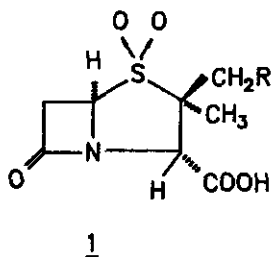


OXIDATION STUDIES ON  $\beta$ -LACTAM ANTIBIOTICS:  
 2 $\beta$ -HETEROARYLTHIOMETHYLPENAMS

Rajeshwar Singh\*, Maya P. Singh, and Ronald G. Micetich  
 SynPhar Laboratories Inc.  
 4290 - 91A Street  
 Edmonton, Alberta, Canada T6E 5V2


Abstract - The structural determination (by  $^1\text{H}$  and  $^{13}\text{C}$ -nmr) of the various products obtained by the m-chloroperbenzoic acid oxidation of 2 $\beta$ -heteroarylthiomethyl penicillins is reported.

The  $\beta$ -lactamase inhibitory activity <sup>1-4</sup> of penicillanic acid sulfones (1) has led us to study the oxidation of simple 2 $\beta$ -heteroarylthiomethyl derivatives of 6 $\beta$ -aminopenicillanic acid having two thioether functions, the nuclear 1-S and the C<sub>2</sub>, CH<sub>2</sub>S - moiety, each of which is susceptible to oxidation to sulfoxide and sulfone. We have used both m-chloroperbenzoic acid (mCPBA) and H<sub>2</sub>O<sub>2</sub>-CH<sub>3</sub>COOH as oxidant and by varying the stoichiometry of the reagents, we have studied the sequence of oxidation (scheme).



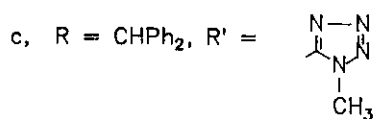
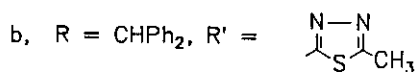
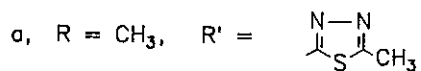
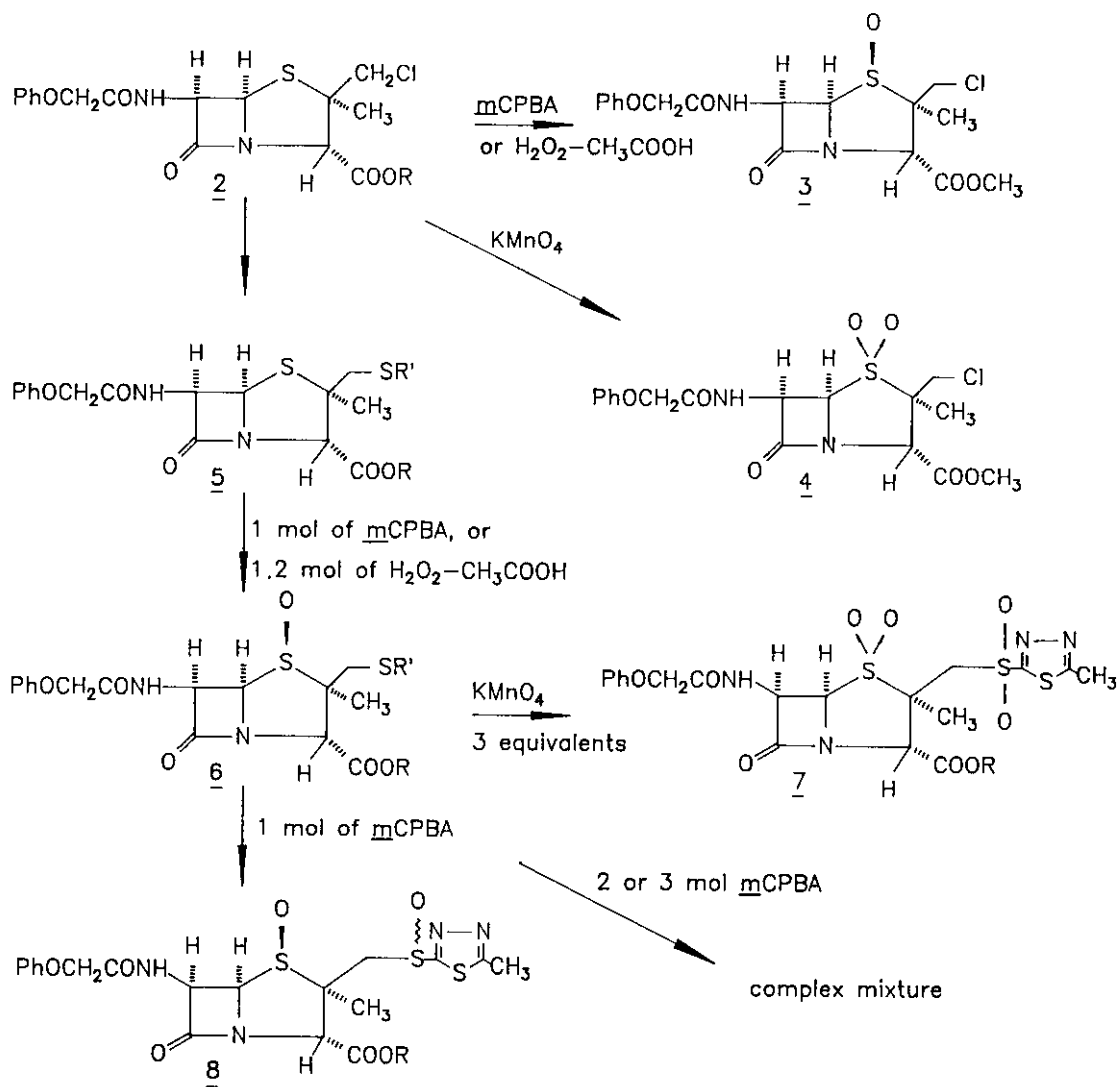
R = H (Sulbactam)

