shielded than those in adamantane which are flanked by three methylene groups. Consequently, the signals at 32.1 and 27.7 ppm in the spectrum of **2** are assigned to bridgehead carbons b and d, respectively.

The ^{13}C NMR spectrum of 4-homoisotwistane (**4**) is assigned by comparison of experimental and calculated chemical shifts. The spectrum shows eight signals (Table I). According to the proton off-resonance decoupling and the T_1 values the signals at 33.0, 30.8, and 24.7 ppm correspond to CH groups while those at 32.2, 31.8, 27.0, 26.2, and 15.2 ppm correspond to CH_2 groups. Grant's additivity rule[27] was used to calculate the shifts of carbons a and b (16.2 and 32.7, respectively). To calculate the chemical shifts of the other carbons the shifts of bicyclo[2.2.2]octane[28] were taken as the basis and the influence of the trimethylene bridge was estimated using the additivity increments. For carbons c, d, e, f, g, and h (see Table I, footnote *b*) the following values were obtained: 32.1, 33.9, 26.7, 26.7, 24.6, and 29.2 ppm, respectively. Therefore, the signals at 15.2, 30.8, 33.0, and 24.7 ppm are assigned to carbons a, c, d, and g, respectively, whereas the signals at 32.2 and 31.8 ppm, as well as the signals at 27.0 and 26.2 ppm, could not be assigned in this way.

Acknowledgments. This work was supported by a grant from the Research Council of the Republic of Croatia (Yugoslavia) and by the Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung. We thank Professors P. v. R. Schleyer and J. K. Crandall for helpful discussions and D. E. Sunko for use of equipment.

Registry No.—**1a**, 25763-45-5; **1b**, 57443-88-6; **2**, 281-46-9; **3**, 700-56-1; **4**, 43000-53-9.

References and Notes

(1) Part II: K. Mlinaric-Majerski, Z. Majerski, and E. Pretsch, *J. Org. Chem.*, **40**, 3772 (1975).
(2) (a) Rugjer Boskovic Institute; (b) ETH, Zürich.
(3) Taken in part from M.S. Thesis of K. Mlinaric-Majerski.
(4) J. E. Nordlander, F. Ying-Hsiueh Wu, S. P. Jindal, and J. B. Hamilton, *J. Am. Chem. Soc.*, **91**, 3962 (1969); P. v. R. Schleyer, E. Funke, and S. H. Liggero, *ibid.*, **91**, 3965 (1969).
(5) R. E. Leone, J. C. Barborak, and P. v. R. Schleyer in "Carbonium Ions", Vol. 4, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1972, Chapter 33, p 1931.
(6) Z. Majerski and K. Mlinaric, *J. Chem. Soc., Chem. Commun.*, 1030 (1972).
(7) Such a cation has also been suggested as one of the intermediates in the sulfuric acid catalyzed rearrangements of 1- and 3-homoadamantanols[8] and in the Lewis acid catalyzed rearrangement of homoadamantane.[9a]
(8) J. Janjatovic, D. Skare, and Z. Majerski, *J. Org. Chem.*, **39**, 651 (1974).
(9) (a) R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem., Forsch.*, **18**, 17 (1971); (b) *ibid.*, **18**, 71 (1971).
(10) Preliminary accounts of this work were reported as the first paper of this series: K. M. Majerski and Z. Majerski, *Tetrahedron Lett.*, 4915 (1973).
(11) 4-Homoadamantanone-*5*-^{13}C was prepared[1] in 46% overall yield by the addition of $(CH_3)_3Si^{13}CN$ to adamantanone followed by $LiAlH_4$ reduction of the α-trimethylsilyloxy nitrile and Demjanow–Tiffeneau ring enlargement of the resulting α-aminomethyl alcohol. This synthetic procedure appears to be a general and convenient method for the preparation of ^{13}C-labeled ketones and their derivatives.
(12) Such a set of 11-carbon tricyclic structures has also been independently constructed by Osawa, Inamoto, Engler, and Schleyer.[13b]
(13) (a) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973); (b) P. v. R. Schleyer and E. Osawa, private communications.
(14) A. Krantz and C. Y. Lin, *J. Chem. Soc. D.*, 1287 (1971); *J. Am. Chem. Soc.*, **95**, 5662 (1973).
(15) N. Takaishi, Y. Inamoto, K. Aigami, K. Tsuchihashi, and H. Ikeda, *Synth. Commun.*, **4**, 225 (1974); N. Takaishi, Y. Fujikura, Y. Inamoto, H. Ikeda, K. Aigami, and E. Osawa, *J. Chem. Soc., Chem. Commun.*, 371 (1975); N. Takaishi, Y. Fujikura, Y. Inamoto, H. Ikeda, and K. Aigami, *Ibid.*, 372 (1975).
(16) M. Farcasiu, K. R. Blanchard, E. M. Engler, and P. v. R. Schleyer, *Chem. Lett.*, 1189 (1973).
(17) N. Takaishi, Y. Inamoto, and K. Aigami, *Chem. Lett.*, 1185 (1973); *J. Org. Chem.*, **40**, 276 (1975); *J. Chem. Soc., Perkin Trans. 1*, 789 (1975); N. Takaishi, Y. Inamoto, K. Tsuchihashi, K. Yashima, and K. Aigami, to be published.
(18) (a) $T_1(O_2)$ is approximately 100 sec: H. Jaeckle, U. Haeberlen, and D. Schweitzer, *J. Magn. Reson.*, **4**, 198 (1971); (b) W. Buchner, *ibid.*, **17**, 229 (1975).
(19) For example, H. L. Goering and G. N. Fickes, *J. Am. Chem. Soc.*, **90**, 2848, 2856, 2862 (1968).
(20) On this basis a small excess of the label should also be expected at positions a, c, and g (see Table I, footnote *b*) in **3**. However, this excess is probably too small to be detected, since it would be spread over five carbon atoms.
(21) The product mixture of the rearrangement–hydride transfer reduction of 2-homoadamantanol in sulfuric acid is essentially the same as that from 4-homoadamantanol: Z. Majerski, K. M. Majerski, and B. Goricnik, unpublished results.
(22) The formation of 4-homoisotwistane in CF_3SO_3H-catalyzed rearrangement of homoadamantane appears to proceed also via **7**: Y. Inamoto, private communication.
(23) E. M. Engler, M. Farcasiu, A. Sevin, J. M. Cense, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 5769 (1973).
(24) J. T. Clerc, E. Pretsch, and S. Sternhell, "^{13}C-Kernresonanzspektroskopie", Akademische Verlagsgesellschaft Frankfurt am Main, 1973, p 88; D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984 (1964); J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *ibid.*, **92**, 1338 (1970).
(25) G. E. Maciel, H. C. Dorn, R. L. Greene, W. A. Kleschick, M. R. Peterson, Jr., and G. H. Wahl, Jr., *Org. Magn. Reson.*, **6**, 178 (1974).
(26) D. Skare and Z. Majerski, *Tetrahedron Lett.*, 4887 (1972).
(27) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **96**, 1827 (1974).
(28) G. E. Maciel and H. C. Dorn, *J. Am. Chem. Soc.*, **93**, 1268 (1971).

