Retention of Stereochemistry in the Ring-opening of Penicillin V Sulphone *p*-Nitrobenzyl Ester

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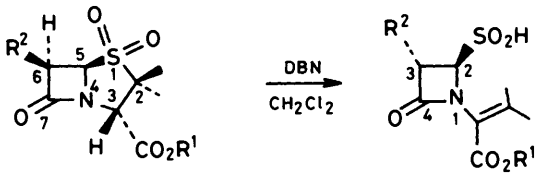
By careful control of the basic catalyst, the solvent, and the temperature, *p*-nitrobenzyl phenoxymethylpenicillinate 1,1-dioxide (penicillin V sulphone *p*-nitrobenzyl ester) (**1d**) can be converted into (2*R*,3*R*)-1-[2-methyl-(*p*-nitrobenzyloxycarbonyl)prop-1-enyl]-4-oxo-3-phenoxyacetamidoazetidine-2-sulphinic acid (**3**) with almost complete retention of stereochemistry at C-5 and C-6 of the starting ester (**1d**). The sulphinic acid (**3**) is unstable, but its sodium salt is readily methylated by iodomethane to afford the stable crystalline sulphone (**6**).

R. J. Stoodley and his co-workers have shown[1] that penicillin sulphone esters (**1a**), (**1b**), and (**1c**) react with organic bases such as DBN (1,5-diazabicyclo[4.3.0]non-5-ene) to afford oxoazetidinesulphinic acids (**2a**), (**2b**), and (**2c**). The β-elimination from readily available starting materials is an attractive reaction for the synthesis of monocyclic β-lactams, and for the subsequent synthesis of novel fused β-lactams.



(**1**) (**2**)

a; R^1 = Me, R^2 = $PhCH_2CONH$
b; R^1 = 4-$O_2NC_6H_4CH_2$, R^2 = $PhCH_2CONH$
c; R^1 = Me, R^2 = $PhOCH_2CONH$
d; R^1 = 4-$O_2NC_6H_4CH_2$, R^2 = $PhOCH_2CONH$

The utility of this reaction is, however, reduced by the epimerisation that occurs at the 6-position of the starting compounds (**1**). This epimerisation, catalysed by a trace of the organic base, is more rapid than the subsequent ring-opening which itself requires an excess of the base.[1] The 6-epimers (or 3-epimers in the case of the product monocyclic β-lactams with their different numbering systems) are less useful, as most of the biologically active β-lactams and fused β-lactams, except penems,[2] possess (*R*) geometry, *i.e.* that of the starting compounds (**1**), at this carbon atom.

The driving force for the epimerisation is presumably the attainment of the less strained, *trans*, arrangement of the groups at C-5 and C-6 of the β-lactam rings of the sulphones (**1**), so that such epimerisation is a likely consequence of carbanion formation at C-6, or possibly at C-5.

Formation of a carbanion at C-3 of the sulphone (**1**) is probably the initial step in the β-elimination reaction. Increasing the acidity of the proton at C-3, and decreasing the base strength, might therefore be ways of discriminating in favour of carbanion formation at C-3 and thus of bringing about β-elimination without epimerisation. The *p*-nitrobenzyl ester (**1d**) should be slightly more acidic at C-3 than its analogues. The C-3 proton is sterically more crowded than the one at C-6, so that a base less bulky than DBN would also assist in the desired discrimination.

When the sulphone (**1d**) was treated with a solution of potassium acetate in a mixture of dimethylformamide (DMF) and dichloromethane (1:2) at 5—10 °C for 18 h, there was obtained a new oxoacetidinesulphinic acid (**3**) in *ca.* 20% yield; *ca.* 67% of the starting sulphone (**1d**) was recovered, so that the through-put yield is *ca.* 60%. That this product (**3**) was of the required *cis*-relationship is shown by the characteristic coupling constant $J_{2,3}$ of 5 Hz for the protons at C-2 and C-3. Typically this coupling constant is 4—6 Hz for *cis* configurations and 2—3 Hz for *trans* configurations.[3]

Potassium acetate in the mixture of DMF and dichloromethane was the best choice for the elimination reaction, but other metallic acetate salts can be used. If the dichloromethane is omitted, then the product is a mixture of epimers (**2d**) and (**3**); the ratio of epimerised acid (**2d**) to the acid (**3**) increased with time, ultimately becoming greater than unity. It was found that the starting sulphone (**1d**) became a mixture of 6-epimers in a similar order to these ratios. In dimethyl sulphoxide (DMSO) the epimer (**2d**) was the major product.

