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6-EPI-PENICILLINS AND 7-EPI-CEPHALOSPORINS

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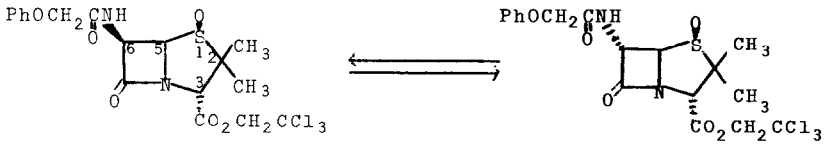
Essentially similar methods (1-4) of non-reversible, base-catalyzed epimerizations of the 6-position of penicillins have recently been described. These procedures failed, however, in attempts to epimerize penicillins which contain a secondary-amide side-chain.(1,4) This communication reports a novel, non-basic, reversible method of epimerizing penicillin sulfoxides at C_6 which is not limited by the nature of the amide side-chain. The primary utility of 6-epi-penicillin sulfoxides is their use as intermediates in a facile conversion to derivatives of 7-epi-cephalosporanic acid.



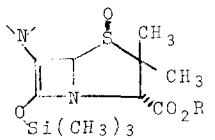
1 2

Crystalline phenoxymethyl penicillin-(s)-sulfoxide-β,β,β-trichloroethyl ester, 1, is transformed to a mixture of starting material and its C_6-epimer 2 upon exposure to N,O-bis-(trimethylsilyl)-acetamide (BSA). The equilibration requires several days at room temperature and occurs in a variety of inert solvents, methylene chloride being preferred. The equilibrium ratio of 2 to 1 is estimated as 4:1. Compound 2, m.p. 150-152°, (5) is easily separated from 1 by fractional crystallization from absolute methanol with yields as high as 50%. Intermediate crops, which co-crystallize as mixtures of 1 and 2, may be recycled for greater conversion to the latter. Final crops contain only 1. Pure 2 is converted to the same equilibrium mixture under identical conditions, thus constituting the first successful conversion of a 6-epi-penicillin derivative to its epimer with the natural configuration at C_6.

Epimerizations of the type 1⇌2 appear to be quite general under BSA catal-

ysis, occurring regardless of the nature of the amide side-chain (secondary or tertiary) or the ester protecting groups. Silyl exchange reagents of structure similar to BSA, e.g. N,O-bis-(trimethylsilyl)-trifluoracetamide (F_3-BSA), also catalyze the equilibration, while many other silylating agents (trimethylchlorosilane, hexamethyldisilizane, N-trimethylsilyl acetamide, dimethylchlorosilane, and trimethylsilylimidazole) fail to effect the same result. The sulfoxide function was found to be necessary for BSA catalyzed epimerizations, perhaps because it increases the acidity of the C_6 proton, either by an inductive effect or through homoenolic stabilization of an incipient anion at C_6. The β-lactam carbonyl is known for its "ketone-like" behavior and the conversion of ketones to silyl-enol-ethers under conditions similar to those described here has been demonstrated.(6) Such factors might permit formation of the planar enamine-silylenol-ether intermediate 3 from either 1 or 2: this in turn reverts to a mixture of epimers via a desilylation-reprotonation process from either the α- or β-face of the molecule.

Cephalosporins and their respective sulfoxides fail to epimerize in similar fashion (at C_7), even though superficially the latter system appears to allow an analogous mechanistic pathway. Apparently the sulfoxide function has less effect on the acidity of the C_7 proton in the cephalosporin series; and, as a result, the silylated acetamides are incapable of inducing silyl-enol-ether formation. This may be attributed in part to resonance structures such as 5, involving the sulfur atom. Similar resonance forms have been proposed (7) as being responsible for the 260 mμ absorption in cephalosporins. Our nmr dilution and solvent studies have shown that the secondary amide protons of cephem sulfoxides are more weakly hydrogen bonded to the β-sulfoxide oxygen than in their penam counterparts (8), consistant with a comparatively lower $S^+ \rightarrow O^-$ dipole moment in the former. Such a reduction of charge separation in cephem oxides would be expected to re-



