A New Degradation of Penicillins

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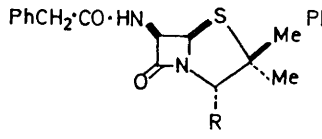
Summary Potassium benzylpenicillinate (**1**) is converted into compound (**7**) by mercury(II) acetate in acetic acid at room temperature.

REACTIONS in which the 1,2-, 3,4-, and 1,5-bonds of penicillanic acid derivatives are selectively cleaved are of considerable current interest because the products are of potential value in the synthesis of β-lactam antibiotic analogues.[1]

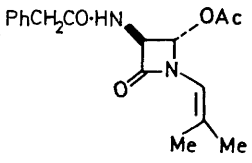
Recently, we reported[2] that mercury(II) acetate in hot acetic acid converted penicillins *e.g.*, (**1**) into monocyclic azetidinones *e.g.*, (**3**). Clearly this degradation involved the rupture of the 1,2- and 1,5-bonds of the penicillin but the timing of these steps was not established. We now present evidence which indicates that the degradation is triggered by the 1,5-bond scission.

When compound (**1**) was added to a stirred solution of mercury(II) acetate (2 mol. equiv.) in acetic acid at room

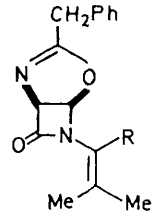
temperature, an amorphous salt was precipitated (75%). The salt is considered to possess structure (**7**) on the basis of elemental analysis and the following evidence.



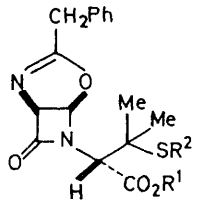
(1) R = $CO_2^-K^+$
(2) R = $CO_2{\cdot}CH_2CCl_3$



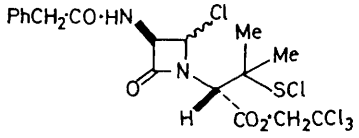
(3)



(4) R = H
(5) R = CO_2Me



(6) R^1 = Me, R^2 = H
(7) $R^1 = R^2$ = HgOAc



(8)

The i.r. spectrum of the salt showed peaks at 1765 (β-lactam C=O) and 1575 (CO_2^-) cm^{-1}; however, there were no absorptions diagnostic of amide I and II bands.

The n.m.r. spectrum [$(CD_3)_2SO$] of the salt initially contained very broad signals; however, after 12 h† a sharp spectrum, characteristic of the oxazoline (**4**), was obtained. Repetition of the reaction on a preparative scale yielded (**4**)‡ (30%), m.p. 108—110°, $[\alpha]_D$ — 49° ($CHCl_3$).

A freshly prepared solution of the salt in dimethyl sulphoxide was treated with an excess of diazomethane in ether to give (48% after silica gel chromatography) the ester (**6**),‡ $[\alpha]_D$ + 38° ($CHCl_3$), which was converted (65% after silica gel chromatography) into the oxazoline (**5**),[3] m.p. 120—122°, $[\alpha]_D$ + 46° ($CHCl_3$), by mercury(II) acetate in dimethyl sulphoxide.

When heated in acetic acid, the salt afforded (40% after silica gel chromatography) the acetate (**3**),[2] m.p. 68—70°, $[\alpha]_D$ — 18° ($CHCl_3$), which was also obtained (95%) from the reaction of (**4**) with acetic acid at room temperature. Consequently, the conversion of (**1**) into the acetate (**3**) involves the intermediacy of the salt (**7**) and possibly the oxazoline (**4**).

Only one other procedure is available for the selective cleavage of the 1,5-bond of a penicillanic acid derivative without the loss of the sulphur atom: this is the chlorine-induced conversion of (**2**) into the sulphenyl chlorides (**8**).[4] The last-mentioned compounds have been shown to be versatile intermediates in the synthesis of novel β-lactam derivatives.[5]

We thank the S.R.C. for financial support.

(*Received, 15th May* 1973; *Com.* 685.)

† A black precipitate, presumably mercury(II) sulphide, was deposited during the reaction.

‡ The composition of all new compounds was confirmed by elemental analysis and/or by mass spectroscopy. Structural assignments are based on i.r. and n.m.r. spectroscopic evidence.

[1] "Cephalosporins and Penicillins", ed. E. H. Flynn, Academic Press, New York, 1972; R. J. Stoodley, *Progr. in Org. Chem.*, 1973, **8**, 102.
[2] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1973, **32**.
[3] J. C. Sheehan in "Molecular Modification in Drug Design", Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D.C., 1964, p. 15; D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.
[4] S. Kukolja, *J. Amer. Chem. Soc.*, 1971, **93**, 6267; S. Kukolja and S. R. Lammert, *Croat. Chem. Acta*, 1972, **44**, 423.
[5] S. Kukolja, *J. Amer. Chem. Soc.*, 1972, **94**, 6270, 7590.