OXIDATION STUDIES ON β-LACTAM ANTIBIOTICS: 2β-HETEROARYLTHIOMETHYLPENAMS

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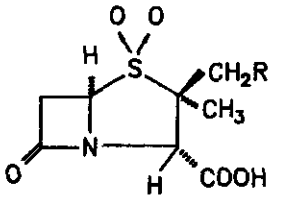
Abstract - The structural determination (by ^{1}H and ^{13}C-nmr) of the various products obtained by the m-chloroperbenzoic acid oxidation of 2β-heteroarylthiomethyl penicillins is reported.

The β-lactamase inhibitory activity [1-4] of penicillanic acid sulfones (1) has led us to study the oxidation of simple 2β-heteroarylthiomethyl derivatives of 6β-aminopenicillanic acid having two thioether functions, the nuclear 1-S and the C_2, CH_2S - moiety, each of which is susceptible to oxidation to sulfoxide and sulfone. We have used both m-chloroperbenzoic acid (mCPBA) and H_2O_2-CH_3COOH as oxidant and by varying the stoichiometry of the reagents, we have studied the sequence of oxidation (scheme).



1

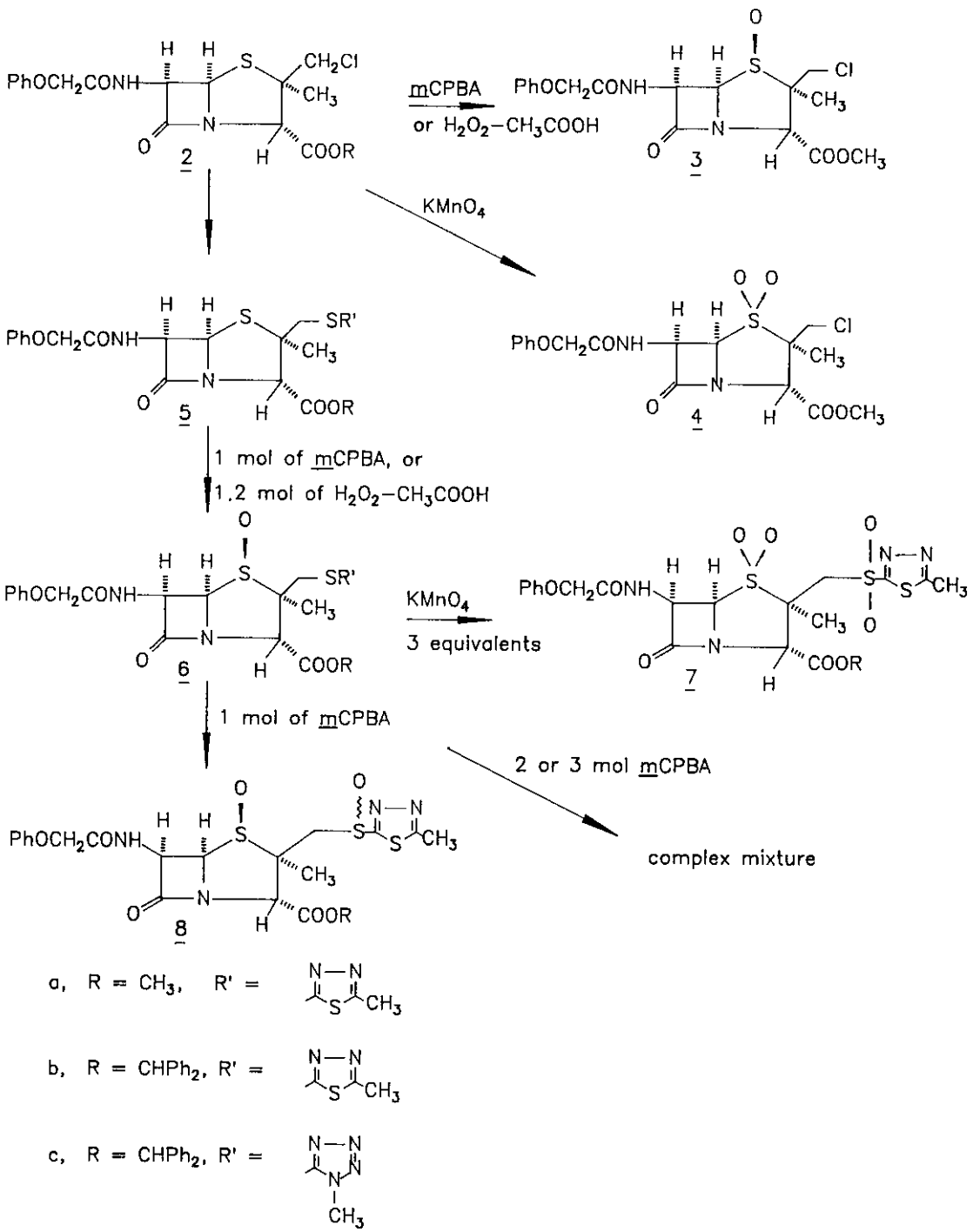
R = H (Sulbactam)

