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THE DETERMINATION OF STEREOCHEMISTRY AND REACTIONS OF 3-HYDROXY, 3-METHYL CEPHALOSPORINS

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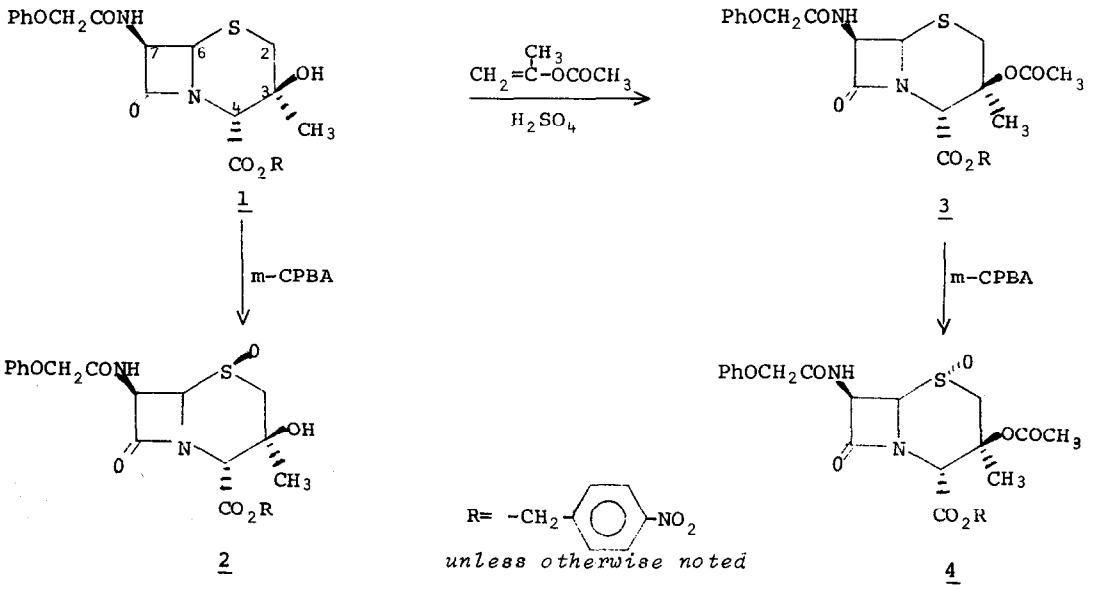
In the preceding communication (1), we reported the facile preparation of a novel class of cephalosporins, 3-hydroxy-3-methyl-cepham derivatives, 1, via acid catalyzed ring expansion of penicillin sulfoxides. This communication describes some additional chemical and spectroscopic properties of these compounds, and thus establishes the S configuration at C_3 (*i.e.*, 3β-hydroxyl).



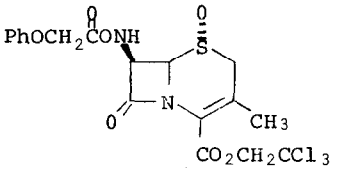
1 3

2 4

Oxidation of the parent 3-hydroxy, 3-methyl cepham ester, 1, (m-chloroperbenzoic acid/CH_2Cl_2) provides a sulfoxide, 2, (m.p. 224-225°) possessing the β-configuration (1), as anticipated from previous analogy in cephalosporins (2). Derivatives of the 3-hydroxy group of 1 are readily prepared under mild conditions affording, for example, the previously described 3-O-acetate, 3, and a corresponding 3-O-trimethylsilyl ether (1). In contrast, however, the 3-hydroxy

function of the β-sulfoxide 2 resists analogous functionalization even under more strenuous conditions.

These observations may be explained by a *cis* relationship between the hydroxyl at C_3 and the β-oxygen attached to sulfur in 2, since the reduced reactivity of the 3-hydroxyl function of 2 can be attributed to the added steric hindrance provided by the sulfoxide oxygen as well as to internal hydrogen bonding. Complementary to the rationale is the oxidation (m-chloroperbenzoic acid CH_2Cl_2 r.t.) of the 3-acetoxy cepham 3 which leads almost exclusively to the less hindered α-sulfoxide 4 (m.p. 190-192°). The α-configurational assignment at position 1 of 4 was verified by the treatment of 4 (R= $-CH_2CCl_3$) with triethylamine to provide the known 3-cephem α-sulfoxide 5 (3) by elimination of the elements of acetic acid.



