

excess water, the reaction mixture was filtered, the solid precipitate was washed several times with methylene chloride, and the combined brown-colored methylene chloride filtrate and washings were washed with water till neutral, dried (magnesium sulfate), and evaporated to dryness to yield 300 mg. of a brown, solid material. Thin layer chromatography showed at least five different compounds. Chromatography of the crude product (300 mg.) on basic alumina and elution with petroleum ether, followed by benzene and then chloroform, allowed the recovery of a total of 280 mg. of material (collected in 14 fractions). The hexane-benzene (3:2) fraction yielded 78 mg. of pure orange brownish crystals whose physical constants

turned out to be identical with those of the dimer XIII obtained in the ascorbic acid reduction. All the other chromatography fractions consisted of mixtures (several spots on t.l.c.) which could not be separated into the pure components even after repeated chromatography on various absorbents. There was reason to believe that chemical changes were taking place on the column during the chromatographic purification.

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Selective Reductions. VII. Reaction of Lithium Trimethoxyaluminumhydride with Selected Organic Compounds Containing Representative Functional Groups¹

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*The stoichiometry of the reaction of excess lithium trimethoxyaluminumhydride with 56 selected organic compounds containing representative functional groups under standardized conditions (tetrahydrofuran solution, 0°) was examined in order to define the characteristics of the reagent for selective reductions. Compounds containing active hydrogen, such as alcohols, thiols, and amines, rapidly liberate the theoretical quantity of hydrogen. Aldehydes and ketones utilize 1 mole of hydride in undergoing reduction to the alcohol, although cinnamaldehyde utilizes 2. Carboxylic acids, anhydrides, acid chlorides, esters, and lactones utilize hydride corresponding to reduction to the alcohol stage. Epoxides react much slower than with lithium aluminum hydride, suggesting that the reagent should be useful for reduction of many functional groups in the presence of the epoxide structure. Moreover, in the case of unsymmetrical epoxides the products exhibit a high stereoselective opening of the ring. Nitriles and amides utilize hydride corresponding to reduction to the amine. Cyclohexanone oxime and pyridine do not react under the standard conditions, but nitro compounds, azobenzene, azoxybenzene, and picoline N-oxide are reduced. Disulfides and sulfoxides undergo reduction, but sulfones, sulfonic acids, and cyclohexyl tosylate are relatively inert. Consequently, in its behavior the reagent resembles lithium aluminum hydride much more closely than it does lithium tri-*t*-butoxy-aluminumhydride previously explored with this series of compounds. However, there are significant differences which should lead to useful applications. In particular, the presence of only a single reactive hydrogen*

should make possible a number of selective reductions which are impractical with lithium aluminum hydride because of the presence of four hydrogens which exhibit variable reducing capabilities in the reduction.

Introduction

The addition of 3 moles of an alcohol to 1 mole of lithium aluminum hydride in an appropriate solvent provides a simple, convenient means of preparing derivatives which exhibit reducing properties significantly different from those of the parent reagent.^{3,4} For example, lithium tri-*t*-butoxyaluminumhydride, prepared in this manner, has proven to be a valuable reagent for the selective reduction of acid chlorides to aldehydes,^{3,5} for the stereospecific reduction of steroidal ketones,⁶ and for certain selective reductions in complex molecules.⁷⁻⁹ A systematic survey of the characteristics of this reagent has revealed that it is an exceedingly mild reducing agent, approaching sodium borohydride in its behavior.¹⁰

The addition of 3 moles of ethyl alcohol to lithium aluminum hydride produces a product which is not homogeneous.^{4,11} Nevertheless, this material has proven to be valuable for the preparation of aldehydes

(3) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **80**, 5372 (1958).

(4) H. C. Brown and C. J. Shoaf, *ibid.*, **86**, 1079 (1964).

(5) H. C. Brown and B. C. Subba Rao, *ibid.*, **80**, 5377 (1958).

(6) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1431 (1958).

(7) J. Fajkos, *Chem. Listy*, **52**, 2134 (1958).

(8) J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959).

(9) C. Tamm, *Helv. Chim. Acta*, **43**, 338 (1960).

(10) H. C. Brown and P. M. Weissman, *Israel J. Chem.*, **1**, 430 (1963).

(11) An apparently homogeneous material, sodium triethoxyaluminumhydride, has been synthesized by the reaction of sodium hydride with "monomeric" aluminum ethoxide: G. Hesse and R. Schrödel, *Ann.*, **607**, 24 (1957).

