Tetrahedron Letters No.45, pp. 4011-4017, 1965. Pergamon Press Ltd.
Printed in Great Britain.

MECHANISM OF SODIUM BOROHYDRIDE REDUCTION OF PYRIDINIUM IONS. III. FORMATION OF PIPERIDINES

Paul S. Anderson,* William E. Krueger,* and
Robert E. Lyle+

The Department of Chemistry
University of New Hampshire,
Durham, New Hampshire

(Received 7 September 1965)

The reduction of 1- substituted pyridinium ions has been reported to lead to tetrahydropyridines with the exception of 1-phenyl pyridinium bromide[1] salts which are converted to a mixture of dihydropyridines.[2] The early reports of Panouse[3] and Ferles[4] indicated the isolation of piperidines was also observed. Since the initial report of the formation of piperidines by this method, numerous examples of the reduction have been reported and no indication of piperidine formation has been made.[1] A careful examination of the product of several pyridinium ions by gas chromatography (See Table I), has indeed confirmed the report of Panouse[3] and Ferles[4], that complete saturation of the heterocyclic ring can occur.

The formation of the tetrahydropyridine has been shown to occur by initial attack of the hydride ion on a carbon atom adjacent to the positive nitrogen.[5] The completely saturated ring was

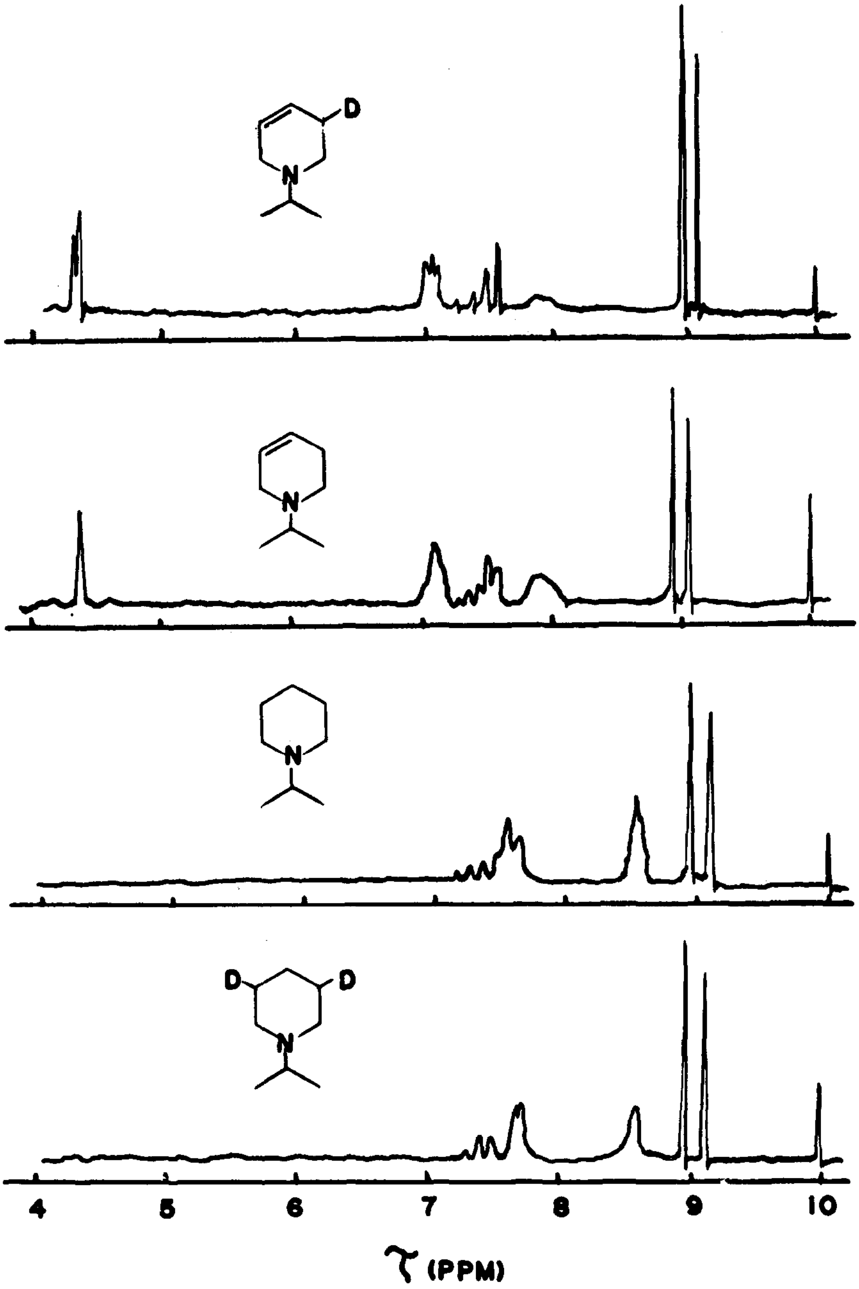
---

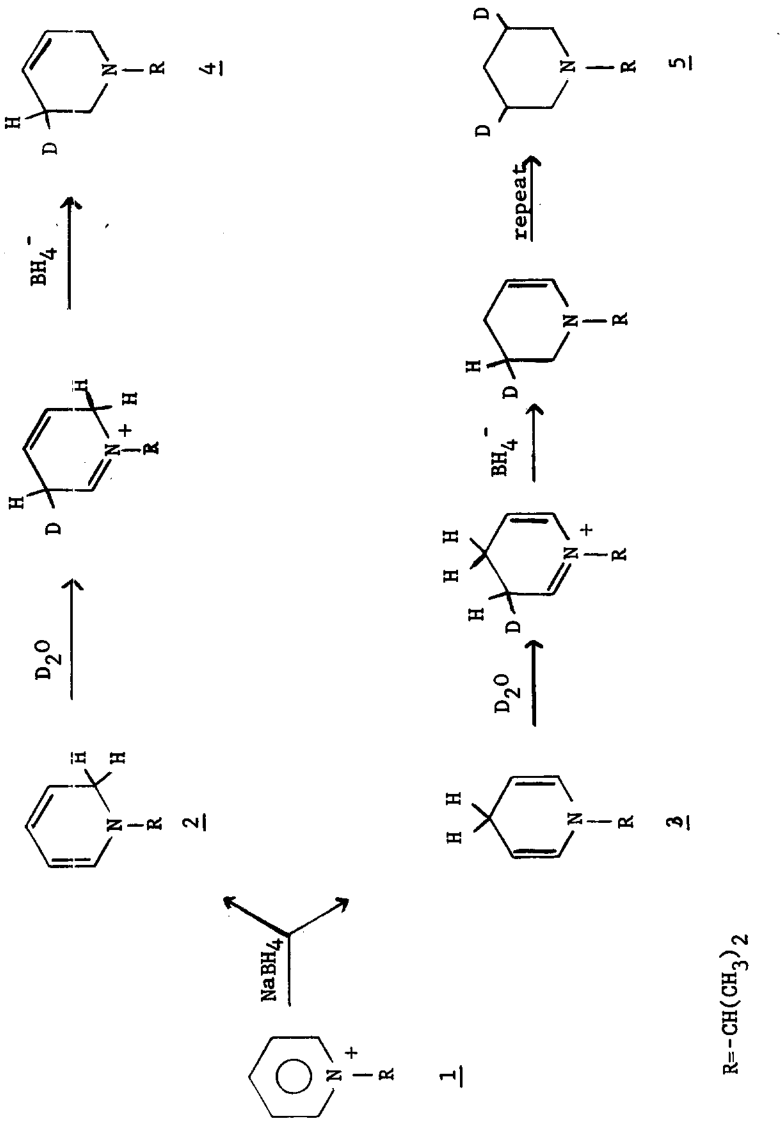
* Abstracted from the theses of P.S.A. and W.E.K. Presented to the Graduate School in partial fulfillment of the Ph.D. Degree.

\+ Author to whom inquires should be addressed.

