Studies Related to Penicillins. Part 28.[1] β-Elimination Reactions of Sulphones derived from Penicillins leading to *cis*-3-Acylamino-4-oxoazetidine-2-sulphinic Acids†

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The reactions of the 3-acetyl and 3-formyl derivatives of (3*S*,5*R*,6*R*)-2,2-dimethyl-6-phenoxyacetamidopenam 1,1-dioxide, i.e. compounds (**5e,f**), and of *p*-nitrophenyl (3*S*,5*R*,6*R*)benzylpenicillinate 1,1-dioxide (**1f**) with 1,5-diazabicyclo[5.3.0]non-5-ene (DBN) followed by iodomethane have been studied. In the case of penam dioxide (**5e**), epimerisation at position 6 competes with the β-elimination at position 3 and a mixture of the *trans*- and *cis*-azetidinones (**11a**) and (**12a**) is isolated. No epimerisation is observed with compounds (**5f**) and (**1f**), which react to give the corresponding *cis*-azetidinones (**12b,c**). It is possible to avoid the epimerisation of the penam dioxide (**5e**), and to isolate the *cis*-azetidinesulphinate salt (**13**), by using potassium t-butoxide in place of DBN. The *cis*-azetidinesulphinic acid (**8c**) is also isolable from the reaction of the penicillinate dioxide (**1f**) with DBN followed by acidic work-up. It undergoes *O*-methylation of the sulphinic acid group in the presence of diazomethane to give the methyl sulphinate (**19**), as a mixture of diastereoisomers. Saponification of the *p*-nitrophenyl ester of the *cis*-azetidinesulphinic acid (**8c**) is effected by sodium hydroxide to give the disodium salt (**18b**), which undergoes methylation in the presence of iodomethane to afford the dimethyl derivative (**12d**).

We have reported[2] that the penicillinate dioxides (**1a**—**e**) react with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to give, after acidic work-up, the azetidinesulphinic acids (**2a**—**e**). In the case of the penicillinate dioxide (**1a**), it was shown that the base initially brought about an equilibration reaction with the 6-epimer (**3a**);[3] the latter compound then underwent β-elimination. Whilst the afore-cited reactions are of intrinsic interest, their potential for the synthesis of novel antibacterially active β-lactam derivatives is hampered by the epimerisation [6-*epi*-penicillin salts, *e.g.* (**4a**), are very much less active than their counterparts, *e.g.* (**4b**)[4]].

The epimerisation and β-elimination reactions are triggered by the formation of carbanionic intermediates at positions 6 and 3, respectively.[5] In principle, therefore, it should be possible to promote the latter reaction over the former by increasing the acidity of the 3-hydrogen atom. Indeed, in a recent study,[6] we reported that this was feasible. Thus the chloroacetylpenam dioxide (**5a**) was found to react with DBN to give the oxathiazabicyclononane oxide (**6a**). Furthermore, the hydroxyacetylpenam dioxide (**5b**) was also converted into compound (**6a**) when treated with DBN followed by thionyl chloride. Clearly, the *cis*-acylaminoazetidinesulphinate salts (**7a,b**) were implicated in the afore-cited reactions.

Whereas a 1:1.6 mixture of the oxathiazabicyclononane oxides (**6a,b**) was produced on treatment of the diazoacetylpenam dioxide (**5c**) with DBN followed by acidic work-up,[6] compound (**6c**) was the sole product from the corresponding reaction of the diazoacetylpenam dioxide (**5d**). In the former instance, the substrate (**5c**) underwent a competitive epimerisation at position 6 and β-elimination at position 3; in the latter case, epimerisation of the substrate (**5d**) occurred prior to the β-elimination.

† Part of this work was carried out in the Department of Organic Chemistry at the University of Newcastle upon Tyne.

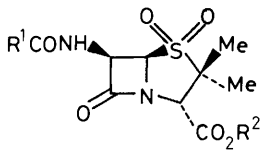
In this paper, we describe further studies involving penam dioxides of types (**1**) and (**5**) which have led to the synthesis of *cis*-acylaminoazetidinesulphinic acids and their derivatives.

Results and Discussion

In the hope that it could be converted into the *cis*-azetidinesulphinic acid (**8a**), the acetylpenam dioxide (**5e**) was sought. It was expected that compound (**5e**) would be accessible from the diazoacetylpenam dioxide (**5c**),[6] using the Wolfrom procedure;[7] corresponding reductions of diazo ketones derived from penicillanic acids have been reported previously.[8] Indeed, treatment of compound (**5c**) in acetone with hydriodic acid provided the crystalline acetylpenam dioxide (**5e**) in excellent yield.

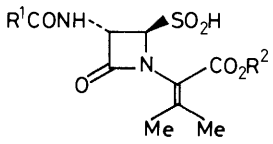
When treated in deuteriochloroform with DBN, the acetylpenam dioxide (**5e**) was transformed into a new product which appeared to be a mixture of the sulphinate salts (**7c**) and (**9**) on the basis of ^{1}H n.m.r. spectroscopy. However, an acidic work-up afforded non-β-lactam materials rather than the sulphinic acids (**8a**) and (**10**). Suspecting that the last-cited compounds were unstable, interception of the sulphinate salts (**7c**) and (**9**) with iodomethane was examined. Following silica-gel fractionation of the product, two crystalline substances were isolated. The first-eluted material, obtained in 37% yield, was formulated as the *trans*-azetidinone (**11a**). The second-eluted material, isolated in 29% yield, was considered to be the *cis*-azetidinone (**12a**).

The structures assigned to compounds (**11a**) and (**12a**) were based upon analytical and spectral considerations. In particular, the β-lactam hydrogens of the former material appeared as a one-proton doublet (*J* 2 Hz) at δ 5.05 and a one-proton doublet (*J* 7 and 2 Hz) at δ 5.10 in the ^{1}H n.m.r. spectrum ($CDCl_3$); those of the latter material were present as a one-proton doublet (*J* 5 Hz) at δ 5.12 and a one-proton double doublet (*J* 10 and 5 Hz) at δ 6.07. The values of the vicinal



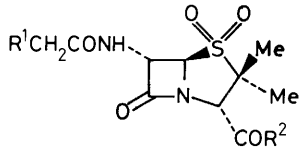
(1)

a; $R^1 = CH_2Ph$, $R^2 = Me$
b; $R^1 = CH_2Ph$, $R^2 = CH_2C_6H_4NO_2$-*p*
c; $R^1 = CH_2Ph$, $R^2 = CH_2CH_2I$
d; $R^1 = CH_2OPh$, $R^2 = Me$
e; $R^1 = OCH_2Ph$, $R^2 = Me$
f; $R^1 = CH_2Ph$, $R^2 = C_6H_4NO_2$-*p*
g; $R^1 = CH_2OPh$, $R^2 = CH_2C_6H_4NO_2$-*p*



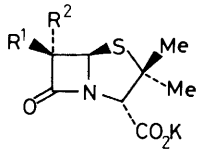
(2)

a; $R^1 = CH_2Ph$, $R^2 = Me$
b; $R^1 = CH_2Ph$, $R^2 = CH_2C_6H_4NO_2$-*p*
c; $R^1 = CH_2Ph$, $R^2 = CH_2CH_2I$
d; $R^1 = CH_2OPh$, $R^2 = Me$
e; $R^1 = OCH_2Ph$, $R^2 = Me$



