Tetrahedron Letters No. 14, pp. 1133-1135, 1970. Pergamon Press. Printed in Great Britain.

ASYMMETRIC HYDROBORATION OF 1-METHYL-1,2,3,6-TETRAHYDROPYRIDINE

Robert E. Lyle and Courtland K. Spicer

Department of Chemistry, University of New Hampshire, Durham, N. H. 03824

(Received in USA 15 January 1970; received in UK for publication 19 February 1970)

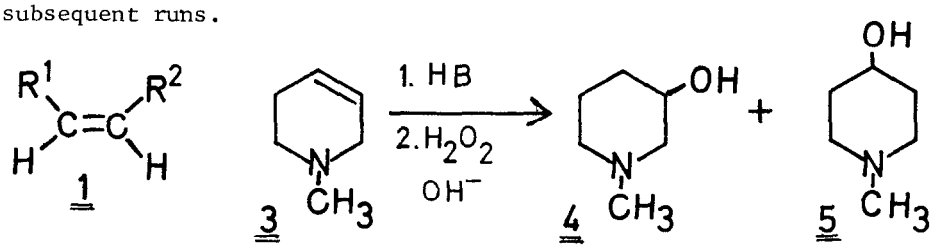
The stereochemical course of the hydroboration of the double-bonds of acyclic cis-alkenes (1) and unhindered methylene derivatives with (+)- or (-)-di-3-pinanylborane (2) can be generalized.[1] The generalization has prompted the consideration of several models for the transition states to correlate this generalization.[2-5] Unfortunately these correlations have not been applicable to other types of olefinic systems, in some cases because the hydroboration reagent is probably not di-3-pinanylborane.[2] Notable among the exceptional alkenes are the carbocyclic analogs of cis-alkenes which may be anomalous because of steric factors or because of the stereochemical relationship of the faces of the double bonds. While the acyclic cis-double bonds have equivalent faces if $R_1=R_2$ (1) or enantiotopic faces if $R_1 \neq R_2$ (1), the cyclic alkenes that were investigated either are highly hindered, such as 1-methylcyclohexene (trisubstituted) or 2,2,2-bicyclooctene (carbon bridges over both faces); have diastereotopic faces, such as norbornene or 3-substituted cyclohexene; or produce no chiral product such as cyclohexene.[6,7] Except for the norbornene these alkenes give alcohols of the opposite configuration to that predicted.

A cyclic alkene which would resemble the acyclic alkenes in having enantiotopic faces and yet have minimal steric hindrance to approach to the faces is found in the tetrahydropyridines. The hydroboration of 1-methyl-1,2,3,6-tetrahydropyridine (3) with diborane was shown to give about 75% of 1-methyl-3-piperidinol (4) and 25% of the achiral 1-methyl-4-piperidinol (5).[8] The separation of the two piperidinols was possible by gas chromatography, so a study of the reaction with the chiral hydroboration reagent, (-)-di-3-pinanylborane, was initiated. If the reaction took the same course as the acyclic cis-alkenes then the S-1-methyl-3-piperidinol† would be the expected product

†The cis-alkenes give the R-alkanols; however, a reversal in priorities[9] of the groups in the piperidinols causes the same reaction pathway to give the S-configurational assignment.

from reaction with (-)-di-3-pinanylborane from (+)-α-pinene. The cyclic alkenes, with the exception of the norbornenes, would lead to a prediction of the formation of R-1-methyl-3-piperidinol from this reaction.

The hydroboration of 1-methyl-1,2,3,6-tetrahydropyridine (3) with (-)-3-pinanylborane prepared from α-pinene of 80.5% optical purity gave a 70% yield of piperidinols shown to be 71% 1-methyl-3-piperidinol and 29% 1-methyl-4-piperidinol. Separation of the piperidinols gave the pure 3-isomer $[\alpha]_D^{27}$ +1.56° (c 2.56 in absolute ethanol). Comparable results were obtained in subsequent runs.



