Tetrahedron Letters,Vol.26,No.4,pp 497-500,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

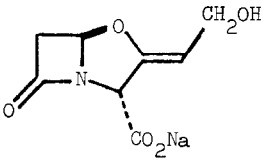
A SYNTHESIS OF 4-CARBOXY-3-METHYLCEPH-3-EM 1,1-DIOXIDE INVOLVING A NEW STRATEGY FOR THE RING ENLARGEMENT OF PENICILLANATE 1,1-DIOXIDES

G.D. Sriyani Ananda and Richard J. Stoodley*

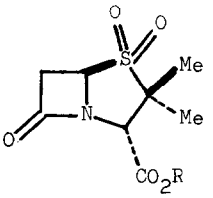
Department of Organic Chemistry, The University, Newcastle upon Tyne, NE1 7RU

Summary: The title compound has been prepared from sulbactam sodium salt by a six-step sequence.

Many penicillins are hydrolysed by β-lactamases and they are therefore ineffective against bacteria that produce these enzymes. Sodium clavulanate (1)[1] and sulbactam sodium salt (2a)[2] are powerful β-lactamase inactivators which are capable of protecting penicillins from such enzymic destruction. In consequence, combinations of penicillins and these compounds can play a useful role in the treatment of infections caused by β-lactamase-producing bacteria.



(1)

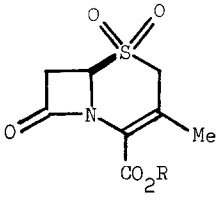


(2)

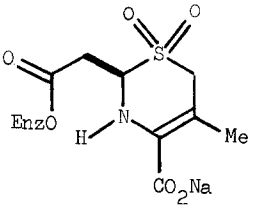
a; R = Na

b; R = CH_2Ph

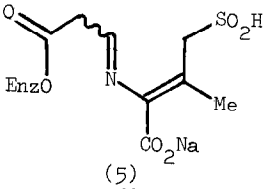
As part of a programme aimed at defining structural features of β-lactam derivatives that are necessary for β-lactamase inhibition, the cephem dioxide (3a) attracted our attention. Were it to act as a substrate for the enzyme, a species of type (4) would be generated which might isomerise to an intermediate of type (5). Analogous processes are believed to be implicated in the inactivation of β-lactamases by compounds (1)[3] and (2a).[4] We now report on the synthesis and biological testing of the salt (3a).



(3)



(4)



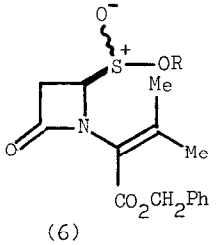
(5)

a; R = Na

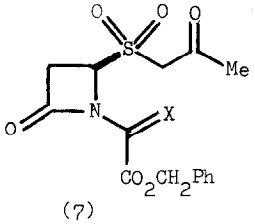
b; R = CH_2Ph

c; R = H

When treated with 1,5-diazabicyclo[4.3.0]non-5-ene in dichloromethane,[5] sulbactam benzyl ester (2b)[6] was converted into the sulphinic acid (6a), $[\alpha]_D$-13° ($CHCl_3$), in 87% yield. The derived sodium salt (6b) reacted with chloroacetone in acetone containing a trace of sodium iodide to give the sulphone (7a) (80% yield after SiO_2 chromatography), $[\alpha]_D$ -53° ($CHCl_3$). That the afore-cited reaction had led to the sulphone (7a) rather than the sulphinate (6c) was suggested by the presence of a strong band at 1 330 cm^{-1} (attributed to the symmetrical stretch of a sulphone moiety[7]) in the i.r. region. Moreover, ^1H n.m.r. spectroscopy revealed that the product was a single entity [a diastereoisomeric mixture would have been expected for the sulphinate structure (6c)]. Finally, the ease with which the methylene protons of the acetonyl group underwent deuterium exchange [the AB-system (J 14 Hz) centred at δ 3.80 disappeared on addition of D_2O to the $CDCl_3$ solution] left little doubt that the sulphone formulation (7a) was the correct one.



(6)



(7)

a; R = H

b; R = Na

c; R = CH_2COMe

a; X = CMe_2

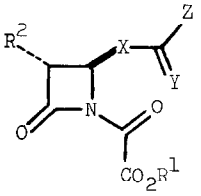
b; X = O

Ozonolysis of the sulphone (7a) in dichloromethane at -78°C (with a Me_2S work-up) provided the oxamide (7b), $[\alpha]_D$ -78° (EtOH), as a slightly impure foam in essentially quantitative yield.

