# Reductions with Metal Hydrides. XIV. Reduction of 2-Tetrahydropyranyl and 2-Tetrahydrofuranyl Ethers

ERNEST L. ELIEL, BERNARD E. NOWAK, RONALD A. DAIGNAULT,[1] AND VICTOR G. BADDING

*Department of Chemistry, University of Notre Dame, Notre Dame, Indiana*

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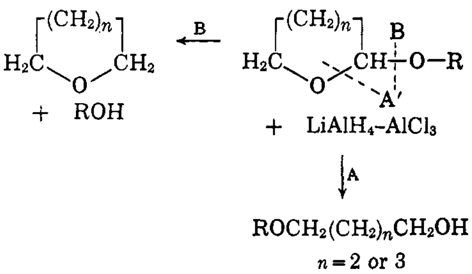
The reduction of a number of 2-tetrahydropyranyl and 2-tetrahydrofuranyl ethers with lithium aluminum hydride–aluminum chloride has been studied. The products are 5-hydroxypentyl or 4-hydroxybutyl ethers on one hand and alcohols and tetrahydropyran or -furan on the other. Factors affecting the ratio of ring cleavage (to give hydroxy ethers) *vs.* exocyclic cleavage are discussed.

In a previous publication[2] we have described the cleavage of acetals and ketals with lithium hydride–aluminum chloride ("mixed hydride"[4]) to give simple ethers (from acyclic ketals) or β- or γ-hydroxy ethers (from five- and six-membered cyclic ketals). We have now applied this cleavage reaction to 2-tetrahydropyranyl and 2-tetrahydrofuranyl ethers. These ethers are readily prepared by addition of alcohols to the commercially available 2,3-dihydropyran or the readily prepared 2,3-dihydrofuran (from rearrangement of the commercially available 2,5-dihydro isomer). Being acetals, they would be expected to be subject to the previously discovered hydrogenolysis, the only question being as to whether cleavage takes place in the ring (Scheme I, path A) to give 5-hydroxypentyl or 4-hydroxybutyl ethers or exocyclically (Scheme I, path B) to give the starting alcohols and tetrahydropyran or -furan. If path A prevails, the cleavage will constitute a convenient synthetic method for 5-hydroxypentyl and 4-hydroxybutyl ethers, to supplement the previously described[2] synthesis of 3-hydroxypropyl and 2-hydroxyethyl ethers. Path B, on the other hand, is without synthetic utility.

SCHEME I



The results of the cleavage of a number of 2-tetradropyranyl ethers with "mixed hydride" are shown in Table I and the results for a series of 2-tetrahydrofuranyl ethers in Table II.

Although the material balances are poor in some instances (especially entries 1, 3, 6, and 13), presumably due to water solubility of the lower hydroxy ethers and due to volatility and water solubility of the corresponding alcohols, in most instances material recovery is between 65 and 100%. In some critical cases, yields were checked by analytical gas chromatography using an internal standard. In the discussion following, it should be kept in mind that the isolated or analytical yields of hydroxy ethers (A) represent minimum actual yields, whereas 100 − % recovered alcohol (B) is the maximum possible yield of hydroxy ether A.

For the purpose of determining optimal conditions, several of the compounds shown in Tables I and II were also reduced with lithium aluminum hydride–boron trifluoride.[5] The yields with this reagent are shown in Table III.

The identification of the 14 hydroxy ethers prepared in the present work is based on infrared and n.m.r. spectra and, in the case of the twelve new compounds, elemental analysis. 5-*n*-Butoxy-1-pentanol (Table I) and 4-benzyloxy-4-butanol (Table II) had been previously described in the literature and their refractive indices and the boiling point of the former agreed with those reported. An authentic sample of 5-*t*-butoxy-1-pentanol was prepared from 5-chloro-1-pentanol and potassium *t*-butoxide with temporary protection (to ring closure) of the alcohol function by dihydropyran. Authentic 4-cyclohexyloxy-1-butanol was obtained from phenol and butyrolactone followed by reduction of the carboxylic acid function and the aromatic ring. Both authentic samples were identical in physical properties with the corresponding reaction products.

The primary purpose of the present work was to establish a new preparative method for hydroxy ethers of the general formulas, $RO(CH_2)_4OH$ and $RO(CH_2)_5OH$, hitherto not readily accessible. As indicated in Tables I–III, such ethers may now be synthesized in moderate to good yields by a convenient method from readily available starting materials. The combination of lithium aluminum hydride with aluminum chloride is best when R is tertiary, whereas for secondary and especially primary R boron trifluoride is the preferred Lewis acid. It is well known that no reduction at all of tetrahydropyranyl and tetrahydrofuranyl ethers occurs with lithium aluminum hydride in the absence of a Lewis acid.[7]

A second purpose of our work was to throw light on the factors which determine the extent of ring (A, Scheme I) *vs.* side chain (B, Scheme I) cleavage. These factors have proved relatively complex, but some discussion is in order.

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[1] From the Ph.D. Thesis of R. A. Daignault. We gratefully acknowledge support of this work under National Institutes of Health Grant GM-08848 and National Science Foundation Grant G-14251.

[2] E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Am. Chem. Soc.*, **84**, 2371 (1962); see also ref. 3.

[3] Previous paper: E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Am. Chem. Soc.*, **84**, 2377 (1962).

[4] E. L. Eliel, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **22**, 129 (1961).

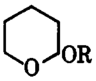
[5] A. R. Abdun-Nur and C. H. Issidorides, *J. Org. Chem.*, **27**, 67 (1962). The active reagent is probably a combination of $B_2H_6$ and $BF_3$; see also footnote 6.

[6] Since diborane is reported to be very little soluble in ether and would thus be expected to escape before reduction, it is unlikely that it is the actual reducing agent. More likely, a combination of $BH_3$ and $BF_3$, either a dimer or a compound $BH_2F$ or $BHF_2$, is involved. This needs to be established.

[7] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 678–681.

