The Influence of the 2-Alkoxy Group and of C-5 Substituents on the Direction of Reductive Cleavage of 2-Alkoxytetrahydrofurans by AlH_2Cl in Ether Solution[1]

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The AlH_2Cl hydrogenolysis of ether solutions of 2-alkoxytetrahydrofurans in which the alkoxy group is either CH_3O, C_2H_5O, i-C_3H_7O, or t-C_4H_9O, gives only those products resulting from ring C—O bond cleavage. However, substituents at C-5 of 2-methoxytetrahydrofuran exert a strong effect on the ratio of ring to *exo* C—O bond cleavage. Thus, alkyl (electron donor) groups at C-5 promote an increase in the amount of *exo* cleavage, the proportion increasing from 62.5 to 100% as the C-5 alkyl group is changed from CH_3 to t-C_4H_9. In contrast, electron withdrawing substituents, CH_3OCH_2— and C_6H_5, at C-5 favor ring cleavage to the extent of 93 and 84% respectively.

The results are interpreted in terms of the influence that these substituents exert through their electronic properties on the relative ease of attainment of the transition state leading to either ring C—O or *exo* C—O bond cleavage. However, evidence is provided to show that the bulk steric effect of these substituents also controls, though to a minor extent, the proportion of ring to *exo* cleavage.

Les hydrogénolyses par AlH_2Cl de solutions éthérées de tétrahydrofurannes alcoolates-2, où le group alcoolate est soit CH_3O, C_2H_5O, i-C_3H_7O, ou t-C_4H_9O, conduisent uniquement aux produits résultant de la rupture de la liaison C—O du cycle. Cependant, les substituants sur C-5 dans le méthoxy-2 tétrahydrofuranne, exercent un effet important sur le rapport: rupture de la liaison C—O du cycle sur rupture de la liaison C—O exocyclique. C'est ainsi que des groupes alkyles (donneurs d'électrons) sur C-5 favorisent le pourcentage de clivage exocyclique; les pourcentages augmentant de 62.5 à 100% si le groupe alkyle passe de CH_3 à t-C_4H_9. Au contraire, des substituants en C-5 attracteurs d'électrons, CH_3OCH_2— et C_6H_5, favorisent la rupture du cycle jusqu'à des proportions de 93 et 84% respectivement.

Les résultats sont interprétés en fonction de l'influence qu'exercent ces substituants, par leurs propriétés électroniques, sur la facilité relative de formation de l'état de transition conduisant ultérieurement à la rupture de la liaison C—O soit du cycle soit exocyclique. Cependant, des preuves ont été apportées afin de montrer que l'encombrement stérique de ces substituants contrôle également, bien qu'à un degré moindre, les proportions de clivage cyclique et exocyclique.

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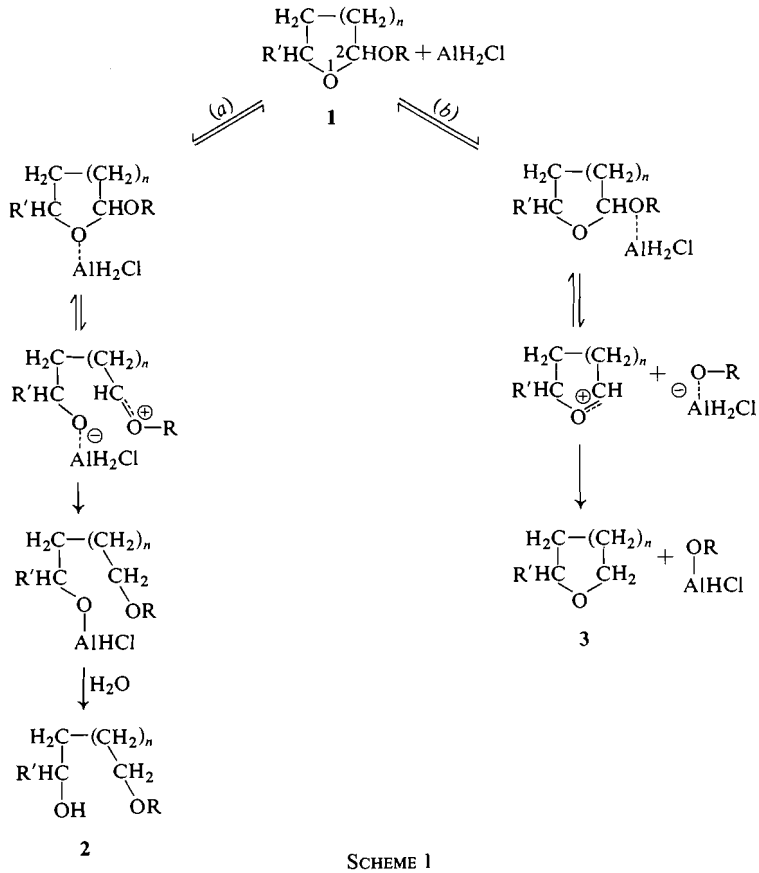
Introduction

It has been shown (1) that the proportion of ring C—O bond cleavage to side chain C—O bond cleavage of 2-alkoxytetrahydropyrans (Scheme 1, **1**, $n = 2$) resulting from the hydrogenolysis by a 1:1 mixture of $AlCl_3$ and $LiAlH_4$ in ether depends upon the nature of the alkyl group of the 2-alkoxy substituent and also upon the nature of the C-6 substituent. The percent ring cleavage increased in the order 30, 60, 60, 82, 87 when the alkyl group of the 2-alkoxytetrahydropyran was CH_3, C_2H_5, n-C_4H_9, i-C_3H_9, and t-C_4H_9 respectively (**1**, $R' = H$ in each case). This was attributed to the relative electron donor ability of the alkyl group of the 2-alkoxy moiety to facilitate attainment of the transition state leading to the intermediate oxocarbonium ion involved in ring cleavage compared to the ease of obtaining the alternate intermediate oxocarbonium ion involved in the departure of the 2-alkoxy group with simultaneous ring retention (Scheme 1, routes *a* and *b* respectively, $n = 2$, $R' = H$, R = alkyl). Attainment of the transition state leading to the oxocarbonium ion was considered to be the slow and rate determining step, while hydride addition to this ion was fast and nonreversible. A similar explanation, involving the C-6 substituent was advanced to explain the 6, 60, and 80% proportion of ring cleavage found in the $LiAlH_4$–$AlCl_3$ hydrogenolysis respectively of the *cis–trans* mixture of 6-methyl-2-methoxy-

[1]In part from the thesis of P. C. Loewen submitted to the Faculty of Graduate Studies, University of Alberta as part of the requirements for the Ph.D. degree, 1969, and the thesis of Miss L. P. Makhubu submitted to the Faculty of Graduate Studies, University of Alberta as part of the requirements for the M.Sc. degree, 1967.



