Rearrangement of an Isothiazolidinone to a β-Lactam. A Model for Penicillin Biosynthesis

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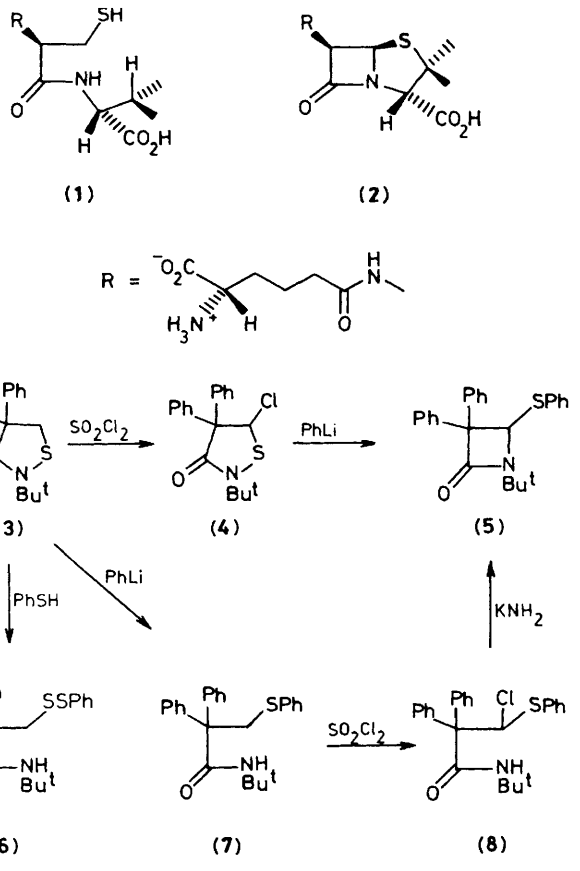
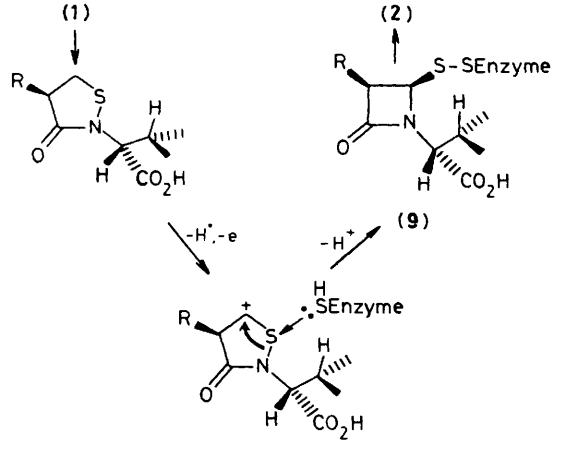
Based on novel syntheses of a β-lactam from an isothiazolidinone, a mechanism of formation of the β-lactam ring in penicillin biosynthesis is proposed.

Investigation of the biosynthesis of penicillins and related β-lactam antibiotics has shown that isopenicillin N (**2**) is derived from the tripeptide,[δ-(L-α-aminoadipoyl)]-L-cysteinyl-D-valine (**1**),[1]† but the mechanism of this transformation has not been elucidated. Although isothiazolidinones have been proposed as intermediates in this conversion, attempts to prepare β-lactams from isothiazolidinones, *in vitro*, have failed to date.[2] In this report the preparation of β-lactam (**5**) from isothiazolidinone (**3**) is described and a mechanism for the formation of the β-lactam ring in penicillin biosynthesis is proposed.



Treatment of (**3**)[2] with sulphuryl chloride (CCl_4, 20 °C) afforded (**4**)‡ [71%; m.p. 92—94 °C (decomp.); ^1H n.m.r. δ(CCl_4) 1.49 (s, 9H), 6.18 (s, 1H), and 7.0—7.5 (m, 10H)], which reacted with phenyl-lithium (Et_2O, −78 °C) to give the β-lactam (**5**) [86%; oil; ^1H n.m.r. δ(CCl_4) 1.42 (s, 9H), 5.53 (s, 1H), and 6.9—7.3 (m, 15H)]. Reaction of (**3**) with phenyl-lithium (Et_2O, −78 °C) afforded the amide (**7**) [82%; m.p. 80—81 °C; ^1H n.m.r. δ(CCl_4) 1.25 (s, 9H), 3.83 (s, 2H), 5.3 (br. s, 1H), and 6.9—7.4 (m, 15H)], identical to a sample prepared from 2,2-diphenyl-3-phenylthiopropanoic acid.[3] The chloride (**8**), produced by treatment of (**7**) with sulphuryl chloride (CCl_4, 20 °C) [60%; oil; ^1H n.m.r. δ(CCl_4) 1.22 (s,



Scheme 1

† δ-(α-Aminoadipoyl) = 5-amino-5-carboxypentanoyl.

‡ All new compounds gave satisfactory n.m.r., i.r., and high resolution mass spectral data and, with the exceptions of (**4**) and (**8**), satisfactory microanalytical data.

9H), 5.3 (br. s, 1H), 6.22 (s, 1H), and 6.9—7.6 (m,15 H)], reacted with potassium amide (NH_3, −78 °C) to give (**5**) in 82% yield. These syntheses establish that a β-lactam can be prepared from an isothiazolidinone.

Rearrangement of the oxidized isothiazolidinone (**4**) to the β-lactam (**5**) most likely proceeds by nucleophilic attack of the phenyl anion at sulphur. An analogous mechanism could be involved in the *in vivo* transformation (**1**) → (**2**) (Scheme 1). A most attractive hypothesis is that the nucleophile promoting the biological rearrangement could be a thiol residue of the penicillin synthetase enzyme, as formation of the disulphide (**9**) is fundamental to a proposed mechanism for the formation of the thiazolidine ring.[4,5] Support for this hypothesis comes from the spontaneous reaction of (**3**) with thiophenol (CCl_4, 20 °C) to give disulphide (**6**) [94%; hard oil; ^1H n.m.r. δ(CCl_4) 1.23 (s, 9H), 3.75 (s, 2H), 5.1 (br. s, 1H), and 7.0—7.4 (m, 15H)].

The only alternative mechanism proposed for the formation of the β-lactam ring in (**2**),[5,6] that is consistent with all biosynthetic studies, does not rationalize formation of a disulphide. The mechanism proposed in Scheme 1 accounts for the decisive role of the thiol group in (**1**) in binding the substrate to the enzyme during penicillin biosynthesis.[7]

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