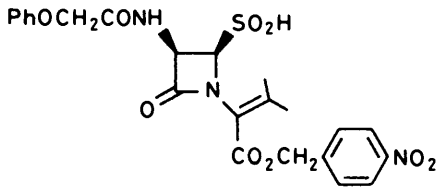
Reaction between the sulphone (**1d**) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in dichloromethane at room temperature afforded only the epimerised product (**2d**), but at −30 °C the product is a mixture of the two epimers (**2d**) and (**3**), with *ca.* 80% of the mixture being the epimerised product (**2d**).

In hydroxylic solvents, the effect of base upon the sulphone (**1d**) is to open the β-lactam ring.[4] Thus with sodium 2-hydroxyethanethiolate (**4**) the product is *p*-nitrobenzyl-2-amino-3-methyl-3-sulphinobutanoate (**5**).

The sulphinic acid (**3**) is rather labile, especially in solution, but is readily susceptible to further chemical manipulation. Treatment with sodium hydrogen carbonate produces the sodium salt of the acid; this with iodomethane affords the stable methyl sulphone (**6**). This sulphone formation can be used to separate the product of required stereochemistry from the mixture produced by the DBU reaction above; the epimeric acid (**2d**) thus produces the epimeric sulphone (**7**). The coupling constants of the C-2 and C-3 protons in these sulphones (**6**) and (**7**) were 5 Hz and 2 Hz respectively.

Experimental

M.p.s were obtained using a microscope hot-stage and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 257 instrument. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. T.l.c.s. were run on Merck silica gel 60 F_{254} plates and were visualised under u.v. light. Column chromatographs were run on Merck Kieselgel 60 (70—230 mesh ASTM) deactivated with 10% water. Preparative centrifuging-accelerated radial thin-layer chromatographs were run on a Chromatotron model 7924T, and h.p.l.c. was carried out on a Waters Millipore Liquid Chromatographer 440. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. ^{1}H N.m.r. spectra were recorded on a



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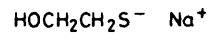

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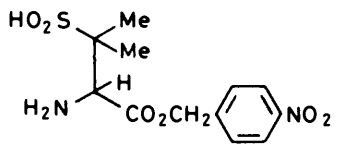

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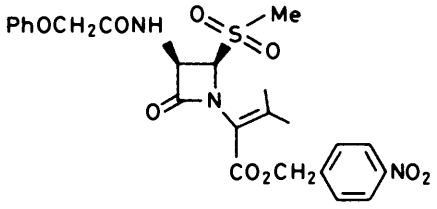

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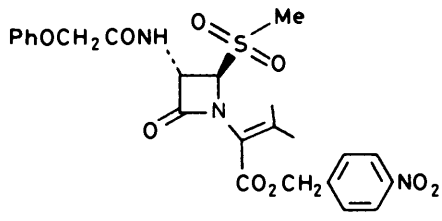

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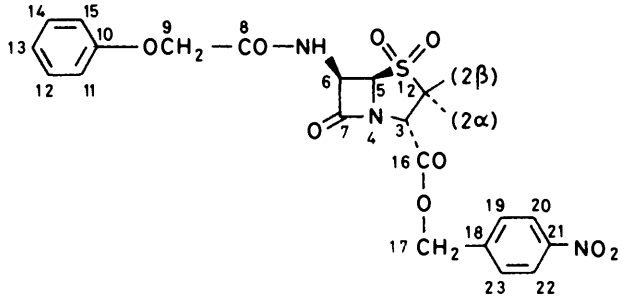
Perkin-Elmer R32 instrument at 90 MHz. Additional ^{1}H n.m.r. spectra, and ^{13}C n.m.r. spectra, were recorded in Fourier transform mode on a Jeol JNM FX-200 instrument. Chemical shifts are in p.p.m. downfield from $SiMe_4$. ^{13}C N.m.r. assignments were deduced by a combination of methods, including NNE, OFR, SEL, NEO, and INEPT techniques.