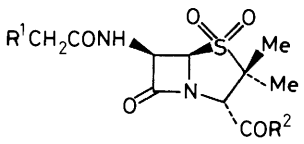
(3)

a; $R^1 = Ph$, $R^2 = OMe$
b; $R^1 = OPh$, $R^2 = Me$



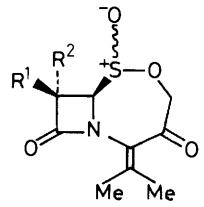
(4)

a; $R^1 = H$, $R^2 = NHCOCH_2Ph$
b; $R^1 = NHCOCH_2Ph$, $R^2 = H$



(5)

a; $R^1 = OPh$, $R^2 = CH_2Cl$
b; $R^1 = OPh$, $R^2 = CH_2OH$
c; $R^1 = OPh$, $R^2 = CHN_2$
d; $R^1 = Ph$, $R^2 = CHN_2$
e; $R^1 = OPh$, $R^2 = Me$
f; $R^1 = OPh$, $R^2 = H$



(6)

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

coupling constants indicated[9] that the β-lactam hydrogen atoms were *trans*-disposed in compound (**11a**) and *cis*-orientated in compound (**12a**).

Presumably, in the presence of DBN, the acetylpenam dioxide (**5e**) undergoes a competitive β-elimination [to give the sulphinate salt (**7c**)] and an epimerisation-β-elimination sequence [to give the 6-epimer (**3b**) and thence the sulphinate salt (**9**)].

In the hope of limiting the epimerisation reaction, the acetylpenam dioxide (**5e**) was treated in tetrahydrofuran (THF) at −78 °C with potassium t-butoxide (1 mol equiv.). Evaporation of the solvent left a solid which was purified by dissolution in acetone and addition of diethyl ether. The resulting amorphous precipitate (which was hygroscopic), obtained in 58% yield, was the salt (**13**) on the basis of its spectroscopic properties. In particular, in the ^1H n.m.r. spectrum (D_2O), the β-lactam hydrogen atoms appeared as two one-proton doublets (J 5 Hz) at δ 3.92 and 5.22.

Interestingly, although the salt (**13**) was stable in deuterium oxide over a period of 1 day, non-β-lactam products resulted when the material was acidified. Clearly, as suspected earlier, the sulphinic acid (**8a**) was a labile entity.

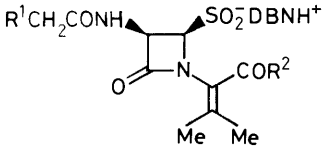
To verify its structure, the salt (**13**) was treated with an excess of iodomethane in *N*,*N*-dimethylformamide (DMF). The crystalline product, isolated in 70% yield [based on (**5e**)] after silica-gel chromatography, was identified as the *cis*-azetidinone (**12a**). Evidently, in the case of the acetylpenam dioxide (**5e**) the rates of β-elimination at position 3 and epimerisation at position 6 are influenced by the base and/or solvent.

The 3-hydrogen atom of the formylpenam dioxide (**5f**) is expected to be more acidic than that of the acetylpenam dioxide (**5e**). It was therefore of interest to examine the behaviour of compound (**5f**) under β-elimination conditions.

It was envisaged that the formylpenam dioxide (**5f**) would be accessible from the dihydroxyethylpenam dioxide (**14**). Two routes to the last-cited compound were examined. In procedure *A*, the hydroxyacetylpenam oxide (**15a**)[6] was treated with sodium borohydride in ethanol to give the crystalline dihydroxyethylpenam oxide (**15b**) in 64% yield; oxidation of compound (**15b**) with potassium permanganate in aqueous acetic acid provided the crystalline dihydroxyethylpenam dioxide (**14**) in 83% yield. In procedure *B*, the hydroxyacetylpenam dioxide (**5b**)[6] was subjected to the action of sodium borohydride in THF; work-up gave compound (**14**) in 55% yield. From the common precursor [the hydroxyacetylpenam oxide (**15a**)], the overall yield of the dihydroxyethylpenam dioxide (**14**) was 53% by route *A* and 48% by route *B*. The dihydroxyethylpenam derivatives (**14**) and (**15b**) were isolated as single diastereoisomers, indicating high stereoselectivity in the reduction of the 3-carbonyl groups of compounds (**5b**) and (**15a**).

Oxidative cleavage of the glycol group of the dihydroxyethylpenam dioxide (**14**) was achieved by the action of sodium periodiate in aqueous dioxane. The resultant product, isolated as a syrup in 85% yield after azeotropic removal of water with benzene, was the formylpenam dioxide (**5f**).

There was no evidence for the formation of the sulphinic acid (**8b**) when the formylpenam dioxide (**5f**) was subjected to the



(7)

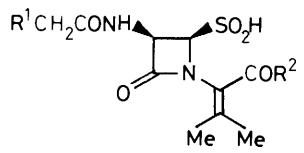
a; R^1 = OPh, R^2 = CH_2Cl

b; R^1 = OPh, R^2 = CH_2OH

c; R^1 = OPh, R^2 = Me

d; R^1 = OPh R^2 = H

e; R^1 = Ph, R^2 = $OC_6H_4NO_2$-*p*



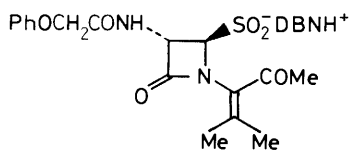
(8)

a; R^1 = OPh, R^2 = Me

b; R^1 = OPh, R^2 = H

c; R^1 = Ph, R^2 = $OC_6H_4NO_2$-*p*

d; R^1 = OPh, R^2 = $OCH_2C_6H_4NO_2$-*p*



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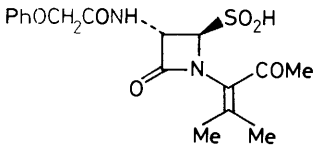

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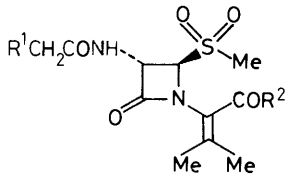


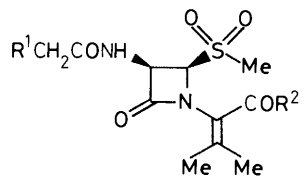
(11)

a; R^1 = OPh, R^2 = Me

b; R^1 = Ph, R^2 = OMe

c; R^1 = Ph, R^2 = $OCH_2C_6H_4NO_2$-*p*

d; R^1 = OPh, R^2 = OMe



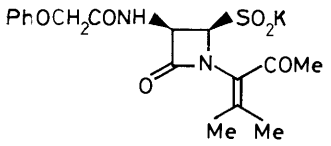
(12)

a; R^1 = OPh, R^2 = Me

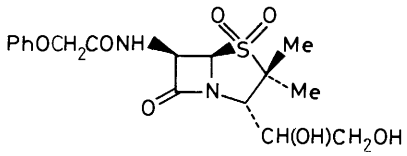
b; R^1 = OPh, R^2 = H

c; R^1 = Ph, R^2 = $OC_6H_4NO_2$-*p*

d; R^1 = Ph, R^2 = OMe



(13)



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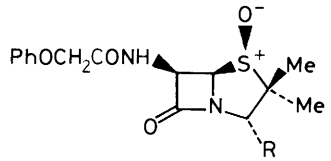


(15)

a; R = $COCH_2OH$

b; R = $CH(OH)CH_2OH$

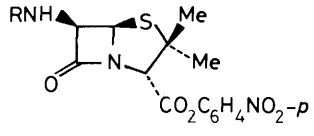
action of DBN in deuteriochloroform followed by an acidic work-up. However, when the reaction was monitored by ^1H n.m.r. spectroscopy, a species corresponding to the sulphinate salt (**7d**) was detected. This material was trapped by the addition of iodomethane; following silica-gel fractionation of the product, the syrupy *cis*-azetidinone (**12b**) was isolated in 31% yield. The ^1H n.m.r. spectrum ($CDCl_3$) of compound (**12b**) featured a one-proton doublet (*J* 5 Hz) at δ 5.48 and a one-proton double doublet (*J* 10 and 5 Hz) at δ 5.91 for the β-lactam hydrogen atoms.

