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New Functionalized Monocyclic *beta*-Lactams Suitable Precursors for Anhydro 2-Azacephams[1]

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Abstract. The anhydro 2-azacephams **9** were prepared starting from penicillanate sulphoxides **1** *via* 4-aminosulphinyl-2-oxoazetidines **3** and **4** and 4-aminosulphonyl-2-oxoazetidines **6** and **8** New functionalized monocyclic *beta*-lactams **5** and **7** were also produced as precursors for other *beta*-lactam species

INTRODUCTION

Previously, the 2-oxoazetidine-4-sulphinic acid amides were declared as suitable intermediates for the preparation of some cephalosporin species It was noted that the 2-oxoazetidine-4-sulphinyl chlorides **2** (R=V, R^1=H, R^3=pNB) in reaction with aniline produced aminosulphinyl derivative **3** (R=V, R^1=H, R^2=C_6H_5, R^3=pNB) which was used for conversion to 3-*exo*-methylene cepham sulphoxide [2]

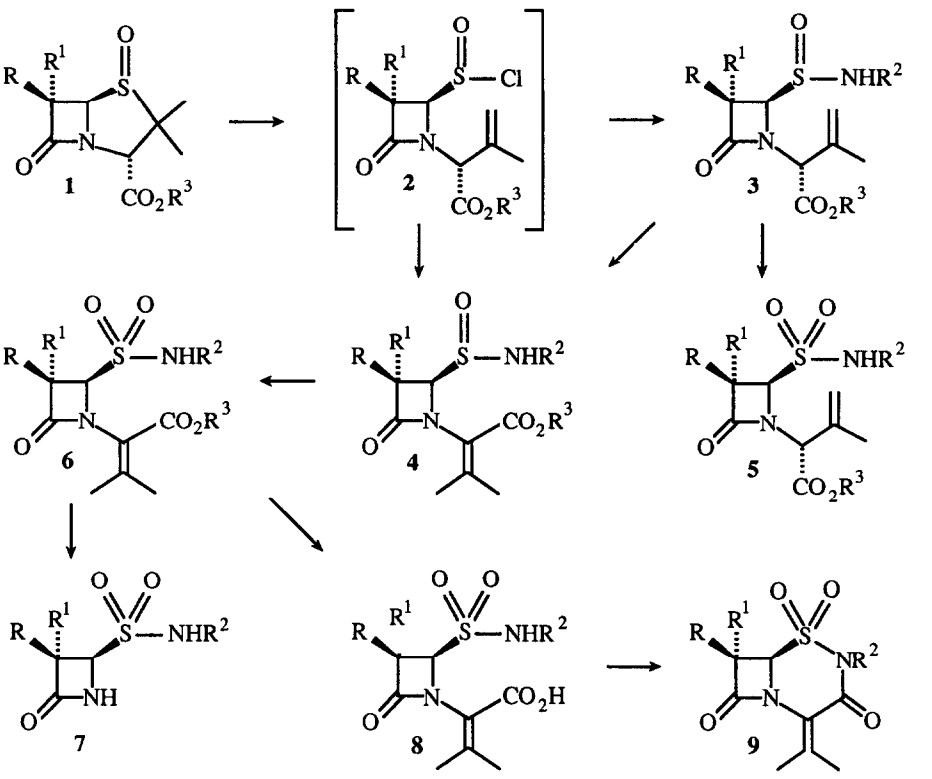
Now, we have found that the 2-oxoazetidine-4-sulphinamides **3** are also useful intermediates for the synthesis of some novel monocyclic and fused *beta*-lactams In this paper we report the preparation of the 2-oxoazetidine-4-sulphinamides and sulphonamides as well as their intramolecular cyclization into the new anhydro 2-azacephams

RESULTS AND DISCUSSION

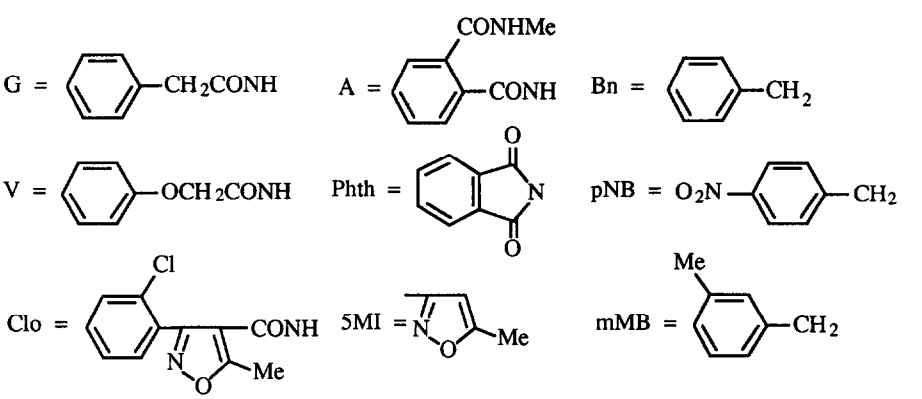
Starting from the penam sulphoxides **1** we have generated 2-oxoazetidine-4-sulphinyl chlorides **2** by the well-established methodology[3] and used them *in situ* for the preparation of the 2-oxoazetidine-4-sulphinamides **3** (Scheme 1) Thus in the reaction of **2** (R=V, R^1=H, R^3=Me and pNB) with 3-amino-5-methylisoxazole (3A5MI) the mixture of epimers **3** (R=V, R^1=H, R^2=5MI, R^3=Me and pNB), with different configuration at sulphur was formed

The authors dedicate this paper to Dr B Gašpert for his 65th birthday

Scheme 1



R = H, Br, G, V, A, Clo, Phth
R^1= H, Br,
R^2= H, Me, Bn, 5MI,
R^3= Me, Bn, pNB, mMB



Both epimers **3**, with methyl as well as with p-nitrobenzyl ester group, were partially separated from the mixture by crystallization Furthermore, in the case of the sulphinamides **3** with G, Clo and Phth side chains at C-3 only one epimer was isolated from the epimeric mixtures

The compounds **3** were isomerized into corresponding structural isomers **4** by the action of triethylamine in dichloromethane Moreover, the isomerization of the compounds **3** into **4** was detected also in part during the aminolysis of the sulphinyl chlorides **2** with 3A5MI, while in reaction of **2** with methylamine the mixture of epimers **4** was produced predominantly Furthermore, in the course of the reaction with methylamine we have found the specific amine attack at the phthalimido group Thus, in the reaction of the sulphinyl chlorides **2** (R=Phth, R^1=H, R^3=pNB) with methylamine, besides the aminolysis and the double bond isomerization, the regioselective nucleophilic attack at the phthalimido carbonyl was performed yielding the mixture of epimers **4** (R=A, R^1=H, R^2=Me, R^3=pNB) Therefore, the transformation of the phthalimido group into the secondary-amido moiety, which may be hydrolyzed by the well-known methods,[4,5] performs a new possibility for the removal of the phthaloyl protective group in the presence of a generally highly reactive azetidinone carbonyl

The sulphinamides **3** were oxidized into the 2-oxoazetidine-4-sulphonamides **5** The oxidation with hydrogen peroxide and formic acid in dichloromethane was performed selectively at sulphur giving sulphonamide **5** in high yield Under the same reaction conditions the sulphinamides **4** were oxidized into **6** On the other hand, by the oxidation of the compound **4** with potassium permanganate in the presence of acetic acid besides sulphonamide **6** the derivative **7** was partially prepared The latter compound without butenoate group at the azetidinone nitrogen was formed by treating the sulphonamide **6** with potassium permanganate under the same reaction conditions [6]

The 2-oxoazetidine-4-sulphonamides **6** were transformed into derivatives **8** with deprotected carboxylic group Thus, the hydrogenolysis of the benzyl and p-nitrobenzyl ester of the compounds **6** with palladium on charcoal gave the acid **8** in moderate yield Cleavage of the m-methylbenzyl ester under similar conditions was performed and found to be possible but not a good method for producing the acid **8** with cloxacillin side chain at C-3 position Attempts to cleave the methyl ester of the compound **6** (R=V, R^1=H, R^2=Bn, R^3=Me) by using method with Me_3SiI failed giving rise to the degradation of the azetidinone ring The acid **8** was isolated in high yield after cleavage of the benzyl ester group of the compound **6** (R=Br, R^1=Br, R^2=Bn, R^3=Bn) by using method with $AlCl_3$ [7]

All the prepared sulphonamides **5**, **6**, **7** and **8** with V, G, A, Phth and Clo side chain at C-3 possess the values of coupling constants for the vicinal 4-H and 3-H protons between 4 5 and 5 3 Hz (Table 1) These values supported retention of the *cis* relationship between the 4-H and 3-H on the *beta*-lactam ring as in starting penicillanate sulphoxides **1** Both, *cis* (J 4 5 and 4 7 Hz) and *trans* (J 1 8 and 2 1 Hz), coupling constants for the 4-H and 3-H are present in ^{1}H NMR spectra of the compounds **7** (R=H, R^1=H, R^2=Bn) and **8** (R=H, R^1=H, R^2=5MI) with two geminal 3α-H and 3β-H

