DHI (14.1 g., 0.1 mole) in 75 ml. of methanol. After an hour of reflux and standing at room temperature for 2 hours, the reaction mixture was decomposed with 10% sodium hydroxide and worked up in the usual way. Analysis of the product on a Tide detergent column gave 73% *trans*-alcohol and 27% *cis*-alcohol. No ketone was found.

A similar reduction using KBH_4 in 67% aqueous methanol gave the same product composition within experimental error.

Reductions of DHI with $NaBH_4$ in anhydrous isopropyl alcohol, 65% aqueous isopropyl alcohol, anhydrous diglyme, *t*-butyl alcohol and with sodium trimethoxyborohydride in isopropyl alcohol are summarized in Table III.

Preparation of $NaB(O\text{-}Pr\text{-}i)_3H$ and Reduction of DHI.—Sodium hydride (1.14 g.) was added to isopropyl borate[9] (8.6 g., 0.045 mole) in 100 ml. of sodium-dried diglyme in a flask which was previously flamed under a nitrogen atmosphere. During the entire operation dry nitrogen was passed through the system. The reaction mixture was heated at about 130° for 85 min. At one point the temperature reached about 135° and the contents turned brown.

A solution of DHI (3.9 g., 0.028 mole) in 20 ml. of diglyme was added and the reaction mixture was stirred overnight, then heated on a steam-bath for 3 hours and kept overnight at room temperature. The reaction mixture was hydrolyzed with water and 10% sulfuric acid and diluted with about 1 liter of water. The product was extracted with ether and the ether solution was washed with saturated sodium bicarbonate solution and with water and dried over anhydrous magnesium sulfate. The ether was distilled leaving a concentrated orange residue weighing 6 g. which was analyzed with a Carbowax 20M column at 155° and contained 77% *trans*-alcohol and 23% *cis*-alcohol. Reduction had occurred to only a limited extent.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND RADIATION LABORATORY[1] OF THE UNIVERSITY OF NOTRE DAME, NOTRE DAME, IND.]

Reduction with Metal Hydrides. XII. Reduction of Acetals and Ketals with Lithium Aluminum Hydride–Aluminum Chloride

BY ERNEST L. ELIEL, VICTOR G. BADDING AND MARK N. RERICK

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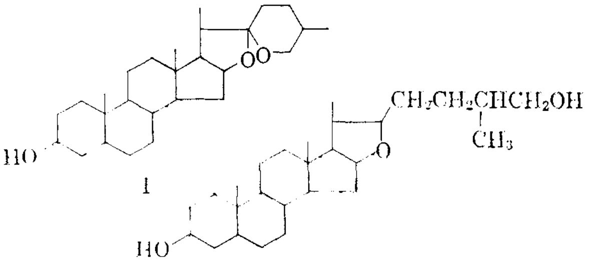
The reduction of acetals and ketals to ethers in high yield by means of lithium aluminum hydride–aluminum chloride is described.

In 1951, Doukas and Fontaine reported[2] that spirostanes such as I are reduced to furostanols, such as II, by the addition of solid lithium aluminum hydride (LAH) to an ethereal solution of the spirostane saturated with anhydrous hydrogen chloride or hydrogen bromide. This report was noteworthy for two reasons. The combination of reagents employed was rather unusual. (Neither LAH nor hydrogen halides by themselves affected I and combinations of LAH with hydrogen sulfide, sulfur dioxide and *p*-toluenesulfonic acid were also ineffective.) Also conversion of I to II exemplifies reduction of a ketal to an ether for which no procedures giving acceptable yields were then available. In general, of course, the ketal function is resistant to the attack of LAH and, in fact, ketal formation often is employed to protect ketone groups during the reduction of other functions (such as ester groups) in a molecule.[3]



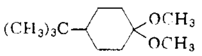
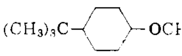
I

II

When subsequent work in our laboratory and elsewhere[4] disclosed that the reducing properties of LAH may be considerably modified by the addition of Lewis acids, especially aluminum chloride, it became likely that the active ingredient in the reagent employed by Doukas and Fontaine[2] was a LAH–aluminum chloride combination. We therefore studied[5] the action of such a combination on a variety of acetals and ketals with the results shown in Table I.

TABLE I

REDUCTION OF ACETALS AND KETALS

Compound reduced	Product	Yield, %
$C_6H_5CH(OCH_3)_2$	$C_6H_5CH_2OCH_3$	88
$C_6H_5CH(OC_2H_5)_2$	$C_6H_5CH_2OC_2H_5$	73^b
$n\text{-}C_3H_7CH(OC_2H_5)_2$	$n\text{-}C_4H_9OC_2H_5$	ca. $47^{a,b}$
$C_6H_5C(OC_2H_5)_2CH_3$	$C_6H_5CH(CH_3)OC_2H_5$	81
$(CH_3)_2C(OC_4H_9\text{-}n)_2$	$(CH_3)_2CHOC_4H_9\text{-}n$	84^c
$C_6H_{10}(OCH_3)_2{}^d$	$C_6H_{11}OCH_3{}^e$	74
$C_6H_{10}(OC_2H_5)_2{}^d$	$C_6H_{11}OC_2H_5{}^e$	78
$C_6H_{10}(OC_3H_7\text{-}n)_2{}^d$	$C_6H_{11}OC_3H_7\text{-}n^e$	74
$C_6H_{10}(OC_4H_9\text{-}n)_2{}^d$	$C_6H_{11}OC_4H_9\text{-}n^e$	61
 $(CH_3)_3C$ OCH_3 OCH_3	 $(CH_3)_3C$ OCH_3	92^f

[a] 1.25 moles of hydride per mole acetal. [b] Product codistilled with ethanol. [c] Product codistilled with 1-butanol. [d] C_6H_{10} is cyclohexylidene. [e] C_6H_{11} is cyclohexyl. [f] 75.5% *trans* isomer, 16.5% *cis* isomer by gas chromatography.

The reductions all proceeded to give ethers: $RR'C(OR'')_2 \rightarrow RR'CHOR''$. Yields were good,

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[1] The Radiation Laboratory is operated under contract with the Atomic Energy Commission. This paper is taken in part from the Ph.D. dissertation of Victor G. Badding.

[2] H. M. Doukas and T. D. Fontaine, *J. Am. Chem. Soc.*, **73**, 5917 (1951); **75**, 5355 (1953).

[3] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 673-680.

[4] For a review and references, see E. L. Eliel, *Rec. Chem. Progr.*, **23**, 129 (1961).

