(6*R*)-6-(SUBSTITUTED METHYL)PENICILLANIC ACID SULFONES: NEW POTENT β-LACTAMASE INHIBITORS

S. ADAM*, R. THEN and P. ANGEHRN

F. Hoffmann-La Roche AG,
4002-Basel, Switzerland

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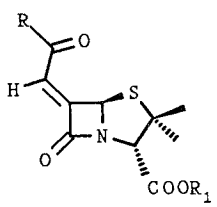
A series of (6*R*)-6-(substituted methyl)penicillanic acid sulfones has been prepared starting from the corresponding 6-(substituted methylene)penicillanates. The new sulfones **9a**, **9b**, **9c** and **9d** have been shown to be potent β-lactamase inhibitors.

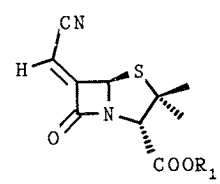
Production of β-lactamases is by far the most common mechanism of acquired resistance to β-lactam antibiotics. These enzymes efficiently hydrolyze the amide bond of the β-lactam nucleus, yielding products devoid of antibiotic activity. Inhibition of these enzymes has found clinical application, *i.e.* clavulanic acid which is used in combination with the potent but (otherwise) β-lactamase-sensitive antibiotic amoxicillin and so protects it from inactivation[1,2].

In earlier accounts we described the synthesis and biological activities of 6-acylmethylenepenicillanates **1** (R_1 = Piv.; Fig. 1), potent broad spectrum β-lactamase inhibitors[3~6]. We also reported similar properties for the related penem **2**[7] as well as for **3**, a vinylogous analogue of 6-formylmethylenepenicillanate[8] (Fig. 2). Unfortunately, it turned out that application of these inhibitors *in vivo*, especially for therapeutic purposes, is limited due to their instability in biological fluids[9]. This instability was also reflected in another series lacking the carbonyl function: *i.e.* **5**; in that case the instability in the test medium of the corresponding pivaloyloxymethyl ester was such that no true β-lactamase-inhibition value could be determined (Table 2). Our efforts at designing potential prodrugs of **1a**, endowed with improved chemical stability led to no concomitant *in vivo* activity improvement[10]. Herein we report further work done on some of the 6-(substituted methylene)penicillanates in a further attempt to obtain inhibitors with greater chemical stability but still endowed with potent β-lactamase activity. The rationale behind the work reported here was simply the following: Hydrogenation of the 6 exocyclic double bond in **1** should relieve the β-lactam

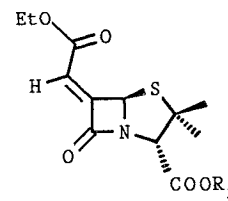
Fig. 1. Structure of compounds **1**, **5** and **6**.



1a R = $-CH_3$
$R_1 = -CH_2OCOC(CH_3)_3$ = Piv
1b R = $-CH_2O-Ph$
$R_1 = -CH_2OCOC(CH_3)_3$
1c R = $-CH_3$ R_1 = –PNB
1d R = $-CH_2O-Ph$ R_1 = –PNB



5a $R_1 = -CH_2OCOC(CH_3)_3$
5b R_1 = –PNB



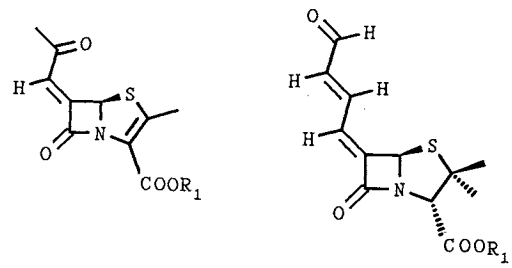
6a $R_1 = -CH_2OCOC(CH_3)_3$
6b R_1 = –PNB

strain and so improve the chemical stability, but in doing so, the preformed Michael acceptor incorporating the ketone (which is a requisite for the inhibition[11]) disappears. At this stage (reminiscent from the published work on sulbactam[12]) we anticipated that introduction of the sulfone functionality might provide another adequate "activation" for potential β-lactamase inhibition. Furthermore the new chemical entity would bypass the need for using the pivaloyloxymethyl ester and allow the use of the *p*-nitrobenzyl (PNB) ester as the carboxyl protecting group which we anticipated could be readily removed by hydrogenolysis (past experience called for its use rather than the benzyl ester). The same reasoning was applied to **5**. In addition, for comparison purposes, we also included **6** which had turned out to be practically inactive (though containing a preformed Michael acceptor) (Table 2).