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Previously reported ring expansions of penicillin sulfoxides in acetic anhydride (4,5) provide direct routes to 3-acetoxy, 3-methyl cepham derivatives. In the latter instance the 3-acetoxy group was also assigned the β-configuration on the basis of NMR (5) and verified via x-ray crystallographic analysis (6). In the former report (4) no definite configurational assignments were made, however our re-examination of this work suggests that the identical stereochemical assignment is justified. It thus appears that the mechanistic refinement previously suggested (1) may be applicable in an even broader sense to include mixed sulfenic-carboxylic anhydrides since the stereospecificity of these rearrangements is well accommodated by this proposal.

As illustrated in Table I, a change in solvent ($CDCl_3$ → DMSO-d_6) induces a downfield shift of ∿ 1.5 ppm in the resonances for both -NH and -OH in the cepham sulfide (1, R= $-CH_3$) indicative of intermolecular H-bonding to DMSO. The corresponding β-sulfoxide (2, R= $-CH_3$), however, exhibits only a negligible shift during the same solvent change. Thus, the strong inference of intramolecular H-bonding of both -NH and -OH to the sulfoxide oxygen requires that all three groups be situated on the β-face. As would be anticipated, the -NH signal of the α-sulfoxide 4 undergoes a solvent induced shift comparable to that observed in 3

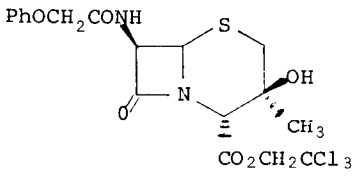
Compound	Solvent	Chemical Shift (δ ppm) -NH	-OH
1, R= $-CH_3$	$CDCl_3$	8.55	4.00
	$DMSO-d_6$	10.02	5.51
	△ sulfide	-1.47	-1.51
2, R= $-CH_3$	$CDCl_3$	8.09	6.47
	$DMSO-d_6$	8.27	6.64
	△ sulfoxide	-0.18	-0.17

TABLE I: Hydrogen Bonding Studies via Solvent Induced Shifts

since intramolecular H-bonding between the amide and the α-sulfoxide is not possible. Mechanistic considerations (1) had implied the β-orientation of H_4, and this was verified by the detection of long-range coupling between H_4 and $H_{2\beta}$ in both sulfide (1, R= $-CH_3$, J= 1 Hz) and sulfoxide (2, R= $-CH_3$, J= 4 Hz).

Nuclear Overhauser studies revealed a rather small enhancement of the H_4 signal upon irradiation of the C_3-methyl (∿ 7% in 1, R= $-CH_3$ and ∿ 10% in 2, R= $-CH_3$). Even though the two groups in question are *trans*, mutual relaxation probably occurs because of their proximity due to the relative flexibility of the six-membered ring.

Additional evidence in support of the β-disposition of the 3-hydroxy group arises from a structural modification that occurs to 6 during silica gel chromatography. Scission of the β-lactam bond of 6 is accompanied by concurrent acylation of the 3-hydroxy group to afford lactone 7. Models verify that lactone formation is possible only with a β-3-hydroxy group. Some of the pertinent 100 MHz resonances for 7 include the following: in $CDCl_3$ the upfield pair of signals ($H_{2\alpha}$ @ 2.95δ) of the usual AB quartet attributable to the C_2 methylene



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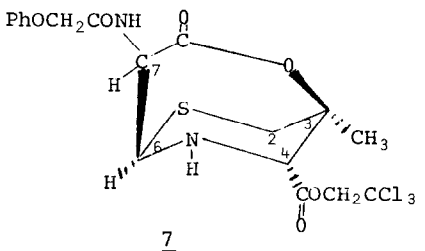
Silica gel



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protons is additionally split by H_6 ($J_{2\alpha-6}$ = ∿ 1 Hz). The H_7 double doublet (5.36δ) collapses to a doublet upon irradiation of H_6 or a D_2O wash. Both H_4 and H_6 appear at ∿ 4.5δ (as a shoulder on $PhOC\underline{H}_2$-). The amine N<u>H</u> appears as a diffuse region centered at 2.75δ and washes out with D_2O. IR confirms loss of β-lactam absorption, and a new carbonyl band attributable to the lactone at 1740 cm^{-1} appears in its place. In addition to the parent peak (P) at m/e 496, peaks of significant intensity occur at m/e 452 ($P-CO_2$), 438 ($452-CH_2$), 420 ($P-CO_2S$), 406 ($P-CO_2SCH_2$) and 345 ($P-NHCOCH_2OPh$) in the mass spectrum of <u>7</u>.

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