

TABLE VIII  
REACTION OF *n*-BUTYRONITRILE WITH LITHIUM  
TRITHOXALUMINOHYDRIDE AT 25°

		Diglyme,	THF,	Ether,
		25 ml.	25 ml.	25 ml.
LiAlH <sub>4</sub> solution	molarity	0.46	0.41	0.41
	mmoles	11.5	10.2	10.2
Ethyl alcohol added	ml.	2.00	1.75	1.75
	mmoles	33	30	30
Butyronitrile solution	ml.	10.0	10.0	10.0
	molarity	1.00	1.00	1.00
	mmoles	10.0	10.0	10.0
	Reaction time	min.	15.0	15.0
Aldehyde yield	%	15	25	59

hydrazine gave a derivative corresponding to a 68% yield of *n*-butyraldehyde, melting at 123–124°

**Preparation of Lithium Di-*t*-butoxyomomethoxyaluminumohydride in Ether and Reduction of Butyronitrile.**—Methyl alcohol (0.80 ml., 20 mmoles) was added by means of a hypodermic syringe to 50 ml. of 0.40 *M* lithium di-*t*-butoxyaluminumohydride in ether over a 7-min. period. Hydrogen evolution was measured as 0.58 l. at 25° (737 mm.), or 22.0 mmoles. The solution remained crystal clear. Analysis showed it to be 0.40 *M* in hydride and gave a hydride/aluminum ratio of 1.04/1.00.

From this solution, 20 ml. (8.0 mmoles) was added in 3 min. to 0.576 g. of *n*-butyronitrile (8.3 mmoles) in 10 ml. of anhydrous ether at 0°. After 1 hr., no physical changes were evident in the reaction mixture and no hydrogen evolution had occurred. Upon

hydrolysis, 20 ml. of hydrogen was collected at 25° (738 mm.), 0.8 mmole at STP. *n*-Butyraldehyde, isolated with 2,4-dinitrophenylhydrazine, amounted to 1.56 mmoles, corresponding to a 21.6% yield based upon hydride utilization.

**Preparation of Lithium Triethoxyaluminumohydride in Ether.**—In the apparatus described previously, 32.1 ml. of ethyl alcohol (0.549 mole) was added to 300 ml. of 0.61 *M* lithium aluminum hydride (0.183 mole) in ether over a 45-min. period at room temperature. Hydrogen evolution was measured as 14.68 l. at 25° (739 mm.) or 0.565 mole at STP. Considerable white precipitate formed which was allowed to settle overnight. The clear solution was transferred under dry nitrogen pressure through a sintered glass disk into a clean dry flask. An analysis of a 5-ml. sample of the clear solution gave 77.8 ml. of hydrogen at 26° (740 mm.) or 2.98 mmoles, and 0.9345 g. of aluminum 8-hydroxyquinolate or 2.03 mmoles. The solution was therefore 0.60 *M* in hydride and had a hydride/aluminum ratio of 1.47/1.00.

**Reduction of Capronitrile with Lithium Triethoxyaluminumohydride in Ether.**—This reaction is typical of other nitrile reductions. In the previously described apparatus 10 ml. of 0.65 *M* lithium triethoxyaluminumohydride (6.5 mmoles) solution in ether giving a hydride/aluminum ratio of 1.47/1.00 was added to 0.624 g. of capronitrile (6.4 mmoles) in 5 ml. of ether. The nitrile was weighed out using a hypodermic syringe. The addition time for the hydride solution was 6 min. The reaction mixture immediately took on an orange color and became cloudy and viscous, becoming more viscous as the reaction proceeded. No hydrogen evolution was evident during the reaction. Hydrolysis after 15 min. showed no unreacted hydride. Following the usual aldehyde analysis, 1.0655 g. of 2,4-dinitrophenylhydrazone was obtained, melting at 104–106°, corresponding to 3.81 mmoles of caproaldehyde, a 59.5% yield.

[CONTRIBUTION FROM THE RICHARD B. WETHERILL LABORATORY OF PURDUE UNIVERSITY, LAFAYETTE, IND.]

## Selective Reductions. IV. The Partial Reduction of Nitriles with Lithium Triethoxyaluminumohydride—A Convenient Aldehyde Synthesis<sup>1,2</sup>

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The reaction of nitriles with "lithium triethoxyaluminumohydride" (from the treatment of 1 mole of lithium aluminum hydride in ether with 3 moles of ethanol or 1.5 moles of ethyl acetate) produces an addition product which is readily hydrolyzed to the corresponding aldehyde. A simple study of the variables has led to conditions which provide the basis for a relatively simple, but broadly general, synthetic procedure. Aliphatic and aromatic nitriles of widely varying structural types have been transformed into the aldehydes, generally in yields of 70 to 90%. The factors influencing the selective reduction of nitriles by hydride reagents are discussed.

