Transformations of Penicillins. Part VI.[1] Preparation and Reactions of Thiosulphonate *S*-Esters derived from Penicillin *S*-Oxides

By Robin D. Allan, Derek H. R. Barton,* Moopil Girijavallabhan, and Peter G. Sammes, Chemistry Department, Imperial College, London SW7 2AY

The sulphenic acids derived by heating penicillin sulphoxides react with arenesulphinic acids to form the corresponding arenethiosulphonate *S*-esters. These esters are themselves versatile derivatives and react with nucleophiles to form the corresponding sulphides, liberating the arenesulphinic acid. This two-step process greatly extends the range of substituents that can be introduced onto the penicillin sulphur atom after opening of the thiazolidine ring. A novel reaction was obtained with the thiosulphonate ester (2; R = Me) and sodium azide, which gave the symmetrical disulphide (6).

PREVIOUS papers in this series have illustrated the synthetic utility of the sulphenic acid intermediates obtained by heating penicillin *S*-oxides. The interest in many of these processes lies in the fact that the transient sulphenic acid can be trapped to give derivatives potentially useful for conversion into penicillin and cephalosporin analogues. Because of the transient nature and low concentrations of the sulphenic acids such trapping reactions generally have to be extremely efficient in order to compete with normal decay processes such as ring expansion, rearrangement, *etc.* As a consequence it was considered desirable to prepare an isolable derivative of the sulphenic acid which would behave as a moderated sulphenic acid, particularly with respect to nucleophilic substitution reactions. Since thiosulphonate *S*-esters are known to react efficiently with stabilised carbanions[2] to produce substituted sulphides, an attempt to prepare the thiosulphonate derivatives from penicillin *S*-oxides was made. The reaction of the trichloroethyl ester (1; R = O·CH_2·CCl_3) with toluene-*p*-sulphinic acid[3] was carried out in dry benzene using diethylaniline to buffer the solution. After 26 h at reflux no starting sulphoxide remained. Isolation of the principal products by crystallisation gave the thiosulphonate (2; R = Me) in 81% yield. Although the initial product expected was the βγ-unsaturated isomer (3; R = O·CH_2·CCl_3), none of this was detected amongst the products. Presumably conjugation was completely effected during the trapping reaction. The generality of this reaction was established by using, as an alternative, *p*-methoxybenzenesulphinic acid, which afforded the corresponding ester (2; R = MeO) in 85% yield.

Because of the potential usefulness of substituted hydrazide systems for protection of carboxylic acids,[4] some examples of the trapping reaction were also performed with the hydrazide derivatives (1; R = NMe·NMe_2) and (1; R = NPr^i·$NHPr^i$). In the former case the trapping reaction was much faster (3 h) than in the case of the trichloroethyl ester (26 h reaction time), and the reaction with the latter hydrazide was even faster (1·5 h). This is presumably caused by a steric buttressing effect by the acid derivative on the adjacent *gem*-dimethyl group (Scheme). Such an effect has been noticed previously[5] and can be explained in terms of compression of the *syn*-methyl group against the sulphoxide bond leading to a more efficient electrocyclic opening of the thiazolidine ring forming the sulphenic acid and relieving steric strain.

The products from the hydrazide derivatives were the βγ-unsaturated isomers (3; R = NMe·NMe_2) and (3; R = NPr^i·$NHPr^i$) rather than the conjugated analogues. Treatment of these isomers with bases failed to effect the conjugation of the double bond. As expected for hydrazide derivatives and as established for amides,[6] the proton adjacent to the hydrazide function is less acidic than that of the corresponding trichloroethyl derivative. That the isolation of the hydrazide βγ-isomers (3) is not due to the presence of a sterically controlled equilibration of the double bond in these series is indicated by the absence of epimers about the point of hydrazide attachment.

The di-isopropylhydrazide (3; R = NPr^i·$NHPr^i$) was accompanied by another compound. Prolonged heating of the former effected its complete conversion into the new product, which was isomeric with the starting thiosulphonate. Its n.m.r. spectrum showed that it had lost the doubly bonded methylene group and contained a new quaternary methyl group. It was assigned the structure (4) on the basis of its spectral properties. The trimethylhydrazide behaved in a similar manner although, in this instance other reactions interfered and the rearranged product was not isolated in a pure state.

