Tetrahedron Letters No. 32, pp 2915 - 2918.
© Pergamon Press Ltd. 1978. Printed in Great Britain.

0040-4039/78/0801-2915$02.00/0

A NEW ROUTE TO 3-METHYLENECEPHAMS

J.R. Corfield and C.G. Taylor

Dista Products Limited,

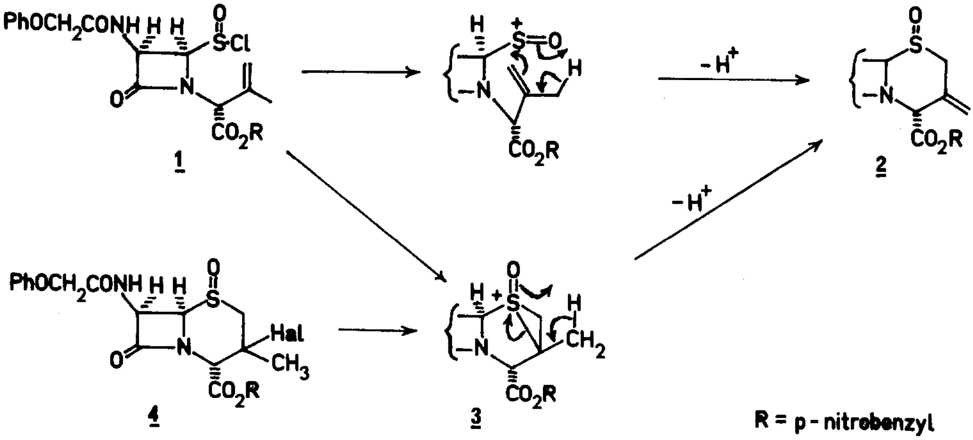
Fleming Road, Speke, Liverpool L24 9LN, U.K.

(Received in UK 2 June 1978; accepted for publication 12 June 1978)

3-Methylenecephams are key intermediates in the synthesis of certain cephalosporin antibiotics.[1] We wish to report a new synthesis of a 3-methylenecepham which also has some interesting mechanistic aspects.

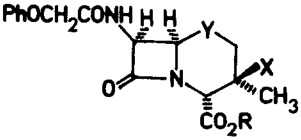
A convincing mechanism for a reaction in which a 3-methylenecepham is produced must be capable of accounting for the formation of that product in spite of the greater thermodynamic stability of the isomeric 2- and 3-cephems. Thus, Kukolja et al.[2] have proposed an ene mechanism to describe the reaction in which the sulphinyl chloride 1 reacts with certain Lewis acids to yield a 3-methylenecepham 2 (Scheme). An alternative view of the reaction, however, involves the formation from 1 of an episulphoxonium ion 3, which is an oxidised form of the well-established episulphonium ion encountered in the classic rearrangement of a penicillin sulphoxide to a 3-cephem.[3] We hypothesized that 3 might undergo a sigmatropic hydrogen shift (Scheme) in order to generate the neutral product 2 via loss of a proton, a reaction which finds analogy in the facile sigmatropic elimination observed in certain episulphoxides.[4] The possibility of generating an episulphoxonium ion from a 3-halo-3-methylcepham 4 using an electrophilic metal salt to assist the removal of the halide ion therefore merited investigation.

The 3-bromo-3-methyl cepham 5b was prepared by the method of the Fujisawa group.[5] Oxidation of 5b with m-chloroperbenzoic acid (mCPBA) in chloroform at 0-5° gave a high yield of the R-sulphoxide 6b as a foam,[6] whereas oxidation with iodobenzene dichloride in aqueous pyridine at -30° gave a 60% yield of the S-sulphoxide 7b (m.p. 147-149°). Sulphoxide stereochemistry was determined by dehydrohalogenation of both 6b and 7b in chloroform using pyridine or triethylamine and comparison of the resulting 3-cephems with authentic material.[7] By a similar method were prepared 6a (foam), 7a (m.p. 164-166°) and 6c (foam).

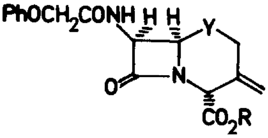


R = p-nitrobenzyl

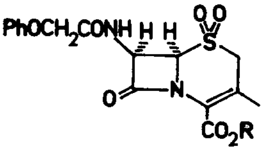
Scheme



	Y		X
5	S	a	Cl
6	S''''O	b	Br
7	S◀O	c	I
10	SO$_2$		



	Y
8	S◀O
9	S''''O
12	SO$_2$



11

Treatment of 7b with mercury(I) perchlorate (0.5 mole) in dimethoxyethane (DME) for 18 hr. at 15-20° gave the desired 3-methylenecepham 8[2] in 76% yield. This product was identical with authentic material.[7] Acetonitrile, dioxan, THF and acetone were also satisfactory solvents. Mercury(II) perchlorate (1 mole) was also able to effect the same transformation but no other metal salt was successful, although many were examined in a number of solvents. Generally, no reaction was observed except at elevated temperatures when quantities of the 3-cephem were formed, though in some cases there was evidence of participation by the anion. 7a was very inert and no successful reactions were observed using it. The utility of mercury(I) and mercury(II) salts in metal-assisted reactions of alkyl halides is well known.[8]

