

BOROXYDRIDE REDUCTION OF 1,3-DIMETHYLPYRIDINIUM IODIDE IN STRONGLY ALKALINE MEDIUM

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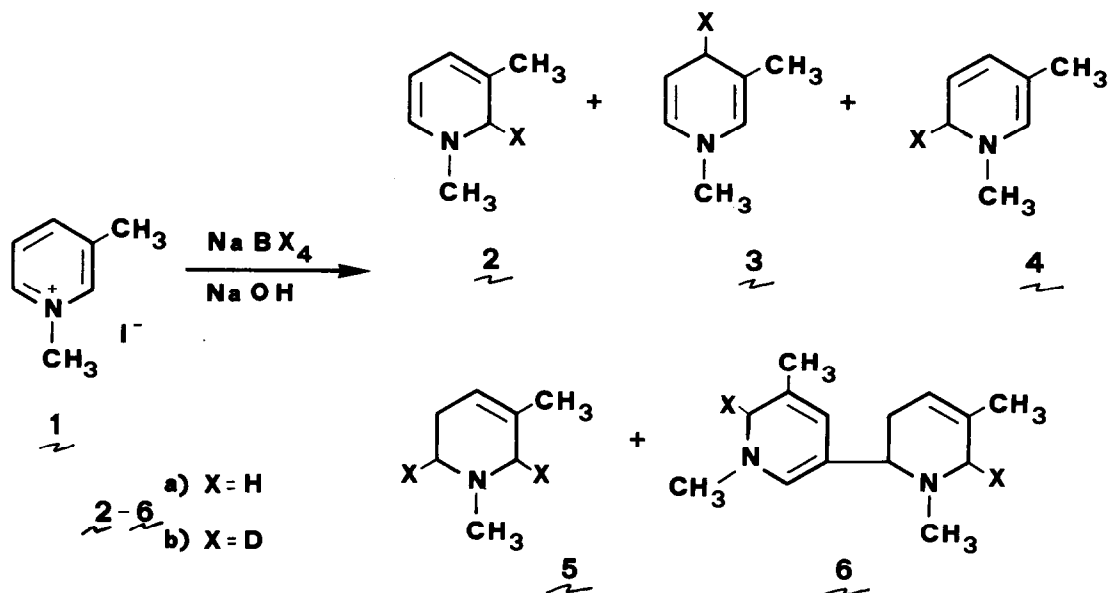
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In connection with our previous work on dihydropyridines,² we have investigated the preparation of alkyldihydropyridines by reduction of the corresponding pyridinium salts with NaBH₄. Close examination of the pertinent literature reveals some controversial points. Thus, according to Kinoshita,³ the reduction of an alkyldihydropyridinium salt with NaBH₄ in strongly alkaline medium yields dihydropyridines, whereas according to Panouse⁴ and Ferles⁵ tetrahydro and hexahydropyridines are formed. Therefore, we reduced 1,3-dimethylpyridinium iodide **1** in 0.8 N NaOH/MeOH with NaBH₄ following Kinoshita's method: a broad band appeared in the uv spectrum at ca. 335 nm, indicative of the formation of a 1,2- or a 1,6-dihydropyridine system. When the reduction of the salt was complete, the reaction mixture was extracted with CH₂Cl₂ and the solvent evaporated. On distillation, the crude residue did not give dihydropyridines, but two major products, namely the tetrahydropyridine **5a**⁵ (bp 128-130°/760 torr; hydrochloride mp 163-5°) and the dimer **6a** (bp 108-110°/0.01 torr) identified on the basis of molecular weight (218, from mass spectrum) and spectroscopic properties: ¹H nmr (see Table I); ¹³C nmr (CDCl₃, 25.18 MHz) δ 131.5, 123.5, 110.0 (s, vinyl C), 133.4, 119.7, 118.7 (d, vinyl CH), 62.8 (d, C-2), 59.9 (t, C-6), 55.3 (t, C-6'), 42.7 (q, N-CH₃), 42.3 (q, N'-CH₃), 33.3 (t, C-3), 20.9, 20.7 ppm (q, C-CH₃); uv λ max (MeOH) 332 nm; ir (liquid film) $\bar{\nu}$ 1610 and 1670 cm⁻¹. Since it has been recently reported^{6,7} that alkyldihydropyridines could be isolated by alkaline reduction of pyridinium salts with NaBH₄ in a two-phase system, we have carried out a series of experiments following this procedure. In a typical run, **1** (10.0 g, 0.042 mol) was rapidly added to a stirred mixture of NaBH₄ (1.3 g, 0.034 mol), 10 N NaOH (30 ml), methanol (30 ml), and light petroleum ether (150 ml); after three minutes the hydrocarbon phase was separated and evaporated yielding a mixture of products (2.5 g), that were not resolved, and whose composition, changing as a function of time, was established by a careful ¹H nmr analysis.

