $CH_2$·$CCl_3$), 7·70 (3H, s), 7·92 (3H, s), 5·96 (2H, q, *J* 7 Hz, O·$CH_2$·$CH_3$), 6·42 (2H, s, $CH_2Ph$), 6·98 (2H, s, S·$CH_2$), and 8·82 (3H, t, *J* 7 Hz, $CH_3$·$CH_2$) (Found: C, 47·8; H, 4·6; N, 5·0. $C_{22}H_{25}Cl_3N_2O_6S$ requires C, 47·9; H, 4·6; N, 5·1%).

*Liberation of the* β-*Lactam* NH *Group*.—(a) *From the dihydropyran adduct* (8). The adduct (5·0 g) in ether was treated with an excess of diazomethane [from *N*-nitrosomethylurea (20 g)] in ether (200 ml) at 0° for 6 days. The remaining excess of diazomethane was quenched with acetic acid and the solvent was removed *in vacuo*. Purification of the residual foam by preparative t.l.c. afforded the *minor isomer* of (15) as the least polar material (35 mg), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1770 (β-lactam), 1760 (ester), 1670 (amide), 1620 (C=C), and 1550 $cm^{-1}$ (amide), τ 2·7br (5H, s, Ph), 3·40 (1H, d, *J* 10 Hz, NH), 4·30 (1H, dd, *J* 4 and 10 Hz, 3-H), 4·60 (1H, d, *J* 4 Hz, 2-H), 5—5·5 (4H, m), 6·1 (2H, m), 6·42 (2H, s, $CH_2Ph$), 8—8·4 (4H, m), 8·65 (3H, s), and 9·00 (3H, s) (Found: C, 48·8; H, 4·7; N, 9·65. $C_{24}H_{27}Cl_3N_4O_5S$ requires C, 48·9; H, 4·9; N, 9·5%). The more polar, *major isomer* of (15) (2·7 g) had $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (β-lactam and ester), 1760 (amide), 1620 (C=C), and 1510 $cm^{-1}$ (amide), τ 2·7 (5H, s, Ph), 3·74 (1H, d, *J* 9 Hz, NH), 4·43 (1H, dd, *J* 4 and 9 Hz, 3-H), 4·88 (1H, d, *J* 4 Hz, 2-H), 5·33 and 5·52 (2H, ABq, *J* 12 Hz, $CH_2$·$CCl_3$), 5·28 and 5·72 (2H, ABq, *J* 17 Hz, $CH_2N_2$), 6·25 (2H, m), 6·38 (2H, s, $CH_2Ph$), 8—8·3 (4H, m), 8·66 (3H, s), and 9·04 (3H, s) (Found: C, 48·9; H, 4·65; Cl, 17·9; N, 9·5; S, 5·4%). Thus the two compounds are isomers of 2,2,2-trichloroethyl 3ξ-[(2*R*,3*R*)-2-(3,4-dihydro-2*H*-pyran-5-ylthio)-4-oxo-3-phenylacetamidoazetidin-1-yl]-4,4-dimethyl-Δ¹-pyrazoline-3ξ-carboxylate.

The major pyrazoline (100 mg) in t-butyl alcohol (2 ml) and potassium t-butoxide (30 mg) in t-butyl alcohol (2 ml) were mixed and left at room temperature for 2 min, then poured into a mixture of ether and water. The ether layer was separated and washed with water, the aqueous fractions being back-washed with more ether (2 × 5 ml). The combined organic extract was dried and evaporated *in vacuo* to give, after preparative t.l.c., the disulphide (17) and (3R,4R)-4-(3,4-*dihydro*-2H-*pyran*-5-*ylthio*)-3-*phenylacetamidoazetidin*-2-*one* (16) (40 mg, 74%), m.p. 152—154° (benzene), $[\alpha]_D^{28}$ −7° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (β-lactam), 1620 (amide), and 1520 $cm^{-1}$ (amide), τ 2·70 (5H, s, Ph), 3·20 (1H, d, *J* 8 Hz, amide NH), 3·45br (1H, s, β-lactam NH), 3·52 (1H, s, vinylic H), 4·58 (1H, dd, *J* 4 and 8 Hz, 3-H), 5·30 (1H, d, *J* 4 Hz, 4-H), 6·20 (2H, m), 6·42 (2H, s, $CH_2Ph$), and 8·10 (4H, m) (Found: C, 60·1; H, 5·7; N, 9·1. $C_{16}H_{18}N_2O_3S$ requires C, 60·4; H, 5·7; N, 8·8%). The same compound was obtained by treating the major pyrazoline isomer, or the mixture of isomers, with zinc dust in glacial acetic acid. Thus the pyrazoline (0·5 g) in 1 : 9 water–acetic acid (25 ml) was stirred at room temperature with zinc duct (1·0 g) for 1 h; the solution was filtered and evaporated and the residue extracted into ethyl acetate (150 ml). The extract was washed with water (150 ml), saturated sodium hydrogen carbonate solution (100 ml), and finally water (100 ml), dried, and evaporated to afford the sulphide (16) (0·26 g, 95%), m.p. 152—154° (from benzene).

