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C(2)-SPIROEPOXY-CEPHEMS

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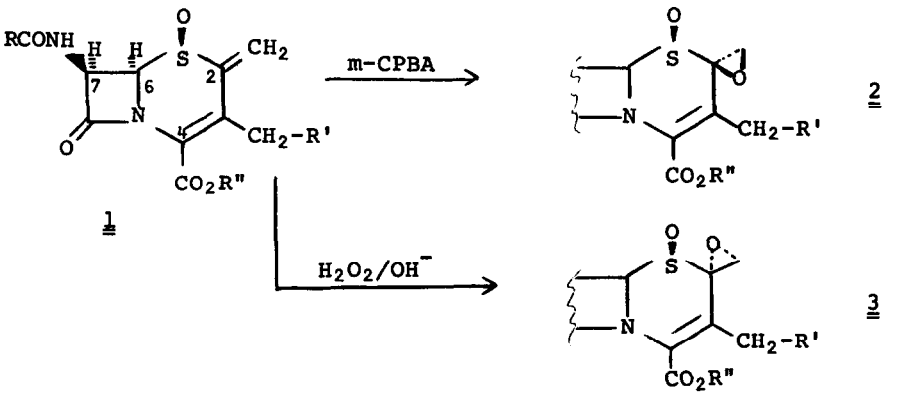
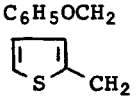
We have reported several syntheses of interesting β-lactam derivatives derived from the diene sulfoxide system 1[1].

We now wish to report the synthesis of a C(2)-spiroepoxy cephem and attempts to use this derivative in an approach into ring expanded cephalosporins.

Treatment of 1(a)[2] in $CHCl_3$ with m-CPBA (5°, 30 min.) gave after work up and chromatography, 30-40% of a single epoxide isomer 2(a) [232°]. Alternatively, reaction of 1(a) with alkaline H_2O_2[3] gave the other epoxide isomer 3(a) [180-181°] in 45-55% yield plus a trace of isomer 2(a).



1 2 3

Where	R	R'	R"
(a)	CH_3	H	TCE
(b)	$C_6H_5OCH_2$	H	TCE
(c)	$C_6H_5OCH_2$	OAc	TCE
(d)		OAc	TCE

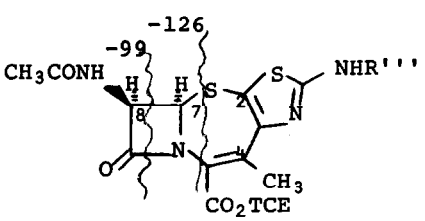
TCE = trichloroethyl

Other diene sulfoxides 1(b), 1(c) and 1(d) also form a single epoxide isomer [3(b) (45-50%, 195°, 3(c) (35%) and 3(d) (12%)] with alkaline hydrogen peroxide. No attempt was made to synthesize the other isomer of 3(b-d).

The evidence for structures 2 and 3 was provided by physical data and subsequent chemical reactions, *ie*, the conversion of the two spiroepoxy isomers into a common product 5. Thus the ir showed the β-lactam stretch at 1809 cm^{-1}, the mass spec. showed a mol. ion at M-18, each isomer analyzed correctly and their respective nmr spectrums showed loss of the C(2)-exomethylene protons. There was a significant difference in the nmr ($DMSOd_6$) spectrums of isomers 2(a) and 3(a), primarily in the position (δ) of the epoxide methylene-AB(J=4Hz), 3.26, 3.60 vs 3.84, 3.90 and the H(6) doublet (J=5Hz), 5.50 vs 5.16 for the peracid isomer 2(a) vs the H_2O_2 isomer 3(a). The stereochemical assignments of the spiroepoxides are based on the fact that protons (or methyl groups) located vicinal and trans diaxial [in this case the hydrogens of the epoxy methylene group of 2(a)] to the β-sulfoxide are shielded[4].

Our initial goal was to prepare the sulfide-spiroepoxide, which we felt would react with acids, for example, HBr, to open the epoxide and hence the ring at S(1)-C(2), to give the thiol-ω-bromoketone, which would then spontaneously close to give the 3-keto-ring expanded cephem. Attempts to reduce the sulfoxide-spiroepoxide, however, gave intractable material and the products isolated were nonlactam in structure. Similar results were obtained with the sulfoxide-spiroepoxide by the reaction with various nucleophiles (N_3^-, Br^-, ROH, RSH including 2-mercaptobenzothiazole) under conditions commonly used for opening epoxides. It seemed apparent that initial opening of the epoxide was occurring readily and that the product depended on the fate of the sulfenic acid functionality. What we really needed was an intramolecular trapping agent.

Reaction of crude 3(a) with 5 equiv. of thiourea in ETOH at 60°/30 min. gave, after work up and chromatography, 24% of the tricyclic ring expanded cephem 4(R'''=H) as well as a non-β-lactam containing product. The same reaction with N-methylthiourea gave the corresponding N-methyl derivative of 4(R'''=CH_3) in 4% yield.



