A New Oxidative Two-atom Expansion of the β-Lactam Ring of a 6β-Aminopenicillanate

John Steele and Richard J. Stoodley*

Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU, U.K.

Methyl 6*β*-(dihydro-4*H*-1,3,5-dioxazin-5-yl)penicillanate is converted into methyl (6*S*,9*S*)-8,8-dimethyl-2-oxo-5-oxa-7-thia-1,4-diazabicyclo[4.3.0]non-3-ene-9-carboxylate by the action of potassium permanganate in aqueous acetic acid.

Recently, we have shown[1] that penicillanate 1,1-dioxides, *e.g.* (**1a**), react by an epimerisation–*β*-elimination sequence, in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene, to give azetidinonesulphinic acids, *e.g.* (**2**). In the hope that it would undergo the *β*-elimination reaction without epimerisation, we attempted to prepare the sulphone (**1b**). We now report an unprecedented rearrangement which occurred as a consequence of oxidation of the penicillanate (**3a**) with potassium permanganate.

When the acid (**3b**) was stirred with 41% aqueous formaldehyde–ether and the crude product (isolated from the ether layer) treated with diazomethane, the penicillanate (**3a**), m.p. 125—127 °C, $[\alpha]_D$ +233° (EtOH), was obtained (51% after SiO_2 chromatography).

The penicillanate (**3a**) reacted with potassium permanaganate (2.2 mol. equiv.) in 80% aqueous acetic acid (conditions that are usually effective for transforming penicillanates into penicillanate 1,1-dioxides[2]) to give compound *A* (56% after SiO_2 chromatography), m.p. 149—151 °C, $[\alpha]_D$ −310° (EtOH). The constitution of compound *A*, as $C_9H_{12}N_2O_4S$, was established by elemental analysis and mass spectroscopy. Spectroscopic considerations revealed the presence of a $-CO_2Me$ group [ν_{max} 1 750 cm^{-1}; δ_H 3.78 (3H, s); δ_C 52.7 (q) and 168 p.p.m. (s)], an unstrained $-C(O)N<$ moiety [ν_{max} 1 690 cm^{-1}; δ_C 151 p.p.m. (s)], and a $-CH{:}N-$ function [δ_H 7.76 (1H, s); δ_C 147 p.p.m. (d)], suggesting that compound *A* was bicyclic. Additionally, compound *A* incorporated a CMe_2 moiety [δ_H 1.47 and 1.70 (2 × 3H, s); δ_C 23.6 and 33.5 (2 × q), and 53.9 p.p.m. (s)] and two CH groups [δ_H 4.80 and 6.52 (2 × 1H, s); δ_C 69.9 and 95.1 p.p.m. (2 × d)]. In common with the penicillanate (**3a**), compound *A* showed in the mass spectrum a base peak at *m/z* 174 attributable to the ion (**4**). On the basis of the foregoing information, compound *A* was considered to possess either the structure (**5**) or (**6**).

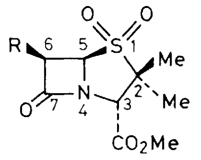
In the hope of differentiating between the two structures, compound *A* was treated with sodium borohydride in ethanol. Following silica gel chromatography a dihydro-derivative, m.p. 134—136 °C (decomp.), $[\alpha]_D$ +44° (EtOH), was isolated (81%). The 360 MHz ^1H n.m.r. spectrum of this material indicated that it possessed the structure (**7a**). In particular, the chemical shift of the bridgehead proton (δ 6.68) was very similar to that of compound *A* (δ 6.52); furthermore, the methylene proton at δ 4.07 was coupled (*J* 8 Hz) to the amino-proton at δ 6.24, as well as (*J* 16 Hz) to the methylene proton at δ 3.67.

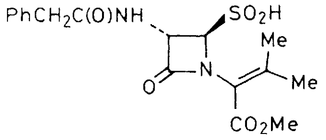
It is well established that *N*- and *O*-acylhydroxylamines can be differentiated by i.r. spectroscopy.[3] Corroboratory evidence that the dihydro-derivative possessed the structure (**7a**) was deduced by its conversion into the *N*-acetyl compound (**7b**) (96%), m.p. 167—169 °C (decomp.), $[\alpha]_D$ −26° (EtOH) [ν_{max} 1 750 (ester CO), 1 680, and 1 665 cm^{-1} (amide CO)], in the presence of acetic anhydride and pyridine.