(b) *From the isobutyl ether* (11). Reaction of the vinyl ether (0·72 g) with an excess of diazomethane in ether afforded a mixture of the corresponding pyrazoline adducts (0·7 g), which was immediately treated with zinc dust (1·5 g) in 1 : 9 water–acetic acid (60 ml) at room temperature for 3 h. Work-up in the normal manner afforded (3R,4R)-4-(2-*isobutoxyvinylthio*)-3-*phenylacetamidoazetidin*-2-*one* (19) (0·18 g, 42%), m.p. 99·5—101° (from ether), $[\alpha]_D^{25}$ +11° (*c* 0·76 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3300 (NH), 1765 (β-lactam), 1665 (amide), and 1545 $cm^{-1}$ (amide), τ 2·75br (5H, s, Ph), 2·98 (1H, d, *J* 8 Hz, NH), 3·62 (1H, s, NH), 3·52 (1H, d, *J* 12 Hz, O·C*H*=), 3·54 (1H, dd, *J* 4·5 and 8 Hz, 3-H), 5·21 (1H, d, *J* 12 Hz, S·C*H*=), 5·34 (1H, d, *J* 4·5 Hz, 4-H), 6·42 (2H, s, $CH_2Ph$), 6·67 (2H, d, *J* 6 H, O·$CH_2$), 8·16 (1H, m), and 9·09 (6H, d, *J* 6 Hz, $Me_2CH$) (Found: C, 61·0; H, 6·6; N, 8·3. $C_{17}H_{22}N_2O_3S$ requires C, 61·0; H, 6·6; N, 8·4%).

(c) *From the ester* (14). The ester (0·685 g) was treated with an excess of diazomethane in ether for 7 days at 0—5° before work-up in the normal manner. The crude mixture was immediately treated with zinc dust (1·5 g) in 1 : 9 water–acetic acid for 4 h at room temperature to give, after chromatography through silica (1 : 10 ethyl acetate–benzene as eluant), (3R,4R)-4-(*ethoxycarbonylmethylthio*)-3-*phenylacetamidoazetidin*-2-*one* (21) (0·195 g, 50%), m.p. 118·5—120° (ethyl acetate–light petroleum), $[\alpha]_D^{22}$ +17° (*c* 0·97 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3300 (NH), 1765 (β-lactam), 1730 (ester), 1670 (amide), and 1540 $cm^{-1}$ (amide), τ 2·70br (5H, s, Ph), 2·80 (1H, d, *J* 8 Hz, NH), 2·75br (1H, s, NH), 4·52 (1H, dd, *J* 4·5 and 8 Hz, 3-H), 4·97 (1H, d, *J* 4·5 Hz, 4-H), 5·84 (2H, q, *J* 7·5 Hz, O·$CH_2$), 6·40 (2H, s, $CH_2Ph$), 6·82 (2H, s, S·$CH_2$), and 8·73 (3H, t, *J* 7·5 Hz, $CH_3$·$CH_2$) (Found: C, 55·9; H, 5·8; N, 8·8; S, 9·8. $C_{15}H_{18}N_2O_4S$ requires C, 55·9; H, 5·6; N, 8·7; S, 9·9%).

