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Reductions with Metal Hydrides. X. The Stereochemistry of Reduction of 3,3,5-Trimethylcyclohexanone with Complex Aluminohydrides

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The stereochemistry of reduction of 3,3,5-trimethylcyclohexanone with lithium aluminum hydride in diethyl ether is independent of the proportion of reactants and order of their addition, giving in all cases $55 \pm 3\%$ of the axial alcohol trans-3,3,5-trimethylcyclohexanol. Higher proportions of the axial alcohol are formed with various lithium aluminum alkoxyhydrides. It is proposed that alkoxyhydrides are not involved in the reduction of 3,3,5-trimethylcyclohexanone with LiAlH$_4$ but that, as soon as they are formed, they disproportionate to lithium aluminum tetraalkoxide (insoluble) and lithium aluminum hydride which latter species is the only effective reducing agent throughout the reaction. Similar results are observed in tetrahydrofuran as a solvent, except that the proportion of axial alcohol formed is about 15–20% greater than in diethyl ether.

Lithium aluminum hydride, discovered by Schlesinger, Bond and Finholt,[1] is one of the most useful reducing agents in organic chemistry.[2] The ketone function frequently has been reduced by this reagent and the stereochemistry of the resulting carbinols, in cases where two epimeric products may result, has been a matter of interest.[3,4] Although the reduction of a ketone (which requires one equivalent of hydride) by the LiAlH$_4$ reagent (which has four disposable hydride equivalents) may, in principle, involve three intermediate stages—LiAlH$_3$(OR), LiAlH$_2$(OR)$_2$ and LiAlH(OR)$_3$—not much is known about the actual role these intermediates play, if any. Cram and Greene[5] observed that the reduction of 3-cyclohexyl-2-butanone with lithium aluminum hydride gave the *threo* and *erythro* isomers of 3-cyclohexyl-2-butanol in the same ratio, regardless of whether the ketone was added to the solution of hydride (in which case hydride was in excess during the reduction) or whether hydride was added slowly to ketone (in which case ketone was in excess most of the time). The authors inferred it to be unlikely that in the former case most of the reduction was effected by LiAlH$_4$ and in the latter by species of the type LiAlH$_n$(OR)$_{4-n}$ (n = 1, 2 or 3), because this most probably would have given rise to differences in product composition, but they did not prove this point. They further inferred (incorrectly, as it now appears) that the second, third and fourth stage of the reduction involved alkoxyhydride species, but that these species are much faster reducing agents than LiAlH$_4$ and that they are therefore necessarily involved in preference to

LiAlH$_4$ even when a large excess of the latter reagent is available, as in the early stages of the "direct addition" procedure.[6] The observation that the ratio of epimeric products is independent of the order of mixing of the reactants has also been made in the case of the lithium aluminum hydride reduction of 3-cholestanone which gives 9–12% 3-β-cholestanol upon "normal" addition[7] and 13% 3-β-cholestanol upon "inverse" addition.[8] On the other hand, it has been found[9–11] that alkoxyaluminohydrides are less effective reducing agents than the AlH$_4^-$ species. This is clearly incompatible with the assumption (see above) that the second, third and fourth stage in the LiAlH$_4$ reduction involve alkoxyaluminohydride species which react much faster than lithium aluminum hydride itself.

The present work was undertaken to throw further light on this puzzling problem. The substrate chosen for study was 3,3,5-trimethylcyclohexanone (dihydroisophorone), because of its ready accessibility, because it gives the two diastereoisomeric reduction products *trans*-3,3,5-trimethylcyclohexanol (T) and *cis*-3,3,5-trimethylcyclohexanol (C) in nearly equal amounts with excess hydride,[12] and because the product mixture can be analyzed easily by gas chromatography on
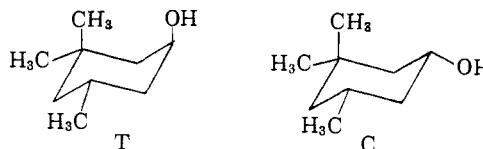
a Carbowax column. The latter two points make it possible to detect even small variations of the product isomer ratio T/C.

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(1) A. E. Finholt, A. C. Bond and H. I. Schlesinger, *J. Am. Chem. Soc.*, **69**, 1199 (1947).

(2) Reviews: (a) W. G. Brown, "Reductions by Lithium Aluminum Hydride," in R. Adams, ed., "Organic Reactions," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1951; (b) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956; (c) V. M. Mićović and M. L. Mihailović, "Lithium Aluminum Hydride in Organic Chemistry," Naukna Knjiga, Belgrade, Yugoslavia, 1955.

(3) W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(4) D. M. S. Wheeler and J. W. Huffman, *Experientia*, **16**, 516 (1960).

(5) D. J. Cram and F. D. Greene, *J. Am. Chem. Soc.*, **75**, 6005 (1953).

