Synthesis of 7-Oxo-3-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylates: Analogues of Clavulanic Acid

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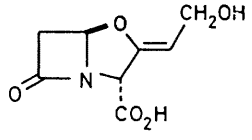
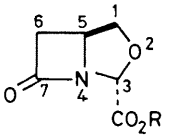
Summary 4-Iodomethylazetidin-2-one is converted into the title compounds when treated sequentially with glyoxylic acid esters and sodium hydride

THE disclosure that clavulanic acid (**1**), a metabolite of *Streptomyces clavuligerus*,[1] is a potent irreversible inhibitor of a wide range of clinically important β-lactamases[2] has prompted the preparation of several structurally related compounds[3] We now describe the synthesis of the title compounds (**2**), the first examples of isoclavams †

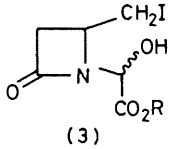


(1)



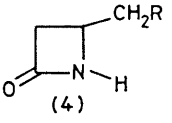
(2)

a; R = Bu^t d, R = $CH_2C_6H_4NO_2$-*p*
b; R = Me e, R = H
c; R = CH_2Ph f; R = Na



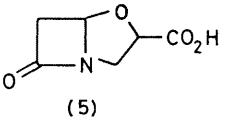
(3)

a, R = Bu^t



(4)

a; R = I
b; R = OH
c; R = $OSO_2C_6H_4Me$-*p*



(5)

It was planned to generate the isoclavam ring system by final closure of the 1,2-bond from precursors of type (**3**) This approach defined the iodide (**4a**) as the key intermediate

Sequential treatment of 4-vinylazetidin-2-one[4] with ozone (MeOH, −78 °C) and sodium borohydride gave the alcohol (**4b**)‡ (65%), m p 60—66 °C (after sublimation), esterification (*p*-$MeC_6H_4SO_2Cl$, C_5H_5N, −30 → 0 °C) of the alcohol (**4b**) afforded the tosylate (**4c**)‡ (50%), m p 102—103 °C, which was converted into the iodide (**4a**)‡ (80%), m p 105—107 °C, by sodium iodide (Me_2CO, 56 °C)

A solution of the iodide (**4a**) in tetrahydrofuran reacted with t-butyl glyoxylate in the presence of triethylamine[5] to give the syrupy alcohol (**3a**)‡ (80% after SiO_2 chromatography), as a 1 : 1 mixture of isomers Sodium hydride in tetrahydrofuran converted the alcohol (**3a**) into the isoclavam (**2a**)‡¶ (50%), m p 63—65 °C By similar reaction sequences, the iodide (**4a**) was transformed into the syrupy isoclavams (**2b**),‡¶ (**2c**),‡¶ and (**2d**) ‡¶

Attempts to derive the acid (**2e**) or the salt (**2f**) from the esters (**2a**—**d**) were unrewarding due to the ease with which the β-lactam linkages were cleaved

Recently, clavam-2-carboxylic acid (**5**) has been isolated from culture fluids of *Streptomyces clavuligerus*, its methyl ester is claimed to possess antifungal activity[6]

We thank the S R C and N R D C for financial support

(*Received, 16th October* 1979, *Com* 1102)

† The trivial name 'clavam' has been proposed (ref 6) for 7 oxo 4 oxa-1-azabicyclo[3 2 0]heptane By analogy, 'isoclavam' is suggested for 7-oxo-3-oxa-1-azabicyclo[3 2 0]heptane These systems, when referred to by their trivial names, are numbered as in penicillins [*i e*, (**2**)], *cf* ref 6

‡ This compound was identified by its spectral properties, its composition was confirmed by elemental analysis and/or mass spectroscopy

¶ Although the relative configuration of the 3 and 5-positions was not established the isolation of this compound as a single isomer suggests that the 3 carboxylic acid group and the 5 hydrogen atom are *cis* orientated This stereochemical arrangement represents the thermodynamically favoured situation in related systems (A G Brown, D F Corbett, and T T Howarth, *J C S Chem Comm*, 1977, 359, P H Bentley and E Hunt, *ibid*, 1978, 518)

[1] T T Howarth, A G Brown, and T J King *J C S Chem Comm*, 1976 266
[2] A G Brown D Butterworth, M Cole, G Hanscomb, J D Hood, C Reading and G N Rolinson *J Antibiotics*, 1976 **29**, 668
[3] P H Bentley, G Brooks, M L Gilpin, and E Hunt, *Tetrahedron Letters*, 1979, 1889, E Hunt, *J C S Chem Comm*, 1979, 686, and references therein
[4] E J Moriconi and W-C Meyer, *J Org Chem*, 1971, **36**, 2841
[5] R Scartazzini H Peter, H Bickel, K Heusler, and R B Woodward, *Helv Chim Acta*, 1972, **55**, 408, J Finkelstein, K G Holden, and C D Perchonock, *Tetrahedron Letters*, 1978, 1629
[6] D Brown, J R Evans, and R A Fletton, *J C S Chem Comm*, 1979, 282