Finally, we have investigated the behaviour of some reactive carboxylic acid derivatives **8** and found them to be suitable precursors for the formation of the new 2-azacephams species **9** (Table 2) Thus, stirring the compounds **8** in dichloromethane with DCC provided the anhydro 2-azacephams **9** with G and Phth side chain The intramolecular cyclization proceeded also in good yield (67-87 %) when the carboxylic group of compound **8** (R=H, R^1=H, R^2=Bn) was transformed into the acid chloride, which in the presence of triethylamine yielded **9** without side chain at C-7 Furthermore, the compounds **8** with A, V, Clo side chain at

Table 1. ^{1}H NMR Data of the Compounds **5**, **6**, **7** and **8**

Compound					^{1}H NMR (δ, ppm)	
No	R	R^1	R^2	R^3	*cis* 4-H / 3-H	Rest of the signals
5	V	H	5MI	Me	5 46 (1H, d, **J 5.0**Hz,4-H) 6 01 (1H, dd, **J 5.0** and 10 3 Hz, 3-H)	(90MHz, $CDCl_3$) δ 1 91 (3H, s, =CMe), 2 18 (3H, s, OCMe), 3 79 (3H, s, OMe), 4 44 (2H, bs, CH_2CO), 4 90 (1H, s, NCHCO), 5 00 and 5 17 (2H, 2bs, $=CH_2$), 6 82-7 41 (5H, m, C_6H_5O), 7 75 (1H, d, J 10 3Hz, CONH)
5	Phth	H	5MI	pNB	5 57 (1H, d, **J 4.5**Hz, 4-H), 5 76 (1H, d, **J 4.5**Hz, 3-H)	(300MHz, $CDCl_3$) δ 2 02 (3H, s =CMe), 2 22 (3H, s, OCMe), 4 98 (1H, s, NCHCO), 5 09-5 35 (4H, m, $=CH_2$, OCH_2), 5 97 (1H, s, =CH), 7 51 and 8 15 (4H, 2d, J 8 4Hz, $C_6H_4NO_2$), 7 69-8 05 (4H, m, Phth)
5	Clo	H	5MI	mMB	5 44 (1H, d, **J 5.0**Hz, 4-H), 5 95 (1H, dd, **J 5.0** and 9 6Hz, 3-H)	(300MHz, $CDCl_3$) δ 1 79 (3H, s, =CMe), 2 31 (3H, s, PhMe), 2 35 and 2 72 (6H, bs, 2 OCMe), 4 85 (1H, s, NCHCO), 4 90 and 5 10 (2H, 2s, $=CH_2$), 5 08 and 5 13 (2H, ABq, J 12.0Hz, OCH_2,), , 6 04 (1H, s, =CH), 6 37 (1H, d, J 9 6Hz, CONH), 7 01-7 26 and 7 41-7 55 (8H, 2m, $2C_6H_4$)
6	V	H	5MI	Me	5 54 (1H, d, **J 5.2**Hz, 4-H), 6 06 (1H, dd, **J 5.2** and 10 4 Hz, 3-H)	(300MHz, $CDCl_3$) δ 2 09 and 2 22 (6H, 2s, CMe_2), 2 26 (3H, s, OCMe), 3 71(3H, s, OMe), 4 46 and 4 57 (2H, ABq, J 15 0Hz, CH_2CO), 4 57 (1H, s, SNH), 6 07 (1H, s, =CH), 6 95-7 37 (5H, m, C_6H_5O), 7 76 (1H, d, J 10 4Hz, CONH)
6	V	H	5MI	pNB	5 59 (1H, d, **J 5.2**Hz, 4-H), 6 03 (1H, dd, **J 5.2** and 10 5Hz, 3-H)	(300MHz, $CDCl_3$) δ 2 11 and 2 20 (6H, 2s, CMe_2), 2 24 (3H, s, OCMe), 4 35 and 4 50 (2H, ABq, J 15 1Hz, CH_2CO), 5 26 (2H, s, OCH_2), 6 00 (1H, s, =CH), 6 90-7 35 (5H, m, C_6H_5O), 7 52 and 8 22 (4H, 2d, J 8 8Hz, $C_6H_4NO_2$), 7 77 (1H, d, J 10 5Hz, CONH)
6	V	H	Bn	Me	4 80 (1H, d, **J 5.3**Hz, 4-H), 5 83 (1H, dd, **J 5.3** and 10 8Hz, 3-H)	(90MHz, $CDCl_3$) δ 2 09 and 2 25 (6H, 2s, CMe_2), 3 69 (3H, s, OMe), 4 09-4 41 (5H, m, CH_2CO, $SNHCH_2$), 6 87-7 44 (10H, m, $2C_6H_5$), 7 77 (1H, d, J 10 8Hz, CONH)
6	G	H	5MI	pNB	5 44 (1H, d, **J 5.3**Hz, 4-H) 5 84 (1H, dd, **J 5.3** and 9 9 Hz, 3-H)	(90MHz, $CDCl_3$) δ 1 99 and 2 15 (6H, 2s, CMe_2), 2 28 (3H, s, OCMe), 3 59 (2H, s, CH_2CO), 5 19 (2H, s, OCH_2), 5 81 (1H, s, = CH), 6 84 (1H, d, J 9 9Hz, CONH), 7 28 (5H, s, C_6H_5), 7 45 and 8 17 (4H, 2d, J 8 9Hz, $C_6H_4NO_2$)
6	G	H	Bn	pNB	4 67 (1H, d, **J 5.0**Hz, 4-H) 5 73 (1H, dd, **J 5.0** and 10 3Hz, 3-H),	(90MHz, $CDCl_3$) δ 2 06 and 2 24 (6H, 2s, CMe_2), 3 59-3 98 (5H, m, CH_2CO, $SNHCH_2$), 5 21 (2H, bs, OCH_2), 6 68 (1H, d, J 10 3Hz, CONH), 7 00-7 36 (10H, m, $2C_6H_5$), 7 42 and 8 19 (4H, 2d, J 8 8Hz, $C_6H_4NO_2$)
6	G	H	Me	pNB	4 67 (1H, d, **J 5.0**Hz, 4-H) 5 73 (1H, dd, **J 5.0** and 10 3Hz, 3-H)	(90MHz, $CDCl_3$) δ 2 06 and 2 24 (6H, 2s, CMe_2), 3 59-3 98 (5H, m, CH_2CO, $SNHCH_2$), 5 21 (2H, bs, OCH_2), 6 68 (1H, d, J 10 3Hz, CONH), 7 00-7 36 (10H, m, $2C_6H_5$), 7 42 and 8 19 (4H, 2d, J 8 8Hz, $C_6H_4NO_2$)

