Removal of Sulphur-protecting Groups in the Synthesis of a 4-Mercapto-β-lactam

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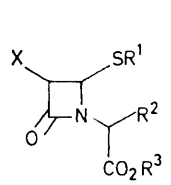
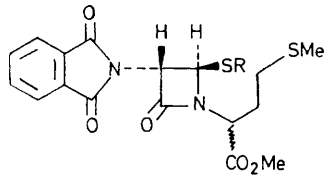
Summary 4-Mercapto-1-(1-methoxycarbonyl-3-methylthiopropyl)-3-phthalimidoazetidin-2-one (**2**) was obtained from its *S*-*p*-nitrobenzyl (**3**) and its *S*-trityl (**5**) derivatives; the synthesis of these 4-aralkylthio-β-lactams and the removal of the *S*-protecting groups are described.

IN a previous paper it was suggested that β-lactams of the type (**1**) in which the side chain, R^2, contains a functional group allowing ring closure on the sulphur atom, may serve as intermediates for the synthesis of β-lactams structurally related to penicillins and cephalosporins.[1] A problem which arose during the development of this synthetic approach was the removal of the sulphur-protecting group R^1 without the disruption of the sensitive 4-membered ring. This problem has now been solved as exemplified by the synthesis of the 4-mercapto-β-lactam (**2**).

Condensation of DL-methionine methyl ester with *O*-ethyl thioformate in methanol gave compound (**6**)†[2] (78%, b.p. 140—150°/0·05 mm). This thioamide was treated with sodium hydride and *p*-nitrobenzyl chloride in toluene to give the thioformimidate (**7**) which was converted into the β-lactams (**3**) by interaction with phthaloylglycyl chloride, and triethylamine [22%, based on (**6**)]. The two *trans*-diastereoisomers were obtained, one of them crystalline,† m.p. 139—140° (from carbon tetrachloride), δ (C_6D_6 + $CDCl_3$)‡ (for the ring hydrogens) 5·00 (d) and 5·20 (d, *J* 2·8 Hz), and the other non-crystalline δ (C_6D_6) 5·08 (d and 5·29 (d, *J* 2·5 Hz). The two *p*-nitrobenzylthio-β-lactams were hydrogenated on 10% palladium on charcoal in acetic acid–dioxan to the respective *p*-aminobenzylthio-derivatives (**4**) (57%) which were treated with $HgSO_4$ in dilute mineral acid and methanol to give the respective



(1) X = Amino or potential amino-group
R^1 = S-protecting group
R^2 = Side chain
R^3 = O-protecting group



(2) R = H
(3) R = *p*-NO_2·C_6H_4·CH_2
(4) R = *p*-NH_2·C_6H_4·CH_2
(5) R = Trityl

HCS·NH·CH(CH$_2$·CH$_2$SMe)CO$_2$Me
(6)

RS·HC:N·CH(CH$_2$·CH$_2$·SMe)CO$_2$Me
(7) R = *p*-NO$_2$·C$_6$H$_4$·CH$_2$
(8) R = Me
(9) R = Trityl

mercury mercaptides. Treatment with hydrogen sulphide afforded the *trans*-mercapto-β-lactams (**2**) (60%). The isomer (**2**) [δ(C_6D_6) 2·00 (1H, d, *J* 10 Hz, SH), 4·99 (1H, dd, *J* 2·5 Hz and 10 Hz, ring 4-H), 5·29 (1H, d, *J* 2·5 Hz, ring 3-H)] which was obtained by the deblocking of the non-

† Satisfactory microanalysis and spectral properties.

‡ A few drops of $CDCl_3$ were added to assist dissolution of the sample in C_6D_6.

crystalline isomer (**3**) was treated with trityl chloride in chloroform to give the β-lactam (**5**) (63%), m.p. 174—175°, δ (C_6D_6) 5·17 (d) and 5·70 (d, *J* 2·5 Hz). The other isomer (**2**), δ (C_6D_6) 1·82 (1H, d, *J* 9 Hz, SH), 4·85 (1H, dd, *J* 2·5 and 9 Hz, ring 4-H), and 5·19 (1H, d, *J* 2·5 Hz, ring 3-H), deriving from the crystalline isomer (**3**) was similarly converted into the tritylthio-β-lactam (**5**), m.p. 142—143°, δ (C_6D_6) 5·20 (d), and 5·67 (d, *J* 2·5 Hz).

The successful stepwise removal of the *S*-*p*-nitrobenzyl group[3] prompted us to examine also the use of the trityl protecting group which is removable by heavy metal salts without the need of a preliminary hydrogenation.[4] The tritylthio-β-lactams (**5**) were therefore independently prepared by treatment of the thioformimidate (**9**) and triethylamine with phthaloylglycyl chloride (79%). In this case also only the *trans* isomers of (**5**)† were obtained. These compounds were identical in physical and spectral properties with the tritylthio-β-lactams (**5**) obtained by tritylation of the mercapto-lactams (**2**). The tritylthioformimidate (**9**) could not be obtained by a direct *S*-tritylation of the thioamide (**6**) This thioamide was therefore treated with methyl iodide and sodium hydride to give the methylthioformidate (**8**).[2] On warming with tritylthiol under reduced pressure an exchange reaction occurred giving the required thioimidate (**9**).

Detritylation of the two isomeric β-lactams (**5**) with mercury(II) chloride in methanol at 40—50° afforded the respective mercury mercaptides which were converted into the free thiols (**2**) (29%) by treatment with hydrogen sulphide. The spectral properties of these compounds were identical to those of the 4-mercapto-β-lactams (**2**) obtained from the *p*-nitrobenzylthio-β-lactams (**3**).

The preparation of some 4-mercapto-β-lactams by the degradation of penicillins and their use as intermediates in the synthesis of bicyclic β-lactams has been recently described.[5]

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