TABLE I

REDUCTION OF 2-TETRAHYDROPYRANYL ETHERS WITH MIXED HYDRIDE



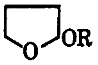
$\longrightarrow$ $RO(CH_2)_5OH$ (A) or ROH (B) + tetrahydropyran

| Entry | R | Yield, % A | B.p., °C. (mm.) | $n^{20}D$ | Calcd., % C | Calcd., % H | Found, % C | Found, % H | Yield, % B |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $(CH_3)_2CH$ | 43 | 98–100 (12) | 1.4313 | 65.71 | 12.41 | 66.00 | 12.00 | *a* |
| 2 | $(CH_3)_3C$ | 72 | 106 (10) | 1.4348 | 67.45 | 12.58 | 67.52 | 12.78 | *a* |
| 3 | *n*-$C_4H_9$ | 10 | 120 (10)[b] | 1.4376[b] | | | | | 38 |
| 4 | 3-Methyl-2-butyl | 51 | 114–116 (11) | 1.4362 | 68.91 | 12.73 | 69.10 | 12.49 | 13 |
| 5 | *t*-Amyl | 79 | 118–120 (13) | *a* | 68.91 | 12.73 | 69.04 | 12.71 | *a* |
| 6 | Neopentyl | 27 | 111–112.5 (10) | 1.4305 | 68.91 | 12.73 | 68.72 | 12.70 | 15 |
| 7 | Cyclohexyl | 45[c] | 138–139.5 (18) | 1.4660 | 70.91 | 11.91 | 71.25 | 11.91 | 38 |
| 8 | *n*-$C_6H_{13}$ | 11 | 117–118 (8.5) | *a* | 70.16 | 12.85 | 69.91 | 12.71 | ~90 |
| 9 | *cis*-3,3,5-[d] | 38[e] | 114–116 (0.5) | *a* | 73.63 | 12.36 | 73.34 | 12.31 | 42 |
| 10 | *trans*-3,3,5-[d] | 62[f] | 110–112 (0.7) | *a* | 73.63 | 12.36 | 73.59 | 12.42 | 5 |
| 11 | $C_6H_5CH_2$ | *g* | ... | ... | ... | ... | ... | ... | 90 |
| 12 | $C_6H_5CH_2CH_2$ | *g* | ... | ... | ... | ... | ... | ... | 94 |
| 13 | $CF_3C(CH_3)_2$ | *g* | ... | ... | ... | ... | ... | ... | 47 |

[a] Not determined. [b] C. Crisnan [*Ann. chim.*, [13] **1**, 457 (1956)] reported b.p. 129° (20 mm.), $n^{26}D$ 1.4353. [c] Isolated yield, confirmed by gas chromatographic analysis. [d] 3,3,5-Trimethylcyclohexyl. [e] Isolated yield; v.p.c. indicated 51% actual yield. [f] Isolated yield; v.p.c. indicated 98% actual yield. [g] None isolated; yield small or nil.

TABLE II

REDUCTION OF 2-TETRAHYDROFURANYL ETHERS WITH MIXED HYDRIDE



$\longrightarrow$ $RO(CH_2)_4OH$ (A) or ROH (B) + tetrahydrofuran

| Entry | R | Yield, % A | B.p., °C. (mm.) | Calcd., % C | Calcd., % H | Found, % C | Found, % H | Yield, % B |
|---|---|---|---|---|---|---|---|---|
| 14 | $(CH_3)_3C$ | 58 | 72–74 (10)[a] | 65.71 | 12.41 | 65.57 | 12.27 | *b* |
| 15 | Cyclohexyl | 63 | 112–120 (8) | 69.69 | 11.71 | 70.28 | 11.80 | ~15 |
| 16 | *n*-$C_6H_{13}$ | 27[c] | 100–104 (2) | 68.89 | 12.73 | 68.83 | 12.81 | 40 |
| 17 | $C_6H_5CH_2$ | 4 | 116 (4)[d] | | | | | 83 |

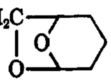
[a] $n^{18}D$ 1.4301. [b] Not determined. [c] Isolated yield; analytical yield (by v.p.c.) was 54%. [d] $n^{25}D$ 1.5168. T. D. Perrine [*J. Org. Chem.*, **18**, 1356 (1953)] reported b.p. 155–167° (12 mm.), $n^{25}D$ 1.5130.

TABLE III

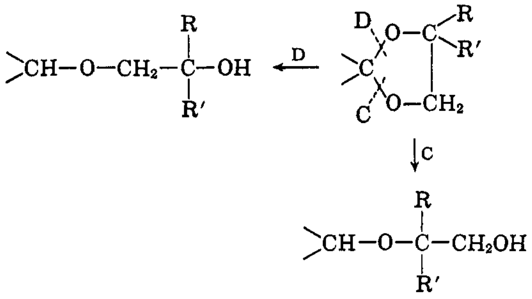
REDUCTION OF 2-TETRAHYDROPYRANYL AND 2-TETRAHYDROFURANYL ETHERS WITH LITHIUM ALUMINUM HYDRIDE–BORON TRIFLUORIDE

| No. | Starting material | Yield of $RO(CH_2)_nOH$, % |
|---|---|---|
| 18 | 2-*t*-Butoxytetrahydrofuran | 16 |
| 19 | 2-Cyclohexyloxytetrahydrofuran | 69 |
| 20 | 2-*n*-Hexyloxytetrahydrofuran | 66 |
| 21 | 2-Benzyloxytetrahydrofuran | 48 |
| 22 | 2-*t*-Butoxytetrahydropyran | 46 |
| 23 | 2-Cyclohexyloxytetrahydropyran | 69 |
| 24 | 2-*n*-Hexyloxytetrahydropyran | 41 |
| 25 | 2-Benzyloxytetrahydropyran | 25 |
| 26 | 6-Methoxytetrahydropyran-2-methanol | None[a] (39) |
| 27 | 6,8-Dioxabicyclo[3.2.1]octane[b] | None[a] (80) |

[a] The only product isolated was tetrahydropyran-2-methanol, b.p. 180–192°, in the yield shown (lit.[30] b.p. 182°). [b]



SCHEME II



Leggetter and Brown[8] have studied in detail the previously discovered[2] cleavage of unsymmetrical ketals and have discerned two factors governing the direction of opening (C or D, Scheme II) of such ketals. One factor[8b] is related to substituent polarity; when R, in Scheme II, is electron donating (*e.g.*, methyl[2]), mode C predominates, but, when R is electron withdrawing ($CH_2Cl$, $CH_2OR$), mode D is favored. Thus cleavage occurs away from the electron donor and close to the electron acceptor. This polar effect may best be accounted for in terms of the energy profile shown in Figure 1. According to Leggetter and Brown,[8b] formation of the oxocarbonium ion intermediates $I_i$ and $I_{ii}$ (perhaps better represented as internal ion pairs in the ether solvent) is rate determining. The transition states $T_i$ and $T_{ii}$ reflect the stability of the corresponding intermediates $I_i$ and $I_{ii}$ and so, if $I_i$ is more stable than $I_{ii}$, product i will be formed in predominance over ii. Since electron-donating R (and R′) will stabilize $I_i$ over $I_{ii}$ (by alleviating positive charge on oxygen), whereas electron-withdrawing R will have the opposite effect (by enhancing the charge in $I_i$ more than in $I_{ii}$), it is clear that electron-donating R will favor product i,

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[8] (a) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **41**, 2671 (1963); (b) *ibid.*, **42**, 990 (1964); (c) *ibid.*, **42**, 1005 (1964).

