The 2,3-Diazabicyclo[2.2.1]heptyl Ring System. II.[1] The Elimination Mechanism of the Intermediates Formed by Hydroboration of 2,3-Dicarbomethoxy-2,3-diazabicyclo[2.2.1]hept-5-ene

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The intermediates formed in the hydroboration of 2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]hept-5-ene under appropriate conditions yield the partially fragmented products, 4-(N,N′-dicarbomethoxyhydrazino)cyclopentene and 3-(N,N′-dicarbomethoxyhydrazino)cyclopentanol. These products have been shown to arise *via* a *trans*-β-elimination mechanism. A study with different nucleophiles shows a correspondence between the elimination and the nucleophilicity of the group which attacks the boron atom. In this regard, sodium borohydride was found to be particularly effective in causing the elimination.

According to recent reports,[2-4] hydroboration of a variety of different allyl derivatives results in β elimination of the organoborane intermediate. Brown and Cope,[3b] postulate both *cis*- and *trans*-elimination mechanisms. In another study, Pasto and Cumbo[5] cite evidence for a *cis* elimination and a boron trifluoride catalyzed *trans* elimination of β-ethoxyorganoboranes. However, to date most of the intimate mechanistic details of such eliminations are largely unknown.

Our interest in this field was aroused by the discovery that partial fragmentation–rearrangement accompanies hydroboration–oxidation of 2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]hept-5-ene (I). As we reported in the preceding paper,[1] products II and IV can be obtained in substantial yields with appropriate conditions.

It appeared desirable to undertake an investigation of the mechanism of this reaction for several reasons. First of all, it seemed likely that the formation of II was the result of β elimination of organoboron intermediates. If this proved to be the case, the rigid bicyclic structure I offered special advantage in examining the details of such eliminations. In this regard, the stereochemistry of the reaction could be deduced from information already in hand. Finally, the formation of II and IV appeared to be especially sensitive to a variety of different reaction conditions. This paper reports the details of our study of the mechanism of the formation of II *via* hydroboration–oxidation of I.

Results and Discussion

Preliminary experiments were made with I to determine the time required for hydroboration of the carbon–carbon double bond, and to ascertain the extent of any concurrent reaction with the carbomethoxyhydrazino part of the molecule. Hydroboration was conducted in tetrahydrofuran at 0° using a 1:1 ratio of borane[6] to I. The mixture was kept at 0° and aliquots were removed periodically and analyzed for residual hydride.[7] The reaction proceeded smoothly, with 1 mole of hydride per mole of I being consumed in *ca.* 2 hr. Further utilization of hydride occurred at a very much reduced rate. After 7 hr the uptake of hydride was less than 1.1 moles per mole of I. Thus, the amount of any side reaction is negligible in a few hours at 0°. On the basis of this, the standard time of hydroboration for all studies (except Figure 1) was selected as 3 hr at 0°.

In order to see if II and IV arise from the same reaction pathway, I was hydroborated with deuterioborane in tetrahydrofuran at 0°. For this experiment a 1:1 ratio of deuterioborane to I was used. After reaction at 0° the hydroboration mixture was divided into two parts and worked up as in expt 1 and 6 of Table I. One part was oxidized immediately at 0° by addition of an aqueous solution of hydrogen peroxide and sodium hydroxide. Deuterated III was recovered by column chromatography in 94% yield. This product showed 90–95% incorporation of one deuterium atom at ring position C-6 as based on nmr analysis. The nmr spectrum showed the disappearance of one proton in the two-proton multiplet at τ 8.3.[8] The remainder of the hydroboration mixture was treated with 1 molar equiv of sodium hydroxide and then refluxed (60°) for 3 hr. After oxidation at 0° with aqueous hydrogen peroxide and sodium hydroxide, deuterated II was recovered by column chromatography in 86% yield. A 90–95% incorporation of one deuterium was found at C-3. The nmr spectrum showed the disappearance of one proton in the four-proton methylene doublet centered at τ 7.50.[8]

These deuterium-labeling results indicate that II and III are formed from common organoboron intermediates. The fragmentation which subsequently leads to II can be accounted for readily in terms of β elimination of such intermediates (*vide infra*).