As expected for thiosulphonates, reactions with stabilised carbanions resulted in displacement of the sulphinic acid and formation of a substituted sulphide.[2] For example, treatment of the hydrazide derivative (3; R = NMe·NMe_2) with diethyl sodiomalonate in benzene at room temperature afforded the malonate derivative (5), and related nucleophiles behaved similarly.

[1] Part V, I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *J.C.S. Perkin I*, 1973, 1187.

[2] L. G. S. Brooker and S. Smiles, *J. Chem. Soc.*, 1926, 1726; D. T. Gibson, *ibid.*, 1931, 2637; S. Hayashi, M. Furukawa, J. Yamamoto, and K. Nigata, *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 1188.

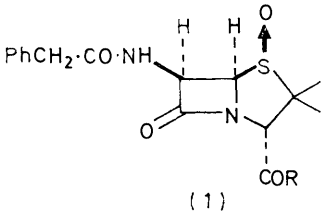
[3] For a review on the preparation of sulphinic acids see W. E. Truce and A. M. Murphy, *Chem. Rev.*, 1951, **48**, 69.

[4] D. H. R. Barton, M. Girijavallabhan, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 929.

[5] D. H. R. Barton, I. H. Coates, P. G. Sammes, and C. M. Cooper, following paper; *cf.* R. D. G. Cooper, *J. Amer. Chem. Soc.*, 1970, **92**, 5010.

[6] 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.

A novel reaction was observed between the trichloroethyl derivative (2; R = Me) and sodium azide in aqueous dioxan. Nitrogen was liberated and the disulphide (6) was isolated in 50% yield. Displacement of a sulphinic acid residue must occur, followed by reduction of the sulphenyl azide intermediate by more azide ion to give nitrogen and the thiolate ion. The latter then reacts with more of the starting thiosulphonate to produce the disulphide.



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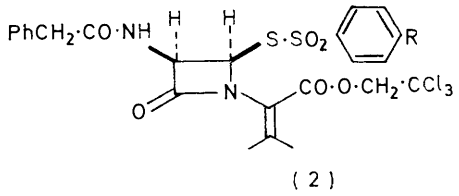

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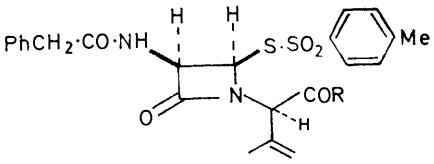

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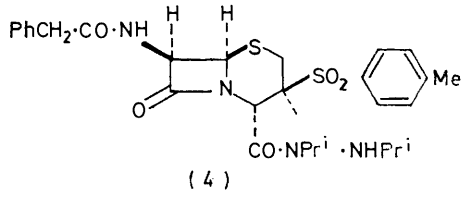

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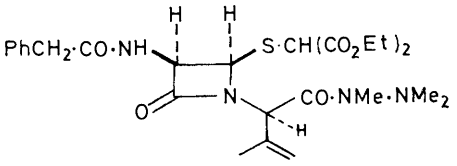

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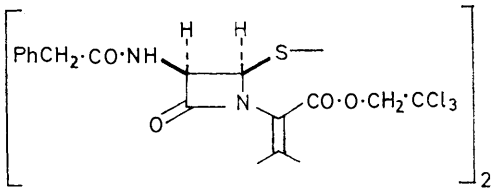

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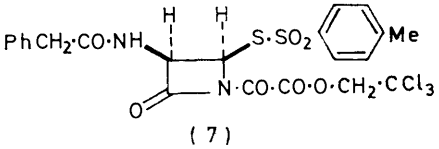

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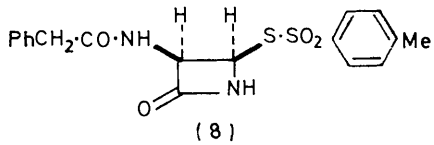

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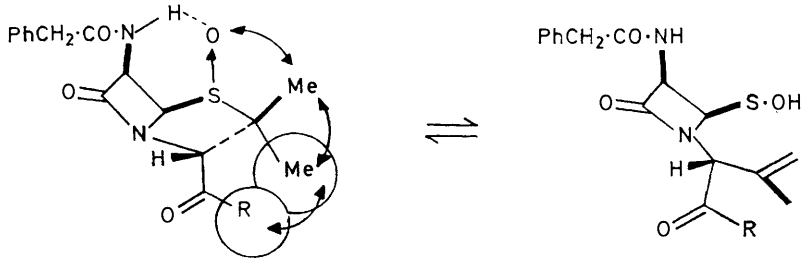

SCHEME

Ozonolysis of the thiosulphonate (2; R = Me) was readily effected to produce the oxamide (7), and subsequent hydrolysis with dilute phosphoric acid liberated the free amide (8). However, this product decomposed on chromatography. Thiosulphonate presumably behaves as an efficient leaving group under these conditions.

