Vinylic Sulphoxides from Penicillins

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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 report[1] 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 sulphoxides[3] 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° (*c* 0·9, $CHCl_3$).† 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° (*c* 0·9, $CHCl_3$). 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 bond[2] 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° (*c* 1·4, dioxan), could also be converted into the ester (**8**), $[\alpha]_D^{20}$ +263° (*c* 1·3, $CHCl_3$), 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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