Studies Related to Penicillins. Part 24.[1] A Novel Thiazolidine Ring Enlargement of Penam Dioxides

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In the presence of hydrochloric acid, (3*S*,5*R*,6*R*)-3-diazoacetyl-2,2-dimethyl-6-phenoxyacetamidopenam 1,1-dioxide (**4c**) was converted into the corresponding 3-chloroacetyl derivative (**4b**), which reacted with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to give (7*R*,8*R*)-2-isopropylidene-8-phenoxyacetamido-5-oxa-6-thia-1-azabicyclo[5.2.0]nonane-3,9-dione 6-oxide (**9a**). The last-cited compound was also produced when (3*S*,5*R*,6*R*)-3-hydroxyacetyl-2,2-dimethyl-6-phenoxyacetamidopenam 1,1-dioxide (**4d**) was subjected to the action of DBN followed by thionyl chloride. Whereas a 1:1.6 mixture of the oxathiazabicyclononane oxide (**9a**) and its 8*S*-diastereoisomer (**9b**) resulted when the diazoacetylpenam dioxide (**4c**) was treated with DBN followed by hydrochloric acid, (7*R*,8*S*)-2-isopropylidene-8-phenylacetamido-5-oxa-6-thia-1-azabicyclo[5.2.0]nonane-3,9-dione 6-oxide (**9c**) was the sole product from the corresponding reaction involving (3*S*,5*R*,6*R*)-3-diazoacetyl-2,2-dimethyl-6-phenylacetamidopenam 1,1-dioxide (**4e**). Corresponding enlargements of the thiazolidine ring of (3*S*,5*R*)-3-diazoacetyl-2,2-dimethylpenam 1,1-dioxide (**6d**) and its 6*S*-chloro derivative (**6e**) were induced by DBN followed by hydrochloric acid to give (7*R*)-2-isopropylidene-5-oxa-6-thia-1-azabicyclo[5.2.0]nonane-3,9-dione 6-oxide (**9d**) and its 8*S*-chloro derivative (**9e**). In all cases, the oxathiazabicyclononane oxides were produced as single diastereoisomers although their configuration at position 6 was not established.

Some time ago, we reported[2] that the chloroacetylpenam (**1a**) [prepared from penicillin V potassium salt (**1b**) by a three-step sequence] reacted with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to give the cepham (**2a**). The ring expansion was presumed to involve the intermediate thiolate (**3a**), derived by a β-elimination process. More recently, we showed[3] that penicillinate dioxides, *e.g.* (**4a**), reacted with DBN to give (after acidification) azetidinesulphinic acids, *e.g.* (**5**). Initially, the base brought about[4] an equilibration of the penicillinate (**4a**) with its 6-epimer (**6a**); the latter then underwent β-elimination.

It is well established that sulphinate salts undergo *S*-alkylations with alkyl halides;[5] for example, we have shown that the sulphinate (**7**) is transformed into the sulphone (**8**) when treated with chloroacetone in *N*,*N*-dimethylformamide.[6] Accordingly, we expected that DBN would convert the chloroacetylpenam dioxide (**4b**) into the cepham dioxide (**2b**), by way of the sulphinate (**3b**). Epimerisation of the acylamino substituent was not likely to present a problem in the last-cited situation, since the acidity of the 3-hydrogen atom of the precursor (**4b**) was expected to outweigh that of the 6-hydrogen atom.[2] We now report on the unexpected outcome of this reaction and its consequences.

Results and Discussion

The diazoacetylpenam (**1c**)[7] [prepared in virtually quantitative yield by subjecting the salt (**1b**) to the action of $Et_3NH^+Cl^-$ in CH_2Cl_2, $ClCO_2Et$ in CH_2Cl_2, and CH_2N_2 in Et_2O] was oxidised to the diazoacetylpenam dioxide (**4c**), isolated as a crystalline solid in 42% yield, by the action of potassium permanganate in aqueous acetic acid. The conversion of the diazoacetylpenam dioxide (**4c**) into the chloroacetylpenam dioxide (**4b**) was achieved in 92% yield by stirring a solution of the former in dichloromethane with 4M hydrochloric acid.

The chloroacetylpenam dioxide (**4b**) reacted with DBN in deuteriochloroform to give, after work-up and purification on silica gel, a crystalline product in 54% yield. Mass spectrometry and elemental analysis established that the material was derived from the precursor (**4b**) by the loss of the elements of hydrogen chloride. However, the compound showed properties markedly different from those of the cepham dioxide (**2b**),[8] which had been prepared earlier from the cepham (**2a**) by oxidation with *m*-chloroperoxybenzoic acid. Spectroscopic considerations left little doubt that the dehydrochlorination product was the oxathiazabicyclononane oxide (**9a**), as a single diastereoisomer (but of undefined stereochemistry at sulphur). In particular, ^1H n.m.r. spectroscopy ($CDCl_3$) revealed signals for the vinylic methyl groups as two three-proton singlets at δ 1.93 and 2.31, for the methylene group at position 4 as two one-proton doublets (*J* 14 Hz) at δ 3.79 and 5.42, and for the *cis*-oriented β-lactam hydrogen atoms as a one-proton doublet (*J* 4 Hz) at δ 4.83 and a one-proton double doublet (*J* 10 and 4 Hz) at δ 5.94.

Clearly, the oxathiazabicyclononane oxide (**9a**) had arisen from the intermediate (**3b**) by an intramolecular displacement, in which an oxygen atom of the sulphinate moiety had acted as the nucleophile. This was a surprising outcome since, as already indicated, intermolecular reactions of sulphinate salts with alkyl halides are dominated by *S*-alkylations. Moreover, that there should be a preference to form the seven-membered rather than the six-membered ring was also unusual.

It is conceivable that the sultine (**9a**) arises from the cepham dioxide (**2b**) by the pathway outlined in the Scheme, in which the species (**10**)—(**12**) are postulated as intermediates. However, this possibility was eliminated by the finding that compound (**2b**)[8] was recovered unchanged (in 88% yield) when subjected to the action of DBN in deuteriochloroform followed by an acidic work-up.

