Studies Related to Penicillins. Part 21.[1] β-Elimination Reactions of *S,S*-Dioxides of Penicillanic Esters [2]

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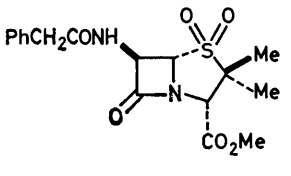
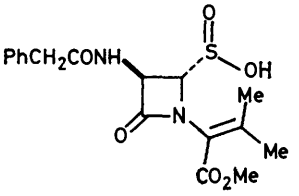
In the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), methyl benzylpenicillinate 1,1-dioxide (3a) is converted into (2*S*,3*R*)-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-oxo-3-phenylacetamidoazetidine-2-sulphinic acid (5a). Corresponding reactions are observed with the *p*-nitrobenzyl and 2-iodoethyl esters of benzylpenicillinic acid 1,1-dioxide (3b and c), with methyl phenoxymethylpenicillinate 1,1-dioxide (3d), with methyl benzyloxypenicillinate 1,1-dioxide (3i), with methyl 6β-phthalimidopenicillanate 1,1-dioxide (3h), with methyl 6α-chloropenicillanate 1,1-dioxide (4b), and with *p*-nitrobenzyl penicillanate 1,1-dioxide (4c). Unidentified non-β-lactam products are produced when methyl penicillinate 1,1-dioxide (3e), methyl methylpenicillinate 1,1-dioxide (3f), and benzyl 6β-triphenylmethylaminopenicillanate 1,1-dioxide (3g) are treated with DBN.

The sodium salt of compound (5a) reacts with methyl iodide to give methyl 3-methyl-2-[(2*R*,3*S*)-2-methylsulphonyl-4-oxo-3-phenylacetamidoazetidin-1-yl]but-2-enoate (6a). Similar reactions occur with the sodium salts of the sulphinic acids derived from the sulphones (3b), (3d), (4b), and (4c).

METHODS for the selective cleavage of the non-β-lactam-associated bonds of the bicyclic backbone of penicillanic acid derivatives are of interest because the products of such reactions may serve as precursors of β-lactam-antibiotic analogues. Recently, we reported [3] that the 5-*epi*-penicillinate *S,S*-dioxide (1) was converted



(1)



(2)

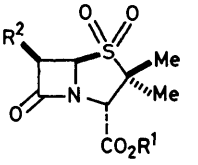
into the oxoazetidinesulphinic acid (2) in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). We now define the scope of this novel isomerisation.

RESULTS AND DISCUSSION

Previously, it was noted that the penicillinate *S,S*-dioxide (3a) was equilibrated with the 6-epimer (4a) in the presence of a trace of DBN.[3] The sulphone (3a), when treated with an excess of the base in dichloromethane, afforded the crystalline oxoazetidinesulphinic acid (5a) in 80% yield. The structure of the last-described material followed from elemental analysis, its spectroscopic properties [which were identical with those of the enantiomer (2)], and its optical rotation, $[\alpha]_D$ −176° ($CHCl_3$) {which was opposite in sign but similar in magnitude to that of the enantiomer (2), $[\alpha]_D$ +160° ($CHCl_3$)}. Furthermore, the sodium salt of the sulphinic acid (5a), when stirred with methyl iodide in *N,N*-dimethylformamide, was transformed (55%) into the methyl sulphone (6a), which was characterised analytically and spectroscopically. It is well established that sulphinate salts act as sulphur nucleophiles towards alkyl halides.[4]

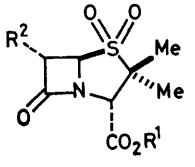
To establish whether the foregoing isomerisation could be effected with a benzylpenicillinate *S,S*-dioxide containing an ester group which might be convertible into a carboxyl at a later stage, the *p*-nitrobenzyl ester (3b) was prepared (70%) by oxidation of the penicillinate (7a) [5] with potassium permanganate in aqueous acetic acid.[6] The sulphone (3b) reacted with DBN to give the oxoazetidinesulphinic acid (5b) (60%) as a sticky foam. The product was characterised by its spectral properties and by its conversion into the methyl sulphone (6b) (55% after SiO_2 chromatography).

Previously, it was suggested [3] that the isomerisation of the 5-*epi*-penicillinate *S,S*-dioxide (1) to the oxoazetidine sulphinic acid (2) proceeded by an *E1cB* mechanism. With a view to providing some support for this pathway, the behaviour of the iodoethyl ester (3c) was examined. It was hoped that the anion (8) would be intercepted intramolecularly by the electrophilic carbon atom of the iodomethyl group and that the γ-lactone (9) would be produced. The sulphone (3c) was prepared (98%) by



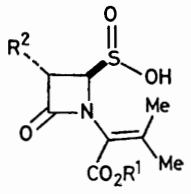
(3)

a; R^1 = Me, R^2 = $PhCH_2CONH$
b; R^1 = *p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$, R^2 = $PhCH_2CONH$
c; R^1 = ICH_2CH_2, R^2 = $PhCH_2CONH$
d; R^1 = Me, R^2 = $PhOCH_2CONH$
e; R^1 = Me, R^2 = HCONH
f; R^1 = Me, R^2 = MeCONH
g; R^1 = $PhCH_2$, R^2 = Ph_2CHN
h; R^1 = Me, R^2 = phthalimido
i; R^1 = Me, R^2 = $PhCH_2OCONH$



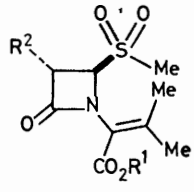
(4)

a; R^1 = Me, R^2 = $PhCH_2CONH$
b; R^1 = Me, R^2 = Cl
c; R^1 = *p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$, R^2 = H
d; R^1 = K, R^2 = H



(5)

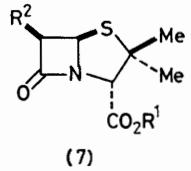
a; R^1 = Me, R^2 = $PhCH_2CONH$
b; R^1 = p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$, R^2 = $PhCH_2CONH$
c; R^1 = ICH_2CH_2, R^2 = $PhCH_2CONH$
d; R^1 = Me, R^2 = $PhOCH_2CONH$
e; R^1 = Me, R^2 = phthalimido
f; R^1 = Me, R^2 = $PhCH_2OCONH$
g; R^1 = Me, R^2 = Cl
h; R^1 = p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$, R^2 = H



(6)

a; R^1 = Me, R^2 = $PhCH_2CONH$
b; R^1 = p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$, R^2 = $PhCH_2CONH$
c; R^1 = Me, R^2 = $PhOCH_2CONH$
d; R^1 = Me, R^2 = Cl
e; R^1 = p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$, R^2 = H

oxidation of the penicillinate (7b) with potassium permanganate; the reaction of the bromoethyl ester (7c), itself obtained (92%) from potassium benzylpenicillinate (7d) and 1,2-dibromoethane in *N*,*N*-dimethylformamide, with sodium iodide in hot acetone provided the iodoethyl ester (7b) in 96% yield. In the presence of DBN, the



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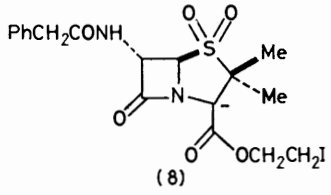

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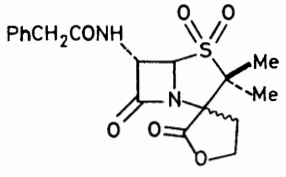


(9)

a; R^1 = p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$, R^2 = $PhCH_2CONH$
b; R^1 = ICH_2CH_2, R^2 = $PhCH_2CONH$
c; R^1 = $BrCH_2CH_2$, R^2 = $PhCH_2CONH$
d; R^1 = K, R^2 = $PhCH_2CONH$
e; R^1 = H, R^2 = $PhCH_2CONH$
f; R^1 = H, R^2 = $PhOCH_2CONH$
g; R^1 = Me, R^2 = $PhOCH_2CONH$
h; R^1 = Me, R^2 = $MeCOCH{:}C(Me)NH$
i; R^1 = H, R^2 = $MeCOCH{:}C(Me)NH$
j; R^1 = H, R^2 = H_2N
k; R^1 = $PhCH_2$, R^2 = Ph_3CNH
l; R^1 = Me, R^2 = phthalimido
m; R^1 = Me, R^2 = $PhCH_2OCONH$

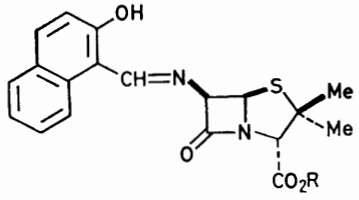
sulphone (3c) was converted (63%) into the syrupy sulphinic acid (5c), which was characterised by its spectroscopic properties; there was no evidence for the formation of the γ-lactone (9). Evidently, if involved, the anion (8) undergoes the elimination in preference to the internal alkylation.

