On the Reduction of β-Lactams with Diborane

Peter G. Sammes* and Steven Smith

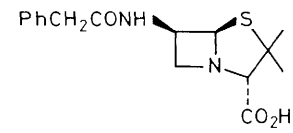
Department of Organic Chemistry, The University, Leeds LS2 9JT, U.K.

Reduction of β-lactams and penicillins with diborane produces 1,3-amino-alcohols and not, as previously reported, azetidines.

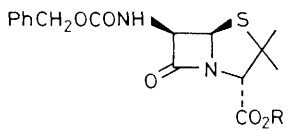
As part of a programme studying carrier–receptor proteins involved in penicillin allergy, Nataraj *et al.* described the preparation of 7-deoxy-penicillin G (**1**).[1] Because of our current interest in β-lactamase inhibition,[2] use of compound (**1**) as a competitive inhibitor was contemplated and occasioned a re-investigation of the previous work.

In place of the starting benzyl ester (**2**) used in the route of Nataraj *et al.* we employed the benzhydryl ester (**3**).† Reduction of (**3**) with diborane (generated externally) was carried out in dry tetrahydrofuran at −10 °C, and after quenching with saturated ammonium chloride, ether extraction, and chromatography through silica gel, the reaction afforded one major product (35%), which did not analyse as the ester of the azetidine (**1**) but as the amino-alcohol (**4**) [ν_{max} ($CHCl_3$) 3425, 3345, and 1720—1730 cm^{-1}; δ ($CDCl_3$) 0.99 (3H, s, Me), 1.56 (3H, s, Me), 3.9—3.5 (4H, m, CH_2OH, 3-*H*, 6-*H*), 4.79 (1H, d, *J* 7 Hz, 5-*H*), 5.09 (2H, s, $PhCH_2O$), 5.60 (1H, br. s, N*H*), 6.95 (1H, s, Ph_2CH), and 7.1—7.5 (15H, m, aromatic)]. Amongst other products the reduction produced a small quantity of benzhydryl alcohol and the thiazolidine (**5**) (24%). No evidence for formation of the expected azetidine could be found. The products (**4**) and (**5**) can arise by the process depicted in Scheme 1, in which ring opening is preferred to iminium ion formation and subsequent reduction. The amino-alcohol (**4**) was further characterised by benzoylation, which gave the *O*-benzoate (**6**); lack of *N*-benzoylation reflects the extremely weak basicity of the thiazolidine nitrogen.[3] The amino-alcohol (**4**) also formed a non-crystalline hydrochloride, initial $[\alpha]_D$ +82.7° (*c* 1.0, MeOH), for which epimerisation at position 5 in methanol[4] leads to mutaroration, $[\alpha]_D^{21}$ + 55.2° after 5 h.

† All new compounds gave satisfactory microanalytical and spectroscopic data.

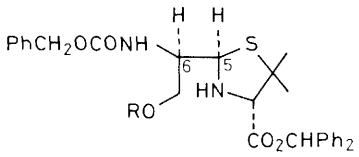


(1)



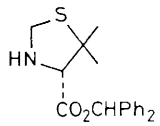
(2) R = $PhCH_2$

(3) R = Ph_2CH

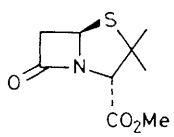


(4) R = H

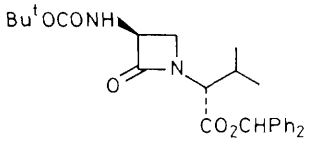
(6) R = PhCO



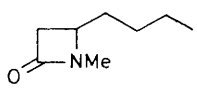
(5)



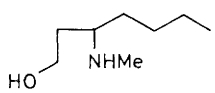
(7)



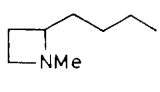
(8)



