Total Synthesis of β-Lactamase Inhibitors related to Clavulanic acid

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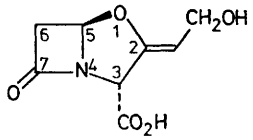
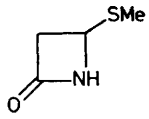
Summary (*E*)-3-Methoxycarbonylmethylene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane (**6**), its geometric isomer (**7**), and a related vinyl chloride (**8**) have been obtained by a three-step synthesis from 4-methylthioazetidin-2-one.

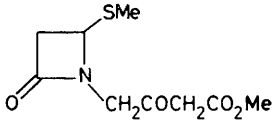
A RECENT communication[1] from these laboratories described a simple synthesis of the 7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane ring system, which is found in the natural β-lactamase inhibitor clavulanic acid (**1**).[2] We now report an alternative synthesis of this ring system which provides an important extension to the methodology in that it allows incorporation of an exocyclic double bond at the C-2† position and thus gives compounds which have a closer structural analogy to (**1**).



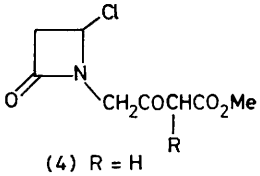
(1)



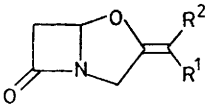
(2)



(3)



(4) R = H
(5) R = Cl



(6) $R^1 = CO_2Me$; $R^2 = H$
(7) $R^1 = H$; $R^2 = CO_2Me$
(8) $R^1 = CO_2Me$; $R^2 = Cl$

Alkylation of racemic 4-methylthioazetidin-2-one (**2**)[3]‡ using methyl γ-bromoacetoacetate in the presence of 2 equiv. of NaH in dimethylformamide gave the β-keto ester (**3**) in 43% yield. Reaction of (**3**) with 1 equiv. of chlorine in CCl_4 gave (**4**), which, without purification, was treated with K_2CO_3 in dimethylformamide to give the fused β-lactam (**6**) in 26% yield. When the crude chloride (**4**) was treated with triethylamine in a 1 : 1 mixture of methylene dichloride and diethyl ether the geometric isomer (**7**) (7%) was obtained in addition to (**6**) (8%). Compounds (**6**) and (**7**) were not interconverted under either of the above cyclisation conditions.

A third bicyclic compound (**8**) was obtained in small amounts (*ca.* 0·5%) from both of the above cyclisation experiments. This product is assumed to arise because of contamination of crude (**4**) with the dichloride (**5**). When (**3**) was treated with 2 equiv. of chlorine and the resulting product was cyclised in the presence of K_2CO_3, (**8**) was obtained as the only bicyclic product in 40% yield.

The assignments of double-bond geometries to (**6**) and (**7**) follow from their ^1H n.m.r. spectra.[4,5] In (**6**) the vinyl proton appears at δ 5·45§ and the C-3 protons at δ 3·88 and 5·02 whereas (**7**) gives absorptions for the vinyl proton at δ 4·93 and the C-3 protons at δ 3·70 and 4·51. The structural assignments are also supported by the ^{13}C n.m.r. spectra[6] in that the ester carbonyl of (**6**) absorbs at lower field (δ 167·6§) than that of (**7**) (δ 165·1).¶ For (**8**) the assignment of double bond geometry is based on the correspondence of the absorptions for its C-3 protons (δ 3·98 and 5·05) with those for (**6**), since it is expected[5] that replacement of the vinylic hydrogen in (**6**) or (**7**) with chlorine should have little effect on the chemical shifts of the C-3 protons.

In comparison to (**1**),[2] compounds (**6**)—(**8**) showed moderate activity as irreversible inhibitors of β-lactamases from a number of bacteria.[7] For example, when (**6**) was combined *in vitro* with ampicillin at a level of 10 μg ml^{-1} it reduced the minimum inhibitory concentration of ampicillin from 500 to 4 μg ml^{-1} against a β-lactamase producing strain of *Staphylococcus aureus*.[8]

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† Numbering of the ring system, as in (**1**), follows that used for penicillins. See footnote in preceding communication.

‡ Spectral properties of all new compounds were in accord with the proposed structure.

§ Chemical shifts from Me_4Si for solutions in $CDCl_3$.

¶ Further evidence for these stereochemical assignments was obtained by comparison of the chemical shifts of the vinyl protons in (**6**) and (**7**) with those in 3-(CO_2Me)-(**6**) and 3-(CO_2Me)-(**7**) (P. H. Bentley, P. D. Berry, G. Brooks, M. L. Gilpin, E. Hunt, and I. I. Zomaya, *J.C.S. Chem. Comm.*, 1977, 748); the structure of 3-(CO_2Me)-(**6**) has been established by *X*-ray analysis (T. J. King, unpublished results).

[1] A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, 359.
[2] A. G. Brown, D. Butterworth, M. Cole, G. Hanscomb, J. D. Hood, and C. Reading, *J. Antibiotics*, 1976, **29**, 668; T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266.
[3] Prepared from 4-acetoxyazetidin-2-one using the method of K. Clauss, D. Grimm, and G. Prossel, *Annalen*, 1974, 539.
[4] B. Miller, H. Margulies, T. Drabb, Jr., and R. Wayne, *Tetrahedron Letters*, 1970, 3801.
[5] L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 1960, 2881.
[6] J. B. Stothers, 'Carbon-13 N.M.R. Spectroscopy,' Academic Press, New York and London, 1972, Ch. 8, p. 298.
[7] C. Reading, unpublished results from these laboratories.
[8] P. A. Hunter, unpublished results from these laboratories.