When the R-sulphoxide 6b was subjected to our best reaction conditions (mercury(I) perchlorate, DME, 18 hr., 20°) a 75% yield of the 3-methylenecepham 9 (m.p. 187-189°; nmr (d_6-DMSO,δ) 3.51 and 4.23 (ABq, 2H, J=12.5 Hz), 4.55 (S,2H), 4.58 (d, 1H, J=4.5 Hz), 5.2-5.6 (m, 6H)) was obtained. 9 could be isomerized to the corresponding 3-cephem using triethylamine in chloroform. 6a did not react with mercury(I) perchlorate but 6c resembled 6b in its behaviour.

The similarity in the behaviour of 6b and 7b in this reaction was surprising. The most ready formation of the episulphoxonium ion would be predicted to occur when the lone pair on sulphur and the halogen atom at C-3 are trans to one another, as in 7b, thus permitting closure of the three-membered ring without interference from the departing metal-halogen complex. Differences in reactivity between 6b and 7b would thus be expected but were not observed. Evidence for the proposed mechanism was therefore sought in the behaviour of the sulphone 10b. Oxidation of either 6b or 7b with excess mCPBA in refluxing chloroform gave an 85% yield of 10b (m.p. 187-188° dec.), which could be dehydrohalogenated ($CHCl_3$,Et_3N) to the corresponding 3-cephem 11 (m.p. 182-183°). On treating 10b with mercury(I) perchlorate in DME at 20° for 24 hr., no reaction was observed; more forcing conditions (2 hr. at reflux) yielded a 9:1 mixture of 11 and 12 (m.p. 179-180°; nmr ($CDCl_3$,δ) 3.70 and 3.97 (ABq, 2H, J=15 Hz), 4.52 (S,2H), 5.23 (d, 1H, J=4.5 Hz), 5.27 (S, 3H), 5.47 (S, 1H), 5.60 (S, 1H), 6.17 (q, 1H, J=4.5 and 11 Hz)). 12 was not converted into 11 under the conditions of the reaction. These results show that in both the R- and S-sulphoxides the lone pair on sulphur participates in the reaction, implying the intermediacy of a bridged species which is presumably the proposed episulphoxonium ion. The kinetically-controlled product mixture obtained from the sulphone 10b, however, is consistent with a simple metal-assisted elimination reaction via a transition state having a high degree of carbonium ion character at C-3, Whether an episulphoxonium ion is also an intermediate in Kukolja's reaction remains an open question. It will be noted that the successful reaction of both 6b and 7b implies the existence of two epimeric episulphoxonium ions (a situation which also occurs in the case of the episulphonium ion), both of which are capable of yielding a 3-methylenecepham, since the retention of sulphoxide stereochemistry in both conversions excludes the possibility of a common intermediate.

Acknowledgement

We thank Mr. G. Maciak (Eli Lilly and Co., Indianapolis) for analytical data and Mr. M. Whyment and Mr. N. Howell for technical assistance. We are also indebted to Prof. J.E. Baldwin, Dr. L.D. Hatfield and Dr. R.D.G. Cooper for many helpful discussions.

References

(1) R.R. Chauvette and P.A. Pennington, J. Am. Chem. Soc., 96, 4986 (1974); R.R. Chauvette and P.A. Pennington, J. Med. Chem., 18, 403 (1975); R. Scartazzini, P. Schneider and H. Bickel, Helv. Chim. Acta, 58, 2437 (1975); R. Scartazzini and H. Bickel, Helv. Chim. Acta, 57, 1919 (1974); G.A. Koppel, M.D. Kinnick and L.J. Nummy, J.Am. Chem. Soc., 99, 2822 (1977).

(2) S. Kukolja, S.R. Lammert and M.R. Gleissner, J. Am. Chem. Soc., 98, 5040 (1976)

(3) E.H. Flynn, ed., 'Cephalosporins and Penicillins', Academic Press, New York, 1972, p. 203.

(4) J.E. Baldwin, G. Höfle and Se Chun Choi, J.Am. Chem. Soc., 93, 2810 (1971)

(5) T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi and T. Oku, Tetrahedron Letters, 3001 (1973); British Patent 1453301.

(6) All new compounds were characterised by ms, nmr and ir and, where crystalline, had acceptable elemental analyses.

(7) We thank Dr. T.S. Chou (Eli Lilly and Co., Indianapolis) for providing us with samples.

(8) A. McKillop and M.E. Ford, Tetrahedron, 30, 2467 (1974) and references therein.