Total Synthesis of Clavulanic Acid Analogues *via* Isomerisation of 7-Oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-enes

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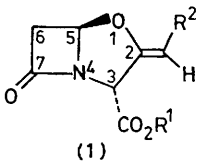
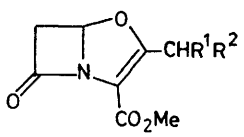
Summary Sodium *Z*-3-benzylidene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate (**1b**), a novel clavulanic acid analogue, has been prepared *via* the isomerisation of the bicycloheptene (**2a**).

As part of a programme concerned with the total synthesis of clavulanic acid analogues,[1] we have prepared and studied the isomerisation of the novel bicycloheptenes (**2**). The latter were readily obtained from the acetate (**3**),[2] by a route previously demonstrated[3] in these laboratories for the



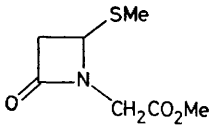
(1)

a; R^1 = Me, R^2 = Ph
b; R^1 = Na, R^2 = Ph
c; R^1 = H, R^2 = CH_2OH

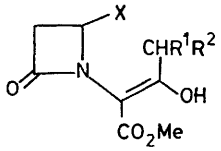


(2)

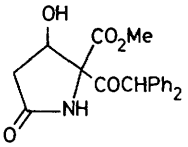
a; R^1 = Ph, R^2 = H
b; R^1 = Me, R^2 = H
c; R^1 = R^2 = Ph
d; R^1 = R^2 = Me



(3)



(4a–d) X = SMe
(5a–d) X = Cl
} R^1, R^2 as for (2)



(6)

synthesis of (**2**, R^1 = R^2 = H) carrying a triphenylmethylamino group at C-6.† The intermediate β-keto esters (**4a**—**d**), which are largely enolised as shown, were isolated as oils in yields of 67—83%. Following chlorinolysis[3] of (**4a**—**d**) the crude chlorides (**5a**—**d**) were each cyclised by adding 1 equiv. of triethylamine to an ice-cold ethereal solution and filtering the mixture after 10—15 min. Evaporation furnished the essentially pure, racemic bicycloheptenes (**2a**—**d**), in near quantitative yield. Further purification by rapid silica-gel chromatography led to a poor recovery of these sensitive materials. The observed spectral characteristics‡ confirmed the proposed structures for (**2a**—**d**); *e.g.* (**2a**) showed *inter alia* ν_{max} ($CHCl_3$): 1805 (lactam C=O), 1700 (ester C=O), and 1625 (C=C) cm^{-1}; λ_{max} (EtOH): 273 nm; δ 3·98 (q, *J* 14 Hz, CH_2Ph) and 5·77 (dd, *J* 2·5, *J'* 0·5 Hz, 5-H).

Exposure of (**2a**) to a further quantity (0·3—1 equiv.) of triethylamine in CH_2Cl_2 for 2—3 h, followed by chromatography, furnished only the racemic analogue (**1a**) in 54% yield from (**4a**). A similar yield of (**1a**) was also obtained, without isolation of (**2a**), by treating (**5a**) with K_2CO_3 in dry dimethylformamide. Compound (**1a**) displayed *inter alia* ν_{max} ($CHCl_3$): 1800 (lactam C=O), 1750 (ester C=O), and 1680 (C=C) cm^{-1}; λ_{max} (EtOH) 265 nm; δ 5·20 (br,s, exchanges with D_2O containing DBN, 3-H), 5·57 (br, s, vinyl-H), and 5·86 (d, *J* 2·2 Hz, 5-H).† Whilst the product was expected to have the same relative stereochemistry at C-3 and C-5 as in clavulanic acid by virtue of its formation under basic conditions,[4] the configuration of the double-bond could only be guessed.[5] The observed shift of the vinyl proton in the n.m.r. spectrum, however, agrees well with that predicted for (**1a**), δ = 5·8, if the coefficients of Matter *et al.*[6] are applied to the bicycloheptane (**1**, R^1 = Me, R^2 = CO_2Me)[7] of established configuration.

All attempts to isomerise (**2b**—**d**) under similar basic or other conditions have failed. Interestingly, a compound isolated from (**2c**) or (**5c**) after treatment with K_2CO_3 followed by aqueous work up was identified as a mixture of the diastereoisomeric γ-lactams (**6**) from spectroscopic data. Finally, keeping a dilute aqueous tetrahydrofuran solution of (**1a**) at pH 9·5 with NaOH until 1 equiv. had been consumed provided, after freeze-drying, the amorphous sodium salt (**1b**) in 83% yield. Compound (**1b**) is a potent inhibitor of several β-lactamases.

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† The numbering, shown in (**1**), follows that used in penicillins, rather than that based on the bicycloheptane system. Chemical shifts are p.p.m. from Me_4Si for solutions in $CDCl_3$. DBN is 1,5-diazabicyclo[4.3.0]non-5-ene.

‡ Satisfactory analytical and spectroscopic data were obtained for all new compounds.

[1] (a) Clavulanic acid, a naturally occurring β-lactamase inhibitor, has the structure (**1c**). See T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266; (b) A total synthesis of (±)-clavulanic acid has been reported by us. See P. H. Bentley, P. D. Berry, G. Brooks, M. L. Gilpin, E. Hunt, and I. I. Zomaya, *J.C.S. Chem. Comm.*, 1977, 748.

[2] Prepared from (±)-4-methylthioazetidin-2-one (K. Clauss, D. Grimm, and G. Prossel, *Annalen*, 1974, 539) by alkylation (ref. 3) with methylbromoacetate.

[3] A. J. Eglington, *J.C.S. Chem. Comm.*, 1977, 720. Lithium *NN*-bis(trimethylsilyl)amide was used for generation of the ester enolate; CCl_4 was the solvent for the chlorinolysis. The cyclisation conditions also differ (see text).

[4] Recently a synthetic 3-*epi* analogue was shown to epimerise at C-3 under basic conditions: P. H. Bentley, unpublished results.

[5] The structure of a related analogue (**1**, R^1 = Me, R^2 = 2,5-dichloro-3-thienyl), prepared by us in an identical fashion has been confirmed by *X*-ray crystallographic analysis to have the relative stereochemistry depicted in (**1**): T. J. King, unpublished data.

[6] U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, 1969, **25**, 691. For limitations of this approach: *ibid.*, p. 2023.

[7] See ref. (1b), addition of [*Z gem* (Ph)–*Z gem* (CO_2R)] to the observed chemical shift for the vinyl proton of this compound (5·2) gives 5·78. On the same basis the predicted value for the *E*-isomer of (**1a**) is 6·18.