An Unexpected Outcome of the Reaction of a Racemic Carbapen-1-em with Osmium(VIII) Oxide

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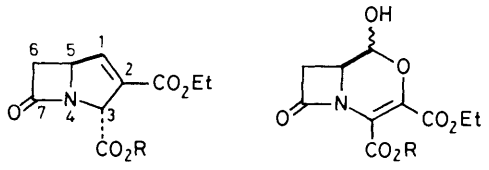
t-Butyl 2-ethoxycarbonylcarbapen-1-em-3-*exo*-carboxylate (**1a**) reacts with osmium(VIII) oxide to give t-butyl (1*SR*,5*SR*,7*RS*,8*RS*)-1-ethoxycarbonyl-8-hydroxy-2-oxa-6-azabicyclo[3.2.1]octane-7-carboxylate (**7a**).

Recently, we described[1] a simple synthesis of carbapenems of the type (**1**). As part of a programme aimed at utilising these heterocycles as precursors of novel bicyclic β-lactam derivatives, we considered the possibility of deriving iso-oxacephems of the type (**2**). It was envisaged that osmium(VIII) oxide would react with carbapenems of the type (**1**) to give *cis*-diols of the type (**3**) (the *cis*-hydroxylation was expected to occur from the *exo*-face since this appeared to be least hindered). An oxidative cleavage of the diol system would then generate intermediates of the type (**4**) which were expected to cyclise spontaneously to target systems of the type (**2**). We now report an unexpected outcome in our attempts to reduce this plan to practice.

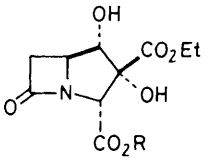
When treated with osmium(VIII) oxide (1 mol. equiv.) in pyridine (using a $Na_2S_2O_5$ work-up), the carbapenem (**1a**) was converted into compound A, m.p. 121 °C, in 82% yield (after SiO_2 chromatography and recrystallisation). Analytical evidence indicated that the product was derived from the starting material by the addition of the elements of H_2O_2. Although its i.r. spectrum [ν_{max} (KBr) *inter alia* 3 420br., 3 320, 1 775, 1 750, and 1 720 cm^{-1}] was in accord with the diol structure (**3a**), the ^{1}H-n.m.r. spectrum of compound A [δ (360 MHz, $CDCl_3$) *inter alia* 2.59 (1H, dd, *J* 19 and 2.5 Hz), 2.83 (1H, dd, *J* 19 and 8 Hz), 4.32 (1H, ddd, *J* 8, 6, and 2.5 Hz), and 3.82 (1H, s)] showed significant differences from that of the known carbapenam (**5**)[2] [δ ($CDCl_3$) *inter alia* 2.66 (1H, dd, *J* 15.5 and 2 Hz, 6β-H), 3.05 (1H, dd, *J* 15.5 and 5 Hz, 6α-H), 3.75 (1H, dd, *J* 5 and 2 Hz, 5-H), and 4.48 (1H, d, *J* 4.5 Hz, 3-H)].

Compound A reacted with lead(IV) acetate (1 mol. equiv.) in dichloromethane to give compound B, m.p. 140—141 °C, in 61% yield after recrystallisation. Compound B possessed the constitution expected for the iso-oxacephem (**2a**). How-

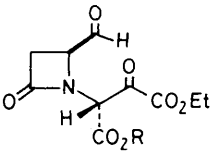


(1)
a; R = Bu^t

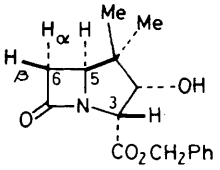
(2)
a; R = Bu^t



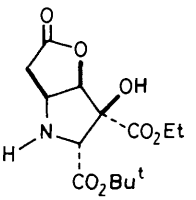
(3)
a; R = Bu^t



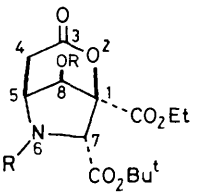
(4)



