Reduction of Organic Compounds by Alkoxyaluminoxyhydrides

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The introduction of alkoxy groups into lithium aluminoxyhydride, sodium aluminoxyhydride, and aluminium hydride usually results in modification of the steric requirements and thus of the reducing properties of the parent hydrides. The reactions of these alkoxyaluminoxyhydrides with organic compounds are reviewed with special regard to selective reductions of functional groups in the presence of other reducible substituents, to partial reductions of esters, acid halides, amides, and nitriles to aldehydes, to stereospecific reductions of cyclic ketones and steroids and to hydro-geolytic reactions of these alkoxyaluminoxyhydrides in comparison with common metal hydrides.

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1. Introduction

Alkali metal aluminoxyhydrides and alkali metal borohydrides display extremely different reactivities when applied as reducing agents. Since their discovery more than 20 years ago, considerable work has been devoted to modify the reducing ability of lithium aluminoxyhydride as well as to increase that of sodium borohydride and to thus fill the gap between the most widely used representatives of these groups of metal hydrides. Whereas the reducing action of sodium borohydride, limited practically to aldehydes, ketones, and acid chlorides, could be greatly increased by the addition of certain metal salts and by the introduction of alkoxy groups into the hydride, modification of the powerful reducing capacity of lithium aluminoxyhydride by the introduction of alkoxy substituents led to a series of lithium alkoxyaluminoxyhydrides with different reactivity and selectivity. A wide variety of alkoxyhydrides with differentiated reactivities has similarly been derived from sodium aluminoxyhydride and aluminoxyhydride.

Of the great number of alkoxyaluminoxyhydrides, especially the methoxy, ethoxy, and t-butoxy derivatives of lithium aluminoxyhydride find regular application in synthetic organic chemistry. In many cases, the alkoxy derivatives of aluminoxyhydride and sodium aluminoxyhydride as well as the recently introduced 2-methoxyethoxy derivative of the latter are also utilized with success.

This review deals with the preparation and properties of these alkoxyaluminoxyhydrides with regard to their selectivity and stereospecificity in reduction reactions. For comprehensive reviews including also other metal hydrides see Ref.1.
2. Preparation of Alkoxyalumino- and Alkoxyalumino-hydrides

2.1. Lithium Alkoxyalumino-hydrides

The reagents are conveniently prepared in situ by treating standardized solutions of lithium aluminohydride (LiAlH₄) in ether, tetrahydrofuran, or diglyme with a definite amount of the corresponding alkyloxy compound, such as alcohol, ester, ketone, or phenol. Of the great number of reagents prepared by this route only the most important are discussed further.

Addition of 3 molar equivalents of methanol to LiAlH₄ in tetrahydrofuran or diglyme leads to a stable solution of LiAlH₄(OCH₃)₃, which shows no tendency to disproportionate. Addition of a fourth mole of methanol yields LiAl(OCH₃)₄, which is precipitated from the solution. A different course of the methoxyalumino-hydride formation was observed in ether, in which addition of 3 equivalents of methanol leads to insoluble LiAlH₄(OCH₃)₂₂.₃.₄

By treating LiAlH₄ in ether, tetrahydrofuran, or diglyme with 2 mol of ethanol, nearly pure LiAlH₄(OCH₃)₂ is formed; the reaction with 3 mol of ethanol affords a product which appears to be largely LiAlH₄(OCH₃)₃, accompanied, however, by significant amounts of the diethoxy and tetraethoxy derivatives for the sake of simplicity, the formulae LiAlH₄(OCH₂)₃ and LiAlH₄(OCH₃)₂ will be used throughout this review for the adducts prepared by addition of 2 or 3 mol of ethanol, respectively, to LiAlH₄. In both cases, ethanol can be replaced by the half amount of ethyl acetate²–⁶.

Unlike 2-propanol, the adducts of which with LiAlH₄ always disproportionate to the insoluble tetra-i-propoxy derivative and to the parent hydride, t-butanol (3 mol) gives with LiAlH₄ in tetrahydrofuran as solvent stable solutions of LiAlH₄(OH–t-C₄H₉)₃,₅,₈,₉; according to association measurements, this compound appears to be monomeric over a wide range of concentrations¹⁰.

Sometimes, separate preparation and isolation of this hydride is recommended rather than the formation in situ¹¹; isolated in pure form, LiAlH₄(OH–t-C₄H₉)₃ can be sublimed under vacuum at 280° without decomposition⁹.

Adducts with other hydroxy compounds are also formed. Thus, LiAlH₄ reacts with sterically hindered 2,6-di-t-butylphenol under evolution of only 2 equivalents of hydrogen; and 9,10-dihydro-9,10-ethano-9-anthrol liberates 3 equivalents of hydrogen and thus resembles t-butanol. The complex hydride resulting from the reaction of LiAlH₄ with di-ethylene glycol monoethyl ether can be used for reductions at temperatures up to 200 °C.

Comparison of the I.R. spectra of different lithium alkoxyalumino-hydrides

\[
\text{LiAlH₄(OR)ₙ} \quad R = CH₃, C₂H₅, t-C₄H₉ \quad n = 1–4
\]

shows that monoalkoxy-hydrides exhibit interactions of the form Al—O—Al, whereas dialkoxy-hydrides show little tendency to form secondary valences. Bands associated with Al—H vibrations are found between 600 and 800 cm⁻¹ as well as between 1500–1800 cm⁻¹. The spectra of LiAl(OR)₄ are much simpler than those of the less symmetric hydrogen-containing alkoxyalumino-hydrides.¹⁴

Comparison of the I.R. spectra of independently prepared LiAlH₄(OH–t-C₄H₉)₃ (Al—H stretching band at 1760 cm⁻¹ and no shoulder or weak band at 1860 cm⁻¹) and AlH₄(OH–t-C₄H₉)₂ (Al—H stretching band at 1860 cm⁻¹) indicates that the equilibrium concentration of the latter hydride in the tetrahydrofuran solutions of the former is less than 1°/₁₀. This result contrasts with the earlier assumption that in solutions of LiAlH₄(OH–t-C₄H₉)₂ an equilibrium exists according to Scheme A and that AlH₄(OH–t-C₄H₉)₃ is thus the actual reducing species in reductions with LiAlH₄(OH–t-C₄H₉)₃.¹⁵,¹⁶

\[
\text{LiAlH₄(OH–t-C₄H₉)₃} \quad \overset{\text{LiAlH₄(OH–t-C₄H₉)₂}}{\Rightarrow} \quad \text{AlH₄(OH–t-C₄H₉)₃} \quad \overset{\text{LiAlH₄(OH–t-C₄H₉)₂}}{\Rightarrow} \quad \text{LiO–t-C₄H₉}
\]

Scheme A

Lithium mono-, di-, and tri-t-butoxy alumino-hydrides all show similar N.M.R. spectra.¹⁷

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2.2. Alkoxyaluminoxyhydrates

Depending on the ratio of reactants, slow addition of a calculated quantity of alcohol to AlH₃ in tetrahydrofuran affords alkoxyaluminoxyhydrates of the type

\[ [\text{RO} \cdot \text{AlH₃-n}]_n \quad R = \text{CH₃}, \text{C₂H₅}, \text{t-C₃H₇}, \text{n-C₄H₉}, \text{t-C₆H₄} \]

\[ n = 1, 2, 3 \quad x \geq 2 \]

Ref. 10, 18, 19, 20.

The stability of AlH₂(OR) towards disproportionation into AlH₃ and AlH(OR)₂ decreases with increased branching of the alkyl side chain at C-α; the degree of association (x) decreases in the same order. The stability of AlH(OR)₂ increases in the reverse order. In tetrahydrofuran, AlH(OR)₂ exist as dimers (1), trimers, or insoluble polymers (2).  

\[ \text{t-C₆H₄-O-} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \]

\[ \text{t-C₆H₄-O-} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \]

[AlH(OR)₂]₂

\[ [\text{AIH(O-t-C₆H₄)₂}]_2 \]

2

3. Reactions of Alkoxyaluminoxyhydrates

3.1. Reactions with Active Hydrogen Compounds

LiAlH(OCH₃)₃ 33 and NaAlH₃(OCH₂CH₂OH)₃ 34 react rapidly with alcohols, phenols, thiols, and primary amines under evolution of 1 and 2 mol of hydrogen, respectively. Benzyl alcohols containing electron-donor groups on the ring which facilitate formation of a resonance-stabilized carbonium ion readily undergo hydrogenolysis to the corresponding methyl derivatives when treated with NaAlH₃(OCH₂CH₂OH)₃ in xylene at elevated temperatures (140°) 35-38. Addition of equimolar amounts of methanol or water converts NaAlH₃(OCH₂CH₂OH)₃ into half-methanolized or half-hydrolyzed hydrides of unknown structure which show markedly increased reducing power in comparison with that of the parent hydride (see Section 3.9).