R = Cl

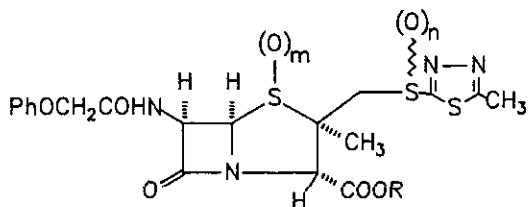
R =  (YTR 830)

2 $\beta$ -Heteroarylthiomethylpenicillins(5)<sup>5</sup>, required as a starting material, was prepared by the reaction of 2 $\beta$ -chloromethylpenicillins(2) with 5-mercaptoheteroaryls in DMF and water. The 2 $\beta$ -chloromethyl-6 $\beta$ -phenoxyacetamidopenicillins

Scheme



(2) were prepared by the method of Kamiya *et al.*<sup>6</sup> using the corresponding *unsym*-azetidinone disulfide and cupric chloride in dichloromethane. Compound 2, containing only the 1S-nuclear thio function, on treatment with either 1.2 equivalents of H<sub>2</sub>O<sub>2</sub>-CH<sub>3</sub>COOH (1.2:4, room temperature, 48 h) or *m*CPBA (0°C, 0.5 h) in dichloromethane gave the corresponding 1β-sulfoxide 3<sup>7</sup> whereas oxidation with 2 equivalent of KMnO<sub>4</sub> in CH<sub>3</sub>COOH-H<sub>2</sub>O (85:15) gave the corresponding sulfone 4<sup>8</sup>. Oxidation of the 2β-heteroarylthiomethylpenicillins (5) prepared by the reported method<sup>5</sup> with one equivalent of *m*CPBA (0°C, 0.5 h) or 1.2 equivalent of H<sub>2</sub>O<sub>2</sub>-CH<sub>3</sub>COOH (1.2:4, room temperature, 48 h) in dichloromethane gave compound 6 in which the nuclear sulphur is oxidized. Compounds 6 (a,b) upon further oxidation with another equivalent of *m*CPBA (0-10°C, 2 h) afforded a mixture of isomers (α and β sulfoxide at CH<sub>2</sub>S-) 8 (a and b) in which both thioether functions were oxidized to sulfoxide. Compound 6c treated with *m*CPBA under similar conditions did not give the requisite disulfoxide compound 8c, indicating that the nature of the heterocyclic moiety is important in determining the oxidation pattern of the compound. Compound 6 (a and b) when treated with three equivalents of KMnO<sub>4</sub> in acetic acid - water (85:15) gave the disulfones 7 (a and b) which were also obtained from oxidation of compounds 5 (a and b) with KMnO<sub>4</sub> (4 equivalents) in acetic acid - water. Compounds 5c and 6c on treatment with KMnO<sub>4</sub> did not give the disulfone 7c but gave only the monosulfone in which the ring S is oxidized<sup>9</sup>. Compound 6a on further oxidation with two equivalents of *m*CPBA (room temperature, 6 h) gave a mixture of compounds (tlc showed two spots) which were separated by column chromatography (silica gel column, ethyl acetate: hexane (80:20) as eluant). The nmr spectrum of the first fraction (8%) showed a mixture of compounds 9 and 10, and the second fraction (35%) showed the presence of a mixture of compounds 8a (α and β-isomer). Oxidation of compound 6a with three equivalents of *m*CPBA (room temperature, 24 h) gave three fractions after chromatographic separation. The first fraction (8%) was identified as compound 7a, and the second fraction (16%) as a mixture of compounds 9 and 10, whereas the third fraction was identified as 8a.