We are aware of only one other example in which a presumed

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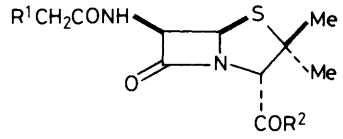
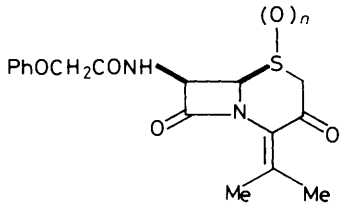


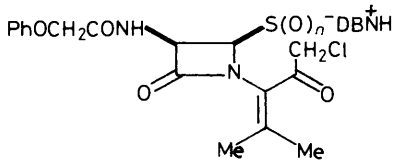
(1)

a ; R^1 = OPh , R^2 = CH_2Cl
b ; R^1 = OPh , R^2 = OK
c ; R^1 = OPh , R^2 = CHN_2
d ; R^1 = Ph , R^2 = OK
e ; R^1 = Ph , R^2 = CHN_2



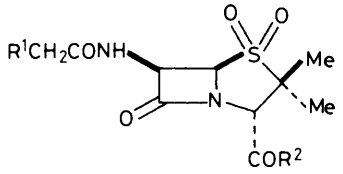
(2)

a ; n = 0
b ; n = 2



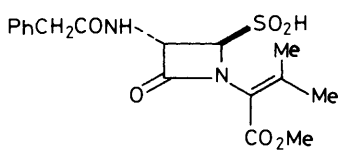
(3)

a ; n = 0
b ; n = 2

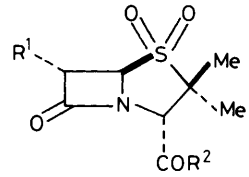


(4)

a ; R^1 = Ph , R^2 = OMe
b ; R^1 = OPh , R^2 = CH_2Cl
c ; R^1 = OPh , R^2 = CHN_2
d ; R^1 = OPh , R^2 = CH_2OH
e ; R^1 = Ph , R^2 = CHN_2

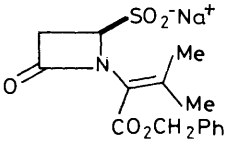


(5)

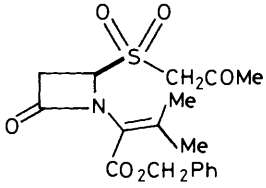


(6)

a ; R^1 = $NHCOCH_2Ph$, R^2 = OMe
b ; R^1 = $NHCOCH_2OPh$, R^2 = CHN_2
c ; R^1 = $NHCOCH_2Ph$, R^2 = CHN_2
d ; R^1 = H , R^2 = CHN_2
e ; R^1 = Cl , R^2 = CHN_2
f ; R^1 = H , R^2 = ONa



(7)



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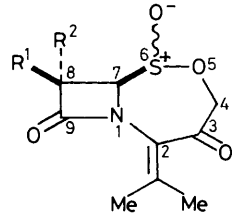
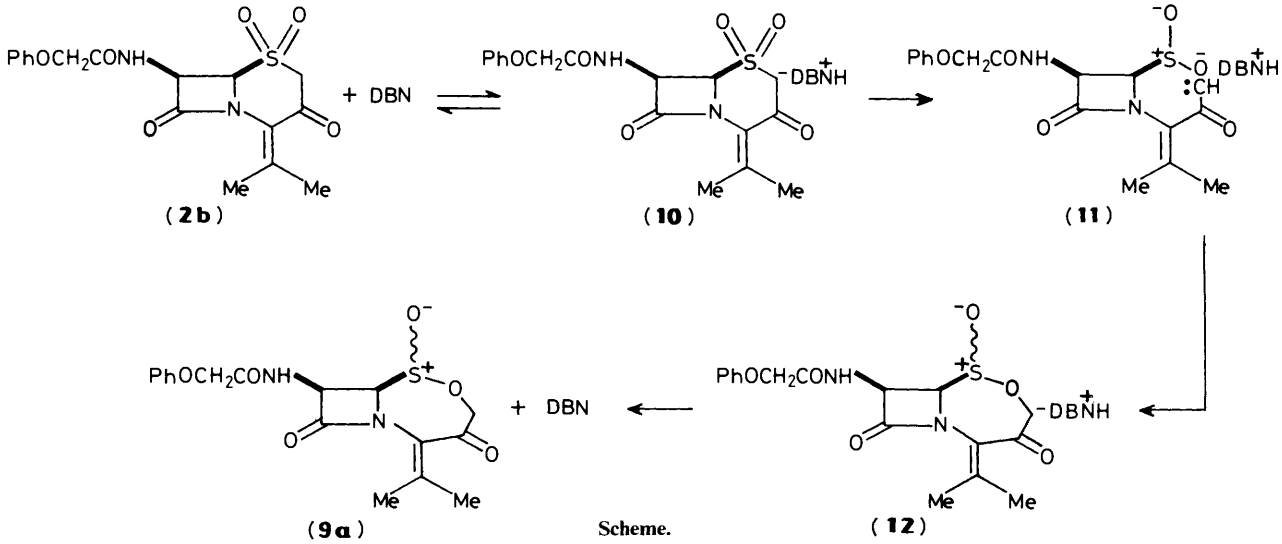


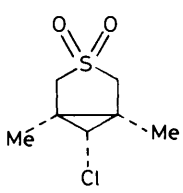
(9)

a ; R^1 = $NHCOCH_2OPh$, R^2 = H
b ; R^1 = H , R^2 = $NHCOCH_2OPh$
c ; R^1 = H , R^2 = $NHCOCH_2Ph$
d ; R^1 = R^2 = H
e ; R^1 = H , R^2 = Cl



(2b) (10) (11) (12) (9a)

Scheme.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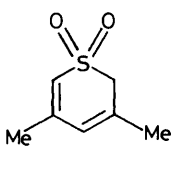
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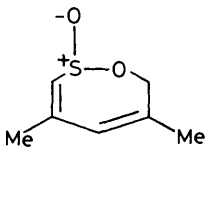
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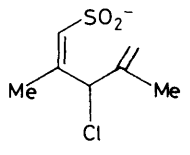
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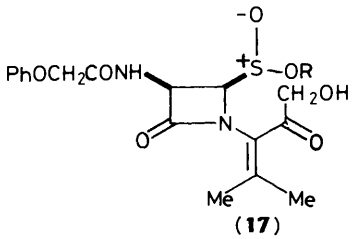
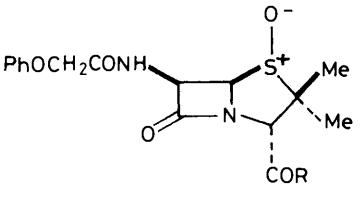
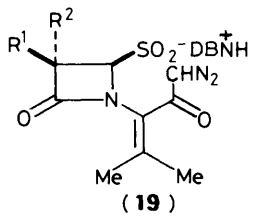
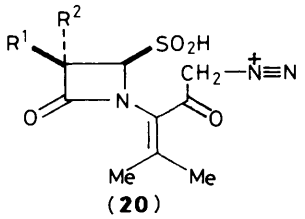
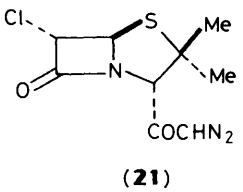

(17)
a ; R = DBNH
b ; R = H


(18)
a ; R = CHN_2
b ; R = CH_2OH


(19)
a; R^1 = $NHCOCH_2OPh$, R^2 = H
b; R^1 = H, R^2 = $NHCOCH_2OPh$
c; R^1 = H, R^2 = $NHCOCH_2Ph$


(20)
a ; R^1 = $NHCOCH_2OPh$, R^2 = H
b ; R^1 = H, R^2 = $NHCOCH_2OPh$


(21)

sulphinate intermediate had the opportunity of cyclising to give either a six- or a seven-membered ring. Thus Gaoni[9] observed that the thiabicyclohexane dioxide (**13**) was transformed into a *ca.* 1:1 mixture of the thiopyran dioxide (**14**) and the oxathiacycloheptadiene oxide (**15**) by the action of butyllithium in tetrahydrofuran. The anion (**16**) was suggested to give rise to the thiopyran dioxide (**14**) by an intramolecular S_N2' displacement involving the sulphur atom of the sulphinate, and to the oxathiacycloheptadiene oxide (**15**) by an intramolecular S_N2' displacement involving an oxygen atom of the sulphinate.