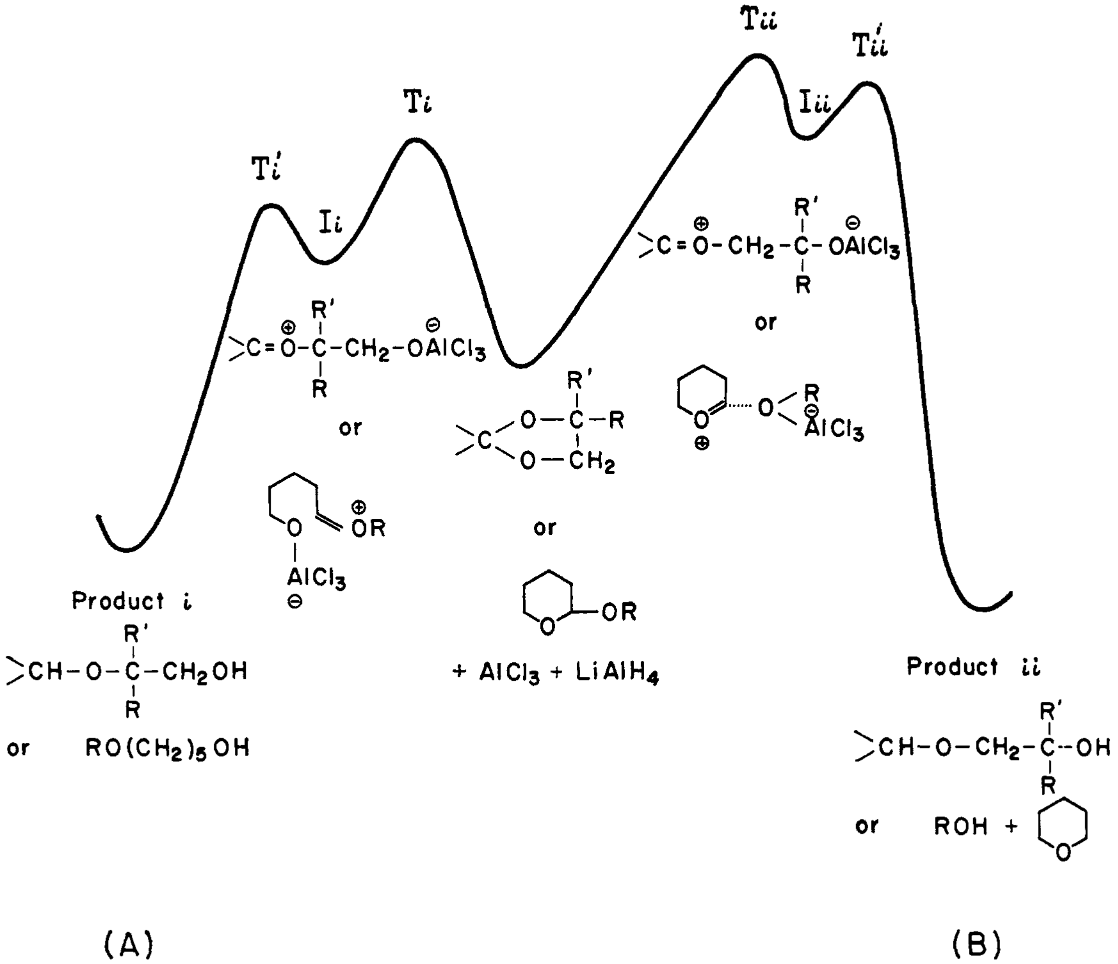


Figure 1.

whereas electron-withdrawing R will favor product ii. This interpretation implies the kinetic form

$$\text{reactant} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \text{intermediate} \xrightarrow{k_2} \text{product}$$

$$k_2 \gg k_{-1}$$

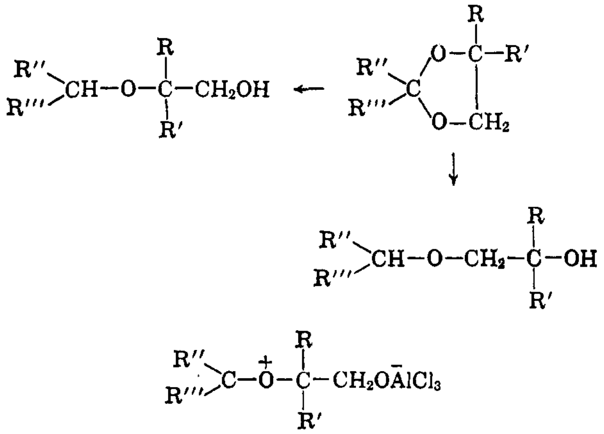
That $I_i$ and $I_{ii}$ reflect the energy of $T_i$ and $T_{ii}$ is in accordance with the Hammond postulate,[9] since $I_i$ and $I_{ii}$ are relatively unstable intermediates. It must be pointed out, however, that by the same token $I_i$ and $I_{ii}$ also reflect the energy of the transition states $T_i'$ and $T_{ii}'$, and there is nothing in Leggetter and Brown's argument which precludes that $T_i'$ and $T_{ii}'$ are the rate-determining transition states. If this were so, the kinetic form of the reaction would be

$$\text{reactant} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \xrightarrow{k_2} \text{product}$$

$$k_2 \ll k_{-1}$$

In this case the intermediates are formed reversibly and reduction itself is the rate-determining step. Although the two kinetic forms are, in principle, distinguishable (see below), both are compatible with Leggetter and Brown's evidence.

SCHEME III



(unstable if R, R', R'', R''' ≠ H)

R, R' electron donating

A second factor discerned by Leggetter and Brown[8c] is steric. In the case of *ketals* only, when R and R' ≠ H, cleavage is observed[2] to go counter to the polar factor (Scheme III) to give exclusively the tertiary alcohol. The reason, according to Leggetter and Brown,[8c] lies in the instability of the oxocarbonium ion precursor of the primary alcohol. This intermediate, shown in Scheme III, is an isostere of a 1-*t*-butyl-2,2-dialkylethylene which is destabilized by about 4.3 kcal./mole through steric compression of the *cis*-alkyl and *t*-butyl groups.[10]

Since the compounds studied in the present work are all acetals rather than ketals, the steric factor of Leggetter and Brown[8c] is not operative as such and our re-

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(9) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(10) R. B. Turner, D. E. Nettleton, and M. Perelman, *ibid.*, **80**, 1430 (1958).

