Conversion of Penicillins into Biosynthetically Significant Peptides

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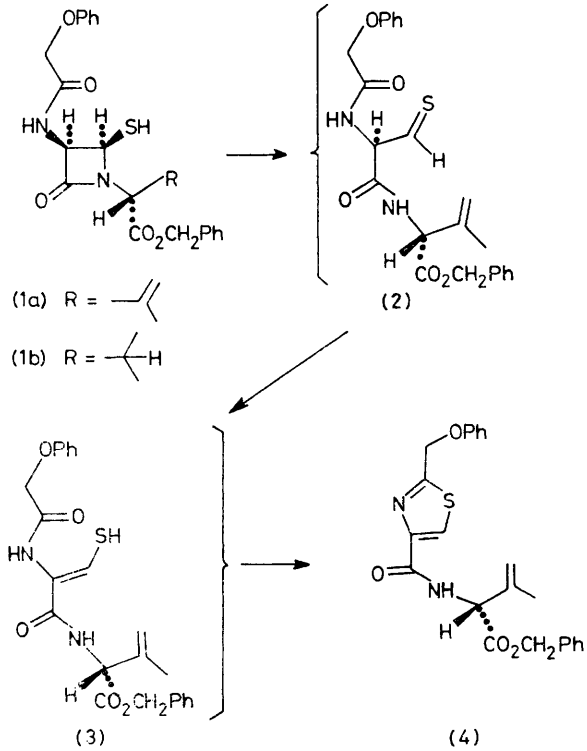
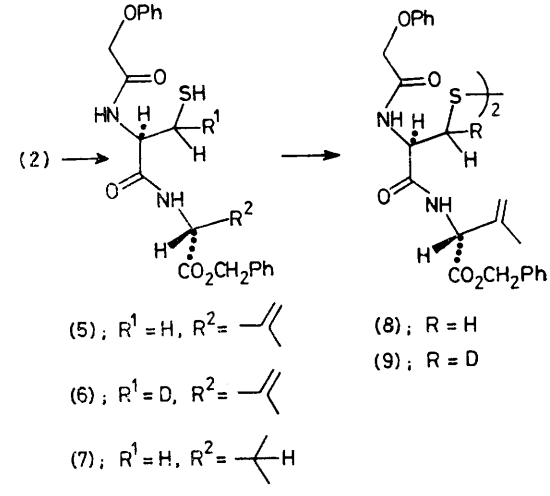
Summary Mild acid treatment of the 4-mercapto-azetidin-2-one (**1**) gave the thioaldehyde (**2**) which was intercepted by reduction to the peptide (**5**), prior to enolization; a similar sequence with the dihydro-derivative (**11**) provided the cysteinyl-valine peptide (**7**), which represents a formal reversion of penicillin biosynthesis.

PREVIOUSLY we showed that the penicillin-derived mercapto-azetidinone (**1a**) was converted into the thiazole (**4**) by way of intermediates suggested to be the thioaldehyde (**2**) and its tautomer (**3**), Scheme 1.[1] We have now found that the thioaldehyde (**2**) has a sufficiently long lifetime to enable its clean interception in a chemical reaction, adding further support to the existence of this transient species.[2]



SCHEME 1

Thus treatment of (**1a**) with methanolic acetic acid (20:3 v/v) in the presence of sodium cyanoborohydride at 25 °C gave the dipeptide (**5**) (97%), which was oxidized (iodine in tetrahydrofuran) to the crystalline disulphide (**8**), m.p. 146—150 °C (chloroform–ethyl acetate),† Scheme 2. This substance (**8**) was identical in all respects with a synthetic sample obtained from L-cystine-t-butyl ester by sequential phenoxyacetylation (phenoxyacetyl chloride, triethylamine), deprotection (trifluoroacetic acid; 15 min; 25 °C), and coupling with D-isodehydrovaline benzyl ester[3] (dicyclohexylcarbodiimide, 1-hydroxybenztriazole).

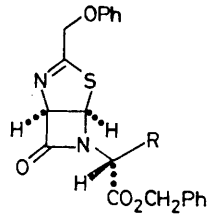


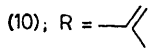
SCHEME 2

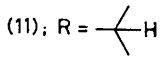
The possible intermediacy of the enethiol (**3**) was eliminated when reduction of (**2**) was repeated in deuteriated methanolic acetic acid, which provided (**5**) containing no carbon-bound deuterium. Similarly, the possibility of direct reductive opening of (**1**) to (**5**) was checked by reduction in methanolic acetic acid with sodium cyanoborodeuteride, whereupon the monodeuteriopeptide (**6**) was obtained, oxidized as before to the dimer (**9**). This substance was shown to consist of a pair of diastereomeric dideuterio-compounds (as a dimer) in a ratio of 3:1 (270 MHz ^{1}H n.m.r. spectroscopy in $CDCl_3$). Thus the single proton α to the disulphide bond appeared as a pair of doublets (ratio of areas 3:1), δ 2·97 (*J* 11 Hz) and 3·08 (*J* 3 Hz), respectively.‡ This lack of stereospecificity militates against a direct reduction of (**1**) and is more consistent with a stereoselective reduction, *via* (**2**).

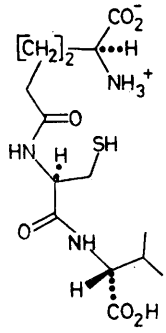
† All new compounds have given satisfactory analytical and spectral data.

‡ The coupling of a pair of epimers, such as (**6**) necessarily may yield the dimer (**9**) as three possible stereochemically distinct substances. However, selection in the coupling reaction and magnetic differences in the product, as a result of a single deuterium substitution, which is not involved in the reaction, are likely to be very small. Therefore, we consider the area ratios to represent the epimer ratios, in the thiol (**6**).



(10); R = 

(11); R = 



(12)

Finally, catalytic reduction of the precursor (**10**) [tris(triphenylphosphine)rhodium(I) chloride; benzene; 1 atm; room temp.; 35 h] gave the dihydro-derivative (**11**) (71%), m.p. 51 °C (from methanol), which after hydrolysis, as before,[1] gave the thiol (**1b**), m.p. 95—97 °C (from methylene chloride–ether). Reduction of the derived thioaldehyde gave the saturated dipeptide (**7**) (70%). This last sequence represents a formal reversal of the proposed biosynthesis of penicillins from the Arnstein tripeptide (**12**).[4]

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[1] J. E. Baldwin and M. A. Christie, *J.C.S. Chem. Comm.*, 1978, 239.
[2] For some previous attempts to make and intercept thioaldehyde peptides, *cf.* J. Cheney, C. J. Moores, J. A. Raleigh, A. I. Scott, and D. W. Young, *J.C.S. Perkin I*, 1974, 239.
[3] J. E. Baldwin, S. B. Haber, C. Hoskins, and L. I. Kruse, *J. Org. Chem.*, 1977, **42**, 1239. The benzyl ester was prepared by the degradation of penicillin V benzyl ester described herein.
[4] H. V. R. Arnstein and J. C. Crawhill, *Biochem. J.*, 1957, **67**, 180; for a recent assessment of current knowledge of penicillin biosynthesis, *cf.* E. P. Abraham, in 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' Special Publication No. 28, The Chemical Society, London, 1977, p. 1.