It was of interest to examine alternative routes to the oxathiazabicyclononane oxide (**9a**) and, in this respect, the hydroxyacetylpenam dioxide (**4d**) became of interest. It was envisaged that the last-cited compound would react with DBN to give the sulphinate salt (**17a**), which, under appropriate conditions, would be convertible into compound (**9a**).

When treated with dilute sulphuric acid in dioxane, the diazoacetylpenam dioxide (**4c**) was transformed into the crystalline hydroxyacetylpenam dioxide (**4d**), albeit in very poor yield (14% after recrystallisation). Since the overall yield of compound (**4d**) from the diazoacetylpenam (**1c**) was only *ca.* 6%, a more efficient route was sought. The crystalline diazoacetylpenam oxide (**18a**), obtained in 85% yield by oxidation of the diazoacetylpenam (**1c**)[7] with sodium periodate in aqueous methanol, reacted with dilute sulphuric acid in dioxane to give the hydroxyacetylpenam oxide (**18b**) in 44% yield after recrystallisation. The last-cited compound was transformed into the hydroxyacetylpenam dioxide (**4d**) in 88% yield by oxidation with potassium permanganate in aqueous acetic acid. Overall, the latter sequence provided compound (**4d**) in 33% yield based upon the diazoacetylpenam (**1c**).

In the hope of deriving the sulphinic acid (**17b**), a suspension of the hydroxyacetylpenam dioxide (**4d**) in deuteriochloroform was treated with DBN. The solution formed was believed to contain the sulphinate salt (**17a**), on the basis of ^1H n.m.r. spectroscopy, but an acidic work-up and extraction into ethyl acetate provided only a low recovery of non-β-lactam material. However, when the afore-cited reaction was repeated and thionyl chloride was introduced into the mixture prior to work-up, the oxathiazabicyclononane oxide (**9a**) was produced in 87% yield.

The foregoing results establish, for the first time, that epimerisation at position 6 of *cis*-6-acylaminopenam dioxides can be divorced from the β-elimination reaction at position 3. Although not isolated, the sulphinates (**3b**) and (**17a**) are clearly implicated in the reactions of compounds (**4b** and **d**) with DBN. The 3-hydrogen atoms of compounds (**4b** and **d**) are expected to be more acidic than the 3-hydrogen atom of the penicillinate (**4a**) and, presumably, it is this effect which promotes the β-elimination reactions. It was of interest therefore to examine the behaviour of the diazoacetylpenam dioxide (**4c**) towards DBN. Such a study was expected to give an indication of the ranking of the diazoacetyl function as an acidifying group.

The diacetylpenam dioxide (**4c**) reacted with DBN in deuteriochloroform to give, after an acidic work-up (with gas evolution), two products that were separated by silica gel chromatography. The less-mobile material, isolated in 28% yield, was identified as the oxathiazabicyclononane oxide (**9a**). The more-mobile material, obtained in 44% yield, was identified as an isomer of compound (**9a**) on the basis of mass spectrometry and elemental analysis. Spectroscopic considerations left little doubt that the product possessed structure (**9b**). In particular, the ^1H n.m.r. spectrum featured two three-proton singlets at δ 2.10 and 2.21 for the vinylic methyl groups and two one-proton doublets (*J* 14 Hz) at δ 3.66 and 5.27 for the 4-methylene group; the *trans*-orientated β-lactam protons appeared as a one-proton double doublet (*J* 7 and 2 Hz) at δ 4.80 and a one-proton doublet (*J* 2 Hz) at δ 5.17.

Presumably, in the afore-cited reaction there is a competition between a β-elimination reaction of the substrate (**4c**) [to give the sulphinate salt (**19a**)] and an epimerisation of the substrate (**4c**) [to give the 6-epimer (**6b**)] followed by a β-elimination reaction of the 6-epimer (**6b**) [to give the sulphinate salt (**19b**)]. Acidification generates the species (**20a** and **b**) which then give rise to the products (**9a** and **b**). Evidently, the diazoacetyl function is a poorer promoter of the β-elimination reaction than the chloroacetyl or hydroxyacetyl moieties; however, it is superior to the methoxycarbonyl group.

To examine the influence of the acylamino substituent upon the epimerisation/β-elimination processes, the diazoacetylpenam dioxide (**4e**) was synthesized. It was obtained from the diazoacetylpenam (**1e**)[7] [prepared in 83% yield by subjecting the salt (**1d**) to the action of $Et_3NH^+Cl^-$ in CH_2Cl_2, $ClCO_2Et$ in CH_2Cl_2, and CH_2N_2 in Et_2O] in 43% yield by oxidation with potassium permanganate in aqueous acetic acid.

The crystalline diazoacetylpenam dioxide (**4e**) reacted with DBN in deuteriochloroform to give, after an acidic work-up

(with gas evolution), the oxathiazabicyclononane oxide (**9c**) as a single crystalline diastereoisomer in 97% yield. The structure of the last-cited compound followed from its spectroscopic properties; in particular its ^{1}H n.m.r. spectrum ($CDCl_3$) featured two three-proton singlets at δ 2.17 and 2.28 for the vinylic methyl groups, two one-proton doublets (*J* 14 Hz) at δ 3.70 and 5.26 for the 4-methylene group, and a one-proton double doublet (*J* 7 and 2 Hz) at δ 4.63 together with a one-proton doublet (*J* 2 Hz) δ 5.14 for the *trans*-orientated β-lactam protons.

Evidently, the substrate (**4e**) equilibrates with its 6-epimer (**6c**) and the latter compound undergoes the β-elimination [to give the sulphinate (**19c**)] faster than the former. Seemingly, therefore, deprotonation at position 6 occurs more readily with a phenylacetamido than with a phenoxyacetamido group.

To determine the generality of the ring-expansion reaction of diazoacetylpenam dioxides, compounds (**6d** and **e**) were sought. Sequential treatment of sulbactam sodium salt (**6f**)[10] with triethylamine hydrochloride in dichloromethane, ethyl chloroformate in dichloromethane, and diazomethane in diethyl ether provided compound (**6d**) as a crystalline solid in 72% yield. Oxidation of the diazoacetylpenam (**21**)[11] with potassium permanganate gave, after fractionation on silica gel, the diazoacetylpenam dioxide (**6e**) as a slightly impure foam in *ca.* 25% yield.