(6) The same point has been made for sodium borohydride by E. R. Garrett and D. A. Lyttle, *ibid.*, **75**, 6051 (1953), and H. C. Brown, E. J. Mead and B. C. Subba Rao, *ibid.*, **77**, 6209 (1955); however, these authors based their assertion on kinetic studies. See also H. Haubenstock and E. L. Eliel, *ibid.*, **84**, 2368 (1962).

(7) (a) H. R. Nace and G. L. O'Connor, *ibid.*, **73**, 5824 (1951); (b) E. L. Eliel and J.-C. Richer, *J. Org. Chem.*, **26**, 972 (1961).

(8) W. G. Dauben, R. A. Micheli and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).

(9) H. C. Brown and R. F. McFarlin, *ibid.*, **80**, 5372 (1958), especially footnote 16.

(10) C. J. Shoaf, Ph.D. Dissertation, Purdue University, 1957; *Dissertation Abstr.*, **17**, 1904 (1957).

(11) G. Hesse and R. Schrödel, *Ann.*, **607**, 24 (1957).

(12) K. D. Hardy and R. J. Wicker, *J. Am. Chem. Soc.*, **80**, 640 (1958).

The results of various reductions of dihydro-isophorone with lithium aluminum hydride and related reagents in diethyl ether are shown in Table I. With hydride alone (entries 1–3), one obtains 55% T (axial hydroxyl) and 45% C, a ratio very similar to that of 58% β-isomer and 42% α-isomer reported for the reduction of the analogously constituted 2-cholestanone.[13] In analogy with the earlier work cited above[5] we find the product ratio to be insensitive both to the amount of hydride used (compare entries 1 and 2) and the order of addition (compare 2 and 3).

Entries 4–6 and 8–9 (Table I) refer to lithium aluminum hydride modified by addition of alcohol prior to use in reduction. Methanol (entry 4),

TABLE I

REDUCTION OF DIHYDROISOPHORONE WITH LiAlH₄ AND MODIFIED LiAlH₄ REAGENTS IN DIETHYL ETHER

Entry	Addend	Moles addend / Mole LiAlH₄	Equiv. hydride[a] / Mole ketone	trans-(axial)-Alcohol,[a,b] %
1	......	..	1.24	52
2	......	..	8.4	55
3	......	..	1.00, 1.00	54,[c] 55[d]
4	Methanol	3	1.25	75[e]
5	Ethanol	3	1.2	83
6	Isopropyl alc.	3	1.3, 2	54, 54
7	Acetone	2	1.1	57
8	t-Butyl alc.	2	1.1	63
9[f]	t-Butyl alc.	3	1.07	73
10	Cyclohexanone	3	1.09	58[g]
11	d-Camphor	3	1.08	67
12	Al chloride	3.7	3.0, 3.6	86, 85
13[h]	Al chloride	4.2	0.91	0.0
14	Al chloride	0.34	..	12

[a] Figures separated by a comma represent the results of separate experiments. [b] Product composition was determined by gas chromatographic analysis using a Tide detergent column or a Carbowax 20M column (Aerograph instrument). [c] Inverse addition of hydride; 9% ketone found in product. [d] Inverse addition of hydride; 3% ketone found in product. [e] About 3% ketone in product. [f] Commercial LiAl(O–Bu-t)₃H from Metal Hydrides, Inc., gave 70% trans-(axial) alcohol. [g] About 48% unreduced ketone found in product. [h] Thermodynamic control. About 23% unreduced ketone in product; due to the instability of the AlH₃ solution, there was some question on the equivalents of hydride available for reduction.

ethanol (entry 5) and t-butyl alcohol (entry 9) yield a reagent which produces a greater amount of T than does LiAlH₄ alone, the maximum increase being from 55 to 83% for the ethanol-modified reagent. The modified reagent is presumably[9,10,14] a lithium aluminum trialkoxyhydride, LiAlH(OR)₃, although there is still some question about the exact composition of the ethoxide.[10] At first sight, the greater amount of T formed with these reagents might have been ascribed to their greater bulk, expected to impede approach to the ketone from the axial side required to form the equatorial alcohol C.[3] However, as has been pointed out before in another connection,[9] this is not the whole explanation, for the greatest amount of T is formed with
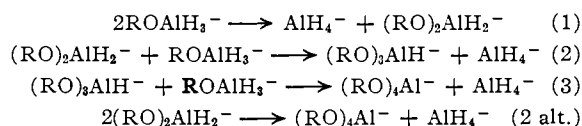
(13) W. G. Dauben, E. J. Blanz, J. Jiu and R. A. Micheli, J. Am. Chem. Soc., 78, 3752 (1956). Their yield—52% β, 37% α—has been normalized to add up to 100% here.

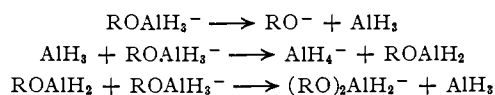(14) See also H. C. Brown, C. J. Shoaf and C. P. Garg, Tetrahedron Letters, No 3, 9 (1959).

lithium aluminum triethoxyhydride (entry 5) and not with the presumably more bulky tri-t-butoxy-hydride (entry 9). The di-t-butoxyhydride,[9] entry 8, gives only slightly more T than LiAlH₄ alone.