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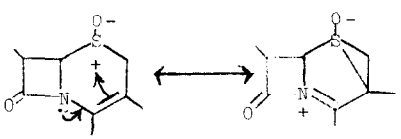
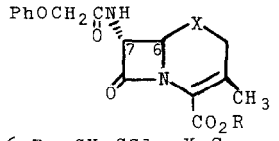


4 5

duce both the electrostatic and/or homoconjugative contributions to C_7, which may in turn effect the enolizability of the "ketone-like" β-lactam carbonyl.

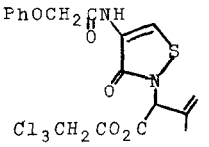
The C_7-epi-cephalosporins are, however, readily accessible via an acid-catalyzed ring expansion of the appropriate C_6-epi-penicillin sulfoxide, similar to that previously described by Morin, et. al., (9) affording the corresponding 7-epi-desacetyl cephem ester, such as 6, (24%). Compound 6 (m.p. 169-170°, MeOH) was separated from a biproduct, isothiazolone, 7, (9) by chromotography over silica gel using a benzene-ethylacetate elution gradient.



6 R=-CH_2CCl_3;X=S

8 R=-H;X=S

11 R=-CH_2CCl_3;X=S(O)



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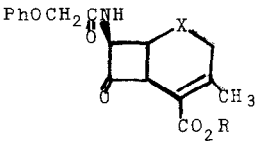

9 R=-H;X=S

10 R=-CH_2CCl_3;X=S(O)

The β,β,β-trichloroethyl group was removed with zinc dust in aqueous hydrochloric acid-acetonitrile at room temperature, (10) to provide the 7-epi-phenoxymethyl-desacetoxy cephalosporanic acid, 8, (m.p. 169-170°, mixture m.p. with 6 depressed) in 78% yield. Acid 8 displayed significantly reduced antimicrobial activity when compared to its epimer 9. This was not surprising in view of similar results obtained for the 6-epi-penicillins. (3,4) Neither of the epimeric sulfoxides, 10 (m.p. 175-176°, EtOH) or 11 (m.p. 213-214°, $CHCl_3$/EtOH), shows any evidence of interconversion to its C_7 epimer upon extended BSA treatment, as previously described.

A recent communication reported the 7-epimerization of an intact cephalosporin sulfoxide ester, (11) but, the epimerized sulfoxide ester was not converted to the corresponding, reduced 7-epi-cephalosporanic acid.

The nmr spectra of the 6-epi-penicillin sulfoxides and 7-epi-cephalosporin derivatives are identical in most respects to their counterparts with the normal cis-β-lactam proton configuration, (8,9) with the exception of the epimerized center. In $CDCl_3$ (TMS internal standard, 60 MHz) the H_6 quartet shifts upfield from 6.16δ ($J_{5,6}$=4) in 1 to 5.42δ ($J_{5,6}$=1.5) in 2. In the cephem series the H_7 quartet of 9 appears at 5.87δ ($J_{6,7}$=4.5), but moves to 5.02δ ($J_{6,7}$=1.8) in 6 and 5.04δ ($J_{6,7}$=2.0) in 8. Such changes are in agreement with earlier reports. (1-4,11) All new compounds had ir and nmr spectra, as well as elemental

analysis, consistent with their proposed formulations.

This conversion of a 6-epi-penicillin derivative to its natural isomer may be important when coupled with the Bose synthesis (12) of penicillins having C_5-C_6 *trans* geometry, as a potential route for their conversion to the natural isomers with a *cis* β-lactam configuration.

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5. Compound 2a exhibits unusual crystallization behavior, often crystallizing with a mole of solvent, m.p. 98°, re-solidifying and re-melting at 150-152° after loss of methanol (verified by nmr). On other occasions it crystallized directly in its 150-152° form.

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