SCHEME I

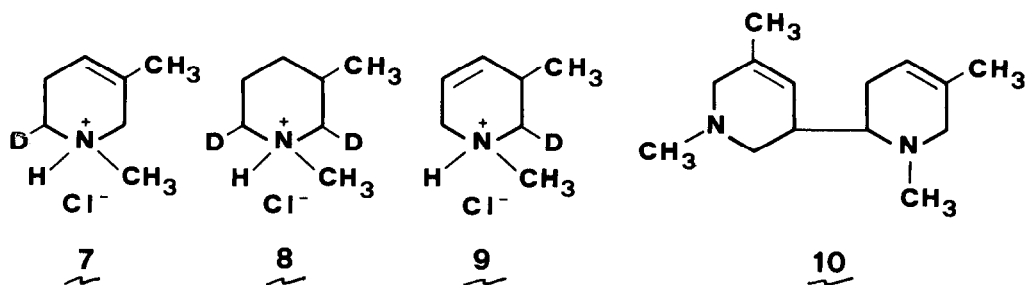


Spectra recorded immediately after evaporation of the solvent gave the following composition: 1,3-dimethyl-1,2-dihydropyridine 2a, 62%; 1,3-dimethyl-1,4-dihydropyridine 3a, 11%; 1,3-dimethyl-1,6-dihydropyridine 4a, 11%; 1,3-dimethyl-1,2,5,6-tetrahydropyridine 5a, 11%; 1,1',5,5'-tetramethyl-1,1',2,3,6,6'-hexahydro-2,3'-bipyridine 6a, 5%⁸ (Scheme I). Nmr spectra were also recorded after 24, 40, 72, 144, and 168 hours: they clearly demonstrate a gradual decrease in the amount of 2a,

TABLE I- ¹H nmr data for compounds 2a-6a (100 MHz, CDCl₃, TMS as internal standard)

Compd	δ, ppm	Assignment	J, Hz	Compd	δ, ppm	Assignment							
<u>2a</u>	5.81, bd	1, H-6	5, 6	<u>5a</u>	5.33, m	1, H-4							
	5.55, m	1, H-4	5, 4		2.87, m	2, H-2							
	4.60, dd	1, H-5			2.50, m	2, H-6							
	3.67, bs	2, H-2			2.31, s	3, N-CH ₃							
	2.58, s	3, N-CH ₃			2.10, m	2, H-5							
	1.62, bs	3, C-CH ₃			1.50, s	3, C-CH ₃							
<u>3a</u>	5.8-5.4	2, H-2 + ³ H-6	5, 6	<u>6a</u>	5.8-5.4	3, H-2, ³ H-4 + H-4'							
	4.35, dt	1, H-5	5, 4 α		3.0	3.61, bs	2, H-6'						
	2.8, m	2, H-4	5, 4 β					3.12	1, H-6α (or β)				
	2.72, s	3, N-CH ₃						2.8	1, H-6β (or α)				
	1.62, bs	3, C-CH ₃						2.58, s	3, N'-CH ₃				
	<u>4a</u>	5.8-5.4	2, H-2 + ³ H-4					5, 4	9.0	2.4-2.0	3, H-2 + ³ H-3		
5.24, ddt		1, H-5	5, 2	1.0				2.18, s				3, N-CH ₃	
3.58, bd		2, H-6	5, 6 α		4.0	1.66, 1.64	6, C-CH ₃ + C'-CH ₃						
2.52, s		3, N-CH ₃	5, 6 β										
1.62, bs		3, C-CH ₃											

