Synthesis of a 7-Oxo-1,4-diazabicyclo[3.2.0]hept-3-ene-2-carboxylate (Δ^1-Azapenem) and a Related 3,7-Dioxo-1,4-diazabicyclo[3.2.0]heptane-2-carboxylate, a Fused β,γ-Lactam†

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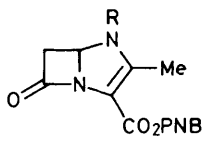
The Δ^1-azapenem (**3**) is synthesised by cyclisation of the azetidinone isothiocyanate (**7**) followed by *S*-alkylation; the intermediate 7-oxo-3-thioxo-1,4-diazabicyclo[3.2.0]heptane-2-carboxylate (**8**) can be oxidised by benzeneseleninic anhydride to give a fused β,γ-lactam.

The recent literature[1] describes many new β-lactam-containing ring structures, of natural and synthetic origin, that display potentially useful biological properties. As part of our studies on new β-lactams we have already described the synthesis of the Δ^2-azapenem ring system[2] (**1**) analogous to the penem structure first reported by Woodward.[3] We now report the synthesis of the Δ^1-azapenem (**3**)† in an attempt to prepare an unsubstituted Δ^2-azapenem corresponding to (**2**). In addition, we describe the synthesis of a related fused β,γ-lactam that possesses the 3,7-dioxo-1,4-diazabicyclo-[3.2.0]heptane ring system (**9**). This ring system is isomeric to a 4,7-dioxo-1,3-diazabicyclo[3.2.0]heptane recently described by Pearson.[4]

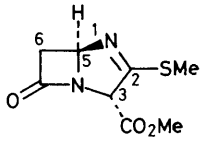
Treatment of 4-acetoxyazetidinone with sodium t-butylthiolate in ethanol at room temperature gave the crystalline azetidinone sulphide (**4**)[5] in good yield. Alkylation

† Formula (**3**) shows the non-standard (penicillin-derived) numbering system used in conjunction with the Δ^1- and Δ^2-azapenem trivial names. In all other cases standard systematic nomenclature and numbering are used.

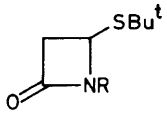


(1) R = Et or Ph

(2) R = H

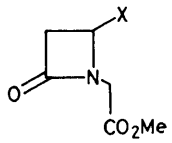


(3)



(4) R = H

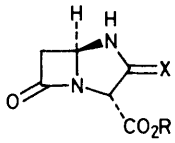
(5) R = CH_2CO_2Me



(6) X = SC≡N

(7) X = N=C=S

PNB = $CH_2C_6H_4NO_2$-*p*



(8) X = S, R = Me

(9) X = O

(9a) X = O, R = Me

(9b) X = O, R = PNB

(9c) X = O, R = K (salt)

All compounds described are racemic; for convenience only one enantiomer is shown.

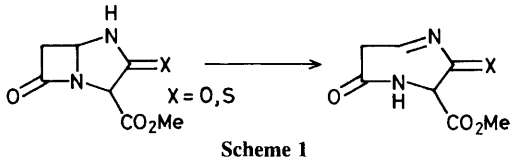
($BrCH_2CO_2Me$, dimethylformamide, K_2CO_3) at room temperature gave the azetidinone acetate (**5**). Subsequent chlorinolysis (Cl_2, CCl_4, −20 °C) gave the 4-chloroazetidinone which without purification was treated with KSCN (MeCN, 20 °C) to afford a mixture of the thiocyanate (**6**) and the isothiocyanate (**7**). Heating this mixture at 40 °C for 1 h caused complete (by n.m.r.) isomerisation of one compound into the other which we presumed to be the isothiocyanate.‡ Reaction with KSCN could, therefore, be performed at 40 °C with isolation of only the presumed isothiocyanate which was stable to normal handling and chromatography (silica), as an oil in 78% yield; ν($CHCl_3$) 2040, 1780, and 1750 cm^{-1}; δ ($CDCl_3$) *inter alia* 5.5 (dd, *J* 1.8 and 4.4 Hz, H-4).

