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**University of New Hampshire, Ph.D., 1966
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AMINOALCOHOLS BY THE HYDROBORATION
OF UNSATURATED AMINES

BY

COURTLAND KOLBUS SPICER

B. A., University of Connecticut, 1959

M. S., University of Vermont, 1961

A THESIS

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This thesis has been examined and approved.

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Courtland K. Spicer

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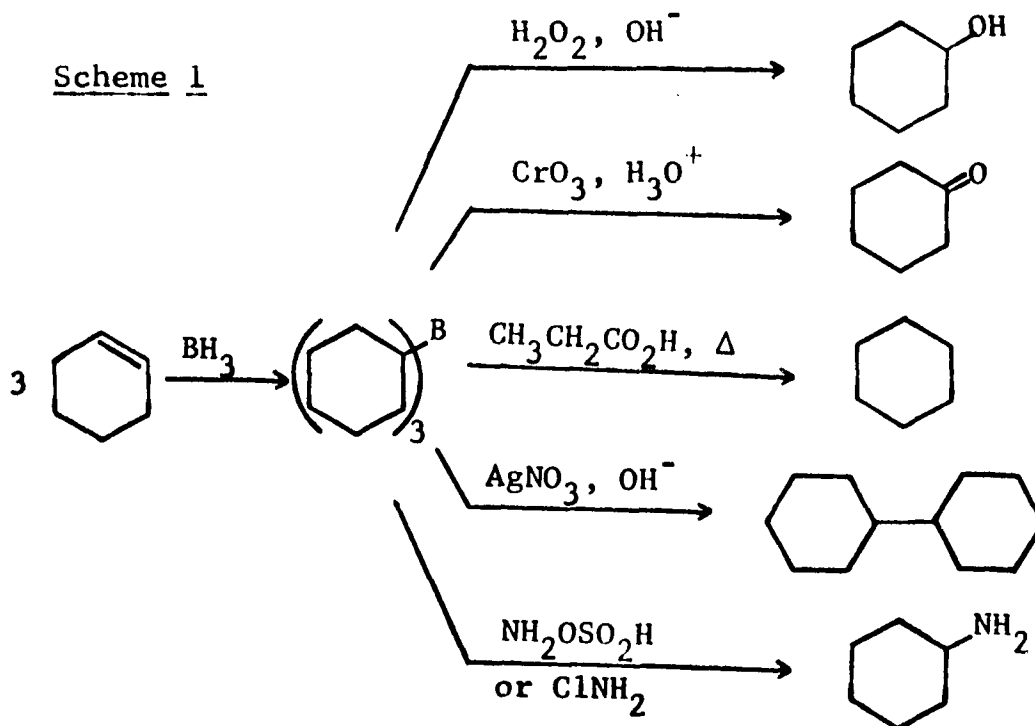
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INTRODUCTION

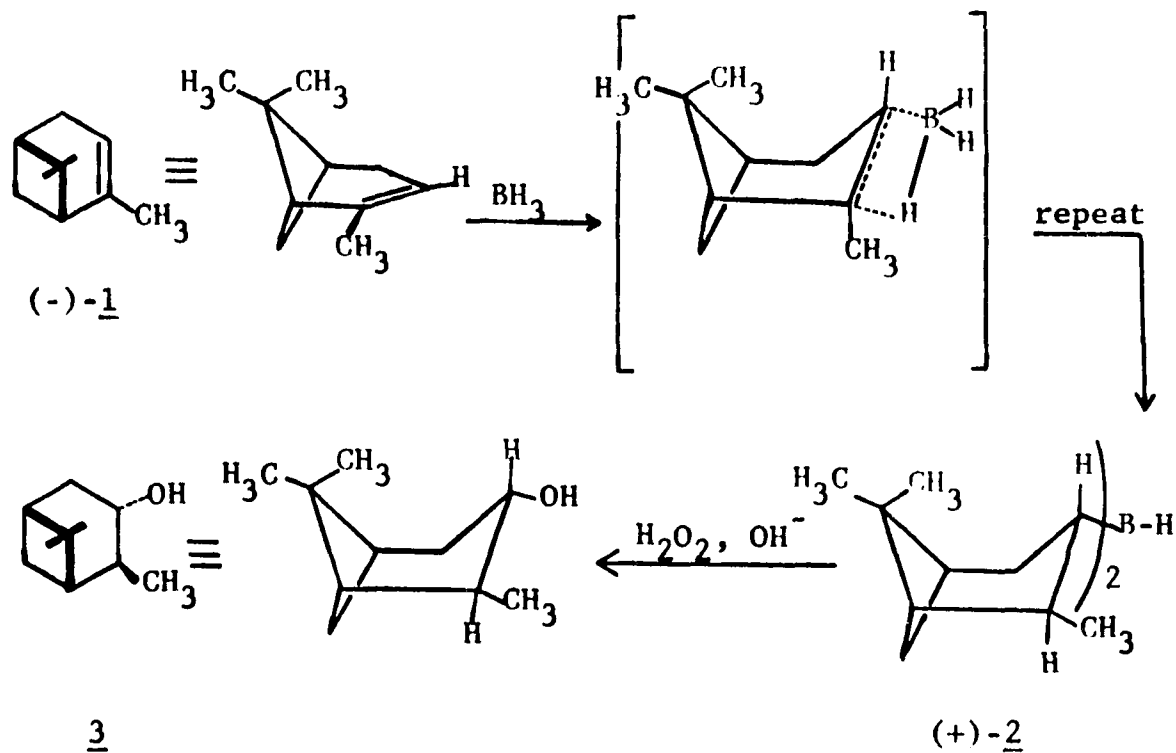
One of the more useful synthetic tools available to the organic chemist is the hydroboration reaction.¹ The extensive work of H. C. Brown and his collaborators since 1956 established the procedures for conveniently preparing organoboranes by the addition of boron hydrides to carbon-carbon multiple bonds. Much of the synthetic usefulness of the reaction has centered around the subsequent conversion of the organoborane thus produced to alcohols¹, carbonyl compounds¹, alkanes¹, coupled products¹, and amines.² This may be illustrated by the reaction of cyclohexene with diborane to give tricyclohexylborane, which is then treated with the appropriate reagent (Scheme 1). For the purposes of this thesis, further discussion will be limited to the preparation of alcohols from olefins.



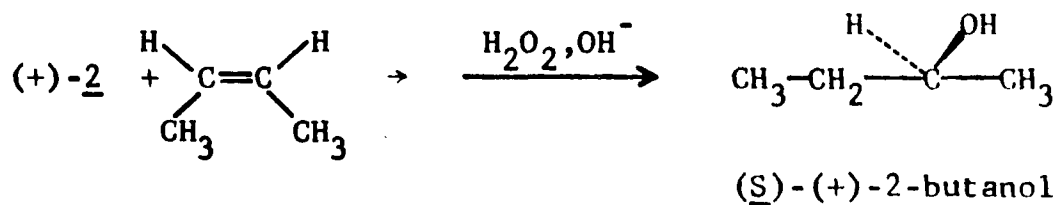
Brown found that the hydroboration of olefins proceeds via a cis-addition of a boron hydride bond to a carbon-carbon double (or triple) bond in an anti-Markownikoff manner such that the predominant product has the boron bonded to the less highly substituted carbon atom. Oxidation of the alkylborane thus formed gives an alcohol in which the hydroxyl group has the same position as that formerly occupied by the boron. Thus hydroboration is an important synthetic tool, for it produces the isomeric alcohol to that formed by hydration of an olefin. Hydroboration was found to be somewhat sensitive to electronic effects, but this reaction was particularly susceptible to steric influences. The attack of diborane occurs preferentially from the less hindered side of the double bond, probably via a four-center transition state, so that the overall reaction is stereoselective.

It was also found that diborane actually reacts as the monomer, borane (BH_3), and it is often convenient to regard the reagent as such. The three active hydrogens of a borane molecule may each attack a double bond, depending on the steric influences of adjacent groups, and thus the organoborane produced may be a mono-, di-, or trialkylborane.

These observations can be illustrated by the reaction of borane with the terpene α -pinene (1).

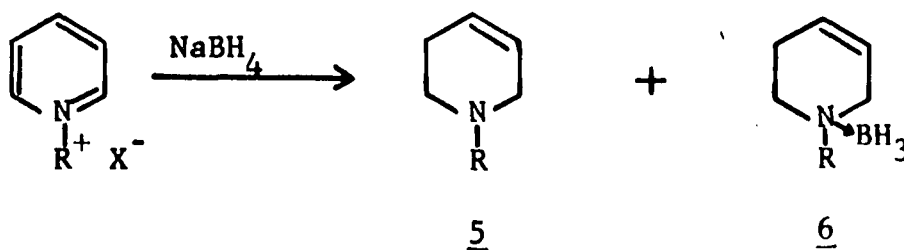


Since α -pinene is available in the optically active form, Brown³, as well as other workers⁴, has described its use in the preparation of optically active alcohols by asymmetric induction. For example, the hydroboration of cis-2-butene with (+)-diisopinocampheylborane [(+)-2] gave 2-butanol (4) in 86% optical purity.



Since the absolute configuration of (+)-diisopinocampheylborane is known⁵, Brown³ proposed an empirical model for relating the absolute configuration of the alcohols produced by hydroboration. It was found that this method, while yielding straightforward results for the hydroboration of unhindered and acyclic olefins, was less reliable when reaction times were short, as with hindered and trans olefins, for alcohols of much lower optical purity were obtained. In addition, the products were of exactly the opposite configuration from that predicted by the simple model. At least one olefin was found^{3c} to undergo reaction by both simple addition and displacement of α -pinene, further complicating this method for establishing absolute configurations.

As a result of a continuing study^{6,7} in these Laboratories of the sodium borohydride reduction of pyridinium ions, a number of partially reduced pyridines, especially tetrahydropyridines (5), were available. It was observed that such reductions often gave the products as the amineborane derivatives (6). This is interesting since hydroborations can be run using amineboranes^{8,9} as the source of diborane.



The expected products of hydroboration of tetrahydropyridines are 3- and 4-piperidinols. These piperidinols are of considerable pharmacological interest because their derivatives and related compounds have shown activity as analgesics¹⁰,

anesthetics¹¹, psychotomimetics¹², hypotensive drugs¹³, anti-malarials¹⁴, antispasmodics¹⁵, antihistaminics¹⁶, and anti-depressants.^{15b} Piperidinols are also related structurally to a number of naturally-occurring compounds, such as carpaine¹⁷, cassine¹⁸, the tropane alkaloids¹⁹, pseudoconhydrine²⁰, febrifugine²¹, retamin²², veratramine²³, and hydroxypipericolic acid.²⁴

At the outset of this thesis research in 1961, there were only a few references in the literature to the hydroboration of unsaturated amines.²⁵⁻²⁷ During the development of this thesis, several nitrogen-containing alkenes were reported to have been hydroborated, including dehydroproline derivatives²⁸⁻³⁰, baikian³¹, several enamines³²⁻³⁵, benzomorphans^{9,36}, deoxycodine³⁷, Δ^8 -dehydrosparteine²², and dimethylallylamine.^{8g}

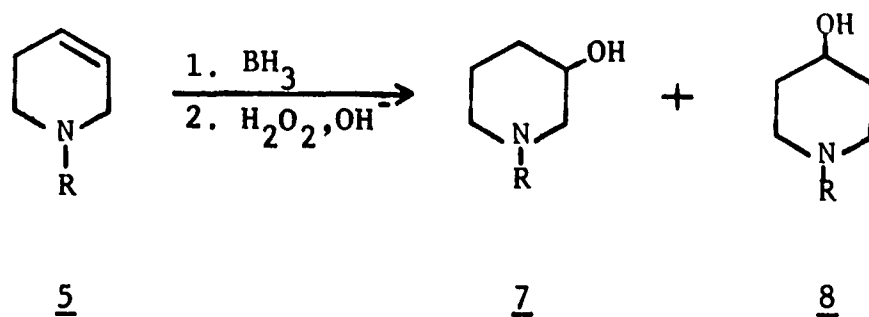
In view of the synthetic utility of the hydroboration reaction it was decided to extend its scope to a number of olefinic amines in order to prepare various piperidinols and other aminoalcohols. The product analysis of such reactions would be utilized to attempt to determine any role the heterocyclic nitrogen might play in the reaction.

DISCUSSION AND RESULTS

Hydroboration of N-Alkyl-1,2,5,6-tetrahydropyridines

The conversion of substituted tetrahydropyridines to piperidinols by hydration has been reported.³⁸ This method can lead to molecular rearrangements, is not stereospecific, and usually gives only the most highly substituted alcohol (Markownikoff addition). The preparation of piperidinols by hydroboration seemed to provide a valuable companion method in view of the accessibility of a variety of N-alkyltetrahydropyridines available by the sodium borohydride reduction of pyridinium ions.^{6,7}

Exploratory experiments³⁹ in these laboratories by Carle and Nudd in 1960 demonstrated that the hydroboration-oxidation of several N-alkyl-1,2,5,6-tetrahydropyridines (5) give as product a mixture of the expected N-alkylpiperidinols. However, the relative amounts of the isomeric N-alkyl-3-piperidinols (7) and N-alkyl-4-piperidinols (8) were not determined.



R = n-C₄H₉, -CH₂-Ph,

-CH₂CH₂-Ph

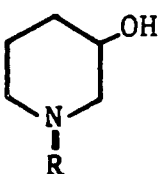
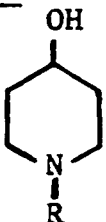
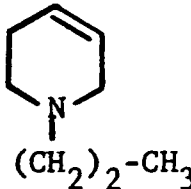
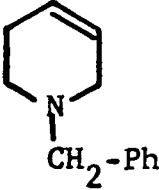
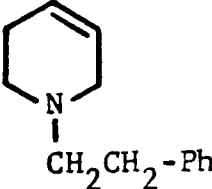
The distilled product mixtures from these preliminary reactions were available and were subjected to detailed gas chromatographic analyses at an initial stage of this research. A summary of the overall yield and product composition is reported in Table I.

Several conclusions can be made from these results. One is that the yields of piperidinols are relatively modest. This can be explained at least in part by the fact that the starting tetrahydropyridines were obtained by the sodium borohydride reduction of the appropriate alkyl halide pyridinium salt. This reaction has been shown^{6b,7f} to lead to (10-30%) N-alkylpiperidines, which are not readily separated from tetrahydropyridines by distillation. Thus the starting amines contained considerable amounts of inert piperidines mixed with the tetrahydropyridines.

It can also be seen that the isomer distribution substantially favors the 3-piperidinols (7) over the 4-piperidinols (8) by a factor of about three to one. These results were quite unexpected from a consideration of steric factors, since the hydroboration of 3-substituted cyclohexene (9) was reported⁴⁰ to give products of equal isomer distribution. Thus the carbons of the 3,4-double bond in the tetrahydropyridines studied would be expected to be equivalent in reactivity toward attacking borane reagent, being two atoms removed from the possible steric influence of the N-alkyl group. That this was not the case means that the ring nitrogen is exerting some influence so that the reaction course is fundamentally different from that with related carbocyclic compounds. The nature of this influence and directive effects in the hydroboration of tetrahydropyridines will be discussed

Table I

Hydroboration of N-Alkyl-1,2,5,6-tetrahydropyridines

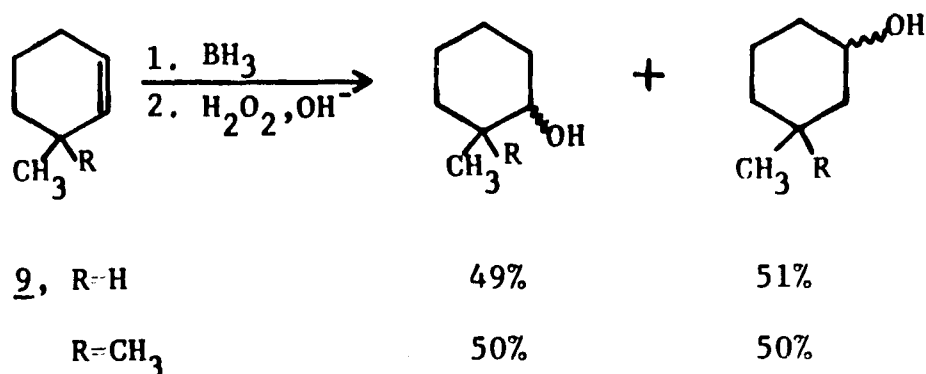
<u>Tetrahydro- pyridine</u>	<u>Yield of Piperidinols, %^a</u>	<u>Relative Yields, %^b</u>		<u>Gas Chromatographic Column</u>
				
 (CH ₂) ₂ -CH ₃	34 ^c	79	21	2 m. 5% Carbowax 20M on Chromosorb W, 150°, 10 psi
 CH ₂ -Ph	42-70 ^d	76	24	1 m. 5% Carbowax 20M on Haloport-F, 173°, 15 psi
 CH ₂ CH ₂ -Ph	58-65 ^e	74	26	1 m. 5% Carbowax 20M on Chromosorb W, 173°, 20 psi

^a Distilled material; yields are based on starting tetrahydropyridine.

^b Calculated from the areas under the respective peaks in the gas chromatogram. These percentages represent the average of at least two separate injections.

^c One experiment; ^d five experiments; ^e three experiments.

later.



The possibility of the formation of an intermediate amineborane was obvious, and it thus became an objective of this research to examine the role, if any, that such an amineborane would have on the direction of hydroboration of cyclic unsaturated amines. It should be pointed out here that the predominance of 3-piperidinols over 4-piperidinols was interesting from a synthetic standpoint, since synthetic routes to the 3-piperidinols are considerably more limited than those routes to the 4-piperidinols. This fact is reflected in the prices of commercially available compounds.⁴¹

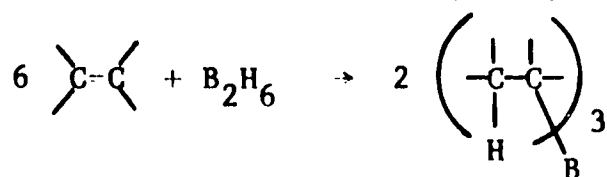
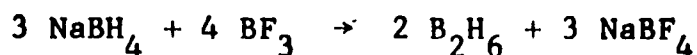
Another conclusion from the data in Table I is that, at least for the compounds studied, the size of the N-alkyl group of the tetrahydropyridines seems to have little effect on the isomer distribution with hydroboration.

Hydroboration of N-Methyl-1,2,5,6-tetrahydropyridine by the In Situ Generation of Diborane

N-Methyl-1,2,5,6-tetrahydropyridine (10) was chosen as a model compound for these hydroboration studies in order to minimize any possible steric effect of the size of the N-alkyl group and because the lower boiling points of the expected

N-methylpiperidinols would facilitate analysis by gas chromatography. The properties of the piperidinols 11 and 12 were well established, thereby simplifying product identification. Initial experiments were conducted using 10 prepared by the sodium borohydride reduction of pyridinium methiodide according to the procedure of Anderson^{6b}, but in the majority of later reactions 10 from a commercial source⁴² was employed.

The title compound, 10, was treated with diborane generated in situ by the addition of boron trifluoride etherate to a mixture of sodium borohydride and 10 in diglyme (diethylene glycol dimethyl ether). The diborane which was produced could combine with the amine and/or olefin according to the stoichiometry below, illustrating the formation of the trialkylborane.