6	Phth	H	5MI	pNB	5 73 (1H, d, **J 5.4**Hz, 4-H), 5 83 (1H, d, **J 5.4**Hz, 3-H)	(90MHz, $CDCl_3$) δ 2 12 and 2 26 (6H, 2s, CMe_2), 2 32 (3H, s, OCMe), 5 21 (2H, bs, OCH_2), 6 05 (1H, bs, =CH), 7 50 and 8 18 (4H, 2d, J 9 0Hz, $C_6H_4NO_2$), 7 60-7 86 (4H, m, Phth)
6	A	H	Me	pNB	5 16 (1H, d, **J 4.9**Hz, 4-H) 5 94 (1H, dd, **J 4.9** and 10 4Hz, 3-H)	(300MHz, $CDCl_3$) δ 2 15 and 2 31 (6H, 2s, CMe_2), 2 86 (3H, d, J 4 5Hz, SNMe), 2 98 (3H, d, J 4 9Hz, CONMe), 5 31 and 5 38 (2H, ABq, J 13 2Hz, OCH_2), 6 38 (1H, m, SNH), 6 97 (1H, d, J 10 4Hz, CONH), 7 18 (1H, q, J 4 9Hz, CONH), 7 44-7 52 (4H, m, C_6H_4), 7 54 and 8 25 (4H, 2d, J 8 7Hz, $C_6H_4NO_2$)
7	G	H	Bn		4 85 (1H, d, **J 4.7**Hz, 4-H), 5 57 (1H, dd, **J 4.7** and 9 5Hz, 3-H)	(90MHz, DMSO-d_6) δ 3 56 (2H, bs, CH_2CO), 4 15-4 20 (2H, m, NCH_2), 7 25 and 7 38 (10H, 2bs, $2C_6H_5$), 7 87-7 93 (1H, m, SNH), 8 49 (1H, d, J 9 5Hz, CONH), 9 24 (1H, bs, N_1H)
7	H	H	Bn		3 29 (1H, dd, **J 4.7** and 15 2 Hz, 3α-H), 4 71 (1H, dd, J 2 1 and **4.7**Hz, 4-H)	(90MHz, DMSO-d_6) δ 2 96 (1H, dd, J 2 1 and 15 2Hz, 3β-H), 4 23 (2H, d, J 5 9Hz, NCH_2), 7 33 (5H, s, C_6H_5), 7 96 (1H, t, J 5 9Hz, SNH), 8 92(1H, s, N_1H)
8	G	H	5MI		5 68 (1H, d, **J 5.2**Hz, 4-H), 6 0 (1H, dd, **J 5.2** and 9 3Hz, 3-H)	(300MHz, $CDCl_3$) δ 1 95 and 2 07 (6H, 2s, CMe_2), 2 35 (3H, s, OCMe), 3 67 (2H, s, CH_2CO), 6 12 (1H, s, =CH), 6 63 (1H, d, J 9 3Hz, CONH), 7 27-7 31 (5H, m, C_6H_5)
8	G	H	Bn		4 94 (1H, d, **J 5.2**Hz, 4-H), 5 84 (1H, dd, **J 5.2** and 10 3Hz, 3-H)	(300MHz, $CDCl_3$) δ 2 07 and 2 25 (6H, 2s, CMe_2), 3 56 and 3 64 (2H, ABq, J 14 8Hz, CH_2CO), 3 98 -4 02 (3H, m, $SNHCH_2$), 6 77 (1H, d, J 10 3Hz, CONH), 7 11-7 37 (10H, m, $2C_6H_5$)
8	G	H	Me		5 24 (1H, d, **J 5.2**Hz, 4-H), 5 88 (1H, dd, **J 5.2** and 10 3 Hz, 3-H)	(300MHz, $CDCl_3$) δ 2 07 and 2 25 (6H, 2s, CMe_2), 2 53 (3H, d, J 4 5Hz, NMe), 3 63 (2H, ABq, J 15 1Hz, CH_2CO), 4 16 (1H, m, SNH), 6 84 (1H, d, J 10 3Hz, CONH), 7 26-7 40 (5H, m, C_6H_5)
8	V	H	5MI		5 78 (1H, d, **J 4 8**Hz, 4-H), 6 09 (1H, dd, **J 4.8** and 10 5Hz, 3-H)	(300MHz, $CDCl_3$) δ 2 05 and 2 19 (6H, 2s, CMe_2), 2 27 (3H, s, OCMe), 4 50 and 4 59 (2H, ABq, J 15 0Hz, CH_2CO), 6 23 (1H, s, =CH), 6 91-7 40 (5H, m, C_6H_5O), 7 78 (1H, d, J 10 5Hz, CONH)
8	Phth	H	5MI		5 68 (1H, d, **J 4.9**Hz, 4-H), 5 82 (1H, d, **J 4.9**Hz, 3-H)	(90MHz, DMSO-d_6) δ 2 17 (6H, s, CMe_2), 2 27 (3H, s, OCMe), 3 31 (2H, bs, SNH, COOH), 5 89 (1H, s, =CH), 7 92 (4H, s, Phth)
8	A	H	Me		5 24 (1H, d, **J 5.0**Hz, 4-H), 5 65 (1H, dd, **J 5.0** and 8 7Hz, 3-H)	(300MHz, DMSO-d_6) δ 2 01 and 2 19 (6H, 2s, CMe_2), 2 64 (3H, d, J 4 5Hz, CONMe), 2 75 (3H, d, J 4 7Hz, SNMe), 7 17 (1H, q, J 4 7Hz, SNH), 7 48-7 56 (4H, m, C_6H_4), 8 38 (1H, q, J 4 5Hz, CONH), 9 07 (1H, d, J 8 7Hz, CONH)
8	H	H	5MI		5 34 (1H, dd, J 1 8 and **4.5** Hz, 4-H), 3 55 (1H, dd, J **4.5** and 15 3Hz, 3α-H)	(300MHz, DMSO-d_6) δ 1 89 and 2 13 (6H, 2s, CMe_2), 2 35 (3H, s, OCMe), 3 21 (1H, dd, J 1 8 and 15 3Hz, 3β-H), 6 07 (1H, s, =CH), 11 32 (1H, bs, SNH), 13 05 (1H, b, COOH)

C-3 as well as with bromine atoms at C-3 formed mixed anhydrides with ethyl chloroformate which *in situ* produced anhydro 2-azacephams **9** Moreover, during removal of benzyl ester group with $AlCl_3$ [7] compound **6** (R=Br, R^1=Br, R^2=MI, R^3=Bn) was *in situ* transformed into **9** (R=Br, R^1=Br, R^2=H)

Table 2 Yields and Some Physicochemical Data of the Compounds **9**

Compound **9**			Yield	m p	IR	^{1}H NMR (δ, ppm)		
R	R^1	R^2	(%)	(°C)	(ν, cm^{-1})	6-H	7-H	J (Hz)
G	H	Bn	93 2[a]	176-178	1795, 1695, 1670	4 98	6 16	4 3
G	H	5MI	58 5[a]	180-183	1790, 1715, 1670	5 28	6 27	4 3
G	H	Me	59 6[a]	powder	1785, 1700, 1660	4 97	6 19	4 3
Phth	H	5MI	60 0[a]	195-197	1815, 1790, 1740	5 41	6 01	4 4
A	H	Me	87 4[c]	212 214	1795, 1690, 1670	5 13	6 33	4 3
H	H	Bn	87 0[b]	160-162	1780, 1700, 1620	4 86	3 58	4 8
H	H	5MI	67 0[b]	170-175	1800, 1715, 1610	5 15	3 73	4 5
Br	Br	Bn	68 7[c]	150-152	1790, 1700, 1605	5 26		
Br	Br	H	83 3[d]	108-110	1805, 1705, 1630	6 27		
V	H	5MI	85 1[c]	138-139	1810, 1715, 1610	5 43	6 34	4 5
Clo	H	5MI	23 0[c]	powder	1795, 1720, 1690	5 28	6 35	4 2

Method a) DCC, b) acid chloride, c) mixed anhydride, d) $AlCl_3$

In conclusion, the new anhydro 2-azacephams **9** represent further structural variants based on the natural penicillins and may be useful precursors for other *beta*-lactam species

EXPERIMENTAL

M p s. were obtained using a Fisher-Johns apparatus and are uncorrected IR spectra were recorded on a Perkin-Elmer 257G instrument ^{1}H NMR spectra were recorded on a Jeol FX-90 Q(90MHz) and Varian XL-GEM 300(300MHz), chemical shifts δ were recorded in ppm downfield from $SiMe_4$ Mass spectra were scanned on a Shimadzu GCMS-QP 1000 A instrument operating at 70 eV T l c were run on Merck Kieselgel HF_{254} plates and compounds were visualized under UV light or I_2 vapour adsorption following cool water flush Column chromatography was performed on Merck Kieselgel 60 (70-230 mesh ASTM)

***4-Aminosulphinyl-2-oxoazetidine* 3 and 4**

General procedure Toluene was heated in an equipment having a Dean-Stark water trap to remove azeotropically any moisture To the resulting dried toluene (50 mL), 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 0 °C The formed 2-oxoazetidine-4-sulphinyl chlorides **2** reacted *in situ* with amines to provide epimeric mixture of sulphinamides [2]

3 (R=V, R^1=H, R^2=5MI, R^3=Me) The sulphinyl chlorides **2**, formed under the general procedure starting from 6-phenoxyacetamidopenicillanate sulphoxide methyl ester[8] (1 9 g, 5 0 mmol), were stirred with 3A5MI (2 1 g, 21 mmol) for two hours The reaction mixture was filtered, mother liquor dried (Na_2SO_4) and evaporated in vacuum yielded 1 88 g (79%) a mixture of sulphinamides with R_f 0 35 and 0 45 in (CH_2Cl_2 MeOH = 20 1), The epimer with R_f 0 35 crystallized from toluene to give 0 29 g (12 2%), m p 185-190 °C, IR (KBr) ν 1770s, 1755m, 1670m, 1625m cm^{-1}, ^{1}H NMR (90MHz, $CDCl_3$) δ 1 99 (3H, s, =CMe), 2 15 (3H, s, OCMe), 3 85 (3H, s, OMe), 4 43 (2H, bs, CH_2CO), 5 05 (1H, s, NCHCO), 5 09 and 5 27 (2H, 2bs, $=CH_2$), 5 37 (1H, d, J 4 5Hz, 4-H), 5 79 (1H, s, =CH), 5 84 (1H, dd, J 4 5 and 9 5Hz, 3-H), 6 95-7 34

(5H, m, C_6H_5O), 7 70 (1H, d, J 9 5Hz, CONH), 8 29 (1H, s, SNH) ppm, Anal $C_{21}H_{24}O_7N_4S$ (476 5) calc'd C 52 93, H 5 08, N 11 76, S 6 73%, found C 52 42, H 5 32, N 12 02, S 6 34%, The epimer with R_f 0 45 crystallized from the mixture of methanol-ether to give 0 61 g (25 6%), m p 146-148 °C, IR (KBr) ν 1778s, 1730s, 1690s, 1625m cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 1 97 (3H, s, =CMe), 2 29 (3H, s, OCMe), 3 82 (3H, s, OMe), 4 42 and 4 62 (2H, ABq, J 15Hz, CH_2CO), 5.06 (1H, s, NCHCO), 5 06 and 5 22 (2H, 2bs, $=CH_2$), 5 31 (1H, d, J 4 7Hz, 4-H), 5 78 (1H, s, =CH), 5 97 (1H, dd, J 4 7 and 9 5Hz, 3-H), 6 74-7 29 (5H, m, C_6H_5O), 8 35 (1H, s, SNH), 8 44 (1H, d, J 9 5Hz, CONH) ppm, Anal $C_{21}H_{24}O_7N_4S$ (476 5) calc'd C 52 93, H 5 08, N 11 76, S 6 73%, found C 52 70, H 5 69, N 12 12, S 7 05%

