

SODIUM BOROHYDRIDE REDUCTION OF MONOCYCLIC 1,2,3-TRIAZINE N-OXIDES[#]Heihachiro Arai, Akio Ohsawa, Hidefumi Ohnishi, and Hiroshi Igeta^{*}School of Pharmaceutical Sciences, Showa University, Shinagawa-ku,
Tokyo 142, Japan

Abstract --Reduction of 4,6-disubstituted 1,2,3-triazine 2-oxides with sodium borohydride afforded the corresponding 1,4,5,6-tetrahydro-1,2,3-triazine 2-oxides as main products. The mechanism was examined using NaBH_4 in CH_3OD and NaBD_4 in CH_3OH .

While sodium borohydride (SBH) reacts with neither pyridine nor pyridazine, the reagent reacts with more electron deficient rings such as 3-cyanopyridine, pyridine 3-carboxylate, and quaternary salts of pyridine and pyridazine to give 1,2- and 1,4-dihydro and/or tetrahydro derivatives.¹

These facts prompted us to investigate the behaviour of monocyclic 1,2,3-triazines and their N-oxides,² having strongly electron deficient rings, towards SBH.

Reduction of 4-methyl-6-phenyl- and 4,6-dimethyl-1,2,3-triazine (5a and 5b) with SBH (excess) in methanol at 0°C afforded the corresponding 2,5-dihydro-1,2,3-triazines (4a and 4b) quantitatively² and reduction of 4,6-dimethyl-1,2,3-triazine 1-oxide with SBH under similar conditions gave 4b in 85% yield together with 5b, no other products being obtained.

Present report is concerned with the first example of the attack of hydride upon the β -position of six-membered heteroaromatic N-oxides.

Reduction of 1,2,3-triazine 2-oxides (1) with SBH was carried out under the conditions described above. After evaporation of the solvent the products were purified by column chromatography (Al_2O_3) to give 1,4,5,6-tetrahydro-1,2,3-triazine 2-oxides (2 and 3), in which the N-oxide group remained, together with 4 and 5, in the yields shown in Table on the next page.

[#]Dedicated to Professor Kyosuke Tsuda on the occasion of his 75th birthday.

Table

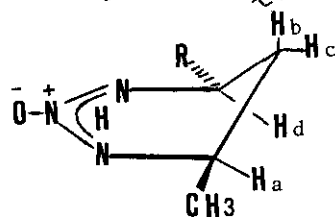
	$\xrightarrow[\text{MeOH}]{\text{SBH}}$					
1		2	3	4	5	1(SM)
a: R=Ph		62	0*	36	trace	trace
b: R=Me		63	20	5	2	5

Yield: % *3a was not detected by nmr and tlc of the reaction mixture.

