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THERMAL TRANSFORMATION OF 6-PHENYLTHIOACETAMIDOPENICILLIN SULFOXIDE

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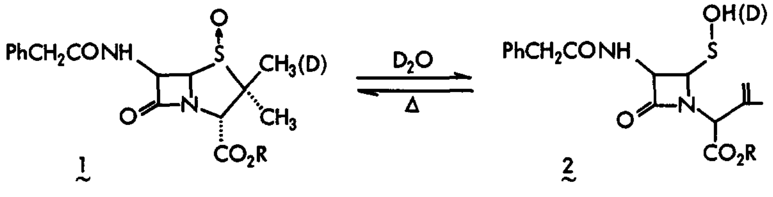
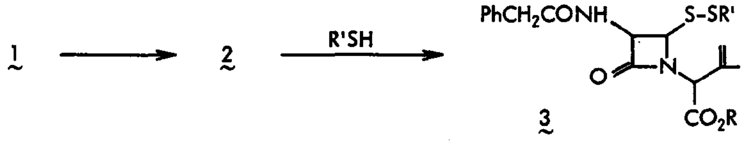
There is growing evidence that penicillin sulfoxide ester (1) is in a thermal equilibrium with the sulfenic acid (2).[1-4] Thus, on refluxing a solution of 1 in benzene containing deuterium oxide, deuterium is incorporated into the 2-methyl group (eq. 1). Another evidence of synthetic significance is that, in the presence of a thiol e.g. 2-mercaptobenzothiazole, the sulfenic acid furnishes the disulfide (3) as a result of intermolecular thiol trapping.[5,6] We carried out the reaction with 6-phenylthioacetamidopenicillin sulfoxide p-nitrobenzyl ester (4) to realize an intramolecular thioamido trapping, because the functional group is known as a good nucleophile.[7] The compound 4 was prepared by the condensation reaction of 6-aminopenicillanic acid sulfoxide p-nitrobenzyl ester with phenyldithioacetic acid using dicyclohexylcarbodiimide.

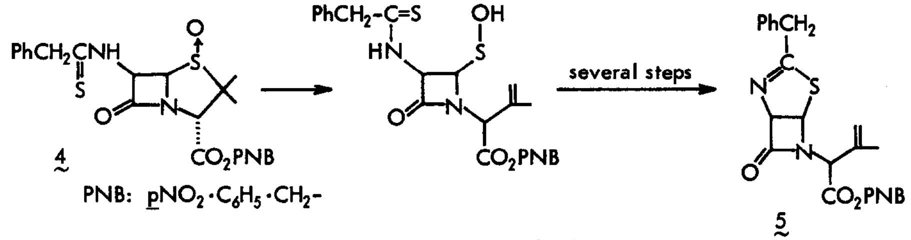


(eq. 1)

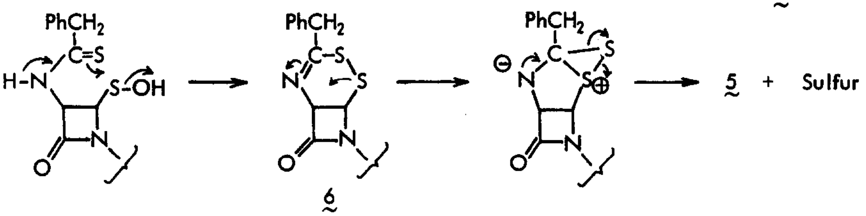


(eq. 2)

When a solution of 1 (penicillin G sulfoxide p-nitrobenzyl ester) in toluene containing deuterium oxide was refluxed for 3 hrs, 56% deuterium incorporation was observed into the 2β-methyl group with no other chemical change. Treatment of 4 under entirely identical conditions afforded, as a major product, the thiazoline derivative 5 in 59% yield in addition to the recovered 4, in which no deuterium incorporation was observed



(eq. 3)



(eq. 4)

(eq. 3). The structure of 5 was established by comparison with an authentic sample prepared by the reported method.[8] These results demonstrate that, while the sulfenic acid from 1 exchanges protons and then returns to the deuterated 1, the sulfenic acid from 4, once formed, is not allowed to recyclize to 4 and instead immeadiately attacked by the thioamido-sulfur. We conceive that the sulfenic acid functions as an electrophile towards the thioamide, as towards a thiol,[2c] thereby affording the 6-membered disulfide (6) which, however, does not survive under the reaction conditions and undergoes concecutive thermal rearrangements, as pictured in eq. 4, to give finally the stable 5 by liberating sulfur. The results observed in the thioamido compound (4) suggest that under suitable conditions the amido group in 1 might participate in reactions with the sulfenic acid.

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