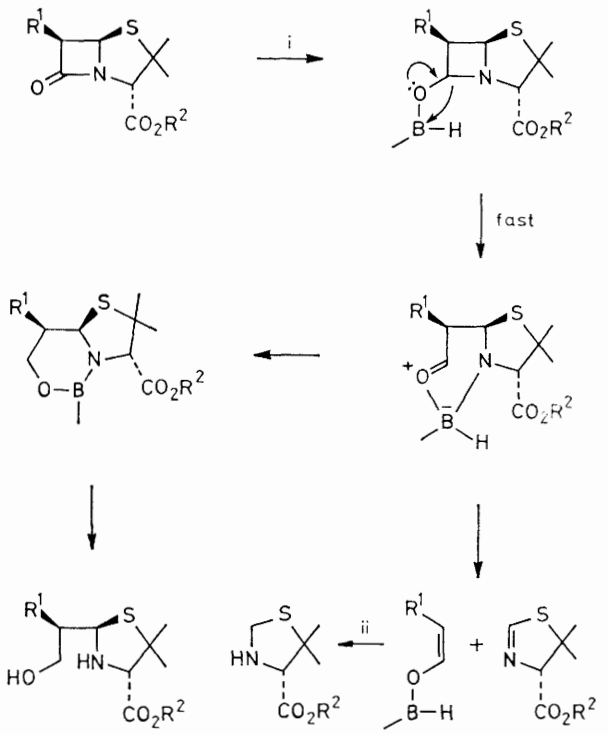
(9)



(10)



(11)



Scheme 1. *Reagents:* i, B_2H_6; ii, B_2H_6 and work-up.

In order to check that formation of the amino-alcohol of type (**4**) was not confined to the diborane reduction of penicillin, the β-lactam derivatives (**7**), (**8**), and (**9**) were also examined. In each case the principal product was the amino-alcohol, in yields of 72, 22, and 78% respectively, rather than the corresponding azetidine. Use of methyl penicillinate (**7**) illustrates that absence of the carbamate side chain does not adversely influence the course of the reduction, whilst use of the monocyclic β-lactams (**8**) and (**9**) indicates that the reaction path leading to amino-alcohols is general and not limited to fused systems. In the reduction of the simple β-lactam (**9**) the reaction products were compared with an authentic sample of the corresponding azetidine, prepared by cyclisation of the amino-alcohol (**10**). None of the azetidine (**11**) was detected amongst the diborane reduction products of the azetidinone (**9**). Furthermore, the azetidine (**11**) was unaffected by exposure to the standard diborane reduction work-up conditions.

We conclude that diborane reduction of β-lactam derivatives results in the formation of 1,3-amino-alcohols rather than azetidines.

We thank Hoeschst (U.K.) Ltd., and the S.E.R.C. for a CASE Studentship (to S.S.), and Dr. S. Petursson (Sir William Dunn School of Pathology, University of Oxford) for providing details of his results in this area before publication.

Received, 2nd August 1982; Com. 907

References

1 C. V. Nataraj, C. Mandal, and P. K. Bhattacharyya, *Proc. Indian Acad. Sci., Sect. A*, 1978, **87**, 1; F. A. Jang, W. R. Pilgrim, J. P. Poyser, and P. J. Siret, 'Topics in Antibiotic Chemistry,' ed. P. G. Sammes, Ellis Horwood Ltd., Chichester, 1980, vol. 4, p. 217.

2 V. Knott-Hunziker, S. G. Waley, B. S. Orlek, and P. G. Sammes, *FEBS Lett.*, 1979, **99**, 59; B. S. Orlek, P. G. Sammes, V. Knott-Hunziker, and S. G. Waley, *J. Chem. Soc., Perkin Trans.* 1, 1980, 2322.

3 'The Chemistry of Penicillins,' eds. H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, Princeton, New Jersey, 1949, p. 1944.

4 J. J. Herak, M. Kovačević, and B. Gaspert, *Croat. Chem. Acta*, 1978, **51**, 265; C. A. Schneider and A. L. DeWeck, *Helv. Chim. Acta*, 1967, **50**, 2011.