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Cis and *trans*–4–Oxoazetidine–2–Sulphonic Acid Derivatives; Preparation and X-Ray Structure Determination[1]

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Cis and *trans*–4–oxoazetidine–2–sulphonic acid derivatives were prepared starting from penicillanate sulphoxides (**1**) and (**4**). The methylsulphonates (**5**), (**7**), (**8**) and (**9**) were formed by oxidation of 4–oxoazetidine–2–sulphinates (**2**), (**3**), and (**6**). Generally, 4–oxoazetidine–2–sulphonates were labile entities and hydrolyzed under mild conditions into sulphonic acids. These were isolated as acids (**12**) and salts (**10**), (**11**) and (**14**). The conformational isomers of the sulphonate (**9a**) were detected by ^{1}H NMR spectroscopy and confirmed by variable temperature experiments. X-Ray structure analyses of **9a** were performed but there wasn't any evidence for intramolecular hydrogen bonding.

INTRODUCTION

The bactericidal properties exhibited by some monocyclic β-lactams have stimulated a growing interest in the preparation of new species. Among these, the 4–oxoazetidine–2–sulphonic acid derivatives are interesting compounds for the preparation of potential monobactams, and for the subsequent synthesis of novel fused β-lactams.

There are only two reports in the literature that describe the preparation of 4–oxoazetidine–2–sulphonic acid derivatives. The betaine, 3–amino–4–oxoazetidine–2–sulphonic acid was formed by the degradation of thiazolinoazetidinone.[2] Furthermore, some alkylsulphonates, derived from sulbactam, were prepared in our laboratory.[3]

In this paper, we report studies involving the preparation and structure determination of some *cis* and *trans*–4–oxoazetidine–2–sulphonic acid derivatives.

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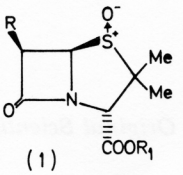
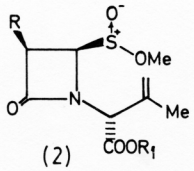


(1)

a; R = Pht, $R_1 = CH_2C_6H_4NO_2$
b; R = $PhCH_2CONH$, $R_1 = CH_2C_6H_4NO_2$
c; R = $PhOCH_2CONH$, R_1 = Me
d; R = $PhOCH_2CONH$, $R_1 = CH_2C_6H_4NO_2$
e; R =  , $R_1 = CH_2C_6H_4Me$



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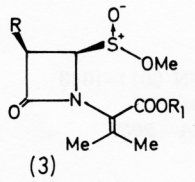

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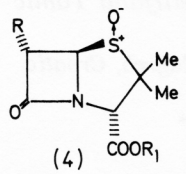
b; R = $PhCH_2CONH$, $R_1 = CH_2C_6H_4NO_2$
c; R = $PhOCH_2CONH$, R_1 = Me
d; R = $PhOCH_2CONH$, $R_1 = CH_2C_6H_4NO_2$
e; R =  , $R_1 = CH_2C_6H_4Me$



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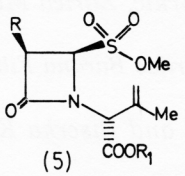

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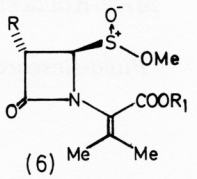

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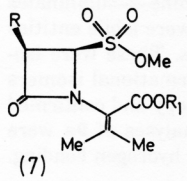
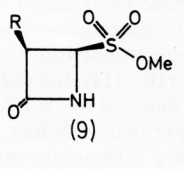


(7)

a; R = Pht, $R_1 = CH_2C_6H_4NO_2$
b; R = $PhCH_2CONH$, $R_1 = CH_2C_6H_4NO_2$
c; R = $PhOCH_2CONH$, R_1 = Me
d; R = $PhOCH_2CONH$, $R_1 = CH_2C_6H_4NO_2$
e; R =  , $R_1 = CH_2C_6H_4Me$



(9)

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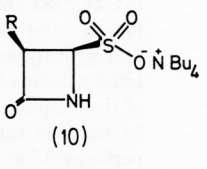

(10)

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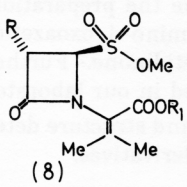
b; R = $PhOCH_2CONH$



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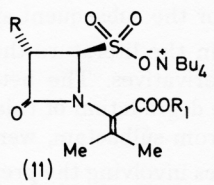

(11)

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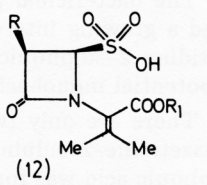
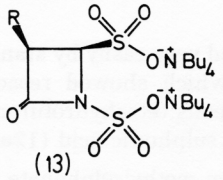


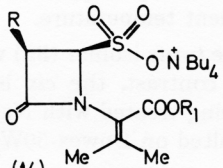
(12)

a; R = Pht $R_1 = CH_2C_6H_4NO_2$
b; R = $PhCH_2CONH$, $R_1 = CH_2C_6H_4NO_2$
c; R = $PhOCH_2CONH$, R_1 = Me
d; R =  , $R_1 = CH_2C_6H_4Me$



(13)

a ; R = $PhCH_2CONH$



(14)

a; R = Pht, $R_1 = CH_2C_6H_4NO_2$

b ; R = $PhCH_2CONH$ $R_1 = CH_2C_6H_4NO_2$

c ; R = $PhOCH_2CONH$ R_1 = Me

RESULTS AND DISCUSSION

Chemistry

S. Kukolja and his co-workers have shown that penicillin sulphoxide ester (**1**) can react with *N*–chlorosuccinimide (NCS) and alcohol to afford 4–oxoazetidine–2–sulphinate (**2**).[4]

Using this procedure, we prepared the corresponding sulphinates starting from the penicillanate sulphoxides (**1**) and (**4**).[5,6,7,8]

The complex mixture of *R* and *S* sulphinates (**2**) and in part *R* and *S* sulphinates (**3**) were obtained. These were treated with triethylamine and the sulphinates (**2**) were completely isomerized into isomers (**3**). The sulphinates were used for the preparation of some new *cis* and *trans* 4–oxoazetidine–2–sulphonates.

Thus, by the oxidation of sulphinate (**2a**) with $KMnO_4$, sulphonate (**5a**) was obtained in 53% yield. Under the same reaction conditions, the *cis*–sulphonate (**7a**) and *trans*–sulphonate (**8a**) were prepared by the oxidation of sulphinates (**3a**) and (**6a**).

During the oxidation of the sulphinate (**3b**) with $KMnO_4$, besides oxidation on sulphur, the complete substituent was removed from β-lactam nitrogen and sulphonate (**9a**) was isolated in 30% yield. The same compound was also prepared when sulphonate (**7b**) was treated with $KMnO_4$.[9,10]

The ^1H NMR spectrum (DMSO–d_6) of the sulphonate (**9a**) featured dual peaks, which indicated conformational isomers. These were confirmed by variable NMR temperature experiments at 20 °C and 60 °C. The hindered rotation could not be explained by intramolecular hydrogen bonding of the SO's to the azetidine NH. An X-ray structure analysis of **9a** was performed and there wasn't any evidence for intramolecular hydrogen bonding.

The use of an oxidant such as H_2O_2 gave sulphonates (**7**) in a better yield. Thus, the oxidation of sulphinate (**3b,c**) with H_2O_2 in dichloromethane gave the sulphonate (**7b,c**) in an about 70% yield.

Besides the type of the oxidant, the acid also affected the yield of the sulphonate. Particularly when the sulphinate (**3c**) was oxidized with $KMnO_4$ in 80% acetic acid-ethylacetate mixture, instead of the sulphonate (**7c**), sulphonic acids were formed and isolated as tetrabutylammonium salts (**10b**) and (**14c**).

Indeed, the ease of hydrolysis of the methylsulphonate function of compounds **7** and **8** was demonstrated by the formation of sulphonic acid under mild conditions. The

sulphonate (**7b**) was hydrolyzed to sulphonic acid (**12b**) by standing in dichloromethane at ambient temperature.

Moreover, the *trans* isomer (**8a**) was hydrolyzed very easily by standing at ambient temperature. In contrast, the *cis* isomer (**7a**), which showed reasonable stability, hydrolyzed by being treated with $NaHCO_3$ in aqueous tetrahydrofuran. The resultant product was desalted on Dowex-50W(H^+) to yield sulphonic acid (**12a**).