In the past the Stephen reaction has been the recommended procedure for converting a nitrile into the corresponding aldehyde.<sup>5</sup> However, while it is usually satisfactory for aromatic nitriles, it has proved less than satisfactory for aliphatic derivatives.<sup>6,7</sup>

It was suggested that the controlled reduction of aliphatic nitriles at low temperatures by lithium aluminum hydride provides a convenient synthetic route.<sup>8</sup> Unfortunately, the experimental details have not appeared and numerous workers have experienced difficulty with this synthesis.<sup>9</sup>

(1) Previous studies in this general area of research have appeared in connection with other series. For a survey of the results of these investigations, see H. C. Brown, *J. Chem. Educ.*, **38**, 173 (1961), and H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., Chapter 17.

(2) Based upon a thesis submitted by C. P. Garg in January, 1962, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Research assistant on a grant provided by the Parke, Davis and Co., 1957–1958.

(4) Research assistant on Contract DA-33-008-ORD-992 supported by the Office of Ordnance Research, U. S. Army.

(5) H. Stephen, *J. Chem. Soc.*, 1874 (1925).

(6) E. Mosetti, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 218–257.

(7) C. J. Claus and J. L. Morgenthau, Jr., *J. Am. Chem. Soc.*, **73**, 5005 (1951); J. W. Williams, *ibid.*, **61**, 2248 (1939); E. Lieber, *ibid.*, **71**, 2862 (1949); J. A. Knight and H. D. Zook, *ibid.*, **74**, 4560 (1952); S. Peitra and C. Trincherà, *Gazz. chim. ital.*, **85**, 1705 (1955); C. F. H. Allen, M. R. Gilbert, and D. M. Young, *J. Org. Chem.*, **2**, 231 (1937).

(8) L. Friedman, Abstracts of Papers, 116th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1949, p. 5-M.

(9) N. C. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956.

Recently, sodium triethoxyaluminumohydride has been applied successfully for the conversion of various aromatic nitriles to the corresponding aldehydes, but it was reported that this procedure is not applicable to the selective reduction of aliphatic nitriles.<sup>10</sup>

We have had considerable success in utilizing alkoxy substituted lithium aluminumohydrides, conveniently synthesized by treating lithium aluminum hydride with the appropriate alcohol,<sup>11,12</sup> for selective reductions. Thus, lithium tri-*t*-butoxyaluminumohydride reduces both acid chlorides<sup>13</sup> and phenyl esters<sup>14</sup> into the corresponding aldehydes. Lithium trimethoxyaluminumohydride has proved valuable for the stereoselective reduction of bicyclic ketones.<sup>15</sup> Finally, lithium di- and triethoxyaluminumohydrides have provided a convenient synthetic route from the dimethylamides to the corresponding aldehydes.<sup>16</sup>

It was recently observed that lithium triethoxyaluminumohydride<sup>17</sup> reacts with *n*-butyronitrile and capro-

(10) G. Hesse and R. Schrödel, *Angew. Chem.*, **68**, 438 (1956); *Ann.*, **607**, 24 (1937).

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

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

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

(14) H. C. Brown and P. M. Weissman, manuscript in preparation.

(15) H. C. Brown and H. R. Deck, manuscript in preparation.

(16) H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **81**, 502 (1959); **86**, 1089 (1964).

(17) It is convenient to refer to the product from the reaction of 3 moles of ethanol, or 1.5 moles of ethyl acetate, with 1 mole of lithium aluminum

nitrile to yield the aldehyde in a yield of 60 to 70%.<sup>12</sup> This promising observation suggested the desirability of a systematic exploration of this reaction with the objective of developing a general synthetic procedure, applicable to both aliphatic and aromatic nitriles.<sup>18</sup>

### Results and Discussion

**The Reaction of Various Alkoxy Substituted Lithium Aluminum Hydrides with *n*-Butyronitrile.**—It appeared desirable to explore the relative utility of a number of alkoxy substituted lithium aluminum hydrides as selective reducing agents for nitriles. Accordingly, *n*-butyronitrile was selected as a representative aliphatic nitrile and it was treated with a number of "lithium trialkoxyaluminumhydrides," under standard conditions (ether solution, 0°, 1 hr. reaction time). The reagents were synthesized *in situ* by treating a standard solution of lithium aluminum hydride in ethyl ether with 3 molar equivalents of the alkoxy carrier (alcohol, ester, ketone, or phenol). With the exception of the reagents previously examined,<sup>12</sup> no attempt was made to establish the precise nature of the reagents thus synthesized.

The reagent was treated at 0° with 1 molar equivalent of *n*-butyronitrile (normal addition) and allowed to stand for 1 hr. Methanol was then added (hydrogen evolved, if any, was measured), and an aliquot taken for aldehyde analysis with 2,4-dinitrophenylhydrazine. In the cases of lithium aluminum hydride and lithium diethoxyaluminumhydride the reagents were added to the nitrile (reverse addition) to avoid the possible effects of a temporary excess of the reducing agent.

The results are summarized in Table I.

