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SOME OBSERVATIONS REGARDING β-LACTAM-CLEAVAGE REACTIONS OF PENICILLANATE 1,1-DIOXIDES AND RELATED COMPOUNDS

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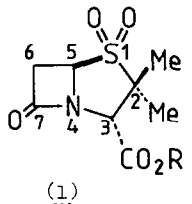
Summary: 1,5-Bond ruptures may follow, but do not accompany, 4,7-bond cleavages of penicillanate 1,1-dioxides.

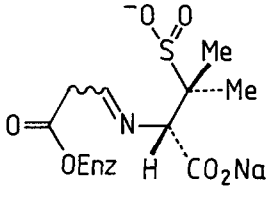
Many penicillins are hydrolysed by β-lactamases and they are therefore ineffective against bacteria that produce these enzymes. Sulbactam sodium salt (1a) is a powerful β-lactamase inactivator which is capable of protecting penicillins from such enzymic destruction.[1] In consequence, combinations of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



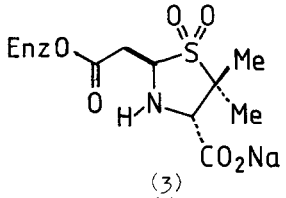
(1)

a; R = Na

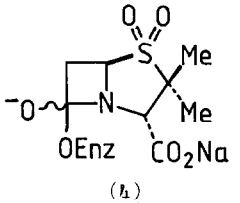
b; R = CH_2Ph



(2)



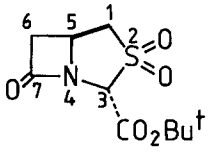
(3)



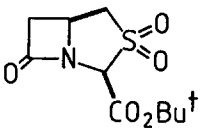
(4)

Knowles and his co-workers have shown[2] that the inactivation of sulbactam sodium salt (1a) by the β-lactamase from Escherichia coli involves further reactions of species (2). By analogy with penicillanate substrates, species (2) may be expected to arise from precursor (3). However, since such an intermediate could not be detected, the possibility that the initially formed enzyme-substrate complex (4) underwent direct conversion into species (2) was considered by the Harvard workers.

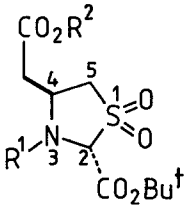
Recently, we reported[3] that the isopenam dioxides (5) and (6) reacted with trifluoroacetic acid to give, following esterification with diazomethane, the corresponding thiazolidine dioxides (7a) and (8a). These results established that the ruptures of the 4,7-bonds of compounds (5) and (6) were not accompanied by cleavages of the 2,3-bonds. Moreover, intermediates (7c) and (8c), which were clearly implicated, must have undergone intramolecular acyl transfers to give the acids (7b) and (8b) faster than isomerisations to the imine sulphinic acid (9).



(5)



(6)

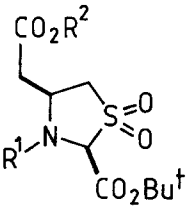


(7)

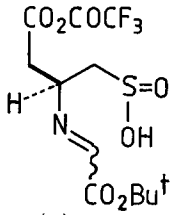
a; R^1 = $COCF_3$, R^2 = Me

b; R^1 = $COCF_3$, R^2 = H

c; R^1 = H, R^2 = $COCF_3$

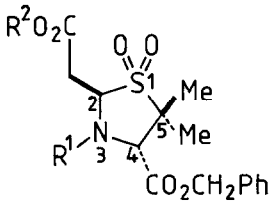


(8)



(9)

In the present study, the penicillanate dioxide (1b),[4] $[\alpha]_D$ +171° ($CHCl_3$), was treated in deuteriochloroform with trifluoroacetic acid (1 mol. equiv.). When the reaction was complete (n.m.r. spectroscoy), the solution was evaporated and the residue treated with diazomethane. Following silica-gel purification, a crystalline material, m.p. 116-117°C, $[\alpha]_D$ -14° ($CHCl_3$), was isolated in 62% yield. On the basis of its analytical and spectroscopic properties, the compound was assigned structure (10a). Its stereostructure was inferred by n.O.e.-difference spectroscopy ($CDCl_3$); thus irradiation of the singlet at δ 1.60, attributed to the 5β-methyl group, caused a > 2% enhancement of the singlet at δ 4.70, assigned to H_4, and 2% enhancements of the multiplets centred at δ 2.90 and 3.40, due to the methylene protons of the 2-substituent.

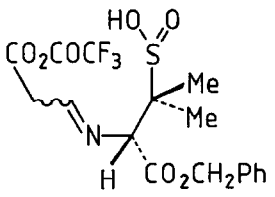


(10)

a; $R^1 = COCF_3$, $R^2 = Me$

b; $R^1 = COCF_3$, $R^2 = H$

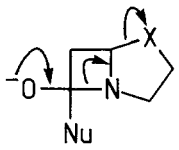
c; $R^1 = H$, $R^2 = COCF_3$



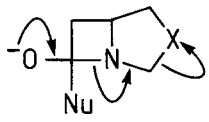
(11)

The formation of the thiazolidine dioxide (10a) means that the acid (10b) is the product of the reaction of the penicillanate dioxide (1b) with trifluoroacetic acid. On the basis of this result and those described earlier, we conclude that β-lactam-cleavage reactions of compounds (1b), (5) and (6) by trifluoroacetic acid result in the formation of the corresponding thiazolidine dioxides (10c), (7c) and (8c) as intermediates rather than the imine sulphinic acids (11) and (9).

The failure to observe processes of types (12a) and (13a) has, we believe, a stereoelectronic basis. In heterolytic fragmentations, a partial requirement is that the bonds undergoing rupture must possess an antiperiplanar relationship;[5] this geometry is precluded in intermediates of types (14a) and (15a) (where the bonds that have to be cleaved are emphasized by heavy lines). In consequence, we infer that species (3) is an obligatory intermediate in the reaction of sulbactam sodium salt (1a) with β-lactamases. Obviously, the aforecited stereoelectronic requirements cannot be realized in any species of types (14) and (15) (where X = a heteroatomic substituent). Necessarily, therefore, intermediate (17) (which has not been detected)[6] is implicated in the inactivation of β-lactamase by sodium clavulanate (16).

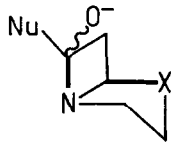


(12)

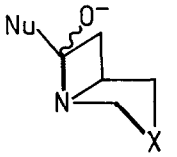


(13)

a; X = SO_2

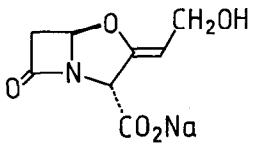


(14)

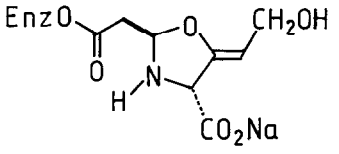


(15)

a; X = SO_2



(16)



(17)

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References and Footnotes

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

3 P.H. Crackett, C.M. Pant and R.J. Stoodley, J.C.S.Chem.Commun., 1983, 1284.

4 This compound was obtained in 80% yield (after SiO_2 chromatography) from the reaction of sulbactam sodium salt (1a) with benzyl bromide in N,N-dimethylformamide.

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