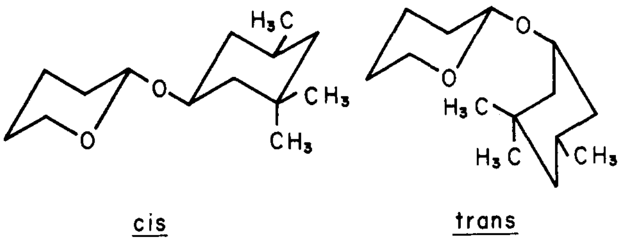

Figure 2.

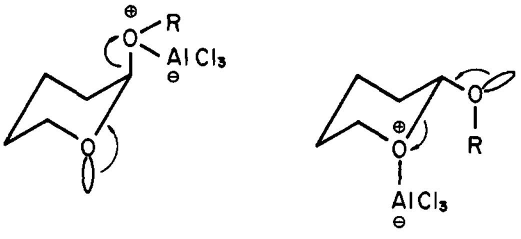

Figure 3.

sults will be rationalized in terms of their polar factor[8b] plus whatever additional steric factors we feel should be considered.

Comparison of tertiary, secondary and primary alkyl substituents (R in Scheme I), *e.g.*, entries 2 and 5 *vs.* 1, 4, and 7 *vs.* 3, 6, and 8 in Table I or 14 *vs.* 16 in Table II, suggests that tertiary R promotes path A, whereas primary R promotes path B. Since tertiary alkyl is generally considered to be more electron donating than primary alkyl, this is in accordance with the energy profile embodied in Figure 1. Complete predominance of path B for R = $C_6H_5CH_2$, $C_6H_5CH_2CH_2$, and $CF_3(CH_3)_2C$ (Table I, entries 11–13) may be similarly explained in terms of the electron-withdrawing properties of phenyl and trifluoromethyl.

An equivalent way of explaining the direction of cleavage is to say that the Lewis acid, $AlCl_3$ (or possibly $AlCl_2H$), coordinates preferentially on the ring (intermediate $I_i$, product A) when R is tertiary but preferentially on the exocyclic oxygen (intermediate $I_{ii}$, product B) when R is primary. When the argument is put in this fashion, it becomes evident that steric effects may influence the site of coordination. Such steric effects had previously[2] been implicated in the cleavage of propylene acetals and ketals but were not considered in the later work[8b] establishing the importance of polar factors.[11] The present work suggests that these steric effects are not without importance. Thus, 2-neopentyloxytetrahydropyran (see Table I, entry 6) gives more ring cleavage than other primary derivatives (entries 3 and 8). More convincingly, *trans*-3,3,5-trimethylcyclohexyl-2-tetrahydropyranyl ether (Figure 2) gives much more ring cleavage than the *cis* isomer (Table I, entries 9 and 10). Since polar effects must be very nearly the same in the two stereoisomers, it would appear that interference of the *syn*-axial[12] methyl group in the *trans* isomer with coordination of $AlCl_3$ at the exocyclic oxygen is responsible for the absence of products B formed *via* intermediate $I_{ii}$ (Figure 1). It is possible that the decreasing importance of path B with increasing bulk of R (*e.g.*, from primary to tertiary) is also due to steric rather than polar factors.

Decreasing ease of coordination with increasing bulk is implied by the lesser basicity of di-*sec*-butyl ether compared to di-*n*-butyl ether[13] and of diisopropyl ether compared to diethyl ether[14] toward boron trifluoride.

Ease of coordination (of steric origin) may also explain the generally greater extent of ring (*vs.* side-chain) cleavage of tetrahydrofuranyl compared to the corresponding tetrahydropyranyl ethers, evident from a comparison of Tables II and I (*e.g.*, entries 15 *vs.* 7 and 16 *vs.* 8 and 17 *vs.* 11). It is known[15] that tetrahydrofuran is a stronger base than tetrahydropyran.

An analogous explanation may apply to the much lesser extent of ring cleavage of 6-methyl-2-isopropoxytetrahydropyran (*ca.* 2%, see below) and 6-hydroxymethyl-2-methoxytetrahydropyran (Table III, entry 26; see also entry 27) compared to similar compounds unsubstituted in the 6-position (Table I, entry 1; Table III, entry 23).

We have been mindful of the possibility that conformational factors might influence the mode of ring cleavage of tetrahydropyranyl and (though to a much lesser extent) of tetrahydrofuranyl ethers. It is known from sugar chemistry[16] that pyranosides tend to exist preferentially in the conformation in which the acetal group is axial (owing to the "anomeric effect," an interaction of the exocyclic C–O dipole with the unshared p-electrons of the ring oxygen) and simple 2-pyranyl ethers, by the same token, should exist mainly in the conformation with axial OR.[16b] Exceptions might conceivably exist where R is bulky (*e.g.*, *t*-butyl, neopentyl, *trans*-3,3,5-trimethylcyclohexyl) in which case steric effects might outweigh polar ones and the equatorial conformation of the ether might be preferred. If this preference carried over into the transition state for acetal cleavage, side-chain cleavage might be the preferred mode in unhindered (axial) ethers, as shown in Figure 3, whereas ring cleavage might compete more effectively in the hindered (equatorial) ethers. The reason is evident from Figure 3: the lone pair on the ring oxygen is favorably situated for an *anti* elimination of the axial ether oxygen but not of the equatorial ether oxygen, so that with the equatorial ether fragmentation[17] might be expected to occur.

To see whether experimental evidence for differences between axial and equatorial 2-tetrahydropyranyl ethers could be obtained, we synthesized *cis*- and *trans*-6-methyl-2-isopropoxytetrahydropyran by addition of isopropyl alcohol to 6-methyl-5,6-dihydropyran (prepared from commercially available[18] 6-hydroxymethyl-5,6-dihydropyran *via* the tosylate).[19] The stereoisomers were separated by preparative gas chromatography and their configuration was readily assigned from their n.m.r. spectra. One isomer showed a narrow acetal

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[11] We are referring to a direct bulk effect opposing coordination of the Lewis acid, not the more subtle indirect steric effect demonstrated in ref. 8c.

[12] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p. 43.