On the other hand, LiAlH(O-t-C₆H₄)₃ reacts only slowly with primary and secondary alcohols, and even more slowly with phenols and thiols; it is practically inert towards tertiary alcohols as well as primary amines 9, 39. According to Brown et al., the following reactions (Scheme B) take place simultaneously between this hydride and primary alcohols:

\[ \text{LiAlH(O-t-C₆H₄)₃} + R-\text{CH₂-OH} \]

\[ \text{H₂} + \text{LiAlH(O-t-C₆H₄)₃} \]

\[ \text{LiAlH(O-t-C₆H₄)₃} + \text{R-CH₂-OH} \]

\[ \text{O-CH₂-R} \]

\[ \text{O-CH₂-R} \]

Scheme B

2.3. Sodium Alkoxyaluminoxyhydrates

For the preparation of sodium trialkoxyaluminoxyhydrates, the synthesis from sodium hydride and trialkoxylaluminum has been recommended 21-25; however, according to conductivity measurements, the composition of these hydrides is not homogeneous and does not correspond precisely to the formulae cited 22. Sodium di- or tri-alkoxy and bis- or tris-[2-methoxyethoxy]-aluminoxyhydrates were obtained by refluxing Na₃AlH₆ or NaAlH₄ with trialkoxylaluminum in tetrahydrofuran 26 or with tris-[2-methoxyethoxy]-aluminum in aromatic hydrocarbons 27, respectively. A series of sodium alkoxo-, aryloxy-, α-alkoxyalkoxy-, and α-dimethylamino-alkoxyaluminoxyhydrates was synthesized by allowing metallic aluminum and sodium, both suspended in aromatic solvents, to react under hydrogen pressure and at elevated temperatures (160–190°) with aliphatic alcohols, phenols, methylphenols, xyleneols, α-alkoxyalkanols, or α-dimethylaminoalkanols 28-32.


Alkoxyaluminohydrides have also been used for partial reductions of some unsaturated primary alcohols. Thus in contrast to LiAlH₄, which reduces 1-hydroxalk-2-ene-4,6-diyne (3, Scheme C) to allenolols (1-hydroxy-3,5,6-trienes, 4) as main products and allenynolols (1-hydroxylalka-3,4-dien-6-yne, 5) as minor products, the use of LiAlH₄(OCH₃)₂ or LiAlH₄(OCH₂C₂H₅) affords improved yields of 5 together with 4 as a minor product; the reaction using the LiAlH₄-butane-2,3-diol complex affords only 4⁴⁰:

\[
R-\text{C=C-}\equiv\text{C}=\text{CH}=\text{CH}-\text{CH}_2=\text{OH} \quad \rightarrow
\]

3

4

\[
R=\text{CH}=\text{C}=\text{CH}=\text{CH}=\text{CH}-\text{CH}_2=\text{CH}_2=\text{OH} \quad + \quad R-\text{C=C=CH}=\text{CH}-\text{CH}_2=\text{CH}_2=\text{OH}
\]

Scheme C

The complex of LiAlH₄ with an α-D-glucosurano derivative proved similarly effective to dimethoxyaluminohydride or lithium dimethoxylaluminohydride⁴² in the partial reduction of a triple bond in unsaturated primary alcohols and the elucidation of the configuration of the latter.

3.2. Reactions with Aldehydes and Ketones

3.2.1. Reductions without Regard to Stereospecificity

Saturated aldehydes and ketones may be rapidly reduced with NaAlH₄(OCH₃)₃,⁴² LiAlH₄(OCH₃)₃,⁴⁴,³⁹ LiAlH₄(=C₄H₆)₄,⁴⁵, or NaAlH₄(OCH₂OCH₃)₂⁴⁴ to the corresponding alcohols. In the case of the latter hydride, however, the sterically hindered 2,4,6-trimethylacetophenone reacts predominantly in the enol form, yielding only about 10% of the carbonyl.⁴⁴ Hydroxy-, alkoxy-, and amino-substituted aromatic aldehydes and ketones react with NaAlH₄(OCH₂OCH₃)₂ at a substantially higher rate than with LiAlH₄ and give substituted hydroxymethyl alcohols in high yields; at higher temperatures, these aldehydes and ketones, in which the position of the substituent on the ring allows the formation of a stabilized carboxonium ion, readily undergo hydrogenolysis with NaAlH₄(OCH₂OCH₃)₂ giving substituted toluenes, diarylmethanes, or methylxanthathenes in high yields.⁴⁵-⁴⁸

2.4-Dihydroxydiphenylmethane

A 70% solution of sodium bis[2-methoxyethyl]-aluminohydride (12.1 g, 60 mmol) in xylene is added with stirring to a hot solution of 2,4-dihydroxbenzenophenone (4.28 g, 20 mmol) in xylene (90 ml). Stirring and heating is continued. The initially formed light yellow precipitate dissolves to give a deep-red solution as the temperature reaches 143°C. The reaction mixture is stirred for 1 hr at this temperature, then cooled with an ice bath, diluted with ether, and decomposed by the addition of 20% sulfuric acid. The organic layer is separated and the aqueous layer extracted with ether. The combined organic solutions are washed with water, shaken with solid sodium carbonate, again washed with water, and dried with sodium sulfate. The solvents are distilled off and the residue is distilled in vacuo; yield: 3.3 g (82%), b. p. 162–163°C/1 mm, m. p. 76–76.5°C, from benzene.

z,β-Unsaturated carbonyl compounds are reduced by NaAlH₄(OCH₂OCH₃)₂ either to the unsaturated or saturated alcohols, depending on the reaction conditions, in 80–97% yields.⁴³,⁴⁴ On the other hand, the behavior of both LiAlH₄(OCH₃)₃ and LiAlH₄(=C₄H₆)₄ towards these compounds appears to depend on the structure of the carbonyl compound.

LiAlH₄(OCH₃)₃, previously reported to simultaneously reduce both the double bond and the carbonyl group in cinnamaldehyde,⁵⁳ affords a 90% yield of the unsaturated alcohol in the reduction of 3-oxocyclopentene and reduces 5-oxo-endo-tricycle[5.2.1.0²₉]dec-3-ene (5,6-dihydro-endo-dicyclopentadien-1-one, 6) to yield approximately equal amounts of the unsaturated alcohol (7) and saturated ketone (8), along with minor amounts of alcohol ⁹⁴⁵:

\[
\begin{array}{c}
\text{HO} \\
\text{H} \\
\end{array}
\]

6

\[
\begin{array}{c}
\text{HO} \\
\text{H} \\
\end{array}
\]

7

\[
\begin{array}{c}
\text{HO} \\
\text{H} \\
\end{array}
\]

9

Scheme D

LiAlH\(_4\) (O → C\(_2\)H\(_3\))\(_3\), which only reduces the carbonyl function of cinnamaldehyde\(^9\), gives the highest yield of 8 from reduction of 6 and a 89\% yield of cyclopentanol (in comparison to 100\% with NaBH\(_4\)) in the reduction of 3-oxocyclopentenone\(^4\). On the other hand, this hydride effected selective saturation of the conjugated double bond of 5-oxo-endo-tricyclo[5.2.1.0\(^2\),6\]dec-3-8-diene (10)\(^4\) and of 2-oxo-cis-bicyclo[3.2.0]hepta-3,6-diene (11)\(^4\); the products, obtained in high yields,

![Chemical structures](image)

were the corresponding ketones with intact isolated double bond.

Table 1. Reduction of 5-Oxo-endo-tricyclo-
[5.2.1.0\(^2\),6\]dec-3-ene (6) with Metal Hydrides\(^4\) (Scheme D)

<table>
<thead>
<tr>
<th>Hydride</th>
<th>Product composition, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiAlH(_4) (ethyl ether)</td>
<td>67 12 21</td>
</tr>
<tr>
<td>LiAlH(_4) (tetrahydrofuran)</td>
<td>0 67.2 100 0-32.8</td>
</tr>
<tr>
<td>LiAlH(OCH(_3))(_3)</td>
<td>45 41 14</td>
</tr>
<tr>
<td>LiAlH(O → C(_2)H(_3))(_3)</td>
<td>0 84.5 15.5</td>
</tr>
<tr>
<td>NaBH(_4)</td>
<td>0 0 100</td>
</tr>
<tr>
<td>AlH(_3)</td>
<td>64.3 86 7 32.7 1.5-19.2</td>
</tr>
</tbody>
</table>

In the reduction of mesityl oxide, LiAlH\(_4\) is the preferred reagent and affords a better yield of the unsaturated alcohol as well as a cleaner product than does LiAlH(O → C\(_2\)H\(_3\))\(_3\)\(^4\).

LiAlH(O → C\(_2\)H\(_3\))\(_3\) was successfully used in the selective reduction of one carbonyl group in cyclic diketones (for this application in the steroid series see Section 3.3.). Thus, 1,4-dioxo-cis-trans-\(\Delta^6\)-octalin (12) was reduced (Scheme E) to the ketol 13, which after Wolff-Kishner reduction gave 1-hydroxy-\(\Delta^6\)-octalin (14) in 64\% yield (5-25\% after reaction with LiAlH\(_4\) and Wolff-Kishner reduction)\(^4\).

![Chemical structures](image)

3.2.2. Stereospecific Reductions of Monocyclic and Bicyclic Ketones

The results obtained to date on reductions of monocyclic and bicyclic ketones with alkoxymetal hydrides (Tables 2 and 3) reveal that LiAlH(OCH\(_3\))\(_3\) is more stereoselective than either LiAlH\(_4\), LiAlH(OCH\(_3\))\(_3\), or LiAlH(O → C\(_2\)H\(_3\))\(_3\). In comparison with LiAlH\(_4\), LiAlH(OCH\(_3\))\(_3\) gives preferential attack from the less hindered side of the carbonyl plane in rigid ketone systems. Thus, bicyclic ketones such as norcamphor, camphor, isopinocamphene, and fenchone are reduced by LiAlH(OCH\(_3\))\(_3\) to the thermodynamically less stable of the two possible alcohols in high isomeric purity. In the less rigid monocyclic systems such as 2-methylcyclohexanone and 2-methylcycloheptanone, this hydride gives substantially less amounts of the more stable alcohol than does LiAlH\(_4\) or LiAlH(O → C\(_2\)H\(_3\))\(_3\).