When treated sequentially with DBN and dilute hydrochloric acid, compounds (**6d** and **e**), were converted into the corresponding oxathiazabicyclononane oxides (**9d** and **e**), each as a single diastereoisomer. The former product was isolated as a crystalline solid in 74% yield; the latter, which was also crystalline, was obtained in 63% yield. The ^{1}H n.m.r. spectra ($CDCl_3$) featured the vinylic methyl signals as two three-proton singlets [at δ 1.92 and 2.29 for compound (**9d**) and at δ 2.02 and 2.32 for compound (**9e**)] and the 4-methylene signals as two one-proton doublets [at δ 3.74 and 5.41 (*J* 14 Hz) for compound (**9d**) and at δ 3.79 and 5.40 (*J* 14 Hz) for compound (**9e**)]; the signals for the β-lactam hydrogen atoms of compound (**9d**) appeared as a two-proton doublet (separation 4 Hz) at δ 3.23 and a one-proton triplet (separation 4 Hz) at δ 4.67, whereas those of compound (**9e**) appeared as two one-proton doublets (*J* 1 Hz) at δ 4.69 and 4.98.

The present findings are of interest in a number of respects. First, they provide further insights into the factors which influence epimerisations at position 6 and β-eliminations at position 3 of penicillin-derived sulphones. Secondly, they reveal protocols for effecting a two-atom ring-enlarging rearrangement of the five-membered ring of 3-chloroacetyl, 3-hydroxyacetyl, and 3-diazoacetyl derivatives of 2,2-dimethylpenam 1,1-dioxides. Thirdly, they provide access to oxathiazabicyclononane oxides; as well as representing a new class of bicyclic β-lactam derivatives, such compounds feature the 1,2,3-oxathiazepane ring, a hitherto unknown heterocyclic entity.

Experimental

Ethereal diazomethane was prepared by adding a solution of 'Diazald' in diethyl ether to potassium hydroxide in aqueous ethanol.[12] For chromatographic and instrumental details, see Part 20.[13]

Preparation of (3S,5R,6R)-3-*Diazoacetyl*-2,2-*dimethyl*-6-*phenoxyacetamidopenam* 1,1-*Dioxide* (**4c**).—Triethylamine hydrochloride (1.38 g, 10 mmol) was added to a stirred suspension of the potassium penicillinate (**1b**) (3.88 g, 10 mmol) in dichloromethane (40 cm^3) and, after 0.5 h, the mixture was cooled (CCl_4–solid CO_2) and treated with ethyl chloroformate (2.87 cm^3, 30 mmol) (added in one portion). After a further 0.75 h, the mixture was washed with aqueous sodium hydrogen carbonate followed by water. The organic layer was then dried ($MgSO_4$), concentrated to half its volume, and slowly added to an excess of diazomethane in diethyl ether at 0 °C. After 1.5 h, the solvent was evaporated off to leave (3*S*,5*R*,6*R*)-3-diazoacetyl-2,2-dimethyl-6-phenoxyacetamidopenam (**1c**)[7] (3.70 g, 99%) as a syrup; $\nu_{max.}$(film) 3 440 (NH), 2 120 (C=$\overset{+}{N}$=$\overset{-}{N}$), 1 775 (β-lactam C=O), 1.685 (amide C=O), and 1 630 cm^{-1} (diazoketone C=O); δ(60 MHz; $CDCl_3$) 1.53 and 1.69 (each 3 H, s, together 2-Me_2), 4.18 (1 H, s, 3-H), 4.52 (2 H, s, CH_2OPh), 5.43 (1 H, d, *J* 4 Hz, 5-H), 5.75 (1 H, dd, *J* 8 and 4 Hz, 6-H), 5.80 (1 H, s, $COCHN_2$), and 6.8—7.45 (6 H, m, Ph and CONH).

A solution of potassium permanganate (2.30 g, 14.6 mmol) in water (50 cm^3) was added in drops over 1 h to a stirred, ice-cooled solution of the diazoacetylpenam (**1c**) (3.70 g, 9.9 mmol) in 4:1 acetic acid–water (75 cm^3). After a further 1 h, sulphur dioxide was bubbled into the mixture (until the purple colour was discharged), which was then extracted with dichloromethane. The organic layer was washed with water followed by aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated to leave a foam (2.25 g), which was crystallised from ethyl acetate–hexane to give *compound* (**4c**) (1.70 g, 42%). After a further recrystallisation, the sample possessed m.p. 131—133 °C; $[\alpha]_D$ +167° (1% in CH_2Cl_2); $\nu_{max.}$(KBr) 3 330 (NH), 2 120 (C=$\overset{+}{N}$=$\overset{-}{N}$), 1 805 (β-lactam C=O), 1 685 (amide C=O), and 1 630 and 1 615 cm^{-1} (diazoketone C=O); $\lambda_{max.}$(EtOH) 216 (ε 10 000), 259 (9 800), 260 (9 400), 268 (9 600), 275 (9 800), and 280 nm (8 800); δ(60 MHz; $CDCl_3$) 1.40 and 1 60 (each 3 H, s, together 2-Me_2), 4.28 (1 H, s, 3-H), 4.50 (2 H, s, CH_2OPh), 4.80 (1 H, d, *J* 4 Hz, 5-H), 5.80 (1 H, s, $COCHN_2$), 6.15 (1 H, dd, *J* 10 and 4 Hz, 6-H), 6.70—7.35 (5 H, m, Ph), 8.15br (1 H, d, *J* 10 Hz, CONH) [addition of D_2O caused the double doublet at δ 6.08 to collapse to a doublet (*J* 4 Hz), and the doublet at δ 8.15 to disappear]; *m/z* (e.i.) 406 (M^+) and 219 ($C_{11}H_{11}N_2O_3^+$, base peak) (Found: C, 50.3; H, 4.5; N, 13.5; S, 7.6. $C_{17}H_{18}N_4O_6S$ requires C, 50.25; H, 4.45; N, 13.8; S, 7.9%).

