Sodium Borohydride Reduction of Conjugated Aldehydes and Ketones

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The reduction of conjugated aldehydes and ketones by sodium borohydride leads, in general, to substantial amounts of fully saturated alcohol products. In alcohol solvents the formation of saturated β-alkoxy alcohols (involving solvent addition to the double bond) is observed. This product is enhanced by added solvent conjugate base and depressed by addition of trialkyl borate. The structural features which control the extent of simple carbonyl reduction, 1,4 reduction, and solvent addition have been examined, as well as the effects of different solvents on the course of the reaction.

Sodium borohydride reduction of carbon–carbon double bonds has been observed in conjugated esters,[3] nitroalkenes,[4] and enol acetates.[5] These examples are apparently widely regarded as exceptions to the general rule that double bonds are inert to sodium borohydride. Based on the early literature report[6] that crotonaldehyde, cinnamaldehyde, and mesityl oxide yield only allylic alcohols with this reagent, most recent textbooks[7] either state or imply that carbonyl-conjugated double bonds are unaffected by sodium borohydride. Conversely, lithium aluminum hydride is often viewed as a less selective reagent based on the well-documented complete reduction of cinnamyl derivatives.[8]

In connection with another study requiring allylic alcohols, the sodium borohydride procedure was applied to 2-cyclohexenone. A very substantial percentage of the product was the fully reduced cyclohexanol. Examination of the literature revealed several similar reports[9-13] of conjugated ketone double-bond reduction, all of which involved substituted cyclohexenones. Although the number of specific examples of enone complete reduction exceeds those where only the carbonyl group is affected, the former are still viewed as abnormal.[13]

To clarify this question, we have examined the reduction of a number of unsaturated aldehydes and ketones under a variety of conditions.

(1) NDEA Title IV Predoctoral Fellow.

(2) Alfred P. Sloan Fellow, 1967–1969.

(3) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963); S. B. Kadin, *ibid.*, **31**, 620 (1966); J. A. Meschino and C. H. Bond, *ibid.*, **28**, 3129 (1963); H. LeMoal, R. Carrie, and M. Bargain, *Compt. Rend.*, **251**, 2541 (1960).

(4) H. Shechter, D. E. Ley, and E. B. Robinson, Jr., *J. Amer. Chem. Soc.*, **78**, 4984 (1956).

(5) W. G. Dauben and J. F. Eastham, *ibid.*, **73**, 4463 (1951); W. G. Dauben, R. A. Micheli, and J. F. Eastham, *ibid.*, **74**, 3852 (1952).

(6) S. W. Chaikin and W. G. Brown, *ibid.*, **71**, 122 (1949).

(7) For example, see H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 40; R. T. Morrison and R. N. Boyd, "Organic Chemistry," 2nd ed, Allyn and Bacon, Inc., Boston, Mass., 1966, p 639; C. D. Gutsche, "The Chemistry of Carbonyl Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 65; J. March, "Advanced Organic Chemistry," McGraw-Hill Book Co., San Francisco, Calif., 1968, p 679; A. Liberles, "Introduction to Theoretical Organic Chemistry," The Macmillan Co., New York, N. Y., 1968, p 510; L. O. Smith, Jr., and S. J. Cristol, "Organic Chemistry," Reinhold Publishing Co., New York, N. Y., 1966, p 442.

(8) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948); F. A. Hochstein and W. G. Brown, *ibid.*, **70**, 3483 (1948); M. J. Jorgenson, *Tetrahedron Lett.*, 599 (1962).

(9) F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkranz, *Chem. Ind.* (London), 1482 (1954).

(10) T. L. Jacobs and R. B. Brownfield, *J. Amer. Chem. Soc.*, **82**, 4033 (1960).

(11) N. W. Atwater, *ibid.*, **83**, 3071 (1961).

(12) W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965); K. Igbal and W. R. Jackson, *ibid.*, *C*, 616 (1968).

