Synthesis of *trans*- and *cis*-β-Lactams Related to Penicillin. Nucleophilic Substitution of a 3-Chloro-β-lactam

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Summary β-Lactams having a common nitrogen atom with valine methyl ester and carrying a benzylthio-substituent at the 4-position, and a phthalimido (**8**), chloro (**9**), azido (**10**), or amino (**11**) substituent at the 3-position of the ring have been synthesized.

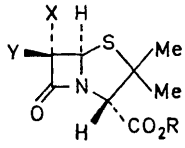
PENICILLINS (**1**) and cephalosporins (**4**) have the common structural feature (**5**) and are believed to employ the same mode of action when inhibiting the synthesis of bacterial cell walls.[1] The synthesis of new β-lactams having the partial structure (**5**) is therefore of considerable interest.

We have recently investigated the preparation of monocyclic β-lactams (**6**) having a common nitrogen atom with α-amino-acid esters and carrying a thiosubstituent in the 4-position, and a potential amino-group at the 3-position of the ring. If the side chain, R^1, contains a functional group allowing ring closure on the sulphur, compounds (**6**) may serve as intermediates in a general method for the synthesis of bicyclic β-lactams structurally related to penicillin and cephalosporin. The present paper deals with the preparation and the stereochemistry of some model compounds in which the amino-acid moiety is valine.

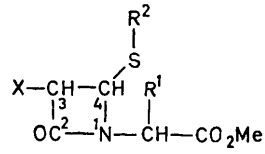
N-Thioformyl-L-valine methyl ester $[\alpha]_D^{20} - 8°$ (*c* 2; $CHCl_3$), prepared by thioformylation[2] of L-valine methyl ester with ethyl thioformate, was treated with sodium hydride in tetrahydrofuran and then alkylated with benzyl bromide to give (**7**) (**85**%) b.p. 95—110° at 0·02 mmHg, ν_{max} ($CHCl_3$) 5·75 (CO_2Me), 6·25 (C=N) μm. Phthaloylglycyl chloride was added during 5 h to a solution of the imidate (**7**) and triethylamine in methylene dichloride. Chromatography of the crude product over silica gel afforded the β-lactam (**8**) (39%), m.p. 88—89°.[3]† The n.m.r. spectrum indicated the presence of two partially overlapping AB patterns characteristic[4] of two *trans*-β-lactams: δ (C_6D_6) 5·17 (d, *J* 2·6 Hz) and 5·23 (d, *J* 2·6 Hz) (total 1H); and 5·39 (d, *J* 2·6 Hz) and 5·41 (d, *J* 2·6 Hz) (total 1H); no *cis*-isomer could be isolated. Since only β-lactams of *cis*-stereochemistry can be expected to have

† All the new β-lactams were fully characterized by elemental analysis, and i.r., ^1H n.m.r., and mass spectra.

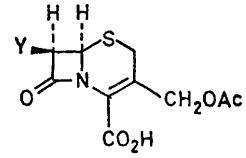
antibacterial activity, another route for their preparation was developed.



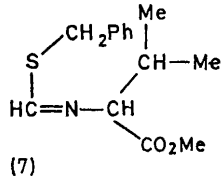
(1) X=H, Y=acylamino, R=H
(2) X=Cl, Y=H, R=Me
(3) X=OSO_2Me, Y=H, R=CH_2Ph



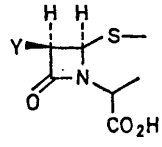
(6) R^1 = side chain
R^2 = protecting group
X = phthalimido, N_3, or halogen



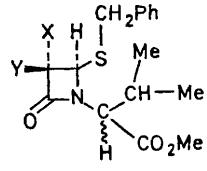
(4) Y= acylamino



(7)



(5) Y= acylamino



(8) X=phthalimido, Y=H
(9) X=Cl, Y=H
(10) X=H, Y=N_3
(11) X=H, Y=NH_2

A solution of (**7**) and triethylamine in toluene was treated with chloroacetyl chloride to give, after column chromatography on alumina, the chloro-β-lactam (**9**) (45%).[3] N.m.r. spectroscopy revealed the presence of a mixture of two *trans*-isomers, subsequently separated into its components by column chromatography on Florisil. The n.m.r. spectrum of the first compound to be eluted, m.p. 52—53°, $[\alpha]_D^{25}$ − 65° (*c* 1; $CHCl_3$), showed the characteristic[4] AB pattern: δ (C_6D_6) 4·38 (d, *J* 1·9 Hz, 1H); 4·55 (d, *J* 1·9 Hz, 1H) as did the second compound (an oil): δ (C_6D_6) 4·33 (d, *J* 1·7 Hz, 1H) and 4·68 (d, *J* 1·7 Hz, 1H). A solution of the lactam (**9**) (as two *trans*-isomers), and sodium azide in dimethyl sulphoxide was kept in the dark at 85—95° for 24 h to afford after silica gel thick-layer chromatography the *cis*-azido-β-lactam (**10**) (25%) as a mixture of two diastereoisomers which were separated by chromatography on Florisil. The n.m.r. spectra of these compounds display AB patterns characteristic of *cis*-β-lactams;[4] the first eluted, m.p. 53—54°: δ (C_6D_6) 3·96 (d, *J* 4·7 Hz, 1H) and 4·81 (d, *J* 4·7 Hz, 1H), and the second, m.p. 76–77° δ (C_6D_6) 3·98 (d, *J* 5 Hz, 1H) and 4·40 (d, *J* 5 Hz, 1H).

Reduction of (**10**), m.p. 53—54°, with zinc in 90% acetic acid gave the *cis*-amino-β-lactam (**11**) (70%), δ ($CDCl_3$) 4·31 (d, *J* 4·6 Hz, 1H); 5·03 (d, *J*4·6 Hz, 1H), toluene-*p*-sulphonate, m.p. 137—138°.

The nucleophilic substitution of a chlorine atom by an azido-group in position 3 of a β-lactam ring opens a new route for the preparation of β-lactams bearing sulphur and nitrogen substituents at the same positions as in the natural penicillins and cephalosporins and having the same stereochemistry. It has been reported[5,6] that attempts to perform similar substitutions in (**2**)[5] and in (**3**)[6] resulted in the cleavage of the β-lactam ring, while 3-chloro-4,4-diethoxycarbonyl-1-phenyl-β-lactam could not be converted into the respective 3-amino analogue.[7]

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