6α-Deuteriopenicillin. Steric Control of Fast Reversible Protonation[1]

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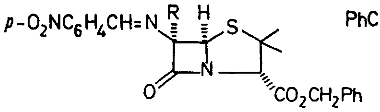
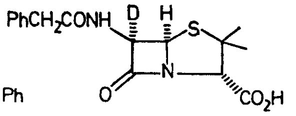
Summary Even under equilibrating conditions, steric control of deuterium approach to the anion (V) gives the thermodynamically less stable isomer (I) as the principal product.

MANY electronegative groups have been introduced at the 6-position of the penicillin nucleus utilizing Schiff bases such as (I).[2] The simplest substituent would be deuterium, and since the bioactivity of 6α-deuteriopenicillin (IV) might be significantly different from that of normal penicillin, we have investigated its synthesis.



(I) R = H
(II) R = Li
(III) R = D



(IV)

However, when (I) was converted into (II) with phenyllithium in tetrahydrofuran (THF) at −78 °C and then treated with 99·5% D_2O containing CD_3CO_2D, the 6α-protio-compound (I) was recovered, with at most a few percent of the 6α-deuterio Schiff base (III).[3] The reagents and technique were the same as those described previously.[2a,2b,4] We believed that (II) was formed under these conditions, because (i) the difference in pK_a between benzene and (I) must be *ca.* 30,[5] (ii) the reaction between (I) and phenyl-lithium is visible in that an intense blue colour appears instantaneously, and (iii) although (III) is sluggish toward weak electrophiles such as methyl iodide without activation by *e.g.*, $HCONMe_2$, it reacts rapidly with stronger electrophiles such as t-butyl hypochlorite[6] and *N*-bromosuccinimide[2c] to give the 6-halogeno-derivatives. Previous work had shown that (II) retains its configuration in THF since protonation gives back (I) and not the more stable 6-epimer (VI).[2a,4]†

Other workers had also obtained only recovered (I) and negligible amounts of (III), despite careful experimental techniques.[7] We therefore sought other conditions for the preparation of (III).

When (I) is treated with triethylamine at room temperature, equilibrium with a few percent of the anion (V) is rapidly established as shown by the pale blue colour, and within a few minutes, depending on the solvent, >85% of the thermodynamically more stable (VI) is obtained.[4] The reaction cannot be followed further because a second and

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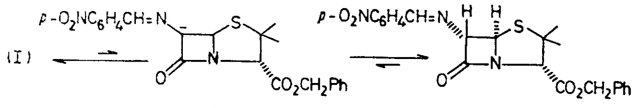
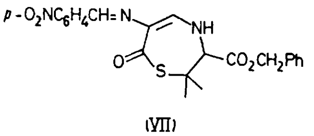
† Lithiated (VI) also retains its configuration in THF (ref. 2c).

irreversible isomerization to the thiazepine (VII) occurs almost as quickly as the equilibrium (I) ⇌ (VI).[4] Despite the greater stability of (VI), however, irreversible protonation of (V) under other conditions (THF–HCONMe$_2$, Li salt, −10 to −78 °C) favours (I) over (VI) by a 2:1 ratio,[4] doubtless owing to steric approach control.



(V) (VI)



(VII)

We now report that steric approach control of protonation also prevails under conditions of rapid equilibration. Treatment of (I) at room temperature for 5—10 s with Et$_3$N in acetonitrile containing a molar excess of D$_2$O afforded mixtures of (VI) and (I). Compound (VI), of course, was deuteriated because it passed through the anion (V). More interesting was the fact that recovered (I) was also deuteriated [*i.e.*, contained (III)] to varying extents, depending on reaction time. At 10% epimerization, there was 40—50% of (III) in recovered (I) + (III), and at *ca.* 40% epimerization > 70% (III). From these data it can be seen that protonation of anion (V) in acetonitrile at 25 °C occurs preferentially from the less hindered α face, giving (I) and (VI) in a *ca.* 4:1 ratio.

The latter mixture of (I), (III), (VI), and (VII) was converted into penicillin G by known methods,[4] with isomers separated *en route*, and in this way a sample of penicillin G containing > 70% of 6α-deuteriopenicillin (IV) was obtained. Its antimicrobial activity was similar to that of penicillin G itself.