[5] For a preliminary communication of some of these results, see E. L. Eliel and M. N. Rerick, *J. Org. Chem.*, **23**, 1088 (1958).

generally in the 70–90% range except when isolation difficulties were encountered because the product ether (RR'CHOR'') codistilled with the by-product alcohol (R''OH). Best yields were obtained when the ratio of aluminum chloride to LAH was 4:1 and the ratio of LAH to ketal 1:2 (100% excess). The latter ratio was dictated by the unavoidable wastage of hydride which occurs when standardized LAH solution is added to a solution of aluminum chloride in anhydrous ether, as evidenced by evolution of hydrogen. Most of this probably is occasioned by the presence of $AlCl_2OH$ (or similar species) in commercial $AlCl_3$. When an insufficient amount of hydride was used in the reduction, a red color, possibly due to accumulation of the oxocarbonium ion $RR'C{=}OR^+$, was observed, yields suffered and by-products appeared. Thus, in the reduction of acetophenone diethyl ketal with a deficient amount of the mixed reagent, some 1,3,5-triphenylbenzene was obtained. This was also the principal product of the reaction of this ketal with ethereal aluminum chloride. The rationale of the $AlCl_3$:LAH ratio employed is less obvious. Other work in our laboratory[4] has suggested that a 3:1 or 4:1 ratio of the constituents[6] is needed to produce some of the special effects of the "mixed hydride" reagent, *e.g.*, in the reduction of triphenylethylene oxide to 2,2,2-triphenylethanol.[7] According to work by Wiberg,[8] this ratio of reagents probably produces $AlHCl_2$: $LiAlH_4 + 3AlCl_3 \rightarrow LiCl + 4AlHCl_2$. Tentative confirmation of the desirability of using $AlCl_3$ and LAH in at least a 3:1 ratio comes from studies on the reduction of cyclohexanone ethylene ketal with mixed hydride summarized in Table II.

TABLE II

REDUCTION OF CYCLOHEXANONE ETHYLENE KETAL WITH DIFFERENT RATIOS OF REAGENTS

Mole			Product or recovered ketal, %	
Ketal	$LiAlH_4$	$AlCl_3$	Product	Ketal
1	0.5	2.0	88	[a]
1	.5	1.5	83	[a]
1	.5	0.5	64	25
1	.5	0.166	*ca.* 9	*ca.* 58

[a] Not isolated.

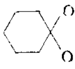
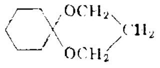
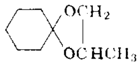
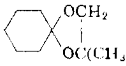
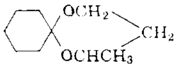
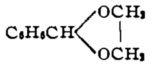
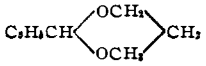
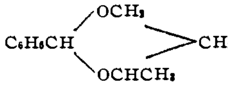
A ratio of $AlCl_3$ to LAH of 3:1 or greater is required to produce the reduction product, cyclohexyl β-hydroxyethyl ether, in optimum yield. At lower chloride:hydride ratios, unreduced ketal is recovered and the amount of reduction product is not in excess of that calculated on the basis that the true reducing agent is $AlHCl_2$ (66.7% for a 1:1 ratio, 22% for a 1:3 ratio of $AlCl_3$ to LAH[9]). However, we have not made a thorough and detailed study of the stoichiometry of the ketal reduction, and the conclusions here presented must be considered tentative.

The reduction of 4-*t*-butylcyclohexanone dimethyl ketal with mixed hydride (Table I, last entry) is of interest in that the possible *cis* and *trans* isomers of 4-*t*-butylcyclohexyl methyl ether were obtained in a ratio (18:82) very similar to the ratio of *cis*- and *trans*-4-*t*-butylcyclohexanol obtained in the reduction of 4-*t*-butylcyclohexanone with mixed hydride (20:80).[10]

Following the successful reduction of simple ketals with mixed hydride, we undertook the reduction of some cyclic ketals with the results shown in Table III. In all cases, the easily isolable hydroxyether products were obtained in over 80% yield, and in view of the ready accessibility of cyclic acetals and ketals, the mixed hydride reduction of these compounds recommends itself as a very convenient synthesis of a variety of β- and γ-hydroxyethers.[11]

TABLE III

REDUCTION OF CYCLIC KETALS

Entry	Compound reduced	Product	Yield, %
1		$C_6H_{11}OCH_2CH_2OH^a$	88
2		$C_6H_{11}OCH_2CH_2CH_2OH^a$	92
3		$C_6H_{11}OCH(CH_3)CH_2OH^a$ $C_6H_{11}OCH_2CH(CH_3)OH^a$	69[b] 16[b]
4		$C_6H_{11}OCH_2C(CH_3)_2OH^a$	89[b]
5		$C_6H_{11}OCH(CH_3)CH_2CH_2OH^a$ $C_6H_{11}OCH_2CH_2CHOHCH_3{}^a$	62[c] 31[b]
6		$C_6H_5CH_2OCH_2CH_2OH$	89
7		$C_6H_5CH_2OCH_2CH_2CH_2OH$	83
8		$C_6H_5CH_2OCH(CH_3)CH_2CH_2OH$ $C_6H_5CH_2OCH_2CH_2CHOHCH_3$	62[c] 32[b]

[a] C_6H_{11} is cyclohexyl. [b] Analysis by gas chromatography and infrared comparison with authentic samples. [c] Assumed structure of the major fraction in the gas chromatogram.

Of special interest in Table III is the reduction of unsymmetrical ketals (entries 3, 4, 5 and 8). In the reduction of the propylene ketal (entry 3) and the 1,3-butylene acetal and ketal (entries 8, 5), the product of hydrogenolysis of the primary ether function (*i.e.*, the primary alcohol–secondary ether) predominates over the product of hydrogenolysis of the secondary ether function (*i.e.*, the secondary alcohol–primary ether). Curiously, the opposite

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(6) The 4:1 reagent is probably equivalent to a 3:1 reagent containing excess $AlCl_3$. It is doubtful that the extra mole of $AlCl_3$ plays any part other than to ensure that the $AlCl_3$:LAH ratio is at least 3:1, even when the aluminum chloride reagent is somewhat impure.

(7) M. N. Rerick and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2356 (1962).

(8) E. Wiberg and M. Schmidt, *Z. Naturforsch.*, **6b**, 333. 460 (1951); see also G. G. Evans, J. K. Kennedy and F. P. DelGreco, *J. Inorg. Nucl. Chem.*, **4**, 40 (1957).

(9) Considering that 1 mole of $AlHCl_2$ per mole ketal is needed and that 1 mole of $AlCl_3$ produces 4/3 mole of $AlHCl_2$, thus for each mole of $AlCl_3$, 4/3 mole of ketal may be reduced. This assumes that the aluminum chloride becomes unavailable once it has participated in reduction—in whatever form it may then be.