Phenoxymethylpenicillinic acid (7f), in common with benzylpenicillinic acid (7e), is a primary low-cost penicillin which is produced by direct fermentation. Accordingly, it was appropriate to examine the behaviour of an ester of its *S*,*S*-dioxide towards DBN. The sulphone (3d), prepared (73%) by oxidation of the penicillinate (7g) [5] with potassium permanganate, reacted with DBN to give the sulphinic acid (5d) (65%) as a hygroscopic foam. The structure (5d) was established on the basis of its analytical and spectral properties and by its conversion into the methyl sulphone (6c) (91% after SiO_2 chromatography).

The foregoing examples suggest that the conversions of benzylpenicillinate ester *S*,*S*-dioxides (3; R^2 = $PhCH_2CONH$) and phenoxymethylpenicillinate ester *S*,*S*-dioxides (3; R^2 = $PhOCH_2CONH$) into sulphinic acids of type (5; R^2 = $PhCH_2CONH$ and $PhOCH_2CONH$) are likely to be general reactions.

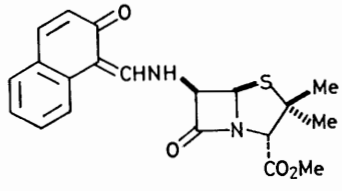
To define further the capabilities of the aforementioned rearrangement, the behaviour of the sulphones (3e and f) towards DBN was investigated. However, in each case, non-β-lactam products were isolated; these were not further investigated.

The preparation of the sulphones (3e and f) is worthy of comment. The former derivative was obtained (27% after SiO_2 chromotography) by the oxidation of the Schiff's base (10a) with potassium permanganate; compound (10a) was prepared (82%) by treating the known imine (10b)[7] with diazomethane. Although spectro-



(10)

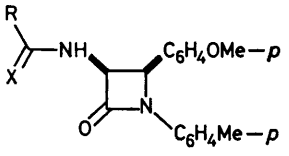
a; R = Me
b; R = H



(11)

scopic evidence indicated that the precursor of the sulphone (3e) possessed the structure (10a), the tautomer (11) is presumably implicated in the oxidation. The sulphone (3f) was obtained (49% after SiO_2 chromatography (from the penicillanate (7h) by oxidation with

potassium permanganate; the reaction of the enamine (7i), prepared (95%) from 6α-aminopenicillanic acid (7j) and pentane-2,4-dione, provided the ester (7h) (92%). Recently, Bose and his co-workers have effected the oxidative cleavage of enamines of type (12a) to amides of type (12b) by using ruthenium(IV) oxide.[8]

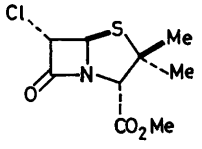


(12)

a; X = MeOOCCH
b; X = O

In the hope of effecting the isomerisation of a penicillanate *S,S*-dioxide containing a protected 6-amino-group, which might be deprotected at a later stage, the triphenylmethylamino-, phthalimido-, and benzyloxycarbonylamino-penicillanate *S,S*-dioxides (3g, h, and i) were prepared. The compounds, isolated in respective yields of 75, 73 and 64%, were derived from the penicillinates (7k),[9] (7l),[10] and (7m) by oxidation with potassium permanganate; the reaction of 6α-aminopenicillanic acid (7j) with benzyloxycarbonyl chloride followed by diazomethane provided the route to the penicillanate (7m) (48% after SiO_2 chromatography). Whereas non-β-lactam products, which were not further examined, resulted when the sulphone (3 g) was treated with DBN, the sulphinic acids (5e and f) were isolated in respective yields of 79 and 59% from the sulphones (3h and i). The sulphinic acid (5e) was isolated in a crystalline state, as a hemihydrate, and the sulphinic acid (5f) as a foam; both compounds were unambiguously characterised by their analytical and spectroscopic properties.

Finally, the behaviour of the penicillanate *S,S*-dioxides (4b and c) towards DBN was studied. The former compound was prepared (92%) by the oxidation of the known penicillanate (13) [11] with potassium permanganate whereas the latter compound was obtained



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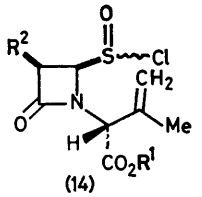
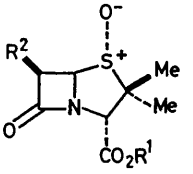


(14)

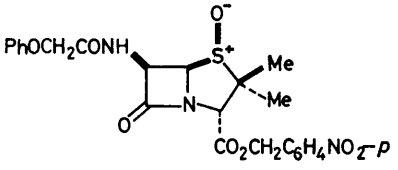
a; R^1 = Me, R^2 = phthalimido
b; R^1 = *p*-NO_2·C_6H_4·CH_2, R^2 = phthalimido
c; R^1 = *p*-NO_2·C_6H_4·CH_2, R^2 = $PhOCH_2CONH$

(89%) from the reaction of the penicillanate *S,S*-dioxide (4d) [12] with *p*-nitrobenzyl bromide in *N,N*-dimethylformamide. In the presence of DBN, the sulphones (4b and c) were converted into the sulphinic acids (5g and h) in respective yields of 62 and 97%; both compounds, which were isolated as syrups, were characterised by their spectroscopic properties and by their conversion into the methyl sulphones (6d) (40% after SiO_2 chromatography) and (6e) (77% after SiO_2 chromatography).



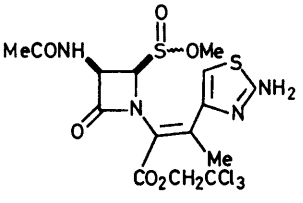
(15)

a; R^1 = Me, R^2 = phthalimido
b; R^1 = *p*-NO_2·C_6H_4·CH_2, R^2 = phthalimido

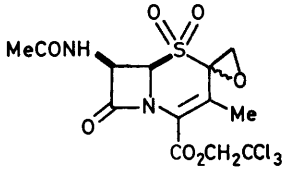


(16)

In conclusion, the reaction of sulphones of penicillanate esters with DBN constitutes a useful route to oxoazetidinesulphinic acids of type (5). In view of the diverse chemistry associated with the sulphinic acid moiety,[4] such compounds are of considerable potential in the synthesis of analogues of the β-lactam antibiotics. Hitherto, the only other examples of oxoazetidinesulphinic acid derivatives in the literature are the sulphinyl



(17)



(18)

chlorides (14a—c), prepared by thermolysis of the corresponding sulphoxides (15a), (15b), and (16) in the presence of sulphuryl chloride or *N*-chlorosuccinimide,[13] and the methyl sulphinate (17), obtained by treating the cephem *S,S*-dioxide (18) with thiourea followed by diazomethane.[14] The chlorine atom of sulphinyl chlorides of type (14) is reported to be readily displaced by nitrogen, oxygen, and sulphur nucleophiles.[13]

EXPERIMENTAL

For general experimental deails, see Part 20.

