

Vinylic Sulphoxides from Penicillins

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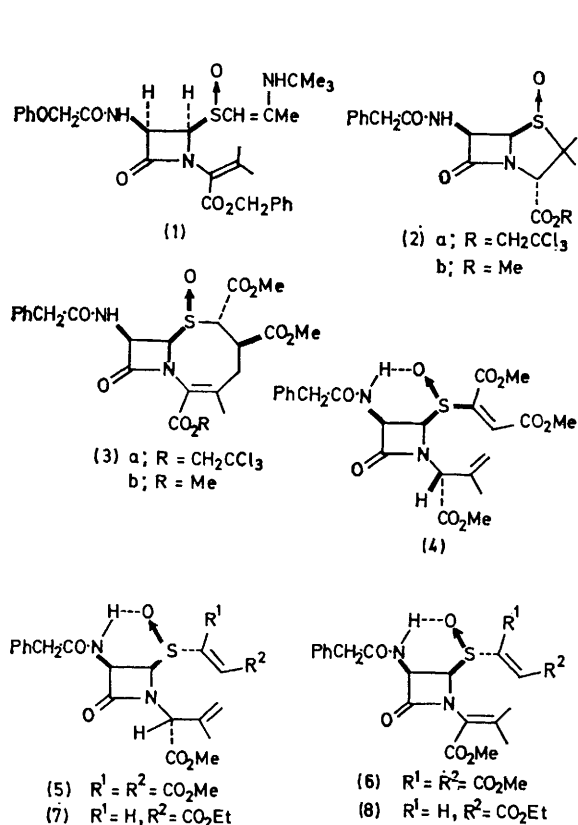
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Summary The sulphenic acid intermediates produced thermally from penicillin sulphoxides can be added across acetylenic esters to produce conjugated sulphoxides in good yield.

A RECENT report¹ on the preparation of the conjugated sulphoxide (**1**) from a penicillin prompts us to report a different route to similar systems.

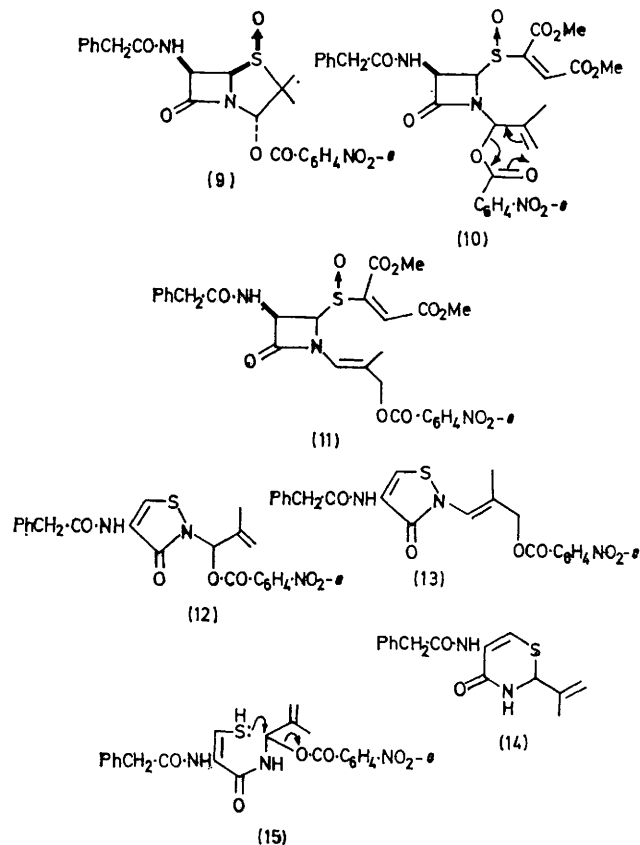
Shelton and Davis have demonstrated the ease of addition of *t*-butylsulphenic acid across electrophilic systems such as acetylenic esters.² In examining the chemistry of penicillin sulphoxides³ it has also been found that their derived sulphenic acids react with acetylenic esters such as dimethyl acetylenedicarboxylate. In initial experiments with the trichloroethyl ester (**2a**) difficulty was experienced in separating the initial reaction products. Chromatography