Reaction of the Diazoacetylpenam Dioxide (**4c**) *with Hydrochloric Acid.*—A solution of the diazoacetylpenam dioxide (**4c**) (0.262 g, 0.645 mmol) in dichloromethane (5 cm^3) was stirred with 4M hydrochloric acid (2 cm^3). After 3 h, when the reaction was complete (t.l.c.), the mixture was diluted with dichloromethane and washed with aqueous sodium hydrogen carbonate followed by water. Evaporation of the dried ($MgSO_4$) organic layer gave (3S,5R,6R)-3-*chloroacetyl*-2,2-*dimethyl*-6-*phenoxyacetamidopenam* 1,1-*dioxide* (**4b**) (0.246 g, 92%) as a chromatographically homogeneous foam with the following properties: $[\alpha]_D$ +124° (1% in $CHCl_3$); $\nu_{max.}$(film) 3 350 (NH), 1 795 (β-lactam C=O), 1 735 (chloroketone C=O), and 1 665 cm^{-1} (amide C=O); $\lambda_{max.}$(EtOH) 211 (ε 8 100), 220sh (6 900), 271 (800), and 278 nm (520); δ(60 MHz; $CDCl_3$) 1.41 and 1.62 (each 3 H, s, together 2-Me_2), 4.48 (2 H, s, CH_2OPh), 4.58 (1 H, s, 3-H), 4.65 (2 H, s, $COCH_2Cl$), 5.00 (1 H, d, *J* 4 Hz, 5-H), 6.36 (1 H, dd, *J* 10 and 4 Hz, 6-H), 7.20—7.60 (5 H, m, Ph), and 8.38 (1 H, d, *J* 10 Hz, CONH) [addition of D_2O caused the doublet at δ 8.38 to disappear and the double doublet at δ 6.36 to collapse to a doublet (*J* 4 Hz)]; *m/z* (e.i.) 414 (M^+) and 107 ($C_7H_7O^+$, base peak) (Found: C, 49.5; H, 4.8; N, 6.4. $C_{17}H_{19}ClN_2O_6S$ requires C, 49.2; H, 4.6; N, 6.75%).

Reaction of the Chloroacetylpenam Dioxide (**4b**) *with DBN.*—A solution of the chloroacetylpenam dioxide (**4b**) (0.141 g, 0.34 mmol) in deuteriochloroform (0.8 cm^3) was treated dropwise with a 40% solution of DBN in deuteriochloroform until the reaction was complete (^{1}H n.m.r. spectroscopy). The mixture was diluted with ethyl acetate and washed with dilute hydrochloric acid followed by brine. Evaporation of the dried (Na_2SO_4) organic phase and purification of the product by

silica gel chromatography [EtOAc–light petroleum (1:2) as eluant] gave (7R,8R)-2-*isopropylidene*-8-*phenoxyacetamido*-5-*oxa*-6-*thia*-1-*azabicyclo*[5.2.0]*nonane*-3,9-*dione* 6-*oxide* (**9a**) (0.070 g, 54%). The sample, after recrystallisation from chloroform–diethyl ether, displayed m.p. 180—182 °C (decomp.); $[\alpha]_D$ +300° (0.4% in CH_2Cl_2); $\nu_{max.}$(KBr) 3 300 (NH), 1 775 (β-lactam C=O), 1 690 (enone C=O), and 1 665 cm^{-1} (amide C=O); $\lambda_{max.}$(EtOH) 218 (ε 10 300), 250 (5 000), 261 (4 500), 267 (4 000), and 274 nm (3 000); δ(60 MHz; $CDCl_3$) 1.93 and 2.31 (each 3 H, s, together CMe_2), 3.79 and 5.42 (each 1 H, d, *J* 14 Hz, together 4-H_2), 4.52 (2 H, s, CH_2OPh), 4.83 (1 H, d, *J* 4 Hz, 7-H), 5.94 (1 H, dd, *J* 10 and 4 Hz, 8-H), 6.80—7.42 (5 H, m, Ph), and 7.9br (1 H, d, *J* 10 Hz, CONH) [addition of D_2O caused the double doublet at δ 5.94 to collapse to a doublet (*J* 4 Hz) and the doublet at δ 7.9 to disappear]; *m/z* (e.i.) 378 (M^+) and 77 ($C_6H_5^+$, base peak) (Found: C, 53.8; H, 4.6; N, 7.3%; M^+, 378.0914. $C_{17}H_{18}N_2O_6S$ requires C, 53.95; H, 4.8; N, 7.4%; *M*, 378.0885).

Reaction of the Diazoacetylpenam Dioxide (**4c**) *with Sulphuric Acid.*—3M Sulphuric acid (5 cm^3) was added to a stirred solution of the diazoacetylpenam dioxide (**4c**) (0.410 g, 1.01 mmol) in dioxane (40 cm^3). After 24 h, the mixture was neutralised with aqueous sodium hydrogen carbonate and extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) organic layer and crystallisation of the residue from chloroform–diethyl ether gave (3S,5R,6R)-3-*hydroxyacetyl*-2,2-*dimethyl*-6-*phenoxyacetamidopenam* 1,1-*dioxide* (**4d**) (0.056 g, 14%), m.p. 174—176 °C (decomp.); $[\alpha]_D$ +142° (1% in CH_2Cl_2); $\nu_{max.}$(KBr) 3 450 and 3 420 (OH and NH), 1 805 (β-lactam C=O), 1 735 (ketone C=O), and 1 710 cm^{-1} (amide C=O); $\lambda_{max.}$(EtOH) 221 (ε 3 800), 262 (900), 268 (1 250), and 275 nm (1 100); δ(60 MHz; $CDCl_3$–CD_3SOCD_3) 1.38 and 1.60 (each 3 H, s, together 2-Me_2), 4.40 (2 H, d, separation 6 Hz, $COCH_2OH$), 4.53 (3 H, s, CH_2OPh and 3-H), 5.14 (1 H, d, *J* 4 Hz, 5-H), 5.18 (1 H, t, separation 6 Hz, CH_2OH), 6.14 (1 H, dd, *J* 10 and 4 Hz, 6-H), 6.78—7.44 (5 H, m, Ph), and 8.25br (1 H, d, *J* 10 Hz, CONH) [addition of D_2O caused the doublet at δ 4.40 to collapse to a broad singlet, the triplet at δ 5.18 and the doublet at δ 8.25 to disappear, and the double doublet at δ 6.14 to collapse to a doublet (*J* 4 Hz)]; *m/z* (e.i.) 396 (M^+) and 77 ($C_6H_5^+$, base peak) (Found: C, 51.2; H, 5.0; N, 6.9%; M^+, 396.1028. $C_{17}H_{20}N_2O_7S$ requires C, 51.5; H, 5.1; N, 7.05%; *M*, 396.0991).