TABLE I  
YIELDS OF *n*-BUTYRALDEHYDE IN THE REDUCTION OF *n*-BUTYRONITRILE BY ALKOXY SUBSTITUTED LITHIUM ALUMINUM HYDRIDE

Reagent <sup>a</sup>	Mode of addition <sup>b</sup>	Hydride utilization, % <sup>c</sup>	Yield of aldehyde, % <sup>d</sup>
LiAlH <sub>4</sub>	R	100	29
Li(EtO) <sub>2</sub> AlH <sub>2</sub>	R	100	51
Li(MeO) <sub>3</sub> AlH	N	7-10 <sup>e</sup>	10
Li(EtO) <sub>3</sub> AlH	R	100	67
Li(EtO) <sub>3</sub> AlH	N	100	69
Li( <i>n</i> -PrO) <sub>3</sub> AlH	N	100	69
Li( <i>n</i> -BuO) <sub>3</sub> AlH	N	100	77
Li( <i>n</i> -AmO) <sub>3</sub> AlH	N	100	62
Li( <i>n</i> -HexO) <sub>3</sub> AlH	N	100	62
Li( <i>i</i> -BuO) <sub>3</sub> AlH	N	100	46
Li( <i>i</i> -PrO) <sub>3</sub> AlH	N	50-60 <sup>e</sup>	12
Li(C <sub>6</sub> H <sub>11</sub> O) <sub>3</sub> AlH	N	30-40 <sup>e</sup>	13
Li(C <sub>6</sub> H <sub>5</sub> O) <sub>3</sub> AlH	N	6-10 <sup>e</sup>	0
Li(C <sub>6</sub> H <sub>5</sub> O) <sub>3</sub> AlH	N	60-70 <sup>e,f</sup>	0

<sup>a</sup> Prepared by treating lithium aluminum hydride in ether with the alkoxy carrier (alcohol, phenol, ester, or ketone). <sup>b</sup> R, hydride added to nitrile; N, nitrile added to hydride. <sup>c</sup> In all cases 1 mole of nitrile was used per mole of available "hydride." The reaction was carried out for 1 hr. at 0°, except where otherwise indicated. <sup>d</sup> As 2,4-dinitrophenylhydrazine. <sup>e</sup> Reagent largely insoluble in ether. <sup>f</sup> Ether solution refluxed for 1 hr.

**The Reaction of Lithium Triethoxy- and Tri-*n*-butoxyaluminumhydride with Representative Aliphatic Nitriles.**—The above results indicated that the best yields are obtained with lithium triethoxy- (69%), tri-*n*-propoxy- (69%), and tri-*n*-butoxyaluminumhydride (77%). Accordingly, we adopted the first and third of these as our preferred reagents and examined their

utility for the reduction of a group of aliphatic nitriles possessing major structural variations in the  $\alpha$ -position—*n*-butyronitrile, isobutyronitrile, trimethylacetonitrile, and cyclopropanecarbonitrile. We also examined the behavior of these nitriles toward lithium aluminum hydride to have a basis for estimating the advantages of these alkoxy derivatives.

The results are summarized in Table II.

TABLE II  
ALDEHYDE YIELDS IN THE REDUCTION OF NITRILES BY LITHIUM ALUMINUM HYDRIDE AND SOME ALKOXY DERIVATIVES

Nitrile <sup>a</sup>	Yield of aldehyde, % <sup>b</sup>		
	LiAlH <sub>4</sub>	Li-(EtO) <sub>2</sub> -AlH <sub>2</sub>	Li-( <i>n</i> -BuO) <sub>3</sub> -AlH
<i>n</i> -Butyronitrile	29	51	69
Isobutyronitrile	59	79	81
Trimethylacetonitrile	68		89
Cyclopropanecarbonitrile	38-48 <sup>d</sup>		69

<sup>a</sup> One mole of nitrile was used per mole of available "hydride." The reactions were carried out by the procedures used for the experiments listed in Table I. <sup>b</sup> By analysis with 2,4-dinitrophenylhydrazine. <sup>c</sup> 0.5 hr. at 0°, followed by 0.5 hr. at 36° (reflux). The reaction was incomplete under the usual conditions (1 hr. at 0°). <sup>d</sup> L. I. Smith and E. R. Rogier, *J. Am. Chem. Soc.*, **73**, 4047 (1951); isolated yields.

It is evident that both lithium triethoxyaluminumhydride and lithium tri-*n*-butoxyaluminumhydride give consistently good yields with all four nitriles. On the other hand, it was observed that the reaction of lithium tri-*n*-butoxyaluminumhydride with trimethylacetonitrile was incomplete under the usual conditions (1 hr. at 0°), and required refluxing of the ether solution to achieve completion. It is obviously undesirable, in a general procedure, to require alteration of the conditions for individual reactants. Moreover, it was apparent that hydrolysis of the reaction intermediate would produce a mixture of 3 moles of alcohol with approximately 1 mole of aldehyde. It is obviously much easier in most cases to remove the more volatile, water-soluble ethyl alcohol from the aldehyde product than the less volatile, water-insoluble *n*-butyl alcohol. Accordingly, we decided to adopt lithium triethoxyaluminumhydride as our preferred reagent, with lithium tri-*n*-butoxyaluminumhydride in reserve for cases where the presence of ethanol might be undesirable.

