Selective Reductions. XIX. The Rapid Reaction of Carboxylic Acids with Borane–Tetrahydrofuran. A Remarkably Convenient Procedure for the Selective Conversion of Carboxylic Acids to the Corresponding Alcohols in the Presence of Other Functional Groups

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Aliphatic and aromatic carboxylic acids are reduced rapidly and quantitatively to the corresponding alcohols by borane in tetrahydrofuran, either at 0° or 25°. Even sterically hindered acids, such as 1-adamantanecarboxylic acid, dicarboxylic acids, such as adipic acid, phenolic acids, and amino acids undergo facile and quantitative reduction with borane. Aliphatic carboxylic acids are reduced at faster rates than aromatic carboxylic acids. Unlike more conventional, very powerful reducing agents, such as lithium aluminum hydride, the mildness of the reagent, borane, permits the presence of other functional groups less susceptible to the reducing action of the reagent, groups such as ester, nitro, halogen, nitrile, keto, etc. The remarkable utility of this reagent for the selective reduction of carboxylic acids was confirmed by the selective conversion of adipic acid monoethyl ester to ethyl 6-hydroxyhexanoate and *p*-cyanobenzoic acid to *p*-cyanobenzyl alcohol in yields of 88 and 82%, respectively. This reaction provides a highly convenient synthetic procedure for the selective reduction of the carboxylic acid group where this is required in synthetic operations.

Reduction of carboxylic acids to the corresponding alcohols has been examined with a variety of complex metal hydrides and metal hydrides, such as lithium aluminum hydride, lithium trimethoxyaluminohydride (LTMA), lithium tri-*tert*-butoxyaluminohydride (LTBA), aluminum hydride, "mixed hydride," etc.[3] Lithium aluminum hydride has been widely applied for such reductions. However, lithium aluminum hydride and lithium trimethoxyaluminohydride are exceedingly powerful reducing agents capable of reducing practically all organic functional groups, whereas lithium tri-*tert*-butoxyaluminohydride is a mild reducing agent which does not reduce the carboxylic acid group. Consequently, this introduces a severe limitation in utilizing these reagents for the selective reduction of carboxylic acids to alcohols in the presence of other reducible functional groups in multifunctional molecules. Recently, the development of aluminum hydride as a reducing agent in our laboratories made it possible to overcome some of the limitations of lithium aluminum hydride, to achieve, for example, the selective reduction of the carboxylic acid group in the presence of nitro and halogen substituents. Unfortunately, aluminum hydride is highly reactive toward other functional groups, such as ester, nitrile, keto group, epoxide, etc., so that its utilization for selective reductions is not broadly applicable.

We recently reported an extensive investigation of the approximate rates and stoichiometry of the reaction of borane in tetrahydrofuran (THF) with organic compounds containing representative functional groups.[4] During the course of this investigation, it was observed that carboxylic acids, such as hexanoic acid and benzoic acid, are reduced by borane to the corresponding alcohols rapidly and quantitatively under remarkably mild conditions (eq 1).

$$\mathrm{RCOOH} \xrightarrow[0^\circ]{\mathrm{BH_3\text{-}THF}} \underset{>95\%}{\mathrm{RCH_2OH}} \qquad (1)$$

R = alkyl or aryl

The results of this investigation suggested that the unique reduction characteristics of borane should permit selective reduction of the carboxylic acid group to the corresponding primary alcohol in the presence of many other less reactive functional groups. Accordingly, we undertook a detailed study of the scope of the reduction and its applicability for multifunctional molecules. The results of this investigation are reported in the present paper.

Results and Discussion

Stoichiometry.—Simple carboxylic acids, such as hexanoic acid or benzoic acid, should require one borane unit or a total of three "active hydrides"[5] for the reduction to alcohol stage, one hydride for the reaction with the acidic hydrogen and two hydrides for the reduction. Similarly, dicarboxylic acids, such as adipic acid, should need a total of six "active hydrides" for complete reduction.

With acids containing hydroxy groups, such as salicylic acid, a total of four "active hydrides" (two for the acidic hydrogens present in the molecule and two for the reduction) would be required for the reduction.

Finally, amino acids, such as *p*-aminobenzoic acid,

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(3) (a) For a summary of the literature, see N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, pp 322–372; (b) H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1458 (1966); (c) H. C. Brown and P. M. Weissman, *ibid.*, **87**, 5614 (1965); (d) H. C. Brown and P. M. Weissman, *Israel J. Chem.*, **1**, 430 (1963); (e) H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1464 (1966); (f) N. M. Yoon and H. C. Brown, *ibid.*, **90**, 2927 (1968); (g) R. F. Nystrom, *ibid.*, **81**, 610 (1959); (h) E. E. Eliel, *Rec. Chem. Progr.*, **22**, 129 (1961); (i) E. C. Ashby and J. Prather, *J. Amer. Chem. Soc.*, **88**, 729 (1966).

(4) (a) H. C. Brown, P. Heim, and N. M. Yoon, *ibid.*, **92**, 7161 (1970); (b) H. C. Brown and B. C. Subba Rao, *ibid.*, **82**, 681 (1960); (c) H. C. Brown and W. Korytnyk, *ibid.*, **82**, 3866 (1960).

(5) It is convenient to discuss the utilization of the reagents in terms of moles of hydride taken up per mole of acid. However, it should not be confused that free "hydride" ion is the active species. An "active hydride" refers to one B–H bond, 1 equiv of borane.

might require a maximum of eight "active hydrides," three for the reaction with "active hydrogens" present on nitrogen and oxygen, two for the reduction, and the remaining three (1 mol of borane) for the formation of an amine–borane complex.

General Procedure for Rate and Stoichiometry Studies. Effect of Structure of the Acid on the Reactivity.—In order to understand the influence of the structure of the carboxylic acid on the rate of this reaction, the reactivity of a series of acids of representative structural features was examined toward borane. The general procedure adopted was to add 4 mmol of acid to 6.66 mmol of borane solution in sufficient THF to give 20 ml of solution. This makes the reaction mixture 0.33 *M* in BH_3 and 0.2 *M* in substrate. The solutions were maintained at constant temperature (*ca.* 25°) and aliquots were removed at appropriate intervals of time and analyzed for "residual hydride" by hydrolysis. In the case of dicarboxylic acids and amino acids, the concentration of borane alone was increased to 0.5 *M*.

