

OXIDATION STUDIES OF BETA-LACTAM ANTIBIOTICS

THE 6(7)-IMINOETHERS OF PENICILLINS AND CEPHALOSPORINS

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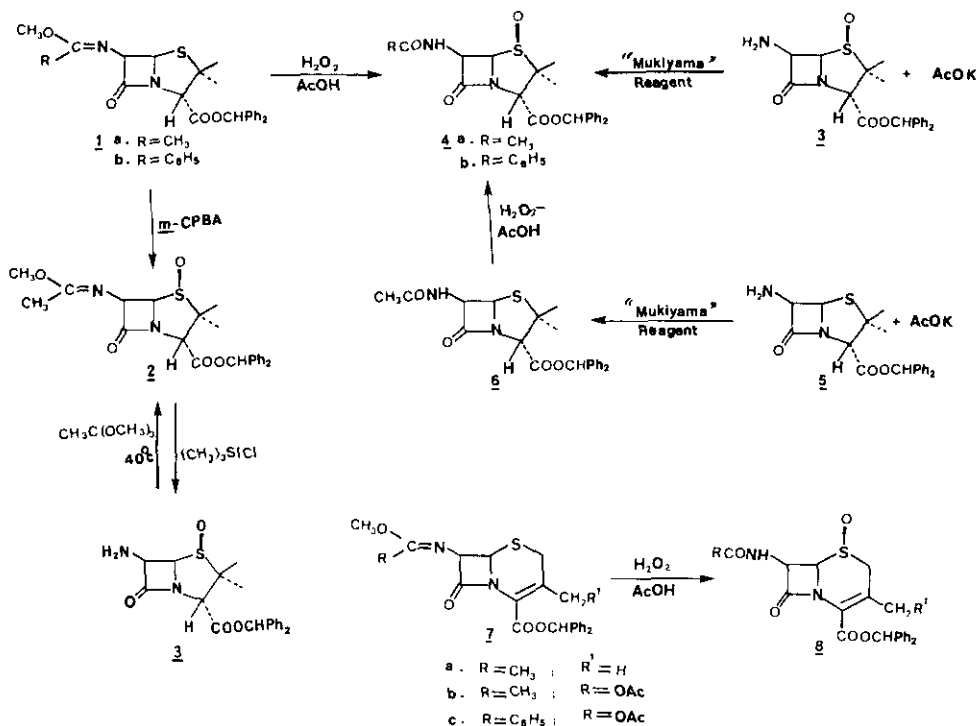
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Abstract - The oxidation of the 6-iminoethers of penicillins using m-CPBA gave the 1 β -sulfoxide of the respective 6-iminoether; whereas with $H_2O_2-CH_3CO_2H$, the 6-iminoetherpenicillins and 7-iminoethercephalosporins gave the respective 1 β -sulfoxides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

In continuation of our studies on β -lactam antibiotics¹, we required the 1 α -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 1 β -sulfoxide¹. The accepted explanation for this preference is that the proton of the 6 β -amide moiety at the C-6 or C-7 position binds to the oxidant and directs the oxidation from the hindered β -face². 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 1 α -sulfoxide (oxidation from the less hindered α -face should be normally preferred). In confirmation, are the reports that 6-phthalimidopenicillin³, the Schiff bases of penicillins and cephalosporins⁴, and the N-nitroso derivatives of the 6-amidopenicillins⁵, all provide the 1 α -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 1 α -sulfoxides⁴, the oxidation of the 6(7) β -iminoethers of penicillins and cephalosporins as a possible route to the 1 α -sulfoxides and in particular the 1 α -sulfoxides of 6-APA (6-aminopenicillanic acid), 7-ADCA (7-aminodesacetoxycephalosporanic acid), and 7-ACA (7-aminoccephalosporanic 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, 2, have been reported⁶.



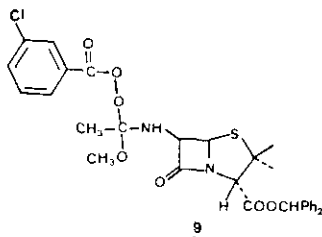
The oxidation of benzhydryl 6 β -(1-methoxy-1-methylmethylene)iminopenicillanate, 1a, with *m*-chloroperbenzoic acid in dichloromethane gave benzhydryl 6 β -(1-methoxy-1-methylmethylene)-iminopenicillanate-1 β -sulfoxide, 2, in 48% yield - a result quite different from that of the Schiff bases which provide the α -sulfoxides⁴. The identity of the product 2 was confirmed by preparing the same compound, 2⁶ (identical ir and nmr spectra), by the reaction of trimethyl orthoacetate with benzhydryl 6 β -aminopenicillanate-1 β -sulfoxide, 3, made in turn from 6-aminopenicillanic acid 1 β -sulfoxide, 3⁷. Compound 2 on treatment with excess trimethylsilyl chloride and quinoline, (1 equivalent) in chloroform gave benzhydryl 6 β -aminopenicillanate-1 β -sulfoxide, 3₂ as a major product, along with the expected benzhydryl 6 β -acetamidopenicillanate-1 β -sulfoxide, 4a⁸, as a minor product.

When compound 1 was oxidised with hydrogen peroxide and acetic acid in dichloromethane the product (66%) was benzhydryl 6 β -acetamidopenicillanate-1 β -sulfoxide, 4a. Similarly compound 1b on oxidation with $\text{H}_2\text{O}_2\text{-CH}_3\text{CO}_2\text{H}$ gave 4b. The identity of compound 4a was confirmed by two alternate synthesis - coupling potassium acetate with benzhydryl 6-aminopenicillanate-1 β -sulfoxide, 3, using Mukaiyama's reagent and the procedure of Kametani⁹; or by the

oxidation of benzhydryl 6 β -acetamidopenicillanate, 6, with H₂O₂-CH₃CO₂H in dichloromethane.