In the light of the experience gained in the present studies with the substrates (**5e,f**) and in earlier studies[6] with the substrates (**5a,b**), attention was re-focussed upon penicillinate dioxides of type (**1**). In addition to their susceptibility to nucleophilic attack, *p*-nitrophenyl esters are known to increase the acidity of adjacent hydrogen atoms compared with alkyl esters. Indeed, the *p*-nitrophenyl ester (**16a**) has been reported[10] to undergo the anhydropenicillin rearrangement [to give compound (**17**)] in the presence of DBN. Accordingly, it was decided to examine the behaviour of the activated ester (**1f**) under basic conditions.

When treated sequentially in dichloromethane with triethylamine hydrochloride, ethyl chloroformate, and *p*-nitrophenol, potassium benzylpenicillinate (**4b**) was converted into the *p*-nitrophenyl ester (**16b**). Without purification, this material was treated with potassium permanganate in aqueous acetic acid; recrystallisation of the product gave the penicillinate dioxide (**1f**) in the 64% yield [based upon (**4b**)].

Gratifyingly, the penicillinate dioxide (**1f**) reacted in dimethyl sulphoxide with DBN followed by iodomethane to give the methylsulphonyl derivative (**12c**), isolated as a crystalline solid in 64% yield after silica-gel chromatography. The ^1H n.m.r. spectrum ($CDCl_3$) of compound (**12c**) featured the β-lactam hydrogen atoms as a one-proton doublet (*J* 5 Hz) at δ 5.12 and a one-proton double doublet (*J* 10 and 5 Hz) at δ 5.94.

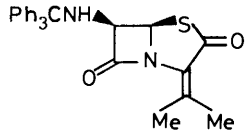
It was possible to isolate the *cis*-azetidinesulphinic acid (**8c**), contaminated with *ca.* 25% of *p*-nitrophenol, by treatment of the penicillinate dioxide (**1f**) with DBN followed by an acidic work-up. The acid (**8c**) was somewhat unstable and had to be processed rapidly. By contrast its sodium salt (**18a**) (which still contained *p*-nitrophenol) showed a reasonable shelf-life. In the ^1H n.m.r. spectrum ($CDCl_3$) of the acid (**8c**), the β-lactam hydrogen atoms resonated as a doublet (*J* 5 Hz) at δ 4.82 and a double doublet (*J* 8 and 5 Hz) at δ 5.32. In the spectrum (D_2O) of the salt (**18a**), they appeared as doublets (*J* 5 Hz) at δ 4.07 and 5.09.



(16)

a; R = CPh_3

b; R = $COCH_2Ph$



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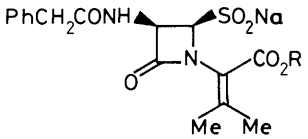
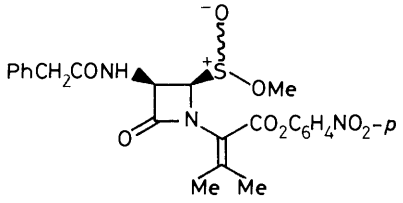


(18)

a; R = $C_6H_4NO_2$-*p*

b; R = Na



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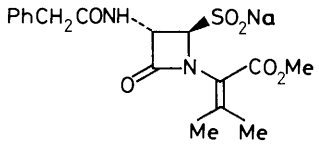

(20)

Table 1. Chemical shifts (δ) of representative hydrogen atoms of 3-acylamino-4-methylsulphonylazetidin-2-ones (in $CDCl_3$)

Compound	H_a[a]	H_b[b]	$MeSO_2$
(**11a**)	5.10	5.05	2.93
(**11b**)[2]	5.13	5.18	3.18
(**11c**)[2]	4.98	5.16	2.93
(**11d**)[2]	5.19—5.35		3.05
(**12a**)	6.07	5.12	2.64
(**12b**)	5.91	5.48	2.53
(**12c**)	5.94	5.12	2.44
(**12d**)	5.85	5.06	2.48

[a] H_a Refers to the β-lactam hydrogen adjacent to the acylamino entity. [b] H_b Refers to the β-lactam hydrogen atom next to the methylsulphonyl group.

Table 2. Chemical shifts (δ) of the β-lactam hydrogen atoms of 3-acylamino-4-oxoazetidine-2-sulphinic acids and their salts

Compound	Solvent	H_a[a]	H_b[b]
(**2a**)[2]	$CDCl_3$	5.18	4.71
(**2b**)[2]	$CDCl_3$	5.30	4.72
(**2c**)[2]	$CDCl_3$	5.17	4.80
(**2d**)[2]	$CDCl_3$	5.33	4.82
(**2e**)[2]	$CDCl_3$	*ca.* 5.1	4.73
(**8c**)	$CDCl_3$	5.32	4.82
(**13**)	D_2O	5.22	3.92
(**18a**)	D_2O	5.09	4.07
(**18b**)	D_2O	5.23	4.20
(**20**)	D_2O	5.30	4.30

[a] H_a Refers to the β-lactam hydrogen atom adjacent to the acylamino entity. [b] Refers to the β-lactam hydrogen atom adjacent to the sulphur group.

The sulphinic acid (**8c**) was converted, by the action of the diazomethane, into the methyl sulphinate (**19**) [40% yield based upon (**1f**) after SiO_2 chromatography], isolated as a syrupy 1.5:1 mixture of diastereoisomers. It was possible to separate the isomers by semi-preparative h.p.l.c. but only the minor diastereoisomer was obtained in an analytically pure state. The β-lactam hydrogen atoms of the major diastereoisomer appeared as a one-proton doublet (*J* 5 Hz) at δ 4.98 and a one-proton double doublet (*J* 9 and 5 Hz) at δ 5.52 in the ^1H n.m.r. spectrum ($CDCl_3$). In the minor diastereoisomer, they showed similar multiplicities and coupling constants and resonated at δ 4.76 and 5.50.

The ease of hydrolysis of the *p*-nitrophenyl ester function of compound (**8c**) was demonstrated by the formation of the disodium salt (**18b**) and *p*-nitrophenol in the presence of sodium hydroxide. In the ^1H n.m.r. spectrum (D_2O) of the mixture, the β-lactam hydrogen atoms absorbed as doublets (*J* 5 Hz) at δ 5.20 and 5.23. Treatment of the mixture in DMF with iodomethane, and purification of the product by silica-gel chromatography, gave the crystalline dimethyl derivative (**12d**) [30% based on (**1f**)].