All of the acids examined react instantaneously and quantitatively to evolve hydrogen, forming triacyloxyboranes. Simple carboxylic acids, such as propionic acid and benzoic acids, are reduced rapidly and quantitatively in 1 hr. Introduction of alkyl substituents α to the carbonyl group (propionic acid *vs.* trimethylacetic acid) does not influence the rate of reduction, revealing insensitiveness of the reaction to steric effects. However, introduction of electron-withdrawing substituents, such as halogen, α to the carbonyl group, decreases the rate of reduction (trichloroacetic acid *vs.* propionic acid). The results are summarized in Table I.

TABLE I
RATES OF REACTION OF BORANE WITH REPRESENTATIVE CARBOXYLIC ACIDS IN TETRAHYDROFURAN AT 25°[a,b]

Registry no.	Acid	Reduction,[c] % 0.5 hr	1.0 hr	3.0 hr	6.0 hr	12.0 hr	24.0 hr	48.0 hr
79-09-4	Propionic	95	100	100				
65-85-0	Benzoic	99	99					
75-98-9	Trimethylacetic	95	100	100				
79-11-8	Chloroacetic	100	100	100				
76-03-9	Trichloroacetic			8	18	37	48	61
90-64-2	Mandelic		80	88	92	100	100	
69-72-7	Salicylic		87	100				
150-13-0	*p*-Aminobenzoic[d]		100	100				
124-04-9	Adipic[d]	93	96	98	100			

[a] Unless otherwise indicated, reaction mixtures were 0.33 *M* in BH_3 and 0.2 *M* in the compound. [b] In all of the acids, the hydrogen evolution from the acidic hydrogen is instantaneous and complete. Hydrogen evolution from the amino group in *p*-aminobenzoic acid is slow and incomplete (38%) [c] Reactions were monitored by the decrease in the hydride concentration. [d] Solutions were 0.5 *M* in BH_3 and 0.2 *M* in the acid.

Competition Experiments.—Extensive study of the reaction of typical organic functional groups with excess borane gave a rough indication of the relative ease of reduction by this reagent of representative functional groups.[4] It has been established that borane is essentially inert toward nitro (both aliphatic and aromatic), sulfone, sulfide, disulfide, tosylates, and halogen (both alkyl and aryl). However, functional groups, such as ketone, esters, and nitriles, are reduced fairly rapidly by this reagent. Consequently, before undertaking to test the feasibility of selective reduction of carboxylic acid groups in the presence of such functional groups, it appeared desirable to establish the reactivities of these groups relative to the carboxylic acid group by means of competitive experiments. Accordingly, equimolar amounts of a carboxylic acid and a compound containing the functional group were allowed to compete for a limited quantity of borane in THF. The borane was added slowly to the reaction mixture, maintained at −15°. After 12 hr the mixture was hydrolyzed and analyzed by glpc using an internal standard.

The ease of reduction of carboxylic acids by this reagent is remarkable. Thus, the acid group is reduced completely in the presence of an ester (*n*-octanoic acid *vs.* ethyl hexanoate) and a nitrile (benzoic acid *vs.* benzonitrile). Even in the presence of a ketone, the carboxylic acid group is preferentially reduced (*n*-hexanoic acid *vs. p*-chloroacetophenone).

Representative results are summarized in Table II.

Synthetic Utility.—In order to establish the synthetic utility, product studies for the reduction of representative carboxylic acids were carried out. The rate and stoichiometric studies previously discussed indicated that for complete reduction 1 mol of borane is required per 1 mol of the carboxylic acid group. We established that simple acids, such as hexanoic acid, undergo rapid and quantitative reduction using only the stoichiometric quantity of borane. With carboxylic acids containing functional groups, such as halogen, nitro, etc., which are essentially inert toward borane, we utilized a modest excess of borane, 1.33 mol of BH_3 per 1 mol of RCO_2H (33% excess). The borane in THF was added slowly to the acid in THF at 0°. After the addition was completed, the reaction mixture was allowed to warm up to room temperature in the course of 1 hr (procedure A). In extending this procedure to the hydroxy acids and amino acids, the amount of borane used was increased by $^1/_3$ equiv for each equiv of active hydrogen present in the molecule. With amino acids an additional mol of borane per mol of acid was utilized to overcome the difficulties resulting from the formation of less reactive amine–borane complexes.

With the carboxylic acids containing more reactive functional groups, such as ester, keto, nitrile, etc., the precise stoichiometric amount of borane was utilized (1 mol of borane per mol of carboxylic acid group). The borane in THF was added drop by drop slowly to the acid in THF maintained at −15°. After the addition was completed, the mixture was allowed to warm up to room temperature and allowed to remain there overnight for a total reaction time of 12 hr (procedure B).

Simple carboxylic acids, such as *n*-hexanoic acid and benzoic acid, were converted into *n*-hexyl alcohol and benzyl alcohol in yields of 99 and 89%, respectively.

Even a sterically hindered carboxylic acid, such as 1-adamantanecarboxylic acid, was converted without difficulty into 1-adamantanemethanol in a yield of 95% (eq 2).

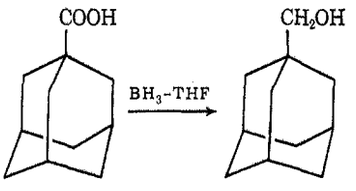
Dicarboxylic acids, such as adipic acid and phthalic acid, were converted into their corresponding diols in yields of 99 and 95%, respectively.