Reaction of Methyl Benzylpenicillinate 1,1-Dioxide (3a) *with 1,5-Diazabicyclo*[4.3.0]*non-5-ene* (*DBN*).—DBN (7 cm^3, 56.7 mmol) was added in one portion to a stirred solution of the sulphone (3a) [15] (15.0 g, 39.5 mmol) in dichloromethane (30 cm^3). After 20 min the dark red solution was diluted

with dichloromethane and washed with dilute hydrochloric acid. The organic layer was extracted with aqueous sodium hydrogen carbonate, which was acidified and extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) organic extract left a residue which crystallised when triturated with chloroform. Ether was added and the crystals of (2R,3S)-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phenylacetamido*-4-*oxoazetidine*-2-*sulphinic acid* (5a) (12.0 g, 80%) were collected by filtration; m.p. 136—137 °C (from $CHCl_3$); $[\alpha]_D$ −176° (0.9% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 280 (NH), 1 785 (azetidinone CO), 1 730 (ester CO), and 1 600br cm^{-1} (H-bonded amide CO); $\lambda_{max.}$ (EtOH) 210 nm (ε 16 000); δ($CDCl_3$) 2.0 and 2.23 (each 3H, s, CMe_2), 3.62 (2 H, s, $PhCH_2$·CO), 3.80 (3 H, s, CO_2Me), 4.71 (1 H, d, *J* 2 Hz, CH·C*H*·S), 5.18 (1 H, dd, *J* 2 and 6 Hz, NH·C*H*·CH), 7.25 (5 H, s, Ph), 8.20 (1 H, d, *J* 6 Hz, CO·N*H*·CH), and 9.75br (1 H, s, SO_2H) [addition of D_2O caused the signals at 8.20 and 9.75 to disappear and that at 5.18 to collapse to a d (*J* 2 Hz)]; *m/z* 346 ($M^+ - H_2O_2$) and 91 ($C_7H_7^+$, base peak) (Found: C, 53.6; H, 5.05; N, 7.2. $C_{17}H_{20}N_2O_6S$ requires C, 53.7; H, 5.25; N, 7.35%).

Reaction of the Sodium Salt of the Sulphinic Acid (5a) *with Methyl Iodide*.—The sulphinic acid (5a) (0.380 g, 1 mmol) was added to a stirred solution of sodium hydrogen carbonate (0.084 g, 1 mmol) in water (5 cm^3) which was then evaporated. The dried (*in vacuo* over $CaCl_2$) salt was dissolved in *N*,*N*-dimethylformamide (3 cm^3) and treated with methyl iodide (0.284 g, 2 mmol). Work-up after 24 h afforded *methyl* 3-*methyl*-2-[(2R,3S)-2-*methylsulphonyl*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]*but*-2-*enoate* (6a) (0.217 g, 55%); m.p. 170—171 °C (from $CHCl_3$—Et_2O); $[\alpha]_D$ −43° (1.0% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 340 (NH), 1 785 (azetidinone CO), 1 710 (ester CO), 1695, 1 680, and 1 660 (amide CO), and 1 315 and 1 140 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 212 (ε 16 800) and 235sh nm (10 000); δ($CDCl_3$) 2.19 and 2.40 (each 3 H, s, CMe_2), 3.18 (3 H, s, SO_2Me), 3.73 (2 H, s, $PhCH_2$·CO), 3.88 (3 H, s, CO_2Me), 5.13 (1 H, d, *J* 6 Hz, NH·C*H*·CH), 5.18 (1 H, s, CH·C*H*·S), 6.63br (1 H, d, *J* 6 Hz, CO·N*H*·CH), and 7.48 (5 H, s, Ph) [addition of D_2O caused the signal at 6.63 to disappear and those at 5.13 and 5.18 to merge to a s (2H)]; *m/z* 315 ($M^+ - CH_3O_2S$) and 91 ($C_7H_7^+$, base peak) (Found: C, 55.1; H, 5.55; N, 7.15. $C_{18}H_{22}N_2O_6S$ requires C, 54.8; H, 5.6; N, 7.1%).

Reaction of p-*Nitrobenzyl Benzylpenicillinate* (7a) *with Potassium Permanganate*.—A stirred solution of the penicillinate (7a) [5] (9.00 g, 19.2 mmol) in 4 : 1 acetic acid–water (140 cm^3) was treated dropwise over 2.5 h with potassium permanganate (6.60 g, 41.8 mmol) dissolved in water (60 cm^3). After a further 1 h, 30% hydrogen peroxide was added until the permanganate 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 left p-*nitrobenzyl benzylpenicillinate* 1,1-*dioxide* (3b) (6.70 g, 70%); m.p. 88—90 °C (from $CHCl_3$—Et_2O); $[\alpha]_D$ +90° (0.7% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 400 (NH), 1 800 (azetidinone CO), 1 755 (ester CO), and 1 675 cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 211 (ε 17 800) and 264 nm (15 600); δ($CDCl_3$) 1.30 and 1.58 (each 3 H, s, CMe_2), 3.65 (2 H, s, $PhCH_2$·CO), 4.56 (1 H, s, N·C*H*·CMe_2), 4.77 (1 H, d, *J* 4.6 Hz, CH·C*H*·S), 5.30 (2 H, s, O·CH_2·C_6H_4), 6.13 (1 H, dd, *J* 4.6 and 9.6 Hz, NH·C*H*·CH), 7.04 (1 H, d, *J* 9.6 Hz, CO·C*H*·CH), 7.34 (1 H, s, $CHCl_3$), 7.38 (5 H, s, Ph), and 7.53 and 8.24 (each 2 H, d, *J* 8 Hz, C_6H_4) [addition of D_2O caused the signal at 7.04 to disappear and that at 6.13 to collapse to a d (*J* 4.6 Hz)]; *m/z* 435 ($M^+ - H_2O_2S$) and 91 ($C_7H_7^+$, base peak) (Found: C, 46.4; H, 3.85; N, 6.65; S, 5.15. $C_{23}H_{23}O_8N_3S.CHCl_3$ requires C, 46.4; H, 3.85; N, 6.75; S, 5.15%).

Reaction of p-*Nitrobenzyl Benzylpenicillinate* 1,1-*Dioxide* (3b) *with DBN*.—A solution of DBN (2.3 cm^3, 18.6 mmol) in dichloromethane (2 cm^3) was added to a stirred solution of the sulphone (3b) (5.00 g, 8.06 mmol) in dichloromethane (5 cm^3). Work-up after 30 min, as described in the preparation of the compound (5a), gave (2*R*,3*S*)-3-(1-*p*-nitrobenzyloxycarbonyl-2-methylprop-1-enyl)-4-oxo-3-phenylacetamidoazetidine-2-sulphinic acid (5b) (3.00 g, 74%) as a sticky foam; $[\alpha]_D$ −53° (1.1% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 300br and 3 000br (NH and OH), 1 770 (azetidinone CO), and 1 735—1 610br cm^{-1} (ester and amide CO); $\lambda_{max.}$ (EtOH) 214 (ε 19 700) and 267br nm (12 900); δ($CDCl_3$) 2.05 and 2.25 (each 3 H, s, CMe_2), 3.62 (2 H, s, $PhCH_2$·CO), 4.72 (1 H, d, *J* 2 Hz, CH·C*H*·S), 5.30 br (3 H, s, CO_2·CH_2·C_6H_4 and NH·C*H*·CH), 6.70br (1 H, s, CO·N*H*·CH), 7.30 (5 H, s, Ph), 7.42 and 8.12 (each 2 H, d, *J* 8 Hz, C_6H_4), and 8.90br (1 H, s, SO_2H) (addition of D_2O caused the signals at 6.70 and 8.90 to disappear); *m/z* 483 ($M^+ - H_2O$) and 91 ($C_7H_7^+$, base peak).

Reaction of the Sodium Salt of the Sulphinic Acid (5b) *with Methyl Iodide*.—The sulphinic acid (5b) (0.360 g, 0.72 mmol) in dichloromethane (3 cm^3) was added to a stirred solution of sodium hydrogen carbonate (0.060 g, 0.72 mmol) in water (3 cm^3) which was then evaporated. The dried (*in vacuo* over $CaCl_2$) salt was stirred in acetone (5 cm^3) and methyl iodide (0.204 g, 1.44 mmol) for 12 h. The mixture was then evaporated and the residue partitioned between dichloromethane and water. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica gel chromatography ($CHCl_3$ as eluant) gave *p-nitrobenzyl* 3-*methyl*-2-[(2R,3S)-2-*methylsulphonyl*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]*but*-2-*enoate* (6b) (0.199 g, 55%) as a chromatographically homogeneous syrup; $[\alpha]_D$ +15° (0.9% in EtOH); $\nu_{max.}$ (film) 3 380 (NH), 1 785 (azetidinone CO), 1 700 (ester CO), 1 685 cm^{-1} (amide CO), and 1 320 and 1 145 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 215 (ε 14 400) and 261 nm (9 900); δ($CDCl_3$) 2.08 and 2.23 (each 3 H, s, CMe_2), 2.93 (3 H, s, SO_2Me), 3.56 (2 H, s, $PhCH_2$·CO), 4.98 (1 H, dd, *J* 2 and 6 Hz, NH·C*H*·CH), 5.16 (1 H, d, *J* 2 Hz, CH·C*H*·S), 5.30 (2 H, s, O·CH_2·C_6H_4), 7.01 (1 H, d, *J* 6 Hz, CO·N*H*·CH), 7.30 (5 H, s, Ph) and 7.53 and 8.18 (each 2 H, d, *J* 8 Hz, C_6H_4) [addition of D_2O caused the signal at 7.01 to disappear and that at 4.98 to collapse to a d (*J* 2 Hz)]; *m/z* 436 ($M^+ - CH_3O_2S$) and 91 ($C_7H_7^+$, base peak) (Found: $M^+ - CH_3O_2S$, 436.1525 $C_{23}H_{22}N_3O_6$ requires *M*, 436.1509).