**dl-endo-Fenchyl Alcohol**\(^1^\):

*Lithium Trimethyloxalylhydride in Tetrahydrofuran*: In a 1000-ml flask, lithium aluminium hydride (15.2 g, 0.4 mol) is added to distilled tetrahydrofuran (750 ml). The mixture is stirred overnight, the solids are allowed to settle, and an aliquot of the clear solution is analyzed for dissolved hydride. A sufficient quantity of the clear solution is placed in a 1000-ml three-neck flask, fitted with condenser, stirrer, and addition funnel, to provide 0.3 mol of the reagent. The solution is cooled to 0 \(^\circ\)C and methanol (36.6 ml, 28.8 g, 0.9 mol) is gradually added (exo-thermic reaction) as the hydrogen evolved is vented.

**dl-endo-Fenchyl Alcohol**: To the stirred solution of lithium trimethyloxalylhydride prepared as described above, dl-fenchone (53 g, 0.25 mol) is added dropwise at such a rate that the temperature can be maintained at ~0 \(^\circ\)C. The solution is stirred at 0 \(^\circ\)C for 1 hr and the residual hydride is destroyed by water. The reaction mixture is transferred to a separatory funnel, ether is added, and the mixture is treated with a saturated solution of sodium potassium tartrate. The organic phase is separated, the aqueous layer is extracted with ether, and the combined ether extracts are dried with anhydrous magnesium sulfate. The solvents are removed using a rotary evaporator and the residue is distilled in vacuo; yield: 30.7 g (80\%); b.p. 43 45 /1 mm; isomeric purity: 97\% (G.L.C. analysis); p-nitrobenzoate, m.p. 93 94.5 \(^\circ\)C.

On the other hand, LiAlH(OCH\(_3\))\(_3\), NaAlH\(_2\)(OC\(_2\)H\(_5\))OCH\(_3\), and LiAlH(O → C\(_2\)H\(_3\))\(_3\) (the latter with some exceptions) reduce monocyclic and bicyclic ketones to two epimeric alcohols in a ratio close to that realized with LiAlH\(_4\).

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In the case of 3,3,5-trimethylcyclohexanone (15), LiAlH(O−t-C₆H₄)₃ yields (in contrast to LiAlH₄) preferentially the more stable trans-alcohol resulting from the attack at the less hindered side of the C=O plane. Compared to LiAlH₄, the stereospecificity of LiAlH(O−t-C₆H₄)₃ observed in the reduction of 5-oxobicyclo[2.2.1]heptene (dehydroanacampor) and 3-exo-dimethylaminomethyl-2-oxobicyclo[2.2.1]heptane is low.

The failure of LiAlH(O−t-C₆H₄)₃ to give higher stereoselectivity (expected because of its larger steric requirements) was ascribed to different mechanisms involved in the reductions of hindered ketones with LiAlH(O−t-C₆H₄)₃ and LiAlH(OCH₃)₃. In addition, the significantly different composition of products arising from the reduction of 2,4-dioxodicyclohexylmethane by LiAlH₄, LiAlH(OCH₃)₃, and LiAlH(O−t-C₆H₄)₃ has led to the assumption that not LiAlH(OCH₃)₃ but AlH(OCH₃)₃, formed according to the Scheme F, was the actual reducing agent.

3 CH₂OH + LiAlH₄ →
AlH(OCH₃)₂ + CH₃O⁻Li⁺ + 3 H₂

Scheme F

The relatively high association recently found for solutions of LiAlH(OCH₃)₃ in tetrahydrofuran allows the assumption that molecular aggregation of this hydride, producing a reducing agent bulkier than monomeric LiAlH(O−t-C₆H₄)₃, may be responsible for the higher stereoselectivity of the former hydride.

The kinetic results obtained for the reaction of LiAlH(O−t-C₆H₄)₃ with monocyclic ketones appear to rule out “product development control” for the reduction of 3,3,5-trimethylcyclohexanone (15), 4-t-butylcyclohexanone (16), 3,5 dimethylcyclohexanone (17), and 3,3,5,3-tetramethylcyclohexanone (18);

“steric approach control” seems to be operative in the formation of the equatorial alcohol from 15.

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**Table 2. Stereospecific Reduction of Monocyclic Ketones with Metal Hydrides**

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Yield of trans-alcohol, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAH$^a$</td>
<td>LTMA$^b$</td>
</tr>
<tr>
<td>![Structure 15]</td>
<td>76−79$^c$</td>
</tr>
<tr>
<td>![Structure 16]</td>
<td>74−76$^c$</td>
</tr>
<tr>
<td>![Structure 17]</td>
<td>82$^d$</td>
</tr>
<tr>
<td>![Structure 18]</td>
<td>98$^e$</td>
</tr>
<tr>
<td>![Structure 19]</td>
<td>81$^e$</td>
</tr>
<tr>
<td>![Structure 20]</td>
<td>42$^f$</td>
</tr>
<tr>
<td>![Structure 21]</td>
<td>90−91$^g$</td>
</tr>
<tr>
<td>![Structure 22]</td>
<td>91−93$^g$</td>
</tr>
<tr>
<td>![Structure 23]</td>
<td>16−17$^h$</td>
</tr>
<tr>
<td>![Structure 24]</td>
<td>94$^i$</td>
</tr>
<tr>
<td>![Structure 25]</td>
<td>58−63$^i$</td>
</tr>
<tr>
<td>![Structure 26]</td>
<td>52−54$^i$</td>
</tr>
<tr>
<td>![Structure 27]</td>
<td>53−62$^i$</td>
</tr>
</tbody>
</table>

---

$^a$ LAH = LiAlH₄; LTMA = LiAlH(OCH₃)₃; LTEA = LiAlH(OCH₂CH₃)₃; LTBA = LiAlH(O−t-C₆H₄)₃; SDMA = NaAlH₃(OCH₂CH₃)₂.

$^b$ Ref. 51; the reaction with disobenzyleborane gives cis-alcohols in 92−94% purity.

$^c$ Ref. 52.

$^d$ Ref. 53.

$^e$ Ref. 54.

$^f$ Ref. 55.

$^g$ Ref. 56; the reduction with disocamphylborane gives cis-alcohols in 35−36% of trans-alcohol.

$^h$ Ref. 57.

$^i$ Ref. 58.

$^j$ Ref. 59.

$^k$ Ref. 60.

$^l$ Ref. 61; the reduction with NaBH₄ yielded 85% of trans-alcohol.

$^m$ Ref. 62.

$^n$ Ref. 63; the reaction was also performed with NaBH₄, NaBH(OCH₃)₃, and NaBH(O−t-C₆H₄)₃.

$^o$ Ref. 64.

$^p$ Ref. 65.

$^q$ Ref. 66; the reaction was also performed with NaBH₄, NaBH(OCH₃)₃, and NaBH(O−t-C₆H₄)₃.

$^r$ Ref. 67.

$^s$ Ref. 68; the reaction with AlH(O−t-C₆H₄)₃ afforded 74−80% of trans-alcohol.

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Table 3. Stereospecific Reduction of Bicyclic Ketones with Metal Hydrides

<table>
<thead>
<tr>
<th>Ketone</th>
<th>LAH&lt;sup&gt;a&lt;/sup&gt; Yield (%&lt;sub&gt;d&lt;/sub&gt;)</th>
<th>LTMA&lt;sup&gt;a&lt;/sup&gt; Yield (%&lt;sub&gt;d&lt;/sub&gt;)</th>
<th>LTBA&lt;sup&gt;a&lt;/sup&gt; Yield (%&lt;sub&gt;d&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norecamphor&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>89&lt;sup&gt;d&lt;/sup&gt;</td>
<td>98&lt;sup&gt;d&lt;/sup&gt;</td>
<td>93&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>90&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>92&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camphor&lt;sup&gt;i&lt;/sup&gt;</td>
<td>92&lt;sup&gt;d&lt;/sup&gt;</td>
<td>99&lt;sup&gt;a&lt;/sup&gt;</td>
<td>93&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>90&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>94&lt;sup&gt;k&lt;/sup&gt;-95&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>97&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Oxobicyclo[2.2.1]hept-2-ene (Dehydronornocamphor)&lt;sup&gt;b,a&lt;/sup&gt;</td>
<td>91</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Isopinocamphone&lt;sup&gt;c&lt;/sup&gt;-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>89</td>
<td>98</td>
<td>84</td>
</tr>
<tr>
<td>Fenchone&lt;sup&gt;b&lt;/sup&gt;-&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>97</td>
</tr>
<tr>
<td>7-Isopropyliden-5-oxobicyclo[2.2.1]hept-2-ene&lt;sup&gt;b&lt;/sup&gt;-&lt;sup&gt;e&lt;/sup&gt;</td>
<td>89</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>7-Isopropyliden-2-oxobicyclo[2.2.1]heptane&lt;sup&gt;b&lt;/sup&gt;-&lt;sup&gt;e&lt;/sup&gt;</td>
<td>94</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>2-exo-Dimethylaminomethyl-3-oxobicyclo[2.2.1]-heptane&lt;sup&gt;b&lt;/sup&gt;-&lt;sup&gt;j&lt;/sup&gt;</td>
<td>82</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>3-Oxobicyclo[3.1.0]hexane&lt;sup&gt;b&lt;/sup&gt;-&lt;sup&gt;k&lt;/sup&gt;-&lt;sup&gt;k&lt;/sup&gt;</td>
<td>89</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>2-Oxobicyclo[3.2.1]octane&lt;sup&gt;b&lt;/sup&gt;-&lt;sup&gt;k&lt;/sup&gt;-&lt;sup&gt;k&lt;/sup&gt;</td>
<td>90</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>(−)-Cedran-2-one&lt;sup&gt;b&lt;/sup&gt;-&lt;sup&gt;n&lt;/sup&gt;-&lt;sup&gt;x&lt;/sup&gt;</td>
<td>70</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>(−)-Isocedran-2-one&lt;sup&gt;b&lt;/sup&gt;-&lt;sup&gt;n&lt;/sup&gt;-&lt;sup&gt;n&lt;/sup&gt;</td>
<td>93, 6</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> LAH = LiAlH₄; LTMA = LiAlH(OCH₃)₃; LTBA = LiAlH(O-i-C₄H₉).<br><sup>b</sup> Predominating isomer is endo.<br><sup>c</sup> Ref.13; the reduction with LiAlH(OCH₃)₃ yielded 85% of endo-alcohol.<br><sup>d</sup> Ref.15.<br><sup>e</sup> Ref.16.<br><sup>f</sup> Ref.17.<br><sup>g</sup> Ref.18.<br><sup>h</sup> Ref.19; the reduction was also performed with Al(O-i-C₄H₉).<br><sup>i</sup> Ref.20; the reduction with Al(O-i-C₄H₉)₂ yielded 90-95% of endo-alcohol.<br><sup>j</sup> Predominating isomer is exo.<br><sup>k</sup> The reduction with NaAlH₄(OCH₃)₂ yielded 88-89% of exo-alcohol.<br><sup>l</sup> Ref.21.<br><sup>m</sup> Ref.22.<br><sup>n</sup> Ref.23; the reduction with Al(O-i-C₄H₉)₂ yielded 75-80% of exo-alcohol.<br><sup>p</sup> Ref.24.<br><sup>q</sup> Ref.25.<br><sup>r</sup> Predominating isomer is 2-exo-dimethylaminomethyl-3-endo-hydroxybicyclo[2.2.1]heptane.<br><sup>s</sup> Ref.26; also other 2-exo-dimethylaminomethyl derivatives were reduced.<br><sup>t</sup> Reductions were also performed with NaBH₄.<br><sup>u</sup> Predominating isomer is cis.<br><sup>v</sup> Ref.27.<br><sup>w</sup> The reductions were also performed with Al(O-i-C₄H₉).<br><sup>x</sup> Ref.28.<br><sup>y</sup> Predominating isomer is (−)-cedran-2-ol, the isomer present in minor amount is (−)-neocedran-2-ol.<br><sup>z</sup> Ref.29.<br><sup>aa</sup> Predominating isomer is (−)-neoisocedran-2-ol, the isomer present in minor amount is (−)-isocedran-2-ol.
The isomer ratio in the reduction product of 2,2-dimethyl-4-p-butylicyclohexanone \(^{37}\) (19) appears to be more determined by the eclipsing factor \(^{22}\) than by steric approach factors. The relative rate constants determined for attack of compounds 15-19 from the axial and equatorial side using LiAlH\(_4\), LiAlH(OCH\(_3\))\(_3\), and LiAlH(O—\(\equiv\)C\(_4\)H\(_9\))\(_3\), as well as NaBH\(_4\) or NaBH(O—\(\equiv\)C\(_3\)H\(_9\))\(_3\), support the concept of “steric approach control” but suggest that “product development control” plays at best a minor role, especially in the reductions with aluminohydrides \(^{39}\).