EXPERIMENTAL

I.r. spectra were recorded with a Unicam SP 200 spectrometer and u.v. spectra with a Unicam SP 800 spectrometer for ethanolic solutions. ^{1}H N.m.r. spectra were recorded with a Varian T60 instrument for solutions in deuteriochloroform using 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°. Phosphoric acid solutions were prepared

from orthophosphoric acid. M.p.s were determined with a Kofler hot-stage apparatus. Solutions were dried over anhydrous sodium sulphate.

Reaction of the Trichloroethyl Ester (1; R = O·CH_2·CCl_3) *with Toluene*-p-*sulphinic Acid.*—To a solution of toluene-*p*-sulphinic acid (8·0 g; freshly prepared by neutralisation of the sodium salt with 1 equiv. of concentrated hydrochloric acid, followed by extraction with dichloromethane) in dry benzene (80 ml) was added freshly distilled *NN*-diethylaniline (20 ml). The solution, when tested with damp indicator paper, showed a pH value of *ca.* 5·0. The trichloroethyl ester (1; R = O·CH_2·CCl_3) (5·0 g) was then added and the resulting solution was heated to reflux under dry, oxygen-free nitrogen for 26 h. It was then cooled, diluted with benzene (120 ml), and extracted first with aqueous 15% v/v phosphoric acid (3 × 30 ml), then with dilute sodium hydrogen carbonate solution (20 ml), and finally with water (50 ml). The benzene extract was evaporated under reduced pressure and the oily residue was poured into rapidly stirred 1 : 4 cyclohexane–light petroleum at 60°. The precipitated oil was re-treated a further two times by this procedure to give a crystalline precipitate, which was recrystallised from benzene–cyclohexane, to give (3R,4R)-1-[2-*methyl*-1-(2,2,2-*trichloroethoxycarbonyl*)-*prop*-1-*enyl*]-3-*phenylacetamido*-4-(p-*tolylsulphonylthio*)-*azetidin*-2-*one* (2; R = Me) (5·2 g, 81%), m.p. 88—90°, $[\alpha]_D^{25}$ +28° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3300 (NH), 1775 (β-lactam), 1690 (amide), 1340, and 1150 cm^{-1} (SO_2), $\lambda_{max.}$ 225 and 250 nm (ε 15,800 and 7350), τ 2·4 (2H, m, aromatic), 2·8 (7H, m, aromatic), 4·2 (1H, d, *J* 5 Hz), 5·4—5·2 (3H, m), 6·40 (2H, s), 7·6 (3H, s), and 7·9 (3H, s) (Found: C, 48·6; H, 4·1; Cl, 17·5; N, 4·3; S, 10·4. $C_{25}H_{25}Cl_3N_2O_6S_2$ requires C, 48·4; H, 4·0; Cl, 17·2; N, 4·5; S, 10·3%).

Reaction of the Trichloroethyl Ester (1; R = O·CH_2·CCl_3) *with* p-*Methoxybenzenesulphinic Acid.*—In a similar manner, *p*-methoxybenzenesulphinic acid (5·0 g), buffered with diethylaniline, and the ester (4·0 g) were heated in benzene (40 ml) at reflux for 15 h. After precipitation from cyclohexane–light petroleum at 60° the solid was recrystallised from benzene to give (3R,4R)-4-(p-*methoxyphenylsulphonylthio*)-1-[2-*methyl*-1-(2,2,2-*trichloroethoxycarbonyl*)*prop*-1-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (2; R = OMe) (5·7 g, 84%), m.p. 87—89°, $[\alpha]_D^{25}$ +42° (*c* 1·8 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3300 (NH), 1780 (β-lactam), 1690 (amide), 1340, and 1150 cm^{-1} (SO_2), $\lambda_{max.}$ 241 and 265 (ε 18,000 and 12,000), τ 2·3 (2H, d, aromatic), 2·8 (5H, m, aromatic), 3·2 (2H, d, aromatic), 4·2 (1H, d, *J* 4·5 Hz), 5·2—5·4 (3H, m), 6·25 (3H, s, MeO), 6·50 (2H, s, PhCH_2), 7·9 (3H, s), and 8·1 (3H, s) (Found: C, 47·1; H, 3·9; Cl, 16·5; N, 4·3; S, 10·3. $C_{25}H_{25}Cl_3N_2O_7S_2$ requires C, 47·2; H, 3·9; Cl, 16·7; N, 4·4; S, 10·1%).

