Tetrahedron Letters No. 47, pp 4703 - 4706.

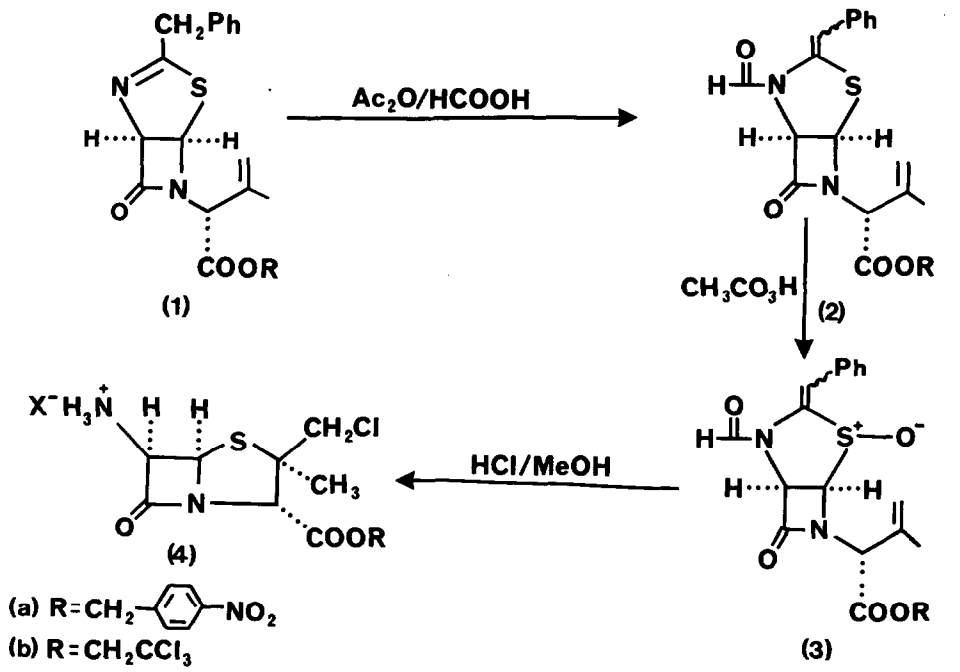
0040-4039/78/1115-4703$02.00/0

THE REARRANGEMENT OF p-NITROBENZYL 2R-[(1R,5R)-3-BENZYLIDENE-4-FORMYL-6-OXO-4,7-DIAZA-2-THIABICYCLO[3,2,0]HEPTAN-7-YL]-3-METHYLBUT-3-ENOATE 2'-OXIDE

S.J. Eagle and J. Kitchin*
Glaxo-Allenburys Research (Greenford) Ltd., Greenford, Middlesex.

The 2-halomethyl penam system has been synthesised by a variety of routes in recent years.[1] These modified penicillins have been used for the preparation of 3-halo-3-methyl cephams and hence the Δ^3-cephem system, 3-methylene cephams,[2] and 2-methyl 3H-cephems.[3]

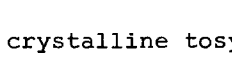
In this communication we report the rearrangement of a modified, penicillin-derived thiazoline, to give a 6-amino-2-chloromethylpenam ester.



The thiazoline (1a), prepared by the method of Cooper and José,[4] was formylated[5] to give (2a)[6] in 75% yield, as a foam, λ_{max} (ethanol) 280 nm (ε 21,600), $[\alpha]_D$ -365° (C 0.49 $CHCl_3$), ν_{max} ($CHBr_3$) 1772, 1740, and 1685 cm^{-1}; n.m.r. ($CDCl_3$) τ1.37 (1H, s), 1.81 and 2.53 (4H, ABq, J8), 2.69 (5H, s), 3.23 (1H, s), 3.99 (2H, ABq, J4), 4.76 (2H, s), 4.92 (1H, s), 5.10 (1H, s), 5.15 (1H, s), and 8.33 (3H, s).

Oxidation with peracetic acid gave a quantitative yield of the sulphoxide (3a), as a single diastereoisomer, λ_{max} (ethanol) 268 nm (ε 17,700), $[\alpha]_D$ -593° (C 0.45 $CHCl_3$), ν_{max} ($CHBr_3$) 1774, 1735, and 1680 cm^{-1}; n.m.r. ($CDCl_3$) τ 1.54 (1H, s), 1.72 and 2.65 (4H, ABq, J9), 2.3 to 2.7 (6H, m), 3.84 (2H, d, J4), 4.59 (2H, d, J4), 4.76 (2H, s), 5.05 and 5.14 (each 1H, br s), 5.21 (1H, s), and 8.61 (3H, s).

Reaction of the sulphoxide (3a) with three equivalents of hydrogen chloride in a 3:1 mixture of methanol and tetrahydrofuran at 0-5° for 1.25 hr. gave an 80% yield of the chloromethyl penam (4a, X = Cl) as an amorphous solid[7] on precipitation by ether; λ_{max} (ethanol) 264 nm (ε 10,300), $[\alpha]_D$ + 106° (C 1.5 CH_3OH), ν_{max} (Nujol) 3000 to 2400, 1784, and 1745 cm^{-1}, n.m.r. (DMSO-d_6) τ1.72 and 2.28 (4H, ABq, J8), 4.38 and 4.84 (4H, each d, J4) 4.60 (2H, s), 5.01 (1H, s), 6.09 (2H, s), and 8.52 (3H, s).