(1) Based upon a thesis submitted by P. M. Weissman in Aug., 1964, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Graduate Research Assistant on Research Grant DA-ARO(D)-31-124-117 supported by the U. S. Army Research Office (Durham).

in high yields from the corresponding nitriles¹² and dimethylamides.¹³

On the other hand, the use of methyl alcohol does lead to the synthesis of a homogeneous material, lithium trimethoxyaluminumhydride.⁴ Moreover, preliminary observations indicated that, in contrast to lithium tri-*t*-butoxyaluminumhydride, the reducing potential of the trimethoxy derivative must be high, approaching that of lithium aluminum hydride itself.¹⁴ Accordingly, it appeared desirable to undertake a systematic exploration of the reactions of lithium trimethoxyaluminumhydride with some 56 organic compounds, comprising the more common functional groups, in order to define the area of its probable utility.¹⁵

Results and Discussion

In order that the data might be compared with the earlier results obtained with lithium tri-*t*-butoxyaluminumhydride,¹⁰ as well as with the results realized with other reagents now under study,¹⁶ it was desirable to standardize the reaction conditions. Consequently, all reactions were carried out in tetrahydrofuran at 0°. In the present case, we utilized a reaction mixture which was 0.4 *M* in the reagent and 0.1 *M* in the organic substrate. If the reaction did not proceed at a significant rate at 0°, it was repeated at 25°. In a few cases the compound undergoing reduction utilized so many equivalents of hydride that it was necessary to increase the hydride/compound ratio. This was done by maintaining the concentration of the reagent at 0.4 *M*, while decreasing the molar concentration of the substrate.

The general procedure involved placing, with the aid of a hypodermic syringe, 8.0 mmoles of lithium aluminum hydride (representing 32 mmoles of hydride) of a standardized solution in tetrahydrofuran into a flask flushed with nitrogen. The solution was cooled to 0° and 24 mmoles of methanol was then slowly added in sufficient tetrahydrofuran to give a total volume of 15 ml. The compound to be tested was then added in 5.0 ml. of tetrahydrofuran solution. The gas evolved (presumed to be hydrogen) was collected and measured. After the desired reaction period, usually 0.5 and 3.0 hr., dilute, aqueous sulfuric acid was added and the hydrogen evolved was collected and measured. A blank experiment was performed, side by side, in which pure solvent was added without compound. From the data, it was possible to calculate the number of millimoles of hydride utilized by the compound to evolve hydrogen and the number of millimoles of hydride utilized for reduction.

Alcohols, Phenols, Amines, and Thiols. It was of interest to examine a number of representative compounds containing "active hydrogen" to see whether they would react with the reagent. It was noted pre-

(12) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **86**, 1085 (1964).

(13) H. C. Brown and A. Tsukamoto, *ibid.*, **86**, 1089 (1964).

(14) For a survey of the characteristics of the various hydride reducing agents, see H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, Chapter 17.

(15) An unexpected development, which did not arise out of the present systematic survey, was the discovery that lithium trimethoxyaluminumhydride achieves the reduction of bicyclic ketones with unusually high stereospecificity. This development is described in the accompanying paper: H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.*, **87**, 5620 (1965).

(16) Research in progress with N. M. Yoon.

viously that tertiary alcohols fail to react with lithium tri-*t*-butoxyaluminumhydride and that the reaction of primary and secondary alcohols, as well as phenol, fail to liberate the theoretical quantity of hydrogen.¹⁰ Evidence was presented to support the conclusion that a portion of the alcohol or phenol reacted to displace *t*-butyl alcohol from the reagent and that it was the failure of this material to react that was responsible for the partial yields of hydrogen. *n*-Hexylamine failed to evolve any hydrogen with the reagent and 1-hexanethiol reacted only slightly, whereas benzenethiol reacted completely in 0.5 hr.¹⁰

These results are to be contrasted with the behavior of lithium trimethoxyaluminumhydride. With this reagent, all of these active hydrogen compounds evolved the theoretical quantity of hydrogen well within the first observation period (usually 0.5 hr.). The results are summarized in Table I.

Table I. Reaction of Lithium Trimethoxyaluminumhydride with Representative "Active Hydrogen" Compounds in Tetrahydrofuran at 0°

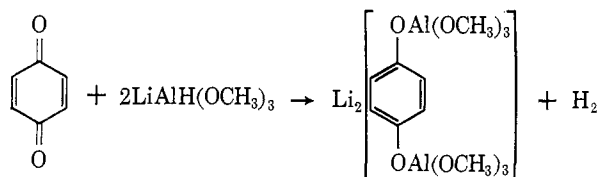
Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydride used for reduction ^b
1-Hexanol	0.5	1.03		0
Benzyl alcohol	0.5	0.96		0
3-Hexanol	0.5	1.09		0
3-Ethyl-3-pentanol	0.5	1.08	1.06	0
Phenol	0.5	0.99	0.96	0
<i>n</i> -Hexylamine	0.5	2.00	2.00	0
1-Hexanethiol	0.5	1.00	1.04	0
Benzenethiol	3.0	1.02	1.00	0

^a 2.00 mmoles of compound except where otherwise indicated, to 8.0 mmoles of reagent. ^b Millimoles per mmole of compound. ^c Hydrogen evolved from blank minus the hydrogen evolved on hydrolysis of the reaction mixture after the indicated reaction period.

