The Reaction of Penicillin Sulphoxides with Vinyl Ethers

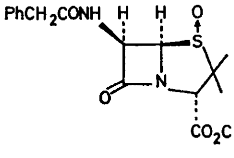
By I. Ager, D. H. R. Barton,* G. Lucente, and P. G. Sammes

(*Chemistry Department, Imperial College, London* SW7 2AY)

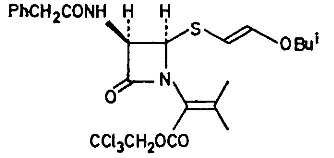
Summary The sulphenic acid intermediates produced thermally from penicillin sulphoxides can be trapped intermolecularly with vinyl ethers and with keten acetals.

The sulphenic acids produced by heating penicillin sulphoxides are versatile intermediates for the modification of the penicillins.[1] Their part in deuterium exchange,[2] sulphoxide isomerisation,[3] reduction,[4] and trapping with thiols[5] has been reported and the use of dihydropyran as a trapping agent has also been noted.[6] The latter reagent is a vinyl ether and hence further examples of such reactions have been studied. Isobutyl vinyl ether was heated with the (*S*)-sulphoxide (**1**) in dioxan under nitrogen for 44 h. Separation of the reaction mixture by chromatography (alumina) using ethyl acetate–benzene as eluant afforded one major, but unstable product, shown to be the *trans*-substituted vinyl ether (**2**),[†] ν_{max} 3300, 1765, 1740, 1680 cm^{-1}. Small quantities of the corresponding *cis*-isomer could also be detected in the reaction mixture. The vinyl ether was unstable and, on heating in toluene containing a catalytic amount of toluene-*p*-sulphonic acid, readily eliminated isobutanol to form the dihydro-thiazine (**3**), m.p. 115·5—116·5°, $[\alpha]_D^{23}$ −454° (*c* 1, $CHCl_3$). The mass spectrum of the latter compound was extremely characteristic, with strong peaks at *m/e* 217 and 99, corresponding to the ions (a) and (b). The isobutyl ether (**2**) was resistant to mild solvolytic conditions, *i.e.* 0·06N methanolic HCl, and a similar stability was noted for the analogous dihydropyran product (**4**).[6] However, under more forcing conditions, namely 0·05N methanolic HCl under reflux, smooth solvolysis of the isobutyl ether (**2**) proceeded, giving the dimethyl acetal (**5**) as a crystalline solid, m.p. 90—91°, $[\alpha]_D^{23}$ −15° (*c* 1·0, $CHCl_3$). The dihydropyranyl ether (**4**) also solvolysed under these conditions, but it afforded an epimeric mixture of all four possible stereoisomers (**6**). The vinyl ether (**2**) was readily converted into its unsubstituted β-lactam derivative (**7**), m.p. 99−101°, $[\alpha]_D^{25}$ +11° (*c* 0·7, $CHCl_3$) by application of the pyrazoline method for removing the nitrogen substituent.[7]

When 1,1-diethoxyethene was reacted with the sulphoxide (**1**), the corresponding vinyl ether was not produced. Instead *in situ* hydrolysis occurred and the product was the corresponding ester (**8**), ν_{max} 3320, 1770, 1730, 1670, and 1540 cm^{-1}, which was immediately converted into its free β-lactam derivative (**9**) by the addition of diazomethane followed by zinc–acetic acid reduction. The β-lactam (**9**) had m.p. 118—120°, $[\alpha]_D^{22}$ +17° (*c* 1·0, $CHCl_3$).



(1)



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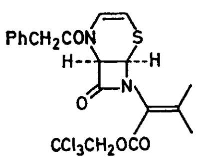

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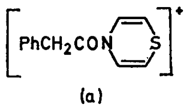
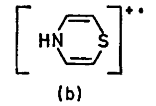
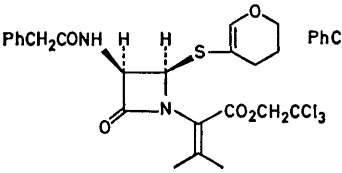


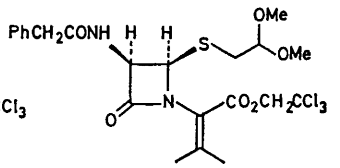
(a)



(b)



(4)



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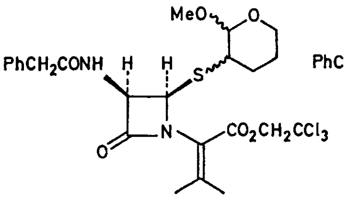
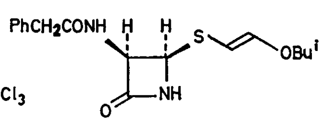
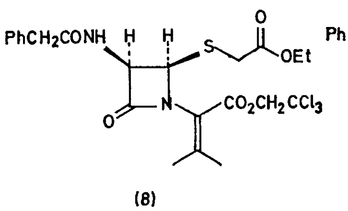


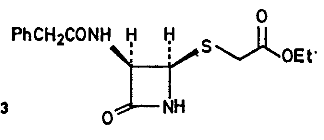
(6)



(7)



(8)



(9)

All new compounds showed the expected spectroscopic properties and analysed correctly.

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[†] Assigned the *trans*-configuration on the basis of its ^1H n.m.r. spectrum, J_{trans} 12 Hz.

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[7] D. H. R. Barton, D. G. T. Greig, P. G. Sammes, and M. V. Taylor, *Chem. Comm.*, 1971, 845.