TABLE II

RELATIVE REACTIVITIES OF CARBOXYLIC ACIDS TO OTHER FUNCTIONAL GROUPS TOWARD BORANE IN TETRAHYDROFURAN[a]

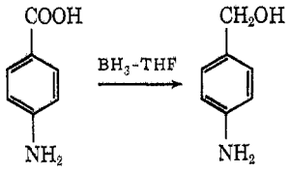
Expt	Registry no.	Compounds used	Mmol	Borane, mmol	Reaction products	Mol %
1	124-07-2	*n*-Octanoic acid	10.0		*n*-Octyl alcohol	50
				10.0	*n*-Octanoic acid[b]	0
	123-66-0	Ethyl hexanoate	10.0		*n*-Hexyl alcohol	<0.2
					Ethyl hexanoate	50
2		Benzoic acid	10.0		Benzyl alcohol	48
				10.0	Benzoic acid[b]	2
	100-47-0	Benzonitrile	10.0		Benzylamine[b]	<0.2
					Benzonitrile	49.8
3[c]	142-62-1	*n*-Hexanoic acid	15.0		*n*-Hexyl alcohol	40
				15.6	*n*-Hexanoic acid	10
	99-91-2	*p*-Chloroacetophenone	15.0		*p*-Chlorophenylethanol	7
					p-Chloroacetophenone	43

[a] Borane in THF was added to the THF solution of the compounds at −15°. [b] Not determined directly; estimated by difference. [c] Data taken from ref 4c.



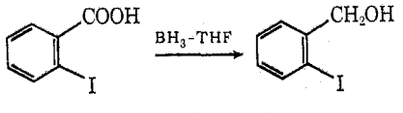
(2)

The presence of acidic or basic functional groups, such as the phenolic or amino group, did not interfere in the smooth reduction of the carboxylic acid group to the alcohol. Thus, salicylic acid was reduced to *o*-hydroxybenzyl alcohol in 92% yield. Similarly, *p*-aminobenzoic acid was converted to *p*-aminobenzyl alcohol in 80% yield (eq 3).



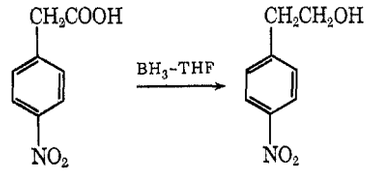
(3)

Carboxylic acids containing halogen substituents were quantitatively and cleanly converted into the corresponding halogen-substituted alcohols. For example, chloroacetic acid and 2-bromododecanoic acid were converted into 2-chloroethanol and 2-bromododecanol in essentially quantitative yield. Similarly, 11-bromoundecanoic acid was reduced to 11-bromoundecanol in a yield of 91%. Further, *o*-iodobenzoic acid and *o*-bromobenzoic acid were converted into *o*-iodobenzyl alcohol and *o*-bromobenzyl alcohol in yields of 92 and 93%, respectively (eq 4).



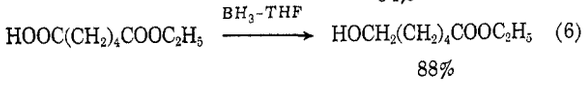
(4)

Finally, we examined *p*-nitrophenylacetic acid, adipic acid monoethyl ester, and *p*-cyanobenzoic acid to test the utility of this procedure for selective reductions. The products, 2-*p*-nitrophenylethanol, ethyl 6-hydroxyhexanoate, and *p*-cyanobenzyl alcohol, were all obtained in excellent yield, confirming the value of this procedure for selective reductions (eq 5–7). The results are summarized in Table III. Work-up procedures for the individual compounds are discussed in detail in the Experimental Section.



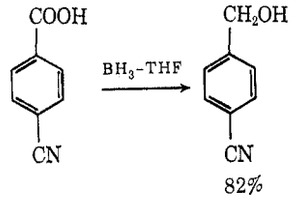
(5)

94%



(6)

88%



(7)

82%

Scope and Applicability.—Preliminary exploratory studies have established many unusual reducing characteristics of borane, quite different from those observed for aluminum hydride, lithium aluminum hydride, and its alkoxy derivatives. The reactivity of various functional groups toward borane decreases in the order carboxylic acids ≥ olefins > ketones > nitriles > epoxides > esters > acid chlorides. This is in marked contrast to the order of reactivity exhibited by these groups toward lithium aluminum hydride and its alkoxy derivatives (which are "basic"). This difference in behavior has been attributed to the Lewis acid character of borane.

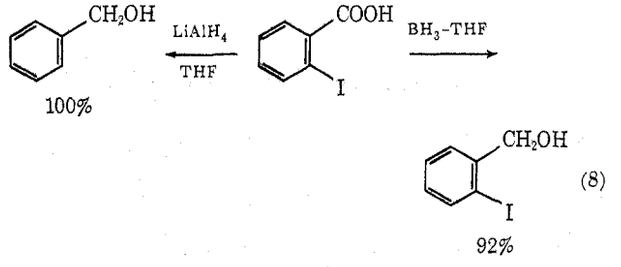
For achieving the conversion of the carboxylic acid group to the $-CH_2OH$ grouping, borane has three major advantages over the conventional reagents, such as lithium aluminum hydride, aluminum hydride, etc. First, the reaction is exceedingly rapid and quantitative, free of side products. Second, the stoichiometric quantity of borane is adequate to bring the reaction to completion in a reasonable time under mild conditions. Third, the unique reducing characteristics exhibited by borane enable the reaction to tolerate the presence of almost any other functional group, such as nitro, halogen (alkyl and aryl), nitrile, ester, epoxide, sulfone, sulfide, sulfoxide, tosylate, disulfide, etc. No other hydride reagent currently available exhibits such a unique selectivity.

In utilizing lithium aluminum hydride, the reduction of the carboxylic acids often requires conversion of the acid to other derivatives with more favorable properties, such as ester or acid chloride, to achieve smooth reduction. However, borane reduces even sterically hindered acids and polycarboxylic acids directly to the alcohol stage with exceptional ease in a single step.

p-Aminobenzoic acid has been reduced to *p*-aminobenzyl alcohol with lithium aluminum hydride in 20% yield,[6] whereas the use of borane has improved the yield to 80%. Indeed, borane has been the reagent of choice for such transformations involving amino acids to amino alcohols.[7]

Recently, borane has been successfully applied to the specific reduction of C-terminal carboxyl groups in model peptides and proteins without affecting the peptide linkage.[8] This opens up many major applications for borane in biological chemistry, such as specific modification of peptides and proteins. With some additional research in this area, it should be possible to develop this reaction as a general procedure for C-terminal determination in proteins.