An unexpected development of these experiments was the discovery that reasonable yields of aldehydes could be obtained from aliphatic nitriles containing one or more branches in the  $\alpha$ -position by the use of lithium aluminum hydride itself.

**Effect of Reaction Conditions on Aldehyde Yield.**—It appeared desirable to explore in detail the effect on the aldehyde yield of a number of possible variables in the reaction of lithium triethoxyaluminumhydride with *n*-butyronitrile.

First, it is evident that there is no significant difference in the yield realized whether the hydride reagent is added to *n*-butyronitrile at 0°, or whether the nitrile is added to the hydride (Table I). The latter procedure is obviously preferable, since it permits the synthesis and utilization of the reagent in the same flask.

The reagent was prepared at -80, 0, and 25°, brought to 0°, and treated with the nitrile. The yield of aldehyde was 52% for reagent prepared at -80°, 69% for the reagent synthesized at 0°, and 62% for reaction obtained at 25°. Fortunately, this result also favors a simple procedure—the reagent is prepared by adding ethyl alcohol or ethyl acetate prefer-

hydride, as "lithium triethoxyaluminumhydride" even though the evidence is that this is merely the major component, with significant quantities of the diethoxy derivative also present. See discussion in ref. 12.

(18) A preliminary communication reporting this development was published previously: H. C. Brown, C. J. Shoaf, and C. P. Garg, *Tetrahedron Letters*, No. 3, 9 (1959).

ably to the lithium aluminum hydride solution maintained at  $0^\circ$ . After the reagent is prepared, the nitrile is added without altering the temperature of the reaction flask.

*n*-Butyronitrile was treated with the hydride and the reaction product permitted to stand for various lengths of time at  $0^\circ$  before it was hydrolyzed and the aldehyde yield determined. The yield decreased with increasing time: 69% for 0.25 hr., 67% for 1.0 hr., 45% for 3 hr. It is evident that the reaction mixture should be hydrolyzed in a period no longer than the recommended 1-hr. reaction time.

Finally, we varied the ratio of nitrile to hydride. However, optimum results were realized with the theoretical ratio of 1 mole of nitrile to 1 mole of lithium triethoxyaluminumhydride.

**Scope of the Reaction.**—The above results lead to the following recommended procedure. In a round-bottom flask fitted with a stirrer, thermometer, pressure-equalized dropping funnel, and condenser, flushed with nitrogen, is placed an appropriate quantity of a standardized solution of lithium aluminum hydride in ethyl ether (approximately 1.0 *M*). The flask is immersed in an ice-bath. To the stirred reaction mixture (at  $0^\circ$ ) the appropriate quantity of ethyl acetate (1.5 moles per mole of lithium aluminum hydride) is added over a period of 15 min.<sup>19</sup> The solution becomes somewhat opaque because of the formation of a small quantity of white, insoluble material. The reaction is stirred for an additional 15 min., and then the nitrile (1 mole per mole of reagent) is introduced into the reaction mixture. There is a rapid exothermic reaction, and the solution becomes highly viscous. The reaction mixture is stirred for no more than 1 hr., and is hydrolyzed with 5 *N* sulfuric acid for isolation of the aldehyde, or with methanol if the objective is to analyze an aliquot with 2,4-dinitrophenylhydrazine.

This procedure was applied to seventeen representative nitriles. The results are summarized in Table III.

TABLE III

YIELDS OF ALDEHYDES IN THE REDUCTION OF REPRESENTATIVE NITRILES BY LITHIUM TRIETHOXYALUMINOHYDRIDE

Nitrile	Yield of aldehyde, %	
	By analysis with 2,4-dinitrophenylhydrazine	By isolation
<i>n</i> -Butyro-	69	
<i>n</i> -Capro-	69	55
Isobutyro-	81	
Trimethylaceto-	89	74
Phenylaceto- <sup>a</sup>	0	
$\gamma$ -Phenoxybutyro-	66	
$\gamma$ -Phenylbutyro-	73	
Cyclohexanecarbo-	76	71
Cyclopropanecarbo-	69, 89 <sup>b</sup>	66 <sup>b</sup>
Cinnamo-	61	
Benzo-	96	76
<i>o</i> -Tolu-	87	
<i>o</i> -Chlorobenzo-	87	
<i>p</i> -Chlorobenzo-	92	84
<i>p</i> -Aniso-	81	
$\alpha$ -Naphtho-	80	
Nicotino-	58 <sup>c</sup>	
Adipo-	60	

<sup>a</sup> Ref. 12. <sup>b</sup> Lithium tri-*n*-butoxyaluminumhydride was used for the reduction. <sup>c</sup> Apparent low yield of aldehyde due to the solubility of the 2,4-dinitrophenylhydrazone in hydrochloric acid.