[13] J. Deters, Ph.D. Dissertation, University of Notre Dame, Notre Dame, Ind., 1964.

[14] H. C. Brown and R. M. Adams, *J. Am. Chem. Soc.*, **64**, 2557 (1942).

[15] D. E. McLaughlin, M. Tamres, S. Searles, and S. Nukina, *J. Inorg. Nucl. Chem.*, **17**, 112 (1961).

[16] (a) *Cf.* ref. 12, pp. 375–377; (b) see also C. B. Anderson and D. T. Sepp, *Chem. Ind.* (London), 2054 (1964); J. T. Edward and I. Puskas, *Can. J. Chem.*, **40**, 711 (1962).

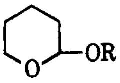
[17] C. A. Grob, *Bull. soc. chim. France*, 1360 (1960); see also ref. 12, p. 108.

[18] We are indebted to the Shell Chemical Co. for a generous sample of this compound.

[19] R. Zelinski and H. J. Eickel, *J. Org. Chem.*, **23**, 462 (1958).

TABLE IV

2-TETRAHYDROPYRANYL ETHERS

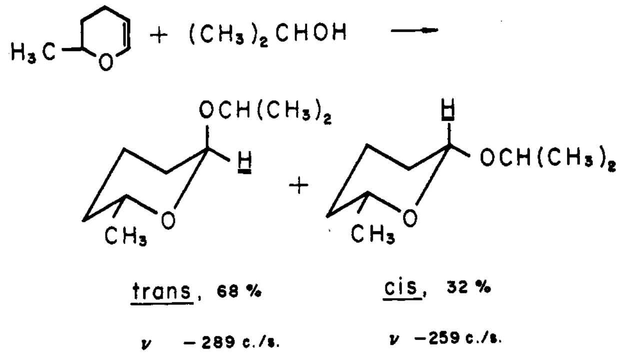


| R | B.p., °C. (mm.) | $n^{20}D$ | Calcd., % C | Calcd., % H | Found, % C | Found, % H | Yield, % |
|---|---|---|---|---|---|---|---|
| $(CH_3)_2CH$ | 154–155 (745)[a] | 1.4256[a] | | | | | 62 |
| $(CH_3)_3C$ | 54–56 (10)[b] | 1.4300[b] | | | | | 69 |
| *n*-Butyl | 70–72 (11)[c] | 1.4324[c] | | | | | 80 |
| 3-Methyl-2-butyl | 73–74 (11) | 1.4342 | 69.70 | 11.72 | 69.66 | 11.76 | 81.5 |
| *t*-Amyl | 69.5–71 (12) | 1.4361 | 69.70 | 11.72 | 69.81 | 11.84 | 83.5 |
| Neopentyl | 76 (18) | 1.4285 | 69.70 | 11.72 | 69.82 | 11.90 | 78 |
| Cyclohexyl | 57.5–58.5 (0.8) | 1.4670 | 71.68 | 10.96 | 71.62 | 11.07 | 92.5 |
| *n*-Hexyl | 94 (3)[d] | 1.4397[d] | | | | | 90 |
| Benzyl | 100 (2)[e] | 1.5134[e] | | | | | 51 |
| *cis*-3,3,5-[f] | 82–84 (0.7) | *g* | 74.28 | 11.58 | 73.76 | 11.51 | 82 |
| *trans*-3,3,5-[f] | 80 (0.7) | *g* | 74.28 | 11.58 | 74.04 | 11.44 | 78 |
| $(CF_3)C(CH_3)_2$ | 56–58 (10) | *g* | 50.94 | 7.13 | 51.01 | 7.29 | 56 |

[a] Lit.[24a] b.p. 43° (10 mm.), $n^{20}D$ 1.4255. [b] $n^{25}D$ 1.4268. Lit.[24b] b.p. 56° (13 mm.), $n^{25}D$ 1.4268. [c] R. I. Longley, W. S. Emerson, and T. C. Schafer [*J. Am. Chem. Soc.*, **74**, 2012 (1952)] reported b.p. 70–72° (12 mm.), $n^{25}D$ 1.4294. [d] Lit.[30] b.p. 119° (20 mm.), $n^{20}D$ 1.4401. [e] G. F. Woods and D. N. Kramer [*J. Am. Chem. Soc.*, **69**, 2246 (1947)] reported b.p. 107° (3 mm.), $n^{20}D$ 1.5128. [f] Trimethylcyclohexyl. [g] Not determined.

proton signal at −289 c.p.s. (relative to tetramethylsilane at 60 Mc.p.s.), whereas the broad signal of the acetal proton of the other isomer appeared at −259 c.p.s. Since it is known[20] that equatorial protons in cyclohexane systems resonate at lower frequencies and are narrower in signal width than axial protons, the isomer with the −289 c.p.s. signal was assigned the *trans* conformation and that with the −259 c.p.s. signal the *cis* conformation (Scheme IV).

SCHEME IV



The assignment presupposes that the compounds exist predominantly in the conformations shown. The alternative conformation of the *cis* isomer would involve an unfavorable *syn*-axial[12] methyl–isopropoxy interaction. (The corresponding methyl–hydroxyl interaction in a cyclohexane is unstable by about 2 kcal./mole[21a]). The alternative conformation of the *trans* isomer would involve axial methyl (disfavored by about 1.7 kcal./mole[21b]) and equatorial isopropoxyl. That the latter is actually *less* stable than axial isopropoxyl follows from analogy with the pyranosides[16] and is confirmed by the signal position and width of the acetal proton in 2-isopropoxytetrahydropyran, −275.8 c.p.s., corresponding to approximately 56% axial isopropoxyl and 44% equatorial isopropoxyl on the reasonable assumption[21] that the equatorial methyl group at position 6 (Scheme IV) does not affect the chemical shift of the acetal proton appreciably.[22]

Unfortunately, the mixed hydride reduction of *both* stereoisomers of 6-methyl-2-isopropoxytetrahydropyran gave almost exclusively isopropyl alcohol and tetrahydropyran; the expected ether–alcohol 1-isopropoxy-5-hexanol, $(CH_3)_2CHO(CH_2)_4CHOHCH_3$, was obtained in only 2.2% yield from the *cis* isomer and 0.9% yield from the *trans* isomer. As the difference between these two yields is not experimentally significant, no conclusion is possible as to whether, in fact, the *trans* (axial) isomer gives more exocyclic cleavage and the *cis* (equatorial) more ring cleavage, the only indication being that ring cleavage in both cases is very much less favored than in the case of the 6-unsubstituted 2-isopropoxytetrahydropyran.