In view of the greater stereoselectivity of LiAlH(OR)₃ as compared to LiAlH₄ toward dihydro-isophorone, it is at first sight surprising that the product ratio T/C is insensitive to the amount of hydride used in the reduction and to the order of addition. If, regardless of the amount of hydride used, each LiAlH₄ molecule were completely used up as to reducing capacity [being, so-to-speak, "zipped down" to LiAl(OR)₄] as suggested by Cram and Greene,[5] our findings could be explained. However, this would require that LiAlH$_n$(OR)$_{4-n}$ is much more reactive in the reduction of ketones than LiAlH₄, an assumption clearly incompatible with the findings of Brown and McFarlin.[9] Therefore another explanation is required. We propose that the reason for our findings and those of the earlier workers is that *as soon as the first stage of reduction is accomplished, the resulting reagent, LiAlH₃(OR), very rapidly disproportionates to LiAlH₄ and LiAl(OR)₄.* The entire reduction is therefore effected by the species LiAlH₄, regardless of the order of addition.

The disproportionation, looked at in more detail, probably involves the stages

$$2ROAlH_3^- \longrightarrow AlH_4^- + (RO)_2AlH_2^- \quad (1)$$
$$(RO)_2AlH_2^- + ROAlH_3^- \longrightarrow (RO)_3AlH^- + AlH_4^- \quad (2)$$
$$(RO)_3AlH^- + ROAlH_3^- \longrightarrow (RO)_4Al^- + AlH_4^- \quad (3)$$
$$2(RO)_2AlH_2^- \longrightarrow (RO)_4Al^- + AlH_4^- \quad (2 \text{ alt.})$$

Each stage, in turn, probably is made up of individual steps of the following type, since it is not likely that two negative ions react with each other

$$ROAlH_3^- \longrightarrow RO^- + AlH_3$$
$$AlH_3 + ROAlH_3^- \longrightarrow AlH_4^- + ROAlH_2$$
$$ROAlH_2 + ROAlH_3^- \longrightarrow (RO)_2AlH_2^- + AlH_3$$

Corroborative evidence for the disproportionation hypothesis comes from entries 6, 7 and 10 in Table I. When a secondary alcohol such as isopropyl alcohol, or a ketone reducible to a secondary alcohol, such as acetone or cyclohexanone, is added to lithium aluminum hydride, the resulting reagent has the same stereoselectivity, within the limits of experimental error, as LiAlH₄ alone. It is particularly striking that isopropyl alcohol is quite out of line with methanol and ethanol on one side and t-butyl alcohol on the other. The logical explanation is that most secondary alcohols (and ketones reducible to secondary alcohols) do not yield stable LiAlH$_n$(OR)$_{4-n}$ reagents, but that these reagents, if formed, very rapidly disproportionate to LiAlH₄ and an insoluble tetraalkoxide (which does, in fact, precipitate from solution[10]). In the reduction of a ketone, such as 3,3,5-trimethylcyclo-hexanone, the primary product, is, of course, an alkoxyaluminohydride and disproportionation of this gives back the LiAlH₄: 4LiAlH$_n$(OR)$_{4-n}$ → nLiAlH₄ + (4 − n)LiAl(OR)₄.

If one explains the difference between primary and secondary alkoxyhydrides on the basis of a much greater tendency to disproportionate [to AlH₄⁻ and Al(OR)₄⁻] on the part of the latter,[10]

the question arises why the trend is reversed with t-alkoxyhydrides. It is possible that t-alkoxyhydrides, because of the larger bulk of the alkoxy group, disproportionate less rapidly than sec-alkoxyhydrides, but this kinetic explanation seems unpalatable since it requires a non-monotonous trend in the series prim. alkoxyhydride, sec. alkoxyhydride, tert. alkoxyhydride. We rather believe that the impediment to disproportionation in the case of the t-alkoxyhydrides is a thermodynamic one, based on the known difficulty of forming tetra-t-butoxyaluminohydride. In fact, our result with $LiAlH_4$ and two moles of t-BuOH (Table I, entry 8) is compatible with the assumption that the reagent formed under these circumstances was $^2/_3$ LiAl(O-t-Bu)$_3$H and $^1/_3$ $LiAlH_4$. The calculated product composition for such a reagent (from entries 1 and 9) would be 66% $trans$, in agreement with the 63% found, especially in view of the fact that the reagent was in slight excess and somewhat more than one-third of the reduction may thus have been effected by LAH. Unfortunately, the precipitate of LiAl-(O-t-Bu)$_3$H expected on the basis of this interpretation was not formed. More detailed product studies involving different ratios of LAH, 3,3,5-trimethylcyclohexanone and t-butyl alcohol are required to clear up this point.