9; R = CH<sub>3</sub>, m = 1, n = 2

10; R = CH<sub>3</sub>, m = 2, n = 1

The nmr data of the oxidation products are summarized in Table-1 ( $^1\text{H}$ -nmr) and Table-2 ( $^{13}\text{C}$ -nmr).

#### Structural determination of oxidation products:

The structures of the oxidation products were determined on the basis of their  $^{13}\text{C}$ -nmr data. It is clear from Table 2, that when the nuclear sulphur is oxidized to sulfoxide (3) there is a remarkable change in the chemical shifts of carbons  $\text{C}_2$  (67.05  $\rightarrow$  80.87),  $\text{C}_3$  (65.10  $\rightarrow$  64.54),  $\text{C}_5$  (67.99  $\rightarrow$  75.94),  $\text{C}_6$  (59.53  $\rightarrow$  55.83),  $\text{C}_2$ - $\beta\text{CH}_2$  (52.63  $\rightarrow$  43.25), and  $\text{C}_2$ - $\alpha\text{CH}_2$  (22.00  $\rightarrow$  14.50). When the nuclear sulphur is oxidized to sulfone (4), there is comparatively lower chemical shift for  $\text{C}_2$ ,  $\text{C}_3$ , and  $\text{C}_6$ , but more for  $\text{C}_5$  (67.99  $\rightarrow$  62.24),  $\text{C}_2$ - $\beta\text{CH}_2$  (52.63  $\rightarrow$  43.96) and  $\text{C}_2$ - $\text{CH}_3$  (22.00  $\rightarrow$  16.41) as compared to the starting material. The oxidation of compound 5a with 1 equivalent of mCPBA gave the compound 6a in which the change in chemical shift compared to compound 3 is the same, and it indicated that the nuclear sulphur was oxidized to the sulfoxide. Further oxidation of compound 6a gave the compound 8a (mixture of  $\alpha$  and  $\beta$  isomers at  $-\text{CH}_2\text{S}-$ ) in which the chemical shifts (see Table 2) indicate that nuclear sulphur as well as the  $-\text{CH}_2\text{S}-$  function has been oxidized to sulfoxides.

Oxidation of compound 6a with 2 equivalents of mCPBA gave compound 9, 10 and 8a, and oxidation with 3 equivalents of mCPBA gave compound 7a, 9, 10 and 8a. The  $^{13}\text{C}$ -chemical shifts of these compounds summarized in Table 2 indicate that compound 7a is a sulfone, compound 9 is a sulfoxide at nuclear sulphur and sulfone at  $-\text{CH}_2\text{S}-$  function, compound 10 is a sulfone at nuclear sulphur and sulfoxide at  $-\text{CH}_2\text{S}-$  function.

Thus it is clear from the oxidation studies on the 2 $\beta$ -heteroarylthiomethylpenicillins that the nuclear sulphur is oxidized to the sulfoxide in preference to the side chain sulphur, but oxidation of the side chain sulphur follows immediately after the oxidation of the nuclear sulphur depending on the substituent at the side chain sulphur<sup>9</sup>. Once the disulfoxide is formed both nuclear and side chain sulphur atoms become equally susceptible to oxidation to yield the respective sulfones unlike the case of the 3-heteroarylthiomethylcephalosporins<sup>10</sup>.