Reaction of Potassium Benzylpenicillinate (7d) *with* 1,2-*Dibromoethane*.—A stirred solution of the salt (7d) (1.41 g, 3.79 mmol) in *N*,*N*-dimethylformamide (20 cm^3) was treated with 1,2-dibromoethane (3.56 g, 18.9 mmol). After 24 h the mixture was evaporated to leave a syrup which, on addition of ether, afforded 2-*bromoethyl benzylpenicillinate* (7c) (1.54 g, 92%); m.p. 97—99 °C (from CH_2Cl_2–Et_2O); $[\alpha]_D$ +237° (0.3% in EtOH); $\nu_{max.}$ (KBr) 3 300 (NH), 1 790 (azetidinone CO), 1 750 (ester CO), and 1 655 cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 221 (ε 2 700), 252sh (250), 258 (230), 264 (150), and 268 nm (100); δ($CDCl_3$) 1.47 (6 H, s, CMe_2), 3.52 (2 H, t, separation 5.5 Hz, CH_2·CH_2Br), 3.60 (2 H, s, $PhCH_2$·CO), 4.40 (1 H, s, N·C*H*Me_2), 4.43 (2 H, t, separation 5.5 Hz, CO_2·CH_2·CH_2), 5.45—5.78 (2 H, m, NH·C*H*·CH), 6.32br (1 H, d, *J* 8.5 Hz, CO·N*H*·CH), and 7.22 (5 H, s, Ph) [addition of D_2O caused the signal at 6.32 to disappear and that at 5.43—5.78 to collapse to 2 d (each *J* 4 Hz)]; *m/z*

442 and 440 (M^+) and 268 and 266 $C_8H_{13}BrNO_2S^+$, base peaks) (Found: C, 48.9; H, 4.7; N, 6.35. $C_{18}H_{21}BrN_2O_4S$ requires C, 49.0; H, 4.75; N, 6.35%).

Reaction of 2-Bromoethyl Benzylpenicillinate (7c) *with Sodium Iodide*.—A mixture of the bromoethyl ester (7c) (1.42 g, 3.22 mmol), sodium iodide (4.83 g, 32.2 mmol), and acetone (10 cm³) was heated under reflux. After 0.5 h, the cooled mixture was diluted with dichloromethane and water. Evaporation of the dried ($MgSO_4$) organic layer left *2-iodoethyl benzylpenicillinate* (7b) (1.51 g, 96%); m.p. 88—90 °C (from CH_2Cl_2–Et_2O); $[\alpha]_D$ +221° (0.3% in EtOH); $\nu_{max.}$ (KBr) 3 320 (NH), 1 790 (azetidinone CO), 1 750 (ester CO), and 1 655 cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 219 (ε 3 200), 251 (700), 257 (650) 263 (500), and 268sh nm (400); δ($CDCl_3$) 1.41 (6 H, s, CMe_2), 3.26 (2 H, t, separation 6 Hz, CH_2·CH_2I), 3.59 (2 H, s, PhCH_2·CO), 4.36 [3 H, s and t (separation 6 Hz), N·CH·CMe_2 and CO_2·CH_2·CH_2], 5.41—5.74 (2 H, m, NH·CH·CH·S), 6.17br (1 H, d, *J* 8.5 Hz, CO·NH·CH), and 7.20 (5 H, s, Ph) [addition of D_2O caused the signal at 6.17 to disappear and that at 5.41—5.74 to collapse to 2 d (each *J* 4 Hz)]; *m/z* 488 (M^+) and 313 ($C_8H_{13}INO_2S^+$, base peak) (Found: C, 44.1; H, 4.3; N, 5.7. $C_{18}H_{21}IN_2O_4S$ requires C, 44.3; H, 4.3; N, 5.75%).

Reaction of 2-Iodoethyl Benzylpenicillinate (7b) *with Potassium Permanganate*.—The penicillinate (7b) (0.488 g, 1 mmol) was oxidised with potassium permanganate as described for the derivative (7a). Work-up after 1 h afforded *2-iodoethyl benzylpenicillinate 1,1-dioxide* (3c) (0.510 g, 98%); *m.p.* 142—144 °C (from CH_2Cl_2–Et_2O); $[\alpha]_D$ +154° (0.3% in EtOH); $\nu_{max.}$ (KBr) 3 140 (NH), 1 800 (azetidinone CO), 1 760 (ester CO), and 1 665 cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 220 (ε 3 000), 253 (700), 259 (650), 266 (550), and 284sh nm (200); δ($CDCl_3$) 1.37 and 1.59 (each 3 H, s, CMe_2), 3.26 (2 H, t, separation 6 Hz, CH_2·CH_2I), 3.55 (2 H, s, PhCH_2·CO), 4.38 (2 H, t, separation 6 Hz, CO_2·CH_2·CH_2), 4.47 (1 H, s, *N*·$CH$$Me_2$), 4.73 (1 H, d, *J* 4.5 Hz, CH·CH·S), 6.03 (1 H, dd, *J* 10 and 4.5 Hz, NH·CH·CH), 7.06br (1 H, d, *J* 10 Hz, CO·NH·CH), and 7.19 (5 H, s, Ph) [addition of D_2O caused the signal at 7.06 to disappear and that at 6.03 to collapse to a d (*J* 4.5 Hz)]; *m/z* 521 (MH^+) and 91 ($C_7H_7^+$, base peak) (Found: C, 41.6; H, 3.95; N, 5.35. $C_{18}H_{21}N_2O_6S$ requires C, 41.5; H, 4.05; N, 5.4%).

Reaction of the Sulphone (3c) *with DBN*.—A solution of the sulphone (3c) (0.206 g, 0.4 mmol) in deuteriochloroform (0.8 cm³) was treated dropwise with a 20% solution of DBN in deuteriochloroform until the starting material had disappeared (n.m.r. spectroscopy). The mixture was diluted with ethyl acetate and washed with dilute hydrochloric acid. The organic layer was then extracted with aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer left a syrupy residue (0.048 g), which contained no β-lactam component (i.r. spectroscopy). The sodium hydrogen carbonate solution was acidified and extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$) organic extract left a syrup which was (2*R*,3*S*)-1-[1-(2-iodoethoxycarbonyl)-2-methylprop-1-enyl]-3-phenylacetamido-4-oxoazetidine-2-sulphinic acid (5c) (0.129 g, 63%); $[\alpha]_D$ +89° (0.37% in EtOH); $\nu_{max.}$ (film) 3 310 (NH and OH), 1 770 (β-lactam CO), 1 725 (ester CO), and 1 670br cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 219 nm (ε 2 300); δ($CDCl_3$) 1.91 and 2.20 (each 3 H, s, CMe_2), 3.10—3.35 (2 H, m, CH_2·CH_2I), 3.57 (2 H, s, PhCH_2·CO), 4.20—4.45 (2 H, m, O·CH_2·CH_2), 4.80 (1 H, d, *J* 2 Hz, CH·CH·S), 5.17 (1 H, dd, *J* 5 and 2 Hz, NH·CH·CH), 6.64br (1 H, s, OH), 7.15 (5 H, s, Ph), and 7.80br (1 H, d, *J* 5 Hz, CO·NH·CH) [addition of D_2O caused the signals at 6.64 and 7.80 to disappear and that at 5.17 to collapse to a d (*J* 2 Hz)]; *m/z* 545 (M^+ — H_2O_2S) and 91 ($C_7H_7^+$, base peak).