Chemistry

The starting 6-(substituted methylene)penicillanates **1**, **5** and **6** as well as the 6-(substituted methyl)penicillanates **7** were prepared according to previously employed conditions[13]. The oxidation at

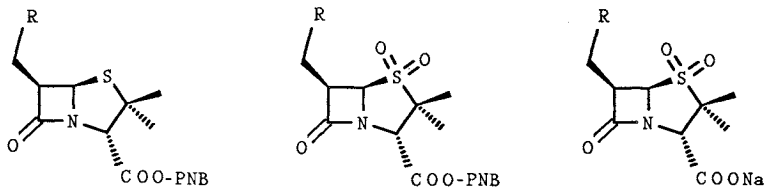
Fig. 2. Structure of compounds **2** and **3**.



2 **3**

$R_1 = -CH_2OCOC(CH_3)_3$

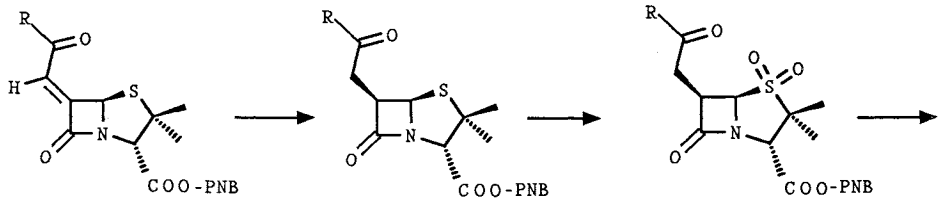
Fig. 3. Structure of compounds **7**, **8** and **9**.



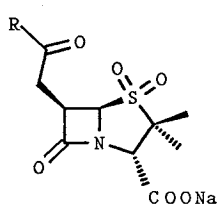
7c, 7d **8c, 8d** **9c, 9d**

c R=–CN
d R=–CO_2Et

Scheme.



1c, 1d **7a, 7b** **8a, 8b**



9a, 9b

1c, 7a, 8a, 9a R=–CH_3
1d, 7b, 8b, 9b R=–CH_2O–Ph

room temperature of compounds **7** with an excess (2.2 equiv.) of *m*-chloroperbenzoic acid (*m*-ClPBA) led rapidly and quantitatively to a mixture of the corresponding α and β sulfoxides (kinetic products of the reaction). Subsequent heating of the reaction mixture for a few hours at 60°C led to the sulfones **8** which were isolated in relatively good yields after work up of the reaction mixture followed by flash chromatography of the crude product. The β-sulfoxides of **7b**, **7c** and **7d** were also isolated from the oxidation mixtures in low yield. Tetrahydrofuran (THF) was found to be the most appropriate solvent for this oxidation (when compared to chloroform and dichloromethane). Removal of the PNB ester was readily achieved by hydrogenolysis using an equal weight of 10% palladium on carbon in ethyl acetate (EtOAc). The acids were isolated quantitatively as their sodium salts **9** after treatment of the hydrogenation mixture with 1 equiv. of sodium 2-ethylhexanoate (2 N in EtOAc).

Biological Results

Inhibition of β-Lactamases

Table 1 shows the inhibitory properties of the new compounds using partially purified enzyme preparations: Against the β-lactamase from *Proteus vulgaris* 1028, **9a**, **9b**, **9c** and **9d** are more active than sulbactam. When compared to clavulanic acid **9a**, **9b** and **9d** are only slightly superior and **9c** less potent. Against the constitutive penicillinase from *Klebsiella pneumoniae*, the new sulfones are only slightly superior when compared to sulbactam and less active when compared to clavulanic acid. **9b**, **9c**, **9d** and to a lesser degree **9a** are good inhibitors of the 1024 enzyme of *Escherichia coli*, a β-lactamase

Table 1. Inhibitory properties of (6*R*)-6-(substituted methyl)penicillanic acid sulfones against isolated β-lactamases.

