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REDUCTION OF PYRIDAZINE COMPOUNDS WITH SODIUM BOROHYDRIDE

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Reduction of heterocyclic compounds using complex metal hydrides is a recent advance in heterocyclic chemistry[1] and affords a route towards obtaining saturated nitrogen heterocycles. We wish to report here the first examples of the reduction of pyridazine compounds and the mechanism of their reduction. Using sodium borohydride, $NaBH_4$, we have obtained the tetrahydroderivatives (IIa-c) from bicyclic azolopyridazines with a bridgehead nitrogen (Ia-c).

The reaction mixture, comprising the compound and $NaBH_4$ (10 molar equivalents) in ethanol, was heated under reflux, cooled, and the unreacted $NaBH_4$ decomposed with dilute acid. It was then made basic with NaOH, evaporated to dryness under reduced pressure and the residue extracted with chloroform. Evaporation of the solvent yielded the tetrahydro-derivatives, IIa-c, as a clean crystalline residue in high yields.

IIa, m.p. 115-116° was obtained in 72 % yield after 4.5 hr of reflux. NMR spectrum indicated three sets of methylene protons centered at τ = 8.05 (m), 7.17 (t) and 6.80 (t) and characterized as the C-7, C-8 and C-6 protons respectively. A broad singlet at 4.92 τ resulted from the N-5 proton and a sharp singlet at 3.30 τ integrated for the two protons at C-2 and C-3.

IIb, m.p. 126-127° was obtained in 85 % yield after 2 hr of reflux. NMR spectrum, τ= 8,01 (m, 7-CH_2), 7.07 (t, 8-CH_2), 6.74 (dt, 6-CH_2), 4.06 (t, 5-NH) and 2.09 (s, 3-CH).

IIc, m.p. 158-159° was obtained in 91 % yield after 1 hr of reflux. NMR spectrum, τ= 8.11 (m, 7-CH_2), 7.0 (t, 8-CH_2), 6.74 (dt, 6-CH_2) and 2.61 (t, 5-NH).

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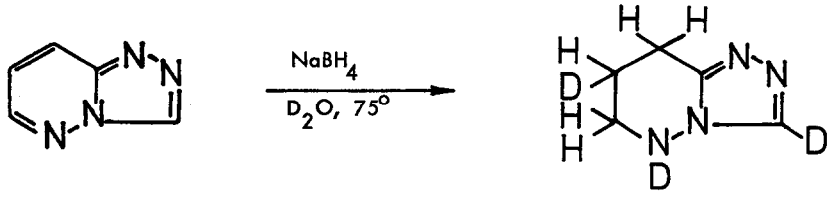
The NMR spectra of the reaction products clearly showed that reduction occurred at the pyridazine nucleus to give a tetrahydro compound. By analogy with the reaction pathways proposed for the $NaBH_4$ reduction of pyridinium salts[2], the reduction of the pyridazine nucleus may be expected to proceed via an intermediate dihydro-derivative. It is also important, from the mechanistic point, to determine whether the C = C or C = N bond of the pyridazine nucleus is reduced first. While we were unable to detect a dihydroreduction product, we noticed that 7,8-dihydro-s-triazolo(4,3-b)pyridazine (III) obtained by catalytic reduction[3], underwent reduction with $NaBH_4$ in ethanol with extreme ease even at room temperature to give a compound identical with IIb. This fact strongly suggested that reduction of the C = C bond occurred before reduction of the C = N bond.

The importance of an immonium moiety in borohydride reductions is well established in the case of pyridinium[2], thiazolium[4] and azolium[5] salts. In order that the pyridazine compounds may undergo reduction, it is essential that an immonium ion be formed first by protonation of the 5-nitrogen by the protic solvent medium in which the reaction is carried out. A hydride ion derived from $NaBH_4$ would then attack the electron-deficient carbon at the 8-position of the immonium ion system and the resulting enamine moiety would reform an immonium ion which would undergo protonation at the C-7 position and be subsequently reduced further to the tetrahydro compound. If hydride attack were to occur initially at the C-6 position of the immonium ion system, the C=N bond would be reduced before the C=C bond, and the resulting 5,6-dihydro-intermediate would lack the enamine structure and could not undergo further reduction.