There is one result in the literature which apparently contradicts our findings, namely, the reduction of 2-butanone to optically active 2-butanol by means of a reagent prepared from lithium aluminum hydride and (+)-camphor.[15] If the actual reducing agent in this reduction is $LiAlH_4$ rather than an optically active alkoxyhydride, it is hard to understand how an optically active product could be obtained, unless one is willing to invoke some rather nebulous "asymmetric induction" caused by the mere presence of the active isoborneol complex (formed by reduction of camphor), and the optical purity claimed for the 2-butanol ($ca.$ 20%) is rather too high for that. In view of this apparent inconsistency, we reduced 3,3,5-trimethylcyclohexanone with the $LiAlH_4$-camphor reagent. The result (entry 11, Table I) clearly shows that the reducing agent in this case is not $LiAlH_4$ but is (presumably) of the type $LiAlH_n(OR)_{4-n}$. It is quite reasonable that the bulky isobornyloxy-complex formed in the reduction of camphor would be disproportionate with difficulty, resembling in this respect the tri-t-butoxy complex (entry 8) more than a typical complex derived from an unhindered secondary alcohol.

Entries 12–14 in Table I are concerned with aluminum chloride modified hydride reagents.[16] Under conditions of kinetic control (entry 12) a 4:1 AlCl$_3$–LiAlH$_4$ reagent gives the largest amount

of T (axial) alcohol observed in ether as a solvent, in agreement with observations made in other cases.[7b,16,17] It is not clear whether this is strictly due to the bulk of the reagent (presumably[16] solvated AlHCl$_2$) or whether, by analogy with the alkoxyhydrides ($vide$ $supra$), electronic factors also play a part. Under conditions of thermodynamic control (entry 13), the 4:1 reagent yields exclusively the stable isomer C; this again is in accord with earlier observations.[7b,16,17] Of special interest is the reduction with a reagent obtained by adding one-third mole AlCl$_3$ to one mole $LiAlH_4$—which leads to precipitation of LiCl and formation,[1] in solution, of AlH$_3$ (entry 14). This reagent gives more equatorial (C) isomer than any of the other reducing agents operating under kinetic control. Although the possibility of equilibration is not entirely excluded, it is more likely that the product of the AlH$_3$ reduction was kinetically controlled. The large amount of C formed may reflect the formation of a ketone–AlH$_3$ complex prior to reduction.[18] Whereas ordinarily the axial approach of hydride to 3,3,5-trimethylcyclohexanone is somewhat hindered by the axial methyl group in the 3-position, such hindrance is unimportant when reduction is intramolecular, occurring within the ketone–AlH$_3$ complex, and under such circumstances the more stable equatorial isomer predominates in the product.[3] The large difference in steric result between reduction with aluminum hydride (entry 14) and reduction with lithium aluminum hydride (entries 1–3) rules out any major participation of the AlH$_3$ species in the $LiAlH_4$ reduction of ketones[4,19]; for if as little as half the reduction with $LiAlH_4$ involved AlH$_3$ as the reducing species, this half would give only 12% T and, in order to get 55% T over-all, the other half of the reduction would have to give essentially pure T. This seems quite unlikely, in the light of the results with the alkoxyaluminum hydrides (entries 4, 5, 9) which are far from completely stereoselective.

In Table II are summarized our results on reductions of dihydroisophorone with lithium aluminum hydride and hydride–alcohol combinations in tetrahydrofuran. It should be noted, first of all, that the results are parallel to those in ether (Table I) in that the proportion of hydride and order of addition are unimportant (entries 1–3), and in that methanol and t-butyl alcohol effect a great increase in the amount of T (entries 4 and 6; here again methanol is more effective than t-butyl alcohol) whereas isopropyl alcohol is ineffective (entry 5). This suggests that the mechanism of reduction in THF is generally similar to that in ether, and, in particular, that the effective reducing agent in the absence of added methanol or t-butyl alcohol is $LiAlH_4$ throughout the reduction. There is, however, a marked solvent effect which leads to much greater stereoselectivity in THF than is observed in ether.[20] This suggests that the hy-

(15) A. A. Bothner-By, $J. Am. Chem. Soc.$, **73**, 846 (1951). ADDED IN PROOF.—Professor P. S. Portoghese, University of Minnesota, has kindly informed the authors that, after careful purification, the 2-butanol obtained by reduction of 2-butanone with LAH-d-camphor is optically $inactive$ (paper submitted to $J. Org. Chem.$), the activity observed by Bothner-By presumably being due to an impurity. On the other hand, O. Červinka, $Coll. Czech. Chem. Comm.$, **26**, 673 (1961), reports the formation of $active$ 2-phenyl-1-methylpiperidine from 1-methyl-2-phenyl-3,4,5,6-tetrahydropyridinium perchlorate and LAH-d-camphor. From this work and ours, it appears that an isobornyloxyhydride species is, in fact, formed, but that it does not invariably cause asymmetric reduction.

(16) E. L. Eliel, $Rec. Chem. Progr.$, **22**, 129 (1961).