The absolute configuration of 3-piperidinol was determined by the synthetic scheme shown in Figure 1, which related S-(+)-arginine hydrochloride (6) with S-(-)-3-piperidinol (8)† This same configurational assignment was made recently by correlating mannitol with S-(-)-3-piperidinol.[10] The conversion of S-(-)-3-piperidinol, $[\alpha]_D^{23}$ -1.6°, obtained by resolution of the racemate with (+)-10-camphorsulfonic acid, to 1-methyl-3-piperidinol (4) $[\alpha]_D^{22}$ -2.4° (c 12.5 in absolute ethanol) confirmed the configuration as S-(-)-1-methyl-3-piperidinol and the hydroboration product as being of the R-configuration.

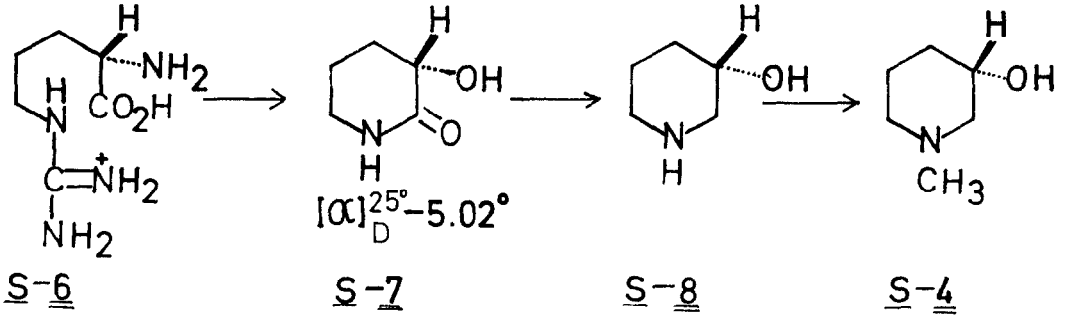


Figure 1

†S-6 was converted to S-7 by reported procedures[12] and S-7 was reduced to S-8 by lithium aluminum hydride.

The formation of the R-1-methyl-3-piperidinol (4) from the reaction with (-)-di-3-pinanylborane places the tetrahydropyridine in the same group as the hindered cyclic alkenes. This suggests that the hydroboration is occurring with the Lewis salt of the amine rather than the base form. The bulk and stereochemistry of the substituted borane attached to the nitrogen of the tetrahydropyridine would preclude the possibility of evaluating any of the current models for hydroboration with this reaction.[11]

We thank the National Institutes of Health for a Public Health Service Fellowship, 1962-1965, to one of us (CKS) and for a research grant CA-04143.

References

1. H. C. Brown, "Hydroboration," Benjamin, New York, 1962, chapter 14.

2. H. C. Brown, N. R. Ayyangar, and G. Zweifel, J. Amer. Chem. Soc., 86, 397 and 1071 (1964).

3. A. Streitwieser, Jr., L. Verbit, and R. Bittman, J. Org. Chem., 32, 1530 (1967).

4. D. R. Brown, S. F. A. Kettle, J. McKenna, and J. M. McKenna, Chem. Comm., 667 (1967).

5. K. R. Varma and E. Caspi, Tetrahedron, 24, 6365 (1968).

6. D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, J. Amer. Chem. Soc., 90, 4877 (1968).

7. K. Mislow and M. Raban, "Topics in Stereochemistry," vol. 1, eds., E. L. Eliel and N. L. Allinger, Interscience, New York, 1967.

8. R. E. Lyle, K. P. Carle, C. R. Ellefson, and C. K. Spicer, J. Org. Chem., in press.

9. R. S. Cahn, J. Chem. Ed., 41, 116 (1969), and references cited therein.

10. C. C. Deane and T. D. Inch, Chem. Comm., 812 (1969).

11. J. D. Morrison, Surv. Prog. Chem., 3, 147 (1966), and H. S. Mosher and J. D. Morrison, "Asymmetric Reactions in Organic Chemistry," Prentice-Hall, New York, In Press. The authors of this paper express appreciation to JDM for an opportunity to see a preprint of Chapter 6 of the book and for helpful discussion.

12. a) P. Hamilton and P. Ortiz, Biochem. Preparations, 4, 76 (1955);
b) K. Felix and H. Müller, Z. Physiol. Chem., 174, 112 (1928).