suggested to be formed by an initial attack at the 4-position of the pyridine ion by Ferles[4]. Some support for this postulate was obtained from the reduction of 1-isopropylpyridinium iodide (1) with sodium borohydride in deuterium oxide. A similar procedure was described by Cervinka[6] in a study of the mechanism of the reduction of pyridinium ions by formic acid. On the basis of these mechanisms of the sodium borohydride reactions, 1-isopropyl-1,2,5,6-tetrahydropyridine (4) should contain one deuterium in the 5-position, as has been previously demonstrated[5], and the 1-isopropyl piperidine (5) should contain a total of two deuterium atoms in the 3- and 5-positions. The nuclear magnetic resonance spectra (Figure 1) confirm the monodeuteration in the tetrahydropyridine (4) and is consistent with the dideuteration of the piperidine (5) derivative. The integral of the doublet at 9.0τ was considered to result from the resonance of the six methyl hydrogens. This calibration then indicates the presence of two hydrogens under the broad peak at 7.9τ resulting from the hydrogens at the 5-position of undeuterated 1-isopropyl-1,2,5,6-tetrahydropyridine. The tetrahydropyridine (4) separated from the reduction in deuterium oxide showed the equivalent of one hydrogen under this peak. A similar consideration of the integral of the peak at 8.55τ in the n.m.r. spectra of 1-isopropylpyridine showed six hydrogens in the normal product and four hydrogens from the reduction in deuterium oxide. That the two deuterium atoms are located at the 3- and 5-positions is indicated by the change of the triplet at 7.58τ due to the 2- and 6-protons to a doublet in the 3,5-d_2-1-isopropyl piperidine (5).