Reaction of the Diazoacetylpenam (**1c**) *with Sodium Periodate* (*with* N. S. Watson).—A solution of sodium periodiate (1.61 g, 7.5 mmol) in water (30 cm^3) was added to a stirred solution of the diazoketone (**1c**)[7] (2.61 g, 6.97 mmol) in methanol (30 cm^3). After 18 h, the mixture was partitioned between chloroform and water. Evaporation of the dried ($MgSO_4$) organic layer gave (1S,3S,5R,6R)-3-*diazoacetyl*-2,2-*dimethyl*-6-*phenoxyacetamidopenam* 1-*oxide* (**18a**) (2.32 g, 85%) as a crystalline solid. A sample recrystallised from chloroform–diethyl ether showed m.p. 161—163 °C; $[\alpha]_D$ +283° (0.1% in $CHCl_3$); $\nu_{max.}$(KBr) 3 360 (NH), 2 130 (C=$\overset{+}{N}$=$\overset{-}{N}$), 1 780 (β-lactam C=O), 1 685 (amide C=O), and 1 640 cm^{-1} (diazoketone C=O); $\lambda_{max.}$(EtOH) 217 (ε 11 800), 253 (12 600), 269 (10 900), and 276 nm (10 400); δ(60 MHz; $CDCl_3$) 1.27 and 1.79 (each 3 H, s, together 2-Me_2), 4.58 (1 H, s, 3-H), 4.61 (2 H, s, OCH_2Ph), 5.13 (1 H, d, *J* 4 Hz, 5-H), 5.98 (1 H, s, $COCHN_2$), 6.20 (1 H, dd, *J* 10 and 5 Hz, 6-H), 6.94—7.56 (5 H, m, Ph), and 8.4br (1 H, d, *J* 10 Hz, CONH) [addition of D_2O caused the double doublet at δ 6.20 to collapse to a doublet (*J* 5 Hz), and the doublet at δ 8.4 to disappear]; *m/z* (e.i.) 362 ($M^+ - N_2$), 312, 250, and 219 ($C_{11}H_{11}N_2O_3^+$, base peak) (Found: C, 52.3; H, 4.6; N, 13.9. $C_{17}H_{18}N_4O_5S$ requires C, 52.3; H, 4.65; N, 14.35%).

Reaction of the Diazoacetylpenam 1-*Oxide* (**18a**) *with Sulphuric Acid.*—3M Sulphuric acid (18 cm^3) was added to a stirred solution of the diazoacetylpenam oxide (**18a**) (3.11 g, 7.97 mmol) in dioxane (120 cm^3). After 24 h, the mixture was neutralised with aqueous sodium hydrogen carbonate and extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) organic layer and crystallisation of the residue from chloroform–diethyl ether gave (1S,3S,5R,6R)-3-*hydroxyacetyl*-2,2-*dimethyl*-6-*phenoxyacetamidopenam* 1-*oxide* (**18b**) (1.34 g, 44%), m.p. 151—153 °C (decomp.); $[\alpha]_D$ +236° (1% in CH_2Cl_2); $\nu_{max.}$(KBr) 3 430 and 3 370 (OH and NH), 1 790 (β-lactam C=O), 1 725 and 1 700 (ketone C=O), and 1 670 cm^{-1} (amide C=O); $\lambda_{max.}$(EtOH) 225 (ε 3 900), 264 (1 050), 270 (1 450), and 276 nm (1 250); δ(60 MHz; CD_3SOCD_3) 1.14 and 1.56 (each 3 H, s, together 2-Me_2), 4.31 (2 H, d, separation 6 Hz, $COCH_2OH$), 4.50 (1 H, s, 3-H), 4.60 (2 H, s, CH_2OPh), 5.3br (1 H, t, separation 6 Hz, CH_2OH), 5.50 (1 H, d, *J* 4 Hz, 5-H), 5.96 (1 H, dd, *J* 10 and 4 Hz, 6-H), 6.75—7.40 (5 H, m, Ph), and 8.2br (1 H, d, *J* 10 Hz, CONH) [addition of D_2O caused the signals at δ 5.3 and 8.2 to disappear, the doublet at δ 4.31 to collapse to a singlet, and the double doublet at δ 5.96 to collapse to a doublet (*J* 4 Hz)]; *m/z* (e.i.) 380 (M^+) and 107 ($C_7H_7O^+$, base peak) (Found: C, 53.8; H, 5.2; N, 7.2. $C_{17}H_{20}N_2O_6S$ requires C, 53.65; H, 5.3; N, 7.35%).

Reaction of the Hydroxyacetylpenam Oxide (**18b**) *with Potassium Permanganate.*—A solution of potassium permanganate (0.611 g, 3.87 mmol) in water (20 cm^3) was added in drops over 0.5 h to a stirred ice-cooled solution of the hydroxyacetylpenam oxide (**18b**) (0.688 g, 1.76 mmol) in 4:1 acetic acid–water (40 cm^3). After a further 1 h, the mixture was treated with 10% hydrogen peroxide solution (until the purple colour was discharged) and extracted with dichloromethane. The organic extract was washed with water followed by aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated to give a crystalline residue (0.613 g, 88%), identical with the hydroxyacetylpenam dioxide (**4d**) by ^1H n.m.r. spectroscopy.

Reaction of the Hydroxyacetylpenam 1,1-*Dioxide* (**4d**) *with DBN Followed by Thionyl Chloride.*—A solution of 95% DBN (0.08 cm^3, 0.61 mmol) in dichloromethane (1 cm^3) was added to a stirred suspension of the hydroxyacetylpenam dioxide (**4d**) (0.250 g, 0.63 mmol) in dichloromethane (5 cm^3). After 10 min, the mixture was treated with thionyl chloride (0.05 cm^3, 0.69 mmol). After a further 0.5 h, the mixture was diluted with dichloromethane and washed with aqueous sodium hydrogen carbonate followed by water. Evaporation of the dried ($MgSO_4$) organic layer left a residue which was crystallised from chloroform–diethyl ether to give material (0.208 g, 87%) identical (^1H n.m.r. spectroscopy) with the oxathiazabicyclononane oxide (**9a**) derived from the chloroacetylpenam dioxide (**4b**).

Reaction of the Diazoacetylpenam Dioxide (**4c**) *with DBN Followed by Hydrochloric Acid.*—A 40% solution of 95% DBN in deuteriochloroform was added in drops to a solution of the diazoacetylpenam dioxide (**4c**) (0.251 g, 0.62 mmol) in deuteriochloroform (1 cm^3) until the starting material had disappeared (^1H n.m.r. spectroscopy). The mixture was then diluted with dichloromethane and washed with dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic phase left a syrup which contained two components (t.l.c.). The mixture was fractionated by silica gel column chromatography [EtOAc–light petroleum (1:2) as eluant].

The first-eluted material was (7R,8S)-2-*isopropylidene*-8-*phenoxyacetamido*-5-*oxa*-6-*thia*-1-*azabicyclo*[5.2.0]*nonane*-3,9-*dione* 6-*oxide* (**9b**) (0.103 g, 44%). After recrystallisation from

chloroform–light petroleum, the sample possessed m.p. 177—179 °C (decomp.); $[\alpha]_D$ +50° (0.5% in EtOH); $\nu_{max.}$(KBr) 3 350 (NH), 1 760 (β-lactam C=O), and 1 690 cm^{-1} (amide and enone C=O); $\lambda_{max.}$(EtOH) 211 (ε 12 000), 246sh (4 200), 262sh (3 500), 268 (3 000), and 275 nm (2 200); δ(60 MHz; $CDCl_3$) 2.10 and 2.21 (each 3 H, s, together CMe_2), 3.66 and 5.27 (each 1 H, d, *J* 14 Hz, 4-H_2), 4.43 (2 H, s, CH_2OPh), 4.80 (1 H, dd, *J* 7 and 2 Hz, 8-H), 5.17 (1 H, d, *J* 2 Hz, 7-H), and 6.66—7.42 (6 H, m, Ph and CONH) [addition of D_2O caused the double doublet at δ 4.80 to collapse to a doublet (*J* 2 Hz) and the integral for the multiplet at δ 6.66—7.42 to be reduced to 5 H); *m/z* (e.i.) 378 (M^+) and 124 (base peak) (Found: C, 53.6; H, 4.6; N, 7.4%; M^+, 378.0892. $C_{17}H_{18}N_2O_6S$ requires C, 53.95; H, 4.8; N, 7.4%; *M*, 378.0886).

