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THE PREPARATION AND HYDRIDE REDUCTION OF SOME TETRAHYDROFURANYL ACETALS.

by

© PETER CECIL LOEWEN

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY.

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1969

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled

THE PREPARATION AND HYDRIDE REDUCTION OF SOME TETRAHYDROFURANYL ACETALS.

submitted by PETER CECIL LOEWEN, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

A number of 2-alkoxy-5-substituted tetrahydrofurans and 2-aryloxytetrahydrofurans have been prepared. The hydrogenolysis at room temperature in ether solution of these acetals with the species $AlClH_2$ (from a 1:1 molar ratio of $LiAlH_4$ and $AlCl_3$) has been examined and the relative amounts of exo and endo C-O bond cleavage have been measured.

Miss L. Makhubu had previously found that all 2-alkoxy-tetrahydrofurans gave exclusively endo or ring cleavage apparently because of the strong electron donor ability of the ring oxygen. Substituents at C-5 of the C-2 alkoxy acetals have been found to affect the direction of hydrogenolysis of the acetals. Alkyl groups at C-5 resulted in the formation of some exo cleavage product. The proportion of exo cleavage was found to increase as the size and electron donor ability of the alkyl group increased. An electron withdrawing group at C-5 resulted in predominantly endo cleavage. These results have been explained in terms of the inductive effect of the C-5 substituent upon the relative stabilities of the oxocarbonium ions from exo and endo cleavage. The C-5 substituents also exhibited a steric effect but it was of minor importance.

The C-3 methoxy substituent had no effect upon the direction of hydrogenolysis of 2-methoxytetrahydrofuran since exclusively endo cleavage has been found for both the substituted and unsubstituted acetals. The principal influence of the C-3 methoxy group was to retard very markedly the rate of reduction. This has been

attributed to the electron withdrawing effect of the C-3 substituent.

The hydrogenolysis of all the 2-aryloxytetrahydrofurans was found to give exclusively exo cleavage. This has been attributed to a strong complex formation between the π-electron system of the aryl ring and the aluminum species thus leading to cleavage of the exo C-O bond only. Polar and steric factors were considered to be unimportant.

The acetal, 2-benzyloxytetrahydrofuran, was found to give increasingly larger amounts of exo cleavage product as the reducing species was changed from AlH_3 to AlH_2Cl to $AlCl_2H$. This has been attributed to the increase in the Lewis acidity of the aluminum species which affected the strength of the complex formed with the aryl ring of the benzyl group.

The 2-aryloxytetrahydrofurans and pyrans were found to react with $AlCl_3$ in ether solution to give the corresponding phenol and dihydrofuran or pyran along with varying amounts of a rearrangement product. Similarly, 2-benzyloxytetrahydrofuran gave exo cleavage in the presence of $AlCl_3$.

The stereospecific synthesis of cis-5-methyl-2-methoxytetrahydrofuran has been attempted with no success. However, it has been concluded that the cis and trans isomers of 5-methyl-2-methoxytetrahydrofuran did not react to give different products even though the isomer ratio (60 : 40, cis/trans or trans/cis) paralleled the 60 : 40 exo to endo cleavage ratio.

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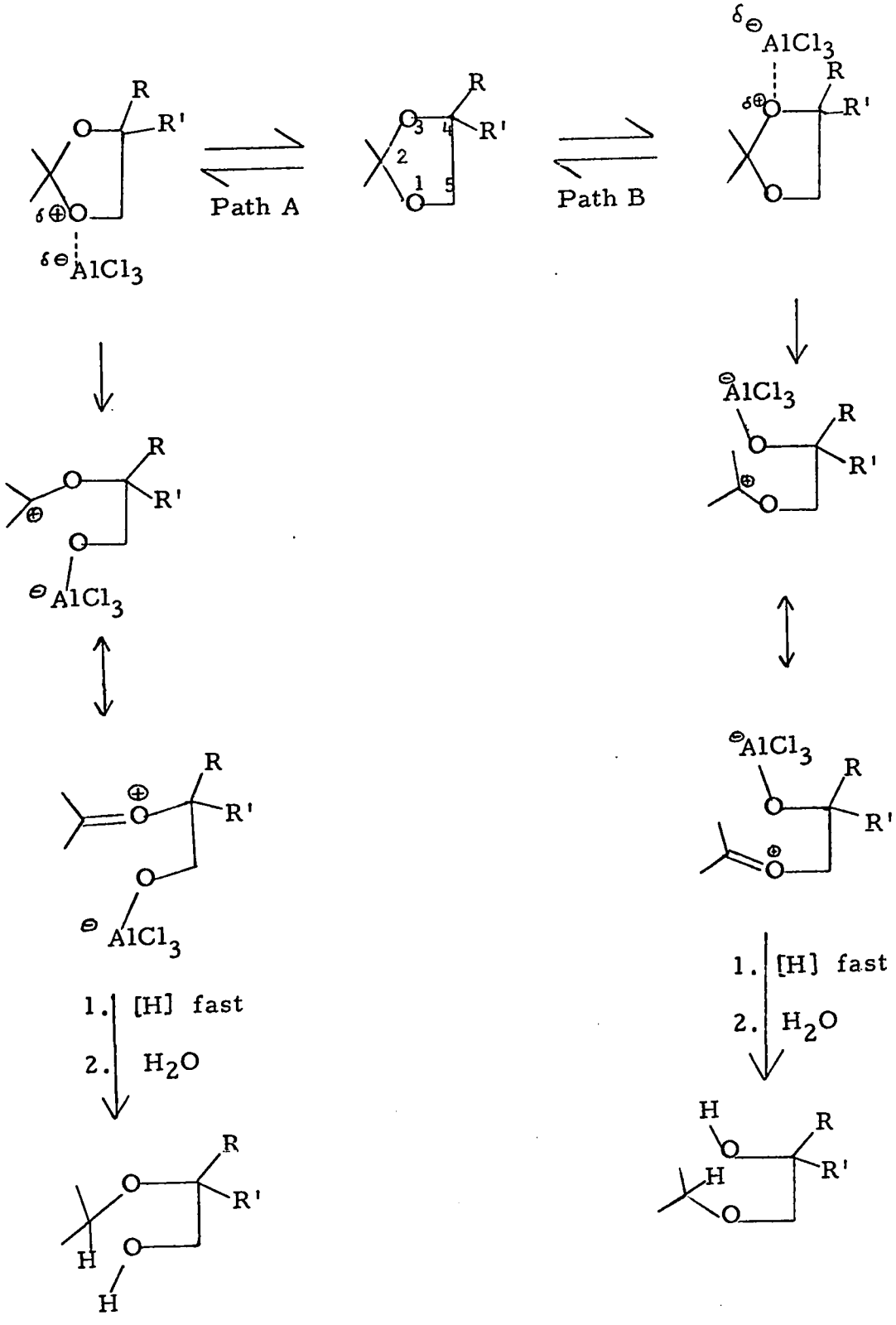
INTRODUCTION

A. The Problem

A considerable amount of work has been reported concerning the $LiAlH_4$ - $AlCl_3$ hydrogenolysis of 1,3-dioxolanes (1), 1,3-dioxanes (2) and tetrahydropyranyl acetals (3, 4). Leggetter and Brown concluded that the substituents on C-4 or C-5 of the dioxolane ring, by their polar effect could stabilize or destabilize the intermediate oxocarbonium ion believed to be formed as one step of the reaction, and thus exert a profound effect on the direction of C—O bond cleavage.

The mechanistic sequence proposed by Leggetter and Brown (1) for the two possible directions of cleavage of the dioxolane ring is shown in Scheme 1. Path A is favored if R and R' are electron donating (alkyl) because of the increased stabilization of the intermediate oxocarbonium ion, while path B is favored when R and R' are electron withdrawing ($-CH_2-Cl$ or $-CH_2OR$) since the oxocarbonium ion in path A would be destabilized relative to that in path B.

A similar explanation was used by Diner and Brown to explain the results of the hydrogenolysis of the tetrahydropyranyl acetals (3) (Scheme 2, n = 2). Electron donating groups (R = alkyl) attached to the exocyclic oxygen favored endocyclic cleavage

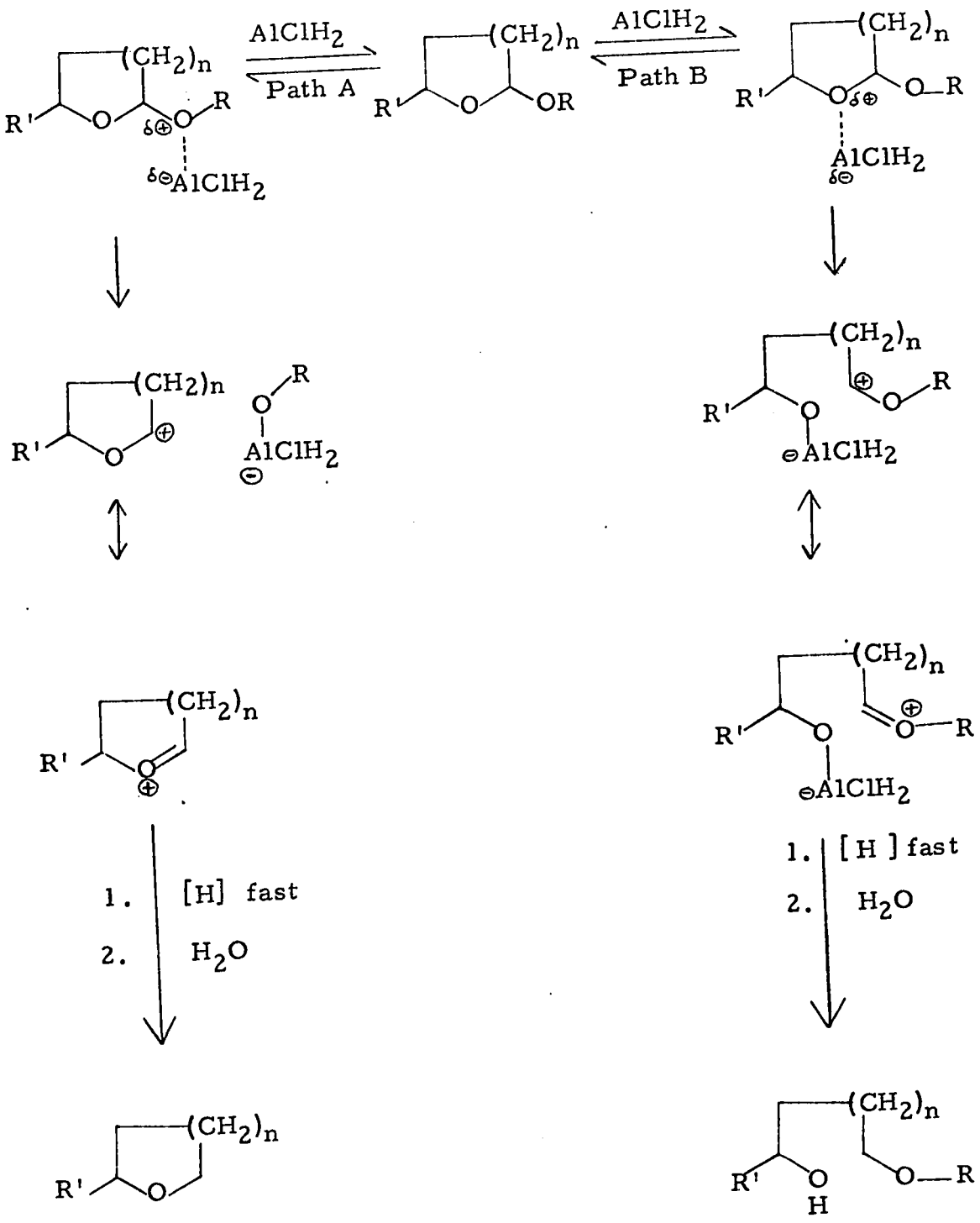


Scheme 1

(path B) while electron donating groups (R' = alkyl) attached to C-6 favored exocyclic cleavage (path A). In contrast, an electron withdrawing group at either of these positions had just the opposite effect. Although steric factors were thought to play some part in the reaction, the inductive effect of the substituents, R and R', were believed to provide the overriding directing influence.

In extending this study to the tetrahydrofuranyl acetals, Miss Makhubu synthesized a number of 2-alkoxytetrahydrofurans and found that they all hydrogenolyzed to give products arising from endocyclic cleavage only (Scheme 2, n = 1, R = alkyl, R' = H) (5). The explanation given was the strong Lewis basicity of the ring oxygen which caused practically exclusive association of the Lewis acid (which is simultaneously the reducing species) with the ring oxygen (Scheme 2, n = 1, path B). The Lewis acid reducing species formed from the equimolar mixture of $LiAlH_4$ and $AlCl_3$ used by Miss Makhubu (5), Diner and Brown (3) and Leggetter and Brown (1) has been shown by Ashby and Prather (6) to be $AlClH_2$.

Hydrogenolysis of 5-methyl-2-methoxytetrahydrofuran (Scheme 2, n = 1, R = CH_3, R' = CH_3) was found by Miss Makhubu to give products which came from cleavage of both the exo and endo C–O bonds in the ratio of 60 to 40 respectively. On the other hand 5-methoxymethyl-2-methoxytetrahydrofuran gave exclusively endocyclic cleavage (Scheme 2, n = 1, R = CH_3, R' = CH_3O-CH_2-).



Scheme 2 (n = 1 or 2)

The fact that the electron donating methyl group at C-5 favored exocyclic cleavage, while the electron withdrawing methoxymethyl group at C-5 favored endocyclic cleavage, agreed with the view that polar factors greatly influence the direction of cleavage in the 5-substituted compounds. However, the results were not entirely conclusive since the disubstituted tetrahydrofurans were mixtures of cis and trans isomers and these isomers were not separated. Accordingly, the importance of any steric influence could not be assessed. It was therefore necessary to examine the problem further to clarify this question.

The objectives of the current investigations were as follows:

(i) to discover whether both steric and polar factors were involved in determining the direction of hydrogenolysis of the 5-substituted-2-alkoxytetrahydrofurans. The synthesis and subsequent hydrogenolysis of a number of 2,5-disubstituted tetrahydrofurans with substituents not only of different sizes but of different electron donor ability was the proposed route to determine which directing effect was predominant.

(ii) to determine whether in the 5-substituted-2-alkoxytetrahydrofurans, the cis and trans isomers cleaved in the same direction or actually gave different relative amounts of exo and endo cleavage. Either a separation of the two isomers, particularly those of 5-methyl-2-methoxytetrahydrofuran, or a stereospecific synthesis of one of the isomers followed by its hydrogenolysis was

necessary for a solution of this problem.

(iii) to synthesize and study the direction of hydrogenolysis of 2-aryloxytetrahydrofurans and of 3-substituted-2-alkoxytetrahydrofurans as had been done for the analogous substituted tetrahydropyrans studied by Diner (3, 7).

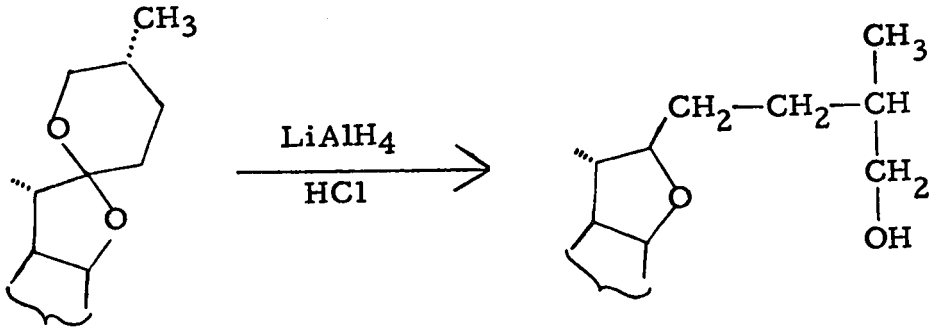
B. Literature Survey

1. Brief History of the Development of the Hydrogenolysis of Acetals and Ketals.

In 1947, $LiAlH_4$ was first introduced as a reducing agent (8) and since that time has been used for the reduction of a large number of functional groups, particularly carbonyl groups. Ethers are unaffected by this reagent and, hence, are useful solvents for $LiAlH_4$ reductions. Since acetals and ketals are geminal diethers, they also, as would be expected, are usually unaffected by $LiAlH_4$. Accordingly it has been common practice to protect the carbonyl group of ketones and aldehydes by converting them to ketals and acetals. This permits $LiAlH_4$ reduction of other functional groups with the protected carbonyl group remaining unaffected (8, 9). A very extensive review of the use of hydrides has been made by Gaylord covering these and many other aspects of hydride reductions (9).

In 1953, it was found that the addition of hydrochloric acid to the $LiAlH_4$ system drastically changed the properties of this

reducing species making the hydrogenolysis of acetals and ketals possible under these conditions. For example, spirostanols were reduced to furostanols by $LiAlH_4$ in the presence of HCl or HBr (Scheme 3).



Scheme 3

This specific direction of reductive cleavage was attributed to the in situ formation of $AlCl_3$ which formed a $LiAlH_4$ - $AlCl_3$ complex considered to be the actual reducing species (11). Since that time the "mixed hydride" ($LiAlH_4$ - $AlCl_3$) has been used to reduce a variety of acetals, ketals, hemithioacetals and hemithioketals (12, 13). A review of these reactions has been published by Eliel (14).

2. Nature of the Reducing Species.

As early as 1947 Finholt and coworkers (15) found that the reaction of a 3 to 1 molar ratio of $LiAlH_4$ and $AlCl_3$ gave solutions of an unstable AlH_3. Much more recently Ashby and Prather (6) have shown that AlH_3, AlH_2Cl and $AlHCl_2$ are obtained from 1 to 3, 1 to 1 and 3 to 1 molar ratio mixtures of $AlCl_3$ and $LiAlH_4$. The

equations illustrating the formation of these hydride species are shown below.

$$LiAlH_4 + 3\,AlX_3 \rightarrow 4\,AlX_2H + LiX$$

$$LiAlH_4 + AlX_3 \rightarrow 2\,AlXH_2 + LiX$$

$$3\,LiAlH_4 + AlX_3 \rightarrow 4\,AlH_3 + 3\,LiX$$

where X = I, Br, Cl

The different hydride species could be identified by a characteristic infrared absorption for each and by elemental analysis, as described by Ashby and Prather (6).

This work was verified and extended in a report by Diner, Davis and Brown (16). They found that the interconversion of the hydride species

$$AlH_3 \rightleftarrows AlH_2Cl \rightleftarrows AlHCl_2$$

was a fast and reversible reaction which could be accomplished by the addition of appropriate amounts of $AlCl_3$ or $LiAlH_4$ to solutions of any one of the species.

In a gradual addition of $AlCl_3$ to an equimolar portion of $LiAlH_4$, initially AlH_3 is formed which is rapidly transformed to $AlClH_2$ as more $AlCl_3$ is added. If a ketal or acetal is present, it therefore comes into contact first with AlH_3. However, reduction with AlH_3 is quite slow (16) and most of the reduction is done by the species AlH_2Cl (a much more reactive reducing species) after complete addition of $AlCl_3$.

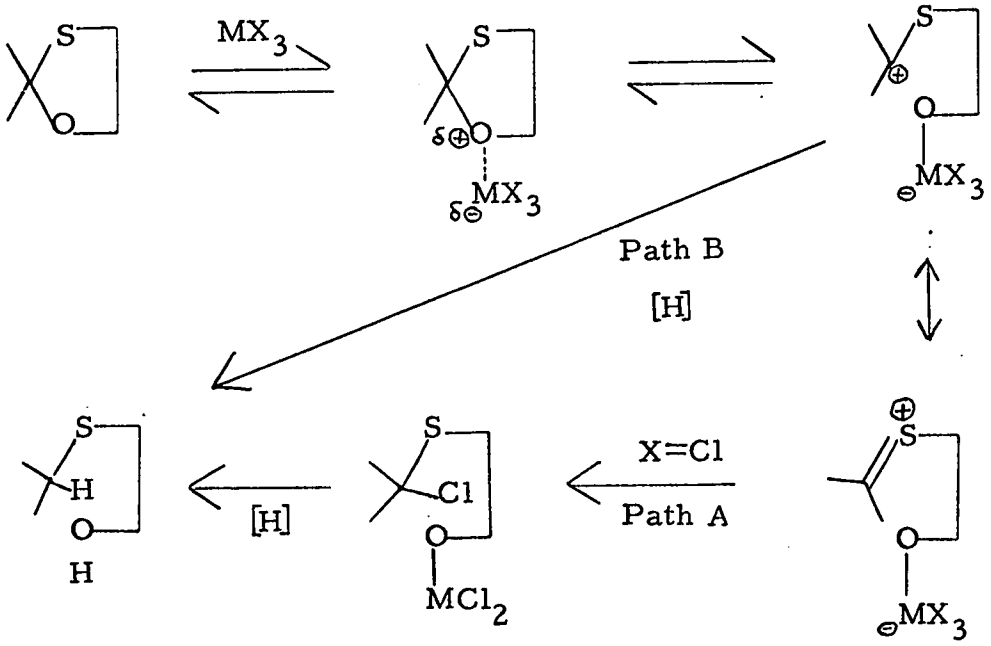
3. Hydrogenolysis of Acetals and Ketals.

Following the publication of the review of the action of mixed hydrides on a large number of compounds including acetals and ketals (14), the mixed hydride reduction of several cyclic acetals and ketals was studied (12). This was followed in turn by a similar study using the ethylene hemithioketal of 4-t-butyl-cyclohexanone in 1962 (13, 17). Eliel and coworkers could not achieve reduction of this hemithioketal using BF_3 as the Lewis acid (13) while Leggetter and Brown were able to do so (17).

Eliel and coworkers had proposed the formation of an intermediate α-chlorothioether when $AlCl_3$ was used with $LiAlH_4$. This is shown in path A of the mechanistic sequence in Scheme 4. If BF_3 were used in place of $AlCl_3$, this halo intermediate could not be formed since the fluorine on BF_3 is not as nucleophilic as the chlorine in $AlCl_3$ (18). Since it is known that α-chloroethers are readily reduced by $LiAlH_4$, this information suggested that α-chloroether formation was a prerequisite to the final step of hydrogenolysis.

However, Leggetter and Brown showed that a prior mixing of BF_3 and the oxathiolane followed by addition of $LiAlH_4$ did result in reductive cleavage (17). The addition sequence of reagents employed by Eliel et al involved initially the formation of a mixture of $LiAlH_4$ and BF_3 and their subsequent admixture with reducible material. This procedure produced BH_3 which, because of its

insolubility in the solvent, was lost from the reaction medium before reduction of the hemithioketal could occur. Since the main argument supporting the view that the α-chloroether is first formed was thus no longer tenable, Leggetter and Brown proposed simply a direct reduction of the intermediate oxocarbonium ion as shown in path B of Scheme 4, a possibility that Eliel had also earlier envisaged (11).

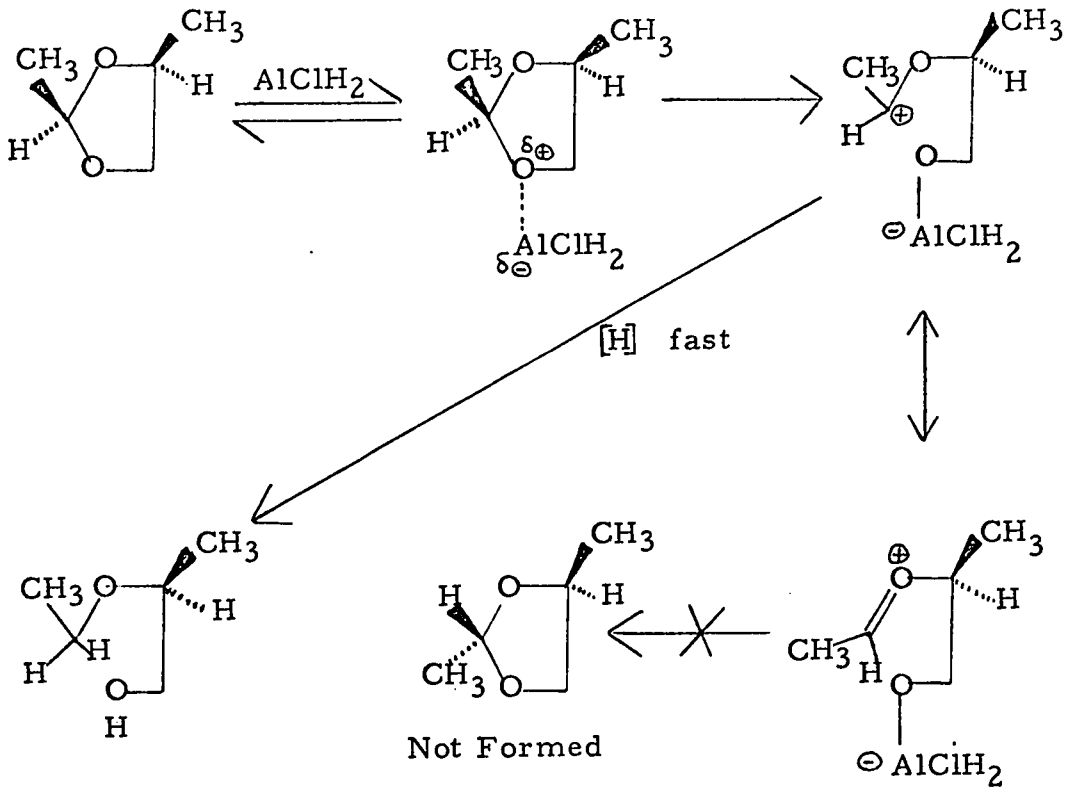


Scheme 4

Following their first report (17), Leggetter and Brown carried out an extensive study of the cleavage of cyclic acetals and ketals (1) investigating the factors influencing the direction and ease of ring cleavage. It was found that polar or inductive effects of the various substituents best explained the observed results. The mechanistic scheme proposed to explain the results is shown in

Scheme 1 and is quite similar to that shown in Scheme 4 which was also proposed by Leggetter and Brown for the hydrogenolysis of the oxathiolane (17).

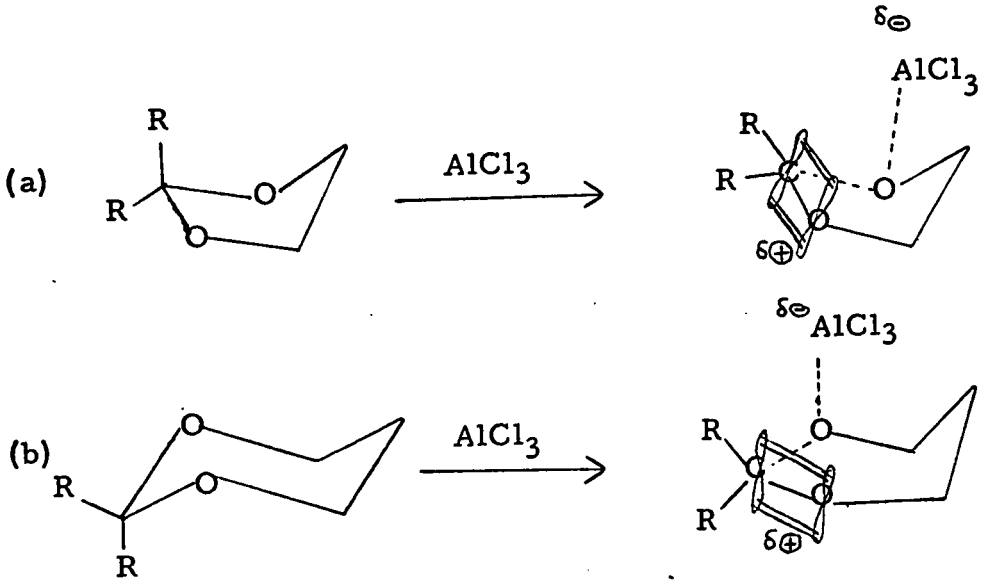
As previously mentioned, electron donating groups at R and R' (Scheme 1) favor cleavage by path A because they assist the adjacent oxygen atom in its stabilization of the intermediate carbonium ion thus producing an "oxocarbonium ion". If R and R' were electron withdrawing groups, they would lower the ability of the adjacent oxygen atom to stabilize the carbonium ion in path A but would have little effect on the stability of the carbonium ion formed in path B. This would result in predominant cleavage by path B. Since it is the relative ease of formation of these two intermediate oxocarbonium ions which determines the product ratios, their rate of formation was considered to be the rate determining step. This assumption received further verification (19) when no isomerization of the recovered cis- or trans-2,4-dimethyl-1,3-dioxolane was found after partial hydrogenolysis (Scheme 5). The formation of the oxocarbonium ion apparently is the slow step and the ion is immediately reduced before it has a chance to revert to the other isomer.



Scheme 5

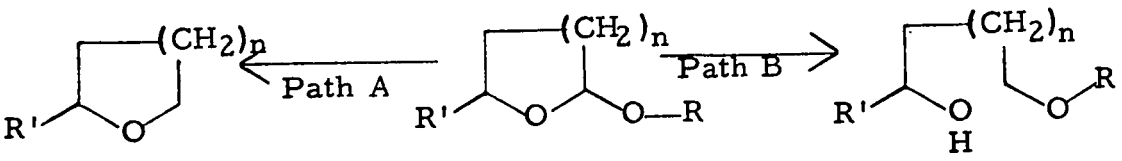
Further work by Leggetter, Diner and Brown (2) disclosed that the ring size affected the rate of cyclic acetal cleavage. The five-membered 1,3-dioxolane ring was reduced faster than the corresponding six-membered 1,3-dioxane ring. This was attributed to the greater ease of formation of the oxocarbonium ion in a five-membered ring than in a six-membered ring. The five-membered ring is very nearly a planar structure, usually thought to exist in a slightly puckered conformation (24). The overlap of an oxygen "p" orbital with an empty "p" orbital being formed on the carbon, as the C—O bond breaks, requires very little distortion of

the ring from its original shape (Scheme 6-a). In the dioxane ring, however, a very considerable amount of distortion from the chair conformation must occur for effective overlap to take place between an oxygen "p" orbital and the empty C-2 "p" orbital being formed (Scheme 6-b).



Scheme 6

Two reports have appeared concerning the reduction of tetrahydropyranyl acetals (3, 4) one of which (4) also included four tetrahydrofuranyl acetals. The two possible paths of reduction of the 2-alkoxytetrahydropyrans and furans are shown in Scheme 7.



Scheme 7 (n = 1 or 2)

In the first report which appeared (4) the authors employed a 1 to 4 molar proportion of $LiAlH_4$ and $AlCl_3$ as the reducing mixture. From the results of their work, they concluded that while polar effects were in some cases important, they could not alone explain the direction of reduction in all of the 2-alkoxytetrahydropyrans and furans studied. Steric effects must play some role in directing the course of reduction.

Support for the view that steric effects rather than polar factors were the predominating influence in directing the course of hydrogenolysis was obtained from their reduction of the tetrahydrofuranyl acetals (4). They found 58%, 63%, 27% and 4% endocyclic cleavage where R was t-C_4H_9, cyclohexyl, n-C_6H_{13} and C_6H_5-CH_2- respectively (Scheme 7, n = 1, R' = H). This view was based on the following rationale. A bulky tertiary group such as R = t-C_4H_9- would sterically shield the exocyclic oxygen atom and this would cause preferential complexation of the aluminum species at the ring oxygen. This would result in cleavage by path B (Scheme 7, n = 1). On the other hand a smaller R group (R = $C_6H_5CH_2$) with a primary carbon attached to the exo oxygen would present much less steric interference to complexation with the exo oxygen allowing cleavage to occur by path A (83% for R = $C_6H_5CH_2$-). Mention was also made in this report of the possibility that the higher basicity of the tetrahydrofuran ring oxygen might in some way be affecting the direction of cleavage by causing some association between the

ring oxygen and the aluminum species (Lewis acid).

The report by Diner and Brown (3) included the hydrogenolysis of not only the 2-alkoxy and 2-aryloxytetrahydropyrans but also the 6-methyl and 6-methoxymethyl-2-alkoxytetrahydropyrans. They concluded that the steric effects of the groups at R and R' (Scheme 7, n = 2) over a wide range of substituents were only minor. Polar effects were thought to be the major directing influence as found for the 1,3-dioxolanes, and only if the polar effects due to the two substituents, R and R', were closely alike did the steric effects become important.

The mechanistic sequence proposed by Diner and Brown (3) has already been shown in Scheme 2 where n = 2. A gradual change from 0 to 30 to 60 to 82 to 87% of ring cleavage was found as R was changed from C_6H_5- to CH_3- to C_2H_5- to i-C_3H_7- to t-C_4H_9-, with R' = H in all cases. The more strongly electron donating groups R = i-C_3H_7 and R = t-C_4H_9 would stabilize the intermediate oxocarbonium ion formed in path B (Scheme 2), relative to that formed in path A. Hence, preferential ring cleavage occurs for these two substituents while relatively less ring cleavage occurs for the weaker electron donating groups. An electron withdrawing group such as R = C_6H_5 has just the opposite effect. Hence, the oxocarbonium ion arising from path A is more stable and only side chain cleavage occurs.

Groups (R') at C-6 (Scheme 2) were also found to affect the

direction of hydrogenolysis. An electron donating group R' = CH_3 (with R = CH_3) favors path A by enhancing the stability of the intermediate oxocarbonium ion of path A while an electron withdrawing group R' = CH_3OCH_2 (with R = CH_3) favors path B or ring cleavage because it destabilizes the oxocarbonium ion of path A relative to that in path B.

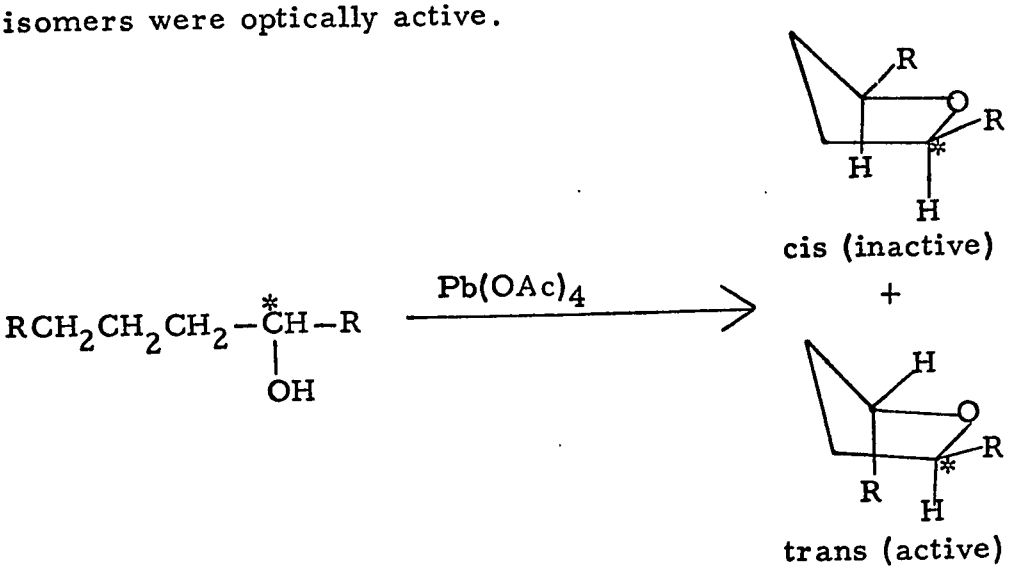
Only when the polar effects of the substituents, R and R', cancelled did steric effects become important. This was observed when R' = CH_3 and R = i-C_3H_7 in which case predominant side chain cleavage occurred. Here the ring oxygen was considered to be shielded by the C-6 methyl group.

In the case of the 6-methoxymethyl-2-methoxytetrahydropyran, Diner and Brown did not feel that additional complexation of the methoxymethyl oxygen with the aluminum species was an important reason for the preferential ring cleavage occurring in this compound. Conclusive evidence disproving this hypothesis was not given, however.

4. Conformation and Isomer Distribution of the 2,5-Disubstituted-tetrahydrofurans.

Mihailovic and coworkers recently verified earlier work assigning the cis and trans isomer configurations of the 2,5-dialkyltetrahydrofurans on the basis of their optical activity (20). Lead tetraacetate oxidation of a number of optically active hydroxy compounds gave mixtures of cis and trans disubstitutedtetrahydrofurans as shown in Scheme 8. The isomers were separated by

preparative gas liquid chromatography (g.l.c.) and the physical constants (including optical rotation) measured. The cis isomers having a plane of symmetry were optically inactive while the trans isomers were optically active.



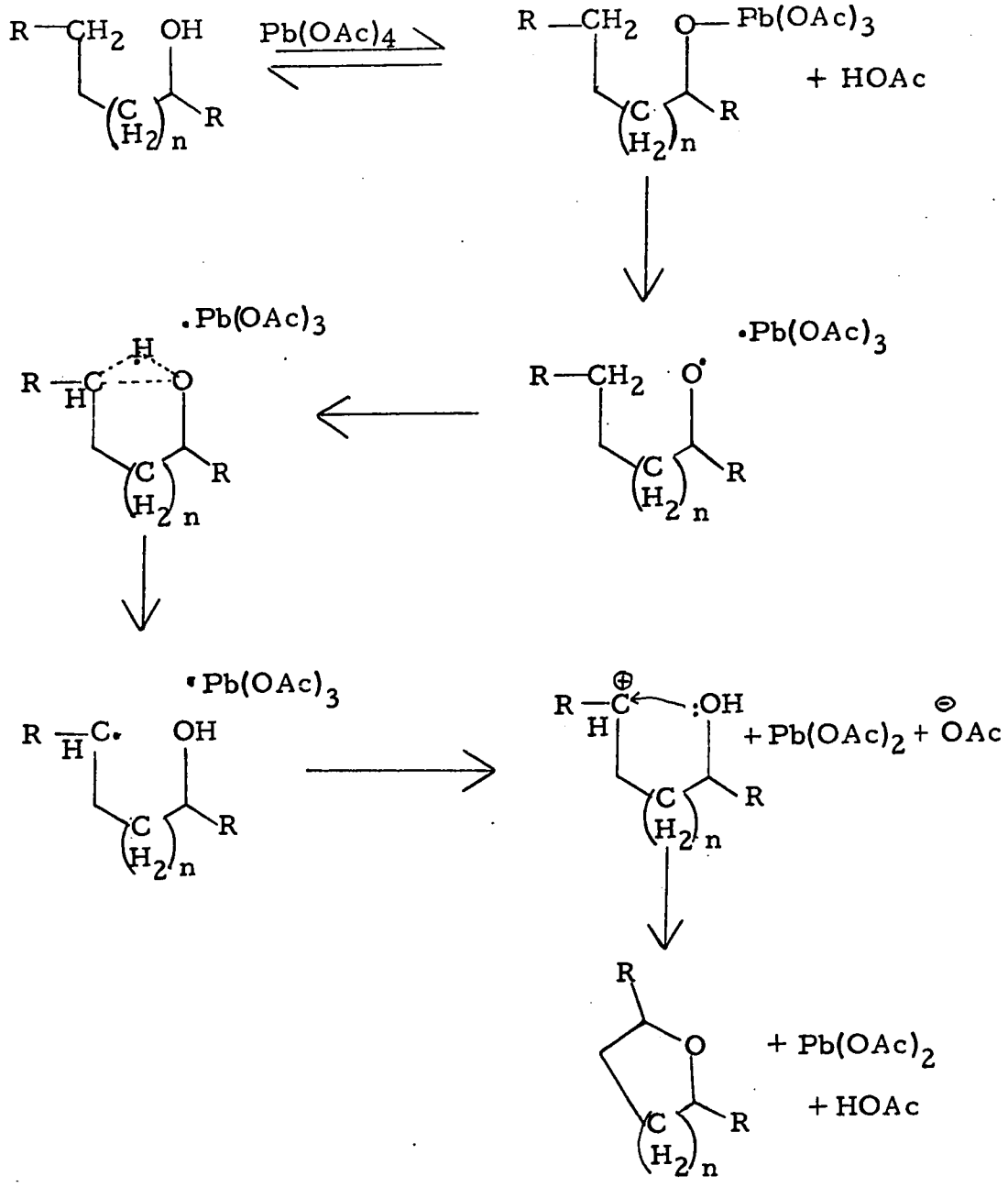
(* - denotes center of optical activity)

(Ac = $CH_3-\overset{O}{\overset{\|}{C}}-$)

Scheme 8

Mihailovic and Miloradovic (21) had previously proposed the following mechanism outlined in Scheme 9 for the oxidative cyclization of alcohols.