Aldehydes and Ketones. Aldehydes and ketones were reduced rapidly to the alcohol stage, utilizing 1 equiv. of hydride per carbonyl group, according to the equation $R_2CO + LiAlH(OCH_3)_3 \rightarrow Li[R_2CHOAl(OCH_3)_3]$. Cinnamaldehyde utilized 2 molar equiv. of "hydride" to form hydrocinnamyl alcohol. This was surprising. In the case of lithium aluminum hydride this reduction has been attributed to the intervention of a cyclic mechanism requiring the presence of at least two hydrides on the aluminum atom.¹⁷ However, there does not appear to be any simple manner in which a similar cyclic mechanism can operate with lithium trimethoxyaluminumhydride. A simple reduction of the aldehyde group, without participation of the double bond, is achieved by the use of the *t*-butoxy reagent.¹⁰ The experimental results for these derivatives are summarized in Table II.

Quinones. Benzoquinone utilized 1 equiv. of hydride for reduction and a second for hydrogen evolution. This corresponds to reduction to the hydroquinone stage. No hydrogen was evolved in the corresponding reduction of *p*-benzoquinone by lithium

(17) F. A. Hochstein and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3484 (1948).



tri-*t*-butoxyaluminumhydride.¹⁰ The failure to obtain hydrogen in this case may be the result of the previously discussed side reaction of alcohols and phenols with the *t*-butoxy reagent, although there exists the possibility that the reduction in the earlier case proceeded to the formation of 4-hydroxycyclohexadienone. We are exploring this possibility.

Table II. Reaction of Lithium Trimethoxyaluminumhydride with Representative Aldehydes and Ketones in Tetrahydrofuran at 0°

Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydride used for reduction ^b
<i>n</i> -Hexaldehyde	0.5	0	0.99	0.99
	3.0	0	0.97	0.97
Benzaldehyde	0.5	0	0.91	0.91
	3.0	0	1.01	1.01
2-Heptanone	0.5	0	1.05	1.05
	3.0	0	0.99	0.99
Norcamphor	0.5	0	0.95	0.95
	3.0	0	0.99	0.99
Acetophenone	0.5	0	1.08	1.08
	3.0	0	0.93	0.93
Benzophenone	0.5	0	0.88	0.88
	3.0	0	0.93	0.93
Cinnamaldehyde ^d	0.5	0	2.02	2.02
	3.0	0	2.10	2.10

^a See Table I, footnote *a*. ^b See Table I, footnote *b*. ^c See Table I, footnote *c*. ^d Gas chromatographic examination showed a quantitative yield of hydrocinnamyl alcohol.

The failure to realize a simple stoichiometric relationship with anthraquinone indicates that the reaction does not follow a single course. Evidently reduction is proceeding to form both 9,10-anthracenediol and 9,10-dihydro-9,10-anthracenediol. The results are summarized in Table III.

Table III. Reaction of Lithium Trimethoxyaluminumhydride with Representative Quinones in Tetrahydrofuran at 0°

Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydride used for reduction ^b
<i>p</i> -Benzoquinone	0.5	0.96 ^e	1.99	1.03
	3.0	0.96	2.05	1.09
Anthraquinone ^d	0.5	0.48 ^e	2.04	1.56
	1.0	0.51	2.02	1.51
	3.0	0.59	2.22	1.63

^a See Table I, footnote *a*. ^b See Table I, footnote *b*. ^c See Table I, footnote *c*. ^d Inverse addition: solution of reagent added to suspension of anthraquinone. ^e Hydrogen evolved immediately following addition.

Carboxylic Acids and Acyl Derivatives. Carboxylic acids rapidly evolved 1 mole of hydrogen, with the reduction to the alcohol stage then proceeding more slowly, utilizing 2 additional equiv. of hydride. In

order to realize a complete reaction in a reasonable time, it proved convenient either to increase the hydride to compound ratio to 8:1 or to increase the reaction temperature to 25°.

The acid anhydrides also utilized the full 4 equiv. of hydride, corresponding to reduction to the alcohol or glycol stage. In some cases the reaction proceeded relatively sluggishly at 0°, but the use of an excess of reagent and a temperature of 25° caused the reaction to proceed to essential completion within 3 hr. in all cases examined. Finally, acid chlorides reacted readily at 0°, the reactions being complete within 1 hr.

We explored the possibility of achieving a partial reduction to aldehyde by adding 2 moles of the reagent to 1 mole of the carboxylic acid. However, 2,4-dinitrophenylhydrazine failed to indicate the formation of aldehyde. The experimental data are summarized in Table IV.