(13) (a) J. W. Wheeler and R. H. Chung, *J. Org. Chem.*, **34**, 1149 (1969). (b) Cyclopentenone appears to be particularly susceptible to conjugate reduction. *Cf.* P. L. Southwick, N. Latif, B. M. Fitzgerald, and N. M. Zaczek, *ibid.*, **31**, 1 (1966); H. C. Brown and H. M. Hess, *ibid.*, **34**, 2206 (1969).

Results and Discussion

As the following data clearly demonstrate, reduction of a conjugated double bond is a substantial competing process in the sodium borohydride reduction of both cyclic and acyclic ketones. Acrolein (6) and crotonaldehyde (7) (in contrast to the early report of Chaikin and Brown[6]) also exhibit some conjugate reduction. Table I compares results obtained with borohydride in 50% aqueous ethanol with those from LiAlH₄ reduction; the much greater carbonyl selectivity of the latter is evident. The cyclic ketones with sodium borohydride are more prone to conjugate reduction than the acyclic analogs, while both types show the anticipated effects of β-alkyl substitution. In keeping with simple steric arguments, the aldehydes exhibit a greater preference for direct carbonyl reduction; one β-methyl group (7) lowers the amount of 1,4 reduction, but interestingly, the effect is not so great as that of a single α-methyl substituent (as in methacrolein, 8), where only carbonyl reduction is observed.

Two substituted 2-cyclohexenones, 5-methyl- and 5-*t*-butyl-, were also subjected to the reduction conditions used to obtain the data in Table I. Both gave results similar to those from the unsubstituted 4 (eq 1).
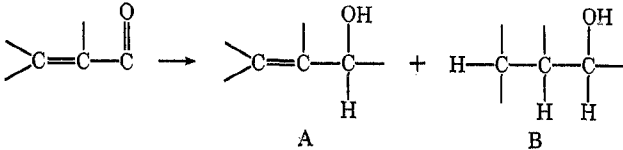

	a	b	a	b	
R = CH₃	49%	90%	51%	9%	(1)
R = *t*-butyl	42%	92%	58%	7%	
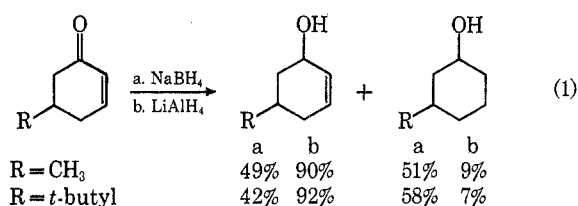
Again, as in the case of 1 and 4, LiAlH₄ reduction led to a small amount of saturated ketone after hydrolysis. This product almost certainly arises by conjugate hydride addition; the saturated alcohol may be derived from hydroalumination of the allylic alcoholate[8] or reduction of the saturated ketone formed during hydrolysis.[14]
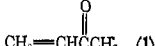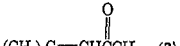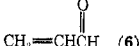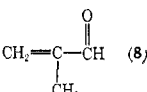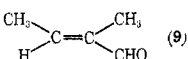
In the original work of Chaikin and Brown[6] the reductions of 3 and 7 were carried out in aqueous solution. Repetition of these reactions in water gave exactly the same results as shown for aqueous alcohol in Table I. We can only conclude that these authors were unable, because of analytical limitations, to observe the relatively small amount (8% for each) of conjugate reduction product formed from these systems.

Isopropyl alcohol (*i*-PrOH) is widely used as a solvent for sodium borohydride reductions, and the

(14) J. A. Marshall, N. H. Andersen, and A. R. Hochstetler, *ibid.*, **32**, 113 (1967).