Trapping of the Hydrazide Derivatives with Toluene-p-*sulphinic Acid.*—(a) *The trimethylhydrazide* (1; R = NMe·NMe_2). The hydrazide (5 g), toluene-*p*-sulphinic acid (8·0 g, 2·5 equiv.), and diethylamine (25 g, 5 equiv.) in dioxan (100 ml) were heated at reflux for 3 h. (A control reaction showed that a similar reaction time was required with benzene as solvent.) The reaction mixture was worked up in the normal manner to give, after column chromatography, (3R,4R)-1-[(1R)-2-*methyl*-1-(NN′N′-*trimethylhydrazinocarbonyl*)*prop*-2-*enyl*]-3-*phenylacetamido*-4-(p-*tolylsulphonylthio*)*azetidin*-2-*one* (3; R = NMe·NMe_2) (4·6 g, 70%), m.p. 143—145°, $[\alpha]_D$ −186° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 and 3350 (NH), 1775 (β-lactam), 1680 and 1670 (amide), and 1340 and 1150 cm^{-1} (SO_2), τ 2·05—2·85 (*ca.* 9H, m), 3·38 (1H, d, *J* 8 Hz, NH), 4·0 (1H, d, *J* 4 Hz, 4-H), 4·50 (1H, s), 4·80 (1H, dd, *J* 4 and 8 Hz, 3-H), 5·10br (s) and 5·28br (s) (2H, CH_2=C), 6·25 (2H, s, PhCH_2), 7·0 (3H, s, CO·NMe), 7·35 and 7·38 (NMe_2), and 8·0 (3H, s, MeC=) (Found: C, 57·5; H, 5·9; N, 10·4; S, 11·9. $C_{26}H_{32}N_4O_5S_2$ requires C, 57·35; H, 5·9; N, 10·3; S, 11·8%).

(b) *The* NN′-*Di-isopropylhydrazide* (1; R = NPr^i·$NHPr^i$). The hydrazide (5·0 g) in dry benzene (80 ml) was heated with toluene-*p*-sulphinic acid (8·0 g) and diethylaniline (25 ml) at reflux for 1·5 h. The solution was cooled, diluted with ethyl acetate (100 ml), and washed with 15% v/v phosphoric acid until all the base had been removed, followed by dilute aqueous sodium hydrogen carbonate and, finally, water. The organic extract was evaporated to small bulk *in vacuo* and the residue precipitated from hot light petroleum several times. The residual oil was then chromatographed through silica gel (120 g) to give two products.

The first component eluted (benzene as solvent) was recrystallised from benzene–cyclohexane to give (3S,4S,6R,7R)-4-(NN′-*di-isopropylhydrazinocarbonyl*)-3-*methyl*-7-*phenylacetamido*-3-(p-*tolylsulphonyl*)*cepham* (4) (1·3 g, 20%), m.p. 178—179°, $[\alpha]_D^{25}$ +49° (*c* 1·4 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3450, 3350 (NH), 1775 (β-lactam), 1690 (amide), 1660, 1520, 1330, and 1155 (SO_2) cm^{-1}, τ 2·3 (2H, d, aromatic), 2·8 (7H, m, aromatic), 3·7 (1H, s), 4·3—4·6 (2H, β-lactam), 5·9 (1H, m), 6·2br (1H, s), 6·45 (2H, s), 6·68br (2H, s), 6·75 (1H, m, CON·CH), 7·6 (3H, s), 8·35 (3H, s), and 8·8—9·2 (2 × *Me*$_2$CH) (Found: C, 59·2; H, 6·4; N, 9·6; S, 11·0. $C_{19}H_{38}N_4O_5S_2$ requires C, 59·4; H, 6·5; N, 9·55; S, 10·9%).

When a sample of the thiosulphonate (3; R = NPr^i·$NHPr^i$) was heated in benzene for a long period (10 h) it was gradually converted into the cepham derivative (4). Treatment of the same thiosulphonate with either triethylamine or diazabicyclononene in tetrahydrofuran for several h did not induce isomerisation of the double bond.

