Synthesis of Penems by Ring Contraction of a 2-Thiacephem

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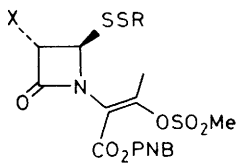
2-Thiacephems prepared from penicillanic acid undergo ring contraction to penems with triphenylphosphine.

We have previously described the synthesis of 1-oxa-[1] and 1-aza-penems[2] using a phosphine-mediated desulphurisation step. We now report an extension of this approach to the synthesis of penems. Since Woodward's original route to these compounds,[3,4] two related penem ring forming reactions have been reported.[5,6]†

Prior to these latter reports we had found that treatment of the azetidinone methanesulphonate[5] (**1a**) with a large excess of hydrogen sulphide in benzene effected rapid and high-yield displacement of mercaptobenzothiazole.

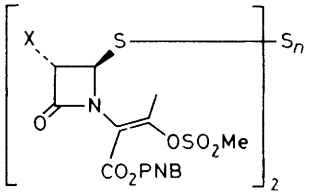
Direct chromatography of the reaction mixture over silica gel gave, as a foam, an azetidinone methanesulphonate, ν (film) 1780 and 1730 cm^{-1}, in 60—80% yield, the structure of which was initially thought to be the hydrodisulphide (**2**). Subsequent molecular weight determination and combustion analysis suggested a mixture of tri- and tetra-sulphides (**3a**) as more probable alternative structures. A recent report[7] on the stability of the hydrodisulphide derived from *N*-acetyl penicillamine would indicate that the above described polysulphides arise from the initially formed hydrodisulphide (**2**).

Treatment of (**3a**) with sodium hydrosulphide in a shaken biphasic solvent system (H_2O–ethyl acetate), hydrogen sulphide (H_2O, Na_2CO_3–ethyl acetate, shaken), or alternatively potassium thioacetate (tetrahydrofuran, 0 °C, homogeneous) gave rapidly the 2-thiacephem[8] (**4a**)‡§ {m.p. 161 °C decomp., $[\alpha]_D$ + 221°, ν ($CHCl_3$) 1782 and 1725 cm^{-1}, ^1H n.m.r. δ ($CDCl_3$) 2.30 (s, CH_3), 2.94 (dd, *J* 16 and 2 Hz, H-7), 3.80 (dd,

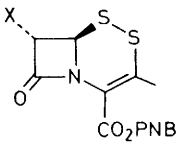


(1a) X = H
(1b) X = Cl
R =

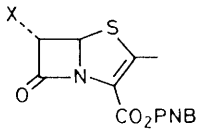
(2) X = H, R = H



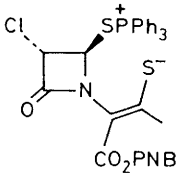
(3a) X = H, *n* = 1 and 2
(3b) X = Cl, *n* = 1



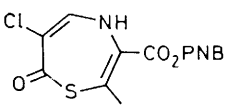
(4a) X = H
(4b) X = Cl



(5a) X = H
(5b) X = Cl



(6)



(7)

PNB = *p*-$NO_2C_6H_4CH_2$–

† The validity of a third penem ring forming reaction has been disproved. See F. DeDinno, E. Linek, and B. G. Christensen, *J. Am. Chem. Soc.*, 1979, **101**, 2210; S. Oida, A. Yoshida, T. Hayashi, E. Nakayanna, S. Sato, and E. Ohki, *Tetrahedron Lett.*, 1980, 619; S. W. McCombie, A. K. Ganguly, V. M. Girijavallabhan, P. D. Jeffrey, S. Lin, and P. Pinto, *Tetrahedron Lett.*, 1981, 3489.

‡ Assumed from mechanistic considerations to be the 6*R* isomer.

§ All new compounds gave satisfactory combustion analysis and/or high resolution mass measurement.

J 16 and 5 Hz, H-7), and 4.63 (dd, *J* 5 and 2 Hz, H-6)} which was purified immediately by short-path chromatography. The potassium thioacetate procedure was found to be considerably more reproducible than the other methods and up to 50% of isolated product could be obtained. Treatment of (**4a**) with triphenylphosphine in chloroform gave, as the sole product, the *p*-nitrobenzyl penem ester (**5a**),[4,5] 76%, $[\alpha]_D$ *ca.* 0°.¶

Anticipating that the presence of a 7α-substituent in the cyclic disulphide (**4b**) would favourably influence the stereochemical course of the ring contraction to give the 5*R*-penem, we prepared the 3α-chloroazetidinone methanesulphonate (**1b**) from 6α-chloropenicillanic acid.[9] Treatment with hydrogen sulphide gave the trisulphide (**3b**) [ν (film) 1792 and 1734 cm^{-1}] which was cyclised as before to give the 7α-chloro-2-thiacephem (**4b**) in 30% yield; ^1H n.m.r. δ ($CDCl_3$) 2.30 (s, CH_3), 4.63 (d, *J* 2 Hz, H-7), and 4.73 (d, *J* 2 Hz, H-6).

Desulphurisation of (**4b**) with triphenylphosphine in a range of solvents gave as the sole β-lactam product the 5*S*-chloropenem (**5b**) in 50% yield; ^1H n.m.r. δ ($CDCl_3$), 2.44 (s, CH_3), 5.49 (d, *J* 3.5 Hz, H-5), and 5.90 (d, *J* 3.5 Hz, H-6). A similar result was obtained with tri-n-butylphosphine. The absence of the *trans*-isomer indicates that the intermediate (**6**) formed by attack of triphenylphosphine on the disulphide (**4b**) reacts *via* synchronous displacement of the phosphine sulphide. In contrast, trimethyl phosphite-induced desulphurisation of (**4b**) gave only the thiazepine (**7**) with no trace of either *cis*- or *trans*-chloropenems as determined by ^1H n.m.r. spectroscopy. The thiazepine (**7**) presumably results from attack of the intermediate enethiolate on the β-lactam carbonyl.

¶ For 5*R*-(**5a**), $[\alpha]_D^{20} = +136°$.[4]

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