Tetrabutylammonium Borohydride. Borohydride Reductions in Dichloromethane

Douglas J. Raber* and Wayne C. Guida

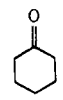
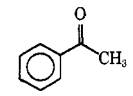
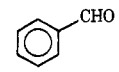
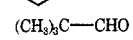
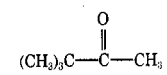
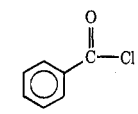
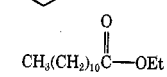
Department of Chemistry, University of South Florida, Tampa, Florida 33620

Received September 26, 1975

The utility of tetrabutylammonium borohydride as a reducing agent has been investigated. The high solubility of this reagent in dichloromethane permits reductions to be carried out in high yields in the absence of protic solvents. The selectivity of tetrabutylammonium borohydride in dichloromethane toward organic carbonyl compounds is similar to that exhibited by sodium borohydride in aqueous or alcoholic media. At room temperature acid chlorides are reduced extremely rapidly, aldehydes and ketones are reduced at convenient rates, and esters are reduced quite slowly. Synthetic procedures and results are reported for the reduction of a variety of aldehydes and ketones.

The preparation of quaternary ammonium borohydrides (tetramethylammonium, tetraethylammonium, and benzyltrimethylammonium borohydride) was reported by Banus, Bragdon, and Gibb in 1952.[1] The tetramethyl derivative exhibited solubilities similar to those of the alkali metal borohydrides, and consequently the quaternary ammonium derivatives did not appear to offer any advantages as synthetic reagents. Subsequently, Sullivan and Hinckley reported[2] the preparation of quaternary ammonium borohydrides which contained long chain alkyl groups: cetyltrimethylammonium borohydride and tricaprylmethylammonium borohydride. These compounds are soluble in

Table I
Reduction of Representative Carbonyl Compounds with Tetrabutylammonium Borohydride at 30°C

No.	Compd	1 equiv[a]		2 equiv[a]		4 equiv	
		$t_{1/2}$, min	Max %	$t_{1/2}$, min	Max %	$t_{1/2}$, min	Max %
1		2100	75	850	98	550	98
2		2600	69	1100	94	600	98
3		100	92	120[b]	92	40[b]	96
4		1250	94				
5		>10 000	40				
6		*c*	100				
7		*d*	25				

[a] This refers to the number of equivalents of reducing agent per mole of substrate; the concentration of the carbonyl compound was 1 M in each case. [b] $k \simeq 6 \times 10^{-3}$ l. mol^{-1} s^{-1}; none of the other substrates afforded a linear plot when the data were analyzed in terms of second-order kinetics (cf. ref 10c). Even benzaldehyde failed to follow second-order kinetics when only a single equivalent of reducing agent was used. [c] The reduction of benzoyl chloride was extremely rapid at room temperature and did not stop at the aldehyde state even at −78°C. [d] The reduction of ethyl laurate was followed for 96 h, at which time only 25% had been reduced.

nonpolar aprotic solvents such as benzene and hexane. In benzene, acid chlorides and aldehydes are reduced readily, "ketones only very slowly, even at elevated temperatures; and esters, not at all at room temperature and only slowly at higher temperatures".[2] Quaternary ammonium borohydrides have thus appeared to offer few advantages in organic synthesis; their utility has been restricted by the poor solubility of short-chain tetraalkylammonium derivatives in aprotic solvents and by the poor ability of the long-chain analogues to reduce ketones.

The ability to carry out borohydride reductions in nonhydroxylic solvents would nevertheless be quite useful. For instance, the reduction of aldehydes and ketones with sodium borohydride in the commonly employed aqueous or alcoholic solvents can be complicated by side reactions such as the formation of hydrates, acetals, ketals, or ethers.[3] In addition many organic compounds are not adequately soluble in those solvents. While borohydride reductions have been carried out in aprotic media, the available combinations of reagents and solvents have not been without disadvantages. For example, sodium borohydride shows very limited solubility[4] in ethereal solvents such as diethyl ether, tetrahydrofuran, and dimethoxyethane, and while it exhibits useful solubility[4] in diglyme and dimethylformamide, the water miscibility and high boiling points of the latter make work-up of reactions in these solvents quite inconvenient. Furthermore, Brown, Mead, and Subba Rao have shown[5a] that in diglyme sodium borohydride reduces ketones only very slowly, the reduction of acetone at 25°C being incomplete even after 96 h. Lithium borohydride is adequately soluble in many ethereal solvents, but its much greater reactivity decreases its synthetic utility; in contrast to sodium borohydride the lithium derivative readily reduces esters as well as aldehydes and ketones.[5]

Brändström, Junggren, and Lamm[6] recently prepared tetra-*n*-butylammonium borohydride and showed that it can be used to prepare solutions of diborane in dichloromethane by reaction with alkyl halides, but the reactions of tetrabutylammonium borohydride with carbonyl compounds were not reported. Our own use[7] of tetrabutylammonium borohydride as a mild and selective reagent for the reduction of oxonium ions indicated that this readily available[6] compound might be a versatile reagent for carrying out carbonyl reductions in aprotic solvents. Additional support for this idea was provided by the work of Hutchins, who found tetrabutylammonium cyanoborohydride to be an effective reducing agent in HMPA.[8]

We hoped that the high solubility of tetrabutylammonium borohydride in dichloromethane[6] would allow the use of that solvent for the reduction of aldehydes and ketones. Dichloromethane offers many advantages as a reaction medium: it is a powerful solvent for many organic compounds and (in contrast to many ethereal solvents) is relatively inexpensive; its low boiling point (41°C) and water immiscibility greatly facilitate the reaction work-up. We have therefore carried out an investigation of the reactions of a series of carbonyl compounds with tetrabutylammonium borohydride in dichloromethane.

