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THE MECHANISM OF THE REDUCTION OF PYRIDINIUM IONS WITH SODIUM BOROHYDRIDE

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THE reduction of 1-methylpyridinium iodide with potassium borohydride was described by Panouse[1] as producing a 1,2,5,6-tetrahydropyridine. This reaction is most unusual for it appears that sodium borohydride has caused the reduction not only of a carbon-nitrogen double bond of the aromatic system, but also a carbon-carbon double bond. The type of product of the reaction, however, has been confirmed by many authors who have caused the reduction of a variety of pyridinium ions to the corresponding tetrahydropyridines.[2] In only a few cases have dihydropyridines been isolated from sodium borohydride reductions. The sodium borohydride reductions of 3-cyanopyridine methiodide,[2a] 1-alkyl- or 1-aryl-3-carbamoylpyridinium salts,[3a] and 1-phenylpyridinium chloride[3b] are such examples.

These dihydropyridines were shown to be substituted 1,6-dihydropyridines. It was reported, however, that 1,4-dihydropyridine derivatives

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[1] J.S. Panouse, *C.R. Acad. Sci., Paris* **233**, 260, 1200 (1951).

[2a] K. Schenker and J. Druey, *Helv. Chim. Acta* **42**, 1960 (1959);
[b] R. Lyle, E. Perlowski, H. Troscianiec and G. Lyle, *J. Org. Chem.* **20**, 1761 (1955);
[c] K. Schenker, *Angew. Chem.* **72**, 638 (1960);
[d] K. Schenker, *Ibid.* **73**, 81 (1961);
[e] Seiichi Saito and Everette L. May, *J. Org. Chem.* **27**, 948 (1962);
[f] John W. Huffman, *Ibid.* **27**, 948 (1962).

[3a] References in E.N. Shaw, *Pyridines and Its Derivatives* Vol. II (Edited by E. Klingsburg), pp. 47-55. Interscience, New York (1961);
[b] M. Saunders and E.H. Gold, *J. Org. Chem.* **27**, 1439 (1962).

were also produced, and 1,2-dihydropyridines were detected in the ultraviolet absorption spectra of the reaction mixtures.[3a] The success of the sodium borohydride reduction of pyridinium salts to tetrahydropyridines led to an investigation of the nature of the dihydropyridine or pyridines which might be intermediate in the formation of the tetrahydropyridine and the pathway of the conversion of this dihydropyridine to the product.

An investigation of the changes in the ultraviolet absorption spectra of the reduction reactions which were known to produce significant yields of tetrahydropyridines showed in each case that the long-wavelength band attributed to 1,2-dihydropyridines was the strongest or only band observed. This observation was found with 3-acyl-, 3-ethoxycarbonyl-, 3- and 4-alkyl- and 4-aryl-pyridines (see Table 1). That substituted 1,4-dihydro[4] and 1,6-dihydropyridines[2a] were resistent to further reduction by sodium borohydride strongly suggested that the 1,2-dihydropyridines were intermediate

TABLE 1

Ultraviolet Absorption Maxima, above 300 mμ, of Dihydropyridines

Pyridinium ion	$Na_2S_2O_4$ Reduction λ_{max} (mμ)*	$NaBH_4$ Reduction λ_{max} (mμ)*
1-Alkyl- or 1-aryl	(no reduction)	350-355(4)
1,4-Dialkyl	(no reduction)	335(2)
1-Methyl-4-phenyl	(no reduction)	355
1-Alkyl-3-carbamoyl	355-360(4)	364-370, 410-415(4)
1-Alkyl-3-ethoxycarbonyl	353-355(2)	362,425(2)
1-Alkyl-3-benzoyl	384-385(3)	366,374, 468-475(4)
1-Methyl-3-benzoyl-4-phenyl	374	360,485
1-Methyl-3,5-diphenyl		320,415

* The numbers in parantheses indicate the number of compounds studied.

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[4] D.A. Nelson, Thesis, University of New Hampshire (1960).

in the formation of the substituted tetrahydropyridines.

The fact that these dihydropyridines contain enamine systems suggested that the second reductive step of the sodium borohydride reaction proceeded by an initial attack of an electrophile on the enamine system to produce an intermediate having an unsaturated ammonium group, which was attacked by the borohydride ion producing the tetrahydropyridine. This pathway was indicated by the isolation only of substituted 1,2-dihydropyridines from the reactions of 1,3,5-trisubstituted pyridinium ions with sodium borohydride in various solvent media; thus 1-methyl-3,5-diphenylpyridinium iodide, 1,3,5-trimethylpyridinium iodide, and 1-methyl-5-bromo-3-methoxycarbonylpyridinium bromide all gave 1,2-dihydropyridines.[5] Thus the substituents sterically interfere with the attack of the electrophile at the terminal enamine carbon.