The different pathways (see below) for the formation of these two products are confirmed, and it is evident that the relative amount of piperidine and tetrahydropyridine is an indication of the relative rates of attack of the hydride on the 2- and 4-positions.


D
N
D
N
N
D
D
N
4
5
6
7
8
9
10
τ (PPM)



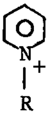
R=-CH(CH$_3$)$_2$

It will be noted from Table I that as the alkyl group increases in size, the relative amount of the piperidine increases Methyl < Butyl < Benzyl < Isopropyl. This is consistent with the hypothesis that a large substituent on the nitrogen sterically interferes with the approach of the hydride ion to a carbon atom adjacent to the quaternary nitrogen. The attack at the 4-position of course would remain unhindered, and the product would become more largely determined by attack at the latter position.

TABLE I

GLC ANALYSIS OF PRODUCTS FROM

SODIUM BOROHYDRIDE REDUCTION OF PYRIDINIUM IONS*

	4 %	5 %
$-CH_3$	100	0
$-CH_2-CH_2-CH_2-CH_3$	95	5
$-CH_2-Ph$	88	12
$-CH(CH_3)_2$	72	28

* Two meter 5% silicone grease on Chromosorb diatomaceous earth column.

Recently, in discussing the reaction of pyridinium ions with cyclopentadienyl anion, attack at the 2- or 4-position was reported.[7,8] A consideration of the starting materials indicated that those pyridinium ions with which 2-attack[7] resulted, had a 1-methyl substituent, but the 1-benzyl pyridinium ions seem to lead largely to products resulting from attack at the 4-position.[8] We thus wish to propose that one of the important factors in determining the position of attack of a nucleophile on a pyridinium ion is the possible steric interference to the approach of the nucleophile to the pyridine carbons. This effect is particularly important when the reaction with the nucleophile is irreversible.[9] Compare for example, the effect of reversible reactions in which the thermodynamic stability of the dihydropyridine becomes important.

Acknowledgement: The authors wish to express appreciation to the National Cancer Institute of the National Institutes of Health for Grant CA 04143 and continuation grants. The assistance of Mrs. Donna Amoruso Moffett, NSF Undergraduate Research Participant, in checking the reduction reactions is gratefully acknowledged.

The n.m.r. spectra were determined using a Varian A-60 spectrometer made available by Grant G 22718 from the National Science Foundation.

References

1. P.S. Anderson and R.E. Lyle in "Advances in Heterocyclic Chemistry". A. R. Katritzky and J.M. Lagowski ed., Vol. II, Academic Press, New York, N.Y. In Press.
2. M. Saunders and E.H. Gold, J. Org. Chem., 27, 1439 (1962).
3. J.J. Panouse, Compt. rend. 233, 260 and 1200 (1951). J.J. Panouse, Bull soc. chim. France, 53D and 60D (1953).
4. M. Ferles, Collection Czech. Chem. Commun., 23, 479 (1958).
5. R.E. Lyle, D.A. Nelson, and P.S. Anderson, Tetrahedron Letters, No. 13, 553 (1962), and P.S. Anderson and R.E. Lyle, Tetrahedron Letters, No. 3, 153 (1964).
6. O. Cervinka and O. Kriz, Collection Czech. Chem. Commun., 30, 1700 (1965).
7. K. Hafner, Angew. Chem., 70, 419 (1958) See page 421.
8. J.A. Berson, E.M. Evleth, Jr., and Z. Hamlet, J. Am. Chem. Soc., 87, 2888 (1965) see footnote 22.
9. R.E. Lyle and G.J. Gauthier, Tetrahedron Letters, In Press.