Lithium aluminum hydride causes extensive hydrogenolysis of the carbon–halogen bonds in both aliphatic and aromatic substrates.[9] Thus the yield of 2-chloroethanol from chloroacetic acid utilizing lithium aluminum hydride has been reported to be 5%.[10] Use of aluminum hydride improved the yield to 69%.[3f] (Similarly, use of "mixed hydride" increased the yield of 3-bromopropanol from 3-bromopropionic acid to 50%.[3g]) In the present study, use of borane dramatically enhanced the yield of 2-chloroethanol to 100%. Similarly, iodo- and bromo-substituted benzoic acids on reduction with lithium aluminum hydride undergo extensive hydrogenolysis of the carbon–halogen bond. Particularly, it has been reported that *o*-iodobenzoic acid reacts with lithium aluminum hydride to yield only benzyl alcohol (dehalogenated product) and none of the desired product.[11] Use of borane in the present study yielded *o*-iodobenzyl alcohol in 92% yield and none of the dehalogenated product (eq 8).



(8)

The applicability of borane for such specific transformations is further evidenced by the successful selective reduction of the carboxyl function in the presence of ester or cyano group where both lithium aluminum hydride and aluminum hydride would fail. Indeed, since the original suggestion that it should be possible to reduce the carboxyl group selectively in the presence of an ester group,[4c] there have been a number of such applications of borane.[12]

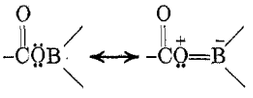
Finally, even carboxylic acids containing keto groups can be successfully reduced to the corresponding keto alcohols in reasonably good yield[13] (eq 9).

$$C_6H_5COCH_2CH_2COOH \xrightarrow[THF]{BH_3} \underset{60\%}{C_6H_5COCH_2CH_2CH_2OH} \quad (9)$$

Mechanism. Trialkoxylboroxine as Final Reduction Product.—Previous studies[4b,c] have established that the first step in these reactions involves formation of the triacyloxyborane[14] (eq 10). It is postulated that

$$3RCOOH + BH_3 \xrightarrow{\text{very fast}} (RCO)_3B + 3H_2 \quad (10)$$

the carbonyl group in triacyloxyborane must be "activated" as a consequence of resonance involving the boron atom and the lone pair on oxygen (eq 11).

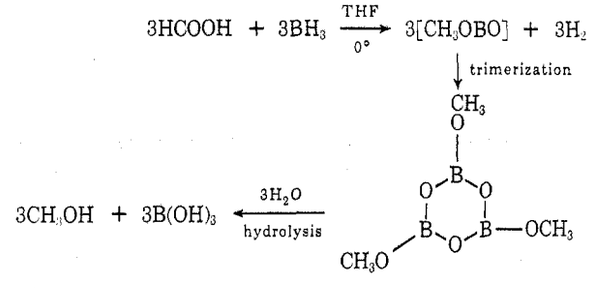


(11)

According to this interpretation, the carbonyl group in triacyloxyborane should resemble those in aldehydes and ketones, much more than those in derivatives such as esters, acid chlorides, etc.[15] Consequently, this moiety undergoes further reaction with borane.

The stoichiometry of the reaction suggests that the final product should be the trialkoxyboroxine. This substance should give the alcohol and boric acid on hydrolysis. Indeed, this proposal has now been confirmed. Reaction of 1 mol of formic acid with 1 mol of borane resulted in the formation of trimethoxyboroxine, isolated in 78% yield, and identified by its proton nmr (singlet at δ 3.59) (Scheme I).

SCHEME I



(6) A. P. Phillips and A. Maggiolo, *J. Org. Chem.*, **15**, 659 (1950).

(7) (a) M. Siddiqueullah, R. McGarth, L. C. Vining, F. Sala, and D. W. Westlake, *Can. J. Biochem.*, **45**, 1881 (1967); (b) A. V. Emes and L. C. Vining, *ibid.*, **48**, 613 (1970); (c) C. K. Wat, V. S. Malik, and L. C. Vining, *Can. J. Chem.*, **49**, 3653 (1971).

(8) (a) A. F. Rosenthal and M. Z. Atassi, *Biochim. Biophys. Acta*, **147**, 410 (1967); (b) M. Z. Atassi and A. F. Rosenthal, *Biochem. J.*, **111**, 593 (1969).

(9) (a) H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, **34**, 3918 (1969); (b) H. C. Brown and S. Krishnamurthy, manuscript in preparation.

(10) E. L. Eliel and J. T. Traxler, *J. Amer. Chem. Soc.*, **78**, 4049 (1956).

(11) G. J. Karabatsos and R. L. Shone, *J. Org. Chem.*, **33**, 619 (1968).

(12) (a) N. L. Allinger and L. A. Tushaus, *J. Org. Chem.*, **30**, 1945 (1965); (b) C. C. Schroff, W. S. Stewart, S. J. Uhm, and J. W. Wheeler, *ibid.*, **36**, 3356 (1971); (c) W. S. Johnson, J. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron, Suppl.*, **8**, Part II, 541 (1966); (d) R. A. Firestone, E. E. Harris, and W. Reuter, *Tetrahedron*, **23**, 943 (1967); (e) S. Hagishita and K. Kuriyama, *ibid.*, **28**, 1435 (1972).

(13) B. C. Subba Rao and G. P. Thakar, *Current Science*, **32**, 404 (1963).

(14) Hydrogen evolution is instantaneous and quantitative even at −20°, indicating the remarkable ease with which triacyloxyboranes are formed. Recently, it has been reported that the triaryloxyboranes initially formed can undergo dismutation to acid anhydrides and oxybisdiacyloxyboranes and the resulting dismuted products undergo further reduction with borane–THF to the alcohol stage; see A. Pelter, M. G. Hutchings, T. E. Levitt, and K. Smith, *Chem. Commun.*, 347 (1970). However, the rates of reduction of carboxylic acids observed in the present study are far faster than the rates of dismutation for triacyloxyboranes in the majority of instances. This indicates that dismutation need not be an important factor in the presence of excess borane–THF.

(15) A detailed study of the unusual chemistry of triacyloxyboranes is underway with Mr. Thomas P. Stocky.