Two reactions with the same stoichiometry (0.025 moles of 10 and 0.040 moles of BH_3) and work-up were performed. They differed in that in reaction I the mixture of reactants was heated under equilibration conditions (100° for 2 hr.) and reaction II was run at room temperature. After oxidation and work-up, reaction I gave ca. 37% yield of N-methylpiperidinols with 71% of the 3-isomer (11) and 29% of the 4-isomer (12). Reaction II gave ca. 38% yield with the relative yields of 75% of 11 and 25% of 12.

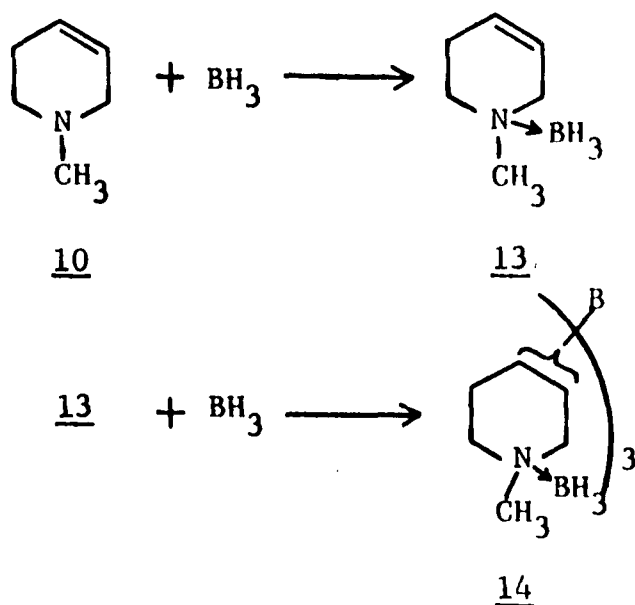
Another similar reaction (reaction III) with the same stoichiometry as reactions I and II was run, but with the reaction time limited to 10 minutes at room temperature. Oxidation and the usual work-up gave only ca. 9% yield of piperidinols with the relative yields of 72% of 11 and 28% of 12. About 25% of unreacted tetrahydropyridine 10 was also obtained from the ether extract of the basified reaction mixture.

It was apparent that N-methyltetrahydropyridine was giving results analogous to those with the N-butyl, N-benzyl, and N- β -phenethyl homologs. Also, heating the organoborane intermediate did not appreciably alter the yield or the distribution of isomers. The fact that a short reaction time gave a considerably lower yield of products but the same relative amounts of the 3- and 4-piperidinols, gave rise to the working hypothesis that borane was initially attacking the nitrogen atom in a fast step and the addition of borane to the carbon-carbon double bond was proceeding more slowly. This result also suggested that the distribution of isomers represented the kinetic, as well as the thermodynamic mixture of products.

The low yields in the above reactions could not be explained by the presence of N-methylpiperidine in the starting material. The sodium borohydride reduction of pyridinium methiodide has been shown to give only N-methyl-1,2,5,6-tetrahydropyridine (10)^{6b,7f}, so 10 prepared by this method was free of N-methylpiperidine, as was 10 obtained commercially.

A possible explanation for the lower yields was incorrect reaction stoichiometry. If one molar equivalent of borane were involved in reaction with the basic nitrogen of 10 initially and completely, then the reaction of 0.025 mole of 10 and 0.040 mole of BH_3 would give 0.025 mole of N-methyl-

1,2,5,6-tetrahydropyridine amineborane (13), with only 0.015 mole of BH_3 in excess. Even though the trialkyl borane was formed and the borane was used most efficiently, only a calculated 0.0067 mole of BH_3 would be in excess. In view of the reactivity of diborane, this small excess of borane could have been destroyed by reaction with small amounts of impurities in starting materials and solvent.



A second possible cause of the low yield was that the hydroboration reaction had not gone to completion in 2 hours. Brown found⁴³ that the addition of boron trifluoride etherate to a sodium borohydride solution in diglyme does not generate diborane smoothly because of the intermediate formation of sodium diborohydride ($\text{NaBH}_4 \cdot \text{BH}_3$), whereas the reverse addition of a diglyme solution of sodium borohydride to a solution of boron trifluoride etherate in diglyme does generate diborane smoothly. The latter mode of addition had not been used because of the possibility of reaction of 10 with the boron trifluoride etherate, a strong Lewis acid.

An experiment was designed to improve the yield of

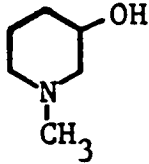
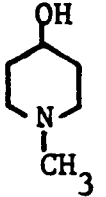
piperidinols by using a longer reaction time and a larger excess of diborane. In order to demonstrate the synthetic usefulness of hydroboration as applied to tetrahydropyridines, this reaction (reaction IV) was run on a larger scale than those previously mentioned. Thus, 0.25 mole of tetrahydropyridine 10 was treated with a calculated 0.718 mole of BH_3 at room temperature for 12 hr. After oxidation and the usual work-up, there was obtained an 83.5% yield of crude piperidinols 11 and 12 in the relative amounts of 74.5% of 11 and 25.5% of 12. Although reaction IV did not establish whether the excess diborane or the longer reaction time was responsible for the higher yield of piperidinols, it seems likely on the basis of subsequent experiments that both factors contributed. The results of reactions I-IV are summarized in Table II.

Cleavage of Diglyme

In the reactions described above, an unknown compound always was present in the isolated product mixtures. The initial hypothesis was that this compound was N-methyl-2-hydroxymethylpyrrolidine (15), perhaps arising via neighboring-group participation in a rearrangement of the intermediate organoborane (16). 3-Substituted piperidines are known to undergo such rearrangements.⁴⁴

Table II

Hydroboration of N-Methyl-1,2,5,6-tetrahydropyridine (10)

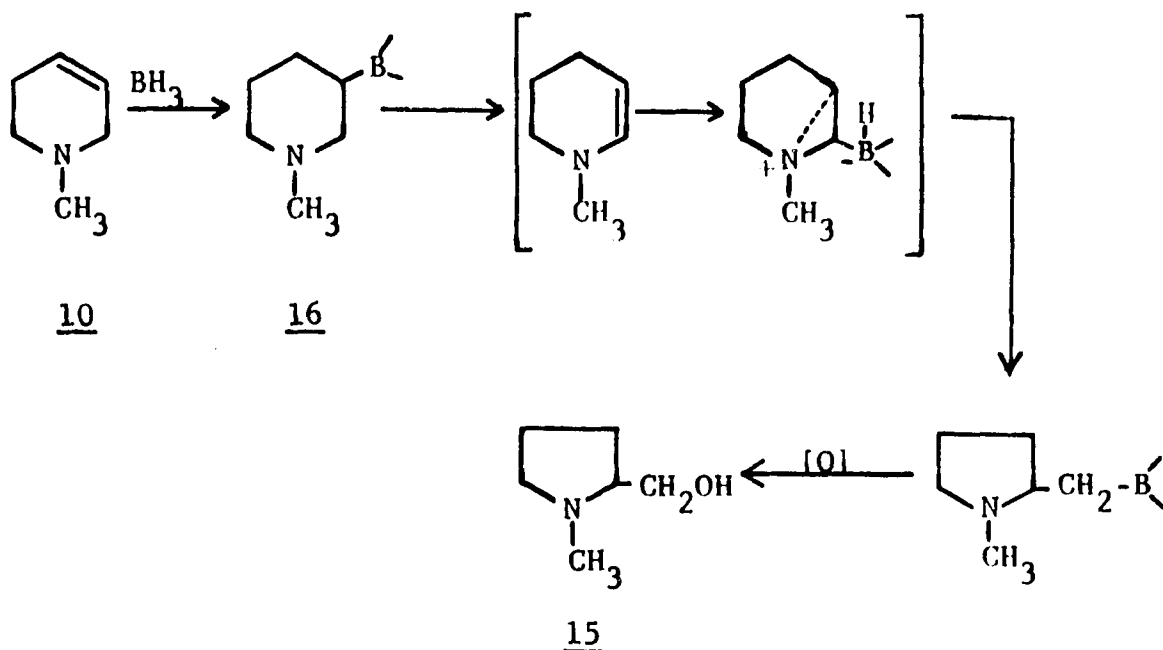
Reaction Number	Moles of <u>10</u>	Moles of BH_3^{a}	Reaction Temp.	Reaction Time ^b	Yield of Piperidinols, % ^c	Relative yields, % ^d	
							
I	0.025	0.040	100°	2 hr.	37	71	29
II	0.025	0.040	25°	2 hr.	38.5	75	25
III	0.025	0.040	25°	10 min.	9	72	28
IV	0.25	0.718	25°	12 hr.	83.5	74.5	25.5

^a Generated in situ.

^b Reaction time after completion of diborane generation.

^c Yields are based on starting tetrahydropyridine 10 and are calculated from the gas chromatogram.

^d Relative yields are calculated from the areas under the respective peaks in the gas chromatogram.

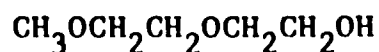


Comparison of the gas chromatographic retention times of the unknown compound with that of authentic 15⁴⁵ showed this hypothesis to be incorrect. Authentic 15 had a retention time shorter than either the N-methyl-3- or -4-piperidinols and was not present in either these reaction mixtures or in those of any subsequent experiments.

The unknown compound 18 had a retention time intermediate between those of piperidinols 11 and 12 and interfered somewhat with the gas chromatographic analysis of these compounds. A small amount of unknown 18 from a distilled hydroboration reaction mixture was collected by preparative gas chromatography. Compound 18 was a colorless liquid with an infrared spectrum containing strong bands at $3650-3450\text{ cm}^{-1}$, indicative of either an oxygen-hydrogen or nitrogen-hydrogen stretching vibration of a hydroxyl group or an amine, and at $1150-1040\text{ cm}^{-1}$, indicative of the carbon-oxygen stretching vibration of alcohols and ethers. The infrared spectrum was similar to, but not identical with, that of diethylene glycol

monoethyl ether, suggesting that 18 might be diethylene glycol monomethyl ether.

A small portion of a distilled hydroboration reaction mixture containing 11, 12 and 18 was taken up in anhydrous ether, and hydrogen chloride gas was passed through the solution. The resulting white precipitate was separated by filtration, and the filtrate, which was now free of basic compounds, was analyzed by gas chromatography. Unknown compound 18 was still present. Comparison of the infrared spectra and gas chromatographic retention times of unknown 18 and authentic diethylene glycol monomethyl ether⁴⁶ showed that they were the same compound.



18

In view of the importance of diglyme as a reaction solvent, these results were communicated⁴⁷, with the suggestion that the diglyme cleavage was proceeding analogously to that of the reductive cleavage by diborane of other ethers.⁴⁸⁻⁵⁰ It is equally possible, however, that the diglyme cleavage resulted from reaction with hydrochloric acid during the work-up procedures.

Hydroboration of N-Methyl-1,2,5,6-tetrahydropyridine by the External Generation of Diborane

The results of reactions I-IV suggested the intermediacy of an amineborane in the hydroboration of tetrahydropyridines, but it was decided to investigate this possibility in greater detail. Therefore, a series of experiments were designed in which the reaction stoichiometry was carefully

controlled. These reactions were run in tetrahydrofuran into which was bubbled diborane which was generated in an external flask. This procedure eliminated any possible complications arising from the presence of inorganic salts, such as sodium borohydride, and the strong Lewis acid, boron trifluoride etherate. Also, diborane is much more soluble in tetrahydrofuran than in diglyme, and being lower boiling, tetrahydrofuran is easily removed during the work-up of reaction mixtures.

The reaction of the tetrahydropyridine 10 with one molar equivalent of borane (BH_3) and the removal of solvent by distillation gave the expected amineborane 13 (reaction V). This compound was obtained crude as an oil, the infrared spectrum of which contained strong bands at 2360 and 2270 cm^{-1} , characteristic of the boron-hydrogen stretching frequency of amineboranes, with a strong shoulder at 2320 cm^{-1} , the overtone of the boron-hydrogen deformation frequency at 1160-1180 cm^{-1} . Strong absorption in the 2400-2200 and 1170 cm^{-1} regions of the infrared spectrum has been previously shown^{51,52} to be characteristic of the borane addition compounds of tertiary amines. Similar absorption bands have been observed in the spectra of a number of tetrahydropyridine amineboranes which were produced from the sodium borohydride reduction of pyridinium ions.^{6b,53} The infrared spectrum of 13 also contained bands of medium intensity at 3040 and 3005 cm^{-1} , characteristic of the carbon-hydrogen stretching frequency of olefins.

A purer sample of 13 was obtained using a procedure similar to that of reaction V. The nuclear magnetic resonance (nmr) spectrum (Fig. 1) of this sample of 13 showed a multiplet at 5.74 ppm due to two vinyl hydrogens, a multiplet at 3.30

ppm due to two allylic hydrogens at carbon-2, a triplet at 2.90 ppm due to two methylene hydrogens at carbon-6, a multiplet at 2.26 ppm due to two allylic hydrogens at carbon-5, and a singlet at 2.50 ppm due to the three N-methyl hydrogens. These assignments were made by analogy with the nmr spectrum of 13 with that of 1,2,5,6-tetrahydropyridine (5, R H)⁵⁴, which has similar chemical shifts for the respective analogous hydrogens. The nmr spectrum of amineborane 13 was found to be similar in band shape with that of 10, except that there was a downfield shift of the resonance bands of the methylene hydrogens at the 2- and 6-positions by about 0.5 ppm and the N-methyl by 0.28 ppm. This observation is consistent with the fact that hydrogens on carbon atoms adjacent to a positively charged nitrogen are deshielded, and thus their absorptions are found at lower field than those of the parent basic compounds. Thus the infrared and nmr spectroscopic data clearly support the assignment of 13 as N-methyl-1,2,5,6-tetrahydropyridine amineborane.

The molar refraction⁵⁵ of 13 was found to be 35.84. The calculation of a theoretical value for this compound was somewhat limited because the only literature value^{8g} for the atomic refraction of a quaternary boron (2.5) was expressed in only two significant figures. If it is assumed that this value for boron is exact, the calculated value for the molar refraction of N-methyl-1,2,5,6-tetrahydropyridine amineborane (13) is 36.76, which is in excellent agreement with the experimental value.

Alkaline oxidation of 13 from reaction V gave only a trace amount of piperidinol 11. This indicates that virtually no organoborane, such as 16, was present in 13, since oxidation of 16 would have converted it to piperidinol 11.

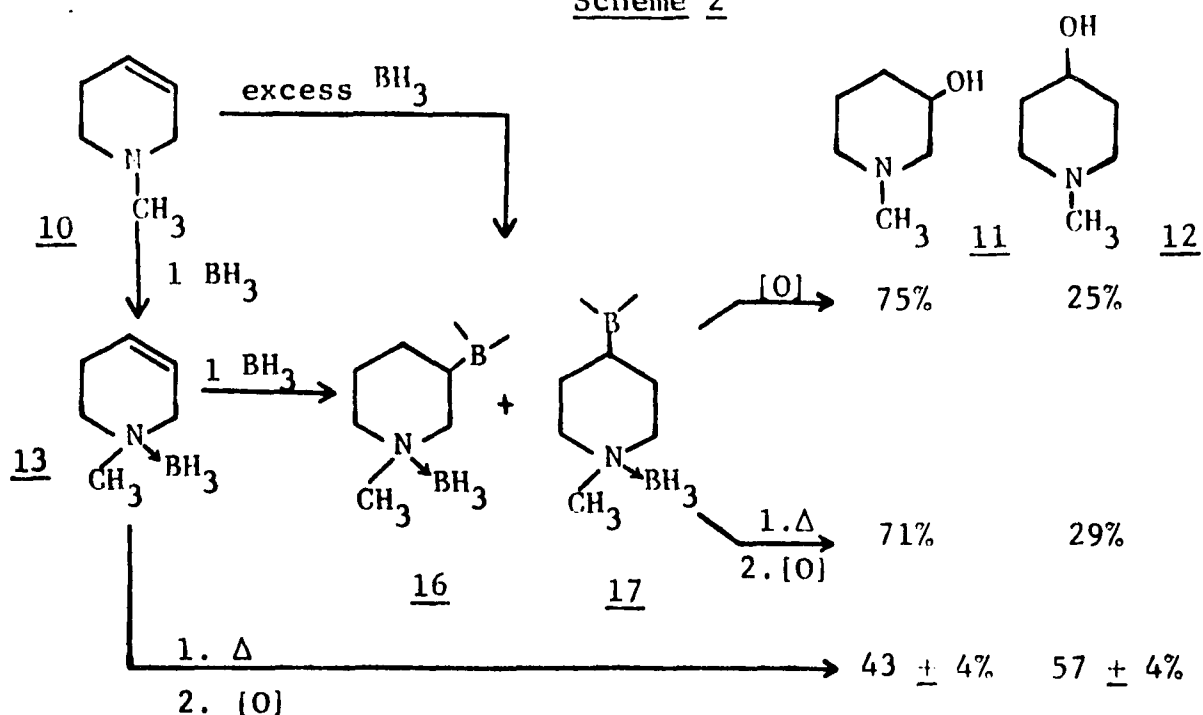
Thermal equilibration of amineborane 13 from reaction

V by heating in diglyme and subsequent alkaline oxidation (reaction VI) gave a mixture of piperidinols 11 and 12, in the relative amounts of ca. 43% of 11 and 57% of 12. This ratio of products was quite different from the previous hydroborations of 10 in which 11 was favored by a factor of 3:1. The interpretation of this result is that the amineborane 13 underwent a substantial amount of self-hydroboration, probably via the thermal dissociation of 13 to diborane, which then added to the olefinic double bond. Such a dissociation-addition mechanism of amineborane hydroborations has been proposed by Hawthorne^{8a,8c,8d,8f} and Ashby.^{8b}

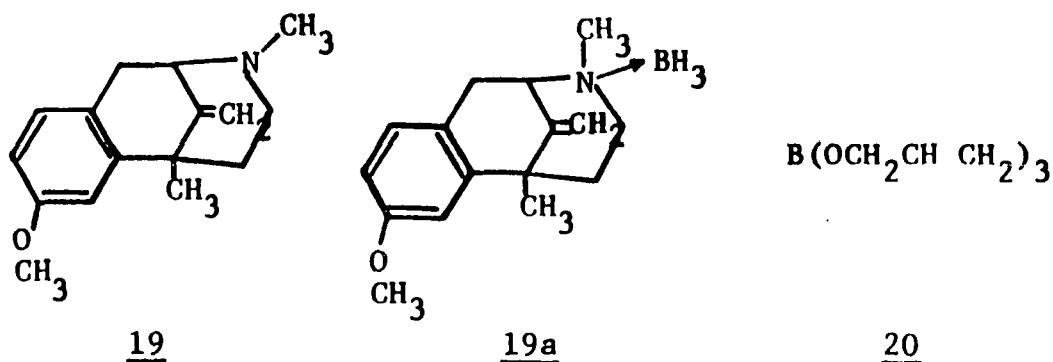
The reaction of tetrahydropyridine 10 with a two molar equivalent of borane (BH_3) and subsequent alkaline oxidation (reaction VII) gave the expected 3- and 4-piperidinols in the relative amounts of 73% of 11 and 27% of 12, the same ratio as had been previously obtained with reactions in which diborane was generated in situ.

The results of Reactions I-VII are summarized in Scheme 2. These results demonstrate that the working hypothesis was correct in that the hydroboration of unsaturated amines proceeds stepwise, such that the first mole of borane reacts with the nitrogen atom to form an amineborane, such as 13, and the second mole of borane adds to the carbon-carbon double bond.