An identical compound (**12a**) was prepared when methylsulphonate (**5a**) was treated with triethylamine during which the hydrolysis of the methylsulphonate function and isomerization of the double bond were performed.

Moreover, when methylsulphonate (**9a**) was treated with pyridinesulphurtrioxide complex, the hydrolysis of the methylsulphonate function was performed together with the sulphonation at N_1. The resultant product was isolated as a ditetrabutylammonium salt (**13a**).

TABLE I

Crystal data and details of the structure determination

a) Crystal data	
Formula	$C_{12}H_{14}N_2O_5S$
M_r	298.31
a (Å)	4.892(3)
b (Å)	9.558(2)
c (Å)	14.48(1)
β (°)	94.51(3)
V (Å^3)	675.1(2)
D_{calc} (g cm^{-3})	1.467
Z	2
Crystal system	monoclinic
Space group	$P2_1$
Crystal size (mm)	0.1 × 0.2 × 0.3
Linear absorption coefficient (cm^{-1})	2.48
F (000)	312
b) Data Collection	
Diffractometer	Enraf-Nonius-CAD4F
Radiation	Mo$K\alpha$ (λ = 0.71073 Å) graphite-monochromator
Temperature (K)	297(1)
Θ_{min}, Θ_{max} (°) for cell det.	4, 17
No of reflections for cell det.	25
Θ_{min}, Θ_{max}	2, 25
ω scan(°)	$\Delta\omega = 1.0 + 0.35 \tan\Theta$
$h\ k\ l$ limits	0 → 4, 0 → 9 −13 → 13
Reflections measured	1746
Reflections observed with $I > 2\sigma(I)$	1190
c) Refinement	
No of parameters	206
Quantity minimized, $\sum\omega \mid \mid F_o \mid - \mid F_c \mid \mid^2$	$w^{-1} = (\sigma^2(F_o) + 0.0003\ F_o^2)k$
R, R_w	0.044, 0.042
Max. parameter shift, $(\Delta/\sigma)_{max}$	0.234 (C12,x)
Residual electron density, $(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$	(e Å^{-3}) 0.23, −0.24

Solution of the Structure

A suitable crystal of compound **9a** was obtained from ethylacetate solution at ambient temperature for 2 days. The crystallographic data and details of data collection and refinement are listed in Table I.

Reference reflections $\bar{1}$ 0 3, $\bar{1}$ 1 1, $\bar{1}$ 1 0 showed a variation at about 0.6 %. Data reduction was performed by Enraf-Nonius SDP/VAX package.[11] Lorentz and polarization effects were corrected. The structure was solved by direct methods using the program SHELX86.[12] Scattering factors and anomalous dispersion corrections were those included in the SHELX77.[13] The hydrogen atoms of phenyl and methyl (C13) groups were derived on the stereochemical grounds. The others were located from a difference Fourier map. The structure was refined by the full-matrix least-squares method using the program SHELX77. For interatomic distances, bond and torsion angles calculations the program PLATON was used. Drawings were prepared by the PLUTON and ORTEP II.[15] PLATON and PLUTON are incorporated in the EUCLID package.[14] Calculations were carried out on the microVAXII in the X-Ray Laboratory of Rudjer Bošković Institute, Zagreb, Croatia. Final atomic coordinates of the non-hydrogen atoms and equivalent isotropic temperature factors are listed in Table II.

Molecular and Crystal Structure of (9a)

Interatomic distances, bond and selected torsion angles are listed in Tables III and IV. The molecular structure is presented by the ORTEP drawing in Figure 1. The diagram illustrating the packing of molecules in the crystal lattice *via* hydrogen bonds is given in Figure 2; hydrogen bond geometry is displayed in Table V.

TABLE II

Final atomic coordinates and equivalent isotropic thermal parameters ($\times 10^4$)

	X	Y	Z	UEQ(A*A)
S	0.7317(2)	0.9453(0)	0.4690(1)	324(4)
O2	1.0200(6)	0.9404(6)	0.4604(2)	444(11)
O3	0.5754(7)	0.8222(4)	0.4520(3)	435(13)
O4	1.0186(9)	1.2494(5)	0.2742(3)	578(16)
O5	0.3110(7)	0.8683(5)	0.2182(3)	565(15)
O6	0.6760(7)	0.9949(5)	0.5685(2)	492(13)
N1	0.7557(9)	1.2064(5)	0.4004(3)	363(15)
N2	0.7401(8)	0.9427(6)	0.2546(3)	331(12)
C2	0.5858(10)	1.0839(6)	0.3968(4)	300(15)
C3	0.6459(10)	1.0693(6)	0.2925(3)	306(17)
C4	0.8478(11)	1.1908(6)	0.3148(4)	381(19)
C5	0.5574(10)	0.8513(6)	0.2158(4)	381(19)
C6	0.6774(11)	0.7223(7)	0.1725(5)	560(23)
C7	0.3504(13)	0.5228(7)	0.1417(4)	542(22)
C8	0.1520(13)	0.4535(10)	0.0878(5)	694(24)
C9	0.0736(13)	0.4971(8)	0.0023(6)	676(27)
C10	0.1957(16)	0.6141(9)	-0.0324(4)	716(28)
C11	0.3952(14)	0.6869(7)	0.0225(4)	563(23)
C12	0.4717(11)	0.6429(6)	0.1114(4)	387(17)
C13	0.8766(14)	1.0801(7)	0.6234(4)	593(23)

$$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \vec{a}_i \vec{a}_j$$

TABLE III

Bond lengths (Å) and angles (degrees)

S	– O2	1.427(3)	O6	– S	– C2	102.9(2)
S	– O3	1.414(4)	O2	– S	– C2	108.8(2)
S	– O6	1.561(4)	O2	– S	– O6	109.7(2)
S	– C2	1.000(6)	O3	– S	– O2	109.1(2)
O4	– C4	1.198(7)	O3	– S	– O6	106.4(2)
O5	– C5	1.220(6)	O3	– S	– O2	118.8(2)
O6	– C13	1.461(7)	S	– O6	– C13	120.8(3)
N1	– C2	1.434(7)	C2	– N1	– C4	96.3(4)
N1	– C4	1.360(7)	C3	– N2	– C5	119.4(4)
N2	– C3	1.421(8)	N1	– C2	– C3	87.4(4)
N2	– C5	1.341(7)	S	– C2	– C3	113.5(4)
C2	– C3	1.567(7)	S	– C2	– N1	112.2(4)
C3	– C4	1.542(8)	N2	– C3	– C4	120.0(4)
C5	– C6	1.522(9)	C2	– C3	– C4	84.1(4)
C6	– C12	1.494(8)	N2	– C3	– C2	122.6(5)
C7	– C8	1.368(10)	O4	– C4	– N1	133.6(6)
C7	– C12	1.380(9)	N1	– C4	– C3	91.2(4)
C8	– C9	1.334(11)	O4	– C4	– C3	135.2(5)
C9	– C10	1.381(11)	O5	– C5	– N2	121.9(5)
C10	– C11	1.395(10)	N2	– C5	– C6	115.7(4)
C11	– C12	1.378(8)	O5	– C5	– C6	122.3(5)
			C5	– C6	– C12	113.1(5)
			C8	– C7	– C12	121.7(6)
			C7	– C8	– C9	121.2(7)
			C8	– C9	– C10	119.3(7)
			C9	– C10	– C11	120.0(6)
			C10	– C11	– C12	120.4(6)
			C7	– C12	– C11	117.3(5)
			C6	– C12	– C11	121.3(6)
			C6	– C12	– C7	121.4(5)

TABLE IV

Selected torsion angles (degrees)

O3	– S	– O6	– C13	154.7(4)
O2	– S	– O6	– C13	25.0(5)
C2	– S	– O6	– C13	–90.7(5)
N1	– C2	– S	– O3	–171.6(4)
N1	– C2	– S	– O2	–40.5(5)
C3	– C2	– N1	– C4	–7.8(4)
C4	– C3	– N2	– C5	–164.6(5)
C2	– C3	– N2	– C5	92.1(6)
N2	– C3	– C2	– S	15.8(6)
C4	– C3	– C2	– N1	6.9(4)
C3	– C4	– N1	– C2	7.9(4)
N1	– C4	– C3	– N2	–131.7(5)
N1	– C4	– C3	– C2	–7.2(4)
O5	– C5	– N2	– C3	–5.7(8)
C6	– C5	– N2	– C3	176.9(5)
O5	– C5	– C6	– C12	16.5(9)
N2	– C5	– C6	– C12	–166.1(5)
C5	– C6	– C12	– C7	–101.0(7)