The question of the configuration of the organoborane intermediates is pertinent to a mechanistic description of the elimination. In the preceding paper[1] we established that oxidation of the reaction intermediates affords the *exo* epimer III (Scheme I) in high yield. Brown has accumulated convincing evidence that hy-

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(1) Part I: E. L. Allred, C. L. Anderson, and R. L. Smith, *J. Org. Chem.*, **31**, 3493 (1966). For a preliminary communication of a part of these results, see E. L. Allred, C. L. Anderson, and R. L. Smith, *Tetrahedron Letters*, **No. 9**, 951 (1966).

(2) P. Binger and R. Koster, *ibid.*, **No. 4**, 156 (1961).

(3) (a) H. C. Brown and K. A. Keblys, *J. Am. Chem. Soc.*, **86**, 1791 (1964); (b) H. C. Brown and O. J. Cope, *ibid.*, **86**, 1801 (1964).

(4) J. G. Sharefkin and S. H. Pohl, *J. Org. Chem.*, **29**, 2050 (1964).

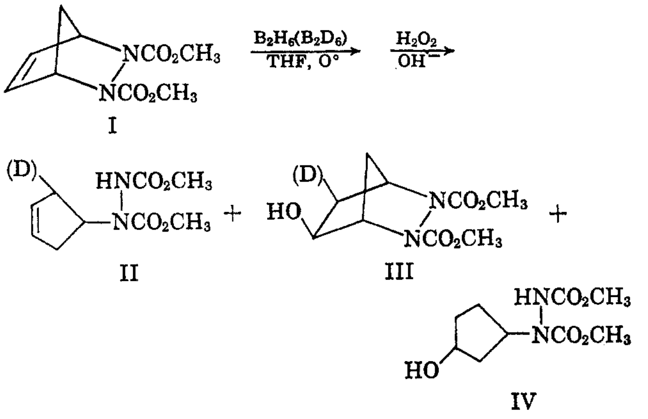
(5) (a) D. J. Pasto and C. C. Cumbo, *J. Am. Chem. Soc.*, **86**, 4343 (1964). (b) A very recent study of the elimination of β-substituted organoboranes was reported by D. J. Pasto, R. Snyder, and N. P. Bolasurbramaniyan at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstracts, p 4S.

(6) Diborane exists in tetrahydrofuran solution as the borane derivative; see B. Rice and H. S. Uchida, *J. Phys. Chem.*, **59**, 650 (1955).

(7) Analysis was made by the procedure of Brown and Keblys.[3a] Following the lead of these workers, the stoichiometry is discussed in terms of the "hydride" utilized. One mole of borane, BH_3, yields 3 moles of hydrogen on hydrolysis, corresponding to the presence of three "hydrides." Addition of 1 mole of "double bond" results in the up-take of 1 mole of "hydride." Hydrolysis then results in the evolution of 2 moles of hydrogen, showing the presence of 2 moles of residual "hydride."

(8) See ref 1 for the nmr data for II and III.

SCHEME I



droboration involves *cis* addition of the boron–hydrogen bond to the carbon–carbon double bond, and that subsequent oxidation to the alcohol proceeds with retention of configuration.[9] On this basis, the boron–carbon bond is in the *exo* configuration. Thus, the elimination must occur in a *trans* manner.

It was observed previously that the method of generating diborane and the temperature of oxidation greatly affected the formation of II and IV.[1] This suggested that the elimination may be a consequence of nucleophilic attack on boron. To check this possibility, tetrahydrofuran solutions of the organoboranes formed from a 1:1 ratio of borane to I were treated with a few different nucleophiles for varying lengths of time and at temperatures of 0 and 60°.[10] Following the treatment, the reaction mixture was oxidized with alkaline hydrogen peroxide at 0° and the products II, III, and IV were separated by careful chromatography on a Florisil column. Infrared spectra were used to follow the course of separation and for estimating product yields. In all cases, the total recovered product yield (II, III, and IV) was greater than 90%. The product compositions are believed to be reliable to *ca.* ±3%. The results of this study are summarized in Table I.