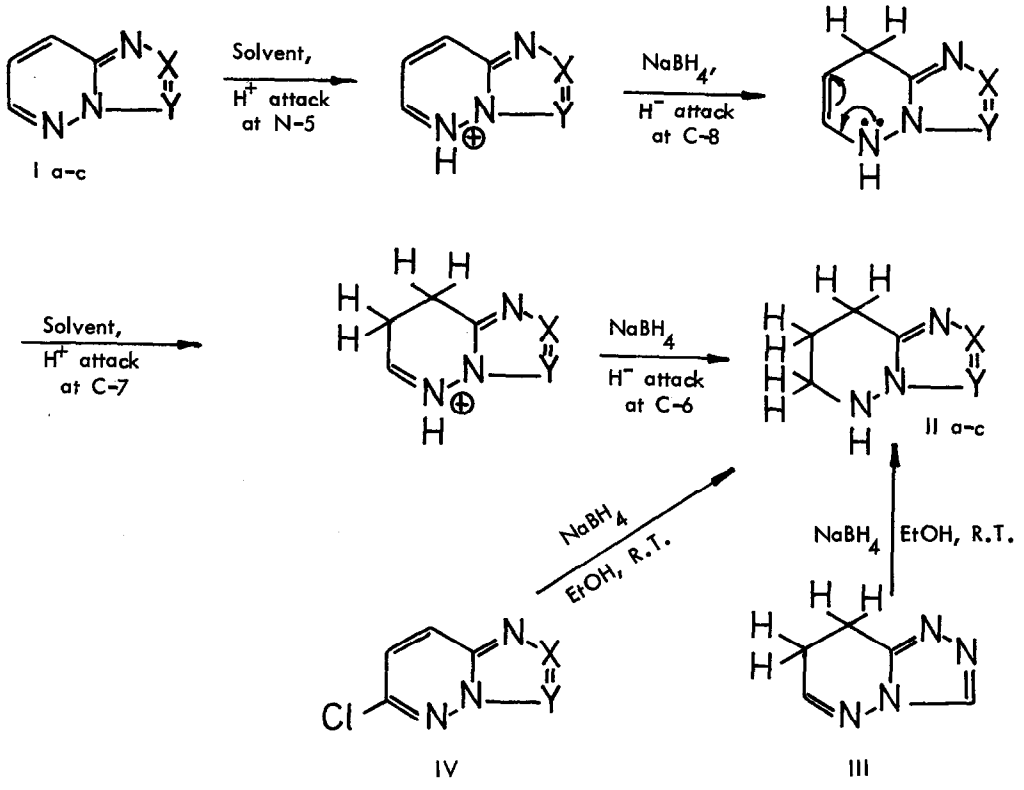
Using deuterium oxide as the solvent, it has been possible to follow the various steps involved in the reduction. The $NaBH_4$ reduction of s-triazolo(4,3-b)pyridazine (Ib) in deuterium oxide gave a deuterated tetrahydropyridazine, the mass spectrum of which gave a parent peak at m/e, 127, corresponding to the presence of three deuterium atoms. It was also found that Ib completely and rapidly exchanged its hydrogen atom at C-3 for deuterium when dissolved in deuterium oxide[6]. The tetrahydro-s-triazolo(4,3-b)pyridazine (IIb), on the other hand, rapidly exchanged both N-5 and C-3 hydrogens. However, there was no evidence for any exchange between deuterium and the hydrogen atoms of the 6-, 7-, or 8-methylene groups even after 2 hr at 80°.



A comparison of the NMR spectra of the deuterated and undeuterated tetrahydro-s-triazolo(4,3-b)pyridazine revealed that the third deuterium atom is attached at C-7.

Likewise in the deuterated tetrahydro-tetrazolo(1,5-b)pyridazine there are two deuterium atoms present in the molecule, one at the N-5 and the other at the C-7 position.

On the basis of this information the gross mechanism of the $NaBH_4$ reduction of bicyclic azolo pyridazines with a bridgehead nitrogen may be represented as follows:



a, X = Y = CH

b, X = N, Y = CH

c, X = Y = N

A reduction path similar to the one envisaged here has been proposed to explain the formation of piperidines from the borohydride reduction of pyridine and picoline methiodides, through initial formation of a 1,4-dihydropyridine[7]. However, in the bicyclic compounds, complete reduction of the pyridazine nucleus does not occur because it is part of the remaining heteroaromatic system and protonation of the 4-nitrogen would disrupt the aromaticity of the 5-membered ring. In the simple pyridazine itself, borohydride reduction in ethanol proceeded to completion giving rise to a mixture of tetra- and hexahydro-derivatives, as shown by NMR spectra. The borohydride reduction of 6-chloro-substituted pyridazines (IV) to give II at greatly enhanced rates at room temperature, is also consistent with the mechanism of protonation of the enamine moiety.

The present finding not only enlarges the collection of examples of borohydride reduction of heterocycles, but also provides a useful and simple synthetic route for the preparation of reduced pyridazine compounds of interest. The nmr spectra, mass spectra and elemental analyses are fully in accord with the assigned structures of the products.

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