Mihailovic and Miloradovic found that the formation of the five-membered tetrahydrofuran ring was preferred to the formation of a six-member tetrahydropyran ring. This was attributed to a difference in reactivity between the δ - and ε -hydrogens involved, respectively, in the 1,5- and 1,6-hydrogen transfers. A difference



(n = 1 or 2) (Ac = $CH_3-C(=O)-$)

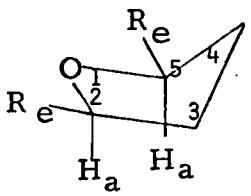
Scheme 9

in the free energies of activation (probably steric or entropy factors) in going to the corresponding transition states was the explanation. More simply, the six-membered transition state of the 1,5-hydrogen transfer is preferred to the less easily attained seven-membered transition state of the 1,6-hydrogen transfer.

The cyclization does not affect the stereochemistry of the C—O bond. As a result the oxidation process starting from an optically active alcohol gives an optically inactive cis isomer (having a plane of symmetry) and an optically active trans isomer (Scheme 8). On this basis, it was possible to definitely assign the structures of the cis and trans isomers by simply determining the optical rotations of the two isomers. In fact it was found in all cases that one isomer was optically active and the other was not.

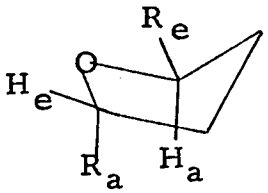
The cis isomer had a lower boiling point and lower refractive index than did the trans isomer. This agreed with studies on the 1,3-dimethylcyclopentane (22, 23) which showed that the low boiling isomer was the cis isomer. Also, it had been shown that the low boiling cis isomer in the cyclopentane compound was thermodynamically more stable than was the trans isomer by 0.53 kcal/mole (23). These findings were not consistent with a planar conformation of the cyclopentane ring in which the cis isomer should be less stable than the trans isomer. The results, however, were consistent with a puckered, envelope (C_s) conformation resulting in the cis isomer being more stable because of the quasi diequatorial

disposition of the alkyl groups (Structure 1-a), while the trans isomer has a conformation of lower stability due to the quasi equatorial axial disposition of the alkyl substituents (Structure 1-b).



(a)

cis quasi diequatorial



(b)

trans quasi equatorial axial

Structure 1

The nuclear magnetic resonance (n.m.r.) spectra of these compounds are noteworthy since the signals for the α-protons on carbons 2 and 5 for the trans isomer are shifted downfield relative to the position of signals for the α-protons of the cis isomer. This was attributed to a deshielding effect of the axial methyl group on the axial α-proton. For example in the spectrum of 2,5-dimethyltetrahydrofuran, the cis α-proton signal was centered at $\delta = 3.93$ ppm while the trans α-proton signal fell at $\delta = 4.13$ ppm, a shift of 12 Hz.

Gagnaire and Monzeglio (25) also reported the stereospecific synthesis, physical properties and n.m.r. spectra of a number of 2,5-disubstituted tetrahydrofurans. The constants for the 2,5-dimethyltetrahydrofuran agreed with those reported by Mihailovic et al (20) with the n.m.r. signals for the cis α-protons being shifted upfield relative to those of the trans α-protons. However, for the 2,5-bis-tosyloxymethyltetrahydrofuran, they

found that there was no difference between the positions of the α-proton signals for the cis and trans isomers. In addition they showed that for the 2,5-bis-hydroxymethyltetrahydrofuran, the chemical shifts of the α-proton signals were in the opposite direction relative to those for the 2,5-dimethyl compound. The cis α-proton of the bis-hydroxymethyl compound absorbed at δ = 4.15 ppm while the trans α-proton absorbed at δ = 4.10 ppm. This is a difference of 3 Hz but in the opposite direction from that found in the spectra of the dimethyl compound.

Hence, the chemical shifts of the α-proton signals in the n.m.r. spectra do not appear to be reliable criteria, generally, for assignment of cis or trans configuration in the 2,5-disubstituted tetrahydrofurans. Only isolation and comparison of the physical constants or a stereospecific synthesis can reliably be used to assign the isomer configuration.

5. Basicity of the Tetrahydrofuran Oxygen.

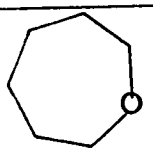
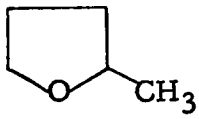
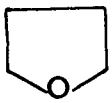
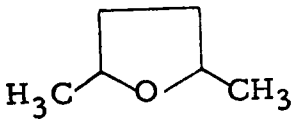
Brown and Adams in 1942 reported a study of the stabilities of the boron trifluoride complexes with tetrahydrofuran, dimethyl ether and diethyl ether (26). The dissociation constants for the complexes were 0.0011×10^2, 0.184×10^2 and 0.420×10^2 respectively for tetrahydrofuran, dimethyl ether and diethyl ether. This indicated that a much more stable complex was being formed with tetrahydrofuran, thus illustrating the stronger Lewis basicity or electron donor ability of the cyclic ether as compared to that of

the acyclic ethers. This property was attributed to steric factors controlling the approach of the BF_3 to the ether oxygen and not to inductive effects.

In 1962 Arnett and Wu (27) reported the basicities of a number of cyclic and acyclic ethers, determined in an aqueous sulphuric acid solution. A selection of the results pertinent to the present work is given in Table 1.

Table 1

pKa Values for the Basicity of Various Ether Oxygens Towards Aqueous Acid*

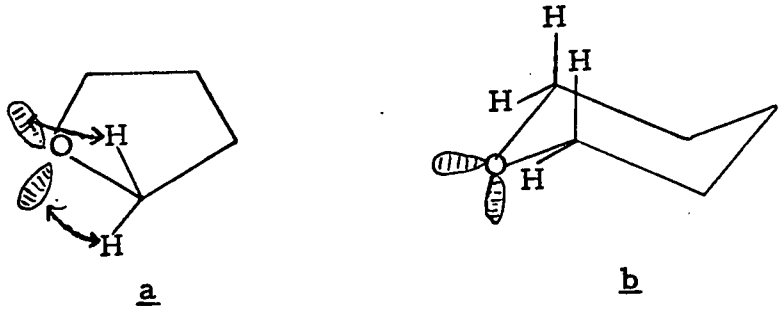
Ether	pKa	Ether	pKa
	-2.02		-2.65
	-2.08		-2.79
 cis	-2.44	C_2H_5-O-C_2H_5	-3.59
trans	-2.65	CH_3-O-CH_3	-3.83

* Taken from the work of Arnett and Wu (27)

The ethers in Table 1 are listed in order of their decreasing basicity as indicated by the pKa values. This order of decreasing basicity parallels the decrease in I strain found by Brown and coworkers (28, 29) in going from five- and seven- to six-membered

ring ethers attributed to the greater internal strain in the free base, which is relieved upon protonation. In fact tetrahydrofuran has been shown to be thermodynamically less stable by 2.9 kcal/mole than tetrahydropyran (30).

Ether oxygens are known to be sp^3 hybridized, forming C-O-C bond angles of around 110° (31). In tetrahydrofuran and hexamethylene oxide, a considerable nonbonded interaction takes place between the nonbonding electron pairs on the oxygen and the electrons engaged in bonding hydrogens to the adjacent carbons. This is illustrated in Structure 2-a and is considered by Arnett and Wu to be one factor adding to the high I strain of the molecule.



a b

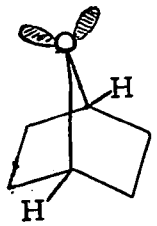
Structure 2

Coordination of the oxygen electrons with a proton may result in a decrease of this nonbonded interaction by reducing the electron density on the oxygen. This relief of the electron orbital interaction reduces the I strain of the system resulting in stabilization of the protonated molecule.

In tetrahydropyran, the electron pair orbitals of the oxygen are staggered as shown in Structure 2-b, resulting in very little interaction with the adjacent C-H bonding orbitals. This staggered

arrangement possesses the smallest interaction possible in a cyclic system. Any deviation from this arrangement, as is found in tetrahydrofuran, results in an increase in the orbital interaction and a corresponding increase in Lewis basicity. Since there is very little I strain to start with in the tetrahydropyran molecule, protonation is not assisted by the formation of a more stable molecule and hence the basicity is less.

Support for this argument arose when 7-oxabicyclo [2,2,1]-heptane (Structure 3) was found to have a pKa = -2.80, nearly identical to that of tetrahydropyran. The oxygen is contained in a five-membered ring but the eclipsing of unshared oxygen electron pair orbitals with the adjacent C-H bond orbitals is eliminated by the strained bicyclo system. Hence, although the molecule probably has a higher I strain than has tetrahydrofuran, complexation with a proton has no effect in relieving nonbonded orbital interactions and a basicity similar to that of tetrahydropyran is therefore found.



Structure 3

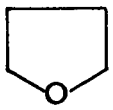
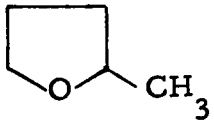
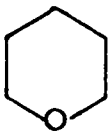
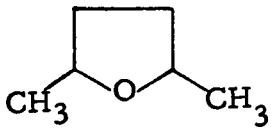
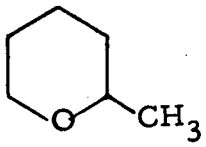
In 1963 Cioffi and Zenchelsky (32) reported a study of the relative basicities of a number of cyclic ethers towards $SnCl_4$. The association constants for the $SnCl_4$ complex formation with a number of ethers are given in Table 2 and they illustrate the order of

decreasing Lewis basicity in the series: tetrahydrofuran > tetrahydropyran > 2-methyltetrahydropyran > 2-methyltetrahydrofuran > 2,5-dimethyltetrahydrofuran.

Table 2

Association Constants for the Reaction

$SnCl_4 + 2\ Base \rightarrow SnCl_4 \cdot 2\ Base$*

Base	$K\left(\frac{l^2}{mole^2}\right)$	Base	$K\left(\frac{l^2}{mole^2}\right)$
	6×10^7		1×10^5
	8.2×10^5		0.3×10^5
	2.5×10^5		

*Taken from the work by Cioffi and Zenchelsky (32).

In contrast to the explanation of Arnett and Wu (27) for the observed order of basicity, Cioffi and Zenchelsky concluded that the order of base strength is determined by steric considerations alone, since inductive and other electronic effects should be negligible in saturated compounds. They based their explanation on the assumption that tetrahydropyran must change from the stable valence angle of $90 \pm 5^{\circ}$ (measured by Allen and Hibbert (33)) to a less stable tetrahedral valence angle during complex formation,

causing a considerable increase in the molecule's I strain (28, 34). Tetrahydrofuran on the other hand is already in a near sp^3 or tetrahedral arrangement and less energy is required (or the I strain increment is less) in the formation of the $SnCl_4$ complex. The F strain (35) involved in the approach of the $SnCl_4$ molecule to the ether oxygen should be nearly the same for both cyclic ethers. Since less energy is required to form the complex with tetrahydrofuran, the complex is more easily formed and the basicity appears to be higher than that of tetrahydropyran.

However, a serious flaw in this argument is evident since the C-O-C bond angle is known to be around 110° (31) not the $90 \pm 5^{\circ}$ found by Allen and Hibbert (33). In other words, the tetrahydropyran oxygen is already in a tetrahedral arrangement and the proposed increase in I strain of the molecule could not have originated in the fashion predicted.

Methyl groups increase the F strain by inhibiting the approach of the $SnCl_4$ to the ring oxygen. For this reason, the alkylated compounds have a lower basicity than the nonalkylated compounds. The fact that a large difference in basicity between the mono- and dimethyltetrahydrofurans was found by Cioffi and Zenchelsky (32) while only a small difference was found by Arnett and Wu (27) can be explained by the larger size of the $SnCl_4$ compared to a proton. This would cause a greater or more pronounced F strain when $SnCl_4$ was used as the Lewis acid since the effect of the methyl

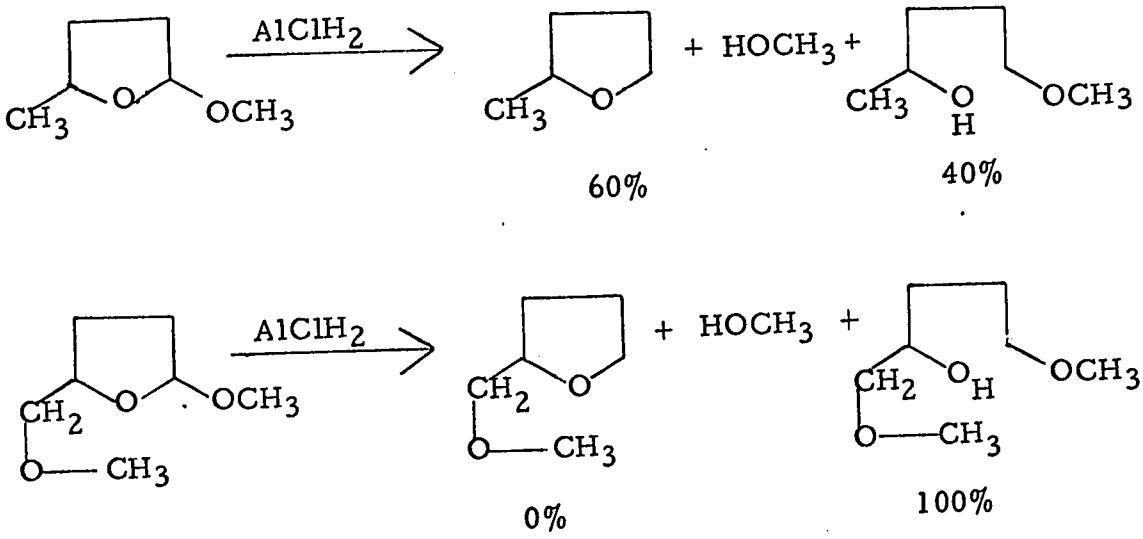
groups would be accentuated by interaction with a larger Lewis acid.

Hence, the order of basicity found by Cioffi and Zenchelsky is probably more applicable to the complexation of $AlCl_3$ or one of the "mixed hydrides", say $AlClH_2$, with a tetrahydrofuranyl acetal's ring oxygen. However, the explanation employed by Cioffi and Zenchelsky (32) is not valid while that of Arnett and Wu can be applied to both sets of results.

RESULTS AND DISCUSSION

A. Synthesis of the 5-Substituted-2-alkoxytetrahydrofurans*

Miss Makhubu found that $AlClH_2$ reduction of 5-methyl-2-methoxytetrahydrofuran gave a 60 to 40 exo to endo cleavage ratio while the 5-methoxymethyl-2-methoxytetrahydrofuran gave exclusively endo cleavage (Scheme 10).



(Percentages refer to proportion of the products)

Scheme 10

These results were attributed to the predominating polar effect of the substituents on C-5 which controlled the course of the hydrogenolysis reaction. Steric effects of the substituents were considered to be unimportant (5).

However, two points regarding the steric effect of the C-5 substituents were not clarified and required further study. The

* cis-trans mixtures were formed in all cases and the names used in the following discussion refer to isomer mixtures.

first problem was whether or not there was a steric effect present in the hydrogenolysis of the cis compared to the trans isomer of 5-methyl-2-methoxytetrahydrofuran. This had not been investigated due to the fact that the isomers could not be separated (5). The attempts made in the present work to solve this problem will be discussed later. The second problem was the possibility of complex formation between the aluminum species and the methoxymethyl oxygen which could promote association with the adjacent ring oxygen and thus overcome the steric effect of that substituent. Such preferred association of the Lewis acid with the ring oxygen could lead to exclusive ring cleavage and hence would explain the direction of cleavage observed. If this were so, it would be unnecessary to invoke a predominating polar effect as the cause of the direction of hydrogenolysis in this particular case. To assist in the solution to this second problem, some other 2-alkoxytetrahydrofurans substituted at C-5 by suitable groups would be useful.

It was felt that the 2-alkoxytetrahydrofurans with the bulkier isopropyl or t-butyl groups at the C-5 position would suitably expand the study. A phenyl group at the C-5 position was also considered helpful since it would be an electron withdrawing group as well as provide a steric effect at least as large as that of the isopropyl group. The A values determined from the cyclohexane system are in the range of 2.0 to 3.1 kcal/mole for the phenyl group and 1.8 to 2.5 kcal/mole for an isopropyl group (24-b)

indicating the slightly larger steric size of the phenyl ring. This dual nature of the C-5 phenyl group would cause a competition between steric and polar effects in the same molecule and this might be revealing.

In this section the synthesis of these compounds is described. As will be shown in Section 10 below, the γ-substituted-γ-butyrolactones can be easily converted to the corresponding 5-substituted-2-alkoxytetrahydrofurans by the method of Korte and coworkers (36, 37). This fact made the γ-substituted lactones the most desirable intermediates for the synthesis of the 5-substituted tetrahydrofuranyl acetals. Initially, work was concentrated upon the preparation of γ-isopropyl-γ-butyrolactone since Miss Makhubu had already made an unsuccessful attempt to synthesize this lactone. Quite a large number of approaches were attempted before a successful preparation of the lactone was finally found.

The unsuccessful attempts to produce the lactone as well as a number of unsuccessful attempts to prepare, directly, the 5-isopropyl-2-methoxytetrahydrofuran without producing the lactone, are described below. The reason for the description of these unsuccessful attempts is that they are interesting in their own right and, as well, they lead up to the eventual successful synthesis of the isopropyl lactone and subsequently the acetal. The procedure finally evolved to prepare the 5-isopropyl-2-methoxytetrahydrofuran was then adapted to the preparation of the corresponding 5-t-butyl

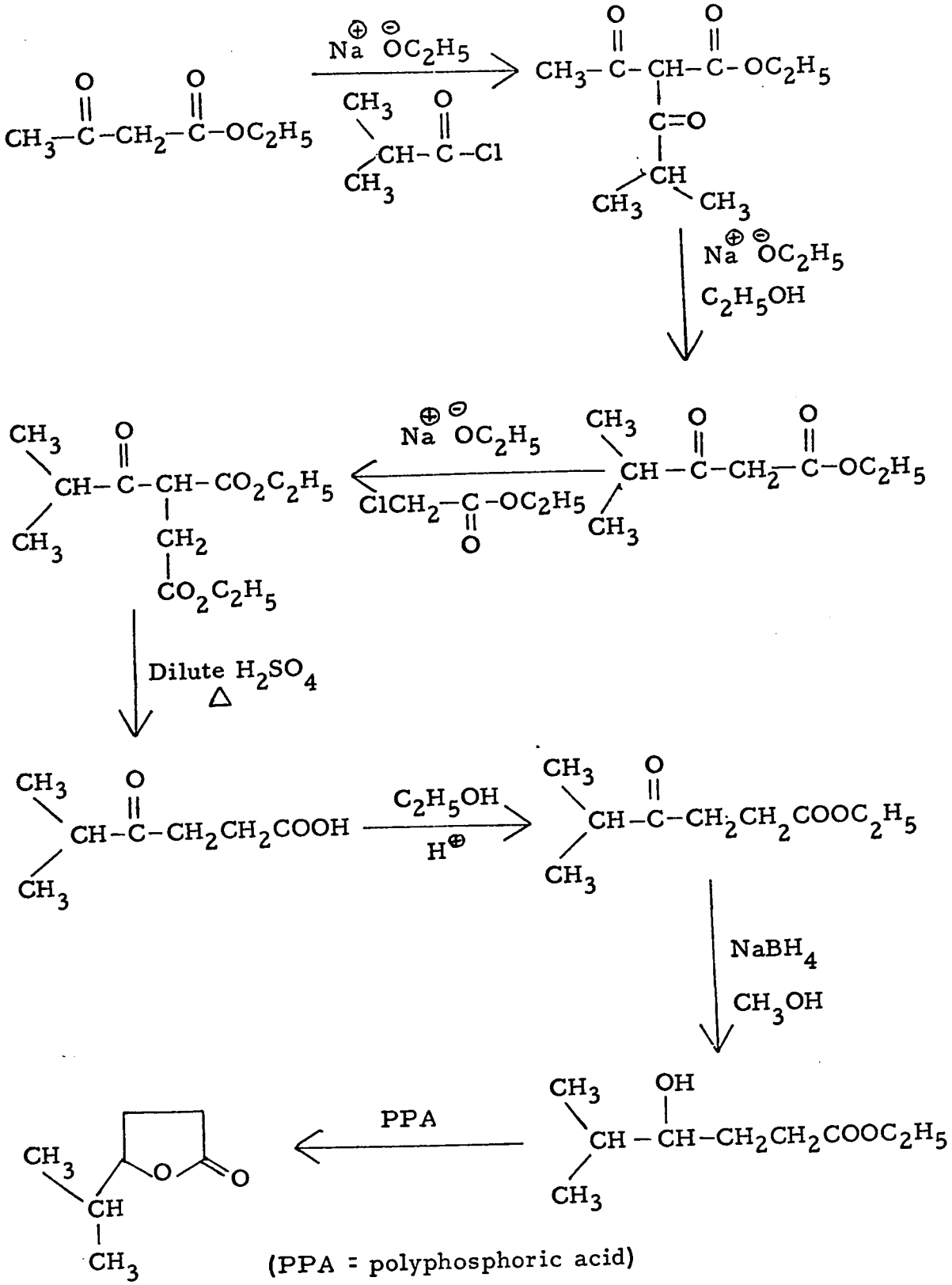
and 5-phenyl-2-methoxytetrahydrofurans.

1. Attempted preparation of γ-isopropyl-γ-butyrolactone by acetoacetic ester condensations.

The first attempt to synthesize the γ-isopropyl-γ-butryolactone was a continuation of a reaction sequence initiated by Miss Makhubu (5). Her proposed route had seemed promising in the initial stages but difficulty had arisen in the last step. This proposed sequence is a modification of a combination of published procedures (36, 38) and is shown in Scheme 11.

Miss Makhubu reported the successful synthesis of all the intermediates, each in moderate yield, up to ethyl β-isobutyryl-propionate. However, the final steps of sodium borohydride reduction and acid catalyzed cyclization did not produce any lactone. At this point, Miss Makhubu was forced to abandon the synthesis.

There seemed to be no reason why the final reactions would not be possible and the present work was started in an attempt to prepare ethyl β-isobutyrylpropionate and study the cyclization reaction. However, difficulty was encountered immediately. Absolutely no product was recovered from the attempt tc form β-isobutyrylpropionic acid by hydrolysis of the preceding ester with refluxing dilute sulfuric acid and by subsequent decarboxylation. Since the yields of the steps up to this point had been very poor as well as unreliable, the complete failure of this ester hydrolysis step prompted the abandonment of this procedure. No reason for the failure of this hydrolysis could be given.

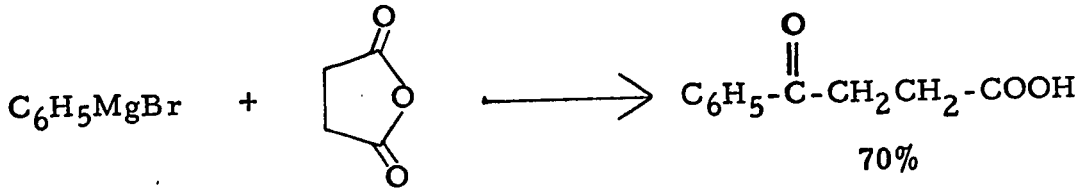


(PPA = polyphosphoric acid)

Scheme 11

2. Attempted preparation of γ-isopropyl-γ-butyrolactone by the action of isopropylmagnesium bromide on succinic anhydride and diethyl succinate.

The next attempt involved the addition of Grignard reagents to succinic anhydride and diethyl succinate. A comprehensive review of Grignard reagents and their reactions with many different compounds, including anhydrides and esters, is contained in a book by Kharasch and Reinmuth (39). The direct addition of one equivalent of phenylmagnesium bromide to succinic anhydride is known to give the keto acid in a 70% yield (39, 40) (Scheme 12).



Scheme 12

A similar addition of a limited amount of Grignard reagent to diethyl succinate gives the keto-ester corresponding to the above keto acid (39).

On the basis of these reports it was proposed that the addition of one equivalent of isopropylmagnesium bromide to either diethyl succinate or succinic anhydride would give the desired keto-ester or acid. However, after several attempts with different reaction conditions, absolutely no product was isolated and only the unreacted anhydride or ester was recovered.

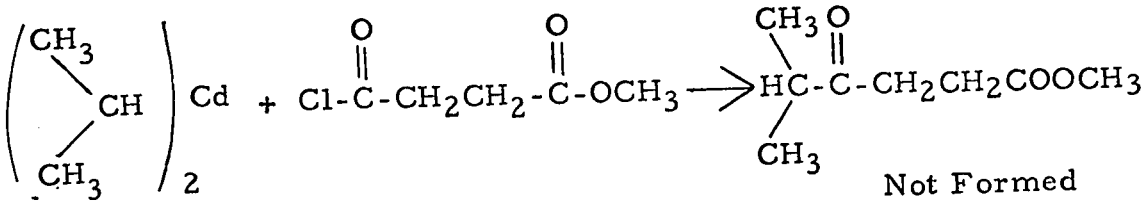
The isopropylmagnesium bromide provides a secondary

carbanion which do not add to certain carbonyl functions as well as the primary Grignard reagents or phenylmagnesium bromide. Therefore, it was no doubt the lower reactivity of the isopropylmagnesium bromide which was responsible for the failure of this reaction.

3. Attempted preparation of γ-isopropyl-γ-butyrolactone by the action of diisopropylcadmium on β-carbomethoxypropionyl chloride.

This synthetic sequence involved the attempted addition of the organocadmium reagent, diisopropylcadmium, to an acyl halide, β-carbomethoxypropionyl chloride. This type of reaction is a mild form of Grignard alkylation which can form ketones in the presence of other functional groups such as the carbonyl group of ketones or esters. Two extensive reviews have been published on the topic (41, 42).

It was proposed that the addition of diisopropylcadmium to β-carbomethoxypropionyl chloride would give the desired methyl β-isobutyrylpropionate (Scheme 13). The synthesis of the β-carbomethoxypropionyl chloride is well known and reasonably easy (43), making this an attractive procedure. However, the reaction did not proceed as desired and no identifiable material was recovered.

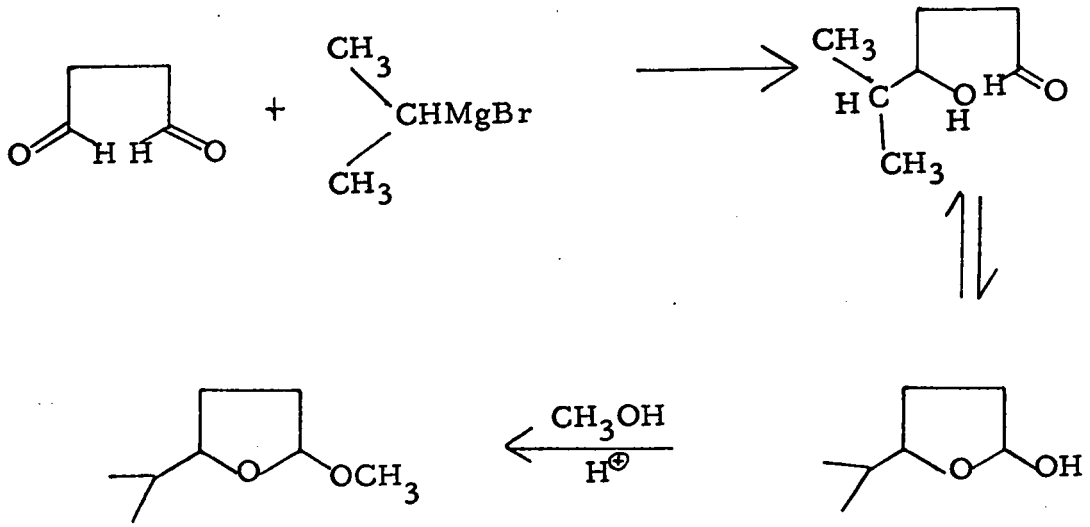


Scheme 13

It was subsequently found that secondary organocadmium compounds are not thermally stable relative to the primary compounds (44). The anion, therefore, is not stable enough to react with an acyl halide before the anion decomposes (44) in refluxing tetrahydrofuran.

4. Attempted preparation of 5-isopropyl 2-methoxytetrahydrofuran by the action of isopropylmagnesium bromide on succindialdehyde.

It was thought that one equivalent of the isopropylmagnesium bromide would add to one carbonyl group of succindialdehyde, forming the desired secondary hydroxy group γ-to the remaining carbonyl. Upon workup in acidic methanol, the hydroxy aldehyde could form the hemi-acetal which would be converted to the methoxy acetal as shown in Scheme 14.



Scheme 14

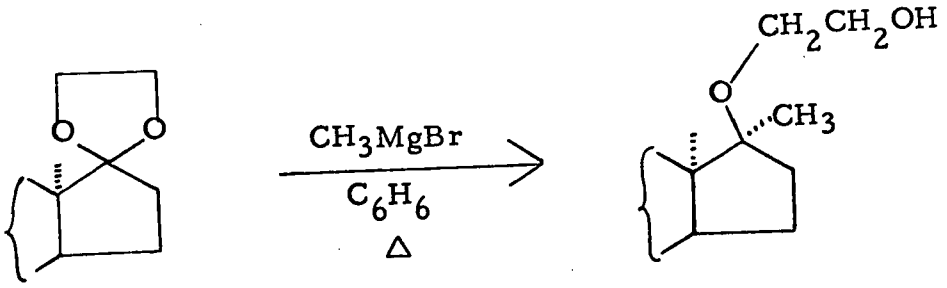
However, all attempts to isolate the dialdehyde in a pure form for reaction with the Grignard reagent were unsuccessful.

The literature preparation of succindialdehyde (45) involves hydrolysis of the dioxime and produces the dialdehyde in aqueous solution. Although a boiling point was given, no instructions could be found for separation of the aldehyde from the aqueous solution. When it was found from the previous experiments that isopropylmagnesium bromide was relatively ineffective in carbonyl additions, this sequence and the aldehyde preparation were not continued.

5. Attempted preparation of 5-substituted 2-methoxytetrahydrofuran by the action of a Grignard reagent on 2,5-dimethoxy-2,5-dihydrofuran.

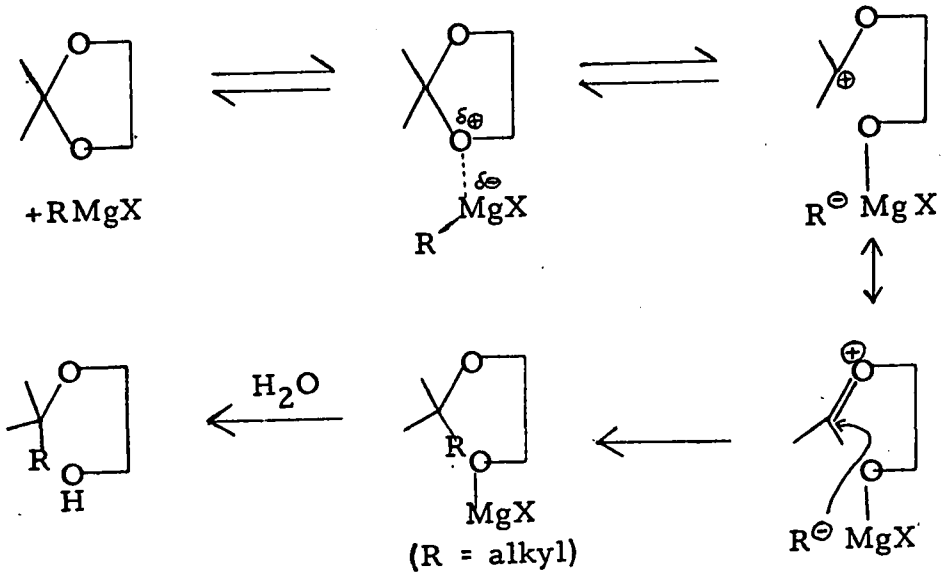
While the present work was in progress, a report appeared in the literature (46) describing the reaction of cyclic ketals with Grignard reagents in refluxing benzene, a reaction on which a considerable amount of earlier work had been done (47, 48). This idea of Grignard reagents reacting with ketals suggested that 5-substituted-2-methoxytetrahydrofurans could be made from 2,5-dimethoxy-2,5-dihydrofuran.

Ketals and acetals are usually stable under Grignard reaction conditions in ether, but the energy barrier of the reaction is overcome by heating the reagents in refluxing benzene. By this procedure, the dioxolane ring has been successfully cleaved in a large number of steroidal ketals (46). An example of this is shown in Scheme 15.



Scheme 15

The mechanism proposed for this reaction (46) involves the initial complexation of the Grignard reagent with one of the oxygen atoms of the dioxolane ring, followed by anionic attack on the partially formed (or possibly completely formed) oxocarbonium ion as shown in Scheme 16.

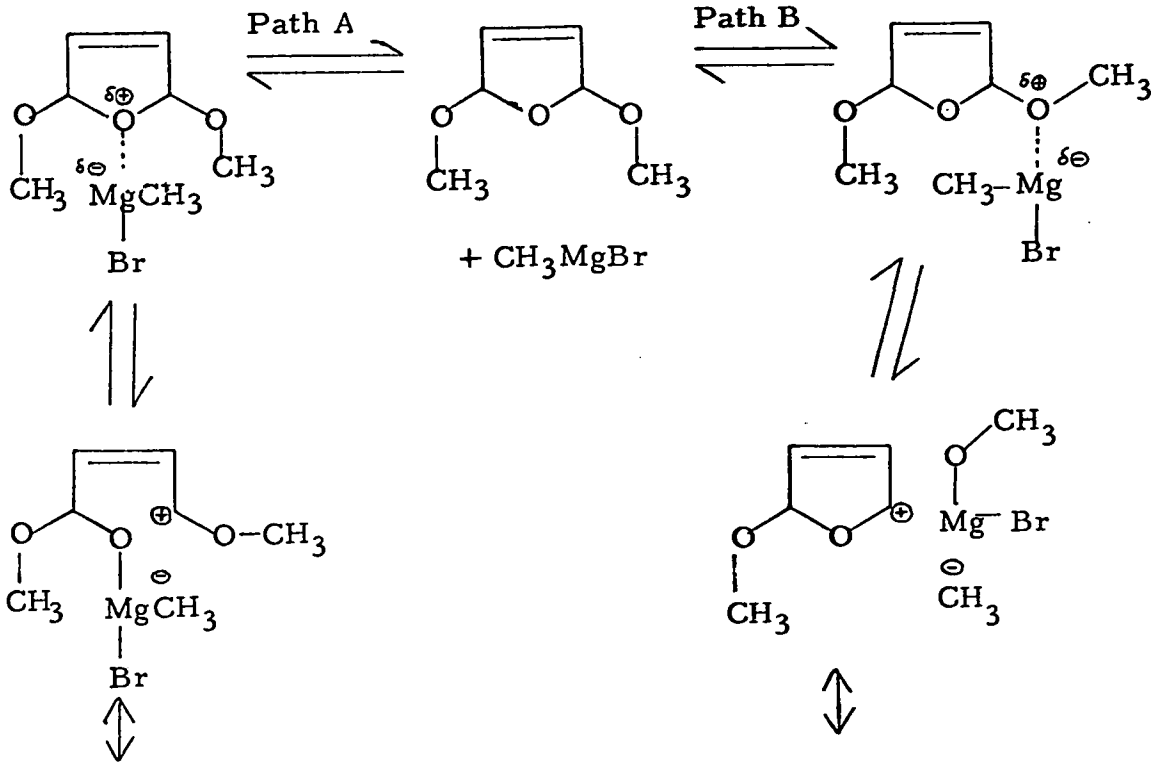


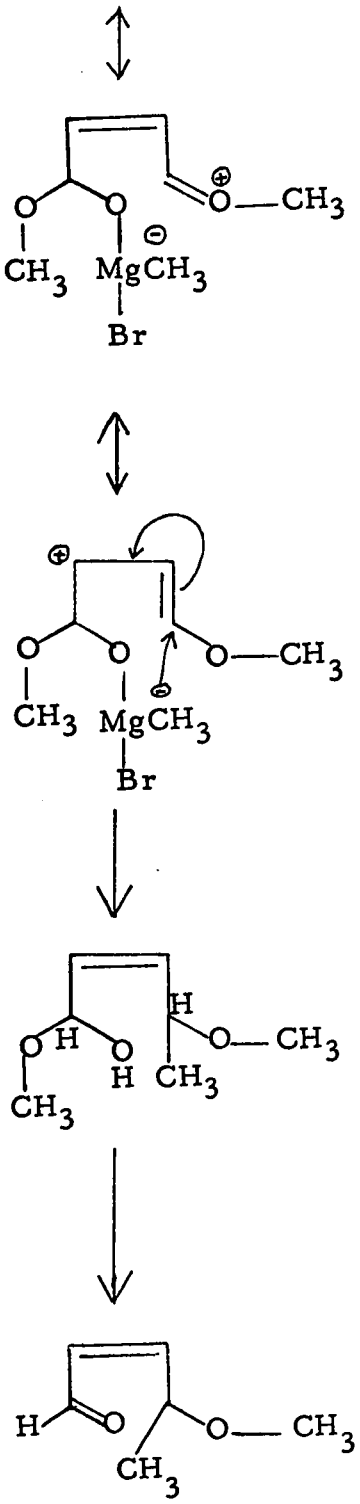
Scheme 16

In order to determine whether this type of reaction would be useful for the preparation of tetrahydrofuranyl acetals with a substituent at C-5, a trial reaction was carried out in which methyl-

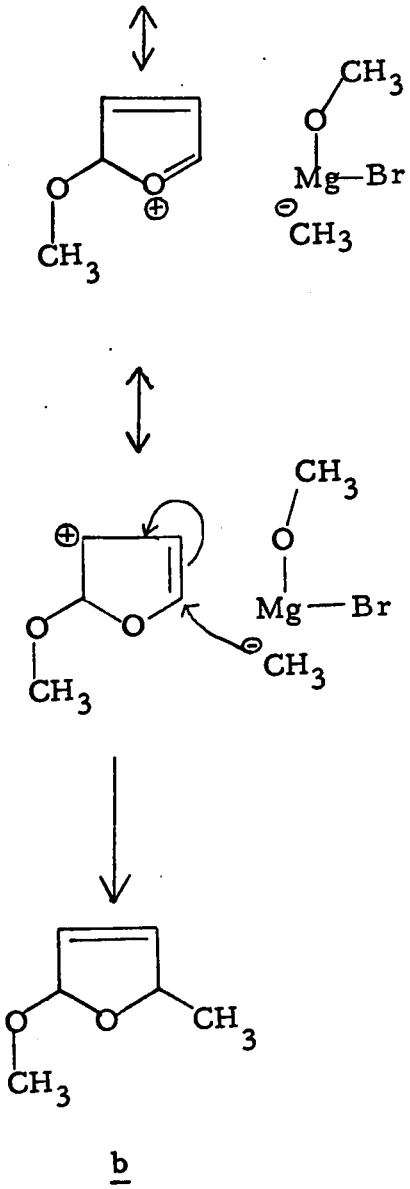
magnesium iodide was added to 2,5-dimethoxy-2,5-dihydrofuran in an attempt to prepare 5-methyl-2-methoxy-2,5-dihydrofuran. The production of this unsaturated acetal would be useful in the stereospecific synthesis of one isomer of 5-methyl-2-methoxy-tetrahydrofuran to be discussed later. The dihydrofuran could also be reduced to the saturated acetal. If this series of reactions were successful, they could be repeated starting with isopropyl-magnesium bromide although, in this case, the reaction might fail because of the poor reactivity of this Grignard reagent.

