Syntheses Based on 1,2-Secopenicillins; the Synthesis of the 1-Oxadethiapenem Ring System

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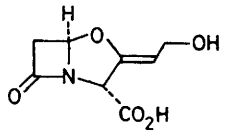
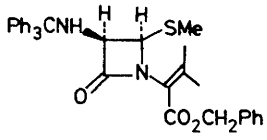
Summary The new 7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene ring system has been synthesised from the readily available secopenicillin (**2**).

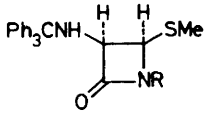
RECENTLY the novel fused bicyclic β-lactams, clavulanic acid (**1**),[1] thienamycin,[2] and MM 4550 and MM 13902[3] have been isolated from *Streptomyces* species. Other new fused bicyclic β-lactams, such as the 1-carbadethiacephem,[4] 1-oxadethiapenam,[5,6] and penem[7] systems have also been synthesised. We now report an easy synthesis of the 7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene (1-oxadethiapenem) system, in which there is an endocyclic double bond, as opposed to the exocyclic double bond of clavulanic acid (**1**).



(1)

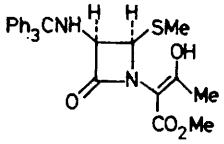


(2)

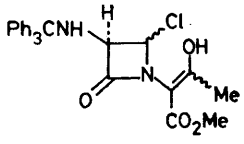


(3), R = H

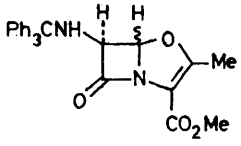
(4), R = CH_2CO_2Me



(5)



(6)



(7)

The secopenicillin (**2**), readily prepared from benzyl 6β-triphenylmethylaminopenicillanate,[8] was oxidised with potassium permanganate to give (3*R*,4*R*)-4-methylthio-3-triphenylmethylaminoazetidin-2-one (**3**).[9] The azetidinone (**3**) was treated with methyl bromoacetate and sodium hydride in tetrahydrofuran (THF) to give methyl 2-[(3*R*,4*R*)-4-methylthio-2-oxo-3-triphenylmethylamino-azetidin-1-yl]acetate (**4**) (67%).† Reaction of the ester enolate of (**4**), generated by means of lithium *N*-isopropylcyclohexylamide in THF at −70 °C, with acetyl chloride gave the desired keto ester (**5**) (75%), m.p. 154—156 °C;†‡ the i.r. [ν_{max} ($CHCl_3$) 1760, 1730sh, 1715sh, 1655, and 1615 cm^{-1}] and ^1H n.m.r. spectra indicated that (**5**) existed mainly in the enol form. A dichloromethane solution of (**5**) was treated with 1 equiv. of chlorine in dichloromethane§ for 1 min to give the unstable chloroazetidinone (**6**). Treatment of (**6**), without purification, with a mixture of silver tetrafluoroborate, silver oxide, and pyridine in dichloromethane gave a mixture of the (5*R*,6*R*)- and (5*S*,6*R*)-methyl 3-methyl-7-oxo-6-triphenylmethylamino-4-oxa-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates (**7**) as a glass [15% from (**5**)]; ν_{max} (CH_2Cl_2) 1800 (β-lactam C=O), 1705 (ester C=O), and 1630 cm^{-1} (C=C); λ_{max} (EtOH) 261 nm (ε 6,400); δ ($CDCl_3$) 2·18 (s) and 2·24 (s) (3H, 3-Me, 2 isomers), 3·84 (3H, s, CO_2Me), 4·2—4·8 (2H, m, 5-CH and 6-CH), and 7·0—8·0 (15H, m, ArH); *m/e* 440·1758 (M^+). The compound was unstable and needed careful, rapid chromatography. Prolonged chromatography of (**7**) on silica gel led to substantial losses of material, and failed to separate the stereoisomers.

Product (**7**), in contrast to clavulanic acid (**1**), was only a weak inhibitor of β-lactamases.

(*Received, 20th July* 1977; *Com.* 745.)

† New compounds had spectroscopic and elemental and/or mass spectral data in accord with structures indicated.

‡ Methyl α-bromoacetoacetate failed to react with (**3**) to give (**5**).

§ Solutions of chlorine in dichloromethane had to be used when freshly prepared, as on standing they decolourised and appeared to form phosgene. It was found that solutions of chlorine in carbon tetrachloride were more stable.

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