Results and Discussion

Kinetic Studies. Our first goal was to determine the reactivity of dichloromethane solutions of tetra-*n*-butylammonium borohydride toward various types of carbonyl compounds, and this was done by monitoring the progress of the reactions by infrared spectroscopy. The changes in intensity in the carbonyl absorption of aliquots of reaction solutions permitted a quantitative measurement of the consumption of the substrate. The results are summarized in Table I and in Figures 1 and 2.

The data clearly demonstrate large differences in reactivity for the various classes of carbonyl derivatives as summarized by the following series (in order of decreasing reactivity): acid chlorides > aldehydes > ketones > esters. At one extreme, the reduction of benzoyl chloride (6) with tet-

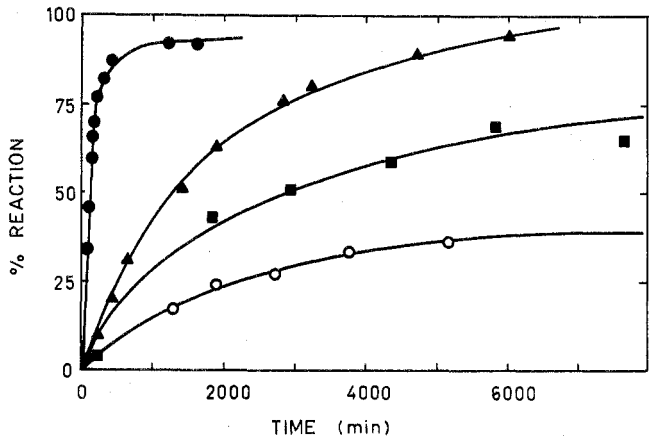


Figure 1. Rates of reduction of carbonyl compounds (●, benzaldehyde; ▲, acetophenone; ■, pivalaldehyde; ○, pinacolone) with tetrabutylammonium borohydride (1 equiv of reducing agent per mole of carbonyl compound) at 30°C in dichloromethane. The concentration of the carbonyl compound was 1 M in each case.

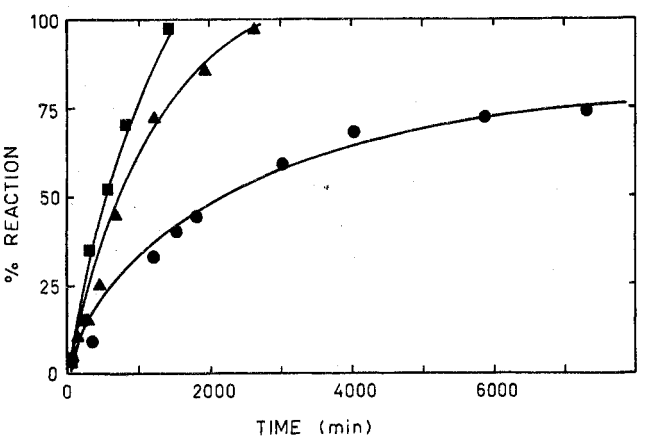


Figure 2. Rates of reduction of cyclohexanone (1 M) with tetrabutylammonium borohydride (■, 4 equiv; ▲, 2 equiv; ●, 1 equiv) at 30°C in dichloromethane.

rabutylammonium borohydride is essentially instantaneous; even at −78°C the reaction proceeds rapidly. The other extreme is represented by ethyl laurate (7): this ester is only 25% reduced after 4 days at 25°C. Both aldehydes and ketones undergo reduction at 25°C at rates which are useful for synthetic purposes.

Figure 1 shows that as expected the rate of reduction is highly dependent on the steric bulk of the substituents; thus replacement of a phenyl group by a *tert*-butyl group results in a substantial decrease in rate for both pinacolone (5) and pivalaldehyde (4) relative to acetophenone (2) and benzaldehyde (3), respectively. Similar effects have been found for other borohydride reductions.[9]

Figure 2 and Table I show the effects of variation of the concentration of borohydride relative to the concentration (1 M) of the carbonyl compound. As expected for a bimolecular process, the rate of reduction increases as the concentration of tetrabutylammonium borohydride is increased. Somewhat unexpected is the dependence of the total extent of reaction upon the concentration of borohydride relative to that of the carbonyl compound. Thus, while the reaction with aldehydes proceeds readily and nearly to completion with only 1 equiv of tetrabutylammonium borohydride, it is preferable to use 4 equiv of the reducing agent in the case of ketones; otherwise the reaction is inconveniently slow or does not proceed to completion.

Mechanistic Considerations. The reaction of borohydride ion with aldehydes and ketones in aqueous or alcoholic solutions is considered to proceed stepwise with successive replacement of each of the four hydrides with alkoxide groups generated by reduction of the carbonyl derivative (eq 1).[10] Under these conditions the reaction of bor-

Figure 3. Rates of reduction of cyclohexanone (1 M) with tetrabutylammonium borohydride (1 M) (▲, in the presence of 1 molar equiv of ethanol; ●, in the absence of ethanol) at 30°C in dichloromethane.

$$BH_4^- \xrightarrow{R_2C=O} R_2CHOBH_3^- \xrightarrow{R_2C=O} (R_2CHO)_2BH_2^- \xrightarrow{R_2C=O}$$
$$(R_2CHO)_3BH^- \xrightarrow{R_2C=O} (R_2CHO)_4B^- \xrightarrow{\text{work-up}} R_2CHOH \quad (1)$$

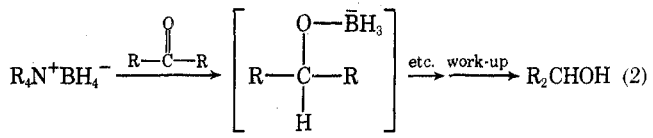
ohydride ion with aldehydes and ketones is rapid and exhibits clean second-order kinetics. This has been interpreted as evidence[10] that the first step of eq 1 is rate limiting; otherwise different kinetic behavior would be expected.

