The Reduction of Thiazolium Salts with Sodium Borohydride

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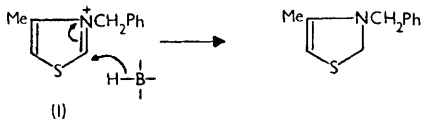
THIAMINE undergoes reduction at its thiazolium nucleus with sodium borohydride to yield either a di-[1] or tetra-hydro[2]-derivative depending on the solvent. We have used this reducing agent in aqueous solution to obtain tetrahydro-derivatives (thiazolidines) from a variety of thiazolium salts.[3]

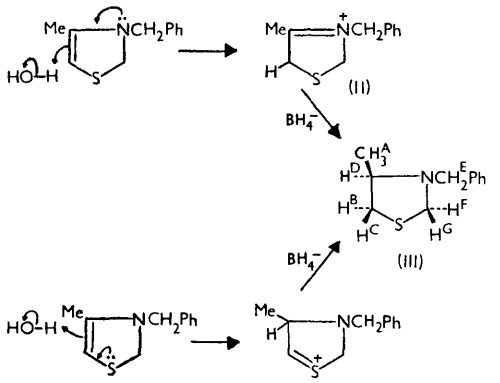
[1] H. Hirano, *J. Pharm. Soc. Japan*, 1958, **78**, 1387.
[2] G. E. Bonvicino and D. J. Hennessy, *J. Amer. Chem. Soc.*, 1957, **79**, 6325.
[3] G. M. Clarke and P. Sykes, unpublished results.

By analogy with the reaction pathways proposed for the reduction of pyridinium salts by hydride ion derived from sodium borohydride[4] or the formate ion,[5] the reduction of thiazolium cations could proceed by two alternative pathways. In both, initial attack by borohydride at the electron-deficient 2-position yields a dihydro-derivative (4-thiazoline):



(I)

This dihydro-derivative may then be protonated by the solvent either at C–5 or C–4:



Subsequent attack of borohydride on either cation gives the thiazolidine (III). Carrying the reduction out in deuterium oxide[6] will result in the introduction of one atom of deuterium into the thiazolidine, whichever pathway is followed. The position taken up by this deuterium atom will determine whether the lone pair involved in the protonation step is provided by nitrogen or sulphur.

We reduced 3-benzyl-4-methylthiazolium chloride in water and obtained 3-benzyl-4-methylthiazolidine (III). Its n.m.r. spectrum is reproduced in Fig. 1. The presence of the electronegative substituents and the flexibility of the ring do not allow unequivocal assignments of J_{BD} and J_{CD}, and hence τ_B and τ_C using the Karplus equation.

3-Benzyl-4-methylthiazolium bromide exchanges its hydrogen atom at C–2 for deuterium when dissolved in deuterium oxide.[7] We reduced this thiazolium salt under two sets of conditions. In the first experiment, the solution of the thiazolium salt in deuterium oxide was left standing at room temperature for 46 hours to allow the exchange at C–2 to go to completion before the sodium borohydride was added. The n.m.r. spectrum of the resultant dideuterated 3-benzyl-4-methylthiazolidine is reproduced in Fig. 2. In the second experiment, the reducing agent was added 5 minutes after the thiazolium salt was dissolved in the deuterium oxide. The mass spectrum of the product showed that it was a mixture of mono- (~2 parts) and di-deuterated (~1 part) 3-benzyl-4-methylthiazolidine. Its n.m.r. spectrum is identical with that of the dideuterated thiazolidine obtained in the first experiment except in the τ6 region and this part of the spectrum is reproduced as the upper curve in Fig. 2 (as well as the τ6·9—7·6 region).

In the spectrum of the dideuterated product of the first experiment (Fig. 2, lower) the AB quartet at τ ~6 has given way to two broad singlets corresponding to hydrogen in the 2-position *cis* and *trans* to the 4-methyl group; the broadening is due to geminal H–D coupling.[8] In the spectrum of the product from the second experiment (Fig. 2, upper), the broad singlets due to the dideuterated product may be seen under the quartet due to the monodeuterated product.

The coupling constant for the splitting of the resonance due to the 4-methyl group is exactly the same as in the undeuterated thiazolidine. If the deuterium had entered at position-4, one would expect a coupling constant of only ~1c./sec.[8] The eight lines of the AB position of the ABX system of the undeuterated thiazolidine in the τ6·9—7·6 region (Fig. 1) have given way to two broad doublets corresponding to hydrogen in the

[4] R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Tetrahedron Letters*, 1962, 533; P. S. Anderson and R. E. Lyle, *ibid.*, 1964, 153.

[5] O. Červinka and O. Kříž, *Coll. Czech. Chem. Comm.*, 1965, **30**, 1700.

[6] The hydrogen of sodium borohydride does not exchange with the deuterium of deuterium oxide. (P. R. Girardot and R. W. Parry, *J. Amer. Chem. Soc.*, 1951, **73**, 2368).

[7] R. Breslow, *J. Amer. Chem. Soc.*, 1957, **79**, 1762.

[8] Splittings due to H–D coupling are $\frac{1}{6{\cdot}55}$ times the splittings due to corresponding H–H coupling. (H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, 1959, **31**, 1278).