until it completely disappears, and a corresponding increase in the amount of $\underline{6a}$. $\underline{2a}$ could not be isolated by distillation of the reaction mixture *in vacuo*, since heating increases the rate of dimerization and consequently the product obtained is $\underline{6a}$ rather than $\underline{2a}$. The high $\underline{2a}:\underline{3a}+\underline{4a}$ ratio indicates a predominant attack of BH_4^- ion to the most hindered position. $\underline{2a}$ is a primary reduction product and not an artefact derived from the rearrangement of $\underline{3a}$ (or $\underline{4a}$). This was demonstrated by repeating the reduction of $\underline{1}$ in the same conditions as above, but replacing NaBH_4 by NaBD_4 . Analysis of nmr spectra of the reaction mixture immediately after evaporation of the hydrocarbon phase, gave the following composition: $\underline{2b}$, 76%; $\underline{3b}$, 11%; $\underline{4b}$, 11%; $\underline{5b}$, 2%. No 1,3-dimethyl-6-deutero (or 4-deutero) 1,2-dihydropyridine was detected, thus excluding the isomerization of $\underline{3b}$ (or $\underline{4b}$) to $\underline{2b}$. Nmr spectra of the mixture of deuterated compounds were also recorded after 24, 48, 120 and 144 hours: they clearly demonstrate a gradual decrease in the amount of $\underline{2b}$, until it disappears, while a corresponding amount of $\underline{6b}$ is formed. Furthermore, we reduced $\underline{1}$ with LiAlH_4 in anhydrous ethyl ether: again dihydropyridines were not isolated and the predominant products were the dimer $\underline{6a}$ and the tetrahydropyridine $\underline{5a}$. When the mixture of the products $\underline{2a}$ - $\underline{6a}$ freshly obtained from the evaporation of the hydrocarbon phase was treated with NaBD_4 in 0.5 N $\text{NaOH}/\text{H}_2\text{O}$, the gradual fading of the dihydropyridine uv absorption band was noticed, until it completely disappears. The solution was extracted with CH_2Cl_2 , the solvent evaporated and the residue distilled. The fraction boiling between 50° and 70° at 20 torr by treatment with an ethereal HCl solution gave a mixture of hydrochlorides that was shown by ^1H and ^{13}C nmr spectra⁹ to be formed by the deuterated products $\underline{7}$ (60%), $\underline{8}$ (13%), and $\underline{9}$ (10%), together with the hydrochloride of the already existing tetrahydropyridine $\underline{5a}$. The formation of $\underline{7}$, $\underline{8}$, and $\underline{9}$ demonstrates the ability of the enamine system present respectively in $\underline{2}$, $\underline{3}$ and $\underline{4}$ to undergo complete and direct reduction by NaBH_4 in alkaline medium. In a separated experiment, $\underline{6a}$ in 0.5 N $\text{NaOH}/\text{H}_2\text{O}$ was also treated with NaBH_4 ; the reduction proceeded slowly and was complete after 12 hr, to yield $\underline{10}$, bp $170^\circ/20$ torr, mw 220 (from mass spectrum), uv (H_2O) end-



absorption at ca. 210 nm, ^{13}C nmr (CDCl_3 , 25.18 MHz) δ 132.5, 131.1 (s, vinyl C), 121.8, 118.9 (d, vinyl CH), 61.0, 37.2 (d, C-2 and C-3'), 59.3, 59.0, 53.5, 25.2 (t, methylene C), 45.9, 40.0 (q, N- CH_3), 20.9, 20.7 ppm (q, C- CH_3). The experimental evidence demonstrates: i) the remarkable regioselectivity of attack of the BH_4^- ion on the salt 1, in agreement with previous findings¹⁰⁻¹² concerning other nucleophilic reactions on 3-methylpyridinium cations, and ii) the ability of the enamine system present in 2, 3, 4 and 6 to undergo direct reduction by NaBH_4 in alkaline solution. In this case the mechanism commonly postulated for the further reduction of the dihydro to tetrahydropyridines in solution of low pH^{13,14} cannot be operative since it involves, as a key step, the protonation of the enamine system to an imonium cation. Obviously some alternative mechanism must be operative in those cases where a pyridinium salt is directly reduced to a tetrahydro derivative by NaBH_4 in alkaline solution. Further work on this point is under way in our laboratory.

References and Notes

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- 8) The composition of the mixture was evaluated as follows: the integrals of the signals due to the C-5 protons gave a 2a:3a:4a ratio corresponding to 6.2:1.1:1.1. The integrals of the signals due to the N-methyl protons gave a 3a:4a:5a:6a ratio of 1:1:1:0.5.
- 9) Typical peaks in the all decoupled ^{13}C nmr spectrum (D_2O , dioxane as internal reference, δ 67.4 from TMS) are, for 7: a triplet at δ 50.8 ppm, C-6, $J_{\text{C}_6-\text{D}} = 22.3$ Hz; for 8 a triplet at δ 61.3 ppm, C-2 and a triplet at δ 55.3 ppm, C-6; for 5a·HCl a singlet at δ 51.2 ppm, C-6. 9 has been identified from the presence in the ^1H nmr spectrum (D_2O , 100 MHz) of a doublet at δ 1.16 ppm, C- CH_3 , $J_{\text{CH}_3-\text{C}_3-\text{H}} = 7$ Hz decoupled by irradiating the C_3 -H signal at δ 2.8 ppm.
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