SCHEME 1

tetrahydropyran, and the separate *cis* and *trans* isomers of 2-methoxy-6-methoxymethyltetrahydropyran (1).

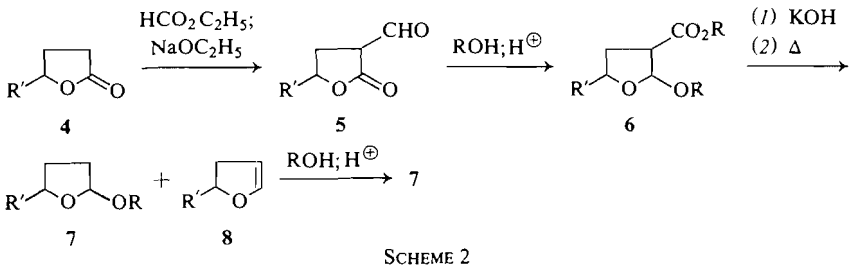
The present paper describes the results of the extension of this study to the hydrogenolysis by 1:1 $LiAlH_4$–$AlCl_3$ (*i.e.* AlH_2Cl (2, 3)) of 2-alkoxytetrahydrofurans and of some 5-substituted 2-methoxytetrahydrofurans (Scheme 1, **1**, $n = 1$).

Results and Discussion

Preparation of 2-Alkoxytetrahydrofurans and 5-Substituted 2-Alkoxytetrahydrofurans

The unsubstituted 2-alkoxytetrahydrofurans were prepared by the reaction of the appropriate alcohol with α-formyl-γ-butyrolactone (previously obtained from the base-catalyzed reaction of γ-butyrolactone (**4**, R′ = H) with ethyl formate), followed by alkaline hydrolysis and subsequent decarboxylation of the product (Scheme 2), a procedure based on that of Korte *et al.* (4, 5). For R′ = H, the yield of the ester **6** decreased in the order 90, 41, 29, ~0% when R was CH_3, C_2H_5, *i*-C_3H_7, and *t*-C_4H_9 respectively, a result thought to be due to the relatively greater steric interference of R as its bulk increased. Decarboxylation of the 2-alkoxy-3-carboxytetrahydrofuran in the conversion of **6** to **7** was accompanied by the dihydrofuran **8**. However, by the acid-catalyzed reaction of the mixture of **7** and **8** with the alcohol ROH, **7** could be obtained quite readily, free of **8**.

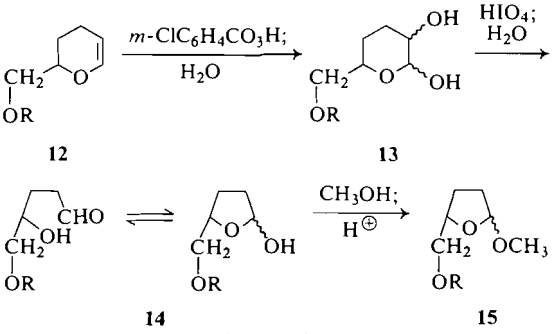
The same procedure shown in Scheme 2 was used to convert the γ-substituted γ-butyrolactones **4** (R′ = CH_3, *i*-C_3H_7, *t*-C_4H_9) to the corresponding 2-methoxy-5-substituted tetrahydrofurans. Apart from the commercially available γ-valerolactone (**4**, R′ = CH_3), the required γ-alkyl-γ-butyrolactones were made satisfactorily by the reaction of the appropriate



SCHEME 2

methyl ketones **9** ($R' = i\text{-}C_3H_7$ or $t\text{-}C_4H_9$) with dimethylamine and titanium tetrachloride (Scheme 3), a method which produces the terminal enamine **10** (6), which was then condensed with ethyl bromoacetate to provide the γ-ketoester **11** (7). The ester **11** could then be reduced and the product subsequently cyclized to the γ-substituted γ-butyrolactone **4** (Scheme 3). This method was unsuccessful for the preparation of γ-phenyl-γ-butyrolactone from acetophenone, since the conversion of **11** ($R' = C_6H_5$) to **4** ($R' = C_6H_5$) with sodium borohydride (Scheme 3) was quite unsatisfactory. However, **4** ($R' = C_6H_5$) could be obtained in satisfactory yield from the base-catalyzed reaction of styrene oxide with diethyl malonate, and the product hydrolyzed and decarboxylated.

We were unable to prepare γ-methoxymethyl-γ-butyrolactone (**4**, $R' = CH_3OCH_2$) to take advantage of its conversion to **7** ($R' = CH_3OCH_2$, $R = CH_3$) by the route shown in Scheme 2. However, 2-methoxy-5-methoxymethyltetrahydrofuran was made satisfactorily by the reaction of a peroxy acid with the methyl ether of 2-hydroxymethyl-2,3-dihydro-3*H*-pyran (**12**, $R = CH_3$) to produce the diol **13** (8) which in turn was oxidized with metaperiodic acid (Scheme 4). To avoid extensive decomposition, the product **14** was not isolated or purified, but instead subjected directly to acid-catalyzed reaction with methanol to produce the acetal **15** ($R = CH_3$).

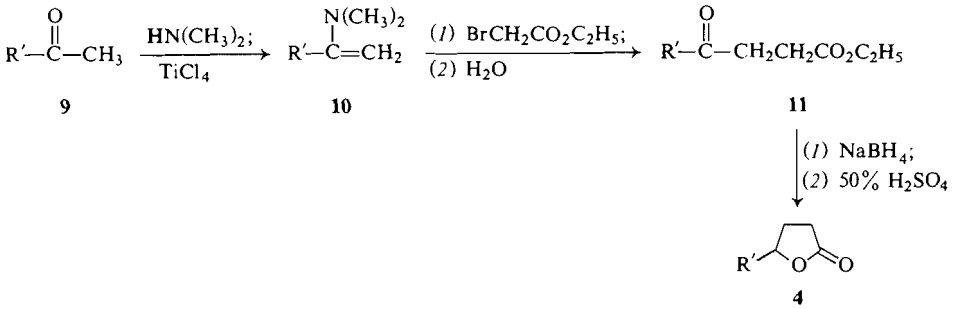


SCHEME 4

Hydrogenolyses

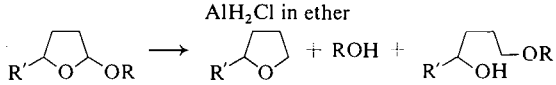
(a) Of 2-Alkoxytetrahydrofurans

Only two products were obtained from the hydrogenolysis of each of the 2-alkoxytetrahydrofurans (*cf.* routes *a* and *b* in Scheme 1, $n = 1$). These usually were easily identified by comparison of the g.l.c. retention times with those of authentic samples. In all cases of doubt, the products were isolated by preparative g.l.c. and then identified by comparison of their p.m.r. and i.r. spectra and physical constants with those of authentic compounds. In those



