Synthesis of Ethyl 3-Methyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate and the Reaction of 4-Acetoxyazetidin-2-one with Ethyl α-Diazoacetoacetate

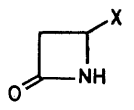
By GERALD BROOKS, T. TREFOR HOWARTH, and ERIC HUNT*

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

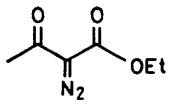
Summary Ethyl 3-methyl-7-oxo-4-oxa-1-azobicyclo[3.2.0]-hept-2-ene-2-carboxylate (**4**) has been obtained by a four-step synthesis from 4-methylthioazetidin-2-one and has been compared with the products obtained from the rhodium(II) acetate-catalysed reaction of 4-acetoxy-azetidin-2-one with ethyl α-diazoacetoacetate; this latter reaction did not give compound (**4**), as was previously claimed, but yielded ethyl 2-(4-acetoxy-2-oxoazetidinyl)-3-oxobutyrate as the major β-lactam product.

A RECENT communication[1] claimed a new synthesis of the 7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene ring system from 4-acetoxyazetidin-2-one (**1**). In particular, this paper described the reaction of compound (**1**) with ethyl α-diazoacetoacetate (**3**) in the presence of rhodium(II) acetate to give a β-lactam product which was assigned structure (**4**) on the basis of its spectral properties. In fact, the spectral data quoted for this product are not in accordance with those expected for structure (**4**).† We have therefore prepared compound (**4**) using an established synthesis[2] and have reinvestigated the products obtained from the rhodium(II) acetate-catalysed reaction of (**1**) with (**3**).

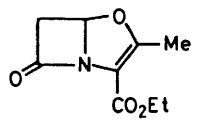
Starting with 4-methylthioazetidin-2-one, and using the previously described general route,[2] the bicyclic β-lactam



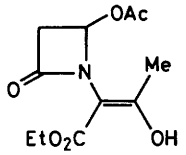
(1) X = OAc
(2) X = SMe



(3)



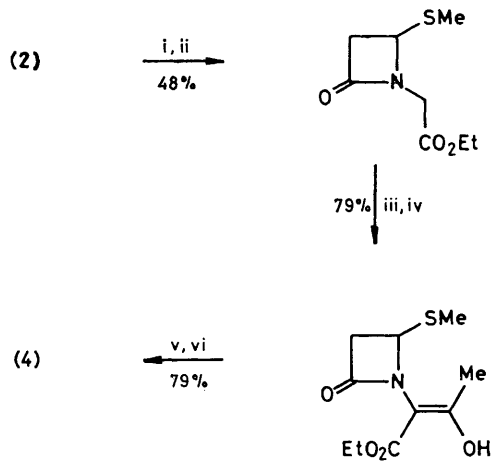
(4)



(5)

(**4**) was obtained as a gum in an overall yield of 30%. The synthesis is outlined in the Scheme.‡ Compound (**4**) had λ_{max} (EtOH) 269 nm (ε 6100); ν_{max} ($CHCl_3$) 1810, 1705, and 1635 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1·30 (3 H, t, *J* 7 Hz), 2·25 (3 H, s), 3·37 (1 H, dd, *J* 17, 1·5 Hz), 3·62 (1 H, dd, *J* 17,

† Most noteworthy was the chemical shift quoted for the C-5 proton, which, at δ ($CDCl_3$) 6·2, was at much lower field than that observed in compounds of similar structure (P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, *J. Chem. Soc., Chem. Commun.*, 1977, 905; P. H. Bentley and E. Hunt, *J. Chem. Soc., Chem. Commun.*, 1978, 518).



SCHEME. *Reagents:* i, NaH (1 equiv.), dimethylformamide, 0 °C, 10 min; ii, $BrCH_2CO_2Et$ (1·1 equiv.), 0 °C, 1 h; iii, $LiN(SiMe_3)_2$ (2 equiv.), tetrahydrofuran, −70 °C, 10 min; iv, MeCOCl (1 equiv.), −70 °C, 1·5 h; v, Cl_2 (1 equiv.), CCl_4, 0 °C, 5 min; vi, Et_3N (1 equiv.), tetrahydrofuran, 0 °C, 5 min. Overall yields of each step are given.

3 Hz), 4·24 (2 H, q, *J* 7 Hz), and 5·85 (1 H, dd, *J* 3, 1·5 Hz); *m/e* 197·0674 (M^+) (Calc. *M*, 197·0688). The n.m.r. spectrum of this compound is clearly different from that quoted[1] for the β-lactam product obtained from the rhodium(II) acetate reaction.

When we investigated the reaction between (**1**) and (**3**) under the previously described[1] conditions we were unable to detect (t.l.c.) the bicyclic compound (**4**). Chromatography of the complex reaction mixture on silica gel gave one β-lactam product as a pale yellow oil (7·5%). To this product we have assigned structure (**5**) on the basis of its spectral properties: λ_{max} (EtOH) 258 nm (ε 9400); ν_{max} ($CHCl_3$) 1775, 1755, 1655, and 1625 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1·30 (3 H, t, *J* 7 Hz), 2·08 (6 H, s), 2·93 (1 H, dd, *J* 15, 2 Hz), 3·31 (1 H, dd, *J* 15, 4 Hz), 4·24 (2 H, q, *J* 7 Hz), 6·13 (1 H, dd, *J* 4, 2 Hz), and 12·35 (1 H, s, enolic OH); *m/e* 257·0901 (M^+) (Calc. *M*, 257·0899).

Compound (**5**) was also obtained in 39% yield when (**4**) was treated with acetic acid (1 : 1 tetrahydrofuran–glacial acetic acid, 20 °C, 2 h). Compound (**5**) showed no tendency to cyclise to (**4**) on prolonged treatment with either rhodium(II) acetate in toluene or triethylamine (1 equiv.) in dichloromethane.

(*Received, 26th March* 1981; *Com.* 346.)

‡ All new compounds had spectral properties in accordance with their proposed structure; compound (**4**) is unstable, and it was not possible to obtain an analytically pure sample.

[1] J. Cuffe and A. E. A. Porter, *J. Chem. Soc., Chem. Commun.*, 1980, 1257.
[2] A. J. Eglington, *J. Chem. Soc., Chem. Commun.*, 1977, 720; P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, *J. Chem. Soc., Chem. Commun.*, 1977, 905.