Compound	IC_{50} (μM) for the β-lactamase		
	Proteus vulgaris 1028[a]	*Klebsiella pneumoniae* NCTC 418[b]	*Escherichia coli* 1024[c]
Sulbactam	0.11	2.8	8.0
Clavulanic acid	0.03	0.02	85.0
9a	0.013	1.35	24.0
9b	0.018	1.8	18.0
9c	0.06	1.5	9.5
9d	0.017	2.35	12.0

β-Lactamase type:
[a] Inducible, chromosomally determined cephalosporinase (type Ic).
[b] Constitutive penicillinase (type II).
[c] Constitutive chromosomal cephalosporinase (type I).

Table 2. Inhibitory properties of 6-(substituted methylene)penicillanates against isolated β-lactamases.

Compound	IC_{50} (μM) for the β-lactamase					
	Proteus vulgaris 1028[a]		*Klebsiella pneumoniae* NCTC 418[b]		*Escherichia coli* 1024[c]	
	−E	+E	−E	+E	−E	+E
Sulbactam	0.11	—	2.8	—	8.0	—
1a	0.16	0.015	0.19	0.0005	32.0	1.5
1b	0.7	0.011	3.5	0.06	29.0	0.75
5a	*	*	90.0*	13.0*	*	*
6a	100.0	65.0	100.0	100.0	100.0	29.0

E: Test carried out in the presence of 10 μl of hog liver esterase following the procedures described in reference 4, after a 15 minutes preincubation time of the β-lactamase and inhibitor.
* Compound unstable. No true β-lactamase-inhibition value could be determined.
β-Lactamase type:
[a] Inducible, chromosomally determined cephalosporinase (type Ic).
[b] Constitutive penicillinase (type II).
[c] Constitutive chromosomal cephalosporinase (type I).

Table 3. *In vitro* synergy with ampicillin against β-lactamase-producing isolates.

Compound	MIC (μg/ml) inhibitor + ampicillin[a]		
	Klebsiella pneumoniae NCTC 418	*Proteus vulgaris* 1028	*Escherichia coli* 1024
Sulbactam	3.1 + 3.1	1.6 + 1.6	12 + 12
9a	> 12 + 50	0.4 + 1.6	12 + 50
9b	50 + 25	12.5 + 6.3	ND
9c	12 + 25	1.6 + 6.3	< 50 + 6
9d	25 + 25	1.6 + 1.6	25 + 25

ND: Not done.

[a] Figures presented were selected on the basis of minimal drug concentration required for inhibition, as read from checkerboard titration experiments. MICs of ampicillin alone were in all instances greater than 50 μg/ml. Medium: Mueller-Hinton broth (Difco). Inoculum: 10^5 cfu/ml.

Table 4. Therapeutic activity in combination with ampicillin (A) against experimental septicemias in mice. (ED_{50}, mg/kg, sc)

	Proteus vulgaris 1028	*Staphylococcus aureus* 887
A + Sulbactam	1.8 + 12.5	10 + 10
A + **9a**	0.6 + 12.5	20 + 20
A + **9c**	0.6 + 12.5	12 + 12
A + **9b**	28 + 28	ND
A + **9d**	> 25 + 25	ND

ND: Not done.

ED_{50} single compounds, > 50 mg/kg, sc.

against which clavulanic acid has little activity. Table 3 shows that the new sulfones (**9a**, **9c** and **9d**) considerably reduced the MIC values of ampicillin against *Proteus vulgaris* and that they are as effective as sulbactam against this organism. As can be seen, synergism was less pronounced against the other β-lactamase-producing organisms. Their performance *in vivo* is given in Table 4: In combination with ampicillin **9a** and **9c** are better synergists than sulbactam against systemic infection with *Proteus vulgaris* 1028 after subcutaneous administration. The other compounds were less active in mice.