A comparison of the ^1H n.m.r. spectra of some compounds prepared in this work and earlier studies[2] revealed some diagnostic features, which are summarised in Tables 1 and 2. In the case of the 3-acylamino-4-methylsulphonylazetidin-2-ones (**11a—d**) and (**12a—d**) (Table 1), the chemical shifts of the β-lactam hydrogen atoms are markedly dependent upon their geometry. Thus with the *trans*-substituted derivatives (**11a—d**), both absorb in the δ 4.98—5.35 region. With the *cis*-substituted compounds (**12a—d**), the hydrogen atom adjacent to the acylamino function is significantly deshielded (absorbing in the δ 5.85—6.07 region) in comparison with that of the *trans*-substituted compounds; however, the hydrogen atom adjacent to the methylsulphonyl group shows a chemical shift (in the δ 5.06—5.48 region) which is similar to that of its *trans*-substituted relatives. The chemical shifts of the methylsulphonyl hydrogen atoms are also diagnostic of geometry; in the *trans*-azetidinones (**11a—d**), they resonate in the δ 2.93—3.18 region, whereas in the *cis*-azetidinones (**12a—d**) they appear in the δ 2.44—2.64 region.

With the 3-acylamino-4-oxoazetidine-2-sulphinic acids (**2a—e**) and (**8c**) (Table 2), the β-lactam hydrogen atom adjacent to the acylamino function appears at lower field (in the δ 5.1—5.33 region) than that next to the sulphino group (in the δ 4.71—4.82 region); the chemical shift of these protons do not appear to be influenced by their stereochemical relationship. In the sulphinate salts (**13**), (**18a,b**), and (**20**), the β-lactam hydrogen atom adjacent to the sulphinate group experiences a substantial up-field shift (to δ 3.92—4.30) whereas that adjacent to the acylamino group is essentially unaltered (absorbing in the δ 5.09—5.30 region).

The present findings are of interest in a number of respects. First, they provide further insights into the factors which promote β-eliminations at position 3, at the expense of epimerisations at position 6, of penicillin-derived sulphones. Secondly, they provide access to (2*R*,3*R*)-3-acylamino-4-oxo-

acetidine-2-sulphinic acids and their derivatives. As well as their intrinsic interest, such compounds are of potential value in the synthesis of novel β-lactams. Hitherto, related sulphinic acids have been prepared from penicillin sulphoxides by oxidation with *N*-chlorosuccinimide followed by hydrolysis of the derived azetidinesulphinyl chlorides[11] and from cephalosporin sulphones by electrolytic or zinc reduction.[12] Very recently, Davis and Wu have reported[13] that the sulphinic acid (**8d**) can be obtained in *ca.* 20% yield from the penicillinate dioxide (**1g**) by the action of potassium acetate in a mixture of DMF and dichloromethane. Sulphinic acid methyl esters have also been described; they can be prepared from 2-spiroepoxycephalosporin sulphones by the action of thiourea followed by diazomethane[14] and from azetidinedisulphides by electrolysis in the presence of acidic methanol.[15]

Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows: THF was distilled from calcium hydride immediately prior to use; DMF was distilled *in vacuo* from calcium hydride and stored over 4 Å molecular sieves; dimethyl sulphoxide was stored over 4 Å molecular sieves. Light petroleum refers to that fraction boiling in the range 40—60 °C. Ethereal diazomethane was generated by adding a solution of Diazald in diethyl ether to potassium hydroxide in aqueous ethanol.[16] ^{1}H N.m.r. spectra at 300 MHz were measured using either a Varian XL300 or a Bruker AC300 spectrometer. Electron impact (e.i.) mass spectra were determined using an AEI MS9 instrument operating at 70 eV; a Kratos MS45 spectrometer was employed to record chemical ionization (c.i.) (using NH_3 as the carrier gas) and fast atom bombardment (f.a.b.) (using *m*-nitrobenzyl alcohol as the matrix) mass spectra. Semi-preparative h.p.l.c. was carried out using a column (25 × 0.8 cm) of Spherisorb S10 silica, a Constametric III pump, and a Cecil CE212 variable wavelength detector (set at 280 nm). For other chromatographic and instrumental details, see Part 20.[17]

Preparation of (3S,5R,6R)-3-*Acetyl*-2,2-*dimethyl*-6-*phenoxyacetamidopenam* 1,1-*Dioxide* (**5e**).—A solution of freshly distilled 57% hydriodic acid (1.2 cm^3, 9.1 mmol) in acetone (5 cm^3) was added in drops to a stirred solution of the diazoacetylpenam dioxide (**5c**)[6] (1.06 g, 2.61 mmol) in acetone (20 cm^3). After 15 min, the mixture was diluted with dichloromethane and washed with aqueous sodium thiosulphate. Evaporation of the dried ($MgSO_4$) organic phase gave the *title compound* (**5e**) (0.970 g, 98%) as a syrup which crystallised on addition of diethyl ether. After recrystallisation from ethyl acetate–light petroleum, the sample (0.690 g, 70%) displayed m.p. 125—127 °C; $[\alpha]_D$ +157° (1% in CH_2Cl_2); $\nu_{max.}$(KBr) 3 430 (N–H), 1 805 (β-lactam C=O), 1 730 (ketone C=O), and 1 700 cm^{-1} (amide C=O); $\lambda_{max.}$(EtOH) 222 (ε 4 700), 262 (1 050), 268 (1 400), and 275 nm (1 200); δ(60 MHz; $CDCl_3$) 1.36 and 1.57 (each 3 H, s, 2-Me_2), 2.28 (3 H, s, COMe), 4.30 (1 H, s, 3-H), 4.53 (2 H, s, CH_2OPh), 4.84 (1 H, d, *J* 5 Hz, 5-H), 6.17 (1 H, dd, *J* 10 and 5 Hz, 6-H), 6.74—7.45 (5 H, m, C_6H_5), and 8.1br (1 H, d, *J* 10 Hz, CONH) [addition of D_2O caused the double doublet at δ 6.17 to collapse to a doublet (*J* 5 Hz) and the doublet at δ 8.1 to disappear]; *m/z* (e.i.) 380 (M^+, base peak) (Found: C, 53.7; H, 5.3; N, 7.2%; M^+, 380.1044. $C_{17}H_{20}N_2O_6S$ requires C, 53.65; H, 5.3; N, 7.35%; M^+, 380.1042).

Reaction of the Acetylpenam Dioxide (**5e**) *with DBN followed by Iodomethane.*—95% DBN (0.282 cm^3, 2.16 mmol) was added to a stirred solution of the acetylpenam dioxide (**5e**) (0.696 g, 1.83 mmol) in dichloromethane (10 cm^3) followed, after 0.5 h, by iodomethane (3.24 cm^3, 10 mmol). After 15 h, the mixture was diluted with dichloromethane and washed with dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography (light petroleum–EtOAc; gradient elution) gave two major products.