SCHEME 3

TABLE 1. Room temperature hydrogenolysis of unsubstituted and 5-substituted 2-alkoxytetrahydrofurans by AlH_2Cl in ether



A B C

Experiment	Compound A R′	Compound A R	Reduction* time (h)	Extent of reduction (%)	Total recovery (%)	Reduction products as % of product B	Reduction products as % of product C
1	H	CH_3	2.25	100	86†	0	100
2	H	C_2H_5	2.25	100	82†	0	100
3	H	i-C_3H_7	2.25	100	80†	0	100
4	H	t-C_4H_9	2.25	100	86†	0	100
5‡	CH_3OCH_2	CH_3	2.0	100	85	6.5	93.5
6‡	CH_3	CH_3	2.0	100	80	62.5	37.5
7‡	i-C_3H_7	CH_3	2.0	100	90	86	14
8‡	t-C_4H_9	CH_3	2.0	62	80	~100	trace
			8.0	100	95	~100	trace
9‡	C_6H_5	CH_3	2.0	85	92	15.7	84.3
			48.	100	90	15.5	84.5
10‡	CH_3	i-C_3H_7	3.0	100	80	6.8	93.2

*This time generally was more than enough for complete reaction. Most were complete in a fraction of the time indicated and in these cases no starting material remained. All products were stable to the reaction conditions.

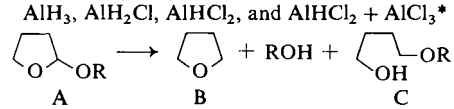
†Recovery was based on the actual % yield of product C obtained by distillation and does not include B or CH_3OH since the latter could not be estimated by g.l.c.

‡*cis–trans* mixtures of A were reduced in each case. The p.m.r. spectra indicated that the two isomers were present in the ratio from 1:1 to 2:3.

cases wherein authentic compounds were not available or reported, the isolated products were characterized in the usual way. All hydrogenolysis products were stable under the reaction conditions. Product ratios were determined by g.l.c. peak areas, uncorrected for detector response since usually the observed areas corresponded well within 5% of the expected area, and only a few deviated at the most by 10%. In all cases there was no doubt as to the preferred direction of reductive cleavage. The results of the hydrogenolysis reactions are shown in Table 1 in which structure A represents the substituted or unsubstituted 2-alkoxytetrahydrofuran while structures B and C represent the products from *exo* cleavage and ring (*endo*) cleavage respectively.

Experiments 1–4 in Table 1 show that when R′ = H in A, only ring cleavage occurs, regardless of whether R is CH_3, C_2H_5, i-C_3H_7, or t-C_4H_9. This is in sharp contrast to the findings for the hydrogenolysis of the analogous 2-alkoxytetrahydropyrans where both ring and *exo* cleavage products were formed, with the latter decreasing in relative amount as the alkyl group changed from CH_3 to t-C_4H_9. It is clear that exclusive ring cleavage occurs regardless of the inductive or steric effect of the alkyl substituent R. Since it has been shown that there is a stronger association of Lewis acids with tetrahydrofuran than with the analogous acyclic ether (9–11), it is possible that this factor submerges any inductive or steric influence of the alkyl group R and hence the Lewis acid AlH_2Cl associates exclusively or nearly so with the ring oxygen, the first step in the reductive cleavage of the C—O bond of acetals. It is to be expected that the stronger association of the Lewis acid with the ring oxygen would produce a greater extent of C—O bond breaking in the transition state, resulting in the strong preference for ring cleavage (route *a*, Scheme 1, $n = 1$, R′ = H). That a polar effect of the alkyl group is still operative, although it is unable to manifest itself in terms of the direction of reductive cleavage, is clearly shown by the competitive reaction of a 1:1 mixture of 2-ethoxy- and 2-t-butoxytetrahydrofuran with a limited amount of AlH_2Cl, sufficient to hydrogenolyze only one-half of the total acetal. It was found again that only ring cleavage products were obtained, but the ratio of the 2-t-butoxy- to 2-ethoxytetrahydrofuran reduced was 78:22, thus showing that the t-butyl group is more

TABLE 2. Room temperature hydrogenolysis of ether solution of 2-benzyloxytetrahydrofuran by AlH_3, AlH_2Cl, $AlHCl_2$, and $AlHCl_2 + AlCl_3$*



A B C

($R = C_6H_5CH_2^-$)

Experiment no.	Reagent	Extent of reduction (%)	Total material recovery (%)	% reduction product as B	% reduction product as C
1	AlH_3	67.5	84	20.5	79.5
2	AlH_2Cl	100	95	48.5	51.5
3	$AlHCl_2$	100	90	90.5	9.5
4	$AlHCl_2:AlCl_3$ (4:1)	100	91	91.3	8.7

*All reactions were allowed to proceed for 2 h.

effective in facilitating attainment of the transition state leading to oxocarbonium ion formation.