The second compound, eluted with benzene–ethyl acetate mixtures, was recrystallised from benzene–cyclohexane to yield (3R,4R)-1-[(1R)-NN′-*di-isopropylhydrazinocarbonyl*-2-*methylprop*-2-*enyl*]-3-*phenylacetamido*-4-(p-*tolylsulphonylthio*)*azetidin*-2-*one* (3; R = NPr^i·$NHPr^i$) (4·5 g, 70%), as a foam, $[\alpha]_D^{25}$ −117° (*c* 1·5 in $CHCl_3$), $\nu_{max.}$ 3450 and 3350 (NH), 1770 (β-lactam), 1690 and 1600 (amide), and 1340 and 1150 cm^{-1} (SO_2), τ 2·4 (2H, m, aromatic), 2·7 (7H, m, aromatic), 3·4 (1H, d, *J* 8 Hz, NH), 4·2 (1H, d, *J* 5 Hz, 4-H), 4·7br (1H, s), 4·95 (1H, dd, *J* 5 and 8 Hz, 3-H), 5·35br (s) and 5·6br (s) (2H, C=CH_2), 5·9 (1H, m, CO·NH), 6·2—6·9 (4H, m), 7·6 (3H, s, Ar*Me*), 8·25 (3H, s, MeC=C), and 8·6—9·2 (2 × *Me*$_2$CH). A sample was precipitated from dioxan for analysis (Found: C, 58·9; H, 6·5; N, 9·0; S, 10·4. $C_{29}H_{38}N_4O_5S_2$,0·5$C_4H_8O_2$ requires C, 59·0; H, 6·7; N, 8·9; S, 10·2%).

Reaction of the Hydrazide (3; R = NMe·NMe_2) *with Diethyl Sodiomalonate.*—A solution of the hydrazide (600 mg) in dry benzene (15 ml) was added to a freshly prepared solution of diethyl sodiomalonate (370 mg, 2 equiv.) in benzene (15 ml) with stirring at room temperature. After 15 min the solution was made just acidic with 5% v/v phosphoric acid and then extracted with ethyl acetate. The extract was washed with aqueous 1% w/v sodium hydrogen carbonate and water. Evaporation of the extract afforded a pale yellow oil which was precipitated from light petroleum as an amorphous solid, (3R,4R)-4-

[(*bisethoxycarbonyl*)*methylthio*]-1-[(1R)-2-*methyl*-1-NN'N'-*trimethylhydrazinocarbonylprop*-2-*enyl*]-3-*phenylacetamidoazetidin*-2-*one* (5) (475 mg, 80%), $[\alpha]_D^{20}$ −117° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 3400, 1765, 1720, 1690, 1680, 1520, and 1460 cm^{-1}, τ 2·7br (5H, s, aromatic), 3·21 (1H, d, *J* 8 Hz, NH), 4·25 (1H, d, *J* 4 Hz), 4·44br (1H, s), 4·58 (1H, dd, *J* 4 and 8 Hz), 4·95 and 5·05 (2H, CH_2=C), 5·65 (1H, s), 5·85 (4H, q, *J* 7 Hz, 2 × CH_2Me), 6·40 (2H, s, PhCH_2), 7·15 (3H, s, CONMe), 7·5 and 7·6 (2 × NMe), 8·08 (3H, s), and 8·80 (6H, t, *J* 7 Hz, 2 × *Me*CH_2) (Found: C, 57·1; H, 6·5; N, 9·95; S, 5·9. $C_{26}H_{36}N_4O_7S$ requires C, 56·9; H, 6·6; N, 10·2; S, 5·8%).