3 (R=V, R^1=H, R^2=5MI, R^3=pNB) The sulphinyl chlorides **2,** formed under the general procedure starting from 6-phenoxyacetamidopenicillanate sulphoxide p-nitrobenzyl ester (5 0 g, 10 mmol), were stirred with 3A5MI (4 0 g, 40 mmol) for two hours and treated as was noted above yielded 5 0 g (83 6%) crude sulphinamides with R_f 0 50 and 0 55 in (CH_2Cl_2 MeOH=20 1), the epimer with R_f 0 50 crystallized from toluene to give 0 5 g (16 7%), m p 196-198 °C, IR (KBr) ν 1775s, 1755m, 1665m, 1625m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 02 (3H, s, =CMe), 2 25 (3H, s, OCMe), 4 45 and 4 54 (2H, ABq, J 15 1Hz, CH_2CO), 5 07 (1H, bs, NCHCO), 5 07 and 5 19 (2H, 2bs, $=CH_2$), 5 39 (1H, d, J 5 1Hz, 4-H), 5 35 (2H, bs, OCH_2), 5 76 (1H, bs, =CH), 5 85 (1H, dd, J 5 1 and 9 0Hz, 3-H), 6 91 -7 36 (5H, m, C_6H_5O), 7 49 (1H, d, J 9 0Hz, CONH), 7 49 and 8 21 (4H, 2d, J 8 8Hz, $C_6H_4NO_2$) ppm, The epimer with R_f 0 55 was purified by silica gel chromatography with dichloromethane-methanole (20 1) as eluant, IR (KBr) ν 1790s, 1750s, 1690s, 1630m, 1610m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 1 97 (3H, s, =CMe), 2 29 (3H, s, OCMe), 4 55 (2H, bs, CH_2CO), 4 99 (1H, s, NCHCO), 5 10 and 5 23(2H, 2bs, $=CH_2$), 5 20 (1H, d, J 4 8Hz, 4-H), 5 29 and 5 37 (2H, ABq, J 12 9Hz, OCH_2), 5 73 (1H, bs, =CH), 5 91 (1H, dd, J 4 8 and 9 5Hz, 3-H), 6 81-7 36 (5H, m, C_6H_5O), 7 51 and 8 25 (4H, 2d, J 8 3Hz, $C_6H_4NO_2$), 8 07 (1H, d, J 9 5Hz, CONH)ppm

3 (R=G, R^1=H, R^2=5MI, R^3=pNB) The sulphinyl chlorides **2,** formed under the general procedure starting from 6-phenylacetamidopenicillanate sulphoxide p-nitrobenzyl ester[9] (3 0 g, 6 2 mmol), were stirred with 3A5MI (2 5 g, 25 mmol) for two hours and treated as was noted above yielded 2 86 g (81%) mixture of epimers **3** The epimer with R_f 0 50 (CH_2Cl_2 EtOAc=7 3) after silica gel chromatography crystallized from mixture dichloromethane-ether 1 43 g (40 5%) , m p 157-160 °C, IR (KBr) ν 1770s, 1740m, 1705m, 1620m cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 1 92 (3H, s, =CMe), 2 35 (3H, s, OCMe), 3 61 (2H, s, CH_2CO), 4 94 (1H, bs, NCHCO), 5 07 and 5 19 (2H, 2bs, $=CH_2$), 5 13 (1H, d, J 4 8Hz, 4-H), 5 28 (2H, s, OCH_2), 5 57 (1H, bs,= CH), 5 77(1H, dd, J 4 8 and 9 0Hz, 3-H), 7 22 (5H, bs, C_6H_5), 7 44 (1H, d, J 9 0Hz, CONH), 7 49 and 8 21 (4H, 2d, J 8 8Hz, $C_6H_4NO_2$) ppm, Anal $C_{26}H_{27}O_8N_5S$ (596 6) calc'd C 54 83, H 4 78, N 12 29, S 5 63%, found C 54 99, H 4 61, N 12 22, S 5 17%

3 (R=Phth, R^1=H, R^2=5MI, R^3=pNB) The sulphinyl chlorides **2,** formed under the general procedure without CaO starting from 6-phthalimidopenicillanate sulphoxide p-nitrobenzyl ester[10] (1 5 g, 3 0 mmol), were stirred with 3A5MI (1 2 g, 12 mmol) for four hours at 10 °C and treated as was noted above The residue was purified by silica gel chromatography with dichloromethane-ethyl acetate (4 1) as eluant, 1 09 g (61 2%) the epimer with R_f 0 76 (CH_2Cl_2 MeOH=9 1) was separated as a foam, IR (KBr) ν 1795bs, 1730vs, 1623m cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 190 (3H, s, =CMe), 2 27 (3H, s, OCMe), 4 76 (1H, bs, NCHCO), 4 92 and 5 06 (2H, 2bs, $=CH_2$), 5 25 (2H, bs, OCH_2), 5 67 (1H, d, J 5 4Hz, 4-H), 6 09 (1H, d, J 5 4Hz, 3-H), 7 20 (1H, bs, =CH), 7 52 and 8 20 (4H, 2d, J 9 0Hz, $C_6H_4NO_2$), 7 71-7 95 (4H, m, Phth), 8 05 (1H, bs, SNH) ppm

3 (R=Clo, R^1=H, R^2=5MI, R^3=mMB) The sulphinyl chlorides **2,** formed under the general procedure starting from cloxacillline sulphoxide m-methylbenzyl ester[11] (2 0g, 3 6 mmol) were stirred with 3A5MI (1 1 g, 11 mmol) for three hours at 15 °C and treated as was noted above The crude material was chromatographted and epimer with R_f 0 40 (CH_2Cl_2 EtOAc=4 1) was separated (0 93 g, 48 6%), IR (film) ν 1785vs, 1740vs, 1670s, 1620s cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 1 84 (3H, s, =CMe), 2 35 (6H, bs, 2 OCMe), 2 77 (3H, s, MePh), 4 92-4 95 (2H, m, NCHCO, =CH), 4 98-5 20 (4H, m, OCH_2, =CH, 4-H), 5 69-5 83 (2H, m, 3-H, =CH), 6 71 (1H, d, J 9 0Hz, CONH), 7 13 -7 52 (8H, m, $2C_6H_4$) ppm

4 (R=V, R^1=H, R^2=5MI, R^3=Me). The epimer **3** (R=V, R^1=H, R^2=5MI, R^3=Me) with m p 185-190 °C (0 3 g, 0 6 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0 12 g, 1 2 mmol), solution was

stirred for two hours at RT, washed with water, dried (Na_2SO_4) and evaporated The residue was chromatographed on silica gel with dichloromethane-methanol (20 1) as eluant to give 0 23 g (80 4%) sulphinamide with R_f 0 28 (CH_2Cl_2 MeOH=20 1), IR (film) ν 1780s, 1730m, 1695m, 1625m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 06 and 2 19 (6H, 2s, CMe_2), 2 25 (3H, s, OCMe), 3 76(3H, s, OMe), 4 31 and 4 40 (2H, ABq, J 15 0Hz, CH_2CO), 5 34 (1H, d, J 5 0Hz, 4-H), 5 60 (1H, dd, J 5 0 and 8 8 Hz, 3-H), 5 80 (1H, s, =CH), 6 84-7 32 (5H, m, C_6H_5O), 7 92 (1H, d, J 8 8Hz, CONH), 8 43 (1H, s, SNH) ppm

The epimer **3** (R=V, R^1=H, R^2=5MI, R^3=Me) with m p 146-148 °C was treated as noted above yielded sulphinamide **4** with R_f 0 30 (CH_2Cl_2 MeOH=20 1), IR (film) ν· 1790s, 1730m, 1695m, 1625m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 11 and 2 25 (6H, 2s, CMe_2), 2 31 (3H, s, OCMe), 3 78(3H, s, OMe), 4 46 and 4 64 (2H, ABq, J 15 0Hz, CH_2CO), 5 26 (1H, d, J 5 3Hz, 4-H), 5 79 (1H, dd, J 5 3 and 9 5Hz, 3-H), 5 81 (1H, s, =CH), 6 79-7 31 (5H, m, C_6H_5O), 8 45 (1H, d, J 9 5Hz, CONH), 8 64 (1H, s, SNH) ppm, Anal $C_{21}H_{24}O_7N_4S$ (476 5) calc'd C 52 93, H 5 08, N 11 76, S 6 73%, found C 53 20, H 5 36, N 11 98, S 6 60%