Eliel *et al.* (12) have reported the hydrogenolysis of four 2-alkoxytetrahydrofurans by a mixture of $AlCl_3$ and $LiAlH_4$ and found that generally both *exo* and *endo* cleavage occurred. The percentage of *exo* and *endo* cleavage products actually obtained by them in each case where the alkyl group was *t*-butyl, cyclohexyl, *n*-hexyl, and benzyl were, respectively, a trace and 58, 15 and 63, 40 and 27, 83 and 4. They concluded from this that the steric effect of the C-2 alkoxy group was more important than was the basicity of the ring oxygen in directing the course of reductive cleavage. The discrepancy between our results and those reported (12) might be due to the fact that we employed as reducing system a 1:1 mixture of $AlCl_3$ and $LiAlH_4$ which provides AlH_2Cl (2, 3) whereas Eliel *et al.* (12) used a 4:1 mixture of $AlCl_3$ and $LiAlH_4$, which provides a 1:4 mixture of $AlCl_3$ and $AlHCl_2$ (2, 3). This view is supported by the data in Table 2 which show the results of the hydrogenolysis of 2-benzyloxytetrahydrofuran by the series of reagents AlH_3, AlH_2Cl, $AlHCl_2$, and the 4:1 mixture of $AlHCl_2$ with $AlCl_3$ (Eliel's reagent). The latter two hydrogenolyzing reagents provide the *exo* and *endo* cleavage products, B and C, in the proportion 90.5:9.5 and 91.3:8.7 respectively, nearly the same as the proportion of 83:4 reported (12). However, reduction by AlH_2Cl provides the same products in the proportion *exo*:*endo* = 48.5:51.5. The failure to obtain exclusive ring cleavage with AlH_2Cl as was found for the alkoxytetrahydrofurans may be due to the electron withdrawing character of the phenyl group which would then cause the benzyloxy moiety to destabilize the transition state leading to ring cleavage, thus overcoming to some extent the overwhelming tendency of the Lewis acid to coordinate with the ring oxygen which is followed by ring cleavage. AlH_3 also provides the *exo* and *endo* cleavage products, but in the proportion 20.5:79.5. It is clear from the data in Table 2 that those hydrogenolyzing agents which are the strongest Lewis acids provide the greatest proportion of *exo* cleavage.

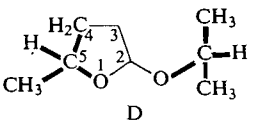
(b) Of 5-Substituted 2-Alkoxytetrahydrofurans

Hydrogenolysis of the 5-alkyl-2-methoxytetrahydrofurans, as *cis–trans* mixtures, provides both *exo* and *endo* cleavage products B and C. As the C-5 alkyl group R′ is changed from CH_3 to i-C_3H_7 to t-C_4H_9, the percent *exo* cleavage is respectively 62.5, 86, and ~100% (experiments 6–8, Table 1). It is clear that in these three cases, the greater "basicity" of the ring oxygen is counteracted by other forces. Two factors, either separately or in concert, could account for these results. The first is due to the electron donor property of the C-5 alkyl group (R′) competing progressively more effectively in lowering the energy required to attain the transition state leading to the formation of the oxocarbonium ion involved in ring retention, than does the *exo* oxygen's alkyl group in attaining the alternate oxocarbonium ion (*i.e.* route *b* is preferred over route *a* in Scheme 1). The second factor is due to the steric effect of the C-5 alkyl substituent, added to that of the C-2 methoxy group, decreasing the ease of associa-

tion of the Lewis acid with the ring oxygen, thus causing preference for route *b* (Scheme 1). It is to be noted that such a steric effect has been advanced to account for the lower "basicity" of 2-methyltetrahydrofuran and of 2,5-dimethyltetrahydrofuran compared to that of tetrahydrofuran itself (10, 11).

In an attempt to determine the relative effectiveness of the polar and steric influences, substituents were incorporated in structure **1** at C-5, which provided the bulk required, but were electron withdrawing in character. If the steric effect is predominant, hydrogenolysis of these C-5 substituted 2-methoxytetrahydrofurans should provide primarily B, the product from *exo* cleavage (route *b*, Scheme 1). On the other hand, if the polar effect is of predominant importance, then the ring cleavage product C should be preferred (route *a*, Scheme 1). In this connection it is known that the phenyl group has an effective bulk slightly greater than that of the isopropyl group, as shown by their respective A values of 2.1–3.0[2] and 1.8–2.5 kcal/mol determined in the cyclohexane system (13). Experiments 5 and 9 (Table 1) show that hydrogenolysis of 2-methoxy-5-methoxymethyltetrahydrofuran and of 2-methoxy-5-phenyltetrahydrofuran (both as *cis–trans* mixtures) provide the ring cleavage products in the proportion of 93.5 and 84.5% respectively. This appears to show that it is the electronic rather than the steric effect which is of major importance in determining the direction of reductive cleavage. However, the ability of oxygen ethers and of the phenyl group to associate with Lewis acids such as $AlCl_3$, and thus quite likely with AlH_2Cl, might cause the C-5 substituents, $R' = CH_3OCH_2$ and C_6H_5, to assist in keeping the AlH_2Cl in the vicinity of the ring oxygen, rather than with the C-2 oxygen atom, and in this way favor ring cleavage.

A further attempt to determine the relative effectiveness of polar and steric influences was made by hydrogenolyzing 5-methyl-2-isopropoxytetrahydrofuran. In this compound the polar effects on the acetal unit of the isopropyl group and of the portion of the structure at C-5



D

should be similar since the latter moiety approximates the isopropyl group in its electron donor ability. This feature is shown in structure D in which the comparable sections are emphasized. In this case only the bulk of the substituents and the relative "basicity" of the two oxygen atoms should control the direction of reductive cleavage. Experiment 10, Table 1, shows that ring cleavage occurs to the extent of 93.2%. This clearly demonstrates the importance of the greater "basicity" of the ring oxygen. If steric effects were predominant in controlling the direction of cleavage, one would expect that 5-methyl-2-isopropoxytetrahydrofuran (experiment 10) would suffer *exo* cleavage *at least* to the same extent as did 5-methyl-2-methoxytetrahydrofuran (experiment 6). This is clearly not the case, and fortifies our view that electronic factors as well as the "basicity" of the ring oxygen play dominant roles in the direction of reductive cleavage of 2-alkoxytetrahydrofurans. However, the fact that 2-isopropoxytetrahydrofuran undergoes *only* ring cleavage (experiment 3) while 5-methyl-2-isopropoxytetrahydrofuran provides, upon hydrogenolyses, as much as 6.8% of the *exo* cleavage product, B, might be interpreted as evidence that some steric effect is exerted by the C-5 substituent. Hence the steric effect of the C-5 substituent could provide at least some of the reason why hydrogenolysis of 5-alkyl-2-methoxytetrahydrofuran produces an increasing proportion of *exo* cleavage product B ($62.5 \rightarrow 86 \rightarrow 100\%$) as the C-5 group is changed from CH_3 to $i\text{-}C_3H_7$ to $t\text{-}C_4H_9$.