The first-eluted material (0.270 g, 37%) was identified as (3S,4R)-1-(1-*acetyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphonyl*-3-*phenoxyacetamidoazetidin*-2-*one* (**11a**), m.p. 160 °C (from $CHCl_3$–light petroleum); $[\alpha]_D$ +49° (0.3% in CH_2Cl_2); $\nu_{max.}$(KBr) 1 775 (β-lactam C=O), 1.690 (enone C=O), 1 670 (amide C=O), and 1 655 cm^{-1}; $\lambda_{max.}$(EtOH) 216 (ε 16 400), 250 (6 800), 266sh (4 800), and 273sh nm (3 200); δ(300 MHz; $CDCl_3$) 2 02, 2.07, and 2.40 (each 3 H, s, CMe_2 and COMe), 2.93 (3 H, s, SO_2Me), 4.50 (2 H, s, CH_2OPh), 5.05 (1 H, d, *J* 2 Hz, 4-H), 5.10 (1 H, dd, *J* 7 and 2 Hz, 3-H), 6.83—6.87, 6.94—6.99, and 7.24—7.30 (2, 1, and 2 H, each m, C_6H_5), and 7.38br (1 H, d, *J* 7 Hz, CONH); *m/z* (c.i.) 412 (MNH_4^+, 9%) 395 (MH^+, 11), 317 (33), 315 (M^+ − CH_3O_2S, 50), 223 (52), and 140 (100) (Found: C, 54.9; H, 5.5; N, 7.0; S, 7.9. $C_{18}H_{22}N_2O_6S$ requires C, 54.8; H, 5.6; N, 7.1; S, 8.15%).

The second-eluted material (0.210 g, 29%) was identified as (3R,4R)-1-(1-*acetyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphonyl*-3-*phenoxyacetamidoazetidin*-2-*one* (**12a**), m.p. 64 °C (from $CHCl_3$–light petroleum); $[\alpha]_D$ −48° (0.2% in CH_2Cl_2); $\nu_{max.}$(KBr) 1 790 (β-lactam C=O) and 1 690 cm^{-1} (enone and amide C=O); $\lambda_{max.}$(EtOH) 215 (ε 18 700), 246 (7 400), 266sh (4 900), and 273sh nm (3 200); δ(300 MHz; $CDCl_3$) 2.16, 2.22, and 2.40 (each 3 H, s, CMe_2 and COMe), 2.64 (3 H, s, SO_2Me), 4.60 (2 H, AB, q, *J* 15 Hz, separation of inner lines 3 Hz, CH_2OPh), 5.12 (1 H, d, *J* 5 Hz, 4-H), 6.07 (1 H, dd, *J* 10 and 5 Hz, 3-H), 6.95—6.99, 7.02—7.08, and 7.32—7.38 (2, 1, and 2 H, each m, C_6H_5), and 7.88br (1 H, d, *J* 10 Hz, CONH); *m/z* (c.i.) 412 (MNH_4^+, 8%), 395 (MH^+, 2), and 315 (M^+ − CH_3O_2S, 24) (Found: C, 54.5; H, 5.6; N, 7.0; S, 8.4. $C_{18}H_{22}N_2O_6S$ requires C, 54.8; H, 5.6; N, 7.1; S, 8.15%).

Reaction of the Acetylpenam Dioxide (**5e**) *with Potassium t-Butoxide Followed by Iodomethane.*—Freshly sublimed potassium t-butoxide (0.114 g, 1.02 mmol) was added to a stirred, cooled (Me_2CO–solid CO_2) solution of the acetylpenam dioxide (**5e**) (0.390 g, 1.02 mmol) in dry THF (6 cm^3). After 1 h, the solvent was removed by evaporation and the residue was dissolved in acetone. Addition of diethyl ether to the solution induced the precipitation of potassium (2*R*,3*R*)-1-(1-acetyl-2-methylprop-1-enyl)-4-oxo-3-phenoxyacetamidoazetidine-2-sulphinate (**13**) (0.255 g, 59%) as a hygroscopic solid; m.p. 108—110 °C (decomp.); $[\alpha]_D$ −28° (0.4% in EtOH); $\nu_{max.}$(KBr) 3 400br (N–H), 1 760 (β-lactam C=O), and 1 680 and 1 650 cm^{-1} (amide C=O); $\lambda_{max.}$(EtOH) 218 (ε 14 700), 231sh (8 500), 269 (4 200), 275 (3 700), and 320 nm (3 500); δ(60 MHz; D_2O) 2.00 and 2.13 (each 3 H, s, CMe_2), 2.34 (3 H, s, COMe), 3.92 (1 H, d, *J* 5 Hz, 2-H), 4.64 (2 H, s, CH_2OPh), 5.22 (1 H, d, *J* 5 Hz, 3-H), and 6.76—7.56 (5 H, m, C_6H_5) (the spectrum was unchanged over 24 h).

Iodomethane (0.105 cm^3, 1.69 mmol) was added to a stirred solution of the potassium salt (**13**) (0.160 g, 0.38 mmol) in dry DMF (5 cm^3). After 24 h, the mixture was diluted with ethyl acetate and washed with water (2 ×) and brine. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography [light petroleum–EtOAc (2:1) as eluant] gave material (0.105 g, 70%) that was identical to the (3*R*,4*R*)-azetidinone (**12a**) by 300 MHz ^{1}H n.m.r. spectroscopy.

Preparation of (1S,3S,5R,6R)-3-(1,2-*Dihydroxyethyl*)-2,2-*dimethyl*-6-*phenoxyacetamidopenam* 1-*Oxide* (**15b**).—Sodium borohydride (0.056 g, 1.48 mmol) was added to a stirred suspension of the hydroxyacetylpenam oxide (**15a**)[6] (0.550 g, 1.45 mmol) in ethanol (50 cm^3). After 30 min, the mixture was

diluted with dichloromethane and washed with dilute hydrochloric acid followed by water. The dried ($MgSO_4$) organic layer was then evaporated. Methanol was added to the residue and the solvent was removed by evaporation (× 3). The product was then recrystallised from methanol–chloroform to give the *title compound* (**15b**) (0.356 g, 64%); m.p. 171—173 °C (decomp.); $[\alpha]_D$ +55° (1% in CH_2Cl_2); $\nu_{max.}$(KBr) 3 510, 3 430, and 3 360 (OH and NH), 1.765 (β-lactam CO), and 1 665 cm^{-1} (amide CO); $\lambda_{max.}$(EtOH) 219 (ε 9 200), 264 (1 200), 270 (1 600), and 277 nm (1 400); δ(60 MHz; CD_3SOCD_3) 1.30 and 1.53 (each 3 H, s, 2-Me_2), 3.5br (4 H, s, $CHOHCH_2OH$), 4.55 (3 H, s, CH_2OPh and 3-H), 5.1br (1 H, s, CH_2OH), 5.25 (1 H, d, *J* 5 Hz, 5-H), 5.78 (1 H, dd, *J* 10 and 5 Hz, 6-H), 6.75—7.45 (5 H, m, C_6H_5) and 8.2br (1 H, d, *J* 10 Hz, CONH) [addition of D_2O caused the integral for the signal at δ 3.5 to reduce to 3 H, the singlet at δ 5.1 and the doublet at δ 8.2 to disappear, and the double doublet at δ 5.78 to collapse to a doublet (*J* 5 Hz)]; *m/z* (e.i.) 382 (M^+) and 364 ($M^+ - H_2O$, base peak) (Found: C, 53.4; H, 5.9; N, 7.4. $C_{17}H_{22}N_2O_6S$ requires C, 53.4; H, 5.8; N, 7.35%).