Table IV. Reaction of Lithium Trimethoxyaluminumhydride with Representative Carboxylic Acids and Acyl Derivatives in Tetrahydrofuran at 0°

Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydride used for reduction ^b
Caproic acid	0.5	1.05	2.13	1.13
	3.0	1.05	2.41	1.41
	3.0 ^d	1.05	3.11	2.11
Benzoic acid	0.5	1.0	1.33	1.33
	3.0	1.0	2.13	1.13
	6.0	1.0	2.62	1.62
Acetic anhydride ^f	3.0 ^e	1.0	3.11	2.11
	0.5 ^d	0	2.16	2.16
	3.0 ^d	0	3.16	3.16
Succinic anhydride	3.0 ^{d,e}	0	4.22	4.22
	0.5 ^d	0	2.89	2.89
	3.0 ^d	0	3.86	3.86
Phthalic anhydride ^f	0.5 ^d	0	3.57	3.57
	3.0 ^d	0	4.03	4.03
	0.5	0	2.02	2.02
Caproyl chloride	3.0	0	2.01	2.01
	0.5	0	1.84	1.84
Benzoyl chloride	1.0	0	2.00	2.00

^a See Table I, footnote *a*. ^b See Table I, footnote *b*. ^c See Table I, footnote *c*. ^d Millimoles of compound. ^e 25°. ^f A white precipitate was observed.

For comparison, in the case of lithium tri-*t*-butoxyaluminumhydride there was observed no reduction of carboxylic acids, half-reduction of anhydrides (to form the hydroxy acid in the case of cyclic derivatives), and complete reduction of acid chlorides.¹⁰

Esters and Lactones. Esters and lactones reacted rapidly to take up two hydrides per mole of compound. Consequently, reduction must be proceeding to the alcohol stage in the case of the esters and to the glycol stage in the case of the lactones. Isopropenyl acetate utilized nearly 3 moles of hydride. Presumably the reduction is proceeding to form both isopropyl alcohol (from the intermediate acetone) and ethanol (from the acetate group). These results are summarized in Table V.

In contrast to the ready reduction of esters, described above, lithium tri-*t*-butoxyaluminumhydride failed to react with ethyl benzoate and exhibited only a

Table V. Reaction of Lithium Trimethoxyaluminumhydride with Representative Esters and Lactones in Tetrahydrofuran at 0°

Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydride used for reduction ^b
Ethyl caproate	0.5	0	2.17	2.17
Ethyl benzoate	0.5	0	2.12	2.12
	3.0	0	2.07	2.07
Phenyl acetate	0.5	0	2.03	2.03
	3.0	0	1.99	1.99
γ-Butyrolactone	0.5	0	1.93	1.93
	3.0	0	1.93	1.93
Phthalide	0.5	0	2.02	2.02
	3.0	0	2.06	2.06
Isopropenyl acetate	0.5 ^d	0	2.88	2.88
	3.0	0	2.53	2.53
	6.0	0	2.59	2.59

^a See Table I, footnote a. ^b See Table I, footnote b. ^c See Table I, footnote c. ^d 1.00 mmole compound.

very slow reduction of ethyl caproate. Lactones were reduced, but at a relatively slow rate. Finally, phenyl acetate utilized one hydride rapidly, with the second being utilized at a much slower pace. This observation led to the development of a new procedure for the conversion of aliphatic carboxylic acids into aldehydes.¹⁸

Epoxides. The reaction of the reagent, lithium trimethoxyaluminumhydride, with epoxides was relatively slow, requiring 3 hr. at 25° to achieve reduction of terminal epoxides and more than 12 hr. for internal epoxides. This suggests that the reagent may prove useful for the selective reduction of more reactive groups, such as carboxylic acids and esters, in the presence of the epoxide structure. The sensitivity of the reaction rate to the structure of the epoxide is also promising, suggesting the possibility of achieving the selective reduction of one epoxide grouping in the presence of a second, less reactive arrangement.

The reduction of unsymmetrical epoxides by this reagent appears to be highly selective, with transfer of the hydride occurring almost exclusively to the less substituted carbon atom. The results are summarized in Table VI.

Amides and Nitriles. Primary amides, such as caproamide and benzamide, reacted to liberate 2 moles of hydrogen, but this does not prevent the further uptake of 2 equiv. of hydride to form the amine, after hydrolysis. Tertiary amides underwent rapid reduction to the amine stage without liberation of hydrogen. Finally, both capronitrile and benzonitrile utilized 2 equiv. of hydride, indicating reduction to the amine stage.

Gas chromatographic examination of the reduction products of caproamide and capronitrile indicated the formation of *n*-hexylamine in a yield of 83% from the amide and 69% from the nitrile. No attempt was made to establish optimum conditions for the reduction or the recovery of the amine, so that these figures can only be considered in the nature of lower limits to the possible yield. It is particularly noteworthy that no hydrogen evolution was observed in the reduction of capronitrile. Considerable hydrogen is evolved from

(18) P. M. Weissman and H. C. Brown, *J. Org. Chem.*, in press.