TABLE III

PRODUCTS OF REDUCTION OF CARBOXYLIC ACIDS WITH BORANE IN TETRAHYDROFURAN[a]

Compd	Procedure	Time, hr	Hydride/compd	Product	Yield,[b] %
Benzoic acid	A	1.0	4.0	Benzyl alcohol	89
1-Adamantanecarboxylic acid	A	1.0	4.0	1-Adamantanemethanol	95
Adipic acid	A	6.0	7.0	1,6-Hexanediol	100
Phthalic acid	A	6.0	7.0	Phthalyl alcohol	95
Salicylic acid	A	3.0	5.0	*o*-Hydroxybenzyl alcohol	92
p-Aminobenzoic acid	A	4.5	8.0	*p*-Aminobenzyl alcohol	80
Chloracetic acid	A	0.5	4.0	Chloroethanol	100[c]
2-Bromododecanoic acid	A	1.0	4.0	2-Bromododecanol	92
11-Bromoundecanoic acid	A	1.0	4.0	11-Bromoundecanol	91
o-Iodobenzoic acid	A	1.0	4.0	*o*-Iodobenzyl alcohol	92
o-Bromobenzoic acid	A	1.0	4.0	*o*-Bromobenzyl alcohol	93
p-Nitrophenylacetic acid	A	2.0	4.0	2-*p*-Nitrophenyl ethanol	94
Adipic acid monoethyl ester	B	16.0	3.0	Ethyl 6-hydroxyhexanoate	88
p-Cyanobenzoic acid	B	12.0	3.0	*p*-Cyanobenzyl alcohol	82

[a] Reactions were carried out on a 25-mmol scale. [b] Unless otherwise indicated, the reported yields are isolated yields. [c] Determined by glpc.

Conclusions

The facile reaction of borane with olefins led to the discovery of hydroboration reaction and the exploration of the remarkable chemistry of organoboranes.[16] The rapid and quantitative reduction of amides to amines by borane resulted in numerous applications of this procedure for such conversions in medicinal, pharmaceutical, and biological chemistry.[17] The subject of the present study, the selective reduction of carboxylic acids in the presence of almost any functional group, provides yet another major application for the reagent, borane–THF.

Experimental Section

Materials.—Tetrahydrofuran was dried with excess lithium aluminum hydride, distilled under nitrogen, and stored over 5-Å molecular sieves. Borane solution in THF was prepared from sodium borohydride and boron trifluoride etherate.[18,19] The borane–THF solution was standardized by hydrolyzing a known aliquot of the solution with glycerine–water–THF mixture and measuring the hydrogen evolved. For most experiments the concentration was approximately 2 *M* in BH_3.

Carboxylic acids used were the commercial products of the highest purity. They were further purified by distillation or recrystallization when necessary. In all of the cases, physical constants agreed satisfactorily with constants in the literature.

All glassware was dried thoroughly in a drying oven and cooled under a dry stream of nitrogen. All reduction experiments were carried out under a dry nitrogen atmosphere. Hypodermic syringes were used to transfer the solution.

Rates of Reduction of Carboxylic Acids.—Reduction of benzoic acid is representative. A 100-ml flask was dried in an oven and cooled down in a dry nitrogen atmosphere. The flask was equipped with a rubber syringe cap, a magnetic stirring bar, and a reflux condenser, connected to a gas buret. The flask was immersed in a water bath at room temperature (*ca.* 25°) and 6.6 ml (6.6 mmol) of 1.0 *M* borane solution in THF was introduced into the reaction flask, followed by 9.4 ml of THF. Then 4 mmol of benzoic acid in 4 ml of THF was introduced slowly. Now the reaction mixture was 0.33 *M* in BH_3 and 0.2 *M* in acid. Hydrogen evolution, 4 mmol, was almost instantaneous, which corresponds to 1 mmol of hydrogen evolution per mmol of the acid. The mixture was stirred well.

At the end of 30 min, a 5.0-ml aliquot of the reaction mixture was removed with a hypodermic syringe and injected into a hydrolyzing mixture in a 1:1 mixture of 2 *N* sulfuric acid and ethylene glycol. The hydrogen evolved was measured with a gas buret. This indicated that 2.99 mmol of hydride has reacted per mmol of the acid, indicating the completion of the reaction. An aliquot taken at the end of 1 hr showed no further hydride utilization.

The results for other acids are summarized in Table I.

Reduction of Hexanoic Acid with a Stoichiometric Quantity of Borane in THF.—A clean, dry 25-ml flask, equipped with a side arm fitted with a silicone rubber stopple, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, was cooled down with nitrogen. Then 5 ml (10 mmol) of a 2 *M* solution of hexanoic acid was injected into the reaction flask, followed by 1 ml of *n*-dodecane as the internal standard. The flask was immersed in an ice bath and cooled to 0°. Then 4.3 ml (10 mmol) of 2.33 *M* borane solution in THF was added slowly. There was evolved 260 ml (10.1 mmol) of hydrogen during the course of the addition. The ice bath was removed and replaced by a water bath (*ca.* 25°). At the end of 0.5 hr, 1 ml of the reaction mixture was hydrolyzed with water and analyzed by glpc on a 5% Carbowax 20M column, 6 ft × 0.125 in., indicating the presence of 97% *n*-hexyl alcohol. At the end of 1 hr a 99% yield of *n*-hexyl alcohol was realized. The reaction mixture was devoid of any residual hydride.

A similar study was made utilizing 3.3% of excess borane. *n*-Hexyl alcohol was formed in 100% yield in 30 min. Hydrolysis of the reaction mixture with water indicated the presence of 2.5 mmol of residual hydride.

Competitive Experiments. Reaction of *n*-Octanoic Acid and Ethyl Hexanoate with a Limited Quantity of Borane in THF.—The experimental set-up was the same as in the previous experiments. To the reaction flask was added 5 ml (10 mmol) of a 2 *M* solution of octanoic acid in THF, followed by 5 ml (10 mmol) of a 2 *M* solution of ethyl hexanoate in THF; 1 ml of *n*-dodecane was added to serve as an internal standard. The mixture was stirred well and a minute sample was withdrawn and analyzed by glpc. The mixture was cooled to −15° using an ice–salt bath. Then 4.3 ml (10 mmol) of a 2.33 *M* solution of BH_3 was added slowly, drop by drop, over a period of 20 min. There was evolved 9.9 mmol of hydrogen during the course of addition (hydrogen evolution was instantaneous even at −15°). The mixture was stirred for 12 hr, allowing it to warm up to room temperature slowly. The mixture was hydrolyzed with water. There was observed no hydrogen evolution, indicating the complete utilization of borane. The aqueous phase was saturated with anhydrous potassium carbonate. Gas chromatographic examination of the ethereal layer indicated the presence of 10 mmol of *n*-octyl alcohol, traces of *n*-hexyl alcohol, and 9.9 mmol of ethyl hexanoate (recovered as unreacted).

