Azapenems: Synthesis of 4-Substituted 7-Oxo-1,4-diazabicyclo[3.2.0]-hept-2-ene Carboxylates

By GRAHAM JOHNSON and BARRY C. ROSS
(*Dept. of Chemistry, Hoechst Pharmaceutical Research Laboratories, Walton Manor, Walton, Milton Keynes* MK7 7AJ)

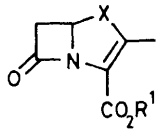
Summary 2-Aza-1-thiacephems prepared from penicillanic acid are desulphurised with triphenylphosphine in good yield to give azapenems.

RECENT advances both in the isolation of natural products and in synthetic chemistry have afforded potentially important new bicyclic β-lactam antibiotics and β-lactamase inhibitors. Many of these compounds are characterised by the possession of the strained 7-oxo-1-azabicyclo[3.2.0]hept-2-ene nucleus with a carbon, an oxygen, or a sulphur atom at the 4-position (**1**—**3**), and are respectively represented by thienamycin (carbapenems),[1] the clavems (oxapenems),[2] and penems.[3,4] In this communication we describe the synthesis of the azapenems which possess the hitherto unreported 7-oxo-1,4-diazabicyclo[3.2.0]hept-2-ene nucleus (**4**).

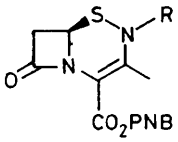
We expected that both the β-lactam and the cyclic enamide structure present in the azapenems (**4**) would be of limited stability. Accordingly we directed our attention towards the generation of a suitably stable precursor capable of mild and efficient transformation into the target structure. We have achieved this objective through the synthesis of the previously undescribed 2-aza-1-thiacephem nucleus (**5**) which undergoes smooth desulphurisation at room temperature to afford the corresponding azapenem in good yield. The 2-aza-1-thiacephem (**5a**) was synthesised thus: treatment of the vinyl methanesulphonate (**6**), prepared from 6-amino-penicillanic acid,[5] with aniline in the presence of a strong tertiary amine base {Et_3N or 1,4-diazabicyclo[2.2.2]-octane (DABCO)} gave the phenylenamide (**7a**).† Cyclisation of (**7a**)‡ into the 2-aza-1-thiacephem (**5a**) [ν (film) 1782, 1715 cm^{-1}; δ ($CDCl_3$) 2·20 (s, Me), 2·83 (dd, *J* 16 and 2 Hz, H-7), 3·80 (dd, *J* 16 and 5 Hz, H-7), 4·50 (dd, *J* 2 and 5 Hz, H-6); $[\alpha]_D$ −257° (*c* 1·18, $CHCl_3$)] was effected in 62% yield by treatment with finely divided silver acetate[7] in refluxing benzene.§ Desulphurisation of (**5a**) with triphenylphosphine in acetonitrile at room temperature gave the *N*-phenylazapenem (**4a**). Purification was achieved by direct crystallisation from acetonitrile followed by washing the solid with benzene (to remove co-precipitated triphenylphosphine sulphide) or by rapid column chromatography to give (**4a**) as a yellow crystalline solid in 83% yield [m.p. 144·5—145 °C; ν($CHCl_3$) 1796, 1690 cm^{-1}; δ($CDCl_3$), 2·23 (s, Me), 3·30 (dd, *J* 16 and 1 Hz, H-6), 3·76 (dd, *J* 16 and 2·5 Hz, H-6), 5·68 (dd, *J* 1 and 2·5 Hz, H-5); λ_{max} (EtOH) 268, 333 nm (ε 10 880, 17 600), $[\alpha]_D$ + 17° (*c* 0·486, $CHCl_3$)].

The *N*-ethyl derivative (**4b**) was prepared by two alternative, but related, procedures. Treatment of the vinyl methanesulphonate (**6**) with ethylamine (CH_2Cl_2, −20 °C) gave the enamide (**7b**) as a crystalline solid in 88% yield. This was followed by treatment with silver acetate[7] in refluxing benzene to give after several hours the cyclic sulphenamide (**5b**) [m.p. 110—112 °C; ν($CHCl_3$) 1775, 1706 cm^{-1}; δ($CDCl_3$) 2·43 (s, Me), 2·77 (dd, *J* 15 and 2 Hz, H-7), 3·80 (dd, *J* 15·5 and 5 Hz, H-7), 4·38 (dd, *J* 2 and 5 Hz, H-6); $[\alpha]_D$ −199° (*c* 0·422, $CHCl_3$)] as a colourless crystalline solid in 50% yield. Alternatively treatment of (**6**) with ethylamine in the presence of silver acetate[7] ($EtNH_2$, 1 equiv. AgOAc, $CHCl_3$, room temperature) gave the acyclic sulphenamide methanesulphonate (**8**) in 75% yield. Treatment of (**8**) with either triethylamine or DABCO gave the cyclic sulphenamide (**5b**) in 33% yield. N.m.r. evidence suggests that this ring closure proceeds *via* the allene (**9**).

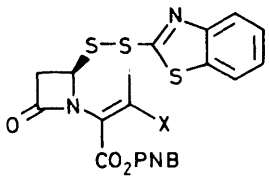
Desulphurisation of (**5b**) with triphenylphosphine in pure acetonitrile proceeded smoothly. Rapid chromatography gave the crystalline *N*-ethyl azapenem (**4b**) in 50% yield [m.p. 116—117 °C; ν($CHCl_3$) 1790, 1680 cm^{-1}; δ($CDCl_3$) 2·29 (s, Me), 3·20 (dd, *J* 16 and 1 Hz, H-6), 3·77 (dd, *J* 16 and 2·5 Hz, H-6), 5·13 (dd, *J* 1 and 2·5 Hz, H-5); λ_{max} (EtOH) 271, 321 nm (ε 11 200, 16 700), $[\alpha]_D$ 0° (*c* 0·886, $CHCl_3$)]. Compared with (**4a**) *N*-ethyl azapenem (**4b**) exhibited reduced stability, both in solution and as the crystalline solid. The low order or absence of optical activity found for both phenyl and ethyl azapenems suggests that



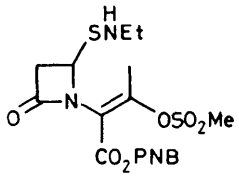
(1) X = CH_2: carbapenem
(2) X = O: oxapenem (clavem)
(3) X = S: penem
(4) X = NR: azapenem
(4a) X = NPh
(4b) X = NEt
R^1 = CH_2–C$_6$H$_4$–NO_2 (PNB)



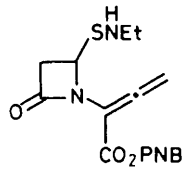
(5)
a; R = Ph
b; R = Et



(6) X = OSO_2Me
(7a) X = NHPh
(7b) X = NHEt



(8)



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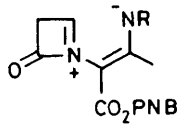

(10)

† All new compounds gave satisfactory combustion analysis or accurate mass measurement values.

‡ This reaction contrasts with the reported[6] thermal cyclisation of related enamides to give 3-aminocephems.

§ Optimisation of this step required the use of high dilution (*ca.* 1 mg/ml) and highly purified solvents to avoid generation of dimeric and other unwanted products.

the achiral 1,5-dipole (**10**) is an intermediate in the final ring contraction. The azapenem ring system has been confirmed by an *X*-ray structure determination.

Attempted hydrogenolysis of the *p*-nitrobenzyl ester under a variety of conditions gave after work-up only decomposition products indicating the low chemical stability of this system.

(*Received*, 13*th August* 1981; *Com.* 995.)

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