Conclusion

The chemical modifications reported here have been successful in so far that they have transformed an inactive 6-(substituted methylene)penicillanate **6a** (Table 2) into a true β-lactamase inhibitor **9c** (Table 1) whilst, the same structural modifications onto **1a** and **1b** (already potent β-lactamase inhibitors, Table 2), have had a detrimental effect on the inhibitory potency of the resulting compounds **9a** and **9b**, though they still are good β-lactamase inhibitors, comparable to sulbactam (Table 1).

Experimental

The conditions were the same as described[13] unless otherwise quoted.

p-Nitrobenzyl (6*R*)-6-(Cyanomethyl)penicillanate *S*,*S*-Dioxide (**8c**)

A solution of **7c** (2.5 g, 6.61 mmol) in 150 ml THF was treated under stirring at 20°C with *m*-ClPBA (2.66 g, 13.9 mmol). The temperature rose to 30°C. The stirred mixture was then heated at 60°C for 24 hours. The excess of peracid was destroyed as usual by the dropwise addition at 5°C of 2 ml of a 10% aqueous solution of sodium sulfite to the stirred mixture which was then concentrated under reduced pressure. The residue was partitioned between EtOAc and water. The organic phase was separated and washed successively with dilute cold $NaHCO_3$ aq. and water, dried, filtered and concentrated under reduced pressure. The residue was rapidly flash chromatographed. Elution with EtOAc-cyclohexane (1 : 1) furnished the sulfone **8c** in 63% yield (1.7 g, 4.17 mmol) as colorless crystals: IR (KBr) cm^{-1} 2262, 1803, 1761, 1324, 1119; MS *m/z* 407 (M), 343 (M − SO_2), 328, 83; ^1H NMR (60 MHz, $CDCl_3$) δ 1.35 and 1.56 (2 × s, 2-CCH_3), ~2.94 (dd, J_{gem} = 16.5 Hz, J_{68} = 8 Hz) and ~3.39 (dd, $J_{68'}$ = 9 Hz) (8-CH_2), ~4.1 (m, 6-CH), 4.02 (s, 3-CH), 4.73 (d, J_{56} = 4.8 Hz, 5-CH), 5.32 (nearly a s, O−CH_2−), 7.58 and 8.26 centers of AA'BB'-spectrum (aromatic H); MP: 125 ~ 126°C.

Further elution with EtOAc-cyclohexane (7 : 3) furnished the corresponding β-sulfoxide in 25% yield (0.66 g, 1.7 mmol).

Sodium (6*R*)-6-(Cyanomethyl)penicillanate *S*,*S*-Dioxide (**9c**)

To a stirred suspension of 2 g prereduced 10% Pd/C in 50 ml EtOAc was added a solution of **8c** (1.6 g, 3.9 mmol) in 50 ml EtOAc. The stirred mixture was hydrogenated at atmospheric pressure for 40 minutes. The catalyst was removed by filtration through $MgSO_4$. The filtrate was concentrated to a volume of 5 ml. Under cooling and stirring the solution was treated with 1.9 ml 2 N solution of sodium 2-ethylcaproate in EtOAc. Addition of 500 ml ethyl ether precipitated the Na salt. The crystalline salt was filtered, thoroughly washed with ether and dried to give 0.98 g of **9c** (3.3 mmol, 85% yield): IR (KBr) cm^{-1} 2264, 1782, 1626, 1389, 1315, 1115; ^1H NMR (60 MHz, DMSO-d_6) δ 1.35 and 1.46 (2×s, 2-CCH_3), ~3.16 (m, ~d, J=~8 Hz, 8-CH_2), 5.86 (s, 3-CH), ~4.2 (m, 6-CH), 5.04 (d, J=4.5 Hz, 5-CH); MP: 160°C (dec.).

p-Nitrobenzyl (6*R*)-6-(2-Oxo-3-phenoxypropyl)penicillanate *S*,*S*-Dioxide (**8b**)