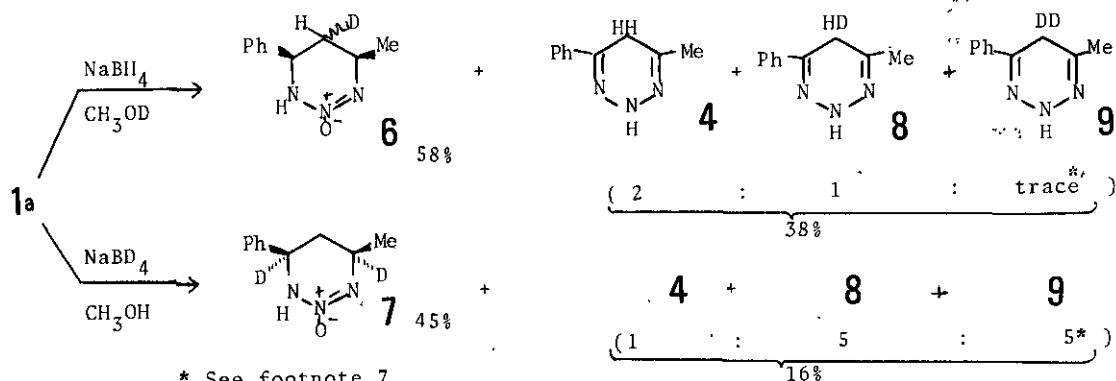
The structures inclusive of stereochemistry of 2a, 2b, and 3b were elucidated by nmr, mass, and ir spectral analyses, i.e., 2a:³ nmr (100 MHz, in CD₃OD with a trace of pyridine-d₅); δ 1.30 (3H, d, $J=6$ Hz, 4-Me), 1.48 (1H, ddd, $J=11, 11, 13$ Hz, Hc), 2.36 (1H, ddd, $J=5, 5, 13$ Hz, Hb), 3.89 (1H, m, Ha), 4.75 (1H, dd, $J=5, 11$ Hz, Hd), 7.34 (5H, s, 6-Ph). Mass (CI);⁵ m/e 192 (M^++1), 176 (M^++1-O), 146, 131, 104. Ir (KBr); 3210, 3125, 1575, 1500, 1451, 1428, 1335, 1275, 1241 cm⁻¹. The coupling constants, $J_{ab}=J_{bd}=11$ Hz and $J_{ac}=J_{cd}=5$ Hz in the nmr spectrum of 2a, indicate that Ha and Hd are in cis configuration.

Similarly, the protons Ha and Hd of 2b and 3b are in cis and trans configuration, respectively.⁶

Next, in order to clarify the mechanism of the reduction, the reduction of 1a was carried out with NaBH₄/CH₃OD and with NaBD₄/CH₃OH (Scheme 1).



Scheme 1



The nmr spectrum of 6 showed two signals due to H(eq) and H(ax) in the 5-position at δ 1.33-1.61 (br m, Hc) and 2.22-2.46 (br m, Hb), respectively; the ratio of H:D was estimated to be approx. 1:1 from the integration of the nmr

signals and neither the 4- nor the 6-position of the compound was deuterated.

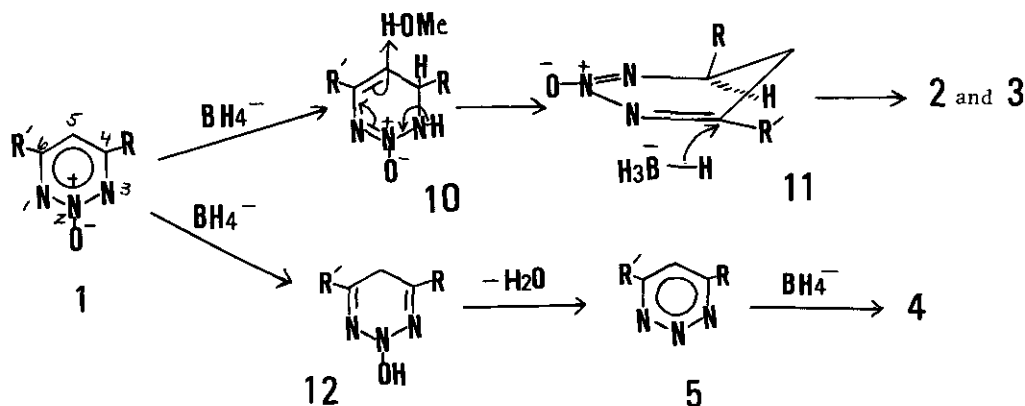
On the other hand, the signals due to the protons at the 5-position of 7 were observed at δ 1.48 (1H, d, $J=13$ Hz, Hc) and 2.36 (1H, d, $J=13$ Hz, Hb), whereas those in the 4- and 6-positions were not observed, showing full deuteration of these positions.

These results clearly indicate that the proton in the 5-position of 2 originated from the solvent, and two protons in the 4- and 6-positions from SBH.

In addition, the proton at the 5-position of 1a was not exchanged with D-atom upon treatment with triethylamine or NaOD in CD_3OD .

