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PREPARATION OF A NOVEL CEPHALOSPORIN SULFONIUM SALT

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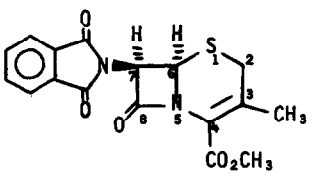
No example of an S-alkylated penicillin or cephalosporin has yet been reported, presumably because the ring sulfur atoms are quite unreactive toward the usual alkylating reagents. However, we have now found that on reaction of ester 1[1] with methyl fluorosulfonate[2] in CH_2Cl_2 (72 hr, r.t., Ar), analytically pure sulfonium salt 2 (mp 143-144.5° dec.) crystallizes in 30%



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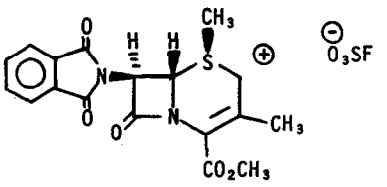

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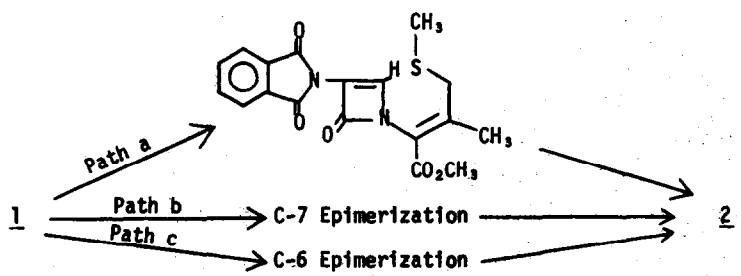
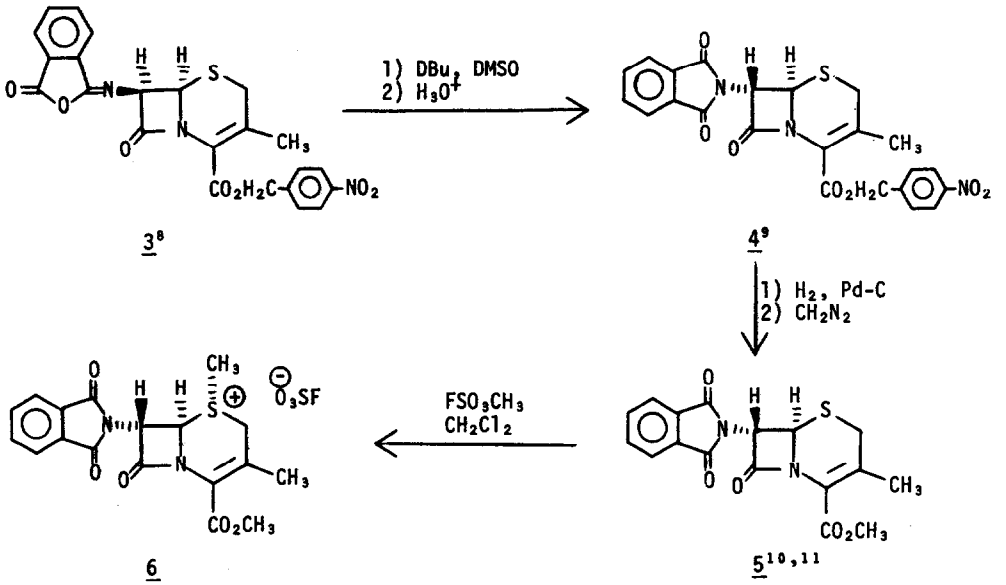
yield;[3] pmr (DMSO-d_6) δ 2.37 (s, 3H, 3-CH_3), 2.96 (s, 3H, S-CH_3), 3.82 (s, 3H, CO_2CH_3), 4.01 (d, J=16, 1H, H2), 4.51 (d, J=16, 1H, H2), 5.52 (broad d, J=2.5, 1H, H6), 6.54 (sharp d, J=2.5, 1H, H7), 8.00 (s, 4H, aromatic). The 2.5 Hz coupling between the β-lactam protons is characteristic of trans β-lactam stereochemistry.[4] The relative stereochemistry of the methyl group on sulfur was assigned on the basis of a 17% N.O.E. observed between the methyl group and the C-6 proton.[5]

There are three fundamentally different mechanisms possible for the formation of 2 from 1 (see diagram). Since 2 is optically active ($[\alpha]_D^{DMSO}$ = +24±3°[6]), it cannot be formed