4 (R=G, R^1=H, R^2=5MI, R^3=pNB) The epimer **3** (R=G, R^1=H, R^2=5MI, R^3=pNB) with m p 157-160 °C (0 62 g, 1 1 mmol) was treated as noted above yielded **4** (0 57 g, 91%), R_f 0 32 (CH_2Cl_2 EtOAc=7 3), m p 92-94 °C, IR (KBr) ν 1790s, 1730m, 1670m, 1625m cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 2 18 and 2 22 (6H, 2s, CMe_2), 2 34 (3H, s, OCMe), 3 61(2H, s, CH_2CO), 5 11(1H, d, J 5 0Hz, 4-H), 5 25 (2H, s, OCH_2), 5 46 (1H, dd, J 5 0 and 8 4 Hz, 3-H), 5 63 (1H, s, =CH), 7 24 (5H, s, C_6H_5), 7 26 (1H, d, J 8 4Hz, CONH), 7 47 and 8 18 (4H, 2d, J 8 5Hz, $C_6H_4NO_2$) ppm, Anal $C_{26}H_{27}O_8N_5S$ (596 6) calc'd C 54 83, H 4 78, N 12 29, S5 63%, found C 55 10, H 4 85, N 12 22, S 5 36%

4 (R=Phth, R^1=H, R^2=5MI, R^3=pNB) The epimer **3** (R=Phth, R^1=H, R^2=5MI, R^3=pNB) with R_f 0 76 (CH_2Cl_2 MeOH=9 1) was treated with triethylamine as noted above yielded **4** as a foam, IR (KBr) ν 1780–1800bs, 1730vs, 1620m cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 2 14 (6H, bs, CMe_2), 2 31 (3H, s, OCMe), 5 08 and 5 23 (2H, ABq, J 13 5Hz, OCH_2), 5 58 (1H, d, J 5 4Hz, 4-H), 5 71 (1H, bs, =CH), 6 0 (1H, d, J 5 4Hz, 3-H), 7 45 and 8 16 (4H, 2d, J 9 0Hz, $C_6H_4NO_2$), 7 70-7 94 (4H, m, Phth) ppm

4 (R=Clo, R^1=H, R^2=5MI, R^3=mMB) The epimer **3** (R=Clo, R^1=H, R^2=5MI, R^3=mMB) with R_f 0 40 (CH_2Cl_2 EtOAc=4 1) was treated with triethylamine as noted above The crude material was chromatographed on silica gel and **4** with R_f 0 21 (CH_2Cl_2 EtOAc=4 1) was isolated, m p 94-96 °C, IR (film) ν 1795vs, 1730s, 1685s, 1625s cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 1 95 and 2 22 (6H, 2s, CMe_2), 2 33 and 2 35 (6H, 2s, 2 OCMe), 2 77 (3H, s, MePh), 4 96 (1H, d, J 4 5Hz, 4-H), 5 13 (2H, bs, OCH_2), 5 61 (1H, dd, J 4 5 and 8 5 Hz, 3-H), 5 72 (1H, s, =CH), 6 69 (1H, d, J 8 5Hz, CONH), 7 04-7 55 (8H, m, $2C_6H_4$) ppm

4 (R=Br, R^1=Br, R^2=5MI, R^3=Bn) The sulphinyl chlorides **2** formed under the general procedure starting from 6,6-dibromopenicillanate sulphoxide benzyl ester[12] (7 0 g, 15 0 mmol) were stirred with 3A5MI (4 5 g, 45 mmol) for three hours at RT and treated as was noted above The residue was treated with triethylamine yielded 1 85 g **4** with R_f 0 51 (CH_2Cl_2 EtOAc=4 1), m p 58-60 °C, IR (CH_2Cl_2) ν 1805vs, 1730s, 1625m cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 1 88 and 2 13 (6H, 2s, CMe_2), 2 31 (3H, s, OCMe), 5 13 (2H, s, OCH_2), 5 56 (1H, s, 4-H), 5 67 (1H, s, =CH), 7 35 (5H, s, C_6H_5), 8 32 (1H, s, SNH) ppm

4 (R=Br, R^1=Br, R^2=Bn, R^3=Bn) The sulphinyl chlorides **2**, formed under the general procedure starting from 6,6-dibromopenicillanate sulphoxide benzyl ester[12] (7 0 g, 15 0 mmol) were stirred with benzylamine (4 mL, 37 5 mmol) and treated as noted above The crude material was chromatographed on silica gel with dichloromethane-ethyl acetate (6 1) as eluant yielded 3 1g (36%) sulphinamide **4** with R_f 0 74 (CH_2Cl_2 EtOAc=4 1), IR (KBr) ν 1800vs, 1730s cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 1 84 and 2 26 (6H, 2s, CMe_2), 3 68-4 40 (3H, m, $SNHCH_2$), 5 07 and 5 24 (2H, ABq, J 12Hz, OCH_2), 5 09 (1H, s, 4-H), 7 10-7 30 (10H, m, $2C_6H_5$) ppm

4 (R=G, R^1=H, R^2=Me, R^3=pNB) The sulphinyl chlorides **2,** formed under the general procedure starting from 6-phenylacetamidopenicillanate sulphoxide p-nitrobenzyl ester[9] (3 0 g, 6 2 mmol), were stirred with methylamine (1 mL, 22 5 mmol) and treated as noted above The residue was chromatographed on silica gel and 1 63g (51 1%) sulphinamide **4** with R_f 0 66 (CH_2Cl_2 MeOH=10 1) was separated, IR (KBr) ν 1780s, 1730m, 1690–1660bm cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 12 and 2 26 (6H, 2s, CMe_2), 2 47 (3H, d, J 5 4 Hz, NMe), 3 63 (2H, ABq, CH_2CO), 4 68 (1H, d, J 5 0Hz, 4-H), 5 28 (2H, s, OCH_2), 5 80 (1H, dd, J 5 0 and

9 9 Hz, 3-H), 7 19 (1H, d, J 9 9Hz, CONH), 7 26-7 38 (5H, m, C_6H_5), 7 50 and 8 24 (4H, 2d, J 8 7Hz, $C_6H_4NO_2$) ppm

4 (R=V, R^1=H, R^2=Bn, R^3=Me) The sulphinyl chlorides **2**, formed under the general procedure starting from 6-phenoxyacetamidopenicillanate sulphoxide methyl ester[9] (1 9 g, 5 0 mmol), were stirred with benzylamine (2 3g, 21 0 mmol) and treated as noted above The residue was chromatographed on silica gel and 1 8g (74 4%) mixture of sulphinamides **4** with R_f 0 45 and 0 46 (CH_2Cl_2 MeOH=20 1) was obtained, IR (KBr) ν 1780s, 1725m, 1705–1670m, 1600w cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) δ 213 and 2 26 (6H, 2s, CMe_2), 3 75 (3H, s, OMe), 4 13-4 50 (5H, m, CH_2N, CH_2CO, SNH), 4 95 (1H, d, J 5 0Hz, 4-H), 5 87 (1H, dd, J 5 0 and 10 0Hz, 3-H), 6 75-7 37 (5H, m, C_6H_5O), 8 47 (1H, d, J 10 0Hz, CONH) ppm for epimer in excess

4 (R=G, R^1=H, R^2=Bn, R^3=pNB) The sulphinyl chlorides **2**, formed under the general procedure starting from 6-phenylacetamidopenicillanate sulphoxide p-nitrobenzyl ester[9] (2 1 g, 4 3 mmol), were stirred with benzylamine (1 8 mL, 17 2 mmol) and treated as noted above The residue was chromatographed on silica gel and 1 78g (69 4%) mixture of sulphinamides **4** with R_f 0 33 and 0 42 (CH_2Cl_2 EtOAc=3 7) was obtained, IR (KBr) ν 1760bs, 1720–1690bm, 1680–1650bm cm^{-1}, ^1H NMR (90MHz, DMSO-d_6) δ 2 11 and 2 25 (6H, 2s, CMe_2), 3 53 (2H, s, CH_2CO), 3 81-4 36 (3H, m, $SNHCH_2$), 4 78 (1H, d, J 5 4Hz, 4-H), 5 24 (2H, bs, OCH_2), 5 70 (1H, dd, J 5 4 and 9 0Hz, 3-H), 6 65 (1H, d, J 9 0Hz, CONH), 7 07-7 35 (10H, m, $2C_6H_5$), 7 44 and 8 17 (4H, 2d, J 9 0Hz, $C_6H_4NO_2$) ppm for epimer in excess, Anal $C_{30}H_{30}O_7N_4S$ (590 66) calc'd C 61 00, H 5 12, N 9 48, S5 43%, found C 61 16, H 5 94, N 9 48, S 5 96%