Table VI. Reaction of Lithium Trimethoxyaluminumhydride with Representative Epoxides in Tetrahydrofuran at 0°

Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydrides used for reduction ^b
1,2-Butylene oxide	0.5 ^d	0.08	0.73	0.65
	3.0 ^d	0.08	1.21	1.13
Styrene oxide ^e	0.5	0	0.28	0.28
	3.0 ^d	0	0.97	0.97
Cyclohexene oxide	3.0	0	0.27	0.27
	3.0 ^d	0	0.43	0.43
	12.0 ^d	0.08	0.86	0.76
1-Methyl-1,2-cyclohexene oxide ^f	1.0	0.03	0.18	0.15
	6.0	0.03	0.21	0.18
	24	0.03	0.46	0.43

^a See Table I, footnote a. ^b See Table I, footnote b. ^c See Table I, footnote c. ^d 25°. ^e Ratio of primary to secondary alcohol, 1:99. ^f Only tertiary alcohol and unreacted epoxide found in gas chromatographic examination.

such nitriles in their reaction with lithium aluminum hydride and this side reaction is believed responsible for the condensations and decreased yields which are observed in these reductions.^{18,20} The results are summarized in Table VII.

Table VII. Reaction of Lithium Trimethoxyaluminumhydride with Representative Amides and Nitriles in Tetrahydrofuran at 0°

Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydride used for reduction ^b
Caproamide	3.0 ^d	1.95	2.51	0.56
	24.0 ^d	1.94	4.15	2.21
Benzamide	0.5 ^d	1.83	1.71	0
	12.0 ^d	1.75	2.93	1.18
	3.0 ^{d,e}	2.04	3.83	1.79
N,N-Dimethylcaproamide	0.5	0	2.09	2.09
	3.0	0	2.05	2.05
N,N-Dimethylbenzamide	0.5	0	1.98	1.98
	3.0	0	2.01	2.01
Capronitrile	0.5	0	1.28	1.28
	3.0	0.04	1.99	1.95
Benzonitrile	0.5	0	1.43	1.43
	3.0	0	1.84	1.84
	6.0	0	1.85	1.85

^a See Table I, footnote a. ^b See Table I, footnote b. ^c See Table I, footnote c. ^d 1.00 mmole of compound. ^e 25°.

Lithium tri-*t*-butoxyaluminumhydride does not react with these compounds under these conditions, either to evolve hydrogen or to transfer hydride for reduction.¹⁰

Nitro Compounds and Their Derivatives. 1-Nitropropane reacted at a moderate pace with the apparent consumption of 6 moles of hydride per mole of compound. Nearly 3 moles of hydrogen was evolved during the reduction, indicating that 3 moles of hydride was being utilized for reduction. This corresponds to reduction to the amine. Nitrobenzene reacted much more sluggishly and required 24 hr. at 25° to take up 4 equiv. of hydride, with 2 hydrides being utilized for reduction and 2 for hydrogen evolution,

(19) L. M. Soffer and E. W. Parrota, *J. Am. Chem. Soc.*, **76**, 3580 (1954); L. M. Soffer and M. Katz, *ibid.*, **78**, 1705 (1956).

(20) R. F. Nystrom, *ibid.*, **77**, 2544 (1955).

corresponding to the stoichiometry expected for reduction to the azobenzene. At 0° there is a relatively rapid uptake of 3 hydrides, corresponding to reduction to azoxybenzene, and no significant further reduction is observed in 24 hr. This suggests that the reduction could be controlled to yield azoxybenzene at 0° and azobenzene at 25°.

The reaction proceeds only very sluggishly with both azobenzene and azoxybenzene at 0°. However, at 25° azoxybenzene is slowly reduced, showing a utilization of 4 hydrides in 48 hr., corresponding to reduction to hydrazobenzene. Azobenzene is also reduced to the hydrazobenzene stage, but the reaction is quite slow and is not yet complete even after 48 hr. at 25°. The results are summarized in Table VIII.

Table VIII. Reaction of Lithium Trimethoxyaluminumhydride with Nitro Compounds and Their Derivatives in Tetrahydrofuran at 0°

Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydride used for reduction ^b
1-Nitropropane ^f	3.0 ^d	2.23	4.76	2.53
	24.0 ^d	2.75	5.48	2.73
	3.0 ^{d,e}	2.99	6.02	3.04
Nitrobenzene ^f	24.0 ^d	1.54	3.26	1.72
	3.0 ^{d,c}	1.54	3.08	1.54
	24.0 ^{d,c}	1.96	4.00	2.04
Azobenzene	48.0 ^{d,c}	2.13	4.27	2.14
	24.0	0.31	0.75	0.44
	48.0 ^e	0.8	1.59	0.79
Azoxybenzene	24.0 ^d	0.33	0.96	0.63
	24.0 ^{e,g}	1.5	3.02	1.52
	48.0 ^{e,g}	1.93	4.00	2.07

^a See Table I, footnote a. ^b See Table I, footnote b. ^c See Table I, footnote c. ^d 1.00 mmole of compound. ^e 25°. ^f The reaction mixtures became gelatinous as the reduction proceeded. ^g 2.5 mmoles of compound, 15.0 mmoles of hydride.