Studies of borohydride reductions in aprotic media have afforded additional mechanistic information. For example, the reactivities of borohydride salts in aprotic solvents are highly dependent on the nature of the cation. While lithium borohydride reduces ketones in anhydrous pyridine,[11] the sodium salt reduces them very slowly[12] or not at all.[11] This difference in reactivity could be a result of ion pairing effects as well as of electrophilic catalysis by lithium ions.[12,13] The importance of the former effect is suggested by the observation that lithium and sodium borohydride react with acetone at the same rate in aqueous solution[13] where the salts should be largely dissociated. In isopropyl alcohol (where more association of the ions would be expected) the lithium derivative reacts several times more rapidly.[13]

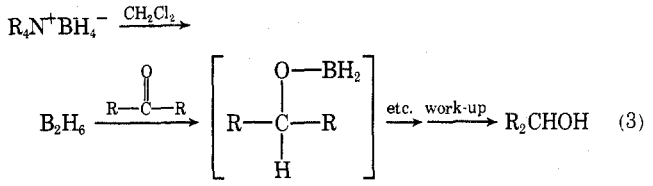
The importance of electrophilic catalysis is illustrated by the observation that the addition of lithium salts enhances the rate of reductions by sodium borohydride in nonaqueous solvents.[5,13] Similarly, the large rate difference in sodium borohydride reductions in aqueous or alcoholic solutions relative to reactions in aprotic media has been attributed to electrophilic catalysis by the hydroxylic solvent.[11,12] Our own work tends to support this interpretation. Thus, the overall rate of reaction of tetrabutylammonium borohydride with ketones and aldehydes in dichloromethane is much slower than comparable reductions with sodium borohydride in aqueous or alcoholic media. Figure 3 clearly shows that the addition of an equivalent amount of ethanol results in a substantial (ca. twofold) increase in the rate of reduction of cyclohexanone (1) by tetrabutylammonium borohydride in dichloromethane. Nevertheless, reduction does occur in the absence of ethanol, and one must conclude that electrophilic catalysis (by either protic solvent or metal ions) is not a prerequisite for reduction.

Earlier work has shown that sodium borohydride reduc-

tions of ketones in aprotic solvents are extremely slow. There was some initial confusion in the literature because rapid reduction can occur during aqueous work-up of aliquots of reaction mixtures.[11] Brown found essentially no reduction of acetone by sodium borohydride in diglyme, DMF, acetonitrile, or pyridine after 24 h at 0°C.[13] Similarly, Ritchie observed no reduction of cyclohexanone by sodium borohydride in pyridine after 72 h at room temperature. While the conditions used by those workers were not the same as those utilized by us, the earlier results concerning the reduction of ketones appear to be in sharp contrast with those summarized in Table I. The facile reduction of primary alkyl halides by tetrabutylammonium borohydride in dichloromethane[6] to liberate diborane suggested the possibility of a similar reaction between tetrabutylammonium borohydride and the solvent (dichloromethane).[14] The actual reducing agent in the ketone reductions of Table I might therefore be diborane (eq 3) rather than borohydride ion (eq 2). That diborane is indeed produced



(2)



(3)

by such a reaction was shown by the isolation of a moderate yield (50%) of cyclohexanol following oxidative work-up of a solution of cyclohexene and tetrabutylammonium borohydride in dichloromethane which had been maintained at room temperature for 40 h.

In order to ascertain whether or not the rate of production of diborane is sufficiently rapid to account for the reduction of ketones, several additional experiments were carried out. The rate of decomposition of tetrabutylammonium borohydride in dichloromethane at 30°C was determined by monitoring the 2240-cm^{-1} band[11] of aliquots of the solution; the decomposition followed first-order kinetics and exhibited a half-life of approximately 2300 min. We also found that the reduction of cyclohexanone (1) by diborane is quite rapid: the reaction of a dichloromethane solution of cyclohexanone (1 M) and diborane (0.5 M) is complete within 15 min at room temperature. On the other hand, only two of the three hydrides per boron exhibit this high reactivity. Thus when only an equivalent amount of diborane was employed (1 M cyclohexanone, 0.17 M B_2H_6) the reduction proceeded rapidly to ca. 67% completion; further reduction was extremely slow. Similar behavior was observed by Brown and Korytnyk for the reduction of cyclohexanone by borane in tetrahydrofuran.[15]

Comparison of the results of the borane reductions with the data in Figure 2 lead to the conclusion that diborane alone cannot be responsible for the reduction of cyclohexanone. Thus in 2300 min one-half of the original borohydride ion has been converted to diborane. In the case where 1 equiv (0.25 mol) of borohydride was employed this would correspond to the formation of 0.06 mol of diborane, which would account for only 37% reduction of cyclohexanone even if all three hydrides per boron were utilized. Since transfer of the third hydrogen is slow, 37% represents an upper limit. If transfer of that hydrogen were considered negligible, only 25% reduction would be expected. However, the actual reduction of cyclohexanone proceeded to greater