4 (R=A, R^1=H, R^2=Me, R^3=pNB) The sulphinyl chlorides **2**, formed under the general procedure starting from 6-phthalimidopenicillanate sulphoxide p-nitrobenzyl ester[10] (1 5 g, 3 0 mmol) were stirred with methylamine (1 mL, 22 5 mmol) for three hours and treated as noted above The residue was chromatographed on silica gel and 1 36g (81 3%) mixture of sulphinamides **4** with R_f 0 60 and 0 55 (CH_2Cl_2 MeOH=9 1) was obtained, IR (film) ν 1780s, 1730sh, 1615s, 1650m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 20 and 2 31 (6H, 2s, CMe_2), 2 81 (3H, d, J 5 0 Hz, CONMe), 2 92 (3H, d, J 4 7Hz, SNMe), 4 90 (1H, d, J 4 9Hz, 4-H), 5 28 and 5 36 (2H, ABq, J 13 7Hz, OCH_2), 6 12 (1H, q, J 5 0Hz, CONH), 5 18 (1H, dd, J 4 9 and 10 2Hz, 3-H), 7 15 (1H, q, J 4 7Hz, SONH), 7 23-7 48 (4H, m, C_6H_4), 7 55 and 8 26 (4H, 2d, J 8 5Hz, $C_6H_4NO_2$) , 8 01 (1H, d, J 10 2Hz, CONH) ppm for epimer in excess

***4-Aminosulphonyl-2-oxoazetidine* 5, 6 and 7**

General procedures

A The compound **3** or **4** (5 0 mmol) was dissolved in dichloromethane (35 mL) and formic acid (7 mL), added 30% aqueous H_2O_2 (2 8 mL) and mixture was stirred at RT [11] The organic layer was separated, washed with water, dried (Na_2SO_4), filtered and evaporated

B The compound **4** (6 0 mmol) was dissolved in chloroform and stirred with m-chloroperbenzoic acid (m-CPBA) (6 0 mmol) for 20 min at -10 °C and for one hour at RT The sodium bisulphite (1N, 36 mL) was added, stirred for five minutes and organic layer was separated, washed with water, dried (Na_2SO_4), filtered and evaporated

C The compound **4** (4 0 mmol) was dissolved in 80% acetic acid (25 mL) and ethyl acetate (25 mL), cooled to 0 °C and saturated aqueous solution of $KMnO_4$ (25 mL) was added dropwise as long as the pink colour persisted The colour of the solution was discharged by adding 30% aqueous H_2O_2 The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and evaporated

5 (R=V, R^1=H, R^2=5MI, R^3=Me) The mixture of sulphinamides **3** (R=V, R^1=H, R^2=5MI, R^3=Me) was treated under the general procedure A yielded sulphonamide **5**, R_f 0 20 (CH_2Cl_2 MeOH=20 1), IR (KBr) ν 1795s, 1750m, 1690s, 1620m, 1605m cm^{-1}

5 (R=Phth, R^1=H, R^2=5MI, R^3=pNB) The sulphinamide **3** (R=Phth, R^1=H, R^2=5MI, R^3=pNB) was treated under general procedure A yielded sulphonamide **5** as a foam, R_f 0 58 (CH_2Cl_2 MeOH=9 1), IR (KBr) ν 1805s, 1790s, 1735vs, 1615m cm^{-1}

5 (R=Clo, R^1=H, R^2=5MI, R^3=mMB) The mixture of sulphinamides **3** (R=Clo, R^1=H, R^2=5MI, R^3=mMB) was treated under general procedure A yielded sulphonamide **5** as a foam, R_f 0 55 (CH_2Cl_2 MeOH=10 1), IR (KBr) ν 1795vs, 1745s, 1680vs, 1620s cm^{-1}

6 (R=V, R^1=H, R^2=5MI, R^3=Me). The sulphinamide **4** (R=V, R^1=H, R^2=5MI, R^3=Me) was treated under general procedure A yielded sulphonamide **6** as a foam, R_f 0 24 (CH_2Cl_2 MeOH=20 1), IR (KBr) ν 1790s, 1735m, 1700s, 1620m cm^{-1}

6 (R=G, R^1=H, R^2=5MI, R^3=pNB) The sulphinamide **4** (R=G, R^1=H, R^2=5MI, R^3=pNB) was treated under general procedure A yielded sulphonamide **6** ; R_f 0 57 (CH_2Cl_2 MeOH=8 1), IR (KBr) ν 1785s, 1730m, 1665s, 1615m cm^{-1}

6 (R=Br, R^1=Br, R^2=Bn, R^3=Bn) The sulphinamide **4** (R=Br, R^1=Br, R^2=Bn, R^3=Bn) was treated under the general procedure B yielded sulphonamide **6** , R_f 0 88 (CH_2Cl_2 EtOAc=4 1), m p 120-122 °C, IR (KBr) ν 1780vs, 1730s, 1640s cm^{-1}, ^{1}H NMR (90MHz, $CDCl_3$) δ 2 09 and 2 28 (6H, 2s, CMe_2), 4 09 (2H, d, J 5 8Hz, NCH_2), 4 63 (1H, t, J 5 8Hz, SNH), 5 08 and 5 34 (2H, ABq, J 11 7Hz, OCH_2), 5 32 (1H, s, 4-H), 7 29-7 35 (10H, m, $2C_6H_5$) ppm

6 (R=Br, R^1=Br, R^2=5MI, R^3=Bn) The sulphinamide **4** (R=Br, R^1=Br, R^2=5MI, R^3=Bn) was treated under the general procedure B yielded sulphonamide **6**, R_f 0 25 (CH_2Cl_2 EtOAc=4 1), m p 168-170 °C, IR (KBr) ν 1780vs, 1765vs, 1625s cm^{-1}, ^{1}H NMR (90MHz, $CDCl_3$) δ 2 06 and 2 15 (6H, 2s, CMe_2), 2 37 (3H, s, OCMe), 5 05 (2H, s, OCH_2), 5 70 (1H, s, 4-H), 6 07 (1H, s, =CH), 7 31 (5H, s, C_6H_5) ppm

6 (R=Clo, R^1=H, R^2=5MI, R^3=mMB) The sulphinamide **4** (R=Clo, R^1=H, R^2=5MI, R^3=mMB) was treated under the general procedure A yielded sulphonamide **6** as a foam, R_f 0 55 (CH_2Cl_2 MeOH=10 1), IR (film) ν 1795vs, 1735m, 1685bs, 1620s cm^{-1}, (90MHz, $CDCl_3$) δ 1 84 and 2 11 (6H, 2s, CMe_2), 2 26 and 2 33 (6H, 2s, 2 OCMe), 2 72 (3H, s, MePh), 5 01 (2H, bs, OCH_2), 5 36 (1H, d, J 5 0Hz, 4-H), 5 71-5 92 (2H, m, 3-H, =CH), 6 41 (1H, d, J 10 0Hz, CONH), 7 01-7 62 (8H, m, $2C_6H_4$) ppm

6 (R=Phth, R^1=H, R^2=5MI, R^3=pNB) The sulphinamide **4** (R=Phth, R^1=H, R^2=5MI, R^3=pNB) was treated under the general procedure A yielded sulphonamide **6**, R_f 0 60 (CH_2Cl_2 MeOH=9 1), IR (KBr) ν 1790bs, 1730vs, 1615m cm^{-1}

6 (R=V, R^1=H, R^2=Bn, R^3=Me) The sulphinamide **4** (R=V, R^1=H, R^2=Bn, R^3=Me) (1 8 g, 3 7 mmol) was treated under the general procedure A yielded sulphonamide **6** (1 77 g, 95%), R_f 0 55 (CH_2Cl_2 MeOH=20 1), IR (KBr) ν 1785s, 1735m, 1690s, 1605m cm^{-1}

6 (R=A, R^1=H, R^2=Me, R^3=pNB) The sulphinamide **4** (R=A, R^1=H, R^2=Me, R^3=pNB) (1 53g, 2 7mmol) was treated under the general procedure A yielded sulphonamide **6** (1 23 g, 79 5%), R_f 081 (CH_2Cl_2 MeOH=9 1) , IR (film) ν 1790s, 1730s, 1670–1640bs cm^{-1}

6 (R=G, R^1=H, R^2=Bn, R^3=pNB) The sulphinamide **4** (R=G, R^1=H, R^2=Bn, R^3=pNB) (1 36 g, 2 3 mmol) was treated under the general procedure A yielded sulphonamide **6** (1 18 g, 84 0%), R_f 0 60 (CH_2Cl_2 EtOAc=4 1), IR (KBr) ν 1790s, 1750-1730bm, 1695-1670bm cm^{-1}, Anal $C_{30}H_{30}O_8N_4S$ (606 66) calc'd C 59 40 H 4 98, N 9 23, S 5 28%, found C 59 33, H 4 89, N 9 21, S 5 51%

6 (R=G, R^1=H, R^2=Me, R^3=pNB) The sulphinamide **4** (R=G, R^1=H, R^2=Me, R^3=pNB) (1 8 g, 3 45 mmol) was treated under the general procedure A yielded sulphonamide **6** (1 34 g, 73 3%), R_f 0 34 (CH_2Cl_2 EtOAc=4 1), IR (KBr) ν 1785s, 1730m, 1700-1675bm cm^{-1}, Anal $C_{24}H_{28}O_8N_4S$ (530 56) calc'd C 54 33 H 4 94, N 10 56, S 6 04%, found C 54 53, H 4 81, N 10 53, S 7 03%