TABLE I

Substrate	NaBH₄, 50% aqueous EtOH			LiAlH₄, ether		
	Yield, %[a]	% A	% B	Yield, %[b]	% A	% B
CH₂=CHCCH₃ (1)	86	57	43	79	83	7[d]
CH₃CH=CHCCH₃ (2)	90	65	35	85	98	1
(CH₃)₂C=CHCCH₃ (3)	89	92	8	82	100	0
(4)	90	59	41	97	94	2[c]
(5)	90	70	30[d]	88	100	0
CH₂=CHCH (6)	70	85	15	70	96	2
CH₃CH=CHCH (7)	91[b]	92	8	94	100	0
CH₂=C—CH (8) CH₃	100	≥99	≤1	98	100	0
(9)	95	≥99	≤1	82	100	0

[a] Determined by vpc. [b] Distilled yield. [c] The LiAlH₄ reductions of 1 and 4 also gave 10 and 4%, respectively, saturated ketone products; small amounts of analogous materials were obtained from 2 and 6. [d] 84% *cis* and 16% *trans*-3-methylcyclohexanol.

behavior of conjugated carbonyl compounds in this medium was therefore of interest. An unprecedented observation was the formation of saturated 3-isopropoxy alcohol product (eq 2). The data for reduction of compounds 1–9 are shown in Table II.

TABLE II

REDUCTION BY SODIUM BOROHYDRIDE IN
ISOPROPYL ALCOHOL

Substrate	Yield,[a] %	Product distribution[b,c]		
		% A	% B	% C
1	90	10	30	60
2	85[c]	34	33	33
3	85	65	34	1
4	65	25	48	27[d]
5	85	63	37[e]	0
6	69	53	26	21
7	85	59	15	26
8	65	≥95	≤4	≤1
9	84	98	2	0

[a] Overall distilled yield. [b] The products A, B, and C are designated in eq 2. [c] Determined by vpc. [d] 85% *cis*- (lower retention time) and 15% *trans*-3-isopropoxycyclohexanol. [e] 88% *cis*- and 12% *trans*-3-methylcyclohexanol.

The ethereal products for several of these systems could be identified by alternate synthesis *via* isopropoxymercuration–reduction. The oxymercuration is known[15] to be primarily controlled by inductive effects and allylic alcohols tend on this basis to give largely the 3-solvoxy product.[16] However, alkyl substituents directly attached to the double bond completely override the effect of the more remote hydroxyl group, as shown by the data in Table III. The reaction is in general regiospecific,[17] with only crotyl alcohol (16) showing

(15) J. Halpern and H. B. Tinker, *J. Amer. Chem. Soc.*, **89**, 6427 (1967).
(16) M. R. Johnson and B. Rickborn, *Chem. Commun.*, 1073 (1968); *J. Org. Chem.*, **34**, 2781 (1969).
(17) A. Hassner, *ibid.*, **33**, 2684 (1968).

evidence of any alternate positional isomer. The 2-alkoxy alcohols in all cases examined have markedly lower vpc retention times than the 3-alkoxy analogs. Compound 11 showed no evidence of positional isomer formation, but, like the cyclic compounds 13 and 14, gave a diastereomeric mixture of 3-alkoxy derivatives. In order of increasing vpc retention times, the ratio was *ca.* 30% to 70%; the sodium borohydride in *i*-PrOH reduction of the corresponding enone 2 gave the same two ethereal products, but in a ratio of *ca.* 60% to 40%. Similar reversal in product distribution is observed for the two reactions using enone 4 and allylic alcohol 13.