The results of kinetic studies of the reduction of \(p,p'\)-disubstituted benzophenones by LiAlH(O—\(\equiv\)C\(_4\)H\(_9\))\(_3\), show that in the transition state the C\(=\)O groups interact with a center carrying a significant negative charge; this eliminates the possibility of reduction by a neutral aluminohydride species and is consistent with hydride donation by an anion of the type Al\(^{10}\)(O—\(\equiv\)C\(_4\)H\(_9\))\(_3\)H\(^{17}\).

For the reduction of ketones with optically active alkoxyaluminohydride complexes see a recent review on asymmetric synthesis \(^{34}\).

### 3.3. Reactions with Steroids

The application of LiAlH(O—\(\equiv\)C\(_4\)H\(_9\))\(_3\) in the steroid series has made possible a number of reductions of high selectivity and stereospecificity not achieved with LiAlH\(_4\) or NaBH\(_4\) \(^{58,73,76,77}\).

The differences in the rates of reduction of 3-, 7-, and 17-keto-steroids allow reduction to occur selectively at the C-3 carbonyl \(^{16}\). For example, the reduction of 3,17-dioxoestr-5(10)-ene (20; Scheme G) gives rise to two hydroxyketo ones 21 and 22 in a ratio of 15:1 (5:1 with NaBH\(_3\)) \(^{38}\).

![Scheme G](image)

The slow rate of reduction of \(\alpha,\beta\)-unsaturated ketones made it possible to selectively reduce 17- and 7-keto groups in the presence of a conjugated 3-keto group. Thus, 3,17-dioxyoestr-4-ene (23) was converted into 17\(\beta\)-acetoxy-3-oxyoestr-4-ene (24; Scheme H) in 55% yield and 3\(\beta\)-acetoxy-7,17-dioxyoestr-5-ene into 3\(\beta\),17\(\beta\)-diaoxyoestr-7-oxyoestr-5-ene in 66% yield \(^{16}\).

![Scheme H](image)

In addition, an angular 10-formyl group could be partially reduced in the presence of a 3-keto group \(^{26}\); when NaBH\(_4\) was used as the reducing agent, borate complexes were formed and the corresponding hydroxyalkyl derivative could only be isolated after treatment with a mannotol/methanol/sulfuric acid mixture.

The high stereospecificity achieved with LiAlH(O—\(\equiv\)C\(_4\)H\(_9\))\(_3\) is illustrated by the almost quantitative yields of equatorial alcohols obtained from 3-keto-steroids \(^{57,80,84}\) as well as the high or nearly quantitative yields of 3\(\beta\)-76,80,81, 7\(\beta\)-76, and 17\(\beta\)-hydroxy derivatives \(^{76}\) obtained in the reductions of 3-, 7-, and 17-keto-steroids, respectively. In addition, 16-keto-steroids are selectively reduced to 16\(\beta\)-alcohols \(^{85}\). Thus, 3-oxocholesta-4-ene and 3-oxocholesta-5-ene afford 3\(\beta\)-hydroxycholesta-4,5-ene \(^{58,84,86}\) and 3\(\beta\)-hydroxycholesta-5-ene \(^{58,84}\), respectively. Both products are practically free of 3\(\alpha\)-isomers (1%). Cholesterol-3-one gives the nearly pure (98.5% \(^{\circ}\)) 3\(\beta\)-epimer \(^{77,84}\).

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Reduction of Organic Compounds by Alkoxyaluinohydrides

3β-Hydroxycholesten-4-ene⁸⁸:
Dry 1-butanol (12 g, 160 mmol) is added dropwise with stirring to a 0.5 M solution (100 ml) of lithium aluminohydride in ether. The white precipitate is allowed to settle, the ether decanted, and the solid lithium tri-1-butoxyaluminohydride dissolved in diglyme (40 ml). To this solution is added at -40° to -50° a solution of 3-oxocholesterol-4-ene (15 g, 39 mmol; m.p. 79-80°) in ether/benzene (8:1, 200 ml, cooled to 0°). The mixture is allowed to stand at 0° overnight and is then hydrolyzed by treatment with ice, 5% sodium hydroxide, and sodium potassium tartrate. The ether solution is dried and evaporated and the residue recrystallized from ethyl acetate; yield: 13 g (87%); m.p. 126-129°. The product is sufficiently pure and contains 1% of 3α-isomer. One more recrystallization from ethyl acetate affords the pure product in large needles; m.p. 131-132°; α<sub>D</sub> +46° (cf. Ref. ⁸⁸).

Similar results are observed when the keto-steroid is substituted by bromine in the 2α-, 2β-, 4α-, 4β- and 16β-positions⁷⁵, ⁷⁶, ⁷⁸. For example, the reduction of 2α-bromocholestan-3-one affords a crude product whose physical constants are almost identical with those of the pure 3β-alcohol⁷⁸. Unlike NaBH₄, LiAlH₄(O-1-C₆H₅)₃ does not epimerize the bromine in the unstable 2β- or 16β-bromoketones⁷⁶. Whereas during the reduction of 16α-bromo-17-keto-steroids (25) by other hydrides in a polar medium an inversion occurs at C-16, the reduction with LiAlH₄(O-1-C₆H₅)₃ in non-polar solvents gives rise to 16α-bromo-17-epimeric alcohols 26 and 27⁸⁸ (Scheme I).

Scheme I

Apart from its stereospecificity, LiAlH₄(O-1-C₆H₅)₃ displays other advantages in comparison with LiAlH₄ or NaBH₄. Thus, when severe reaction conditions are required in order to reduce the keto group in conjugated ketones, the double bond is not attacked⁷⁶. Reduction of keto groups proceeds without fission of acetoxyl⁷⁶, ⁸², ⁸⁵, ⁸⁹-⁹², benzoyloxy⁹³, or even formyloxy groups⁹⁹ at C-3, C-16, or C-17; and epoxide⁷⁶, ⁹⁴ as well as lactone rings⁹⁴ remain unaffected. Thus in contrast to LiAlH₄ or NaBH₄, LiAlH₄(O-1-C₆H₅)₃ proved unique in the cardenolide and bufadienolide series in selectively reducing the carbonyl or formyl groups and leaving intact the butenolide as well as hexadienolide rings⁹⁵. Unlike LiAlH₄, which reduces a δ-eno lactone (28) to a diol, LiAlH₄(O-1-C₆H₅)₃ affords two ketols⁹⁵, ⁹⁶ and ⁹⁷ (Scheme J), in a ratio of 96:4.

Scheme J

The 3-enamine grouping used to protect the 3-keto group in the reduction of 3,17-keto-steroids⁸⁵, ⁹⁶ (31, 32) is not attacked by LiAlH₄(O-1-C₆H₅)₃; the same applies to the amide group in 20-acetamino-or 18-benzylamino-steroids⁸², ⁹⁷.