Since 2-isopropoxytetrahydropyran is itself conformationally heterogeneous but does give rise to ring as well as exocyclic cleavage, the almost exclusive exocyclic cleavage observed with the 6-methyl derivative cannot be blamed on a rapid equilibration of the *cis* and *trans* isomers with reduction then occurring *via* the *trans* isomer to give only exocyclic cleavage. Rather some other factor is responsible, the most likely being steric interference by the 6-methyl group with coordination of $AlCl_3$ at the ring oxygen (*vide supra*). Because of the small amount of ring cleavage, we were not able, either, to determine whether the stereoisomeric 6-methyl-2-isopropoxytetrahydropyrans are equilibrated faster than they are reduced. Such a determination would have indicated which of the transition states T or T′ in Figure 1 is rate determining, since equilibration prior to reduction would occur if T′ but not if T were the higher-energy transition state.

Change from aluminum chloride to boron trifluoride (compare Tables I and II with III) seems to have a general leveling effect as regards ring *vs.* exocyclic cleavage. The data are not extensive enough to warrant discussion of this point, but it is clear that

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(20) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958); see also ref. 16b.

(21) See ref. 12: (a) p. 52; (b) p. 44.

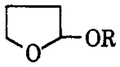
(22) *Cf.* E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962), regarding the corresponding situation in a 3-methylcyclohexanol. The effect of equatorial methyl at C-3 on the carbinol proton at C-1 is a shift of −0.5 c.p.s. for equatorial H, and of 1.5 c.p.s. for axial H.

$LiAlH_4$–$BF_3$ is a better reagent than $LiAlH_4$–$AlCl_3$ for the synthesis of $RO(CH_2)_nOH$ ($n$ = 4 or 5) when R is primary or secondary.

The starting materials used in this investigation were prepared by the standard method: addition of alcohol to 2,3-dihydropyran or -furan in the presence of mineral acid. The properties and yields of the starting materials are summarized in Tables IV and V. Excess dihydropyran[23] was the solvent for the pyranyl ethers while tetrahydrofuran was used (as diluent) in the synthesis of the tetrahydrofuranyl ethers from the less readily available 2,3-dihydrofuran. An alternative synthesis of 2-tetrahydrofuranyl ethers, from tetrahydrofuran and $t$-butyl perbenzoate in the presence of alcohols, is also available,[24] but, in our hands, proved less convenient for the preparation of these ethers in variety and was used only for 2-$t$-butoxytetrahydrofuran.

TABLE V

2-TETRAHYDROFURANYL ETHERS



| R | B.p., °C. (mm.) | Calcd., % C | Calcd., % H | Found, % C | Found, % H | Yield, % |
|---|---|---|---|---|---|---|
| $(CH_3)_3C$ | 42–44 (17)[a] | | | | | 68 |
| Cyclohexyl | 90–92 (10) | 70.55 | 10.66 | 70.56 | 10.64 | 55 |
| $n$-Hexyl | 83–84 (10)[b] | | | | | 78 |
| Benzyl | 102 (4) | 74.13 | 7.92 | 74.35 | 8.04 | 66 |

[a] $n^{20}_D$ 1.4192. Lit.[24] b.p. 40° (11 mm.), $n^{20}_D$ 1.4194. [b] Lit.[24a] b.p. 87–88° (10 mm.).

## Experimental

**2,3-Dihydrofuran.**[25]—Potassium $t$-butoxide was prepared by dissolving 12 g. of potassium in 200 ml. of sodium-dried $t$-butyl alcohol. A mixture of 70 g. of this solution and 70 g. (1 mole) of 2,5-dihydrofuran was placed in a 0.5-l. stainless steel autoclave which was sealed and heated at 170° for 6 hr. The cooled solution was poured into a round-bottom flask and distilled through a spinning-band column to give 55.3 g. (79%) of 2,3-dihydrofuran: b.p. 53–55° (745 mm.), $n^{20}_D$ 1.4200; lit.[25] b.p. 53.4°, $n^{20}_D$ 1.4282. The characteristic[26] infrared bands at 3120, (w), 1615 (s), and 710 cm.$^{-1}$ (m) were observed.

**2-Cyclohexyloxytetrahydrofuran.**—A solution of 7 g. (0.1 mole) of 2,3-dihydrofuran, 10 g. (0.1 mole) of cyclohexanol, and a trace of $p$-toluenesulfonic acid in 25 ml. of tetrahydrofuran was heated on the steam bath in a flask equipped with a reflux condenser. As the reaction became exothermic, external heating was interrupted to be resumed when the reaction subsided. After 1-hr. total heating the solution was cooled and neutralized with methanolic sodium methoxide. The tetrahydrofuran and methanol were then pumped off with an aspirator and the residue was distilled to yield 9.3 g. (55%) of 2-cyclohexyloxytetrahydrofuran (see Table V).

Other 2-tetrahydrofuranyl ethers (Table V) were prepared similarly except the 2-$t$-butoxy compound which was prepared from tetrahydrofuran and $t$-butyl perbenzoate in 68% yield.[24a]

**2-(*cis*-3,3,5-Trimethylcyclohexyl)tetrahydropyran.**[27]—A solution of 14.2 g. (0.1 mole) of *cis*-3,3,5-trimethylcyclohexanol[28] and a trace of $p$-toluenesulfonic acid in 16.8 g. (0.2 mole) of dihydropyran was placed in a flask equipped with a reflux condenser and heated cautiously on the steam bath until an exothermic reaction set in. Heating was then interrupted, to be resumed when the reaction subsided. After an hour of heating, the solution was neutralized with methanolic sodium methoxide, the solvent was pumped off at water aspirator pressure, and the residue was distilled: b.p. 82–84° (0.7 mm.), yield 18.5 g. (88%) (see Table IV). Other 2-tetrahydropyranyl ethers (Table IV) were prepared similarly.

**6,8-Dioxabicyclo[3.2.1]octane**[29] was prepared from 34.2 g. (0.3 mole) of 6-hydroxymethyl-5,6-dihydropyran[18] in 150 ml. of dry benzene using a trace of $p$-toluenesulfonic acid to catalyze ring closure, according to the method of Whetstone.[29] The product, 17.5 g. (51%), boiled at 64–66° (38 mm.) and solidified: m.p. 46–48°; lit.[29,30] b.p. 68–70° (39 mm.), m.p. 50°.