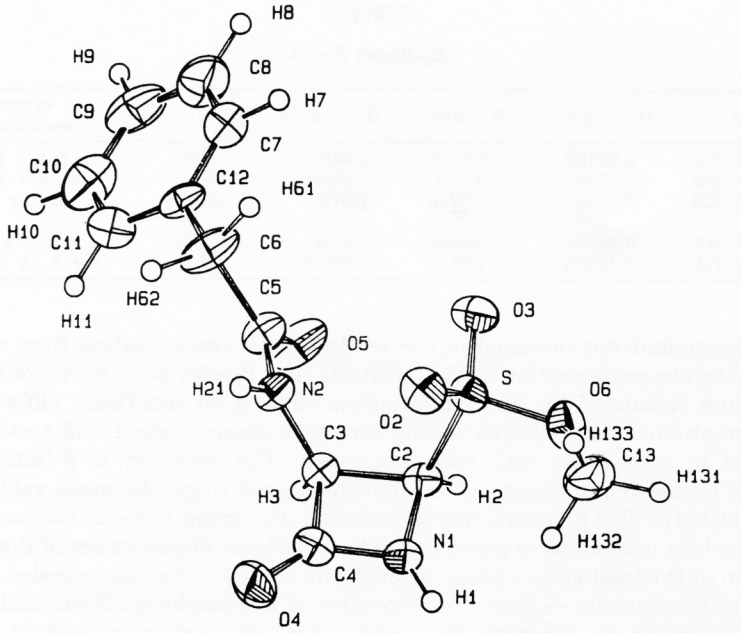


Figure 1. The ORTEP drawing of the **9a** molecule with atom numbering; thermal ellipsoids are at 50% level.

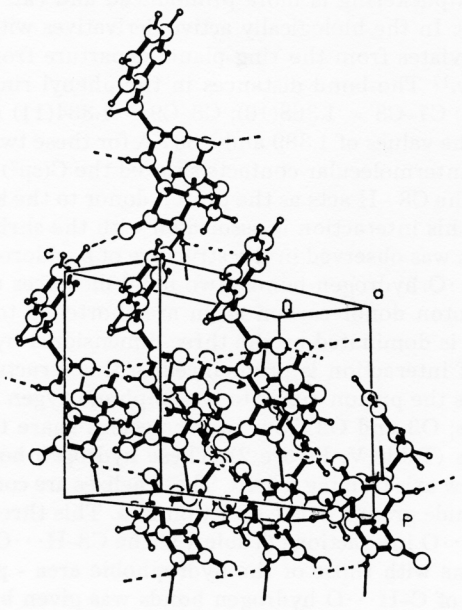


Figure 2. Crystal packing of **9a**. Broken lines denote the hydrogen bonds.

TABLE V

Hydrogen bonds

D – H ··· A	D ··· A(Å)	D – H(Å)	H ··· A(Å)	∢D–H···A(°)	symmetry operation on A
N1 – H1 ··· O3	2.994(6)	0.87(7)	2.54(6)	114(5)	–x + 1, y + 1/2, –z + 1
N1 – H1 ··· O2	3.150(6)	0.87(7)	2.30(6)	168(6)	–x , y + 1/2, –z + 1
N2 – H21··· O5	2.970(6)	0.92(5)	2.07(5)	167(6)	x – 1, y , z
C2 – H2 ··· O2	3.286(6)	0.89(5)	2.56(5)	139(4)	x + 1, y , z
C8 – H8 ··· O4	3.434(9)	1.08	2.565(9)	137	x + 1, y – 1 , z

The compound was obtained in the semisynthetic route starting from compound **1b** with absolute configuration 6*R*(3*R*), 5*R*(2*R*). The Bijvoet pairs were not measured. The *R*-values calculated for both enantiomers showed no significant difference. The 3*R*, 2*R* enantiomer was selected during structure determination and torsion angles were listed in accordance with this assignment. The geometry of β-lactam ring is dominated by the requirements of the four-membered rings; the mean value of bond angles is 89.8(4)°. The β-lactam ring is puckered; the mean value of torsion angles is 7.4(4)°. The best least-squares plane showed a significant displacement of the C4 atom. Calculation of the least-square plane through the N1, C2, C3 atoms revealed departure of C4 from this plane by –0.183(5) Å. Inspection of the Cambridge Structural Database (version 4, 1991)[16] on β-lactam ring, which has not been associated to any ring, revealed 155 crystal structures (with $R < 0.07$). Puckering of β-lactam ring at the C2 site (numbering for C4 is C2 in unsubstituted β-lactam), with deviation from the three-atom plane in the range 0.06–0.10 Å, was detected in 28 structures. However, in the present structure this puckering is more pronounced and can be associated with the C–H···O interactions. In the biologically active derivatives with the β-lactam moiety, the nitrogen atom deviates from the ring plane; departure from the plane is directly related to the activity.[17] The bond distances in the phenyl ring are shorter than the usual ones (Table III): C7–C8 = 1.368(10); C8–C9 = 1.334(11) Å. After corrections on the riding motion,[18] the values of 1.389 and 1.337 Å for these two bonds were obtained. An inspection of the intermolecular contacts showed the C(sp^2) - H···O (carbonyl) interaction (Table V). The C8 - H acts as the proton donor to the keto oxygen of β-lactam ring; most probably, this interaction is associated with the shrinkage of aromatic C–C bond. The same effect was observed in the structure of *p*–chloro–*trans*–cinnamic acid[19] which exhibits C–H···O hydrogen bonds; two bond distances of the aromatic system which include the proton donor carbon atom are shortened to 1.369(3) and 1.365(3) Å. Molecular packing is dominated by the three-dimensional hydrogen bond network. The C–H···O type of interaction is pronounced in this structure. The nitrogen of β-lactam ring appears as the proton donor to the sulphon oxygen atoms exhibiting bifurcated hydrogen bonds; O3 and O2 from two molecules share the same proton in the N–H···O interactions (Table V, Figure 2). These hydrogen bonds connect molecules along the two-fold screw axis forming a helix. These helixes are connected *via* N2–H···O5 hydrogen bonds of amide groups in the direction of **a**. This three-dimensional network is completed by C–H···O interactions (Table V). The C8–H···O4 interaction connects the hydrophilic regions with those of the hydrophobic area - phenyl rings. The crystallographic evidence of C–H···O hydrogen bonds was given by Taylor & Kennard,[20] on the basis of 113 crystal structures determined by neutron diffraction. Discussion

of the role of these interactions on molecular packing and conformation was given by Berkovich-Yellin & Laiserowitz.[21,22]

EXPERIMENTAL

M.p.s. were obtained using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 G instrument.

^{1}H NMR spectra were recorded on a Jeol FX 90Q instrument operating at 90 MHz. Chemical shifts δ were recorded in p.p.m. downfield from $SiMe_4$. T.l.c. were run on Merck Kieselgel HF_{254} plates and were visualized under UV light or I_2 vapor adsorption following cool water flush. Column chromatography was performed on Merck Kieselgel 60 (70–230 mesh ASTM) activated at 105 °C.

General Preparation of 4-oxoazetidine-2-sulphinates (2) and (3)

Toluene was heated in an equipment having a Dean-Stark water trap to remove azeotropically any moisture. To the resulting dried toluene (50 cm^3), penicillanate sulphoxide (**1**) (1.5 mmol), calcium oxide* (6 mmol) and *N*-chlorosuccinimide (1.5 mmol) were added. The mixture was refluxed for 1.5 hours and then cooled to 5 °C. Dry methanol was added and the reaction mixture was stirred at 5 °C for 2 hours. The reaction mixture was washed with water, dried over $MgSO_4$ and evaporated to provide sulphinate (**2**).[4] The obtained compound **2** was dissolved in dichloromethane and stirred with triethylamine at 5 °C for 1 hour. The reaction solution was washed with water, dilute hydrochloric acid and water. The organic layer was dried over $MgSO_4$ and evaporated. The crude sulphinate (**3**) was purified.