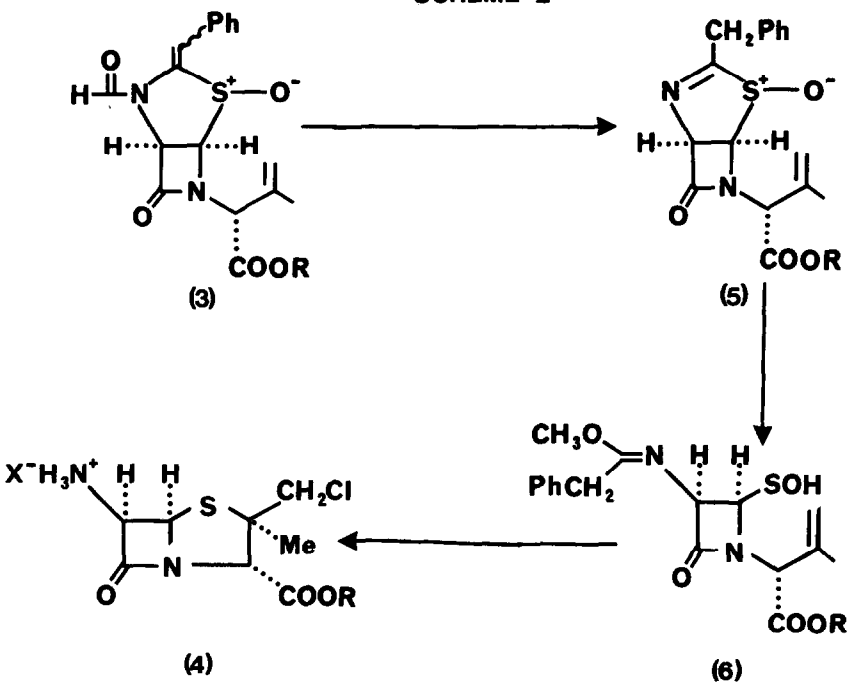
The crystalline tosylate (4a, X = ) m.p. 115 to 120° (d), was prepared in 50% yield from (3a) <u>via</u> the free amine.

This series of reactions was also applied to thiazoline (1b), to give the crystalline derivatives (2b) m.p. 117 to 118° and (3b) m.p. 163 to 164°, and (4b, X = Cl) as an amorphous solid.

The preparation of the cepham isomer of (4a, X = Cl) has been published[8]. Confirmation of the penam structure was also obtained by acylation of (4a, X = Cl) to give derivatives displaying the spectral characteristics[9] of the penam ring system.

We have outlined a possible mechanism (Scheme I), although we have no direct evidence for the proposed intermediates.

SCHEME I



We believe the first step is the methanolysis[10] of the formyl group of (3) to give the thiazoline sulphoxide (5), which undergoes ring opening (possibly *via* nucleophilic attack of methanol at the C=N- system) to give intermediates containing iminoether and sulphenic acid functions. The iminoether function can be cleaved to give amines with methanol[11] and under acidic conditions the sulphenic acid moiety adds to the double bond to give a thiiranium ion, which can be trapped by chloride ion[1b].

The ease with which the thiazoline sulphoxide (5) ring opens is in marked contrast to the thiazoline sulphoxides prepared by Kishi and co-workers[12] However, the presence of an acidic methylene group at C-3 in (5) maybe the reason for this difference.

Cooper[13] has reacted a C-3 phenoxymethyl thiazoline with m-chloro-perbenzoic acid in the presence of trifluoroacetic acid to give penams and cephams, probably *via* a sulphenic acid as intermediate.

REFERENCES

1. (a) S. Kukolja and S.R. Lammert, J. Amer. Chem. Soc., 94, 7169 (1972);
   (b) S. Kukolja, S.R. Lammert, M.R. Gleissner, and A.I. Ellis, J. Amer. Chem. Soc., 97, 3192 (1975);
   (c) T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, Tetrahedron Letters, 3001 (1973);
   (d) H. Tanida, T. Tsuji, T. Tsushima, H. Ishitobi, T. Irie, T. Yano, H. Matsumura, and K. Tori, Tetrahedron Letters, 3303, (1975).
2. S. Kukolja, M.R. Gleissner, A.I. Ellis, D.E. Dorman, and J.W. Paschal, J. Org. Chem., 41, 2276 (1976).
3. T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Oku, J. Amer. Chem. Soc., 98, 2342 (1976).
4. R.D.G. Cooper and F.L. José, J. Amer. Chem. Soc., 92, 2575 (1970).
5. C.W. Huffman, J. Org. Chem., 23, 727 (1958).
6. Only a single geometrical isomer of undetermined configuration was detected by n.m.r. spectroscopy.
7. Crude (4a, X = Cl) contains ca. 8% of the isomeric cepham.[8]
8. A. Nudelman and R.J. McCaully, J. Org. Chem., 42, 2887 (1977).
9. (a) S. Kukolja, N.D. Jones, M.O. Chaney, T.K. Elzey, M.R. Gleissner, J.W. Paschal, and D.E. Dorman, J. Org. Chem., 1975, 40, 2388;
   (b) K. Tori, T. Tsushima, Y. Tamura, H. Shigemoto, T. Tsuji, H. Ishitobi, and H. Tanida, Tetrahedron Letters, 3307 (1975).
10. J.P. Greenstein and M. Winitz, "Chemistry of the Amino Acids", John Wiley and Sons, Inc., New York, 1961, p. 920.

    The corresponding N-acetyl analogue of (3a) under identical conditions gave an 8% yield of (4a, X = Cl).
11. W.H.W. Lunn, R.W. Burchfield, T.K. Elzey, and E.V. Mason, Tetrahedron Letters, 1307 (1974).
12. H. Tanino, S. Nakatsuka, and Y. Kishi, Tetrahedron Letters, 581 (1976).
13. R.D.G. Cooper, J. Amer. Chem. Soc., 94, 1018 (1972).

(Received in UK 19 September 1978)