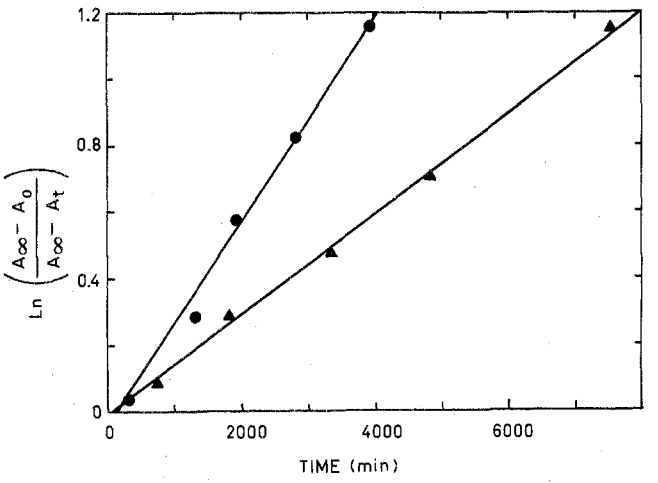


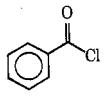
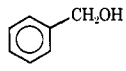
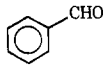
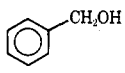
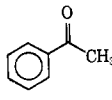
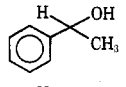
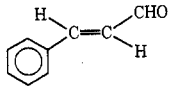
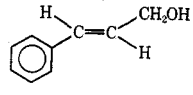
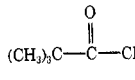
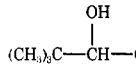
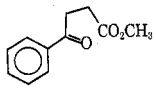
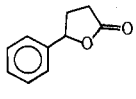
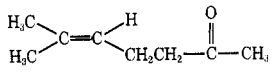
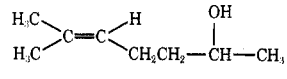
Figure 4. First-order decomposition of tetrabutylammonium borohydride at 30°C in dichloromethane [●, in the absence of ethanol, $k = (3.0 \pm 0.1) \times 10^{-4}$ s^{-1}; ▲, in the presence of 1 molar equiv of ethanol, $k = (1.52 \pm 0.03) \times 10^{-4}$ sec^{-1}]. The lines are least-squares fits of the experimental points.

than 50% within this time period, indicating that at least a substantial proportion of the reduction of cyclohexanone proceeds via direct reaction with borohydride ion (eq 2).

Thus, one must consider two alternative pathways for the initial reaction of the borohydride ion: direct hydride reduction of the carbonyl compound (eq 2) and initial reaction of the borohydride ion with solvent to give diborane as the reducing agent (eq 3).[16] Table I clearly shows that the reduction of aldehydes proceeds via eq 2 as the major pathway; these reactions are too fast to be reconciled with prior decomposition of tetrabutylammonium borohydride. On the other hand, the rates of ketone reductions are comparable to the rate of diborane production and eq 3 may represent a significant pathway in these cases. However, the addition of an equivalent amount of ethanol causes a substantial change in the reaction. Thus, while ethanol enhances the rate of cyclohexanone reduction (Figure 3), it actually decreases the rate of borohydride decomposition (Figure 4). Under these conditions the rate of borane production is much too slow to account for the reduction of cyclohexanone by the pathway of eq 3. Thus, the addition of protic solvent must result in electrophilic catalysis of the direct reduction of ketone by borohydride ion, and the pathway represented by eq 2 becomes increasingly important.

Synthetic Applications. The data in Table I suggested the general procedures to be followed for preparative reductions: Aldehydes (1 M) are reduced at a convenient rate with a single equivalent of borohydride; for preparative work we have used a 50% excess (1.5 equiv). Ketones (1 M) are reduced at a convenient rate only when a substantial excess of reducing agent is employed; for preparative reactions we have utilized 4 equiv of tetrabutylammonium borohydride. The results of a series of reductions are presented in Table II. Isolated yields and purities are consistently high, and the experimental procedure is straightforward. A typical reduction was accomplished by allowing a dichloromethane solution of the carbonyl derivative (1 M) and tetrabutylammonium borohydride to stand at room temperature for 0.25–48 h. The reaction mixture was then quenched by stirring with dilute alkaline hydrogen peroxide. The aqueous phase was extracted with dichloromethane, and the combined organic solutions were washed with saturated aqueous sodium sulfite, dried over sodium sulfate, and evaporated at reduced pressure. The crude product was taken up in diethyl ether and the insoluble ammonium salts were removed by filtration through a short col-

Table II
Reduction of Representative Carbonyl Compounds[a] with Tetrabutylammonium Borohydride

No.	Compd	Equiv[b]	Time, h	Product	% yield[c]	Purity,[d] %
6		4	0.25		98	99
3		1.5	24		91	99
1		4	24		86	99
2		4 4	45 2[e]		93 90	98 98
8		1.5	17		73	90
5		4 4	48 5.5[e]		82[d,f] 97	94
7	$CH_3(CH_2)_{10}CO_2Et$	4	96	$CH_3(CH_2)_{10}CH_2OH$	25[d,f]	
9		4	40		98	90
10		4	24		87	98

[a] The solutions were approximately 1 M in the carbonyl compound; reductions were carried out at room temperature. [b] This refers to the number of equivalents of reducing agent per mole of substrate. [c] Isolated yield after Kugelrohr distillation. [d] Estimated by GLC. [e] The reduction was performed in refluxing chloroform. [f] The major impurity was unreacted starting material.

umn of alumina. Kugelrohr distillation then afforded the final product.

The use of aqueous hydrogen peroxide in the work-up not only serves to destroy any unreacted hydride, but also facilitates the hydrolysis of the borate esters formed in the reduction.[17] If this step is omitted, much lower yields result. The dichloromethane solution was washed with aqueous sodium sulfite in order to destroy any peroxides in the organic phase prior to distillation.