#### EXPERIMENTAL

Ir Spectra were recorded on a Nicolet DX-FT IR spectrophotometer and nmr spectra on a Bruker AM-300 spectrometer using tetramethylsilane as internal standard.

Reactions were monitored by thin layer chromatography (plate coated with silica gel 60F<sub>254</sub> of thickness 0.2 mm). The spectroscopic data are summarized in Table 1 ( $^1\text{H}$ -nmr) and Table 2 ( $^{13}\text{C}$ -nmr).

Methyl 2 $\alpha$ -methyl-2 $\beta$ -(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-6 $\beta$ -phenoxy-acetamidopenam-3 $\alpha$ -carboxylate (5a):

To a solution of methyl 2 $\beta$ -chloromethyl-2 $\alpha$ -methyl-6 $\beta$ -phenoxyacetamidopenam-3 $\alpha$ -carboxylate 2a (3.98 g, 10 mmol) in 72 ml of DMF:H<sub>2</sub>O (5:1) was added NaHCO<sub>3</sub> (0.966 g, 11.5 mmol) and 5-mercapto-1,3,4-thiadiazole (1.52 g, 11.5 mmol). The reaction mixture was stirred at room temperature for 24 h, then diluted with water and extracted with ethyl acetate. The organic extract was washed with water (X5), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to a foamy residue (4.66 g) which was chromatographed over silica gel using ethyl acetate - hexane (80:20) as eluant. The desired compound 5a was obtained as a white foam upon concentration of the selected fractions, yield 1.2 g (25%); ir(KBr): 3386, 3280, 1787, 1750, 1693 cm<sup>-1</sup>.

Diphenylmethyl 2 $\alpha$ -methyl-2 $\beta$ -(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-6 $\beta$ -phenoxyacetamidopenam-3 $\alpha$ -carboxylate(5b):

It was prepared by a similar method as discussed above for compound 5a using diphenylmethyl-2 $\beta$ -chloromethyl-6 $\beta$ -phenoxyacetamidopenam-3 $\alpha$ -carboxylate (2b) as starting material. The desired compound 5b was obtained as white foam, yield 31%; ir(KBr): 3345, 3066, 2955, 1795, 1745, 1696 cm<sup>-1</sup>.

Diphenylmethyl 2 $\alpha$ -methyl-2 $\beta$ -(1-methyl-1,2,3,4-tetrazol-5-yl)thiomethyl-6 $\beta$ -phenoxyacetamidopenam-3 $\alpha$ -carboxylate (5c):

Prepared by similar method as described for compound 5a using 2b and 5-mercapto-1-methyl-1,2,3,4-tetrazole. The desired compound 5a was obtained as off white foam, yield 15%; ir(KBr): 3370, 3059, 2961, 1779, 1748, 1702 cm<sup>-1</sup>.

Methyl 2 $\beta$ -chloromethyl-2 $\alpha$ -methyl-6 $\beta$ -phenoxyacetamidopenam-3 $\alpha$ -carboxylate-1 $\beta$ -sulfoxide (3):

Method A:

To an ice cooled solution of 2a (3.98 g, 10 mmol) in dichloromethane (100 ml), mCPBA (2.15 g, 10 mmol, 80%) was added in portions over 15 min and the reaction mixture was stirred at the same temperature for another 30 min. The separated solid was filtered and the filtrate (dichloromethane portion) was washed successively with NaHCO<sub>3</sub>, water and brine solution. The dichloromethane layer was then separated and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to provide crude 3 which was purified by column chromatography using silica gel as adsorbent and ethyl acetate-hexane (80:20) as eluant. The desired product was obtained as a white foam, yield: 2.9 g (70%); ir (KBr): 3377, 2967, 1802, 1757, 1692 cm<sup>-1</sup>.

Method B:

To a solution of 2a (0.80 g, 2 mmol) in dichloromethane (20 ml), AcOH (960 mg, 8 mmol) and 30% H<sub>2</sub>O<sub>2</sub> (0.272 mg, 2.4 mmol) was added and the mixture was stirred at room temperature for 48 h. The reaction mixture was worked up as usual and purified over silica gel column using ethyl acetate - hexane (80:20) as eluant to obtain the desired compound 3 as white foam, yield 700 mg (84%).