The results must be considered quite satisfactory. In spite of the wide range of structures examined, the

(19) For larger quantities a longer addition time and a colder bath will be required to control this exothermic reaction.

yields are generally in the range of 70 to 90%, with but one exception, phenylacetonitrile. This derivative appears to react with the reagent preferentially at the acidic  $\alpha$ -hydrogen.<sup>12</sup> In contrast, the yields realizable by the application of the Stephen's procedure to the same aldehydes are very good in some cases, but very poor in others (Table IV).

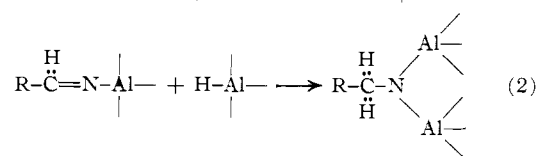
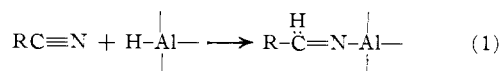
TABLE IV

COMPARISON OF ALDEHYDE YIELDS FROM NITRILES BY THE STEPHEN REACTION AND THE REDUCTION WITH LITHIUM TRIETHOXYALUMINOHYDRIDE

Nitrile	Yield of aldehyde, %	
	Stephen reduction <sup>a</sup>	$\text{Li}(\text{EtO})_3\text{AlH}$ reduction
Capro-	0	69
Isocapro-	31	
Isobutyro-		81
$\gamma$ -Phenoxybutyro-		66
Cinnamo-	40, 65	61
Benzo-	97	96
<i>o</i> -Chlorobenzo-	Nearly quant.	87
<i>p</i> -Chlorobenzo-	Nearly quant.	92
<i>o</i> -Tolu-	9	87
$\alpha$ -Naphtho-	7	80

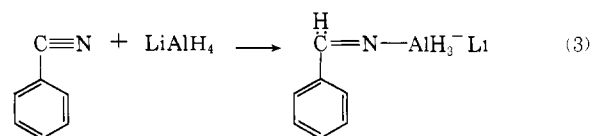
<sup>a</sup> Ref. 6.

**Theoretical Considerations.**—It is appropriate to consider here the factors which appear to control the reduction of a nitrile to the amine stage or to the aldehyde. It is apparent that the reduction to the amine stage requires the uptake of 2 equivalents of "hydride" from the reagent (2), whereas the aldehyde synthesis must involve the uptake of 1 mole of hydride, followed by hydrolysis of the intermediate imine derivative (1).



The reactions of lithium aluminum hydride are so fast that there has been relatively little quantitative work on the rates of its reactions. On the other hand, the related derivative, sodium borohydride, reacts considerably faster with ketones than with esters, and faster with imines than with nitriles.<sup>1</sup> Consequently, it is not surprising that in the treatment of 4 moles of *n*-butyronitrile with 1 mole of lithium aluminum hydride most of the reaction proceeds *via* a double addition, resulting in only a modest yield of aldehyde (Table II).

The steric and electronic characteristics of the phenyl group appear to stabilize the initial imine derivative, permitting the isolation of excellent yields of aldehyde from the reaction of 1 mole of the aromatic nitrile with 1 mole of lithium aluminum hydride<sup>12</sup> (3).

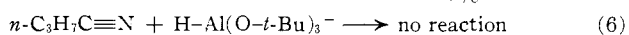
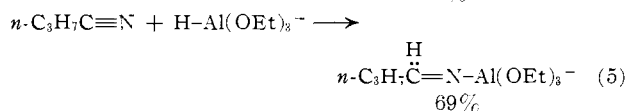
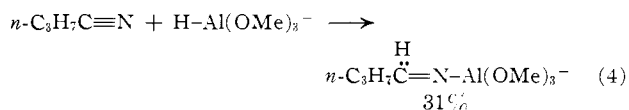


It is pertinent that the phenyl substituents in acetophenone and benzophenone have been observed to decrease greatly the reactivity of the carbonyl group toward sodium borohydride.<sup>20</sup>

(20) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84**, 373 (1962).

Branching in the  $\alpha$ -position evidently favors the first addition over the second, resulting in improved aldehyde yields (Table II). Presumably, this is the result of the increased inductive influence of the branched alkyl groups and their larger steric requirements in reducing the rate of nucleophilic attack at the imine carbon.<sup>20</sup>

Similarly, it appears that an increase in the steric requirements of the substituents attached to aluminum also favors a single addition (4, 5). If the steric requirements of the substituents are too large, even the first stage fails to occur (6).



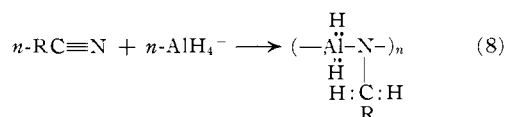
This interpretation does not provide a complete accounting of the available information. It fails to explain why the reduction is favorable in ethyl ether, but results in very poor yields in the better solvating media, tetrahydrofuran and diglyme.<sup>12</sup> Moreover, it does not account for the report that sodium triethoxyaluminumhydride does not reduce aliphatic nitriles to aldehydes in satisfactory yields.<sup>10</sup> These results indicate that both the lithium ion and a poor solvating medium are essential features of the selective reduction.

