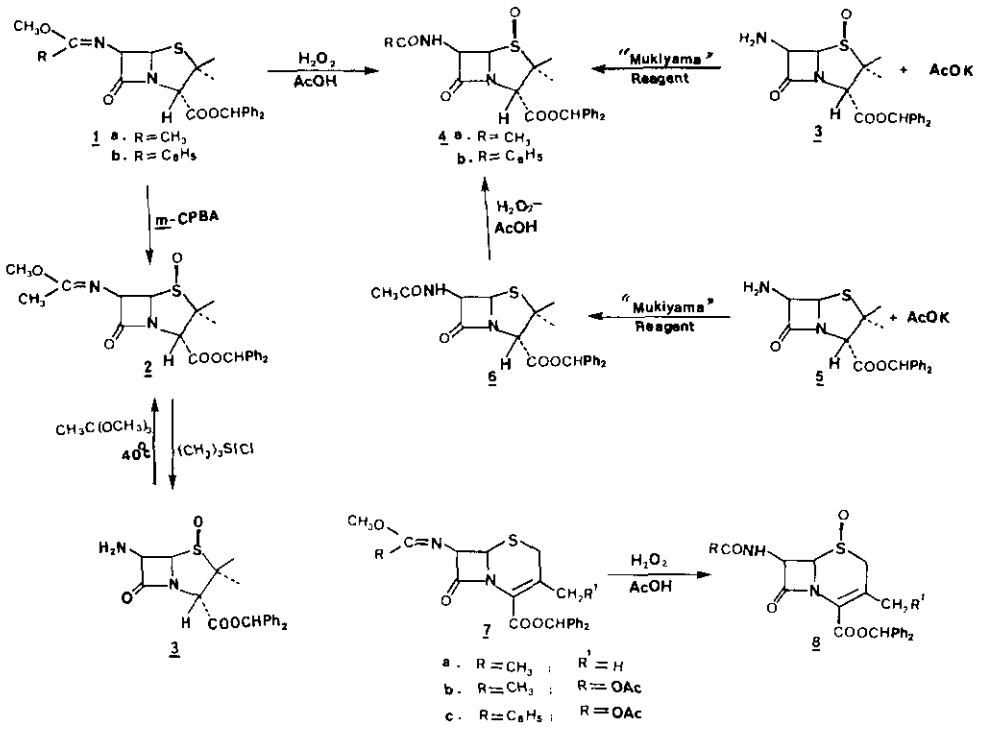
OXIDATION STUDIES OF BETA-LACTAM ANTIBIOTICS
THE 6(7)-IMINOETHERS OF PENICILLINS AND CEPHALOSPORINS

Ronald G. Micetich and Rajeshwar Singh
Faculty of Pharmacy and Pharmaceutical Sciences
University of Alberta
Edmonton, Alberta, Canada T6G 2N8

Abstract - The oxidation of the 6-iminoethers of penicillins using m- CPBA gave the 1 β-sulfoxide of the respective 6-iminoether; whereas with H_2O_2-CH_3CO_2H, the 6-iminoetherpenicillins and 7-iminoethercephalosporins gave the respective 1 β-sulfoxides of the 6(7)-amido compounds.

In continuation of our studies on β-lactam antibiotics[1], we required the 1α-sulfoxides of various β-lactam antibiotics. Penicillins and cephalosporins on oxidation with readily available oxidants such as m-chloroperbenzoic acid (m- CPBA) or peracetic acid, give a preponderance of the 1β-sulfoxide[1]. The accepted explanation for this preference is that the proton of the 6β-amide moiety at the C-6 or C-7 position binds to the oxidant and directs the oxidation from the hindered β-face[2]. The obvious assumption is that if this directive influence is removed then steric factors should prevail and oxidation will then produce a predominance of the 1α-sulfoxide (oxidation from the less hindered α-face should be normally preferred). In confirmation, are the reports that 6-phthalimidopenicillin[3], the Schiff bases of penicillins and cephalosporins[4], and the N-nitroso derivatives of the 6-amidopenicillins[5], all provide the 1α-sulfoxides as the major, if not the only, product of oxidation. In view of the report that the Schiff bases of penicillins and cephalosporins are oxidised to the 1α-sulfoxides[4], the oxidation of the 6(7)β-iminoethers of penicillins and cephalosporins as a possible route to the 1α-sulfoxides and in particular the 1α-sulfoxides of 6-APA (6-aminopenicillanic acid), 7-ADCA (7-aminodesacetoxycephalosporanic acid), and 7-ACA (7-aminocephalosporanic acid), appeared reasonable. The steric bulk of the 6(7)β-iminoethers should further facilitate α-oxidation. The preparation of the 6(7)β-iminoethers of penicillins, 1, and cephalosporins, 7, have been reported[6].