Methyl 2 $\alpha$ -methyl-2 $\beta$ -(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-6 $\beta$ -phenoxy-acetamidopenam-3 $\alpha$ -carboxylate-1 $\beta$ -sulfoxide (6a):

Prepared by similar methods as described for compound 3 using compound 5a as starting material. The desired product was obtained as white foam, yield 82%; ir(KBr): 3386, 2935, 1798, 1756, 1691, cm<sup>-1</sup>.

Diphenylmethyl 2 $\alpha$ -methyl-2 $\beta$ -(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-6 $\beta$ -phenoxy-acetamidopenam-3 $\alpha$ -carboxylate-1 $\beta$ -sulfoxide (6b):

Prepared by similar methods as described above for compound 3 using compound 5b as starting material. The desired product was obtained as a white foam, yield 60%; ir(KBr): 3394, 3041, 2951, 1798, 1752, 1693 cm<sup>-1</sup>.

Diphenylmethyl 2 $\alpha$ -methyl-2 $\beta$ -(1-methyl-1,2,3,4-tetrazol-5-yl)thiomethyl-6 $\beta$ -phenoxy-acetamidopenam-3 $\alpha$ -carboxylate-1 $\beta$ -sulfoxide (6c):

Prepared by similar methods as described for compound 3 using compound 5c as starting material. The desired product was obtained as a white foam, yield 85%; ir(KBr): 3379, 3066, 3032, 2978, 1800, 1754, 1691 cm<sup>-1</sup>.

Methyl 2 $\beta$ -chloromethyl-2 $\alpha$ -methyl-6 $\beta$ -phenoxyacetamidopenam-3 $\alpha$ -carboxylate 1,1-dioxide (4):

To a solution of methyl 2 $\beta$ -chloromethyl-2 $\alpha$ -methyl-6 $\beta$ -phenoxyacetamidopenam-3 $\alpha$ -carboxylate 2 (797 mg, 2 mmol) in 40 ml of AcOH-H<sub>2</sub>O (17:3), potassium permanganate (663.6 mg, 4.2 mmol) was added in portions. The reaction mixture was stirred at room temperature for 3 h, excess KMnO<sub>4</sub> was decomposed with H<sub>2</sub>O<sub>2</sub>, the reaction mixture was diluted with ice cold water, and the solid that separated was extracted with dichloromethane. The organic phase was washed successively with aqueous NaHCO<sub>3</sub> solution, water and brine; dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was chromatographed over silica gel using ethyl acetate-hexane (80:20) as eluant. The pure compound was obtained as a white foam, yield 490 mg (57%); ir(KBr): 3407, 2950, 1807, 1760, 1701 cm<sup>-1</sup>.

Methyl 2 $\alpha$ -methyl-2 $\beta$ -(2-methyl-1,3,4-thiadiazol-5-yl)sulphonylmethyl-6 $\beta$ -phenoxyacetamido-penam-3 $\alpha$ -carboxylate 1,1-dioxide (7a):

Prepared by the similar method as described for compound 4. Oxidation of either compound 6a with 3 equivalents of  $\text{KMnO}_4$  or compound 5a with 4 equivalents of  $\text{KMnO}_4$  gave the product 7a as a white foam, yield 25%; ir(KBr): 3402, 2943, 1810, 1758, 1700  $\text{cm}^{-1}$ .

Diphenylmethyl 2 $\alpha$ -methyl-2 $\beta$ -(2-methyl-1,3,4-thiadiazol-5-yl)sulphonylmethyl-6 $\beta$ -phenoxyacetamidopenam-3 $\alpha$ -carboxylate 1,1-dioxide (7b):

Prepared by the similar method as described for compound 4. Oxidation of either compound 6b with 3 equivalents of  $\text{KMnO}_4$  or compound 5b with 4 equivalents of  $\text{KMnO}_4$  gave the product 7b as a white foam, yield 21%; ir(KBr): 3402, 2943, 1810, 1751, 1698  $\text{cm}^{-1}$ .