The oxidation of the cephalosporins 7 with H₂O₂-CH₃CO₂H proceeded similarly to give the benzhydryl 7 β -acetamidocephalosporin-1 β -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).



This facilitates oxidation at the hindered β -face; and regeneration of the 6-iminoether in the absence of water. With H₂O₂-CH₃CO₂H a similar reaction probably occurs resulting in formation of the 1 β -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 6 β -(1-methoxy-1-methylmethylene)iminopenicillanate-1 β -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 CH₂Cl₂ 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 NaHCO₃ and then brine. The organic phase was dried (Na₂SO₄) and concentrated. The residue was dissolved in CH₂Cl₂ (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 CH₃ and NH₂. The CH₂Cl₂-hexane filtrate was concentrated and dried under vacuum to give an amorphous solid (1.1g, 48.5%); IR $\gamma_{\text{max}}^{\text{KBr}}$: 2950, 1788, 1750, 1670; NMR(CDCl₃): 0.92 and 1.68 (ss, 3H, 3H, gem-CH₃), 2.08 (s, 3H, CH₃C(OCH₃)), 3.68 (s, 3H, OCH₃), 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, CHPh₂), 7.42 (m, 10H, CHPh₂).

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

To a solution of 1a (2.19g, 0.005 mole) in CH₂Cl₂ (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 NaHCO₃, and brine. The organic phase was dried (Na₂SO₄), 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 CH₂Cl₂), and triethylamine (0.50g, 5 mmole) were added over 5 min to a stirred solution of benzhydryl 6 β -aminopenicillanate-1 β -sulfoxide, 3 (0.6g, 1.5 mmole) and potassium acetate (0.5g, 5.3 mmole) in CH₂Cl₂ (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 Na₂SO₄ 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 CHCl₃, 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 (Na₂SO₄), and concentrated. The residue was chromatographed over silica gel using CH₂Cl₂-ethyl acetate as eluant, giving 0.2g (50.7%) of product 3 as an amorphous solid; IR $_{\text{max}}^{\text{KBr}}$ cm⁻¹ 3423, 2952, 1787, 1751; NMR (CDCl₃); 0.93 and 1.70 (s,s,3H, 3H, gem,CH₃), 2.60(bs,2H,NH₂), 4.70(d,1H,J=4.5Hz,5-H), 4.77(s,1H,3-H), 4.93(d,1H,J=4.5Hz,6-H), 7.07(s,1H,CHPh₂), 7.43(m,10H,CHPh₂); 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.

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

 Using $\text{H}_2\text{O}_2\text{-CH}_3\text{CO}_2\text{H}$.

Comp No.	Yield	mp °C	Molecular Formula (Mol. Wt.)	IR(KBr) cm^{-1}	NMR (CDCl_3) δ -values
<u>4a</u>	66	190	$\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$ (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, $J=4.5\text{Hz}$, 5-H), 6.13(q, 1H, $J_1=10.5\text{Hz}$, $J_2=4.5\text{Hz}$, 6-H), 7.06(s, 1H, CHPh_2), 7.43(m, 1H, CHPh_2 and NH).
<u>4b</u>	72	150-151	$\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$ (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, $J=4.5\text{Hz}$, 5-H), 6.36 (q, 1H, $J_1=10.5\text{Hz}$, $J_2=4.5\text{Hz}$, 6-H), 7.06(s, 1H, CHPh_2), 7.43(m, 13H, CHPh_2 and 3H of $\text{C}_6\text{H}_5\text{CO}$), 7.93(m, 3H, 2H of $\text{C}_6\text{H}_5\text{CO}$ and NH).
<u>8a</u>	62	200	$\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$ (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, $J=13\text{Hz}$, 2- CH_2), 4.96(d, 1H, $J=4.5\text{Hz}$, 6-H), 5.90 (q, 1H, $J_1=8\text{Hz}$, $J_2=4.5\text{Hz}$, 7-H), 7.00(s, 1H, CHPh_2), 7.46(m, 10H, CHPh_2), 8.26(d, 1H, $J=8\text{Hz}$, NH).
<u>8b</u>	62	213	$\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_7\text{S}$ (496)	3277, 2950, 1795, 1743, 1687	2.00(s, 6H, CH_3CO and OCOCH_3), 3.70 and 4.00 (ABq, 2H, $J=18\text{Hz}$, 2- CH_2), 4.70 and 5.07(ABq, 2H, $J=14\text{Hz}$, 3- CH_2), 5.00(d, 1H, $J=4.5$ Hz, 6-H), 6.00(q, 1H, $J_1=3\text{Hz}$, $J_2=4.5\text{Hz}$, 7-H), 7.03(s, 1H, CHPh_2), 7.43(m, 10H, CHPh_2), 8.33(d, 1H, $J=8\text{Hz}$, NH).
<u>8c</u>	57	162-163	$\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_7\text{S}$ (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, $J=4.5\text{Hz}$, 6-H), 4.83 and 5.33(ABq, 2H, $J=18\text{Hz}$, 3- CH_2), 6.40(q, 1H, $J_1=8\text{Hz}$, $J_2=4.5\text{Hz}$, 7-H), 7.01(s, 1H, CHPh_2), 7.46(m, 14 H, CHPh_2 , NH and 3H of $\text{C}_6\text{H}_5\text{CO}$), 7.90(m, 2H, 2H of $\text{C}_6\text{H}_5\text{CO}$).

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