

THE REACTION OF N-BENZYLOXYPYRIDINIUM BROMIDE  
WITH SODIUM BOROHYDRIDE: MECHANISTIC ASPECTS

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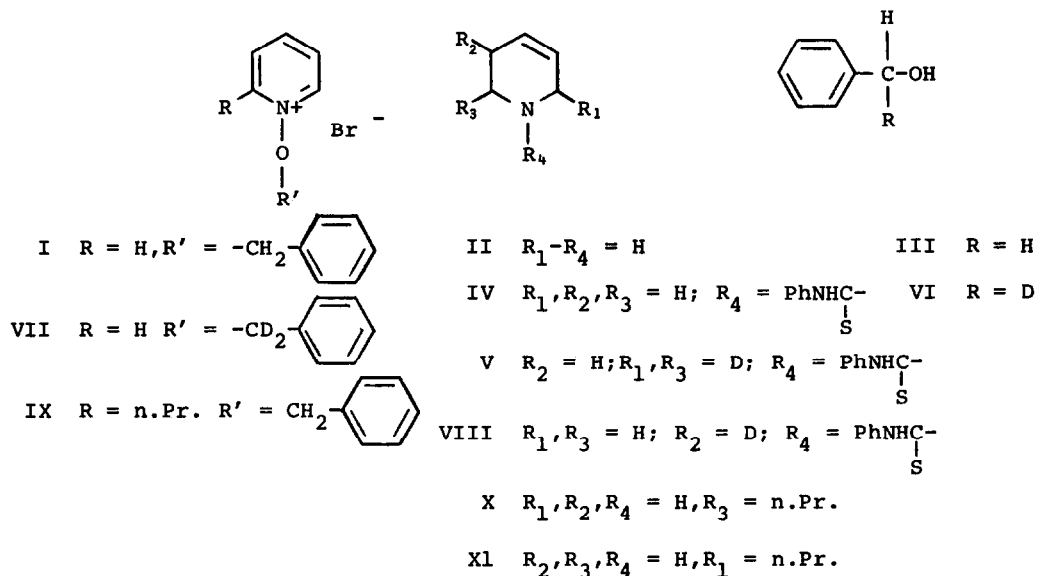
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The reduction of N-alkyl pyridinium salts with sodium borohydride is a well-known reaction, yielding in most cases the corresponding 1, 2, 3, 6-tetrahydropyridine derivatives.<sup>1</sup> The mechanistic aspects of this reaction have been studied and a mechanism proposed.<sup>2</sup> We wish to report our studies on the analogous reduction of N-benzyloxy pyridinium bromides.

The literature describes one example of this reaction; the reduction of N-methoxy pyridinium perchlorate to pyridine.<sup>3</sup> Subsequent to completion of our work, the reduction of N-alkoxy pyridinium salts has been reported to yield a mixture of the corresponding tetrahydro pyridine, pyridine and piperidine derivatives.<sup>4</sup>

In our studies, we have found that treatment of simple N-benzyloxy pyridinium bromides with sodium borohydride affords as the major products the corresponding tetrahydropyridines and benzylalcohol. (e.g. I → II and III)