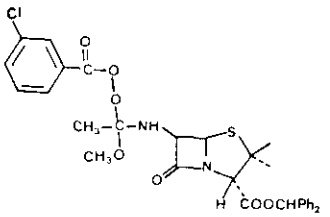


The oxidation of benzhydryl 6β-(1-methoxy-1-methylmethylene)iminopenicillanate, 1a, with m-chloroperbenzoic acid in dichloromethane gave benzhydryl 6β-(1-methoxy-1-methylmethylene)-iminopenicillanate-1β-sulfoxide, 2, in 48% yield - a result quite different from that of the Schiff bases which provide the 1α-sulfoxides[4]. The identity of the product 2 was confirmed by preparing the same compound, 2[6] (identical ir and nmr spectra), by the reaction of trimethyl orthoacetate with benzhydryl 6β-aminopenicillanate-1β-sulfoxide, 3, made in turn from 6-amino-penicillanic acid 1β-sulfoxide, 3[7]. Compound 2 on treatment with excess trimethylsilyl chloride and quinoline, (1 equivalent) in chloroform gave benzhydryl 6β-aminopenicillanate-1β-sulfoxide, 3, as a major product, along with the expected benzhydryl 6β-acetamidopenicillanate-1β-sulfoxide, 4a[8], as a minor product.

When compound 1 was oxidised with hydrogen peroxide and acetic acid in dichloromethane the product (66%) was benzhydryl 6β-acetamidopenicillanate-1β-sulfoxide, 4a. Similarly compound 1b on oxidation with H_2O_2-CH_3CO_2H gave 4b. The identity of compound 4a was confirmed by two alternate synthesis - coupling potassium acetate with benzhydryl 6-aminopenicillanate-1β-sulfoxide, 3, using Mukaiyama's reagent and the procedure of Kametani[9]; or by the

oxidation of benzhydryl 6β-acetamidopenicillanate, 6, with H_2O_2-CH_3CO_2H in dichloromethane. The oxidation of the cephalosporins 7 with H_2O_2-CH_3CO_2H proceeded similarly to give the benzhydryl 7β-acetamidocephalosporin-1β-sulfoxides, 8.

These results can be explained by initial addition of the m-chloroperbenzoic acid to the β-iminoether group to form a reactive intermediate of the type 9 (using the penicillin as an example).



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This facilitates oxidation at the hindered β-face; and regeneration of the 6-iminoether in the absence of water. With H_2O_2-CH_3CO_2H a similar reaction probably occurs resulting in formation of the 1β-sulfoxide; but in addition hydrolysis of the iminoether produces the 6(7)-amido moiety.

EXPERIMENTAL

Ir spectra were recorded on a Nicolet DX-FTIR spectrophotometer and nmr spectra on a Varian EM-360A spectrometer using tetramethylsilane as an internal standard. Representative examples are given. The data on the compounds are summarised in Table 1.

Benzhydryl 6β-(1-methoxy-1-methylmethylene)iminopenicillanate-1β-sulfoxide, 2.

m-Chloroperbenzoic acid (1.08g, 0.0062 mole) was added in small portions to a solution of 1a (2.19g, 0.005 mole) in CH_2Cl_2 under stirring and ice cooling over 10 min. The reaction mixture was stirred in the ice bath for 30 min. The solid that separated was filtered and the filtrate washed with aqueous $NaHCO_3$ and then brine. The organic phase was dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2 (20 ml) and then diluted with hexane, when a solid separated out and was collected (820 mg). Attempts to purify this solid by chromatography were unsuccessful - the nmr spectrum of the crude solid showed signals due to CH_3 and NH_2. The CH_2Cl_2-hexane filtrate was concentrated and dried under vacuum to give an amorphous solid (1.1g, 48.5%); IR γ_{max}^{KBr} cm^{-1}: 2950, 1788,1750,1670; NMR($CDCl_3$) : 0.92 and 1.68 (ss, 3H,3H,gem.CH_3), 2.08(s,3H,$CH_3C(OCH_3)$), 3.68(S,3H,OCH_3), 4.82 (s,1H,3-H), 4.97 (d,1H,J=5Hz,5-H), 5.30(d,1H,J=5Hz,6-H), 7.05(s,1H,$CHPh_2$), 7.42(m,10H,$CHPh_2$).

