

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

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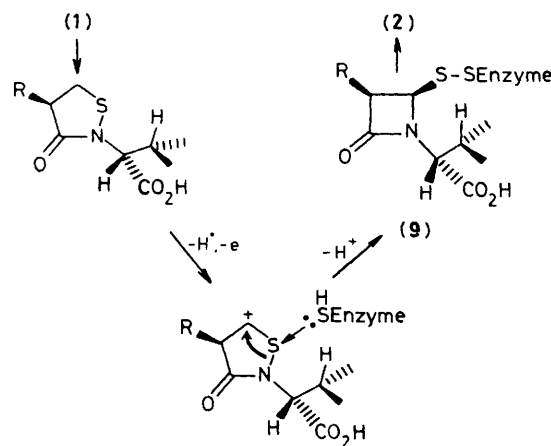
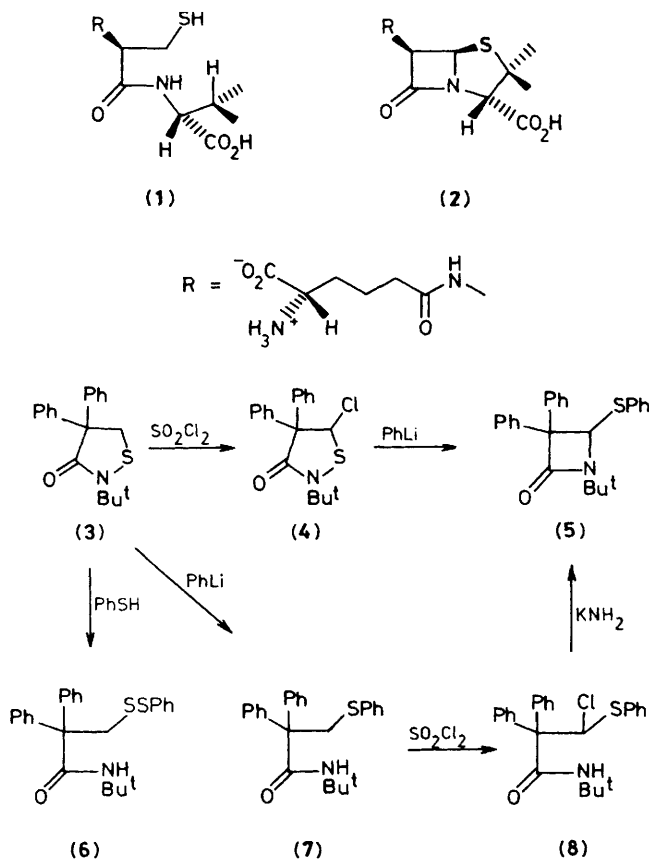
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Based on novel syntheses of a β -lactam from an isothiazolidinone, a mechanism of formation of the β -lactam ring in penicillin biosynthesis is proposed.

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),[†] 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. $\delta(\text{CCl}_4)$ 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. $\delta(\text{CCl}_4)$ 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. $\delta(\text{CCl}_4)$ 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. $\delta(\text{CCl}_4)$ 1.22 (s,



Scheme 1

[‡] 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.

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

9H), 5.3 (br. s, 1H), 6.22 (s, 1H), and 6.9–7.6 (m, 15H)], 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) \rightarrow (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. $\delta(\text{CCl}_4)$ 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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