The reduction of the cyclic sulfite mixture obtained from 3β,5-dihydroxy-5β-cholestan-6-one and containing compounds with axial SO- (33a; ⁹%); and equatorial SO-groups (33b; 91%) affords the 3,5-cyclic sulfite of 3β,5,6-trihydroxy-5β-cholestan with axial SO-groups (34a; 6%); and the 5,6-cyclic sulfite with equatorial SO-group (35; 57%).

Scheme K

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Reduction of the cyclic sultate (33c) of 3z,5-di-hydroxy-5z-cholestan-6-one proceeds without rearrangement, yielding the 6β-hydroxy-sultate (34b)\(^9\). The partial reduction of 5α- and 5β-cholestan-3-one ethylene ketal gives different results depending on the type of cyano derivative and hydride used. The highest yields (42\%\(\)) of the 5α-formyl derivative were obtained with LiAlH\((OC\_3H\_2)\_3\). In the case of the 5β-cyano derivative, LiAlH\((OC\_3H\_2)\_3\) fails to react and the reduction with LiAlH\((OC\_3H\_2)\_3\) gives rise to a 5β-aminoethyl derivative and a Schiff base in equal yields (32\%\(\))\(^9\).

### 3.4. Reactions with Carboxylic Acids and Acid Anhydrides

Carboxylic acids and acid anhydrides are easily reduced to the corresponding alcohols and diols by LiAlH\((OC\_3H\_2)\_3\)\(^3\),\(^3\),\(^3\),\(^1\) or more rapidly by NaAlH\((OC\_3H\_2)\_3\)\(^3\),\(^3\),\(^3\),\(^1\). Using the latter hydride, excellent yields of the same products can also be obtained by reducing the sodium or bromomagnesium salts of carboxylic acids\(^3\),\(^3\). A certain selectivity is displayed by this hydride in the reduction of ketocarboxylic acids to diols\(^3\),\(^3\),\(^1\) or lactones\(^3\),\(^3\). Hydroxy-, alkoxy-, and amino-substituted aromatic carboxylic acids can easily be reduced with NaAlH\((OC\_3H\_2)\_3\)\(^3\) to give the corresponding hydroxymethyl derivatives in high yields. Under more severe conditions (80–145\(\^\circ\)), hydrogenolysis of the α- and ρ-substituted carboxylic acids takes place, affording high yields of the corresponding methylphenols, methylnaphtols, dihydroxyanilines, or toluidines\(^5\),\(^3\),\(^3\).

LiAlH\((OC\_3H\_2)\_3\) does not attack carboxylic acids and thus offers a possibility of selectively reducing other substituents in the presence of a free carboxylic group\(^5\),\(^3\),\(^3\). On the other hand, cyclic anhydrides are reduced by this hydride to form lactones\(^3\),\(^3\),\(^3\),\(^1\). However, the use of LiAlH\(_2\) at low temperatures (−55\(\^\circ\))\(^3\) and an even more versatile method using NaN\(_3\) (108) have been recommended instead of the use of LiAlH\((OC\_3H\_2)\_3\) for lactone synthesis.

NaAlH\((OC\_3H\_2)\_3\) reacts with acid anhydrides similarly to LiAlH\((OC\_3H\_2)\_3\) or NaAlH\((OC\_3H\_2)\_3\)\(^2\),\(^2\),\(^2\).

### 3.5. Reactions with Esters and Lactones

Esters of aliphatic and aromatic carboxylic acids react relatively slowly with NaAlH\((OC\_3H\_2)\_3\)\(^2\),\(^2\) or more rapidly with LiAlH\((OC\_3H\_2)\_3\)\(^3\),\(^3\),\(^3\),\(^3\),\(^10\). The reaction with NaAlH\((OC\_3H\_2)\_3\)\(^3\),\(^3\) in aromatic hydrocarbons at 80\(\^\circ\) is very rapid, giving excellent yields of the same products\(^5\),\(^3\),\(^10\). Using this hydride, aromatic allylic alcohols can be prepared by the reduction of conjugated esters (reverse addition at 20–30\(\^\circ\)) in high yields\(^2\). For this purpose, LiAlH\((OC\_3H\_2)\_3\) has been suggested to be generally useful\(^1\).

#### 4-Hydroxybenzyl Alcohol\(^1\)

A hot solution of 4-hydroxybenzoic acid (6.08 g, 36.6 mmol) in benzene (80 ml) is added rapidly with stirring to a solution of sodium bis-[2-methoxyethoxy]-aluminoxyhydroxide (16.7 g, 82.5 mmol) in benzene (80 ml). The reaction mixture is heated under reflux for 15 min, cooled with an ice bath, and decomposed with water (15 ml). The benzene layer is separated; the highly viscous aqueous layer is stirred with water (85 ml) for 1 hr, decomposed by passing gasous carbon dioxide through the mixture for 1 hr, and extracted with ether (3 x 200 ml). The organic layers are combined, dried with sodium sulfate, and evaporated under reduced pressure. The residue is recrystallized from water; yield: 3.2 g (70\%\(\)); m.p. 109.5 110.5\(\^\circ\).

A selective reduction of ethyl Vitamin-A-carboxylate is achieved with NaAlH\((CH\_2)\_3(OH)\_2\), which when used in n-C\(_6\)H\(_5 \_a\) aliphatic hydrocarbon solution does not affect the conjugated double bond system and gives Vitamin A in a yield of 95\%\(^5\),\(^10\),\(^11\). Various 4-methylhexahydropyrazin-1-yl derivatives can be prepared in excellent yields by hydrogenolysis of 1-substituted 4-ethoxybenzocarboxyhexahydropyrazines with NaAlH\((OC\_3H\_2)\_3\)\(^11\). Although LiAlH\((OC\_3H\_2)\_3\) can be used for the reduction of α-aminoesters to α-aminoaldehydes, AlH\((OC\_3H\_2)\_3\) appears to be the preferred reagent, giving higher product yields\(^11\).

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\(^{105}\) D. Taur et al., Tetrahedron 24, 2453 (1968).


\(^{110}\) H. Poosner, Angew. Chem. 72, 819 (1960).

LiAlH(O—t-C₄H₉)₃ does not react with alkyl esters of aromatic carboxylic acids and reduces alkyl esters of aliphatic carboxylic acids at a very slow rate. A great difference between the transfer rates of the first and second hydride to phenyl esters led to the development of a new method for the conversion of carboxylic acids into the corresponding aldehydes via the phenyl esters (Scheme L).

\[ R-\text{COOC₃H₅} + \text{LiAlH(O—t-C₄H₉)} \rightarrow R-\text{CHO} + \text{LiAl(O-t-C₄H₉)} \]

**Scheme L**

The highest aldehyde yields (≈ 70%) are obtained by the reduction of phenyl esters of unsubstituted aliphatic, acyclic, and aliphatic carboxylic acids. An exception is phenyl cyclopropanecarboxylate which, like phenyl benzoate, fails to give the corresponding aldehyde.

Alternatively, NaAlH₃(OOC₃H₇OCH₃)₂ can be used for reduction of esters to aldehydes according to Scheme M:

\[ 2R'-\text{COOR} + \text{NaAlH₃(OOC₃H₇OCH₃)} \rightarrow 2R'-\text{CHO} + \text{NaAlO(O-t-C₄H₉)} \]

**Scheme M**

In this case, the highest aldehyde yields (80–90%) are obtained from methyl or 2-methoxyethyl esters of aliphatic carboxylic acids; the yields decrease with the length or branching of the R₂ substituent, t-butyl and phenyl esters being completely unreactive. Esters of aryl- and aralkanecarboxylic acids give generally lower yields (30–50%).

The reactivities of both LiAlH(O—t-C₄H₉)₃ and NaAlH₃(OOC₃H₇OCH₃) are compared in Table 4 with those of AlH₂(t-C₄H₉)₂ and NaAlH₄, recommended earlier for the aldehyde synthesis from esters.

Lactones are reduced by LiAlH(OOC₃H₇OCH₃) and NaAlH₃(OOC₃H₇OCH₃) to the corresponding diols as rapidly as with LiAlH₄. On the other hand, the unusually slow reduction of lactones by LiAlH(O—t-C₄H₉)₃ to diols is utilized for the partial reduction of δ-lactones to lactols.

Whereas LiAlH₄ reduces both carbonyl groups in a δ-enol lactone system, LiAlH(O—t-C₄H₉)₃ affords ketols in high yields. In the latter case, the separate preparation and isolation of LiAlH(O—t-C₄H₉)₃ rather than its formation in situ is advisable because better yields and cleaner products are obtained.

Using LiAlH₃(OCC₂H₅)₂, it is possible to reduce terpene lactones of the type 36 to the lactols, giving isochroman derivatives (37) in 89–96% yields.

**Scheme N**

### 3.6. Reactions with Carboxylic Acid Halides

Aliphatic and aromatic carboxylic acid chlorides are rapidly reduced by LiAlH(OCH₃)₃. LiAlH(O—t-C₄H₉)₃, NaAlH₃(OOC₂H₅)₂, or NaAlH₃(OOC₂H₅OCH₃)₂ to the corresponding alcohols in yields comparable to those obtained using LiAlH₄. These alkoxyhydrides can therefore find useful application in acid chloride reductions where the presence of other reducible substituents or conjugated double bonds makes the use of a more selective reagent necessary. Thus, cinnamyl alcohol and ring-substituted cyclopropenyl carbinals can be prepared in good yield from the corresponding unsaturated acid chlorides by reduction with LiAlH(O—t-C₄H₉)₃.

Of special interest is the partial reduction of carboxylic acid chlorides (reverse method) to the corresponding aldehydes by using one equivalent of LiAlH(O—t-C₄H₉)₃ in tetrahydrofuran or better in diglyme according to Scheme O.

\[ R-\text{Cl} + \text{LiAlH(O—t-C₄H₉)} \rightarrow R-\text{CHO} + \text{LiCl} + \text{Al(O—t-C₄H₉)} \]

**Scheme O**

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Table 4. Synthesis of Aldehydes by Partial Reduction of Carboxylic Acid Esters.