(2R,3R) 3-Phthalimido-1-(1'-p-nitrobenzyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphinic Acid Methyl Ester (**3a**)

Crude **3a** was purified by silica-gel chromatography with dichloromethane-ethylacetate (9:1) as eluant and crystallized from ethanol to yield **3a** (77.1% based on **1a**); m.p. 131–133 °C; R_f 0.52 in CH_2Cl_2–EtOAc (9:1); IR (KBr) 1785s, 1760s, 1715vs, 1630w, 1600m, 1515s, 1385s, 1340m, 1280w, 1205m, 1100m, 970m, 710m cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28 and 2.33 (6H, 2s, CMe_2), 3.70 (3H, s, OMe), 4.92 (1H, d, J = 5.8 Hz, C_2H), 5.36 (2H, s, OCH_2), 5.78 (1H, d, J = 5.8, C_3H), 7.56 and 8.26 (4H, 2d, J = 9 Hz, $C_6H_4NO_2$) and 7.72–7.96 (4H, m, Pht);

Anal. $C_{24}H_{21}N_3O_9S$ (527.51)

calc'd: C 54.65; H 4.01; N 7.96; S 6.08%,

found: C 54.36; H 4.34; N 7.96; S 6.08%.

(2R,3R) 3-Phenylacetamido-1-(1'-p-nitrobenzyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphinic Acid Methyl Ester (**3b**)

Crude **3b** was purified by silica-gel chromatography with dichloromethane–ethylacetate (4:1) as eluant to yield foam (62.4% based on **1b**); R_f 0.44 and 0.50 in CH_2Cl_2–EtOAc (1:1), IR (KBr) 3300m, 1780vs, 1730s 1675s, 1520vs, 1350vs, 1220s, 980s cm^{-1}; ^{1}NMR ($CDCl_3$) for the predominant isomer δ 2.11 and 2.24 (6H, 2s, CMe_2), 3.60 (3H, s, OMe), 3.61 (2H, s, CH_2CO), 4.71 (1H, d, J = 5.3 Hz, C_2H), 5.28 (2H, s, OCH_2), 5.46 (1H, dd, J = 5.3 and 9.0 Hz, C_3H), 6.84 (1H, d, J = 9.0 Hz, CONH), 7.30 (5H, s, C_6H_5), 7.49 and 8.21 (4H, 2d, J = 8.9 Hz, $C_6H_4NO_2$);

Anal. $C_{24}H_{25}O_8N_3S$ (515.55)

calc'd: C 55.91; H 4.89; N 8.15; S 6.22%,

found: C 56.24; H 5.01; N 8.24; S 5.84%.

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* Procedures 3a and 6a were done without calcium oxide.

*(2R,3R) 3–Phenoxyacetamido–1–(1'–methyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphinic Acid Methyl Ester (***3c***)*

Crude **3c** oil was then triturated with ether and the epimer with m.p. 130–132 °C was separated by filtration (37.1%); R_f 0.68 in CH_2Cl_2–EtOAc (5:3); IR (KBr) 3250–3310m, 1760s, 1717m, 1675m, 1595w, 1585w, 1520m, 1485m, 1430m, 1380–1360m, 1230s, 1180m, 1105s, 1075–1055m, 980w, 880m cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 and 2.27 (6H, 2s, CMe_2), 3.67 (3H, s, OMe), 3.78 (3H, s, OMe), 4.55 (2H, s, OCH_2), 4.86 (1H, d, J = 5.0 Hz, C_2H), 5.78 (1H, dd, J = 5.0 and 9.4 Hz, C_3H), 6.89–7.32 (5H, m, C_6H_5O), 8.13 (1H, d, J = 9.4 Hz, NHCO);

Anal. $C_{18}H_{22}O_7N_2S$ (410.44)

calc'd: C 52.67; H 5.40; N 6.80; S 7.81%,

found: C 52.49; H 5.91; N 6.48; S 7.72%.

Another epimer was separated from the mother liquor by chromatography on silica-gel to give an oily compound (25.9%); R_f 0.68 in CH_2Cl_2–EtOAc (5:3); IR(film) 3395m, 1785s, 1730s, 1690s, 1645vw, 1605m, 1515m, 1440m, 1390–1370m, 1300m, 1230s, 1180m, 1130m, 1085–1065m, 980m cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 and 2.25 (6H, 2s, CMe_2), 3.71 (3H, s, OMe), 3.78 (3H, s, OMe), 4.55 (2H, s, OCH_2), 5.05 (1H, d, J = 5.3 Hz, C_2H), 5.73 (1H, dd, J = 5.3 and 9.7 Hz, C_3H), 6.99–7.33 (5H, m, C_6H_5O), 8,05 (1H, d, J = 9,7 Hz, NHCO).

*(2R,3R) 3–(3'–o–Chlorophenyl–5'–methyl–4'–isoxazolylcarboxamido)–1–(1–m–methylbenzyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphinic Acid Methyl Ester (***3e***)*

Purification of crude **3e** by silica-gel chromatography with benzene-ethylacetate (2:1) as eluant afforded predominantly the epimer with R_f 0.63. Further elution produced second epimer with R_f 0.48; IR (CH_2Cl_2) 3390m, 1780vs, 1720m, 1670m, 1600s, 1510s, 1380–1360m, 1330w, 1205s, 1125m, 1055w, 980vs, 880vw cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (3H, s, Me), 2.24 and 2.35 (6H, 2s, CMe_2), 2.77 (3H, s, Me), 3.66 (3H, s, OMe), 4.70 (1H, d, J = 5.3 Hz, C_2H), 5.06 and 5.22 (2H, 2d, J = 12.3 Hz, CH_2Ph), 5.59 (1H, dd, J = 5.3 and 9.0 Hz, C_3H), 6.55 (1H, d, J = 9.0 Hz, NHCO), 7.14–7.35 (4H, m, C_6H_4), 7.40–7.59 (4H, m, C_6H_4);

Anal. $C_{28}H_{28}N_3O_7SCl$ (586.07)

calc'd: C 57.38; H 4.82; N 7.17; S 5.47; Cl 6.05%,

found: C 57.21; H 4.75; N 7.02; S 5.17; Cl 6.20%.

*(2R,3R) 3–Phthalimido–1–(1'–p–nitrobenzyloxycarbonyl–2'–methyl–prop–2'–enyl)–4–oxoazetidine–2–sulphonic Acid Methyl Ester (***5a***)*

Compound **2a** (240 mg, 0.45 mmol) was dissolved in ethylycetate (10 cm^3), water (2 cm^3) and 80% acetic acid (0.1 cm^3) and 4% aqueous solution of $KMnO_4$ (4 cm^3) was added dropwise at 5 °C during 30–40 minutes. The color of the solution was discharged by adding 30% aqueous solution of H_2O_2 (4 cm^3) and manganese dioxide was filtered off. The ethylacetate layer was separated, washed with water, dried (Na_2SO_4) and evaporated. Purification of the residue by silica-gel chromatography in dichloromethane-ethylacetate (9:1) gave **5a** (130 mg, 53%) as a foam; R_f 0.45 in CH_2Cl_2–EtOAc (4:1); IR (KBr) 1800s, 1735vs, 1610w, 1525m, 1385s, 1350m, 1175m, 1160m, 1110m, 985m and 720m cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (3H, bs, Me), 3.86 (3H, s, OMe), 4.91 (1H, s, CHCOO), 5.13–5.20 (2H, m, $=CH_2$), 5.35 (2H, s, OCH_2), 5.49 (1H, d, J = 5.4 Hz, C_2H), 5.72 (1H, m, J = 5.4 Hz, C_3H), 5.59 and 8.25 (4H, 2d, J = 9.0 Hz, $C_6H_4NO_2$), 7.70–7.96 (4H, m, Pht);

Anal. $C_{24}H_{21}O_{10}N_3S$ (543.50)

calc'd: C 53.04; H 3.89; N 5.73; S 5.90%,

found: C 53.64; H 4.00; N 7.69; S 5.32%.

*(2R,3R) 3–Phthalimido–1–(1'–p–nitrobenzyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid Methyl Ester (**7a**)*

Compound **3a** (1230 mg, 2.33 mmol) was dissolved in ethylacetate (30 cm^3), water (12 cm^3) and 80% acetic acid (0.3 cm^3) and 4% aqueous solution of $KMnO_4$ (14 cm^3) was added dropwise at 5 °C during 80 minutes. After addition of water (30 cm^3), the color of the solution was discharged by adding 30% aqueous solution of H_2O_2 (7 cm^3) and the reaction mixture was filtered. The ethylacetate layer was separated, washed with water, dried (Na_2SO_4) and evaporated. Purification of the residue by silica-gel chromatography in dichloromethane-ethylacetate (9:1) gave **7a** (520 mg, 41%) as a foam; R_f 0.58 in CH_2Cl_2–EtOAc (9:1); IR (KBr) 1790s, 1720vs, 1605m, 1520m, 1375s, 1340m, 1285m, 1205s, 1175s, 1100m, 970s and 710s cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 and 2.38 (6H, 2s, CMe_2) 3.27 (3H, s, OMe), 5.36 (2H, s, OCH_2), 5.46 (1H, d, J = 4.5 Hz, C_2H), 5.67 (1H, d, J = 4.5 Hz, C_3H), 7.54 and 8.26 (4H, 2d, J = 9.0 Hz, $C_6H_4NO_2$), and 7.71–7.96 (4H, m, Pht);

Anal. $C_{24}H_{21}O_{10}N_3S$ (543.50)

calc'd: C 53.04; H 3.89; N 7.73; S 5.90%,

found: C 53.15; H 4.09; N 7.64; S 5.65%.