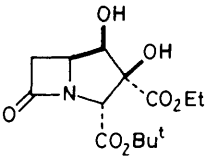
(5)



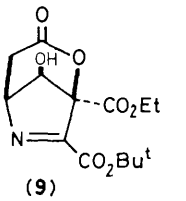
(6)



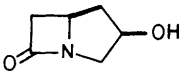
(7)
a; R=H
b; R=MeC(=O)



(8)



(9)



(10)

ever, although its i.r. spectrum [ν_{max} (KBr) *inter alia* 3 400, 1 785, 1 725, and 1 710 cm^{-1}] was compatible with this formulation, its ^{1}H-n.m.r. spectrum [δ (360 MHz, $CDCl_3$) *inter alia* 2.82 (1H, dd, *J* 19 and 4 Hz), 3.02 (1H, dd, *J* 19 and 9 Hz), and 5.01—5.06 (1H, m)] and u.v. spectrum [λ_{max} (EtOH) 225 (ϵ 560) and 250 nm (150)] were not.[3]

A further examination of compound A revealed that it was a basic material and that it gave a crystalline salt (55% yield after recrystallisation), m.p. 120—128 °C (with softening at 82 °C), with toluene-*p*-sulphonic acid in acetone–ether. This excluded the carbapenam structure (**3a**) and suggested that compound A was either the fused γ-lactone (**6**) or the fused δ-lactone (**7a**). Evidently, the *cis*-hydroxylation had occurred from the *endo*-face of the carbapenem (**1a**) to give the *cis*-diol (**8**), which had spontaneously rearranged to the product, *i.e.* either (**6**) or (**7a**).

It is well established that γ- and δ-lactones absorb in the i.r. region at *ca.* 1 770 and 1 745 cm^{-1}, respectively.[4] Accordingly, the fused γ-lactone (**6**) appeared to be the favoured structure for compound A. However, on the basis of Dreiding models, the tertiary alcohol moiety of the intermediate diol (**8**) is better disposed to interact with the β-lactam carbonyl function. Consequently, the δ-lactone structure (**7a**) was preferred over its γ-lactone counterpart (**6**).† In support of this formulation, compound A reacted with acetic anhydride in pyridine to give a diacetate (90% yield after SiO_2 chromatography), m.p. 135—136 °C (with softening at 101 °C) in which the oxygenated methine proton appeared as two doublets‡ (each 0.5H, *J* 6 Hz) at δ 5.40 and 5.50 in the 360 MHz ^{1}H-n.m.r. spectrum ($CDCl_3$). The downfield shift of the oxygenated methine proton upon acetylation [that of the precursor appeared as a doublet (*J* 6 Hz) at δ 4.84 ($CDCl_3$)] is indicative[5] of the presence of a secondary alcohol function in the precursor. Hence, the diacetate is considered to possess the structure (**7b**) and compound A the structure (**7a**).

On the basis of the structure (**7a**) proposed for compound A, compound B is formulated as the pyrroline (**9**).

The aforementioned results are of interest in a number of respects. First, the formation of a rearranged structure in an osmium(VIII) oxidation is unusual and, in the present case, it provides a useful and novel route to 3,5-functionalised derivatives of *trans*-4-hydroxyproline, an amino acid of biochemical and synthetic interest.[6] Secondly, the results reveal a surprising directing effect in the attack of osmium(VIII) oxide on the C=C bond of a carbapenem and imply that compounds incorporating the structural feature (**10**) may be unstable. Finally, although lead(IV) acetate has been used to convert dibenzylamine into *N*-benzylidenebenzylamine (in low yield),[7] we are unaware of its application in effecting the dehydrogenation of compounds incorporating the NH–CH(CO_2R) moiety.

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† The oxygenated methine proton of compound A showed no coupling with the hydroxy proton.

‡ The duplication of this signal (and of others in the spectrum) is attributed to compound (**7b**) existing in solution as two rotameric forms, owing to restricted rotation about the amide linkage.

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