<table>
<thead>
<tr>
<th>Ester</th>
<th>Yield (%) of the corresponding aldehyde&lt;sup&gt;a&lt;/sup&gt;</th>
<th>LTBA&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>SDMA&lt;sup&gt;d&lt;/sup&gt;</th>
<th>ADB&lt;sup&gt;e&lt;/sup&gt;</th>
<th>SAH&lt;sup&gt;c,f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂C-COOM</td>
<td>71 (4)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>92 (4)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl-CH₂-COOM</td>
<td>67 (0.5)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>88&lt;sup&gt;4&lt;/sup&gt;</td>
<td>81&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>C₆H₅-COOR</td>
<td>77 (3)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-C₆H₅-COOR</td>
<td>63 (4)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-C₆H₅-COOM</td>
<td>71 (4)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>88 (5)&lt;sup&gt;m&lt;/sup&gt;</td>
<td>80&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂C-CH&lt;sub&gt;2&lt;/sub&gt;-CH=COOR</td>
<td>33 (0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-C₆H₅-COOR</td>
<td>67 (4)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>81 (5)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>78&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl-CH₂-CH₂-CH₂-COOR</td>
<td></td>
<td></td>
<td>25&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td>NC-CH₃-COOR</td>
<td>84 (8)&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-C₆H₅-COOR</td>
<td>82&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-C₆H₅-CH₃-COOR</td>
<td>82 (8)&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂C=CH-CH=CH-CH₃-COOR</td>
<td>88&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-C₆H₅-COOR</td>
<td>70 (24)&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROOC-CH₃-COOR</td>
<td>70 (4)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>H₂COOR</td>
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<tr>
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<td>78 (8)&lt;sup&gt;m&lt;/sup&gt;</td>
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<td>46&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
<td>DMSO-COOR</td>
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<td></td>
<td></td>
<td>81&lt;sup&gt;n&lt;/sup&gt;</td>
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<sup>a</sup> LTBA = LiAlH₄(OC₆H₄OCH₃)₃; SDMA = NaAlH₄(OH)(OC₆H₄OCH₃)₂; ADB = AlH₃(OC₆H₄OCH₃)₂; SAH = NaAlH₄.
<sup>b</sup> For R = C₆H₅, reduction in tetrahydrofuran at 0°C.
<sup>c</sup> Yields of 2,4-dinitrophenylhydrazones.
<sup>d</sup> For R = CH₃, unless stated otherwise.
<sup>e</sup> Reduction in ether at -70°C.
<sup>f</sup> Reverse addition.
<sup>i</sup> Reduction in toluene, hexane, or ether at -70°C (0.5-1 hr).
<sup>j</sup> Reduction in tetrahydrofuran or tetrahydrofuran/pyridine at -45°C to -65°C (aliphatic esters: 2-5 hr; aromatic esters: 5-7 hr).
<sup>k</sup> Numbers in parentheses denote reaction time (hr).
<sup>l</sup> Analytical yields.
<sup>m</sup> The reduction of the 2-methoxyethoxy ester gave a 87% yield (2 hr).
<sup>n</sup> Reduction of the 4-chlorophenyl ester gave 77% yield at -22°C (8 hr).
<sup>o</sup> For R = C₆H₅.
<sup>p</sup> Yields of NaHSO₃: R—CHO complexes.
<sup>q</sup> The reactivity was improved by grinding with added glass beads.
<sup>r</sup> Only benzyl alcohol (46%) was isolated after a reaction time of 4 hr.
<sup>s</sup> For R = t-C₆H₅.
<sup>t</sup> For R = n-C₆H₅.
p- And m-substituted aromatic aldehydes or dialdehydes are prepared by this method in 60–90% yield, o-substituted aldehydes in somewhat lower yields, and aliphatic or alicyclic aldehydes in yields of 37–60%. As the conjugated double bond is not attacked in this procedure, a number of substituted cinnamaldehydes or aliphatic unsaturated aldehydes and dialdehydes can thus be obtained in good yield.

4-Nitrobenzaldehyde:
Dry r-butanol (60 g, 0.80 mol) is added with stirring to a 0.5 M solution (500 ml) of lithium aluminohydride in ether. The white precipitate is allowed to settle, the ether decanted, and the solid lithium tri-r-butoxyaluminohydride dissolved in diglyme (200 ml). The solution is added over a period of 1 hr to a solution of 4-nitrobenzoyl chloride (45.3 g, 0.244 mol) in diglyme (100 ml) at 75°C (Dry-Ice bath). The mixture is warmed to room temperature over a period of 1 hr and is then poured onto crushed ice. The mixture is filtered, the solid on the flier pressed dry, and extracted several times with 95% ethanol. Evaporation of solvent yields 29.4 g (80%) of crude product; m.p. 103–104°C. Recrystallization from aqueous ethanol gives the pure product in the form of light-brown crystals; yield: 25.4 g (69%); m.p. 104–105°C.

Fluoroaldehydes can also be synthesized by the reduction of fluoroacetal fluorides with LiAlH(O–r-C₃H₇)₃, with other hydrides, hydrogenolysis of the C–CHO bond takes place.

The use of NaAlH(O–r-C₃H₇)₃ was recommended for the reduction of C₉–C₁₈ acid chlorides to aliphatic aldehydes; in this case, however, the reduction to the aldehyde competes with the simultaneous formation of acid and alcohol.

3.7. Reactions with Carboxamides, Imides, and Lactams

Whereas LiAlH(O–r-C₃H₇)₃ is inert toward amides, LiAlH(OCH₃)₃ or NaAlH₂(OH₂OC₃H₇)₃ reduce primary carboxamides to amines as readily as LiAlH₄ or AlH₃. Likewise, tertiary amides are reduced to the corresponding amines, the reaction surprisingly being faster with LiAlH(OCH₃)₃ or NaAlH₂(OH₂OC₃H₇)₃ than with LiAlH₄.

In some cases, reductive cleavage to an alcohol and a secondary amine was observed; thus, the reduction of diphenylformamide with NaAlH₂(OCH₂H₃)₃ affords diphenylamine as the major product, together with the expected N-methylidiphenylamine.

One of the important reactions of tertiary amides is their partial reduction to aldehydes by metal hydrides. For this purpose, different routes have been earlier recommended, based on the partial reduction of the corresponding N-acylcarbazoles. N-acylimidazoles, 1-acylaziridines, 1-acyl-3,5-dimethylpyrazoles, or N-methylnitriles with LiAlH₄. Recently it has been shown that dimethylamines of aliphatic, alicyclic, aromatic, and heterocyclic acids could be, with some exceptions, readily converted into the corresponding aldehydes in yields ranging from 60 to 90% using LiAlH₄(OCH₃)₃ or LiAlH₄(OH₂OC₃H₇)₃ in ether solution at 0°C.

Cyclohexanecarboxaldehyde:
A 1.25 M solution (300 ml) of lithium aluminohydride in ether is placed in a 1000-ml, three-necked flask equipped with condenser, mechanical stirrer, and dropping funnel. The flask is cooled by an ice bath. To the stirred solution is added ethyl acetate (49.6 g, 0.563 mol) over a period of 2 hr and the reaction mixture is stirred for 30 min at 0°C. The stirred slurry of lithium triethoxyaluminohydride thus prepared is added, with ice-cooling, N,N-dimethylcyclohexanecarboxamide (58.2 g, 0.375 mol) at such a rate that vigorous refluxing of the ether is avoided. The reaction mixture is stirred for 1 hr and then decomposed by the addition of 5 N sulfuric acid. The ether layer is separated and the aqueous layer extracted with ether (2 x 100 ml). The combined ether layers are washed with water, shaken with solid sodium hydrogen carbonate, washed again with water, and dried with sodium sulfate. The ether is distilled and the residue distilled in vacuum; yield: 32.8 g (78%); cf. also Ref.119; b.p. 74–78°C/20 mm; nD₂₀: 1.4499.

The hydrides LiAlH₂(OCH₃)₃ and LiAlH₄(OH₂OC₃H₇)₃ proved to be also suitable for the preparation of chloro- or thio-substituted aliphatic aldehydes or those containing isolated double bonds, which aldehydes are hardly accessible by the Rosenmund synthesis. o-Chloro-, o-methoxy-, and p-nitro-sub-

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Substituted benzaldehyde derivatives were also prepared in high yields.\(^{5,6}\) Similarly, N,N-dimethyldifluoroacetamide was successfully reduced by LiAlH\(_4\)(OC\(_2\)H\(_3\))\(_2\) to difluoroacetalddehyde.\(^{143}\) Using the same procedure, the N,N-dimethylamide of 18-hydroxy-2β,16x-cur-19-en-17-0ic acid (38) could be reduced with LiAlD\(_4\)(OC\(_2\)H\(_3\))\(_2\) (Scheme P) affording 17-deuterio Wieland-Gumlich aldehyde (39) in 55% yield.\(^{143}\)

![Scheme P](image)

On the other hand, both LiAlH\(_4\)(OC\(_2\)H\(_3\))\(_2\) and LiAlH\(_4\)(OC\(_2\)H\(_3\))\(_3\) fail to reduce conjugated dimethylamides to the corresponding conjugated aldehydes; thus, the reduction of N,N-dimethylcrotonamide affords no crotonaldehyde, and cinnamaldehyde is obtained in only 7–9% yield\(^{145}\) from the reduction of N,N-dimethylcinnamamide. Similarly, the reduction of dimethylamides of β,γ- and γ,δ-unsaturated cyclopentenyl- and cyclohexenylacetic acids with LiAlH\(_4\)(OC\(_2\)H\(_3\))\(_2\) gives low yields of the unsaturated aldehydes\(^{146}\) and thus in this case the reduction of the corresponding N-methylalanes is recommended. Relatively low yields of butanal\(^{10}\) (41%) and trimethoxyacetaldehyde\(^{147}\) (45%) are obtained by reduction of the corresponding dimethylamides with LiAlH\(_4\)(OC\(_2\)H\(_3\))\(_2\).