Several entries in Table II require comment. As expected (Table I) only the keto group of methyl 3-benzoylpropionate (9) was reduced, and the lactone (which is formed spontaneously upon distillation) was obtained in excellent yield. The reduction of pinacolone (5) is extremely slow (Figure 1), and even after 48 h substantial amounts of unreduced ketone remained. However, when the reduction was conducted at higher temperatures (refluxing chloroform), a reaction time of 5.5 h provided pinacolyl alcohol in excellent yield. Reaction times necessary for reduction of other ketones can also be decreased by this procedure. For example, the reduction of acetophenone (2) in refluxing chloroform requires only 2 h for complete reaction. Although diborane is probably formed during the reduction of ketones, hydroboration of the carbon–carbon double bond in 6-methyl-5-hepten-2-one (10) did not compete with reduction of the keto group; the unsaturated alcohol was isolated in good yield. Although this may appear to contradict the relative reactivities of functional groups toward diborane reported by Brown,[15] hydroboration of olefins is known to take place very slowly in the absence of ethers.[18]

In conclusion, tetrabutylammonium borohydride is a mild and selective reagent for the reduction of organic compounds. It provides a useful complement to the variety of reducing agents which are already available: borohydride reductions can now be conveniently performed in dichloromethane thus avoiding difficulties which sometimes arise with aqueous or alcoholic media.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer; NMR spectra were recorded on a Varian A-60 spectrometer, and chemical shifts are reported in parts per million downfield from Me_4Si. Gas chromatographic analyses were performed on a Varian Model 2400 gas chromatograph equipped with flame ionization detectors and 5 ft × 0.125 in. (o.d.) columns packed with 10% Carbowax 20M on Chromosorb W.

Cyclohexanone, acetophenone, and 6-methyl-5-hepten-2-one were obtained from Aldrich Chemical Co. and were used without purification. Benzoyl chloride and ethyl laurate were obtained from Eastman Organic Chemicals and were used without purification. Pinacolone and cinnamaldehyde (Eastman Organic Chemicals) were distilled prior to use; benzaldehyde (Aldrich Chemical Co.) was washed with 1 M aqueous $KHCO_3$ and distilled prior to use. Pivalaldehyde was prepared via the reaction of *tert*-butylmagnesium chloride with ethyl formate.[19] Methyl 3-benzoylpropionate was prepared via esterification[20] of 3-benzoylpropionic acid.[21] Reagent grade dichloromethane was stored over Linde 4A molecular sieves and used without subsequent purification.

Tetrabutylammonium borohydride was prepared by the reaction between sodium borohydride and tetrabutylammonium chloride[6,22] and was purified by recrystallization from ethyl acetate followed by careful drying under vacuum at 50–60°C. Samples of tetrabutylammonium borohydride purified in this manner showed no loss of active hydrogen after storage at room temperature for more than 1 year. Nevertheless, we stored tetrabutylammonium borohydride at 6°C in a tightly stoppered bottle.

Kinetic Studies. Reductions with Tetrabutylammonium Borohydride. The following general procedure was employed for the reduction of cyclohexanone, acetophenone, pinacolone, benzoyl chloride, pivalaldehyde, and benzaldehyde.

In a 5-ml volumetric flask was placed either 5, 2.5, or 1.25 mmol

of tetrabutylammonium borohydride and approximately 3 ml of dichloromethane. To the resulting solution was added 5 mmol of the appropriate carbonyl compound followed by sufficient dichloromethane to bring the volume to 5 ml. The solution was then placed in a constant-temperature bath at 30.0°C. Aliquots (50 μl) were withdrawn periodically, diluted to 2 ml with dichloromethane, and analyzed by infrared spectroscopy. Matched sodium chloride cells (1 mm path length; the reference cell contained dichloromethane) were used to measure the intensity of the carbonyl absorption.

Beer's law plots of the carbonyl absorbance were found to be linear in the concentration range employed for all compounds except benzaldehyde. The concentrations of the benzaldehyde solutions were determined from a calibration curve.

Reduction of Cyclohexanone (1) with Diborane. A. Using 3 Equiv of Diborane. To a solution of 1.21 g (4.7 mmol) of tetrabutylammonium borohydride in 3 ml of dichloromethane was added dropwise with stirring 0.67 g (4.7 mmol) of methyl iodide. The resulting solution was allowed to stand at room temperature for 15 min and was then cooled in an ice bath while 0.46 g (4.7 mmol) of cyclohexanone was added dropwise. When the addition was complete, the solution was allowed to warm to room temperature and the volume was brought up to 5 ml with dichloromethane. The ir spectrum of an aliquot removed after a reaction time of 15 min showed no carbonyl absorbtion.

B. Using 1 Equiv of Diborane. To a solution of 0.46 g (4.7 mmol) of cyclohexanone in 3 ml of dichloromethane was added 0.40 g (1.6 mmol) of tetrabutylammonium borohydride. Sufficient dichloromethane was added to bring the total volume to 5 ml, and an aliquot of the resulting solution was removed for ir analysis. The reaction solution was cooled in an ice bath and 0.23 g (1.6 mmol) of methyl iodide was added. The reaction mixture was removed from the ice bath and aliquots were periodically removed for infrared analysis. The reaction had proceeded to the extent of ca. 66% after 15 min, and no further decrease of the carbonyl absorption was observed over a period of 24 h at room temperature.

Reduction of Ethyl Laurate (7) with Tetrabutylammonium Borohydride. To a solution of 1.15 g (5 mmol) of ethyl laurate in 5 ml of dichloromethane was added 1.3 g (5.1 mmol) of tetrabutylammonium borohydride. The solution was allowed to stand at room temperature for 96 h and was then quenched by the addition of 10 ml of 3% aqueous hydrogen peroxide and 5 ml of 10% aqueous sodium hydroxide. The mixture was stirred for 2 h, the layers were separated, and the aqueous phase was extracted with two 15-ml portions of dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated at reduced pressure. GLC analysis of the residue showed the presence of 25% lauryl alcohol and 75% unreacted ester.

Reduction of Cyclohexanone (1) with Tetrabutylammonium Borohydride in the Presence of Ethanol. To a solution of 0.92 g (9.4 mmol) of cyclohexanone in 8 ml of dichloromethane was added 0.44 g (9.6 mmol) of ethanol and 0.60 g (2.3 mmol) of tetrabutylammonium borohydride. Sufficient dichloromethane was added to bring the volume to 10 ml, and the general procedure was followed.

