Total Synthesis of Clavulanic Acid Analogues from 7-Oxo-3-vinyl-4-oxa-1-azabicyclo[3.2.0]heptanes

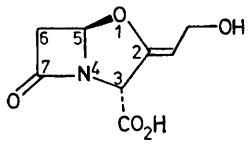
By PETER H. BENTLEY* and ERIC HUNT

(*Beecham Pharmaceuticals Research Division, Chemotherapeutic Research Centre, Brockham Park, Betchworth, Surrey* RH3 7AJ)

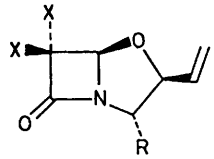
Summary A 3-vinyl group has been incorporated into the 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane ring system by way of the selenoxide elimination process, or by utilising a novel 3-vinylserine derivative, and its transformation to an alkoxyethylidene group demonstrated.

THE novel fused β-lactam, clavulanic acid (**1**),[1] contains the 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane ring system, a simple synthesis of which has recently been described from these laboratories.[2] As part of a programme aimed at the total synthesis[3] of analogues of (**1**), we have prepared and investigated the transformation of the fused β-lactams (**2**),

carrying a vinyl group at C-2,† into the desired 2-alkylidene derivatives. In one process we envisaged allylic bromination of (**2**), followed by reaction of the product (**3**), Z = Br, with nucleophiles to generate (**4**), Z = OR, SR *etc.*

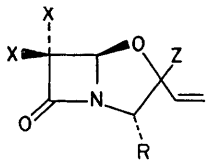


(1)

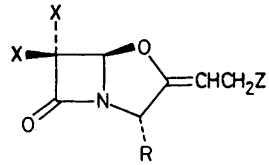


(2)

a; X = H, R = CO_2Me
b; X = R = H
c; X = Br, R = CO_2Me



(3)

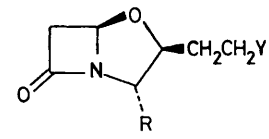


(4)

a; X = Z = Br, R = CO_2Me
b; X = Br, Z = OPr^i, R = CO_2Me
c; X = Br, Z = OMe, R = CO_2Me
d; X = H, Z = OMe, R = CO_2CH_2Ph

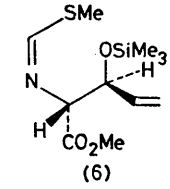
The required vinyl derivatives (**2a**) and (**2b**) were obtained from the racemic bicycloheptanes (**5a**)‡ and (**5b**)‡ respectively. (**5a**) was hydrogenolysed, tosylated (tosyl chloride, pyridine, dichloromethane) to (**5c**), and treated with sodium *o*-nitrophenyl selenide[4] in dimethylformamide–1,2-dimethoxyethane (1 : 2) to provide the selenide (**5d**) (53%).§ Brief exposure to aqueous hydrogen peroxide (10 equiv.; 3 h) in 1,2-dimethoxyethane smoothly transformed (**5d**) into (**2a**) in 70% yield. Similarly (**5b**)¶ was transformed to (**2b**) *via* the selenide (**5e**) in an overall yield of 58%. (**2a**) showed *inter alia*: $\nu_{max.}$ ($CHCl_3$): 1790 and 1745 cm^{-1}; δ ($CDCl_3$; Me_4Si): 4·20 (1H, d, 3-H), 5·2—5·5 (3H, m and d, 5-H and vinyl CH_2), and 5·89 (1H, ddd, vinyl CH). (**2b**) displayed *inter alia*: ν_{max} ($CHCl_3$): 1780 cm^{-1}; δ($CDCl_3$; Me_4Si) 3·05—3·55 (3H, m, 3-H[2] and 6-H), 5·1—5·4 (3H, m, 5-H and vinyl CH_2), and 5·80 (1H, ddd, vinyl CH).

The 6,6-dibromo analogue (**2c**) was also constructed by a longer route,[5] in which the racemic *threo*-amino ester derivative (**6**)[6] was converted into (**7a**) (dibromoacetyl bromide, triethylamine in benzene) in 41% yield. (**7a**) was chlorinolysed and hydrolysed to (**7b**) and cyclisation with silver tetrafluoroborate and silver oxide in dichloromethane provided a 13% yield of a single bicyclic compound assigned structure (**2c**) on the basis of the chemical shift of the C-3 proton in the ^1H n.m.r. spectrum [this shift differentiates (**2c**) from (±)-5-*epi*-(**2c**), the other possible product] and the relative stereochemistry of the starting material (**6**). (**2c**) displayed *inter alia*: ν_{max} ($CHCl_3$): 1810 and 1755 cm^{-1}; δ ($CDCl_3$; Me_4Si): 4·34 (1H, d, 3-H), 5·28 and 5·42 (each 1H, d, vinyl CH_2), 5·44 (1H, s, 5-H), and 5·89 (1H, ddd, vinyl CH).