(10) E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

(11) ε-Hydroxyethers may be obtained in some cases by mixed hydride reduction of tetrahydropyranyl ethers (ref. 4). The potential synthesis of δ-hydroxyethers from tetrahydrofuranyl ethers is under study.

result is found with the isobutylene ketal (entry 4) where the *exclusive* product is the tertiary alcohol-primary ether formed by hydrogenolysis of the tertiary ether function of the unsymmetrical ketal. This contrast between primary–secondary and primary–tertiary ketals may indicate a difference in the mechanism of hydrogenolysis of the two species, or it may be a result of a counterplay of polar and steric influences.

Following our preliminary publication[5] on the hydrogenolysis of acetals and ketals by LAH–$AlCl_3$, Pettit and Bowyer demonstrated[12] that mixed hydride is actually capable of reducing spirostanes (such as I) to furostanols (such as II), thus supporting our initial assumption that the reagent employed by Doukas and Fontaine[2] was, in effect, a LAH–aluminum chloride combination. In their publication,[12] Pettit and Bowyer show that treatment of diosgenin acetate (III) with ethereal aluminum chloride followed by ethanedithiol yields a cyclic mercaptal, IV, which clearly implies the occurrence of a hydride shift, as indicated in Chart I. The authors suggest that a similar hydride shift may occur in the reduction of I to II (or of III to the unsaturated analog of II), such reductions also involving aldehyde intermediates. In order to test the possible generality of such hydride shifts, we carried out the reduction of cyclohexanone ethylene ketal and cyclohexanone trimethylene ketal with lithium aluminum deuteride–aluminum chloride. Mass spectral comparison of the products of these hydrogenolysis reactions, after further reduction, with authentic deuterated samples showed, however, that no hydride shift had occurred. The details of these experiments are summarized in Chart II. They throw some light, if only in a negative way, on the mechanism of the hydrogenolysis of ketals by mixed hydride—a topic whose further discussion must await results of future study. Of course, the absence of hydride shifts in the reduction of cyclic ketals of the type shown in Chart II, in which the two oxygen atoms are exocyclic or in the same ring, does not preclude the occurrence of such shifts in the reduction of the rather different spiroketals exemplified by I and III.

CHART I

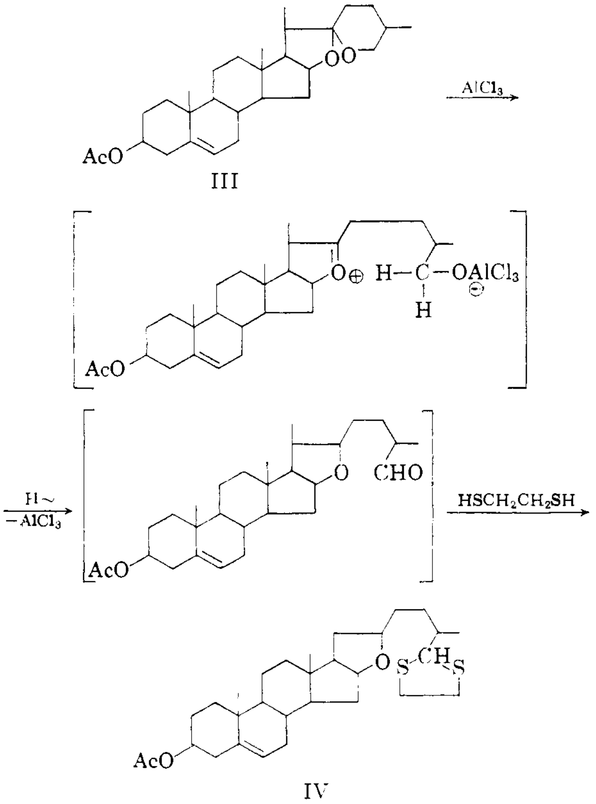
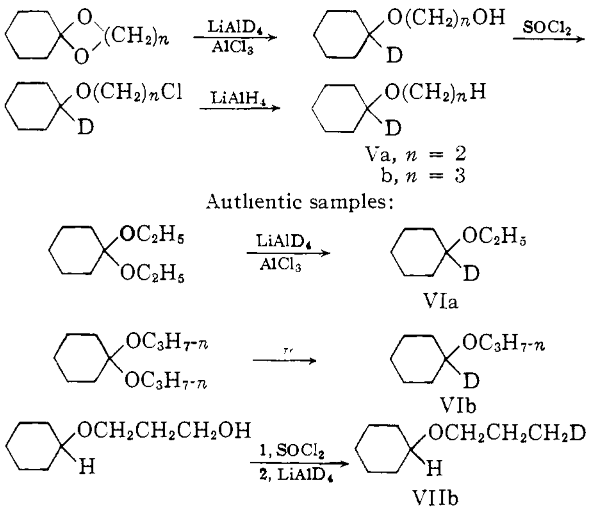


CHART II



Mass spectral patterns
Va ≡ VIa; Vb ≡ VIb; Vb ≢ VIIb

Following preliminary publication of this work[5] four other studies on hydrogenolysis of acetals and ketals have appeared.[13–15] One[13] employs catalytic hydrogenation in the presence of hydrogen chloride. Although the method avoids the use of the expensive lithium aluminum hydride, it gives ethers in only poor yields, along with many side products. The second report[14] refers to the use of lithium aluminum hydride–boron trifluoride. The work-up procedure is stated[14] to be somewhat simpler when aluminum chloride is replaced by boron trifluoride,[16] but it has not yet been explored whether replacement of $AlCl_3$ by BF_3 leads to an efficacious reducing agent in all cases. In our own work we have been able to replace LAH–aluminum chloride by lithium hydride–aluminum chloride with only a catalytic amount of LAH.[17]

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[12] G. R. Pettit and W. J. Bowyer, *J. Org. Chem.*, **25**, 84 (1960).

[13] W. L. Howard and J. H. Brown, *ibid.*, **26**, 1026 (1961); see also L. W. Covert, R. Connor and H. Adkins, *J. Am. Chem. Soc.*, **54**, 1651 (1932).

[14] A-R. Abdun-nur and C. H. Issidorides, *J. Org. Chem.*, **27**, 67 (1962).

[15] (a) E. Frainnet, R. Calas and A. Bazouin, *Bull. soc. chim. France*, 1480 (1960); (b) J. Cheymol, J. Seyden-Penne and J.-M. Benoist, *Compt. rend.*, **252**, 3072 (1961).

[16] The yields are also claimed[14] to be higher. However, in as much as we have improved the yields employing $AlCl_3$ since our original publication[5] by the use of a larger excess of hydride, there is probably no real difference between BF_3 and $AlCl_3$ in this regard.