**6-Methoxytetrahydropyran-2-methanol**[30] was prepared from 22.8 g. (0.2 mole) of 6-hydroxymethyl-5,6-dihydropyran,[18] 38.4 g. (1.2 mole) of methanol, and a trace of $p$-toluenesulfonic acid as described.[30] The product, 22.9 g. (79%), boiled at 87–90° (7 mm.); lit.[30] b.p. 86–91° (7 mm.). It probably contained both stereoisomers.

**2-Isopropoxy-6-methyltetrahydropyran.**—A solution of 14 g. (0.14 mole) of 6-methyl-5,6-dihydropyran and a few crystals of $p$-toluenesulfonic acid in 50.4 g. (0.84 mole) of isopropyl alcohol was heated cautiously at reflux as described earlier. After an hour of heating, the reaction mixture was neutralized with methanolic sodium methoxide and distilled to give 16.4 g. (75%) of 2-isopropoxy-6-methyltetrahydropyran (mixture of geometrical isomers), b.p. 57–59° (16 mm.), $n^{20}_D$ 1.5022.

*Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.53; H, 11.58.

Vapor phase chromatography on a Carbowax 20M column (142°, 46 cc./min. He flow) indicated the presence of two isomers in a ratio of 68:32 (retention times 4.3 and 6.1 min.). The n.m.r. spectrum also showed the two isomers in about a 1:2 ratio through the acetal methine signals at −260 (wide, split) and −288 c.p.s. (narrow), the latter more intense peak corresponding to the equatorial proton (axial ether), which is thus present in the mixture to the extent of 68%.

Separation of the two isomers was effected on a Wilkens Model A-700 preparative gas chromatograph, SE-30 silicone oil column (105°, 200 cc./min. He flow) with repeat automatic injection of 0.2-ml. sample/cycle. From 14 g. of material was recovered 2.7 g. of the *trans* isomer (97% pure by analytical gas chromatography), narrow n.m.r. signal at −289 c.p.s. (at 60 Mc.p.s. downfield from tetramethylsilane), and 1.3 g. of the *cis* isomer, wide n.m.r. signal at −259 c.p.s. (95% pure by analytical gas chromatography).

Reduction of 7.9 g. (0.05 mole) of the mixed acetals (68:32) as described below gave 2.75 g. of a wide-boiling mixture consisting of isopropyl alcohol and 2-methyltetrahydropyran, as suggested by gas chromatography. This was followed by 0.19 g. (2.4%) of material, b.p. 44° (5 mm.), resembling other hydroxy ethers in infrared spectrum, which was presumed to be 6-isopropoxy-2-hexanol; not enough material was available for complete characterization. The material gave a single peak (retention time 16 min. on a Carbowax column at 158°, 55 cc./min. He flow) on a gas chromatogram. Repetition of the experiment using gas chromatography with an internal standard (1-decanol) confirmed that the product was formed in about 2% yield only. Similar analyses of reduction products of the nearly pure *cis* and *trans* ethers indicated formation of the hydroxy ether product in 2.6 and 0.9% yield, respectively.

**4-$t$-Butoxy-1-butanol.**—The reduction is typical of that of tetrahydrofuranyl ethers (Table II). To 100 ml. of chilled anhydrous ether in a three-necked flask equipped with dropping funnel, stirrer, and reflux condenser capped with a drying tube was added 27.4 g. (0.2 mole) of anhydrous aluminum chloride in small portions. The solution was stirred for 0.5 hr. and 46 ml. (0.05 mole) of 1.15 $M$ ethereal lithium aluminum hydride (clear, standardized solution) was added with continued cooling. After further stirring for 0.5 hr., 15.2 g. (0.1 mole) of 2-$t$-butoxytetrahydrofuran in *ca.* 100 ml. of anhydrous ether was added dropwise while the mixture was allowed to warm to room temperature. The solution was then boiled for 2 hr., cooled to ice-bath temperature, and enough water was added to destroy unreacted

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[23] Generously donated by the Electrochemicals Division of E. I. du Pont de Nemours and Co. through the courtesy of Dr. David Scheiber.

[24] (a) S. O. Lawesson and C. Berglund, *Arkiv Kemi*, **17**, 475 (1961); (b) G. Sosnovsky, *J. Org. Chem.*, **25**, 874 (1960); *Tetrahedron*, **13**, 241 (1961).

[25] M. L. A. Fluchaire and G. Collardeau, U. S. Patent 2,556,325 (1951); *Chem. Abstr.*, **46**, 1046*f* (1952).

[26] G. D. Meakins, *J. Chem. Soc.*, 4170 (1953).

[27] Method of R. Paul, *Bull. soc. chim. France*, [5] **1**, 971 (1934).

[28] E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).

[29] R. R. Whetstone, U. S. Patent 2,511,891 (1950); *Chem. Abstr.*, **44**, 8961*c* (1950).

[30] Shell Chemical Co., 110 West 51st St., New York 20, N. Y., Bulletin PD-148, 1963.

hydride. When hydrogen evolution ceased, 10% (by weight) aqueous sulfuric acid was added until two clear layers were obtained. The ethereal layer was separated and the aqueous layer was extracted continuously with ether for 85 hr. The combined ether layers were dried over potassium carbonate and concentrated to give 11.14 g. of crude oil. Distillation yielded 1.3 g., b.p. 42–70° (10 mm.), containing traces of *t*-butyl alcohol and tetrahydropyran (v.p.c.), and 7.59 g., b.p. 72–74° (10 mm.), free of contaminants; the total yield was 8.89 g. (61%) (see Table II).

Continuous extraction was not employed for the other ethers in Table II which appeared to be considerably less water soluble than the *t*-butyl ether.

**5-Cyclohexyloxy-1-pentanol. A. LiAlH$_4$–AlCl$_3$.**—The reduction of 9.2 g. (0.05 mole) of 2-cyclohexyloxytetrahydropyran was carried out as described above (on half the scale indicated). The ethereal solution was concentrated to 50 ml. and a weighed amount of 2-cyclohexyloxytetrahydropyran was added as an internal standard. (A blank gas chromatogram of the crude reaction product without added standard showed complete consumption of starting material.) The solution was then analyzed by gas chromatography. Area response factors were evaluated by submitting mixtures of known composition of 5-cyclohexyloxy-1-pentanol and 2-cyclohexyloxytetrahydropyran to gas chromatography under identical conditions (Carbowax column at 180–190°, 75 cc./min. He flow rate). Three analyses indicated 42.6, 45.7, and 48.5% yields of 1-cyclohexyloxy-5-pentanol, based on starting material.