There are two possible routes by which the Grignard reagent could attack the 2,5-dimethoxy-2,5-dihydrofuran without affecting the double bond. The mechanistic sequence for the two possible paths of the reaction is shown in Scheme 17.





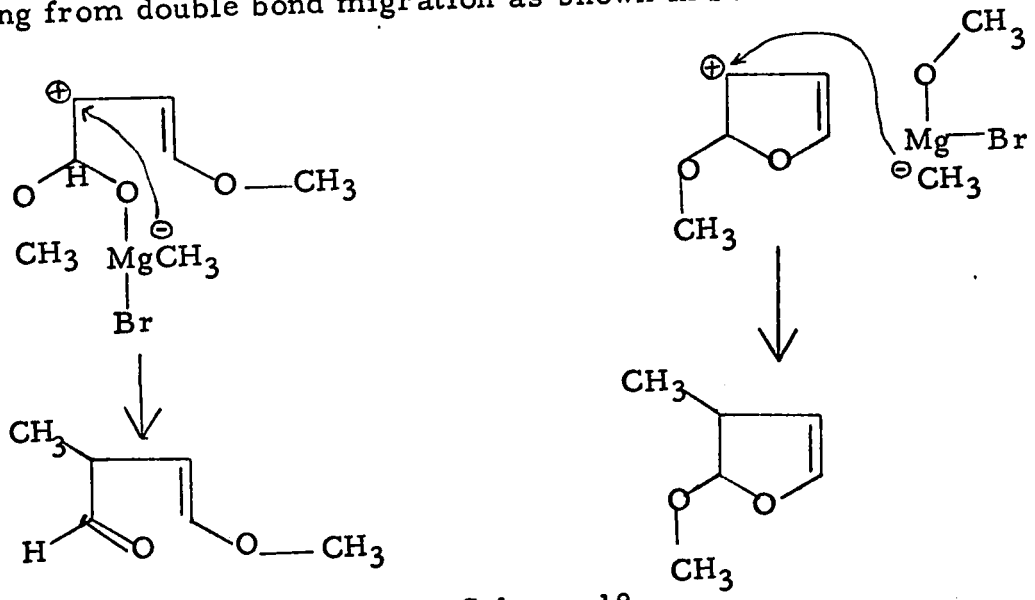
a



b

Scheme 17

As well as the two products shown (Scheme 17 - a and b), there is the possibility of attack at the allylic carbonium ion resulting from double bond migration as shown in Scheme 18.

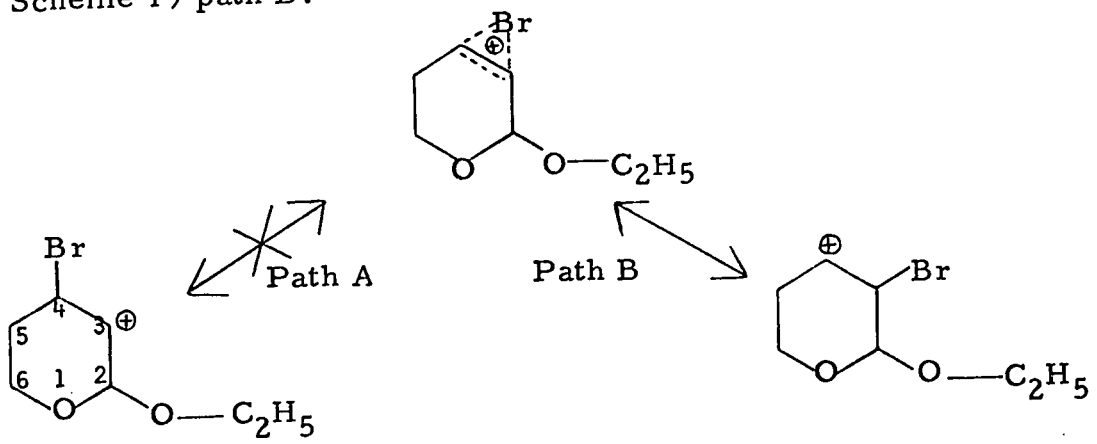


Scheme 18

This possibility was not considered to be too important, however, since a carbonium ion at this position, α- to an anomeric center of an acetal, would be destabilized by the inductive electron withdrawing effect of the geminal diether group. As well, the positive charge on the anomeric carbon is quite highly stabilized by participation of the electrons from oxygen.

The factor of destabilization of the rearranged allylic carbonium ion by the geminal ether group has been found to determine the direction of 3-membered bromonium ion ring opening on a tetrahydropyranyl nucleus. The geminal dioxy group at C-2 destabilizes an incipient positive charge at C-4 less than at C-3 when such a charge is developed by partial C-Br bond breaking (49).

This preferential formation of the carbonium ion at C-4 is shown in Scheme 19 path B.



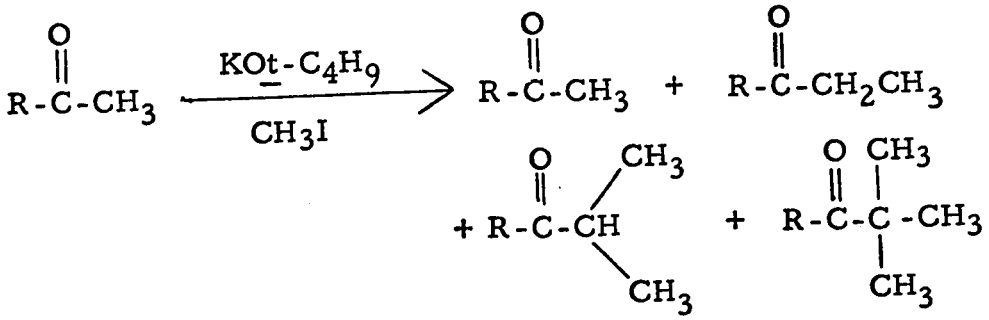
Scheme 19

The major complicating factor directing the reaction away from the desired path B (Scheme 17) was expected to be the stronger basicity of the dihydrofuran ring oxygen compared to that of the exocyclic ether oxygens (26, 27, 32). However, it was thought that the two methoxy groups would present sufficient steric hindrance to complexation at the ring oxygen, to allow some complexation with the exo oxygen atom and subsequent reaction to occur via path B (Scheme 17).

However, several attempts at this reaction in different solvents and at different temperatures gave essentially no reaction. A g.l.c. analysis of the reaction mixture showed the presence of starting material primarily, along with a few very minor peaks. A fast reaction would be expected between a carbonium ion and a Grignard reagent, so it must be concluded that a sufficiently strong complex formation does not occur between either the exo- or endo-cyclic oxygens and the Grignard reagent to initiate the reaction.

6. Attempted preparation of γ-isopropyl- γ-butyrolactone by direct condensation of 3-methyl-2-butanone with ethyl chloroacetate.

An extensive review of alkylation reactions of ketones has been published by Conia (50). Alkylations of ketones with the aid of strong bases such as potassium tertiary butoxide are complicated by the fact that polyalkylation occurs very easily as shown for the case of pinacolone in Scheme 20.

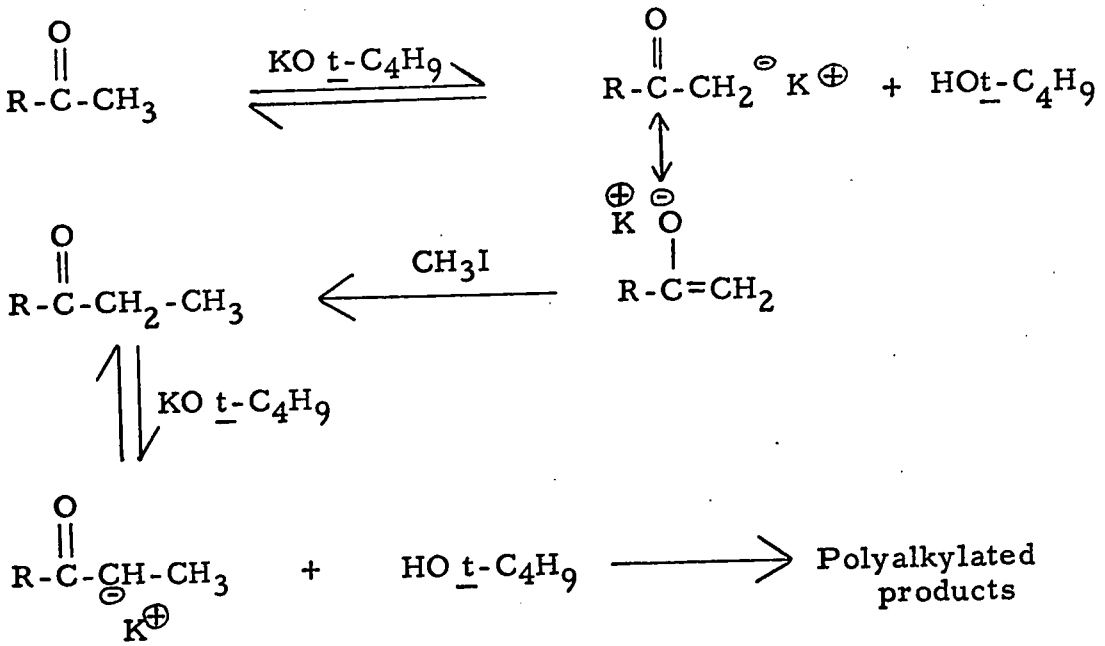


(R = t-C_4H_9)

Scheme 20

The accepted mechanism involves initial abstraction by the base of a hydrogen atom α - to the carbonyl group to form a stabilized carbanion which can react with the alkyl halide. The alkylated material in turn can react further until all of the α-hydrogens are replaced as shown in Scheme 21.

In some cases, polyalkylation and aldol condensations can be eliminated by using a base such as sodium hydride, sodium amide or potassium triphenylmethide which can react rapidly and irreversibly to form the carbanion.



(R = -t-C_4H_9)

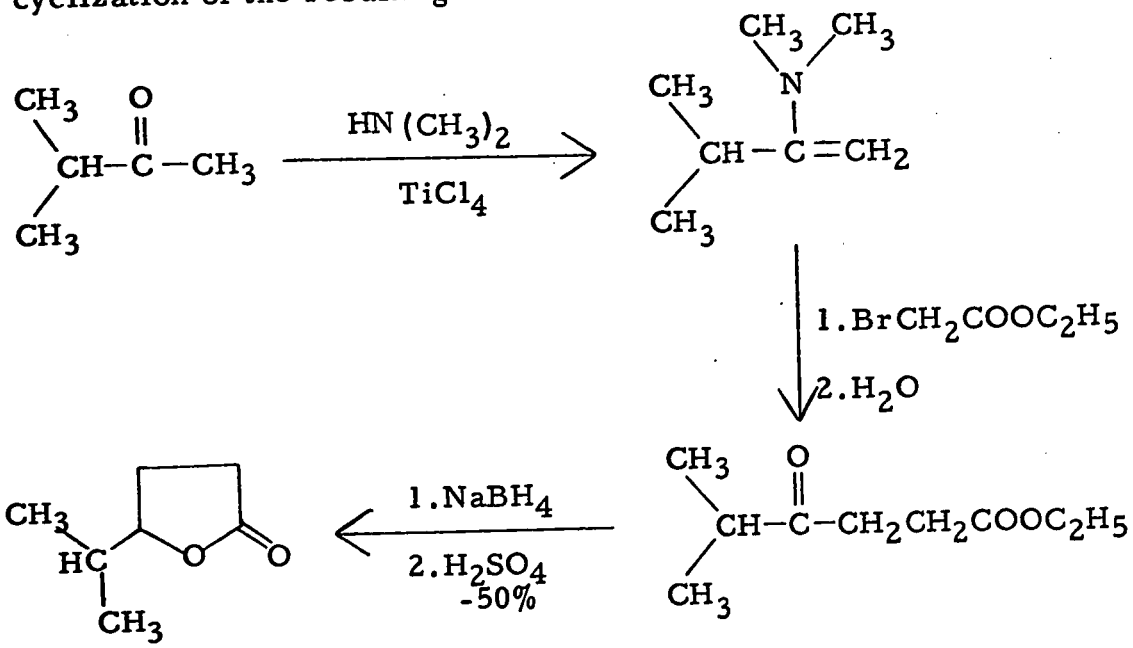
Scheme 21

In the present work, 3-methyl-2-butanone was treated with either sodium hydride or potassium triphenylmethide, and to the product was added ethyl chloroacetate. The resulting reaction mixtures were analyzed by g.l.c.. In both cases a mixture of several products was found. None of the components appeared as a major peak or corresponded to the peak given by the desired ethyl β-isobutyrylpropionate prepared by Miss Makhubu.

7. Successful preparation of γ-isopropyl-γ-butyrolactone by the condensation of ethyl bromoacetate and the dimethylamine enamine of 3-methyl-2-butanone.

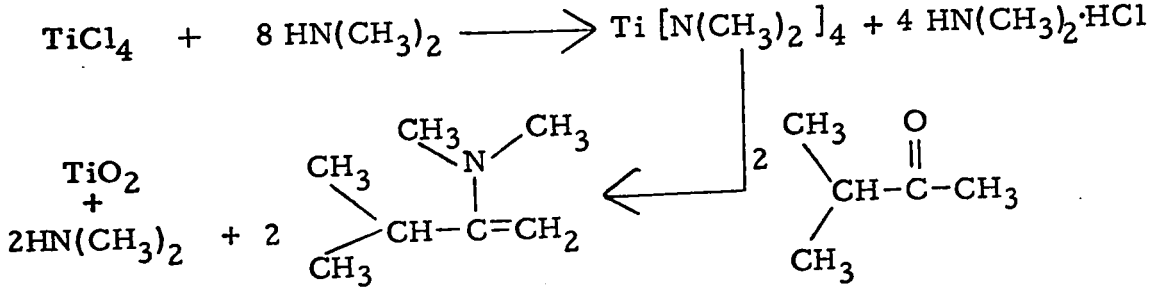
The procedure which successfully produced the γ-substituted-γ-butyrolactone is outlined in Scheme 22. It involves the condensation of an enamine of 3-methyl-2-butanone with ethyl bromoacetate

followed by sodium borohydride reduction and acid catalyzed cyclization of the resulting keto-ester.



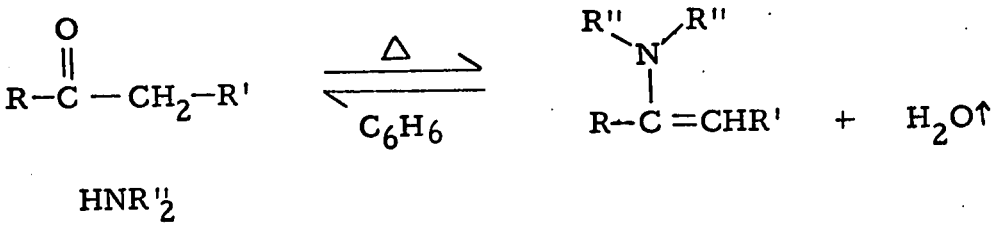
Scheme 22

The enamine synthesis employed in the first step was recently reported in the literature (51) and is a relatively easy, one-step procedure. There is no need to isolate the intermediate tetraamino titanium compound although it can be isolated if necessary. The reaction is shown in Scheme 23. White and Weingarten (51) reported a 57% yield of the dimethylamine enamine of 3 - methyl - 2 - butanone but variable yields of between 35 and 40% were found in the present work.



Scheme 23

Stork and coworkers first introduced the synthesis and use of enamines in 1963 (52). Their synthesis procedure involved the heating of a mixture of ketone and amine in refluxing benzene solution so that water was removed by azeotropic distillation. The removal of water in this manner was necessary in order to force the equilibrium to the right (Scheme 24).

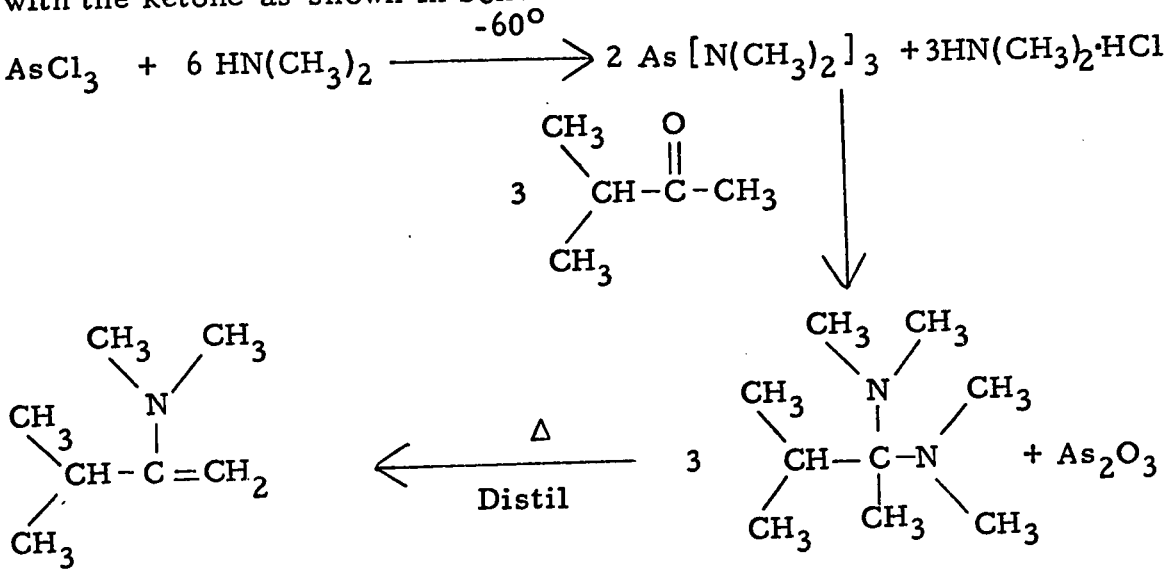


Scheme 24

One major drawback to the Stork synthesis lay in the fact that the enamine with the most highly substituted double bond was always formed. Furthermore, no enamines could be made in which the methyl group of methyl ketones was involved in the double bond formation, even when the methyl group was the only group available for double bond formation. Consequently, the recent reports of enamine synthesis in nonaqueous media proved very useful since terminal enamines could now be formed (51, 53). The two procedures reported (51, 53) were similar in approach, involving the formation of a metal amine compound which subsequently reacted with a ketone to form an enamine and metal oxide. The method starting with titanium tetrachloride (51) is described above. The second method employed arsenic trichloride (53). Both procedures were attempted in the present work but only the former

procedure using titanium tetrachloride was successful.

The preparation starting with arsenic trichloride (53) stipulated that the intermediate tris-dimethylaminoarsine be isolated by distillation and then be reacted in the subsequent step with the ketone as shown in Scheme 25.



Scheme 25

The literature report claimed that any secondary amine could be used for this synthesis but the reaction between tris-dimethylaminoarsine and 3-methyl-2-butanone did not prove successful in the present work.

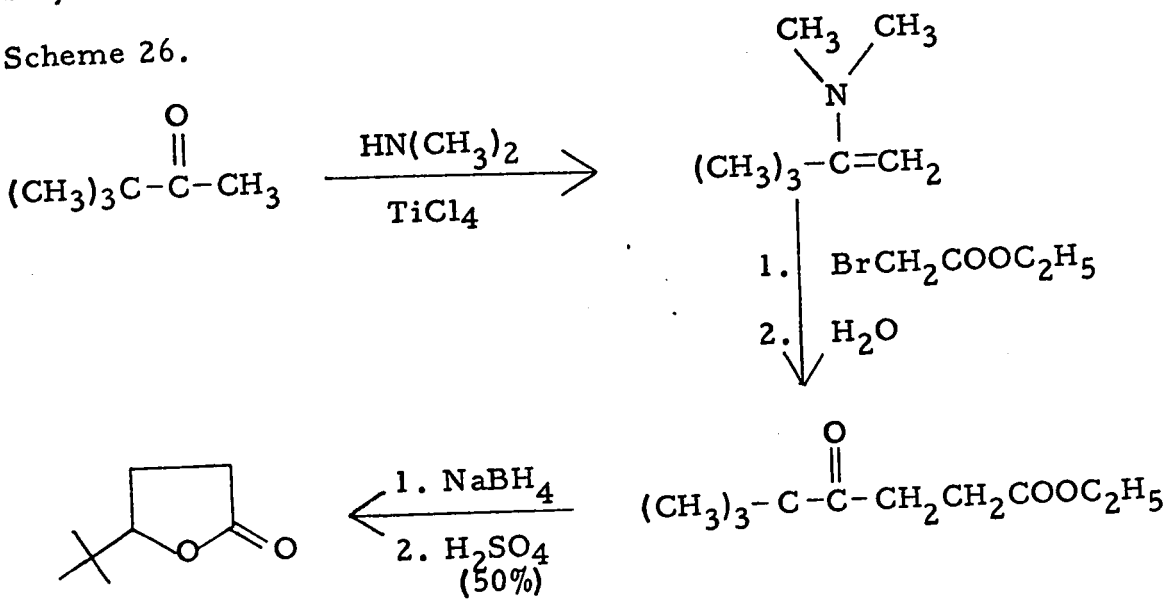
The second step of the synthesis involved a Michael condensation of the enamine with ethyl bromoacetate. The reaction proceeded equally well in either methanol, as described by Stork et al (52), in 1,2-dimethoxyethane or in diethyl ether, in all cases to the extent of about 45%.

Since the last steps of reduction and cyclization of the

ethyl β -isobutyrylpropionate did not work for Miss Makhubu (5) but proved successful in the present work, it may be concluded that polyphosphoric acid as used by Miss Makhubu was unsatisfactory and could not affect the cyclization.

8. Preparation of γ-t-butyl-γ-butyrolactone by a procedure similar to that used to prepare γ-isopropyl-γ-butyrolactone.

The same reaction sequence employed to synthesize γ-isopropyl-γ-butyrolactone was used to synthesize γ-t-butyl-γ-butyrolactone starting from 3,3-dimethyl-2-butanone as shown in Scheme 26.



Scheme 26

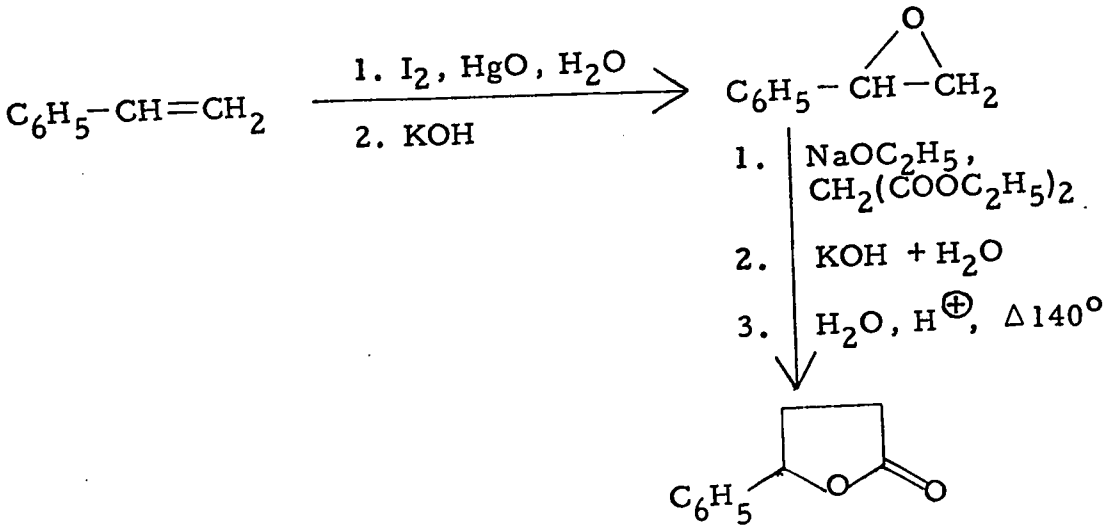
The enamine synthesis proceeded in a 63% yield (95% in the literature (51)) while the Michael condensation step proceeded in a 38% yield and the reduction and cyclization in a 95% yield. The lactone was thus obtained in a 25% overall yield from the pinacolone. Dry solvents were found to be a necessity for the

production of satisfactory yields of products in all steps of the synthesis.

9. Preparation of γ-phenyl-γ-butyrolactone.

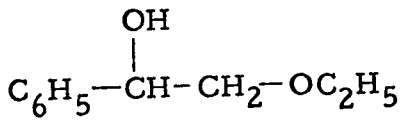
The procedure used to prepare the γ-isopropyl- and γ-t-butyl-γ-butyrolactone was also attempted for the synthesis of γ-phenyl-γ-butyrolactone but with no success. The enamine formation between acetophenone and dimethylamine proceeded only in very poor yield and distillation of the keto-ester and lactone in subsequent steps resulted in extensive charring and tar formation. Only a few drops of product could be isolated.

A simpler and more direct route to this particular lactone was found in the literature (54) and involved the condensation of styrene oxide with diethylmalonate, followed by decarboxylation and cyclization of the product. The starting material, styrene oxide, could be bought, or readily prepared from styrene (55). The reaction sequence for this lactone preparation is shown in Scheme 27.



Scheme 27

Russel and VanderWerf(54) carried out the preparation of the lactone from the epoxide in a continuous sequence without isolating any of the intermediates. When their procedure was used in the present work, only 2-ethoxy-1-hydroxy-1-phenylethane (Structure 4) was obtained in a 63% yield. This product could



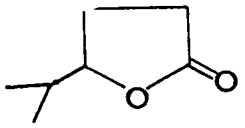
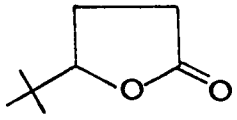
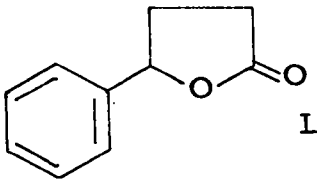
Structure 4

have been formed only from a direct attack of the ethoxide anion on the styrene oxide. This indicated that the reaction between sodium ethoxide and diethyl malonate had not gone to completion before styrene oxide was added or that the reaction of styrene oxide with ethoxide was faster than that with the malonate carbanion from the equilibrium $^{\ominus}OC_2H_5 + CH_2(COOC_2H_5)_2 \rightleftarrows HOC_2H_5 + {}^{\ominus}CH(COOC_2H_5)_2$. A modified procedure was therefore used to prepare sodium malonate. This was accomplished by the addition of diethyl malonate to a suspension of sodium hydride in 1,2-dimethoxyethane (DME). This reaction proceeded quickly and irreversibly with the evolution of hydrogen. The subsequent reactions carried out following the method of Russell and VanderWerf provided the lactone in 54% yield.

The physical constants of the three lactones prepared in this work are listed in Table 3.

TABLE 3

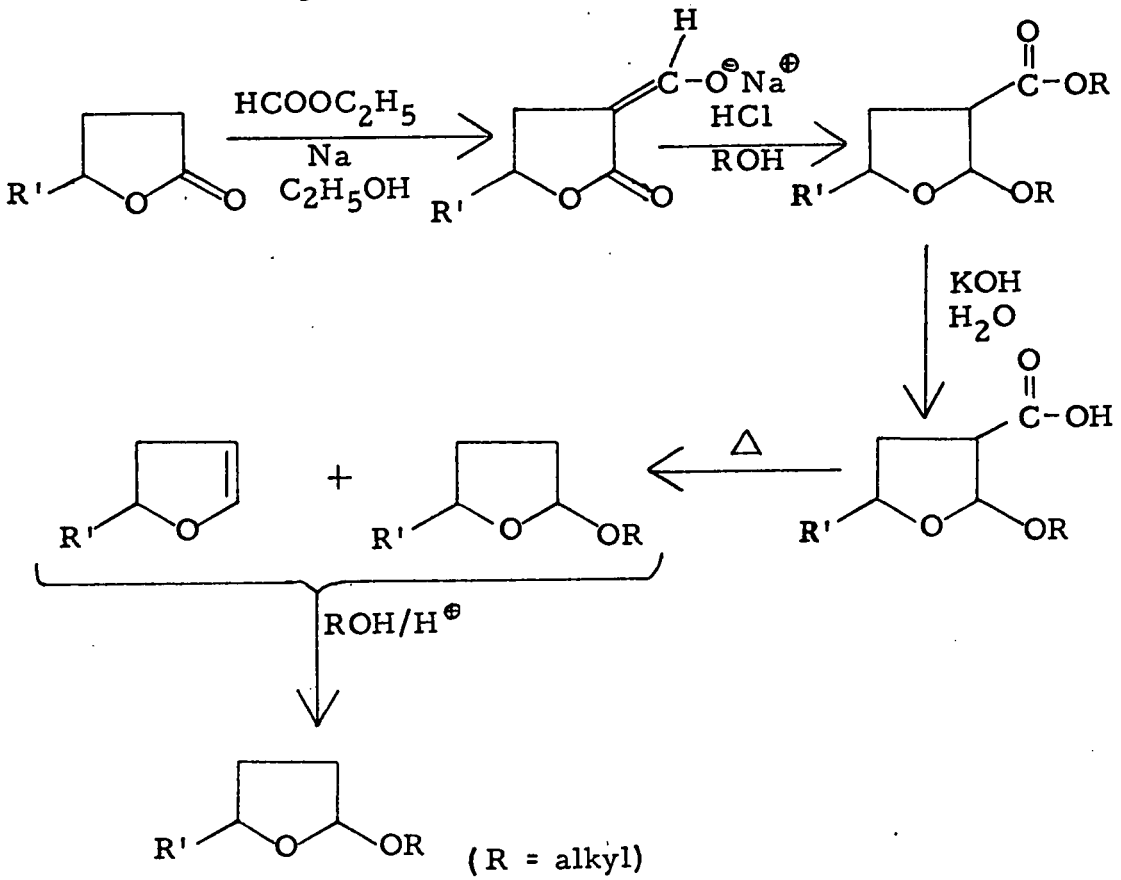
Physical Constants of the γ-Substituted-γ-butyrolactones.

Lactone	Boiling Point	$n_D^{(T)}$	Analysis	
			Calc'd	Found
	56°C at 0.5 mm	1.4416 (20°)	C, 65.64	65.86
			H, 9.37	9.46
	74°C at 2.0 mm	1.4453 (22°)	C, 67.57	66.52*
			H, 9.92	9.88
	132°C at 1.5 mm	1.5392 (23°)		
	Lit. (54) 130°C at 1.5 mm	1.5418 (15°)		

* This was the best analysis obtained even after three distillations.

10. Synthesis of the 5-substituted-2-methoxytetrahydrofurans from γ-substituted-γ-butyrolactones.

The conversion of the three lactones listed in Table 3 to their corresponding 5-substituted-2-methoxytetrahydrofurans was carried out using the procedure of Korte and coworkers (36, 37). This is a reasonably reliable procedure although rather lengthy. However, Miss Makhubu had used it to prepare 2-methoxy-, 2-ethoxy- and 2-isopropoxytetrahydrofuran from γ-butyrolactone as well as 5-methyl-2-methoxytetrahydrofuran from γ-valerolactone (5). The reaction sequence is shown in Scheme 28.

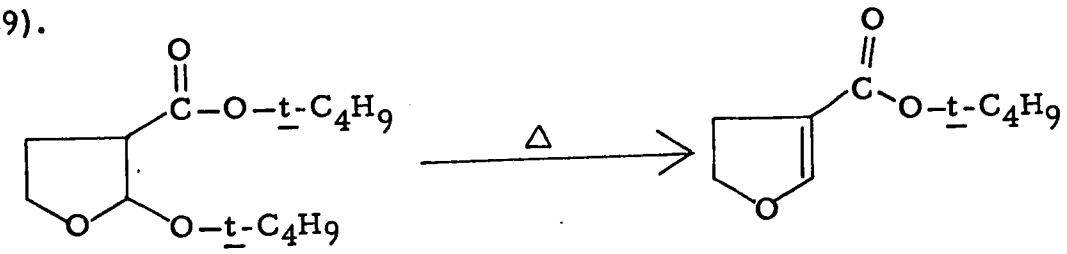


(R = alkyl)

(R' = alkyl or aryl)

Scheme 28

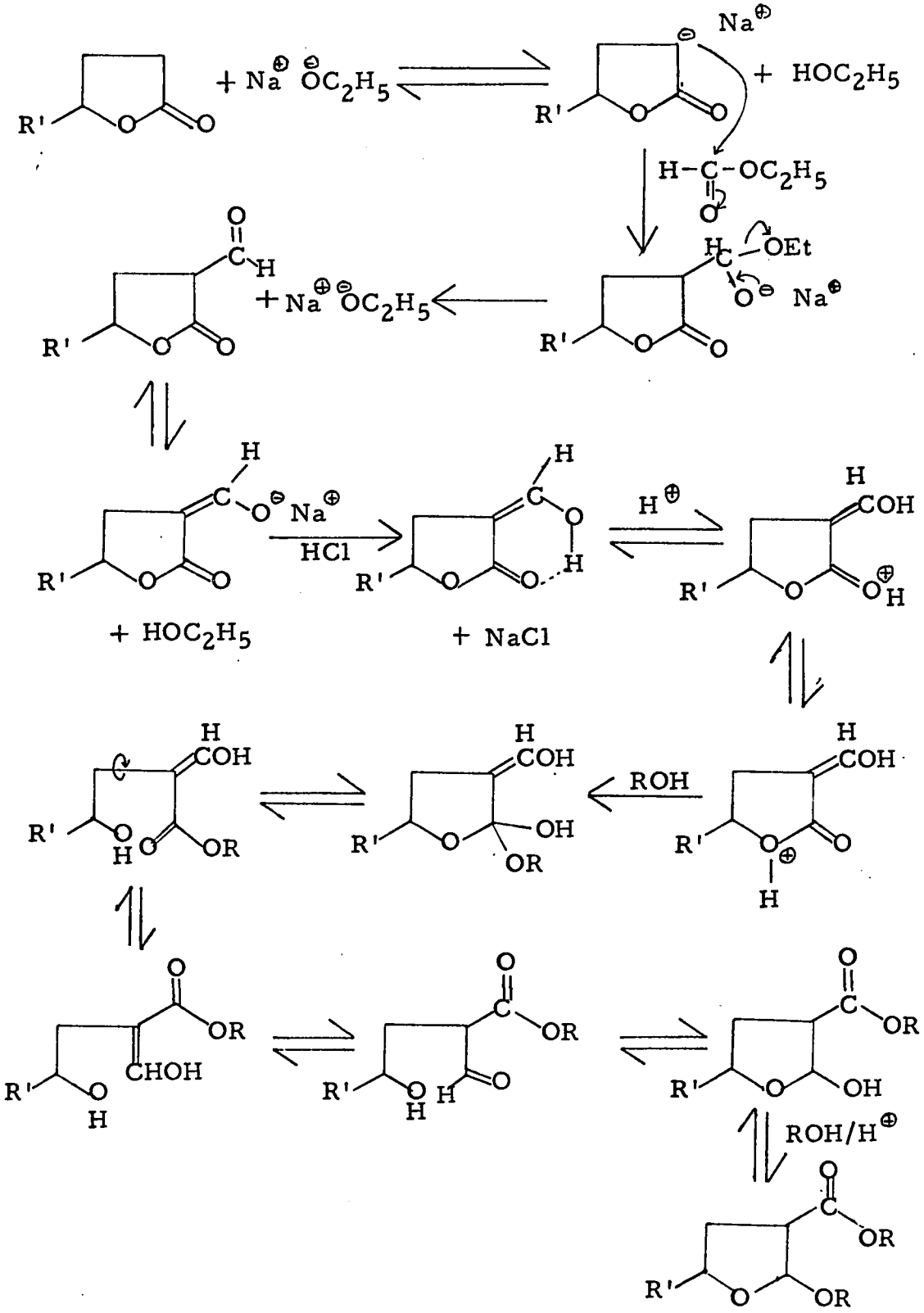
Miss Makhubu obtained the intermediate esters R = CH_3-, C_2H_5- and i-C_3H_7- (R' = H in all cases) in 90%, 41% and 29% yields respectively. For R = t-C_4H_9- and R' = H absolutely no ester was obtained. The lower yield with the bulky isopropoxy group and complete inability to obtain the ester with the t-butoxy group was attributed to steric interference between the C-2 alkoxy and C-3 carboalkoxy functions which facilitated elimination of the alcohol upon attempts at purification by distillation. Instead of the ester, only 3-carbo-t-butoxy-4,5-dihydrofuran was obtained, in good yield, when distillation of the crude t-butyl ester was attempted (Scheme 29).



Scheme 29

The mechanistic sequence for the formation of the ester from the lactone is shown in Scheme 30.

When R' was i-C_3H_7-, t-C_4H_9- and C_6H_5- (R = CH_3- in all cases), the intermediate ester was obtained in the present work in 81%, 72% and 63% yields respectively. Miss Makhubu had obtained a 55% yield of the ester when R' = CH_3-and R = CH_3-(5). The overall yields of the acetals from the lactones found in the present work were 28%, 10% and 54% when R' = i-C_3H_7-, t-C_4H_9-



(R = alkyl; R' = alkyl or aryl)

Scheme 30

and C_6H_5- (R = CH_3- in all cases) respectively.

The only difficulty encountered in the synthetic sequence involved the decarboxylation of the intermediate acid (Scheme 28). Korte and coworkers (36, 37) as well as Miss Makhubu (5) had obtained their results by a simple distillation at 200°C. But in the present work only very poor yields of the acetal were obtained by this method. The method for decarboxylation of furancarboxylic acids (56) was therefore adopted in order to improve yields. This procedure involved heating the carboxylic acid in quinoline at 200-210°C with a trace of cupric sulphate catalyst. The catalyst proved to be necessary for the reaction to occur at a reasonable rate and improved yields of decarboxylated product were obtained in its presence.

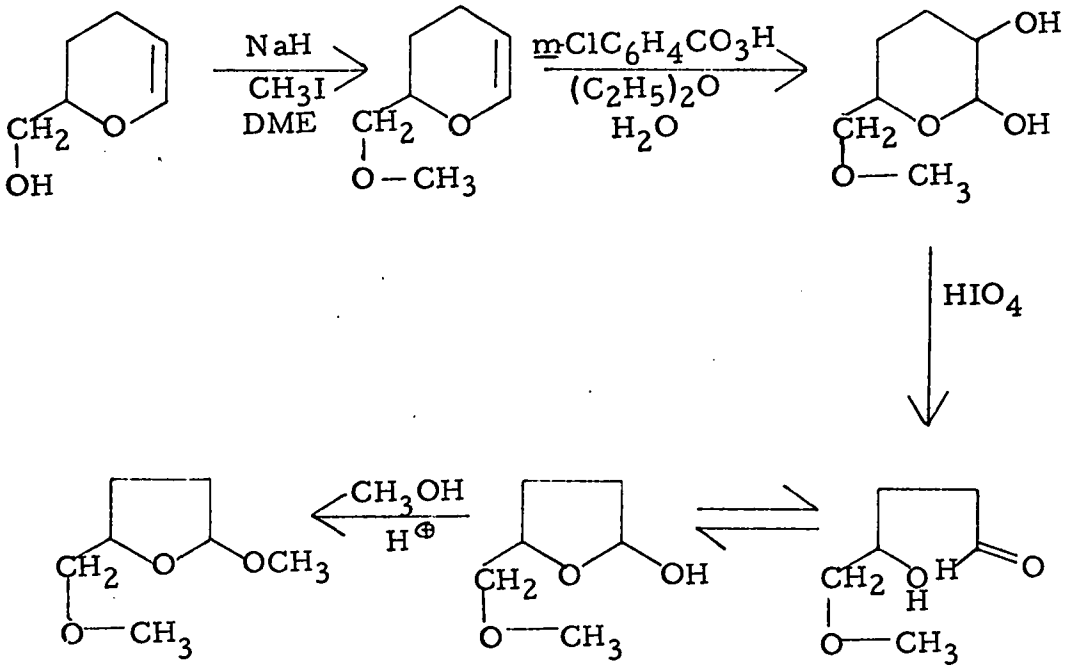
This decarboxylation procedure could be used to prepare the 5-isopropyl- and 5-t-butyl-2-methoxytetrahydrofurans but not the 2-methoxy-5-phenyltetrahydrofuran because of the latter compound's high boiling point (above that of the quinoline solvent). Eventually, a 68% yield of the decarboxylated material was obtained by simply heating the C-5 phenyl substituted acid at 140°C under vacuum. The acid decarboxylated and distilled cleanly without the use of cupric sulphate.