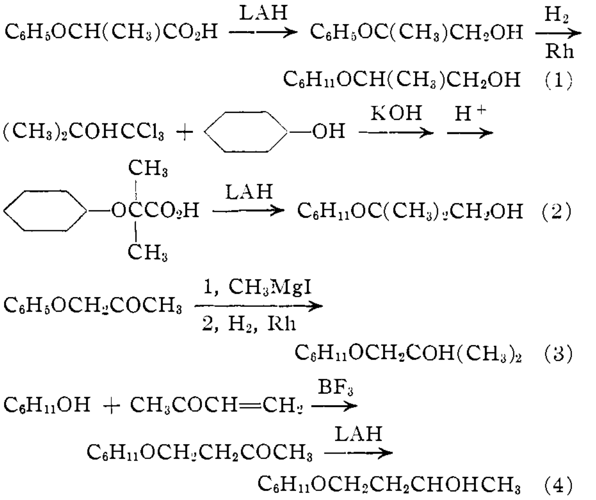
[17] Lithium hydride and aluminum chloride in the presence of a catalytic amount of LAH do, of course, form more LAH: A. E. Finholt, A. C. Bond and H. I. Schlesinger, *J. Am. Chem. Soc.*, **69**, 1199 (1947).

The third report[15a] is concerned with hydrogenolysis of acetals by triethylsilane–zinc chloride, but the primary objective of this reaction seems to be the synthesis of triethylalkoxysilanes rather than of ethers.

The last report[15b] is a negative one: reduction of benzophenone trimethylene ketal with LAH–$AlCl_3$ yields no hydroxyether but either diphenylmethane or benzophenone, depending on proportions of reagents.

Although many of the compounds synthesized in the course of this investigation were already known, authentic samples were prepared for purposes of comparison in most instances, including all cases where two isomeric reduction products were possible (Table I, last entry; Table III, entries 3–5, 8). A few of the compounds obtained are, however, new; their syntheses by alternate routes are shown in Chart III. These syntheses were, in general, quite tedious and serve to emphasize the advantage of the ketal hydrogenolysis method here described, especially in view of the recently reported[18] new and convenient routes to the acetals and ketals required as starting materials.

CHART III



Experimental

All melting and boiling points are uncorrected. Melting points were determined on a Kofler micro-hot-stage.

Mass spectra were recorded by Mr. George Hennion, Jr., on a Consolidated model 21-103A analytical mass spectrometer.

Infrared spectra were recorded by Mr. Charles Lynch, Mr. Joel Livingston and V.B. on a Baird double beam instrument. Gas chromatographic determinations were effected on a Wilkens Instrument and Research, Inc. Aerograph model A-90-B equipped with a Brown 10-Mv. recorder using helium as a carrier gas. Nuclear magnetic resonance spectra were recorded by Mr. Bernard Nowak on a Varian high resolution instrument. Elementary analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

α-Phenethyl Ethyl Ether (α-Methylbenzyl Ethyl Ether).—Anhydrous aluminum chloride (13.33 g., 0.1 mole) was placed in a 500-ml. three-necked flask equipped with a sealed stirrer, reflux condenser protected by a drying tube and a pressure-equalized addition funnel. The flask was cooled in an ice-bath and 100 ml. of Mallinckrodt anhydrous ether (pre-cooled for 30 minutes in a refrigerator) was added slowly with stirring. After all the aluminum chloride was dissolved (30 minutes), 25 ml. (0.025 mole) of 1.0 *M* clear, standardized ethereal lithium aluminum hydride was added with continued cooling and stirring. Thirty minutes later, 9.7 g. (0.05 mole) of acetophenone diethyl ketal[19] dissolved in 100 ml. anhydrous ether was added and the reaction mixture was stirred for 2 hours after removal of the ice-bath. The aluminum complexes were then destroyed by the addition of 100 ml. of 10% aqueous sulfuric acid with cooling (dropwise at first!), the clear ether layer was separated and the aqueous layer was three times extracted with 50-ml. portions of ether. During the hydrolysis, only 510 ml. of hydrogen (at S.T.P.) instead of the expected 1120 ml. was collected. The combined ether layers were dried over anhydrous potassium carbonate and concentrated. Distillation of the residue yielded 6.14 g. (82%) of ethyl α-phenethyl ether, b.p. 72–74° (15 mm.), $n^{25}D$ 1.4834 (lit.[20] b.p. 89° (31 mm.), $n^{25}D$ 1.4846) whose infrared spectrum was identical, except for the appearance of a very small conjugated ketone peak at 1680 $cm.^{-1}$ (probably due to acetophenone), with that of authentic ethyl α-methylbenzyl ether.[20] The gas chromatogram of the ketal reduction product gave evidence of only very minor impurities.

In an earlier experiment where only 0.0156 mole of $LiAlH_4$ solution and 0.063 mole of $AlCl_3$ was used for the above amount of ketal, the reaction mixture turned deep red after about three-fourths of the ketal had been added to the reaction vessel. The yield of ethyl α-phenethyl ether, b.p 70–76° (15–16 mm.), $n^{25}D$ 1.4845, was only 4.77 g. (64%) and there was isolated 0.5 g. (10%) of 1,3,5-triphenylbenzene, m.p. 174° after recrystallization (lit.[21] m.p. 174.3–174.5°).

The same product (1.03 g., m.p. 175°) was obtained in 61% yield by treating ethereal acetophenone diethyl ketal (3.17 g. in 100 ml. of anhydrous ether) with ethereal aluminum chloride (2.78 g. in 50 ml. of anhydrous ether) at reflux for 2 hours. The product was worked up by treatment with 10% aqueous sodium hydroxide, ether extraction, distillation of all volatile material and treatment of the residue with petroleum ether, followed by recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°).

Reduction of other Ketals and Acetals.—In a manner similar to the above, the reductions summarized in Table I were accomplished. Benzaldehyde dimethyl acetal[22] gave benzyl methyl ether, b.p. 60° (12 mm.), $n^{20}D$ 1.5021 (lit.[23] b.p. 170.5° (760 mm.), $n^{20}D$ 1.5022) in 88% yield. Benzaldehyde diethyl acetal[24] gave benzyl ethyl ether b.p. 75–77° (23 mm.), $n^{20}D$ 1.4889 (lit.[25,26] b.p. 70–71.5° (12 mm.), $n^{20}D$ 1.4954) identical in infrared spectrum with an authentic sample. The yield (72%) is probably not optimal since only 1.25 moles of LAH per mole ketal was employed and considerable high-boiling material resulted. *n*-Butyraldehyde diethyl acetal[27] (14.6 g.) gave 3.0 g. of an *n*-butyl ethyl ether–ethanol azeotrope, b.p. 72–90°, $n^{25}D$ 1.3722 (lit.[28] b.p. 73–74° containing 60% *n*-butyl ethyl ether) and 3.3 g. of ethyl *n*-butyl ether, b.p. 90–92° (745 mm.), $n^{25}D$ 1.3790, identical with an authentic sample (lit.[29] b.p. 92.3° (760 mm.), $n^{25}D$ 1.3798); total yield at least 5.1 g. (51%). Acetone di-*n*-butyl ketal[18] gave 7.1 g. of a mixture, b.p. 104–120°, $n^{20}D$ 1.3958, which, according to a gas chromatogram on a 5-ft. silicone oil column at 95°, contained 6.4% ethanol, 24.7% 1-butanol and 68.9% isopropyl *n*-butyl ether. The yield of the ether is thus 4.9 g. (84%). Cyclohexanone dimethyl ketal[18a] similarly gave cyclohexyl methyl ether, b.p. 122° (754 mm.), $n^{20}D$ 1.4362 (lit.[63] b.p.

