β-Lactam-cleavage Reactions of Isopenam-3-carboxylates and their 2,2-Dioxides

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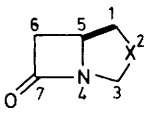
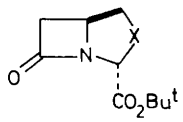
β-Lactam-cleavage reactions of the 3-*exo*- and 3-*endo*-isomers of t-butyl isopenam-3-carboxylate, *i.e.* (**2a**) and (**3a**), and of 3-t-butoxycarbonylisopenam 2,2-dioxide, *i.e.* (**2b**) and (**3b**), induced by trifluoroacetic acid, are not accompanied or followed by 2,3-bond ruptures.

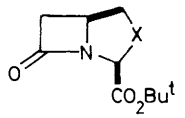
The lethal action of the β-lactam antibiotics against bacteria is associated with the cleavage of the azetidinone linkage by an enzymic nucleophile.[1] A knowledge of the factors which influence such reactions is of fundamental importance and may aid the chemist who seeks to design more effective antibacterial agents. In bicyclic β-lactams of type (**1**) there is the possibility that the rupture of the X(2)–C(3) bond accompanies[2,3] or follows the cleavage of the N(4)–C(7) bond. We



(1)

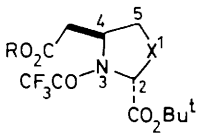


(2)

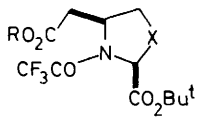


(3)

a; X = S
b; X = SO_2
c; X = O

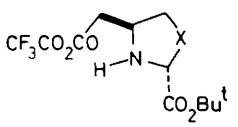


(4)

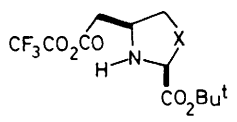


(5)

a; R = Me, X = S
b; R = H, X = S
c; R = Me, X = SO_2
d; R = H, X = SO_2
e; R = H, X = O

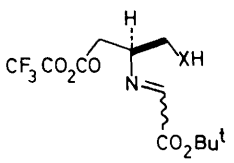


(6)



(7)

a; X = S
b; X = SO_2



(8)

a; X = S
b; X = SO_2

now report that such processes do not contribute significantly to trifluoroacetic acid induced β-lactam-cleavage reactions involving substrates of the type (**1**; X = S and SO_2).

Recently, two of us described the synthesis, in racemic form, of the isopenams (**2a**) and (**3a**).[4] When trifluoroacetic acid (1 mol. equiv.) was added to a deuteriochloroform solution of the isopenam (**2a**), an acidic material was formed. Following esterification with diazomethane and fractionation of the product by silica-gel chromatography, a homogeneous syrup was isolated in 58% yield. The material, of constitution $C_{13}H_{18}F_3NO_5S$ by high-resolution mass spectroscopy, was formulated as the thiazolidine (**4a**) on the basis of its spectroscopic properties. In particular, the compound showed a strong i.r. absorption at 1 695 cm^{-1}, attributable to the amide-carbonyl group. 360 MHz ^1H N.m.r. spectroscopy suggested that the thiazolidine (**4a**) was present in deuteriochloroform as a 1.5 : 1 mixture of rotamers, owing to restricted rotation about the amide bond; for example, there were two signals for the C-2 proton of the thiazolidine ring [δ 5.10 (0.4 H) and 5.22 (0.6 H)]. Evidently, the reaction of the isopenam (**2a**) with trifluoroacetic acid had led to the acid (**4b**).

When allowed to react sequentially with trifluoroacetic acid and diazomethane, the isopenam (**3a**) was converted into the thiazolidine (**5a**) (82% yield after SiO_2 chromatography), m.p. 112—114 °C, ν_{max} (KBr) *inter alia* 1 700 cm^{-1} (amide C=O). 360 MHz ^1H N.m.r. spectroscopy established that the compound was present in deuteriochloroform as a 2 : 1 mixture of rotamers; thus there were two signals for the C-2 proton of the thiazolidine ring [δ 5.38 (0.66 H) and 5.48 (0.33 H)]. Clearly, the acid (**5b**) was the product of the reaction of the isopenam (**3a**) with trifluoroacetic acid.

Presumably, the formation of the acids (**4b**) and (**5b**) involves attack of trifluoroacetic acid at the β-lactam carbonyl groups of the isopenams (**2a**) and (**3a**) to give the mixed anhydrides (**6a**) and (**7a**) as intermediates. Although an analogous reaction was observed with the isoclavam (**2c**) [to give the acid (**4e**)],[3] the present results establish that the β-lactam cleavage is not accompanied by the formation of the imine thiol (**8a**).

Earlier it was reported[4] that the isopenam dioxide (**2b**) was obtained from the isopenam (**2a**) or a 1 : 1 mixture of the isopenams (**2a**) and (**3a**) by oxidation with potassium permanganate. However, in the present study, the isopenam dioxide (**3b**), m.p. 144—145 °C, was isolated in 50% yield after recrystallisation from the oxidation of the isopenam (**3a**).

The isopenam dioxide (**2b**), after reaction with trifluoroacetic acid followed by diazomethane, was converted into a material (64% yield after recrystallisation) of constitution $C_{13}H_{18}F_3NO_7S$. A substance (36% yield after recrystallisation) of identical constitution was isolated from the reaction of the thiazolidine (**4a**) with potassium permanganate. Although the samples differed in their m.p.s (118—120 °C for the former and 111—114 °C for the latter) and their solid-state i.r. spectra [ν_{max} (KBr) *inter alia* 1 745, 1 735, and 1 695 cm^{-1} for the former and 1 725 cm^{-1} for the latter], they were identical by 250 MHz ^1H n.m.r. spectroscopy. In addition to corroborating the structure (**4c**), ^1H n.m.r. spectroscopy indicated that the compound was present in deuteriochloroform as a major rotamer (δ 5.13 for the C-2 proton of the thiazolidine ring). Presumably, the different physical properties of the samples are to be ascribed to different rotamers in the crystals.

When allowed to react sequentially with trifluoroacetic acid and diazomethane, the isopenam dioxide (**3b**) was transformed into the thiazolidine dioxide (**5c**) (62% yield after recrystallisation), m.p. 113—114 °C, ν_{max} (KBr) *inter alia* 1 745 and 1 720 cm^{-1}. The material, which was identical to that obtained (82% yield after recrystallisation) by oxidation of the thiazolidine (**5a**) with potassium permanganate, was considered to exist in deuteriochloroform as a 4 : 1 mixture of rotamers [δ 5.18 (0.8 H) and 5.36 (0.2 H)] by 250 MHz ^1H n.m.r. spectroscopy.

On the basis of the foregoing results, it is clear that the acids (**4d**) and (**5d**) are the respective products of the reactions of the isopenams (**2b**) and (**3b**) with trifluoroacetic acid. Evidently, the intermediates (**6b**) and (**7b**), which are implicated, undergo intramolecular acyl transfers to give the acids (**4d**) and (**5d**) faster than isomerisations to the imine sulphinic acid (**8b**).

Although, to our knowledge, *N*-unsubstituted thiazolidine dioxides have never been isolated or detected (presumably,

because of the ease with which they undergo ring-chain tautomerisation), the present results provide compelling evidence for their fleeting existence.

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