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

(18) Regarding an analogous complex with BH$_3$, see H. C. Brown, H. I. Schlesinger and A. B. Burg, $ibid.$, **61**, 673 (1939), and W. M. Jones, $ibid.$, **82**, 2528 (1960).

(19) N. L. Paddock, $Chemistry & Industry$, 63 (1953).

TABLE II

REDUCTION OF DIHYDROISOPHORONE WITH LiAlH₄ AND
MODIFIED LiAlH₄ REAGENTS IN TETRAHYDROFURAN

Entry	Addend	Moles addend / Mole LiAlH₄	Equiv. hydride / Mole ketone	trans [e] (axial) Alcohol, %
1[a]	......	..	1.44	74
2[b]	......	..	1.0	72
3	......	..	8	74
4	Methanol	3	1.05	92
5[c]	Isopropyl alc.	3	1.05	69
6[d]	Lithium tri-t-butoxy-aluminohydride	..	1.5	88

[a] About 7% ketone in product. [b] Inverse addition of hydride; about 24% ketone in product. [c] 17% ketone in product. [d] Commercial reagent from Metal Hydrides, Inc. [e] Product composition was determined by gas chromatographic analysis using a Tide detergent column or a Carbowax 20M column.

dride species are more solvated in tetrahydrofuran than in ether (in which solvent they have been claimed not to be solvated at all[4]).

From the preparative point of view it is interesting that the C/T ratio can be changed from 100:0 (in the thermodynamically controlled reaction with AlHCl₂, Table I, entry 13) to 8:92 (in the reduction with LiAlH(OCH₃)₃ in THF, Table II, entry 4) depending on the reducing species, solvent and conditions.

In a study of the reduction of 3,4-epoxy-1-butene with lithium aluminum hydride, Fuchs and VanderWerf[21] observed an increase in the relative percentage of 3-buten-1-ol (product of attack at secondary carbon) compared to 3-butene-2-ol (product of attack at primary carbon) from 17% to 30% as the lithium aluminum hydride:epoxide ratio was increased from 0.26:1 to 2.1:1. It was suggested[21] that with the large excess of hydride, the reducing species is largely the aluminohydride (AlH₄⁻) ion, whereas with the limited amount of hydride some of the reduction is effected by the alkoxyhydride ion AlH(OR)₃⁻ which, presumably because of its greater steric requirement, has a greater tendency to attack the primary position. The present work supports the assumption that AlH(OR)₃⁻ has greater effective bulk than AlH₄⁻ and also makes it reasonable that at least the (CH₂=CHCH₂CH₂O)₃AlH⁻ species, being a primary alkoxyhydride, persists long enough in solution to participate in the reduction of the epoxide before it disproportionates.

From our results with primary alkoxyhydrides (Table I, entries 4 and 5) the prediction can be made that, whereas the stereochemistry of the reduction of ketones with LAH is generally independent of the proportions of reagents, as discussed earlier, the stereochemistry of reduction of aldehydes to primary alcohols *should* depend on the proportions of reagent and order of addition. To observe this would, of course, require the use of lithium aluminum deuteride, and at the time the above-described work was completed, no suitable

(20) A similar, though less marked, solvent effect had been reported in ref. 13. Lithium aluminum hydride reduction of cholestan-3-β-yl-7-one acetate in ether gives 57% of the 7-α-ol whereas in THF there is formed 65% of the 7-α-ol.

(21) R. Fuehs and C. A. VanderWerf, *J. Am. Chem. Soc.*, **74**, 3917 (1952).

example was at hand. Subsequently, however, we learned that Professor R. U. Lemieux and Dr. J. Howard (University of Alberta, Canada) had independently (and for an entirely different purpose) obtained data which elegantly confirm the above prediction. These data are shown in Table III. It is seen that little stereoselectivity

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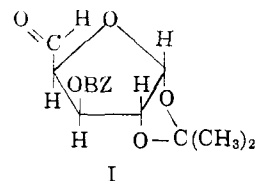
is evidenced with an excess of deuteride (first two entries, reducing agent LiAlD₄), but the stereoselectivity increases when deuteride is used in stoichiometric amount (entry 3) or when its supply is limited by the order of addition (entry 4). In these latter two cases, the reducing agent is evidently *not* all LiAlD₄, thus confirming that the primary alkoxyhydride intermediates function as reducing agents faster than they disproportionate. The conclusion, arrived at here, as in the case of the reduction of dihydroisophorone, is that the alkoxyaluminohydrides are more stereoselective than aluminohydride itself.