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[18] N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, (1960): (a) p. 521, (b) 525, (c) p. 1814.

[19] R. C. Fuson and D. M. Burness, *J. Am. Chem. Soc.*, **68**, 1270 (1946).

[20] K. Mislow, *ibid.*, **73**, 4043 (1951).

[21] G. P. Baxter and A. H. Hale, *ibid.*, **58**, 510 (1936).

[22] E. Fischer and G. Giebe, *Ber.*, **31**, 545 (1898).

[23] W. T. Olson, H. F. Hipsher, C. M. Buess, I. A. Goodman, I. Hart, J. H. Lamneck and L. C. Gibbons, *J. Am. Chem. Soc.*, **69**, 2451 (1947).

[24] L. Claisen, *Ber.*, **40**, 3906 (1907).

[25] C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).

[26] F. Drahowzal and D. Klamann, *Monatsh.*, **82**, 594 (1951).

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133° (760 mm.), $n^{20}\mathrm{D}$ 1.4346) in 74% yield. Its infrared spectrum showed small alcohol and ketone impurities. Cyclohexanone diethyl ketal[18a] gave cyclohexyl ethyl ether, b.p. 66°(42 mm.), $n^{20}\mathrm{D}$ 1.4350 (lit.[30] b.p. 146.2–146.4° (725 mm.), $n^{20}\mathrm{D}$ 1.4401) in 78% yield. Its infrared spectrum was identical (except for the presence of a small band due to carbonyl impurity at 1700 cm.$^{-1}$) with that of an authentic specimen, b.p. 76° (82 mm.), $n^{20}\mathrm{D}$ 1.4374, prepared from β-hydroxyethyl cyclohexyl ether (see below) by conversion to the *p*-toluenesulfonate followed by reduction with lithium aluminum hydride. Cyclohexanone di-*n*-propyl ketal[18a] gave cyclohexyl *n*-propyl ether, b.p. 100–106° (92–96 mm.), $n^{20}\mathrm{D}$ 1.4368 (lit.[30] b.p. 170.5–171.5° (728 mm.), $n^{20}\mathrm{D}$ 1.4394) in 74% yield, identical in infrared spectrum with a sample prepared from α-hydroxypropyl cyclohexyl ether (see below) by conversion to the chloride followed by reduction with lithium aluminum hydride. Cyclohexanone *n*-butyl ketal[18a] similarly gave cyclohexyl *n*-butyl ether, b.p. 76° (11 mm.), $n^{20}\mathrm{D}$ 1.4388 (lit.[30] b.p. 193.5–194.5° (734 mm.), $n^{20}\mathrm{D}$ 1.4385) in 61% yield. The product was gas chromatographically homogeneous and was further identified by comparison of its infrared spectrum with that of an authentic sample (b.p. 80° (15 mm.), $n^{20}\mathrm{D}$ 1.4389) prepared by catalytic hydrogenation of *n*-butyl phenyl ether over a 5% rhodium-on-alumina catalyst.

4-*t*-Butylcyclohexanone Dimethyl Ketal and its Reduction.—When 34 g. (0.32 mole) of trimethyl orthoformate and 38.5 g. (0.25 mole) of 4-*t*-butylcyclohexanone (kindly supplied by the Dow Chemical Co.) in 100 ml. of anhydrous methanol in a flask equipped with a reflux condenser were made to react by the addition of a few crystals of *p*-toluenesulfonic acid, an exothermic reaction set in. After standing for 3 days, the solution was made basic with sodium methoxide in methanol, concentrated and distilled to give 48.0 g. (96%) of 4-*t*-butylcyclohexanone dimethyl ketal, b.p. 106° (10 mm.), $n^{20}\mathrm{D}$ 1.4498. In a second run where more careful temperature control was exercised in the early stages of the reaction, the product crystallized; m.p. 38° after two recrystallizations from petroleum ether.

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.08: H, 11.98.

The ketal showed a split methyl peak (separation about 2c./s. at 60 mc.) in the n.m.r. spectrum.[31]

Reduction of 9.2 g. (0.041 mole) of the above ketal in the usual way gave 6.44 g. (92%) of mixed 4-*t*-butylcyclohexyl methyl ether, b.p. 90° (14 mm.), $n^{20}\mathrm{D}$ 1.4512. An authentic sample of the mixed ethers was prepared in 56% yield by treating mixed 4-*t*-butylcyclohexanol (kindly supplied by the Dow Chemical Co.) with diazomethane in the presence of boron trifluoride etherate[32]; b.p. 90° (14 mm.), $n^{25}\mathrm{D}$ 1.4527. Both samples showed two major components of identical retention times, presumably the *cis* and *trans* isomers of the ether. (In addition, the sample from the ketal showed an impurity which from the gas chromatogram and infrared spectrum appeared to be 4-*t*-butylcyclohexanone, whereas the sample from the diazomethane reaction was similarly shown to be contaminated with the 4-*t*-butylcyclohexanols.) Since the 4-*t*-butylcyclohexanol used to synthesize the authentic ethers was rich in *trans* isomer (*ca.* 75%), it was assumed that the ether obtained from this alcohol was also rich in *trans* isomer. On this basis, then, the *trans* isomer has the higher retention time in the gas chromatogram and the reduction product of the ketal contains 18% *cis* isomer and 82% *trans* isomer (disregarding ketone).

Reduction Using Lithium Hydride–Aluminum Chloride.—To a solution of 13.33 g. (0.1 mole) of aluminum chloride in 100 ml. of anhydrous ether prepared as described above was added a slurry of 0.8 g. (0.1 mole) of lithium hydride in 10 ml. of ether. A few ml. of *ca.* 1 *M* ethereal $LiAlH_4$ was added as a catalyst and the mixture was stirred at reflux for 6 hours. Ten grams (0.05 mole) of 4-*t*-butylcyclohexanone dimethyl ketal in 100 ml. of ether was then added slowly and boiling was continued for 2 hours. After the usual work-up (during which an accidental loss occurred) there was obtained 3.88 g. (46%) of 4-*t*-butylcyclohexyl methyl ether, b.p. 90° (11 mm.), $n^{20}\mathrm{D}$ 1.4517, containing 83% of *trans* and 17% of *cis* isomer. The yield is not the best obtainable.