A consideration of the results in Table I reveals a trend of increasing elimination (II + IV) according to the order of increasing nucleophilicity THF < H_2O < OH^- < BH_4^-. This clearly indicates that boron–carbon cleavage of the intermediates and the resulting β elimination are a consequence of nucleophilic attack on boron. In this regard, Cristol and co-workers[11] found that treatment of the hydroboration intermediate of 2-chlorodibenzobicyclo[2.2.2]octatriene with water gave elimination of boron and chloride while treatment with nonaqueous perbenzoic acid gave chlorohydrin. These observations provide the first identification of a correspondence between the elimination and the nucleophilicity of the group attacking the boron atom.

The labeling, stereochemical, and nucleophilic results are accounted for readily in terms of the mechanistic sequence shown in Scheme II. In this scheme, Y: represents the nucleophile.

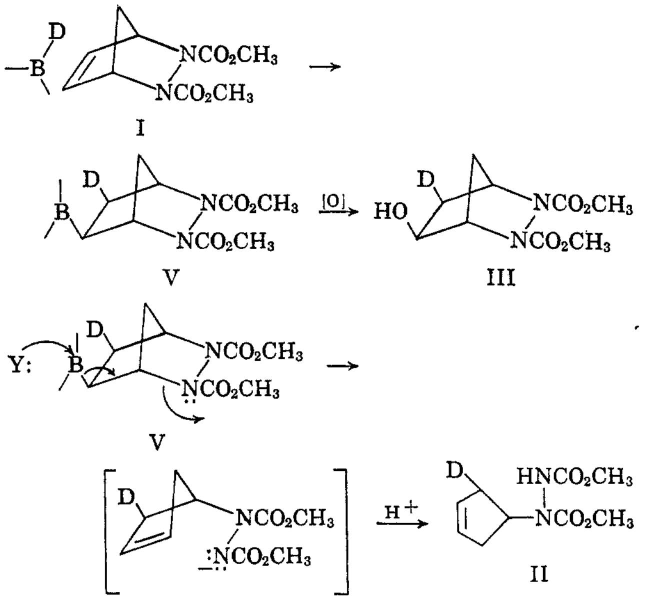
TABLE I

EFFECT OF NUCLEOPHILES ON THE ELIMINATION REACTION OF THE INTERMEDIATES PRODUCED IN THE HYDROBORATION OF I

Expt[a]	Time, hr	Temp, °C	Added nucleophile	Composition of the product, % II	III	IV
1	..	0	...	<3	94	<3
2[b]	8	60	THF	<5	>90	...
3[b]	72	60	THF	<3	>90	<3
4[c]	3	0	OH^-	<3	95	<3
5[c]	1	60	OH^-	50	45	<5
6[c]	3	60	OH^-	86	8	...
7[d]	1	60	H_2O	30	...	...
8[d]	3	60	H_2O	31	65	<3
9[d]	8	60	H_2O	33	...	...
10[e]	3	0	BH_4^-	<5	65	30

[a] A 1:1 ratio of BH_3 to I was used for all hydroborations, except for expt 3 where the ratio was 7:1. Hydroboration was conducted at 0° for 3 hr. The standard oxidation work-up consisted of rapid addition of a twofold excess of aqueous $NaOH–H_2O_2$ at 0°. [b] The excess BH_3 was removed under vacuum and fresh, dry THF was added. [c] Enough 3 *M* NaOH was added to give a 1:1 mole ratio of OH^- to I. The standard oxidation work-up was used at 0°. [d] A 9:1 mole ratio of H_2O to I was used. The standard oxidation work-up was used. [e] A 0.5:1 mole ratio of $NaBH_4$ to I was added at the start of the hydroboration. This result was verified by several similar experiments.