Scheme 2



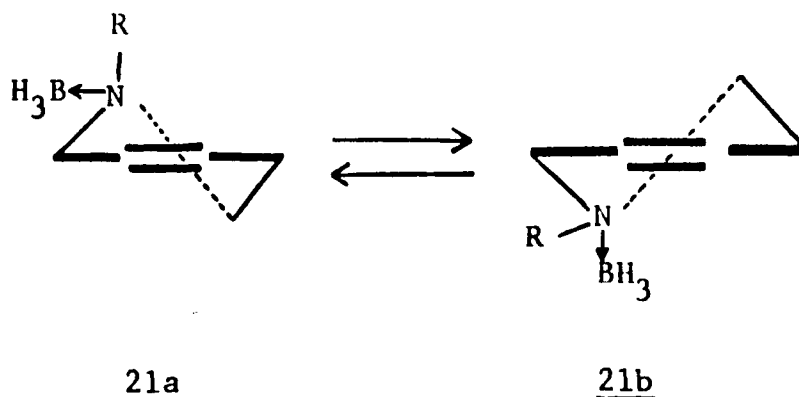
When the above experiments had been completed, support for these conclusions was obtained as a result of a series of papers by Kugita and Takeda.^{9,36} These workers found that the hydroboration of the 9-methylene-6,7-benzomorphan 19 also proceeds stepwise, with the first mole of borane adding to the nitrogen to form amineborane 19a without any addition to the carbon-carbon double bond. Also, by way of analogy, Brown and Cope have reported⁵⁶ that the hydroboration of allyl alcohol leads first to allyl borate (20) before undergoing addition of borane to the double bond.



Directive Effects in the Hydroboration of Tetrahydropyridines

Now that the intermediacy of amineboranes in the hydroboration of tetrahydropyridines was established, there remained the question of the possible directive influences of such amineboranes on hydroboration. Hydroboration has been shown to be influenced by both steric and electronic factors.¹ Steric influences appear to be relatively unimportant in the present case of N-alkyl-1,2,5,6-tetrahydropyridines, for there is no detectable difference in the ratio of isomeric products with change in size of the nitrogen substituent. The alternative possibility is that conformation 21b is solely responsible for the formation of products. It seems unlikely that this possibility is valid for the range of substituents used. Also, inspection of Dreiding and Catalin molecular models⁵⁷ indicates that the 3- and 4-carbons of tetrahydropyridines should be equivalent in reactivity. This system presumably exists in a conformational equilibrium such as 21a \rightleftharpoons 22b. Such a simple conformational change should reduce the steric interactions of the nitrogen substituents and the diborane molecule in the transition state so that there would be no particular preference for direction of attack by di-

borane. This was found to be the case with the related carbocyclic compounds, 3-substituted cyclohexenes (9).⁴⁰



The effect of electronic influences on the direction of hydroboration of olefinic compounds containing various functional groups has been the subject of a systematic study by Brown and coworkers.^{56,58} They found for a series of allylic derivatives of the type $X-CH_2CH=CH_2$, that the percentage addition of boron to the secondary carbon increases with increasing electronegativity of the substituent X . This was explained in terms of a hydridic polarization of the boron-hydrogen bond so that with the inductive effect of an electron-withdrawing substituent, a transition state such as 22a would be favored over transition state 22b. A few examples of Brown's results are summarized in Table III.

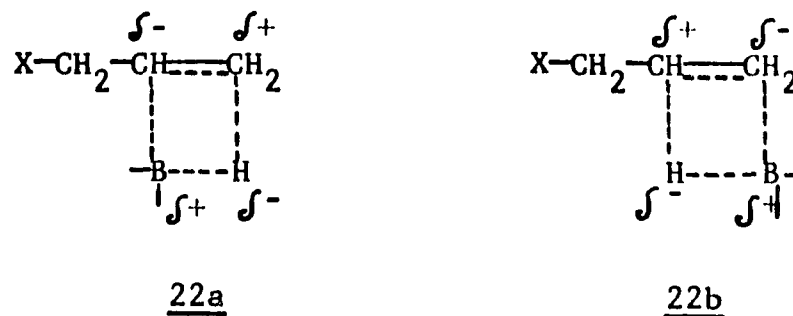


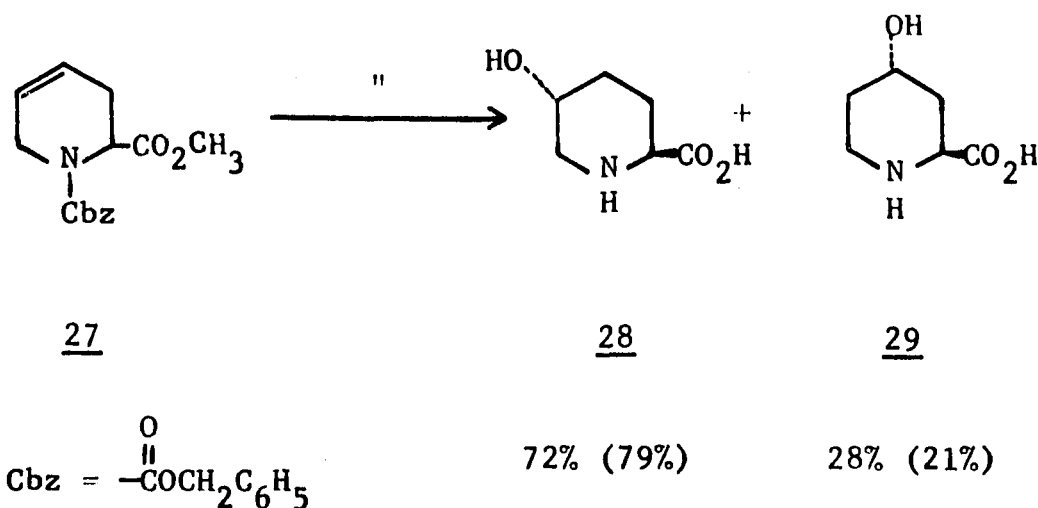
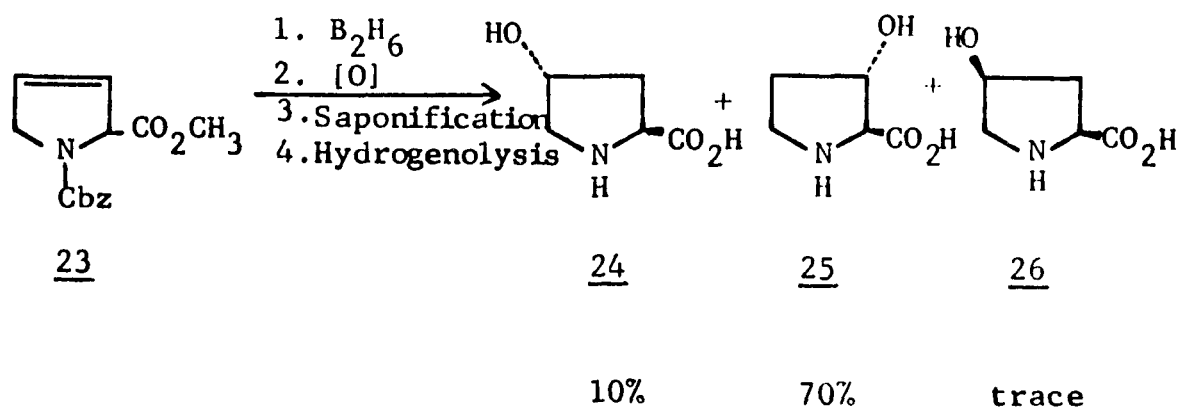
Table III

Hydroboration of Representative Allyl Derivatives^a

Substituent X in $\text{XCH}_2\text{CH}=\text{CH}_2$	% Addition of diborane to <u>2° carbon</u>	<u>1° carbon</u>
CH_3^-	6	94
C_6H_5^-	10	90
$\text{CH}_3\text{CH}_2\text{O}^-$	19	71
$\text{C}_6\text{H}_5\text{CO}_2^-$	25	75
CH_3CO_2^-	35	65
Cl^-	40	60
$p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_3^-$	45	55
F_3C^-	74	26

^a Values from ref. 56

These workers did not report the results of the hydroboration of the corresponding crotonyl derivatives, $XCH_2CH=CHCH_3$; however, they said "the directive influence of the substituent should be much more powerful... (and result) in a dominant addition of the boron to the neighboring 2-position". A test of this prediction is provided by the work of Witkop and his collaborators in which they report the direction of hydroboration of two representative unsaturated amines, N-carbobenzyloxy-3,4-dehydro-DL-proline methyl ester (23)²⁸ and N-carbobenzyloxy-DL-baikian methyl ester (27).³¹



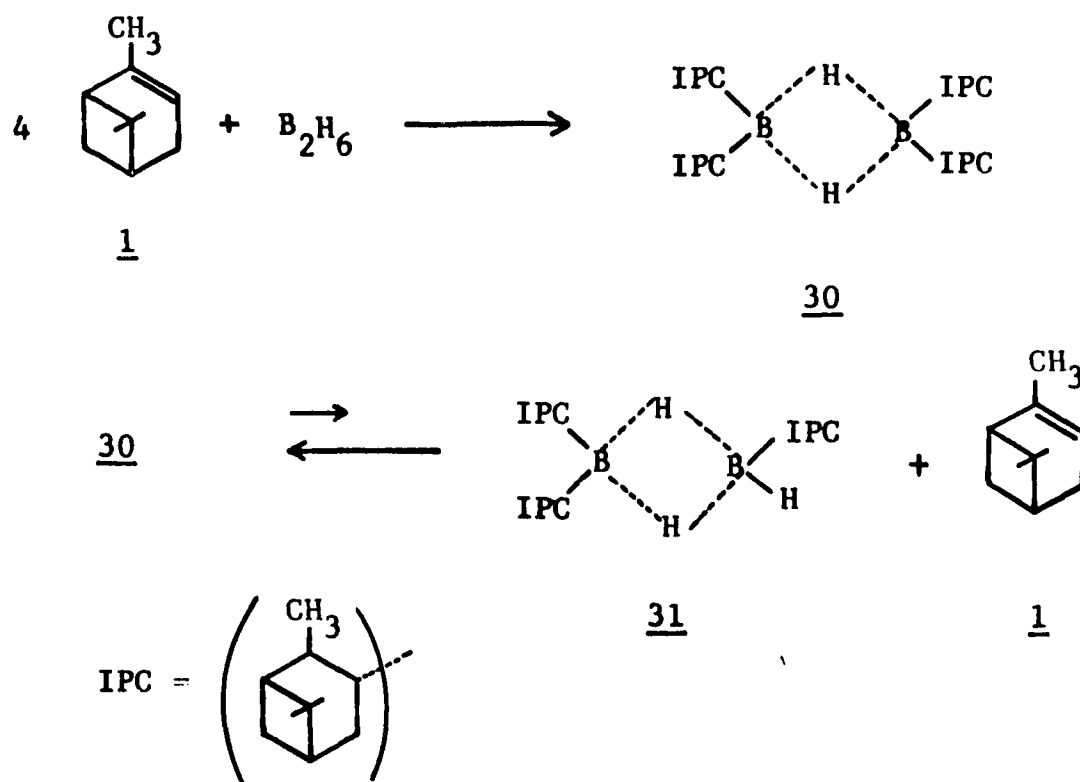
The major product of the hydroboration of 23 was trans-3-hydroxy-DL-proline (25), with trans-4-hydroxy-DL-proline (24) as a minor product. This ratio of products shows the effect of the substantial influence of the 2-carboethoxy group of 23 in directing attack of boron to carbon-3.

Since the carboethoxy group in the six-membered ring 27 is two carbons removed from the double bond, the inductive effect of its electronegativity should be much less important, and the directive influence on the hydroboration of 27 should result from the electronegativity of the nitrogen, which would lead to the prediction of predominant reaction of boron at carbon-5. This was found to be the case, with the hydroboration of 27 giving trans-5-hydroxy-DL-pipecolic acid (28) as the major product (relative 72%)⁵⁹, with trans-4-hydroxy-DL-pipecolic acid as the minor product (28%).⁵⁹

Compound 27 can be considered a tetrahydropyridine, so the results of hydroboration of this system are obviously analogous to the hydroboration of N-alkyltetrahydropyridines. The nitrogen of 27 is non-basic due to its carbobenzyloxy substituent, and the nitrogen of the tetrahydropyridine amineborane 6 is positively charged as well. The relative percentages of 28 and 29 obtained by hydroboration of 27 are virtually the same percentages as those of the analogous piperidinols 7 and 8 from the hydroboration of 6. It is concluded, therefore, that the results of the hydroboration of tetrahydropyridines are consistent with those of Witkop and provide support for and extension of the hypothesis of Brown; i.e., that the direction of hydroboration of unsaturated compounds containing an allylic functional group is influenced markedly by the electronegativity of the substituent.

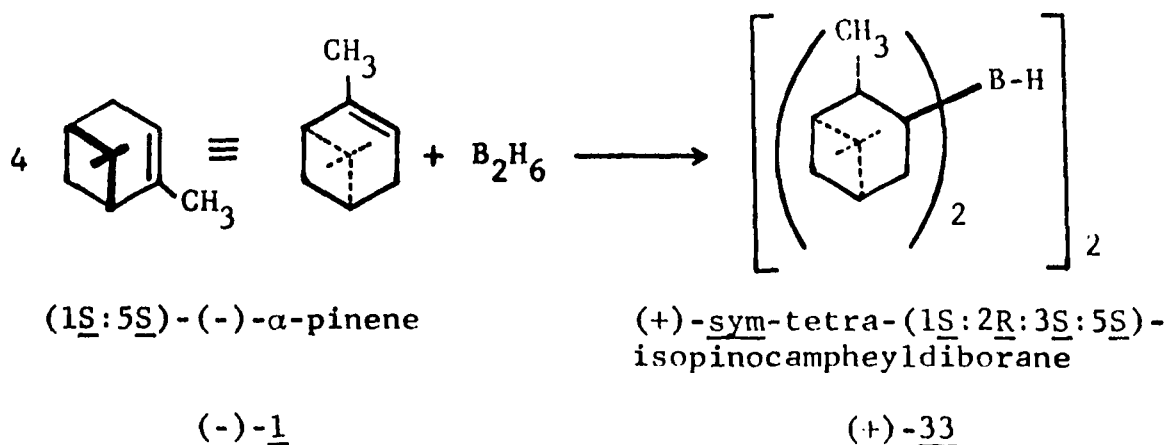
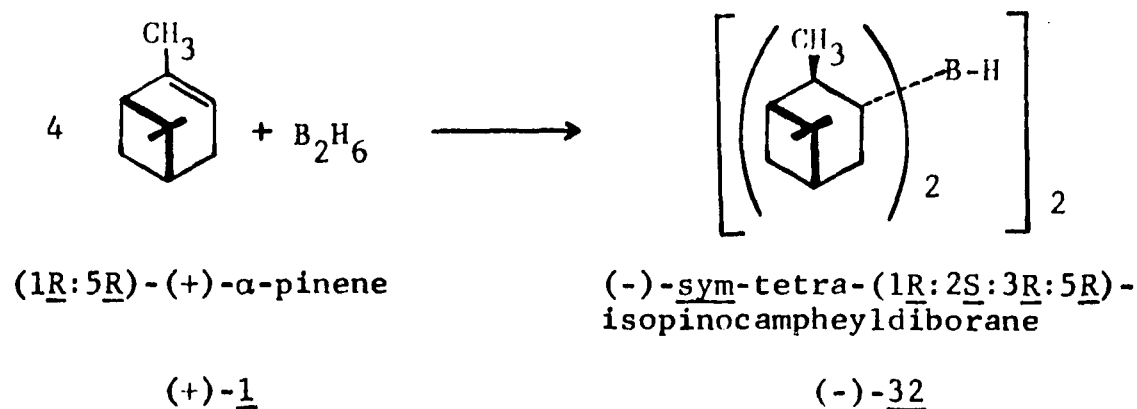
Optically Active Alcohols by Hydroboration of Olefins with
Optically Active Organoboranes

Brown and coworkers have established that the hydroboration of α -pinene proceeds with facility.⁵ With excess α -pinene the dialkylborane which is produced has the dimeric sym-tetraisopinocampheylidborane structure 30, but in the absence of excess α -pinene, the product 30 partially dissociates into the trisopinocampheylidborane 31 and α -pinene.



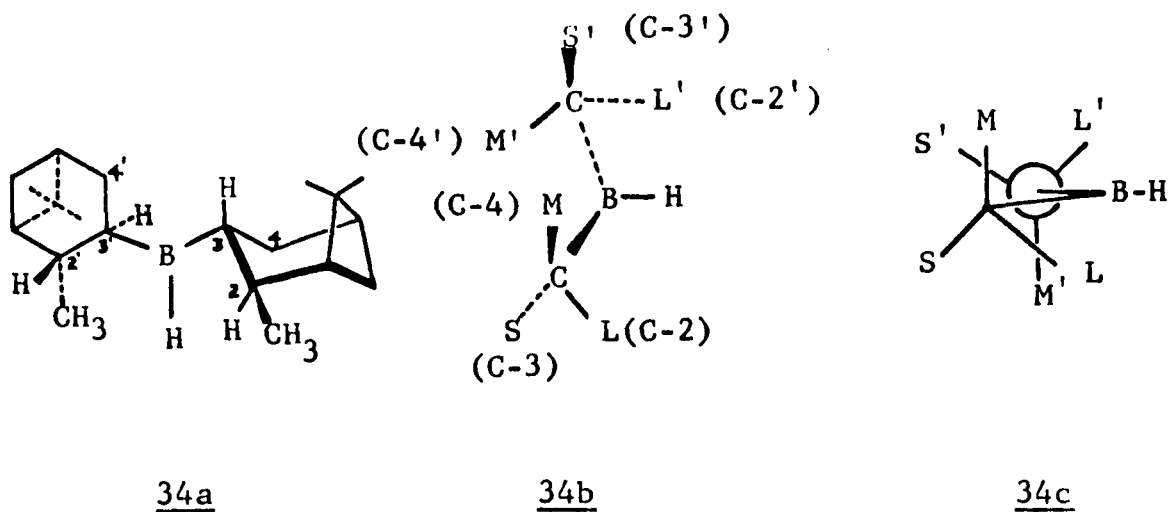
The absolute configuration of (+)- and (-)- α -pinene is known⁶⁰, and the absolute configuration of the two enantiomeric organoboranes (-)-32 and (+)-33 was assigned by Brown as indicated below.⁶¹ It is generally more convenient to refer to the organoboranes (-)-32 and (+)-33 as the monomers (-)- and (+)-diisopinocampheylborane [(-)-2 and (+)-2], and this nomen-

clature will be used where appropriate.