SCHEME I

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TABLE III
ISOPROPOXYMERCURATION–REDUCTION OF ALLYLIC ALCOHOLS

Substrate	Yield, %[a]	% C	% D
CH$_2$=CHCHCH$_3$ (10) (OH)	46	0	100
CH$_3$CH=CHCHCH$_3$ (11) (OH)	32	100	0
(CH$_3$)$_2$C=CHCHCH$_3$ (12) (OH)	26	100	0
(13)	38	100[b]	0
(14)	52	100[c]	0
CH$_2$=CHCH$_2$OH (15)	85	0	100
CH$_3$CH=CHCH$_2$OH[d] (16)	38	96	4
	35	0	100
CH$_2$=C—CH$_2$OH (17) (CH$_3$)			
CH$_3$\C=C/CH$_3$ H \CH$_2$OH	30	0	100

[a] Distilled yield; the remainder was recovered starting material. [b] 75% *trans-* and 25% *cis*-3-isopropoxycyclohexanol. [c] 60% *trans*-3-isopropoxy-*cis*- and 40% *cis*-3-isopropoxy-*trans*-3-methylcyclohexanol. [d] The solvoxymercuration carried out in methanol and ethanol gave higher yields but very similar product distribution.

The formation of isopropoxy-substituted products in the sodium borohydride reductions in *i*-PrOH solution is of mechanistic interest. We propose that the overall reaction occurs as shown in Scheme I. In no instance was any detectable amount of product alcohol (allylic or saturated) adduct to the β position observed; the simplest explanation for this observation is that rapid exchange of alkoxide moiety on boron occurs, and the product alcohol is then present in insufficient amount to compete with the *i*-PrOH. Further, the species which

adds to the enone is the isopropoxide anion *per se*, rather than, e.g., the tetraisopropoxyboronate ion **19**. Although sodium salts of species such as **19** are known to be relatively stable as solids, available evidence suggests that appreciable dissociation (eq 3) may occur in

$$B(OR)_4^- \rightleftharpoons B(OR)_3 + OR^- \qquad (3)$$
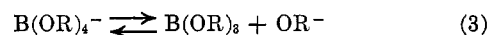
solution.[18] The generation of strong base during reduction is also supported by the observation that attempted reduction of crotonaldehyde by inverse addition of reagents (*i.e.*, addition of NaBH$_4$ in small portions to a solution of the aldehyde in any hydroxylic solvent) leads to extensive polymerization.

Comparison of the data in Tables I and II indicates a solvent effect on the ratio of 1,2 to 1,4 reduction, with the latter enhanced in *i*-PrOH relative to aqueous ethanol. Jackson and Zurqiyah,[12] on the basis of their observation that only conjugate reduction of 3-methylcyclohexenone, carvenone, and cholestenone occurs in pyridine solution, have suggested that the initial hydride transfer from BH$_4^-$ occurs exclusively at the β position, with subsequently formed (in other solvents) alkoxyborohydride species giving a mixture of carbonyl and conjugate reduction. This proposal required that at least 25% fully saturated product be formed; while this was observed with the cyclic enone systems,[12] it does not hold in the present work for compounds **3** and **6–9** (*cf.* Table I). It therefore appears that the initial hydride transfer from BH$_4^-$ can occur at either position.

If the isopropoxide-catalyzed equilibrium between enone and 3-alkoxy ketone **20** (Scheme I) were rapidly established, the amount of ethereal alcohol product should be independent of the isopropoxide ion concentration. This is not the case, as shown by the data in Table IV. All of the systems examined except **3**, **5**, and **9** showed a significant increase in 3-isopropoxy alcohol with added NaO-*i*-Pr. The exceptions have a common feature, the double bond being trisubstituted. The lack of appreciable ether product formation may be associated with either a very low rate of attack by isopropoxide ion or a very small equilibrium constant for formation of **20**. This equilibrium probably strongly favors the unsaturated carbonyl compound in

(18) H. Steinberg, "Organoboron Chemistry," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1964, p 613.