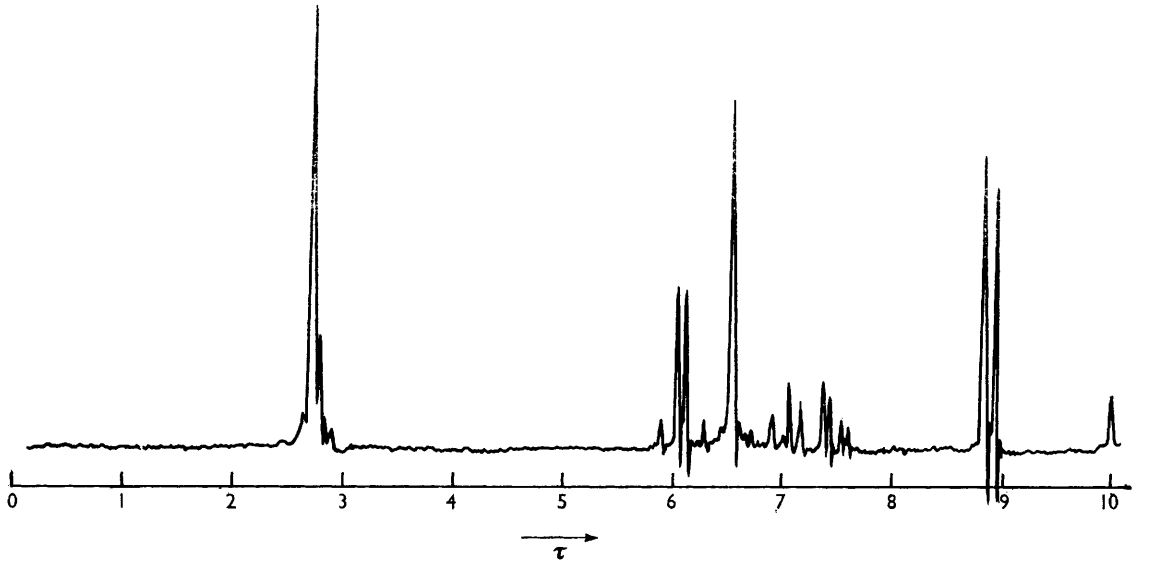


FIGURE 1. 60 *Mc./sec. n.m.r. spectrum of* 3-*benzyl*-4-*methylthiazolidine* (*III*). $\tau_A = 8{\cdot}89$, $\tau_B = 7{\cdot}45$ *or* $7{\cdot}04$, $\tau_C = 7{\cdot}45$ *or* $7{\cdot}04$, $\tau_D = \sim 6{\cdot}5$, $\tau_E = 6{\cdot}54$, $\tau_F = 6{\cdot}16$ *or* $6{\cdot}02$, $\tau_G = 6{\cdot}16$ *or* $6{\cdot}02$.

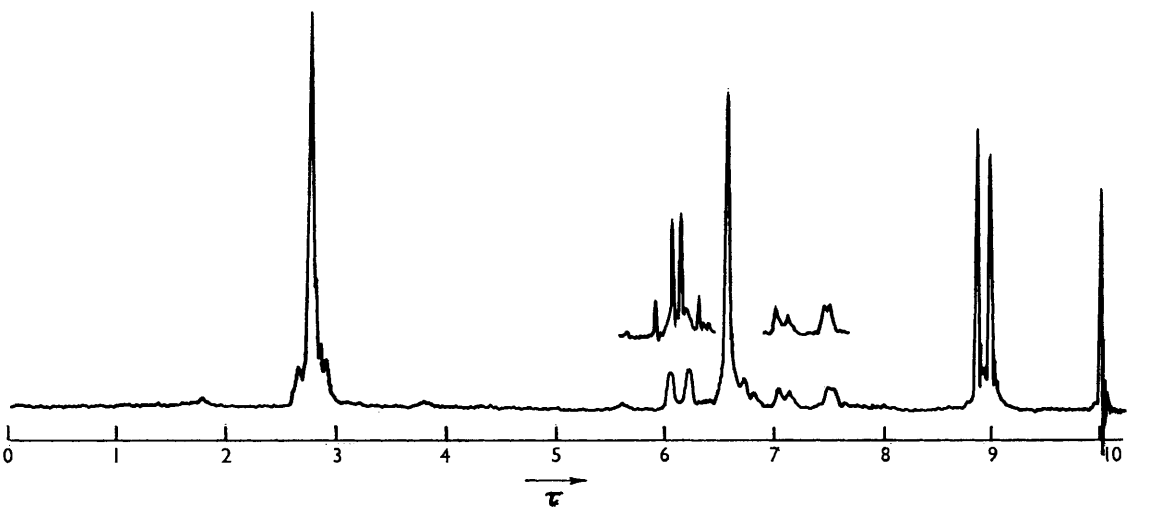


FIGURE 2. 60 *Mc./sec. n.m.r. spectrum of dideuterated* 3-*benzyl*-4-*methylthiazolidine* (*lower curve*) *and part of* 60 *Mc./sec. n.m.r. spectrum of mixture of mono- and di-deuterated* 3-*benzyl*-4-*methylthiazolidine* (*upper curve*).

5-position *cis* and *trans* to the 4-methyl group, split by the hydrogen on C–4; the broadening is again due to geminal H–D coupling.

Integration of the n.m.r. spectra shows that the *cis*- and *trans*-isomers at both C–2 and C–5 are present in equal amounts. This was to be expected in view of the symmetry of the thiazolium cation (I) and the cation (II).

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