Oxidation of compound 6a with one equivalent of mCPBA:

m-Chloroperbenzoic acid (78%, 94 mg, 0.42 mmol) was added to an ice cooled solution of 6a (215.4 mg, 0.42 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at the same temperature (0-10°C) for 2 h and worked up as usual. The residue was chromatographed on silica gel using ethyl acetate-hexane (80:20) as eluant. Compound 8a was obtained as a white foam, yield 160 mg (72%); ir(KBr): 3385, 2934, 1798, 1757, 1692  $\text{cm}^{-1}$ . Similarly the oxidation of compound 6b with one equivalent of mCPBA gave 8b as a white foam, in 71% yield; ir(KBr): 3392, 2938, 1801, 1757, 1692  $\text{cm}^{-1}$ .

Oxidation of compound 6a with two equivalents of mCPBA:

Compound 6a was oxidized with 2 equivalents of mCPBA as described above. The reaction mixture was stirred at room temperature for 6 h and worked up as usual. The tlc of the crude product showed two spots which were separated by column chromatography on silica gel using ethyl acetate-hexane (80:20) as eluant. The fractions, thus obtained corresponding to upper and lower tlc spots were characterized by their nmr spectra. One fraction (8%) corresponding to the upper spot indicated to be a mixture of compounds 9 and 10 whereas the other fraction (35%) corresponding to the lower spot indicated to be a mixture of  $\alpha$  and  $\beta$  isomers of compound 8a.

TABLE 1:  $^1\text{H-nmr}(\text{CDCl}_3)$   $\delta$  values of oxidative products