(d) *From the dihydrothiazine* (12). In a similar manner, this compound (1·4 g) was treated consecutively with diazomethane and then zinc dust to give (1R,6R)-2-*phenylacetyl*-2,7-*diaza*-5-*thiabicyclo*[4.2.0]*oct*-3-*en*-8-*one* (20) (0·6 g, 83%), m.p. 183—185° (ether), $[\alpha]_D^{23}$ −774° (*c* 1·0 in tetrahydrofuran), $\lambda_{max.}$ (EtOH) 275 nm (ε 7500), $\nu_{max.}$ ($CHBr_3$) 3440 (NH), 1780 (β-lactam), and 1680 $cm^{-1}$ (amide), τ [$(CD_3)_2SO$] 1·16 (1H, s, NH), 2·68br (6H, s, Ph and vinylic H), 3·88 (2H, m, vinylic H and 6-H), 4·45 (1H, m, 1-H), and 6·13 (2H, s, $CH_2Ph$) (Found: C, 60·0; H, 4·7; N, 10·7; S, 11·7. $C_{13}H_{12}N_2O_2S$ requires C, 60·0; H, 4·7; N, 10·4; S, 12·3%).

*Bis*-(3,4-*dihydro*-2H-*pyran*-5-*yl*) *Disulphide* (17).—This was obtained from the reaction of the dihydropyran

derivative (15) with potassium t-butoxide. It was also obtained, contaminated with small quantities of the mono- and tri-sulphides, by reaction of dihydropyran with an equivalent amount of sulphur monochloride at 0° for 1 h. The *product* from the reaction of (15) with base had b.p. 65° at $2 \times 10^{-4}$ mmHg, $\nu_{max.}$ ($CHCl_3$) 1610 (C=C), and 1150 $cm^{-1}$ (ether), $\lambda_{max.}$ (EtOH) 245 nm (ε 5300), τ 3·38 (2H, t, *J* 1·4 Hz, O·CH=), 6·10 (4H, t, *J* 5 Hz, $CH_2$·O), 7·72 (4H, m, $CH_2$·C=), and 8·12 (4H, m) (Found: $M^+$, 230·0431. $C_{10}H_{14}O_2S_2$ requires *M*, 230·0435).

*Trapping with Acrylaldehyde.*—The alcohol (22) (2·0 g) in benzene (40 ml) containing acrylaldehyde (8 ml) was heated to reflux for 4 days. The crystalline precipitate was collected, washed with benzene, and dried to give a mixture of the alcohol sulphoxides (25; X = SO) (1·04 g, 54%). N.m.r. analysis showed that this mixture equilibrated to give largely one compound in solution. Recrystallisation from ethanol afforded (1S,4S,6R,7R)-4-*hydroxy*-7-*phenylacetamidocepham* 1-*oxide*, m.p. 210—213°, $[\alpha]_D^{23}$ +141° (*c* 1·00 in $Me_2SO$), $\nu_{max.}$ ($CHBr_3$) 3410 (OH), 3300 (NH), 1778 (β-lactam), 1680 and 1515 (amide), 1022 (sulphoxide), and 705 $cm^{-1}$ (Ph), τ [$(CD_3)_2SO$] 1·94 (1H, d, *J* 9 Hz, NH), 2·69br (5H, s, Ph), 3·70 (1H, d, *J* 3 Hz, OH), 4·50 (1H, dd, *J* 5 and 9 Hz, 7-H), 4·73 (1H, m, $W_{\frac{1}{2}}$ 6 Hz, 4-H), 5·19 (1H, d, *J* 5 Hz, 6-H), 6·32 and 6·49 (2H, ABq, C*H*$_2$Ph), 6·94 (2H, m, S·C*H*$_2$), 7·70, and 8·39 (2H, m, $CH_2$·C*H*$_2$·CH) (Found: C, 54·3; H, 5·1; N, 8·9; S, 10·1. $C_{14}H_{16}N_2O_4S$ requires C, 54·5; H, 5·2; N, 9·1; S, 10·4%).