*(2R,3R) 3–Phenylacetamido–1–(1'–p–nitrobenzyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid Methyl Ester (**7b**)*

Compound **3b** (400 mg, 0.78 mmol) was dissolved in dichloromethane (15 cm^3) and formic acid (1.3 cm^3); 30% aqueous solution of H_2O_2 (4.8 cm^3) was added at 20 °C and the reaction mixture was stirred at 40 °C for 2 hours. Dichloromethane (20 cm^3) and water (10 cm^3) were added and the organic layer was separated, washed with water (10 cm^3), dried (Na_2SO_4) and evaporated in vacuo. Purification of the residue by silica-gel chromatography in dichloromethane-ethylacetate (9:1) gave **7b** (280 mg, 67.9% based on **3b**) as an unstable foam; R_f 0.62 in CH_2Cl_2–EtOAc (4:1); IR (CH_2Cl_2) 3400m, 2950m, 1785vs, 1725s, 1685s, 1510s, 1345s, 1210s, 1160s, 975s cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 and 2.26 (6H, 2s, CMe_2), 3.63 (2H, s, CH_2CO), 3.70 (3H, s, OMe), 5.22 (1H, d, J = 5.3 Hz, C_2H), 5.30 (2H, s, OCH_2), 5.93 (1H, dd, J = 5.3 and 10.1 Hz, C_3H), 6.63 (1H, d, J = 10.1 Hz, CONH), 7.31 (5H, s, C_6H_5), 7.49 and 8.22 (4H, 2d, J = 8.8 Hz, $C_6H_4NO_2$).

*(2R,3R) 3 –Phenoxyacetamido–1–(1'–methyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid Methyl Ester (**7c**)*

Formic acid (2.5 cm^3) and 30% aqueous solution of H_2O_2 (9 cm^3) were added to the solution of **3c** (820 mg, 2.0 mmol) in dichloromethane (20 cm^3). The mixture was stirred for 10 hours at 20 °C, whereafter water (20 cm^3) and dichloromethane (20 cm^3) were added. The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and concentrated in vacuo. The residual oil was purified by silica-gel chromatography in dichloromethane-ethylacetate (5:1) to give **7c** (650 mg, 73.7%) as a foam; R_f 0.73 in CH_2Cl_2–EtOAc (5:3); IR (CH_2Cl_2) 3410m, 1790m, 1380s, 1325m, 1300m, 1270vs, 1220s, 1175s, 1065m, 985s, and 880w cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 and 2.29 (6H, 2s, CMe_2), 3.80 (3H, s, OMe), 3.84 (3H, s, OMe), 4.56 (2H, s, OCH_2), 5.36 (1H, d, J = 5.3 Hz, C_2H), 6.05 (1H, dd, J = 5.3 and 10.5 Hz, C_3H), 6.89–7.42 (5H, m, C_6H_5O), 7.86 (1H, d, J = 10.5 Hz, NHCO);

Anal. $C_{18}H_{22}O_8N_2S$ (426.44)

calc'd: C 50.69; H 5.20; N 6.57; S 7.52%,

found: C 50.24; H 5.40; N 6.48; S 6.92%.

*(2R,3R) 3-Phenoxyacetamido–1–(1'–p–nitrobenzyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid Methyl Ester (**7d**)*

The sulphoxide (**1d**) (10 mmol) was treated as noted in the general procedure. The mixture of the sulphinates (**3d**) was isolated in 69.7% yield [^1H NMR of the predominant isomer ($CDCl_3$) δ 2.17 and 2.29 (6H, 2s, CMe_2), 3.66 (3H, s, OMe), 4.54 (2H, s, OCH_2), 4.80 (1H, d, J = 5.1 Hz, C_2H), 5.31 (2H, s, OCH_2Ph), 5.66 (1H, dd, J = 5.1 and 9.2 Hz, C_3H), 6.87–7.69 (5H, m, C_6H_5O),

7.97 (1H, d, J = 9.2 Hz, NHCO), 8.17–8.32 (4H, 2d, J = 8.8 Hz, $C_6H_4NO_2$)]. The epimeric mixture (3.7 g) was then dissolved in dichloromethane (60 cm^3) and 80% acetic acid (6 g) and 30% aqueous solution of H_2O_2 (25 g) was added dropwise. The reaction mixture was heated at 40 °C for 5 hours. The organic layer was separated, washed with water, saturated aqueous solution of $NaHCO_3$ and water again, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica-gel chromatography using dichloromethane-ethylacetate (5:1) as eluant and **7d** was obtained (3.0 g, 54.8%, based on **1d**); R_f 0.80 in CH_2Cl_2–EtOAc (5:3); IR (CH_2Cl_2) 3400m, 1795s, 1730s, 1705s, 1635w, 1605m, 1520s, 1495s, 1445w, 1350s, 1210s, 1575s, 985s cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 and 2.31 (6H, 2s, CMe_2), 3.81 (3H, s, OMe), 4.56 (2H, s, OCH_2) 5.29 (1H, d, J = 5.2 Hz, C_2H), 5.33 (2H, s, OCH_2Ph), 6.06 (1H, dd, J = 5.2 and 10.3 Hz, C_3H), 6.84–7.57 (5H, m, C_6H_5O), 7.81 (1H, d, J = 10.3 Hz, NHCO), 8.20–8.33 (4H, 2d, J = 8.8 Hz, $C_6H_4NO_2$);

Anal. $C_{24}H_{25}O_{10}N_3S$ (547.53)

calc'd: C 52.64; H 4.57; N 7.68; S 5.86%,

found: C 52.33; H 4.75; N 7.90; S 5.73%.

*(2R,3R) 3–[3'–(o–Chlorophenyl)–5'–methyl–isoxazole–4'–carboxamido]–1–(1'–m–methylbenzyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid Methyl Ester (**7e**)*

To a solution of **3e** (240 mg, 0.4 mmol) in ethylacetate (10 cm^3), glacial acetic acid (0.05 cm^3) was added and cooled to 5 °C. $KMnO_4$ (98 mg, 0.62 mmol) in water (2.5 cm^3) was added dropwise over 30 minutes and the mixture was stirred at 5 °C for a further 30 minutes. Water (10 cm^3) and 30% aqueous solution of H_2O_2 (0.1 cm^3) were added; the organic layer was separated, dried ($MgSO_4$) and evaporated. The residual oil was chromatographed on silica-gel with benzene-ethylacetate (2:1) as eluant to give **7e** (84 mg, 34.3%); R_f 0.76 in C_6H_6–EtOAc (2:1); IR (CH_2Cl_2) 3390w, 1785vs, 1720vs, 1670vs, 1600s, 1490s, 1360vs, 975s cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (3H, s, Me), 2.24 and 2.35 (6H, 2s, CMe_2), 2.77 (3H, s, Me), 3.61 (3H, s, OMe), 5.16 (1H, d, J = 5.3 Hz, C_2H), 5.04 and 5.28 (2H, 2d, J = 12.1 Hz, CH_2Ph), 5.93 (1H, 2d, J = 5.3 and 10.3 Hz, C_3H), 6.26 (1H, d, J = 10.3 Hz, NHCO), 7.16–7.41 (4H, m, C_6H_4), 7.44–7.55 (4H, m, C_6H_4).