Cyclohexanone Ethylene Ketal (1,4-Dioxaspiro [4.5]-decane).—The above ketal[33] (7.1 g., 0.05 mole) dissolved in 100 ml. of ether was reduced by means of a hydride solution prepared from 13.33 g. (0.1 mole) of aluminum chloride in 100 ml. of ether and 25 ml. of 1.0 *M* ethereal lithium aluminum hydride (0.025 mole) as described earlier. After the usual work-up procedure the product was distilled to give 6.32 g. (88%) of 2-cyclohexyloxyethanol, b.p. 100° (14 mm.), $n^{25}\mathrm{D}$ 1.4610 (lit.[34] b.p. 103° (20 mm.), $n^{25}\mathrm{D}$ 1.4590). An authentic sample[35] was prepared as follows: Cyclohexanol was allowed to react with sodium in dry xylene, followed by chloroacetic acid. Extraction with aqueous base followed by acidification and extraction yielded cyclohexyloxyacetic acid in 41% yield, b.p. 100–110° (0.2 mm.), $n^{25}\mathrm{D}$ 1.4662 (lit.[36] b.p. 165° (25 mm.), $n^{25}\mathrm{D}$ 1.4691). Reduction of the acid with ethereal lithium aluminum hydride yielded 2-cyclohexyloxyethanol, b.p. 100° (14 mm.), $n^{25}\mathrm{D}$ 1.4605, in 74% yield. This material was identical in infrared spectrum with the hydrogenolysis product.

Using the different ratios of reagents indicated in Table II in the reduction of cyclohexanone ethylene ketal, the amounts of product and recovered starting material there indicated were obtained. Products were separated by distillation and further analyzed by gas chromatography on a Ucon polar column.

Reduction of Other Cyclic Ketals and Acetals.—Cyclohexanone propylene ketal[33] gave a mixture of cyclohexyloxypropanols, b.p. 100° (12 mm.), $n^{20}\mathrm{D}$ 1.4588, in 85% yield. Gas chromatography indicated that the isomeric composition of this mixture was 17–19% 1-cyclohexyloxy-2-propanol and 81–83% 2-cyclohexyloxy-1-propanol (the duplicate analyses refer to repeat preparations). The analysis was confirmed by quantitative infrared measurements. The authentic samples required for calibration were synthesized as described below. Cyclohexanone trimethylene ketal[3] was reduced to 3-cyclohexyloxy-1-propanol, b.p. 124° (14 mm.), $n^{25}\mathrm{D}$ 1.4625 (lit.[37] b.p. 91–93° (2 mm.), $n^{25}\mathrm{D}$ 1.4600) in 89–92% yield. An authentic sample, prepared in only 9% yield from cyclohexanol, sodium and 3-chloro-1-propanol in *t*-butyl alcohol solution, had b.p. 124° (13 mm.), $n^{25}\mathrm{D}$ 1.4530, and contained several impurities according to its gas chromatogram; nevertheless the infrared spectrum of this material was essentially identical with that of the hydrogenolysis product. Reduction of cyclohexanone 1,3-butylene ketal[33] gave a mixture of hydroxyethers, b.p. 122°(10 mm.), $n^{20}\mathrm{D}$ 1.4613, in 93% yield. The composition, determined for two separate reduction products by gas chromatography, was 69% 3-cyclohexyloxy-1-butanol and 31% 4-cyclohexyloxy-2-butanol. The retention time of the latter component was established by synthesis of an authentic sample as described below. Both ether–alcohols were collected from the gas column. The minor product was identical in infrared spectrum with authentic 4-cyclohexyloxy-2-butanol (see below). The infrared and n.m.r. spectra of the major component were compatible with those to be expected for 3-cyclohexyloxy-1-butanol. Benzaldehyde ethylene acetal[33,38] upon reduction gave 2-benzyloxyethanol, b.p. 135° (13 mm.), $n^{20}\mathrm{D}$ 1.5217 (lit.[39] b.p. 95° (0.25 mm.), $n^{20}\mathrm{D}$ 1.5209) in 89% yield. Its infrared spectrum was identical with that of a commercial sample (Eastman Kodak Co.). Benzaldehyde trimethylene acetal[33,40] was reduced to 3-benzyloxy-1-propanol, b.p. 110° (0.5 mm.), $n^{20}\mathrm{D}$ 1.5152 (lit.[41] b.p. 114°

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(0.9 mm.), n^{20}D 1.5184), in 83% yield. The product was identical in infrared spectrum with authentic 3-benzyloxy-1-propanol, b.p. 110–112° (0.5 mm.), n^{20}D 1.5152, prepared from benzyl chloride, excess 1,3-propanediol and sodium in xylene (61% yield). Benzaldehyde 1,3-butylene acetal[33,42] was reduced to a mixture of benzyloxybutanols, b.p. 96° (0.7 mm.), n^{20}D 1.5093, in 94% yield. Gas chromatography revealed the composition: 66%, 3-benzyloxy-1-butanol and 34%, 4-benzyloxy-2-butanol. The calibration sample of the latter component was synthesized as described below.

Cyclohexanone Isobutylene Ketal and its Reduction.—The ketal was prepared from cyclohexanone and isobutylene glycol[43] by the method of Salmi[33] in 33% yield; b.p. 74° (11 mm.), n^{20}D 1.4460.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.38. Found: C, 70.61; H, 10.66.

Reduction of this ketal with mixed hydride by the general method described earlier gave 1-cyclohexyloxy-2-methyl-2-propanol, b.p. 91–92° (10 mm.), n^{20}D 1.4508, in 89% yield. The infrared spectrum of this product was identical with that of authentic material (see below) and the spectrum as well as the gas chromatogram revealed the absence of the isomeric 2-cyclohexyloxy-2-methyl-1-propanol which was also synthesized (see below).

2-Cyclohexyloxy-2-methyl-2-propanol.—2-Cyclohexyloxy-2-methylpropanoic acid was synthesized from cyclohexanol, potassium hydroxide and 1,1,1-trichloro-2-methyl-2-propanol dihydrate[44] in 10% yield, m.p. 84° (lit. 74–75,[36] 90°[45]). Reduction of this acid with lithium aluminum hydride gave the alcohol in 89% yield, b.p. 104° (11 mm.), n^{20}D 1.4605 (super-cooled), m.p. 51°. The n.m.r. spectrum of the compound was in agreement with the assigned structure.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 70.10; H, 11.70.