Benzhydryl 6β-acetamidopenicillanate-1β-sulfoxide, 4a: Method A

To a solution of 1a (2.19g, 0.005 mole) in CH_2Cl_2(70 ml), hydrogen peroxide (30%, 1.30g, 0.012 mole) and acetic acid (2.40g, 0.04mole) were added under stirring at room temperature. The resulting mixture was stirred for 48 h at room temperature and washed successively with water, aqueous $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated, and the resulting residue chromatographed over silica gel using ethyl acetate-methanol as eluant to give 1.5g (66%) of 4a, mp 190°C.

Method B : 2-Chloro-1-methylpyridinium methyl sulphate (4.5ml of a 32% solution in CH_2Cl_2), and triethylamine (0.50g, 5 mmole) were added over 5 min to a stirred solution of benzhydryl 6β-aminopenicillanate-1β-sulfoxide, 3 (0.6g, 1.5 mmole) and potassium acetate (0.5g, 5.3 mmole) in CH_2Cl_2 (15 ml). The resulting mixture was stirred at room temperature for 45 min and then ethyl acetate (10 ml) was added. The organic layer was washed with dil HCl and water, dried over Na_2SO_4 and concentrated. The residue was chromatographed over silica gel to give 0.35g (53%) of a solid, mp 189-190°C. The IR and NMR spectra are summarised in Table 1. Similarly compound 6 was prepared in 88% yield from the reaction of benzhydryl 6-aminopenicillanate, 5, with potassium acetate in the presence of 2-chloro-1-methylpyridinium methyl sulphate and triethylamine.

Reaction of Compound 2 with trimethylsilyl chloride and quinoline.

To a solution of 2 (the oxidised product of 1a with m-CPBA, 0.45g, 1 mmole) in $CHCl_3$, was added 0.5ml of trimethylsilyl chloride (excess) and quinoline (0.129g, 1 mmole). The resulting solution was stirred at room temperature for 1 h, and the resulting solution washed with water, then dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel using CH_2Cl_2-ethyl acetate as eluant, giving 0.2g (50.7%) of product 3 as an amorphous solid; IRγ_{max}^{KBr} cm^{-1} 3423, 2952, 1787, 1751; NMR ($CDCl_3$); 0.93 and 1.70 (s,s,3H, 3H,gem.C<u>H</u>$_3$), 2.60(bs,2H,N<u>H</u>$_2$), 4.70(d,1H,J=4.5Hz,5-<u>H</u>), 4.77(s,1H,3-<u>H</u>), 4.93(d,1H,J=4.5Hz,6-<u>H</u>), 7.07(s,1H,C<u>H</u>Ph$_2$), 7.43(m,10H,CHP<u>h</u>$_2$); along with 50mg (11.5%) of product 4a. The IR and NMR spectra of this product, 4a, was identical to the spectra of the compound prepared by the oxidation of 6.

ACKNOWLEDGEMENT

We thank the Alberta Heritage Foundation for Medical Research (AHFMR) for the award of an AHFMR Fellowship to RS.

Table 1. Oxidation Products of 6(7)-Iminoethers of Penicillins and Cephalosporins Using H_2O_2-CH_3CO_2H.

