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NOVEL 3-HYDROXY, 3-METHYL CEPHALOSPORINS FROM THE REARRANGEMENT OF PENICILLIN SULFOXIDES

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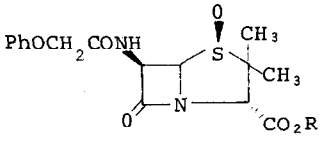
The acid catalyzed ring expansion (1) of penicillin sulfoxide esters, 1, to deacetoxy cephalosporins, 2, has assumed added importance due to the demonstrated oral effectiveness of the broad-spectrum antibiotic, cephalexin (2). We now wish to report additional studies that further aid in elucidating the nature of this conversion, especially with respect to the crucial role of the acid catalyst in determining the products produced.



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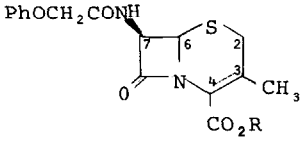

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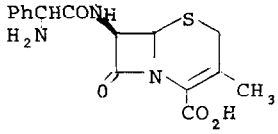
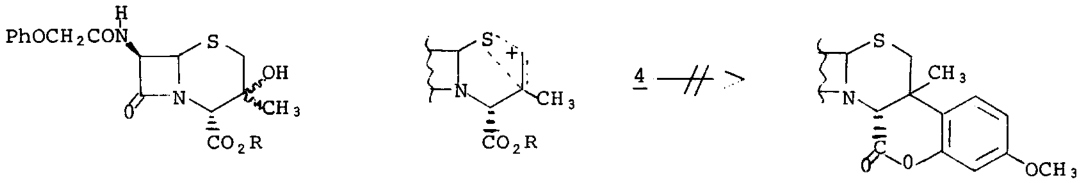


Cephalexin

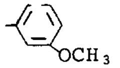
During the course of the study of this rearrangement (3), variable amounts of a new β-lactam containing material could often be isolated in addition to 3-cephem ester 2. The characteristic AB pattern (J_{gem} = 14 Hz) of the C_2 methylene protons and the usual H_7 double doublet (4) of this new compound suggested a cephalosporin derivative. However, the replacement of the vinyl methyl signal (normally found at 2.20 δ in 3-cephem's) with a singlet at higher field (1.26 δ), together with infrared evidence for a saturated ester, and elemental analysis, led to the assignment of the 3-hydroxy, 3-methyl cepham structure, 3, for this novel moiety. Retention of H_7-H_6 cis stereochemistry in 3 was indicated by the coupling constant, J_{6-7} = 4 Hz (4). Treatment of 3 with one equivalent of m-chloroperbenzoic acid affords the corresponding β-sulfoxide, whose configuration is confirmed by NMR hydrogen bonding studies (5-7). The anisotropic effect of the β-sulfoxide (5) upon H_4 indicated that

this hydrogen had retained its original β-orientation.

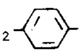
It was subsequently determined that production of 3 (at the expense of 2) was overwhelmingly favored by the use of sulfuric acid, sulfate esters, metal bisulfate salts, and the nitrogen isostere (sulfamic acid). Optimized production of olefin was realized by utilization of alkyl or aryl sulfonic acids as catalysts. This olefin, 2, was ruled out as an intermediate to 3 since the former was completely resistant to acid promoted hydration. The reverse also held, 3 being remarkably resistant to even strenuous acid catalyzed dehydration. The latter conversion could be accomplished, however, by warming 3 in a tertiary amide solvent containing carboxylic or sulfonic anhydrides, suggesting that the corresponding 3-O-acetate and 3-O-sulfonate derivatives of 3 undergo a facile elimination. Such dehydrations proceed in quantative yield.