The results are summarized in Table II.

General Preparative Procedures for the Reduction of Carboxylic Acids to Alcohols.—A series of carboxylic acids of representative structural features was reduced on a 25-mmol scale and the products were isolated to establish the synthetic utility of the

(16) H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1972, pp 255–446.

(17) (a) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964); (b) *J. Org. Chem.*, **38**, 912 (1973), and references cited therein.

(18) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963); H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **90**, 2915 (1968).

(19) One molar solution of borane in tetrahydrofuran is now commercially available from Aldrich Chemical Co., Milwaukee, Wisconsin.

reaction. (Depending upon the other substituents present, the time required may require an increase or decrease.)

A. Sterically Hindered Acids.—The following procedure for the reduction of 1-adamantane carboxylic acid is representative (procedure A). An oven-dried 100-ml flask with a side arm fitted with a silicone rubber stopple, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was cooled down to room temperature under dry nitrogen. Then 4.57 g (25 mmol) of 1-adamantanecarboxylic acid dissolved in 10 ml of THF was placed into the reaction flask. The flask was immersed in an ice bath and cooled to 0°. To this 14.3 ml (33.3 mmol) of 2.33 *M* borane solution in THF was slowly added during a 15-min period. There was evolved 24.5 mmol of hydrogen. The ice bath was replaced by a 25° bath and the mixture was stirred well. At the end of 1 hr, analysis of a minute aliquot of the reaction mixture indicated the completion of the reaction. Excess hydride was carefully destroyed with 10 ml of a 1:1 mixture of THF and water (620 ml of H_2 was evolved, equivalent to 24.5 mmol of residual hydride). The aqueous phase was saturated with anhydrous potassium carbonate. The THF layer was separated and the aqueous layer was extracted with three 20-ml portions of ether. The combined organic phase was dried over magnesium sulfate. The solvents were removed by careful distillation to yield 3.926 g (95%) of 1-adamantanemethanol as a white solid, mp 114.5–115° (lit.[20] mp 115°).

B. Dicarboxylic Acids.—Reduction of adipic acid to 1,6-hexanediol is representative of the general procedure utilized. The experimental set-up was the same as in the previous experiments. A typical reaction setup was assembled and 3.65 g (25 mmol) of adipic acid was placed into the reaction flask, followed by 15 ml of THF. The resulting slurry was cooled to 0° in an ice bath. To this 27 ml (64.5 mmol) of 2.39 *M* borane solution in THF was added dropwise. There was evolved 50.9 mmol of hydrogen. The resulting mixture was stirred for 6 hr at 25°. The excess hydride was destroyed carefully with 15 ml of a 1:1 mixture of THF and water. The aqueous phase was saturated with 8–10 g of potassium carbonate (this is highly essential to drive the water-soluble diol from the aqueous to the THF phase). The THF layer was separated. The aqueous phase was extracted with two 15-ml THF portions and the combined THF extract was dried over magnesium sulfate. Solvent was removed on a rotary evaporator to yield 3.0 g (100%) of pure 1,6-hexanediol, mp 41–42° (lit.[21] mp 41–42°).

Similarly, phthalic acid was converted into the corresponding diol in a yield of 95%.

C. Phenolic Acids.—The following reduction of salicylic acid to *o*-hydroxybenzyl alcohol illustrates the practicality of utilizing borane-THF for such transformations. A typical reaction setup was assembled. To 3.45 g (25 mmol) of salicylic acid dissolved in 10 ml of THF at 0°, 18 ml (42 mmol) of 2.33 *M* borane solution in THF was added dropwise. There was evolved 49.8 mmol of hydrogen. The resulting clear mixture was stirred for 3 hr at 25°, at the end of which analysis of a small aliquot of the reaction mixture indicated the completion of the reaction. Excess hydride was destroyed with water, and the mixture was treated with 30 ml of 3 *N* sodium hydroxide and stirred well for 15 min to form the sodium salt of the phenol. The aqueous phase was separated, and the volatile solvents of the THF phase were removed on a rotary evaporator. The residue of the THF phase was combined with the aqueous phase. The basic aqueous phase was cooled to 0°, carefully neutralized with dilute acetic acid to a pH of 6.7, and extracted six times with 20-ml portions of ether. The ether extract was dried over magnesium sulfate. Stripping off ether yielded 2.84 g (92%) of *o*-hydroxybenzyl alcohol as white plates, mp 78–80°. The material was essentially pure except for a small amount of acetic acid present as the impurity. Recrystallization from boiling benzene yielded 1.97 g as white plates, mp 85–86°; concentration of the mother liquor yielded further crystals (second crop), 0.47 g, mp 82–84°. Yield after recrystallization was 79%.

A variety of work-up procedures, such as the use of methanol or mannitol for removing boric acid as borate ester, and the use of 5% sodium bicarbonate solution instead of the usual potassium carbonate, were examined. They were all less satisfactory (yields ranged from 50 to 66%).

D. Amino Acids.—The following general procedure illustrated for the reduction of *p*-aminobenzoic acid is suggested for the reduction of amino acids. *p*-Aminobenzoic acid (freshly recrystallized from hot water at 80°, mp 187–187.5°), 3.43 g (25 mmol) dissolved in 12.5 ml of THF, cooled to 0°, was treated with 31.9 ml (75 mmol) of 2.35 *M* borane solution in THF. The resulting mixture, which was colorless and homogeneous, was stirred at 25° for 4.5 hr. Then the mixture was cooled to 0° and 15 ml of 3 *N* sodium hydroxide was added to destroy excess hydride and to hydrolyze the amine–borane complex, which required 12 hr at 25°. The pH of the resulting solution was adjusted to 11.0 by adding a few pellets of sodium hydroxide. The aqueous phase was saturated with potassium carbonate, the THF phase was separated, and the aqueous phase was extracted with five 30-ml portions of ether. The combined organic extracts were dried over anhydrous sodium sulfate. Stripping off the solvents on a rotary evaporator gave 2.46 g (80%) of *p*-aminobenzyl alcohol as pale brownish crystals, mp 60–63° (lit.[6] mp 63–64°).