Reaction of Methyl Phenoxymethylpenicillinate (7g) *with Potassium Permanganate*.—The penicillinate (7g) [5] (15.0 g, 41.2 mmol) was oxidised with potassium permanganate, as described for the derivative (3b). Work-up gave *methyl phenoxymethylpenicillinate 1,1-dioxide* (3d) (12.0 g, 74%); m.p. 126—128 °C (from MeOH); $[\alpha]_D$ +120° (1% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 400 (NH), 1 790 (azetidinone CO), 1 740 (ester CO), 1 690 (amide CO), and 1 325 and 1 120 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 215 (ε 10 400), 263 (1 200), 270 (1 600), and 276 nm (1 400); δ($CDCl_3$) 1 38 and 1 62 (each 3 H, s, CMe_2), 3.82 (3 H, s, CO_2Me), 4.53 (3 H, s, O·CH_2·CO and N·CH·CMe_2) 4.83 (1 H, d, *J* 4.5 Hz, CH·CH), 6.18 (1 H, dd, *J* 4.5 and 10.8 Hz, CO·NH·CH), 6.18—7.40 (5 H, m, Ph), and 8.18br (1 H, d, *J* 10.8 Hz, CO·CH·CH) [addition of D_2O caused the signal at 8.18 to disappear and that at 6.18 to collapse to a d (*J* 4.5 Hz)]; *m/z* 396 (M^+) and 107 ($C_7H_6O^+$, base peak) (Found: C, 51.6; H, 5.1; N, 7.1%; M^+, 396.1002. $C_{17}H_{20}N_2O_7S$ requires C, 51.5; H, 5.05; N, 7.05%; *M*, 396.0991).

Reaction of Methyl Phenoxymethylpenicillinate 1,1-Dioxide (3d) *with DBN*.—DBN (0.6 cm³, 4.86 mmol) dissolved in dichloromethane (2 cm³) was added in one portion to a stirred solution of the sulphone (3d) (1.32 g, 3.33 mmol) in dichloromethane (3 cm³). Work-up after 20 min, as described in the preparation of the compound (5c), gave (2R,3S) *1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3-phenoxyacetamido-4-oxoazetidine-2-sulphinic acid* (5d) (0.858 g, 65%) as a white foam; $[\alpha]_D$ −40° (1.0% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 340br (NH and OH), 1 775 (azetidinone CO), 1 720 (ester CO), and 1 675br cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 220 (ε 17 200), 263 (5 700), 269 (5 700), and 276 nm (4 600); δ($CDCl_3$) 2 03 and 2 27 (each 3 H, s, CMe_2), 3 73 (3 H, s, CO_2Me), 4 56 (2 H, s, O·CH_2·CO), 4.82 (1 H, d, *J* 2 Hz, CH·CH·S), 5.33 (1 H, dd, *J* 2 and 6 Hz, NH·CH·CH), 6.60br (1 H, s, SO_2H), 6.70—7.40 (5 H, m, Ph), and 8.20 (1 H, d, *J* 6 Hz, CO·NH·CH) [addition of D_2O caused the signal at 8.20 to disappear and that at 5.40 to collapse to a d (*J* 2 Hz)]; *m/z* 362 (M^+ — H_2O_2) and 77 ($C_6H_5^+$, base peak) (Found: C, 51.3; H, 4.7; N, 7.1. $C_{17}H_{20}N_2O_7S$ requires C, 51.5; H, 5.05; N, 7.05%).

Reaction of the Sodium Salt of the Sulphinic Acid (5d) *with Methyl Iodide*.—The sulphinic acid (5d) (0.198 g, 0.5 mmol) was converted into the sodium salt and treated with methyl iodide as described for the compound (5b). Work-up after 48 h gave *methyl 3-methyl-2-[(2R,3S)-2-methylsulphonyl-4-oxo-3-phenoxyacetamidoazetidin-1-yl]but-2-enoate* (6c) (0.186 g, 91%); m.p. 128—129 °C (from $CHCl_3$–Et_2O); $[\alpha]_D$ +15° (1.0% in EtOH); $\nu_{max.}$ (KBr) 3 400br (NH), 1 785 (β-lactam CO), 1 700 (ester CO), 1 685 and 1 675sh (amide CO), and 1 315 and 1 140 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 225 (ε 10 900), 236sh (9 100), 263sh (4 800), and 276 cm^{-1} (2 200); δ($CDCl_3$) 2.10 and 2.30 (each 3 H, s, CMe_2), 3.05 (3 H, s, SO_2Me), 3.85 (3 H, s, CO_2Me), 4.55 (2 H, s, O·CH_2·CO), 5.19—5.35 (2 H, m, NH·CH·CH·S), and 6.80—7.55 (6 H, m, Ph and CO·NH·CH); *m/z* 379 (M^+—CH_3O) and 331 (M^+—CH_3O_2S, base peak) (Found: C, 52.4; H, 5.1; N, 7.05. $C_{18}H_{22}N_2O_7S$ requires C, 52.7; H, 5.35; N, 6.85%).

Reaction of 6β-(2-Hydroxy-1-naphthylideneamino)penicillanic Acid (10b) *with Diazomethane* (with J. R. Jackson).—An excess of diazomethane in ether was added to a stirred suspension of the acid (10b)[7] (3.70 g, 10 mmol) in chloroform and the resulting solution was evaporated to leave an orange syrup. Crystallisation from ethanol and filtration afforded *methyl 6β-(2-hydroxy-1-naphthylideneamino)penicillanate*

(10a) (3.15 g, 82%) as an orange solid; m.p. 148—149 °C; $[\alpha]_D$ +18° (2.5% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 420 (OH), 1 765 (azetidinone CO), 1 730 (ester CO), and 1 620 cm^{-1} (CN); $\lambda_{max.}$ (EtOH) 232 (ε 45 700), 306 (9 500), 317 (9 200), 354 (5 800), 368 (5 600), 409 (4 200), and 428 nm (4 100); δ($CDCl_3$) 1.52 and 1.68 (each 3 H, s, CMe_2), 3.80 (3 H, s, OMe), 4.56 (1 H, s, N·C*H*·CMe_2), 5.30 (1 H, d, *J* 5 Hz, N·C*H*·CH), 5.73 (1 H, d, *J* 5 Hz, CH·C*H*·S), 7.05—8.15 (6 H, m, $C_{10}H_6$), and 9.40 (1 H, s, C·CH:N); *m/z* 384 (M^+) and 183 (base peak) (Found: C, 62.4; H, 5.35; N, 7.1. $C_{20}H_{20}N_2O_4S$ requires C, 62.5; H, 5.25; N, 7.3%).

Reaction of Methyl 6β-(2-*Hydroxy*-1-*naphthylideneamino*)-*penicillanate* (10a) *with Potassium Permanganate*.—A cooled (ice–NaCl) stirred solution of the penicillanate (10a) (2.14 g, 5.57 mmol) in 4 : 1 acetic acid–water (150 cm^3) was treated dropwise over 0.5 h with potassium permanganate (3.08 g, 19.5 mmol) dissolved in water (100 cm^3). Work-up after a further 1 h, as described in the preparation of the sulphone (3b), gave a syrup (1.66 g) which was purified by silica gel chromatography [EtOAc–light petroleum (1 : 3) as eluant] to afford *methyl penicillinate* 1,1-*dioxide* (3e) (0.441 g, 27%); m.p. 165—167 °C (from $CHCl_3$—Et_2O); $[\alpha]_D$ +70° (1.8% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 380 (NH), 1 805 (azetidinone CO), 1 750 (ester CO), 1 690 (amide CO), and 1 325 and 1 120 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 216 (ε 800) and 224sh nm (600); δ($CDCl_3$) 1.42 and 1.66 (each 3 H, s, CMe_2), 3.90 (3 H, s, CO_2Me), 4.60 (1 H, s, N·C*H*·CMe_2), 4.90 (1 H, d, *J* 4.8 Hz, CH·C*H*·S), 6.29 (1 H, dd, *J* 4.8 and 10.4 Hz, NH·C*H*·CH), 7.25 (1 H, d, *J* 10.4 Hz, CO·N*H*·CH), and 8.38 (1 H, s, N·CHO) [addition of D_2O caused the signal at 7.25 to disappear and that at 6.29 to collapse to a d (*J* 4.8 Hz)]; *m/z* 226 (M^+—O_2S) and 113 (base peak) (Found: C, 41.0; H, 4.8; N, 9.6. $C_{10}H_{14}N_2O_6S$ requires C, 41.4; H, 4.85; N, 9.65%).