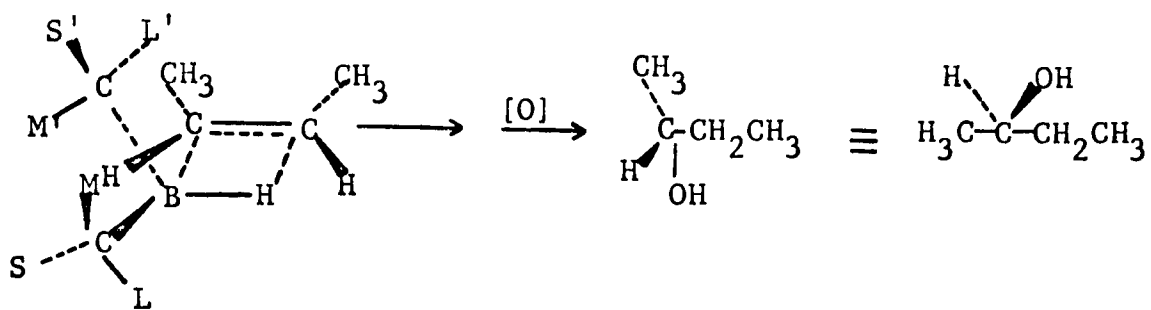
It was reported that optically active diisopinocampheylborane underwent reaction with a number of acyclic and cyclic olefins to give diisopinocampheylalkylboranes, which upon alkaline peroxide oxidation yielded optically active alcohols of optical purities as high as 91%.^{3a,4} The stereospecificity of the reaction suggested the possibility of correlating the absolute configuration of the diisopinocampheylborane reagent with that of the products. On the basis of conformational analysis, Brown proposed the most stable conformation of (-)-diisopinocampheylborane [from (+)- α -pinene] to be 34. The visual conception of this model was simplified by using the symbols S, M, and L for the small, medium and

large groups at C-3, C-4, and C-2, respectively, as in 34b. Morrison has used a modified Newman projection (34c) to describe the same reagent.⁶²



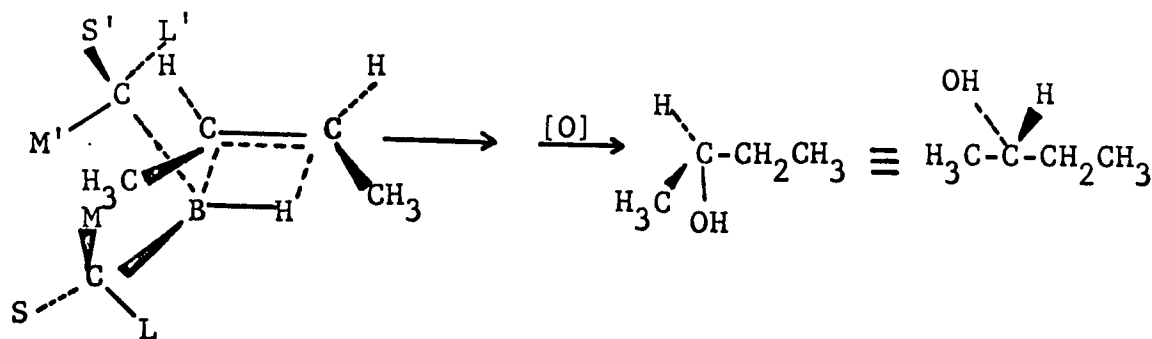
Since the addition of such an organoborane reagent to a double bond is known to proceed via a four-center transition state⁴⁰, it is obvious that such a rigid transition state should have highly specific steric requirements and should be influenced by the steric requirements of both the diisopinocampheylborane and the olefin. For example, the hydroboration of cis-2-butene with (-)-diisopinocampheylborane [(-)-2] can proceed through the possible transition states

35a and 35b.



35a

(R)-(-)-2-butanol



35b

(S)-(+)-2-butanol

Transition state 35a would be favored on steric grounds because the methyl group of the cis-2-butene is directed toward the small hydrogen atom (S'), minimizing steric interactions, whereas in transition state 35b, the methyl group of the cis-2-butene is positioned toward the methylene group (M) at C-4 of the organoborane reagent. Transition state 35a will give an organoborane which will be oxidized to (R)-(-)-2-butanol [(R)-(-)-4], but transition state 35b will lead to the other enantiomeric 2-butanol.

Brown found that the hydroboration of cis-2-butene with (-)-diisopinocampheylborane, followed by oxidation, gave (R)-(-)-2-butanol^{3a}, the product predicted on the basis of the transition state model. The alcohol was obtained in optical purity of 87%. Similarly, the hydroboration of a number of cis-acyclic, cyclic, and bicyclic olefins with diisopinocampheylborane gave the products of predicted absolute configuration in each case. However, the hydroboration of some trans and hindered olefins with this reagent was found to proceed slowly, with the displacement of α -pinene from the organoborane, and gave products of lower optical purity and of exactly the opposite configurations from those predicted on the basis of the simple addition transition state model.^{3b} In these cases, the reaction was found to be taking a new path involving the reaction of the olefin with the less hindered dissociation product, triisopinocampheylidiborane (31).

The difficulty in applying this simple model of the transition state for predicting the absolute configuration of alcohols is dramatically illustrated by the reaction of 2,3,3-trimethyl-1-butene with diisopinocampheylborane.^{3c} This reaction proceeded by both addition (simple addition transition state model) and displacement (configuration opposite of that

predicted from simple model), and was termed "mechanistically complex."

Thus the use of diisopinocampheylborane and triisopinocampheylidiborane to prepare optically active alcohols was demonstrated, but the steric models proposed by Brown, while useful conceptually on an empirical basis, fail to yield consistent, predictable results, and as Morrison has pointed out, such models "should not be given great credence as predictive tools unless a large number of examples have been successfully accommodated."⁶²

Hydroboration of N-Methyl-1,2,5,6-tetrahydropyridine with Diisopinocampheylborane

The preparation of optically active piperidinols was of interest because of their relation to optically active naturally occurring compounds. In order to prepare optically active N-methyl-3-piperidinol as a model compound, the asymmetric induction hydroboration of N-methyl-1,2,5,6-tetrahydropyridine (10) was attempted.

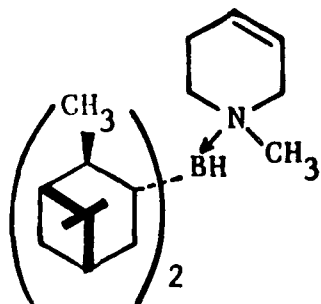
Using a procedure similar to that of Brown³, the title compound 10 was hydroborated with (-)-diisopinocampheylborane [(-)-2], prepared from (+)- α -pinene of ca. 94% optical purity.⁶³ A molar ratio of one mole of 10 to two moles of (-)-2 was used. This reaction gave a 69.5% yield of a mixture of N-methyl-3-piperidinol (11) and N-methyl-4-piperidinol (12) in the relative amounts of 71% of 11 and 29% of 12. A pure sample of 11, isolated as an oil by gas chromatography, was optically active ($[\alpha]_D^{27} +1.56^\circ$), and was identical with an authentic sample of racemic 11 in all respects except optical rotation. Because N-methyl-4-piperidinol is a symmetrical compound, it is not capable of optical activity, and no attempt was made to investigate its optical rotation.

In a similar reaction, 10 was hydroborated with (-)-diisopinocampheylborane [(-)-2], prepared from (+)- α -pinene of ca. 93% optical purity.⁶³ This reaction gave a 63% yield of a mixture of piperidinols 11 and 12 in the relative amounts of 75% of 11 and 25% of 12. Isolation by preparative gas chromatography gave (+)-N-methyl-3-piperidinol [(+)-11], $[\alpha]_D^{26} +1.56^\circ$.

The relative amounts of piperidinols 11 and 12 obtained above were in about the same ratios as had been previously obtained by the hydroboration of 10 with diborane. This suggested that the hydroboration of 10 with diisopinocampheylborane and with diborane is subject to similar electronic influences.

In these reactions the reasonable assumption was made that the hydroboration proceeded via prior formation of an amineborane such as 36, with the subsequent addition of diisopinocampheylborane to the carbon-carbon double bond of 36, in a manner analogous to that found to be the case in the hydroboration of tetrahydropyridine 10 with diborane. The bulky diisopinocampheylborane substituent of 36 must then exert some steric influence on the direction of addition of the diisopinocampheylborane reagent, as evidenced by the fact that the N-methyl-3-piperidinol which was obtained was optically active. Stated another way, if there were no steric influences on the reaction, then asymmetric induction could not have occurred, since it is precisely because of steric influences that asymmetric induction with diisopinocampheylborane

is possible.



36

Absolute Configuration of 3-Piperidinol

The preparation of optically active N-methyl-3-piperidinol has not been described in the literature. Therefore, the absolute configuration of this compound was not known, and no decision could be made as to the optical purity of the sample of 11 obtained by the hydroboration of N-methyl-1,2,5,6-tetrahydropyridine with diisopinocampheylborane. This information could be provided by establishing rigorously the absolute configuration of N-methyl-3-piperidinol by an alternative synthesis, starting with an optically active compound of known absolute configuration and proceeding via optically active 3-piperidinol (42).

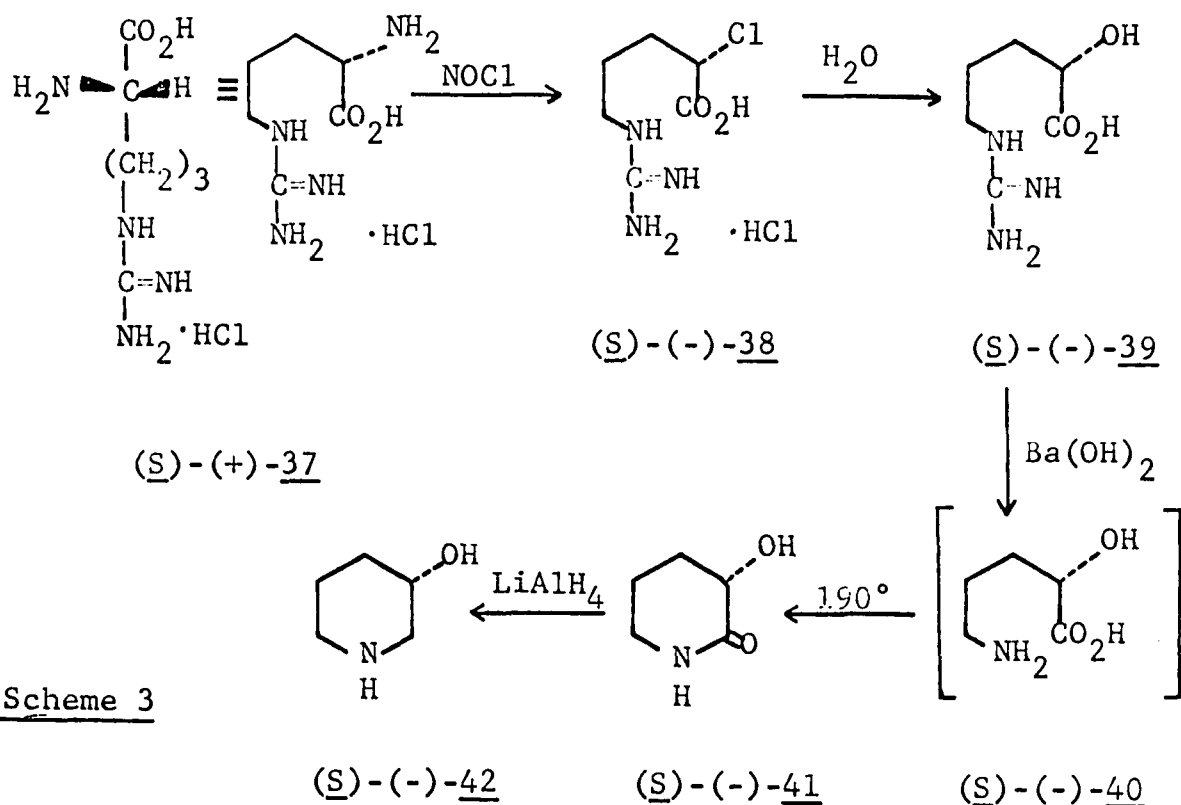
The procedure chosen for the syntheses of optically active 42 and 11 employed as starting material the readily available amino acid, L-(+)-arginine hydrochloride [L-(+)-37] [(S)-(+) -arginine hydrochloride] [(S)-(+) -37]⁶⁴, the absolute configuration of which is known.⁶⁵ Following the procedure of Hamilton and Ortiz⁶⁶, L-(+)-37 was converted by reaction with nitrosyl chloride to optically pure (S)-(-)- α -chloro- δ -guanidino- η -valeric acid hydrochloride [(S)-(-)-38] in 64.6% yield. This compound was hydrolyzed in ca. 83% yield to the

α -hydroxy analog, L-(-)-argininic acid [L-(-)-39] [(S)-(-)- α -hydroxy- \int -guanidino-n-valeric acid] [(S)-(-)-39], of ca. 70% optical purity. It is known that the above two reactions both proceed with retention of configuration⁶⁶⁻⁶⁸; i.e., these reactions stereospecifically converted the α -amino group of 37 to the α -hydroxy group of 39 without changing the configuration of the carbon atom to which they are attached.

L-(-)-Argininic acid [L-(-)-39] was treated with barium hydroxide solution by the procedure of Felix and Müller⁶⁹ to give crude (S)-(-)-3-hydroxy-2-piperidone [(S)-41] in 3.5-9.5% yield, starting from 39. The optical purity of hydroxy lactam 41 was ca. 83%, based on comparison of its optical rotation, $[\alpha]_D -5.02^\circ$, with a literature value of $[\alpha]_D -6.0^\circ$.⁷⁰ The cyclization reaction above also gave 5.6-10.8% yields of racemic and partially racemic 39. Since the reactions in which 39 was converted to 41 did not involve the asymmetric center, the absolute configuration of (-)-41 must be S.

Optically active hydroxy lactam 41 was reduced with lithium aluminum hydride in 71% yield to (-)-3-piperidinol [(-)-42], $[\alpha]_D -4.2^\circ$, which must also have the S configuration, since the reduction did not involve the asymmetric center. The synthetic sequences described above are summarized

in Scheme 3.



Scheme 3

Optical Resolution of 3-Piperidinol

The remaining step in the preparation of optically active N-methyl-3-piperidinol was the methylation of the secondary amine, (-)-3-piperidinol [(S)-42]. However, the quantity of optically active 42 available from the synthetic sequence starting with 37 was insufficient to permit further reaction. It was hoped that an optical resolution of racemic 42 would provide more material, as well as information as to the specific rotation of optically pure 3-piperidinol.

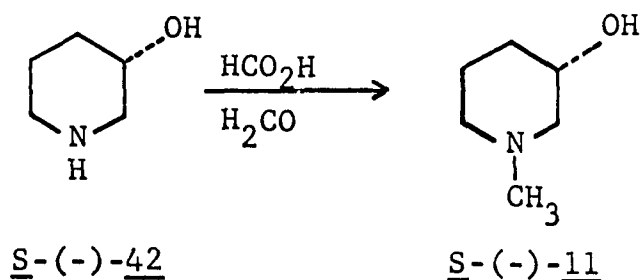
3-Piperidinol (42) formed a crystalline salt on reaction with (+)-10-camphorsulfonic acid in acetone or ethanol-ether solutions. Slow recrystallization of the salt gave a dextrorotatory diastereomer. Regeneration of 42 from the salt by treatment with base produced the dextrorotatory enan-

tiomer of 42, $[\alpha]_D^{22.5} +3.2^\circ$.

The mother liquors from the crystallization of the (+)-10-camphorsulfonic acid salt did not crystallize. Re-generation of 42 from the liquors gave the levorotatory enantiomer of 42, $[\alpha]_D^{23} -1.6^\circ$. Although this material was not completely resolved, it provided the necessary quantity of (-)-42 for conversion to optically active N-methyl-3-piperidinol (11).

Absolute Configuration of N-Methyl-3-piperidinol

A difference in the sign of the D line rotation between S-42 and S-11 was not anticipated; however, since the reversal of the sign of rotation between two closely related optically active compounds of the same absolute configuration is not without precedent, it was necessary to establish rigorously that (-)-42 and (-)-11 both have the same absolute configuration. Thus (-)-3-piperidinol [(-)-42] was converted in 72% yield to (-)-N-methyl-3-piperidinol [(-)-11], $[\alpha]_D^{23} -2.4^\circ$, by the Eschweiler-Clarke methylation procedure.⁷¹ Since the absolute configuration of (-)-42 had been established as S, the conversion of this compound to (-)-N-methyl-3-piperidinol [(-)-11] established the absolute configuration of (-)-11 as S (Scheme 4).



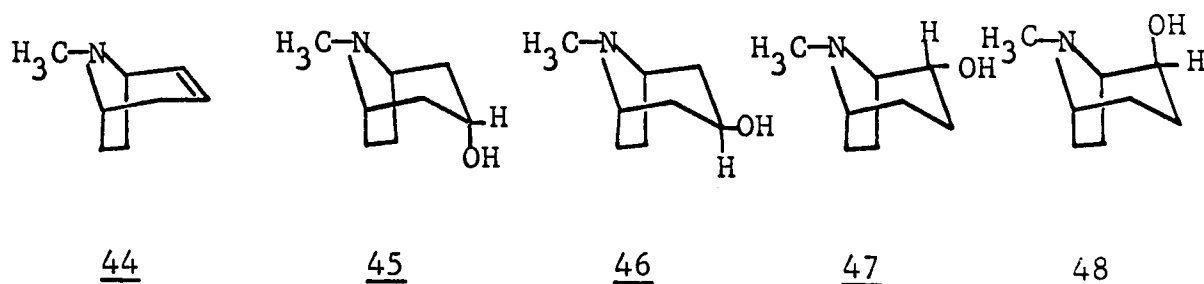
Scheme 4

If it is assumed that the sample of (-)-42 from the cyclization sequence starting with 37 is optically pure, then the sample of (-)-42, $[\alpha]_D -1.6^\circ$, from the resolution of 42 with (+)-10-camphorsulfonic acid can be no greater than 38.1% optically pure. This sample of (-)-42 was converted to (-)-11 with a specific rotation of -2.4° , which also can be no greater than 38.1% optically pure, and thus the specific rotation of optically pure (-)-11 can be no greater than -6.3° . Continuing this correlation and assuming that the optically pure enantiomers of 11 have equal and opposite signs of optical rotation, the optical purity of (+)-11, $[\alpha]_D +1.56^\circ$, from the asymmetric induction hydroboration of 10 can be no greater than 24.8%. This straightforward correlative approach is undoubtedly subject to some error, but it does indicate the order of magnitude of the degree of asymmetric induction of the hydroboration of 10 with (-)-diisopinocampheylborane.

Since (-)-11 has the S configuration, then (+)-11 must have the R configuration. Therefore, the hydroboration of N-methyl-1,2,5,6-tetrahydropyridine (10) with (-)-diisopinocampheylborane [(-)-2] gave R-(+)-N-methyl-3-piperidinol [R-(+)-11] in an optical purity of about 25%. The available evidence does not permit speculation about the nature of the Brown hydroboration transition state model as applied to this tetrahydropyridine system, especially since the validity of this model has not been rigorously proven. In the absence of such evidence, the asymmetric induction hydroboration of 10 must be considered on an empirical basis only, providing a useful correlation between (-)-2 and R-(+)-11, of the type encouraged by Morrison.⁶²

Hydroboration of Tropidine by the In Situ Generation of Diborane

Hydroboration-oxidation of the bicyclic unsaturated amine, tropidine (44), may in principle lead to four isomeric tropanols: tropine (45), pseudo-tropine (46), 2- α -tropanol (47), and 2- β -tropanol (48).⁷² From consideration of molecular models it is apparent that the tropidine molecule is quite rigid and not subject to the facile conformational changes which are possible with N-methyl-1,2,5,6-tetrahydropyridine. Thus conformational considerations in any mechanistic analysis are simplified. The preparation of the isomeric 2-tropanols was of interest because synthetic routes to these compounds either have been laborious or have utilized difficultly obtained or costly starting materials.^{72,73} The four isomeric tropanols are related to a number of potent pharmacological agents and to the group of bicyclic bases known as the tropane alkaloids. For these reasons a study of the chemistry of the tropane system was of practical as well as theoretical interest, and it was decided to extend the study of the hydroboration of unsaturated amines to tropidine.



The title compound, tropidine (44), prepared by the dehydration of tropine (45), was hydroborated by the in situ generation of diborane. This reaction gave a 68% yield of a mixture of the four predicted isomeric tropanols in the relative amounts of (in order of gas chromatographic elutions) 3% 2- β -tropanol (48), 50 \pm 3% tropine (45), 43 \pm 3% 2- α -tropanol (47), and 4% pseudo-tropine (46).