SCHEME II



To the best of our knowledge expt 10 (Table I) represents the first recognition that sodium borohydride can cause elimination of β heterosubstituted organoboranes. The effectiveness of sodium borohydride is indicated by the efficiency of elimination at 0°. In the present case the amount of elimination is reflected by the yield of IV since II is hydroborated readily under the reaction conditions.[1] This elimination is all the more impressive because V eliminates much more slowly than the boron derivatives of allyl ethyl and allyl phenyl ethers.[3b] These observations make it clear that for most synthetic applications *in situ* hydroboration is not the method of choice with α- or β-heterosubstituted alkenes.

Another striking aspect of the results in Table I is that water-promoted elimination appears to stop far short of the amount of elimination effected by hydroxide ion. The elimination at 60° by hydroxide ion advances from 50% at 1 hr (expt 5) to 86% at 3 hr (expt 6). In

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(9) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, pp 12–16, 71–72, and Chapter 8.

(10) In this study, care was taken to exclude boron trifluoride[5a] and sodium borohydride from the tetrahydrofuran solution of borane by using diborane which had been generated from sodium borohydride and boron trifluoride and then passed through a diglyme solution of sodium borohydride; see G. Zweifel, K. Nagase, and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 188 (1962).

(11) S. J. Cristol, F. P. Parungo, and D. E. Plorde, *ibid.*, **87**, 2870 (1965).

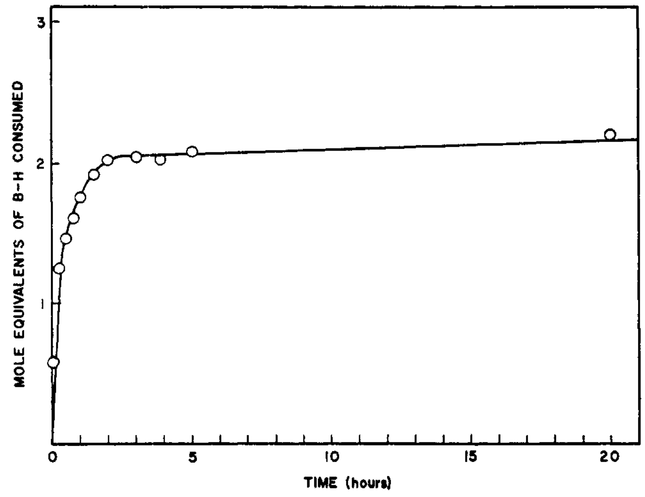
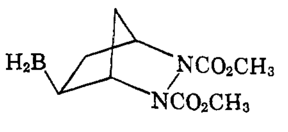
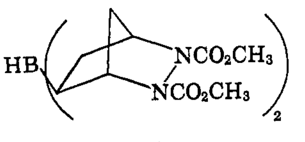


Figure 1.—The degree of alkylation of borane by I in tetrahydrofuran at 0° (three I per BH_3 equivalent).

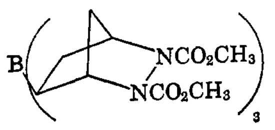
contrast, the elimination with water at 60° remains constant at *ca.* 31% for 1, 3, and 8 hr (expt 7, 8, and 9). These observations suggested that organoborane intermediates such as Va, Vb, and Vc may undergo elimination differently. This point was explored by determining the degree of alkylation of borane by I at 0°, and by scrutinizing the change of water-promoted elimination as the I:BH ratio was varied.



Va



Vb



Vc

The degree of alkylation was established by treating a 3:1 molar ratio of I with borane in tetrahydrofuran. Samples were removed and analyzed for residual hydride at appropriate intervals of time. As shown in Figure 1, the reaction proceeded smoothly to the dialkylborane stage Vb, but only very slowly beyond this. After 20 hr only 2.2 equiv of hydride had been consumed. This indicates that with the standard conditions hydroboration does not proceed appreciably beyond Vb.