In all cases the resulting distillate from the decarboxylation proved to be a mixture of the acetal and olefin. This mixture was simply stirred with methanol and a trace of p-toluenesulfonic acid to give the acetal.

11. Preparation of 5-methoxymethyl-2-methoxytetrahydrofuran, 5-methyl-2-methoxytetrahydrofuran and 2-isopropoxy-5-methyl-tetrahydrofuran.

The acetal 5-methyl-2-methoxytetrahydrofuran was prepared by the method of Korte and coworkers (36, 37) in about a 20% yield from γ-valerolactone. This procedure had previously been used by Miss Makhubu to prepare this acetal (5).

The synthesis of 5-methoxymethyl-2-methoxytetrahydrofuran initially presented a problem to Miss Makhubu, but it was finally prepared by her according to the sequence of reactions in Scheme 31 (5).

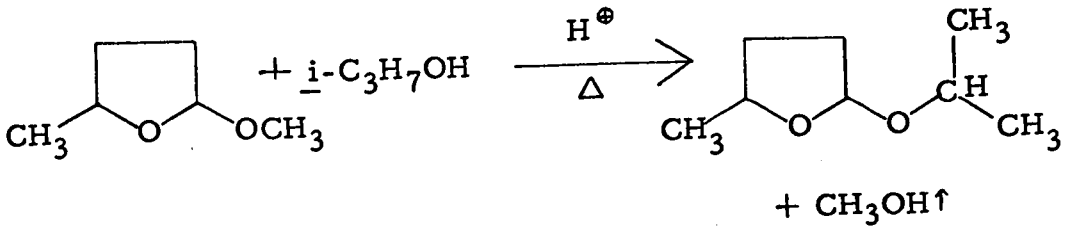


(DME = 1,2-dimethoxyethane)

Scheme 31

This preparation was successfully repeated in the present work and 5-benzyloxymethyl-2-methoxytetrahydrofuran was prepared by the same route except that benzyl chloride rather than methyl iodide was used in the first alkylation step of the 2-hydroxymethyl-3,4-dihydro-2H-pyran.

The acetal, 2-isopropoxy-5-methyltetrahydrofuran, was prepared from 5-methyl-2-methoxytetrahydrofuran by an acid catalyzed exchange reaction in isopropyl alcohol solution. The methanol was distilled out of the solution as it was formed and after treatment with sodium carbonate, the new acetal was distilled out of the reaction flask in a 60% yield (Scheme 32).

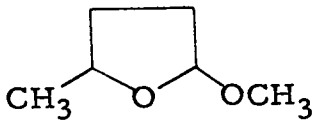
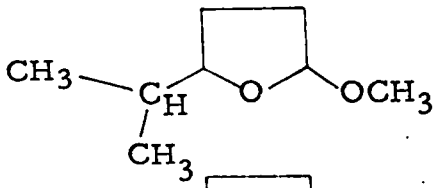
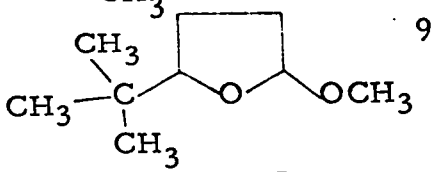
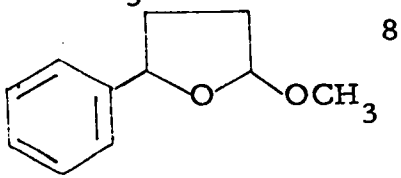
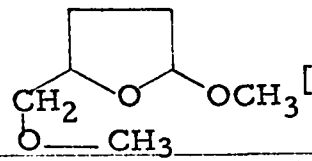


Scheme 32

The physical constants of the acetals prepared in the present work are listed in Table 4. The figures in parenthesis are the constants obtained by Miss Makhubu for the same compounds (5).

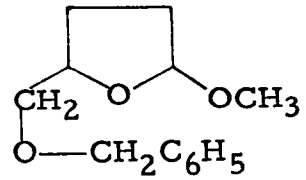
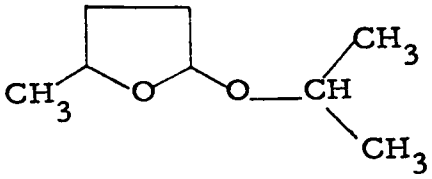
TABLE 4

Physical Constants of cis-trans Mixtures of the 5-Substituted-2-alkoxytetrahydrofurans.

Acetal	Boiling Point (°C)	$n_D(T)$	Analysis Calc'd	Analysis Found
	110° at 695 mm [108-109° at 695 mm]*	1.4080 (22°) [1.4127 (30°)] *	C, 62.06 H, 10.34	62.11 * 10.54
	80° at 95 mm	1.4172 (25°)	C, 66.63 H, 11.19	66.67 11.31
	97° at 110 mm	1.4257 (23°)	C, 68.31 H, 11.46	68.58 11.75
	85° at 0.8 mm	1.5130 (24°)	C, 74.13 H, 7.92	74.37 8.19
	65° at 50 mm [90-93° at 140 mm] *	1.4242 (25°) [1.4248 (23°)] *	C, 57.59 H, 9.65	57.55 * 9.59

* The figures in parentheses are taken from the work of Miss Makhubu (5).

TABLE 4 - Continued

Acetal	Boiling Point (°C)	n_D (T)	Analysis Calc'd	Found
	86-87° at 0.08 mm	1.5014 (24°)	C, 70.25	70.17
			H, 8.16	7.98
	136-138° at 700 mm	1.4112 (25°)	C, 66.63	66.38
			H, 11.18	10.99

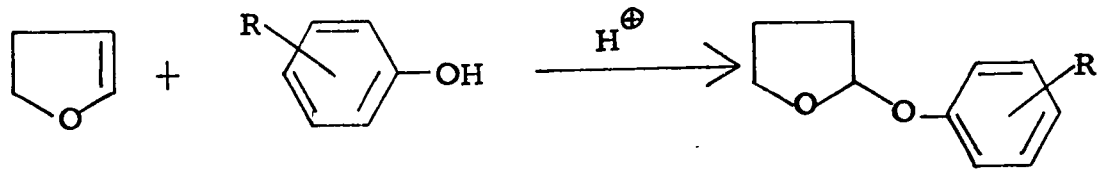
B. Synthesis of 2-Aryloxytetrahydrofurans.

Miss Makhubu attributed the exclusive endocyclic cleavage of all of the 2-alkoxytetrahydrofurans to the strong basicity of the tetrahydrofuran ring oxygen (26, 27, 32) which caused preferential complex formation with the aluminum species to occur at the ring oxygen. The 2-aryloxytetrahydrofurans were not included in Miss Makhubu's study, however, and such a strongly electron withdrawing group would have accentuated any polar effect of the substituents if a polar effect were operative. Diner and Brown (3) in fact had previously found that the 2-aryloxytetrahydropyrans gave exclusively exocyclic cleavage. This indicated a very strong polar influence by the aryl substituents in directing the course of hydrogenolysis.

Since the C-2 aryloxy group had such a pronounced effect in directing the hydrogenolysis of the tetrahydropyranyl acetals, its effect on the direction of hydrogenolysis of tetrahydrofuranyl acetals had to be considered. It was predicted that the 2-aryloxy-tetrahydrofuran molecule would set up a competition in directing the hydrogenolysis between the preferential complexing of the aluminum species at the ring oxygen favoring endo cleavage, and the greater stability of the oxocarbonium ion formed in exo cleavage caused by the phenyl ring destabilizing the oxocarbonium ion formed from endo cleavage.

Five members of the 2-aryloxytetrahydrofuran series were

synthesized by the method which Eliel and coworkers (4) had used to prepare the bulky 2-alkoxytetrahydrofurans. This procedure involved the acid catalyzed addition of the corresponding phenols to 2,3-dihydrofuran (Scheme 33).



Scheme 33

The only problem encountered in this procedure was the removal of excess unreacted phenol from the reaction mixture. After several unsuccessful attempts at washing the reaction mixture with aqueous sodium carbonate and aqueous potassium hydroxide solutions, the more potent "Claisen's Alkali" (57) was found to remove any phenol present, even the relatively unreactive 2,6-dichlorophenol.

The physical constants of the 2-aryloxytetrahydrofurans and of 2-benzyloxytetrahydrofuran are summarized in Table 5.

TABLE 5

Physical Constants of the 2-Aryloxytetrahydrofurans and of 2-Benzyloxytetrahydrofuran.

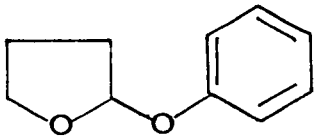
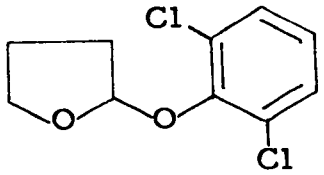
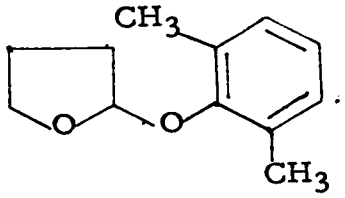
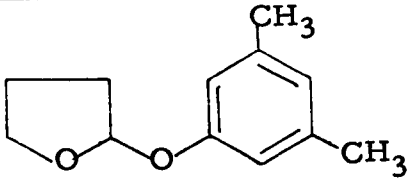
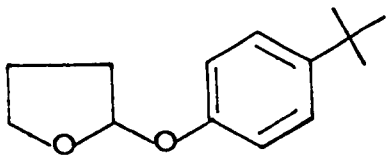
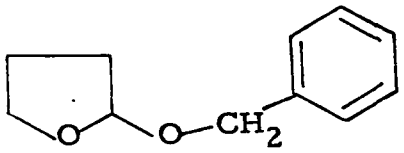
Acetal	Yield (%)	Boiling Point (°C)	n_D(T)	Analysis Calc'd	Found
	82	86° at 2.8 mm	1.5217 (25°)	C, 73.12	73.42
				H, 7.31	7.45
	30	100-102° at 0.8 mm	1.5469 (25°)	C, 51.53	51.73
				H, 4.32	4.72
				Cl, 30.42	30.17
	75.5	95-96° at 1.0 mm	1.5160 (25°)	C, 74.96	75.18
				H, 8.39	8.70

TABLE 5 - Continued

Acetal	Yield (%)	Boiling Point (°C)	n_D(T)	Analysis	
				Calc'd	Found
	54	74° at 0.1 mm	1.5183 (25°)	C, 74.96	75.11
				H, 8.39	8.21
	69.5	92° at 0.1 mm	1.5108 (25°)	C, 76.32	76.46
				H, 9.15	8.85
	80	114° at 7 mm [Lit (4): 102° at 4 mm] *	1.5120 (24°)		

* Figures in parentheses are teken from the work of Eliel and coworkers (4).

C. Attempts to Reduce the γ-Substituted-γ-butyrolactones to the Corresponding Tetrahydrofuranyl Acetals.

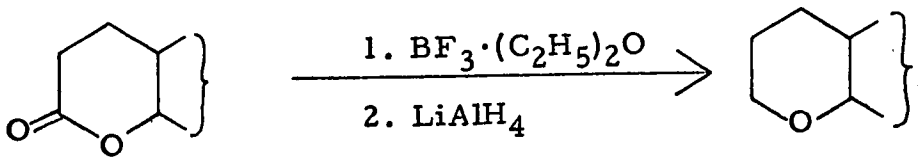
Although the γ-butyrolactones could be converted quite reliably to the corresponding tetrahydrofuranyl acetals(36, 37, 5), the method of Korte and coworkers still involved four steps in which material could be lost, thus lowering the overall yield of the acetal. It would have been very useful if a reliable, one-step reduction of the lactone to the corresponding hemi-acetal (easily converted to the acetal) were available.

A number of reports have appeared in the literature describing this sort of reduction. In most cases the yields reported were quite good but attempts in the present work to repeat the literature procedures were unsuccessful in producing any acetal. These unsuccessful attempts at the direct reduction of the lactone are described below with possible reasons for some of the failures.

1. Attempted reduction of γ-butyrolactone using a $LiAlH_4$-BF_3 solution.

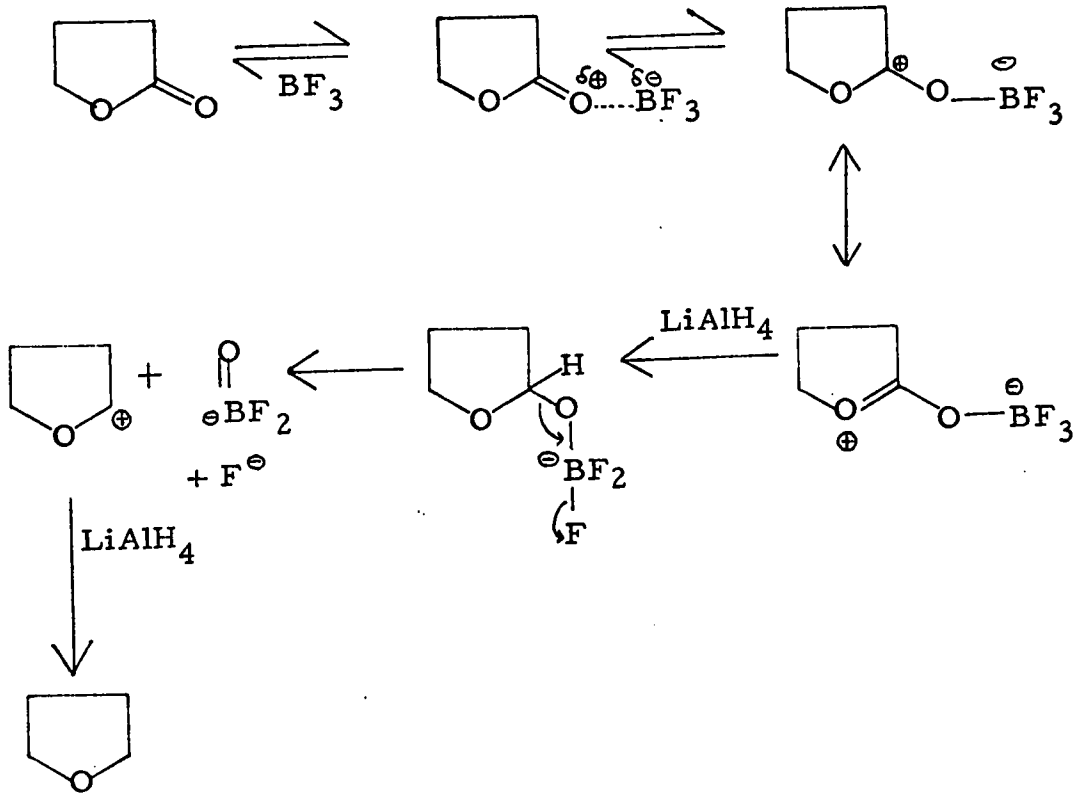
In 1960 and 1961, there appeared two papers (58, 59) describing the reduction of steroidal lactones using different mixtures of boron trifluoride and lithium aluminum hydride. It was reported that the lactones were reduced in different ways depending upon the order of mixing of the three reactants. For example, when a lactone was stirred with boron trifluoride, followed by the addition of lithium aluminum hydride, the carbonyl

oxygen was simply removed leaving the cyclic ether (Scheme 34).



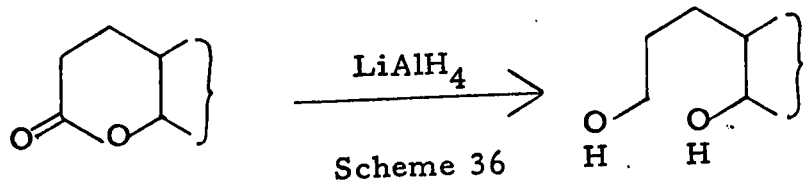
Scheme 34

This reduction was carried out on both "gamma" and "delta" (γ- and δ-) lactones in the steroidal series giving tetrahydrofuran and pyran ethers respectively. The mechanism proposed for the reduction involved initial complexing of BF_3 with the lactone followed by reduction by the hydride species (58). This is shown in Scheme 35.



Scheme 35

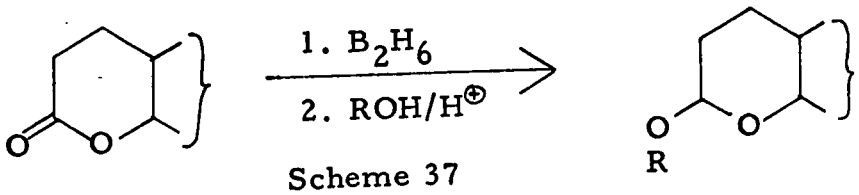
On the other hand, addition of the lactone to a suspension of $LiAlH_4$ in ether gave the diol, as would be expected (Scheme 36).



Scheme 36

Prior mixing of the $LiAlH_4$ and $BF_3 \cdot O(C_2H_5)_2$ produced diborane which was then bubbled into an ether solution of the lactone. When the reaction mixture was worked up by stirring the solution with alcohol and acid, the acetal was obtained as shown in Scheme 37 (58).

$$3\ LiAlH_4 + 4\ BF_3 \longrightarrow 2\ B_2H_6 \uparrow + 3\ LiAlF_4$$



Scheme 37

Since diborane was reported to give the steroidal acetals in a 40 to 50% yield, an attempt was made in the present work to apply this reduction to our simpler lactones. However, absolutely no acetal was recovered from the attempted reductions of γ-butyrolactone even after several attempts with various reaction conditions.

Diborane was first generated in a separate flask and blown into the reaction mixture as described by Pettit and Kasturi (58). However, even after a large excess of diborane had been generated, a 70% recovery of unreacted lactone and absolutely no acetal was found upon distillation of the crude product.

A second attempt involved an <u>in situ</u> preparation of diborane by first mixing the lactone and sodium borohydride followed by the

addition of $BF_3 \cdot O(C_2H_5)_2$. The $NaBH_4$ does not react with the lactone and if B_2H_6 were going to react with the lactone it should have done so during the in situ preparation. However, only the lactone was recovered in an 80% yield by distillation.

Since the diborane reaction was unsuccessful, it was thought that a direct reduction with a weak hydride donor in the presence of BF_3 might yield the acetal. The lactone and $BF_3 \cdot O(C_2H_5)_2$ were stirred while a quarter molar equivalent of $NaBH_4$ was added in small portions. This process is a modification of the previously described procedure for reduction of the lactone to the cyclic ether using $BF_3 \cdot O(C_2H_5)_2$ and $LiAlH_4$. The limited use of a weak hydride donor should have stopped the reaction at the second carbonium ion in Scheme 35 without causing further reduction. Addition of the desired alcohol in an acid solution would then produce the acetal.

However, when this procedure was carried out, only unreacted lactone was recovered, indicating that the $NaBH_4$ molecule was too weak a hydride donor to cause the reduction. In fact, a preferential formation of diborane occurred, and the hydride gas boiled out of the solution. It was expected that the use of one quarter molar equivalent of $LiAlH_4$ would simply carry the reaction to a 25% yield of the ether rather than partial reduction, since it is a very strong hydride donor. Hence, this procedure was abandoned.

2. Attempted reduction γ-butyrolactone using sodium amalgam.

In carbohydrate chemistry, the reduction of sugar lactones to the corresponding hemiacetals using sodium amalgam is a well known reaction (60, 61). This type of reduction was therefore carried out in the present work in an attempt to reduce γ-butyrolactone using the published procedure for the reduction of sugar lactones (62, 63). The only modification employed in the present work was the use of methanol as the solvent rather than acidified water in order that the nonhydroxylated lactone would be soluble, and that the acetal rather than the hydroxyaldehyde (hemiacetal) would be isolated.

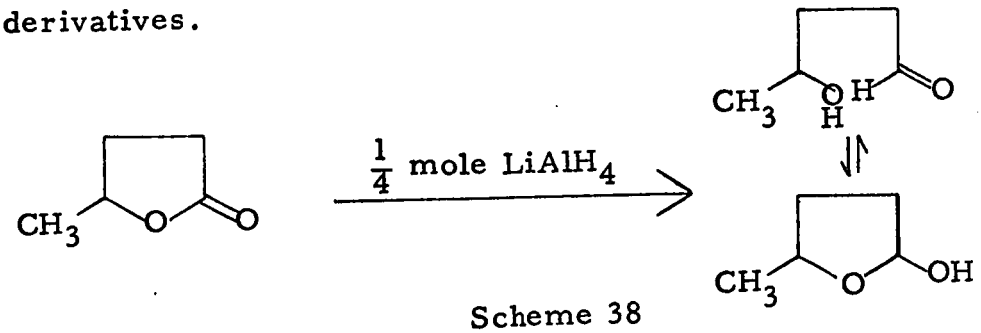
The solution was kept slightly acidic since the literature reports (62) had noted this to be a crucial factor for a successful reduction. In spite of this precaution, absolutely no acetal was isolated from this attempted reduction using 2% sodium amalgam.

Further literature research revealed a statement (64) that an earlier report (65) had noted that nonhydroxylated lactones could not be reduced in this fashion. The original reference (65) could not be found and Arth (64) did not give a reason for the lack of reaction with unsubstituted lactones. However, the present work corroborated the earlier findings (65) and this approach to the reduction of lactones was abandoned.

3. Attempted reduction of γ-butyrolactone using a quarter molar equivalent of $LiAlH_4$.

Arth (64) reported the direct reduction of lactones to the

hydroxy aldehyde (hemi-acetal) using a quarter molar equivalent of $LiAlH_4$ (one equivalent of active hydride) (Scheme 38). The reduction was carried out on a number of different lactones including α-methyl-δ-caprolactone, γ-valerolactone, and α-hydroxy-β,β-dimethyl-γ-butyrolactone giving respectively α-methyl-δ-hydroxy-caproaldehyde, γ-hydroxyvaleraldehyde and α,γ-dihydroxy-β,β-dimethylbutyraldehyde in reasonable yields (64). These products were distillable and gave crystalline 2,4-dinitrophenylhydrazone derivatives.



Scheme 38

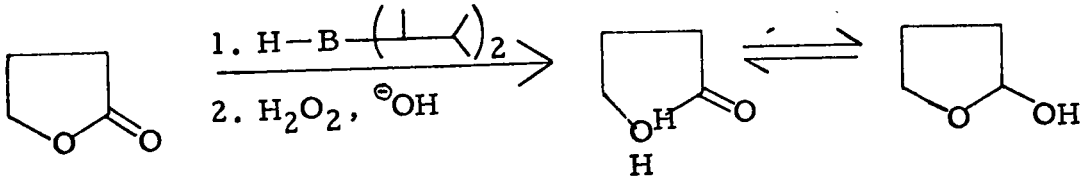
When Arth's procedure was repeated in the present work, the same results could not be obtained. Only the lactone was recovered upon distillation along with a relatively very small amount of the diol and an even smaller amount of what may have been the hydroxy aldehyde. The γ-valerolactone boiled at very nearly the same temperature as the γ-hydroxyvaleraldehyde and the distillation mixture gave only a very small amount of a 2,4-dinitrophenylhydrazone derivative.

Since two attempts at this reduction gave the same results, it was concluded that Arth may simply have been dealing with a mixture of the lactone and a small amount of the hydroxy aldehyde.

The infrared spectrum showed a predominance of the lactone absorption at 1760 cm^{-1} with only a small hydroxyl absorption and a shoulder on the lactone carbonyl absorption which could be attributed to the aldehyde. It was this small amount of aldehyde which gave the weak 2,4-dinitrophenylhydrazone derivative and gave the false impression that the material (which was largely the lactone) was the desired procuct. This procedure was therefore abandoned.

4. Attempted reduction of γ-butyrolactone using disiamylborane.

A report by Brown and Digby (66) indicated that disiamylborane (bis-3-methyl-2-butylborane) was a useful reducing agent for the conversion of such functional groups as (a) aldehydes and ketones to alcohols, (b) unhindered olefins and acetylenes to organoboranes, (c) γ-lactones to hydroxyaldehydes and (d) N,N-dimethylamides to aldehydes. For example, γ-butyrolactone was reduced to 4-hydroxybutyraldehyde in a 73% yield while γ-valerolactone was converted to 4-hydroxyvaleraldehyde in a 76% yield (Scheme 39).



Scheme 39

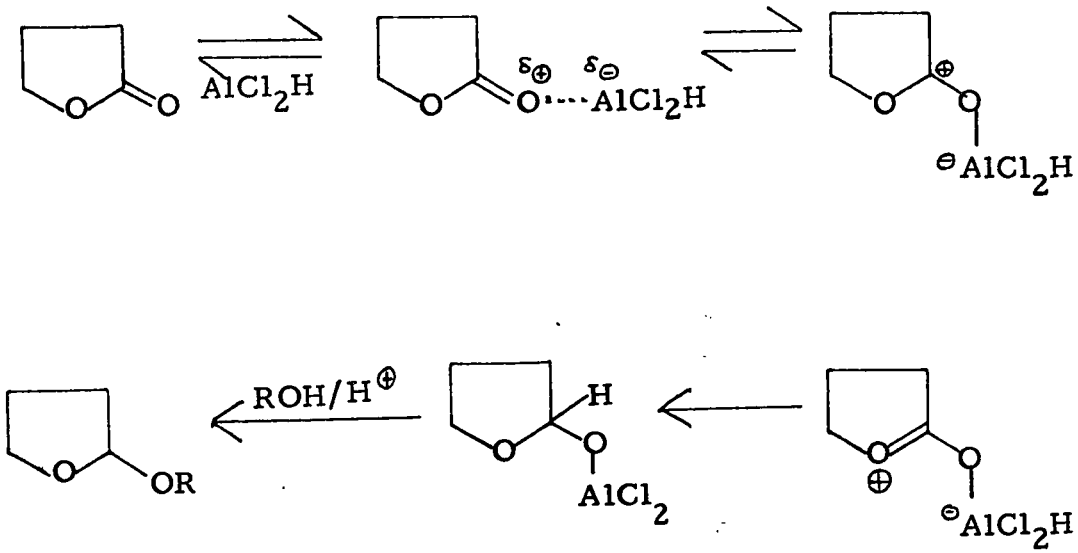
This procedure appeared to be quite promising and disiamylborane was therefore prepared following the procedure of Brown and Zweifel (67). The main difficulty with this reaction arose from the

fact that Brown and Digby did not report the exact reaction conditions (66). Even after several attempts under various conditions, using both oxidative and hydrolysis work-up procedures, no reduction products were found. In all cases only the unreacted lactone was recovered. Since the exact reaction conditions were not described by Brown and Digby, it was not possible to draw any conclusions as to why the reduction did not proceed as they had reported. The procedure was therefore abandoned.

5. Attempted reduction of γ-butyrolactone using $AlCl_2H$.

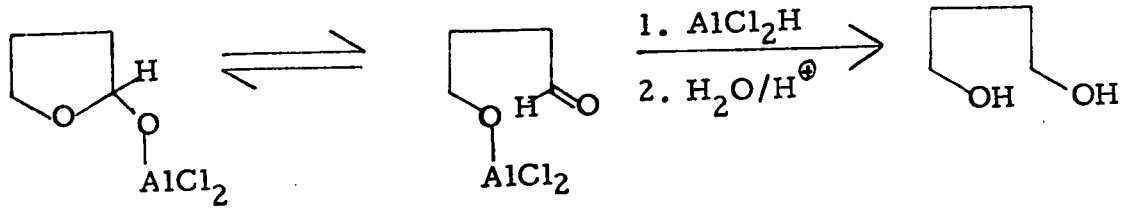
This final attempt at reduction of the lactones was not based on any published procedure but simply on the hypothesis that a reducing species with only one active hydride unit might reduce a lactone only as far as the hemi-acetal. This was similar to the rationale of Brown and Digby (66) who used disiamylborane which has only one active hydride. From other work done in this laboratory, it was shown that $AlCl_2H$ could be produced very easily by using the "mixed hydride" $AlCl_3$ and $LiAlH_4$ in the proportion of 3 to 1 (16). The mechanism by which the reduction of γ-butyrolactone by $AlCl_2H$ might proceed is shown in Scheme 40.

If the mechanism in fact did involve initial complexation of the aluminum species followed by partial carbonium ion formation and intramolecular hydride donation, it was hoped that the reaction would proceed only to the C-2 alumino-oxy species allowing the formation of the acetal during workup with acidified alcohol.



Scheme 40

When the reduction was carried out at -60°C almost no reduction occurred, while at room temperature, the reduction took place directly to the diol. No observable formation of the hydroxy aldehyde or acetal was found in either case. The reduction therefore did not stop at the C-2 alumino-oxy species as hoped, but may have proceeded as shown in Scheme 41. The C-2 alumino-oxy species very quickly decomposed to the anion of the hydroxy aldehyde and the aldehyde would be subject to much faster reduction by the hydride species than was the lactone.



Scheme 41

Since the reaction did not proceed as desired, this method

was abandoned. At this point, there was no longer any necessity for a direct reduction procedure for the lactones. While the above attempts at direct reduction of the lactones had been carried out, parallel experiments which were also in progress had converted all of the lactones to the corresponding acetals by the method of Korte and coworkers (36, 37). However, a report of the direct reduction of sugar lactones to the hemi-acetal appeared recently (68), using a procedure initially reported in 1966 (69) involving the use of sodium borohydride and acetic acid in ether solution. This procedure was not attempted but the fact that the initial report was corroborated by independent work made it look promising. The only question was whether or not the procedure would reduce unsubstituted lactones.

D. Synthesis of Authentic Hydrogenolysis Products.

The hydrogenolysis of the 5-substituted-2-methoxytetrahydrofurans can give two possible products. One is the cyclic 2-substituted tetrahydrofuran resulting from exo cleavage while the other is the acyclic hydroxy ether resulting from endo cleavage. Methanol is also formed from exo cleavage but in the hydrogenolysis experiments performed, it appeared only in very small amounts on the chromatogram when the mixture of products was analyzed by gas liquid chromatography. This low recovery of material was assumed to be due to loss by the reaction or association of methanol

with the aluminum species and its removal by the filtration process.

1. Synthesis of 2-substitutedtetrahydrofurans.

Only two methods for the synthesis of the various 2-substituted tetrahydrofurans were examined. The first procedure was successful but gave a yield of only 20%. The second route provided all of the cyclic ethers in good yields.

(a) Attempted synthesis of 2-substituted tetrahydrofurans by the action of $LiAlH_4$-BF_3 on γ-substituted-γ-butyrolactones.

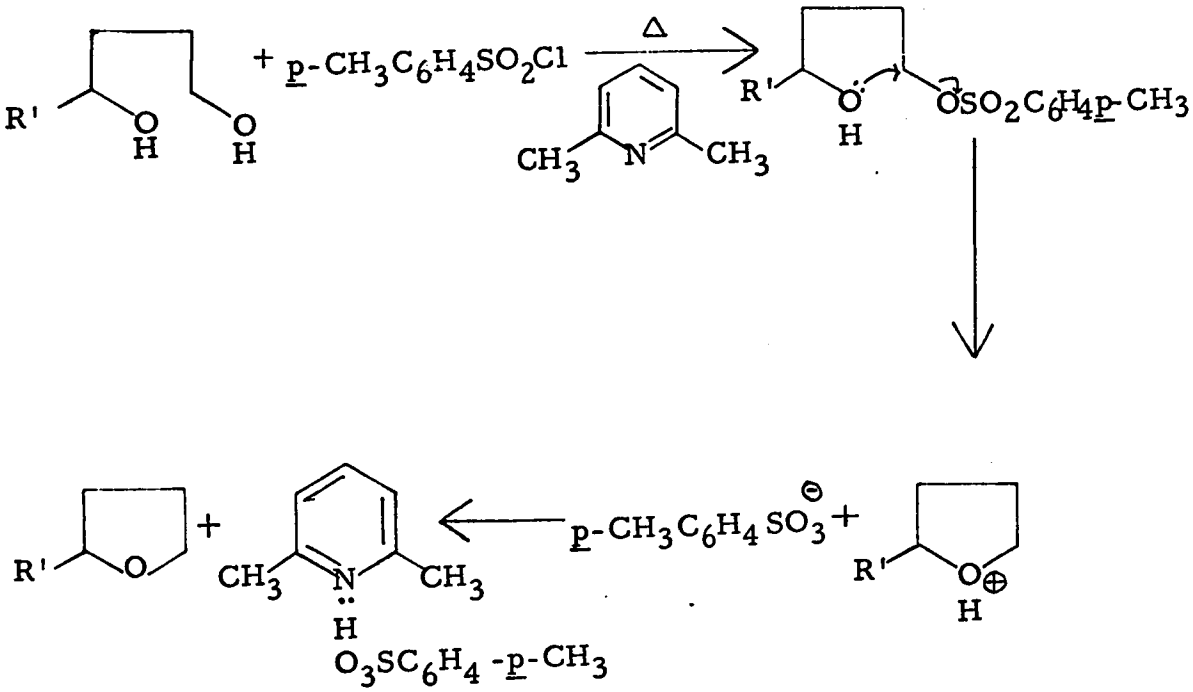
Pettit and Kasturi (58, 59) reported the direct reduction of various steroidal lactones to the corresponding ethers by the action of $LiAlH_4$ on a BF_3-lactone mixture in ether solution (Scheme 34). This work has been mentioned earlier during the discussion of the reduction of lactones to the acetals.

Since no success had been found with the other work reported by these authors, an exploratory reduction only was carried out on γ-butyrolactone. A careful distillation of the reduction mixture gave the desired tetrahydrofuran in just 20% yield. The major product was 1,4-butanediol (> 50% yield). Since most of the reduction produced the diol and not the cyclic ether, this method was abandoned.

(b) Synthesis of the 2-substituted tetrahydrofurans by the action of p-toluenesulphonyl chloride and lutidine on the substituted 1,4-butanediols.

The second synthesis which was examined was based on a report by Reynolds and Kenyon (70) and proved to be quite

successful. The procedure involved the mixing of a 1,4-diol in lutidine or pyridine with subsequent addition of one equivalent of p-toluenesulphonyl chloride at 100°C. The mechanism for this reaction is shown in Scheme 42.



Scheme 42

This procedure worked quite well although some difficulty was encountered in obtaining the cyclic ether in a pure state. In all the cases fractional distillation did not completely separate the mixture of lutidine and cyclic ether. Purification by preparative g.l.c. was necessary and at least two passages of the mixture through the column was required. The 2-t-butyl- and 2-phenyl-tetrahydrofurans obtained by this method gave good analyses, but the isopropyltetrahydrofuran, even after three passages through

the column, was not completely purified. The analysis for carbon was 0.57% off the calculated value although the hydrogen analysis was quite satisfactory (Table 6). The physical constants of the three cyclic ethers prepared in this manner are summarized in Table 6. The yields were not determined since purification by g.l.c. was necessary.

The 1,4-diols required for the synthesis were prepared simply by reducing the corresponding lactones with $LiAlH_4$.

2. Synthesis of the products expected from endo cleavage of the 5-substituted-2-alkoxytetrahydrofurans.

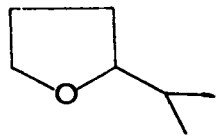
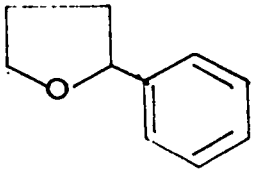
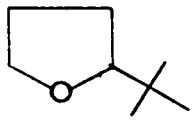
Two procedures were successfully used to synthesize the hydroxy ether products. Selective monomethylation of the primary hydroxy group of the 1,4-diols proved successful in preparing the authentic open chain reduction products expected from the hydrogenolysis of 5-isopropyl- and 5-t-butyl-2-methoxytetrahydrofurans. However, the preparation of the hydroxy ether from 2-methoxy-5-phenyltetrahydrofuran by this method could not be achieved. Synthesis of this latter compound presented a problem and a number of attempts were made before a successful preparation was found. The unsuccessful attempts as well as the successful preparations are described in the following sections.

(a) Synthesis of 2-methyl-6-methoxy-3-hexanol and 2,2-dimethyl-6-methoxy-3-hexanol by the monomethylation of the corresponding 1,4-diols.

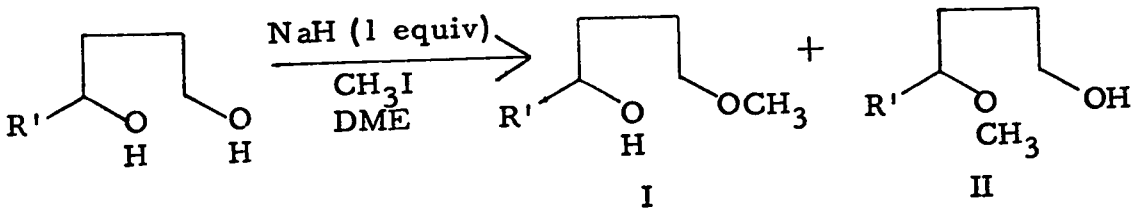
The monomethylation procedure employed was a modification

TABLE 6

Physical Constants of the 2-Substitutedtetrahydrofurans.

Ether	Boiling Points (°C)	$n_D(T)$	Analysis Calc'd	Found
	114° at 700 mm	1.4217 (19°)	C, 73.62	73.05
			H, 12.36	12.35
	80° at 3 mm	1.5283 (23°)	C, 81.04	80.90
			H, 8.16	8.10
	125° at 695 mm	1.4248 (22°)	C, 74.94	74.54
			H, 12.58	12.43

of the method of Diner and coworkers (71) for the alkylation of hydroxy functions. It involved the addition of one equivalent of sodium hydride to a 1,2-dimethoxyethane (DME) solution of the 1,4-diol containing a 100% excess of the methyl iodide. When the reaction mixture was worked up, the gas liquid chromatogram of the product showed that only one major methylation product (I, Scheme 43) was obtained in the two cases where R' = i-C_3H_7- and t-C_4H_9-.



I II

Scheme 43

An attempt to methylate the 1,4-pentanediol (R' = CH_3, Scheme 43), however, resulted in a mixture of the two possible monomethylation products, I and II, in approximately a 5 to 2 ratio. At first sight it appears that a sufficiently bulky group such as i-C_3H_7 or t-C_4H_9 adjacent to a secondary hydroxyl group directs the reaction with sodium hydride away from the secondary hydroxyl group and causes preferential reaction at the less hindered primary hydroxy group. If a bulky group is not present near one of the hydroxyl groups, then both possible monomethylation products are formed. No dimethylation products were found in any of these cases.

However, the attempted monomethylation of 1-phenyl-1,4-butanediol gave a product mixture which g.l.c. showed to be composed of four substances in nearly equal amounts. These could be the two possible monomethylation products, the dimethylated product and the starting diol, although they were not separated and characterized. This was an unexpected result since the phenyl group is at least as bulky as the isopropyl group (according to the A-values) (24-b). These results lead to the conclusion that another factor must be operative in making the benzylic hydroxyl group as reactive as the primary hydroxyl group. The most reasonable explanation is that the inductive or electron withdrawing nature of the phenyl ring helps to stabilize the anion obtained by removal of the proton from the benzylic hydroxyl group. This increase in its acidity would counterbalance any steric effect which prevents a reaction with the secondary hydroxyl group.

The results of Hine and Hine (72) obtained from a study of the relative acidities of a number of weak acids in isopropyl alcohol solution, using sodium isopropoxide as base, corroborates the findings of the present work. Hine and Hine determined the equilibrium constants for the reaction ROH + $\underline{i}$-$C_3H_7O^{\ominus}$ $\rightleftharpoons$ $RO^{\ominus}$ + $\underline{i}$-C_3H_7OH by optical means using suitable indicators and obtained the constants for the alcohols shown in Table 7.