Preparation of (3S,5R,6R)-3-(1,2-*Dihydroxyethyl*)-2,2-*dimethyl*-6-*phenoxyacetamidopenam* 1,1-*Dioxide* (**14**).—(*a*) A solution of potassium permanganate (0.193 g, 1.22 mmol) in water (10 cm^3) was added in drops, over 1 h, to an ice-cooled solution of the dihydroxyethylpenam oxide (**15b**) (0.310 g, 0.81 mmol) in 4:1 acetic acid–water (15 cm^3). After a further 1 h, the colour of the mixture was discharged by adding 30% aqueous hydrogen peroxide and the solution was extracted with dichloromethane. The organic layer was washed with water (2 ×) and aqueous sodium hydrogen carbonate, and then dried ($MgSO_4$) and concentrated to give the *title compound* (**14**) (0.268 g, 83%) as a crystalline solid, m.p. 86—88 °C (from EtOAc–light petroleum); $[\alpha]_D$ +69° (0.4% in EtOH); $\nu_{max.}$(KBr) 3 400 (OH and NH), 1 790 (β-lactam CO), and 1 685 cm^{-1} (amide CO); $\lambda_{max.}$(EtOH) 225 (ε 2 900), 263sh (1 800), 269 (2 300), 276 (2 100), and 285 nm (800); δ(300 MHz; CD_3SOCD_3) 1.45br and 1.54br (each 3 H, s, 2-Me_2), 3.37—3.65 (6 H, m, 3-H and $CHOHCH_2OH$), 4.65br (2 H, s, CH_2OPh), 5.13br (1 H, s, 5-H), 5.95br (1 H, s, 6-H), 6.93—7.00br and 7.27—7.32br (3 and 2 H, each m, C_6H_5), and 8.34br (1 H, d, *J* 10 Hz, CONH) [addition of D_2O caused an immediate sharpening of all signals and a reduction of the integral for the multiplet at δ 3.37—3.65 to 4 H; thus the signal at δ 5.13 appeared as a doublet (*J* 5 Hz), and that at δ 5.95 as a double doublet (*J* 10 and 5 Hz)]; *m/z* (e.i.) 398 (M^+), 177, 107, and 77 ($C_6H_5^+$, base peak) (Found: C, 51.1; H, 5.3; N, 6.9; S, 7.8%; M^+, 398.1158. $C_{17}H_{22}N_2O_7S$ requires C, 51.25; H, 5.55; N, 7.05; S, 8.05%; *M*, 398.1148).

(*b*) Sodium borohydride (0.030 g, 0.79 mmol) was added in small portions to a stirred ice-cooled solution of the hydroxyacetylpenam dioxide (**5b**)[6] (0.580 g, 1.46 mmol) in dry THF. After 30 min, the mixture was diluted with acetone followed by water and extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a solid (0.320 g, 55%) that was identical (^1H n.m.r. spectroscopy) to the dihydroxyethylpenam dioxide (**14**) obtained above.

Preparation of (3S,5R,6R)-3-*Formyl*-2,2-*dimethyl*-6-*phenoxyacetamidopenam* 1,1-*Dioxide* (**5f**).—Sodium periodiate (0.342 g, 1.60 mmol) in water (10 cm^3) was added to a stirred solution of the diol (**14**) (0.636 g, 1.61 mmol) in dioxane (10 cm^3). After 45 min, the mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with water followed by aqueous sodium thiosulphate, dried ($MgSO_4$), and evaporated. Addition of benzene to the residue and re-evaporation (repeated 3 ×) gave the *title compound* (**5f**) (0.497 g, 85%) as a chromatographically homogeneous syrup; $[\alpha]_D$ +75° (1.3% in EtOH); $\nu_{max.}$(film) 3 400 (NH), 1 800 (β-lactam CO), and 1 685 cm^{-1} (formyl and amide CO); $\lambda_{max.}$(EtOH) 221 (ε 5 000), 263 (1 200), 268 (1 600), 275 (1 400), and 318 nm (150); δ(60 MHz; $CDCl_3$) 1.40 and 1.53 (each 3 H, s, 2-Me_2), 4.20 (1 H, s, 3-H), 4.47 (2 H, s, CH_2OPh), 4.73 (1 H, d, *J* 4 Hz, 5-H), 6.06 (1 H, dd, *J* 8 and 4 Hz, 6-H), 6.65—7.30 (5 H, m, C_6H_5), 7.97br (1 H, d, *J* 8 Hz, CONH), and 9.40 (1 H, s, CHO); *m/z* (e.i.) 366 (M^+), 177, 151, 107, and 77 ($C_6H_5^+$, base peak) (Found: M^+, 366.0914. $C_{16}H_{18}N_2O_6S$ requires *M*, 366.0885).

Preparation of (3R,4R)-1-(1-*Formyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphonyl*-3-*phenoxyacetamidoazetidin*-2-*one* (**12b**).—A 30% solution of the 95% DBN in deuteriochloroform was added in drops to a solution of the formylpenam dioxide (**5f**) (0.100 g, 0.273 mmol) in deuteriochloroform (1 cm^3). When the reaction was complete (^1H n.m.r. spectroscopy), iodomethane (0.10 cm^3, 1.56 mmol) was added and the solution was stirred for 2 h. The mixture was then diluted with dichloromethane and washed with dilute hydrochloric acid. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography (light petroleum–EtOAc; gradient elution) gave the *title compound* (**12b**) (0.032 g, 31%) as a chromatographically homogeneous syrup; $[\alpha]_D$ −68° (1.5% in EtOH); $\nu_{max.}$(film) 3 380 (NH), 1 780 (β-lactam CO), and 1 675 cm^{-1} (enal and amide CO); $\lambda_{max.}$(EtOH) 218 (ε 12 500), 255 (6 900), 266sh (5 400), and 274sh nm (3 400); δ(60 MHz; $CDCl_3$) 2.13 and 2.22 (each 3 H, s, CMe_2), 2.53 (3 H, s, SO_2Me), 4.45 (2 H, s, CH_2OPh), 5.48 (1 H, d, *J* 5 Hz, 4-H), 5.91 (1 H, dd, *J* 10 and 5 Hz, 3-H), 6.69—7.23 (5 H, m, C_6H_5), 7.67br (1 H, d, *J* 10 Hz, CONH), and 9.67 (1 H, s, CHO); *m/z* (e.i.) 301 ($M^+ - CH_3O_2S$), 107, and 77 ($C_6H_5^+$, base peak) (Found: $M^+ - CH_3O_2S$, 301.1182. $C_{16}H_{17}N_2O_4$ requires *m/z* 301.1188).

Preparation of p-*Nitrophenol* (3S,5R,6R)-*Benzylpenicillinate* 1,1-*Dioxide* (**1f**).—Triethylamine hydrochloride (3.51 g, 25.5 mmol) was added to a stirred suspension of the monohydrate of potassium benzylpenicillinate (**4b**) (10.0 g, 25.6 mmol) in dry dichloromethane (80 cm^3). After 0.5 h, the mixture was ice-cooled and treated with ethyl chloroformate (2.4 cm^3, 25.1 mmol) followed, after 1 h, by *p*-nitrophenol (3.19 g, 22.9 mmol). The mixture was then allowed to attain room temperature and left overnight, after which it was diluted with dichloromethane and washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate (6 ×), and brine. Evaporation of the dried ($MgSO_4$) organic layer left an amorphous solid (11.7 g) which was predominantly *p*-nitrophenyl (3*S*,5*R*,6*R*)-benzylpenicillinate (**16b**); $\nu_{max.}$(KBr) 3 340br (NH), 1 780 (β-lactam and ester CO), and 1 670 cm^{-1} (amide CO); δ(60 MHz; $CDCl_3$) 1.47 and 1.55 (each 3 H, s, 2-Me_2), 3.56 (2 H, s, CH_2Ph), 4.53 (1 H, s, 3-H), 5.45 (1 H, d, *J* 4 Hz, 5-H), 5.60 (1 H, dd, *J* 10 and 4 Hz, 6-H), 6.29br (1 H, d, *J* 10 Hz, CONH), 7.10—7.35 (7 H, m, C_6H_5 and C_6H_2), and 8.18 (2 H, d, *J* 9 Hz, C_6H_2).