1-Cyclohexyloxy-2-methyl-2-propanol.—1-Phenoxy-2-methyl-2-propanol, b.p. 54° (0.3 mm.), n^{20}D 1.5125 (lit.[46] b.p. 125–125.5° (20 mm.), n^{20}D 1.5120) was prepared in *ca.* 70% yield from phenoxyacetone and methylmagnesium iodide. The crude product was washed with sodium bisulfite solution to remove unchanged starting material. Hydrogenation of the aromatic ring was effected with 5% rhodium-on-alumina (0.6 g. for 6.64 g. of substance) in 40 ml. of absolute ethanol at 49 p.s.i. of hydrogen. After the theoretical amount of hydrogen had been taken up, the solution was filtered, concentrated and distilled to give 5.6 g. (82%) of 1-cyclohexyloxy-2-methyl-2-propanol, b.p. 93–94° (11 mm.), n^{20}D 1.4510. The infrared and n.m.r. spectrum of this material were compatible with the postulated structure.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 70.45; H, 11.65.

2-Cyclohexyl-1-propanol.—2-Phenoxypropanoic acid was reduced by means of ethereal lithium aluminum hydride to 2-phenoxy-1-propanol, b.p. 128° (10 mm.), n^{20}D 1.5261 (lit.[47] b.p. 120° (10 mm.), n^{20}D 1.4760) in 82% yield. Hydrogenation was effected over 5% rhodium-on-alumina as described above and yielded 2-cyclohexyloxy-1-propanol, b.p. 101° (10 mm.), n^{20}D 1.4590, in 91% yield. Its n.m.r. spectrum was compatible with the assigned structure.

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.62, 67.53; H, 10.66, 11.56.

1-Cyclohexyloxy-2-propanol.—Phenoxyacetone was reduced to 1-phenoxy-2-propanol, b.p. 125° (10 mm.), n^{25}D 1.5210 (lit.[47] b.p. 116–117° (10 mm.), n^{25}D 1.5200) in 53% yield by means of ethereal lithium aluminum hydride. Catalytic hydrogenation over 5% rhodium-on-alumina yielded 1-cyclohexyloxy-2-propanol, b.p. 100° (15 mm.), n^{20}D 1.4568 (lit.[48] b.p. 105–106° (20 mm.), n^{20}D 1.4557) in 67% yield. The n.m.r. spectrum of the substance agreed with the assigned structure.

4-Cyclohexyloxy-2-butanol.—To a mixture of 5.0 g. (0.05 mole) of cyclohexanol and 5.0 g. (0.055 mole) of methyl vinyl ketone was added 1 ml. of freshly distilled boron trifluoride etherate. After 3 days the mixture was poured into 100 ml. of 1% aqueous sodium hydroxide and extracted with one 100-ml. and three 50-ml. portions of ether. The ether layers were dried and concentrated and the residue distilled to give 5.04 g. (59%) of 4-cyclohexyloxy-2-butanone, b.p. 68° (0.5 mm.), n^{20}D 1.4533 (lit.[49] b.p. 111–112° (16 mm.), n^{20}D 1.4585). Reduction of this ketone with lithium aluminum hydride gave 4-cyclohexyloxy-2-butanol, b.p. 52° (0.1 mm.), n^{20}D 1.4592, in 87% yield. The n.m.r. spectrum was in agreement with the assigned structure.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 70.15; H, 11.76.

4-Benzyloxy-2-butanol was synthesized from benzyl alcohol and methyl vinyl ketone *via* 4-benzyloxy-2-butanone in exactly the same way as described above for the corresponding cyclohexyl compound. 4-Benzyloxy-2-butanone obtained in 74% yield boiled at 46–60° (0.03 mm.), n^{20}D 1.5022 (lit.[50] b.p. 88–91° (0.5 mm.), n^{28}D 1.5040) and was reduced to 4-benzyloxy-2-butanol, b.p. 77° (0.1 mm.), n^{20}D 1.5080 (lit.[51] b.p. 110–112° (1–2 mm.), n^{25}D 1.5042) in 91% yield. The product appeared homogeneous in a gas chromatogram on Carbowax and the infrared and n.m.r. spectra were in agreement with the assigned structure.

Deuterated Ethers.—**Cyclohexyl-1-*d* ethyl ether (VIa)** was prepared in 52% yield from cyclohexanone diethyl ketal, lithium aluminum deuteride and aluminum chloride in the way indicated earlier for the unlabeled compound, b.p. 74° (75 mm.), n^{20}D 1.4308. The sample was slightly contaminated with cyclohexanone, as shown by infrared analysis. It was purified by gas chromatography and collected for mass spectrometry (Table IV). The purified material was 98.6% monodeuterated, as indicated by a mass spectrum at reduced ionizing voltage.[52]

Cyclohexyl-1-*d* *n*-propyl ether (VIb) was similarly prepared in 63% yield from cyclohexanone di-*n*-propyl ketal, b.p. 60° (12 mm.), n^{20}D 1.4368. This sample, also, contained some cyclohexanone and was purified by gas chromatography before being subjected to mass spectrometry (Table IV). It was 98.4% monodeuterated.

Cyclohexyl *n*-Propyl-3-*d* Ether (VIIb).—3-Cyclohexyloxy-1-chloropropane was prepared from the earlier-described 3-cyclohexyloxy-1-propanol (4.74 g., 0.03 mole) in 2.4 ml. (0.03 mole) of pyridine by the gradual addition of 3.5 ml. (0.045 mole) of thionyl chloride with stirring and cooling in an ice-bath. After 2 further hours stirring at 70° the mixture was poured into 500 ml. of ice-cold 10% hydrochloric and the product twice extracted with 100-ml. portions of ether. The ether solutions were washed successively with three portions each of 10% hydrochloric acid, saturated aqueous bicarbonate and saturated aqueous sodium chloride, and were then combined, dried over potassium carbonate and concentrated. Distillation of the residue gave 3.97 g. (74%) of chloride, b.p. 96° (11 mm.), n^{20}D 1.4626. This product (3.55 g., 0.02 mole) was then reduced with lithium aluminum deuteride (1.68 g., 0.04 mole) in tetrahydrofuran in the usual way,[53] to give 1.8 g. (65%) of cyclohexyl *n*-propyl-3-*d* ether, b.p. 58° (10 mm.), n^{20}D 1.4350 which, after purification by gas chromatography, was subjected to mass spectrometry (Table IV). The sample was 98.4% monodeuterated.