TABLE 7

Relative Acidities of a Number of Alcohols Determined by $K_{eq.}$ for the Reaction $ROH + \underline{i}\text{-}C_3H_7O^{\ominus} \rightleftarrows RO^{\ominus} + \underline{i}\text{-}C_3H_7OH$ (*) (**)

Alcohol	$K_{eq.}$	Alcohol	$K_{eq.}$
CH_3OH	4.0	$CH_3CH_2CH_2OH$	0.50
$C_6H_5CH_2OH$	3.8	$(CH_3)_2CH\text{-}OH$	0.076 (***)
HOH	1.2	$(CH_3)_3C\text{-}OH$	not measurable but < 0.2
CH_3CH_2OH	0.95		

* Determined in isopropyl alcohol solution.

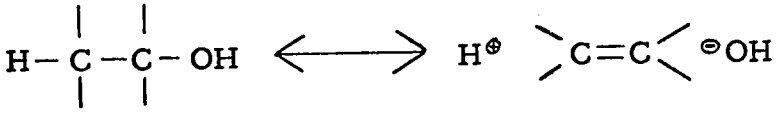
** Taken from the work of Hine and Hine (72).

*** Determined in a separate experiment (72).

It is immediately obvious that benzyl alcohol is nearly as acidic as methanol which agrees with the monomethylation results discussed above. Hine and Hine did not discuss the particular case of benzyl alcohol, but generally explained the observed order of acidity as well as the anomalous value for the acidity of water being less than that of methanol as follows.

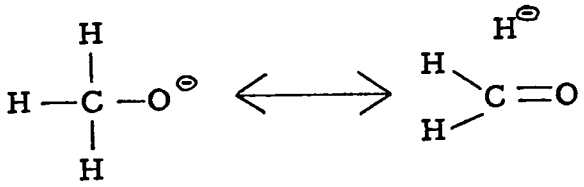
Since the "B strain" hypothesis of Brown and coworkers (35) could not explain the observed order of acidities, Hine and Hine suggested that hyperconjugation might possibly be stabilizing the alcohol relative to the alkoxide anion, thus lowering the alcohol's acidity. In other words the more alkyl substituents there are on

the carbinol carbon (to increase hyperconjugation), the lower is the acidity of the alcohol. Hence, on this basis t-butyl alcohol is less acidic than is ethanol. This is shown in Scheme 44.



Scheme 44

The anomalous acidity of methanol and benzyl alcohol, greater than that of water, was attributed to the complete absence of any possible hyperconjugative stabilization of the alcohol as well as a possible stabilization of the alkoxide anion as shown in Scheme 45.



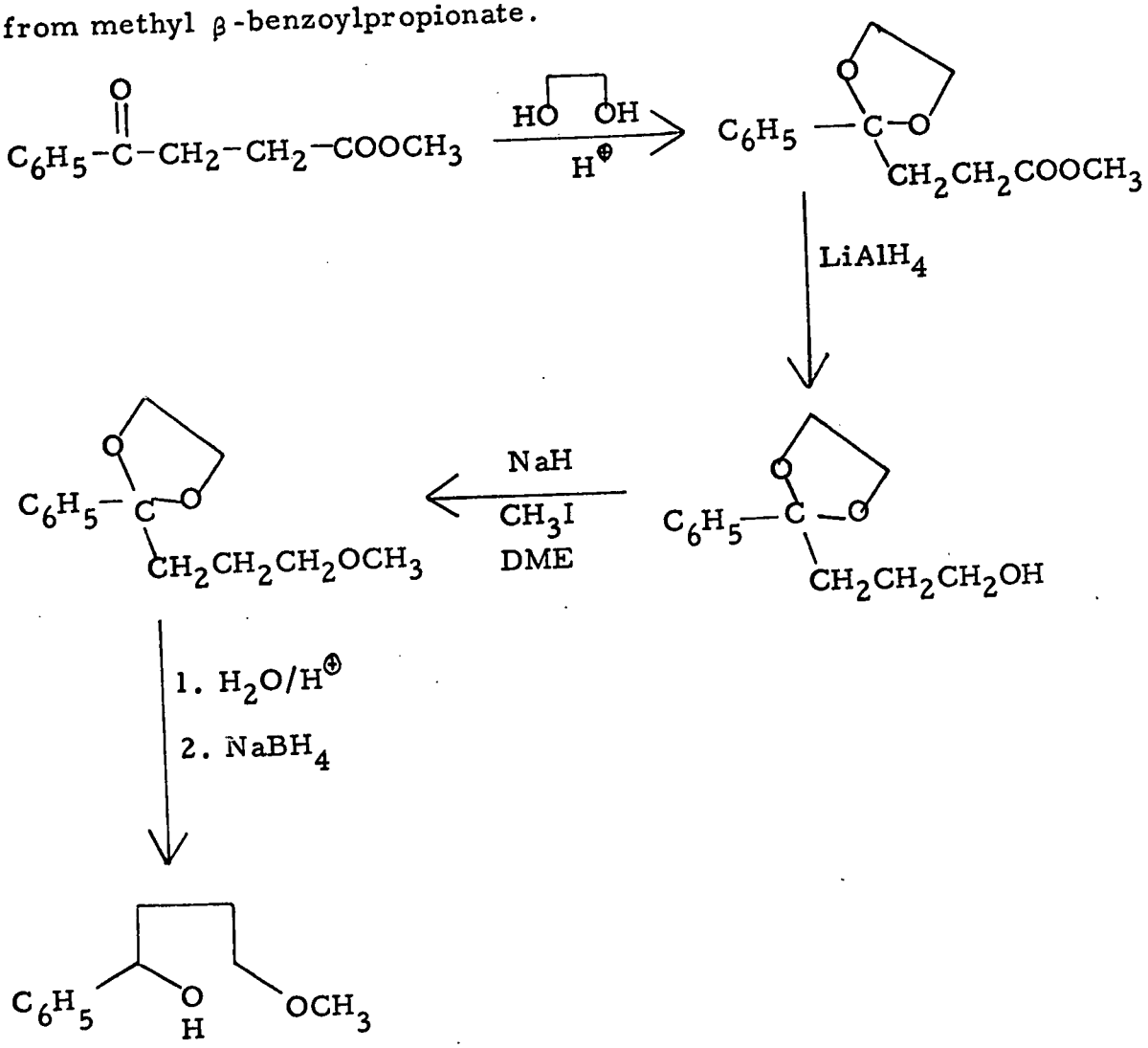
Scheme 45

A better argument than the one of hyperconjugation proposed by Hine and Hine may lie in the inductive effect of the substituents on the carbinol carbon, which can stabilize or destabilize the alkoxide anion. The electron donating methyl groups lower the acidity while an electron withdrawing substituent such as the phenyl ring in benzyl alcohol would increase the acidity.

Whatever the correct explanation, it was obvious that 4-methoxy-1-phenyl-1-butanol could not be prepared in high yield by the selective monomethylation of 1-phenyl-1,4-butanediol. Accordingly the procedure was abandoned.

(b) Attempted preparation of 4-methoxy-1-phenyl-1-butanol from methyl β-benzoylpropionate.

The next reaction sequence proposed for the preparation of 4-methoxy-1-phenyl-1-butanol is shown in Scheme 46 starting from methyl β-benzoylpropionate.



(DME = 1,2-dimethoxyethane)

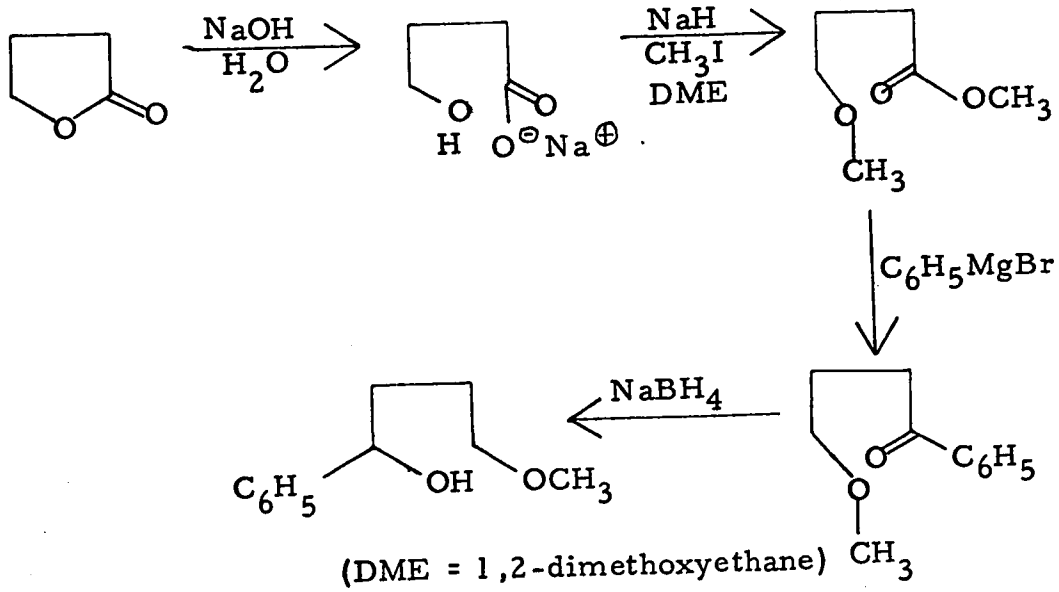
Scheme 46

However, difficulty was encountered in the first step since the formation of the ethylene glycol ketal did not take place. This

was shown by the infrared spectrum of the recovered material which was identical to that of the starting material showing two bands for carbonyl absorptions. No explanation could be proposed for the lack of reaction since Pinder and Smith (73) had been able to prepare the ethylene glycol ketals of acetophenone and a number of substituted acetophenones. Hence the sequence was abandoned.

(c) Attempted preparation of 4-methoxy-1-phenyl-1-butanol from γ-butyrolactone.

The proposed reaction sequence for the preparation of 4-methoxy-1-phenyl-1-butanol from γ-butyrolactone is shown in Scheme 47.

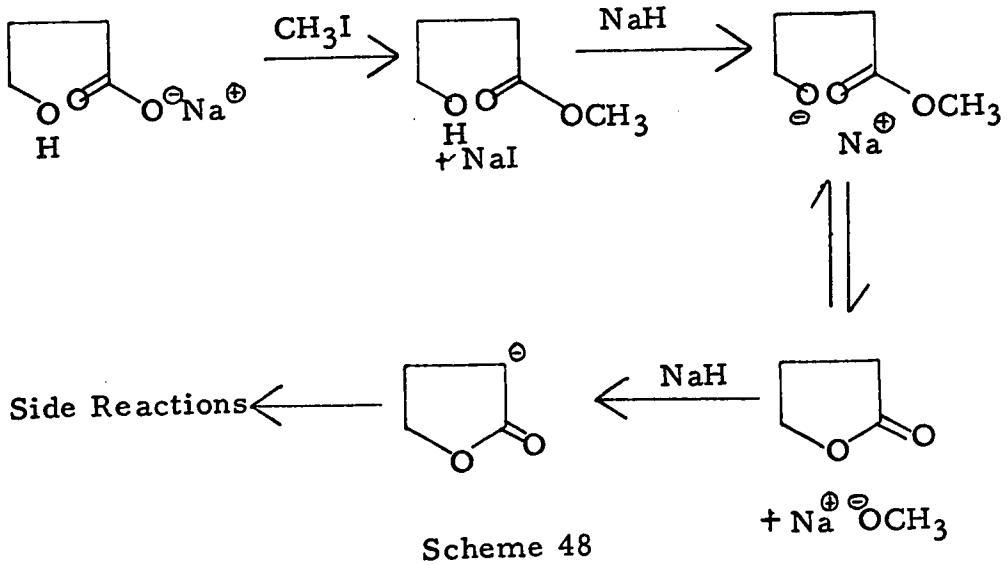


(DME = 1,2-dimethoxyethane)

Scheme 47

The initial formation of the 4-hydroxybutyric acid was reported in the literature (74) and was carried out successfully in the present work. The methylation procedure, however, did not

proceed as proposed since no identifiable material could be isolated readily. A definite explanation was lacking but recyclization to the lactone may have occurred in the presence of methyl iodide. The lactone could then react with sodium hydride resulting in several side reactions, as shown in Scheme 48.

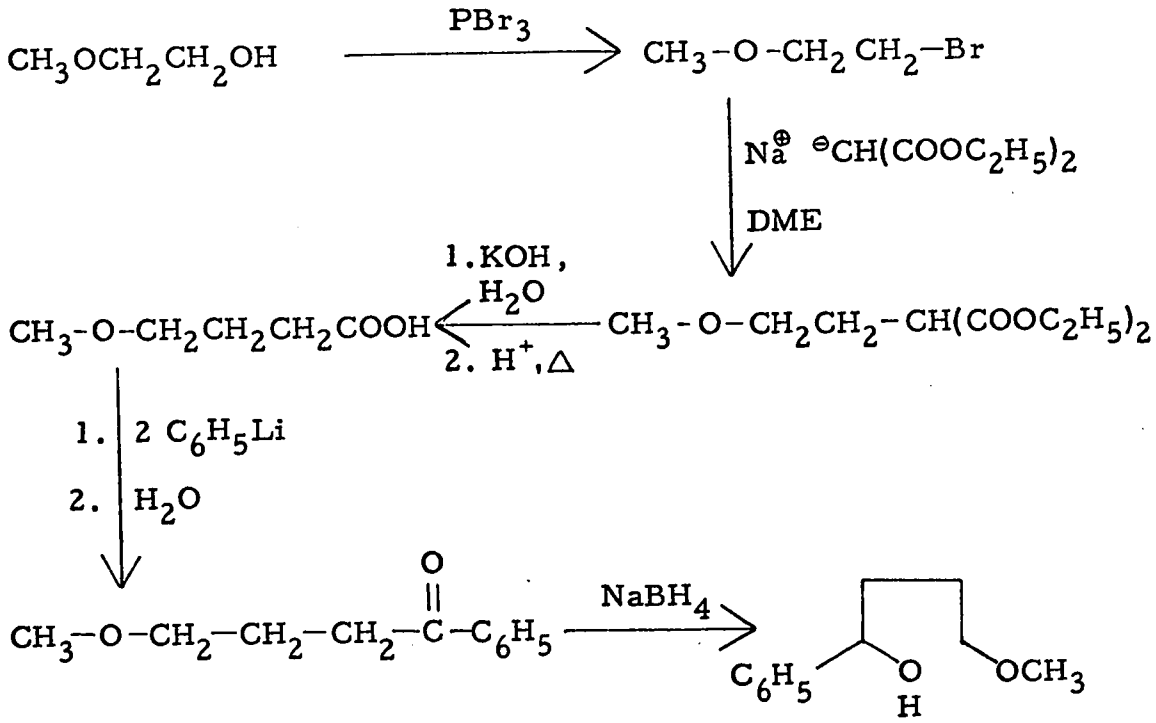


Scheme 48

(d) Preparation of 4-methoxy-1-phenyl-1-butanol from ethylene glycol monomethyl ether.

The synthetic sequence which finally proved to be successful for the preparation of 4-methoxy-1-phenyl-1-butanol is outlined in Scheme 49.

The preparation of 4-methoxybutyric acid was based on the work of Palomaa and Kenetti (75) and all the steps proceeded in good yields. The reaction of the acid with phenyl lithium followed by sodium borohydride reduction gave the desired product.



(DME = 1,2-dimethoxyethane)

Scheme 49

The physical constants of the three hydroxy ethers prepared as described above are listed in Table 8.

3. Synthesis of 4-Benzyloxy- and 4-Aryloxy-1-butanols.

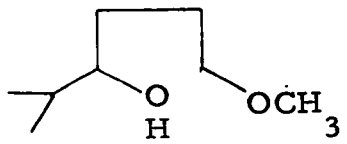
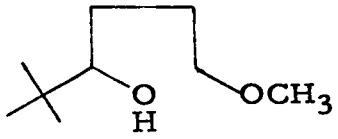
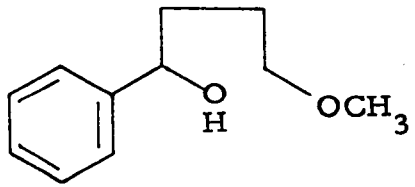
When it appeared that some endo cleavage had occurred during the partial hydrogenolysis of the 2-aryloxytetrahydrofurans, it became necessary to synthesize authentic endo cleavage products. The benzyloxy compound was prepared quite simply but the aryloxybutanols could not be prepared in the same fashion and several attempts were made before a successful synthesis was found.

(a) Preparation of 4-benzyloxy-1-butanol from 1,4-butanediol.

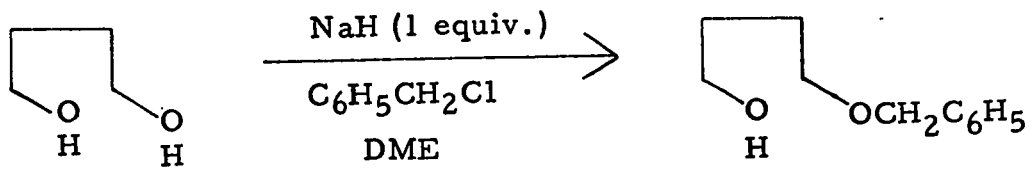
The compound 4-benzyloxy-1-butanol was prepared by the monobenzylation of 1,4-butanediol. This was a modification of the

TABLE 8

Physical Constants of the Authentic Hydroxy Ethers Expected as Hydrogenolysis Products.

Compound	Boiling Point (°C)	$n_D(T)$	Analysis Calc'd	Found
	58° at 1 mm	1.4343 (20)	C, 65.84	65.62
			H, 12.36	12.42
	82-83° at 6 mm	1.4350 (24)	C, 67.45	67.18
			H, 12.58	12.89
	94-95° at 0.1 mm	1.5150 (23)	C, 73.30	73.15
			H, 8.95	8.68

method of Diner and coworkers (71) involving the addition of one equivalent of sodium hydride to the diol in the presence of benzyl chloride as shown in Scheme 50.



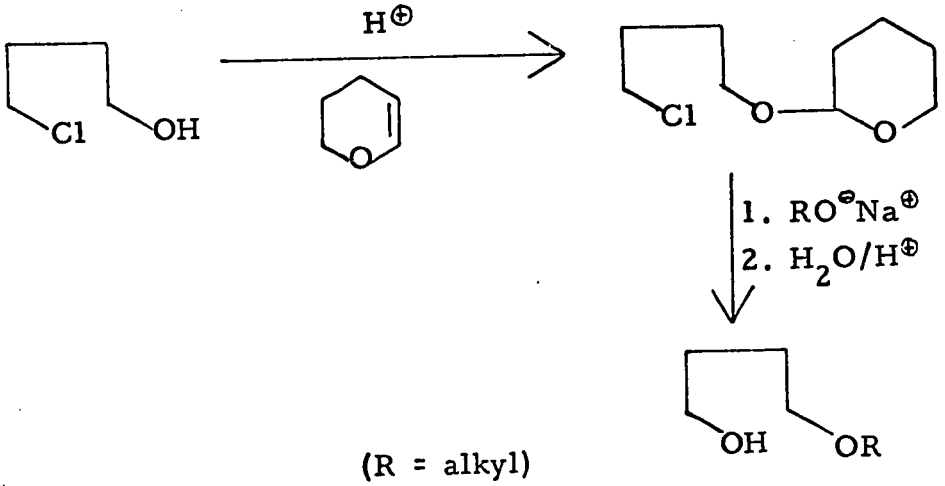
(DME = 1,2-dimethoxyethane)

Scheme 50

The physical constants agreed with those found for the same compound by Eliel and coworkers (4) (Table 8).

(b) Attempted synthesis of 4-aryloxy-1-butanols from 4-chloro-1-butanol.

Two procedures starting with 4-chloro-1-butanol were attempted for the synthesis of the 4-aryloxy-1-butanols neither of which proved to be successful. The first was that used by Eliel and coworkers (4) and by Miss Makhubu (5) to prepare the 4-alkoxy-1-butanols and is outlined in Scheme 51.

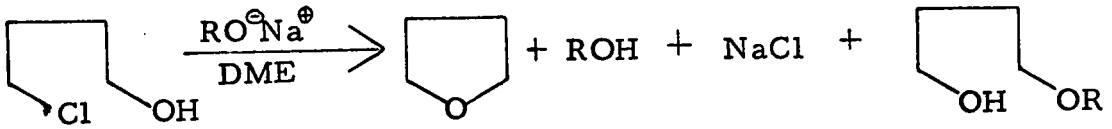


(R = alkyl)

Scheme 51

Although Miss Makhubu was able to get small amounts of the 4-alkoxy-1-butanols by this method, only a very bad mixture of products was found on g.l.c. analysis of the product mixture, when sodium phenoxide was used as the nucleophile.

The second procedure, using 4-chloro-1-butanol, involved a direct reaction between sodium phenoxide and 4-chloro-1-butanol as shown in Scheme 52.



(R = aryl)

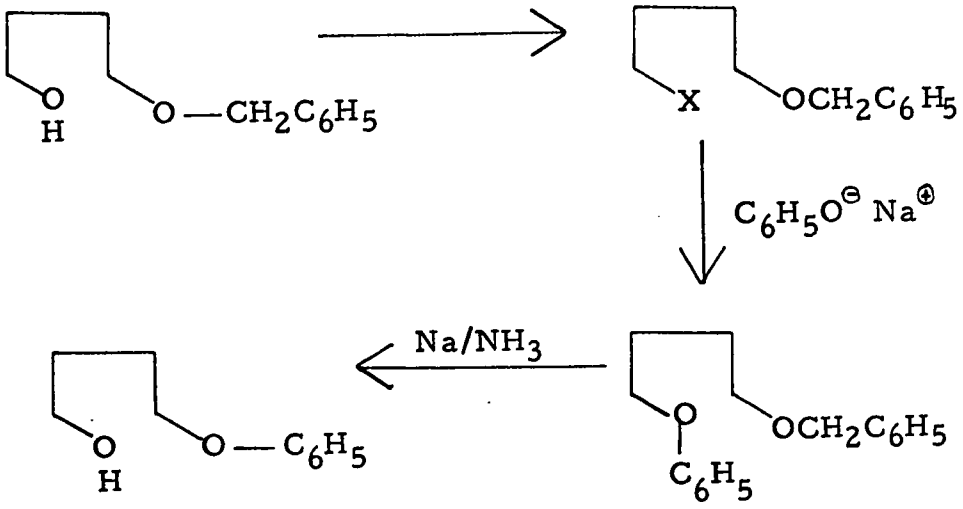
(DME = 1,2-dimethoxyethane)

Scheme 52

Gas liquid chromatography of the products obtained from the reaction showed that only a small amount of the hydroxy ether was formed. Hence, this was also an unsatisfactory method. A reaction seemed to have taken place since sodium chloride had formed, but the reaction could have been a cyclization to form tetrahydrofuran in the presence of a base. Phenol was, in fact, found in reasonable yields (by g.l.c.) but any tetrahydrofuran which may have been formed was no doubt lost during the elimination of 1,2-dimethoxyethane solvent in the isolation procedure. This sequence was abandoned without further study.

(c) Attempted preparation of 4-aryloxy-1-butanols from 4-benzyloxy-1-butanol.

The conversion of the 4-benzyloxy-1-butanol to the chloro, bromo or tosyl compounds followed by condensation with sodium phenoxide was another attempt to prepare the 4-aryloxy-1-butanols. The benzyl group would then be removed by reductive cleavage with sodium in liquid ammonia as shown in Scheme 53.



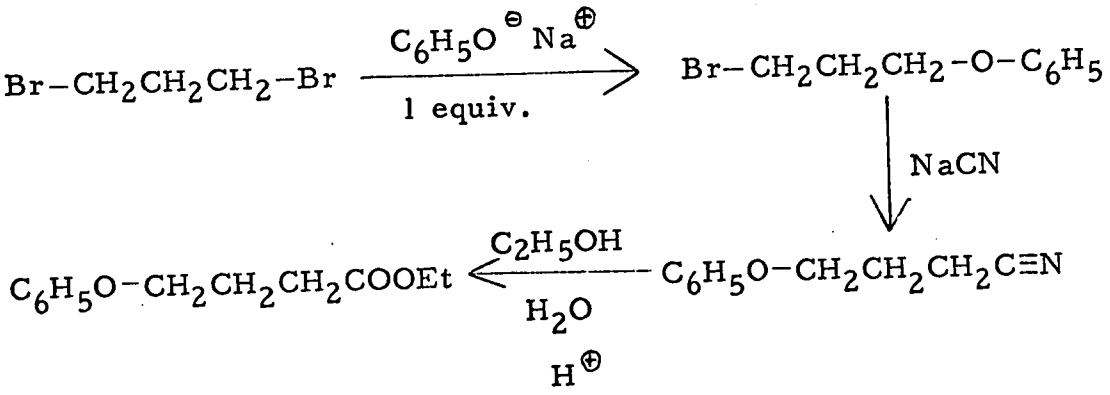
Scheme 53

Difficulty was encountered at the first step of the substitution of the hydroxyl group by bromine since the use of PBr_3 resulted in the production of sufficient acid to cleave the benzyl ether function. The odor of benzyl bromide was clearly apparent. The method of Hooz and Gilani (76) was therefore used to prepare the chloride in a 68% yield but the subsequent reaction with sodium phenoxide was unsuccessful. Similarly, the tosylate was prepared in 81.5% yield but the reaction with sodium phenoxide did not yield any of the

desired product. This procedure was therefore abandoned.

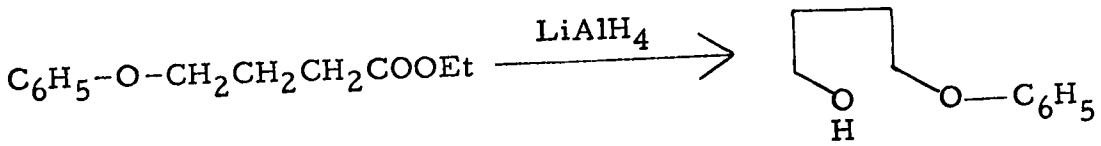
(d) Successful preparation of the 4-aryloxy-1-butanols from 1,3-dibromopropane.

Marvel and Tanenbaum (77) in 1922 reported the preparation of ethyl 4-phenoxybutyrate from 1,3-dibromopropane as shown in Scheme 54.



Scheme 54

The ester produced in this fashion was then reduced using $LiAlH_4$ giving the desired 4-phenoxy-1-butanol as shown in Scheme 55. The complete series of 4-aryloxy-1-butanols was prepared in this way starting with the other substituted phenols.

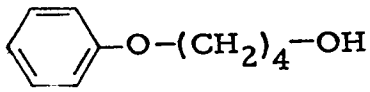
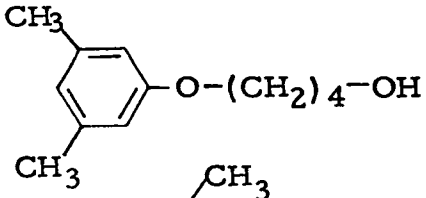
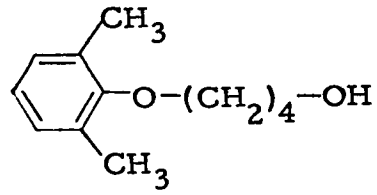
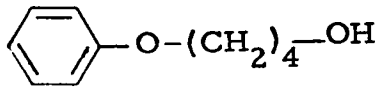


Scheme 55

The physical constants of the authentic 4-benzyloxy- and 4-aryloxy-1-butanols are listed in Table 9.

TABLE 9

Physical Constants of the Authentic 4-Benzyloxy- and 4-Aryloxy-1-butanols.

Compound	Boiling Point (°C)	$n_D(T)$	Analysis	Calc'd	Found
$C_6H_5CH_2O-(CH_2)_4-OH$	105° at 0.4 mm	1.5105 (20)	C,	73.30	73.13
	[116° at 4 mm] *	[1.5130 (25)] *	H,	8.95	8.84
	100-102° at 0.6 mm	1.5260 (22)	C,	72.26	71.94
			H,	8.48	8.73
	120-123° at 0.8 mm	1.5205 (22)	C,	74.19	74.45
			H,	9.34	9.42
	116-118° at 0.9 mm	1.5136 (22)	C,	74.19	74.19
			H,	9.34	9.05
	110-111° at 0.07 mm	1.5380 (22)	C,	51.08	51.12
			H,	5.15	5.32
			Cl,	30.16	30.44

* Figures in parentheses are taken from the work of Eliel and coworkers (4).

E. Hydrogenolysis of the Tetrahydrofuranyl Acetals.

The first hydrogenolyses of the present work were carried out following the procedure described by Leggetter and Brown (1) and used by Miss Makhubu (5). This method involved a prior mixing of the acetal with one molar equivalent of $LiAlH_4$ in an ether solution followed by the dropwise addition of an ether solution of one molar equivalent of $AlCl_3$. As noted by Diner, Davis and Brown (16), this procedure results in the acetal coming into contact first with the AlH_3 species. However, the AlH_3 reacts only slowly with the acetal and it is quickly converted to $AlClH_2$ when the full molar equivalent of $AlCl_3$ is added. Hence, it is the $AlClH_2$ species which causes most if not all of the reduction.

Shortly after the start of this work, a second hydrogenolysis procedure was adopted. This gave results identical to those obtained from the first method but was preferred since it allowed only one aluminum species to be present throughout the reaction. This second method as described by Diner (7) involved a prior mixing of equimolar amounts of $LiAlH_4$ and $AlCl_3$ in dry ether to form the $AlClH_2$ species. The acetal was then added dropwise to this aluminum hydride solution.

Reduction of the 2-aryloxytetrahydrofurans proved to be an extremely fast reaction, being complete within 10 minutes. It is possible that some of this reduction may have been caused by the AlH_3 when the first method was used since AlH_3 does provide a

substantial amount of reduction if the substrate is very reactive. Although there was no difference in the products formed from the two procedures, the second procedure ensured that only $AlClH_2$ was the reducing species. Another advantage to the second procedure was that the two vigorous reactions of the mixed hydride formation and the acetal reduction were not occurring at the same time. Hence, the acetal could be added to an excess of the reducing species in a shorter time than was possible for the addition of the $AlCl_3$ solution to the $LiAlH_4$-acetal solution.

The work-up procedure was also slightly modified from that used by Leggetter and Brown (1) and Makhubu (5). Instead of the addition of an excess of water followed by a continuous extraction of this aqueous solution for six to twelve hours, a small amount of 15% aqueous potassium hydroxide was added slowly until a white, flaky precipitate separated. The formation of this white lithium aluminate ($LiAlO_2$) had previously been found to be a preferred method for working up $LiAlH_4$ reduction reactions (78). The precipitate then was simply separated by filtration and the ether removed by fractional distillation giving yields of recovered material of between 80 and 100%.

Since small amounts of acetal were usually used in the reduction, the product mixtures were analyzed by gas liquid chromatography, comparing the retention times of the products with those of authentic materials. If there was ever any doubt as to the identity of a compound, it was isolated by preparative g.l.c.,

not by distillation, and its spectra and physical constants compared to those of authentic material. However, little difficulty was ever encountered in identifying the hydrogenolysis products from the tetrahydrofuranyl acetals since there were at most only three possible cleavage products if the reduction went in the normal fashion. In all cases only two or three products were found after reduction. Difficulty arose only in the case of the 2-aryloxytetrahydrofurans where a rearrangement was found to occur under certain conditions. A similar rearrangement was not found for any of the acetals with C-2 alkoxy substituents.

The relative peak areas of the hydrogenolysis products found on g.l.c. were used to determine the product ratios, with no corrections applied. The difference in peak size for equimolar amounts of two hydrogenolysis products was checked in a number of cases using equimolar amounts of the two authentic hydrogenolysis products (for example, tetrahydrofuran and phenol from 2-phenoxytetrahydrofuran). In the cases checked, there was found to be at most a 10% variation in peak size and normally the variation was within 5%. Hence, correction of the peak size to give a more exact indication of the molar ratios of products was not necessary.

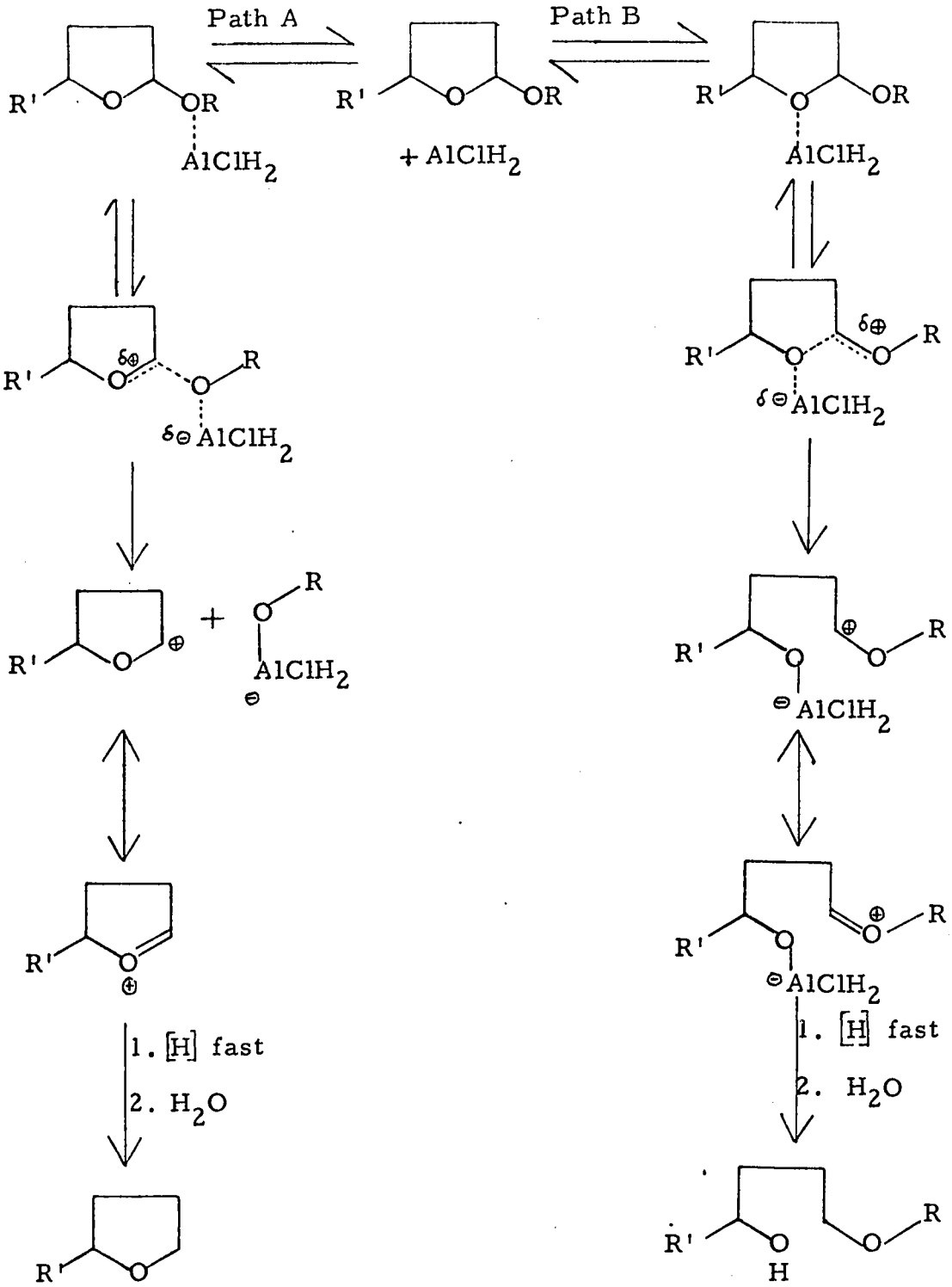
The mechanistic scheme used by Miss Makhubu (5) to rationalize the results of the reduction of the tetrahydrofuranyl acetals was based on the mechanism proposed by Leggetter and Brown to explain the hydrogenolysis of 1,3-dioxolanes (1). The

same mechanism was also used by Diner and Brown (3) to explain the hydrogenolysis of the tetrahydropyranyl acetals. It is shown in Scheme 2 (n = 1 or 2). One modification to this scheme is included in the mechanism to be used in the present work. This involves consideration of a transition state between the complexation of the aluminum species with the acetal and the carbonium ion formation. The mechanistic scheme incorporating the transition state or activated complex is shown in Scheme 56.

The transition state is depicted with a partial bond being formed between the oxygen and aluminum and a partial bond being broken between the oxygen and carbon. The adjacent oxygen is also shown to be assisting in the stabilization of the positive charge being formed.

That the transition state was important in explaining the hydrogenolysis results was pointed out by Eliel and coworkers (4) as a modification to the mechanism of Leggetter and Brown (1). The energy profile for the two possible paths of reduction of the tetrahydropyranyl acetals proposed by Eliel and coworkers (4) is shown in Figure 1.

Positions I and I' correspond to the intermediate oxocarbonium ions while T_i and T_i' correspond to the transition states leading to I and I' respectively. In Figure 1, the relationship of T_i being of lower energy than T_i' will hold when R is a relatively strong electron donating group such as i-C_3H_7 or t-C_4H_9.



Scheme 56

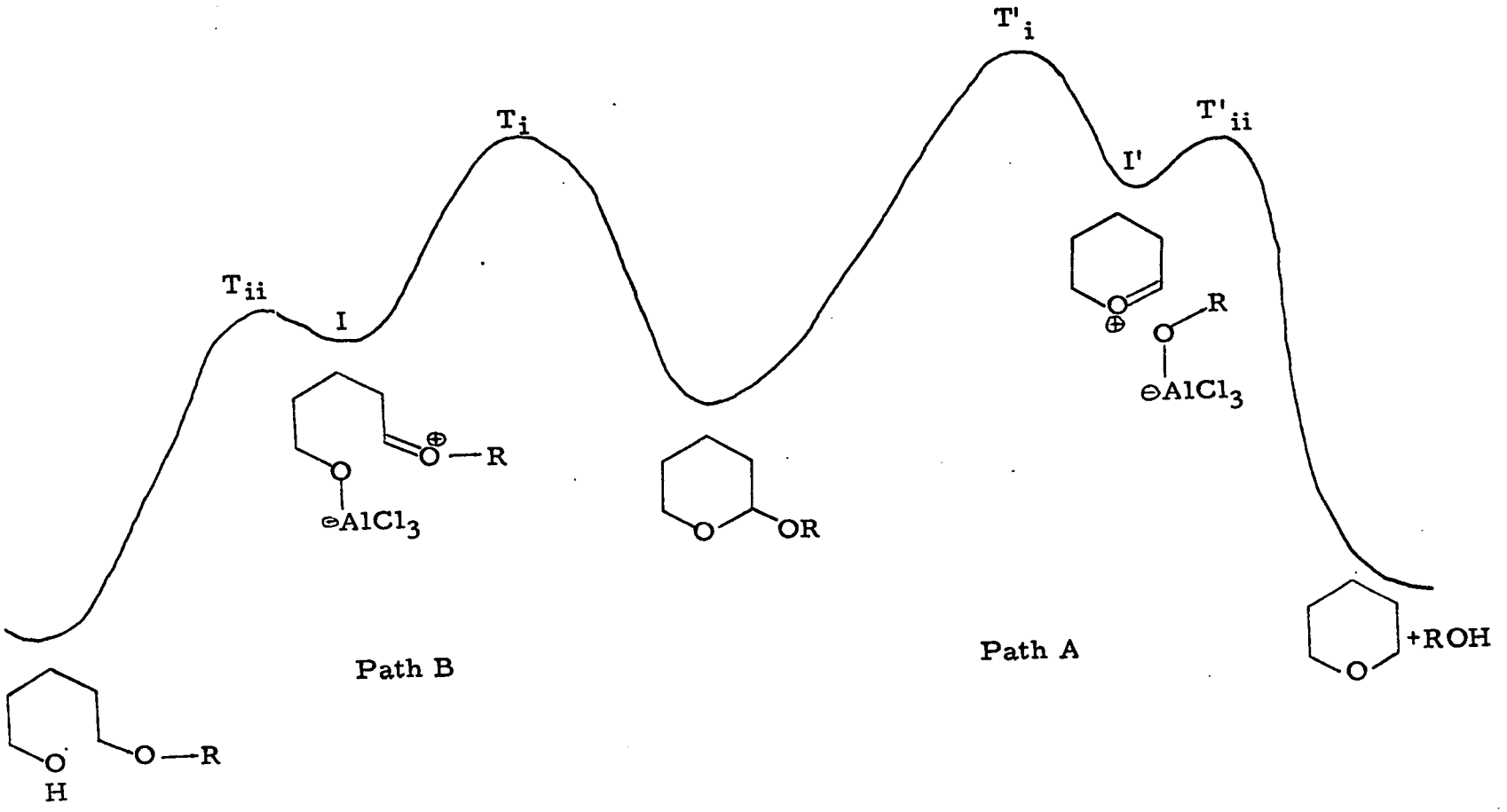


Figure 1. Energy profile for the reductive cleavage of tetrahydropyranyl acetals as proposed by Eliel and coworkers (4).