All of the 5-substituted 2-alkoxytetrahydrofurans were mixtures of the *cis* and *trans* isomers, a fact readily determined by the two sets of quartets in the p.m.r. spectrum of each compound due to the anomeric proton. The signal areas showed that the proportion of isomers ranged from 1:1 to 3:2, but we were unable to determine which of the 3:2 mixture was *cis* or *trans*. Although it has been shown that the signals for the α protons of *trans*-2,5-dimethyltetrahydropyran appear at lower field than do those of the *cis* isomer (14, 15), the signals for the α protons of several other *cis*-

[2]Recent calculations involving phenylcyclohexane (35) show that the energy difference could be as high as 3.6 kcal/mol between the axial phenyl group in the preferred "perpendicular" orientation and the equatorial phenyl group in the preferred "parallel" orientation.

trans-2,5-disubstituted tetrahydrofurans appeared either at nearly the same position in the spectrum or in some cases the *trans* α proton signals occurred at slightly higher field than did those of the *cis* isomer. Accordingly, the p.m.r. spectrum was of no assistance in identifying the *cis* or *trans* isomer. All our attempts to separate the isomers by g.l.c. failed, in spite of the variety of columns employed. Our interest in identifying the *cis* or *trans* isomer lay in the possibility that one isomer might prefer to undergo *exo* cleavage, while the other would prefer *endo* cleavage. This might well have been the situation for 5-methyl-2-methoxytetrahydrofuran since the ratio of *exo*:*endo* cleavage is 62.5:37.5 while the isomer ratio is 3:2. However, since all the other 5-substituted 2-alkoxytetrahydrofurans employed in this work hydrogenolyzed either *exo* or *endo* to the extent of at least 80% while their proportion of *cis–trans* isomers ranged from 1:1 to 3:2, it is unlikely that the relative amount of *cis* and *trans* isomers is an important factor in determining the direction of hydrogenolysis. This view is supported by the results obtained from the treatment of the *cis–trans* mixtures of each of the three compounds 5-methyl-, 5-isopropyl-, and 5-*t*-butyl-2-methoxytetrahydrofuran with an amount of AlH_2Cl insufficient to hydrogenolyze all of the acetal. In all three cases the proportion of *cis–trans* isomers in the remaining unreacted material was the same as that in the starting material, and also the proportion of *exo* to *endo* cleavage was the same as that found when complete hydrogenolysis occurred.

Experimental

All boiling points and melting points are uncorrected.

Gas liquid chromatographic analyses were made with an F and M model 700 instrument equipped with 12 ft × 1/8 in. columns packed with either (*a*) Carbowax 20 M, 20% on Gas-Chrom P (60–80 mesh), (*b*) Apiezon T or Apiezon L, 10% on Chromosorb W (60–80 mesh), or (*c*) butanediol succinate, 20% on Chromosorb W (60–80 mesh). Helium was the carrier gas at a flow rate of ~40 ml/min. For preparative g.l.c., an Aerograph Autoprep, Model A-700 (Wilkens Instrument and Research Co.) was used. The columns employed were (*a*) 12 ft × 1/4 in. packed with Carbowax 20 M, 20% on Gas Chrom P (60–80 mesh), (*b*) 12 ft × 1/4 in., packed with butanediol succinate, 20% on Chromosorb W (60–80 mesh), (*c*) 6 ft × 1/4 in., packed with Apiezon T, 10% on Chromosorb W (30–60 mesh), and (*d*) 12 ft × 1/4 in., packed with 10% Carbowax 20 M and 10% silicone rubber on Chromosorb W (30–60 mesh). Helium was the carrier gas. The type of column and its temperature was dependent on the boiling point of the compounds. For most analyses on the F and M, Model 700, the temperature was linearly programmed to achieve better resolution, with a temperature increase of 15 °C/min starting from 50 °C. The terminal temperature depended upon column stability.

Quantitative analyses by g.l.c. were made by measuring the signal areas directly, uncorrected for detector response since observed and correct areas differed by less than 5% in most cases, though in a few this difference was as much as 10%.

The i.r. spectra were recorded with a Perkin–Elmer Model 337 instrument.

The p.m.r. spectra, all referred to tetramethylsilane, were recorded with a Varian Associates A-60 instrument operated by Mr. R. Swindlehurst and assistants, and an HR-100 spectrometer operated by Mr. G. Bigham. The p.m.r. spectra of all new compounds described below agreed completely with the structures proposed.

Elemental analyses were carried out by Mrs. D. Mahlow of this Department. These agreed well with the expected values.

Solvents were removed by rotary evaporator under reduced pressure unless otherwise stated.

Preparation of 2-Alkoxytetrahydrofurans (see Table 3)

The 2-alkoxy-3-carboalkoxytetrahydrofurans (compounds **1**–**4** in Table 3) were prepared by the published procedure (4). These were saponified (4) and decarboxylated at 100–120° to provide compounds **5**–**7**. Compounds **8** and **9** were prepared by literature directions (12).

Preparation of 5-Substituted 2-Alkoxytetrahydrofurans

cis-trans-5-Methyl-2-methoxytetrahydrofuran

3-Carbomethoxy-5-methyl-2-methoxytetrahydrofuran (5), b.p. 97° at 20 mm, η_D^{26} 1.4310; lit. b.p. 84° at 9 mm (5), was saponified (4) to the acid, yield 92%. The oil was decarboxylated at 100–110° to *cis-trans*-5-methyl-2-methoxytetrahydrofuran; yield 42%, b.p. 108–109° at 695 mm; η_D^{30} 1.4127, η_D^{22} 1.4080.

cis-trans-5-Isopropyl-2-methoxytetrahydrofuran

The reaction of 5.7 g (0.05 mol) of 2-dimethylamino-3-methyl-1-butene (6) with 8.35 g (0.05 mol) of ethyl bromoacetate following general directions (7) provided 2.3 g (32%) of *methyl β-isobutyrylpropionate*, b.p. 86–87° at 8 mm; η_D^{22} 1.4270.

A cold (0°) solution of methyl β-isobutyrylpropionate (2.0 g, 0.013 mol) in 20 ml of dry methanol was vigorously stirred while sodium borohydride (0.25 g, 0.0064 mol) was added in small portions. The mixture was then stirred overnight at room temperature. Excess methanol was then removed and 4 ml of aqueous sulfuric acid (1:1) was added to the stirred residue. The ether extracts (3 × 30 ml) were dried ($MgSO_4$), and freed from solvent. Distillation gave 1.5 g (93%) of γ-isopropyl-γ-butyrolactone, b.p. 56° at 0.5 mm; η_D^{20} 1.4416; lit. b.p. 98° at 15 mm; η_D^{25} 1.4410 (18).