6 (R=V, R^1=H, R^2=5MI, R^3=pNB). The sulphinamide**3** (R=V, R^1=H, R^2=5MI, R^3=pNB) (5 g, 8 4 mmol) was treated under the general procedure A The residue was dissolved in dichloromethane and stirred with triethylamine yielded 3 5 g (68 2%) sulphonamide **6**, R_f 0 65 (CH_2Cl_2 MeOH=9 1), IR (KBr) ν 1795s, 1735m, 1170s, 1620m cm^{-1}

7 (R=G, R^1=H, R^2=Bn) The mixture of sulphinamides **4** (R=G, R^1=H, R^2=Bn, R^3=pNB) (2 0 g, 3 4 mmol) was treated under the general procedure C, The residue was chromatographed on silica gel with dichloromethane-ethylacetate (4 1) as eluant and 0 3 g (23 5%) sulphonamide **7** was separated, R_f 0 92

(nBuOH HOAc H_2O=4 1 1), m p 135-137 °C, IR (KBr) ν 1780vs, 1660s, 1515m, 1320s cm^{-1}, Anal $C_{18}H_{19}O_4N_3S$ (337 43) calc'd C 57 70 H 5 90, N 11 74 S 8 47%, found C 57.89, H 5 13, N 11 25, S 8 9%

7 (R=H, R^1=H, R^2=Bn) a) The sulphinamides **4** (R=H, R^1=H, R^2=Bn, R^3=Bn)[13] were treated under the general procedure C, The residue was stirred in ether and sulphonamide **7** was crystallysed, R_f 0 10 (C_6H_6 EtOAc=3 1), m p 111-113 °C, IR (KBr) ν 1790vs, 1740vs, 1430s, 1330s cm^{-1}, b) The sulphonamide **6** (R=H, R^1=H, R^2=Bn, R^3=Bn)[13] was treated under the general procedure C and the same compound **7** was prepared

***1-(1'-Carboxyl-2'-methyl-prop-1'-enyl)-4-aminosulphonyl-2-oxoazetidine* 8**

General procedures

A1 The compound **6** (0 6 mmol) was dissolved in methanol (25 mL), 10% Pd/C (50 mg) added and treated with hydrogen under pressure (2 5 Atm) The mixture was filtered and mother liquor evaporated The residue was dissolved in dichloromethane (20 mL) and water (20 mL), the aqueous solution of $NaHCO_3$ was added til pH 8 5 after which water layer was separated, washed with dichloromethane and acidified The compound **8** was filtered off or extracted with dichloromethane

B1 The compound **6** (1 mmol) dissolved in dichloromethane (15 mL) and anisole (6 mL) was added into mixture of $AlCl_3$ (3 mmol) in dichloromethane (15 mL) and stirred 30 min at RT The ethyl acetate (15 mL) was added, washed with diluted HCl and extracted with 5% $NaHCO_3$ The water extract was acidified with HCl and extracted with ethyl acetate The organic layer was washed with water, dried and evaporated

8 (R=G, R^1=H, R^2=5MI) The sulphonamide **6** (R=G, R^1=H, R^2=5MI, R^3=pNB) (0 35g, 0 6mmol) was treated under the general procedure A1 yielded 0 14 g (52 4%) acid **8** ; R_f 0 48 (CH_2Cl_2 MeOH=3 2), IR (KBr) ν 1790s, 1680bs, 1620s cm^{-1}

8 (R=G, R^1=H, R^2=Bn) The sulphonamide **6** (R=G, R^1=H, R^2=Bn, R^3=pNB) (0 9 g, 1 5 mmol) was treated under the general procedure A1 yielded 0 52 g (75%) acid **8** , R_f 0 38 (CH_2Cl_2 MeOH=4 1), IR (KBr) ν 1800-1770bs, 1700-1680bm, 1640w cm^{-1}, Anal $C_{23}H_{25}O_6N_3S$ (471 54) calc'd C 58 59, H 5 34, N 8 91, S 6 80%, found C 58 23, H 4 97, N 8 48, S 7 55%

8 (R=G, R^1=H, R^2=Me) The sulphonamide **6** (R=G, R^1=H, R^2=Me, R^3=pNB) (1 2 g, 2 2 mmol) was treated under the general procedure A1 yielded 1 37 g (42 0%) acid **8**, IR (KBr) ν 1785s, 1740-1620bm, 1335m cm^{-1}

8 (R=V, R^1=H, R^2=5MI). The sulphonamide **6** (R=V, R^1=H, R^2=5MI, R^3=pNB) (0 56 g, 0 91 mmol) was treated under the general procedure A1 yielded 0 23 g (52 5%) acid **8**, R_f 0 35 (CH_2Cl_2 MeOH=6 4)), IR (KBr) ν 1795s, 1700bs, 1620m cm^{-1}

8 (R=Phth, R^1=H, R^2=5MI) The sulphonamide **6** (R=Phth, R^1=H, R^2=5MI, R^3=pNB) (0 84 g, 1 4 mmol)was treated under the general procedure A1 yielded 0 49 g (75%) acid **8**, m p 160-165 °C, IR (KBr) ν 1795s, 1780s, 1735vs, 1685m, 1625m cm^{-1}

8 (R=A, R^1=H, R^2=Me) The sulphonamide **6** (R=A, R^1=H, R^2=Me, R^3=pNB) (1 23 g) was treated under the general procedure A1 yielded 0 68 g acid **8**, m p 142 °C decomp , IR (KBr) ν 1785vs, 1720s, 1680s, 1615s cm^{-1}

8 (R=Clo, R^1=H, R^2=5MI) The sulphonamide **6** (R=Clo, R^1=H, R^2=5MI, R^3=mMB) (0 55 g, 0 82 mmol) was treated under the general procedure A1 yielded 0 12 g (26 1%) acid **8**, m p 175-176 °C decomp , R_f 0 79 (EtOAc HOAc H_2O=6 1 1), IR (KBr) ν 1785vs, 1725m, 1610vs, 1560m cm^{-1}

8 (R=H, R^1=H, R^2=Bn) The sulphonamide **6** (R=H, R^1=H, R^2=Bn, R^3=Bn)[13] (0 4 g, 0 93 mmol) was treated

under the general procedure A1 yielded 0 25g (79%) acid **8**, R_f 0 88 (nBuOH HOAc H_2O=4 1 1), IR (KBr) ν 1760vs, 1700s, 1630m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 09 and 2 26 (6H, 2s, CMe_2), 3 17 (2H, d, J 4 1 Hz, α and β 3-H), 4 26 (2H, s, NCH_2), 4 98 (1H, t, J 4 1Hz, 4-H), 7 30 (5H, s, C_6H_5) ppm

8 (R=H, R^1=H, R^2=5MI) The sulphonamide **6** (R=H, R^1=H, R^2=5MI, R^3=Bn)[13] (0 42 g, 1 0 mmol) was treated under the general procedure A1 yielded 0 23 g (69%) acid **8**, R_f 0 91 (nBuOH HOAc H_2O=4 1 1), IR (KBr) ν 1795s, 1760s, 1680vs, 1620vs cm^{-1}

8 (R=Br, R^1=Br, R^2=Bn). The sulphonamide **6** (R=Br, R^1=Br, R^2=Bn, R^3=Bn) (0 59 g, 1 mmol) was treated under the general procedure B1 yielded 0 49 g (98%) acid **8**, R_f 0 66 (EtOAc MeOH=3 1), m p 47-50 °C, IR (film) ν 1805vs, 1700s, 1625m cm^{-1}, ^1H NMR (300MHz, DMSO-d_6) δ 1 98 and 2 23 (6H, 2s, CMe_2), 4 09 and 4 20 (2H, ABX, J 5 7, 6 0 and 15 2Hz, NCH_2), 5 51 (1H, s, 4-H), 7 29-7 39 (5H, m, C_6H_5), 8 49 (1H, dd J 5 7 and 6 0Hz, SNH), 13 5 (1H, b, COOH) ppm

***5-Thia-1,4-diazabicyclo[4 2.0]octane-2-isopropylidene-3,8-dioxo-5,5-dioxide* 9**

General procedures

A2 The compound **8** (1 0 mmol) was dissolved in dichloromethane or tetrahydrofurane, the solution of dicyclohexylcarbodiimide (1 2 mmol) in dichloromethane was added and reaction mixture was stirred for one hour The mixture was filtered and mother liquor was washed with saturated solution of $NaHCO_3$ and water, dried and evaporated

B2 The compound **8** (1 mmol) was dissolved in dichloromethane (15 mL) and triethylamine (1 1 mmol) was added The solution was cooled (-10 °C), added ethyl chloroformate (1 1 mmol) and stirred for one hour at -10 °C and for two hours at RT, after which the reaction solution was evaporated

C2 The compound **8** (1 mmol) was dissolved in thionylchloride (3 mL) and stirred for two hours at RT The solution was evaporated, the residue was dissolved in dichloromethane, added triethylamine till pH 6 5 and stirred for 30 min , washed with water, saturated solution of $NaHCO_3$, dried and evaporated