The second-eluted material (0.066 g, 28%) was identical with the oxathiazabicyclononane oxide (**9a**) on the basis of ^1H n.m.r. spectroscopy.

Preparation of (3S,5R,6R)-3-*Diazoacetyl*-2,2-*dimethyl*-6-*phenylacetamidopenam* 1,1-*Dioxide* (**4e**).—Triethylamine hydrochloride (1.38 g, 10 mmol) was added to a stirred suspension of the potassium penicillinate (**1d**) (3.72 g, 10 mmol) in dichloromethane (40 cm^3). After 0.5 h, the mixture was cooled (CCl_4–solid CO_2) and treated with ethyl chloroformate (2.87 cm^3, 30 mmol) (added in one portion). After 1 h, the mixture was allowed to warm to room temperature and washed with aqueous sodium hydrogen carbonate followed by water. The organic layer was then dried ($MgSO_4$), concentrated to half its volume, and slowly added to an excess of diazomethane in diethyl ether at 0 °C [the diazoacetylpenam (**1e**) was precipitated from the mixture as a yellow solid]. After 1 h, the solvent was evaporated off and the residue was washed (2 ×) with ice-cold diethyl ether to leave (3*R*,5*R*,6*R*)-3-diazoacetyl-2,2-dimethyl-6-phenylactamidopenam (**1e**) [7] (2.96 g, 83% yield) as a pale-yellow solid, $\nu_{max.}$(KBr) 3 330 (NH), 2 120 (C=$\overset{+}{N}$=$\overset{-}{N}$), 1 780 (β-lactam C=O), 1 670 (amide C=O), and 1 635 cm^{-1} (diazoketone C=O); δ(60 MHz; $CDCl_3$) 1.48 and 1.58 (each 3 H, s, together 2-Me_2), 3.62 (2 H, s, CH_2Ph), 4.16 (1 H, s, 3-H), 5.43 (1 H, d, *J* 4 Hz, 5-H), 5.75 (1 H, dd, *J* 8 and 4 Hz, 6-H), 5.80 (1 H, s, $COCHN_2$), 6.87br (1 H, d, *J* 8 Hz, CHN*H*CO), and 7.37 (5 H, s, Ph).

A solution of potassium permanganate (1.31 g, 8.29 mmol) in water (30 cm^3) was added in drops over 1 h to a stirred ice-cooled solution of the diazoacetylpenam (**1e**) (2.03 g, 5.66 mmol) in 4:1 acetic acid–water (40 cm^3). After a further 1 h, 30% hydrogen peroxide solution was added (until the purple colour was discharged) and the mixture was then extracted with dichloromethane. The organic layer was washed with water followed by aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated to leave compound (**4e**) (0.95 g, 43%). After crystallisation from methanol, the sample possessed m.p. 158—161 °C; $[\alpha]_D$ +242° (1% in CH_2Cl_2); $\nu_{max.}$(KBr) 3 280 (NH), 2 120 (C=$\overset{+}{N}$=$\overset{-}{N}$), 1 805 (β-lactam C=O), 1 660 amide (C=O), and 1 640 cm^{-1} (diazoketone C=O); $\lambda_{max.}$(EtOH) 203 (ε 16 800), 151 (10 100), and 277 nm (9 000); δ(60 MHz; $CDCl_3$) 1.40 and 1.59 (each 3 H, s, together 2-Me_2), 3.66 (2 H, s, $COCH_2Ph$), 4.28 (1 H, s, 3-H), 4.76 (1 H, d, *J* 4 Hz, 5-H), 5.80 (1 H, s, $COCHN_2$), 6.13 (1 H, dd, *J* 10 and 4 Hz, 6-H), 7.05br (1 H, d, *J* 10 Hz, CHN*H*CO), and 7.23—7.40 (5 H, m, Ph) (Found: C, 52.1; H, 4.3; N, 14.0; S, 8.0. $C_{17}H_{18}N_4O_5S$ requires C, 52.3; H, 4.65; N, 14.35; S, 8.2%).

Reaction of the Diazoacetylpenam Dioxide (**4e**) *with DBN Followed by Hydrochloric Acid.*—A 40% solution of 95% DBN in deuteriochloroform was added in drops to a solution of the diazoacetylpenam dioxide (**4e**) (0.208 g, 0.533 mmol) in deuteriochloroform (0.8 cm^3) until the starting material had disappeared (^1H n.m.r. spectroscopy). The mixture was then diluted with dichloromethane and washed with dilute hydrochloric acid. Evaporation of the dried (Na_2SO_4) organic phase afforded (7R,8S)-2-*isopropylidene*-8-*phenylacetamido*-5-*oxa*-6-*thia*-1-*azabicyclo*[5.2.0]*nonane*-3,9-*dione* 6-*oxide* (**9c**) (0.187 g, 97%). The sample, after recrystallisation from isopropyl alcohol, displayed m.p. 160—161 °C (decomp.); $[\alpha]_D$ +301° (0.27% in EtOH); $\nu_{max.}$(KBr) 3 300 (NH), 1 700 (β-lactam C=O), 1 695 (enone C=O), and 1 665 and 1 650 cm^{-1} (amide C=O); $\lambda_{max.}$(EtOH) 213 (ε 13 300) and 240sh nm (8 100); δ(60 MHz; $CDCl_3$) 2.17 and 2.28 (each 3 H, s, together CMe_2), 3.57 (2 H, s, CH_2Ph), 3.70 and 5.26 (each 1 H, d, *J* 14 Hz, together 4-H_2), 4.63 (1 H, dd, *J* 7 and 2 Hz, 8-H), 5.14 (1 H, d, *J* 2 Hz, 7-H), 6.4br (1 H, d, *J* 7 Hz, CONH), and 7.23 (5 H, s, Ph) [addition of D_2O caused the double doublet at δ 4.63 to collapse to a doublet (*J* 2 Hz) and the doublet at δ 6.4 to disappear]; *m/z* (e.i.) 344 ($M^+ - H_2O$), 124, and 91 ($C_7H_7^+$, base peak) (Found: C, 56.0; H, 5.2; N, 7.5; S, 8.8. $C_{17}H_{18}N_2O_5S$ requires C, 56.35; H, 5.0; N, 7.75; S, 8.85%).