Preparation of p-*Nitrobenzyl Phenoxymethylpenicillinate 1,1-Dioxide* (**1d**).—A stirred suspension of phenoxymethylpenicillinic acid 1,1-dioxide[5] (4.0 g, 10 mmol) in a mixture of water (15 ml) and butan-1-ol (5 ml) was cooled in an ice-bath whilst potassium carbonate (0.7 g, 5.2 mmol) was added in portions. The clear mixture was azeotropically distilled under reduced pressure with the aid of butan-1-ol (2 × 50 ml). The crystalline potassium phenoxymethylpenicillinate 1,1-dioxide was removed by filtration and dissolved in DMF (10 ml). To this solution were added *p*-nitrobenzyl chloride (1.80 g, 10.5 mmol) and potassium iodide (0.15 g), and the resulting mixture was stirred under nitrogen at room temperature for 24 h. Ethyl acetate (150 ml) and water (50 ml) were added, and the organic layer was separated and washed successively with water, aqueous sodium hydrogen carbonate, and water again, then dried ($MgSO_4$) and evaporated. The product was crystallised from a mixture of ethyl acetate and benzene (1:2.5), to afford brilliant crystals of p-*nitrobenzyl phenoxymethylpenicillinate 1,1-dioxide* (**1d**), solvated with benzene (4.92 g, 80%), m.p. 114—115 °C; $[\alpha]_D$ +82° (*c* 1 in $CHCl_3$); $\nu_{max.}$(KBr) 3 420 (NH), 1 812 (azetidinone CO), 1 762 (ester CO), 1 707

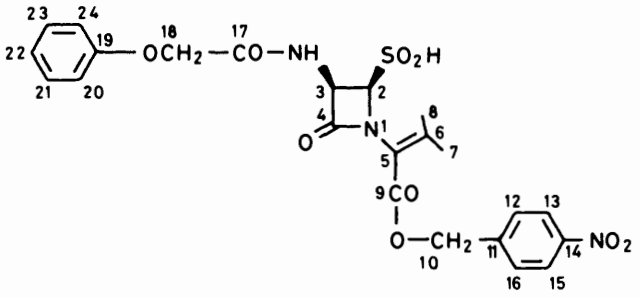


(1d)

(amide CO), and 1 350 and 1 125 cm^{-1} (SO_2); δ_H($CDCl_3$) 1.44 (3 H, s, 2-Me_α), 1.72 (3 H, s, 2-Me_β), 4.62 (2 H, s, PhOCH_2), 4.70 (1 H, s, 3-H), 4.91 (1 H, d, *J* 5 Hz, 5-H), 5.40 (2 H, s, C$H_2C_6H_4NO_2$), 6.28 (1 H, dd, *J* 5, 10 Hz, 6-H), 6.91—7.49 (12.5 H, m, 5 H for Ph and 7.5 H for C_6H_6), 7.62 (2 H, d, *J* 9 Hz, *m*-H of $C_6H_4NO_2$), 8.20 (1 H, d, *J* 10 Hz, CONH), and 8.36 (2 H, d, *J* 9 Hz, *o*-H of $C_6H_4NO_2$); δ_C($CDCl_3$) 173.37 (C-7), 167.86 (C-8), 165.89 (C-16), 156.36 (C-10), 147.47 (C-21), 140.95 (C-18), 129.36 (C-12 and -14), 128.66 (C-19 and -23), 127.90 (benzene carbons), 125.50 (C-20 and -22), 121.78 (C-13), 114.37 (C-11 and -15), 66.52 (C-9), 66.21 (C-17), 65.35 (C-5), 64.29 (C-2), 63.44 (C-3), 55.93 (C-6), 19.72 (2β-C), and 17.43 (2α-C) (Found: C, 59.4; H, 5.1; N, 6.8; S, 4.8. $C_{29}H_{29}N_3O_9S$·1.25C_6H_6 requires C, 59.6; H, 5.0; N, 6.8; S, 5.2%).

In order to remove the solvated benzene, the ester (**1d**) (4 g) was redissolved in dichloromethane (10 ml) and the solution was diluted with n-hexane (10 ml). A white precipitate formed which was filtered off, washed with hexane, and dried *in vacuo*. A white amorphous powder (3.62 g, 96.5%) was obtained, which showed no benzene signal in its ^{1}H n.m.r. spectrum.