To a stirred solution of **7b** (1.8 g, 3.65 mmol) in 100 ml THF at 20°C was added *m*-ClPBA (1.6 g, 8.0 mmol) portionwise. The temperature rose to 31°C. The stirred mixture was then heated at 64°C for 6 hours. After cooling at 0~5°C, the excess of peracid was destroyed by the dropwise addition of a 10% aqueous solution of sodium sulfite. The mixture was then concentrated under reduced pressure. The residue was partitioned between water and EtOAc. The organic phase was separated and washed successively with dilute cold $NaHCO_3$ aq. and water, dried, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography. Eluent cyclohexane - EtOAc (1 : 1). The first colorless foamy eluted material 1.5 g (2.9 mmol, 80%) was the sulfone **8b**: IR (KBr) cm^{-1} 1799, 1760, 1738, 1321, 1185; MS *m*/*z* 516 (M); ^1H NMR (80 MHz, $CDCl_3$) δ 1.35 and 1.52 (2×s, 2-CCH_3), ~3.21 (dd, J_{gem}=19 Hz, J_{68}=6.5 Hz) and ~3.7 (dd, $J_{68'}$=9.5 Hz) (8-CH_2), ~4.2 (m, 6-CH), 4.48 (s, 3-CH), 4.62 (m, nearly a s, $-OCH_2CO-$), 4.87 (d, J=5 Hz, 5-CH), 5.35 (m, nearly a s, $-CO_2CH_2-$), ~6.7~7.4 (m, aromatic H), 7.59 and 8.3 centers of AA'BB'-spectrum (aromatic H).

The second eluted material 0.3 g (0.6 mmol, 17%) was the corresponding β-sulfoxide.

Sodium (6*R*)-6-(2-Oxo-3-phenoxypropyl)penicillanate *S*,*S*-Dioxide (**9b**)

To a prereduced suspension of 2.0 g 10% Pd/C in 50 ml EtOAc was added **8b** (1.5 g, 2.9 mmol) in 50 ml EtOAc. The stirred mixture was hydrogenated for 40 minutes and worked up as for **9c** and the solvent was concentrated under reduced pressure to a volume of 5 ml. Treatment with 1.45 ml of the solution of sodium 2-ethylhexanoate followed by the same work up as for **9c** furnished 1 g of **9b** (2.5 mmol, 86% yield): IR (KBr) cm^{-1} 1781, 1737, 1615, 1388, 1317, 1117; ^1H NMR (60 MHz, D_2O) δ 1.44 and 1.56 (2×s, 2-CCH_3), ~3.15~3.62 (m, 8-CH_2), ~4.1~4.45 (m, 6-CH), 4.25 (s, 3-CH), 4.82~5.05 (m, $-OCH_2CO-$), 5.14 (d, J=4.5 Hz, 5-CH), ~6.7~7.6 (m, aromatic H). MP: 150°C (dec.).

p-Nitrobenzyl (6*R*)-6-Acetonylpenicillanate *S*,*S*-Dioxide (**8a**)

Under stirring at 20°C *m*-ClPBA (5.6 g, 29.1 mmol) was added portionwise to a solution of **7a** (4.3 g, 13.1 mmol) in 300 ml THF. The stirred mixture was then heated at 60°C for 6.5 hours; only traces of β-sulfoxide were still present. The excess of peroxide was destroyed under stirring and cooling by the dropwise addition of 4 ml of a 10% aqueous solution of sodium sulfite. The mixture was then concentrated under reduced pressure. The residue was partitioned between EtOAc and water. The organic phase was separated and washed successively with dilute cold $NaHCO_3$ aq. and water, dried, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography. Elution with cyclohexane - EtOAc (4 : 6) gave 4.5 g (10.5 mmol, 80% yield) of colorless foamy **8a**: IR ($CHCl_3$) cm^{-1} 1800, 1761, 1719, 1329, 1186; CI-MS 442 $(M+NH_4)^+$, 425 $(M+H)^+$; ^1H NMR (80 MHz, $CDCl_3$) δ 1.34 and 1.42 (2×s, 2-CCH_3), 2.23 (s, CH_3CO-), ~3.0 (dd, J_{gem}=19 Hz, J_{68}=6.5 Hz) and ~3.50 (dd, $J_{68'}$=10 Hz) (8-CH_2), ~3.93~4.33 (m, 6-CH), 4.47 (s, 3-CH), 5.85 (d, J=4.8 Hz, 5-CH), 5.35 (nearly a s, $-CO_2CH_2-$), 7.47 and 8.28 centers of AA'BB'-spectrum (aromatic H).