The mechanism of the formation of 2, 3, and 4 from 1 is thereby suggested as shown in Scheme 2. It may be considered that the reduction is initiated by hydride attack on the 4-position (β -position of N-oxide group) of 1 to form 10, which consecutively isomerizes to 11. The intermediate 11 then undergoes hydride attack to form 2 and 3. On the other hand, attack of hydride ion on the 5-position (γ -position of the N-oxide group) of 1 gives 12, followed by dehydration to form 5, which is readily reduced to give 4.

Scheme 2



The predominant formation of 2 whose stereochemistry is *cis* configuration can be explained by the hydride attack on a less hindered site of 11.

Acknowledgement --This work was supported in part by a Grant-in-Aid (No. 56570729) from Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

REFERENCES AND NOTES

1. For example, D.M.Smith, "Comprehensive Organic Chemistry", Vol.4, Pergamon, London, 1979, p3; A.R.Katritzky and J.H.Lagowski, "Chemistry of the Heterocyclic N-Oxides", Academic, London, 1971, p166; C.Kaneko, T.Tsuchiya, and H.Igeta, Chem. Pharm. Bull., 1974, 22, 2894 and references cited therein.
2. A.Ohsawa, H.Arai, H.Ohnishi, and H.Igeta, Chem. Comm., 1981, 1182.
3. Mp 110-111°C (needles from ether); oxidation of 2a with DDQ afforded 1a in 85% yield.
4. All signals due to the protons at 4-, 5-, and 6-positions of 2 and 3 in CD₃OD or CDCl₃ were broad and not assignable. The spectra of the compounds showed clear signals by addition of a trace of pyridine or acetic acid. These phenomena suggest that 2 and 3 exist in a slow equilibrium between 1H- and 3H-forms in neutral media, and in a rapid equilibrium in the presence of base or acid.
5. Molecular ion peaks of 2 and 3 were not observed in EI-mass spectrum.
6. Satisfactory elemental analyses were obtained for 2a and 2b, but not for 3b which could not be kept in the pure state because of its instability. Compound 2b melts at room temperature. Mass (CI);⁵ m/e 130 (M⁺+1), 114 (M⁺+1-O), 86, 70. Nmr (100 MHz, in CD₃OD-trace pyridine);⁴ δ 1.12 [1H, ddd, J=13, 10.7, 10.7 Hz, 5-H(eq)], 1.26 (6H, d, J=6.5 Hz, 2xMe), 2.15 [1H, ddd, J=4.5, 4.5, 13 Hz, 5-H(ax)], 3.72 [2H, m, 4- and 6-H(ax)]. Ir (KBr); 3225, 3120, 1570, 1450, 1425, 1290, 1133 cm⁻¹. Compound 3b also melts at room temperature. Mass (CI);⁵ m/e 130 (M⁺+1), 114 (M⁺+1-O), 86, 70. Nmr (100 MHz, in CD₃OD-trace pyridine-d₅);⁴ δ 1.13 (6H, d, J=6 Hz, 2xMe), 1.57 [2H, dd, J=6, 6 Hz, H(gem) at 5-position], 3.54 (2H, qdd, all the J are 6 Hz, 4- and 6-H). Ir (KBr); 3210, 3125, 1572, 1460, 1404, 1293, 1260, 1136 cm⁻¹.
7. The protons at the 5-position of the 2,5-dihydro compound were exchanged with D-atom of the CH₃OD under the described basic conditions. In the nmr spectrum of the mixture of 4, 8, and 9, the signal due to the proton at the 5-position of 8 appeared in approx. 0.05 ppm higher field than the signal due to the protons at 5-position of 4, and the ratio H₂ : HD : D₂ was calculated from integration ratio of the signals due to the protons at the 5-position, and due to the protons of methyl groups of the dihydro compounds.

Received, 1st September, 1981