Reaction of p-*Nitrobenzyl Phenoxymethylpenicillinate 1,1-Dioxide* (**1d**) *with Potassium Acetate in* DMF–CH_2Cl_2 *Mixture*.—To a solution of potassium acetate (1.1 g, 11.22 mmol) in DMF (50 ml) in an ice-bath were added dichloromethane (100 ml) and the sulphone ester (**1d**) (5.0 g, 9.94 mmol). The complete mixture was stirred at 5—10 °C for 18 h, then extracted with cold water (1 × 300 ml, 2 × 200 ml). The aqueous extracts were combined and washed with fresh dichloromethane (50 ml), then acidified to pH 1.5 with 3M-HCl, and extracted with ethyl acetate (1 × 300 ml, 2 × 150 ml). The ethyl acetate extracts were combined and washed with water (3 × 100 ml), and partitioned with 1% aqueous $NaHCO_3$, which was then re-extracted with ethyl acetate at pH 1.5. The ethyl acetate extracts were washed with water (2 × 100 ml) and saturated aqueous NaCl (100 ml), dried (Na_2SO_4), and evaporated under reduced pressure to dryness in a 35 °C water-bath. A white foam was obtained, which was then crystallised from CH_2Cl_2–ether, yielding (2R,3R)-1-[2-*methyl*-1-(p-*nitrobenzyloxycarbonyl*)*prop*-1-*enyl*)-4-*oxo*-3-*phenoxyacetamidoazetidine*-2-*sulphinic acid* (**3**) (1.02 g, 20%), m.p. 112—113 °C (decomp.); $[\alpha]_D$ −11° (*c* 1 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 300 (NH), 1 787 (azetidinone CO), 1 732 (ester CO), 1 692 (amide CO), and 1 347 and 1 125 cm^{-1} (SO_2H); δ_H($CDCl_3$) 2.18 (3 H, s, =CMe), 2.27 (3 H, s, =CMe), 4.56 (2 H, s, 18-H_2), 4.91 (1 H, d, *J* 5 Hz, 2-H), 5.38 (2 H, s, 10-H_2), 5.62 (1 H, dd, *J* 5, 11 Hz, 3-H), 6.84—7.42 (6 H, m, PhO and SO_2H), 7.58 (2 H, d, *J* 9 Hz, 12- and 16-H), 8.04 (1 H, d, *J* 11 Hz, CONH), and 8.24 (2 H, d, *J* 9 Hz, 13- and 15-H); δ_C($CDCl_3$) 169.53 (C-17), 165.25 (C-4),



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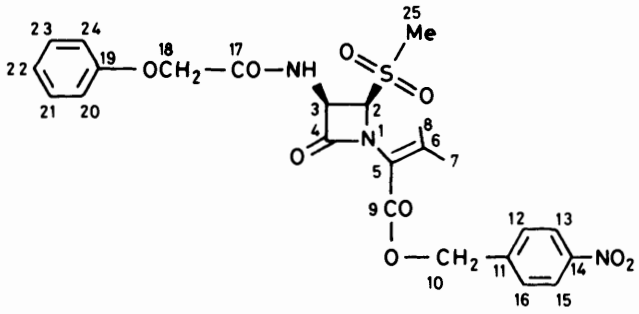

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163.45 (C-9), 157.02 (C-6), 156.93 (C-19), 147.83 (C-14), 142.43 (C-11), 129.73 (C-21 and -23), 128.54 (C-12 and -16), 123.94 (C-13 and -15), 122.34 (C-22), 119.39 (C-5), 114.84 (C-20 and -24), 77.02 (C-2), 66.97 (C-18), 65.76 (C-10), 56.98 (C-3), and 24.16 and 22.29 (C-8 and -7) (Found: C, 53.2; H, 4.7; N, 7.9; S, 6.4. $C_{23}H_{23}N_3O_9S$ requires C, 53.4; H, 4.5; N, 8.1; S, 6.2%).

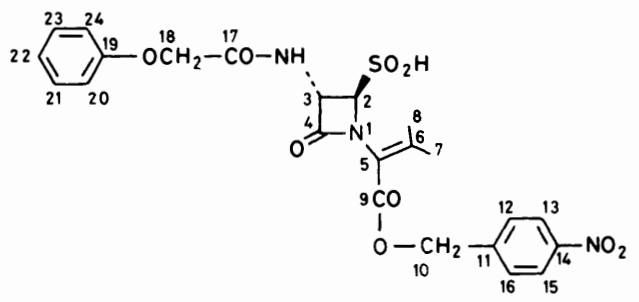
The dichloromethane layer after water extraction was dried ($MgSO_4$) and evaporated. The residue was dissolved in an ethyl acetate–benzene mixture (1:2) and the solution was stirred until crystallisation was complete (about 3 h). Filtration then afforded the product (3.33 g, 67%), m.p. 114—115 °C; $[\alpha]_D$ +82° (*c* 1 in $CHCl_3$); ^1H, ^{13}C, and i.r. spectra showed that this substance was identical with the starting sulphone (**1d**).