Epimerization of Tropanols

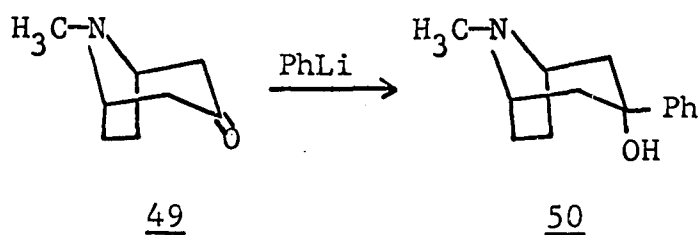
A mixture of tropanols containing 1% 2- β -tropanol (48), ca. 52% tropine (45), ca. 41% 2- α -tropanol (47), and 6% pseudo-tropine (46) was obtained by distillation of the hydroboration mixture. Treatment of this mixture with sodium 3-pentoxide and fluorenone under equilibration conditions gave an equilibrium mixture of 32% 2- β -tropanol, ca. 7% tropine, ca. 10% 2- α -tropanol, and 51% pseudo-tropine. These percentages represent conversions of about 76% of 2- α -tropanol to 2- β -tropanol and about 87% of tropine to pseudo-tropine. The results of this basic equilibration are consistent with the observations that 2- β -tropanol is more stable than 2- α -tropanol⁷² and that pseudo-tropine is more stable than tropine.⁷⁵ Thus the hydroboration of tropidine gave 2- α -tropanol as a major product, and subsequent basic epimerization gave 2- β -tropanol as a major product, demonstrating a new synthetic sequence to the relatively inaccessible isomeric 2-tropanols.

Summarizing the above:

	<u>Reaction mixture</u>	<u>Distillation fraction</u>	<u>After epimerization</u>
2- β -Tropanol (48)	3%	1%	32%
Tropine (45)	50 \pm 3%	52%	7%
2- α -Tropanol (47)	43 \pm 3%	41%	10%
Pseudo-tropine (46)	4%	6%	51%

Directive Effects in the Hydroboration of Tropidine .

The percentages of the products of the hydroboration of tropidine indicated a definite preference for addition of borane to the tropidine molecule from the α side (away from the nitrogen bridge).⁷⁶ The two isomeric tropanols which result from this direction of addition, tropine and 2- α -tropanol, together account for 93% of the tropanols obtained. This direction of addition is exactly opposite to that found to be the case with the reactions of related compounds. The reaction of tropinone (49) with phenyllithium, for example, gives only one isomer (50)⁷⁷, the product resulting from attack from the β side. The kinetically controlled products of the reaction of tropinone and related azabicyclic bases with organometallics⁷⁸, reducing agents⁷⁹, and oxidizing agents⁸⁰ result from the attack of the reagents from the less hindered (β) side; however, the direction of addition of several reducing agents was reversed when the azabicyclic ketone quaternary salt was used.⁷⁹



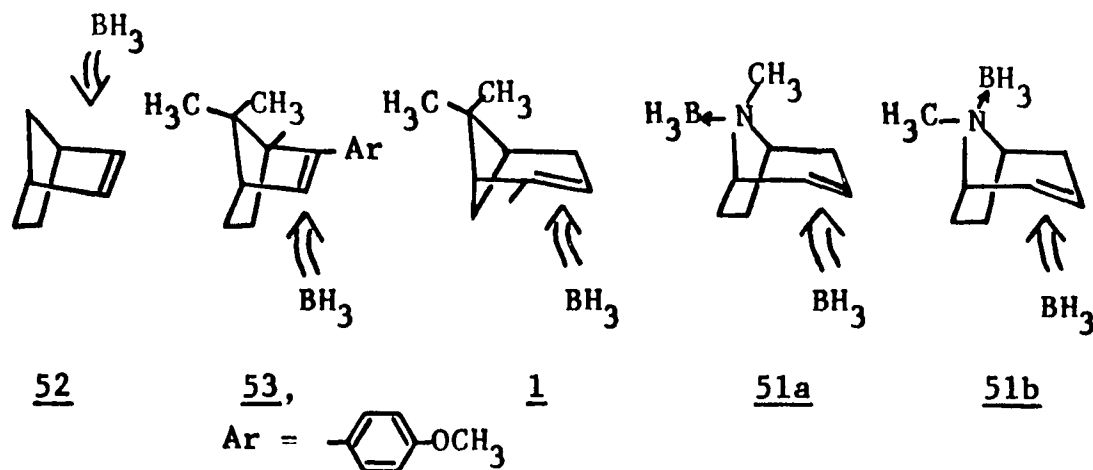
These differences in the steric interference encountered by the several attacking reagents suggested the explanation for the results of the hydroboration of tropidine. The first mole of borane (BH_3) underwent reaction with the basic nitrogen to form tropidine amineborane (51),

the double bond of which was then hydroborated with a second mole of borane. This explanation would be consistent with what was found to be the case with the hydroboration of N-methyl-1,2,5,6-tetrahydropyridine (10).

Tropidine amineborane may be represented by the two diastereomers 51a and 51b (only one enantiomer is given; however, the tropidine used was racemic). It seems likely that the product resulting from equatorial attack of borane on nitrogen (51a) would be favored, by analogy with the work of Fodor^{19a,b} and Closs^{19c}. These workers found that the kinetically controlled products of the reaction of several tropane bases with electrophilic reagents proceeded via equatorial attack. The reaction of borane with the tertiary nitrogen of tropidine should also proceed via equatorial attack since it is unlikely that the formation of 51 is reversible to an appreciable extent under the experimental conditions which were used.

The stereochemistry of the nitrogen in tropidine amineborane (51) is not critical to this discussion because the sizes of the methyl and borane groups are approximately equal. With the prior formation of tropidine amineborane in the hydroboration of tropidine, the N-methyl (or N-borane group) sterically shields the carbon-carbon double bond so that the less hindered side of the molecule is the α side. Hence the preferred direction of addition (of the second mole) of borane is from the α side. This is also consistent with the observation that the hydroboration of norbornene (52) occurs exclusively from the exo side, whereas the hydroboration of p-anisylbornylene (53)⁸¹ and α -pinene (1), both having a gem-dimethyl group, occurs from the less hindered endo side, away from the gem-dimethyl group. The analogy is reasonable, since the tetrasubstituted nitrogen atom in tropidine amineborane is isoelectronic with the gem-dimethyl carbon-6 in p-anisylbor-

nylene and α -pinene.



Direction of Addition of Borane to Bicyclic Olefins

Reaction of Tropidine with One Equivalent of Borane

The reaction of tropidine with one equivalent of borane was investigated to show that the first mole of borane underwent reaction at the basic nitrogen to give tropidine amineborane (51), which then underwent hydroboration with excess diborane. The reaction gave 51 in 71% yield. The white crystalline amineborane 51 was characterized by its infrared spectrum, which contained strong bands at 2420, 2380, 2340, and 2270 cm^{-1} , and a strong doublet at 1160-1150 cm^{-1} . As was previously noted, absorption bands in these regions are characteristic of amineboranes of tertiary amines.^{51,52}

Further evidence for the structural assignment of 51 was provided by nmr spectroscopy. The nmr spectrum of 51 (Fig. 2) showed a singlet at 2.79 ppm due to the three N-methyl hydrogens, a multiplet at 3.46 ppm due to the two bridgehead hydrogens, and a multiplet at 5.78 ppm due to two vinyl hydrogens. The nmr spectrum of amineborane 51 was

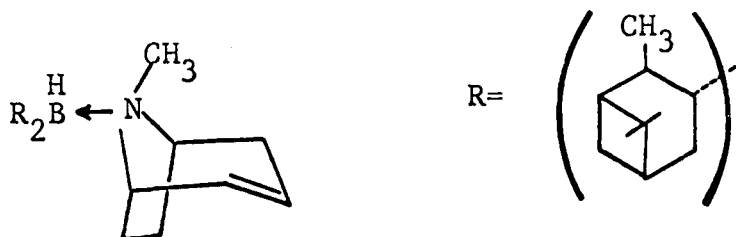
similar to that of tropidine (44) (Fig. 2), but the N-methyl resonance of 51 was shifted downfield by 0.47 ppm, demonstrating the deshielding influence of the positively charged nitrogen of 51.

Hydroboration of Tropidine with Diisopinocampheylborane

The moderate success in the asymmetric induction hydroboration of N-methyl-1,2,5,6-tetrahydropyridine (10) with diisopinocampheylborane prompted the extension of this reaction to the tropidine system. Using a procedure similar to that of Brown³, tropidine was hydroborated with (+)-diisopinocampheylborane [(+)-2], prepared from (-)- α -pinene of ca. 92% optical purity.⁸² A molar ratio of one mole of 44 to two moles of (+)-2 was used. This reaction gave approximately 18% of the four isomeric tropanols in the relative amounts of 61% 2- β -tropanol (48), 6% tropine (45), 6% 2- α -tropanol (47), and 27% pseudo-tropine (46). Because of the low yield of this reaction, it was not possible to isolate sufficient pure 47 or 48 in order to obtain optical rotation data.

Concerning directive influences, it will be noted that the major products in this reaction were 2- β -tropanol and pseudo-tropine, the products resulting from the addition of diisopinocampheylborane to tropidine from the β side.⁷⁶ This preferred direction of addition is opposite to that found in the hydroboration of tropidine with diborane. This suggests that an amineborane such as 54 is not an intermediate in the reaction. In the absence of such a coordinated species, addition of the diisopinocampheylborane to the base tropidine would be favored from the less hindered β side. If amineborane 54 formed, both sides of the double bond would be so protected that the large hydroborating agent could not undergo

reaction. The available evidence does not permit a positive explanation for the distribution of tropanol isomers; however, the low yield of the reaction, as well as the difference in isomer distribution from that obtained by the use of the much smaller hydroborating reagent, diborane, clearly suggests that the addition of diisopinocampheylborane to tropidine was subject to a considerable amount of some type of steric hindrance.



54

Hydroboration of Tropidine with Triisopinocampheylborane

Brown has found^{3b} that triisopinocampheylborane (31), the product formed by slow dissociation of sym-tetra-isopinocampheylborane (30), is a more effective hydroborating agent for hindered olefins than the parent compound 30. The use of 31 was found to require much shorter reaction times and gave products of higher optical purity than hydroboration using diisopinocampheylborane. Triisopinocampheylborane can be formed directly by the reaction of three equivalents of α -pinene with two equivalents of borane.

Since the results of the hydroboration of tropidine with diisopinocampheylborane indicated a substantial steric inhibition of the reaction, the less hindered triisopinocampheylborane was investigated as an asymmetric induction hydroborating agent for tropidine. Following the procedure of Brown^{3b}, tropidine (44) was treated with (+)-triisopino-

campheyldiborane [(+)-31], prepared from (-)- α -pinene of ca. 92% optical purity. This reaction gave about 27% of a mixture of the four isomeric tropanols in the relative amounts of 63% 2- β -tropanol (48), 7% of a mixture of tropine (45) and 2- α -tropanol (47), and 30% pseudo-tropine (46). This relative distribution of products was about the same as that from the previous reaction in which diisopinocampheylborane was the hydroborating agent. Although the total yield of the hydroboration using triisopinocampheylborane was slightly higher than when diisopinocampheylborane was used, it was still too low to permit isolation of pure 47 or 48 for measurement of possible optical rotation.

Hydroboration of N-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine

As an extension of the synthetic application of the hydroboration reaction to the preparation of piperidinols, the hydroboration of N-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (55) with diborane was investigated. This reaction would be expected to lead to only one product, trans-N-methyl-4-phenyl-3-piperidinol (56), resulting from cis, anti-Markownikoff addition of borane to 55. The results of the hydroboration of 55 confirmed this expectation, 55 being converted to 56 in 67-77.5% yields. Piperidinol 56 was identical with an authentic sample which was obtained by the lithium aluminum hydride reduction of N-methyl-4-phenyl-3-piperidone.⁸³ The assignment of the stereochemistry of 56 has been described.⁸³

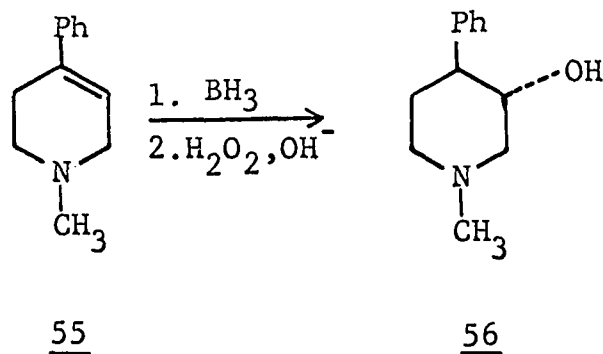


Table IV

Hydroboration of Tropidine

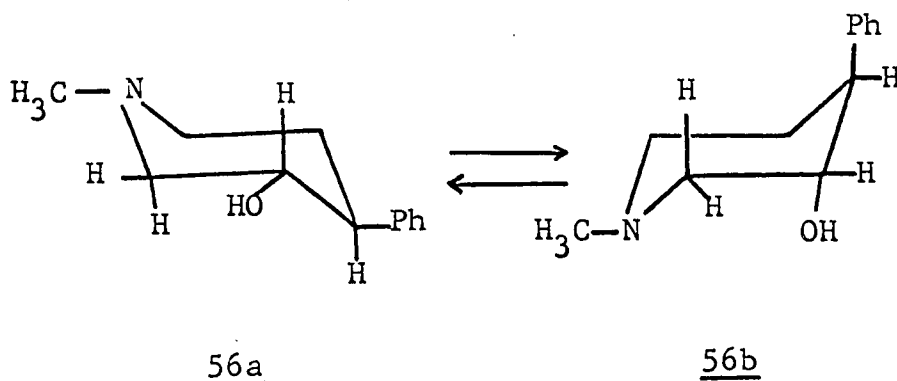
Isomer Distribution of Oxidation Products, %

<u>Hydroborating Agent</u>	<u>Total Yield, %</u>	<u>Tropine (45)</u>	<u>Pseudo-tropine (46)</u>	<u>2-α-Tropanol (47)</u>	<u>2-β-Tropanol (48)</u>
Diborane	68	50 \pm 3	4	43 \pm 3	3
Diisopino- camphylborane (2)	18	6	27	6	61
Triisopino- camphyl-di- borane (31)	27	a	30	a	63

^a The relative amounts of 45 and 47 could not be determined because their respective peaks were not completely resolved on the gas chromatogram. The combined amount of 45 and 47 was 7%, relative to the total quantity of tropanols obtained.

The nmr spectrum of 56 (Fig. 2) contained a multiplet centered at 1.78 ppm due to the six ring methylene hydrogens, a singlet at 2.09 ppm due to the three N-methyl hydrogens, a multiplet centered at 2.81 ppm due to the methine hydrogen at carbon-4, an apparent sextet centered at 3.63 ppm due to the methine hydrogen at carbon-3, a singlet at 4.11 ppm due to one hydroxyl hydrogen, and a multiplet at 7.20 ppm due to five phenyl hydrogens.

Conformation 56a, with equatorial phenyl and hydroxyl groups, would be the preferred conformation for trans-N-methyl-4-phenyl-3-piperidinol. For this conformation the methine hydrogen at carbon-3 is trans-diaxial to the methine hydrogen at carbon-4 and to one of the methylene hydrogens at carbon-2. The absorption due to the carbon-3 methine hydrogen is the X portion of an ABCX system.⁸⁴ Although this type of spin-spin system is theoretically very complex, in practice such a system may give rise to absorptions which are quite simple in appearance due to the equal magnitude of one or more of the coupling constants. Thus the sextet at 3.63 ppm appeared to be the result of the overlap of two triplets with $J_{\text{axial axial}} = 9.74$ cps and $J_{\text{axial equatorial}} = 4.36$ -4.48 cps. The magnitude of J_{ae} is close to that predicted for such a system⁸⁴, but the value of J_{aa} is low by 1-2 cps, which suggests that there is some contribution of 56b to the conformational equilibrium.



EXPERIMENTAL

General

Melting Points. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are corrected.

Infrared Absorption Spectra. Infrared spectra were determined using a Perkin-Elmer Model 137B Infracord spectrophotometer equipped with sodium chloride optics, a Perkin-Elmer Model 21 equipped with sodium chloride optics, or a Perkin-Elmer Model 337 grating spectrophotometer. The University of New Hampshire notebook numbers of spectra determined on the Model 137B are indicated by No.₁₃₇, those determined on the Model 21 by No.₂₁, and those determined on the Model 337 by No.₃₃₇. The spectra of liquids were determined neat, as films. The spectra of solid samples were determined as double mulls in Halocarbon oil 11-14⁸⁵ from 4000 cm^{-1} and 1300 cm^{-1} and in Nujol⁸⁶ mineral oil from 1300 cm^{-1} to 650 cm^{-1} . The absorption bands listed were strong, except for those indicated as medium (m) or weak (w). Bands which exhibited shoulders are indicated as (sh). The positions of the absorption bands are given in wave numbers, cm^{-1} .

Nuclear Magnetic Resonance Spectra. Nuclear magnetic resonance (nmr) spectra were determined using a Varian Model A-60 nmr spectrometer. The spectra were determined in the solvents indicated, and the chemical shifts are given in parts per million (ppm) relative to tetramethylsilane as an internal standard. Spin-spin coupling constants (J) are given in units

of cycles per second (cps).

Optical Rotation Data. Optical rotations were determined using a Franz Schmidt and Haensch polarimeter with a sodium vapor lamp as the light source. The concentrations (g. per 100 ml. of solution) and solvent are indicated for each measurement.

Gas Chromatographic Analysis Data. Gas chromatographic analyses were determined using a Perkin-Elmer Model 154C or an Aerograph Autoprep A-700 chromatograph with helium as the carrier gas. For preparative scale gas chromatographic separations, an Autoprep A-700 or a Perkin-Elmer 222P chromatograph was used. Unless otherwise indicated, chromatographic columns were glass, 4 mm. i.d. The column length, packing material, temperature, and pressure of helium are indicated for each chromatogram.

Calibration curves were not determined for every analysis. Several control experiments with synthetic mixtures of piperidinols of known composition established that the relative peak areas of the components of these mixtures as measured by a planimeter were in excellent agreement with the actual relative quantities. The percentages of each component of hydroboration reaction mixtures were assumed to be the percentage of the total area of the chromatogram. The retention times of products were compared with those of authentic samples for each analysis and were identical in all cases.

Analytical Data. Elemental microanalyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, New York, or with an F and M Model 180 carbon, hydrogen, and nitrogen analyzer in these Laboratories. Analyses determined by Schwarzkopf are indicated by Found^{Sch}, and analyses determined with the F and M analyzer are indicated by Found^{FM}, and

represent an average of two or more determinations.

Hydroboration of N-Alkyl-1,2,5,6-tetrahydropyridines

The product mixtures³⁹ from the hydroborations of N-butyl-1,2,5,6-tetrahydropyridine (5, R $n\text{-C}_4\text{H}_9$), N-benzyl-1,2,5,6-tetrahydropyridine (5, R CH_2Ph), and N- β -phenethyl-1,2,5,6-tetrahydropyridine (5, R $\text{CH}_2\text{CH}_2\text{Ph}$) were analyzed by gas chromatography. The results of these analyses are summarized in Table I.

Hydroboration of N-Methyl-1,2,5,6-tetrahydropyridine (10) by the In Situ Generation of Diborane

N-Methyl-1,2,5,6-tetrahydropyridine (10) was prepared by the sodium borohydride reduction of pyridinium methiodide by the method of Anderson^{6b}, b.p. 111-112°; lit.^{6b} b.p. 112°. However, 10 was obtained from a commercial source⁴² for use in most of the reaction described below.