The lactone (3.6 g, 0.15 mol) was condensed with ethyl formate according to general directions (4) to provide 16 g (81%) of *3-carbomethoxy-5-isopropyl-2-methoxytetrahydrofuran*, b.p. 70° at 1 mm; η_D^{24} 1.4392. This ester (6 g, 0.03 mol) was saponified (4) to give 4.1 g (74%) of the crude viscous

TABLE 3. Physical constants of several 2-alkoxytetrahydrofurans

No.	Compound R	Compound R′	b.p.°/mm Hg	η_D/°C	Literature b.p.°/mm Hg	Literature η_D/°C	Reference
1	CH_3	CO_2CH_3	94/5	1.4357/25	81/13	—	4
2	C_2H_5	$CO_2C_2H_5$	110/19	1.4318/25	—	—	
3	i-C_3H_7	CO_2-i-C_3H_7	108–110/15 (crude)		—	—	
4*	t-C_4H_9	CO_2-t-C_4H_9					
5	CH_3	H	101–102/699	1.4104/24	105–107/	1.4132/14	16
6	C_2H_5	H	110–112/699	1.4105/26	125/	1.4148/20	17
7	i-C_3H_7	H	117–119/699	1.4109/24	132/	1.4147/20	17
8	t-C_4H_9	H	126–127/699	1.4171/25	34–40/10	1.4186/20	12
9	$C_6H_5CH_2$	H	114/7	1.5120/24	102/4		12

*Isolation gave only 3-carbo-t-butoxy-4,5-dihydrofuran, m.p. 45–46°.

liquid *3-carboxy-5-isopropyl-2-methoxytetrahydrofuran.* This crude acid, in 20 ml of quinoline containing a trace of cupric sulfate, was heated at 200–210° under nitrogen. The product, collected in a Dry Ice–acetone cooled flask, contained *5-isopropyl-2-methoxytetrahydrofuran* contaminated with *2-isopropyl-2,3-dihydrofuran.* Treatment of this mixture for 6 h at room temperature with 5 ml of methanol containing a trace of *p*-toluenesulfonic acid, followed by addition of sodium carbonate (2 g), filtration, and distillation, gave *cis-trans-5-isopropyl-2-methoxytetrahydrofuran* (28% from the γ-isopropyl-γ-butyrolactone), b.p. 80° at 95 mm; η_D^{25} 1.4172. The g.l.c. analysis on butanediol succinate column showed two overlapping peaks in the area ratio of ~3:2.

cis-trans-5-t-Butyl-2-methoxytetrahydrofuran

Pinacolone (19) obtained from pinacol hydrate (20), was converted to the enamine 2-dimethylamino-3,3-dimethyl-1-butene (6), yield, 63%, b.p. 105° at 690 mm; η_D^{22} 1.4308; lit. b.p. 57° at 71 mm; η_D^{25} 1.4293 (6).

From the enamine (45 g) and ethyl bromoacetate there was obtained 16 g (38%) of *methyl β-pivalylpropionate* following the directions used for the reaction of methyl α-bromopropionate with enamines (7); b.p. 80° at 4 mm; η_D^{22} 1.4303.

Sodium borohydride reduction of methyl β-pivalylpropionate, followed by acid-catalyzed cyclization of the product as described above for the conversion of methyl β-isobutyrylpropionate to γ-isopropyl-γ-butyrolactone, gave γ-*t*-butyl-γ-butyrolactone; yield, 98% from the ketoester, b.p. 74° at 2 mm; η_D^{22} 1.4453.

Reaction of this lactone with ethyl formate (4) gave a 63% yield of crude *5-t-butyl-3-carbomethoxy-2-methoxytetrahydrofuran* containing 3–4% of unreacted lactone which could not be removed by usual fractional distillation; b.p. of crude, 95% at 3 mm; η_D^{25} 1.4380. The crude ester was saponified (4) and the impure free acid decarboxylated in quinoline as above to provide *cis-trans-5-t-butyl-2-methoxytetrahydrofuran*; yield from the lactone, 10%; b.p. 97° at 110 mm; η_D^{23} 1.4257. The g.l.c. on butanediol succinate showed two separate peaks in the area ratio 55:45.

cis-trans-2-Methoxy-5-phenyltetrahydrofuran

γ-Phenyl-γ-butyrolactone was prepared by the reaction of styrene oxide (21) with diethyl malonate as described (22) but with sodium hydride in 1,2-dimethoxyethane under nitrogen as the condensing system; yield, 54%; b.p. 123° at 0.8 mm; η_D^{23} 1.5392; lit. b.p. 130° at 1.5 mm (22); $\eta_D^{15.4}$ 1.5418 (23).

Reaction of this lactone with ethyl formate (4) gave *3-carbomethoxy-2-methoxy-5-phenyltetrahydrofuran*; yield, 78%; b.p. 125° at 0.5 mm; η_D^{22} 1.5124.

Saponification (4) gave the free acid which was decarboxylated (4) to *cis-trans-2-methoxy-5-phenyltetrahydrofuran* (54% from the lactone); b.p. 85° at 0.8 mm; η_D^{24} 1.5130. The g.l.c. on an Apiezon T column showed a single broad peak for the *cis–trans* mixture.

cis-trans-2-Methoxy-5-methoxymethyltetrahydrofuran

Methylation (25) of 2-hydroxymethyl-3,4-dihydro-2*H*-pyran (24) gave a 70% yield of *2-methoxymethyl-3,4-dihydro-2H-pyran*; b.p. 58–60° at 30 mm; η_D^{24} 1.4458; lit. b.p. 60° at 20 mm; $\eta_D^{17.5}$ 1.4508 (26).

To a solution of 80% *m*-chloroperoxybenzoic acid (55 g, 0.2 mol) in 400 ml of wet ether at 0°, was added dropwise 2-methoxymethyl-3,4-dihydro-2*H*-pyran (26 g, 0.2 mol). The mixture was warmed to room temperature, stirred for 24 h, then freed from ether. A chloroform solution of the residue, separated from the sparingly soluble *m*-chlorobenzoic acid, was washed with aqueous sodium bicarbonate till neutral. The bicarbonate washings in turn were washed with chloroform. The combined chloroform extracts were dried ($MgSO_4$), separated from the solid and freed from solvent to give 30 g (99%) of crude *2,3-dihydroxy-6-methoxymethyltetrahydropyran.* The crude diol (16 g, 0.1 mol) was added dropwise to a solution of periodic acid (22.5 g, 0.1 mol) in 200 ml of a 1:1 mixture of dioxane and water. The resulting mixture was stirred for 12 h, then neutralized with solid sodium bicarbonate. The slightly alkaline solution was extracted continuously for 24 h with chloroform and the extracts dried with $MgSO_4$ containing some sodium thiosulfate to remove iodine. The filtered solution was freed from solvent to give 11.5 g (88.5%) of the crude hemiacetal *cis-trans-2-hydroxy-5-methoxymethyltetrahydrofuran.* This was dissolved in 100 ml of dry methanol containing a few drops of concentrated hydrochloric acid and left at room temperature for 6 h. This was then stirred for 15 min with excess solid sodium bicarbonate. Removal of the solid, and separation of solvent by fractional distillation gave a residue

which was distilled to provide *cis-trans-2-methoxy-5-methoxymethyltetrahydrofuran*; yield, 7.1 g (55%); b.p. 65° at 50 mm; η_D^{25} 1.4242.