Since 1965, when Eliel and coworkers (4) proposed the energy profile diagram, some new information has been obtained by various workers which requires a modification of this diagram if it is to represent all of the known facts. These points are listed here:

(i) Leggetter and Brown have found that the rate of reduction of the carbonium ion from 2,4-dimethyl-1,3-dioxolane was much faster than the rate of isomerization (and presumably therefore, of the cyclization of the acetal (19). There should be very little difference in the steric approach of the hydride to the carbonium ions formed from the tetrahydrofuranyl acetals and the 1,3-dioxolanes because of their similar structure. Hence, the results of the fast reduction of the 1,3-dioxolanes may be extrapolated to apply to the reduction of the tetrahydrofuranyl acetals. The transition state T_{ii} is therefore a very low energy transition state compared to T_i and similarly, T_{ii}' should be at a lower energy state than is T_i'.

(ii) Diner and Brown (3) and Makhubu (5) have proposed a fast initial complex formation between the acetal and the aluminum species which can easily decompose to the starting materials without producing the intermediate oxocarbonium ion. This is substantiated in the studies of the basicities of ethers which have shown that both cyclic and acylic ethers can form complexes with BF_3 (26), protons (27) and $SnCl_4$ (32). Hence, the complex between the acetal and the aluminum species should be included in the energy

profile diagram as a low energy intermediate with only a low energy of activation required for its formation.

(iii) These basicity studies (26, 27, 32) have shown that the tetrahydrofuran oxygen is more "basic" than is the oxygen atom of the acyclic ethers. This, therefore, requires that the intermediate complex at the ring oxygen be of lower energy with a lower energy of activation for its formation than is required for the corresponding complex at the exo oxygen.

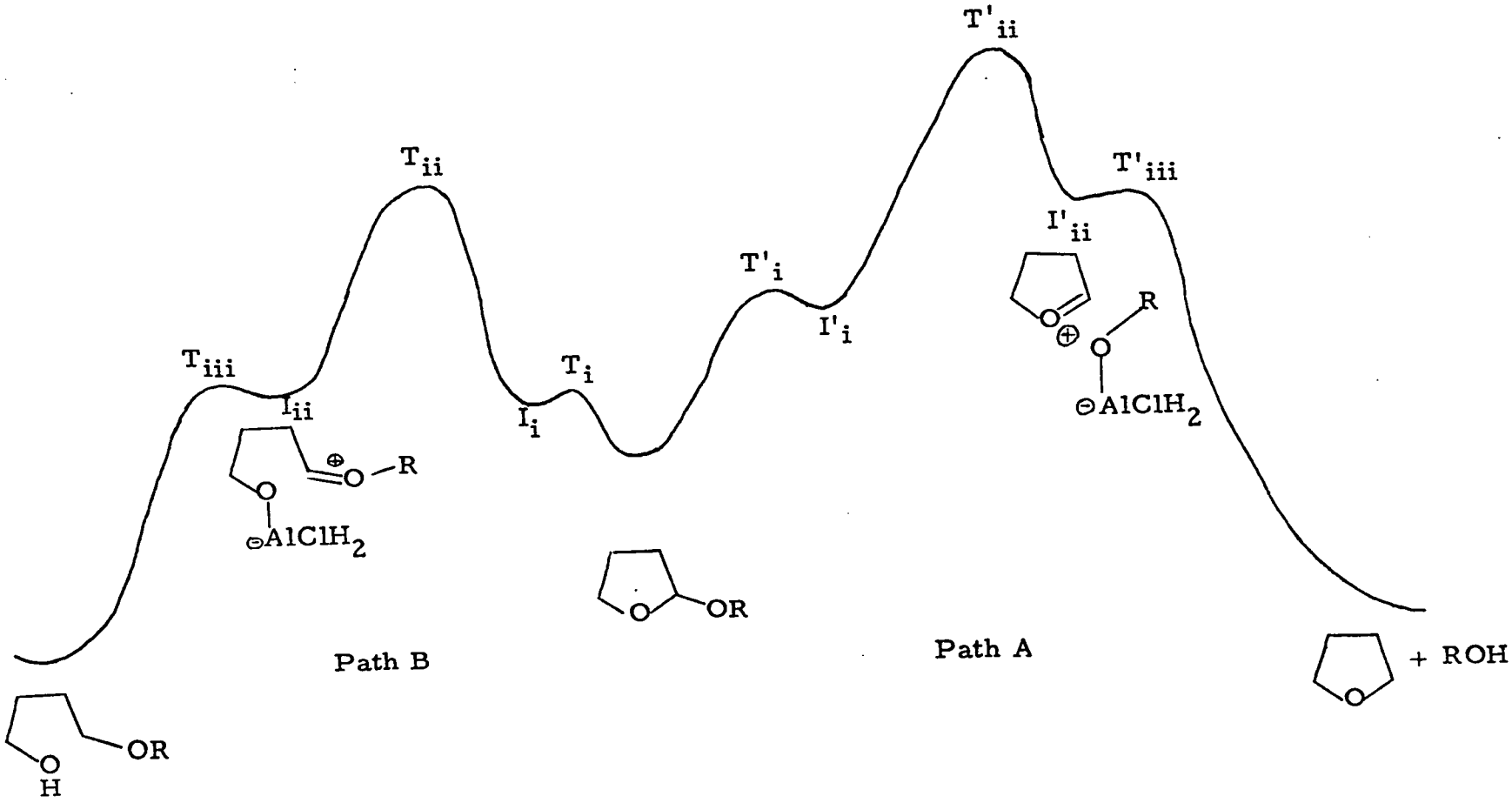
(iv) It may also be postulated that the stronger complex formation at the ring oxygen will result in a more advanced state of breaking of the $C_2 - O_1$ bond. Hence, the stronger the complex formation, the lower is the energy of the transition state leading to the oxocarbonium ion. The postulation is substantiated in the present work. A strong complex formation between $AlCl_3$ and the 2-aryloxytetrahydrofurans sufficiently lowers the transition state energy to oxocarbonium ion formation, that a very fast cleavage of the acetal takes place. It is likely that a strong complex formation stretches the C-O bond to such an extent that very little energy is required to complete cleavage of the bond.

(v) Ashby and Prather (6) have shown that the reducing species involved in the reductions using equimolar ratios of $LiAlH_4$ and $AlCl_3$ is $AlClH_2$. This aluminum species is therefore the Lewis acid as well as the reducing species in the hydrogenolyses carried out in the present work. Eliel and coworkers (4) used a

4 to 1 molar ratio of $AlCl_3$ and $LiAlH_4$ which would result in a 4 to 1 ratio of $AlCl_2H$ and $AlCl_3$ in the reaction solution. Hence, some of the carbonium ion formation, as indicated in their energy profile diagram, may have been caused by $AlCl_3$ alone.

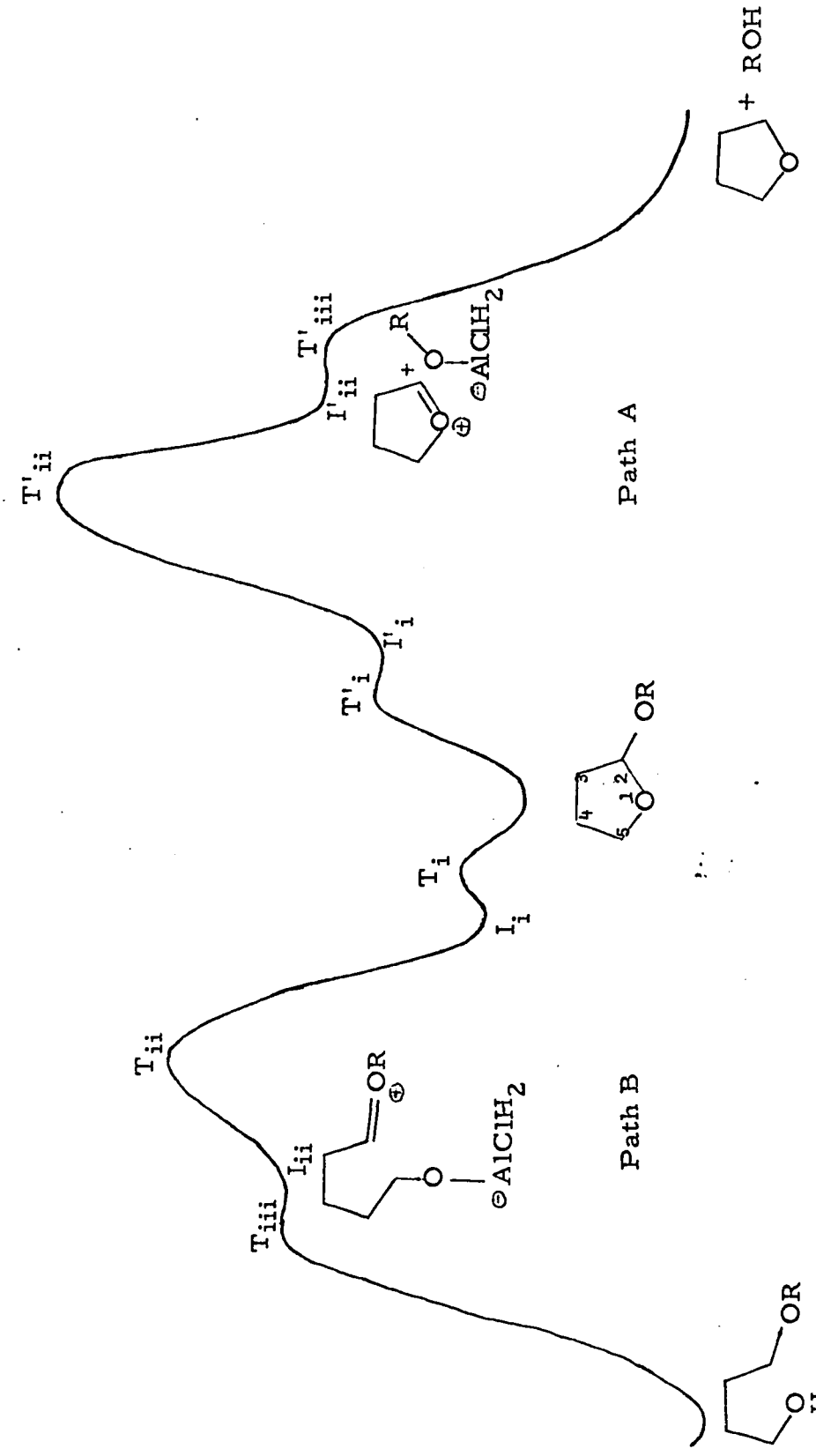
These facts are incorporated in the energy profile diagram shown in Figure 2 where R = t-C_4H_9 or i-C_3H_7. The two possible paths of cleavage shown in Figure 2, path A and path B, correspond to path A and path B in the mechanistic sequence outlined in Scheme 56 (R' = H). Path B is implied to be the most favorable direction of cleavage with the lowest energy intermediates. This would be expected for all cases in which the substituent R is an alkyl group, since Miss Makhubu found exclusive ring cleavage for all of the 2-alkoxytetrahydrofurans. However, the energy diagram in Figure 2 is suitable only for the hydrogenolysis of the 2-alkoxy-tetrahydrofuran when R = t-C_4H_9 or i-C_3H_7. The case of R = CH_3 is shown in Figure 3.

When R = CH_3, I_{ii} should be of higher energy than I_{ii}'. This is a result of the smaller inductive effect of the methyl group stabilizing the oxocarbonium ion from endo cleavage compared to the stabilizing effect of the ethyl residue (C_4-C_5) of the ring on the oxocarbonium ion from exo cleavage. In this latter case of R = CH_3, it is the strong complex formation at the ring oxygen which sufficient-ly lowers the energy of T_{ii} relative to T_{ii}' allowing only I_{ii} to be formed. This is shown in Figure 3.



(R = t-C_4H_9 or i-C_3H_7)

Figure 2. Energy profile for the reductive cleavage of 2-alkoxytetrahydrofurans when R = i-C_3H_7 or t-C_4H_9.



(R = CH_3)

Figure 3. Energy profile for the reductive cleavage of 2-methoxytetrahydrofuran.

The relative energies of the various intermediates will obviously be different for other molecules and the two energy diagrams included here are only for the cases specified.

Except for the added details, there is very little difference between the mechanism outlined in Scheme 56, and that of Leggetter and Brown (1) shown in Scheme 1. The main difference arises from the realization that it is the rate of attaining the transition states T_{ii} and T_{ii}', and not the rate of formation of the oxocarbonium ion which determines the rate and direction of reaction. The relative energies required to approach the two possible transition states determine which direction of cleavage, either exo or endo, will take place. This is really only a difference in terminology since from the Hammond postulate (79) the intermediate oxocarbonium ions, being relatively unstable intermediates, closely reflect the energies of the corresponding transition states. Hence, when the rate of formation of either the oxocarbonium ion intermediate or the transition state is discussed, the rate of formation of the other is automatically implied.

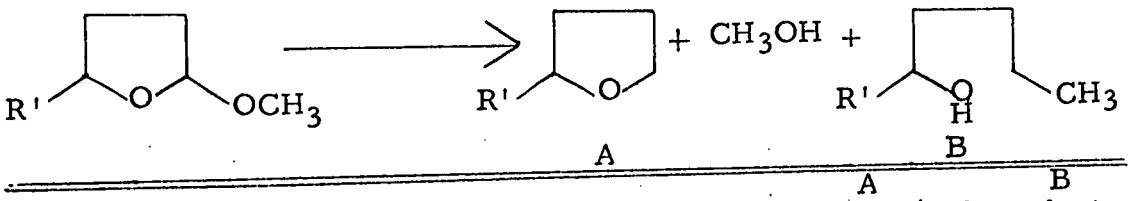
1. Hydrogenolysis of cis-trans Mixtures of the 5-Substituted-2-alkoxytetrahydrofurans.*

Miss Makhubu synthesized and hydrogenolyzed the 5-methyl- and 5-methoxymethyl-2-methoxytetrahydrofurans to determine what effect the substituents at C-5 of the tetrahydrofuranyl acetals would have on the direction of hydrogenolysis. The results are summarized in Table 10.

* In all cases, cis-trans mixtures of the acetals were hydrogenolyzed.

TABLE 10

Hydrogenolysis of cis-trans Mixtures of the 5-Substituted-2-methoxy-tetrahydrofurans with a 1 to 1 Mixture of $LiAlH_4$ and $AlCl_3$.*



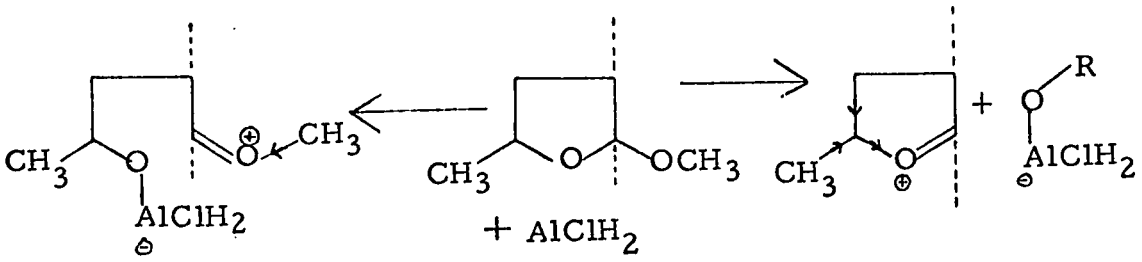
R'	Reduction Time(hr)	Recovery (%)	A as % of product	B as % of product
CH_3	$2\frac{1}{4}$	80	60	40
CH_3-O-CH_2-	$2\frac{1}{4}$	93	0	100

*Taken from the work of Miss Makhubu (5).

The introduction of a methyl group at C-5 resulted in 60% side chain cleavage and only 40% ring cleavage, in contrast to the 100% ring cleavage found for the unsubstituted 2-methoxytetrahydrofuran (5). The increase in exo cleavage could be attributed to both the steric and polar effects of the methyl group. It could be sterically shielding the ring oxygen from complexation with the aluminum species, an explanation similar to that given for the lower basicity of the 2-methyl- and 2,5-dimethyltetrahydrofuran compared to that of tetrahydrofuran (27, 32).

The polar effect can best be explained using the method of Diner (7) which divides the acetal through the anomeric center and considers the inductive contributions of the substituents stabilizing

the two possible carbonium ions. This is shown in Scheme 57.

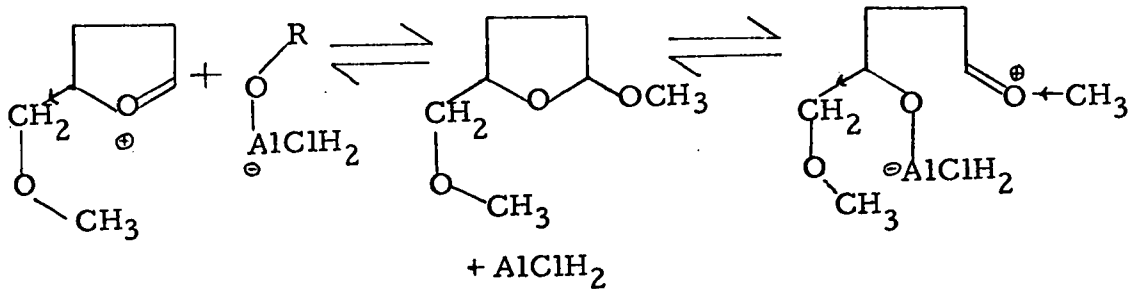


B Scheme 57 A

The oxocarbonium ion resulting from endo cleavage (Scheme 57-B) is stabilized by the inductive effect of only a methyl group. On the other hand, there is effectively an isopropyl group stabilizing the oxocarbonium ion from exo cleavage (Scheme 57-A). Inductive effects are considered to be effective over a distance no greater than two carbon atoms along a chain. The strong basicity of the ring oxygen even though slightly decreased by the methyl substituent (27, 32) still results in the formation of some endo cleavage product. This occurs in spite of the higher stability predicted for the carbonium ion from exo cleavage.

In an attempt to differentiate between steric and polar effects, the 5-methoxymethyl-2-methoxytetrahydrofuran was hydrogenolyzed by Miss Makhubu and found to give exclusively ring cleavage (Table 10). The methoxymethyl group should present at least as great a steric bulk as the methyl group. Hence, if the substituents at C-5 were sterically directing the reaction, similar results would be expected for the 5-methyl- and 5-methoxymethyl-2-methoxytetrahydrofurans. This obviously was not the case.

However, the polar effect of the electron withdrawing methoxymethyl group can explain the results. Again using Diner's method described above, the oxocarbonium ion from exo cleavage (Scheme 58-A) is destabilized relative to the oxocarbonium ion from endo cleavage (Scheme 58-B). On this basis endo cleavage is favored by the C-5 methoxymethyl group, and this is precisely what is observed.



Scheme 58

Miss Makhubu's results from these two hydrogenolyses pointed to a polar effect of the substituents at C-5 directing the course of hydrogenolysis. However, she was not able to synthesize and study the hydrogenolysis of any of the acetals possessing a more bulky substituent at C-5.

In the present work, cis-trans mixtures of the three new acetals were synthesized, having respectively the isopropyl, t-butyl and the phenyl groups at C-5. These new acetals were hydrogenolyzed. As well, the

hydrogenolysis was repeated on those two compounds reported by Miss Makhubu. The results are shown in Table 11.

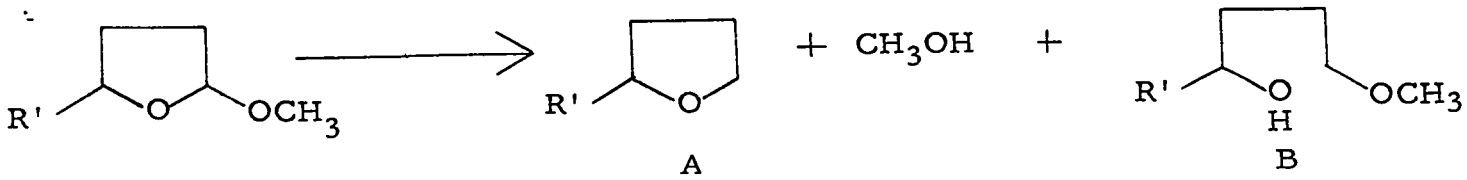
The results in Table 11 clearly show that as the size of the substituent at C-5 increases through the series R' = CH_3, i-C_3H_7, t-C_4H_9, the amount of exo cleavage increases from 60 to 86 to over 99%. This gradient towards more side chain cleavage as the substituent increases in size can be explained in terms of either a steric or a polar effect of the substituent, or by both effects operating together.

The steric shielding of the ring oxygen atom by the substituent on C-5 may force the complex formation and subsequent reduction to take place at the exo carbon-oxygen bond. This would be expected to increase as the size of the substituent group increases and the observed results are in agreement with this explanation.

An explanation similar to that given using Diner's method in Scheme 56 for the polar effect of the C-5 methyl group can be formulated for the C-5 i-C_3H_7 and t-C_4H_9 groups. Both of these groups are electron donating and will stabilize the oxocarbonium ion formed from exo cleavage. Since the inductive effect of the substituents should increase in the order of CH_3 < i-C_3H_7 < t-C_4H_9, there should be a corresponding increase in the stabilization of the oxocarbonium ion formed from exo cleavage (Structure 5). This would result in an increase in exo cleavage when the C-5 substituent (R', Structure 5) was changed from CH_3 to i-C_3H_7 to t-C_4H_9. This is also in agreement with the observed results.

TABLE 11

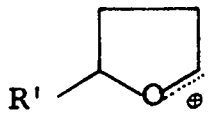
Hydrogenolysis of cis-trans Mixtures of the 5-Substituted-2-methoxytetrahydrofurans with an Equimolar Mixture of $LiAlH_4$ and $AlCl_3$.



A B

R'*	Time (hours)	Recovery %	A	B**	% Reduced
i-C_3H_7	2	90	86	14	100
t-C_4H_9	2	80	>99	trace	62
	8	95	>99	trace	100
C_6H_5	2	92	15.7	84.3	85
	48	90	15.5	94.5	100
CH_3OCH_2	2	85	6.5	93.5	100
CH_3	2	80	62.5	38.5	100

*All of the compounds were cis-trans mixtures and their spectra indicated that the two isomers were present in the ratio of from 2 to 3 (3 to 2) to 1 to 1.
**A and B represent the relative amounts of reduced material in %.



Structure 5

Since both effects would operate in the same direction, it is possible that both are operating simultaneously in the C-5 alkyl substituted acetals. However, the above information does not indicate which effect is predominant or whether one of them can be eliminated.

Additional information was provided by the following observations. When the hydrogenolysis of 5-methoxymethyl-2-methoxytetrahydrofuran was repeated in the present work, 6.5% exo cleavage was found. This was a slight change from the results of Miss Makhubu who reported exclusive endo cleavage. However, this was only a minor change and endo cleavage still predominated to an extent of 93.5%. A repetition of the hydrogenolysis of 5-methyl-2-methoxytetrahydrofuran confirmed the 60 to 40 exo to endo cleavage ratio found by Miss Makhubu when 62.5% exo and 37.5% endo cleavage was found.

The phenyl group at C-5 also exerts an electron withdrawing effect but is of greater bulk than is the C-5 methoxymethyl substituent. The A values, determined in the cyclohexane system, are 2.1 to 3.0 kcal/mole for a phenyl group and 1.8 to 2.5 kcal/mole for an isopropyl group (24-b). This indicates that the phenyl group has a steric effect at least as large if not larger than that of

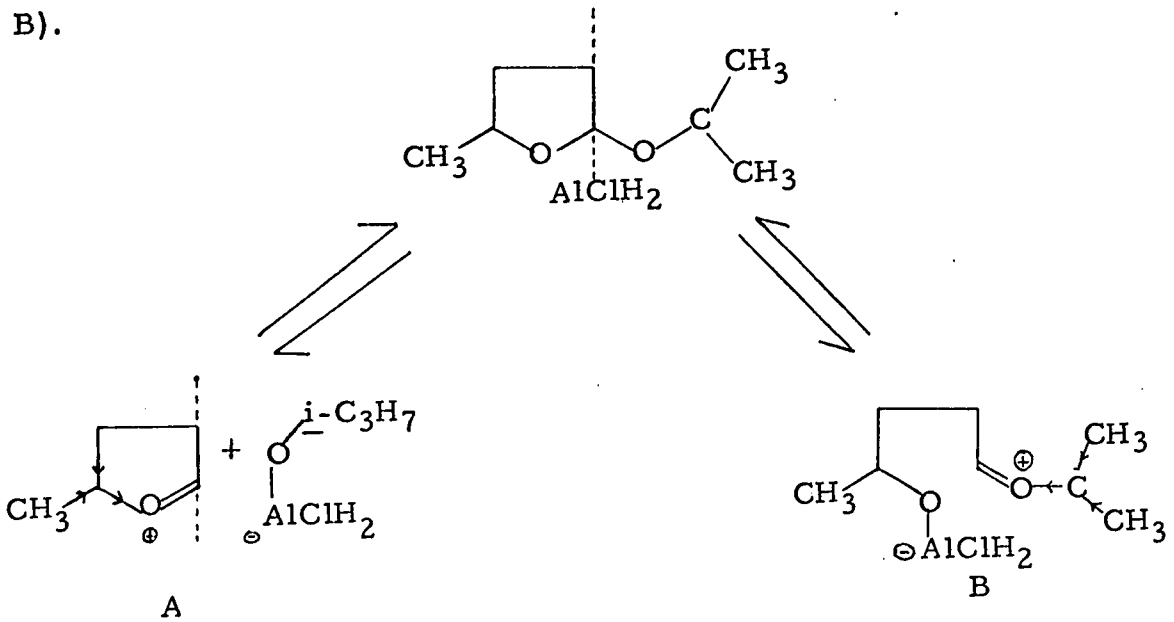
the isopropyl group. If the reductive cleavage is being directed by the steric effect of the C-5 substituents, then both the 5-isopropyl-2-methoxytetrahydrofuran and 2-methoxy-5-phenyltetrahydrofuran should be hydrogenolyzed in the same direction. However, if a polar effect is operative, then, since the isopropyl group is electron donating while the phenyl group is electron attracting, the former compound should experience preferential exo cleavage while the latter should show preferred endo C-O bond cleavage.

When 2-methoxy-5-phenyltetrahydrofuran was hydrogenolyzed, an 84.5% yield of endo cleavage product was found, just the opposite direction of cleavage as was found for the 5-isopropyl-2-methoxytetrahydrofuran (Table 11). Hence, as in the case of the C-5 methoxymethyl and C-5 methyl acetals, this requires that the predominating influence which determines the direction of hydrogenolysis is the polar effect rather than the steric effect of the C-5 substituent.

Although the polar effect seems to be the principal directing influence, the steric effect must be playing some role in directing the reaction. This was concluded from the observation that some exo cleavage product was found in the hydrogenolysis mixture of both the 5-methoxymethyl-2-methoxytetrahydrofuran and 2-methoxy-5-phenyltetrahydrofuran. The strong basicity of the ring oxygen, the electron withdrawing nature of the C-5 substituents and the possibility of association of the aluminum species with the

C-5 substituent all favor endo cleavage. Therefore, there is only one possible explanation for the presence of some exo cleavage. That is, that the steric bulk of the substituent must be sufficient to force 6.5% of the aluminum complexation and subsequent cleavage to involve the exo oxygen in the case of the C-5 methoxymethyl acetal, and 15.5% in the case of the C-5 phenyl acetal. The steric and polar effects of the C-5 substituent are therefore operating simultaneously along with the ring oxygen basicity factor.

In order to investigate further the magnitude of the steric effect of the C-5 substituents in the absence of a polar effect, the 2-isopropoxy-5-methyltetrahydrofuran was chosen for hydrogenolysis. This compound would provide an isopropyl group on the exo oxygen, the polar effect of which is balanced by the inductive equivalent of an isopropyl group attached to the endo oxygen (Scheme 59-A and B).



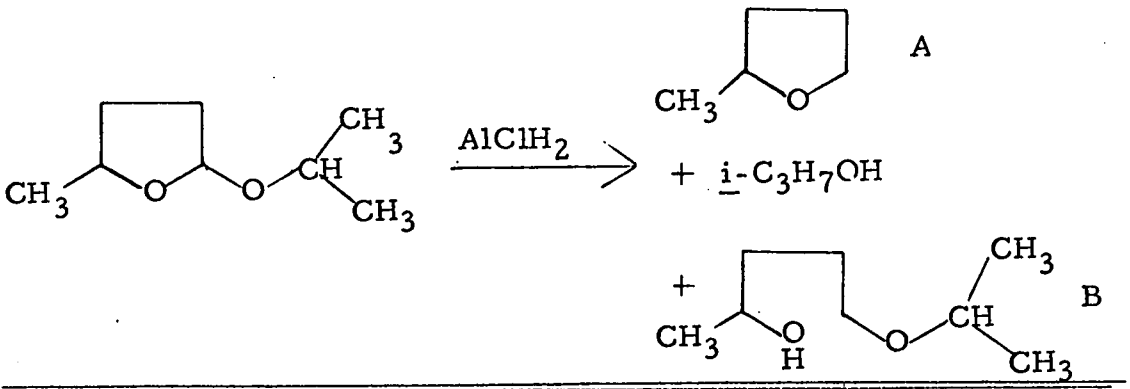
A B

Scheme 59

Hence, only the steric effect of the C-5 methyl group and the strong basicity of the ring oxygen should be operative. The results are shown in Table 12.

TABLE 12

Hydrogenolysis of a cis-trans Mixture of 2-Isopropoxy-5-methyltetrahydrofuran with an Equimolar Mixture of $LiAlH_4$ and $AlCl_3$.



Time (h)	Recovery %	A	B	% Reduced
		as % of product		
3	80	6.8	93.2	100

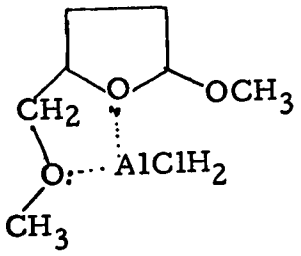
The strong ring oxygen basicity is still the predominant effect causing 93% endo cleavage of the 2-isopropoxy-5-methyltetrahydrofuran. The remaining 7% of exo cleavage must be attributed to the presence of the C-5 methyl group since no exo cleavage was found for the unsubstituted 2-isopropoxytetrahydrofuran (5). It was found in the case of the 2-ethoxytetrahydrofuran that the balancing of the polar effect was not sufficient to cause any

exo cleavage. Therefore, it must be the steric effect of the methyl group which forces 7% of the reaction to occur at the exo oxygen since there is no other effect which can explain its occurrence.

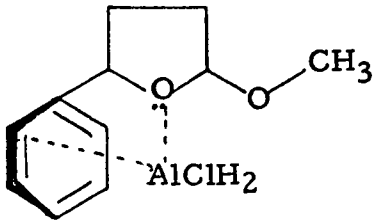
Diner and Brown (3) mentioned the possibility of partial complexation or association between the oxygen of the methoxymethyl group and the aluminum species in close proximity to the tetrahydropyran ring oxygen. This was one possible explanation for the predominant endo cleavage found for the 6-methoxymethyl-2-methoxy tetrahydropyran. However, Diner and Brown concluded on the basis of other results that the polar effect of the substituent was the predominant directing influence in this case and that the association factor was only of minor importance. Since no evidence was given to disprove the association theory, the possibility of an association as is shown in Structure 6-a may occur in the case of the 5-methoxymethyl-2-methoxytetrahydrofuran causing at least some of the predominantly endo cleavage.

There is also a possibility of partial complexation of the π-electron system of the C-5 phenyl group with the aluminum species as shown in Structure 6-b. The strength of such a π-complex is not known but that such a complex does occur is supported by the solubility of $AlCl_3$ in benzene. Structures 6-a and 6-b show complexation occurring simultaneously at both the substituent and the ring oxygens which would require five valence orbitals on the aluminum. This is unlikely and it is most likely that there is a

fast equilibrium between complexation at the two centers mentioned, as well as at the exo oxygen, as is shown in Scheme 60.

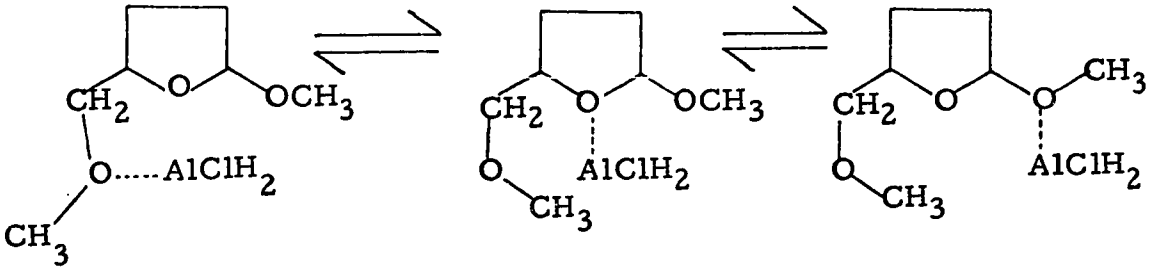


a



b

Structure 6



Scheme 60

It would have been desirable to find a substituent which, while being electron withdrawing, would not complex with the aluminum species or be reduced by the hydride species. Two possibilities which were considered were CF_3- and CCl_3- groups, but both were discarded since the halogen atoms would complex with the aluminum species quite strongly. No other substituent could be found, and this made it impossible to study the effect of an electron withdrawing substituent without the complication of complex formation.

An attempt was made to determine the extent of complexing

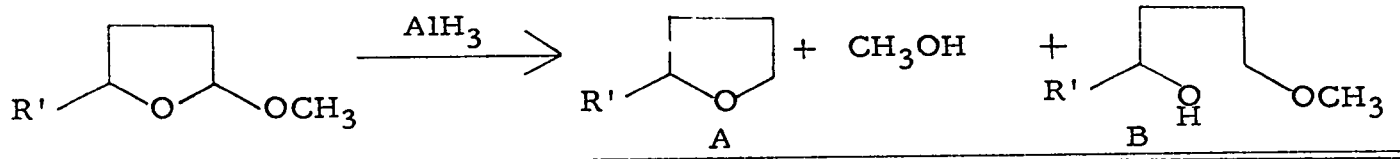
between the aluminum species and the C-5 substituent by carrying out a number of reductions with AlH_3. This nonchlorinated aluminum species is the weakest Lewis acid of the series AlH_3 < $AlClH_2$ < $AlCl_2H$ and it should not complex as strongly with the acetal as does $AlClH_2$. It was proposed that if the ease of complex formation was decreased, there might be a decrease in the amount of complex formation taking place at the endo oxygen. This would allow the steric effect of the phenyl and methoxymethyl groups to become more pronounced. In other words, the weaker complex formation would not assist the oxocarbonium ion formation and this would result in a greater energy being required to reach the transition state for oxocarbonium ion formation. Hence, the relative stabilities of the oxocarbonium ions and the steric effect of the C-5 substituent would become more important. A variation in the exo to endo cleavage ratios using AlH_3 and $AlClH_2$ might result.

The two acetals, 2-methoxy-5-phenyltetrahydrofuran and 5-methoxymethyl-2-methoxytetrahydrofuran, were hydrogenolyzed with AlH_3, giving the results in Table 13.

It is immediately obvious from Table 13 that the reduction with AlH_3 is slower than with $AlClH_2$. This is in agreement with the explanation that AlH_3 forms a much weaker complex than does $AlClH_2$ resulting in an equilibrium not favoring complex formation. The transition state for oxocarbonium ion formation is far more

TABLE 13

Hydrogenolysis of cis-trans Mixtures of 2-Methoxy-5-phenyltetrahydrofuran and 5-Methoxymethyl-2-methoxytetrahydrofuran with AlH_3 Made from a 3 to 1 Mixture of $LiAlH_4$ and $AlCl_3$.



R'*	Time (h)	Recovery (%)	A	B**	% Reduced
CH_3-O-CH_2-	20	85	5.0(5.5)***	85.0(94.5)***	90
C_6H_5	20	90	12.5	56.5	68.7
	48	87	15.5	72.0	87.5
	166	93	21.5	78.5	100

* The compounds were cis-trans mixtures and their n.m.r. spectra indicated that the two isomers were present in a ratio of between 1 to 1 and 3 to 2 (2 to 3).

** A and B represent % of reduced material in the recovered material.

*** The figures in brackets are the relative % of reduced material.

difficult to attain when AlH_3 is used since the complex is not strong enough to assist the reaction by substantial lowering of the activation energy.

For the C-5 methoxymethyl acetal there is, within experimental error, no difference between the endo and exo cleavage ratios for reductions using AlH_3 and $AlClH_2$ (94.5 to 5.5 for AlH_3 and 93.5 to 6.5 for $AlClH_2$). For the C-5 phenyl acetal, however, there is a difference of 6% in the endo to exo cleavage ratio using the two aluminum species (78.5 to 21.5 using AlH_3 and 84.5 to 15.5 using $AlClH_2$). This is only a very small variation and may not be significant. On the other hand, the decrease in endo cleavage can be interpreted as indicating a decrease in the amount of complexation of the phenyl ring with AlH_3 as compared to $AlClH_2$. This then allows more exo complexation to occur, increasing the amount of exo cleavage.

However, since the variation is so small, no definite conclusion can be drawn from this work and no conclusive proof for or against the possibility of association at the C-5 substituent is thus available from the above results. Only during the study of the 2-aryloxy- and 2-benzyloxytetrahydrofurans was complexation between the phenyl ring and the aluminum species found to be very important in determining the direction of cleavage. This topic will be discussed in detail later. However, if complex formation is significant enough to affect the direction of reduction in the 2-aryloxytetrahydrofurans, it should be playing some role in

determining the direction of reduction of the 5-substituted-2-methoxytetrahydrofurans.

In summary, the polar directing effect of the C-5 substituents appears to be the predominant directing influence in the reductive cleavage of the 5-substituted-2-methoxytetrahydrofurans. However, the steric effect of the C-5 substituents shielding the ring oxygen must play some role, since some exo cleavage product is found even though all of the other possible directing effects favor endo cleavage. The strong basicity of the tetrahydrofuran ring oxygen, although decreased by steric shielding from the C-2 and C-5 substituents, is still a factor in determining the direction of reductive cleavage. The importance of the complex formation between the aluminum species and the C-5 substituent could not be definitely determined, but from results found with the 2-alkoxytetrahydrofurans, the complexation factor was concluded to be operative at least to a small extent.

2. Hydrogenolysis of the 2-aryloxytetrahydrofurans with $AlClH_2$.

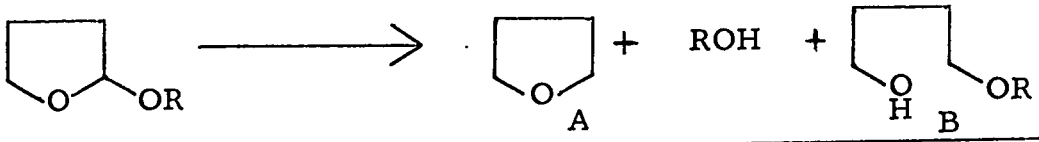
Miss Makhubu stated that the direction of hydrogenolysis found to occur in the 2-alkoxytetrahydrofurans could not be explained on the basis of the inductive effects of the alkyl groups. Instead, the results appeared to be in agreement with the view that the strong basicity of the ring oxygen caused exclusive association of the Lewis acid with the ring oxygen and, consequently, exclusive ring cleavage (5). This latter explanation had previously been suggested by

Eliel and coworkers (4). However, after their study of the hydrogenolysis of four tetrahydrofuranyl acetals, they (4) concluded that the steric bulk of the C-2 alkoxy substituents was an important directing influence, not the ring oxygen basicity.