In some cases, N-methylalanates were used instead of dimethylamides for the aldehyde synthesis; thus, NaAlH\(_4\)(OC\(_2\)H\(_4\)OCH\(_3\))\(_2\) reduces, as does LiAlH\(_4\), N-methyl-N-phenylbenzamide to benzaldehyde or a mixture of benzyl alcohol and benzaldehyde, together with deacetylated amine.\(^{133}\) N-Methylalanates of N,N-disubstituted amino acids undergo a similar reaction on using LiAlH(OC\(_2\)H\(_3\))\(_3\) as the reducing agent; the yields of the corresponding aldehydes, however, in any case do not surpass those obtained with AlH(i-C\(_4\)H\(_9\))\(_2\).\(^{113}\)

Of all mechanisms proposed for the reaction between N,N-disubstituted carboxamides and metal hydrides, that of Weygand (Scheme Q) seems to best explain the formation of different products depending upon the carboxamide, the hydride type, and the reaction conditions.\(^{139}\)

![Scheme Q](image)

According to this theory, a common single intermediate complex (40) is formed in the first step of the reaction; this intermediate can then react in three ways, affording either aldehyde plus secondary amine, alcohol plus secondary amine, or tertiary amine.

Lactams and imides are readily reduced by NaAlH\(_4\)(OC\(_2\)H\(_4\)OCH\(_3\))\(_2\) to the corresponding cyclic imines in high yields.\(^{133}\)

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Treatment of N-benzylphthalimidine (41) or N-benzylphthalimide (43) with NaAlH₄(OC₂H₄OCH₃)₂ (Scheme R) affords N-benzylisoindole (42), whereas the reduction of the imide compound (43) with LiAlH₄ gives only N-benzylisoindoline (44)⁴⁸.

Scheme R

In a number of unsaturated lactams (45), the carbonyl group is simultaneously reduced (Scheme S) with the double bond, regardless of the hydride used. The highest yields (84%) of the corresponding substituted piperidines (46) are obtained with LiAlH₄(OC₂H₅)₂ and LiAlH₄·2AlCl₃¹⁴⁹.

Scheme S

3.8. Reactions with Nitriles

Aliphatic nitriles with relatively acidic hydrogens at C-α give only traces of aliphatic amines in the reduction using NaAlH₄(OC₂H₄OCH₃)₂⁴³,¹³³. Because of the low yield of amine and the large evolution of hydrogen observed when using LiAlH₄¹⁰⁰, LiAlH₄·AlCl₃ complex is recommended for the reduction of aliphatic nitriles to amines¹⁰⁰. LiAlH₄(OC₂H₅)₃¹⁰⁰ or AlH₃⁺ also appear promising for this use, whereas LiAlH₄(O—t-C₄H₉)₃ does not react with aliphatic and aromatic nitriles. A nitrile group directly bound to the aromatic ring is reduced to an amine by group by LiAlH₄(OCH₃)₃³⁳,³⁹ or NaAlH₄(OC₂H₄OCH₃)₂³⁶,⁴³,¹³³ as well as by AlH₃⁴⁹, LiAlH₄¹⁵¹,¹⁵², or NaAlH₄¹⁵². In the series of the heterocyclic nitriles, 3,5-dicyano-1,4-dihydropyridine is obtained as the sole product in excellent yield by reduction of 3,5-dicyanopyridine with NaAlH₄(OC₂H₅OCH₃)₂; other hydrides give mixtures of products¹⁵⁴. The reductions of 3-cyano furan and 3-cyano thiophene with this hydride afford 3- formy l furan and 3-formyl thiophene in yields surpassing those obtained by other available methods¹⁵⁵.

Of special interest is the partial reduction of nitriles, which makes widely varying structural types of aldehydes easily accessible. In contrast to NaAlH₄(OC₂H₅)₃, which is used with great success in the aromatic and heterocyclic series but gives unsatisfactory results in the conversion of aliphatic nitriles²¹,²²,²⁵, LiAlH₄(OC₂H₅)₃ reduces not only aromatic but also aliphatic nitriles within one hour to the corresponding aldehydes in 68–96% yields. Normal addition of the nitrile (1 mol per mol of the reagent) to the hydride solution in ethyl ether at 0°C was found most suitable¹⁴,¹⁵⁰. The partial reduction fails in the case of phenylacetonitrile, α-phthalodinitrile, and 9-cyanofluorene²⁷. A higher yield of cyclopropenecarboxaldehyde is obtained from the corresponding nitrile with LiAlH₄(O—t-C₄H₉)₃ than with LiAlH₄(OC₂H₅)₃⁴.

3.3. Dimethylbutanal (Pivalaldehyde)⁴⁺:

A solution (300 ml) of lithium aluminohydride (0.3 mol) in ether is placed in a 1000-ml flask equipped with condenser, stirrer, thermometer, and dropping funnel. A nitrogen atmosphere is maintained throughout the reaction. To the stirred solution, ethyl acetate (39.6 g, 0.45 mol) is added at 3–7°C over a period of 30 min. Stirring is continued for 30 min. To the stirred slurry of lithium triethoxyaluminohydride thus prepared, trimethylacetonitrile (24.9 g, 0.3 mol) is added over a period of 5 min., whereby the temperature is raised to 10°C and a highly viscous solution is formed. The reaction mixture is stirred at 0°C for 1 hr and then decomposed by the addition of 5 N sulfuric acid (300 ml). The ether layer is separated and the aqueous layer extracted with ether (3 × 50 ml). The combined ether layers are washed with saturated sodium hydrogen carbonate solution (once) and with water (8 × 50 ml). The ether layer is dried with sodium sulfate and distilled through a Todd fractionating column; yield: 25.8 g (74%); b. p. 70.0–72.5 °C/747 mm; nD²⁰: 1.3794.

4-Methylbenzaldehyde⁴⁺:

4-Methylbenzonitrile (5 g, 42 mmol) is added under a nitrogen atmosphere to a solution of sodium triethoxyaluminohydride (13 g, 70 mmol) in tetrahydrofuran (50 ml). The temperature rises to 40°C and the mixture, which is protected from moisture, becomes brown-yellow. After 2 hr, the mixture is poured into dilute sulfuric acid at 0°C and extracted thoroughly with ether. The etheral extract is washed and dried with sodium sulfate. The ether is distilled and the residue repeatedly fractionated under normal pressure; yield: 3.7 g (72%); b. p. 200–202 °C; 2,4-dinitrophenylhydrazone, m. p. 236 °C.

3.9. Reactions with Alkyl and Aryl Halides

LiAlH₄(OCH₃)₃ shows greater reducing power than LiAlH₄ in the reaction with 4-bromotoluene, which affords toluene in 59% yield [LiAlH₄(OCH₃)₃] in comparison to 7% with LiAlH₄.¹⁵⁷ NaAlH₄(OC₂H₅)₃ was also found suitable for the reduction of aromatic halides. It reduces bromobenzene and iodobenzene to benzene in 41 and 96% yield, respectively, but fails to react with chlorobenzene²⁵.

The reducing power of NaAlH₄(OC₂H₅OCH₃)₂ toward aliphatic halides is almost the same as that of LiAlH₄. Similarly to the case with LiAlH₄, an
elimination reaction competes with the reduction of vicinal aliphatic or alicyclic dihalides to hydrocarbons. In comparison with LiAlH₄, however, substantially shorter reaction times and a smaller excess of the hydride can be used, and higher yields of hydrocarbons are obtained in the reduction of aromatic halides with NaAlH₄(OS₂H₂OC₅H₄₃)₂₁⁸,₂⁴,₅₈. Moreover, if instead the half-methanolized hydride prepared in situ corresponding to the above reagent is used, practically quantitative yields of the dehalogenated hydrocarbons are obtained from 1-bromohexane, bromobenzene, or benzyl chloride; and 3-bromochlorobenzene and chlorobenzene are reduced to the chlorobenzene and benzene in 94 and 14 % yields, respectively. The latter yields are not achieved with other hydrides. The half-hydrolyzed hydride can also be used in these reactions.¹⁹⁵

Using NaAlH₄(OS₂H₂OC₅H₄₃)₂, poly-vinyl chloride is dehalogenated to the fully saturated polymer in a yield higher than 95 %; in this case, LiAlH₄ gives a lower yield and the product contains double bonds in the chain.¹⁶⁰

3.10. Reactions with Epoxides

Epoxides are reduced by LiAlH₄(OS₂H₂OC₅H₄₃)₃ more slowly than by AlH₃ or LiAlH₄.²⁰,₃₃,₃⁹,₁₀₀. With LiAlH₄(O→-C₄H₄₃), the reduction is still slower and thus provides a means of selectively reducing aldehyde or ketone groups in the presence of the oxirane ring.⁹,₃⁹. Nevertheless, if prolonged reaction times are used, high yields and high stereoselectivity are obtained in the reduction of epoxides using LiAlH₄(O→-C₄H₄₃).⁹,₃⁹. Whereas in the reduction of styrene oxide with the latter reagent, only secondary alcohol is obtained, using LiAlH₄(OS₂H₂OC₅H₄₃), LiAlH₄, AlH₃, and HAI₄Cl, the primary alcohol is formed in 1, 4, 24, and 26, and 95–99 % yields, respectively.²⁰,₃₃,₁₀₀. A comparative study of the reactivities of alkoxylaminohydrines H₂AlOR and HAI(OR)₂ (R = CH₃, i-C₃H₇, t-C₄H₉) and of hydroxylaluminum halides H₂AlX and HAI₄X (X = Cl, Br, J) towards 2-t-butyl-3,3-dimethylisoxazine(β-diisobutylene oxide) and styrene oxide shows that the hydride reactivity increases in the order

HAI(OR)₂ ≈ H₂AlOR ≈ AlH₃ < H₂AI₄ < HAI₄X and can be correlated with increasing Lewis acidity of the reagents.¹⁹,²⁰.