cis-trans-2-Isopropoxy-5-methyltetrahydrofuran

A solution of 6.8 g (0.05 mol) of 2-methoxy-5-methyltetrahydrofuran in 20 ml of isopropyl alcohol containing a trace of *p*-toluenesulfonic acid was heated in an apparatus arranged for downward distillation while nitrogen was bubbled through the solution. A mixture of methanol and isopropyl alcohol distilled between 60–80°. Distillation was continued till only isopropyl alcohol came over (80°). The cooled residue was stirred with solid sodium bicarbonate, filtered, and fractionally distilled to give 4.3 g (60%) of the furan; b.p. 136–139° at 700 mm; η_D^{25} 1.4112.

The g.l.c. on butanediol succinate showed one broad symmetrical peak.

Preparation of Authentic Hydrogenolysis Products

The 4-Alkoxy-1-butanols from Ring Cleavage of 2-Alkoxytetrahydrofurans

The following compounds were prepared by the general procedure (12) starting with 4-chloro-1-butanol and 3,4-dihydropyran and then using the appropriate alcohol.

4-Methoxy-1-butanol, b.p. 60° at 19 mm; η_D^{26} 1.4194; lit. b.p. 59–63° at 7 mm; η_D^{25} 1.4189 (27).

4-Ethoxy-1-butanol, b.p. 78° at 18 mm; η_D^{26} 1.4201; lit. b.p. 83–84° at 16 mm; η_D^{20} 1.4229 (28).

4-Isopropoxy-1-butanol, b.p. 87° at 15 mm; η_D^{24} 1.4237.

4-t-Butoxy-1-butanol was obtained in 86% yield from AlH_2Cl hydrogenolysis of 2-*t*-butoxytetrahydrofuran (see below for general method); b.p. 95–96° at 17 mm; η_D^{25} 1.4253; lit. b.p. 72–74° at 10 mm; η_D^{18} 1.4301 (12).

Compounds Expected from Ring Cleavage of 5-Substituted-2-alkoxytetrahydrofurans

5-Methoxy-2-pentanol

This compound was obtained as the chief product from the AlH_2Cl hydrogenolysis of 2-methoxy-5-methyltetrahydrofuran by the general procedure described later in this paper; yield, 50%; b.p. 65° at 20 mm; η_D^{25} 1.4220.

6-Methoxy-2-methyl-3-hexanol

A solution of 11 g (0.085 mol) of γ-isopropyl-γ-butyrolactone (see above for preparation of *cis-trans*-5-isopropyl-2-methoxytetrahydrofuran) in 10 ml of dry ether was added dropwise to a solution of lithium aluminum hydride (2.0 g, 0.053 mol) in 100 ml of ether kept at 5° in an ice bath. After the addition, the mixture was stirred for 2 h at room temperature and then an aqueous 15% solution of potassium hydroxide was added till no further lithium aluminate precipitated. The solid was separated and the filtrate freed from ether. The residue was distilled to give *5-methyl-1,4-hexanediol* as a colorless liquid (7.6 g, 69%); b.p. 80° at 0.1 mm; η_D^{19} 1.4553.

To a vigorously stirred solution of this diol (2.5 g, 0.019 mol) and methyl iodide (5.4 g, 0.038 mol) in 50 ml of dry 1,2-dimethoxyethane (DME) was added 0.76 g (0.019 mol) of sodium hydride (obtained from 60% sodium hydride in paraffin washed with pentane and dried under nitrogen) in small portions. The resulting mixture was stirred at room temperature for 2 h, then freed from DME. An ether solution of the residue was filtered and the filtrate dried ($MgSO_4$) and subsequently freed from solid and from ether. The residue when distilled gave *6-methoxy-2-methyl-3-hexanol* as a colorless liquid, b.p. 58° at 1 mm; η_D^{20} 1.4343.

The g.l.c. analysis showed only one symmetrical peak with retention time identical to that of the high boiling product obtained from the hydrogenolysis of 5-isopropyl-2-methoxytetrahydrofuran.

6-Methoxy-2,2-dimethyl-3-hexanol

A solution of lithium aluminum hydride (2.4 g, 0.063 mol) in 100 ml of dry ether was cooled in ice to 5° and added dropwise to a solution of 10 g (0.058 mol) of methyl β-pivalylpropionate (see above for preparation of *cis-trans*-5-*t*-butyl-2-methoxytetrahydrofuran) in 20 ml of ether. The reaction mixture was then treated as described for the analogous reduction of γ-isopropyl-γ-butyrolactone with the hydride; yield of *5,5-dimethyl-1,4-hexanediol*, 8.1 g (81%); b.p. 82–84° at 0.1 mm; η_D^{24} 1.4565.

Monomethylation of this diol followed the same procedure described above for the monomethylation of 5-methyl-1,4-hexanediol, to provide *6-methoxy-2,2-dimethyl-3-hexanol* in 61% yield; b.p. 82–83° at 6 mm; η_D^{24} 1.4350.

The g.l.c. showed a single symmetrical peak with retention time identical to that of the trace amount of high boiling product obtained from the hydrogenolysis of 5-*t*-butyl-2-methoxytetrahydrofuran.

4-Methoxy-1-phenyl-1-butanol

The reaction (29) of diethyl malonate with 1-bromo-2-methoxyethane, but using sodium hydride in dry DME under nitrogen, gave 36 g (45%) of *diethyl (2-methoxyethyl)-malonate*; b.p. 111° at 6 mm; η_D^{22} 1.4238; lit. b.p. 110° at 6 mm (29). Hydrolysis (29) gave 4-methoxybutyric acid (82%); b.p. 93° at 4 mm; η_D^{25} 1.4226; lit. b.p. 105° at 7 mm; η_D^{20} 1.4251 (29). Acid-catalyzed reaction of the acid with methanol gave *methyl 4-methoxybutyrate* (45%), b.p. 100° at 100 mm; η_D^{24} 1.4058.