Hydroborations of I were carried out under standard conditions for several different I:BH ratios. In each case excess water was added and the reaction product was refluxed in tetrahydrofuran (60°). Following oxidation at 0°, the product composition was determined by careful column chromatography. The results are listed in Table II.

Experiments 11 and 12 are particularly instructive in regard to water-promoted elimination. In each case the I:BH ratio is such that the intermediate from hydroboration is the secondary organoborane Vb. The II:III product ratios of 1:1 correspond to elimination of only one alkyl group from Vb. Additional confirmation that elimination stops at this stage is provided by expt 13. The decreasing amount of elimination as the excess of hydride (B–H) increases is also consistent with this observation. This implies that the primary organoborane Va does not yield elimination product with water.

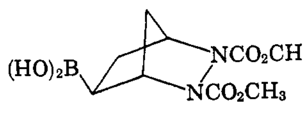
TABLE II

THE WATER-PROMOTED ELIMINATION OF THE INTERMEDIATES PRODUCED BY THE HYDROBORATION OF I[a]

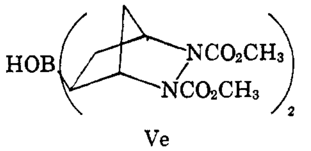
Expt	I:BH ratio	Time, hr (at 60°)	Composition of the product, % II	III	IV
11	1:1.14	3	38[b]	39[b]	<2
12	2:3	3	49	51	<2
13	2:3	6	50	50	<2
14	1:2	3	39	60	<2
8	1:3	3	31	65	<3
15	1:9	3	18	80	<2
16	1:20	3	10	90	<2

[a] Enough water was added for each experiment to make at least a 9:1 mole excess of water to I. The standard oxidation work-up was the same as given in Table I. [b] About 23% of I was recovered unreacted.

The first step for elimination in an aqueous medium undoubtedly involves a rapid conversion of organoboranes Va and Vb to the boronic acid Vd and the borinic acid Ve, respectively.[12] Subsequent steps must involve attack by the nucleophile on the electrophilic boron atom of these derivatives. Apparently water is nucleophilic enough to cause elimination of Ve but not of Vd. This is consistent with theoretical expectations. The boronic acid Vd should be less electrophilic than Ve, owing to the resonance interaction of an additional hydroxyl substituent with the boron atom.[13] Thus, Vd should be less susceptible than Ve to attack by the weak nucleophile, water. It is interesting that hydroxide ion is sufficiently nucleophilic to cause elimination of both Vd and Ve.



Vd



Ve

These observations regarding water and hydroxide ion further confirm the idea of a correspondence between the β-elimination reaction and the nucleophilicity of the group attacking the boron atom.

Experimental Section[14]

2,3-Dicarbomethoxy-2,3-diazabicyclo[2.2.1]hept-5-ene (I).—This compound was prepared according to the procedure of Rodgman and Wright,[15] mp 83–84° (lit.[15] mp 83.5–84°).

Materials.—Tetrahydrofuran and diglyme were freshly distilled (the latter under vacuum at *ca.* 20 mm) from lithium aluminum hydride just before the preparation of each standard stock solution of diborane. Additional tetrahydrofuran was purified similarly prior to use in each experiment. Boron trifluoride etherate was purified by distillation. Sodium borohydride (99%) from Metal Hydrides, Inc., was used without additional purification. Sodium borodeuteride also was obtained from Metal Hydrides, Inc.

General Procedures.—All glassware used in the hydroboration experiments was dried overnight in an oven at 110–125° and

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[12] H. C. Brown, A. Tsukamoto, and D. B. Bigley, *J. Am. Chem. Soc.*, **82**, 4703 (1960).

[13] H. C. Brown and R. F. McFarlin, *ibid.*, **80**, 5372 (1958).

[14] Compounds II, III, and IV had the same melting points and infrared and nmr spectra as reported previously.[1] Infrared spectra were obtained with a Beckman IR-5A spectrophotometer. All nmr spectra were obtained with a Varian A-60 spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard.

