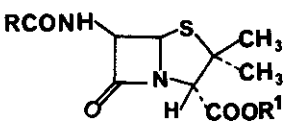
OXIDATION STUDIES ON BETA-LACTAM ANTIBIOTICS

SYNTHESIS OF PENAM AND CEPHEM SULFOXIDES AND SULFONES

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

Abstract - Penicillin and cephalosporin sulfoxides are conveniently prepared by oxidation of the respective penicillin or cephalosporin in methylene chloride using hydrogen peroxide and acetic acid. Replacement of the acetic acid by formic acid produces the respective penicillin and cephalosporin sulfones in high yields.

Considerable attention has been devoted, in recent years, to a study of the conversion of penicillins, 1, and cephalosporins, 2, to the corresponding sulfoxides, 3 and 4, and sulfones, 5 and 6.



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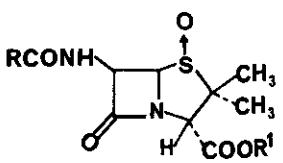

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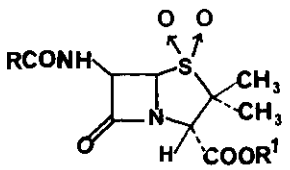

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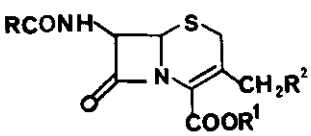

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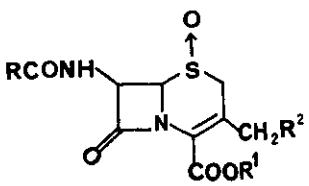

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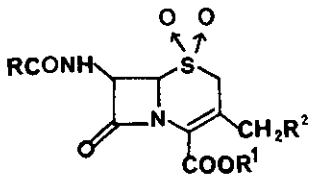

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The pioneering research of Morin and co-workers in converting penicillin sulfoxides, 3, to the desacetoxycephalosporins, 2 (R^2=H), by chemical means[1], generated considerable interest in the penicillin sulfoxides. The use of the desacetoxycephalosporin sulfoxides, 4 (R^2=H) as intermediates for the functionalisation (R^2=halogen) of these compounds[2,3] and, the recent discovery that cephalosporin-1α-sulfoxides[4], and even certain cephalosporin-1β-sulfoxides[5], and cephalosporin-1-sulfones, 6,[5] are bioactive, has sparked interest in these classes of compounds. Penicillin-1-sulfones, 5, long known[6], have only recently become of great importance, with the discovery that β-lactamase inhibitory activity is associated with this class of compound[7-10].

A number of methods exist for the synthesis of the sulfoxides of penicillins, 3, and cephalosporins, 4; and reagents such as sodium periodate[11], ozone[12], peracetic acid (40%)[13], m-chloroperbenzoic acid[14], and iodobenzene dichloride[15], have been utilised as the oxidant. The sulfones of penicillins, 5, and cephalosporins, 6, can be obtained by using m-chloroperbenzoic acid[16], and in the former case also by the use of potassium permanganate[6]. This reagent, potassium permanganate, may not be useful for the preparation of cephem sulfones, 6, due to possible concomitant oxidation of the double bond in the thiazine ring.

Hydrogen peroxide along with organic acids has been used for the oxidation of penicillins and cephalosporins. The organic acid can function as reactant and solvent[17]; or can be employed in large excess[18]; or preferably in a four molar excess in dichloromethane as solvent[19], for the preparation of the sulfoxides of penicillins, 3, or cephalosporins, 4. It is also reported that the use of large amounts of the organic acid result in low yields of the sulfoxides, due to cleavage of the sensitive substrates (penicillins or cephalosporins)[6,18,19]. Mangia from his study of this reaction suggested that formic acid was generally preferred to acetic acid, and that three to four equivalents of the acid was desirable for the preparation of the sulfoxides of penicillins and cephalosporins[19].

In our studies on β-lactam antibiotics, we have had occasion to study this reaction in some detail. In an initial experiment, we found that oxidation of benzyl 6-phenoxyacetamidopenicillanate (the benzyl ester of penicillin V) with hydrogen peroxide in methylene chloride with a four molar excess of formic acid gave a difficultly separable mixture of the sulfoxide, 2, (R=ϕOCH, R^1=$CH\phi_2$, 80%) and the sulfone, 5. Further studies revealed that this method is in fact an excellent method for preparing the sulfoxides, 3 and 4, or the sulfones, 5 and 6. Thus, oxidation with hydrogen peroxide in methylene chloride with acetic acid stopped at the sulfoxide, 3 and 4, stage - the presence of the sulfone was not detected. With formic acid, and, an extended reaction time, high yields of the sulfones, 5 and 6, resulted. Table 1 summarises the data obtained in these studies, the yield percentages being determined from the nmr spectra of the crude products.