On the basis of the aforementioned evidence, the structure (**5**) must be assigned to the product of oxidation of the penicillanate (**3a**) with potassium permanganate (*i.e.*, compound *A*).

One feature of the oxathiadiazabicyclononene derivative (**5**), *i.e.* the stereochemistry of the bridgehead methine group, remained to be established. Although no diagnostic effects were observed with the compound (**5**), nuclear Overhauser effect (n.O.e.) experiments with the derived sulphone, m.p. 123—125 °C, $[\alpha]_D$ −260° (EtOH) [prepared (98%) by oxidation of the compound (**5**) with potassium permanganate] suggested that it possessed the stereostructure (**8a**). Thus the intensity of the 9-proton at δ 4.86 was increased by 10% when the methyl group at δ 1.51 was irradiated and by 2% when the methyl group at δ 1.60 was irradiated; on this evidence, the signal at δ 1.51 was assigned to the 8β-methyl group. The intensity of the 6-proton at δ 5.91 was unaffected by irradiation of the 8β-methyl group but was increased by 2% when the 8α-methyl group was irradiated.

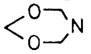
The conversion of the penicillanate (**3a**) into the oxathiadiazabicyclononene derivative (**8b**) provides a rare example of a penicillanate rearrangement involving rupture of the 5,6-bond.[4] Loss of the *N*-protecting group probably does not occur until after oxidation of the nitrogen atom since, under the reaction conditions, the amine (**3c**)[5] was not converted into the compound (**8b**).



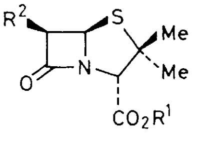


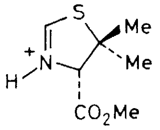
(**1**) a; R = $PhCH_2C(O)NH$

b; R =

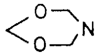


(**2**)





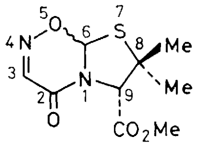
(**3**) a; R^1 = Me, R^2 =

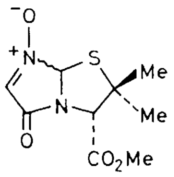


b; R^1 = H, R^2 = NH_2

c; R^1 = Me, R^2 = NH_2

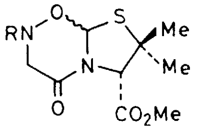
(**4**)

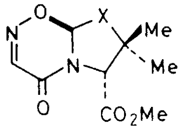




(**5**)

(**6**)

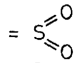




(**7**) a; R = H

b; R = MeCO

(**8**) a; X =



b; X = S

It is noteworthy that the dihydro- and tetrahydro-oxadiazinone rings, present respectively in the compounds (**7**) and (**8a,b**), are hitherto unknown entities. Furthermore, the array of reactive functionality incorporated into the compounds, in addition to ensuring diverse chemistry, is likely to be exploitable in a synthetic context.

We thank the S.E.R.C. for a research studentship (to J. S.) and Dr. I. H. Sadler (Edinburgh University) for performing the n.O.e. experiments.

Received, 30th July 1982; Com. 900

References

1 C. M. Pant, J. Steele, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans.* 1, 1982, 595.

2 A. W. Chow, N. M. Hall, and J. R. E. Hoover, *J. Org. Chem.*, 1962, **27**, 1381.

3 W. Jencks, *J. Am. Chem. Soc.*, 1958, **80**, 4581; O. Exner and B. Kakac, *Collect. Czech. Chem. Commun.*, 1960, **25**, 2530.

4 R. J. Stoodley, *Tetrahedron*, 1975, **31**, 2321; J. Nakano, H. Kando, Y. Nakamura, M. Nakata, and M. Tomita, *Tetrahedron Lett.*, 1976, 2797; D. I. John, N. D. Tyrrell, E. J. Thomas, P. H. Bentley, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1982, 76.

5 B. K. Koe, *Nature*, 1962, **195**, 1200.