NMR Spectrum (neat, Nos. 1557, 1706): 2.22 (singlet), 2.41 (multiplet), 2.80 (multiplet), 5.61 (multiplet). See Fig. 1 for the complete spectrum of 10.

Reaction I. Thermal Equilibration of Organoborane

In a dry 500 ml. 3-necked flask, fitted with a mercury-sealed, mechanical stirrer, dropping funnel, and reflux condenser, were introduced solutions of 2.43 g. (0.025 mole) of N-methyl-1,2,5,6-tetrahydropyridine (10) in 10 ml. of diglyme and 30 ml. of a 1 M solution of sodium borohydride in diglyme. The system was flushed with nitrogen for 0.75 hr. and a slight positive pressure of nitrogen was maintained. Diborane (0.020 mole, 0.040 mole of BH_3) was generated in situ by the dropwise addition of a solution of 7.5 g. (0.052 mole) of boron trifluoride etherate in 10 ml. of diglyme to the

stirred mixture. The resulting mixture was heated on a steam bath with stirring for 2 hr. The reaction mixture was cooled, was made basic with 40 ml. of 6 N sodium hydroxide, and was oxidized by the dropwise addition of 5 ml. of 30% hydrogen peroxide. The resulting mixture was heated on a steam bath for 2 hr. The mixture was cooled, then was acidified with concentrated hydrochloric acid, and excess acid was added. The upper, diglyme layer was removed by decantation and concentrated by distillation. A minimum of water was added to the bottom, aqueous salt layer, and the solution was combined with the concentrate from the diglyme layer. The mixture was steam distilled to remove most of the residual diglyme and diethylene glycol monomethyl ether (18). The residue from the distillation was dissolved in a small amount of water, and solid, anhydrous potassium carbonate was added. The resulting mixture was extracted three times with ether, the ether extracts were dried over potassium carbonate, and the ether was removed from the dried extracts by distillation at atmospheric pressure. The yellow residue was distilled under reduced pressure (water pump) giving 1.44 g. of a colorless oil, b.p. 96-98° at 45 mm. Gas chromatographic analysis (2 m. Carbowax 1500 on 60-100 mesh "Embacel" Kieselguhr, 150°) of this fraction showed it to contain 1.06 g. (37% based on starting tetrahydropyridine 10) of a mixture of N-methyl-3-piperidinol (11) and N-methyl-4-piperidinol (12), contaminated by some diglyme and 18. The relative amounts of piperidinols were 71% of 11 and 29% of 12.

Pure samples of 11 and 12 were collected by trapping them from the gas chromatographic effluent with U-shaped capillary tubes cooled in a Dry Ice-acetone bath. Compounds 11 and 12 were identical with authentic samples of N-methyl-

3-piperidinol (11)⁴⁵ and N-methyl-4-piperidinol (12)⁹⁵, based on comparison of infrared spectra and gas chromatographic retention times.

Reaction II. Organoborane Not Equilibrated

Reaction I was repeated: however, after the generation of diborane was completed, the reaction mixture was stirred at room temperature, rather than 100°, for 2 hr. After oxidation and work-up of the reaction mixture, as described in reaction I, 1.71 g. of an oil was obtained. Gas chromatographic analysis (2 m. Carbowax 1500 on 60-80 mesh "Embacel" Kieselguhr, 150°, and 3 m. 5% Carbowax 20M on Haloport-F, 132°, 8 psi) of this oil showed it to contain 1.10 g. (38.5%) of a mixture of N-methyl-3-piperidinol (11) and N-methyl-4-piperidinol (12). The relative amounts of piperidinols were 75% of 11 and 25% of 12.

Reaction III.

Reaction II was repeated, but after the diborane generation step, the reaction mixture was stirred at room temperature for only 10 min. The reaction mixture was oxidized and worked-up as in reactions I and II, except that the concentrated ether extract was not distilled. The ether extract (2.6 g.) was analyzed by gas chromatography (2 m. 5% Carbowax 20M on Haloport-F, 131°, 4 psi, and 3 m. 5% Carbowax 20M on Haloport-F, 132°, 8 psi) and was shown to contain 0.26 g. (9%) of a mixture of N-methyl-3-piperidinol (11) and N-methyl-4-piperidinol (12). The relative amounts of piperidinols were 72% of 11 and 28% of 12. The ether extract also contained 0.57 g. (24.5% recovery) of N-methyl-1,2,5,6-tetrahydropyridine (10) in addition to diglyme, 18, and lower boiling compounds.

Reaction IV.

A dry 2 l. flask, equipped with magnetic stirrer, condenser, and pressure-equalizing dropping funnel, was flushed by dry nitrogen which exited in an acetone trap. Into the flask were introduced solutions of 22.71 g. (0.60 mole) of sodium borohydride in 500 ml. of diglyme and of 24.30 g. (0.25 mole) of 10 in 50 ml. of diglyme. To the stirred mixture at room temperature (ca. 25°) a solution of 101.9 g. (0.718 mole) of boron trifluoride etherate in 77 ml. of diglyme was added dropwise over a period of 4 hr. This addition was calculated to generate 0.718 mole of BH_3 ; sodium borohydride was in excess. Excess diborane was detected by its reaction with acetone in the trap. The reaction mixture was stirred for 12 hr. at room temperature. Excess boron hydrides were decomposed by the careful addition of water until there was no further visible reaction. The reaction mixture was basified with 60 ml. of 6 N sodium hydroxide, and was oxidized by the dropwise addition of 50 ml. of 30% hydrogen peroxide. The resulting exothermic reaction heated the mixture to 70°. After the completion of the addition of peroxide, the mixture was allowed to cool to room temperature while stirring overnight. The resulting mixture was acidified by the addition of concentrated hydrochloric acid. The mixture was concentrated to near-dryness by distillation at reduced pressure. Water was added to the concentrate and the distillation was repeated to remove by steam distillation most of the residual diglyme and 18. The resulting residue was taken up in a small amount of water, solid anhydrous potassium carbonate was added, and the mixture was extracted with ether. The ether extracts were dried over potassium carbonate, and the ether was removed from the dried

extracts by distillation at room temperature. The residue was shown by gas chromatography (2 m. 5% Carbowax 20M, 131°, 6 psi) to contain 24.01 g. (83.5%) of a mixture of piperidinols 11 and 12 in the relative amounts of 74.5% of 11 and 25.5% of 12. This residue was distilled at reduced pressure (water pump). Two fractions of material boiling over the range 38-106° at 15 mm. were collected. Fraction 1, boiling at 38-75° at 15 mm., 14.21 g., was shown by gas chromatography to contain 5.30 g. of a mixture of piperidinols 11 and 12 in the relative amounts of 91.5% of 11 and 8.5% of 12. Fraction 2, boiling at 75-106° at 15 mm., 18.82 g., contained 16.17 g. of a mixture of 11 and 12 in the relative amounts of 69% of 11 and 31% of 12. Combining the distilled fractions, the yield of piperidinols was thus 21.47 g. (74.7%) with the relative amounts of ca. 75% of 11 and 25% of 12.

Identification of the Product of Diglyme Cleavage

A. Distillation fraction 1 from Reaction IV above was redistilled into several fractions. The fraction boiling at 77-80° at 15 mm. (1.96 g.) was collected and redistilled into several fractions. The fraction boiling at 83-94° at 15 mm. (0.49 g.) was analyzed by gas chromatography (2 m. 5% Carbowax 20M on Haloport-F, 133°, 6 psi) and found to contain 53.5% of 11, 34% of 12, and 12.5% of 18. A small sample of 18 was collected by trapping the gas chromatographic effluent using a glass capillary tube which was cooled in a Dry Ice-acetone bath. The infrared spectrum of 18 contained strong bands at 3650-3450 cm^{-1} and 1150-1040 cm^{-1} and was identical with that of an authentic sample⁴⁶ of diethylene glycol monomethyl ether. The gas chromatographic retention time of 18 was identical with that of authentic diethylene

glycol monomethyl ether.

B. A small portion of the distillation fraction with boiling point 83-94° at 15 mm. which was collected above was taken up in anhydrous ether. Hydrogen chloride gas was passed through the solution and the resulting white precipitate was separated by filtration. The filtrate was concentrated by evaporation to an oil which was found by gas chromatography to be 18 in at least 95% purity. Comparison of the infrared spectra and gas chromatographic retention times of 18 with authentic diethylene glycol monomethyl ether indicated that they were the same compound.

Hydroboration of N-Methyl-1,2,5,6-tetrahydropyridine (10)
by the External Generation of Diborane

Reaction V. Reaction of N-Methyl-1,2,5,6-tetrahydro-
pyridine (10) with One Mole of Borane

In a dry 100 ml. Mini-Lab⁹¹ flask was placed a solution of 3.88 g. (0.040 mole) of 10 in 50 ml. of tetrahydrofuran. The flask was fitted with a sintered glass dispersion tube and was flushed with nitrogen for 0.5 hr. Diborane, (0.020 mole, 0.040 mole of BH_3) diluted with nitrogen, was introduced slowly over a period of 2 hr. The diborane was generated in an external flask by the dropwise addition of a solution of 1.13 g. (0.030 mole) of sodium borohydride in 50 ml. of diglyme to a solution of 8.0 g. (0.0565 mole) of boron trifluoride etherate in 30 ml. of diglyme. After the completion of the sodium borohydride addition, the diborane generator flask was heated for 1 hr. at 70° in order to remove completely the diborane dissolved in the diglyme.

The tetrahydrofuran was removed from the hydroboration reaction mixture by distillation to give a yellow liquid residue. This oil was identified as N-methyl-1,2,5,6-tetrahydropyridine amineborane (13) by its infrared spectrum, which

contained strong bands at 2350, 2320 (sh), 2270 cm^{-1} , and a doublet at 1177 and 1166 cm^{-1} , characteristic of amineborane addition compounds.^{51,52} Gas chromatographic analysis (2 m. 5% Carbowax 20M on Haloport-F, 131°, 3 psi) of this crude amineborane indicated the presence of trace amounts of tetrahydrofuran and 10. Compound 13 was not purified further, but the infrared spectrum was identical with that of a pure sample of 13 which was prepared in a separate experiment.

A 1.70 g. sample of crude 13 was transferred to another flask. To this oil was added 10 ml. of water and then 5 ml. of 6 N sodium hydroxide, and the mixture was oxidized by the dropwise addition of 5 m. of 30% hydrogen peroxide. The resulting mixture was extracted with ether, the ether extracts were concentrated by distillation, and the concentrated extract was analyzed by gas chromatography (2 m. 5% Carbowax 20M on Haloport-F, 132°, 3 psi; also the same column at 6 psi). The chromatogram showed the only basic compounds present to be tetrahydropyridine 10 and a trace of N-methyl-3-piperidinol (11). The amount of 11 was estimated to be less than 5% and was detectable only by the injection of a large sample into the chromatograph. There was no N-methyl-4-piperidinol (12) present to the limits of detection of the chromatograph.

Reaction VI. Thermal Equilibration of N-Methyl-1,2,5,6-tetrahydropyridine Amineborane (13) from Reaction V

A 1.26 g. sample of amineborane 13 from reaction V was added to 20 ml. of diglyme, and this mixture was heated at 150° with stirring for 10 hr. The mixture was cooled, 5 ml. of 6 N sodium hydroxide was added, and the basic mixture was oxidized with 5 ml. of 30% hydrogen peroxide. The solution

was extracted with ether, the ether extracts were concentrated by distillation, and the concentrated extract was analyzed by gas chromatography as in reaction V. The chromatogram showed the piperidinols 11 and 12 to be present in the relative amounts of $43 \pm 4\%$ of 11 and $57 \pm 4\%$ of 12. The presence of a substantial amount of 18 interfered with the analysis and prohibited a more precise determination of the relative amounts of 11 and 12. There was no tetrahydropyridine 10 present.

Reaction VII. Reaction of N-Methyl-1,2,5,6-tetrahydropyridine (10) with Two Moles of Borane

The hydroboration procedure was that of reaction V. Thus, into a solution of 3.88 g. (0.040 mole) of 10 in 50 ml. of tetrahydrofuran was passed 0.040 mole of diborane (0.080 mole of BH_3), generated externally by the dropwise addition of a solution of 2.27 g. (0.060 mole) of sodium borohydride in 70 ml. of diglyme to a solution of 16 g. (0.113 mole) of boron trifluoride etherate in 40 ml. of diglyme. When the addition of diborane was completed, 2 ml. of water was added cautiously to the reaction mixture. The organoborane was oxidized by the addition of 5 ml. of 6 N sodium hydroxide and dropwise addition of 5 ml. of 30% hydrogen peroxide. After stirring the mixture for 0.75 hr., concentrated hydrochloric acid was added until the mixture was acidic, and 15 ml. of excess acid was added. The mixture was concentrated by distillation at reduced pressure. The residue from the distillation was taken up in a small amount of water, and solid anhydrous potassium carbonate was added. The mixture was extracted with ether, the extracts were concentrated by distillation, and the concentrated extract was analyzed by gas chromatography (2 m. Carbowax 20M on Haloport-F, 133° , 6 psi).

The chromatogram showed the relative amounts of piperidinols to be 73% of 11 and 27% of 12.

Alternate Preparation of N-Methyl-1,2,5,6-tetrahydropyridine Amineborane (13)

N-Methyl-1,2,5,6-tetrahydropyridine Amineborane (13).

A 1 M solution (32 ml.) of borane (BH_3) in tetrahydrofuran⁹² was added from a hypodermic syringe over a period of 0.33 hr. to a magnetically stirred solution of 3.88 g. (0.040 mole) of tetrahydropyridine 10 in 25 ml. of n-hexane in a flask cooled in an ice bath. A small amount (ca. 0.2 g.) of a white solid precipitated and was removed by filtration. This precipitate decomposed rapidly in air and was not investigated further.

The filtrate was distilled at reduced pressure to remove tetrahydrofuran and unreacted 10 and gave 3.77 g. (91.6%, based on structure 13) of a light yellow residue, n_D^{20} 1.4812, d_4^{20} 0.8815. This oil was soluble in ether and insoluble in water. The infrared and nmr spectra of the liquid showed it to be N-methyl-1,2,5,6-tetrahydropyridine amineborane (13). The infrared spectrum was almost identical with that of 13 which had been previously prepared (reaction V).

Anal.⁹³ Calcd. for $\text{C}_6\text{H}_{11}\text{NBH}_3$: H(hydridic), 2.72.

Found: H(hydridic), 2.53.

Molar Refraction:⁵⁵ Calcd.: 36.76. Found: 35.84.

IR Spectrum (No. 337 3720): 3040 (m), 3005 (m), 2955, 2350, 2320 (sh), 2270, 1470-1435 (triplet), 1177-1166 (doublet), 1028, 1012, 825, 656.

NMR Spectrum (neat, No. 1555): 2.50 (singlet), 2.26 (multiplet), 2.90 (triplet), 3.30 (multiplet), 5.74 (multiplet). See Fig. 1 for the complete spectrum of 13.

Hydroboration of N-Methyl-1,2,5,6-tetrahydropyridine (10) with Diisopinocampheylborane. A. A slurry of 2.27 g. (0.06 mole) of sodium borohydride in 80 ml. of monoglyme⁸⁷ (1,2-dimethoxyethane) and 21.76 g. (0.16 mole) of (+)- α -pinene⁶³ (α_D^{23} +41.19°, ca. 94% optically pure) were introduced in a dry 200 ml. 3-necked flask, equipped with magnetic stirrer, condenser, and pressure-equalizing dropping funnel, and flushed by nitrogen. The flask was immersed in an ice bath and diborane (0.040 mole, 0.080 mole of BH_3) was generated in situ by the dropwise addition of a solution of 11.4 g. of boron trifluoride etherate in 20 ml. of monoglyme to the stirred α -pinene-sodium borohydride mixture over a period of 0.75 hr. During this time (-)-diisopinocampheylborane [(-)-2] precipitated as a white solid. When the addition of boron trifluoride etherate was complete, the resulting slurry was stirred for an additional 2.75 hr. at 0°.

To the suspension of 0.080 mole of (-)-diisopinocampheylborane prepared above was added dropwise a solution of 3.88 g. (0.040 mole) of N-methyl-1,2,5,6-tetrahydropyridine (10) in 15 ml. of monoglyme. The resulting reaction mixture was stirred for 2.5 hr. at 0° and 12.5 hr. at room temperature. The solution was hydrolyzed with 3 ml. of water, was made basic with 5 ml. of 6 N sodium hydroxide, and was oxidized at 30-64° by the dropwise addition of 8 ml. of 30% hydrogen peroxide. The reaction mixture was stirred for an additional 2.5 hr. and was acidified with 10 ml. of concentrated hydrochloric acid. The mixture was concentrated to a white solid residue by distillation at reduced pressure. The residue was taken up in water, solid potassium carbonate was added, and the basic mixture was extracted with several portions of ether. The combined extracts were dried over potassium carbonate and concentrated by evaporation to a light yellow oil. This oil was

analyzed by gas chromatography (2 m. 5% Carbowax 20M on Haloport-F, 139°, 10 psi) and was shown to contain 3.20 g. (69.5%) of piperidinols 11 and 12 in the relative amounts of 71% of 11 and 29% of 12.

A pure sample of 11 obtained by preparative gas chromatography (Perkin-Elmer Model 222P chromatograph; 10 ft. aluminum column packed with 5% Carbowax 20M on 60-80 mesh HMDS treated Chromosob W) was dextrorotatory: $[\alpha]_D^{27} +1.56^\circ$ (c 2.56, absolute ethanol). The infrared spectrum of (+)-11 (liquid film) was identical with that of a pure sample of racemic 11.

B. In a similar reaction, a suspension of 0.10 mole of (-)-diisopinocampheylborane in monoglyme was prepared by the dropwise addition of a solution of 12.6 ml. (0.10 mole) of boron trifluoride etherate in 30 ml. of monoglyme to a stirred mixture of 3.79 g. (0.10 mole; 25% excess) of sodium borohydride and 27.24 g. (0.20 mole) of (+)- α -pinene⁶³ ($[\alpha]_D^{23.5} +40.67^\circ$, ca. 93% optically pure) in 120 ml. of monoglyme. The diisopinocampheylborane reagent was stirred at 0° for 7 hr.

To the stirred reagent prepared above was added a solution of 4.86 g. (0.050 mole) of 10 in 25 ml. of monoglyme. The reaction mixture was stirred for 2 hr. at 0° and 16.5 hr. at room temperature. The reaction mixture was hydrolyzed with 5 ml. of water and was made basic with 16 ml. of 30% hydrogen peroxide. The oxidized mixture was stirred for an additional 3 hr., and 12 ml. of concentrated hydrochloric acid was added. The acidified mixture was concentrated to a white residue, was made basic with potassium carbonate, and was extracted with ether. The ether extracts were dried and concentrated to an oil, which was shown by gas chromatography (2 m. Carbowax 20M on Chromosorb W, 125°, 4 psi) to contain 3.64 g. (63%) of a mixture of piperidinols in the relative amounts of 75% of 11 and 25% of 12.