When the penicillin, 1a (R=ϕOCH_2, R^1=$CH_2\phi$) was treated in methylene chloride with a mixture of hydrogen peroxide and formic acid (1.2:4) compared to the substrate 1a for 24 h, the product consisted of 80% of the sulfoxide, 3, and 20% of the sulfone, 5. When this ratio was raised to 2.4:8, the product contained 60% sulfoxide, 3, and 40% sulfone, 5. Changing the ratio to 1:12:40 (substrate:H_2O_2:HCOOH) afforded 35% sulfoxide, 3, and 65% sulfone, 5. Doubling the reaction time from 24 h to 48 h gave 16% sulfoxide, 3, and 84% sulfone, 5; and after 72 h gave >95% of the sulfone, 4.

Similar studies were also run on esters of penicillin V using acetic acid. With a ratio of substrate:H_2O_2:CH_3COOH (1:1.2:4) and after 24 h, 67% of the sulfoxide, 3, with starting penicillin, 1, resulted. On increasing the ratio to 1:2.4:8, 87% of the sulfoxide, 3, resulted after 24 h and essentially quantitative yields after 48 h. No evidence of sulfone formation was evident in the nmr spectra of the crude products from these reactions, nor was there evidence of much decomposition in any of these reactions with formic acid or acetic acid.

Corresponding results were obtained with the cephalosporins, 2, as is evident from the data in Table 1.

TABLE 1

OXIDATION OF PENICILLINS AND CHEPHALOSPORINS BY H_2O_2/ORGANIC ACIDS

Compound	R	R^1	R^2	Organic Acid	Molar Ratio of Substrate:H_2O_2 :Organic Acid	Reaction Time (h)	% Yield of Product[a,b] Sulfoxide[c]	Sulfone	mp°c	Reference
1a	ϕOCH_2	$CH_2\phi$	-	HCOOH	1:1.2:4	24	80	20		
	ϕOCH_2	$CH_2\phi$	-	HCOOH	1:2.4:8	24	60	40		
	ϕOCH_2	$CH_2\phi$	-	HCOOH	1:12:40	24	35	65		
	ϕOCH_2	$CH_2\phi$	-	HCOOH	1:12:40	48	16	84		
	ϕOCH_2	$CH_2\phi$	-	HCOOH	1:12:40	72	-	90[d]	124°dec	
	ϕOCH_2	$CH_2\phi$	-	CH_3COOH	1:2.4:8	48	95[d]	-	122-124	Lit 124-125[11]
1b	ϕOCH_2	CH_2CCl_3	-	HCOOH	1:12:40	72	-	76[d]	168-169° dec	
	ϕOCH_2	CH_2CCl_3	-	CH_3COOH	1:2.4:8	48	90[d]	-	146-147	Lit 145-146[14]
1c	ϕOCH_2	$CH\phi_2$	-	CH_3COOH	1:2.4:8	48	91[d]	-	91-92	
2a	ϕOCH	CH_2CCl_3	H	HCOOH	1:2.4:8	24	-	72	215-216 dec	
	ϕOCH	CH_2CCl_3	H	CH_3COOH	1:1.2:4	24	83[d]	-	171-174	
2b		$CH\phi_2$	$OCOCH_3$	CH_3COOH	1:1.2:4	24	90[d]	-	182 dec	
2c		$CH_2CH\phi_2$	$OCOCH_3$	CH_3COOH	1:1.2:4	24	88[d]	-	165 dec	

a. Estimated from the nmr spectrum of the product.

b. The elemental analysis of all new compounds are within acceptable limits.

c. Mixture of R- and S-isomers.

d. Isolated yield of pure product after column chromatography.

The reason for this difference in the oxidation products using acetic acid and formic acid is not clear, but could be a result of the difference in acidity. However, a single experiment in which the benzyl ester of penicillin V was oxidized with hydrogen peroxide in presence of trifluoroacetic acid produced the sulfoxide with considerable amounts of decomposition product. There was no evidence of sulfone formation. Further studies in this area are underway and will be reported in later publications.

GENERAL PROCEDURE FOR SYNTHESIS OF SULFOXIDE OR SULFONE OF PENICILLINS AND CEPHALOSPORINS

A suitable mixture of hydrogen peroxide (30% w/w) and the organic acid (acetic acid for the sulfoxide, formic acid for the sulfone) in the ratio indicated in Table 1 is added slowly to a stirred solution of 2.5 mmole of the substrate (penicillin or cephalosporin) in 35 ml of methylene chloride, kept at room temperature. After the appropriate time (see table), the reaction mixture is washed successively with water, aqueous sodium bicarbonate, and brine, and the organic phase dried (Na_2SO_4), filtered and concentrated to a white foam or solid, pure enough for further reactions. If necessary, further purification can be achieved by recrystallisation or column chromatography on silica.

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