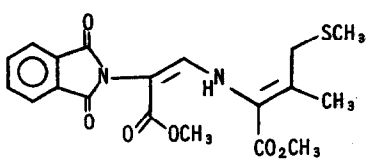
exclusively by path a. Paths b and c lead to enantiomeric products, and so knowledge of the absolute stereochemistry of 2 would reveal the actual reaction path. The absolute stereochemistry of 2 can be inferred from the following sequence of reactions[7]:



3[8] 4[9] 5[10,11] 6

The pmr spectrum of 6 was identical with that of 2, but the optical rotation of 6 was found to be $[\alpha]_D^{DMSO} = -24\pm7°$[6] (opposite in sign to that of 2), indicating that C-6 epimerization is the dominant pathway for the formation of 2 from 1.

The C(6)-S bond of 2 is apparently rather weak. Treatment of 2 with $NaOCH_3$ in CH_3OH-DMSO at -78° for a few minutes gave 7,[11] pmr ($CDCl_3$) δ 2.0 (s, 3H), 2.12 (s, 3H), 3.34 (s, 2H),



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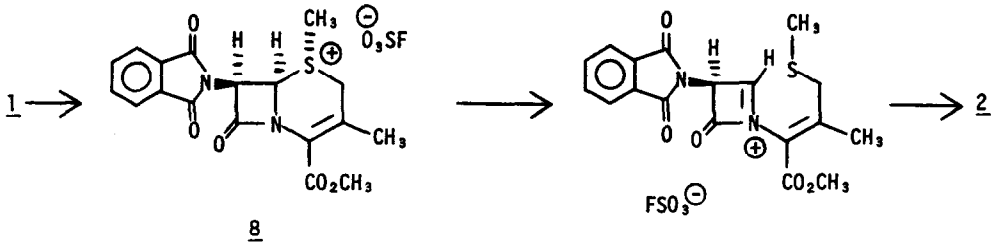
3.67 (s, 3H), 3.84 (s, 3H), 7.55 (overlapping signals, 2H), 7.85 (mult, 4H); the spectrum contained no signals in the δ 4.5-6.5 region.

A mechanism for the conversion of 1 to 2 consistent with the reaction conditions, with C(6)-epimerization and with C(6)-S bond weakening, is shown below:



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2. J. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott, and M. C. Whiting, Chem. Commun., 1533 (1968).
3. Concentration of the mother liquors gives mainly unreacted 1.
4. K. D. Barrow and T. M. Spotswood, Tetrahedron Lett., 3325 (1965); J. L. Luche, H. B. Kagan, R. Parthasarathy, G. Tsoucaris, C. deRango, and C. Zelwer, Tetrahedron, 24, 1275 (1968); D. A. Johnson, D. Mania, C. A. Panetta, and H. H. Silvestri, Tetrahedron Lett., 1903 (1968); G. E. Gutowski, Tetrahedron Lett., 1779 (1970).
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6. Specific rotations are averages of two independent determinations.
7. Crowding of the phthalimido group does not provide a driving force for epimerization of 6 as it undoubtedly does in 8, and the assumption is made here that 6 is formed from 5 by simple S-alkylation. Both 1 and 3 were prepared from 7-aminodeacetoxycephalosporanic acid or its p-nitrobenzyl ester, which in turn are prepared from penicillin V by a well-known route that preserves the natural penicillin stereochemistry about the β-lactam [R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, J. Org. Chem., 36, 1259 (1971)].

8. Paper to be presented (S. Kukolja) at the International Congress of Heterocyclic Chemistry, Ljubljana, Yugoslavia, July 13-18, 1975. Isoimide 3 was prepared from 7-aminodeacetoxycephalosporanic acid p-nitrobenzyl ester by reaction with phthalic anhydride to give the phthalamic acid, followed by cyclization with DCC.
9. Satisfactory analytical and spectroscopic data were obtained for this compound; mp 220-223°, pmr (DMSO-d_6) δ 2.10 (s, 3H), 3.57 (bs, 2H), 5.25 (d, J=2, 1H), 5.35 (d, J=2, 1H), 5.47 (s, 2H), 7.70-8.50 (overlapping signals, 8H).
10. Satisfactory spectroscopic data were obtained for this compound; $[\alpha]_D^{DMSO}$ = +20°, pmr ($CDCl_3$) δ 2.15 (s, 3H), 3.36 (AB, 2H), 3.93 (s, 3H), 5.05 (d, J=2.5, 1H), 5.28 (d, J=2.5, 1H), 7.82 (m, 4H).
11. A satisfactory high resolution mass spectrum was obtained for this compound.