Other Nitrogen Compounds. Cyclohexanone oxime liberated 1 mole of hydrogen, but did not take up any hydride to indicate reduction. On the other hand, phenyl isocyanate rapidly took up 2 moles of hydride, with the third being added at a somewhat slower pace. The uptake of 3 moles of hydride would correspond to reduction to N-methylaniline. Finally pyridine did not react, whereas 4-picoline-N-oxide took up 2 molar equiv. of hydride. These results are summarized in Table IX.

Table IX. Reaction of Lithium Trimethoxyaluminumhydride with Other Nitrogen Compounds in Tetrahydrofuran at 0°

Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydride used for reduction ^b
Cyclohexanone oxime	3.0	1.03	1.09	0
Phenyl isocyanate	0.5	0	1.93	1.93
	3.0	0	2.41	2.41
	6.0	0	2.65	2.65
	3.0 ^d	0	3.08	3.08
Pyridine	3.0	0	0	0
	4-Picoline N-oxide	0.5	0.1	2.27
	3.0 ^d	0.1	2.15	2.05

^a See Table I, footnote a. ^b See Table I, footnote b. ^c See Table I, footnote c. ^d 25°.

Sulfur Compounds. Disulfides reacted with 2 equiv. of the reagent, liberating 1 mole of hydrogen and utilizing 1 mole for reduction. The reaction would therefore appear to be $R_2S_2 + 2LiAlH(OCH_3)_3 \rightarrow 2LiRSAl(OCH_3)_3 + H_2$.

Dimethyl sulfoxide also utilized 2 moles of hydride, 1 for hydrogen evolution and 1 for reduction. This corresponds to reduction to the dimethyl sulfide stage. Methyl *p*-tolyl sulfide showed no reduction in 24 hr.

Diphenyl sulfone appeared to be relatively stable, undergoing only slight reaction in 4 hr. at 25°. Methanesulfonic acid and toluenesulfonic acid liberated hydrogen, but did not undergo reduction under the standard conditions. Finally, cyclohexyl tosylate appeared to undergo slow uptake of hydride. However, gas chromatographic examination of the reaction mixture showed only traces of cyclohexane and cyclohexene. Consequently, it would appear that the hydride is being utilized to reduce the sulfonic ester grouping or being lost through some unknown side reaction.

With the exception of diphenyl disulfide, none of these compounds is reduced significantly by lithium tri-*t*-butoxyaluminumhydride under the standard conditions.¹⁰ Consequently, it would appear that either of these two reagents could be utilized to achieve selective reductions of a number of more reactive groups in the presence of most of these sulfur functions. The experimental data are summarized in Table X.

Table X. Reaction of Lithium Trimethoxyaluminumhydride with Representative Sulfur Derivatives in Tetrahydrofuran at 0°

Compd. ^a	Time, hr.	Hydrogen evolved ^b	Hydride used ^{b,c}	Hydride used for reduction ^b
Di- <i>n</i> -butyl disulfide	0.5	1.02	2.00	0.98
Diphenyl disulfide	0.5	1.05	2.21	1.16
	3.0	1.02	2.14	1.12
Methyl <i>p</i> -tolyl sulfide	24 ^e	0	0.0	0
Dimethyl sulfoxide	12.0	0.49	1.91	1.42 ^f
	3.0 ^e	0.86	2.18	1.32 ^f
Diphenyl sulfone	1.0	0	0.0	0.0
	3.0	0	0.26	0.26
	4.0 ^e	0	0.32	0.32
Methanesulfonic acid ^g	3.0	1.13	1.30	0.17
<i>p</i> -Toluenesulfonic acid (monohydrate)	3.0 ^d	2.98	3.00	0
Cyclohexyl tosylate	3.0 ^e	0	0	0
	6.0 ^e	0	0.11	0.11
	12.0 ^e	0.13	0.33	0.20
	24.0 ^{e,h}	0.20	0.44	0.24

^a See Table I, footnote a. ^b See Table I, footnote b. ^c See Table I, footnote c. ^d 1.00 mmole. ^e 25°. ^f Hydrogen evolved slowly, over 1 to 2 hr. ^g Precipitate observed. ^h Examination of reaction mixture showed only traces of cyclohexane and cyclohexene.

Conclusions

It is evident from this exploratory study that the reagent, lithium trimethoxyaluminumhydride, is an active reducing agent, much closer in its reducing capabilities to lithium aluminum hydride than to the previously investigated lithium tri-*t*-butoxyaluminumhydride. Nevertheless, there are reasons for predicting that it will find useful application in the area of selective reductions.