TABLE IV

SODIUM BOROHYDRIDE REDUCTION WITH ADDED
SODIUM ISOPROPOXIDE[a]

Substrate	% C[b]
1	96
2	43
3	2
4	72
5	0
6	70
7	81
8	30
9	0

[a] One mole of isopropoxide per mole of carbonyl compound. [b] The overall yields were again quite high; the remainder is a mixture of A and B (cf. Table II). The ratio of A to B remains unchanged within experimental error.

all of the systems investigated.[19] Formation of substantial amounts of ethereal alcohol products merely requires that the alkoxy ketone be reduced much faster than the starting material. This behavior is anticipated from the known importance of inductive effects on reduction by sodium borohydride.[21]

The data in Table IV show that, for many systems, reduction in the presence of added alkoxide can be a synthetically useful procedure for the preparation of 3-alkoxy alcohols. This is particularly evident where the solvoxymercuration procedure gives the 1,2 derivative (cf. Table III). Solvent addition is not restricted to *i*-PrOH; crotonaldehyde was reduced by sodium borohydride in a number of common alcohols as solvent, giving the results shown in Table V. The relatively

TABLE V

SODIUM BOROHYDRIDE REDUCTION OF CROTONALDEHYDE IN
VARIOUS ALCOHOL SOLVENTS

Solvent ROH, R	*n*-BuOH	Crotyl alcohol	3-Alkoxy alcohol
Me	7	56	37
Et	9	84	7
n-Pr	11	63	26
i-Pr	15	59	26
n-Bu		(79)	(21)
i-Bu	4	68	28
sec-Bu	2	86	12[a]
t-Bu	7	93	0
Allyl	4	85	11

[a] Mixture of diastereomers.

large amount of solvent incorporation in methanol is presumably due to the methoxide generated by the fairly rapid reaction of borohydride with this medium. Only *t*-butyl alcohol failed to give any measurable solvent addition (or other possible ethereal product, e.g., crotyl or *n*-butyl alcohol adducts); an attempt to force this reaction course by carrying out the reduction in the presence of potassium *t*-butoxide gave extensive polymerization, with negligible volatile products being formed. It is also worth noting in this connection that reductions in water or aqueous alcohol give high yields of carbonyl and conjugate reduction products, and

consequently solvent addition cannot be an important pathway under these conditions. This may be a result of the strongly enhanced rate of reduction in aqueous solvent.

Two systems, methyl vinyl ketone (1) and crotonaldehyde (7), were examined further to see if solvent incorporation could be eliminated by trapping isopropoxide with the Lewis acid triisopropylborate. The results are presented in Table VI. Added borate ester
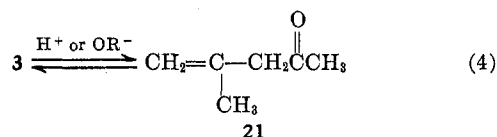
TABLE VI

EFFECT OF B(O-*i*-Pr)₃ ON ISOPROPYL ALCOHOL INCORPORATION

Substrate	Reagent[a]	% C[b]
1		60
1	B(O-*i*-Pr)₃, 1.35	25
7		26
7	B(O-*i*-Pr)₃, 1.35	16
7	NaO-*i*-Pr, 1.0	81
7	B(O-*i*-Pr)₃, 1.35; NaO-*i*-Pr, 1.0	65

[a] Moles per mole of substrate. [b] See eq 2.

does diminish the amount of isopropyl ether formed, but, fails to completely exclude this process. Furthermore, when triisopropyl borate (excess) and sodium isopropoxide were added to the borohydride solution prior to addition of 7, the amount of isopropoxy alcohol was significantly increased relative to the result with neither reagent added. These observations are consistent with the view that the tetraisopropoxyborate anion is appreciably dissociated (eq 3) in *i*-PrOH solution.