It is possible to rationalize these observations on the basis that the lithium ion (solvated to a greater or lesser degree by ether) becomes coordinated to the nitrogen atom of the imine derivative and assists in protecting the double bond from a second addition (7).



Sodium would be much less prone to form a stable coordinate linkage of this kind. Furthermore, the excellent coordinating solvents, tetrahydrofuran and diglyme, should compete more effectively than ether with the imine nitrogen for the lithium ion. Consequently, the present aldehyde synthesis evidently depends for its success on a number of critical factors.

In the reduction of nitriles to amines, it appears that only two of the four hydrides in lithium aluminum hydride are readily available for the reaction.<sup>21,22</sup> The observation that good yields of aldehydes may be realized in the reaction of benzonitrile with lithium aluminum hydride,<sup>12</sup> and of *n*-butyronitrile with lithium di-*t*-butoxyaluminum hydride,<sup>12</sup> both on a 1:1 molar basis, indicates that the second addition does not occur intramolecularly, but involves a second molecule. Consequently, the reaction must largely proceed to the formation of a linear polymer (8), and the low availability of the remaining hydrides must in large part be the result of physical factors.



The reduction of aliphatic nitriles with lithium aluminum hydride is accompanied in many cases by the liberation of hydrogen, presumably from a reaction of an active  $\alpha$ -hydrogen in the nitrile with the hy-

dride reagent.<sup>21-25</sup> This reaction results in some condensation of the nitrile and the appearance of 1,3-diamines in the product.

In the present study we observed relatively little hydrogen evolution. This suggests that the use of the appropriate alkoxy substituted lithium aluminum hydride may be useful for the reduction of nitriles to amines, minimizing the effect of this side reaction and circumventing the difficulties arising from the formation of polymeric intermediates.<sup>26</sup>

### Experimental

**Materials.**—All chemicals were commercial products which were carefully purified by standard methods before use. Special care was given to the drying of the alcohols and esters, utilizing either calcium hydride or potassium carbonate as drying agents. Lithium aluminum hydride solutions in ether were prepared and used as clear solutions. The composition of the solutions was established by the analysis of hydride (by hydrolysis) and confirmed by analysis for aluminum (with 8-hydroxyquinoline).

The nitriles were either commercial products, distilled or recrystallized before use, or they were synthesized by standard methods.

All apparatus was flamed in a dry nitrogen atmosphere and allowed to cool in that atmosphere prior to use.

**Reaction of *n*-Butyronitrile with Lithium Triethoxyaluminumhydride.**—The following experiment is typical of the procedures utilized in the small-scale exploratory studies. In a flask, fitted with stirrer, thermometer, condenser, and a dropping funnel, flushed with nitrogen, was placed 26.5 mmoles of lithium aluminum hydride in 27 ml. of ether. Into this stirred solution, ethyl acetate (3.5 g., 39.8 mmoles) was added over a period of 15 min. at ice-bath temperature. After stirring for another 15 min., 1.83 g. (26.5 mmoles) of *n*-butyronitrile was added to this reagent. There was a rapid exothermic reaction and the solution became quite viscous. The reaction mixture was stirred for an additional hour at 0° and then treated with methanol. Analysis of an aliquot with 2,4-dinitrophenylhydrazine<sup>27</sup> indicated a yield of 69%; m.p. of the hydrazone, as isolated, 118° (lit.<sup>28</sup> 122°).

**Reductions with Lithium Triethoxyaluminumhydride on a Preparative Scale.**—The following procedures described for trimethylacetone nitrile and capronitrile are representative.

**A. Trimethylacetone nitrile.** In a 1-l. flask equipped with a condenser, stirrer, thermometer, and dropping funnel was placed 0.3 mole of lithium aluminum hydride in ether (300 ml.). A nitrogen atmosphere was maintained throughout the reaction. To this stirred solution 0.45 mole of ethyl acetate was added over a period of 75 min., maintaining the temperature at 3–7°. The reaction mixture was stirred for an additional 30 min. Trimethylacetone nitrile (24.9 g., 0.3 mole) was added in 5 min. The temperature rose to 10°, with the formation of a highly viscous solution. The reaction mixture was stirred for 1 hr. (at 0°), and then decomposed with 300 ml. of 5 *N* sulfuric acid. The ether layer was separated and the aqueous layer extracted three times with 50-ml. portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution followed by eight washings with 30-ml. portions of cold water to remove ethanol. Analysis of an aliquot with 2,4-dinitrophenylhydrazine indicated a yield of 77% (the low yield is presumably due to the washings). The ether extract was dried over sodium sulfate and distilled through a Todd fractionating column. Pivalaldehyde, b.p. 70–72.5 at 747 mm., *n*<sub>D</sub><sup>20</sup> 1.3794 (lit.<sup>29</sup> b.p. 71–74° at 730 mm., *n*<sub>D</sub><sup>20</sup> 1.3791), was isolated in a yield of 25.8 g., 74%.