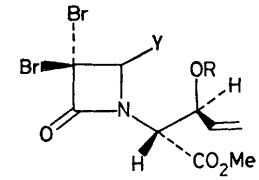


(5)

a; R = CO_2Me, Y = OCH_2Ph
b; R = H, Y = Br
c; R = CO_2Me, Y = $OSO_2C_6H_4Me$-*p*
d; R = CO_2Me, Y = $SeC_6H_4NO_2$-*o*
e; R = H, Y = $SeC_6H_4NO_2$-*o*



(6)



(7)

a; R = $SiMe_3$, Y = SMe
b; R = H, Y = Cl

When (**2c**) was treated with 1,3-dibromo-5,5-dimethylhydantoin in refluxing carbon tetrachloride it was smoothly converted into a mixture containing (**3a**) (1 part) and (**4a**) (4 parts). A solution of this mixture in propan-2-ol was stirred with silver oxide for 1·5 h. Chromatography provided, first, two separable ethers (**3b**) (7% each) and then the desired racemic clavulanates (**4b**) (14% yield), isolated as a mixture of *Z*- and *E*-isomers in the ratio of 5 : 1. [If methanol is used, the ratio of (**3c**) to (**4c**) becomes *ca.* 6 : 1 (total yield 39%)]. However when either (**2a**) or (**2b**) was treated with the same brominating agent, followed immediately by either sodium benzenethiolate or a mixture of propan-2-ol and silver oxide, products corresponding to (**3**) or (**4**) (X = H, Z = Br, SPh, or OPr^i) were not detected.

In the ^1H n.m.r. spectra ($CDCl_3$; Me_4Si), the C-3 proton in the less polar isomer of (**3b**) appears at δ 4·42, while in the more polar isomer it appears at δ 4·67. The former is assigned structure (**3b**), wherein the alkoxy group is *trans* to the C-3 proton, while the latter has the opposite configuration at C-2.[7] The vinyl proton chemical shift serves

† Numbering follows that used in penicillins, indicated in (**1**), rather than that based on the bicycloheptane system.

‡ (**5a**) and (**5b**) were obtained by extensions of the general route (ref. 2) from (±)-methyl *erythro*-5-benzyloxy-2-bromo-3-hydroxypentanoate, and (±)-1,4-dibromobutan-2-ol respectively. The required bromohydrin for the direct synthesis of (**2a**) by the general process (ref. 2) could not be synthesised. Similarly (±)-4-[1-(bromomethyl)-prop-2-enyloxy]azetidin-2-one did not undergo base-induced cyclisation to (**2b**).

§ The spectral properties of all new compounds were in agreement with the proposed structures.

¶ (**5b**) was admixed with its diastereoisomer, from which it was inseparable. The diastereoisomers of (**2b**) were separated by chromatography.

to differentiate[8] *Z*-(**4b**) (δ 4·96) from *E*-(**4b**) (δ 5·26). The relative stereochemistry at C-3 and C-5 in (**3b**) and (**4b**), which was not expected to be altered during these transformations, reflects that in the starting material (**2c**).

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[1] T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266.

[2] A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, 359. See also R. G. Alexander and R. Southgate, *ibid.*, p. 405.

[3] Other independent total syntheses of the 3-alkylidene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane ring system have been reported by us: P. H. Bentley, P. D. Berry, G. Brooks, M. L. Gilpin, E. Hunt, and I. I. Zomaya, *J.C.S. Chem. Comm.*, 1977, 748; P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, *ibid.*, p. 905; E. Hunt, P. H. Bentley, G. Brooks, and M. L. Gilpin, *ibid.*, p. 906.

[4] K. B. Sharpless and M. W. Young, *J. Org. Chem.*, 1975, **40**, 947.

[5] (a) This route is related to a patented disclosure, wherein 3,3-dimethyl serine derivatives, analogous to (**6**), are treated with azidoacetyl chloride and the resulting β-lactams were converted into (±)-1-oxadethiopenicillins: B. G. Christensen and R. W. Ratcliffe, Ger. Offen., 2,411,856, 1974. (b) The related process was first demonstrated for the synthesis of (±)-methyl 6,6-dibromo-3-methyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate: R. J. Ponsford and J. Goodacre, unpublished results from these laboratories.

[6] (**6**) was synthesised from methyl isocyanoacetate and acrolein, *via* (±)-*trans*-4-methoxycarbonyl-5-vinyl-2-oxazoline, by analogy. See ref. 5a and D. Hoppe and U. Schöllkopf, *Annalen*, 1972, **763**, 1.

[7] The structure of (+)-(2*R*)-(**3d**), prepared from (**1**), and having δ(3-H) 4·70, has been confirmed by *X*-ray crystallography: R. J. Ponsford and T. J. King unpublished results.

[8] See cited references in L. M. Jackman and S. Sternhell, 'Application of N.M.R. Spectroscopy in Organic Chemistry,' Pergamon, 1969, p. 187.