R = Cl

R =  (YTR 830)

2β-Heteroarylthiomethylpenicillins(5)[5], required as a starting material, was prepared by the reaction of 2β-chloromethylpenicillins(2) with 5-mercaptoheteroaryls in DMF and water. The 2β-chloromethyl-6β-phenoxyacetamidopenicillins

Scheme



a, R = CH_3, R' =

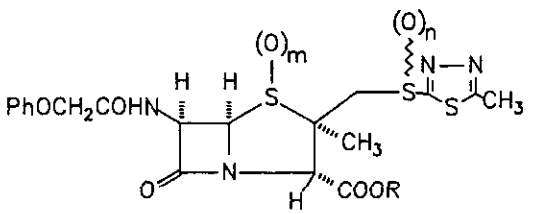
b, R = $CHPh_2$, R' =

c, R = $CHPh_2$, R' =

(2) were prepared by the method of Kamiya et al.[6] 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_2O_2-CH_3COOH (1.2:4, room temperature, 48 h) or mCPBA (0°C, 0.5 h) in dichloromethane gave the corresponding 1β-sulfoxide 3[7] whereas oxidation with 2 equivalent of $KMnO_4$ in CH_3COOH-H_2O (85:15) gave the corresponding sulfone 4[8]. Oxidation of the 2β-heteroarylthiomethylpenicillins (5) prepared by the reported method[5] with one equivalent of mCPBA (0°C, 0.5 h) or 1.2 equivalent of H_2O_2-CH_3COOH (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 mCPBA (0-10°C, 2 h) afforded a mixture of isomers (α and β sulfoxide at CH_2S-) 8 (a and b) in which both thioether functions were oxidized to sulfoxide. Compound 6c treated with mCPBA 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 $KMnO_4$ 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 $KMnO_4$ (4 equivalents) in acetic acid - water. Compounds 5c and 6c on treatment with $KMnO_4$ did not give the disulfone 7c but gave only the monosulfone in which the ring S is oxidized[9].

Compound 6a on further oxidation with two equivalents of mCPBA (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 mCPBA (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_3, m = 1, n = 2

10; R = CH_3, m = 2, n = 1

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

Structural determination of oxidation products:

The structures of the oxidation products were determined on the basis of their ^{13}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 C_2 (67.05 ⟶ 80.87), C_3 (65.10 ⟶ 64.54), C_5 (67.99 ⟶ 75.94), C_6 (59.53 ⟶ 55.83), C_2-βCH_2 (52.63 ⟶ 43.25), and C_2-αCH_2 (22.00 ⟶ 14.50). When the nuclear sulphur is oxidized to sulfone (4), there is comparatively lower chemical shift for C_2, C_3, and C_6, but more for C_5 (67.99 ⟶ 62.24), C_2-βCH_2 (52.63 ⟶ 43.96) and C_2-CH_3 (22.00 ⟶ 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 α and β isomers at -CH_2S-) in which the chemical shifts (see Table 2) indicate that nuclear sulphur as well as the -CH_2S- 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}C-chemical shifts of these compounds summarized in Table 2 indicate that compound 7a is a sulfone, compound 9 is a sufoxide at nuclear sulphur and sulfone at -CH_2S- function, compound 10 is a sulfone at nuclear sulphur and sulfoxide at -CH_2S- function.

Thus it is clear from the oxidation studies on the 2β-heteroarylthiomethyl-penicillins 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[9]. 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[10].

EXPERIMENTAL

Ir Spectra were recorded on a Nicolet DX-FT IR spectrophotometer and nmr spectra on a Brucker AM-300 spectrometer using tetramethylsilane as internal standard. Reactions were monitored by thin layer chromatography (plate coated with silica gel $60F_{254}$ of thickness 0.2 mm). The spectroscopic data are summarized in Table 1 (^{1}H-nmr) and Table 2 (^{13}C-nmr).

Methyl 2α-methyl-2β-(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-6β-phenoxy-acetamidopenam-3α-carboxylate (5a):

To a solution of methyl 2β-chloromethyl-2α-methyl-6β-phenoxyacetamidopenam-3α-carboxylate 2a (3.98 g, 10 mmol) in 72 ml of DMF:H_2O (5:1) was added $NaHCO_3$ (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_2SO_4 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^{-1}.

