Mechanism of Epimerisation of Penicillanic Acid Derivatives

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Summary Under basic conditions, methyl benzyl-5-epipenicillinate 1,1-dioxide (**6**, X = SO_2, R = NH.CO.CH_2Ph) undergoes epimerisation at positions 6 and 3, giving the sulphones (**7**; X = SO_2, R = NH.CO.CH_2Ph) and (**10**), and β-elimination to yield (3*R*,4*R*)-1-(1-methoxycarbonyl-1-methylprop-1-enyl)-3-phenylacetamidoazetidin-2-one-3-sulphinic acid (**9**; X = SO_2H).

IT is well established that a penicillanate ester (**1**; X = S) can equilibrate under basic conditions with its 6-epimer (**2**; X = S), by way of a carbanionic intermediate (**3**; X = S). This epimerisation is often accompanied by the formation of a thiazepinone (**4**), which is considered to arise from the azetinone (**5**; X = S^-). It has been suggested that species (**5**; X = S^-) is a common intermediate in the foregoing reactions, although objections have been lodged against this proposal.[1]

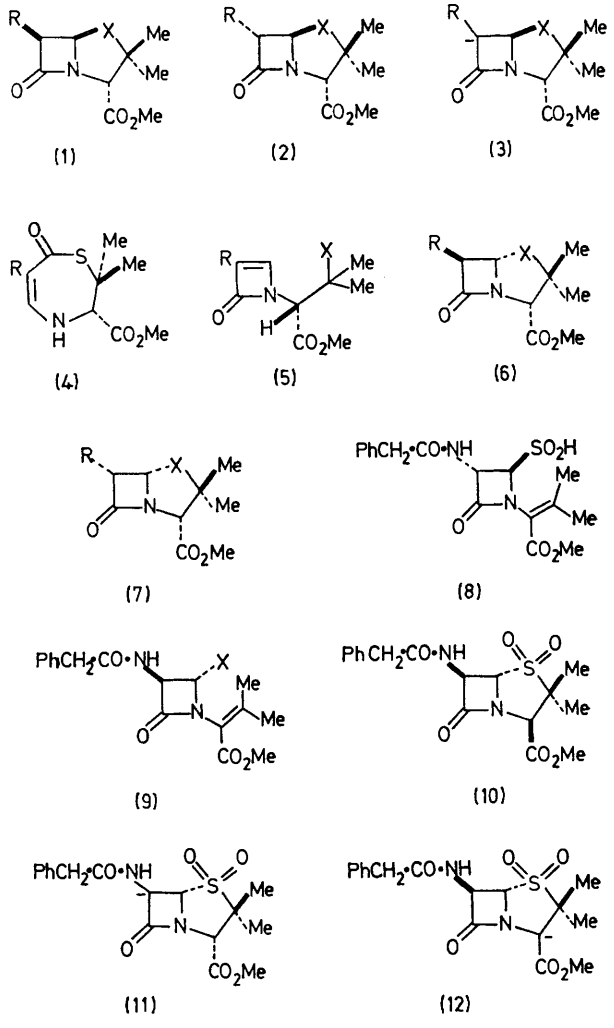
In principle, if an azetinone (**5**; X = S^-) is involved in the epimerisation, there is the possibility of forming a 5-epipenicillanate (**6**; X = S) and a 5,6-diepipenicillanate (**7**; X = S). The failure to observe these products may conceivably be ascribed to an unfavourable thermodynamic situation. Consequently, an examination of the behaviour of a 5-epipenicillanate (**6**; X = S), under conditions in which derivatives (**1**; X = S) and (**2**; X = S) equilibrate, should provide a critical test for the β-elimination pathway. If an azetinone (**5**; X = S^-) intervenes, an equilibrium mixture of the penicillanates (**1**; X = S) and (**2**; X = S) will be produced; if not, interconversion with the 5,6-diepipenicillanate (**7**; X = S) will be the expected result. We have now tested these possibilities with methyl benzyl-penicillinate 1,1-dioxides.

Previously, it was shown that, in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), the sulphone (**1**; X = SO_2, R = NH.CO.CH_2Ph) equilibrated (1 : 2) with the 6-epimer (**2**; X = SO_2, R = NH.CO.CH_2Ph); the mixture then rearranged in a slower reaction to the azetidinone-sulphinic acid (**8**).[2]

The behaviour of methyl benzyl-5-epipenicillinate 1,1-dioxide (**6**; X = SO_2, R = NH.CO.CH_2Ph),† m.p. 128—130 °C, $[\alpha]_D$ −90° ($CHCl_3$), prepared (75%) by oxidation of the 5-epipenicillinate (**6**; X = S, R = NH.CO.CH_2Ph)[3] with potassium permanganate in 80% aqueous acetic acid, towards DBN was more complex. It was not possible to establish an equilibrium situation because of the rapidity with which the base was consumed. However, by performing the reaction in $CDCl_3$ and monitoring it by n.m.r. spectroscopy, it was possible to add sufficient base to deplete the starting material. Work-up at this stage yielded an acidic and a neutral fraction.

The acidic material (23%), m.p. 130 °C, $[\alpha]_D$ +160° ($CHCl_3$), was identical (n.m.r. spectroscopy) with the azetidinone-sulphinic acid (**8**).[2] However, the optical rotation, which was similar in magnitude but opposite in sign, established that the derivative was the enantiomer (**9**; X = SO_2H).†

Separation of the neutral fraction by silica-gel chromatography yielded two new sulphones. The minor, less-polar isomer (17%), m.p. 160 °C, $[\alpha]_D$ −140° ($CHCl_3$), was the 5,6-diepipenicillinate (**7**; X = SO_2, R = NH.CO.CH_2Ph).† The major isomer (43%), m.p. 126—127 °C, $[\alpha]_D$ −164° ($CHCl_3$), was identical (t.l.c. and n.m.r. spectroscopy) with the 6-epimer (**2**; X = SO_2, R = NH.CO.CH_2Ph); however, the optical rotation revealed that the derivative was the enantiomer (**10**).†



The foregoing results demonstrate that the equilibration of the sulphone (**1**; X = SO_2, R = NH.CO.CH_2Ph) with its 6-epimer (**2**; X = SO_2, R = NH.CO.CH_2Ph) and the conversion of the 5-epipenicillanate sulphone (**6**; X = SO_2,

† The composition of new compounds was confirmed by elemental analysis. Structural assignments are based upon i.r., u.v., and n.m.r. spectroscopic evidence.

R = NH.CO.CH_2Ph) into the 5,6-diepimer (**7**; X = SO_2, R = NH.CO.CH_2Ph) involve the carbanionic species (**3**; X = SO_2, R = NH.CO.CH_2Ph) and (**11**), which show no tendency to isomerise to the azetinone (**5**; X = SO_2^-, R = NH.CO.CH_2Ph). Since the ease of β-elimination has been established as sulphones > sulphoxides > sulphides,[4] it is unlikely that azetinones (**5**; X = S^- or SO^-) intervene in the epimerisation at position 6 of penicillanate esters or their sulphoxides.

The results also provide the second example[5] of the epimerisation of a penicillanic acid derivative at position 3. This isomerisation must also proceed by way of a carbanionic species, *i.e.* (**12**), since the sulphinate (**9**; X = SO_2^-), the expected intermediate in the β-elimination pathway, was stable under the reaction conditions. Clearly, the rearrangement of the carbanion (**12**) to the sulphinate (**9**) is an irreversible process.

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