The electrophile which attacks the enamine system could be a proton, from the solvent, or diborane, which might be produced during the sodium borohydride reduction. Indeed, from these reactions the tetrahydropyridines are often isolated as the amine boranes. The nature of the electrophile seemed evident from the fact that when the sodium borohydride reduction of pyridinium ions was run in aprotic solvents, the long wavelength absorption band did not diminish with time.

Thus the dihydropyridine which would be produced as an intermediate appeared to undergo no reaction, as evidenced by no change in the ultraviolet absorption spectra, until a proton source was added.[6]

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[5] The properties of these dihydropyridines will be described in a subsequent publication.

[6] A similar conclusion has been reached by Prof. G. Stork and coworkers regarding the related reduction of enamines of α,β-unsaturated-ketones. The original postulate that borane attack initiated the hydride reduction [G. Stork and G. Birnbau, Tetrahedron Letters 313 (1961)] has now been discarded in favor of initial attack by proton (G. Stork, Harvard Colloquium, April 17, 1962).

The properties of the reaction thus allowed the use of deuterium oxide to study this second step of the reduction. The sodium borohydride reduction of 1-methyl-4-phenylpyridinium iodide, using deuterium oxide as a source of electrophile, gave a deuterated tetrahydropyridine, the mass spectrum of which gave the largest relative abundance, and thus presumably the parent peak, at 174 m/e corresponding to the presence of one deuterium atom.

The infrared spectrum of this deuterated tetrahydropyridine showed a weak band at 2140 cm^{-1}, indicative of saturated C-D stretching,[7] and a medium band at 1265 cm^{-1}, indicative of D-C-H scissoring, concerted vibration. The infrared spectrum differed considerably in the fingerprint region from the spectrum of undeuterated 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, and thus the identity in structure of the deuterated and undeuterated compounds was proved by melting points, melting points of derivatives, and ultraviolet absorption spectra. It was found that the deuterated compound completely and rapidly exchanged the deuterium for hydrogen on warming in aqueous acid. This strongly suggests that the deuterium is indeed located only at the 5-position, for a reasonable mechanism for exchange from a saturated carbon can be written only for this allylic position. Proton attack at the 3-position would form a symmetrical, resonance-stabilized carbonium ion which could eliminate a proton or deuteron, explaining this rapid exchange of isotopes.

A comparison of the proton magnetic resonance spectra of the deuterated and undeuterated 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridines confirmed the location of the deuterium atom. The spectra were nearly identical showing a multiplet due to the resonance of the aromatic hydrogens at 2.3 τ, a doublet (J = 3.5 cps) at 6.95 τ due to the methylene at 2, a triplet

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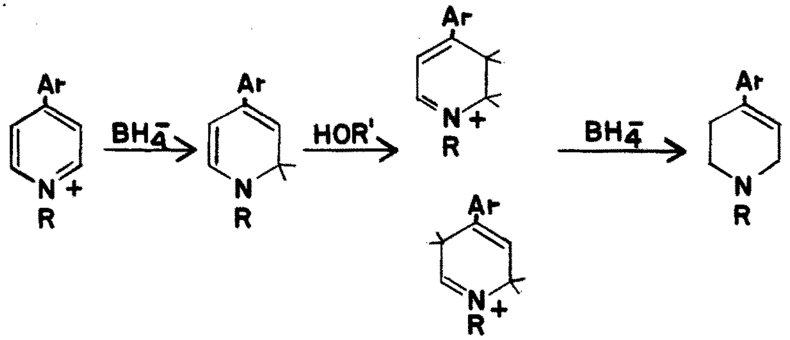
[7] E.J. Corey, Chem. & Ind. 1294 (1954); S. Cristol, J. Org. Chem. **27**, 293 (1962).

(J = 3.5 cps) at 3.97 τ resulting from the vinyl hydrogen at position 3, and a sharp peak at 7.66 τ due to the 1-methyl substituent. The methylene groups on the 5- and 6-positions gave a composite peak (half-band width 3.8 cps) at 7.43 τ which at higher amplification was resolved into a multiplet. In the deuterated sample this peak (half-band width 2.5 cps) could not be resolved, indicating a less complex splitting pattern. The relative peak areas were also in agreement with the presence of only three protons at the 5- and 6-positions of the deuterated compound. The deuterium can be located at the 5- rather than the 6-position on the basis of the exchange reaction in acid, the absence of evidence of deuterium at the 2-position in the NMR, and the fragmentation pattern near 115 m/e $(\mathrm{PhC(CH_2)_2^+})$ in the mass spectra.

On the basis of the ultraviolet absorption spectral studies and the isotopic investigation of the sodium borohydride reduction of pyridinium ions, the gross mechanism of this reaction may be represented as below.[8]



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[8] The results of this investigation do not allow a distinction between an attack of the proton donor at the 3- and 5-positions. The evidence, however, clearly indicates that the protonation step is not reversible under these conditions and that reduction immediately follows protonation, for little or no deuterium is present on the vinyl position in the tetrahydropyridine.