A pure sample of 11 was isolated by preparative gas chromatography (Aerograph A-700 chromatograph: 20 ft. x 3/8 in. aluminum column packed with 20% Carbowax 20M on DMCS treated Chromosorb W), $\alpha_D^{24} +1.56^\circ$ (neat, 1 dm.); $[\alpha]_D^{26} +1.56^\circ$ (c 2.5, 95% ethanol); $n_D^{19} 1.4730$, $n_D^{20.5} 1.4722$, $n_D^{22} 1.4715$. Reported for racemic 11, $n_D^{20} 1.4721$ ⁹⁴ and $n_D^{20} 1.4733$.⁹⁵

Absolute Configuration of 3-Piperidinol (42)

L-(+)-Arginine Hydrochloride (37)⁶⁴ was obtained from a commercial source⁴², $[\alpha]_D^{24} +22.3^\circ$ (c 15, 6 N HCl); reported⁶⁸ $[\alpha]_D^{25} +22^\circ$ (c 15, 6 N HCl).

S-(-)- α -Chloro- δ -guanidino- n -valeric Acid Hydrochloride (38). The procedure used for the preparation of 38 was essentially that of Hamilton and Ortiz.⁶⁶ In a 500 ml. Claisen flask, 50 g. (0.237 mole) of L-(+)-arginine hydrochloride (37) was dissolved in 75 ml. of concentrated hydrochloric acid, and to this was added 37.5 ml. of concentrated nitric acid. The flask was warmed in a water bath at about 60° for 0.5 hr. The excess acid was removed by evaporation under reduced pressure. Three portions of 20 ml. each of concentrated hydrochloric acid were added successively with evaporation to dryness after each addition. The resulting white residue was dissolved in 350 ml. of warm 6 N hydrochloric acid, and the solution was transferred to a 1 l. beaker. The solution was allowed to stand at 40-45° for 34 hr. The salt which precipitated was collected by filtration and washed with 50 ml. of ice-cold concentrated hydrochloric acid. The product was dried under reduced pressure over solid sodium hydroxide to give 20.2 g. (37.1%) of 38, m.p. 149-151°, $[\alpha]_D^{25} -7.9^\circ$ (c 10, H₂O); reported⁶⁶ m.p. 150° (corr.), $[\alpha]_D^{25} -7.5$ (c 10, H₂O).

A second crop of crystals precipitated from the filtrate on cooling in an ice bath. After filtering, washing, and drying, the solid represented 15.0 g. (27.5%) of 38, m.p. 145-148.5°, $[\alpha]_D^{25} -7.8^\circ$ (c 10, H₂O).

S-(-)- α -Hydroxy- \int -guanidino- n -valeric Acid (39) (L-(-)-Argininic Acid. A. The first crop of 38 above, 15.0 g. (0.0653 mole), was dissolved in 1500 ml. of water and heated under reflux for 48 hr. The solution was cooled to room temperature, and 18.75 g. (0.0681 mole) of silver carbonate was added. The mixture was stirred mechanically for 1 hr. and then filtered. Excess silver ion was precipitated from the filtrate as silver sulfide by bubbling hydrogen sulfide through the solution for 2 hr. Excess hydrogen sulfide was displaced from solution by adding Dry Ice, and the mixture was filtered using 7.5 g. of Celite as a filter aid. The precipitate was washed with 100 ml. of water in four portions. The combined filtrate and washings were evaporated by distillation at reduced pressure. The residue was dissolved in 150 ml. of warm water and decolorized with 0.75 g. of Norite. The carbon was removed by filtration and washed with 75 ml. of water in four portions. To the combined filtrate and washings was added 900 ml. of acetone, and the solution was cooled in an ice bath overnight. The white product was isolated by filtration, washed with a solution of 80% acetone-20% water, and dried to give 9.57 g. (83.5%) of 39, m.p. 231-232°d., $[\alpha]_D^{24} -8.1^\circ$ (c 10, H₂O); reported⁶⁶ m.p. 227° (corr.), $[\alpha]_D^{25} -11.5^\circ$ (c 10, H₂O); m.p. 225°⁶⁸, $[\alpha]_D^{25} -11.5^\circ$ (c 10, H₂O).

Anal. Calcd. for C₆H₁₃N₃O₃: C, 41.14; H, 7.48.
Found^{FM}: C, 41.51; H, 7.57.

B. This preparation was repeated exactly as described above, using as starting material the second crop of 38, m.p. 145-148.5°. This reaction yielded 9.50 g. (2.8%) of 39, m.p. 230-230.5°d., $[\alpha]_D^{25} -8.0^\circ$ (c 1.25, H₂O). This material was combined with that obtained above for utilization in the next step (below).

S-(-)-3-Hydroxy-2-piperidone (41). A. L-(-)-Argininic acid (39), 13.0 g. (0.0742 mole), was dissolved in a solution of 54 g. of barium hydroxide in 1040 ml. of water and heated under reflux for 2 hr. Dry Ice was added to the warm solution. The mixture was rewarmed and the barium carbonate was removed by filtration. The filtrate was concentrated to a syrup by distillation at reduced pressure. A small amount of water was added, the solution was filtered, and the filtrate again was concentrated to a syrup. Urea was extracted from this syrup with three portions of hot absolute ethanol. The ethanol-insoluble residue was evaporated to dryness at reduced pressure to give crude S-(-)- α -hydroxy- \int -amino- n -valeric acid [S-(-)-40]. This residue was heated at 190° for 10 min.

A portion of the hydroxy lactam 41 sublimed as needles. This was combined with the unsublimed residue and recrystallized from ethyl acetate to give 0.808 g. (ca. 9.5%) of 41, m.p. 170.5°, $[\alpha]_D^{25} -5.02^\circ$ (c 7.66, H₂O); reported⁷⁰ m.p. 171.5°, $[\alpha]_D^{21} -6.0^\circ$ (c 7.66, H₂O); m.p. 169°. ⁶⁹

Anal. Calcd. for C₅H₉NO₂: C, 52.16; H, 7.88.
Found^{FM}: C, 52.42; H, 8.13.

The filtrate from the ethyl acetate recrystallization was evaporated to dryness and recrystallized from ethyl acetate to give 0.48 g. (ca. 5.6%) of a second crop of 41,

m.p. 137-147°. This was presumably mostly racemic material, which has reported melting points of 134.3°⁷⁰ and 141 to 142°.⁷⁰

B. In another experiment 5.0 g. (0.0285 mole) of L-(-)-argininic acid (39) was heated under reflux in a solution of 22 g. of barium hydroxide in 400 ml. of water. Using the same procedure as in A, there was obtained 0.125 g. (ca. 3.5%) of 41, m.p. 168-169°, and 0.355 g. (10.8%), with m.p. 137-152°.

S-(-)-3-Piperidinol (42). To a magnetically stirred slurry of 0.75 g. of lithium aluminum hydride in 50 ml. of anhydrous ether was added 0.75 g. (0.0652 mole) of optically active hydroxy lactam 41. The reaction mixture was heated under reflux for 42 hr., and the excess lithium aluminum hydride was decomposed by the careful addition of 6 N sodium hydroxide. Anhydrous potassium carbonate and a few potassium hydroxide pellets were added to the resulting slurry which was then triturated with five 30 ml. portions of methylene chloride. The combined methylene chloride layers were dried over anhydrous potassium carbonate and concentrated by evaporation to give 0.47 g. (71%) of white, crystalline product 42, m.p. 88-90°, $[\alpha]_D^{26.8} -4.2^\circ$ (c 7, CH₂Cl₂). The infrared spectrum (Nujol and Halocarbon double mulls) of this material showed the absence of carbonyl absorption and was similar to, but not identical with that of a commercially available⁴² sample of racemic 3-piperidinol. The melting point of (-)-42 was depressed by 30° on admixture with an equal portion of racemic 42.

Optical Resolution of 3-Piperidinol (42)

3-Piperidinol (42) was obtained from a commercial source⁴² and was used without further purification.

(+)-10-Camphorsulfonic Acid (Eastman White Label quality) was obtained from a commercial source⁸⁷ and was used without further purification.

(-)-3-Piperidinol [(-)-42]. A. A warm solution of 10.1 g. (0.10 mole) of racemic 42 in a mixture of 10 ml. of absolute ethanol and 40 ml. of ether was added to a warm solution of 30.2 g. (0.13 mole) of (+)-10-camphorsulfonic acid in 750 ml. of ether and 50 ml. of absolute ethanol. An additional 40 ml. of warm ethanol was added in order to obtain a homogeneous solution. The mixture was cooled to room temperature and was seeded with a few crystals of the salt, m.p. 131.5-135°, $[\alpha]_D^{22} +30.0^\circ$, from a previous small-scale experiment. The solution was cooled to ice-bath temperature and crystallization commenced the next day. After a total of 2 days at ice-bath temperature and 28 days at room temperature, the crystals which had formed were collected by filtration to give 10.09 g. of the (+)-10-camphorsulfonic acid salt of 42, m.p. 131-137°, $[\alpha]_D^{23} +32.0^\circ$ (c 5, absolute ethanol).

Anal. Calcd. for $C_{15}H_{27}NO_5S$: C, 54.03; H, 8.16.
Found^{Sch}: C, 53.99; H, 8.10.

B. A warm solution of 10.1 g. (0.10 mole) of racemic 42 in 300 ml. of acetone was added to a warm solution of 30.2 g. (0.13 mole) of (+)-10-camphorsulfonic acid in 500 ml. of acetone. No precipitation occurred on cooling the mixture to room temperature overnight. The mixture was cooled to ice-bath temperature and crystallization commenced within a few

hours. The mixture was maintained at 0° for an additional 5 days. The salt which formed was isolated by filtration to give 25.22 g. of the (+)-10-camphorsulfonic acid salt of 42, m.p. 134-136.5°. The filtrate from the filtration was enriched in the (+)-(-)-diastereomeric salt and provided partially resolved (-)-42 (see below).

A portion of the salt (8.00 g.) was dissolved in 650 ml. of acetone. The solution was cooled at 0° for 2 days and at room temperature for 27 days. The salt which formed was collected by filtration to give 4.47 g. of the (+)-10-camphorsulfonic acid salt of 42, m.p. 131-133.5°, $[\alpha]_D^{23} +32.4^\circ$ (c 5, absolute ethanol). The infrared spectrum of the salt was identical with that obtained in A.

C. The preparation of the (+)-10-camphorsulfonic acid salt of 42 using equimolar quantities of acid and base with acetone-ethanol or acetone-isopropanol mixtures as solvents gave erratic, non-reproducible results. Although the salts which were obtained were presumably partially resolved, they were not extensively investigated, since the use of excess resolving acid gave more consistent results (A and B).

The filtrate from B above was concentrated by evaporation to give 19.1 g. of an orange oil. Without further purification, the oil was taken up in a small amount of water. The solution was saturated with potassium carbonate and was extracted with methylene chloride. The extracts were combined and dried over solid anhydrous potassium carbonate. The solvent was removed by evaporation to give 5.79 g. of (-)-42 as a viscous oil which partially crystallized on standing, $[\alpha]_D^{23} -1.6^\circ$ (c 12.3, 95% ethanol). Although not completely crystalline, this material was homogeneous to gas chromatographic analysis (1 m. 5% Carbowax 20M on Chromosorb W, 125°, 7 psi).

(+)-3-Piperidinol [(+)-42]. A portion of the salt from B was taken up in a small amount of water. The solution was saturated with potassium carbonate and was extracted with methylene chloride. The extracts were combined and dried over solid potassium carbonate. The solvent was removed by evaporation to leave an oil as residue which crystallized after drying in a desiccator over solid potassium hydroxide to give 0.42 g. of (+)-42, $[\alpha]_D^{22.5} + 3.2^\circ$ (c 11.9, 95% ethanol). This material melted at 55-60° with about half the crystals remaining in the melt. These crystals then melted at 76-85°. Reported^{71a} for racemic 42, m.p. 61-63°.

Absolute Configuration of N-Methyl-3-piperidinol (11)

(-)-N-Methyl-3-piperidinol [(-)-11] was prepared by the Eschweiler-Clarke methylation of (-)-42.⁷¹ Thus, 4.69 g. (0.0464 mole) of (-)-42, $[\alpha]_D^{23} -1.6^\circ$, was mixed with 8 g. of 90% formic acid. To this solution was added 5 g. of 40% formaldehyde. The mixture was heated to reflux while stirring magnetically for 22 hr. To this mixture was added 10 ml. of concentrated hydrochloric acid, and the acidic mixture was concentrated by distillation at reduced pressure. The residue was made basic with saturated sodium hydroxide solution, and the solution was saturated with potassium carbonate. The mixture was extracted with ether, the ether extracts were combined and dried over solid potassium carbonate, and were concentrated by evaporation to give 3.86 g. (72%) of (-)-11, $[\alpha]_D^{22} -2.4^\circ$ (c 12.5, absolute ethanol). The infrared spectrum (liquid film) of the oil was identical with that of authentic racemic 11 and with (+)-11 from the asymmetric hydroboration of N-methyl-1,2,5,6-tetrahydropyridine (10). Gas chromatographic analysis (1 m. 5% Carbowax 20M on Chromosorb W, 125°, 5 psi) indicated a purity of greater than 99%, with no detect-

able 42 present.

Hydroboration of Tropicine (44) by the In Situ Generation of Diborane

Tropine (45) was obtained from a commercial source.⁴² Gas chromatographic analysis indicated that it contained a mixture of 94% tropine and 6% pseudo-tropine, and it was used without further purification.

Tropicine (44) was prepared in 31-33% yields by the dehydration of tropine according to the method of Ladenburg⁷⁴, b.p. 160-164°; lit.⁷⁴ b.p. 162°.

NMR Spectrum (neat, No. 1246): 2.32 (singlet), 3.33 (multiplet), 5.58 (multiplet). See Fig. 2 for the complete spectrum of 44.

Hydroboration-Oxidation of Tropicine (44). A dry 200 ml. 3-necked flask, equipped with magnetic stirrer, condenser, and pressure-equalizing dropping funnel, was flushed with dry nitrogen which was exited in an acetone trap. Into the flask were introduced solutions of 1.49 g. (0.0394 mole) of sodium borohydride in 40 ml. of diglyme and 3.08 g. of tropidine (0.025 mole) in 10 ml. of diglyme. The mixture was stirred and maintained at 0° by an ice bath, and a solution of 6.7 ml. (ca. 0.0525 mole) of boron trifluoride etherate in 10 ml. of diglyme was added dropwise over a period of 1.5 hr. After the completion of this addition, the resulting mixture was brought to room temperature and stirred for an additional 1.5 hr. The solution was hydrolyzed by adding water carefully until there was no further reaction. This mixture was made basic with 15 ml. of 6 N sodium hydroxide and oxidized at 50-64° with 5 ml. of 30% hydrogen peroxide, which was added dropwise over a period of 0.5 hr. The reaction mixture was stirred

for an additional 1.5 hr. and then acidified with 20 ml. of concentrated hydrochloric acid. The mixture was concentrated to near-dryness by distillation at reduced pressure, and water was added. The residual diglyme and diethylene glycol monomethyl ether (18) were removed by steam distillation. The addition of water and steam distillation was repeated twice. The resulting residue was taken up in a small amount of water, solid potassium carbonate was added, and the basified mixture was extracted with several portions of ether. The combined extracts were dried over potassium carbonate and concentrated by evaporation to leave a light yellow oil as residue. The yield of this crude product was 2.41 g. (68%). This oil was analyzed in detail by gas chromatography (2 m. 5% Quadrol on 60-80 mesh KOH-washed Chromosorb W, 157°, 11 psi). The four predicted tropanol isomers were present in the relative amounts of 3% 2- β -tropanol (48), 50 \pm 3% tropine (45), 43 \pm 3% 2- α -tropanol (47), and 4% pseudo-tropine (46). The gas chromatographic retention times of these compounds were 4.20, 11.2, 12.5, and 16.0 minutes, respectively, and were exactly the same as those of a synthetic mixture containing authentic L-2- β -tropanol (48), tropine (45), L-2- α -tropanol (47), and pseudo-tropine (46). (The percentages of tropine and 2- α -tropanol are reported as ranges because their peaks in the gas chromatogram were not completely resolved). A sample of tropine, m.p. 60-64°: lit.⁷⁵ m.p. 63-64°, was isolated from the reaction mixture by preparative gas chromatography (20 ft. x 3/8 in. aluminum column packed with 20% Carbowax 20M on DMCS treated, acid-washed Chromosorb W) and had the same gas chromatographic retention time as that of an authentic sample⁴² of tropine.

Epimerization of Tropanols. The reaction mixture above was separated into several fractions by distillation. The fraction boiling at 82-89° at 2.4-2.9 mm. (0.768 g.) was analyzed by gas chromatography and found to contain 1% 2- β -tropanol (48), ca. 52% tropine (45), ca. 41% 2- α -tropanol (47), and 6% pseudo-tropine (46).

This material was epimerized by the sodium 3-pentoxide-fluorenone equilibration procedure of Bell and Archer.^{72b} Thus, a 0.187 g. sample of the distillation fraction above was heated in a refluxing solution of 0.15 g. of sodium, 0.75 ml. of toluene, 0.0286 g. of fluorenone, and 1.6 ml. of 3-pentanol while stirring magnetically for 28 hr. The mixture was cooled, and 1.6 ml. of water was added. The basic mixture was extracted with ether, the ether extracts were combined and dried over potassium carbonate, and most of the ether was removed from the dried extract by evaporation. The resulting ethereal residue was analyzed by gas chromatography and was shown to contain the four epimeric tropanols in the relative amounts of 32% 2- β -tropanol (48), ca. 7% tropine (45), ca. 10% 2- α -tropanol (47), and 51% pseudo-tropine (46). Evaporation of the ether from the solution analyzed above gave a yellow oil which partially crystallized on standing. The crystals were collected by filtration and triturated with ligroin (30-60°) to give crude pseudo-tropine (46), m.p. 99-108.5°. One recrystallization from benzene-ligroin (30-60°) gave a pure sample of 46, m.p. 104-108°; lit. m.p. 106-108°⁹⁶; 109-110°⁷⁵.

Preparation of Tropicine Amineborane (51)

Tropicine Amineborane (51). A 1 M solution (8 ml.) of borane (BH₃) in tetrahydrofuran⁹² was added from a hypodermic syringe to a magnetically stirred solution of 1.00 g. (0.00813 mole) of tropidine (44) in 10 ml. of n-hexane in a

flask cooled in an ice bath. The resulting mixture was taken to dryness by distillation at reduced pressure to give 1.12 g. of a white solid residue. This material was recrystallized once from water to give 0.78 g. (71%, based on structure 51) of crystals, m.p. 118-122° d., identified as tropidine amineborane (51) by its infrared (Nujol and Halocarbon double mulls) and nmr spectra. A portion of the crystals was purified by vacuum sublimation to give an analytical sample of 51, m.p. 117-119° d. (softens at 97°). This compound was characterized by a distinctive odor similar to that of camphor.

Anal. Calcd. for $C_8H_{16}BN$: C, 70.12; H, 11.77; N, 10.22. Found^{Sch}: C, 69.93; H, 11.55; N, 10.43.

IR Spectrum (No. 337 4083): 3040 (w), 3015 (w), 2960, 2420, 2380, 2340, 2270, 1440, 1298, 1192, 1180, 1160-1150 (doublet), 1106, 1055, 895, 878, 833, 809, 743, 683, 583.

NMR Spectrum ($CDCl_3$, No. 1683): 2.79 (singlet), 3.46 (multiplet), 5.78 (multiplet). See Fig. 2 for the complete spectrum of 51.

Hydroboration of Tropidine (44) with Diisopinocampheylborane.

In a dry 200 ml. 3-necked flask, equipped with the usual facilities, was introduced 13.62 g. (0.10 mole) of (-)- α -pinene ($\alpha_D^{27.5}$ -40.30°, ca. 92% optically pure). The flask was immersed in an ice bath and was flushed with nitrogen, and the contents were stirred magnetically while 50 ml. of a 1 M solution of borane (0.050 mole of BH_3) in tetrahydrofuran was added over a period of 0.5 hr. After stirring for about 1 hr. (+)-diisopinocampheylborane [(+)-2] precipitated, and the reaction mixture was stirred at 0° for a total of 9 hr.