Reaction of 6β-*Aminopenicillanic Acid* (7j) *with Pentane*-2,4-*dione* (with J. R. Jackson).—Pentane-2,4-dione (3.0 cm^3, 30 mmol) was added to a stirred suspension of the acid (7j) (1.08 g, 5 mmol) in methanol (10 cm^3). After 16 h the resulting solution was concentrated and the syrup was treated with light petroleum. Filtration afforded 6β-(1-*methyl*-3-*oxobut*-1-*enylamino*)*penicillanic acid* (7i) (1.40 g, 94%) as a pale yellow solid; m.p. 161—166 °C (decomp.) (from EtOH); $[\alpha]_D$ +256° (0.5% in EtOH); $\nu_{max.}$ (KBr) 2 440br and 1 930br (H-bonded OH and NH), 1 765 (azetidinone CO), 1 710 (acid CO), and 1 590br cm^{-1} (N-bonded vinylogous carbamate CO); $\lambda_{max.}$ (EtOH) 206 (ε 6 300) and 313 nm (18 200); δ(CD_3SOCD_3; 90 MHz) 1.48 and 1.54 (each 3 H, s, CMe_2), 1.90 and 1.94 (each 3 H, s, MeCO and MeC : C), 4.33 (1 H, s, N·C*H*·CMe_2), 5.11 (1 H, s, CO·CH:C), 5.45—5.70 (2 H, m, NH·C*H*·C*H*·S), and 10.8br (1 H, d, *J* 9 Hz, C·N*H*·CH) [addition of D_2O caused the signals at 5.11 and 10.8 to disappear and that at 5.45—5.70 to collapse to 2 d (each *J* 4 Hz)]; *m/z* 298 (M^+) and 44 (CO_2^+, base peak) (Found: C, 52.2; H, 6.05; N, 9.45. $C_{13}H_{18}N_2O_4S$ requires C, 52.4; H, 6.1; N, 9.4%).

Reaction of 6β-(1-*Methyl*-3-*oxobut*-1-*enylamino*)*penicillanic Acid* (7i) *with Diazomethane* (with J. R. Jackson).—An excess of diazomethane in ether was added to a stirred suspension of the acid (7i) (2.46 g, 8.3 mmol) in chloroform (15 cm^3). Evaporation of the resulting solution left a pale yellow syrup which was crystallised from ethanol–light petroleum. Filtration afforded *methyl* 6β-(1-*methyl*-3-*oxobut*-1-*enylamino*)*penicillanate* (7h) (2.37 g, 92%); m.p. 116—117 °C; $[\alpha]_D$ +240° (0.5% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 480 (NH), 1 780 (azetidinone CO), 1 745 (ester CO), and 1 620 cm^{-1} (vinylogous amide CO); $\lambda_{max.}$ (EtOH) 217 (ε 7 000) and 314 nm (18 900); δ(CD_3SOCD_3; 90 MHz) 1.40 and 1.55 (each 3 H, s, CMe_2), 1.89 and 1.94 (each 3 H, s, MeCO and MeC:C), 3.71 (3 H, s, CO_2Me), 4.50 (1 H, s, N·C*H*·CMe_2), 5.11 (1 H, s, CO·CH:C), 5.44—5.64 (2 H, m, NH·C*H*·C*H*·S), and 10.9br (1 H, d, *J* 9 Hz, C·N*H*·CH) [addition of D_2O caused the signal at 10.9 to disappear and that at 5.44—5.64 to collapse to 2 d (each *J* 5 Hz)]; *m/z* 312 (M^+) and 174 ($C_7H_{12}NO_2S^+$, base peak) (Found: C, 54.0; H, 6.4; N, 9.05. $C_{14}H_{20}N_2O_4S$ requires C, 53.9; H, 6.45; N, 9.0%).

Reaction of Methyl 6β-(1-*Methyl*-3-*oxobut*-1-*enylamino*)-*penicillanate* (7h) *with Potassium Permanganate*.—A stirred solution of the penicillanate (7h) (0.624 g, 2 mmol) in 4 : 1 acetic acid–water (20 cm^3) was treated dropwise over 30 min with potassium permanganate (1.34 g, 8.48 mmol) dissolved in water (10 cm^3). Work-up, as described in the preparation of the sulphone (3b), after a further 1 h gave a syrup which was purified by silica gel chromatography [C_6H_6–Et_2O (7 : 3) as eluant] to yield methyl methylpenicillinate 1,1-dioxide (3f) (0.300 g, 49%) as a gum; $[\alpha]_D$ +120° (1.1% in $CHCl_3$); $\nu_{max.}$ (film) 3 380 (NH), 1 805 (azetidinone CO), 1 755 (ester CO), 1 680 (amide CO), and 1 325 and 1 120 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 212 nm (ε 1 100); δ($CDCl_3$) 1.39 and 1.60 (each 3 H, s, CMe_2), 2.05 (3 H, s, MeCO), 3.78 (3 H, s, CO_2Me), 4.54 (1 H, s, N·C*H*·CMe_2), 4.84 (1 H, d, *J* 4.5 Hz, CH·C*H*·S), 6.10 (1 H, dd, *J* 4.5 and 10 Hz, NH·C*H*·CH), and 7.16 (1 H, d, *J* 10 Hz, CO·N*H*·CH) [addition of D_2O caused the signal at 7.16 to disappear and that at 6.10 to collapse to a d (*J* 4.5 Hz)]; *m/z* 305 (MH^+) and 43 ($C_2H_3^+$, base peak).

Reaction of the Penicillanate (7k) *with Potassium Permanganate*.—The penicillinate (7k) [9] (0.200 g, 0.365 mmol) was oxidised with potassium permanganate, as described for the derivative (3b). Work-up after 10 h afforded *benzyl* 6β-(*triphenylmethylamino*)*penicillanate* 1,1-*dioxide* (3 g) (0.156 g, 74%); m.p. 158—159 °C (from $CHCl_3$–Et_2O); $[\alpha]_D$ +130° (1.0% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 400 (NH), 1 800 (azetidinone CO), 1 755 (ester CO), and 1 320 and 1 120 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 228 (ε 8 500), 257sh (1 000), 263 (950), and 268sh nm (600); δ($CDCl_3$) 1.05 and 1.44 (each 3 H, s, CMe_2), 3.70 (1 H, d, *J* 4 Hz, CH·C*H*·S), 3.90 (1 H, d, *J* 14 Hz, C·N*H*·CH), 4.49 (1 H, s, N·C*H*·CMe_2), 4.75 (1 H, dd, *J* 4 and 14 Hz, NH·C*H*·CH), 5.20 (2 H, s, O·CH_2Ph), and 7.20—7.60 (20H, m, 4 × Ph) [addition of D_2O caused the signal at 3.90 to disappear and that at 4.75 to collapse to a d (*J* 4 Hz)]; *m/z* 580 (M^+) and 243 ($C_{19}H_{15}^+$, base peak) (Found: C, 70.3; H, 5.5; N, 4.8. $C_{34}H_{32}N_2O_5S$ requires C, 70.3; H, 5.5; N, 4.8%).

Reaction of Methyl 6β-*Phthalimidopenicillanate* (7l) *with Potassium Permanganate*.—The penicillanate (7l) [10] (1.08 g, 3.00 mmol) was oxidised with potassium permanganate, as described in the preparation of the sulphone (3b). Work-up gave *methyl* 6β-*phthalimidopenicillanate* 1,1-*dioxide* (3h) (1.05 g, 92%); m.p. 220—221 °C (decomp.) (from $CHCl_3$–light petroleum); $[\alpha]_D$ −164° (0.1% in EtOH); $\nu_{max.}$ (KBr) 1 815 and 1 810 (β-lactam CO), 1 775 (phthalimide CO), 1 755 (ester CO), and 1 725 cm^{-1} (phthalimide CO); $\lambda_{max.}$ (EtOH) 220 (ε 3 400), 240sh (750), and 293 nm (150); δ($CDCl_3$) 1.40 and 1.68 (each 3 H, s, CMe_2), 3.80 (3 H, s, CO_2Me), 4.69 (1 H, s, N·C*H*·CMe_2), 4.80 (1 H, d, *J* 4.5 Hz, N·C*H*·CH), 5.67 (1 H, d, *J* 4.5 Hz, CH·C*H*·S), and 7.65—7.90 (4 H, m, C_6H_4); *m/z* 358 ($M^+ - H_2O_2$) and 214 (base peak) (Found: C, 51.7; H, 4.05; N, 7.05. $C_{17}H_{16}N_2O_7S$ requires C, 52.0; H, 4.1; N, 7.15%).