[15] A. Rodgman and G. F. Wright, *J. Org. Chem.*, **18**, 465 (1953).

purged with dry nitrogen before use. The hydroboration reactions usually were carried out in three-neck, 100-ml, round-bottom flasks equipped with a nitrogen inlet, pressure-equalized dropping funnel, rubber septum fitted inlet, nitrogen exit, and magnetic stirrer. During the course of all reactions a slight positive pressure of nitrogen was kept above the reaction mixture. In the experiments where the solution was refluxed, the dropping funnel was replaced with a water-cooled reflux condenser.

Preparation of Deuterioborane in Tetrahydrofuran.—In a flask fitted with a rubber septum capped side tube (for withdrawing samples with a hypodermic syringe) was placed 80 ml of tetrahydrofuran. The flask was immersed in an ice bath. Deuteriodiborane was generated by the addition of 1.9 g (45 mmoles) of sodium borodeuteride in 28 ml of diglyme to 3.2 g (46 mmoles) of boron trifluoride in diglyme.[16] The deuteriodiborane was passed through sodium borodeuteride in diglyme to remove any traces of boron trifluoride and then into the tetrahydrofuran solvent. Active hydride content[7] of the deuterioborane stock solution was determined by injecting a known amount of the solution into an ethylene glycol–diglyme mixture and measuring hydrogen evolution in a gas buret assembly similar to one described by Wiberg.[17] The solution was 0.3 M in deuterioborane.

This same method was used to prepare standard stock solutions of borane in tetrahydrofuran. These solutions were 0.6 or 1.0 M in borane.

Reaction of I with Diborane.—A 1.06-g (5.0 mmoles) sample of I in 12 ml of tetrahydrofuran was added to 8.4 ml (5.0 mmoles) of 0.6 M borane solution in 20 min at 0° and stirred for 8 hr at 0°. Samples were withdrawn periodically and injected into ethylene glycol–diglyme solution to determine the amount of unreacted hydride. In *ca.* 2 hr 1 mole of hydride per mole of I had been consumed. The amount of hydride reacted remained constant for an additional 5 hr; after 7 hr <1.1 moles of hydride had been used.

Hydroboration of I with Deuteriodiborane.—To 34 ml (10 mmoles) of 0.3 M deuterioborane solution at 0° was added 2.12 g (10 mmoles) of I in 10 ml of tetrahydrofuran. After stirring for 3 hr at 0° the solution was divided into two equal parts.

The first part (22 ml) was hydrolyzed with ice and immediately oxidized at 0° by addition of 2 ml of a 50:50 mixture of 30% hydrogen peroxide and 6 N sodium hydroxide. A 1.14-g yield of crude reaction product was recovered. The infrared spectrum[14] showed this to be almost entirely compound III. Deuterated III was isolated in *ca.* 94% yield by column chromatography on Florisil by the procedure described below. The product was recrystallized from ether–pentane for examination of the nmr spectrum. The nmr spectrum was determined in deuteriochloroform using a degassed and sealed tube. The average of five different integration traces showed 90–95% incorporation of one deuterium atom in the two-proton multiplet at τ 8.3.[8]

The second part (22 ml) was hydrolyzed with ice, treated with 2 ml of 3 N sodium hydroxide, and refluxed for 3 hr at 60°. After oxidization with 2 ml of a 50:50 mixture of 30% hydrogen peroxide and 6 N sodium hydroxide, there was obtained 1.05 g of crude reaction product. The infrared spectrum[14] indicated this to be mostly compound II. Deuterated II was recovered in *ca.* 86% yield by chromatography with Florisil. The product was purified for the nmr spectrum by recrystallization from ether-pentane solvent. The nmr spectrum was determined in deuteriochloroform using a degassed, sealed tube. The average of five different integration traces showed 90–95% incorporation of one deuterium atom in the four-proton methylene doublet found at τ 7.50.[8] As expected the one-proton quintet at τ 5.06[8] became a quartet ($J \sim 7$ cps).