NaAlH₄(OS₂H₂OC₅H₄₃)₂ generally gives higher yields of secondary alcohols in the reductions of styrene oxide, propylene oxide, and 1-butene oxide than does LiAlH₄ or LiBH₄. In the case of aliphatic epoxides, however, the selectively formed propan-2-ol and butan-2-ol are accompanied by a small amount (1–5 %) of ethanol and propan-1-ol, respectively, produced by a novel C=C bond cleavage.¹⁶¹

3.11. Reactions with Quinones

In the reduction of p-benzoquinone, one equivalent of LiAlH₄(OS₂H₂OC₅H₄₃)₃ is used for reduction and another for hydrogen evolution; thus, reduction to the hydroquinone stage takes place. With LiAlH₄(O→-C₄H₄₃), however, no hydrogen is evolved, and side reactions are believed responsible for this course of the reaction. In the reduction of anthraquinone with LiAlH₄(OS₂H₂OC₅H₄₃), a complicated stoichiometric relationship is noted, which is compatible with the observed formation of equal amounts of both 9,10-dihydroxyanthracene and 9,10-dihydroxy-9,10-dihydroanthracene.¹⁵³

3.12. Reactions with Nitro Compounds and Their Derivatives

Aliphatic nitro compounds are reduced by LiAlH₄(OS₂H₂OC₅H₄₃)₃, NaAlH₄(OS₂H₂OC₅H₄₃)₃, or NaAlH₄(OS₂H₂OC₅H₄₃)₂, as well as by LiAlH₄, to amines. Similarly to LiAlH₄, LiAlH₄(OS₂H₂OC₅H₄₃)₃ reacts only slowly with nitrobenzene, azobenzene, or azoxybenzene, and LiAlH₄(O→-C₄H₄₃) fails to react with these compounds.⁹,₁₀₀. No attempts have so far been made to utilize the latter hydride for selective reductions in the presence of these groups. In one case, namely in the reduction of nitrobenzene to azobenzene, the use of NaAlH₄(OS₂H₂OC₅H₄₃)₃ is also mentioned.²⁵.

The reverse addition of nitroarenes to 2 equivalents of NaAlH₄(OS₂H₂OC₅H₄₃)₂ affords azo compounds in yields of those obtained with LiAlH₄.¹⁸,₁₆₃. Using 1.5–1.8 equivalents of NaAlH₄(OS₂H₂OC₅H₄₃)₂, however, azoxy or hydrazo compounds are obtained.⁴₃,₁₆₂,₁₆₃. In the reduction of halogenated nitroarenes with this hydride, iodine and bromine are always eliminated but chloride is retained. The reduction of 2,2'-dinitrophenyl affords benzo[c]cinoline in good yield.¹⁶₃.

3.13. Reactions with Other Nitrogen Compounds

Aldoximes and ketoximes are rapidly reduced by NaAlH₄(OS₂H₂OC₅H₄₃)₂ to amines in yields higher than 95 % comparable to those obtained with LiAlH₄.¹₆,₄₃,₁₃₃. Although both LiAlH₄(OS₂H₂OC₅H₄₃)₃ and LiAlH₄(O→-C₄H₄₃)₃ evolve hydrogen with oximes, no reduction to amines is observed.⁹,₁₀₀.

Phenyl isocyanate reacts with LiAlH₄(OS₂H₂OC₅H₄₃)₃ as well as with LiAlH₄ or AlH₃ with formation of N-methylamidine, whereas with LiAlH₄(O→-C₄H₄₃)₃ the reaction stops at the formamidine stage.²₉,₁₀₉.

Pyridine N-oxide and its 3- or 4-methyl derivatives react with NaAlH₄(OS₂H₂OC₅H₄₃)₂ as with LiAlH₄ giving a mixture of piperidine, 1,2,5,6-tetrahydro-pyridine, and pyridine or their derivatives. Pyridine or substituted pyridines are the main products. In contrast to the reactions with these hydrides, AlH₃...
affords mainly 1,2,5,6-tetrahydropyridine or its methyl derivatives. Pyridine N-oxide is inert towards LiAlH(OH)3. N-Alkoxypropyridinium salts are reduced by NaAlH4(OC3H7)2 to the same mixture of products as is obtained from pyridine N-oxide, but in this case piperidine is obtained as the main product in a yield higher than with NaBH4.

Dihydrocinnoline derivatives which were obtained by the reduction of the corresponding cinnolines (47) with LiAlH(OH)3-C6H5 (Scheme T) and assigned the 1,2-dihydro structure (49) have since been shown by N.M.R. spectrometry to have 1,4-dihydro structures (48) and (52).

Scheme T

LiAlH(OH)3-C6H5 has also been successfully applied to the synthesis of indoloquinolizine derivatives from the corresponding pyridinium salts; reductive cyclization of 3-ethyl-[2-(3-indolyl)-ethyl]-pyridinium bromide (50a) in tetrahydrofuran (Scheme U) leads to the tetracyclic 3-ethyl-1,4,6,7,12,12b-hexahydropyrido[2,3-a]quinolizine (51a) and allyl alcohol (51b) 28%. Whereas the acetooxime derivative (50c) affords diene 52 exclusively, in 50% yield.

Scheme U

3.14. Reactions with Sulfur Compounds

LiAlH(OOCs)3 reduces aliphatic and aromatic disulfides to mercaptans and sulfoxides to sulfides as rapidly as LiAlH4; on the other hand, no reaction is observed with sulfides, sulfones, sulfonic acids, or tosylates. LiAlH(OH)3-C6H5 reduces aromatic disulfides more slowly than LiAlH(OOCs)3 and only negligible formation of alkylmercaptans is noted in the reduction of alkyl sulfides. Because of inertness of LiAlH(OH)3-C6H5 toward other sulfur compounds, this hydride can be utilized for selective reductions in the presence of these groups.

3.15. Reactions with Hydrocarbons

An alkoxyhydride complex formed from LiAlH4 and diethylene glycol monoethyl ether (carbitol) reduces acenaphthylene to acenaphthene in 90% yield and 9,9'-bifluorenylidene to 9,9'-bifluorenyl.

The reduction of methyltripropylium perchlorate with LiAlH(OH)3 affords, in contrast to LiAlH4, NaBH4 or (C6H5)3SnH2, a mixture of 1, 2, 3, and 3-methyltripropylium free of the 7-isomer.

3.16. Reactions with Organometallic Compounds

The reduction of phenyl-(1-phenylethyl)-phosphinyl chloride with LiAlH(OH)3 affords two diastereoisomeric phenyl-(1-phenylethyl)-phosphine oxides.

A series of halogenosilanes was successfully reduced by NaAlH4(OC3H7)2OCH3 in ethyl ether or aromatic hydrocarbons to silanes in yields comparable with those obtained with LiAlH4. In contrast to LiAlH4, no side reactions in the reduction of alkoxylchlorosilanes with LiAlH(OH)3-C6H5 are observed; an exception has been noted in the case of ethoxychlorosilanes, where a partial replacement of the ethoxy groups by tertiary butoxy groups takes place.

In contrast to LiAlH4, which reduces phenyl halides (53) to phenyl hydrides, NaAlH(OOCs)3 (Scheme V) replaces all chloro atoms in 53 by the hydride anion to give 54.

Scheme V

The acid chloride of (carboxycyclopentadienyl)-manganese tricarbonyl can be selectively reduced with LiAlH(O—t-C₄H₉)₃ to give the corresponding aldehyde in 68\% yield\(^{173}\).

\[
\text{LiAlH}_2(O—t-C_4H_9)_2, \quad \text{LiAlH}_2(OC_4H_5)_2, \quad \text{LiAlH}(O—t-C_4H_9)_3, \quad \text{NaAlH}(O—t-C_4H_9)_3, \\
\text{AlH}(O—t-C_4H_9)_3, \text{ and LiAlH}(O—t-C_4H_9)_3—AlH}_3
\]

form complexes with organometallic compounds or salts of metals such as iron, nickel, cobalt, titanium, or chromium. These complexes have been recommended as powerful catalysts to increase the rate of the homogeneous hydrogenation of olefins and diolefins with conjugated double bonds (by a factor of \(10^2—10^3\) in comparison with heterogeneous systems and by a factor of more than 10 compared with other homogeneous systems). Aromatic hydrocarbons are not hydrogenated in the presence of these complexes. The rate of hydrogenation using some of these catalysts is much higher than the rate of hydrocarbon isomerization\(^{174,175,176}\).

A convenient route for the conversion of olefins into aldehydes is via olefin hydroboration and carboxylation of the organoboranes in the presence of an equimolar amount of LiAlH(OCH₃)₃ (Scheme W).

In the presence of this hydride, the latter reaction generally proceeds at a rapid rate at 0—25° and the oxidation of the intermediate product \([A]\) (of unknown structure) with hydrogen peroxide produces aldehydes in 87—98\% yields\(^{177}\).

\[
\begin{align*}
\text{Scheme W} \\
R^1\text{B} + \text{CO} + \text{LiAlH(OCH₃)}_3 & \rightarrow \quad \text{[A]} \quad \text{[O]} \\
& \rightarrow 2R^1\text{OH} + R^2\text{CHO}
\end{align*}
\]

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