When heated in toluene containing trimethyl phosphite (2 mol. equiv.) at ca. 90 °C, the oxamide (7b) was converted into the cephem dioxide (3b) (84% yield after SiO_2 chromatography), m.p. 113-115 °C, $[\alpha]_D$ -11° (EtOH). In accord with its structure, compound (3b) showed a strong i.r. absorption (KBr) at 1 795 cm^{-1} for the β-lactam carbonyl group, a u.v. absorption (EtOH) at 260 nm (ε 10 300) for the cephalosporin chromophore,[8] and ^1H n.m.r. absorptions (300 MHz, $CDCl_3$) at δ 3.47 (dd, J 16 and 5 Hz) and 3.57 (dd, J 16 and 2 Hz) for the 7-methylene group, and at δ 3.66 and 3.86 (each d, J 18 Hz) for the 2-methylene group.

Careful hydrogenolysis of the benzyl ester (3b) over 10% palladium-charcoal in ethyl acetate provided the acid (3c) (30% yield after recrystallisation), m.p. 141-144 °C, $[\alpha]_D$ +78° (EtOH), which was converted into the salt (3a) by the action of sodium 2-ethylhexanoate in acetone. The salt (3a), which was unchanged in deuterium oxide over a 24-h period, did not act as an ampicillin synergist against β-lactamase-producing bacteria.

The synthesis of the cephem dioxide (3b), reported herein, is of interest in two respects. Firstly, the strategy for deriving such a compound from a penicillanate 1,1-dioxide is new. Hitherto, cephem dioxides have been prepared by oxidation[9] of the corresponding cephems (which are usually derived by ring expansion of penicillanate 1-oxides[10]) with peracids. Second, the demonstration that the (7b) → (3b) transformation can be induced by trimethyl phosphite is noteworthy in that a six-membered ring is constructed in the reductive coupling reaction. Previously, trialkyl phosphites have been shown to be useful reagents for effecting the reductive cyclisation of azetidinone trithiocarbonates of type (8a) to penems of type (9),[11,12] of azetidinone thioesters of type (8b) to penems of type (9b),[12-14] and of azetidinones of type (8c) to carbapenams of type (9c).[13,15]

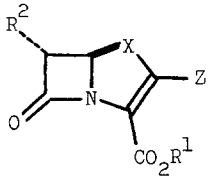


(8)

a; X = Y = S, Z = SR

b; X = S, Y = O, Z = R

c; X = CH_2, Y = O, Z = H, SR



(9)

a; X = S, Z = SR

b; X = S, Z = R

c; X = CH_2, Z = H, SR

Acknowledgements We thank the Association of Commonwealth Universities for a research studentship (to G.D.S.A.) and Pfizer Central Research for the biological testing of the salt (3a).

References

1 T.T. Haworth, A.G. Brown, and T.J. King, J.Chem.Soc.,Chem.Commun., 1976, 266.

2 A.R. English, J.A. Retsema, A.E. Girard, J.E. Lynch, and W.E. Barth, Antimicrob. Agents Chemother., 1978, 14, 414.

3 R.L. Charnas, J. Fischer, and J.R. Knowles, Biochemistry, 1978, 17, 2185; R.L. Charnas and J.R. Knowles, ibid., 1981, 20, 3214; C. Reading and P. Hepburn, Biochem.J., 1979, 179, 67.

4 D.G. Brenner, J.R. Knowles, and G. Rihs, Biochemistry, 1981, 20, 3680; C. Kemal and J.R. Knowles, ibid., 1981, 20, 3688.

5 C.M. Pant, J. Steele, and R.J. Stoodley, J.Chem.Soc.,Perkin Trans. 1, 1982, 595.

6 P.H. Crackett and R.J. Stoodley, Tetrahedron Lett., 1984, 25, 1295.

7 A.D. Cross, 'An Introduction to Practical Infra-Red Spectroscopy', Butterworths, London, 1964, 2nd Edn., p. 78.

8 P.V. Demarco and R. Nagarajan in 'Cephalosporins and Penicillins: Chemistry and Biology', ed. E.H. Flynn, Academic Press, London, 1972, pp. 360-366.

9 R.G. Micetich, R. Singh, and S.N. Maiti, Heterocycles, 1984, 22, 531.

10 R.B. Morin, B.G. Jackson, R.A. Mueller, E.R. Lavagnino, W.B. Scanlon, and S.L. Andrews, J.Am.Chem.Soc., 1963, 85, 1896; ibid., 1969, 91, 1401.

11 A. Afonso, F. Hon, J. Weinstein, A.K. Ganguly, and A.T. McPhail, J.Am.Chem.Soc., 1982, 104, 6138.

12 A. Yoshida, T. Hayashi, N. Takeda, S. Oida, and E. Ohki, Chem.Pharm. Bull., 1983, 31, 768.

13 C. Battistini, C. Scarafile, M. Foglio, and C. Franceschi, Tetrahedron Lett., 1984, 25, 2395.

14 E. Perrone, M. Alpegiani, A. Bedeschi, F. Giudici, and G. Franceschi, Tetrahedron Lett., 1984, 25, 2399.

15 A. Yoshida, Y. Tajima, N. Takeda, and S. Oida, Tetrahedron Lett., 1984, 25, 2793.

(Received in UK 2 November 1984)