9 (R=G, R^1=H, R^2=Bn) The acid **8** (R=G, R^1=H, R^2=Bn) (0 35 g, 0 74 mmol) was treated under the general procedure A2. The residue was chromatographed on silica gel with dichloromethane-ethyl acetate (9 1) as eluant to give 0 31 g (93 2%) of compound **9**, R_f 0 61 (CH_2Cl_2 EtOAc=9 1), m p 176-178 °C, m/e 453 (M^++1), IR (KBr) ν 1795s, 1695m, 1670s, 1620w cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 03 and 2 32 (6H, 2s, CMe_2), 3 65 (2H, bs, CH_2CO), 4 98 (2H, ABq, J 15 2Hz, NCH_2), 4 98 (1H, d, J 4 3Hz, 6-H), 6 16 (1H, dd, J 4 3 and 10 0Hz, 7-H), 6 64 (1H, d, J 10 0Hz, CONH), 7 26-7 42 (10H, m, $2C_6H_5$) ppm, Anal $C_{23}H_{23}O_5N_3S$ (453 51 calc'd C 60 91, H 5 11, N 9 26, S 7 07%, found C 61 04, H 5 31, N 9 15, S 7 55%

9 (R=G, R^1=H, R^2=5MI) The acid **8** (R=G, R^1=H, R^2=5MI) (0 3 g, 0 65 mmol) was treated under the general procedure A2 to give 0 17 g (58 5%) of compound **9**, R_f 0 53 (CH_2Cl_2 EtOAc=4 1), m p 180-183 °C, IR (KBr) ν 1790s, 1715s, 1670s, 1610m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 09 and 2 33 (6H, 2s, CMe_2), 2 48 (3H, s, OCMe), 3 64 (2H, bs, CH_2CO), 5 28 (1H, d, J 4 3Hz, 6-H), 6 10 (1H, s, =CH), 6 27 (1H, dd, J 4 3 and 10 0Hz, 7-H), 6 75 (1H, d, J 10 0Hz, CONH), 7 22-7 37 (5H, m, C_6H_5) ppm

9 (R=G, R^1=H, R^2=Me) The acid **8** (R=G, R^1=H, R^2=Me) (0 3 g, 0 78 mmol) was treated under the general procedure A2 to give 0 23 g (59 6%) of compound **9**, R_f 0 67 (CH_2Cl_2 EtOAc=4 1), m/e 377 (M^++1), IR (KBr) ν 1785s, 1700s, 1660s, 1620m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 04 and 2 34 (6H, 2s, CMe_2), 3 19 (3H, s, NMe), 3 65 (2H, bs, CH_2CO), 4 97 (1H, d, J 4 3Hz, 6-H), 6 19 (1H, dd, J 4 3 and 10 4Hz, 7-H), 6 72 (1H, d, J 10 4Hz, CONH), 7 25-7 39 (5H, m, C_6H_5) ppm

9 (R=Phth, R^1=H, R^2=5MI) The acid **8** (R=Phth, R^1=H, R^2=5MI) (0 24 g, 0 5 mmol) was treated under the general procedure A2 to give 0 14 g (60%) of compound **9**, m p 195-197 °C, R_f 091 (CH_2Cl_2 MeOH=9 1), IR (KBr) ν 1815s, 1790m, 1740vs, 1725s, 1610m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 20 and 2 39 (6H, 2s, CMe_2), 2 46 (3H, s, OCMe), 5 41 (1H, d, J 4 4Hz, 6-H), 6 01 (1H, d, J 4 4Hz, 7-H), 6 27 (1H, s, =CH), 7 68-7 92 (4H, m, Pht) ppm

9 (R=A, R^1=H, R^2=Me) The acid **8** (R=A, R^1=H, R^2=Me) (1 44 g, 1 0 mmol) was treated under the general procedure B2 The residue was chromatographed on silica gel with dichloromethane-methanol (19 1) as eluant to give 0 37 g (87 4%) of compound **9**, m p 212-214 °C, R_f 0 67 (CH_2Cl_2 MeOH=9 1), m/e 420 (M^+), IR (KBr) ν 1795vs, 1690s, 1670s, 1645s cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 09 and 2 37 (6H, 2s, CMe_2), 3 01 (3H, d, J 4 9Hz, CONMe), 3 24 (3H, s, SNMe), 5 13 (1H, d, J 4 3Hz, 6-H), 6 22 (1H, b, CONH), 6 33 (1H, dd, J 4 3 and 9 6Hz, 7-H), 7 48-7 68 (4H, m, C_6H_4), 7 77 (1H, d, J 9 6Hz, CONH) ppm

9 (R=V, R^1=H, R^2=5MI). The acid **8** (R=V, R^1=H, R^2=5MI) (0 15 g, 0 3 mmol) was treated under the general procedure B2 to give 0 12 g (85 1%) of compound **9**, m p 138-139 °C, R_f 0 60 (CH_2Cl_2 EtOAc=5 3), IR (KBr) ν 1810m, 1715s, 1610m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 15 and 2 38 (6H, 2s, CMe_2), 2 50 (3H, s, OCMe), 4 55 and 4 59 (2H, ABq, J 15 3Hz, CH_2CO), 5 43 (1H, d, J 4 5Hz, 6-H),

6 14 (1H, s, =CH), 6 34 (1H, dd, J 4 5 and 10 5Hz, 7-H), 6 91-7 34 (5H, m, C_6H_5O), 7 96 (1H, d, J 10 5Hz, CONH) ppm

9 (R=Clo, R^1=H, R^2=5MI) The acid **8** (R=Clo, R^1=H, R^2=5MI) (0 33 g, 0 58 mmol) was treated under the general procedure B2 The residue was chromatographed on silica gel with dichloromethane-ethyl acetate as eluant to give 0 2 g (62 0%) compound **9**, R_f 0 64 (CH_2Cl_2 EtOAc=4 1), IR (film) ν 1795vs, 1720s, 1610vs, 1690s, 1590s cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 10 and 2 33 (6H, 2s, CMe_2), 2 49 and 2 74 (6H, 2s, 2 OCMe), 5 28 (1H, d, J 4 2Hz, 6-H), 6 07 (1H, s, =CH), 6 35 (1H, dd, J 4 2 and 9 6Hz, 7-H), 6 65 (1H, d, J 9 6Hz, CONH), 7 50-7 60 (4H, m, C_6H_4) ppm

9 (R=Br, R^1=Br, R^2=Bn) The acid **8** (R=Br, R^1=Br, R^2=Bn) (0 25 g, o 5 mmol) was treated under the general procedure B2 The residue was chromatographed on silica gel with dichloromethane as eluant to give 0 16 g (67 8%) compound **9**, m p 150-152 °C, R_f 0 85 (CH_2Cl_2), IR (film) ν 1790s, 1700s, 1605s, 1360vs, 1225vs cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 11 and 2 35 (6H, 2s, CMe_2), 4 97 (2H, s, NCH_2), 5 26 (1H, s, 6-H), 7 29-7 44 (5H, m, C_6H_5) ppm

9 (R=H, R^1=H, R^2=Bn) The acid **8** (R=H, R^1=H, R^2=Bn) (0 34 g, 1 0 mmol) was treated under the general procedure C2 to give 0 28 g (87%) of compound **9**, m p 160-162 °C, R_f 0 80 (C_6H_6 EtOAc=3 1), m/e 320 (M^+), IR (KBi) ν 1780vs, 1700s, 1620m cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 07 and 2 32 (6H, 2s, CMe_2), 3 52 (1H, dd, J 2 2 and 15 2Hz, β 7-H), 3 58 (1H, dd, J 4 8 and 15 2Hz, α 7-H), 4 86 (1H, 2d, J 2 2 and 4 8Hz, 6-H), 4 99 (2H, s, NCH_2), 7 30-7 48 (5H, m, C_6H_5) ppm

9 (R=H, R^1=H, R^2=5MI) The acid **8** (R=H, R^1=H, R^2=5MI) (0 33 g, 1 0 mmol) was treated under the general procedure C2 to give 0 21 g (67%) of compound **9**, m p 170-175 °C, R_f 0 65 (C_6H_6 EtOAc=3 1), m/e 311 (M^+), IR (KBr) ν 1800vs, 1715s, 1610s cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) δ 2 15 and 2 35 (6H, 2s, CMe_2), 2 50 (3H, s, OCMe), 3 59 (1H, dd, J 2 5 and 15 9Hz, β 7-H), 3 73 (1H, dd, J 4 5 and 15 9Hz, α 7-H), 5 15 (1H, 2d, J 2 5 and 4 5Hz, 6-H), 6 17 (1H, s, =CH) ppm

9 (R=Br, R^1=Br, R^2=H). The sulphonamide **6** (R=Br, R^1=Br, R^2=5MI, R^3=Bn) (0 58 g, 1 mmol) was treated under the general procedure B1 to give 0 32 g (83 3%) of compound **9**, m p 108-110 °C, R_f 0 53 (EtOAc MeOH=3 1), IR (film) ν 1805vs, 1705s, 1630m cm^{-1}, ^1H NMR (300MHz, DMSO-d_6) δ 1 90 and 2 25 (6H, 2s, CMe_2), 3 40 (1H, b, NH), 6 55 (1H, s, 6-H) ppm

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