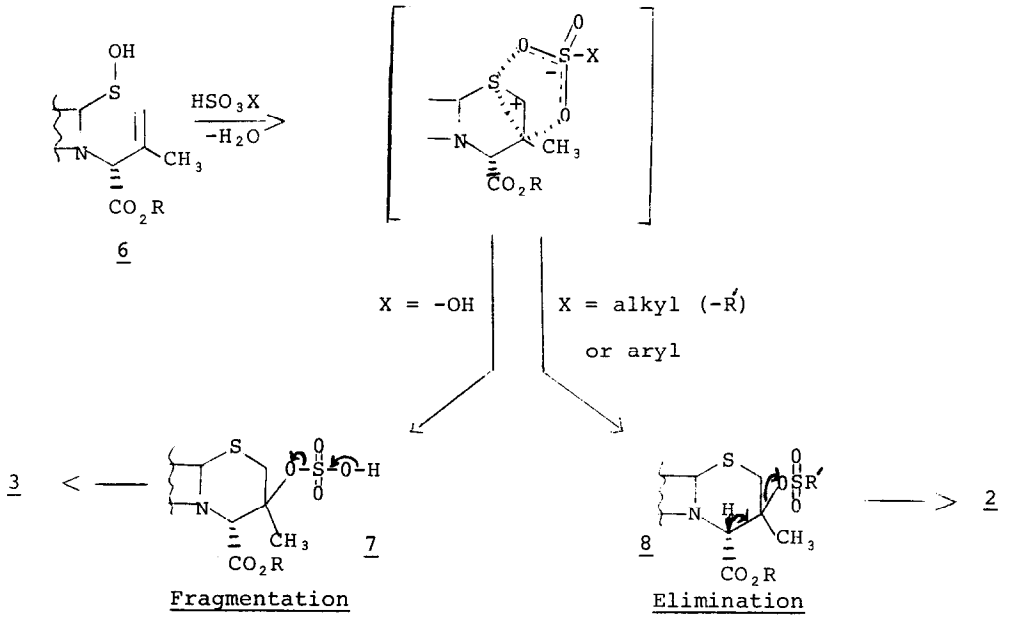


3 4 5

Speculation that episulfonium ion 4 might be a common precursor to both 2 and 3 could not be substantiated by external trapping with hydride (from $[C_6H_5]_3Si\text{-}H$), azide ion, or alcohols. An internal trapping experiment (4, R =  → 5) likewise failed.

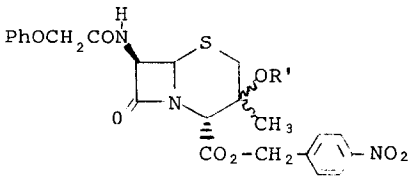
The above evidence warrants consideration of the involvement of esters 7 or 8, both arising from the well-documented sulfenic acid intermediate 6 (8), through a mixed sulfenic-sulfonic anhydride or its ion-pair counterpart. The mode of decomposition may then be responsible for the different reaction courses taken with sulfuric acid and alkyl (or aryl) sulfonic acids.

Formation of the 3-hydroxy-3-methyl cephams of this type is a general reaction and proceeds as described for a large number of amide side chains and ester protecting groups, providing such are stable to reaction conditions. For convenience, however, esters that tend to lend crystallinity to the products (e.g., 3 R = -CH$_2$-  -NO$_2$, mp 214-215°, yield 50%) are desirable for ease of isolation. In contrast to earlier reports (1), ring expansion occurs under



these conditions on the unprotected penicillin V-sulfoxide without concomitant decarboxylation providing 3 (R = -H) albeit in lower yield.

Compound 3 (R = $-CH_2-C_6H_4-NO_2$) was readily characterized by crystalline derivatives as represented below.



	R'	Reagent	m.p.
9	$-COCH_3$	$CH_2=C(OCOCH_3)-CH_3$, H^+	70-72°
10	$-Si(CH_3)_3$	BSA	146-148°
11	$-COCH_2COCH_3$	diketene	138-140°

The 4-nitrobenzyl ester function could be removed from 3 (R = $-CH_2C_6H_5NO_2$[p]) via either catalytic hydrogenation or chemical reduction (Zn°, H^+) to afford 3-hydroxy, 3-methyl-7β-(2-phenoxyacetamido)cepham-4 α-carboxylic acid 3 (R = -H, mp 154-155°), which displayed significantly reduced microbiological activity in comparison to its 3-cephem counterpart (2, R = -H).

Mechanistic considerations suggest a β-configuration for the 3-hydroxy group of 3. The following communication (7) provides extensive spectral and chemical evidence in support of this proposal.

All the above compounds have acceptable elemental analysis and spectral properties consistent with their proposed formulations. Melting points are uncorrected.

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2. C. W. Ryan, R. L. Simon, and E. M. Van Heyningen, *J. Med. Chem.*, 12, 310 (1969).

3. a. From this point on, R=p-nitrobenzyl, unless otherwise stated.

   b. Reaction conditions for conversion of 1 (m.p. 180-181°) → 2 (m.p. (m.p. 190-191°) or 3 are as follows: Reflux 1 in a mixture of N,N-dimethylacetamide/benzene boiling at ∿100°C in the presence of a catalytic amount of the appropriate acid.

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8. R. D. G. Cooper and F. L. José, *J. Am. Chem. Soc.*, 92, 2575 (1970).