Reaction of Methyl 6β-Phthalimidopenicillanate 1,1-*Dioxide* (3h) *with DBN*.—A stirred solution of the sulphone (3h) (0.470 g, 1.20 mmol) in dichloromethane (3 cm^3) was treated with DBN (0.186 g, 1.50 mmol) dissolved in dichloromethane (1 cm^3). Work-up after 30 min, as described for the preparation of the sulphinic acid (5c), gave (2R,3S)-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phthalimido*-4-*oxoazetidine*-2-*sulphinic acid* (5e) (0.371 g, 79%); m.p. 144—146 °C (from EtOH); $[\alpha]_D$ +106° (0.5% in EtOH); $\nu_{max.}$ (KBr) 3 400 (OH), 1 775 (phthalimide and azetidinone CO), and 1 720 cm^{-1} (phthalimide and ester CO); $\lambda_{max.}$ (EtOH) 221 (ε 4 800), 242sh (1 900), and 280sh nm (400); δ($CDCl_3$) 2.11 and 2.23 (each 3 H, s, CMe_2), 3.80 (3 H, s, CO_2Me), 5.14 and 5.67 (each 1 H, d, *J* 2.5 Hz, N·CH·CH·S), and 7.60—8.00 (6 H, m, C_6H_4 and SO_2H) (addition of D_2O caused the signal at 7.60—8.00 to sharpen and its integral to reduce to 4 H); *m/z* 358 ($M^+ - H_2O_2$) and 104 ($C_7H_4O^+$, base peak) (Found: C, 50.8; H, 3.95; N, 6.95. $C_{17}H_{16}N_2O_7S·0.5H_2O$ requires C, 50.9; H, 4.25; N, 7.0%).

Reaction of 6β-*Aminopenicillanic Acid* (7j) *with Benzyloxycarbonyl Chloride followed by Diazomethane*.—A cooled (ice-bath) stirred solution of the acid (7j) (2.16 g, 10.0 mmol) in 1M-sodium hydroxide (10 cm^3, 10 mmol) was treated dropwise with benzyloxycarbonyl chloride (1.5 cm^3, 10 mmol). After 30 min the mixture was washed with ether, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$) organic layer left a syrupy residue which was treated with an excess of diazomethane in dichloromethane. Evaporation after 30 min and purification of the product by silica gel chromatography [EtOAc–light petroleum (4 : 1) as eluant] gave *methyl benzyloxypenicillinate* (7m) (1.74 g, 48%); m.p. 115—117 °C (from EtOAc–light petroleum); $[\alpha]_D$ +168° (0.7% in EtOH); $\nu_{max.}$ (KBr) 3 380 (NH), 1 790 (azetidinone CO), 1 750 (ester CO), and 1 725 cm^{-1} (carbamate CO); $\lambda_{max.}$ (EtOH) 215 (ε 11 500), 250 (800), 257 (800), 262 (700), and 267 nm (550); δ($CDCl_3$) 1.47 and 1.63 (each 3 H, s, CMe_2), 3.74 (3 H, s, OMe), 4.41 (1 H, s, N·C*H*·CMe_2), 5.10 (2 H, s, PhCH_2·O), 5.50br (3 H, s, NH·CH·CH·S), and 7.30 (5 H, s, Ph) (addition of D_2O caused the signal at 5.50 to reduce in intensity to 2 H); *m/z* 364 (M^+) and 174 ($C_7H_{12}NO_2S^+$, base peak) (Found: C, 55.7; H, 5.5; N, 7.5; S, 8.65%; M^+, 364.1122. $C_{17}H_{20}N_2O_5S$ requires C, 56.0; H, 5.5; N, 7.7; S, 8.8%; *M*, 364.1093).

Reaction of Methyl Benzyloxypenicillinate (7m) *with Potassium Permanganate*.—The penicillinate (7m) (1.09 g, 2.99 mmol) was oxidised with potassium permanganate, as described in the preparation of the sulphone (3b). Work-up gave *methyl benzyloxypenicillinate* 1,1-*dioxide* (3i) (0.761 g, 64%); m.p. 184—186 °C (from $CHCl_3$–Et_2O); $[\alpha]_D$ +147° (1.0% in EtOH); $\nu_{max.}$ (KBr) 3 360 (NH), 1 805 (azetidinone CO), 1 760 (ester CO), and 1 700 cm^{-1} (carbamate CO); $\lambda_{max.}$ (EtOH) 216 (ε 15 500), 251 (800), 257 (900), 264 (650), and 268 nm (500); δ($CDCl_3$) 1.35 and 1.56 (each 3 H, s, CMe_2), 3.75 (3 H, s, OMe), 4.46 (1 H, s, N·C*H*·CMe_2), 4.76 (1 H, d, *J* 5 Hz, CH·C*H*·S), 5.08 (2 H, s, PhCH_2·O), 5.80 (1 H, dd, *J* 12 and 5 Hz, NH·C*H*·CH), 6.28br (1 H, d, *J* 12 Hz, CO·N*H*·CH), and 7.30 (5 H, m, Ph) [addition of D_2O caused the signal at 6.34 to disappear and that at 5.90 to collapse to a d (*J* 5 Hz)]; *m/z* 364 ($M^+ - H_2O$) and 174 ($C_7H_{12}NO_2S^+$, base peak) (Found: C, 51.6; H, 4.95; N, 6.85. $C_{17}H_{20}N_2O_7S$ requires C, 51.5; H, 5.05; N, 7.05%).

Reaction of Methyl Benzyloxypenicillinate 1,1-*Dioxide* (3i) *with DBN*.—DBN (0.18 cm^3, 1.46 mmol) dissolved in dichloromethane (1 cm^3) was added to a stirred solution of the sulphone (3i) (0.396 g, 1 mmol) in dichloromethane (1 cm^3). Work-up after 20 min, as described in the preparation of the sulphinic acid (5c), gave (2R,3S)-3-*benzyloxycarbonylamino*-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*oxoazetidine*-2-*sulphinic acid* (5f) (0.234 g, 59%) as a foam; $[\alpha]_D$ +46° (0.6% in EtOH); $\nu_{max.}$ (film) 3 400br (NH and OH), 1 775 (azetidinone CO), 1 715 (ester CO), and 1 700 cm^{-1} (carbamate CO); $\lambda_{max.}$ (EtOH) 216 (ε 12 500), 262 (2 200), 268 (2 300), and 275 nm (2 200); δ($CDCl_3$) 2.03 and 2.25 (each 3 H, s, CMe_2), 3.77 (3 H, s, CO_2Me), 4.73 (1 H, d, *J* 2 Hz, CH·C*H*·S), 5.00—5.20 (3 H, m, NH·C*H*·CH and PhCH_2·O), 6.30br (1 H, d, *J* 6 Hz, CO·N*H*·CH), and 7.25 (5 H, s, Ph) (addition of D_2O caused the signal at 6.30 to disappear and that at 5.00—5.20 to simplify); *m/z* 362 ($M^+ - H_2O_2$) and 91 ($C_7H_7^+$, base peak) (Found: C, 51.3; H, 5.35; N, 6.8. $C_{17}H_{20}N_2O_7S$ requires C, 51.5; H, 5.05; N, 7.05%).