A solution of potassium permanganate (3.47 g, 22 mmol) in water (30 cm^3) was added in drops to a stirred ice-cooled solution of the crude penicillinate (**16b**) (5.00 g) in 4:1 acetic acid–water (100 cm^3). After 1.5 h, the colour of the mixture was discharged by adding 30% aqueous hydrogen peroxide. The mixture was then extracted (3 ×) with chloroform and the organic phase was washed with water, aqueous sodium hydrogen carbonate, and brine. Evaporation of the dried ($MgSO_4$) organic layer and crystallisation of the residue from acetone gave the *title compound* (**1f**) [3.44 g, 64% based upon (**4b**)] as a white solid, m.p. 198 °C (decomp., with darkening at 175 °C); $[\alpha]_D$ +169° (0.86% in Me_2SO); $\nu_{max.}$(KBr) 3 380 (NH), 1 810 (β-lactam CO), 1 780 (ester CO), and 1 680 cm^{-1} (amide CO); $\lambda_{max.}$(MeCN) 263 nm (ε 12 100); δ(300 MHz; CD_3SOCD_3) 1.52 and 1.60 (each 3 H, s, 2-Me_2), 3.63 (2 H, AB q,

J 14 Hz, separation of inner lines 6 Hz, CH_2Ph), 5.03 (1 H, s, 3-H), 5.50 (1 H, d, *J* 5 Hz, 5-H), 5.90 (1 H, dd, *J* 8 and 5 Hz, 6-H), 7.22—7.32 (5 H, s, C_6H_5), 7.60 and 8.35 (each 2 H, d, *J* 9 Hz, C_6H_2), and 8.80br (1 H, d, *J* 8 Hz, CONH); *m/z* (c.i.) 299 (11%), 298 (11), and 140 (100) (Found: C, 54.5; H, 4.3; N, 8.3; S, 6.6. $C_{22}H_{21}N_3O_8S$ requires C, 54.2; H, 4.35; N, 8.6; S, 6.6%).

Preparation of p-*Nitrophenyl* 3-*Methyl*-2-[(2R,3R)-2-*methylsulphonyl*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]*but*-2-*enoate* (**12c**).—95% DBN (0.068 cm^3, 0.52 mmol) dissolved in dry dimethyl sulphoxide (5 cm^3) was added in drops, over 5 min, to a stirred solution of the penicillinate dioxide (**1f**) (0.243 g, 0.50 mmol) in dry dimethyl sulphoxide (15 cm^3). After 15 min, iodomethane (0.13 cm^3, 2.09 mmol) was added and the mixture was stirred overnight. The mixture was diluted with dichloromethane and washed (3 ×) with water. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica-gel chromatography (light petroleum–Et_2O; gradient elution) gave the *title compound* (**12c**) (0.160 g, 64%), m.p. 92—93 °C (from $CHCl_3$–light petroleum); $[\alpha]_D$ −9° (0.9% in CH_2Cl_2); $\nu_{max.}$(KBr) 3 380 (NH), 1 790 (β-lactam CO), 1 750 (ester CO), and 1 680 cm^{-1} (amide CO); $\lambda_{max.}$(EtOH) 202 (ε 32 800) and 265 nm (12 400); δ(300 MHz; $CDCl_3$) 2.21 and 2.36 (each 3 H, s, CMe_2), 2.44 (3 H, s, SO_2Me), 3.65 (2 H, AB q, *J* 13 Hz, separation of inner lines 13 Hz, $COCH_2Ph$), 5.12 (1 H, d, *J* 5 Hz, CHC*H*S), 5.94 (1 H, dd, *J* 10 and 5 Hz, NHC*H*CH), 6.69br (1 H, d, *J* 10 Hz, CONH), 7.26—7.42 (7 H, m, C_6H_5 and C_6H_2), and 8.28—8.33 (2 H, m, C_6H_2); *m/z* (c.i.) 315 (17%), 283 (85), 257 (82), 157 (71), 118 (52), and 110 (100) (Found: C, 52.5; H, 4.6; Cl, 4.5; N, 7.7; S, 6.0. $C_{23}H_{23}N_3O_8S{\cdot}0.25CHCl_3$ requires C, 52.55; H, 4.4; Cl, 5.0; N, 7.9; S, 6.05%).

Preparation of (2R,3R)-1-(2-*Methyl*-1-p-*nitrophenoxycarbonylprop*-1-*enyl*)-4-*oxo*-3-*phenylacetamidoazetidine*-2-*sulphinic Acid* (**8c**) *and Its Sodium Salt* (**18a**).—95% DBN (0.055 cm^3, 0.42 mmol) in dry dichloromethane (1 cm^3) was added to a stirred suspension of the penicillinate dioxide (**1f**) (0.200 g, 0.41 mmol) in dry dichloromethane (5 cm^3). After 20 min, the mixture was diluted with dichloromethane and washed with dilute hydrochloric acid. The organic layer was then extracted with aqueous sodium hydrogen carbonate. After acidification with dilute hydrochloric acid, the aqueous phase was extracted with dichloromethane (2 ×). Evaporation of the dried ($MgSO_4$) organic layer gave an amorphous solid (0.185 g) comprising mainly a 3:1 mixture of the title sulphinic acid (**8c**) and *p*-nitrophenol; $\nu_{max.}$(KBr) 3 300br (NH), 1 780 (β-lactam CO), 1 745 (ester CO), and 1 670br cm^{-1} (amide CO); δ(300 MHz; $CDCl_3$) [for (**8c**)] 2.11 and 2.28 (each 3 H, s, CMe_2), 3.58 (2 H, s, CH_2Ph), 4.82 (1 H, d, *J* 5 Hz, 2-H), 5.32 (1 H, dd, *J* 8 and 5 Hz, 3-H), 6.70br (1 H, d, *J* 8 Hz, CONH), 7.23—7.30 (7 H, m, C_6H_5 and C_6H_2), and 8.20 (2 H, d, *J* 9 Hz, C_6H_2) [addition of D_2O caused the double doublet at δ 5.32 to collapse to a doublet (*J* 5 Hz) and the doublet at δ 6.70 to disappear].

A portion of the afore-cited mixture (0.135 g) was dissolved in dichloromethane (8 cm^3) and stirred with a solution of sodium hydrogen carbonate (0.022 g, 0.27 mmol) in water (5 cm^3). After 10 min, the aqueous phase was separated and concentrated. The residue, obtained as a yellow solid, was predominantly a 4:1 mixture of the title sodium salt (**18a**) and *p*-nitrophenol; δ(300 MHz; D_2O) [for (**18a**)] 2.14 and 2.28 (each 3 H, s, CMe_2), 3.66 (2 H, s, CH_2Ph), 4.07 (1 H, d, *J* 5 Hz, 2-H), 5.09 (1 H, d, *J* 5 Hz, 3-H), 7.27—7.43 (7 H, m, C_6H_5 and C_6H_2), and 8.31 (2 H, *J* 9 Hz, C_6H_2).