Sodium (6*R*)-6-Acetonylpenicillanate *S*,*S*-Dioxide (**9a**)

Starting from 4.4 g (10.3 mmol) **8a**, 3 g 10% Pd/C, (hydrogenation time: 120 minutes) and following the methodology described for **9c**, 2.9 g (9.4 mmol, 91% yield) of **9a** were obtained: IR (KBr) cm^{-1} 1782, 1730, 1316, 1117; ^1H NMR (60 MHz, DMSO-d_6) δ 1.33 and 1.41 (2×s, 2-CCH_3), 2.14 (s, CH_3CO-),

~2.88 (dd, J_{gem}=16.5 Hz, J_{68}=8 Hz) and ~3.25 (dd, $J_{68'}$=9 Hz) (8-CH_2), 3.78 (s, 3-CH), ~3.9~4.26 (m, 6-CH), 4.94 (d, J=4.8 Hz). MP: 195°C (dec.).

p-Nitrobenzyl (6*R*)-6-[(Ethoxycarbonyl)methyl]penicillanate *S*,*S*-Dioxide (**8d**)

A stirred solution of **7d** (2.35 g, 5.5 mmol) in 50 ml THF was treated portionwise at 20°C with *m*-ClPBA (2.2 g, 11.7 mmol). The mixture was then heated at 60°C for 48 hours. The excess of peracid was destroyed as above. The mixture was concentrated under reduced pressure. The residue was partitioned between water and EtOAc. The organic phase was then washed in sequence with dilute cold aqueous $NaHCO_3$, water, dried, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography. Eluent cyclohexane-EtOAc (4:6). Yield, 1.5 g (2.95 mmol, 53%) of colorless foamy **8d**: IR ($CHCl_3$) cm^{-1} 1806, 1763, 1733, 1332, 1168; CI-MS 472 $(M+NH_4)^+$, 455 $(M+H)^+$; ^1H NMR (80 MHz, $CDCl_3$) δ 1.29 (t, CH_3CH_2–), 1.37 and 1.58 (2×s, 2-CCH_3), ~2.82 (dd, J_{gem}=18 Hz, J_{68}=6.5 Hz) and ~3.43 (dd, $J_{68'}$=11 Hz) (8-CH_2), ~4.1~4.3 (m, 6-CH), 4.25 (q, CH_3CH_2–), 4.55 (s, 3-CH), 4.85 (d, J=5 Hz, 5-CH), 5.39 (nearly a s, $-CO_2CH_2$–), 7.61 and 8.35 centers of AA'BB'-spectrum (aromatic H).

The second eluted material (0.21 g) was the corresponding β-sulfoxide.

Sodium (6*R*)-6-[(Ethoxycarbonyl)methyl]penicillanate *S*,*S*-Dioxide (**9d**)

Starting with 1 g **8d**, 1 g 10% Pd/C, (hydrogenation time: 30 minutes) and following the protocol described for **9c**, 0.74 g (2.1 mmol, 85% yield) colorless **9d** were obtained: IR (KBr) cm^{-1} 1784, 1730, 1628, 1386, 1319, 1207, 1160; ^1H NMR (80 MHz, D_2O) δ 1.31 (t, CH_3CH_2–), 1.48 and 1.59 (2×s, 2-CCH_3), ~2.93 (dd, J_{gem}=18 Hz, J_{68}=7.5 Hz) and ~3.34 (dd, $J_{68'}$=10.5 Hz) (8-CH_2–), 4.29 (q, CH_3CH_2–), 4.33 (s, 3-CH), ~4.16~4.59 (m, 6-CH), 5.13 (d, J=4.5 Hz). MP: 155°C (dec.).

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