(1S,6R,7R)-7-*Phenylacetamidoceph*-3-*em* 1-*Oxide* (26; X = SO).—The alcohol (25; X = SO) (1·0 g) was stirred with triethylamine (0·5 ml) and thionyl chloride (0·25 ml) in tetrahydrofuran (50 ml) at room temperature for 30 min. The mixture was then heated to reflux for a further 90 min. The solvent was evaporated off and the residue partitioned between dichloromethane and water. The mixture was filtered and the organic phase separated and washed with water. The solvent was distilled off and the residue was leached with hot ethyl acetate to give, after concentration and cooling, crystals of the *title compound* (0·43 g, 46%), m.p. 210°, $[\alpha]_D^{24}$ +131° (*c* 1·00 in $Me_2SO$), $\lambda_{max.}$ (EtOH) 247 nm (ε 7570), $\nu_{max.}$ ($CHBr_3$) 3340 (NH), 1774 (β-lactam), 1670 and 1508 (amide), and 1032 $cm^{-1}$ (sulphoxide), τ [$(CD_3)_2SO$] 1·64 (1H, d, *J* 9 Hz, NH), 2·67br (5H, s, Ph), 3·02 (1H, dd, *J* 2 and 9 Hz, 4-H), 4·24 (1H, dd, *J* 5 and 9 Hz, 7-H), 4·88 (1H, t, *J* 8 Hz, 3-H), 5·23 (1H, d, *J* 5 Hz, 6-H), 6·29 and 6·49 (2H, ABq, *J* 15 Hz, C*H*$_2$Ph), and 6·3—6·8 (4H, m) (Found: C, 57·0; H, 4·9; N, 9·6; S, 10·95. $C_{14}H_{14}N_2O_3S$ requires C, 57·8; H, 4·8; N, 9·7; S, 11·0%).

(6R,7R)-7-*Phenylacetamidoceph*-3-*em* (26; X = S).—The ceph-3-em oxide (26; X = SO) (0·4 g) in dimethylformamide (40 ml) was stirred with phosphorus tribromide (0·66 ml) at 0° for 5 min. The mixture was then poured into saturated aqueous sodium hydrogen carbonate (250 ml) and extracted with ethyl acetate (2 × 250 ml). The organic phase was washed with more sodium hydrogen carbonate solution and then water before evaporation to dryness to give the *sulphide* (0·36 g, 96%), m.p. 192—195°, $[\alpha]_D^{24}$ +10·9° (*c* 1·0 in $Me_2SO$), $\lambda_{max.}$ (EtOH) 255 nm (ε 7540), $\nu_{max.}$ ($CHBr_3$) 3390 (NH), 1760 (β-lactam), 1672 (amide), and 1560 $cm^{-1}$ (amide), τ [$(CD_3)_2SO$] 0·90 (1H, d, *J* 9 Hz, 7-NH), 2·70br (5H, s, Ph), 3·19 (1H, d, *J* 8 Hz, 4-H), 4·36 (1H, dd, *J* 5 and 9 Hz, 7-H), 4·57 (1H, ddd, *J* 3, 6, and 8 Hz, 3-H), 4·92 (1H, d, *J* 5 Hz, 6-H), 6·45 (2H, s, $CH_2Ph$), and 6·5—6·9 (4H, m) (Found: C, 61·35; H, 5·3; N, 10·0; S, 11·1. $C_{14}H_{14}N_2O_2S$ requires C, 61·5; H, 5·1; N, 10·2; S, 11·7%).

The same compound was obtained by treatment of the alcohol (25; X = SO) (1·7 g) with phosphorus tribromide (2·8 ml) in dimethylformamide (100 ml) at 0° for 15 min (yield 0·98 g, 65%).

Oxidation of the sulphide (26; X = S) (0·98 g) with peracetic acid (1 equiv.; 40% solution) in 1,2-dichloroethane (250 ml) at 0° for 25 min, followed by normal work-up, afforded the sulphoxide (26; X = SO) [(1*S*)-isomer] (0·78 g, 83%).

(6R,7R)-4ξ-*Hydroxy*-7-*phenylacetamidocepham* (25; X = S).—The sulphoxide (25; X = SO) (0·92 g), potassium iodide (4·0 g), and acetyl chloride (0·32 ml) were stirred in dimethylformamide (10 ml) at 0° for 20 min. The mixture was partitioned between water (500 ml) and ethyl acetate (500 ml), with addition of a small quantity of sodium disulphite to discharge the iodine colour. The aqueous layer was further extracted with ethyl acetate (2 × 250 ml), before the combined organic extract was washed with water (2 × 250 ml). Evaporation of the organic extract afforded the *title alcohol* (0·74 g, 80%), m.p. 158—160°, $[\alpha]_D^{21}$ +167° (*c* 0·8 in $Me_2SO$), $\nu_{max.}$ ($CHBr_3$) 3585 (OH), 3405 (NH), 1760 (β-lactam), 1678 (amide), and 1514 $cm^{-1}$ (amide), τ [$(CD_3)_2SO$] 0·97 (1H, d, *J* 8 Hz, NH), 2·69br (5H, s, Ph), 3·81 (1H, d, *J* 3 Hz, OH), 4·70 (2H, narrow m, 4-H and 7-H), 4·91 (1H, d, *J* 4 Hz, 6-H), 6·44 (2H, s, $CH_2Ph$), 6·90 (1H, ddd, *J* 3, 11, and 14 Hz, 2-*pro*-*R* H), 7·36 (1H, ddd, *J* 3, 3, and 14 Hz, 2-*pro*-*S* H), and 7·9—8·4 (3H, m) (Found: C, 57·4; H, 5·5; N, 9·1; S, 10·5. $C_{14}H_{15}N_2O_3S$ requires C, 57·4; H, 5·5; N, 9·6; S, 11·0%).

