Total Synthesis of Methyl (2*RS*,5*RS*)-3-Methylene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate, a Novel Clavulanic Acid Analogue

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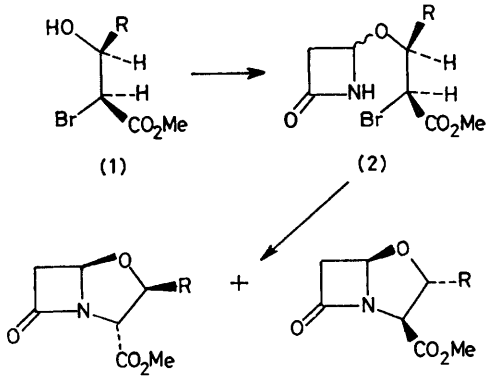
Summary A 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane bearing an arylseleninylmethyl group at C-3 has been constructed and shown to give rise to a novel clavulanic acid analogue (**6a**).

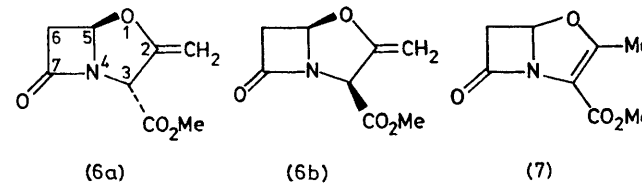
A SYNTHESIS of the 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane ring system has recently been reported[1] from these laboratories, wherein (±)-4-acetoxyazetidin-2-one[2] is first treated with a bromohydrin (**1**) and this is followed by base-induced cyclisation of the intermediate azetidinones (**2**) (Scheme).



SCHEME

Using this procedure we have constructed† the racemic fused β-lactams‡ (**3a**) and (**3b**), by commencing with (±)-methyl *erythro*-2,4-dibromo-3-hydroxybutanoate (**1a**).§ Since attempts to eliminate HBr from (**3a**) to provide the desired analogue (**6a**)[3] proved abortive under a variety of conditions, a mixture of (**3a**) and (**3b**) (*ca.* 1 : 1) was converted into the selenides (**4a**) and (**4b**) (64% yield) by reaction with sodium *o*-nitrophenyl selenide[4] in dimethylformamide–1,2-dimethoxyethane (1 : 1).

Following treatment of the selenides with hydrogen peroxide (10 equiv.; 3 h at 40 °C, 18 h at 20 °C) in 1,2-dimethoxyethane, a mixture of the selenoxides (**5a**) and (**5b**) (50% yield) was isolated after chromatography, together with (**6a**) (9%).



(6a) (6b) (7)

Further elimination was achieved, at the expense of some degradation, by refluxing[5] the selenoxides in carbon tetrachloride–methylene dichloride (2 : 1) for 6 h. Chromatography furnished an inseparable mixture of (**6a**) and (**6b**) (ratio 3 : 7, 48% yield). By analogy,[1] (**6b**) was expected to

† Satisfactory analytical and spectroscopic data were obtained for all new compounds herein reported.

‡ Compounds (**3a**) and (**3b**), which could be separated by careful chromatography, had similar i.r. and n.m.r. spectra. However, in (**3b**) the C-3-H appeared at δ 4·06 (1H, d, *J* 5·5 Hz); in (**3a**) it appeared with C-2-H at δ 4·5—5·0 (2H, m).

§ Compound (**1a**) was prepared from methyl *trans*-4-bromocrotonate by treatment with *N*-bromoacetamide in aqueous dioxan.

epimerise at C-3¶ in the presence of base. Hence a solution of the mixture in $CDCl_3$ was stirred with D_2O containing 1,5-diazabicyclo[4.3.0]non-5-ene for 4—5 min. ^1H N.m.r. spectroscopy** indicated loss of the signals assigned to (**6b**), enhancement of those for (**6a**), and appearance of new signals[6] assigned to the bicycloheptene (**7**). Following aqueous work up, (**6a**) was re-isolated in 23% overall yield from the selenoxides. Compound (**6a**) was a colourless gum, ν_{max} ($CHCl_3$): 1800, 1750, and 1655 cm^{-1}; δ 2·98 (1H, d, J 16 Hz, C-6-H), 3·45 (1H, dd, J 16 and 2·5 Hz, C-6-H), 3·74 (3H, s, OMe), 4·24 (1H, dd, J 3 and 1 Hz, vinyl-H), 4·54 (1H, dd, J 3 and 1 Hz, vinyl-H), 5·00 (1H, t, J 1 Hz, C-3-H), and 5·60 (1H, d, J 2·5 Hz, C-5-H). The mixture of (**6a**) and (**6b**) showed additional signals at δ 4·14 (dd), 4·43 br (s), and 5·37 br (s) assigned to the vinyl-H, C-3-H, and C-5-H, respectively in (**6b**). The more shielded C-3-H in (**6b**) compared to (**6a**) is particularly noteworthy.[1]

(*Received*, 3*rd April* 1978; *Com.* 346.)

¶ Numbering follows that used in penicillins as shown in (**6a**).

** Chemical shifts (δ) are from tetramethylsilane for solutions in $CDCl_3$.

[1] A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, 359.
[2] K. Clauss, D. Grimm, and G. Prossel, *Annalen*, 1974, 539.
[3] Compound (**6a**) lacks the hydroxymethyl group of clavulanic acid, a naturally occurring β-lactamase inhibitor. See T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266.
[4] K. B. Sharpless and M. W. Young, *J. Org. Chem.*, 1975, **40**, 947.
[5] The sluggishness towards elimination observed with (**5a**) and (**5b**) reflects the generally unfavoured *syn*-elimination towards an oxygen atom. See K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, 1973, **95**, 2697.
[6] Observed at δ 2·24 (s, Me) and 5·83 (dd, C-5-H). Compound (**7**) was not subsequently isolated owing to its instability, see P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, *J.C.S. Chem. Comm.*, 1977, 905.