Preparation of Sodium (2R,3R)-1-[2-*Methyl*-1-(p-*nitrobenzyloxycarbonyl*)*prop*-1-*enyl*]-4-*oxo*-3-*phenoxyacetamidoazetidine*-2-*sulphinate*.—The sulphinic acid (**3**) (0.517 g, 1 mmol) was dissolved in cold water (10 ml) with sodium hydrogen carbonate (0.084 g, 1 mmol) and the aqueous solution was freeze-dried, yielding the *sodium salt of the acid* (**3**) as a solid (0.530 g), m.p. 190—192 °C (decomp.); $\delta_C(D_2O)$ (CH_3CN as internal standard) 171.39 (C-17), 168.56 (C-4), 164.38 (C-9), 158.57 (C-6), 157.87 (C-19), 147.96 (C-14), 144.22 (C-11), 130.52 (C-21 and -23), 129.21 (C-12 and -16), 124.47 (C-13 and -15), 122.79 (C-22), 119.67 (C-5), 115.51 (C-20 and -24), 80.15 (C-2), 67.35 (C-18), 66.28 (C-10), 56.79 (C-3), and 24.00 and 21.94 (C-8 and -7) (Found: C, 47.6; H, 4.1; N, 7.0. $C_{23}H_{22}N_3NaO_9{\cdot}2H_2O$ requires C, 48.0; H, 4.5; N, 7.3%).

Reaction of Sodium (2R,3R)-1-[2-*Methyl*-1-(p-*nitrobenzyloxycarbonyl*)*prop*-1-*enyl*]-4-*oxo*-3-*phenoxyacetamidoazetidine*-2-*sulphinate with Iodomethane*.—The sodium salt of the sulphinic acid (**3**) (0.270 g, 0.5 mmol) was dissolved in acetone (10 ml), and iodomethane (0.090 g, 0.64 mmol) was added. The solution was stirred at room temperature for 14 h. T.l.c. (ethyl acetate–benzene 1:1) showed that the starting material had disappeared, and a new spot of R_F 0.44 had formed. The resulting mixture was evaporated to dryness; to the residue were added ethyl acetate (35 ml) and water (10 ml). The organic layer was separated and washed successively with water (2 × 10 ml), 5% aqueous $NaHCO_3$ (2 × 10 ml), 0.5% HCl (5 ml), and water (2 × 5 ml), dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallised from ethyl acetate–hexane, to afford (2R,3R)-[p-*nitrobenzyl*-3-*methyl*-2-(2-*methylsulphonyl*-4-*oxo*-3-*phenoxyacetamidoazetidin*-1-*yl*)*but*-2-*enoate*] (**6**) (0.230 g, 87%), m.p. 95—97 °C; $[\alpha]_D$ −18° (*c* 1 in $CHCl_3$); R_F 0.44 (ethyl acetate–benzene 1:1); $\nu_{max.}(CHCl_3)$ 3 382 (NH), 1 792 (β-lactam CO), 1 720 (ester CO), 1 682 (amide CO), and 1 345 and 1 125 cm^{-1} (SO_2); $\delta_H(CDCl_3)$ 2.19 (3 H, s, =CMe), 2.29 (3 H, s, =CMe), 2.65 (3 H, s, 25-H_3), 4.58 (2 H, s, 18-H_2), 5.24 (1 H, d, *J* 5 Hz, 2-H), 5.32 (2 H, s. 10-H_2), 5.98 (1 H, dd, *J* 5, 11 Hz, 3-H), 6.92—7.36 (5 H, m, PhO), 7.53 (2 H, d, *J* 9 Hz, 12- and 16-H), 7.93 (1 H, d, *J* 11 Hz, CONH), and 8.23 (2 H, d, *J* 9 Hz, 13- and 15-H); $\delta_C(CDCl_3)$ 168.63 (C-17), 164.93 (C-4), 162.36 (C-9), 158.29 (C-6), 156.74 (C-19), 147.76 (C-14), 142.31 (C-11), 129.71 (C-21 and -23), 128.45 (C-12 and -16), 123.89 (C-13 and -15), 122.32 (C-22), 118.72 (C-5), 114.63 (C-20 and -24), 73.23 (C-2), 66.76 (C-18), 65.62 (C-10), 56.57 (C-3), 39.71 (C-25), and 24.31 and 22.34 (C-8 and -7) (Found: C, 54.5; H, 5.1; N, 8.0. $C_{24}H_{25}N_3O_9S$ requires C, 54.2; H, 4.7; N, 7.9%).