To the suspension of 0.050 mole of (+)-diisopino-

camphylborane prepared above was added dropwise a solution of 3.08 g. (0.025 mole) of tropidine (44) in 25 ml. of monoglyme. The resulting mixture was stirred at 0° for 2 hr., the ice bath was removed, and the reaction proceeded at room temperature. An aliquot of the reaction mixture was taken when the reaction had proceeded for 6 hr. at room temperature and was shown by gas chromatography (2 m. 5% Carbowax 20M on HMDS treated Chromosorb W, 133°, 5 psi) to contain α -pinene. After stirring for a total of 12 hr. at room temperature, the reaction mixture was hydrolyzed with water, was made basic with 15 ml. of 6 N sodium hydroxide, and was oxidized at 30-50° by the dropwise addition of 5 ml. of 30% hydrogen peroxide. The reaction mixture was acidified with 15 ml. of concentrated hydrochloric acid and stirred for 0.5 hr. The acidic mixture separated into two layers. The bottom, aqueous layer was separated by decantation, and most of the non-basic material was removed from this solution by extracting with ether. The acidic solution from the extraction was concentrated to a small volume by distillation at reduced pressure. This residue was triturated with several portions of anhydrous ether. The solid residue from the trituration was taken up in water, potassium carbonate was added, and the basic mixture was extracted with several portions of ether. The extracts were combined, were dried over solid potassium carbonate, and were concentrated by evaporation to give 1.74 g. of an oil. This oil was shown by gas chromatography (2 m. 5% Quadrol on 60-80 mesh KOH-washed Chromosorb W, 149°; and 1 m. 20% Quadrol on 60-80 mesh KOH-washed Chromosorb W, 160°) to contain about 0.65 g. (18%) of a mixture of the four epimeric tropanols in the relative amounts of 61% 2- β -tropanol (48), 6% tropine (45), 6% 2- α -tropanol (47), and 27% pseudo-tropine (46). The chromatogram indicated the presence of a substantial amount (the exact quantity was not determined) of unreacted tropidine.

A pure sample of 2- β -tropanol (48) obtained by preparative gas chromatography (1 m. 20% Quadrol on 60-80 mesh KOH-washed Chromosorb W) had an infrared spectrum (liquid film) identical with that of an authentic sample of (+)-L-2- β -tropanol [(+)-(48)].⁷²

Hydroboration of Tropolidone (44) with Triisopinocampheyl-diborane. In a dry 200 ml. 3-necked flask, equipped with the usual facilities and flushed with nitrogen, was introduced 50 ml. of a 1 M solution of borane (0.050 mole of BH_3) in tetrahydrofuran. The flask was immersed in an ice bath, and the solution was stirred magnetically while a solution of 20.4 g. (0.15 mole) of (-)- α -pinene ($\alpha_D^{27.5}$ -40.30°) in 25 ml. of tetrahydrofuran was added over a period of 0.5 hr. The mixture was stirred for an additional 10 hr. at 0°.

To the mixture of 0.050 mole of triisopinocampheyl-diborane [(+)-31] prepared above was added dropwise a solution of 3.08 g. (0.025 mole) of tropolidone (44) in 25 ml. of tetrahydrofuran. The resulting mixture was stirred at 0° for 8 hr. The mixture was hydrolyzed with 2 ml. of water, was made basic with 15 ml. of 6 N sodium hydroxide, and was oxidized at 30-50° for 2 hr. by the addition of 10 ml. of 30% hydrogen peroxide. The reaction mixture was acidified with 15 ml. of concentrated hydrochloric acid and was stirred overnight. The resulting mixture was concentrated by distillation at reduced pressure, and the residue was triturated with anhydrous ether to remove the non-basic material. The remaining acidic residue was taken up in water, potassium carbonate was added, and the basic mixture was extracted with four portions of ether. The extracts were combined, were dried over solid potassium carbonate, and were concentrated by evaporation to give an oil which was shown by gas chroma-

tography (1 m. 20% Quadrol on 60-80 mesh KOH-washed Chromosorb W, 160°, 16 psi) to contain about 0.95 g. (27%) of a mixture of tropanols in the relative amounts of 63% 2- β -tropanol (48), 7% of a mixture of tropine (45) and 2- α -tropanol (47), and 30% pseudo-tropine (46).

The results of the hydroboration of tropidine with diborane, diisopinocampheylborane, and triisopinocampheyl-diborane are summarized in Table IV.

Hydroboration of N-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine by the In Situ Generation of Diborane

N-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine (55) was prepared by the condensation of α -methylstyrene, aqueous formaldehyde, and methylamine hydrochloride according to the procedure of Schmidle and Mansfield³⁸ to give a 54% yield of 55, b.p. 102-106° at 0.3 to 0.5 mm.; lit.³⁸ b.p. 85-90° at 0.8 mm. This material crystallized on standing; m.p. 38-40°; lit.³⁸ m.p. 40-42°.

trans-N-Methyl-4-phenyl-3-piperidinol (56). A. A dry 500 ml. 3-necked flask, equipped with magnetic stirrer, condenser, and pressure-equalizing dropping funnel, was flushed with dry nitrogen, which was exited through an acetone trap. Into the flask, maintained at 0°, were introduced solutions of 21.65 g. (0.125 mole) of N-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (55) in 50 ml. of diglyme and 7.45 (0.20 mole) of sodium borohydride in 50 ml. of diglyme. A solution of 33.5 ml. (ca. 0.26 mole) of boron trifluoride etherate in 25 ml. of diglyme was added dropwise to the stirred mixture over a period of 1.3 hr. while a positive nitrogen pressure was maintained. After completion of this addition, the resulting mixture was brought to room temperature

and stirred for an additional 1.5 hr. The solution was hydrolyzed with 10 ml. of water, was made basic with 30 ml. of 6 N sodium hydroxide, and was oxidized at 45-60° with 30 ml. of 30% hydrogen peroxide, which was added dropwise over a period of 1 hr. The reaction mixture was stirred for an additional hour and then acidified with 30 ml. of concentrated hydrochloric acid. The mixture was concentrated to near dryness by distillation, water was added and the concentration was repeated to remove by steam distillation the residual diglyme and diethylene glycol monomethyl ether (18). The addition of water and steam distillation was repeated twice. The resulting salt and viscous yellow residue was taken up in water, and solid potassium carbonate was added. The basic mixture was extracted five times with ether, and the combined extracts were dried over potassium carbonate and distilled. The fraction boiling at 157-177° at 10 mm. was collected. After standing at room temperature for three weeks, the crude product crystallized to give 16.0 g. (67%) of solid, m.p. 50-72°. Two recrystallizations of the solid from n-heptane gave an analytical sample of trans-N-methyl-4-phenyl-3-piperidinol (56), m.p. 82-84.5°. This compound was identical with a sample obtained by the lithium aluminum hydride reduction of N-methyl-4-phenyl-3-piperidone⁸³, based on comparison of melting points, infrared spectra, and gas chromatographic retention times.

Anal. Calcd. for C₁₂H₁₇NO: C, 75.35; H, 8.96.
Found^{Sch}: C, 75.63; H, 8.92.

IR Spectrum (No. 337 692): 3155-3145, 2920, 2850, 2795, 1603 (w), 1495 (m), 1450 (m), 1260-1255 (doublet), 1135, 1100, 1090, 1070, 1050, 975, 872, 750, 695.

NMR Spectrum (28% w/w in CDCl_3 , No. 1434): 1.78 (multiplet), 2.09 (singlet), 2.81 (multiplet), 3.63 (sextet), 4.11 (singlet), 7.20 (multiplet). See Fig. 2 for the complete spectrum of 56.

At a sweep width of 100 cps, the sextet at 3.63 ppm (methine H at carbon-3) had line spacings of 4.36, 5.36, 4.46, 5.20 and 4.40 cps, respectively. The sextet appeared to be the result of the overlap of two triplets, with $J_{aa} = 9.74$ cps and $J_{ae} = 4.36-4.48$ cps. This portion of the spectrum is reproduced as an enlarged insert in Fig. 2.

The picrate of 56, after recrystallization twice from 95% ethanol, melted at 232-234°.

B. In another experiment 4.43 g. (0.0254 mole) of 55 was hydroborated with diborane which was generated in situ by the reaction of 7.5 g. (0.052 mole) of boron trifluoride etherate with 1.14 g. (0.030 mole) of sodium borohydride. Using the procedure of oxidation and work-up as described in A, 6.0 g. of a viscous oil was obtained. This oil crystallized from an diethyl ether-ligroin (30-60°) mixture to give 3.79 g. (77.5%) of 56, m.p. 71-78°.

It was observed that the reluctance of crude 56 to crystallize from the concentrated ether extracts was due in part to the presence of trace amounts of diglyme and/or 18. However, once crystalline, 56 could be readily recrystallized from n-heptane or ligroin.

trans-N-Methyl-4-phenyl-3-piperidyl Acetate Hydrochloride (57) was prepared by the esterification of the base of the alcohol 56 with acetic anhydride and sodium acetate and was precipitated from an ethereal HCl solution. An analytical sample, m.p. 205-211°, was obtained after two recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47.
Found^{Sch}: C, 62.45; H, 7.74.

IR Spectrum (No. ₂₁ 3578): 2470 (sh), 2430-2390, 1738, 1230, 1072, 1057, 1027, 962, 764, 701.

trans-N-Methyl-4-phenyl-3-piperidyl Benzilate Hydrochloride (58) was prepared by trans-esterification of the base of the alcohol 56 with methyl benzilate, using the method of Cannon.⁹⁷ An analytical sample was prepared by recrystallization from absolute ethanol and melted at 211-216°.

Anal. Calcd. for $C_{26}H_{28}ClNO$: C, 71.30; H, 6.44; N, 3.20. Found^{FM}: C, 70.91; H, 6.71; N, 2.97.

IR Spectrum (No. ₁₃₇ 5231): 3225, 2450-2350, 1740, 1215-1205, 1065, 768, 702.

Fig. 1 NMR Spectra of N-Methyl-1,2,5,6-tetrahydropyridine (10) and N-Methyl-1,2,5,6-tetrahydropyridine Amineborane (13)

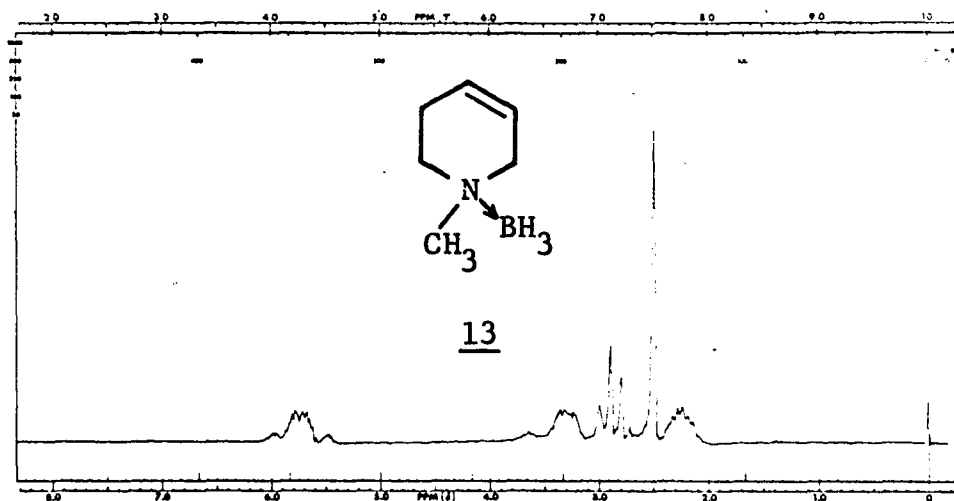
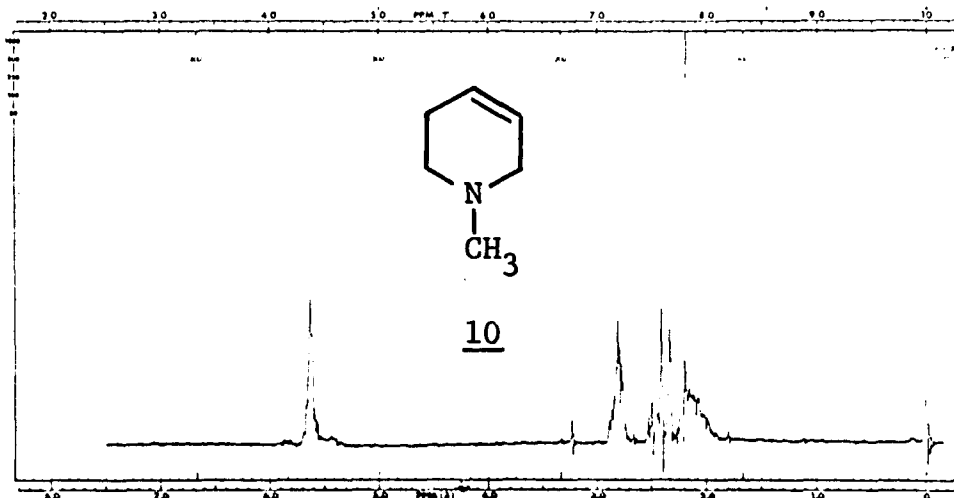
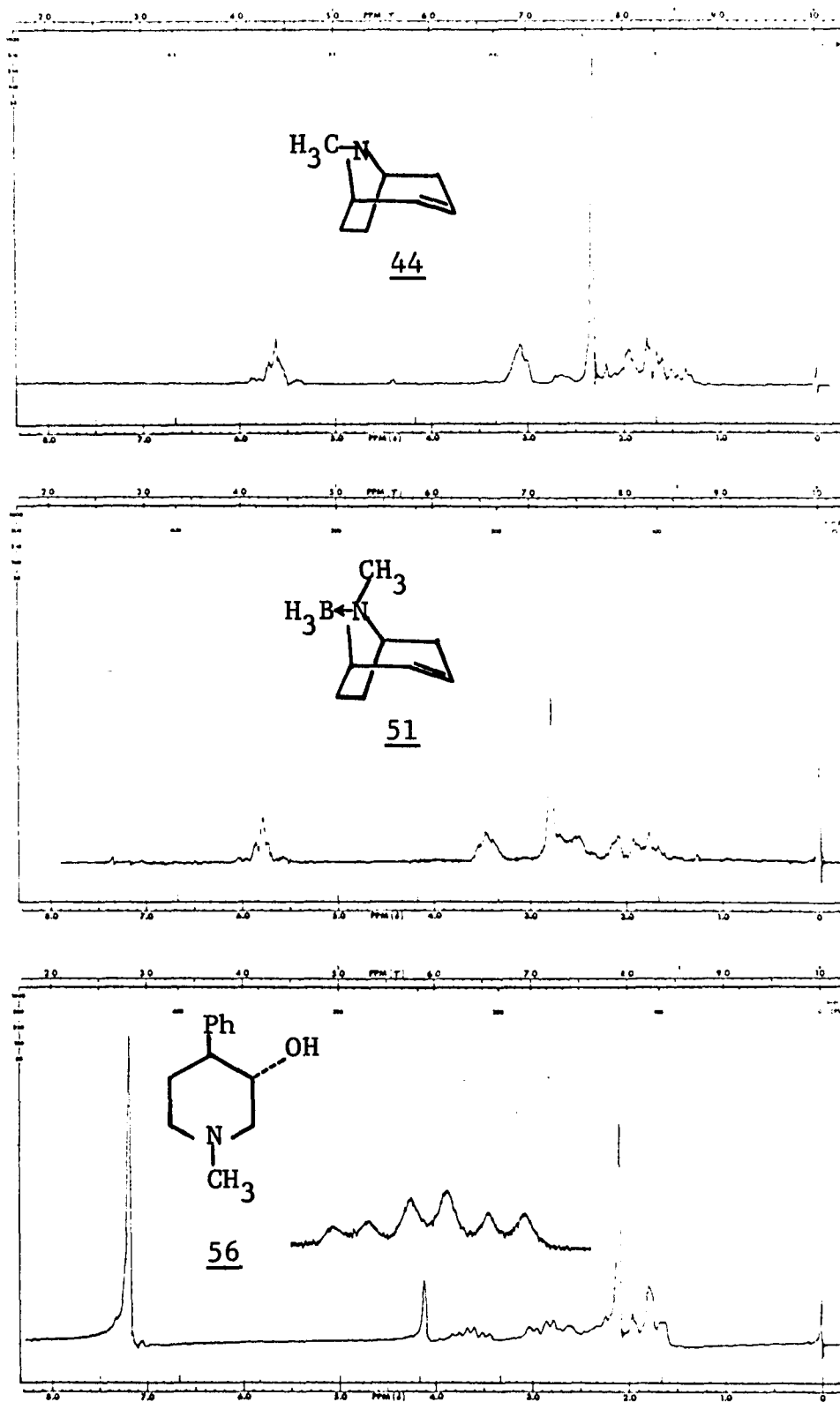


Fig. 2 NMR Spectra of Tropidine (44), Tropidine Amineborane (51), and *trans*-N-Methyl-4-phenyl-3-piperidinol (56)



SUMMARY

1. The conversion of a number of tetrahydropyridines to the corresponding piperidinols in moderate to good yields by the hydroboration reaction was demonstrated. The reaction proceeded such that the formation of N-alkyl-3-piperidinols were favored over the N-alkyl-4-piperidinol isomers by a factor of 3:1. This selectivity was explained in terms of the inductive effect of the allylic nitrogen atom, which directed attack of the boron atom of diborane to the 3-carbon of the tetrahydropyridine. For the systems studied, the size of the N-alkyl group had no substantial effect on the distribution of piperidinol isomers.

2. The reaction of several unsaturated amines with diborane was found to proceed stepwise, with the first mole of borane (BH_3) reacting with the nitrogen atom to form an amineborane, and in a slower, subsequent step, the second mole of BH_3 adding to the carbon-carbon double bond.

3. The asymmetric induction hydroboration of the model compound, N-methyl-1,2,5,6-tetrahydropyridine, gave optically active N-methyl-3-piperidinol of about 25% optical purity.

4. The absolute configuration of (-)-3-piperidinol was established as having the \underline{S} configuration by a cyclization scheme starting with L-(+)-arginine hydrochloride.

5. Racemic 3-piperidinol was partially resolved into both enantiomers. Conversion of (-)-3-piperidinol to (-)-N-methyl-3-piperidinol by methylation established the absolute configuration of (-)-N-methyl-3-piperidinol as \underline{S} .

6. The hydroboration of the bicyclic amine, tropidine, with diborane gave as major products, tropine and 2- α -tropanol, with pseudo-tropine and 2- β -tropanol together accounting for only 7% of the products obtained. This stereospecificity was explained in terms of the steric influence of the intermediate tropidine amineborane, which directed attack of borane to the α side of the tropidine molecule.

7. The hydroboration of tropidine with diisopinocampheylidiborane and the less hindered triisopinocampheylidiborane gave 18-27% yields of a mixture of tropanol isomers in which pseudo-tropine and 2- β -tropanol were the major isomers. This stereospecificity was not explained rigorously, but presumably is due to the substantial steric bulk of the organoborane hydroborating agents.

8. The extension of the hydroboration reaction to unsaturated amines was further demonstrated by the conversion of N-methyl-4-phenyl-1,2,5,6-tetrahydropyridine to trans-N-methyl-4-phenyl-3-piperidinol in good yields.

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