Preparation of (3S,5R)-3-*Diazoacetyl*-2,2-*dimethylpenam* 1,1-*Dioxide* (**6d**).—A stirred suspension of sulbactam sodium salt (**6f**) [10] (1.02 g, 4 mmol) in dichloromethane (25 cm^3) was treated with triethylamine hydrochloride (0.550 g, 4 mmol). After 0.5 h, the mixture was cooled (CCl_4–solid CO_2) and ethyl chloroformate (9.96 cm^3, 10 mmol) added. The mixture was allowed to warm to room temperature after a further 0.5 h, and then washed with aqueous sodium hydrogen carbonate followed by water. The dried ($MgSO_4$) organic phase was concentrated (to *ca.* 10 cm^3) and added in drops to an excess of diazomethane in diethyl ether at 0 °C. Evaporation, after 2 h, left *compound* (**6d**) (0.740 g, 72%). The sample, recrystallised from dichloromethane–light petroleum, showed m.p. 157—159 °C; $[\alpha]_D$ +360° (1% in CH_2Cl_2); $\nu_{max.}$(KBr) 2 120 (C=$\overset{+}{N}$=$\overset{-}{N}$), 1 790 (β-lactam C=O), and 1 640 cm^{-1} (diazoketone C=O); $\lambda_{max.}$(EtOH) 211 (ε 4 700), 250 (10 100), and 275 nm (8 150); δ(60 MHz; $CDCl_3$) 1.42 and 1.62 (each 3 H, s, together 2-Me_2), 3.43 (2 H, d, separation 3 Hz, 6-H_2), 4.10 (1 H, s, 3-H), 4.50 (1 H, t, separation 3 Hz, 5-H), and 5.70 (1 H, s, $COCHN_2$); *m/z* (e.i.) 257 (M^+), 188 ($M^+ - C_2HN_2O$), 165 ($M^+ - N_2O_2S$), and 96 (base peak) (Found: C, 41.9: H, 4.2; N, 16.3. $C_9H_{11}N_3O_4S$ requires C, 42.0; H, 4.3; N, 16.35%).

Reaction of the Diazoacetylpenam Dioxide (**6d**) *with DBN Followed by Hydrochloric Acid.*—A solution of 95% DBN (0.033 cm^3, 0.25 mmol) in deuteriochloroform (0.3 cm^3) was added in drops to a solution of the diazoacetylpenam dioxide (**6d**) (0.062 g, 0.24 mmol) in deuteriochloroform (0.5 cm^3). When the reaction was complete (^1H n.m.r. spectroscopy), the mixture was diluted with chloroform and washed with dilute hydrochloric acid (whereupon effervescence occurred) followed by water. Evaporation left (7R)-2-*isopropylidene*-5-*oxa*-6-*thia*-1-*azabicyclo*[5.2.0]*nonane*-3,9-*dione* 6-*oxide* (**9d**) (0.41 g, 74%). The sample, recrystallised from chloroform–light petroleum, showed m.p. 191—193 °C; $[\alpha]_D$ +475° (0.9% in $CHCl_3$); $\nu_{max.}$(KBr) 1 775 (β-lactam C=O), 1 700 (enone C=O), and 1 605 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 208 (ε 1 600) and 250sh nm (365); δ(60 MHz; $CDCl_3$) 1.92 and 2.29 (each 3 H, s, together CMe_2), 3.23 (2 H, d, separation 4 Hz, 8-H_2), 3.74 and 5.41 (each 1 H, d, *J* 14 Hz, together 4-H_2), and 4.67 (1 H, t, separation 4 Hz, 7-H); *m/z* (e.i.) 165 ($M^+ - O_2S$) and 123 ($M^+ - C_2H_2O_3S$, base peak) (Found: C, 47.2; H, 4.8; N, 6.1. $C_9H_{11}NO_4S$ requires C, 47.15; H, 4.85; N, 6.1%).

Reaction of the Diazoacetylpenam (**21**) *with Potassium Permanganate.*—Potassium permanganate (0.928 g, 5.87 mmol) dissolved in water (12 cm^3) was added in drops, over 2.5 h, to a stirred solution of the diazoacetylpenam (**21**) [11] (0.700 g,

2.7 mmol) in 4:1 acetic acid–water (20 cm^3). After a further 1 h, 30% hydrogen peroxide solution was added until the purple colour was discharged. The solution was then neutralised with aqueous sodium hydrogen carbonate and extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) organic layer and purification of the syrupy residue by silica gel column chromatography (EtOAc–light petroleum; gradient elution) gave (3*S*,5*R*,6*S*)-6-chloro-3-diazoacetyl-2,2-dimethylpenam 1,1-dioxide (**6e**) (0.200 g, 25%) as a slightly impure foam; $\nu_{max.}$(KBr) 2 140 ($C=\overset{+}{N}=\overset{-}{N}$), 1 805 (β-lactam C=O), 1 755w, and 1 635 cm^{-1} (diazoketone C=O); δ(60 MHz; $CDCl_3$) 1.40 and 1.60 (each 3 H, s, together 2-Me_2), 4.15 (1 H, s, 3-H), 4.6br and 5.1br (each 1 H, s, together 5- and 6-H), and 5.75 (1 H, s, $COCHN_2$); *m/z* (e.i.) 233 and 231.

Reaction of the Diazoacetylpenam Dioxide (**6e**) *with DBN.*—A 30% solution of 95% DBN in deuteriochloroform was added in drops to a solution of the crude diazoacetylpenam dioxide (**6e**) (8.80 g, 30 mmol) in deuteriochloroform until the reaction was complete (^1H n.m.r. spectroscopy). The mixture was then diluted with chloroform and washed with dilute hydrochloric acid (whereupon effervescence occurred) followed by water. Evaporation of the dried ($MgSO_4$) organic layer left (7R,8S)-8-*chloro*-2-*isopropylidene*-5-*oxa*-6-*thia*-1-*azabicyclo*[5.2.0]-*nonane*-3,9-*dione* 6-*oxide* (**9e**) (5.00 g, 63%). A sample, recrystallised from chloroform–light petroleum, showed m.p. 160—162 °C; $[\alpha]_D$ +371° (1% in $CHCl_3$); $\nu_{max.}$(KBr) 1 790 (β-lactam C=O), 1 690 (enone C=O), and 1 610 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 230 (ε 12 400), and 312sh nm (240); δ(60 MHz; $CDCl_3$) 2.02 and 2.32 (each 3 H, s, together CMe_2), 3.79 and 5.40 (each 1 H, d, *J* 14 Hz, together 4-H_2), 4.69 and 4.98 (each 1 H, d, *J* 1 Hz, together 7-and 8-H); *m/z* (e.i.) 201 and 199 ($M^+ - O_2S$), and 124 and 123 (base peaks) (Found: C, 40.9; H, 3.7; N, 5.3. $C_9H_{10}ClNO_4S$ requires C, 41.0; H, 3.8; N, 5.3%).

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