Table 14 shows the data upon which their conclusion was based. It must be pointed out that their hydrogenolysis experiments were done using a 4 to 1 mixture of $AlCl_3$ and $LiAlH_4$ while the present work and that of Miss Makhubu was carried out with an equimolar mixture of those two reagents. The difference in reducing species has been shown to have a profound effect upon the direction of cleavage (p. 135 below).

TABLE 14

Hydrogenolysis of 2-Alkoxytetrahydrofuran with a 4 to 1 Mixture of $AlCl_3$ and $LiAlH_4$.*



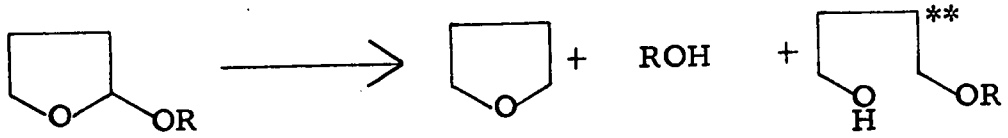
R	Time (h)	% A	% B
t-C_4H_9	2	Trace	58
cyclohexyl	2	15	63
n-C_6H_{13}-	2	40	27
$C_6H_5CH_2$-	2	83	4

* Taken from the work of Eliel and coworkers (4).

Miss Makhubu found exclusively ring cleavage in the hydrogenolysis of four 2-alkoxytetrahydrofurans (Table 15).

TABLE 15

Hydrogenolysis of the 2-Alkoxytetrahydrofurans Using a 1 to 1 Mixture of $LiAlH_4$ and $AlCl_3$.***



A B

R	Time (h)	%A*	%B*
CH_3	2	0	86
C_2H_5	2	0	82
$\underline{i}$-C_3H_7	2	0	80
$\underline{t}$-C_4H_9	2	0	86

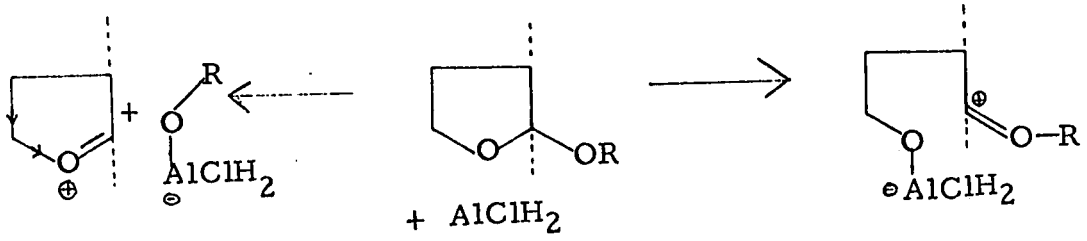
* Refers to % yield of the products after distillation, based on starting acetal.

** Only traces of alcohol and tetrahydrofuran showed on g.l.c..

*** Taken from the work of Miss Makhubu (5).

Since identical results were found for both a small methyl group and a bulky tertiary butyl group, the steric effect of the C-2 alkoxy substituent was considered to be unimportant as a directing effect under the conditions employed for hydrogenolysis. Similarly,

the stabilization of the intermediate carbonium ion by the inductive effect of the alkyl groups could not explain the results. An analysis of the directive effect due to the polar nature of the alkyl group is best made by using the method of Diner (7). In this method, the acetal is divided into two parts at the anomeric center as shown by the dotted line in Scheme 61. The stabilities of the two possible carbonium ions are then considered.



A

B

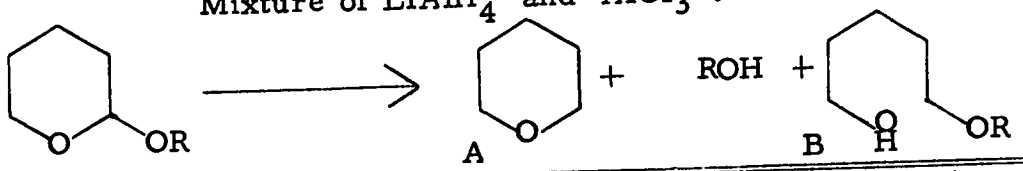
Scheme 61

When R = CH_3, the oxocarbonium ion from endo cleavage (Scheme 61-B) should not be stabilized to the same extent as is the oxocarbonium ion from exo cleavage (Scheme 61-A). The latter oxocarbonium ion is stabilized by what amounts to an ethyl group on the ring residue and, hence, exo cleavage should predominate. When R = C_2H_5, the inductive effect of the two stabilizing groups should just cancel, and exo and endo cleavage should occur in about equal amounts. The groups such as R = i-C_3H_7 and R = t-C_4H_9 should stabilize the oxocarbonium ion from endo cleavage (Scheme 61-B) to a greater extent than that from exo cleavage (Scheme 61-A). Therefore, if the polar effect of the substituents is the predominant directing effect, there should be a gradient from predominantly

exo to predominantly endo cleavage in the 2-alkoxytetrahydrofuran series as R is changed from CH_3 to t-C_4H_9. Diner and Brown (3) had found such a gradient in the hydrogenolysis of the 2-alkoxy-tetrahydropyran series (Table 16). However, such a gradient was not found by Miss Makhubu and the only remaining explanation for the exclusive endo cleavage was the overriding ring oxygen basicity. This relatively strong basicity is well documented in the literature (26, 27, 32).

TABLE 16

Hydrogenolysis of the 2-Aryloxytetrahydropyrans Using a 1 to 1 Mixture of $LiAlH_4$ and $AlCl_3$*.



R	Time (h)	Recovery (%)	%A	%B
CH_3–	16	82	70	30
C_2H_5–	12	85	40	60
i-C_3H_7–	3.5	79	18	82
t-C_4H_9–	21	88	13	87
C_6H_5–	24	72	100	0
p-CH_3–C_6H_4–	24	77	100	0

* Taken from the work of Diner (7).

To complete this study, a tetrahydrofuranyl acetal with an electron withdrawing C-2 substituent was required. Such a group would destabilize the oxocarbonium ion from endo cleavage (Scheme 61-B) relative to the oxocarbonium ion from exo cleavage (Scheme 61-A). This might create a competition between the polar effect and the strong ring oxygen basicity. Eliel and coworkers (4) had hydrogenolyzed 2-benzyloxytetrahydrofuran and found that exo cleavage predominated to an extent of 83%. However, since their results for the other tetrahydrofuranyl acetals did not agree with those found by Miss Makhubu (5), the results for the C-2 benzyloxy acetal could not be compared with Miss Makhubu's results.

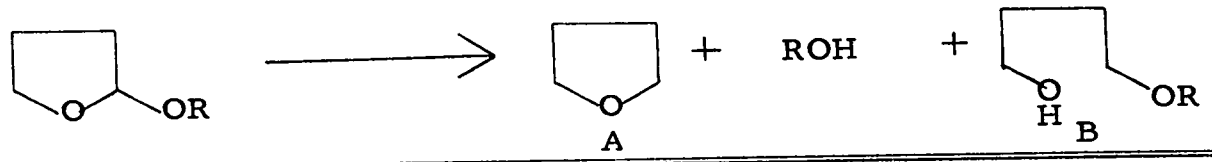
In order to determine what effect an electron withdrawing substituent would have under the reaction conditions used in the present work, the 2-benzyloxytetrahydrofuran was hydrogenolyzed using $AlClH_2$. A number of 2-aryloxytetrahydrofurans were also hydrogenolyzed since Diner and Brown (3) had found that an aryl group apparently exerted a very strong polar effect, giving exclusively exo cleavage in the 2-aryloxytetrahydropyrans (Table 16).

The results from the hydrogenolysis of the 2-aryloxy-tetrahydrofurans are listed in Table 17 along with the results for the hydrogenolysis of 2-benzyloxytetrahydrofuran.

The results shown in Table 17 show that exo cleavage occurs exclusively for all of the 2-aryloxytetrahydrofurans,

TABLE 17

Hydrogenolysis of 2-Aryloxytetrahydrofurans and 2-Benzyloxytetrahydrofuran with a 1 to 1 Mixture of $LiAlH_4$ and $AlCl_3$ ($AlClH_2$).



R	Time (h)*	Recovery (%)	A	B**	% Reduction
C_6H_5-	2	85	100	0	100
2,6-Cl_2-C_6H_3-	2	95	100	0	100
2,6-$(CH_3)_2$-C_6H_3-	2	90	100	0	100
3,5-$(CH_3)_2$-C_6H_3-	2	90	100	0	100
4-t-C_4H_9-C_6H_4-	2	84	100	0	100
$C_6H_5CH_2-$	2	95	48.5	51.5	100

* In all cases reduction was complete within 2 hours.

** A and B represent the relative % of reduced material.

regardless of the substituents on the aryl ring. This direction of cleavage is opposite to that observed for the 2-alkoxytetrahydrofurans (5). Since the phenyl group has been shown to be at least as bulky as the isopropyl group (24-b), the 2,6-disubstituted phenyl rings should sterically shield the exo oxygen to a very considerable extent. Therefore, if a steric effect is directing the reduction, it would be expected to favor the formation of at least some endo cleavage product from the 2-(2,6-dimethylphenoxy)-tetrahydrofuran. However, since only exo cleavage is observed, the steric effect of these substituents is overridden by another factor.

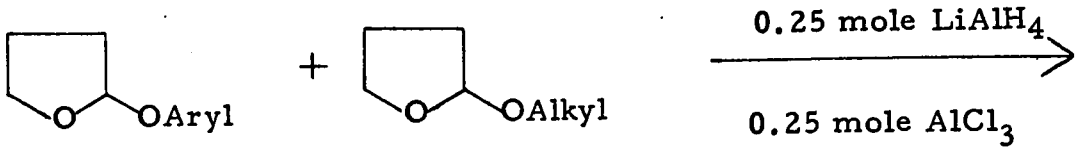
The polar directing effect of the phenyl ring as described by Diner and Brown (3), therefore, appears to be the predominant directing effect. They assumed that the electron withdrawing nature of the phenyl group sufficiently destabilized the oxocarbonium ion from endo cleavage (Scheme 61-B), so that only the oxocarbonium ion from exo cleavage (Scheme 61-A) was formed.

However, a study of the Hammett substituent constants, σ, and the electrophilic substituent constants, σ^+, reveals that, when they are in the para position of the benzene ring, both the phenoxy and methoxy groups exert strong electron donating

effects. The σ values are -0.268 for p-CH_3-O- and -0.320 for p-C_6H_5-O- (80) which indicate that the phenoxy group in fact exerts a larger electron donating effect than does the methoxy group. The σ^+ constants which give a measure of the resonance effect of the substituents are -0.778 for p-CH_3-O- and -0.5 for p-C_6H_5-O- indicating that the phenoxy group still exerts an electron donating effect although smaller than that of the methoxy group (115). Hence, the phenoxy group does not exert a strong electron withdrawing effect as proposed by Diner (7) and it can in fact stabilize the oxocarbonium ion from endo cleavage.

If the phenoxy group did exert an electron withdrawing effect as Diner proposed, then the electron density on the exo oxygen would be decreased and there would be an even greater preference for complexation at the endo or ring oxygen. Therefore, since complex formation at the exo oxygen should be less favorable, a slower reduction should be observed for the C-2 aryloxy acetals than is observed for the C-2 alkoxy acetals. To test this hypothesis, a number of competitive hydrogenolyses were carried out between the 2-aryloxytetrahydrofurans and 2-ethoxytetrahydrofuran. In all cases, there was one

equivalent each of the C-2 aryloxy and alkoxy acetals added to one quarter molar equivalent each of $LiAlH_4$ and $AlCl_3$ (Scheme 62). This forms a one half molar equivalent of $AlClH_2$, which is sufficient hydride to reduce only one half equivalent of one of the acetals (one quarter of all the acetal present) since normally only one of the hydrogen atoms on $AlClH_2$ is active as a hydride source.



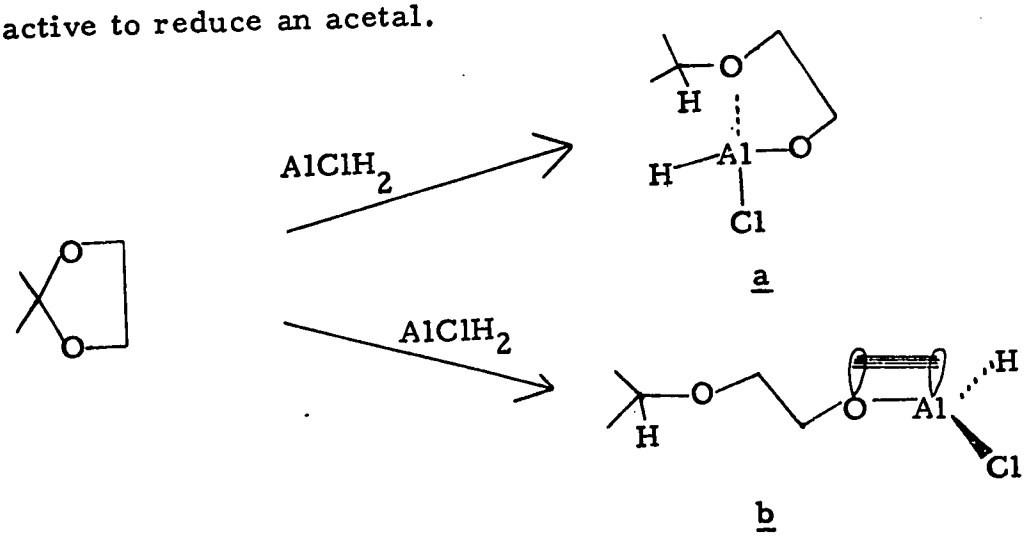
1.0 mole 1.0 mole

Scheme 62

The assumption that only one hydrogen atom of $AlClH_2$ is active is based on work by H. A. Davis (81) who found that only one hydride ion of $AlClH_2$ is donated in the reduction of 1,3-dioxolanes with $AlClH_2$. This was attributed to the formation of the alkoxy aluminum chloro hydride species shown in Scheme 63-a, in which intramolecular complex formation can occur. Complexation with another molecule of acetal apparently does not occur and therefore, reduction of an acetal cannot be accomplished by the species shown in Scheme 63-a. It is interesting to note that this species (Scheme 63-a) can reduce a free aldehyde since complexation is not as important a factor.

The fact that it was intramolecular complexation which was responsible for the limited extent of reduction of the ethylene acetal

by $AlClH_2$ and not simply the weakened Lewis acidity due to overlap of a filled "p" orbital on the oxygen (sp^3 hybrid orbital) with an unfilled "p" orbital on the aluminum (Scheme 63-b) was substantiated by the observation, that the species $HAlClOC_2H_5$ was sufficiently reactive to reduce an acetal.



Scheme 63

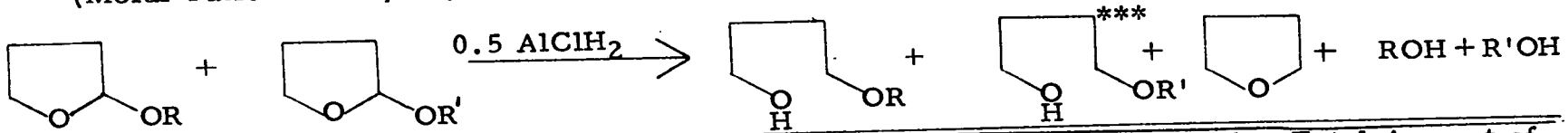
The results for the competitive hydrogenolyses are shown in Table 18.

It was surprising to find that in the first three competitive hydrogenolyses shown in Table 18, only the C-2 aryloxy acetals were reduced and the 2-ethoxytetrahydrofuran was unaffected. Furthermore, the C-2 aryloxy acetals appeared to have been reduced completely rather than just to the extent of 50% as was expected from the work of Davis (81). This complete reduction of the acetal was attributed in part to the in situ formation of $HAlClOC_6H_5$ after the reduction of one molecule of an acetal. This new species was still reactive since no intramolecular complexing could occur

TABLE 18

Competitive Hydrogenolysis of a Mixture of 2-Ethoxytetrahydrofuran and a 2-Aryloxytetrahydrofuran with a limited amount of $AlClH_2$.

(Molar ratio of 2-aryloxytetrahydrofuran : 2-ethoxytetrahydrofuran : $AlClH_2$ = 1 : 1 : 0.5)



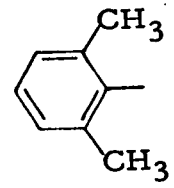
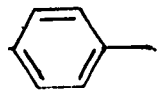
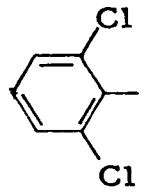
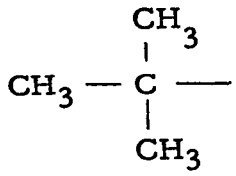
Expt. No.	R and R'	Time (h)	Recovery %	Amount of each acetal reduced*	Total Amount of acetal reduced**
1.		2	95	100	50
	CH_3-CH_2-			0	
2.		2	95	100	50
	CH_3-CH_2-			0	

TABLE 18 - Continued

Expt. No.	R and R'	Time (h)	Recovery %	Amount of each acetal reduced*	Total Amount of acetal reduced**
3.		2	82	100	50
	CH_3-CH_2-			0	
4.		2	98	78	31
	CH_3-CH_2-			22	

* This column gives the total % of each acetal reduced.
** This column gives the total % of all the acetal present which is reduced.
** The products formed from these hydrogenolyses are discussed below.

to prevent complexation with another molecule of acetal. In spite of this complicating factor, it was still obvious that the C-2 aryloxy acetals reacted much faster than did the C-2 alkoxy acetals regardless of whether there were electron donating or withdrawing substituents on the phenyl ring. This was not expected and did not agree with the hypothesis that the strong electron withdrawing effect of the aryl ring should retard the reduction.

As a further check on the validity of the view that an electron donating group should accelerate the reaction, a competitive hydrogenolysis between 2-ethoxy- and 2-t-butoxytetrahydrofurans was carried out (experiment 4, Table 18). It was expected that the relative ease of attainment of the transition states for the cleavage of the two acetals should be reflected in the product ratio from the competitive reduction. The results of this experiment show that the aluminum species reacts preferentially at the ring oxygen in both cases since only ring cleavage products are obtained. Of the reduced material, 78% was 4-t-butoxy-1-butanol and 22% was 4-ethoxy-1-butanol. Hence, it is clear that the C-2 t-butoxy acetal reacts faster than does the C-2 ethoxy acetal. This can be attributed to the fact that the t-butyl group stabilizes the oxocarbonium ion from endo cleavage more than does the ethyl group. That is, it lowers the energy required to reach the transition state leading to the oxocarbonium ion (Structure 7).

Structure 7

A polar effect is therefore definitely operative in determining the rate of cleavage of the C-2 alkoxy acetals and is probably operative in the C-2 aryloxy acetals as well. However, in the latter compounds there has emerged yet another factor, which overrides the polar effect but still directs the reaction such that only exo cleavage occurs. Neither the polar nor the steric effects can satisfactorily explain either the direction of hydrogenolysis of the C-2 aryloxy acetals or their rapidity of reaction. A factor, which must now be considered, is that of a very fast and strong complex formation between the π-electron system of the aryl ring and the aluminum species. This occurs in preference to the complex formation at the ring oxygen. The aluminum species is therefore held in close proximity to the exo oxygen facilitating exo cleavage.

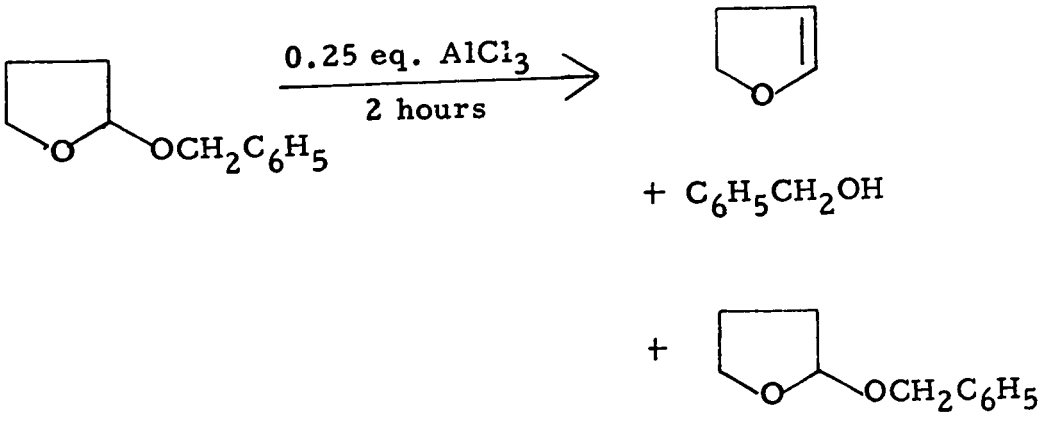
The g.l.c. analysis of the competitive hydrogenolysis mixtures (Table 18) on an Apiezon L column showed small amounts of a high boiling material which were not present when an excess of reducing agent was used, as in the usual 1 to 1 mixture of acetal and $AlClH_2$. The high boiling material was initially attributed to

the formation of some endo cleavage product caused by the $HAlClOC_6H_5$ species. However, it could not be isolated by preparative g.l.c. because of the high boiling point, nor by chromatography on alumina because of the small relative amounts in the mixtures. Their retention times on g.l.c. agreed quite closely to the retention times found for the appropriate authentic 4-aryloxy-1-butanols synthesized for comparison.

However, as will be discussed in detail in section F, these high boiling compounds were actually the result of rearrangement of the acetal in the presence of the aluminum species. The subsequent study of the rearrangement revealed that $AlCl_3$ caused the decomposition of both the 2-aryloxytetrahydrofurans and 2-aryloxytetrahydropyrans within 10 minutes to form predominantly the phenol and 2,3-dihydrofuran (or 3,4-dihydro-2H-pyran). This indicated that a strong complex was formed between the aluminum chloride and the aryl ring. This complex was sufficiently strong that it caused an immediate formation of the oxocarbonium ion from exo cleavage. Although the complex formation will not be as strong with the other weaker Lewis acids ($AlClH_2$), there should still be a marked tendency for it to occur and thus lead to exo cleavage.

The 2-benzyloxytetrahydrofuran was found to give 48.5% exo cleavage and 51.5% endo cleavage with $AlClH_2$. These results (Table 17) are considerably different from those of Eliel and

coworkers (4) who found 83% exo and 4% endo cleavage (Table 14). In an attempt to explain the discrepancy between these results, the C-2 benzyloxy acetal was allowed to react with one-quarter equivalent of $AlCl_3$ alone for two hours. Under these conditions there was obtained a product mixture containing 35.6% of benzyl alcohol and 64.4% of unreacted acetal (Scheme 64). Here, as with the C-2 aryloxy acetals, complex formation with the benzyl group causes cleavage of the acetal although the reaction is slower with the C-2 benzyloxy acetal. Eliel and coworkers were working with a 4 to 1 mixture of $AlCl_3$ and $LiAlH_4$ which would form a 4 to 1 mixture of $AlCl_2H$ and $AlCl_3$. Since both $AlCl_3$ and $AlCl_2H$ are stronger Lewis acids than $AlClH_2$, it is possible that the predominant exo cleavage of 2-benzyloxytetrahydrofuran may have been a result of the large excess of Lewis acid present.



Scheme 64

With the weaker Lewis acid, $AlClH_2$, used in the present work, there would be more of a possibility of an equilibrium

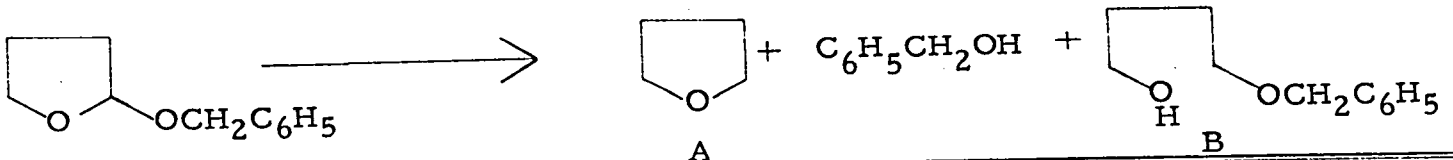
between complex formation at the ring oxygen and complex formation at the phenyl ring of the benzyl group. This would allow the formation of some endo cleavage product along with the exo cleavage product. In order to check this hypothesis, the hydrogenolyses of 2-benzyloxytetrahydrofuran were carried out with AlH_3 and $AlCl_2H$. As well, the conditions of Eliel and coworkers (4:1 mixture of $AlCl_2H$ and $AlCl_3$) were also investigated. If the strength of the complex formation at the phenyl ring were in fact affecting the direction of cleavage, then one might observe a gradient from preferential exo to preferential endo cleavage in changing from $AlCl_2H$ to $AlClH_2$ to AlH_3. The results are shown in Table 19.

The very weak Lewis acid, AlH_3, preferentially complexes at the ring oxygen causing endo cleavage. This occurs in spite of the electron attracting inductive effect of the benzyl system which would be expected to favor exo cleavage.

It can be rationalized that only a strong Lewis acid can form a π-electron complex sufficiently strong to cause exo cleavage. A weak Lewis acid such as AlH_3 cannot initiate the cleavage of the exo C-O bond as quickly as can the stronger $AlCl_2H$ and $AlClH_2$ species. Therefore, more complexation is allowed to occur at the ring oxygen causing endo cleavage. A definite reason for why the preference of reaction at the exo substituent should decrease and the preference for reaction at the

TABLE 19

Hydrogenolysis of 2-Benzyloxytetrahydrofuran Using $AlCl_2H$, $AlClH_2$ and AlH_3.



A B

Species	Time (h)	Recovery %	A	B*	% Reduction
4:1, $AlCl_2H$: $AlCl_3$	2	91	91.3	8.7	100
$AlCl_2H$	2	90	90.5	9.5	100
$AlClH_2$	2	95	48.5	51.5	100
AlH_3	2	84	20.5	79.5	67.5

* A and B represent the relative amounts of reduced product in the recovered material.

endo oxygen should increase, when only the Lewis acidity of the aluminum species was decreased, could not be found.

There is, within experimental error, very little difference between the results for $AlCl_2H$ and for a 4:1 mixture of $AlCl_2H$ and $AlCl_3$. The very small difference between the results in the present work (91.3% exo and 8.7% endo cleavage) and those of Eliel and coworkers (4) (83% exo and 4% endo cleavage) for the 4:1 mixture of $AlCl_2H$ and $AlCl_3$ can be attributed to the difference in work-up procedures.

In the case of $AlClH_2$ and $AlCl_2H$, the polar effect of the benzyl group destabilizing the oxocarbonium ion from endo cleavage relative to that from exo cleavage can be used to explain the substantial amount of exo cleavage. However, when AlH_3 is used, only the strong ring oxygen basicity can explain the preferential (80%) ring cleavage. The polar effect of the benzyl group might be causing some of the 20% exo cleavage. However, there is still a possibility of complex formation at the phenyl ring being the reason for all the exo cleavage. Hence, the factor of complexation of the Lewis acid at either the ring oxygen or C-2 benzyloxy substituent determines the direction of cleavage of 2-benzyloxytetrahydrofuran.

In summary, the 2-aryloxytetrahydrofurans gave exclusively exo cleavage upon reduction with $AlClH_2$. The observation that the acetal, 2-t-butoxytetrahydrofuran reacted four times faster than

did 2-ethoxytetrahydrofuran was interpreted in terms of a polar effect. However, a polar effect could not properly explain the observation that the reduction of the C-2 aryloxy acetals was faster than was the reduction of the C-2 alkoxy acetals. The results were attributed to a strong complex formation between the π-electron system of the aryl ring and the aluminum species, which holds the species in close proximity to the exo oxygen, thus favoring this direction of cleavage. The gradient from preferential exo to preferential endo cleavage of 2-benzyloxytetrahydrofuran, as the Lewis acid-reducing species was changed from $AlCl_2H$ to $AlClH_2$ to AlH_3, was attributed to a different preferential location of complexation for each species. The polar effect of the benzyl ring was concluded to be of only minor importance. The fast reaction between the C-2 aryloxy acetals and $AlCl_3$ supports the hypothesis of a complex formation between the aryl ring and the aluminum species with consequent exo cleavage.

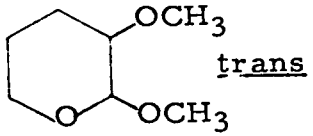
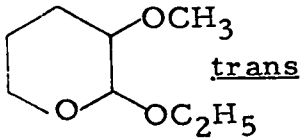
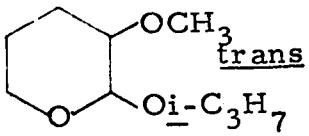
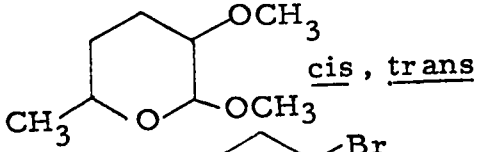
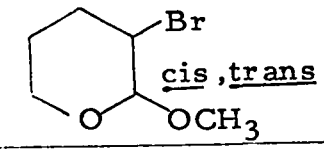
3. Hydrogenolysis of 2,3-dimethoxytetrahydrofuran with $AlClH_2$

Diner (7) reported the hydrogenolysis of several 3-substituted-2-alkoxytetrahydropyrans for which a number of results are shown in Table 20.

The hydrogenolysis of the 2-alkoxy-3-methoxytetrahydropyrans was found to be much slower than was the hydrogenolysis of the 2-alkoxytetrahydropyrans. This was attributed to the electron withdrawing effect of the 3-methoxy group destabilizing

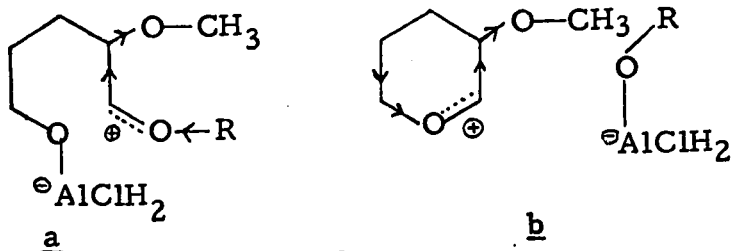
TABLE 20

Hydrogenolysis of Some 3-Methoxy-2-alkoxytetrahydropyrans with $AlClH_2$.*

Acetal	Time (h)	% Reduction	% Recovery	% exo Cleavage	% endo Cleavage
 trans	18 96	0 15	75 80	- 40	- 60
 trans	5	25	88	0	100
 trans	5	22	80	0	100
 cis, trans	22	12	82	100	0
 cis, trans	48	0	80	-	-

* Taken from the work of Diner (7).

the oxocarbonium ions resulting from both endo (Structure 8-a) and exo cleavage (Structure 8-b).



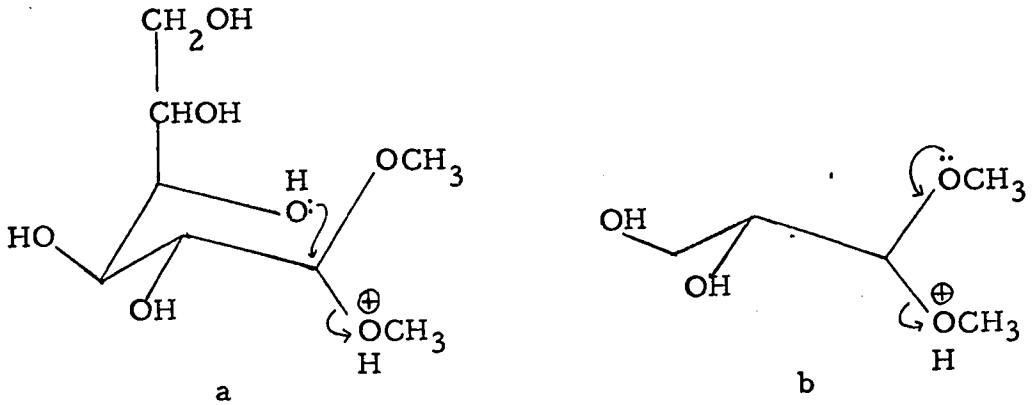
a b

Structure 8

The direction of cleavage was thought to be determined by the predominant or most stable conformation of the tetrahydropyranyl acetal, coupled with the relative stabilities of the two possible oxocarbonium ions determined by inductive effects. The stability of the oxocarbonium ion from endo cleavage (Structure 8-a) should be greater for the 2-alkoxy-3-methoxytetrahydrofuran when R = i-C_3H_7 because of the greater electron donating ability of R compared to that of the "ethyl" group on the ring residue in Structure 8-b. When R = C_2H_5, both of the ions a and b (Structure 8) should be roughly of equal stability and when R = CH_3, the oxocarbonium ion from exo cleavage (Structure 8-b) should be more stable since the "ethyl" group on the ring residue has a greater electron donating ability than the R group in Structure 8-a. However, endo cleavage occurred exclusively when R = i-C_3H_7 or C_2H_5 which was in sharp contrast to the 60% and 82% endo cleavage found respectively for the unsubstituted 2-ethoxy- and 2-isopropoxytetrahydropyrans. When R = CH_3 (Structure 8), 60%

endo cleavage was found to occur, a figure considerably different from the 30% endo cleavage found for the unsubstituted 2-methoxytetrahydropyran. This information clearly indicates that the C-3 methoxy group has a considerable effect in favoring endo cleavage of the 2-alkoxy-3-methoxytetrahydropyrans.

Diner (7) concluded that anchimeric assistance, or neighboring group participation, by the C-3 methoxy group was the factor which favored endo cleavage. The assumption that the C-3 methoxy group could participate in this manner was based on the work of Capon and Thacker (107) who found that D-glucose dimethyl acetal hydrolyzed faster ($k = 110 \times 10^{-4}$ l mole^{-1} sec^{-1}) than did D-glyceraldehyde dimethyl acetal ($k = 1.77 \times 10^{-4}$ l mole^{-1} sec^{-1}). However, these results indicated that it was anchimeric assistance by the C-4 hydroxyl group in D-glucose (Structure 9-a) which was responsible for the accelerated rate of hydrolysis observed. Because there is no hydroxyl group so favorably situated, anchimeric assistance is not possible in the hydrolysis of D-glyceraldehyde dimethyl acetal (Structure 9-b).

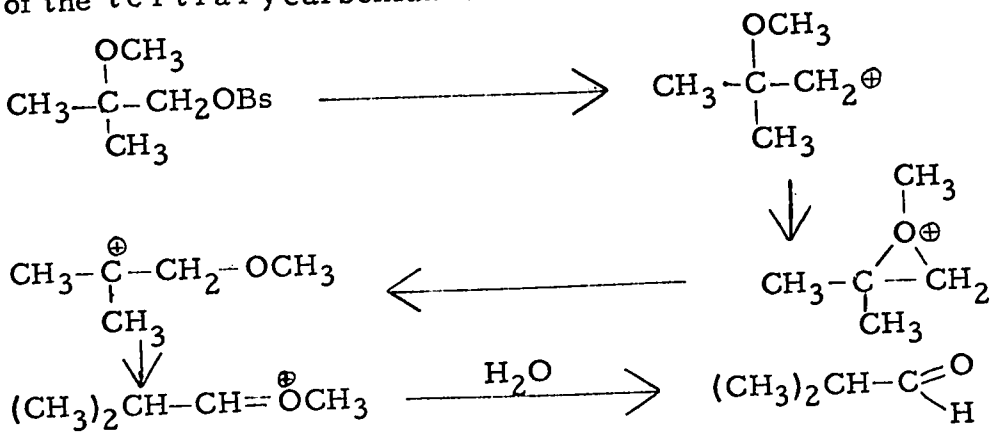


Structure 9

However, Diner failed to consider the several examples which have appeared in the literature and which indicate that the primary effect of an α-OCH_3 group is to inductively destabilize carbonium ion formation at the adjacent carbon. Speck and coworkers have shown that the rate of hydrolysis of α-methoxyacetaldehyde dimethyl acetal ($k = 2 \times 10^{-4}$ l mole^{-1} sec^{-1}) is significantly slower than that of acetaldehyde dimethyl acetal ($k = 0.254$ l mole^{-1} sec^{-1}) (108). Similarly, Böhme and Sell have shown that the rate of hydrolysis of β-chloroethyl ethyl ether ($k = 1.1 \times 10^{-5}$ l mole^{-1}sec^{-1}) is significantly slower than the rate of hydrolysis of β-chloroethyl ethyl thioether($k = 1.7 \times 10^{-1}$ l mole^{-1} sec^{-1}) (109). Winstein and coworkers have shown that there must be at least a small extent of methoxy group participation in two separate reactions in which retention of configuration was found during the replacement of a bromine atom with an acetate group. The reaction of threo (or erythro)-2-bromo-3-methoxybutane with silver acetate in acetic acid gave 3-methoxy-2-butyl acetate with a significant retention of configuration (110). Similarly, trans-1-bromo-2-methoxycyclohexane gave trans-2-methoxycyclohexyl acetate (110). However, it was pointed out that very little participation by the methoxy group was required for the retention of configuration to occur since there appeared to be little nucleophilic overlap with the solvent during the transition state to the carbonium ion formation (112). Hence, methoxy group participation

occurs only to a limited extent.

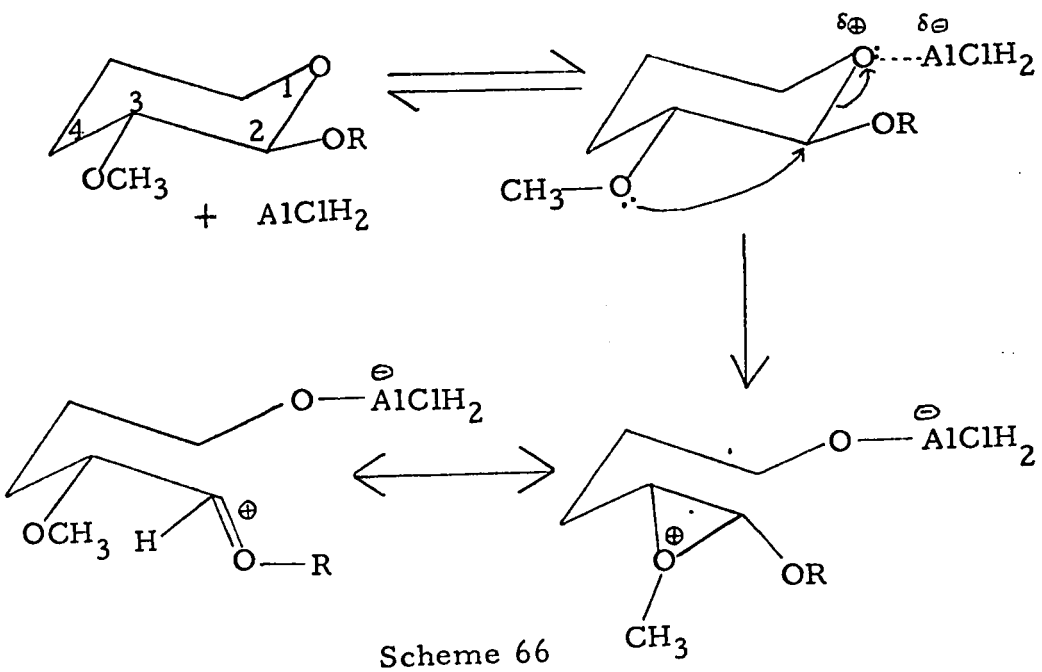
In contrast to these results the rate of hydrolysis of 2-methoxy-2-methylpropyl brosylate was significantly accelerated compared to that of neopentyl brosylate (114). However, a rearranged product, isobutyraldehyde, was obtained from this reaction (Scheme 65) and two possible explanations have been given for the apparently significant participation of the methoxy group in this one reaction. The first was that the steric interaction of the geminal dimethyl groups was relieved by the epoxide formation (112). This is a similar explanation to that given for the faster epoxide formation from the more highly substituted chlorohydrins (112). The second explanation was that the tertiary carbonium ion and the oxocarbonium ion which would be formed after the migration of the methoxy group would be much more stable intermediates than the primary carbonium ion. Hence, while the methoxy group must migrate through the epoxide structure, it does not necessarily make a significant contribution to the carbonium ion stability and the driving force for the reaction is the formation of the tertiarycarbonium ion and the oxocarbonium ion (114).