Preparation of the Trimethylhydrazide (1; R = NMe·NMe_2).—Triethylamine (46 g) was added to a stirred solution of (1*S*,6*R*)-6-phenylacetamidopenicillanic acid *S*-oxide (158 g) in dry tetrahydrofuran (1·5 l) containing ethyl chloroformate (49 g; 1·1 equiv.) at −20° and under nitrogen. After 1 h freshly distilled trimethylhydrazine (33·5 g) was added. After 20 min the solvent was replaced by ethyl acetate and the solution was washed with water, 5% v/v phosphoric acid (3 × 150 ml), and finally water (10 ml portions). After removal of solvent the crude product was crystallised from chloroform to give (1S,6R)-6-*phenylacetamidopenicillano*-(NN'N'-*trimethyl*)*hydrazide* S-*oxide* (1; R = NMe·NMe_2) (120·5 g, 51%), as a monosolvate, m.p. 76—82° (loss of solvent), $[\alpha]_D^{20}$ −140° (*c* 2·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1780 (β-lactam), 1680 (amides), and 1510 cm^{-1}, τ 2·75 (5H, s, Ph), 2·80 (1H, d, *J* 10 Hz, NH), 4·05 (1H, dd, *J* 4 and 10 Hz, 6-H), 4·40 (1H, s, 3-H), 4·98 (1H, d, *J* 4 Hz, 5-H), 6·42 (2H, s, CH_2Ph), 7·07 (3H, s, NMe), 7·42 (6H, s, NMe_2), 8·35 (3H, s, Me), and 8·75 (3H, s, Me) (Found: C, 45·5; H, 5·1; Cl, 20·5; N, 10·6; S, 6·1. $C_{19}H_{26}N_4O_4S,CHCl_3$ requires C, 45·7; H, 5·2; Cl, 20·2; N, 10·7; S, 6·1%).

Reaction of the Thiosulphonate (2; R = Me) *with Sodium Azide.**—Sodium azide (190 mg, 3 equiv.) was added to a solution of the ester (650 mg) in 1 : 9 water–dioxan (10 ml) in portions during 10 min and the solution was then stirred at room temperature for 3 h. Nitrogen evolution occurred. The solution was poured into water–ethyl acetate and the organic extract was washed with water and concentrated. The residue was crystallised from ether to give *bis*-{(2R,3R)-1-[2-*methyl*-1-(2,2,2-*trichloroethoxycarbonyl*)*prop*-1-*enyl*]-4-*oxo*-3-*phenylacetamidoazetidin*-2-*yl*} *disulphide* (6) (244 mg, 50%), m.p. 101—115°, $[\alpha]_D$ 4·15 (*c* 0·67), $\nu_{max.}$ ($CHCl_3$) 3450 and 3350 (NH), 1775 (β-lactam), 1725 (ester), and 1680 cm^{-1} (amide), τ 2·7 (10H, s, 2 × Ph), 3·4 (2H, d, *J* 8 Hz, 2 × Me), and 7·9 (6H, s, 2 × Me) (Found: C, 46·5; H, 4·1; Cl, 22·8; N, 5·75; S, 7·0. $C_{36}H_{36}Cl_6N_4O_8S_2$ requires C, 46·5; H, 3·9; Cl, 22·7; N, 6·0; S, 6·9%).

Ozonolysis of the Thiosulphonate (2; R = Me).—Ozone was passed through a solution of the ester (1·0 g) in dry methanol (25 ml), at 0°, the reaction being monitored by t.l.c. After 1 h, when all the starting material had reacted, the precipitated solid was collected, washed with a little methanol, and dried to give (3R,4R)-3-*phenylacetamido*-4-(p-*tolylsulphonylthio*)-1-(2,2,2-*trichloroethoxyoxaloyl*)*azetidin*-2-*one* (7) (0·86 g, 90%), m.p. 119—121°, $[\alpha]_D$ −15° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 3350 (NH), 1815, 1755, 1700 (CO·N·CO·CO), 1675 (amide), 1330, and 1140 cm^{-1} (SO_2), τ 2·2 (2H, m, aromatic), 2·7 (8H, m), 3·9 (1H, d, *J* 5 Hz, 4-H), 4·8 (1H, dd, *J* 5 and 8 Hz, 3-H), 5·1 (2H, s, CH_2), 6·4 (2H, s, CH_2Ph), and 7·6 (3H, Ar*Me*) (Found: C, 44·4; H, 3·5; Cl, 18·3; N, 4·5; S, 11·0. $C_{22}H_{19}Cl_3N_2O_7S_2$ requires C, 44·5; H, 3·2; Cl, 18·0; N, 4·7; S, 10·8%).

A sample of the oxamide (7) was hydrolysed by stirring with 20% v/v phosphoric acid (in 1 : 2 water–dioxan) for 2 h at room temperature. Extraction with ethyl acetate gave the free amide (8) as an unstable solid. The n.m.r. spectrum showed τ 2·6—2·8 (9H, aromatic), 4·5—4·8 (2H, β-lactam proton as a multiplet), 6·4 (2H, s, CH_2Ph), and 7·5 (3H, s, Ar*Me*).

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