E. Selective Reduction of Acid in the Presence of Halogen Substituents.—The following procedure for the reduction of *o*-iodobenzoic acid is representative. The experimental setup was the same as in the previous experiments. *o*-Iodobenzoic acid, 6.2 g (25 mmol), was placed into the flask, and the flask was immersed in an ice bath and cooled to 0°. Then 14.5 ml (33.3 mmol) of borane–THF was slowly added over a period of 15 min and the solution was vigorously stirred for an additional period of 1 hr, by which time reaction was essentially complete, as indicated by the residual hydride analysis. Excess hydride (24.7 mmol) was carefully destroyed with 15 ml of a 1:1 mixture of THF and water and the aqueous phase was saturated with 5–6 g of potassium carbonate. The THF layer was separated and the aqueous phase was extracted four times with 25-ml portions of ether. The combined organic extracts were dried over magnesium sulfate. Glpc examination of the organic extract revealed the absence of any benzyl alcohol (dehalogenated product). Removal of the solvents gave 5.34 g (92%) of *o*-iodobenzyl alcohol as the white solid, mp 89–90° (lit.[22] mp 91°). A small portion was recrystallized from boiling petroleum ether (bp 30–60°) as needles: mp 90°; nmr ($CDCl_3$, TMS) δ 2.58 (s, 1, -OH), 4.72 (s, 2, $-CH_2-$), 7.0–8.0 (m, 4, aromatic).

F. Selective Reduction in the Presence of the Nitro Substituent.—Since both aliphatic and aromatic nitro groups are essentially inert toward borane, use of excess borane offers no disadvantages. Reduction of *p*-nitrophenylacetic acid to 2-*p*-nitrophenylethanol is representative. To a solution of *p*-nitrophenylacetic acid, 4.53 g (25 mmol) dissolved in 12.5 ml of THF, 14.2 ml (33.3 mmol) of borane in THF was slowly added, evolving 26 mmol of hydrogen. After vigorous stirring for 2 hr at room temperature, the excess hydride (23 mmol) was carefully destroyed with water. The mixture was worked up as in the previous experiments. The solvents were removed in a rotary evaporator to yield 2-*p*-nitrophenylethanol, 3.94 g (94%), as a pale yellow solid: mp 63–64° (lit.[23] mp 63–64°); nmr ($CDCl_3$, TMS) δ 2.7 (s, 1, -OH), 3.0 (t, 2, CCH_2C), 3.95 (t, 2, $-CH_2-$), 7.8 (q, 4, aromatic).

G. Selective Reduction in the Presence of the Ester Group.—Since the esters of aliphatic acids are reduced at a reasonable rate by borane in THF, only a stoichiometric quantity of borane should be employed (procedure B). The procedure described below for the reduction of adipic acid monoethyl ester illustrates the practicality of using BH_3–THF for such conversions. A typical reaction setup was assembled. Into the reaction flask was placed 4.36 g (25 mmol) of adipic acid monoethyl ester (recrystallized from petroleum ether, mp 28–29°), followed by 12.5 ml of THF. The flask was immersed in an ice–salt bath and cooled to −18°. Then 10.5 ml (25 mmol) of 2.39 *M* borane solution in THF was slowly added dropwise over a period of 19 min. There was evolved 25.3 mmol of hydrogen. The resulting clear reaction mixture was stirred well and the ice–salt bath was allowed to equilibrate slowly to room temperature during a 16-hr period. The reaction mixture was hydrolyzed with 15 ml of water at 0°. No hydrogen evolution was observed, indicating the complete utilization of the borane. The aqueous phase was treated with 6 g of potassium carbonate and the THF phase was separated. The aqueous phase was extracted three times with a total of 150 ml of ether. The combined ether extract was washed with 30 ml of a saturated solution of sodium chloride and dried over magnesium sulfate. Removal of the solvent on a rotary

(20) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).

(21) W. A. Lazier, J. W. Hull, and W. J. Amend, *Org. Syn.*, **19**, 48 (1939).

(22) R. G. R. Bacon and W. S. Lindsay, *J. Chem. Soc.*, 1375 (1958).

(23) P. S. Pishchimuka, *J. Russ. Phys. Chem. Soc.*, **48**, 1 (1916).

evaporatory yielded 3.5 g (88%) of ethyl 6-hydroxyhexanoate as a colorless liquid, n^{20}D 1.4374. Distillation yielded 2.98 g (75%) of the material: bp 79° (0.7 mm); n^{20}D 1.4375 [lit.[24] bp 134° (15 mm)]; ir (neat) 3150–3750 (–OH), 1745 cm^{-1} (>C=O); nmr (CCl_4, TMS) δ 1.27 (t, 3, $-CH_3$), 1.0–2.0 [m, 6, $-(CH_2)_3-$], 2.28 [t, 2, $CH_2(C{=}O)O$], 3.53 (t, 2, $HOCH_2-$), 3.75 (s, 1, –OH), 4.17 (q, 2, $O{=}COCH_2-$).

H. Selective Reduction in the Presence of the Cyano Group.—Reduction of *p*-cyanobenzoic acid is representative. The experimental setup and the reaction conditions were the same as in the previous experiments (procedure B). *p*-Cyanobenzoic acid, 3.68 g (25 mmol), was suspended in 30 ml of THF (the acid has low solubility in THF) and to this at −15° 10.5 ml (25 mmol) of borane in THF was slowly added dropwise over a period of 20 min. The resulting mixture was stirred well and the ice–salt bath was allowed to equilibrate to room temperature (*ca.* 25°) slowly over a 12-hr period. Then the reaction mixture was worked up as described in the reduction of adipic acid monoethyl ester. Stripping off the solvent gave a pale yellowish, viscous oil. Distillation *in vacuo* gave 2.73 g (82%) of *p*-cyanobenzyl alcohol as a white solid: bp 108–109° (0.35 mm); mp 39–41° [lit.[25] bp 203° (53 mm), mp 41–42°]; nmr ($CDCl_3$, TMS) δ 3.6 (s, 1, –OH), 4.77 (s, 2, $-CH_2$), 7.6 (q, 4, aromatic).