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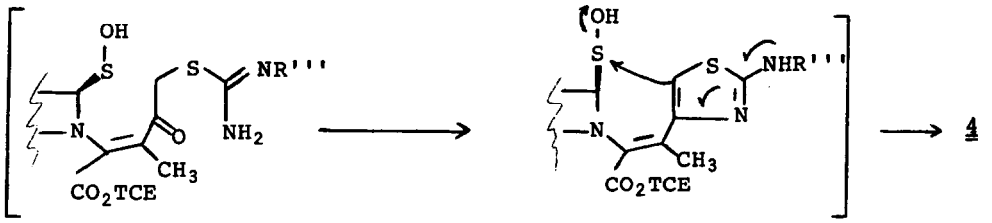
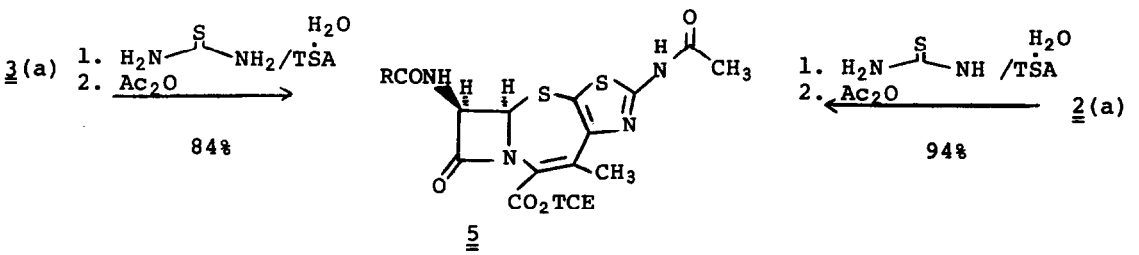
The structure of 4(R'''=H) was evident from physical data. The ir ($CHCl_3$) of 1770 cm^{-1} showed the presence of a β-lactam sulfide. Mass spec. gave a mol. ion at 471, which corresponds to starting material plus thiourea minus two moles of water. The fragmentation showed a small M-99(372), which is the normal mode of β-lactam fragmentation, plus a large M-126(345) which is fragmentation with retention of the β-lactam. The nmr($CDCl_3$) showed loss of the epoxide

methylene, the presence of two methyl groups, the TCE group, the β-lactam protons (reversed), the presence of two replaceable protons, and the side chain amide proton. Thus: (δ), 2.12 (s,3,-C(=O)-CH_3), 2.59(s,3,=C-CH_3), 4.76, 5.00(AB J=12Hz,2,TCE), 5.39(q J=4/7Hz,1,H(8)), 5.80(d J=4Hz,1,H(7)), 6.0(bs,2,NH_2), 6.90(d J=7Hz,1,NH). Compound 4(R'''=H) was readily acetylated with Ac_2O (80°/1 hr.) to give the corresponding N-acetyl derivative 5. Exhaustive oxidation of 5(R=CH_3) with m-CPBA resulted in the uptake of two equivalents of peracid giving first a crystalline sulfoxide (one isomer, 204-205°) followed by the crystalline sulfone (237-238°)[5].

Mechanistically it appears that thiourea opens the epoxide, followed by cyclization to the aminothiazole (loss of one mole of water), then intramolecular sulfenic acid cyclization (loss of the second mole of water) to give the product.

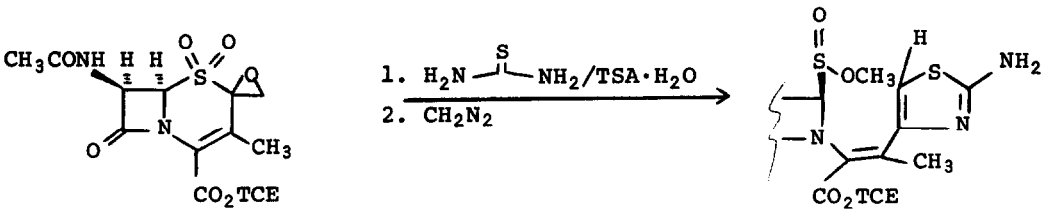


Since protonation of the sulfenic acid or formation of its mixed anhydride should accelerate ring closure[6], we added 0.1 equivalent of toluene sulfonic acid, the yield of 4 increased dramatically from 24 to 46.5% (R'''=H) and from 4 to 49% (R'''=CH_3) using crude 3(a). Using pure isomer 3(a) the overall yield to 5 (R=CH_3) was 84% and it was 94% overall from pure 2(a), thus the conversion of both spiroepoxides 2 and 3 to a common product 5.



From pure 3(b) the overall yield to 5 (R=$C_6H_5OCH_2$) was 85%. However, the cephalosporin epoxide 3(c) failed to give the corresponding tricyclic derivative.

Although we were unsuccessful in isolating the sulfenic acid intermediate we have isolated the sulfinic acid intermediate as a mixture of methyl sulfinates. Thus the sulfone spiroepoxide 6[7] (198-199°) was treated with thiourea-TSA·H_2O, followed by diazomethane, to give mixtures of the methyl sulfinate 7 (28%).



6 7

The free acid obtained from 5 ($R=C_6H_5OCH_2$) showed a low order of microbiological activity.

It is apparent, however, that the α-epoxy-sulfoxide functionality offers a very mild (room temperature and below), nonthermal route to sulfenic acids.

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REFERENCES

1. D. O. Spry, *Tetrahedron Lett.*, 2413 (1973); *Chem. Comm.*, 671 (1973); *Tetrahedron Lett.*, 3611 (1977).
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4. P. V. Demarco and R. Nagarajan in "Cephalosporins and Penicillins: Chemistry and Biology," E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, pp 353.
5. All crystallizations were done from CH_2Cl_2/hexanes and all crystalline compounds analyzed correctly.
6. R. D. G. Cooper and D. O. Spry in "Cephalosporins and Penicillins: Chemistry and Biology," E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, pp 219.
7. Obtained from the peracid (m-CPBA) oxidation of the corresponding diene sulfone.

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