*(2R,3S) 3–Phthalimido–1–(1'–p–nitrobenzyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid Methyl Ester (**8a**)*

Sulphoxide (**4a**) (0.64 mmol) was treated with NCS and methanol as noted in the general procedure and the crude material was purified by silica-gel chromatography with dichloromethane-ethylacetate (9:1) as eluant. The mixture of epimers (**6a**) was separated (220 mg) [^1H NMR (XL–GEM 300 VARIAN) for the predominant epimer ^1H NMR ($CDCl_3$) δ 2.18 and 2.31 (6H, 2s, CMe_2), 3.79 (3H, s, OMe), 5.13 (1H, d, J = 2.8 Hz, C_2H), 5.35 and 5.41 (2H, 2d, J = 13.5 Hz, OCH_2), 5.55 (1H, d, J = 2.8 Hz, C_3H), 7.63 and 8.23 (4H, 2d, J = 8.6 Hz, $C_6H_4NO_2$), 7.78–7.91 (4H, m, Pht], dissolved in ethylacetate (10 cm^3) and 80% acetic acid (2 cm^3), and treated with 4% aqueous solution of $KMnO_4$ (2 cm^3) at 5 °C for 30 minutes. The color of the solution was discharged by adding 30% aqueous solution of H_2O_2. The ethylacetate extract was separated, washed with water, dried ($NaSO_4$), and evaporated. The residue was purified by silica-gel chromatography using CH_2Cl_2–EtOAc (9:1) as eluant and compound **8a** was separated (150 mg, 43% based on **4a**) as a foam; R_f 0.69 in CH_2Cl_2–EtOAc (9:1); ^1H NMR ($CDCl_3$) δ 2.13 and 2.33 (6H, 2s, CMe_2), 3.89 (3H, s, OMe), 5.40 (2H, s, OCH_2), 5.60 (1H, d, J = 2.7 Hz, C_2H), 5.78 (1H, d, J = 2.7 Hz, C_3H), 7.62 and 8.21 (4H, 2d, J = 9.0 Hz, $C_6H_4NO_2$), 7.73–7.96 (4H, m, Pht).

*(2R,3R) 3–Phenylacetamido–4–oxoazetidine–2–sulphonic Acid Methyl Ester (**9a**)*

a) Sulphinate (**3b**) (380 mg, 0.74 mmol) was dissolved in ethylacetate (6 cm^3) and 80% acetic acid (6 cm^3) and 4% aqueous solution of $KMnO_4$ (8.6 cm^3) were added dropwise at 0 °C during 1 hour. After addition of water (3.5 cm^3), the color of the solution was discharged by adding 30% aqueous solution of H_2O_2 (0.2 cm^3). Ethylacetate (20 cm^3) was added, the organic layer was separated and washed with water (2 × 10 cm^3). Water layer was washed with ethylacetate (2 × 10 cm^3). The combined organic layers were dried ($NaSO_4$) and evaporated. Crystallization of the

residue from ethylacetate gave **9a** (66 mg, 29.7%); R_f 0.74 in *n*–BuOH–EtOAc–H_2O (4:2:1); m.p. 141–143 °C; IR (KBr) 3315s, 3290s, 1780vs, 1655vs, 1515s, 1350m, 1155m, 980m, 710s cm^{-1}; ^1H NMR (DMSO–d_6) δ 3.46 and 3.54 (2H, 2s, CH_2CO), 3.86 and 3.98 (3H, 2s, OMe), 4.25 and 5.29 (1H, 2d, J = 5.3 and 5.0 Hz, C_2H), 5.26 and 5.62 (1H, 2dd, J = 5.3, 5.0 and 9.9, 9.3 Hz, C_3H), 7.25 (5H, s, C_6H_5), 7.78 and 8.72 (1H, 2d, J = 9.9, 9.3 Hz, NHCO), 8.63 and 9.39 (1H, 2bs, N_1H)

b) Sulphonate (**7b**) was treated with $KMnO_4$ as noted above. Compound **9a** was isolated in a 33.3% yield.

*(2R,3R) 3–Phenylacetamido–4–oxoazetidine–2–sulphonic Acid Tetrabutyl–ammonium Salt (***10a***)*

Compound **9a** (150 mg, 0.50 mmol) was added to the solution of triethylamine (146 mg, 1.44 mmol) in dichloromethane (5 cm^3) and stirred at 20 °C for 1 hour. The solution was evaporated and the residue dissolved in water (15 cm^3) and desalted on Dowex-50W(H^+). To the resulting acidic water solution, the solution of tetrabutylammoniumhydrogen-sulphate (170 mg, 0.50 mmol) in dichloromethane (30 cm^3) was added and stirred at 20 °C for 3 hours. The organic layer was separated and the water layer was extracted with dichloromethane (2 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the product as an oil which was purified on silica-gel; eluting with dichloromethane-methanol (12:1) yielded **10a** (134 mg, 52%); R_f 0.58 in CH_2Cl_2–MeOH (4:1); IR (KBr) 3325w, 2960s, 2880m, 1770vs, 1680s, 1520m, 1225s, 1200s cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03–1.54 (28H, m, $4CH_2CH_2CH_3$), 3.12–3.30 (8H, m, $4NCH_2$), 3.59 (2H, s, CH_2CO), 4.58 (1H, d, J = 5.3 Hz, C_2H), 5.63 (1H, dd, J = 5.3 and 10.5 Hz, C_3H), 7.30 (5H, s, C_6H_5), 7.76 (1H, d, J = 10.0 Hz, CONH), 8.20 (1H, bs, N_1H).

*(2R,3R) 3–Phenoxyacetamido–4–oxoazetidine–2–sulphonic Acid Tetrabutylammonium Salt (***10b***)*

To the solution of compound **3c** (410 mg, 1 mmol) in ethylacetate (10 cm^3) and 80% acetic acid (4 cm^3), 4% aqueous solution of $KMnO_4$ (15 cm^3, 0.6 g, 3.8 mmol) was added dropwise at 5 °C during 60 minutes. The reaction mixture was stirred for another 60 minutes after which water (2 cm^3) and 30% aqueous solution of H_2O_2 (0.5 cm^3) were added until the color of the solution was discharged. The organic layer was separated, dried (Na_2SO_4) and evaporated. The residue was treated with methanol (3 cm^3) and the solid separated, dissolved in water (10 cm^3) and treated with a solution of tetrabutylammoniumhydrogensulphate (340 mg, 1 mmol) in dichloromethane (10 cm^3). The organic layer was separated, washed with water (1 cm^3), dried (Na_2SO_4) and concentrated to yield a foam (0.17 g, 31.4%); R_f 0.80 in CH_2Cl_2–MeOH (4:1); IR (oil) 3350–3110m, 3000–2850s, 1775s, 1680s, 1530m, 1495s, 1460m, 1380m, 1225vs, 1185s, 1060s, 1010m cm^{-1}; ^1H NMR (DMSO–d_6) δ 1.00–1.84 (28H, m, $4CH_2CH_2CH_3$), 3.20–3.50 (8H, m, $4NCH_2$), 4.46 (1H, d, J = 5.3 Hz, C_2H), 4.62 (2H, s, OCH_2), 5.47 (1H, dd, J = 5.3 and 10.2 Hz, C_3H), 7.02–7.53 (5H, m, C_6H_5O), 8.70 (1H, d, J = 10.2 Hz, NHCO), 8.95 (1H, s, N_1H);

Anal. $C_{27}H_{47}N_2O_6S$ (541.74)

calc'd: C 59.84; H 8.74; N 7.76; S 5.92%,

found: C 59.81; H 9.98; N 7.81; S 5.06%.

*(2R,3S) 3–Phthalimido–1–(1'–p–nitrobenzyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid Tetrabutylammonium Salt (***11a***)*

Compound **8a** (300 mg) was standing at ambient temperature for one week and was chromatographed on silica-gel in dichloromethane-methanol (9:1). A compound with R_f 0.23 was separated, dissolved in methanol (1.5 cm^3) and H_2O (5 cm^3), desalted on Dowex-50W(H^+) and lyophilized. The residue (130 mg) was dissolved in water (10 cm^3) and stirred at 20 °C for 60 minutes with tetrabutylammoniumhydrogensulphate (75 mg) in dichloromethane (10 cm^3). The organic layer was separated; the water layer was washed with dichloromethane (4 × 5 cm^3); the organic extract was dried (Na_2SO_4) and evaporated to yield **11a** (150 mg, foam); IR (KBr) 3700–3300bm, 2970s, 2880m, 1775s, 1730vs, 1615w, 1525m, 1470m, 1400s, 1350m, 1225bs, 1105m, 1085m, 1035m cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91–2.03 (28H, m, $4CH_2CH_2CH_3$), 2.18 and 2.30 (6H, 2s,

CMe_2), 3.27–3.39 (8H, m, $4NCH_2$), 5.30 (1H, d, J = 2.6 Hz, C_2H), 5.38 (2H, bs, OCH_2), 5.62 (1H, d, J = 2.6 Hz, C_3H), 7.30–7.85 (4H, m, Pht), 7.32 and 8.18 (4H, 2d, J = 8.8 Hz, $C_6H_4NO_2$).