(6R,7R)-7-*Phenylacetamidoceph*-3-*em* 1,1-*Dioxide*.—The sulphide (26; X = S) (0·27 g) and peracetic acid (3 mol. equiv.; 40% solution) in 1,2-dichloroethane (90 ml) was set aside at room temperature for 6 days. Work-up in the normal manner, followed by chromatography through silica gel (10 g), eluting with dichloromethane–acetone mixtures, afforded the *sulphone* (0·23 g, 75%), m.p. 196—197° (decomp.), $[\alpha]_D^{21}$ −84° (*c* 0·8 in $Me_2SO$), $\lambda_{max.}$ (EtOH) 241 nm (ε 8200), $\nu_{max.}$ ($CHBr_3$) 3400 (NH), 1794 (β-lactam), 1686 (amide), and 1510 $cm^{-1}$ (amide), τ [$(CD_3)_2SO$] 1·15 (1H, d, *J* 9 Hz, NH), 2·72br (5H, s, Ph), 3·19 (1H, d, *J* 8 Hz, 4-H), 4·11 (1H, dd, *J* 4 and 9 Hz, 7-H), 4·74 (1H, ddd, *J* 2, 6, and 8 Hz, 3-H), 4·77 (1H, d, *J* 4 Hz, 6-H), 5·85br (1H, d, *J* 17 Hz, 2-*pro*-*R* H), 6·23 (1H, dd, *J* 6 and 17 Hz, 2-*pro*-*S* H), and 6·42 (2H, s, C*H*$_2$Ph) (Found: C, 54·6; H, 4·4; N, 8·7; S, 10·4. $C_{14}H_{14}N_2O_4S$ requires C, 54·9; H, 4·6; N, 9·1; S, 10·5%).

(6R,7R)-4ξ-*Ethoxy*-7-*phenylacetamidocepham* (27; X = S).—The olefin (26; X = S) (0·30 g) was stirred with ethanolic 8N-hydrogen chloride (0·5 ml) in tetrahydrofuran (5 ml) at room temperature for 20 h. The mixture was then evaporated to dryness and the residue partitioned between ethyl acetate and aqueous sodium hydrogen carbonate solution. The dried organic extract yielded the *ethoxysulphide* (0·25 g, 63%), m.p. 138—140° (benzene), $[\alpha]_D^{21}$ +127° (*c*. 0·8 in $Me_2SO$), $\nu_{max.}$ ($CHBr_3$) 3395 (NH), 1750 (β-lactam), 1670 (amide), and 1503 $cm^{-1}$ (amide), τ[$(CD_3)_2SO$] 0·99 (1H, d, *J* 9 Hz, NH), 2·70br (8H, s, Ph and benzene), 4·60 (1H, dd, *J* 5 and 9 Hz, 7-H), 4·95 (1H, buried, 4-H), 4·98 (1H, d, *J* 5 Hz, 6-H), 6·1—7·4 (4H, m), 6·45 (2H, s, C*H*$_2$Ph), 7·9—8·4 (2H, m), and 8·87 (3H, t, *J* 7 Hz, C*H*$_3$·$CH_2$) (Found: C, 60·6; H, 6·5; N, 8·1; S, 9·6. $C_{16}H_{20}N_2O_3S$,0·5$C_6H_6$ requires C, 60·6; H, 6·2; N, 7·5; S, 8·5%).

The same ethoxy-sulphide was obtained by treatment of either the hydroxy-sulphide (25; X = S) or the sulphoxide (25; X = SO) with ethanolic hydrogen chloride under the conditions just described. In contrast, reaction of the ceph-3-em oxide (26; X = SO) did not afford any of the ether.

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