Treatment of this compound with lithium hexamethyldisilazide (tetrahydrofuran, −78 °C) followed by quenching with acetic acid gave after chromatography (silica; ethyl acetate–hexane, 1:4) methyl 7-oxo-3-thioxo-1,4-diazabicyclo-[3.2.0]heptane-2-carboxylate (**8**) in 58% yield;§ ν($CHCl_3$) 1800 and 1750 cm^{-1}, δ($CDCl_3$) *inter alia* 5.2 (d, *J* 1.4 Hz, H-2) and 5.5 (quintet, *J* 1.4, 1.4, and 3.6 Hz, H-5). Homoallylic coupling between H-2 and H-5 through the partial double bond of the thioamide was clearly visible (1.4 Hz) and was confirmed by resonance decoupling experiments.

S-Alkylation of the thioamide (**8**) was conveniently achieved by treatment with methyl iodide (MeCN, K_2CO_3, 20 °C) to give the Δ^1-azapenem (**3**), m.p. 83—84.5 °C; ν($CHCl_3$) 1790 and 1755 cm^{-1}; δ($CDCl_3$) *inter alia* 5.6 (quintet, *J* 2.2, 2.8, and 4.9 Hz, H-5) and 5.2 (d, *J* 2.8 Hz, H-3), containing a

‡ At this stage we had no proof of the isothiocyanate structure for the product but it was assumed on the basis of the known thermal rearrangement of thiocyanates to isothiocyanates[6] and the subsequent reaction of the compound which is described.

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



Scheme 1

2-thio-substituent (penem nomenclature) as in thienamycin and related carbapenems. Homoallylic coupling was also observed between H-3 and H-5. An n.m.r. (250 MHz) study in various solvents (*e.g.* $CDCl_3$, CD_3CN, CD_3SOCD_3) showed no evidence of the presence of the Δ^2-isomer corresponding to compound (**3**), the limit of detection being about 1%. This would indicate a free energy difference of at least 2.6 kcal mol^{-1} (1 cal = 4.184 J) between the Δ^1-and Δ^2-forms, which may be compared with an equilibrium Δ^1 : Δ^2 isomer ratio of 3 : 1 for a related carbapenem derivative[7] corresponding to a free energy difference of 0.5 kcal mol^{-1} at 27 °C.

A deuterium exchange study of the Δ^1-azapenem (**3**) (CD_3CN–D_2O, *ca.* 10 : 1) indicated no significant exchange of H-3. Exchange could be observed in the presence of triethylamine but not pyridine (MeCN, D_2O, 29 °C, 5 min). Clearly there is no rapid equilibration between the Δ^1- and Δ^2-forms which would provide a mechanism for fast H-3 proton exchange.

Oxidation of the thioamide moiety of (**8**) with benzeneseleninic anhydride[8] (tetrahydrofuran, 0 °C) gave methyl 3,7-dioxobicyclo[3.2.0]heptane-2-carboxylate (**9a**), a bicyclic β,γ-lactam, in *ca.* 20% yield; ν($CHCl_3$) 1800, 1752, and 1740 cm^{-1}, δ($CDCl_3$) 3.07 (dd, *J* 17 and 1 Hz, H-6), 3.55 (dd, *J* 17 and 3.2 Hz, H-6), 4.83 (s, H-2), and 5.25 (dd, *J* 3.2 Hz and 1 Hz, H-5).

Monocyclic azetidinones with a C-4 substituent possessing an acidic hydrogen, such as OH[9] or SH,[10] are known to undergo readily C-4,N-1 bond cleavage. It is interesting, therefore, that compounds (**8**) and (**9**) show no propensity for β-lactam cleavage of the type shown in Scheme 1. One can only assume that good orbital alignment between the N-1–C-5 bond and the nitrogen lone pair cannot occur owing to the geometrical constraints imposed by the rigid [3.2.0] bicyclic ring system.

Via the *p*-nitrobenzyl ester (**9b**) the potassium salt form (**9c**) of the β,γ-lactam was prepared (10% Pd/C, H_2, 50 lb in^{-2}, EtOAc–H_2O, $KHCO_3$, 20 °C) but showed no interesting biological properties.

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