**B. Capronitrile.**—Lithium triethoxyaluminumhydride (0.3 mole) was prepared in 300 ml. of ether. To the solution (–10°) of the reagent was added 29.1 g. (0.3 mole) of capronitrile in 5 min. The reaction temperature rose to 12° in 10 min. with the formation of a viscous solution. It was allowed to stir for another 50 min. at 3°. The reaction mixture was decomposed by 300 ml. of 5 *N* sulfuric acid. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and water and dried over sodium sulfate. Gas chromatographic examination indicated a 68% yield of aldehyde and nitrile. Distillation through a 12-in. Vigreux column gave 16.6 g., a 55.4% yield, of caproaldehyde, b.p. 51–55° at 53–55 mm.,

(23) L. M. Soffer and E. W. Parrotta, *ibid.*, **76**, 3580 (1954)

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

(25) H. E. Zaugg and B. W. Horrom, *Anal. Chem.*, **20**, 102 (1948)

(26) This possibility is currently under investigation.

(27) H. A. Iddles and C. E. Jackson, *Ind. Eng. Chem., Anal. Ed.*, **6**, 454 (1934); H. A. Iddles, A. W. Low, B. D. Rosen, and R. T. Hart, *ibid.*, **11**, 103 (1939).

(28) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948 pp. 229–230.

(29) K. N. Campbell, *J. Am. Chem. Soc.*, **59**, 1982 (1937)

(21) I. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

(22) L. M. Soffer and M. Katz, *ibid.*, **78**, 1705 (1956).

$n_D^{20}$  1.4042, and 2.5 g., 8.5% yield, of capronitrile, b.p. 73° at 53–55 mm.,  $n_D^{20}$  1.4070.

**C. Cyclohexanecarbonitrile.**—Cyclohexanecarboxaldehyde, b.p. 63–66° at 23–24 mm.,  $n_D^{20}$  1.4507, was obtained in 71% yield.

**D. Benzonitrile.**—Benzaldehyde, b.p. 81–82° at 31 mm.,  $n_D^{20}$  1.5452, was obtained in 76% yield.

**E. *p*-Chlorobenzonitrile.**—Lithium triethoxyaluminumhydride (0.238 mole) was prepared in 238 ml. of ether. Into this stirred solution was added 32.7 g. (0.238 mole) of *p*-chlorobenzonitrile all at once at ice-bath temperature. The reaction mixture was hydrolyzed, after an hour, with 200 ml. of 5 *N* sulfuric acid. Ether was distilled and the resulting aqueous layer was steam distilled. *p*-Chlorobenzaldehyde, m.p. 47–47.5°, was obtained (27.9 g.) in 83.5% yield. Recrystallization from hot water did not change the m.p.

**Reduction with Lithium Tri-*n*-butoxyaluminumhydride on a Preparative Scale.**—The use of lithium tri-*n*-butoxyaluminumhydride is useful in cases where the removal of ethyl alcohol from the product offers difficulties.

**Cyclopropanecarbonitrile.**—In a 1–1, three-necked, round-bottom flask equipped with a condenser, dropping funnel, and stirrer, flushed with nitrogen, was placed 0.3 mole of lithium aluminum hydride in 300 ml. of ether (1 *M* solution). To this solution was added dropwise over a period of 75 min., 0.9 mole (66.6 g.) of 1-butanol, maintaining the temperature at –10 to –5°. The reaction was stirred for another 15 min. To this solution (–10°) was added 20.1 g. (0.3 mole) of cyclopropanecarbonitrile over 15 min., the temperature rising to 8°. The reaction was stirred for 1 hr. at 3° (ice bath) and then decomposed by 300 ml. of 5 *N* sulfuric acid. The ether layer was separated and the heterogen-

eous aqueous layer was extracted three times with 25-ml. portions of ether. The combined ether extracts were washed with sodium bicarbonate solution and water and then dried over sodium sulfate. The ether was concentrated through a small Vigreux column. The ether distillate was extracted with 130 ml. of sodium bisulfite solution (40%) to remove as adduct any aldehyde which would have passed over with the ether. Finally this solution was used to make the adduct of the aldehyde. This adduct was extracted four times with 35-ml. portions of ether to remove 1-butanol. It was decomposed by 42 g. of sodium bicarbonate suspended in 50 ml. of water at 0°. Cyclopropanecarboxaldehyde was steam distilled and the distillate was extracted with ether. The ether was dried over sodium sulfate and concentrated in a Todd fractionating column. Cyclopropanecarboxaldehyde, b.p. 97–98° at 726 mm.,  $n_D^{20}$  1.4302 (lit.<sup>30</sup> b.p. 97–100° at 740 mm.,  $n_D^{20}$  1.4302), was isolated in a yield of 13.8 g., 65.7%.