*(2R,3R) 3–Phthalimido–1–(1'–p–nitrobenzyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid (***12a***)*

a) Compound **7a** (520 mg, 0.96 mmol) was dissolved in THF (10 cm^3). $NaHCO_3$ (75 mg, 0.89 mmol) in H_2O (1 cm^3) was added and the reaction solution was stirred at 65 °C for 90 minutes. The reaction solution was evaporated in vacuo. The residue was chromatographed on silica-gel in dichloromethane-methanol (9:1) and a compound with R_f 0.20 was separated, dissolved in water (4 cm^3) and desalted on Dowex-50W(H^+). The strongly acidic water solution was lyophilized to yield **12a** (260 mg) as a foam; R_f 0.50 in EtOAc–HAc–H_2O (10:2:1); water (K.F.) 8.2%; IR (KBr) 3700–3200bm, 1790s, 1770s, 1725vs, 1520m, 1395s, 1350m, 1215m, 1040w cm^{-1}; ^1H NMR (DMSO–d_6) δ 2.33 (6H, s, CMe_2), 4.81 (1H, d, J = 5.4 Hz, C_2H), 4.97 (6H, bs, SO_2OH and HOH), 5.44 (1H, d, J = 5.4 Hz, C_3H), 5.50 (2H, s, OCH_2), 7.81 and 8.35 (4H, 2d, J = 9.0 Hz, $C_6H_4NO_2$), and 7.97 (4H, s, Pht).

b) Compound **5a** (480 mg, 0.88 mmol) was dissolved in dichloromethane (10 cm^3) and triethylamine (200 mg, 1.98 mmol) was added. The solution was stirred at 5 °C for 4 hours and evaporated in vacuo. The residue was dissolved in water (5 cm^3) and desalted on Dowex–50W(H^+). The acidic water eluant was lyophilized to yield **12a** (360 mg).

*(2R,3R) 3–Phenylacetamido–1–(1'–p–nitrobenzyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid (***12b***)*

a) Compound **3b** (400 mg, 0.78 mmol) was dissolved in dichloromethane (15 cm^3) and formic acid (1.3 cm^3) and then 30% aqueous solution of H_2O_2 (4.8 cm^3) was added. The reaction mixture was stirred at 40 °C for 2 hours. Dichloromethane (20 cm^3) and water (10 cm^3) were added and organic layer was separated, washed with water (10 cm^3), dried (Na_2SO_4) and evaporated. The residue was dissolved in ethylacetate (10 cm^3), triethylamine (100 mg, 1 mmol) was added and the solution was stirred at 20 °C for 1.5 hours. After evaporation of the solvent, the reaction mixture was dissolved in water and desalted on Dowex–50W(H^+). The strongly acidic water solution was lyophilized to yield **12b** (213 mg, 52.6% based on **3b**) as a white powder; m.p. 164–166 °C; R_f 0.58 in CH_2Cl_2–MeOH (4:1); IR (KBr) 3700–3150bm, 3360s, 1765s, 1755s, 1710m, 1680m, 1660m, 1520s, 1350s, 1220vs, 1040s cm^{-1}; ^1H NMR (DMSO–d_6) δ 2.04 and 2.18 (6H, 2s, CMe_2), 3.52 (2H, s, CH_2CO), 4.59 (1H, d, J = 5.4 Hz, C_2H), 5.33 (2H, s, OCH_2), 5.37 (1H, dd, J = 5.4 and 10.1 Hz, C_3H), 6.44 (1H, bs, SO_2OH), 7.27 (5H, s, C_6H_5), 7.67 and 8.23 (4H, 2d, J = 8.6 Hz, $C_6H_4NO_2$), 8.00 (1H, d, J = 10.1 Hz, NHCO).

b) Compound **7b** (240 mg, 0.45 mmol) was dissolved in dichloromethane (5 cm^3) and triethylamine (68 mg, 0.67 mmol) was added. The solution was stirred at 20 °C for 1 hour and evaporated. The residue was dissolved in water (10 cm^3) and desalted on Dowex-50W(H^+). The acidic water solution was lyophilized to yield **12b** (180 mg, 77.8% based on **7b**).

*(2R,3R) 3–Phenoxyacetamido–1–(1'–methyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid (***12c***)*

After separation of compound **10b**, the mother liquor was concentrated under reduced pressure. The residue was treated with methanol (5 cm^3) and acetone (30 cm^3) and stirred for 1 hour. The resulting precipitate was collected, dissolved in water (10 cm^3) and desalted by passing through Dowex–50W(H^+). The strongly acidic water solution was lyophilized to yield **12c** (1.32 g, 32%) as a foam; R_f 0.70 in n–BuOH–HAc–H_2O (4:1:1); IR (KBr) 3350m, 1780s, 1705s, 1600w, 1540m, 1500m, 1440m, 1390w, 1230s, 1035c cm^{-1}; ^1H NMR (DMSO–d_6) δ 2.11 and 2.28 (6H, 2s, CMe_2), 3.82 (3H, s, OMe), 4.67 (2H, s, OCH_2), 4.70 (1H, d, J = 5.6 Hz, C_4H). 5.37 (1H, dd, J = 5.6 and 8.8 Hz, C_3H), 7.02–7.52 (5H, m, C_6H_5O), and 8.83 (1H, d, J = 8.8 Hz, NHCO).

(2R,3R) 3 -[3'(o-Chlorophenyl)-5'-methyl-isoxazole-4'-carboxamido]-1-(1'-m-methylbenzyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphonic Acid (**12d**)

Compound **3e** (700 mg, 1.2 mmol) was dissolved in dry chlorophorm (10 cm^3) and *m*-chloroperbenzoic acid (415 mg, 1.2 mmol) in chlorophorm (4 cm^3) was added. The mixture was stirred at 20 °C for 8 hours, extracted with aqueous sodium hydrogen carbonate and water. The organic layer was dried ($MgSO_4$) and evaporated to yield an oil which was chromatographed on silica-gel using dichloromethane-methanol (4:1) affording **12d** (446 mg, 63.3%); m.p. 178–182 °C; R_f 0.42 in CH_2Cl_2–MeOH(4:1); IR (KBr) 3700–3150bs, 1785s, 1660s, 1610m, 1530m, 1400w, 1295w, 1220vs, 1040m, 770m cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 and 2.04 (6H, 2s, CMe_2), 2.29 and 2.60 (6H, 2s, 2Me), 2.99–3.43 (bs, SO_2OH and HOH), 4.96 (1H, d, J = 4.5 Hz, C_2H), 5.06 (2H, bs, CH_2Ph), 5.49 (1H, 2d, J = 4.5 and 8.6 Hz, C_3H), 6.81 (1H, d, J = 8.6 Hz, CONH), 6.91–7.55 (8H, m, $2C_6H_4$).

(2R,3R) 3-Phenylacetamido-4-oxoazetidine-1,2-disulphonic Acid Ditetrabutylammonium Salt (***13a***)

To pyridine-sulphurtrioxide complex (220 mg, 1.4 mmol), in a vessel compound **9a** (200 mg, 0.70 mmol), and water (15 cm^3) were added. The reaction mixture was then stirred at 50 °C for 30 minutes. The reaction solution was extracted with dichloromethane (2 × 10 cm^3). To the resulting aqueous layer, the solution of tetrabutylammoniumhydrogensulphate (460 mg, 1.40 mmol) in dichloromethane (30 cm^3) was then added and stirred at 20 °C for 2 hours. The organic layer was separated and the water layer was extracted with dichloromethane (3 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated. The crude product was chromatographed on a silica-gel column eluting with dichloromethane-methanol (12:1) to yield **13a** (140 mg, 30.6%); R_f 0.56 in CH_2Cl_2–MeOH (4:1); IR (CH_2Cl_2) 3400w, 2920s, 2850s, 1775s, 1675s, 1510m, 1220s, 885s cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.65 (56H, m, $8CH_2CH_2CH_3$), 3.13–3.23 (16H, m, $8NCH_2$), 3.56 (2H, s, CH_2CO), 4.54 (1H, d, J = 5.0 Hz, C_2H), 5.60 (1H, dd, J = 5.0 and 10.3 Hz, C_3H), 7.27 (5H, s, C_6H_5), 7.73 (1H, d, J = 10.3, CONH);

Anal. $C_{43}H_{82}O_8N_4S_2$ (847.29)

calc'd: C 60.96; H 9.75; N 6.61; S 7.57%,

found: C 60.90; H 10.35; N 6.63; S 6.82%.