COMP. NO.	C <sub>2</sub> - CH <sub>2</sub>	C <sub>2</sub> - CH <sub>3</sub>	C <sub>3</sub> -H	C <sub>5</sub> -H	C <sub>6</sub> - H	C <sub>2</sub> - CH <sub>3</sub>	N <sub>1</sub> - CH <sub>3</sub>	NH
2	3.52 and 3.58 (ABq, J=11.52 Hz, 2H)	1.55 (s, 3H)	5.00 (s, 1H)	5.72 (bs, 1H)	5.69 (dd, J <sub>1</sub> =8.02, J <sub>2</sub> =3.20 Hz, 1H)	----	----	7.5 (d, J=8.02 Hz, 1H)
3	4.0 and 4.3 (ABq, J=12.24 Hz, 2H)	1.35 (s, 3H)	4.67 (s, 1H)	5.06 (d, J=4.59 Hz, 1H)	6.15 (dd, J <sub>1</sub> =9.18, J <sub>2</sub> =4.59 Hz, 1H)	----	-----	8.24 (d, J=9.18 Hz, 1H)
4	3.96 and 4.24 (ABq, J=12.24 Hz, 2H)	1.60 (s, 3H)	4.66 (s, 1H)	4.89 (d, J=4.48 Hz, 1H)	6.27 (dd, J <sub>1</sub> =10.46, J <sub>2</sub> =4.48 Hz, 1H)	----	-----	8.22 (d, J=10.46 Hz, 1H)
5a	3.75 and 3.98 (ABq, J=11.92 Hz, 2H)	1.60 (s, 3H)	4.85 (s, 1H)	5.69 (d, J=4.06 Hz, 1H)	5.85 (dd, J <sub>1</sub> =8.7, J <sub>2</sub> =4.06 Hz, 1H)	2.65 (s, 3H)	-----	7.74 (d, J=8.7 Hz, 1H)
5b	3.72 and 4.05 (ABq, J=14.31 Hz, 2H)	1.40 (s, 3H)	4.93 (s, 1H)	5.72 (d, J=4.62 Hz, 1H)	5.86 (dd, J <sub>1</sub> =9.25, J <sub>2</sub> =4.62 Hz, 1H)	2.64 (s, 3H)	-----	7.76 (d, J=9.25 Hz, 1H)
5c	3.75 and 3.97 (ABq, J=13.83 Hz, 2H)	1.37 (s, 3H)	4.88 (s, 1H)	5.74 (d, J=3.79 Hz, 1H)	5.85 (dd, J <sub>1</sub> =8.59, J <sub>2</sub> =3.79 Hz, 1H)	----	3.86 (s, 3H)	7.82 (d, J=8.59 Hz, 1H)
6a	4.0 and 4.41 (ABq, J=14.03 Hz, 2H)	1.35 (s, 3H)	4.83 (s, 1H)	5.12 (d, J=4.91 Hz, 1H)	6.16 (dd, J <sub>1</sub> =10.52, J <sub>2</sub> =4.91 Hz, 1H)	2.75 (s, 3H)	-----	8.22 (d, J=10.52 Hz, 1H)
6b	4.05 and 4.37 (ABq, J=14.51 Hz, 2H)	1.07 (s, 3H)	4.94 (s, 1H)	5.01 (d, J=4.60 Hz, 1H)	6.16 (dd, J <sub>1</sub> =10.55, J <sub>2</sub> =4.6 Hz, 1H)	2.75 (s, 3H)	-----	8.22 (d, J=10.55 Hz, 1H)
6c	4.14 and 4.37 (ABq, J=14.2 Hz, 2H)	1.07 (s, 3H)	4.97 (s, 1H)	5.03 (d, J=4.64 Hz, 1H)	6.17 (dd, J <sub>1</sub> =10.10, J <sub>2</sub> =4.64 Hz, 1H)	----	3.95 (s, 3H)	8.23 (d, J=10.10 Hz, 1H)
7a	4.30 and 4.36 (ABq, J=15.17 Hz, 2H)	1.80 (s, 3H)	5.01 (s, 1H)	4.95 (d, J=4.42 Hz, 1H)	6.29 (dd, J <sub>1</sub> =10.66, J <sub>2</sub> =4.42 Hz, 1H)	2.91 (s, 3H)	----	8.14 (d, J=10.66 Hz, 1H)
7b	4.24 and 4.28 (ABq, J=13.61 Hz, 2H)	1.52 (s, 3H)	5.20 (s, 1H)	4.87 (d, J=4.33 Hz, 1H)	6.26 (dd, J <sub>1</sub> =10.52, J <sub>2</sub> =4.33, 1H)	1.89 (s, 3H)	----	8.15 (d, J=10.52 Hz, 1H)
8a	3.84 and 4.14 (ABq, J=13.88 Hz, 0.8H) 4.02 and 4.20 (ABq, J=14.27 Hz, 1.2H)	1.44 (s, 1.8H) 1.58 (s, 1.2H)	4.76 (s, 0.4H) 4.85 (s, 0.6H)	5.15 (d, J=4.45 Hz, 0.4H) 5.18 (d, J=4.45 Hz, 0.6H)	6.19 (dd, J <sub>1</sub> =10.06, J <sub>2</sub> =4.64, 1H)	2.89 (s, 1.8H) 2.92 (s, 1.2H)	----	8.11 (d, J=10.43 Hz, 0.4H) 8.17 (d, J=10.43 Hz, 0.6H)
8b	3.86 and 4.18 (ABq, J=13.88 Hz, 0.8H) 3.94 and 4.16 (ABq, J=14.27 Hz, 1.2H)	1.17 (s, 1.2H) 1.18 (s, 1.8H)	4.88 (s, 0.4H) 4.96 (s, 0.6H)	5.10 (d, J=4.64 Hz, 0.4H) 5.11 (d, J=4.64 Hz, 0.6H)	6.19 (dd, J <sub>1</sub> =10.06, J <sub>2</sub> =4.64, 1H)	2.86 (s, 1.8H) 2.87 (s, 1.2H)	----	8.11 (d, J=10.06 Hz, 0.4H) 8.14 (d, J=10.06 Hz, 0.6H)
9	3.8 (m, 2H)	1.56 (s, 3H)	4.74 (s, 1H)	5.22 (d, J=4.68 Hz, 1H)	6.20 (dd, J <sub>1</sub> =11.20, J <sub>2</sub> =4.68 Hz, 1H)	2.94 (s, 3H)	----	8.16 (d, J=11.20 Hz, 1H)
10	3.8 (m, 2H)	1.76 (s, 1.8H) 1.82 (s, 1.2H)	5.07 (s, 0.4H) 5.14 (s, 0.6H)	4.90 (d, J=4.68 Hz, 0.4H) 4.95 (d, J=4.68 Hz, 0.6H)	6.30 (dd, J <sub>1</sub> =11.20, J <sub>2</sub> =4.68 Hz, 1H)	2.90 (s, 3H)	----	8.14 (d, J=11.20, 0.6H) 8.19 (d, J=11.20, 0.4H)