Lithium metal (0.32 g, 0.04 mol) was added to vigorously stirred dry ether (100 ml) which had been flushed with dry nitrogen. To this stirred suspension was added dropwise, 3.14 g (0.02 mol) of bromobenzene. After all the metal had been consumed, the solution under nitrogen was stirred at room temperature for 2 h, and then 1.2 g (0.01 mol) of 4-methoxybutyric acid in 50 ml of ether was added slowly. The solution was stirred overnight at room temperature. Water (10 ml) was then slowly added to the stirred mixture. The ether layer was separated and dried ($MgSO_4$). Removal of the solid and then the solvent gave crude *4-methoxy-1-phenyl-1-butanone*. To this ketone (0.9 g, 0.051 mol), dissolved in 30 ml of dry tetrahydrofuran cooled to −10° in a Dry Ice–acetone bath, was added 1.0 g (0.026 mol) of sodium borohydride. After the addition, the solution was stirred overnight at room temperature and then carefully neutralized with 50% aqueous sulfuric acid using a drop of phenolphthalein as indicator. The excess tetrahydrofuran was removed and the residue dissolved in ether. The solid was separated by filtration and the filtrate freed from ether. Distillation of the residue gave 0.8 g (89%) of *4-methoxy-1-phenyl-1-butanol*; b.p. 94–95° at 0.1 mm; η_D^{23} 1.5150.

The g.l.c. on a column containing Apiezon T showed a single symmetrical peak with retention time identical to that of the high boiling product from the hydrogenolysis of 2-methoxy-5-phenyltetrahydrofuran.

5-Isopropoxy-2-pentanol

This was obtained as the chief product from AlH_2Cl

hydrogenolysis of 2-isopropoxy-5-methyltetrahydrofuran according to the procedure described later in this paper. The alcohol was isolated from the mixture of products by preparative g.l.c. on a butanediol succinate column. The microboiling point was 65–66° at 8 mm; η_D^{24} 1.4225.

Compounds Expected from exo Cleavage; the 2-Alkyltetrahydrofurans and 2-Phenyltetrahydrofuran

Tetrahydrofuran and *2-methyltetrahydrofuran*, from Eastman Kodak Co.

2-Isopropyltetrahydrofuran

The following extensive modification of the general procedure (30) for conversion of a 1,4-diol to the tetrahydrofuran was employed. *p*-Toluenesulfonylchloride (9.8 g, 0.052 mol) in a minimum amount of 2,6-lutidine was added dropwise to a hot (100°) stirred solution of 6.8 g (0.052 mol) of 5-methyl-1,4-hexanediol (prepared above) in 25 ml of 2,6-lutidine. The solution was then stirred for 1 h at 100°, and subsequently distilled. The material boiling at 120–130° was redistilled through a 3-in. Vigreux column; b.p. 114° at 700 mm; g.l.c. showed it to contain 2,6-lutidine (10%). Preparative g.l.c. on a butanediol succinate column at 150° gave pure *2-isopropyltetrahydrofuran*, η_D^{19} 1.4217. The g.l.c. showed one symmetrical peak with retention time identical to that for the low boiling product obtained from the hydrogenolysis of 5-isopropyl-2-methoxytetrahydrofuran.

2-t-Butyltetrahydrofuran

The compound, 5,5-dimethyl-1,4-hexanediol (prepared above) was cyclized to *t-butyltetrahydrofuran* by the modified method used to make 2-isopropyltetrahydrofuran. 2,4,6-Collidine was used in place of 2,6-lutidine and the solution obtained after the period of heating at 100° was stirred into ether. The residue, after removal of solid and solvent, distilled at 125° at 695 mm. The collidine impurity was removed by preparative g.l.c. on a Carbowax column at 150°; η_D^{22} 1.4248.

2-Phenyltetrahydrofuran

$LiAlH_4$ reduction of methyl β-benzoylpropionate (prepared above) by the method used above to reduce methyl β-pivalylpropionate gave *1-phenyl-1,4-butanediol* (84%); b.p. 129–130° at 0.3 mm; η_D^{23} 1.5409. The liquid solidified on standing, m.p. 65–66°.

The diol was cyclized to *2-phenyltetrahydrofuran* by the method used to prepare 2-*t*-butyltetrahydrofuran above but 2,6-lutidine was the base employed. The product boiled at 80° at 3 mm but contained some lutidine. Preparative g.l.c. on an Apiezon T column gave pure material; η_D^{23} 1.5283; lit. b.p. 107 at 15 mm; η_D^{20} 1.5299 (31).

2-Methoxymethyltetrahydrofuran

Reaction of furfuryl alcohol with methyl iodide and sodium hydride (25) gave *2-methoxymethylfuran* (40%); b.p. 80° at 120 mm; η_D^{23} 1.4521; lit. b.p. 134–135° at 762 mm; η_D^{20} 1.4573 (32).

The 2-methoxymethylfuran (5.6 g, 0.05 mol), hydrogenated at 60 p.s.i. and room temperature with rhodium on alumina (33), gave 3.85 g (69%) of 2-methoxytetrahydrofuran; b.p. 90° at 135 mm; η_D^{23} 1.4248; lit. b.p. 140–144° at 715 mm (34).

The g.l.c. showed one symmetrical peak of retention time identical to that of the minor product obtained from hydrogenolysis of 2-methoxy-5-methoxymethyltetrahydrofuran.

General Procedure for the Hydrogenolysis of 2-Alkoxytetrahydrofurans

To a solution of lithium aluminum hydride (0.30 g, 0.0079 mol) in 30 ml of dry ether, cooled to 5° in an ice bath, was added dropwise an ether solution of aluminum chloride, previously prepared by the addition of 1.05 g (0.0079 mol) of the aluminum chloride in small portions to 30 ml of dry ether kept at 5°. The resulting "mixed hydride" (AlH_2Cl (2, 3)) solution was stirred at room temperature for 15 min and then a solution of the 2-alkoxytetrahydrofuran (0.0156 mol) in ether (30 ml) was added dropwise. The resulting mixture was stirred at room temperature for the appropriate time (usually 2 h), whereupon an aqueous 15% solution of potassium hydroxide was slowly dropped in until no further reaction occurred. The colorless precipitate of lithium aluminate was separated by filtration and washed with ether. The combined washings and filtrate were freed from solvent by fractional distillation. The residue (recovery 80–95%) was analyzed by g.l.c. and the products identified by comparison of their retention times with those of authentic substances. In cases of doubt regarding identity the products were isolated by preparative g.l.c. and their i.r. and p.m.r. spectra were compared with those of authentic substances.

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