(2R,3R) 3-Phthalimido-1-(1'-p-nitrobenzyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphonic Acid Tetrabutylammonium Salt (**14a**)

Compound **12a** (240 mg) was dissolved in water (10 cm^3) and tetrabutylammonium hydrogensulphate (150 mg, 0.44 mmol) in dichloromethane (10 cm^3) was added and the mixture was stirred at 20°C for 60 minutes. The organic layer was separated; the water layer was washed with dichloromethane (4 × 5 cm^3); the organic extract was dried (Na_2SO_4) and evaporated to yield **14a** (330 mg) as a foam; IR (KBr) 3700–3200bm, 2970s, 2880m, 1790vs, 1770vs, 1730vs, 1635w, 1615w, 1525m, 1395s, 1350s, 1295m, 1240–1200bs, 1115m, 1035m cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98–1.39 (28H, m, $4CH_2CH_2CH_3$) 2.30 and 2.44 (6H, 2s, CMe_2), 3.02–3.12 (8H, m, $4NCH_2$), 5.02 (1H, d, J = 5.4 Hz, C_2H), 5.31 (2H, bs, OCH_2), 5.40 (1H, d, J = 5.4 Hz, C_3H), 7.52–7.78 (4H, m, Pht), 7.57 and 8.20 (4H, 2d, J = 8.0 Hz, $C_6H_4NO_2$);

Anal. $C_{39}H_{54}N_4O_{10}S$ (770.94)

calc'd: C 60.76; H 7.06; N 7.25; S 4.16%,

found: C 60.65; H 7.20; N 7.48; S 4.51%.

(2R,3R) 3-Phenylacetamido-1-(1'-p-nitrobenzyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphonic Acid Tetrabutylammonium Salt (**14b**)

Compound **12b** (180 mg, 0.35 mmol) and tetrabutylammonium hydrogensulphate (120 mg, 0.35 mmol) were dissolved in a mixture of dichloromethane (30 cm^3) and water (20 cm^3) and

stirred at 20 °C for 3 hours. The organic layer was separated and the water layer was extracted with dichloromethane (3 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated to give **14b** (195 mg, 74.3% based on **12b**); R_f 0.77 in CH_2Cl_2–MeOH (4:1); IR (KBr) 3350w, 2960s, 2880m, 1770vs, 1725m, 1680m, 1520s, 1350s, 1235s, 1035s cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98–1.60 (28H, m, $4CH_2CH_2CH_3$), 2.19 and 2.25 (6H, 2s, CMe_2), 3.06–3.24 (8H, m, $4NCH_2$), 3.56 (2H, s, CH_2CO), 4.86 (1H, d, J = 5.3 Hz, C_2H), 5.25 (2H, s, OCH_2) 5.63 (1H, dd, J = 5.6 and 9.7 Hz, C_3H), 7.26 (5H, s, C_6H_5), 7.51 and 8.19 (4H, 2d, J = 8.6 Hz, $C_6H_4NO_2$), 7.91 (1H, d, J = 9.7 Hz, NHCO);0

Anal. $C_{39}H_{58}O_9N_4S$ (758.99)

calc'd: C 61.72; H 7.70; N 7.38; S 4.22%,

found: C 61.60; H7.97; N 7.16; S 4.06%.

*(2R,3R) 3–Phenoxyacetamido–1–(1'–methyloxycarbonyl–2'–methyl–prop–1'–enyl)–4–oxoazetidine–2–sulphonic Acid Tetrabutylammonium Salt (***14c***)*

In the solution of compound **12c** (1.6 g, 3.9 mmol) in water (10 cm^3), a solution of tetrabutylammoniumhydrogensulphate (1.3 g, 3.8 mmol) in dichloromethane (10 cm^3) was added. The mixture was stirred for 1 hour, whereafter the organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated. The residue was purified on silica-gel chromatography using dichloromethane-methanol (4:1) as eluant and compound **14c** was obtained as an oily solid (1.97 g, 74.6%); IR (film) 3330m, 2970–2880s, 1770s, 1725s, 1685s, 1635w, 1600m, 1530m, 1495s, 1440m, 1390m, 1280–1180s, 1035s cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89–1.90 (28H, m, $4CH_2CH_2CH_3$), 2.19 and 2.25 (6H, 2s, CMe_2), 3.10–3.35 (8H, m, $4NCH_2$), 3.72 (3H, s, OMe), 4.91 (1H, d, J = 5.6 Hz, C_2H), 5.76 (1H, dd, J = 5.6 and 10.3 Hz, C_3H), 6.88–7.36 (5H, m, C_6H_5O), 8.83 (1H, d, J = 10.3 Hz, CONH).

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REFERENCES

1. Presented in part at *XI Meeting of Chemists of Croatia, Zagreb,* 1991.
2. D. Hoppe, G. M. Sheldrick, E. Egert, and P. Karas, *Angew. Chem.* **95** (1983) 912.
3. J. J. Herak, M. Kovačević., and B. Gašpert, *Croat. Chem. Acta.* **62** (1989) 521.
4. S. Kukolja, U.S. Patent, 4.052387, 1977.
5. R. D. G. Cooper, P. V. DeMarco, D. O. Spry, *J. Amer. Chem. Soc.* **91** (1969) 1528.
6. D. H. R. Barton, F. Comer, D. G. T. Greig, and P. G. Sammes, *J. Chem. Soc.* (1971) 3540.
7. R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.* **91** (1969) 1408.
8. R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavaguino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.* **91** (1969) 1401.
9. E. G. Brain, J. A. Elington, C. H. J. Nayler, J. M. Pearson, and J. R. Southgate, *J. Chem. Soc. Perkin I,* (1976) 447.
10. H. Maruyama and T. Hiraoka, *J. Org. Chem.* **51** (1986) 399.
11. B. A. Frenz *The Enraf-Nonius CAD4-SDP,* in *Computing in Crystallography*, Edited by H. Schenk, R. Olthof-Hezenkamp, H. Van Koningveld, and G. C. Bassi, University Press, Delft, 1978, p. 64.
12. G. M. Sheldrick, *SHELX86, Program for structure determination,* University of Cambridge, Cambridge, 1983.
13. G. M. Sheldrick, *SHELX77,* in *Crystallographic Computing 3,* eds. G. M. Sheldrick, C. Kruger, and R. Goddard, Oxford University Press, Oxford, 1985.
14. A. L. Spek, *The EUCLID Package,* in *Computational Crystallography*, Edited by D. Sayre, Clarendon Press, Oxford, 1982, p. 528.

15. C. K. Johnson, *ORTEP II. Report ORNL-5138,* Oak Ridge National Laboratory, Tennessee, USA, 1976.
16. Cambridge Structural Database, version 4 (1991) Cambridge, Crystallographic Data Centre, University Chemical Laboratory, Cambridge, U.K.
17. R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.* **92** (1970) 5489.
18. W. R. Busing, and H. A. Levy, *Acta Cryst.* **17** (1964) 142.
19. J. P. Glusker, D. E. Zacharias, and H. L. Carell, *J. Chem. Soc. Perkin Trans. 2* (1975) 68.
20. R. Taylor and O. Kennard, *J. Amer. Chem. Soc.* **104** (1982) 5063.
21. Z. Berkovich-Yellin and L. Leiserowitz, *J. Amer. Chem. Soc.* **104** (1982) 4052.
22. Z. Berkowich-Yellin and L. Leiserowitz, *Acta Cryst.* **B40** (1984) 159.

SAŽETAK

Derivati *cis*- i *trans*-4-oksoazetidin-2-sulfonskih kiselina. Priprava i određivanje strukture difrakcijom x-zraka

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Pripravljeni su derivati 4-oksoazetidin-2-sulfonskih kiselina polazeći od penicilin-sulfoksida (**1**) i (**4**). Oksidacijom 4-oksoazetidin-2-sulfinata (**2**), (**3**) i (**6**) dobiveni su sulfonati (**5**), (**7**), (**8**) i (**9**). Općenito, 4-oksoazetidin-2-sulfonati su reaktivni spojevi i lako se hidroliziraju u sulfonske kiseline. Izolirane su 4-oksoazetidin-2-sulfonske kiseline (**12**) i soli (**10**), (**11**) i (**14**). Sulfonat (**9a**) pokazuje u otopini prisutnost dvaju konformacijskih izomera što je utvrđeno snimanjem ^{1}H NMR spektara pri različitim temperaturama. Struktura sulfonata (**9a**) određena je i rendgenskom analizom pri čemu nije uočena prisutnost intramolekularnih vodikovih veza.