Novel Synthesis of the 7-Oxo-4-oxa-1-azabicyclo[3.2.0]heptane Ring System

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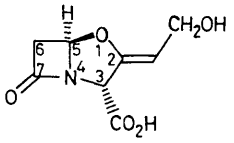
Summary The 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane ring system has been synthesised in two steps from readily available starting materials; the relative stereochemistry of the products was deduced by n.m.r. spectroscopy and base-catalysed epimerisation studies.

RECENTLY we have described the structure elucidation[1] and chemical modification[2] of clavulanic acid (**1**), the first reported naturally occurring fused β-lactam containing the 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane skeleton. We now describe an easy synthesis[3] of this ring system from a readily available starting material (**2**).[4]

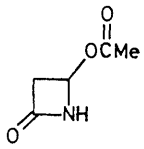
(±)-4-Acetoxyazetidin-2-one (**2**) was condensed with the (±)-bromohydrin (**3**) in the presence of $Zn(OAc)_2.2H_2O$ to give the alkoxyazetidinone (**4**, 10%)† as a mixture of two racemic diastereoisomers. Cyclisation of (**4**) using aqueous benzyltrimethylammonium hydroxide in dimethylformamide gave a 1:1 mixture of (±)-(**5**) and (±)-(**6**) in 61% yield. The diastereoisomers were separated by silica gel chromatography and the relative stereochemistry of the products was deduced from their n.m.r. spectra. The C-3 proton of the less polar product (**5**) was at δ 4·35, whereas the corresponding proton of the more polar product (**6**) appeared at δ 3·86. The C-3 proton in penicillins (**7**), in

† The spectral properties of all new compounds were in accord with the proposed structure.

which the relative configuration of the C-3 and C-5 protons is the same as in (**5**), is usually in the range δ 4·3—4·9.[5] However, in 5-epipenicillins[6] (**8**), in which the relative configuration at C-3 and C-5 is the same as in (**6**), the C-3 proton appears at δ 3·7—4·0.‡ Confirmation that clavulanic acid (**1**) and compound (**5**) have the same relative configuration at C-3 and C-5, corresponding to the thermodynamically more stable molecular configuration, was obtained by epimerisation and exchange studies. Thus, treatment of (**6**) with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)



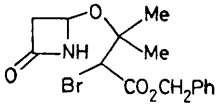
(**1**)



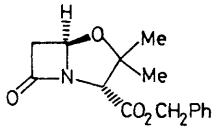
(**2**)

$Me_2C(OH)CH(Br)CO_2CH_2Ph$

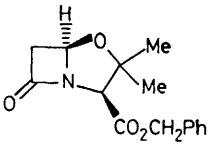
(**3**)



(**4**)



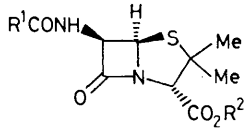
(**5**)



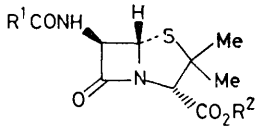
(**6**)

in chloroform resulted in complete conversion into the thermodynamically more stable (**5**). Conversely, treatment of the benzyl ester of (**1**) with DBN under similar conditions did not result in C-3 epimerisation; in the presence of D_2O only exchange of the C-3 proton was observed. The chemical shift of the C-3 proton in both penams and compounds containing the 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane skeleton thus appears to be diagnostic of the relative stereochemistry at C-3 and C-5.

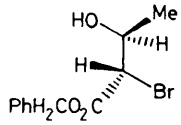
To examine the stereospecificity of the above route, we next investigated the synthesis of a derivative containing three asymmetric centres. Thus condensation of (**2**) with the (±)-*erythro*-bromohydrin (**9**) in the presence of Zn-$(OAc)_2.2H_2O$ gave a mixture of (±)-(**10**) and (±)-(**11**) in 30% yield. Cyclisation of this mixture with cetylbenzyldimethylammonium chloride and sodium hydroxide in a two phase CH_2Cl_2–H_2O system gave (±)-(**12**) and (±)-(**13**) in a



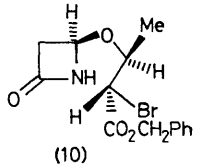
(**7**)



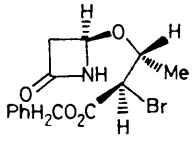
(**8**)



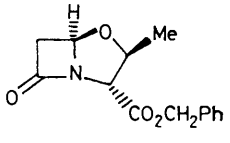
(**9**)



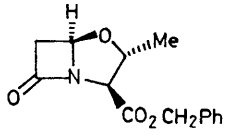
(**10**)



(**11**)



(**12**)



(**13**)

ratio of 1:4 (56%). The relative stereochemistry at C-3 and C-5 of the two racemic diastereoisomers was deduced from the chemical shifts [δ 4·15 for (**12**) and δ 3·62 for (**13**)] of the C-3 protons. The relative stereochemistry at C-2 and C-3 of the products reflects the configuration of the starting bromohydrin (**9**).§

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‡ The possibility that the presence of a 6-acylamino substituent in (**7**) and (**8**) might invalidate these conclusions was discounted because the C-3 proton in penicillanic acid derivatives, in which the 6-position is unsubstituted, also appears in the δ 4·3—4·7 region.

§ Confirmation of the relative stereochemistry of these products has been obtained by more detailed n.m.r. spectral studies; the structure of (**12**) was subsequently confirmed by *X*-ray analysis (T. J. King, unpublished results) of the corresponding methyl ester (D. F. Corbett, unpublished results).

[1] T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266.
[2] A. G. Brown, J. Goodacre, J. B. Harbridge, T. T. Howarth, T. J. King, R. J. Ponsford, and I. Stirling, 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' ed. J. Elks, Chemical Society spl. publication no. 28, 1977; A. G. Brown, T. T. Howarth, I. Stirling, and T. J. King, *Tetrahedron Letters*, 1976, 4203.
[3] For other syntheses of this system, see: B. T. Golding and D. R. Hall, *J.C.S. Perkin I*, 1975, 1517; L. D. Cama, R. A. Firestone, and B. G. Christensen, Abstracts, 10th A.C.S. Middle Atlantic Regional Meeting, Philadelphia, Pennsylvania, 1976.
[4] K. Clauss, D. Grimm, and G. Prossel, *Annalen*, 1974, 539.
[5] P. V. Demarco and R. Nagarajan, 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York and London, 1972, Ch. 8, p. 311.
[6] R. Busson and H. Vanderhaeghe, *J. Org. Chem.*, 1976, **41**, 2561.

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