(24) R. Robinson and L. H. Smith, *J. Chem. Soc.*, 371 (1937).

(25) J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. H. Self, *ibid.*, 103 (1942).

Reduction of Formic Acid with Borane in THF. Isolation of Trimethoxyboroxine.—A typical reaction setup was assembled. Formic acid, 1.1412 g (24.8 mmol) dissolved in 5 ml of THF, was placed in the reaction flask. The flask was immersed in an ice bath and cooled to 0°. To this solution was added dropwise with stirring 10.4 ml (24.8 mmol) of borane in THF. There was evolved 23.6 mmol of hydrogen. The mixture was stirred vigorously for 1.5 hr at 25°. Analysis of a small aliquot of the reaction mixture indicated the absence of any residual hydride. Most of the THF was removed by distillation under nitrogen, yielding a colorless liquid, 1.58 g. Nmr examination of this material indicated a sharp singlet at δ 3.59 (from TMS) characteristic of trimethoxyboroxine (trimethoxyboroxine spectrum in Sadtler No. 9157 exhibits a sharp singlet at δ 3.59); methyl borate was found to exhibit a sharp singlet at δ 3.43 (Sadtler Spectrum No. 10916 for methyl borate exhibits a singlet at δ 3.43). The mixture had 27% of the THF by weight as determined by the integration of the protons of THF. Correcting for the amount of THF, the yield of the boroxine was 78%.

Registry No.—Borane, 13283-31-3; *o*-hydroxybenzyl alcohol, 90-01-7; *o*-iodobenzoic acid, 619-58-9; *o*-iodobenzyl alcohol, 5159-41-1; *p*-nitrophenylacetic acid, 104-03-0; *p*-nitrophenylethanol, 100-27-6; adipic acid monomethyl ester, 627-91-8; ethyl 6-hydroxyhexanoate, 5299-60-5; *p*-cyanobenzoic acid, 619-65-8; *p*-cyanobenzyl alcohol, 874-89-5; formic acid, 64-18-6; trimethoxyboroxine, 102-24-9.

Solvolyses of Axial and Equatorial Epimers of *trans*-2-Decalyl Tosylate and Their 6-Keto and 6-Keto $\Delta^{5(10)}$ Derivatives[1]

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The tosylates of *trans*-2(a and e)-decalols (**1a**-OTs and **1e**-OTs), 6-keto-*trans*-2(a and e)-decalols (**2a**-OTs and **2e**-OTs), and 6-keto-$\Delta^{5(10)}$-*trans*-2(a and e)-decalols (**3a**-OTs and **3e**-OTs) were solvolyzed in trifluoroacetic, formic, and acetic acids and ethanol. Rates in all the solvents and products in acetic acid were investigated. Product patterns from the axial and equatorial **2** tosylates were similar to those reported for the counterparts in the **1** system. Axial to equatorial relative reactivities of the tosylates in the **1** and **2** systems vary insignificantly with solvents being in the range of 3.0 to 5.0 at 50°. Those in the **3** system change from 0.89 in acetic acid and 0.90 in formic acid to 1.29 in ethanol. The greatly reduced ratios for the **3** system in the acids are ascribed to the fact that, while the rates for the axial tosylate are normal, those for the equatorial tosylate are enhanced owing to participation of the 5(10) double bond. The acetates produced from **3e**-OTs show an unusually low inversion–retention ratio, which is compatible with such participation.

Since the *trans*-decalin system is incapable of undergoing chair inversion, it is one of the models most conveniently used for the study of the relationship between conformation and reactivity of cyclohexane derivatives.[2] The higher reactivity of the axial over the equatorial tosylate in conformationally fixed cyclohexane derivatives has been investigated by several workers.[3-9] In the study of solvolyses of *cis*- and *trans*-4-*tert*-butylcyclohexyl tosylates, Winstein and Holness suggested steric acceleration arising from the axial conformation in the initial ground state.[3] Baker and his associates[7,8b] proposed the importance of participation of the β-axial hydrogen in the transition state in solvents of low nucleophilicity and high ionizing power. As an extension of our previous work,[10] we carried out the determination of solvolysis rates and products of the axial and equatorial epimers of *trans*-2-decalyl tosylate (**1**-OTs), 6-keto-*trans*-2-decalyl tosylate (**2**-OTs), and 6-keto-$\Delta^{5(10)}$-*trans*-decalyl tosylate (**3**-OTs) in trifluoroacetic, formic, and acetic acids and ethanol. Effects of solvents and the 5,10 double bond upon the relative reactivity of the epimeric tosylates are reported.[11]

Results

Preparations.—The axial and equatorial epimers of 6-keto-$\Delta^{5(10)}$-*trans*-decalin-2-ol (**3e**-OH, **3a**-OH) were

(1) Presented in part at the 23rd Symposium on Organic Reaction Mechanisms, Kobe, Japan, Oct 1972.

(2) (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, Chapter 8; (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morison, "Conformational Analysis," Interscience, New York, N. Y., 1965, Chapter 2.

(3) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

(4) V. J. Shiner, Jr., and J. G. Jewett, *ibid.*, **87**, 1382, 1383 (1965).

(5) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southan, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968).

(6) K. Okamoto, S. Saito, and H. Shingu, *Bull. Chem. Soc. Jap.*, **42**, 3288, 3298 (1969).

(7) R. Baker, J. Hudec, and K. L. Rabone, *Chem. Commun.*, 197 (1969).

(8) (a) R. Baker, J. Hudec, and K. L. Rabone, *J. Chem. Soc. B*, 1446 (1970); (b) R. Baker and K. L. Rabone, *ibid.*, 1598 (1970).

(9) I. Moritani, S. Nishida, and M. Murakami, *J. Amer. Chem. Soc.*, **81**, 3420 (1959).

(10) H. Tanida, S. Yamamoto, and K. Takeda, *J. Org. Chem.*, **38**, 2077 (1973).

(11) All the compounds used in the present study are *dl* mixtures. For convenience, only one enantiomorph is shown in the figures and according to steroid convention, the hydrogen at C-9 is assigned the β orientation. The same convention was used in the previous work.[10]