Finally, mesityl oxide (3) provides an example of yet another possible side reaction which may occur in sodium borohydride reductions. This compound has long been known[22] to exist in equilibrium (catalyzed by either acid or base) with isomesityl oxide (21) (eq 4).

$$3 \xrightleftharpoons{\text{H}^+ \text{ or OR}^-} \text{CH}_2\text{=}\text{C}\text{—}\text{CH}_2\overset{\overset{\text{O}}{\|}}{\text{C}}\text{CH}_3 \qquad (4)$$
$$\underset{\text{CH}_3}{|} \\ \mathbf{21}$$

The equilibrium (no solvent, 25°) has been shown to favor 3 (ca. 90% 3, 10% 21) by Stross and coworkers.[23] Reduction of different known mixtures of 3 and 21 (eq 5) gave the results shown in Table VII. With
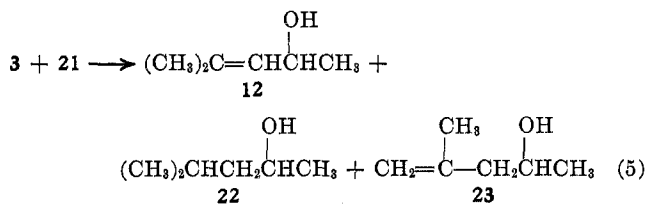
$$3 + 21 \longrightarrow (\text{CH}_3)_2\text{C=CH}\overset{\overset{\text{OH}}{|}}{\text{C}}\text{HCH}_3 +$$
$$\mathbf{12}$$

$$(\text{CH}_3)_2\text{CHCH}_2\overset{\overset{\text{OH}}{|}}{\text{C}}\text{HCH}_3 + \text{CH}_2\text{=}\overset{\overset{\text{CH}_3}{|}}{\text{C}}\text{—}\text{CH}_2\overset{\overset{\text{OH}}{|}}{\text{C}}\text{HCH}_3 \quad (5)$$
$$\mathbf{22} \qquad\qquad \mathbf{23}$$

TABLE VII

Starting material		Reduction conditions	Product distribution		
% 3	% 21		% 12	% 22	% 23
97	3	LiAlH₄, ether	97	0	3
60	40	LiAlH₄, ether	60	0	40
97	3	NaBH₄, 50% aq ethanol	80	16	4
97	3	NaBH₄, 50% aq methanol	87	10	3
60	40	NaBH₄, *i*-PrOH	56	17	25
97	3	NaBH₄, *i*-PrOH	54	28	17

(19) Although there is no direct evidence bearing on the magnitude of this equilibrium constant, Fedor[20] has shown that base converts 4-methoxy-4-methyl-2-pentanone quantitatively (in aqueous solution) into mesityl oxide.

(20) L. R. Fedor, *J. Amer. Chem. Soc.*, **91**, 908 (1969).

(21) H. Kwart and T. Takeshita, *ibid.*, **84**, 2833 (1962).

(22) C. Harries, *Ber.*, **32**, 1326 (1899).

(23) F. H. Stross, J. M. Monger, and H. de V. Finch, *J. Amer. Chem. Soc.*, **69**, 1627 (1947).

both LiAlH$_4$ and sodium borohydride in aqueous solvents, the products furnish no evidence for equilibration between **3** and **21**. In *i*-PrOH, however, the data suggest that equilibrium is approached (presumably catalyzed by sodium isopropoxide) shortly after initiation of reduction. The two entries (Table VII) using *i*-PrOH suggest that an "equilibrium" value of *ca.* 20% **22** is approached from either side; it should be noted that this amount need not correlate directly with the equilibrium percentage of **21**. The nonconjugated ketone is expected to undergo reduction faster than **3**, and hence the amount of **23** formed should be larger than the percentage of **21** present (under rapid equilibration conditions). It is clear that, given the proper circumstances, the homoallylic alcohol could become the major product of borohydride reduction of an enone. In fact, an example is provided by the recent work of Wheeler and Chung,[13] who found the reduction of piperitone (**24**) by sodium borohydride in aqueous base[24] to give mostly **25** (eq 6).[13]

$$\text{24} \quad \xrightarrow[\text{aq CH}_3\text{OH}]{\text{NaBH}_4, \text{OH}^-} \quad \text{25, 46\%} \qquad (6)$$
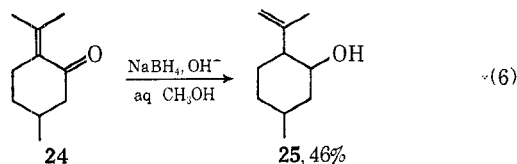
Experimental Section