Comp No.	Yield	mp °C	Molecular Formula (Mol. Wt.)	IR(KBr) cm^{-1}	NMR ($CDCl_3$) δ-values
4a	66	190	$C_{23}H_{24}N_2O_5S$ (440)	3394, 2943, 1790, 1756, 1693	0.96 and 1.70(s,s,3H,3H,gem.CH_3), 2.03 (s,3H,CH_3CONH), 4.21(s,1H,3-H), 5.06 (d,1H,J=4.5Hz,5-H), 6.13(q,1H,J_1=10.5Hz, J_2=4.5Hz,6-H), 7.06(s,1H,$CHPh_2$), 7.43(m, 11H,$CHPh_2$ and NH).
4b	72	150-151	$C_{28}H_{26}N_2O_5S$ (502)	3394,2959, 1797, 1753, 1693	0.93 and 1.73(s,s,3H,3H,gem.CH_3), 4.86 (s,1H,3-H), 5.13(d,1H,J=4.5Hz,5-H), 6.36 (q,1H,J_1=10.5Hz,J_2=4.5Hz,6-H), 7.06(s,1H, $CHPh_2$), 7.43(m,13H,$CHPh_2$ and 3H of C_6H_5CO), 7.93(m,3H,2H of C_6H_5CO and NH).
8a	62	200	$C_{23}H_{22}N_2O_5S$ (430)	3410, 2934, 1787, 1724, 1680	2.00(s,3H,3-CH_3), 2.03(s,3H,CH_3CO), 3.73&3.87 (ABq,2H,J=18Hz,2-CH_2), 4.96(d,1H,J=4.5Hz,6-H), 5.90 (q,1H,J_1=8Hz,J_2=4.5Hz,7-H), 7.00(s,1H, $CHPh_2$), 7.46(m,10H,$CHPh_2$), 8.26(d,1H,J=8Hz, NH).
8b	62	213	$C_{25}H_{24}N_2O_7S$ (496)	3277, 2950, 1795, 1743, 1687	2.00(s,6H,CH_3CO and $OCOCH_3$),3.70 and 4.00 (ABq,2H,J=18Hz,2-CH_2), 4.70 and 5.07(ABq, 2H, J= 14Hz, 3-CH_2), 5.00(d,1H,J=4.5 Hz,6-H), 6.00(q,1H,J_1=8Hz,J_2=4.5Hz 7-H), 7.03(s,1H,$CHPh_2$), 7.43(m,10H,$CHPh_2$), 8.33(d, 1H,J=8Hz,NH).
8c	57	162-163	$C_{30}H_{26}N_2O_7S$ (558)	3402, 2943, 1794, 1739, 1671	2.03(s,3H,$COCH_3$), 3.29 and 3.87(ABq,2H,J=18 Hz,2-CH_2), 4.63 (d,1H,J=4.5Hz,6-H), 4.83 and 5.33(ABq,2H,J=18Hz, 3-CH_2), 6.40(q,1H,J_1=8Hz, J_2=4.5Hz, 7-H), 7.01(s,1H,$CHPh_2$), 7.46(m,14 H,$CHPh_2$,NH and 3H of C_6H_5CO), 7.90(m,2H,2H of C_6H_5CO).

REFERENCES

1. R.G.Micetich, R.Singh and S.N.Maiti, Heterocycles, 1984, 22, 531.
2. R.D.G.Cooper, P.V.Demarco, J.C.Cheng and N.D.Jones, J. Am. Chem. Soc., 1969, 91, 1408.
3. R.D.G.Cooper, P.V.Demarco and D.O.Spry, J. Am. Chem. Soc., 1969, 91, 1528.
4. J.J.de Koning, A.F.Marx, M.M.Poot, P.M.Smid and J.Verweij, "Stereospecific Synthesis of Biologically Active Cephalosporin-R-Sulfoxides" in Recent Advances in the Chemistry of β-Lactam Antibiotics, editor J.Elks, The Chem. Soc., U.K., 1976, 161.
5. S. Uyeo, T.Aoki and W.Nagata, Heterocycles, 1978, 11, 305.
6. R.G.Micetich and R.Singh, Synthesis, in press.
7. R.G.Micetich, Synthesis, 1976, 264; see also Erratum, Synthesis, 1977, 502.
8. T.Hiraoka, K.Iino, Y.Iwano, T.Saito and Y.Sugimura, "Novel Methods for Preparations of 7-Methoxy Cephalosporins and 6-Methoxy Penicillins" in Recent Advances in the Chemistry of β-Lactam Antibiotics, editor J.Elks, The. Chem. Soc., U.K., 1976, 123.
9. T.Kametani, H.Sekine and T.Honda, Heterocycles, 1983, 20, 1577.

Received, 21st January, 1985