through alumina afforded one major component which was shown to be the cyclic 1:1 adduct (**3a**).⁴ Use of the methyl ester (**2b**), by contrast, afforded only two products, the isomeric sulphoxides (**4**) and (**5**), ratio *ca.* 1:1. The former isomer was unstable and, on silica, slowly afforded the cyclic adduct (**3b**) [$\alpha_D^{20} + 76^\circ$ (*c* 0.9, CHCl₃)].[†] Treatment of the mixture of sulphoxides (**4**) and (**5**) with a catalytic



amount of triethylamine in ethyl acetate at room temperature for 30 min afforded the cyclic adduct (**3b**) and the conjugated isomer (**6**), [$\alpha_D^{20} - 125^\circ$ (*c* 0.9, CHCl₃)]. The latter compound was the sole product obtained by brief treatment of the pure sulphoxide (**5**) with triethylamine. Assuming that both of the initial products (**4**) and (**5**) are formed by a *cis*-addition of the sulphenic acid intermediate across the acetylenic bond³ and, as shown by the n.m.r. spectra of the isomers, that in both cases the resulting sulphoxide bond remains hydrogen-bonded to the side-chain phenylacetamido-group, configurational assignments about the trigonal sulphur can be made. The stable isomer (**5**) must be the (*R*)-sulphoxide in which the maleyl residue is held away from the β -lactam nitrogen substituent and the unstable isomer (**4**) must be the (*S*)-sulphoxide in which the maleyl residue is held in a favourable position for cyclisation. Nucleophilic addition to conjugated sulphoxides has ample precedent.⁵

Further stereochemical evidence for the cycloaddition reaction of the sulphenic acid was obtained from reaction of the sulphoxide (**2b**) with ethyl propiolate, which again formed two isomeric adducts, each showing the presence of two *trans*-disposed hydrogen atoms in their n.m.r. spectra



(J_{trans} 16 Hz). The major isomer (**7**), m.p. 180–181°, [$\alpha_D^{20} + 53^\circ$ (*c* 1.4, dioxan), could also be converted into the ester (**8**), [$\alpha_D^{20} + 263^\circ$ (*c* 1.3, CHCl₃)], by treatment with triethylamine in ethyl acetate.

In further experiments dimethyl acetylenedicarboxylate was reacted with the *o*-nitrobenzoate (**9**).⁶ From the mixture of products a major adduct was isolated, which was not the expected compound (**10**) but instead the isomer (**11**), in which the ester had undergone an allylic rearrangement reaction (see arrows, **10**). This reaction had precedent since, on heating the *o*-nitrobenzoate (**9**) in the absence of a trapping agent, two of the products formed were the isothiazolones (**12**), m.p. 157–158°, and (**13**), m.p. 170–172°, the latter arising by further heating of the unrearranged isomer (**12**). Small amounts of the isothiazolones (**12**) and (**13**) were also produced in the trapping reaction of the ester (**9**) with the acetylene derivative. Both could be

[†] All new compounds gave satisfactory microanalyses.

reduced with zinc dust and ammonium chloride to give the same product, shown to be the dihydrothiazinone (**14**), m.p. 152—153°, possibly formed by preferential reduction of the nitrogen-sulphur bond (see **15**).

The reactions described above constitute a convenient

procedure for adding a two-carbon fragment, bearing potential carboxy-groups, to the sulphur atom in penicillins.

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¹ J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 57.

² J. A. Shelton and K. E. Davis, *J. Amer. Chem. Soc.*, 1967, **89**, 718.

³ For a recent review see R. D. G. Cooper and D. O. Spry, 'Cephalosporins and Penicillins' ed. E. H. Flynn, Academic Press, New York, 1972, p. 185.

⁴ I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. Hewitt, B. E. Looker, C. A. Robson, A. Mowat, and W. G. E. Underwood, *J.C.S. Perkin I*, 1973, in the press.

⁵ G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, *Tetrahedron Letters*, 1973, 323.

⁶ D. H. R. Barton, I. H. Coates, and P. G. Sammes, *J.C.S. Perkin I*, 1973, 599.