Decomposition of Tetrabutylammonium Borohydride. A solution of 0.64 g (10 mequiv) of tetrabutylammonium borohydride in 5 ml of dichloromethane was placed in a constant-temperature bath at 30.0°C. Aliquots (50 μl) were withdrawn periodically, diluted to 2 ml with dichloromethane, and analyzed by ir spectroscopy. The same procedure was followed for the decomposition of tetrabutylammonium borohydride in the presence of ethanol: 0.45 g (9.8 mequiv) or 0.23 g (5 mequiv) of ethanol was added to the reaction solutions immediately prior to placing it in the constant-temperature bath. The reaction with the lower concentration of ethanol exhibited behavior intermediate between that of the two cases illustrated in Figure 3.

Synthetic Studies. General Procedure. To a solution of tetrabutylammonium borohydride (15 mequiv for aldehydes, 40 mequiv for ketones) in 10 ml of dichloromethane was added in a single portion 10 mmol of the carbonyl compound. The reaction vessel was stoppered and the solution was allowed to stand for 0.25–48 h (Table II). The reaction was quenched by the addition of 20 ml of 3% hydrogen peroxide followed by 10 ml of 10% sodium hydroxide and the mixture was stirred for ca. 2 h. The layers were separated and the aqueous phase was extracted with three 30-ml portions of dichloromethane. The combined organic solutions were extracted with 20 ml of saturated sodium sulfite, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was taken up in anhydrous diethyl ether, the insoluble tetrabutylammonium salts were removed by filtration, and the ether solution was percolated through a short (ca. 3 cm) column of alumina. The solvent was evaporated under reduced pressure and the crude product was distilled (Kugelrohr).

Reduction of benzoyl chloride (6), benzaldehyde (3), cyclohexanone (1), acetophenone (2), and pinacolone (5) by this procedure afforded products in the yields and purities listed in Table II. The ir and NMR spectra of the products were in agreement with previously published spectra.[23]

Reduction of Benzoyl Chloride (6) at −78°. A solution of 1.0 g (7 mmol) of benzoyl chloride in 20 ml of dichloromethane was cooled to −78°C, and 1.8 g (7.0 mmol) of tetrabutylammonium borohydride in 10 ml of dichloromethane was added dropwise. The resulting solution was poured into ~50 ml of 1 N NaOH, and the layers were separated. The organic layer was washed with two 30-ml portions of 1 N NaOH and was dried over sodium sulfate. GLC analysis indicated a mixture of benzaldehyde and benzyl alcohol in a ratio of 1:15.

Reduction of Acetophenone (2) in Refluxing Chloroform. A solution of 1.1 g (4.3 mmol) of tetrabutylammonium borohydride and 0.50 g (4.2 mmol) of acetophenone in 5 ml of chloroform was heated at reflux for 2 h. Work-up according to the general procedure afforded 0.46 (90%) of 1-phenylethanol (98% pure by GLC).

Reduction of Cinnamaldehyde (8). To a solution of 1.0 g (15.6 mequiv) of tetrabutylammonium borohydride in 3 ml of dichloromethane cooled to 0°C was added slowly 1.32 g (10.0 mmol) of cinnamaldehyde in 10 ml of dichloromethane. The solution was allowed to warm slowly to room temperature (at which point the solution became red) and remain at room temperature for 17 h. Work-up as described in the general procedure (percolation through alumina was omitted) afforded 0.98 g (73%) of cinnamyl alcohol after Kugelrohr distillation (130–160°C, ~1 mm). The distilled product was 90% pure by GLC and exhibited ir and NMR spectra in agreement with those previously reported.[23]

Reduction of Methyl 3-Benzoylpropionate (9). To a solution of 1.4 g (5.4 mmol) of tetrabutylammonium borohydride in 5 ml of dichloromethane was added 1.0 g (5.2 mmol) of methyl 3-benzoylpropionate. The solution was allowed to stand at room temperature for 40 h and was then quenched by the addition of 10 ml of 3% hydrogen peroxide followed by 5 ml of 10% sodium hydroxide. The resulting mixture was stirred for 2 h and was then acidified with 3 M sulfuric acid. The layers were separated, and the aqueous phase was extracted with three 20-ml portions of diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate, and the solvent was evaporated at reduced pressure. Ammonium salts were removed by partitioning the crude product between diethyl ether (100 ml) and water (50 ml). The layers were separated and the aqueous phase was extracted with three 50-ml portions of diethyl ether. The combined ether extracts were dried over sodium sulfate and the solvent was evaporated at reduced pressure. The residue was distilled (Kugelrohr, 150–180°C, ~1 mm) to give 0.82 g (98%) of 4-phenylbutyrolactone. The lactone was 90% pure by GLC and exhibited ir and NMR spectra corresponding to those previously reported.[24] The major by-product was the uncyclized derivative, methyl 4-hydroxy-4-phenylbutyrate.

Reduction of Pinacolone (5) in Refluxing Chloroform. A solution of 2.6 g (10 mmol) of tetrabutylammonium borohydride and 1.0 g (10 mmol) of pinacolone in 10 ml of chloroform was heated at reflux for 5.5 h. The solution was allowed to cool to room temperature and was quenched by the addition of 20 ml of 3% hydrogen peroxide and 10 ml of 10% sodium hydroxide. The mixture was stirred at room temperature for 2.5 h. The layers were then separated, and the aqueous phase was extracted with three 30-ml portions of dichloromethane. The combined organic solutions were extracted with 10 ml of saturated sodium sulfite and dried over sodium sulfate. The solvent was distilled from the crude product through a 6-in. column packed with glass helices, and the residue was taken up in anhydrous diethyl ether. The resulting mixture was percolated through a 3-cm column of alumina and the solvent was distilled as above. The crude product was subjected to Kugelrohr distillation (170–180°C, 1 atm) to give 0.99 g (97%) of pinacolyl alcohol with a purity of 94% by GLC.

Reduction of 6-Methyl-5-hepten-2-one (11). The general procedure provided an 87% yield of 6-methyl-5-hepten-2-ol[25] with a purity of 98% by GLC after Kugelrohr distillation (100–105°C, ~8 mm): NMR ($CDCl_3$) δ 1.1 (d, J = 6 Hz, 3 H), 1.5 (s, 3 H), 1.6 (s, 3 H), 1.8–2.2 (m, 4 H), 3.2 (s, 1 H), 3.7 (m, 1 H), 5.0 (m, 1 H); ir (thin film) 3390, 1670 cm^{-1} (weak).