Starting Materials.—With the exceptions noted below, the unsaturated aldehydes and ketones were commercial materials, spinning band distilled prior to use. Compound **5** was prepared by the method of Cronyn and Riesser.[25] LiAlH$_4$ reduction of acetylacetone gave 3-penten-2-ol (**11**), 65%, bp 65–69° (108 mm), which when subjected to Jones oxidation gave **2**, bp 122°, in 50% yield.[26] All of the starting materials were ≥99% pure by vpc, with the exception of mesityl oxide (**3**) which contained known (very small, except where otherwise noted) amounts of isomesityl oxide (**21**).

Products.—All product ratios were determined by vpc peak area integration; all analyses were carried out on a 4 m × 0.32 cm Carbowax 6M (15%) column at temperatures of from 70 to 103°.[27] The products were in many cases available materials; if not, identification was effected through alternate synthesis, *e.g.*, LiAlH$_4$ reduction for allylic alcohols and solvoxymercuration–reduction for many of the ethereal products. Where the latter procedure gave the alternate isomer, the reduction product was isolated and identified by complete spectral analysis.

The ethereal products obtained from sodium borohydride reduction of crotonaldehyde in various alcohol solvents were characterized by nmr and ir spectra, boiling points, and vpc retention times.[27]

Solvoxymercurations were carried out as described previously,[16] except that reaction times of 24–48 hr (prior to reduction) were used.

Reductions.—All reductions were carried out using 0.5 mol of reagent (LiAlH$_4$ or NaBH$_4$)/mol of unsaturated carbonyl compound. The sodium borohydride used was either commercial material or previously prepared highly purified reagent; this purification had no effect on the results presented here. Commercial reagent grade solvents were used for most reductions. *i*-PrOH dried by distillation from calcium hydride gave identical results with material containing small amounts of water. Two specific procedures will illustrate the general method used.

Crotonaldehyde in 50% Aqueous Ethanol.—Crotonaldehyde 14.0 g, (0.2 mol) was added through a dropping funnel to 3.7 g (0.1 mol) of sodium borohydride in 25 ml of H$_2$O and 25 ml of ethanol at 0°. After stirring at room temperature for 2 hr, the mixture was saturated with salt, extracted with ether, dried (potassium carbonate), vpc analyzed, and distilled to give 12.8 g (91%) of a mixture of *n*-butyl and crotyl alcohol, bp 118–120°.

3-Buten-2-one in *i*-PrOH.—Methyl vinyl ketone (7.0 g, 0.1 mol) was added dropwise at 0° to 1.8 g (0.05 mol) of sodium borohydride in 100 ml of *i*-PrOH. After stirring at room temperature for 8 hr, the mixture was poured into 100 ml of ice water. Potassium carbonate was added to saturate the mixture, after which it was treated as above. After distillation of the solvent, 2-butanol and 3-buten-2-ol were collected at atmospheric pressure; the residue was distilled under vacuum, bp 85° (30 mm), to give 4-isopropoxy-2-butanol. The total yield of distilled material was 90%.

(24) The apparent contradiction to the present work, where we found no rearrangement in aqueous solution, is due to the reduction procedure used by Wheeler and Chung.[18] A basic aqueous borohydride solution was added dropwise to the ketone **24** in methanol. These conditions will clearly favor base-catalyzed processes (rearrangement, aldol condensation, etc.) relative to direct reduction.

(25) M. W. Cronyn and G. H. Riesser, *J. Amer. Chem. Soc.*, **75**, 1666 (1953).

(26) L. P. Kyriakides, *ibid.*, **36**, 530 (1914).

(27) Details, including relative retention times, will be furnished on request.