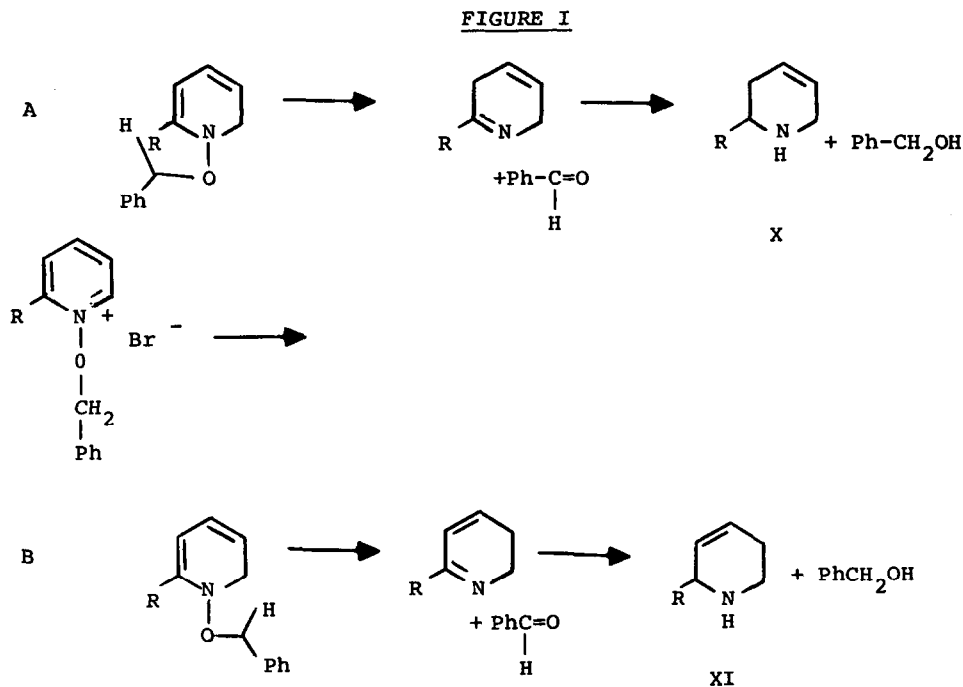


We have undertaken studies designed to investigate the mechanism of this transformation and wish to propose a reaction course which is consistent with and supported by our findings.

Our first studies were intended to ascertain the source of the three hydrogen atoms introduced to the carbon atoms of the heterocyclic ring during the course of the reaction. In these studies, the tetrahydropyridine formed was characterized as its crystalline phenylthiourea derivative IV. Reduction of N-benzyloxy pyridinium bromide (I) with sodium borohydride in deuterium oxide yielded IV containing (workup included treatment with  $H_2O$  to allow N-D, N-H exchange) no deuterium according to an NMR analysis.

Reduction with sodium borodeuteride in water yielded V containing two deuterium atoms per molecule, one in the position two and one in position six. These findings indicate that none of the three hydrogens incorporated in the carbon skeleton of the pyridine ring derive from solvent and two derive from borohydride. A clue to the source of the third hydrogen atom was provided by NMR analysis of the benzyl alcohol generated during reduction with sodium borodeuteride in water which indicated the presence of one methylene deuterium (ie VI). This result suggested that the benzyl alcohol is derived from benz-

aldehyde which in turn resulted from a transfer of a benzylic hydrogen atom to a carbon atom of the heterocyclic nucleus. The conversion of VII to VIII and VI in the presence of sodium borohydride supports this contention. The two mechanistic pathways, each involving an electrocyclic process, shown in Figure I are consistent with the above findings.

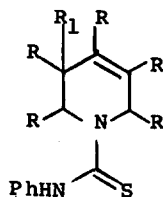
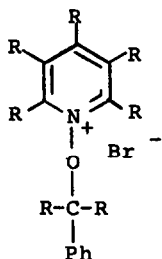


To distinguish between these two possibilities the reduction of N-benzyloxy-2-propylpyridinium bromide (IX) was studied. Assuming that borohydride would initially attack the least hindered alpha position of the pyridinium nucleus, pathway A should result in product X whereas if pathway B is the course of the reaction then the product should be XI.

In fact, the reaction gave X in good yield, consistent with pathway A.

Alternative reaction schemes involving intermolecular hydrogen transfers can be formulated. To explore this aspect, the reduction of an equimolar mixture of XII and XIII was carried out. Intramolecular hydrogen transfer should afford two species XIV and XV whereas intermolecular transfer should yield species XVI - XVII. Mass spectral analysis of the reaction product indicated the

presence of molecular ions corresponding to XIV and XV and the absence of molecular ions corresponding to XVI and XVII, in agreement with an intramolecular pathway.



XII	R = H	XIV	R, R <sub>1</sub> = H	m/e
				218
XIII	R = D	XV	R, R <sub>1</sub> = D	224
		XVI	R = H, R <sub>1</sub> = D	219
		XVII	R = D, R <sub>1</sub> = H	223

The stereochemical aspects of this transformation are currently being studied.

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