TABLE III

REDUCTION OF 1,2-O-ISOPROPYLIDENE-3-O-BENZYL-5-ALDE-
HYDO-α-D-XYLOFURANOSE (I) WITH LITHIUM ALUMINUM
DEUTERIDE IN ETHER[a]

Entry	Mode of addn.	Equiv. LiAlD₄[b] / Aldehyde	Temp., °C.	Equat. isomer,[c] %
1	Direct	4	25	55
2	Direct	4	−70	55
3	Direct	1	25	67
4	Inverse	>1	25	66

[a] Data of R. U. Lemieux and J. Howard, Dept. of Chemistry, University of Alberta, Edmonton, Alberta, Canada; private communication. [b] Equivalents hydride used per mole aldehyde. [c] The product was converted to β-D-xylopyranose-5-d tetraacetate and the relative amounts of equatorial and axial hydrogen at C₅ were determined by n.m.r. spectroscopy; cf. R. U. Lemieux, R. K. Kullnig, W. G. Schneider and H. J. Bernstein, *J. Am. Chem. Soc.*, 80, 6098 (1958). The amount of equatorial and axial hydrogen (as distinct from deuterium) in the xylopyranose is a direct measure of the relative proportions of the two diastereoisomeric xylofuranose-5-d derivatives produced in the reduction.

Experimental

Reductions of Dihydroisophorone (DHI) in Diethyl Ether.—The reactions involving inverse addition of lithium aluminum hydride, prior addition of isopropyl alcohol to lithium aluminum hydride and addition of aluminum chloride to lithium aluminum hydride in a AlCl₃/LAH molar ratio of 0.34 are described in detail below. Other reactions are briefly described. In general, the reaction mixtures were heated under reflux for 2 hours after the addition of DHI and kept overnight before workup. Exceptions are noted under the appropriate experiment. The products were not distilled but the concentrated reaction products were directly analyzed by gas chromatography in order to avoid fractionation of products. Where prior addition of alcohols to hydride was involved, the hydrogen liberated was measured as a check on the stoichiometry. Analyses were carried out on a Carbowax 20M or a Tide detergent column. Relative ratios of the components were usually determined by peak height–half-

width measurement of peaks. This convenient procedure was found to be as satisfactory as the determination of areas with a planimeter, and gave good results with synthetic mixtures. Analyses on the Carbowax 20M and Tide detergent columns agreed very well with each other.

Lithium Aluminum Hydride Reduction. Inverse Addition.—A solution of lithium aluminum hydride in diethyl ether (10 ml. of 1.51 M LAH, 0.0151 mole) was added dropwise to a vigorously stirred solution of DHI (8.47 g., 0.0604 mole) in 40 ml. of ether in a 200-ml. 3-neck flask. During the hydride addition a thick white precipitate formed. After the addition was complete, the reaction mixture was stirred and heated under reflux for 2 hours and allowed to stand overnight at room temperature. Water and 10% sulfuric acid were added to the reaction mixture. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether solution was washed with saturated sodium bicarbonate solution, salt solution, and dried over anhydrous magnesium sulfate. The ether was distilled through a Vigreux column leaving a clear, colorless concentrated residue weighing 15.8 g. which still contained some solvent. This residue was analyzed directly by gas chromatography on a 10-ft. Carbowax 20M column at 160° and a helium flow rate of 30 ml. per min., and contained 54.9% *trans*-alcohol and 45.1% *cis*-alcohol. In addition, 2.6% of ketone was detected.

A duplicate experiment indicated 53.6% *trans*-alcohol, 46.4% *cis*-alcohol and 8.8% ketone. This product analysis was effected on a Tide detergent column.

The direct addition in the usual manner of 1.24 equivalents of hydride per mole of ketone and 8.4 equivalents of hydride per mole of ketone gave 52% and 55%, respectively, of *trans*-alcohol.

Addition of Isopropyl Alcohol to Aluminum Hydride. Reduction of DHI.—An ethereal solution of lithium aluminum hydride (20 ml. of 0.96 M, 0.019 mole) was placed in a 100-ml. 3-neck flask equipped with a pressure equalized addition funnel, magnetic stirrer and Friedrich condenser which led to a Dry Ice trap and hydrogen measuring buret. Dry (distilled from calcium hydride) isopropyl alcohol (3.43 g., 0.057 mole) was added dropwise with stirring, and 0.061 mole of hydrogen was collected. A white precipitate formed during the addition. After stirring for 40 min., a solution of DHI (2.10 g., 0.015 mole) in 5 ml. of ether was added dropwise. The reaction mixture was heated under reflux for 2 hours and allowed to stand overnight at room temperature. The excess hydride was destroyed by the addition of water to the cooled reaction mixture and 0.0065 mole of hydrogen was evolved. After the addition of 10% sulfuric acid the ether layer was separated and the aqueous layer extracted with ether. The combined ether solution was washed with saturated sodium bicarbonate solution, salt solution, and dried over anhydrous magnesium sulfate. The ether was distilled and the concentrated residue was analyzed by gas chromatography on a Tide detergent column at 157° and a helium flow rate of 66 ml. per min., the analysis indicating 53% *trans*-alcohol and 47% *cis*-alcohol. No ketone was detected. Analysis on a Carbowax 20M column at 166° indicated 54% *trans*-alcohol and 46% *cis*-alcohol.

A duplicate experiment gave 54% *trans*-alcohol and 46% *cis*-alcohol. No ketone was detected by either gas chromatography or by infrared.