It was possible to measure approximately the isotope effect for protonation of (V) to (VI). In an experiment taken to 45% epimerization in which the D:H ratio in the total proton pool, including the 6-H in (I), was 86·8:1, the D:H ratio in the epimerized product (VI) was 100:14·65. From this, the apparent $k_H/k_D = ca.$ 12·7, a minimum figure since some of the (VI) must have exchanged more than once. This is about twice the theoretical maximum of 6·9 expected from zero-point effects,[8] and would presumably be even larger if the transition state stood at the midpoint of the reaction co-ordinate.[9] Since (VI) with Et$_3$N gives only small amounts of (V) in equilibrium, the transition state for protonation of (V) should lie much closer to (V) than to (VI).[10] Such abnormally large isotope effects are usually ascribed to proton tunnelling.[11]

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[1] For previous paper in the series: 'Substituted Penicillins and Cephalosporins' see R. A. Firestone and B. G. Christensen, *J. Org. Chem.*, 1973, **38**, 1436.

[2] (a) R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Letters*, 1972, 375; (b) R. A. Firestone, N. Schelechow, and B. G. Christensen, *J.C.S. Chem. Comm.*, 1972, 1106; (c) L. D. Cama and B. G. Christensen, *Tetrahedron Letters*, 1973, 3505; (d) R. Reiner and P. Zeller, *Helv. Chim. Acta*, 1968, **51**, 1905; E. H. W. Bohme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, 1971, **93**, 4324; D. B. R. Johnston, S. M. Schmitt, R. A. Firestone, and B. G. Christensen, *Tetrahedron Letters*, 1972, 4917; G. H. Rasmusson, G. F. Reynolds, and G. E. Arth, *ibid.*, 1973, 145; W. A. Spitzer, T. Goodson, R. J. Smithey, and I. G. Wright, *J.C.S. Chem. Comm.*, 1972, 1138; H. E. Applegate, J. E. Dolfini, M. S. Puar, W. A. Slusarchyk, B. Toeplitz, and J. Z. Gougoutas, *J. Org. Chem.*, 1974, **39**, 2794.

[3] S. Marburg, personal communication.

[4] R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, 1974, **39**, 437.

[5] The pK_a of benzene is 43; A. Streitwieser, Jr., P. J. Scannon, and H. M. Niemeyer, *J. Amer. Chem. Soc.*, 1972, **94**, 7936. The pK_a of (I) is *ca.* 12—13 since it reacts slightly with triethylamine.

[6] Unpublished observations.

[7] The failure to deuteriate penicillin 6-enolates is not without precedent; S. Wolfe and W. S. Lee, *Chem .Comm.*, 1968, 242; S. Wolfe, W. S. Lee, and R. Misra, *ibid.*, 1970, 1067; P. L. Creger, *J. Amer. Chem. Soc.*, 1970, **92**, 1396; M. W. Rathke and A. Lindert, *ibid.*, 1971, **93**, 2318. Recent experiments also show unexpected behaviour of (II). Thus, (III) with PhLi in THF at −78 °C, followed by H$_2$O–AcOH, gave (III) and not (I). Therefore (II) is not simply a tight ion pair (R. Waack, M. A. Doran, E. B. Baker, and G. A. Olah, *J. Amer. Chem. Soc.*, 1966, **88**, 1272; R. Waack, L. McKeever, and M. A. Doran, *Chem. Comm.*, 1969, 117).

[8] K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713.

[9] F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265; R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, *A*, **294**, 273; E. F. Caldin and G. I. Tomalin, *Trans. Faraday Soc.*, 1968, **64**, 2823; S. B. Hanna, C. Jermini, H. Loewenschuss, and H. Zollinger, *J. Amer. Chem. Soc.*, 1974, **96**, 7222. However, see F. G. Bordwell and W. J. Boyle, Jr., *ibid.*, 1971, **93**, 512.

[10] M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, 1936, **32**, 1340; R. P. Bell, *Proc. Roy. Soc.*, 1936, *A*, **154**, 414; G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

[11] E. F. Caldin, *Chem. Rev.*, 1969, **69**, 135.