Diphenylmethyl 2α-methyl-2β-(2-methyl-1,3, 4-thiadiazol-5-yl)thiomethyl-6β-phenoxyacetamidopenam-3α-carboxylate(5b):

It was prepared by a similar method as discussed above for compound 5a using diphenylmethyl-2β-chloromethyl-6β-phenoxyacetamidopenam-3α-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^{-1}.

Diphenylmethyl 2α-methyl-2β-(1-methyl-1,2,3,4-tetrazol-5-yl)thiomethyl-6β-phenoxyacetamidopenam-3α-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^{-1}.

Methyl 2β-chloromethyl-2α-methyl-6β-phenoxyacetamidopenam-3α-carboxylate-1β-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 $NaHCO_3$, water and brine solution. The dichloromethane layer was then separated and dried over Na_2SO_4, 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^{-1}.

Method B:

To a solution of 2a (0.80 g, 2 mmol) in dichloromethane (20 ml), AcOH (960 mg, 8 mmol) and 30% H_2O_2 (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 2α-methyl-2β-(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-6β-phenoxyacetamidopenam-3α-carboxylate-1β-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^{-1}.

Diphenylmethyl 2α-methyl-2β-(2-methyl-1,3,4-thiadiazol-5-yl)thiomethyl-6β-phenoxyacetamidopenam-3α-carboxylate-1β-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^{1}.

Diphenylmethyl 2α-methyl-2β-(1-methyl-1,2, 3,4-tetrazol-5yl)thiomethyl-6β-phenoxyacetamidopenam-3α-carboxylate-1β-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^{-1}.

Methyl 2β-chloromethyl-2α-methyl-6β-phenoxyacetamidopenam-3α-carboxylate 1,1-dioxide (4):

To a solution of methyl 2β-chloromethyl-2α-methyl-6β-phenoxyacetamidopenam-3α-carboxylate 2 (797 mg, 2 mmol) in 40 ml of AcOH-H_2O (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 $KMnO_4$ was decomposed with H_2O_2, the reation mixture was diluted with ice cold water, and the solid that separated was extracted with dichloromethane. The organic phase was washed successively with aqueous $NaHCO_3$ solution, water and brine; dried over Na_2SO_4, 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^{-1}.

Methyl 2α-methyl-2β-(2-methyl-1,3,4-thiadiazol-5-yl)sulphonylmethyl-6β-phenoxyacetamidopenam-3α-carboxylate 1,1-dioxide (7a):

Prepared by the similar method as described for compound 4. Oxidation of either compound 6a with 3 equivalents of $KMnO_4$ or compound 5a with 4 equivalents of $KMnO_4$ gave the product 7a as a white foam, yield 25%; ir(KBr): 3402, 2943, 1810, 1758, 1700 cm^{-1}.

Diphenylmethyl 2α-methyl-2β-(2-methyl-1,3,4-thiadiazol-5-yl)sulphonylmethyl-6β-phenoxyacetamidopenam-3α-carboxylate 1,1-dioxide (7b):

Prepared by the similar method as described for compound 4. Oxidation of either compound 6b with 3 equivalents of $KMnO_4$ or compound 5b with 4 equivalents of $KMnO_4$ gave the product 7b as a white foam, yield 21%; ir(KBr): 3402, 2943, 1810, 1751, 1698 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 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 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 α and β isomers of compound 8a.

TABLE 1: ^{1}H-nmr($CDCl_3$) δ values of oxidative products

COMP. NO.	C_2 - CH_2	C_2-CH_3	C_3-H	C_5-H	C_6 - H	C_2 - CH_3	N_1 - CH_3	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_1=8.02, J_2=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_1=9.18, J_2=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_1=10.46, J_2=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_1=8.7, J_2=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_1=9.25, J_2=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_1=8.59, J_2=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_1=10.52, J_2=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_1=10.55, J_2=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_1=10.10, J_2=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_1=10.66, J_2=4.42 Hz, 1H)	2.91 (s, 3H)	----	8.14 (d, J=10.66 Hz, 1H0
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_1=10.52, J_2=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_1=10.06, J_2=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_1=10.06, J_2=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_1=11.20, J_2=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_1=11.20, J_2=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}C-nmr chemical shift values of oxidation products of 2β-chloromethyl and 2β-(2-methyl-1,3,4-thiadiazol-5-yl)thiomethylpenicillins

COMP. NO.	C_2	C_3	C_5	C_6	C_2-CH_2	C_2-CH_3	C_5'	C_2'	C_2'-CH_3
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)	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.

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