The experiments in which lithium aluminum hydride was modified by the addition of other alcohols as well as acetone, cyclohexanone and camphor prior to reduction of DHI are summarized in Table IV.

The reductions carried out with AlCl₃-modified LAH (entries 12 and 13, Table I) which presumably involve the dichloroaluminum hydride reagent were carried out in a manner similar to that described previously.[17]

Preparation of AlH₃ Solution and Reduction of DHI.—Aluminum chloride (4.6 g., 0.033 mole + 5% excess) was added in several portions to 100 ml. of dry ether in a 500-ml. 3-neck flask equipped with a condenser, addition funnel and Trubore stirrer. The addition was carried out with stirring and ice-bath cooling. Ethereal lithium aluminum hydride (79 ml. of 1.26 M LAH, 0.1 mole) was added dropwise over a 1-hour interval. During the addition a white precipitate appeared. After addition was complete, stirring of the cold mixture was continued for 1.25 hours and the precipitate was then allowed to settle for several hours. The solution was filtered through cotton and stored in a refrigerator. Precipitation occurred continuously on standing.

TABLE IV

Addend	Mole addend	Mole LiAlH₄	Mole DHI	Product,[a] % *trans*-alc.	% *cis*	Mole H₂ evolved during alc. addn.
Methanol[b]	0.045	0.015	0.012	75[c]	25	0.042[d]
Ethanol[e]	.042	.014	.012	83	17	.046[d]
t-Butyl alc.	.025	.013	.023	63	37	.031[f]
t-Butyl alc.	.045	.015	.014	73	27	.050[g]
Acetone[d,e]	.060	.030	.055	57	43	...
Cyclohexa-none[d,h]	.0756	.0252	.023	58	42	...
d-Camphor[i]	.113	.0378	.035	67[j]	33	...

[a] Product analysis effected by gas chromatography on a Carbowax 20M column. [b] The reaction mixture was not heated under reflux in this experiment. [c] About 3% of ketone in product. [d] A precipitate formed during the addition of the "modifier." [e] The reaction mixture was kept overnight at room temperature after addition of DHI and then heated under reflux for 1.5 hours. [f] No precipitate was observed during the addition of the addend. [g] A precipitate appeared toward the end of the addition of the alcohol. [h] The reaction mixture was kept overnight at room temperature and heated under reflux for 2 hours. [i] The reaction mixture was heated under reflux for 1 hour after addition of the camphor; no precipitate was observed either after addition of camphor or of DHI. [j] The isoborneol:borneol ratio obtained was 88:12.

Ten milliliters of the above reagent was added to a 3-neck 200-ml. flask. A solution of DHI (1.4 g., 0.01 mole) in 10 ml. of ether was added and the reaction mixture was heated under reflux for 2 hours, and allowed to stand overnight. There was no significant precipitate formation. Water was added followed by 10% sulfuric acid and the product was extracted with ether. The ether solution was washed with saturated sodium bicarbonate and salt solution and dried over anhydrous magnesium sulfate. The ether was distilled through a Vigreux column leaving a concentrated residue of 2.2 g. which was analyzed by gas chromatography on a Carbowax 20M column at 162°, with a helium flow rate of 49 ml. per min. The alcohol product consisted of 88% *cis*-alcohol and 12% *trans*-alcohol; in addition, there was 22.6% unreduced ketone.

Lithium Aluminum Hydride Reduction in Tetrahydrofuran. Inverse Addition.—A solution of DHI (2.36 g., 0.0168 ml.) in 20 ml. of tetrahydrofuran (THF) was placed in a 3-neck 200-ml. flask equipped with a condenser, equilibrated addition funnel and magnetic stirrer. A lithium aluminum hydride solution in THF (10 ml. of 0.420 M LAH, 0.0042 mole) was added dropwise with stirring over a 15-min. interval. No precipitate was formed. The reaction mixture was heated under reflux for 2 hours and allowed to stand overnight. There was no precipitate formation. Water was added and the precipitate formed was dissolved by the addition of 10% sulfuric acid. The aqueous layer was extracted with ether and the combined ether solution washed with saturated sodium bicarbonate solution and salt solution and dried over anhydrous magnesium sulfate. The solvent was distilled through a Vigreux column leaving a concentrated residue of 7.2 g. This was

TABLE V

Added	Mole addend	Mole LiAlH₄	Mole DHI	Product, % *trans*	*cis*	Mole H₂ evolved during alc. addn.
Methanol	0.0378[a]	0.0126	0.012	92	8	0.0366
Isopropyl alc.	0.0252[b]	0.0084	0.008	69[c]	31	0.0260
LiAl(O—Bu-*t*)₃H[d]	....	....	...	88[e]	12	....