Reaction of p-*Nitrobenzyl Phenoxymethylpenicillinate* 1,1-*Dioxide* (**1d**) *with DBU*.—A procedure similar to that of Stoodley [1] was used. A mixture of the sulphone (**1d**) (0.260 g, 0.5 mmol) and DBU (2 drops) in dichloromethane (20 ml) was stirred at room temperature for 1 h. The mixture was then washed successively with water (2 × 10 ml), 0.1M-HCl (2 × 10 ml), aqueous sodium hydrogen carbonate (5%; 2 × 10 ml), and water (2 × 10 ml), and was then dried ($MgSO_4$) and evaporated. A white foam (0.200 g) was obtained. Examination of the ^1H n.m.r. spectrum of this product (in $CDCl_3$) at 200 MHz showed signals at δ 4.86 (*J* 5 Hz) and 4.95 (*J* 2 Hz), corresponding to the starting compound (**1d**) and its 6-epimer respectively. The ^1H n.m.r. integral ratio was 1:1.7, *i.e.* ~63% of the starting compound (**1d**) had epimerised.

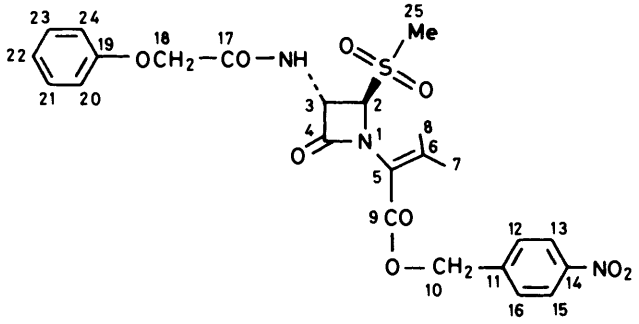
Reaction of p-*Nitrobenzyl Phenoxymethylpenicillinate* 1,1-*Dioxide* (**1d**) *with Excess of DBU*.—Again, Stoodley's procedure [1] was used. A mixture of the sulphone (**1d**) (0.517 g, 1 mmol) and DBU (0.230 g, 1.5 mmol) in dichloromethane (1 ml) was stirred at room temperature for 25 min. The deep red solution was diluted with dichloromethane (10 ml) and washed successively with cold hydrochloric acid (1%; 2 × 5 ml) and water (5 ml). The organic layer was then extracted with aqueous sodium hydrogen carbonate (3%; 2 × 5 ml); this aqueous extract was acidified and back-extracted with dichloromethane (10 ml). Evaporation of the dried organic extract left a residue, which was chromatographed (silica; acetone), and then crystallised from a mixture of dichloromethane and ether, to yield (2R,3S)-1-[2-*methyl*-1-(p-*nitrobenzyloxycarbonyl*)*prop*-1-*enyl*]-4-*oxo*-3-*phenoxyacetamidoazetidine*-2-*sulphinic acid* (**2d**) (0.320 g, 62%), m.p. 107—109 °C; $[\alpha]_D$ −67° (*c* 1 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 340 (NH), 1 775 (β-lactam CO), 1 720 (ester CO), 1 670 (amide CO), and 1 350 and 1 125 cm^{-1} (SO_2H);



(2d)

$\delta_H(CDCl_3)$ 2.01 (3 H, s, =CMe), 2.20 (3 H, s, =CMe), 4.48 (2 H, br s, 18-H_2), 4.80 (1 H, br s, 2-H), 5.24 (3 H, br s, 10-H_2 and 3-H), 6.74—7.30 (5 H, m, PhO), 7.46 (2 H, d, *J* 9 Hz, 12- and 16-H), 7.85 (2 H, br s, collapses on addition of D_2O, CONH and SO_2H), and 8.09 (2 H, d, *J* 9 Hz, 13- and 15-H); $\delta_C(CDCl_3)$ 170.96 (C-17), 162.72 (C-4), 162.52 (C-9), 156.88 (C-6), 156.56 (C-19), 147.56 (C-14), 142.36 (C-11), 129.71 (C-21 and -23), 128.37 (C-12 and -16), 123.65 (C-13 and -15), 122.39 (C-22), 118.62 (C-5), 114.53 (C-20 and -24), 78.41 (C-2), 66.54 (C-18), 65.51 (C-10), 53.45 (C-3), and 23.80 and 22.17 (C-7 and -8) (Found: C, 53.6; H, 4.7; N, 8.0. $C_{23}H_{23}N_3O_9S$ requires C, 53.4; H, 4.5; N, 8.1%).