TABLE 2:  $^{13}\text{C}$ -nmr chemical shift values of oxidation products of 2 $\beta$ -chloromethyl and 2 $\beta$ -(2-methyl-1,3,4-thiadiazol-5-yl)thiomethylpenicillins

COMP. NO.	C <sub>2</sub>	C <sub>3</sub>	C <sub>5</sub>	C <sub>6</sub>	C <sub>2</sub> -CH <sub>2</sub>	C <sub>2</sub> -CH <sub>3</sub>	C <sub>5</sub> '	C <sub>2</sub> '	C <sub>2</sub> '-CH <sub>3</sub>
2	67.05	65.10	67.99	59.53	52.63	22.00	-----	-----	-----
3	80.87	64.54	75.94	55.83	43.25	14.50	-----	-----	-----
4	67.82	67.32	62.24	57.20	43.96	16.41	-----	-----	-----
5a	73.70	67.40	67.80	58.80	46.20	23.8	165.60	164.20	14.80
6a	80.78	65.88	76.34	56.03	35.05	15.60	166.17	163.51	15.15
7a	65.86	66.76	62.46	58.74	56.47	16.08	171.23	166.13	17.70
8a	75.92 (66.74)	66.74 (66.74)	77.32	55.76 (56.00)	57.70 (58.03)	15.06	176.49	169.87 (170.09)	16.20
9	75.89	62.27	77.27	55.96	54.72	15.26	172.16	167.32	16.11
10	66.25 (66.40)	66.61	62.21 (62.09)	57.57 (57.21)	60.97 (59.91)	18.55 (18.69)	176.94	169.91 (171.13)	16.17

Oxidation of compound 6a with three equivalents of mCPBA:

Compound 6a was oxidized with 3 equivalents of mCPBA as described above. The reaction mixture was stirred at room temperature for 24 h and worked up as usual. The tlc of the crude product showed 3 spots which were separated by preparative TLC on silica gel using ethyl acetate-hexane (80:20) as solvent. Fraction A (8%) was compound 7a with some impurities as assigned by nmr, fraction B (16%) was identified as a mixture of compounds 9 and 10 which could not be separated by column chromatography due to same Rf, and fraction C (8.1%) was identified as 8a.

ACKNOWLEDGEMENT

M.P.S. would like to thank the Alberta Heritage Foundation for Medical Research, Alberta, Canada, for the award of Post-Doctoral Fellowship.

REFERENCES

1. N. Aswapokee and H. C. New, J. Antibiotic., 1978, 31, 1238.
2. W. J. Gottstein, L. B. Crast Jr., R. G. Graham, U.G. Haynes, and D.N. McGregor, J. Med. Chem., 1981, 24, 1531.
3. W. J. Gottstein, U. J. Haynes, and D. N. McGregor, J. Med. Chem., 1985, 28, 518.
4. T. W. Hall, S. N. Maiti, R. G. Micetich, P. Spevak, S. Yamabe, N. Ishida, M. Kajitani, M. Tanaka, and T. Yamasaki, "Recent Advances in the Chemistry of  $\beta$ -Lactam Antibiotics", Editors: A.G. Brown and S. M. Roberts, The Royal Society of Chemistry, Berlington House, London, 1984, 242.
5. T. Kamiya, T. Teraji, M. Hashimoto, and O. Nakaguchi, U.S. Patent 3954732; 1976.
6. T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Makaguchi, and T. Oku, Tetrahedron Lett., 1973, 3001.
7. R. G. Micetich, R. Singh, and S. N. Maiti, Heterocycles, 1984, 22, 531.
8. E. Guddal, P. Morch, and L. Tybring, Tetrahedron Lett., 1962, 381.
9. H. Tanaka, M. Tanaka, A. Nakai, S. Yamada, N. Ishida, T. Otani, and S. Torii, J. Antibiotic., 1988, 41, 579.
10. M.P. Singh, R. Singh, P. Spevak, S.N. Maiti, and R.G. Micetich, Abstracts of Papers of 28th InterSci. Conf. on Antimicrob. Agents Chemother., No. 424, Los Angeles, 1988, 183.

Received, 17th January, 1989