Preparation of p-*Nitrophenyl* 2-[(2S,3R)-2-*Methoxysulphinyl*- in the previous experiment] in dichloromethane was treated with an excess of diazomethane in diethyl ether. After 10 min, the mixture was concentrated and the resultant pale-yellow foam was purified by silica-gel chromatography (light petroleum–EtOAc; gradient elution) to give an amorphous solid [0.200 g, 40% based upon (**1f**)] that was mainly the title compound (**19**) as a 1.5:1 mixture of diastereoisomers; $\nu_{max.}$(film) 3 300br (NH), 1 780 (β-lactam CO), 1 740 (ester CO), and 1 675 cm^{-1} (amide CO); $\lambda_{max.}$(EtOH) 266 nm (ε 14 300); δ(300 MHz; $CDCl_3$) 2.14, 2.16, 2.25, and 2.27 (1.2, 1.8, 1.8, and 1.2 H, each s, CMe_2), 3.55—3.57 (2 H, m, CH_2Ph), 3.60 and 3.64 (0.4 and 0.6 H, each d, *J* 5 Hz, CHC*H*S), 4.78 and 4.98 (0.4 and 0.6 H, each d, *J* 5 Hz, CHC*H*S), 5.48 and 5.49 (0.4 and 0.6 H, each dd, *J* 9 and 5 Hz, NHC*H*CH), 6.32br and 6.68br (0.6 and 0.4 H, each d, *J* 9 Hz, CONH), 7.17—7.35 (7 H, m, C_6H_5 and C_6H_2), and 8.21 (2 H, d, *J* 9 Hz, C_6H_2); *m/z* (c.i.) 315 (4%), 140 (34), and 57 (100).

A portion of the afore-cited mixture (0.050 g) was fractionated by h.p.l.c. [hexane–EtOAc (1:1) as eluant] to give fraction *A* (0.018 g, 14%) and fraction *B* (0.013 g, 13%).

Fraction *A* was largely the major diastereoisomer of the title compound (**19**); $[\alpha]_D$ +15° (1.5% in $CHCl_3$); δ(300 MHz; $CDCl_3$) 2.17 and 2.27 (each 3 H, s, CMe_2), 3.56 (2 H, AB q, *J* 16 Hz, separation of inner lines 4 Hz, CH_2Ph), 3.66 (3 H, s, OMe), 4.98 (1 H, d, *J* 5 Hz, CHC*H*S), 5.52 (2 H, dd, *J* 9 and 5 Hz, NHC*H*CH), 6.23br (1 H, d, *J* 9 Hz, CONH), 7.18—7.36 (7 H, m, C_6H_5 and C_6H_2), and 8.23 (2 H, d, *J* 9 Hz, C_6H_2); *m/z* (f.a.b.) 524 (MNa^+, 1%), 502 (MH^+, 1), 422 (100), and 155 (100).

Fraction *B* was the *minor diastereoisomer* of the *title compound* (**19**); $[\alpha]_D$ −10° (1.2% in $CHCl_3$); δ(300 MHz; $CDCl_3$) 2.16 and 2.28 (each 3 H, s, CMe_2), 3.57 (2 H, AB q, *J* 16 Hz, separation of inner lines 4 Hz, CH_2Ph), 3.61 (3 H, s, OMe), 4.76 (2 H, d, *J* 5 Hz, CHC*H*S), 5.50 (1 H, dd, *J* 9 and 5 Hz, NHC*H*CH), 6.60br (1 H, d, *J* 9 Hz, CONH), 7.20—7.35 (7 H, m, C_6H_5 and C_6H_2), and 8.23 (1 H, d, *J* 9 Hz, C_6H_2); *m/z* (f.a.b.) 502 (MH^+, 5%), 501 (M^+, 2), 422 (62), and 155 (100) (Found: C, 54.8; H, 4.9; N, 8.1; S, 6.0. $C_{23}H_{23}N_3O_8S$ requires C, 55.1; H, 4.6; N, 8.4; S, 6.4%).

Preparation of Methyl 3-*Methyl*-2-[(2R,3R)-2-*methylsulphonyl*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]*but*-2-*enoate* (**12d**).—2M Sodium hydroxide (0.9 cm^3, 1.8 mmol) was added to a stirred suspension of the crude sulphinic acid (**8c**) [prepared from the penicillinate dioxide (**1f**) (0.488 g, 1 mmol) by the previously described procedure) in water (5 cm^3). After 15 min, the mixture was filtered and the filtrate concentrated. The residue, after thorough drying (*in vacuo*; P_2O_5), was considered to be mainly a mixture of *p*-nitrophenol and the disodium salt of 3-methyl-2-[(3*R*,4*R*)-2-oxo-3-phenylacetamido-4-sulphinoazetidin-1-yl]but-2-enoic acid (**18b**) by ^1H n.m.r. spectroscopy; δ(300 MHz; D_2O) [for (**18b**)] 2.23 and 2.36 (each 3 H, s, CMe_2), 3.64 (2 H, s, CH_2Ph), 4.20 (1 H, d, *J* 5 Hz, CHC*H*S), 5.23 (1 H, d, *J* 5 Hz, NDC*H*CH), and 7.30—7.47 (5 H, m, C_6H_5).

The material was dissolved in dry DMF (5 cm^3) and iodomethane (0.6 cm^3, 9.6 mmol) was added to the stirred solution. After 15 h, the mixture was diluted with ethyl acetate and washed with water (5 ×). Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography [hexane–EtOAc (1:2) as eluant] followed by recrystallisation of the product from dichloromethane–hexane gave the *title compound* (**12d**) [0.118 g, 30% based on (**1f**)], m.p. 109—110 °C; $[\alpha]_D$ +17° (0.7% in $CHCl_3$); $\nu_{max.}$(KBr) 3 340 (NH), 1 765 (β-lactam CO), 1 735 (ester CO), and 1 690 cm^{-1} (amide CO); $\lambda_{max.}$(EtOH) 213sh nm (ε 11 700); δ(60 MHz; $CDCl_3$) 2.07 and 2.23 (each 3 H, s, CMe_2), 2.48 (3 H, s, SMe),

315 ($M^+ - CH_3O_2S$, 75), 169 (25), 137 (49), and 91 ($C_7H_7^+$, 100) (Found: C, 54.5; H, 5.6; N, 7.1; S, 8.0. $C_{18}H_{22}N_2O_6S$ requires C, 54.8; H, 5.6; N, 7.1; S, 8.15%).

Preparation of Sodium (2R,3S)-1-(2-*Methyl*-1-*methoxycarbonylprop*-1-*enyl*)-4-*oxo*-3-*phenylacetamidoazetidine*-2-*sulphinate* (**20**).—The sulphinic acid (**2a**)[2] (0.100 g, 0.26 mmol) was added to a stirred solution of sodium hydrogen carbonate (0.021 g, 0.25 mmol) in water (2 cm^3). After 15 min, the mixture was washed with dichloromethane and the aqueous phase was concentrated. The product was dried thoroughly (*in vacuo*; P_2O_5) to give an amorphous solid (0.090 g, 90%) which was the title salt (**20**); δ(300 MHz; D_2O) 1.98 and 2.20 (each 3 H, s, CMe_2), 3.68 (2 H, s, CH_2Ph), 3.78 (3 H, s, OMe), 4.30 (1 H, s, CHCHS), 5.30 (1 H, s, NDCHCH), and 7.20—7.45 (5 H, s, Ph).

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