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TABLE IV

MASS SPECTRA OF DEUTERATED MATERIALS

m/e	Va	VIa	Vb	VIb	VIIb
27	23.16	22.73	12.94	12.84	17.66
39	11.69	11.70	17.54	16.85	21.53
41	16.20	16.13	36.45	35.38	41.23
43	7.98	7.75	41.98	41.72	14.93
44	7.18	7.11	7.23	6.99	48.96
45	15.41	15.60	12.32	12.92	6.79
55	13.53	13.62	21.83	21.43	39.23
56	11.28	11.42	24.37	24.21	7.66
57	4.95	4.33	7.82	7.33	100
58	70.80	71.89	100	100	21.77
67	2.81	2.78	4.25	4.02	11.99
82	4.16	4.21	6.63	6.39	25.04
83	10.45	10.49	23.72	23.52	58.13
84	9.59	9.81	55.30	54.72	5.10
85	4.72	3.85	4.35	4.92	0
86	100	100	...	...	...
100	10.30	10.41	64.70	62.08	73.92

Reduction of Cyclohexanone Ethylene Ketal.—The reduction of 5.68 g. (0.04 mole) of this ketal with 0.84 g. (0.02 mole) of lithium aluminum deuteride and 10.66 g. (0.08 mole) of aluminum chloride in anhydrous ether was carried out according to the general procedure described earlier except that the deuteride was added as an ether suspension rather than as a standard solution. The yield of 2-cyclohexyloxyethanol-*d*, b.p. 100° (12 mm.), $n^{20}D$ 1.4629, was 5.07 g. (88%). For purposes of analysis, this sample was transformed into 2-cyclohexyloxy-1-chloroethane in the way described above for the higher (undeuterated) homolog. The chloride, obtained in 78% yield, boiled at 94° (12 mm.), $n^{20}D$ 1.4633, and was reduced to deuterated cyclohexyl ethyl ether, b.p. 70–80° (55 mm.), $n^{20}D$ 1.4302, by means of lithium aluminum hydride in tetrahydrofuran. The product was purified by gas chromatography and then submitted to mass spectrometry. The mass spectrum is shown in Table IV (sample Va). Mass spectrometry at reduced ionizing voltage indicated 97.6% monodeuteration for Va. It is clear from Table IV that Va is identical with VIa (cyclohexyl-1-*d* ethyl ether).

Reduction of Cyclohexanone Trimethylene Ketal.—This experiment was carried out in the same way as that for the lower homolog described above. 3-Cyclohexyloxy-1-propanol-*d*, b.p. 66° (0.3 mm.), $n^{20}D$ 1.4620, was obtained in 91% yield and was converted to the chloride, b.p. 96° (11 mm.), $n^{20}D$ 1.4622, in 78% yield. The chloride, in turn, was reduced to deuterated cyclohexyl *n*-propyl ether, b.p. 58° (10 mm.), $n^{20}D$ 1.4351 (sample designated as Vb) in 52% yield. The sample was purified by gas chromatography prior to mass spectrometry; isotopic purity 97.3%. The mass spectrum, shown in Table IV, clearly indicates that the reaction product Vb is cyclohexyl-1-*d* *n*-propyl ether (VIb) and not cyclohexyl *n*-propyl-3-*d* ether (VIIb), which latter compound was absent in Vb. Infrared spectroscopy confirmed this conclusion: both Vb and VIb have characteristic bands at 1390 and 820 cm.$^{-1}$; the characteristic bands of VIIb at 1370 and 850 cm.$^{-1}$ were absent in Vb.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT AND RADIATION LABORATORY[1] OF THE UNIVERSITY OF NOTRE DAME, NOTRE DAME, IND.]

Reductions with Metal Hydrides. XIII. Hydrogenolysis of Hemithioacetals and Hemithioketals with Lithium Aluminum Hydride–Aluminum Chloride[1]

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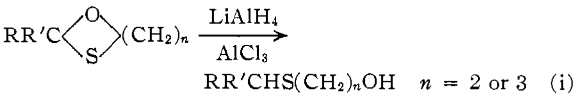
The reduction of cyclic hemithioacetals and hemithioketals with lithium aluminum hydride–aluminum chloride leads to β-hydroxyethyl and γ-hydroxypropyl sulfides, usually in excellent yields. Carbon–oxygen cleavage occurs to the exclusion of carbon–sulfur cleavage. Upon prolonged reaction with the "mixed hydride," further hydrogenolysis of the β-hydroxyethyl sulfide function to an ethyl sulfide function takes place. Tracer studies indicate that this hydrogenolysis proceeds *via* a cyclic sulfonium ion. Both the hydroxyalkyl sulfides and the alkyl sulfides have been transformed into a variety of other products. The mixed hydride reduction serves as a novel and convenient synthesis of thioethers from aldehydes and ketones: $RR'CO \rightarrow RR'CHSCH_2CH_2X$ where $X = OH, H$ or CH_2OH.

In the previous paper,[2] the hydrogenolysis of acetals and ketals to hydroxyethers by "mixed hydride"[3] (lithium aluminum hydride–aluminum chloride in a 1:4 ratio) in ether solution was described. This method has now been extended to hemithioacetals and hemithioketals. In all cases, cleavage of the carbon–oxygen bond occurred exclusively (eq. i), the carbon–sulfur bond remaining intact, as evidenced by the absence of base-soluble mercaptans among the reaction products


$$\xrightarrow[AlCl_3]{LiAlH_4} RR'CHS(CH_2)_nOH \quad n = 2 \text{ or } 3 \quad (i)$$

The compounds reduced and yields of reduction products are shown in Table I.

In most instances, the yields of hydroxysulfides are excellent. In the few cases where yields were low, this was traced to further hydrogenolysis of the β-hydroxyethyl sulfides to ethyl sulfides[4] (eq. ii)

$$RR'CHSCH_2CH_2OH \xrightarrow[AlCl_3]{LiAlH_4} RR'CHSCH_2CH_3 \quad (ii)$$

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[1] The Radiation Laboratory is operated under contract with the Atomic Energy Commission. This paper is taken in part from the Ph.D. dissertations of Louis A. Pilato and Victor G. Badding; for a preliminary report, see *J. Am. Chem. Soc.*, **81**, 6087 (1959).

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[4] Hydrogenolysis of the alcohol function may sometimes be minimized by avoiding an excess of mixed hydride. Thus the difference in yield of *trans*-4-*t*-butylcyclohexyl β-hydroxyethyl sulfide from the two diastereoisomeric 4-*t*-butylcyclohexanone ethylene hemithioketals (Table I) is undoubtedly occasioned by the fact that a larger excess of hydride (leading to more hydrogenolysis) was used with the liquid isomer than with the solid. When the same large excess (200%) was used with the solid isomer, 21% of the ethyl thioether resulted along with 77% of the β-hydroxyethyl thioether. In some instances, however, quite extensive hydrogenolysis seems to be unavoidable because it occurs at a rate comparable to that of the primary hemithioketal cleavage. A case in point is the ethylene hemithioketal of camphor (Table I). The causes responsible for this are not yet completely understood.