In another run on the same scale the products were isolated as described for 4-*t*-butoxy-1-butanol. Fractions collected were 1.90 g. (38%) of cyclohexanol, b.p. 62–65° (19 mm.), $n^{20}\text{D}$ 1.4650, lit.[31] b.p. 67–68° (23 mm.), $n^{20}\text{D}$ 1.4657, and 4.21 (45.5%) of 5-cyclohexyloxy-1-pentanol (see Table I).

**B. Using LiAlH$_4$–BF$_3$.**—In general, the best method for reduction of tetrahydropyranyl and tetrahydrofuranyl ethers using LiAlH$_4$–BF$_3$ is that[5] in which ethereal lithium aluminum hydride and boron trifluoride etherate are mixed prior to addition of the acetal.[6]

An alternative is to add boron trifluoride etherate to a solution of the acetal and lithium aluminum hydride in ether. Mixing of the tetrahydrofuranyl (or -pyranyl) ether with boron trifluoride etherate followed by addition of hydride solution tends to lead to resinification.

A freshly distilled solution of 14.2 g. (0.1 mole) of boron trifluoride etherate was placed in a three-necked flask equipped with stirrer, reflux condenser, and addition funnel and cooled in an ice bath. To this was added, dropwise, 21 ml. (0.025 mole) of a 1.2 *M* clear, standardized ethereal solution of lithium aluminum hydride and approximately 35 ml. of anhydrous ether, and the mixture was stirred for 0.5 hr. A solution of 9.2 g. (0.05 mole) of 2-cyclohexyloxytetrahydropyran in *ca.* 35 ml. of ether was added slowly with stirring and the solution was then allowed to warm to room temperature and stirred for 1 hr., following which it was boiled for 2 hr. It was then cooled, 10% aqueous sulfuric acid was added, the two clear layers were separated, and the aqueous layer was extracted with two portions of ether. The combined ether layers were successively washed with water, saturated aqueous sodium bicarbonate, and brine, following which they were dried over anhydrous potassium carbonate and concentrated. Distillation of the crude residue (9.4 g.) gave 0.6 g. (12%) of cyclohexanol, b.p. 32–34° (1 mm.), identified by infrared spectrum, and 6.3 g. (69%) of 5-cyclohexyloxy-1-pentanol, b.p. 110–111° (1 mm.). Its infrared spectrum was identical with that obtained in the LiAlH$_4$–AlCl$_3$ reduction (*vida supra*).

**5-*t*-Butoxy-1-pentanol (from Pentamethylene Chlorohydrin).**—5-Chloro-1-pentanol (12.25 g., 0.1 mole) and dihydropyran (9.24 g., 0.11 mole) were placed in a flask equipped with a reflux condenser and a few crystals of *p*-toluenesulfonic acid were added. An exothermic reaction set in. After a 2-hr. reflux the reaction mixture was cooled and made basic with a slight excess of methanolic sodium methoxide. The mixture was concentrated at reduced pressure and the residue was diluted with 100 ml. of water. The organic material was extracted with four 50-ml. portions of ether which were combined, dried over sodium sulfate, and concentrated.

The crude 2-(5-chloropentoxy)tetrahydropyran in 100 ml. of anhydrous *t*-butyl alcohol was added to a solution of 13.46 g. (0.12 mole) of commercial potassium *t*-butoxide in 150 ml. of anhydrous *t*-butyl alcohol, and the mixture was stirred at reflux for 20 hr. Excess *t*-butyl alcohol was removed by distillation and the residue was added to 200 ml. of 10% sulfuric acid to hydrolyze the tetrahydropyranyl ether. The organic material was extracted with four 50-ml. portions of ether which were combined, dried over sodium sulfate, and concentrated. Distillation revealed a rather wide boiling range (90–120° at 10 mm.). The fraction boiling at 105–120° (10 mm.), $n^{20}\text{D}$ 1.4492, weighed 1.18 g. and seemed to contain the major amount of the product. Purification was effected by gas chromatography on Tide (10-ft. column, 218°, 48 cc./min. He flow). The main part of the material was collected from the column and proved to be identical in infrared spectrum with the material obtained from reduction of 2-*t*-butoxytetrahydropyran (Table I).

**4-Cyclohexyloxy-1-butanol (from Phenol and γ-Butyrolactone).**—γ-Phenoxybutyric acid, m.p. 59–60° (lit.[32] m.p. 64°) was prepared from phenol and γ-butyrolactone by the method of Reppe[32] in very poor yield. A solution of 13 g. (0.07 mole) of the acid in 70 ml. of anhydrous ether was reduced by addition to 2.2 g. (0.06 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether. Reaction time was 12 hr. at reflux, with stirring. The cooled reaction mixture was decomposed by 10 ml. of water followed by 100 ml. of 10% sulfuric acid. The ether layer was separated and the aqueous layer was extracted with five 50-ml. portions of ether. The combined ether layers were dried over magnesium sulfate, filtered, and concentrated. Distillation of the residue gave 10.5 g. (88%) of 4-phenoxy-1-butanol, b.p. 125° (3 mm.), lit.[33] b.p. 212–215°. Characteristic infrared bands were found at 3.15, 8.1, 9.6, 13.2, and 14.4 μ.

A solution of 10 g. (0.06 mole) of 4-phenoxy-1-butanol in 100 ml. of glacial acetic acid was hydrogenated in a Parr hydrogenation apparatus over 1 g. of platinum dioxide catalyst at about 60 p.s.i. of hydrogen. After the theoretical amount of hydrogen (0.18 mole) was taken up, the solution was filtered and poured into 400 ml. of 10% aqueous sodium hydroxide. The solution was extracted with two 100-ml. and three 50-ml. portions of ether. The combined ether portions were washed several times with water and saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and concentrated, and the residue was distilled to give 4.3 g. (43%) of 4-cyclohexyloxy-1-butanol, b.p. 124–126° (9 mm.), $n^{20}\text{D}$ 1.4629. The infrared spectrum of this material was identical with that of the compound obtained by "mixed hydride" reduction of 2-cyclohexyloxytetrahydrofuran (Table II).

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(31) G. S. Hiers and R. Adams, *J. Am. Chem. Soc.*, **48**, 2385 (1926); E. Waser, H. Sommer, C. Landweer, and C. Gaza, *Helv. Chim. Acta*, **12**, 418 (1929).

(32) W. Reppe, *et al.*, *Ann.*, **596**, 192 (1955).

(33) I. P. Losev and O. V. Smirnova, *Zh. Obsch. Khim.*, **28**, 363 (1958); Engl. transl., p. 359.