For such applications lithium aluminum hydride suffers from the disadvantage of having 4 equiv. of hydride per molecule. As the molecule reacts there are produced a succession of reagents with different reactivities and properties. Consequently, it is difficult to select conditions which will serve to reduce clearly one particular group in the presence of other, less reactive groups. With its one reactive center, lithium trimethoxyaluminumhydride should be free of this difficulty.

Finally, the presence of four active centers in lithium aluminum hydride causes cross-linking (through the aluminum atom) in the reduction of polyfunctional molecules. The resulting polymers precipitate from solution and it becomes difficult to complete the reaction. In the present study we were impressed by our observation that almost invariably the solutions remained clear. Of course, we did not utilize a very large selection of polyfunctional molecules. Nevertheless, it appears quite reasonable that such formation of insoluble polymers should be of much less significance in reductions with a reagent, such as lithium trimethoxyaluminumhydride, containing a monofunctional reaction center.

Experimental Section

Materials. The standard list of compounds examined were essentially the same as those previously utilized. All of the compounds used were commercial products of the highest purity available; they were further purified by distillation, recrystallization, or sublimation when necessary.

The tetrahydrofuran was distilled from lithium aluminum hydride. Solutions of lithium aluminum hydride in this solvent were prepared by adding an excess of the hydride to tetrahydrofuran and stirring the mixture for at least 2 hr. under a dry nitrogen atmosphere. The solution was then filtered, under a slight positive nitrogen pressure, through a 2-in. bed of tightly packed Celite prepared on a sintered glass disk previously sealed into a large cylinder for enclosing the solution. In this way crystal-clear solutions of the reagent were prepared and stored in a 1-l. flask with a rubber septum syringe inlet. The hydride concentration was determined by injecting aliquots of the solution into the hydrolyzing mixture of aqueous glycerol and measuring the hydrogen evolved.

Prepared in this manner and vigorously protected from atmospheric moisture, these solutions of lithium aluminum hydride appeared to be stable indefinitely.

We attempted to prepare standard solutions of lithium trimethoxyaluminumhydride for use in these studies, much in the same manner in which we had earlier used standard solutions of the *t*-butoxy reagent. Unfortunately, tests revealed that the solutions were not stable. Over a period of 1 to 2 weeks a white precipitate would form and the hydride concentration of the supernatant liquid would decrease. For example, one solution, which was 0.67 *M* in hydride shortly after preparation, decreased in concentration to 0.57 *M* within 1 week, and a white precipitate was evident.

In one case we attempted to isolate the reagent. However, after evaporation of the tetrahydrofuran, the admission of air into the flask resulted in a mild explosion.

As a result of these experiences, we decided to utilize solutions freshly prepared by the addition of the

theoretical quantity of methanol to a standard solution of lithium aluminum hydride in tetrahydrofuran. Because of the instability of the solutions of the reagent, we were unable to establish with the desired precision the stoichiometry of the reaction in cases when the compound exhibited a relatively slow utilization of hydride.

Procedure. All reactions and solutions were maintained under a dry nitrogen atmosphere. Hypodermic syringes were used for all transfers. The general procedure may be illustrated by reporting in detail one determination, the reduction of di-*n*-butyl sulfide.

In a dry, 50-ml. erlenmeyer flask, fitted with a rubber syringe cap, magnetic stirring bar, nitrogen inlet, and connection to an inverted gas buret *via* a spiral reflux condenser and a Dry Ice vapor trap, was placed 8.0 mmoles of lithium aluminum hydride (32 mmoles of active hydride) in 9.0 ml. of solution. To this stirred solution, maintained at 0° in an ice bath, there was slowly added 0.769 g. of methanol (24 mmoles) in 6.0 ml. of tetrahydrofuran solution, causing the evolution of 24.64 mmoles of hydrogen. To this solution of the reagent then was added 0.357 g. (2.00 mmoles) of di-*n*-butyl sulfide in 5.0 ml. of tetrahydrofuran solution. It was noted that 2.03 mmoles of hydrogen had been evolved by the time the addition had been completed. The reaction mixture was allowed to remain at 0° for 30 min. It was then hydrolyzed by injecting very dilute aqueous sulfuric acid; 3.94 mmoles of hydrogen was collected. In a blank reaction, performed under identical conditions, but without adding the compound, 7.93 mmoles of hydrogen was evolved upon hydrolysis. Therefore, 3.99 mmoles of hydride (7.93 - 3.94) had been utilized by the compound, 2.03 mmoles to form hydrogen and 1.96 mmoles to reduce the 2.00 mmoles of the di-*n*-butyl disulfide.

Reduction of Cinnamaldehyde. The following experiment will illustrate the technique utilized in cases where the reaction product was subjected to gas chromatographic examination.