**2,4-Dinitrophenylhydrazones.**—Three of the 2,4-dinitrophenylhydrazones have not been previously described in the literature: (1) The bis-2,4-dinitrophenylhydrazone of adipaldehyde, crystallized from glacial acetic acid, m.p. 190°. *Anal.* Calcd.: C, 45.57; H, 3.82; N, 23.62. Found: C, 45.31; H, 3.99; N 21.11. (2) The 2,4-dinitrophenylhydrazone of  $\gamma$ -phenoxybutyraldehyde, crystallized from ethanol, m.p. 112–113°. *Anal.* Calcd.: C, 58.52; H, 4.912; N, 17.06. Found: C, 58.50; H, 5.02; N, 17.22. (3) The 2,4-dinitrophenylhydrazone of  $\gamma$ -phenoxybutyraldehyde, crystallized from ethanol, m.p. 96°. *Anal.* Calcd.: C, 55.8; H, 4.68; N, 16.27. Found: C, 55.67; H, 4.80; N, 16.42.

(30) H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **83**, 4549 (1961)

[CONTRIBUTION FROM THE RICHARD B. WETHERILL LABORATORY OF PURDUE UNIVERSITY, LAFAYETTE, IND.]

## Selective Reductions. V. The Partial Reduction of Tertiary Amides by Lithium Di- and Triethoxyaluminumhydrides—A New Aldehyde Synthesis *via* the Dimethylamides<sup>1,2</sup>

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The reduction of tertiary amides by lithium di- and triethoxyaluminumhydrides, conveniently synthesized *in situ* by the reaction of ethyl alcohol with lithium aluminum hydride, was explored as a useful synthetic route from the carboxylic acid to the corresponding aldehyde. With the exception of the highly hindered amide derivative *N,N*-diisopropyl-*n*-butyramide, a wide variety of *n*-butyryl tertiary amides were readily converted into *n*-butyraldehyde in satisfactory yields. The results realized for the simplest derivative, *N,N*-dimethyl-*n*-butyramide, were especially favorable. Moreover, the same procedure served to convert the dimethylamides of *n*-butyric acid, isobutyric acid, pivalic acid, and benzoic acid into the corresponding aldehydes in yields of 80 to 90%. Accordingly, the scope of this new aldehyde synthesis was explored by applying it to 24 representative acid derivatives. With the exception of conjugated unsaturated derivatives, such as crotonic and cinnamic, wide variation in structural type could be tolerated, with the corresponding aldehyde being produced in yields from 60 to 90%.

The ready availability of carboxylic acids makes it highly desirable to have available convenient synthetic routes from such acids to the corresponding aldehydes. The catalytic hydrogenation of acid chlorides<sup>4</sup> and the Stephen reduction of nitriles<sup>5</sup> have served for many years, but suffer from a number of disadvantages.

The preparation of aldehydes from various acid derivatives by reduction with lithium aluminum hydride has been widely studied.<sup>6</sup> The most successful developments in this direction have involved the selective reduction of a number of tertiary amides. Thus, Wittig and Hornberger synthesized a series of unsaturated aldehydes,  $C_6H_5(\dot{C}H=CH)_nCHO$  ( $n = 1, 2, 4,$

and 5), by the partial reduction of the corresponding *N*-acylcarbazoles with lithium aluminum hydride.<sup>7</sup> Similarly, Weygand and his co-workers demonstrated that the *N*-methylanilides could be utilized to produce a wide variety of aldehydes in good yields (60 to 90%).<sup>8</sup> Moreover, it has been established that the partial reduction of the 1-acyl-3,5-dimethylpyrazoles<sup>9a</sup> or the *N*-acylimidazoles<sup>9b</sup> gives a general synthetic route to aldehydes from carboxylic acids. Finally, we recently reported that lithium aluminum hydride reacts with 1-acylaziridines to provide a synthetic route to the aldehyde.<sup>10</sup>

In these syntheses it is evident that the electronic and steric characteristics of the tertiary amide group are being utilized as a means of controlling the exceedingly powerful reducing action of the reagent, lithium aluminum hydride. The introduction of alkoxy substituents into lithium aluminum hydride provides a simple method of modifying the reducing power of the

(7) G. Wittig and P. Hornberger, *Ann.*, **677**, 11 (1952).

(8) (a) F. Weygand and G. Eberhardt, *Angew. Chem.*, **64**, 458 (1952);

(b) F. Weygand, G. Eberhardt, H. Linden, F. Schäfer, and I. Eigen, *ibid.*, **65**, 525 (1953); (c) F. Weygand and H. Linden, *ibid.*, **66**, 174 (1954).

(9) (a) W. Ried and F. J. Königstein, *ibid.*, **70**, 165 (1958); (b) H. A. Staab and H. Braeunling, *Ann.*, **664**, 119 (1962).

(10) H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **83**, 4549 (1961)

(1) Based upon a thesis submitted by Akira Tsukamoto in June, 1959, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) A preliminary communication reporting some of the results in this paper was published earlier: H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **81**, 502 (1959).

(3) Research assistant on a grant provided by the Eli Lilly and Co., 1957–1959.

(4) K. W. Rosenmund, *Ber.*, **51**, 585 (1918).

(5) H. Stephen, *J. Chem. Soc.*, 1874 (1925).

(6) For a general review of these synthetic routes from carboxylic acid derivatives to the corresponding aldehydes, see E. Mosettig, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, 1954, pp. 218–257.