Hydroboration–Oxidation of Cyclohexene. To a solution of 1.0 g (12 mmol) of freshly distilled cyclohexene in 10 ml of dichlo-

romethane was added 3.2 g (12 mmol) of tetrabutylammonium borohydride. The solution was allowed to stand for 40 h and was then quenched by the addition of 3 ml of water and 3 ml of 3% hydrogen peroxide. Oxidation was effected by dropwise addition of 2 ml of 3 N sodium hydroxide and 3 ml of 30% hydrogen peroxide. The mixture was warmed to 40° for 30 min; it was then allowed to cool to room temperature and was stirred for an additional 1 h. Diethyl ether (100 ml) was added, and the layers were separated. The organic phase was extracted with three 50-ml portions of water, with 10 ml of saturated sodium sulfite, and with 50 ml of saturated sodium chloride. The organic solution was dried over sodium sulfate, percolated through a short column (~3 cm) of alumina, and concentrated at reduced pressure to afford 0.60 g (50%) of cyclohexanol (97% pure by GLC). The product was identical with an authentic sample of cyclohexanol by GLC and ir.

Acknowledgments. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank Mr. Marshall Pepper for preparing several of the compounds used in this study.

Registry No.—**1**, 108-94-1; **2**, 98-86-2; **3**, 100-52-7; **4**, 630-19-3; **5**, 75-97-8; **6**, 98-88-4; **7**, 106-33-2; **8**, 104-55-2; **9**, 25333-24-8; **10**, 110-93-0; tetrabutylammonium borohydride, 33725-74-5; dichloromethane, 75-09-2.

References and Notes

(1) M. D. Banus, R. W. Bragdon, and T. R. P. Gibb, *J. Am. Chem. Soc.*, **74**, 2346 (1952).
(2) E. A. Sullivan and A. A. Hinckley, *J. Org. Chem.*, **27**, 3731 (1962).
(3) (a) E. T. McBee and T. M. Burton, *J. Am. Chem. Soc.*, **74**, 3022 (1952); (b) W. Foerst, Ed., "Newer Methods of Preparative Organic Chemistry", Vol. IV, Academic Press, New York, N.Y., 1968, p 209; (c) T. A. Mashburn and C. R. Hauser, *J. Org. Chem.*, **26**, 1671 (1961); (d) B. J. Bergot and L. Jurd, *J. Heterocycl. Chem.*, **1**, 158 (1964); (e) H. Irie, Y. Tsuda, and S. Uyeo, *J. Chem. Soc.*, 1446 (1959).
(4) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 1050.
(5) (a) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955); (b) J. Kollonitsch, O. Fuchs, and V. Gabor, *Nature (London)*, **173**, 125 (1954).
(6) A. Brändström, U. Junggren, and B. Lamm, *Tetrahedron Lett.*, 3173 (1972).
(7) D. J. Raber and W. C. Guida, *Synthesis*, 808 (1974).
(8) R. O. Hutchins and D. Kandasamy, *J. Am. Chem. Soc.*, **95**, 6131 (1973).
(9) (a) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84**, 373 (1962); (b) K. Bowden and M. Hardy, *Tetrahedron*, **22**, 1169 (1966); (c) H. C. Brown, R. Bernheimer, and K. J. Morgan, *J. Am. Chem. Soc.*, **87**, 1280 (1965); (d) H. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).
(10) (a) E. R. Garrett and D. A. Lyttle, *J. Am. Chem. Soc.*, **75**, 6051 (1953); (b) H. C. Brown, E. J. Mead, and c. J. Shoaf, *ibid.*, **78**, 3616 (1956); (c) H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957); (d) B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970).
(11) (a) C. D. Ritchie, *Tetrahedron Lett.*, 2145 (1963); (b) C. D. Ritchie and A. L. Pratt, *J. Am. Chem. Soc.*, **86**, 1571 (1964).
(12) (a) P. T. Lansbury, R. E. MacLeay, and J. O. Peterson, *Tetrahedron Lett.*, 311 (1964); (b) P. T. Lansbury and R. E. MacLeay, *J. Am. Chem. Soc.*, **87**, 831 (1965).
(13) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **83**, 4372 (1961).
(14) Other mechanisms for the decomposition of tetrabutylammonium borohydride are possible, e.g., decomposition of a tetrabutylammonium borohydride ion pair to give tributylamine, butane, and borane:

$$(Bu)_4N^+BH_4^- \rightarrow (Bu)_3N + BuH + BH_3$$

However, we have not been able to isolate tributylamine from decomposing solutions of tetrabutylammonium borohydride in dichloromethane. Alternatively a radical process might be involved; cf. J. T. Groves and K. W. Ma, *J. Am. Chem. Soc.*, **96**, 6527 (1974).
(15) H. C. Brown and W. Korytnyk, *J. Am. Chem. Soc.*, **82**, 3866 (1960).
(16) Other mechanistic possibilities such as electrophilic catalysis of the reduction by borohydride ion (eq 2) by borane or borane derivatives formed via the pathway of eq 3 are also possible.
(17) H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970).
(18) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithica, N.Y., 1972, p 260.
(19) Cf. K. N. Campbell, *J. Am. Chem. Soc.*, **59**, 1980 (1937).
(20) D. J. Raber and P. Gariano, *Tetrahedron Lett.*, 4741 (1971).
(21) L. F. Somerville and C. F. H. Allen, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 81.
(22) Tetrabutylammonium chloride can be prepared from the less expensive iodide by ion exchange.
(23) Cf. "Sadtler Index of NMR and IR Spectra", Sadtler Research Laboratories, Philadelphia, Pa.
(24) (a) C. H. DePuy, F. W. Breitbeil, and K. K. Ellers, *J. Org. Chem.*, **29**, 2810 (1964); (b) P. M. G. Bavin, D. P. Hansell, and R. G. W. Spickett, *J. Chem. Soc.*, 4535 (1964).
(25) Y. Armand and P. Arnaud, *Ann. Chim. (Paris)*, **9**, 433 (1964).