A Mild and Convenient Synthesis of Penicillin and Cephalosporin Sulfoxides

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In recent years much interest has been directed to the chemistry of penicillin sulfoxides, after Morin and co-workers[1] converted these compounds into desacetoxycephalosporins, and later of cephalosporin sulfoxides as intermediates[2,3] for the functionalization of desacetoxycephalosporins.

For our studies on the chemical reactivities of some penicillin and cephalosporin sulfoxides, we needed a general and inexpensive method for their preparation which is, above all, feasible on a larger scale. A number of synthetic methods are now available. Penicillin sulfoxides have been prepared by oxidation of penicillins with sodium periodate[4], ozone[5],

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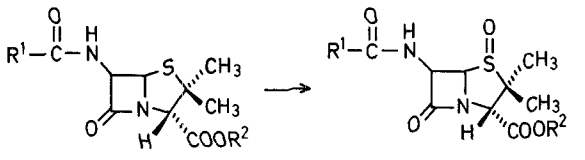
m-chloroperbenzoic acid[6], or 40% peracetic acid[7]. Cephalosporin sulfoxides have been prepared[8] analogously. Although yields were high, the reagents were either expensive or troublesome to handle in large quantities. Hydrogen peroxide, which is a cheaper reagent, was also employed together with an organic acid in a large excess[8] or as a solvent[9], but often this method led to cleavage of the more sensitive substrates with consequent low yields[8,10].

Penicillin and cephalosporin sulfoxides are best prepared in very high yields and in a safe manner by oxidation with hydrogen peroxide in dichloromethane (in dimethylformamide, acetonitrile, or acetone, no or little reaction taking place) in the presence of only a 4 molar excess of formic or acetic acid, which minimizes sulfone formation, acidic decomposition, and reaction times.



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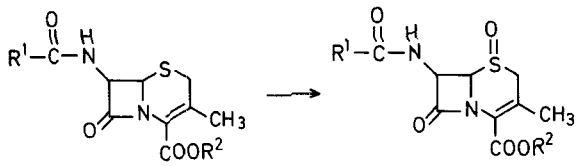

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An incomplete oxidation, giving nevertheless high yield, was obtained in preliminary experiments using 2 mol of acid/mol of substrate even after 48 h reaction, as 2–8% of the starting products **1** or **3** were still present (T.L.C.), while practically quantitative yields of sulfoxides were obtained using 3 or 4 mol of acid. Because of the lower reaction times involved, the latter was the excess of choice (see Table).

Formic acid was generally preferred to acetic acid as it increased the rate of the reaction, except in the oxidation of cephalosporanic acids **3b,c** since it afforded less pure products in this case. The sulfoxides obtained, up to 1 mol scale in this laboratory, are sufficiently pure (>97%) for further reactions without any manipulation and possess the *S*-configuration with minor amounts (<3%) of *R*-sulfoxides[11] in cephalosporins.

Synthesis of Sulfoxides 2 or 4; General Procedure:

The appropriate acid (80 mmol) and 32% hydrogen peroxide (22–26 mmol) are added to a solution or suspension of **1** or **3** (20 mmol) in dichloromethane (70–200 ml, see Table). The reaction mixture is stirred at room temperature (25–30°) until oxidation is complete (T.L.C.: Kieselgel 60 F_{254}, Merck, using benzene/ethyl acetate, 7:3 or acetone/acetic acid, 100:5 as eluents). Recovery of the ester is carried out by washing the organic solvent with water and sodium hydrogen carbonate, drying, and evaporation in vacuo to afford **2** or **4** as white foam. The sulfoxides are purified by column chromatography on silica gel (Merck, Kieselgel 100, 70–80 mesh) using ethyl acetate as eluent. Compound **2b** is obtained by extraction with 5% sodium hydrogen carbonate, separation of the organic phase, and acidification to pH 2. The white precipitate is filtered, washed with little water, and dried.

The acids **4b,c**, which precipitate from the solution during the oxidation, are filtered, washed with little cold dichloromethane, and dried.

Table. Preparation of Penicillin Sulfoxides **2** and Cephalosporin Sulfoxides **4**

Product	R^1	R^2	Yield [%][a]	Acid	Molar ratio Acid:H_2O_2:substrate	Amount of CH_2Cl_2	Reaction time	m.p. (Lit. m.p.)	$[\alpha]_D$
2a	C_6H_5—CH_2	Cl_3C—CH_2	94 (92)	HCOOH	4:1.2:1	200 ml	9 h	174° (174–176°)[6]	+178° (*c* 1, $CHCl_3$)
			93	HCOOH	3:1.2:1	200 ml	12 h	155°	+162° (*c* 1, $CHCl_3$)
			89	HCOOH	2:1.2:1	200 ml	30 h	155°	+160° (*c* 1, $CHCl_3$)
2b	C_6H_5—OCH_2	H	89	HCOOH	4:1.2:1	200 ml	7 h	155° (dec.)[b] (159°)[10]	+174° (*c* 1, CH_3OH)[c]
4a	C_6H_5—CH_2	Cl_3C—CH_2	100 (92)	HCOOH	4:1.1:1	200 ml	15 h	199° (199.5°)[3]	+103° (*c* 1, $CHCl_3$)[d]
4b	C_6H_5—CH_2	H	87	CH_3COOH	4:1.3:1	100 ml	22 h	177° (dec.) (189–190°)[13]	+256° (*c* 1, 0.5 normal $NaHCO_3$)
4c	C_6H_5—OCH_2	H	85	CH_3COOH	4:1.3:1	70 ml	23 h	196° (dec.)[e]	+194° (*c* 1, 0.5 normal $NaHCO_3$)

[a] Yields of the crude crystalline products, which were checked by ^{1}H-N.M.R. and T.L.C. and proved to be practically pure (at least 97%). Values in brackets are yields after column chromatography.

[b] Monohydrate: Lit.[10], hemihydrate.

[c] Lit.[12] $[\alpha]_D = +174°$ (*c* 0.5, acetone).

[d] Lit.[3] $[\alpha]_D = +97°$ (*c* 1, $CHCl_3$).

[e] $C_{16}H_{16}N_2O_6S$ (364.4) calc. C 52.74 H 4.43 N 7.69; found 52.48 4.41 7.72

I.R. (KBr): ν_{max} = 3300, 1790, 1770, 1710, 1670, 1060 cm^{-1}.

4b: ^{1}H-N.M.R. (DMSO-d_6): $\delta = 8.1$ (d, 1H, $J = 8$ Hz); 7.1 (s, 5H); 5.6 (q, 1H, $J = 8$ and 4.5 Hz); 4.7 (d, 1H, $J = 4.5$ Hz); 3.56 (s, 2H); 3.55 (s, 2H); 2.0 ppm (s, 3H).

4c: ^{1}H-N.M.R. (DMSO-d_6): $\delta = 7.98$ (d, 1H, $J = 9$ Hz); 7.3–6.7 (m, 5H); 5.8 (q, 1H, $J = 9$ and 4.8 Hz); 4.8 (d, 1H, $J = 4.8$ Hz); 4.6 (s, 2H); 3.65 (s, 2H); 2.0 ppm (s, 3H).

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