[a] No precipitate was formed either after addition of the methanol or of the DHI. [b] The solution became heterogeneous during the addition of the isopropyl alcohol. [c] 17% of ketone in product. [d] The reagent was obtained from Metal Hydrides, Inc.; the reaction mixture was heated under reflux for 4 hours after addition of DHI. [e] Analysis carried out on a Tide detergent column.

analyzed by gas chromatography on a Carbowax 20M column at 161° and a helium flow rate of 48 ml. per min. indicating a ratio of 71% *trans*-alcohol and 29% *cis*-alcohol. Unreduced ketone (24%) was also present. A duplicate analysis indicated 72% of *trans*-alcohol and 23% of ketone.

Reduction of DHI (7.0 g., 0.05 mole) with 0.7 g. (50% excess) of lithium aluminum hydride in the usual manner (direct addition) gave 73% *trans*-alcohol, as analyzed on a Tide column (analysis on Carbowax 20M indicated 74% *trans*). About 7% of ketone was in the product. Use of a large excess of hydride (0.0168 equivalent reducing 0.00021 mole of DHI) in another direct addition experiment gave 72% *trans*-alcohol.

Reaction of Alcohols with Lithium Aluminum Hydride in THF. Reduction of DHI.—In these experiments (except in the case of lithium aluminum tri-*t*-butoxyhydride) the alcohol was added to the stirred lithium aluminum hydride

solution in THF and the hydrogen evolved was measured in a wet test meter. A solution of DHI was then added and the reaction mixture was heated under reflux for 2 hours and kept overnight at room temperature. It was then worked up in the usual manner. The products were analyzed by gas chromatography on Carbowax 20M. The results are summarized in Table V.

Reductions with Metal Hydrides. XI. Solvent Effect on the Stereochemistry of Reduction with Sodium Borohydride

BY HOWARD HAUBENSTOCK AND ERNEST L. ELIEL

The reduction of 3,3,5-trimethylcyclohexanone with sodium borohydride in anhydrous isopropyl alcohol, anhydrous *t*-butyl alcohol or anhydrous diglyme gives 55% *trans*-3,3,5-trimethylcyclohexanol and 45% *cis* isomer, exactly as reduction with lithium aluminum hydride in ether (previous paper). Higher proportions of *trans*-alcohol (up to a maximum of 82%) are formed in aqueous isopropyl alcohol, anhydrous ethanol and aqueous methanol. The change in product composition is a result of solvent effects rather than of alkoxyborohydride formation in the latter solvents, for (a) sodium trimethoxy-borohydride in isopropyl alcohol gives less *trans*-alcohol than sodium borohydride in aqueous methanol and (b) very little hydrogen (and therefore very little alkoxyborohydride) is formed when sodium borohydride is dissolved in anhydrous ethanol or methanol containing sodium methoxide.

The concepts of "steric approach control" and "product development control" applied to reductions of substituted cyclohexanones have led Dauben and co-workers to postulate that the borohydride species has a greater effective size than the aluminohydride anion.[1] Thus the reduction of menthone with lithium aluminum hydride gives 71% of menthol and 29% of neomenthol whereas with sodium borohydride in methanol it gives 49% of menthol and 51% of neomenthol. It was therefore suggested that the borohydride species, considered effectively larger than the aluminohydride anion, gave more attack from the less hindered equatorial side of the molecule to yield a greater proportion of axial alcohol, neomenthol.

Henbest and co-workers[2] found that reduction of the hindered ketone 3β-acetoxy-9α-bromoergostan-11-one (I) with sodium borohydride in methanol or *tert*-butyl alcohol gave mainly (after acetylation) 3β-acetoxyergostan-11-one while reduction of I with lithium aluminum hydride followed by acetylation gave 3β-acetoxy-9β:11β-epoxyergostane as the major product. This epoxide is presumably formed from the bromohydrin (or aluminum derivative) which is initially produced by reduction of the carbonyl group. These results,

and others, were cited by Dauben[1] as further corroboration of the size difference between the aluminohydride ion and the borohydride ion.

However, Wheeler and Huffman[5] have pointed out that since the aluminohydride ion actually is larger than the borohydride ion, on the basis of a comparison of the Al–H and B–H bond lengths, Dauben's hypothesis rests upon the assumption that solvation of the borohydride ion gives it a greater effective size. This assumption was criticized by Wheeler and Huffman who claimed that neither borohydride ion nor aluminohydride ion is solvated. Furthermore, the different behavior of the two ions in the reduction of 3β-acetoxy-9α-bromoergostan-11-one[2] was ascribed[3] to a difference in mechanism rather than to a difference in size of reagent.

The available evidence suggests that even when consideration is restricted to reductions with sodium borohydride, differences in stereochemistry can be observed when different solvents are used. Thus Dauben found that sodium borohydride in pyridine behaves as a larger reducing agent than sodium borohydride in methanol. Even when only solvents of similar type, *e.g.*, alcohols, are considered, differences can be observed. For example, reduction of Δ⁴-cholestene-3-one with sodium borohydride in isopropyl alcohol is reported to give 95% of the β-alcohol[4] while reduction with sodium borohydride in aqueous methanol gives

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