Methylation of (2R,3S)-1-[2-*Methyl*-1-(p-*nitrobenzyloxycarbonyl*)*prop*-1-*enyl*]-4-*oxo*-3-*phenoxyacetamidoazetidine*-2-*sulphinic Acid* (**2d**).—To a suspension of the sulphinic acid (**2d**) (0.300 g, 0.6 mmol) in water (3 ml) was added sodium hydrogen carbonate (0.051 g, 0.61 mmol). The clear solution was then azeotropically evaporated with the aid of butan-1-ol (2 × 20 ml). The resulting solid was treated with a solution of iodomethane (110 mg, 0.78 mmol) in acetone (5 ml) for 12 h. The mixture was evaporated to dryness. The residue was dissolved in ethyl acetate (20 ml) and the solution was washed successively with 5% aqueous $NaHCO_3$ (2 × 5 ml) and water (2 × 5 ml), dried over anhydrous Na_2SO_4, and evaporated to dryness; the residue was redissolved in 1:1 ethyl acetate–benzene and chromatographed [silica; ethyl acetate–benzene 1:1)], to yield (2R,3S)-[p-*nitrobenzyl* 3-*methyl*-2-(2-*methylsulphonyl*-4-*oxo*-3-*phenoxyacetamido*-*azetidin*-1-*yl*)*but*-2-*enoate*] (**7**) (0.180 g, 56%), m.p. 94—95 °C (from ethyl acetate–ether); $[\alpha]_D$ −16° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 300 (NH), 1 789 (β-lactam CO), 1 722 (ester CO), 1 690 (amide CO), and 1 325 and



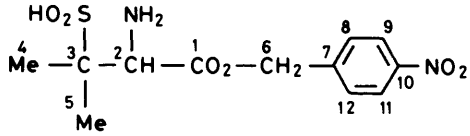
(**7**)

1 130 cm^{-1} (SO_2); $\delta_H(CDCl_3)$ 2.13 (3 H, s, =CMe), 2.27 (3 H, s, =CMe), 3.00 (3 H, s, 25-H_3), 4.56 (2 H, br s, 18-H_2), 5.24 (1 H, dd, *J* 2, 7 Hz, 3-H), 5.33 (1 H, d, *J* 2 Hz, 2-H), 5.42 (2 H, br s, 10-H_2), 6.88—7.50 (5 H, m, PhO), 7.67 (2 H, d, *J* 9 Hz, 12- and 16-H), 7.75 (1 H, d, *J* 7 Hz, CONH), and 8.28 (2 H, d, *J* 9 Hz, 13- and 15-H); $\delta_C(CDCl_3)$ 169.51 (C-17), 162.63 (C-4), 162.56 (C-9), 156.58 (C-19), 155.36 (C-6), 147.30 (C-14), 142.36 (C-11), 129.48 (C-21 and -23), 128.29 (C-12 and -16), 123.60 (C-13 and -15), 122.00 (C-22), 118.55 (C-5), 114.37 (C-20 and -24), 74.08 (C-2), 66.64 (C-18), 65.45 (C-10), 58.53 (C-3), 39.35 (C-25), and 23.70 and 22.27 (C-8 and -7) (Found: C, 53.8; H, 4.9; N, 8.2; S, 6.5. $C_{24}H_{25}N_3O_9S$ requires C, 54.2; H, 4.7; N, 7.9; S, 6.0%).

Reaction of p-*Nitrobenzyl Phenoxymethylpenicillinate* 1,1-*Dioxide* (**1d**) *with DBU at* −30 °C.—A solution of the sulphone (**1d**) (0.500 g, 0.97 mmol) in dichloromethane (5 ml) was cooled to between −30 and −40 °C, then was treated with DBU (0.230 g, 1.51 mmol). The mixture was stirred under nitrogen at this temperature for 3.5 h, then acidified with dil. hydrochloric acid (0.5M; 5 ml). The organic layer was extracted with aqueous sodium hydrogen carbonate (3%; 2 × 5 ml), and this extract was then acidified and back-extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) organic extracts left a residue (0.400 g, 80%), the ^1H n.m.r. spectrum of which showed it to be a mixture of ~20% of the sulphinic acid (**2d**) and ~80% of the epimeric sulphinic acid (**3**). Methylation of the mixed sodium salts of this residue, in the same fashion as described for the sulphinic acid (**3**) (above), afforded a mixture of the corresponding methyl sulphones (**6**) and (**7**). This mixture of epimers was separated on a silica gel column with a mixture of ethyl acetate–benzene (1:2). The component with R_F 0.58 (ethyl acetate–benzene 1:2) (0.280 g) was identified as the (2*R*,3*S*)-methyl sulphone (**7**), and the component with R_F 0.45 (0.060 g) was found to be the (2*R*,3*R*)-methyl sulphone (**6**).