Reaction of Methyl 6α-*Chloropenicillanate* (13) *with Potassium Permanganate*.—The penicillanate (13) [11] (1.25 g, 5.01 mmol) was oxidised with potassium permanganate, as described in the preparation of the sulphone (5c). Work-up yielded *methyl* 6α-*chloropenicillanate* 1,1-*dioxide* (4b) (1.30 g, 92%); m.p. 149—150 °C (from $CHCl_3$—Et_2O); $[\alpha]_D$ +170° (0.8% in $CHCl_3$); $\nu_{max.}$ (KBr) 1 790 (azetidinone CO) and 1 755 cm^{-1} (ester CO); $\lambda_{max.}$ (EtOH) 221 nm (ε 1 300) and 232sh nm (1 100); δ($CDCl_3$) 1 43 and 1.66 (each 3 H, s, CMe_2), 3.95 (3 H, s, CO_2Me), 4.57 (1 H, s, N·C*H*·CMe_2), 4.77 and 5.26 (each 1 H, d, *J* 1.6 Hz, ClCH·CH·S); *m/z* 219 and 217 ($M^+ - O_2S$) and 114 ($C_6H_{10}O_2^+$, base peak) (Found: C, 38.5; H, 4.3; N, 4.7. $C_9H_{12}ClO_5NS$ requires C, 38.3; H, 4.2; N, 4.9%).

Reaction of Methyl 6α-*Chloropenicillanate* 1,1-*Dioxide* (4b) *with DBN*.—*DBN* (0.12 cm^3, 0.97 mmol) in dichloromethane (1 cm^3) was added to a stirred solution of the sulphone (4b) (0.180 g, 0.64 mmol) in dichloromethane (1 cm^3). Work-up after 20 min, as described in the preparation of the sulphinic acid (5c), gave (2R,3S)-3-*chloro*-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*oxoazetidine*-2-*sulphinic acid* (5g) (0.112 g, 62%) as a syrup; $[\alpha]_D$ −85° (0.5% in EtOH); $\nu_{max.}$ (film) 3 200br and 2 960br (OH), 1 786 (azetidinone CO), and 1 710br cm^{-1} (ester CO); $\lambda_{max.}$ (EtOH) 223 nm (ε 8 900); δ($CDCl_3$) 2.00 and 2.26 (each 3 H, s, CMe_2), 3.86 (3 H, s, OMe), 4.88 and 5.13 (each 1 H, d, *J* 2 Hz, ClCH·C*H*·S), and 8.67br (1 H, s, SO_2H) (addition of D_2O caused the signal at 8.67 to disappear); *m/z* 218 and 216 ($M^+ - HO_2S$, base peak) (Found: M^+, 216.0414. $C_9H_{13}{}^{35}ClNO_3$ requires *M*, 216.0427).

Reaction of the Sodium Salt of the Sulphinic Acid (5g) *with Methyl Iodide*.—The sulphinic acid (5g) (0.473 g, 1.68 mmol) was converted into the sodium salt and treated with methyl iodide, as described for the compound (5b). Work-up after 12 h and purification of the product by silica gel chromatography [$CHCl_3$–EtOAc (4 : 1) as eluant] gave *methyl* 3-*methyl*-2-[(2R,3S)-3-*chloro*-2-*methylsulphonyl*-4-*oxoazetidin*-1-*yl*]*but*-2-*enoate* (6d) (0.200 g, 40%) as a chromatographically homogeneous syrup; $[\alpha]_D$ −22° (0.9% in EtOH); $\nu_{max.}$ (film) 1 795 (β-lactam CO), 1 730 (ester CO), and 1 320 and 1 145 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 225 nm (ε 7 500); δ($CDCl_3$) 2.13 and 2.32 (each 3 H, s, CMe_2), 2.95 (3 H, s, SO_2Me), 3.83 (3 H, s, CO_2Me), and 5.20 and 5.25 (each 1 H, d, *J* 2 Hz, ClCH·CH·S); *m/z* 297 and 295 (M^+) and 130 and 128 (base peak) (Found: M^+, 295.0263. $C_{10}H_{14}{}^{35}ClNO_5S$ requires *M*, 295.0281).

Reaction of the Sulphone (4d) *with* p-*Nitrobenzyl Bromide*.—To a stirred susepnsion of the sulphone (4d) [12] (0.510 g, 2.00 mmol) in *N*,*N*-dimethylformamide (6 cm^3) was added

p-nitrobenzyl bromide (0.425 g, 1.97 mmol). After 8 h, the mixture was diluted with ethyl acetate and washed successively with water (3 times) and saturated aqueous sodium chloride. Evaporation of the dried ($MgSO_4$) organic phase left p-*nitrobenzyl penicillanate* 1,1-*dioxide* (4c) (0.645 g, 88%); m.p. 149—151 °C (decomp.) (from EtOAc–light petroleum); $[\alpha]_D$ +154° (0.2% in EtOH); $\nu_{max.}$ (KBr) 1 805 (azetidinone CO) and 1 750 cm^{-1} (ester CO); $\lambda_{max.}$ (EtOH) 212 (ε 10 900) and 262 nm (11 800); δ($CDCl_3$) 1.31 and 1.57 (each 3 H, s, CMe_2), 3.48 (2 H, d, separation 4 Hz, CO·C*H*$_2$·CH), 4.43 (1 H, s, N·C*H*·CMe_2), 4.60 (1 H, t, separation 4 Hz, CH_2·C*H*·S), 5.31 (2 H, s, O·C*H*$_2$·C_6H_4), and 7.50 and 8.20 (each 2 H, d, *J* 8 Hz, C_6H_4); *m/z* 369 (MH^+) and 83 (base peak) (Found: C, 48.6; H, 4.1; N, 7.45. $C_{15}H_{16}N_2O_7S$ requires C, 48.9; H, 4.35; N, 7.6%).

Reaction of the Sulphone (4c) *with DBN*.—The sulphone (4c) (0.210 g, 0.57 mmol) was treated with DBN, as described for the derivative (3c). Work-up afforded (2R,3S)-1-(2-*methyl*-1-p-*nitrobenzyloxycarbonylprop*-1-*enyl*)-4-*oxoazetidine*-2-*sulphinic acid* (5h) (0.204 g, 97%) as a syrup; $[\alpha]_D$ −26° (0.5% in EtOH); $\nu_{max.}$ (film) 3 400br (OH), 1 700 (azetidinone CO), and 1 725 cm^{-1} (ester CO); $\lambda_{max.}$ (EtOH) 215 (ε 12 500) and 261 nm (10 700); δ($CDCl_3$) 2.00 and 2.22 (each 3 H, s, CMe_2), 3.23br (2 H, d, separation 3 Hz, CO·C*H*$_2$·CH), 4.74br (1 H, t, separation 3 Hz, CH_2·C*H*·S), 5.34 (2 H, s, O·C*H*$_2$·C_6H_4), 7.55 and 8.25 (each 2 H, d, *J* 8 Hz, C_6H_4), and 9.55br (SO_2H) (addition of D_2O caused the signal at 9.55 to disappear); *m/z* 303 (M^+ − HO_2S) and 124 (base peak).

Reaction of the Sodium Salt of the Sulphinic Acid (5h) *with Methyl Iodide*.—The sulphinic acid (5h) (0.184, 0.50 mmol) was converted into the sodium salt and treated with methyl iodide as described for the compound (5c). Work-up after 12 h and purification of the product by silica gel chromatography [EtOAc–light petroleum (1 : 1) as eluant] gave p-*nitrobenzyl* 3-*methyl*-2-[(2R)]-2-*methylsulphonyl*-4-*oxoazetidin*-1-*yl*]*but*-2-*enoate* (6c) (0.147 g, 77%) as a chromatographically homogeneous syrup; $[\alpha]_D$ −25° (0.6% in EtOH); $\nu_{max.}$ (film) 1 770 (azetidinone CO) and 1 730 cm^{-1} (ester CO); $\lambda_{max.}$ (EtOH) 216 (ε 11 000) and 259 nm (9 600); δ($CDCl_3$) 2.10 and 2.16 (each 3 H, s, CMe_2), 2.83 (3 H, s, SO_2Me), 3.37 (2 H, d, separation 4 Hz, CO·C*H*·CH), 5.10 (1 H, t, separation 4 Hz, CH_2·C*H*·S), 5.37 (2 H, s, O·C*H*$_2$·C_6H_4), and 7.57 and 8.27 (each 2 H, d, *J* 8 Hz, C_6H_4); *m/z* 382 (M^+) and 137 ($C_7H_7NO_2^+$, base peak) (Found: M^+, 382.0847. $C_{16}H_{18}N_2O_7S$ requires *M*, 382.0835).

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