Utilizing the above techniques, a solution of lithium trimethoxyaluminumhydride in tetrahydrofuran containing 7.46 mmoles of hydride was prepared. To this solution, stirred at 0°, was added 3.5 mmoles of cinnamaldehyde in 5.0 ml. of tetrahydrofuran solution. After 2 hr., a small quantity of ethylene glycol was added, causing the evolution of 0.47 mmole of hydrogen and the precipitation of the lithium and aluminum ions. The organic material was taken up in ether and analyzed by gas chromatography (150-ft. Carbowax 20M capillary column). The analysis showed the presence of 3.44 mmoles of hydrocinnamyl alcohol, a yield of 98%.

Reduction of Styrene Oxide. After the reaction of 2.00 mmoles of styrene oxide with 8 mmoles of the reagent for 3 hr. at 25°, in the usual manner, ethylene glycol was injected. The hydrogen obtained indicated the uptake of 1.94 mmoles of hydride. The organic material was taken up in ether and analyzed on the above column. There was obtained 1.90 mmoles of 1-phenylethanol and 0.02 mmole of 2-phenylethanol, a normalized distribution of 99:1.

Reduction of Caproamide. Caproamide, 1.15 g. (10.0 mmoles), was treated with 80 mmoles of the reagent. There was evolved 19.7 mmoles of hydrogen

over 2 hr. at 0°. The reaction mixture was then allowed to stand at room temperature for 2 hr. The reaction mixture was hydrolyzed using a small quantity of water and alkali and the product was taken up in ether. An aliquot was titrated, indicating a yield of 83%. The solvent was distilled off through a column,

and the solution was subjected to gas chromatographic examination (10% primine on Fluoropak). There was 8.6 mmoles of *n*-hexylamine, a yield of 86%.

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Selective Reductions. VIII. The Stereochemistry of Reduction of Cyclic and Bicyclic Ketones by the Alkoxy-Substituted Lithium Aluminum Hydrides¹

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Contribution from the Richard B. Wetherill Laboratory of Purdue University, Lafayette, Indiana. Received August 20, 1965

*The introduction of alkoxy substituents into lithium aluminum hydride provides a simple, convenient means of modifying the steric requirements and reducing properties of this powerful reducing agent. In order to ascertain the effect of these modifications on the stereochemistry of reduction of monocyclic and bicyclic ketones, a systematic survey was undertaken of the reduction under standard conditions (tetrahydrofuran solution at 0°) of a set of selected monocyclic and bicyclic ketones by lithium aluminum hydride and certain of its alkoxy derivatives. The results reveal that lithium trimethoxyaluminumhydride is more stereoselective than either lithium aluminum hydride or lithium tri-*t*-butoxyaluminumhydride. In the case of bicyclic ketones, the trimethoxy reagent provides the less stable of the two possible alcohols in high isomeric purity. The results confirm the earlier conclusion that the direction of reduction is controlled by the stability of the product in flexible, relatively unhindered ketones and by the steric factor in rigid, sterically congested ketones.*

The stereochemistry of the reduction of ketones by hydride reagents is an interesting problem which has attracted considerable attention.³⁻⁹ In the case of rigid bicyclic ketones, the transfer of hydride from the reagent to the carbonyl group occurs predominantly from the less hindered direction, producing preferentially the more hindered or less stable of the two possible alcohols.⁵ On the other hand, in the less rigid

monocyclic systems, such as 2-methylcyclopentanone⁴ and 2-methylcyclohexanone,³ the transfer of hydride proceeds preferentially to give the more stable of the two possible alcohols.

We had earlier established that the addition of 3 moles of *t*-butyl alcohol to 1 mole of lithium aluminum hydride forms lithium tri-*t*-butoxyaluminumhydride,¹⁰ a reagent with greatly modified reducing characteristics.^{10,11} Similarly, the use of methanol produces lithium trimethoxyaluminumhydride,^{10,12} a more active reducing agent.¹³ Finally, the use of ethanol produces a less homogeneous material,¹² but one which was nevertheless found useful for the selective reduction of nitriles¹⁴ and dimethylamides¹⁵ to aldehydes. It appeared desirable to explore the possible utility of these reagents for the stereoselective reduction of cyclic and bicyclic ketones. Accordingly, we selected a group of model ketones, 2-methylcyclopentanone, 2-methylcyclohexanone, and 2-*t*-butylcyclohexanone for the monocyclics and norcamphor, camphor, and isopinocampone for the bicyclics, and subjected them to reduction by lithium aluminum hydride and its alkoxy derivatives under standard conditions—tetrahydrofuran solution at 0°. The discovery that lithium trimethoxyaluminumhydride is especially effective for the stereoselective reduction of bicyclic ketones led us to extend our study of this reagent to a number of additional bicyclic structures.

Results

In the procedure as it was finally developed, a 0.4 *M* solution of lithium aluminum hydride or of the modified reagent (prepared *in situ* by adding the calculated quantity of alcohol) was cooled to 0°. A measured

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