Conversion of p-*Nitrobenzyl Phenoxymethylpenicillinate* 1,1-*Dioxide* (**1d**) *into Oxoazetidinesulphinic Acids under Various Conditions.*—A large number of experiments were undertaken to explore various combinations of solvents, bases, and reaction temperatures. Alkali metal acetates (K, Li, Na) were effective in this reaction; potassium acetate is the most soluble in the solvent mixture DMF–dichloromethane. In the absence of dichloromethane the reaction went faster but the starting sulphone epimerised rather rapidly. A similar result was obtained using neat DMSO as solvent. Other weak bases, such as pyridinium acetate, produced no reaction. Acetic acid (in a mixture DMF–dichloromethane) also was ineffective. Hydroxylic solvents gave products resulting from opening of the β-lactam ring. After reaction, the mixture was partitioned between water, or aqueous sodium hydrogen carbonate, and ethyl acetate. Work-up of the aqueous extract then afforded a mixture of the epimeric sulphinic acids (**2d**) and (**3**), the ratio of which was determined by ^1H n.m.r. spectroscopy of the methyl groups. In like manner, the ratio of the starting substance (**1d**) to its 6-epimer was found by ^1H n.m.r. examination of the C-5 and C-6 protons. The greatest ratio of (**3**) to (**2d**) (*ca.* 19:1) was attained with the mixture of potassium acetate, DMF, and dichloromethane at 5—10 °C, described above. Omission of the dichloromethane gave a ratio of *ca.* 1:1 for a comparable reaction time; more of the sulphone (**1d**) had been converted, but more had been epimerised. Similar results were obtained using potassium acetate in DMSO.

Reaction of p-*Nitrobenzyl Phenoxymethylpenicillinate* 1,1-*Dioxide* (**1d**) *with Sodium* 2-*Hydroxyethanethiolate* (**4**).—The penicillinate (**1d**) (0.500 g, 0.97 mmol), sodium 2-hydroxyethanethiolate (**4**) (0.100 g, 1. mmol) and methanol (10 ml) were stirred together at room temperature for 3 h. T.l.c. then showed that the starting ester (**1d**) had disappeared. The mixture was adjusted to pH 2 with 10% phosphoric acid, and extracted with ethyl acetate (50 ml). The extract was washed with water and stirred for 2 h. The crystals that formed were removed, washed successively with ethyl acetate and water, recrystallised from a mixture of ethyl acetate, methanol, and water, and dried



(**5**)

in vacuo, to yield p-*nitrobenzyl* 2-*amino*-3-*methyl*-3-*sulphinobutanoate* (**5**) (0.250 g, 79%), m.p. 244—245 °C; $\nu_{max.}$(KBr) 3 450w, 2 600 (NH_3^+), 1 760 (CO), and 1 530 and 1 350 cm^{-1} (SO_2); $\delta_H([^2H_6]DMSO + D_2O)$ 0.84 (3 H, s, Me), 1.07 (3 H, s, Me), 4.49 (1 H, s, 2-H), 5.36 (2 H, s, 6-H_2), 7.69 (2 H, d, *J* 9 Hz,

8- and 12-H), and 8.22 (2 H, d, *J* 9 Hz, 9- and 11-H); $\delta_C([^2H_6]DMSO)$ 166.79 (C-1), 145.65 (C-10), 141.03 (C-7), 127.40 (C-8 and -12), 121.90 (C-9 and -11), 64.36 (C-6), 53.33 (C-2), 49.88 (C-3), and 19.59 and 14.18 (C-4 and -5) (Found: C, 45.7; H, 5.2; N, 8.7; S, 10.6. $C_{12}H_{16}N_2O_6S$ requires C, 45.6; H, 5.1; N, 8.8; S, 10.2%).

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