Separation and Analysis by Column Chromatography.—Floridin Co. 100–200 mesh Florisil was used for all separations and analyses of products from the hydroboration–oxidation of I. For most analyses 40 g of Florisil per 1 g of crude reaction product was used. Solvents employed for elution, listed in order of use, are pentane, dichloromethane, dichloromethane–ether mixtures, ether, and ether–methanol mixtures up to about 5% methanol. Compound II was eluted with dichloromethane and mixtures of dichloromethane containing small percentages of ether. Compound III appeared in the later fractions of mixtures of dichloromethane and ether and with pure ether. Later fractions of ether and the ether–methanol mixtures contained compound IV (when present). Experience indicated where to collect the intermediate product fractions to minimize analytical errors. Infrared absorptions[14] at 3450 (O–H), 3250 (N–H), and mainly at 1525 cm^{-1} (CONH) were used to follow the course of separation and for estimating the product ratios of the few intermediate fractions. The over-all accuracy of the product compositions in Tables I and II is estimated to be *ca.* ±3%.

Effect of Nucleophiles on the Elimination of the Intermediates from the Hydroboration of I.—The details given here for hydroxide ion (expt 5 and 6) are representative of the procedure for the experiments in this series.

A 2.4-g (11.2 mmoles) sample of I in 48 ml of tetrahydrofuran was added to 18.5 ml (11.2 mmoles) of 0.6 M borane solution at 0° during a 15-min period. After stirring for 3 hr at 0°, 4 ml of 3 N sodium hydroxide was added and the reaction mixture was rapidly heated to reflux (60°). An 11-ml sample was removed after 1 hr, cooled to 0°, and oxidized with 1 ml of a 50:50 mixture of 30% hydrogen peroxide and 6 N sodium hydroxide. The oxidized solution was dried with anhydrous magnesium sulfate and filtered using copius amounts of tetrahydrofuran to wash the solid drying agent. The combined filtrate and washings were concentrated under vacuum to give 0.44 g of crude product. This product mixture was separated and analyzed as described above. The results are given in Table I.

A second 11-ml sample was removed after 3 hr and oxidized and analyzed by an identical procedure. The results are included in Table I.

The recovered product yield (II, III, and IV) was >90% in expt 1–10.

The Degree of Alkylation of Borane by I at 0°.—A 9.3-ml (9.3 mmoles) sample of 1.0 M borane in tetrahydrofuran was added very rapidly to 6.0 g (28 mmoles) of I in 82 ml of tetrahydrofuran at 0°. The hydroboration mixture was stirred at 0° and samples were removed at appropriate intervals of time and analyzed for residual hydride (*vide spura*). Even after 20 hr *ca.* 27–30% of the residual hydride remained. The results are illustrated in Figure 1.

Water-Promoted Elimination of the Intermediate from the Hydroboration of I.—The procedure given here for the 2:3 ratio of I to B–H is representative of this series of experiments.

To 4.7 ml (13.1 mmoles of B–H) of 1.0 M borane solution at 0° was added in *ca.* 15 min 2.10 g (9.9 mmoles) of I in 41 ml of tetrahydrofuran. The reaction mixture was stirred at 0° for 3 hr, 2 ml. of water was added, and the solution was rapidly heated to reflux (60°). After 3 hr at 60° one-half (22.3 ml) of the reaction mixture was removed, cooled to 0°, and oxidized with 2 ml of a 50:50 mixture of 30% hydrogen peroxide and 6 N sodium hydroxide. When the oxidized product was worked up as described above, 1.10 g of crude product was isolated. This was analyzed as described before. The results are listed in Table II (expt 12).

The remainder of the reaction mixture was refluxed (60°) for another 3 hr, and then worked up and analyzed. The results are given in Table II (expt 13).

Acknowledgments.—This study was supported by the National Science Foundation, Grant No. GP-3534. We wish to thank Miss Linda Conrad for assistance with many of the chromatographic analyses.

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(16) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 1241 (1961).

(17) K. B. Wiberg, "Laboratory Techniques in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 228.