Scheme 65

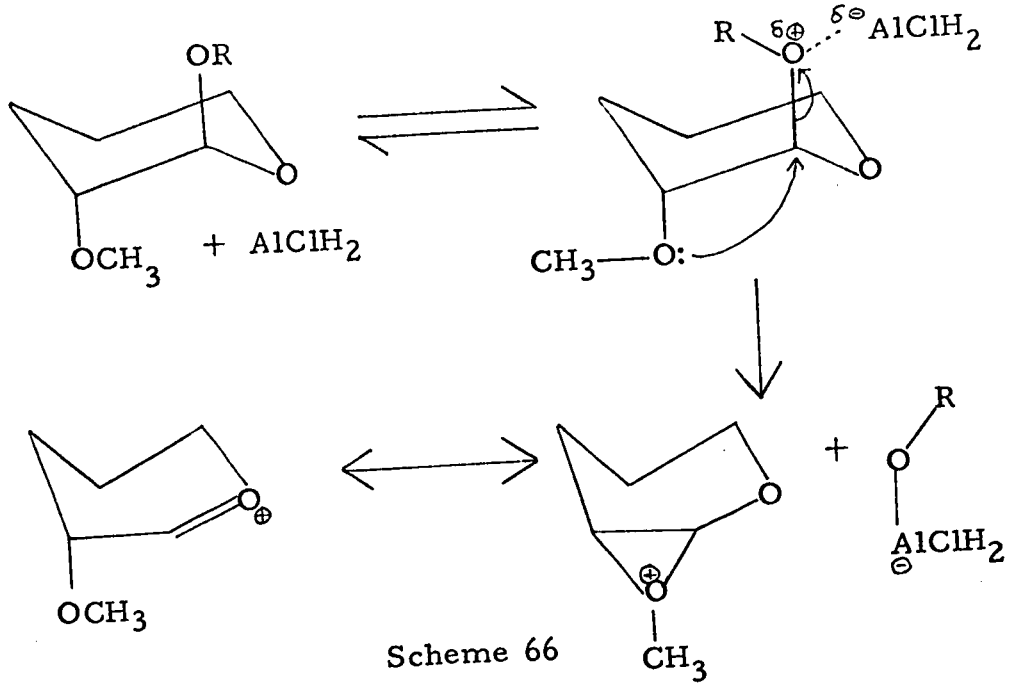
On this basis, it seems unlikely that the participation of the C-3 methoxy group is the major directing effect as Diner (7) had postulated. He based his entire explanation of the observed hydrogenolysis results on the assumption that the C-3 methoxy group participated in the reaction as shown in Scheme 66. The reaction was postulated to take place predominantly (when R = CH_3) or exclusively (when R = C_2H_5 and i-C_3H_7) from the diequatorial conformation (Scheme 66-a) with the C-3 methoxy group anchimerically assisting ring C-O bond cleavage. No reaction could therefore have taken place from the diaxial conformer except when R = CH_3 since, according to Diner, exo cleavage must result from this conformer in order for the C-3 methoxy group to participate (Scheme 66-b).

(a)



Scheme 66

(b)

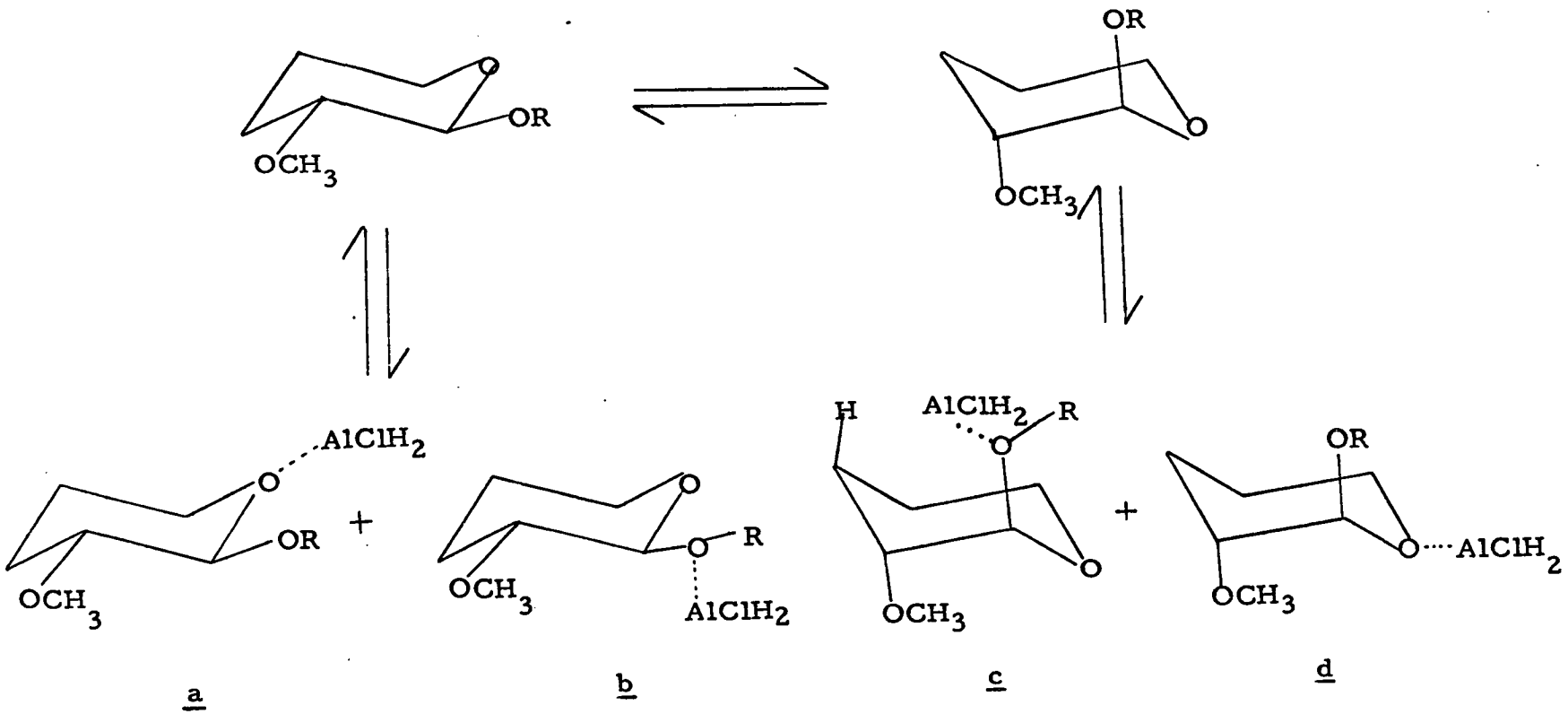


Scheme 66

However, if anchimeric assistance were important then 3-bromo-2-methoxytetrahydropyran should have exhibited some reduction. Winstein and coworkers (113) have shown anchimeric assistance by a bromine atom to be quite important in some solvolysis reactions in spite of the bromine atom's strong electron attracting effect. Hence, anchimeric assistance does not appear to be playing a very important role and the effect of the C-3 substituent is primarily inductive in nature.

Diner (7) showed that the diaxial to diequatorial conformer ratio in the trans-2-alkoxy-3-methoxytetrahydropyran was 60:40 when R = CH_3 and C_2H_5 and 53:47 when R = i-C_3H_7 (Scheme 67). Hence, the two possible conformers are of nearly equal energy.

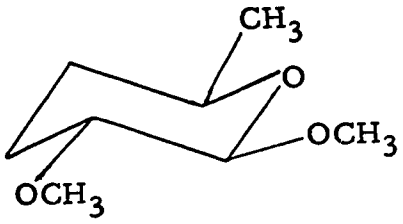
Scheme 67 shows the possible locations at which complexation can occur in the two conformers.


OR
OCH3
OR
OCH3
AlClH2
O
OR
OCH3
+
O
R
OCH3
AlClH2
H
AlClH2
R
O
OCH3
+
OR
O
AlClH2
OCH3
a
b
c
d

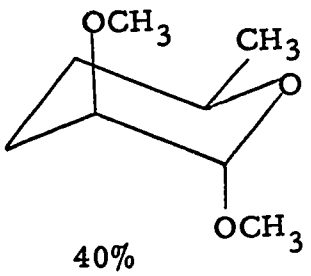
Scheme 67

In the diaxial conformation, a considerable increase in 1,3-interaction would arise if the aluminum species were to complex with the exo oxygen (Scheme 67-c). Since there would be little interference to complexation at the ring oxygen, endo cleavage should therefore be the preferred direction of cleavage from the diaxial conformer. In the diequatorial conformer, there would be an increased gauche interaction with the C-3 methoxy group if complexation were to occur at the exo oxygen (Scheme 67-b). Here again, there should be no hindrance to complexation at the ring oxygen and predominantly endo cleavage results. This rationale appears to hold only when R = C_2H_5 and i-C_3H_7 since when R = CH_3 there is a strong inductive effect which favors exo cleavage and causes 40% exo cleavage in spite of the steric factors just discussed.

The n.m.r. spectrum of 2,3-dimethoxy-6-methyltetrahydropyran obtained by Diner (7) shows a diequatorial to diaxial isomer ratio of approximately 60 to 40 (Scheme 68).



60%

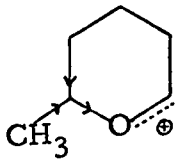


40%

Scheme 68

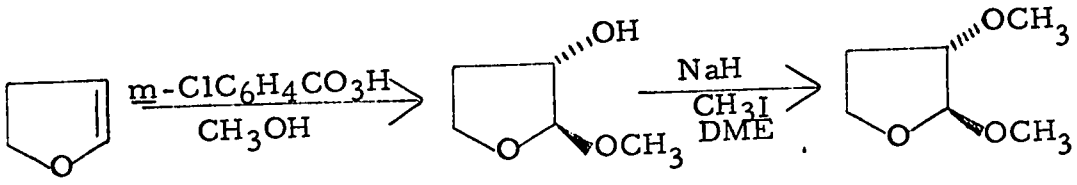
In this case the inductive stabilization of the C-6 methyl group on the oxocarbonium ion from exo cleavage (Structure 10)

appears to be sufficiently strong to cause exclusively exo cleavage. This occurs in spite of the steric factors hindering complexation at the exo oxygen discussed above in reference to the 2-alkoxy-3-methoxytetrahydropyrans. However, a question remains as to whether the effect of the methyl group is entirely polar in nature or partly steric as well. Additional work is required to clarify this problem.



Structure 10

To study further the hydrogenolysis of the tetrahydrofuranyl acetals, the 2,3-dimethoxytetrahydrofuran was prepared and subjected to hydrogenolysis. The procedure used to prepare the acetal was obtained from a report by Sweet and Brown (82). It involved the action of m-chloroperoxybenzoic acid on 2,3-dihydrofuran in methanol solution, followed by methylation using sodium hydride and methyl iodide in 1,2-dimethoxyethane solution (Scheme 69).



Scheme 69

The trans isomer was obtained exclusively by this method. This pure isomer could be isomerized to an equilibrium mixture

of 77% trans and 23% of the cis isomer by stirring in an acidified methanol solution. The isomers were separable on g.l.c. and identifiable in the 60 Mc n.m.r. spectrum by the position of the signal for the anomeric protons. The pure trans isomer gave a sharp singlet at τ5.12 and the cis isomer gave a singlet at τ5.20.

The hydrogenolysis was carried out on the equilibrium mixture using $AlClH_2$ with the results shown in Table 21.

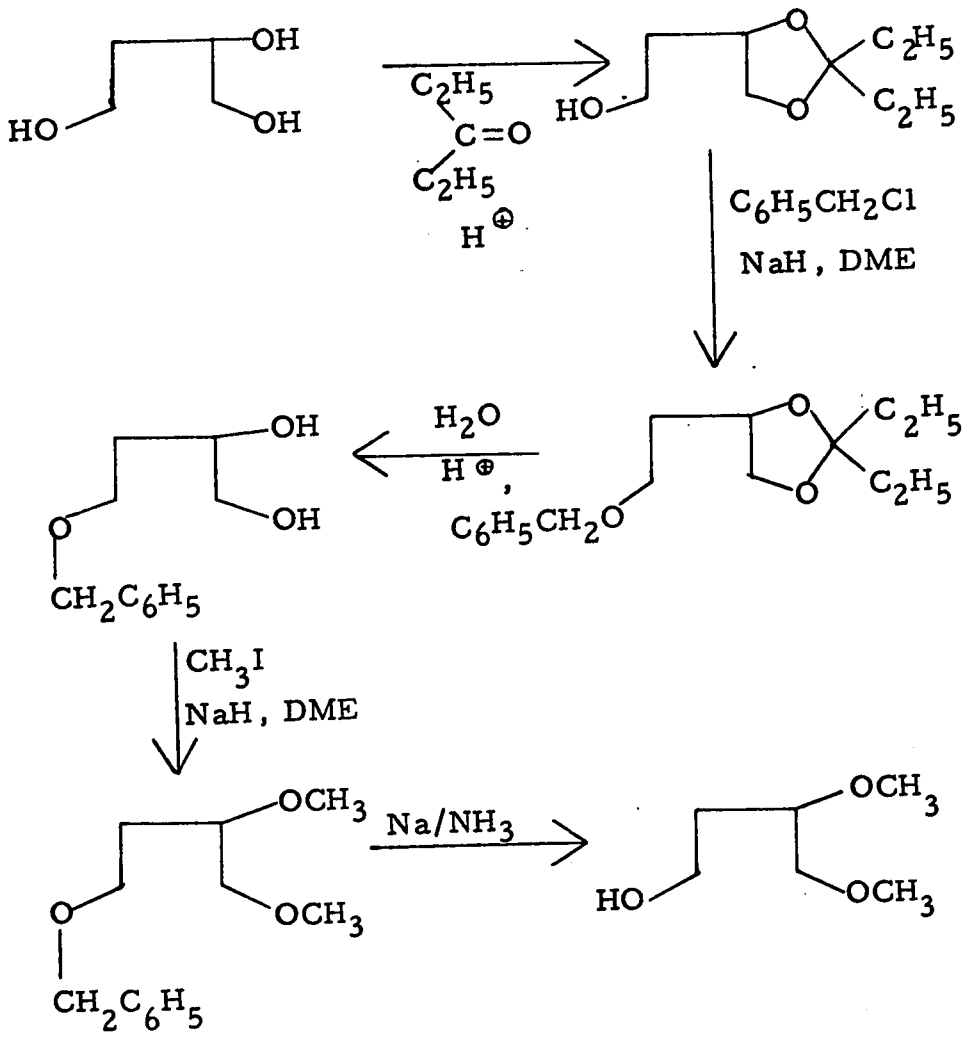
TABLE 21

Hydrogenolysis of the cis:trans mixture of 2,3-dimethoxytetrahydrofuran with $AlClH_2$.

Time (h)	Recovery,%	%Reduced	Ring Cleavage,* %	Side Chain Cleavage,* %
2	95	10	100	0
168	81	80	100	0

* These columns represent the relative amounts of reduced product.

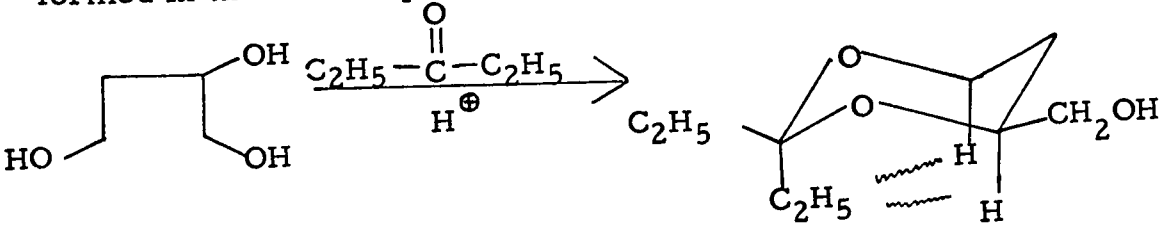
The ring cleavage product was collected by preparative g.l.c.. The microanalysis, n.m.r. and i.r. spectra all agreed with the proposed structure. As well, an authentic sample was prepared from 1,2,4-butanediol by the route shown in Scheme 70. The n.m.r. and i.r. spectra, and analysis were identical with those of the hydrogenolysis product.



(DME = 1,2-dimethoxyethane)

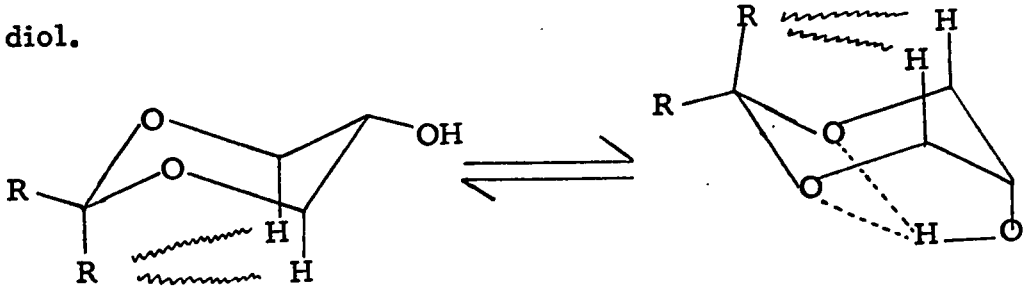
Scheme 70

The only problem which may have arisen in this preparation was the fact that a six-membered dioxane ketal may have been formed in the first step. This is shown in Scheme 71.



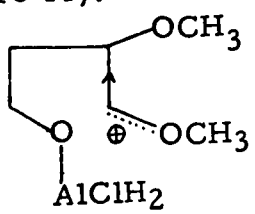
Scheme 71

However, it is known that glycerol preferentially forms five-membered, rather than six-membered ketals (83). This was attributed to the two 1,3-interactions of one of the C-2 alkyl groups as shown in Scheme 72 for glycerol and Scheme 71 for 1,2,4-butanediol.



Scheme 72

The hydrogenolysis of the 2,3-dimethoxytetrahydrofuran was a much slower reaction (requiring 168 hours for 80% reduction) than was the hydrogenolysis of the unsubstituted 2-methoxytetrahydrofuran (requiring only two hours for complete reduction (5)). This was in agreement with Diner's results (7) for the slow hydrogenolysis of the C-3 substituted tetrahydropyranyl acetals. Accordingly, the explanation of the inductive effect of the C-3 methoxy group destabilizing the oxocarbonium ion or increasing the energy of the transition state leading to the oxocarbonium ion from endo cleavage, as proposed by Diner (7), can be applied to the C-3 methoxytetrahydrofuranyl acetal (Structure 11).



Structure 11

The exclusive endo cleavage found in the hydrogenolysis of 2,3-dimethoxytetrahydrofuran was an expected result. All of the 2-alkoxytetrahydrofurans gave endo cleavage and there was no reason for the C-3 methoxy group to favor exo cleavage.

There appears to be little difference in the reactivity of the two isomers since the unreacted acetal after 168 hours still showed about 20% cis and 80% trans isomer to be present on g.l.c. analysis. It is possible that the acetal was isomerized by the aluminum species during the very long reaction period (168 hours). However, a two molar excess of $AlClH_2$ was used during the reduction and any carbonium ion formed should be reduced very quickly before recyclization and isomerization could occur.

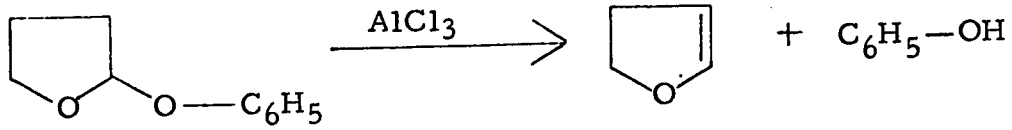
In summary, the C-3 methoxy group has no effect in directing the hydrogenolysis of the 2,3-dialkoxytetrahydrofurans. Exclusively endo cleavage was found for both the C-3 methoxy and the unsubstituted 2-methoxytetrahydrofurans. The principal effect of the C-3 methoxy group appears to be that of retarding the rate of reduction, probably by destabilizing the oxocarbonium ion, i.e. increasing the energy of the transition state leading to oxocarbonium ion formation.

F. Reaction of 2-Aryloxytetrahydrofurans and 2-Aryloxytetrahydropyrans with $AlCl_3$.

As described above all of the C-2 aryloxy acetals were found to react faster with $AlClH_2$ than did 2-ethoxytetrahydrofuran,

regardless of the substituents on the aryl ring (Table 18). A number of competitive hydrogenolyses were then carried out to determine if there were differences in the ease of reactivity among the C-2 aryloxy acetals. During these reactions, between 75 and 100% of all the acetal present appeared to be reduced, in spite of the fact that there was only enough hydride present to reduce 50% of the acetal, assuming that all of the hydride was active. This indicated that a large amount of the acetal reaction was being caused by just the aluminum species in the solution. Because of this complication, no conclusions could be drawn from the competitive reductions and their results are not listed. However, a number of interesting observations were made concerning the reaction of the C-2 aryloxy acetals with $AlCl_3$.

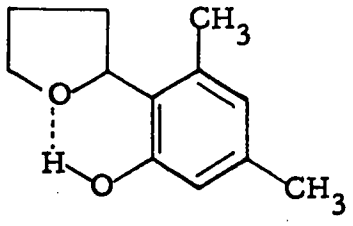
To verify the observation that the acetals were in fact reacting with the aluminum species and to determine what products were being formed, a number of C-2 aryloxy acetals (both tetrahydrofurans and tetrahydropyrans) were each allowed to react with $AlCl_3$ itself. In most cases, a phenol was formed indicating a simple Lewis acid catalyzed cleavage to 2,3-dihydrofuran (which subsequently polymerized) and a phenol. This is shown in Scheme 73 for 2-phenoxytetrahydrofuran.



Scheme 73

In addition to the phenol formation, for each of the 2-aryloxytetrahydrofurans hydrogenolyzed, a small amount of a high boiling material was formed (one high boiling compound for each acetal reacted). However, in the case of the C-2 3,5-dimethylphenoxy acetals, a large amount (74%) of the high boiling material was formed. These were the same high boiling materials that had been found in the attempted competitive reductions. This indicated that the high boiling materials were not the 4-aryloxy-1-butanols arising from reduction of the acetals since there was no feasible route by which such a compound could be formed by the action of $AlCl_3$ alone on the acetal. The high boiling materials were then most likely rearrangement products, whose structural elucidation initially presented a problem because of the difficulty in separating these very minor products from the reaction mixture.

However, when it was found that 2-(3,5-dimethylphenoxy)-tetrahydrofuran gave the rearranged material in 75% yield, it was quite an easy task to separate and purify the high boiling material. This was done in one step by chromatography on an acid-washed alumina column, resulting in a white crystalline solid being obtained. To this compound was assigned the structure shown in Structure 12, on the basis of its elemental analysis, and its n.m.r. and i.r. spectra.



Structure 12

The n.m.r. spectrum is shown in Figure 4. There are two singlets at τ3.45 and τ3.50 which are indicative of two non-equivalent aromatic protons. The multiplet centered at τ4.9, whose integrated area requires it to be due to one proton, is in approximately the same position in the spectrum as is the C_2-H of 2-phenyltetrahydrofuran (τ 5.2). The phenolic proton, which only slowly exchanged with D_2O, was found as a singlet at τ1.0, considerably downfield from where the signal of the proton on the hydroxyl group of a phenol is usually found (τ 4.62 for 3,5-dimethylphenol in $CDCl_3$). This shift can be explained by intramolecular hydrogen bonding between the proton and ring oxygen, as shown in Structure 12. This is an effect similar to that due to the intermolecular hydrogen bonding of any alcohol with dimethylsulfoxide, which results in a marked downfield shift of the hydroxyl proton (84). This would also explain the slow and incomplete exchange with D_2O.

An independent synthesis of the methylated derivative of the phenolic rearrangement product was carried out starting with 3,5-dimethylanisole as shown in Scheme 74.

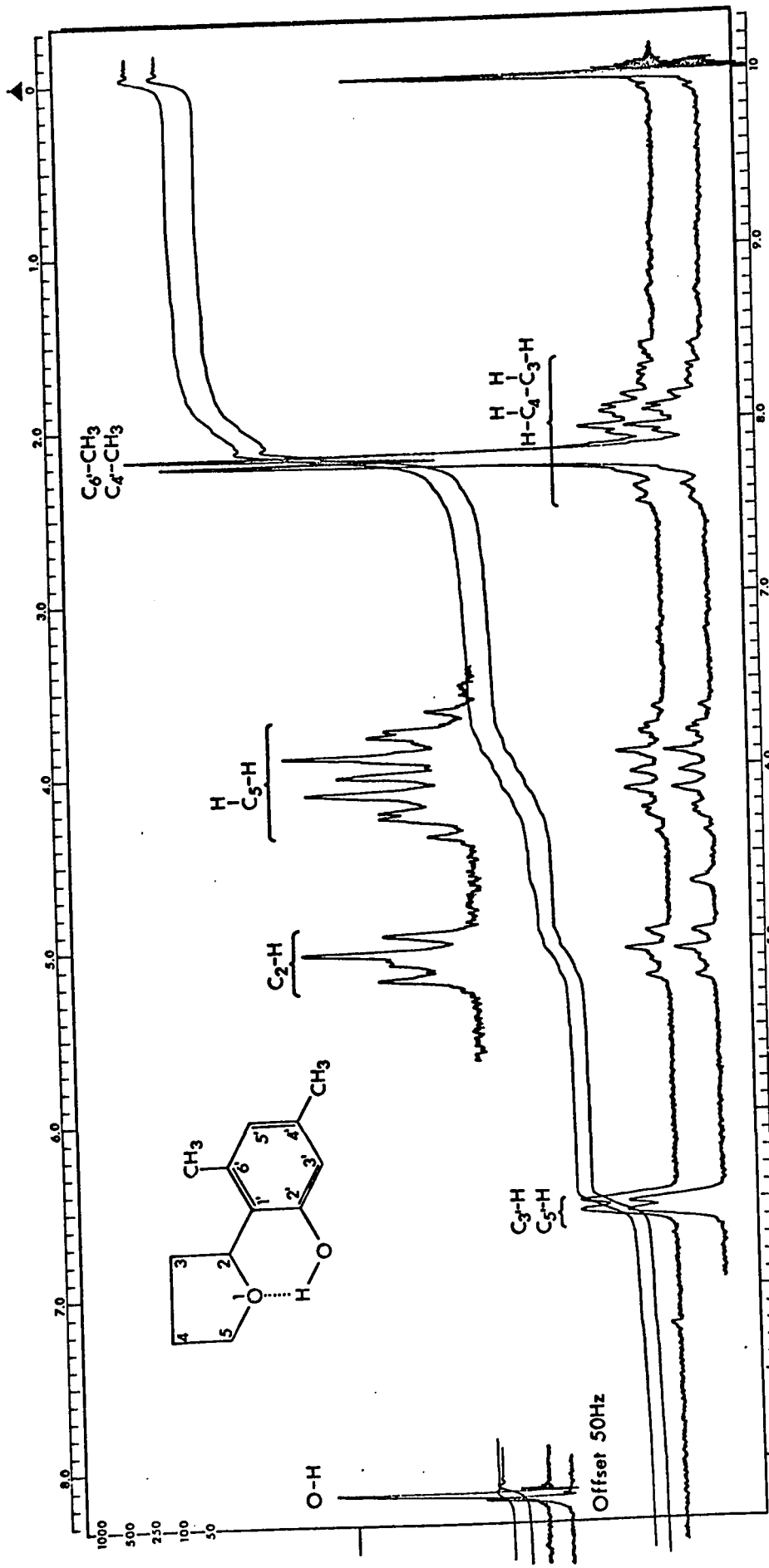
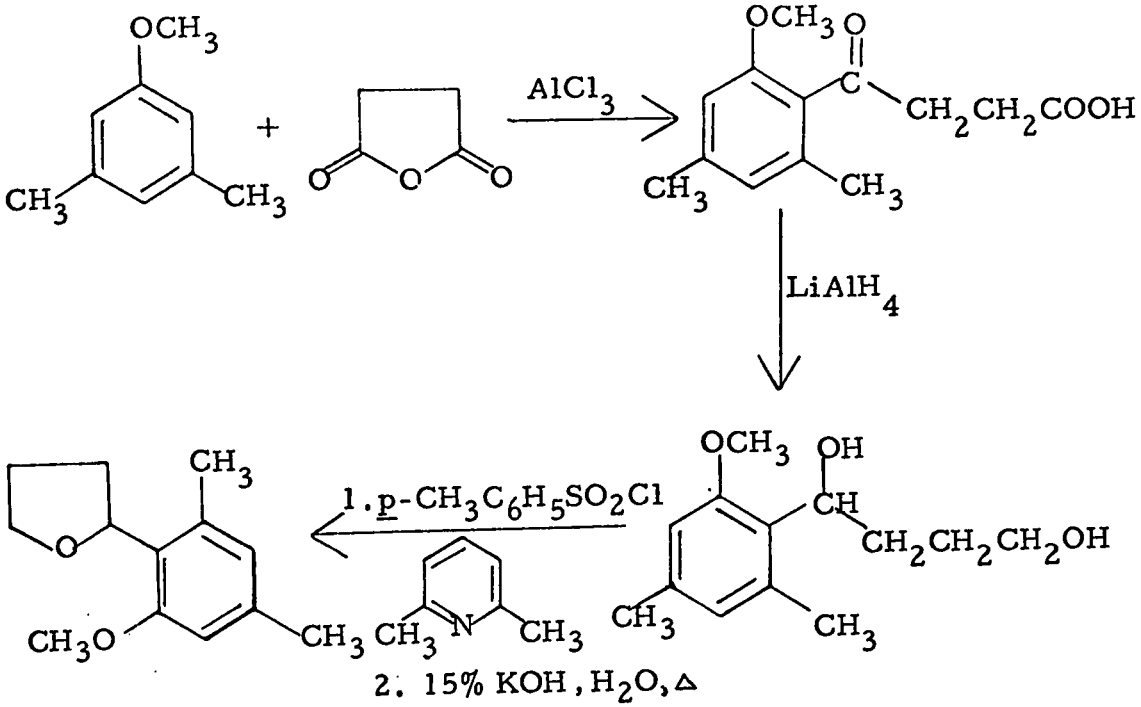
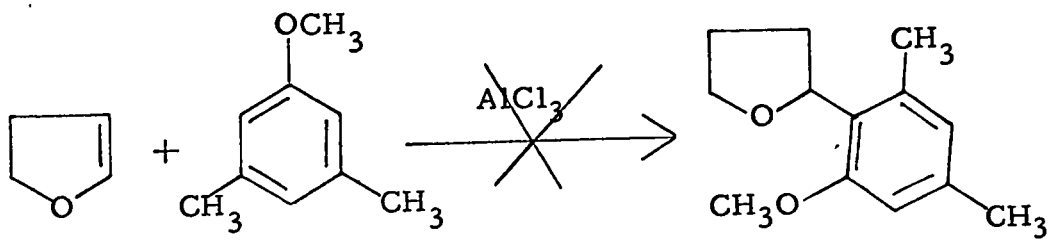


Figure 4. 60 MHz n.m.r. spectrum of 2-(4,6-dimethyl-2-hydroxyphenyl)tetrahydrofuran in $CDCl_3$ referred to tetramethylsilane. The lower spectrum was taken after shaking with D_2O.



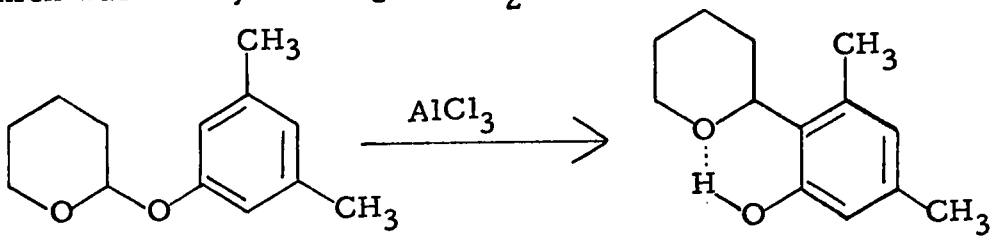
Scheme 74

The n.m.r. and i.r. spectra, and elemental analysis of the synthesized compound all agreed with those of the methylated derivative of the rearrangement product. An attempt was also made to synthesize this compound directly by a Friedel-Crafts reaction between 2,3-dihydrofuran and 3,5-dimethylanisole, using $AlCl_3$, H_2SO_4 and HCl individually as catalysts. Only polymerization of the dihydrofuran took place in all cases (Scheme 75).



Scheme 75

In a similar fashion the rearrangement product from 2-(3,5-dimethylphenoxy)tetrahydropyran was isolated and purified. The elemental analysis, n.m.r. and i.r. spectra all agreed with the proposed structure shown in Scheme 76. The n.m.r. spectrum in $CDCl_3$ showed two singlets at τ 3.48 and τ 3.55, indicative of two nonequivalent aromatic protons, as well as a singlet at τ 1.5 which was slowly exchanged in D_2O.

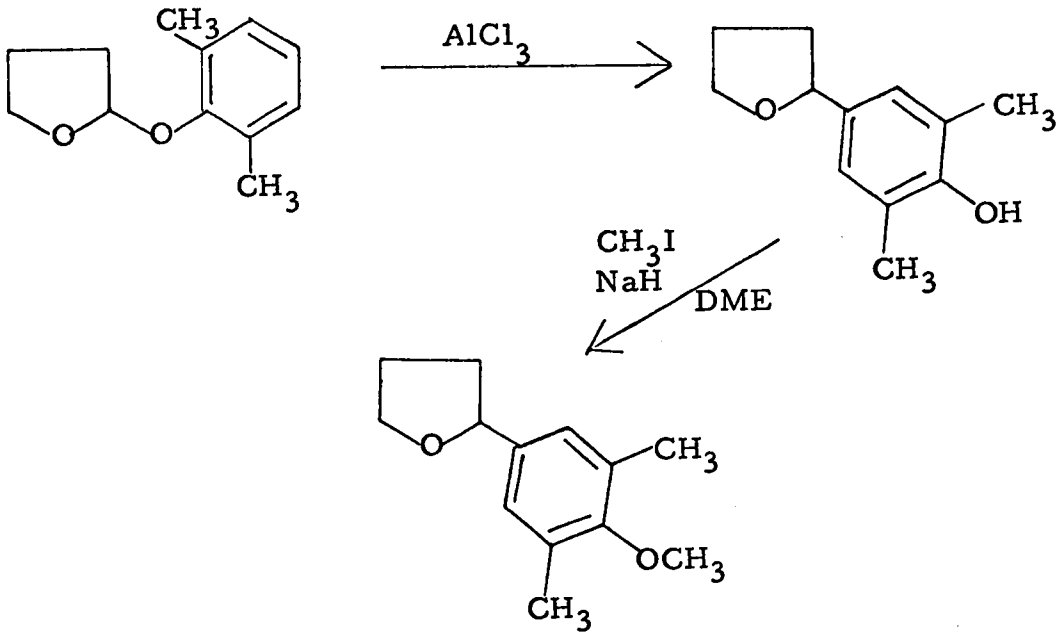


Scheme 76

An authentic sample of the rearranged product was not prepared by an unambiguous route. Instead, the product was identified simply on the basis of the n.m.r. and i.r. spectra and the elemental analysis. The similarity of the spectra to those for the 2-(4,6-dimethyl-2-methoxyphenyl)tetrahydrofuran (which was positively identified) was also considered.

When 2-(2,6-dimethylphenoxy)tetrahydrofuran was treated with $AlCl_3$, only a small amount of this type of rearrangement product was found. A large amount of a completely different rearrangement product, peculiar to this acetal, was found instead. The small amount (16%) of normal rearrangement product, when methylated was distillable and the elemental analysis, n.m.r. and

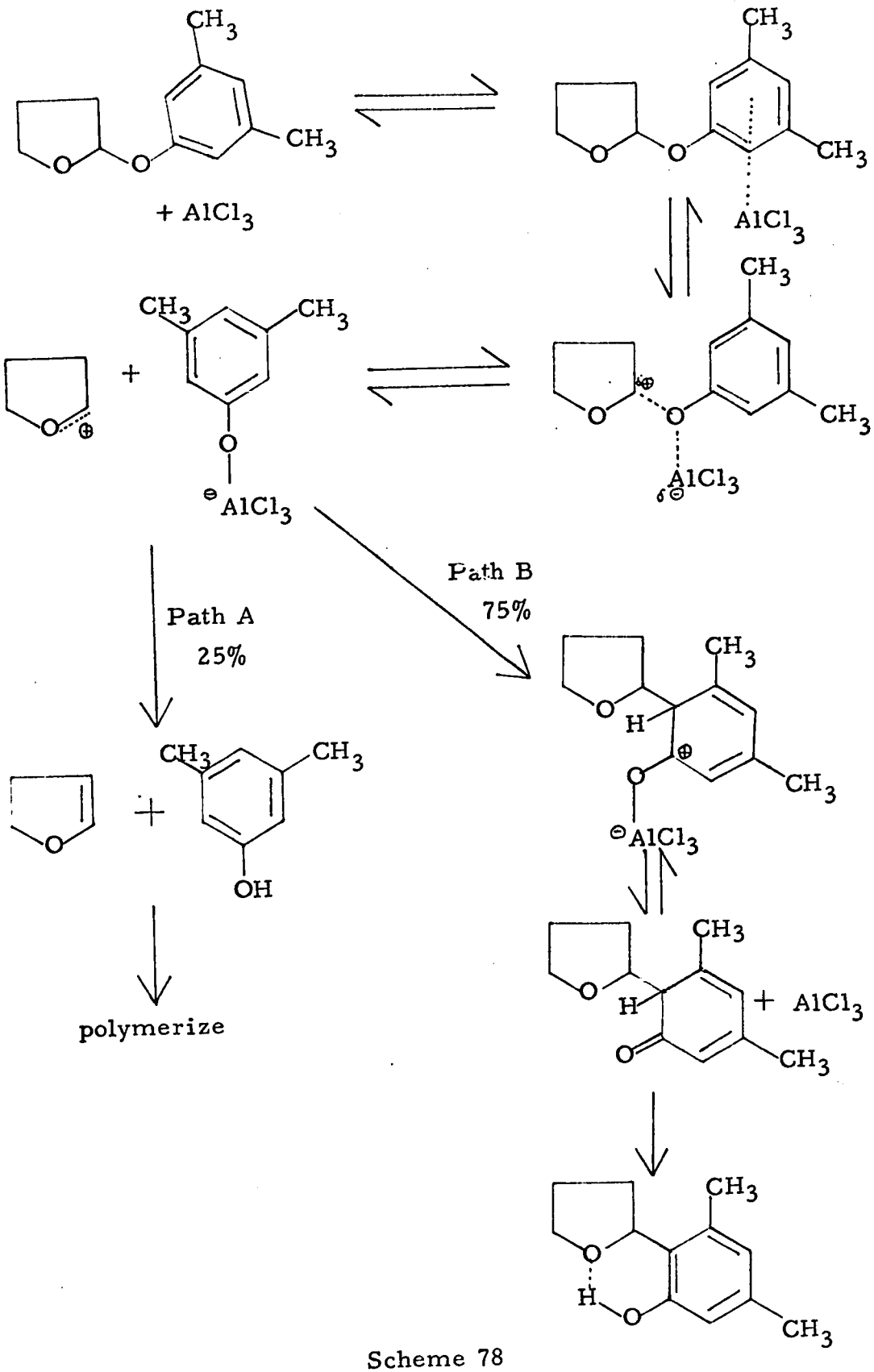
i.r. spectra of this methylated product all agreed with the structure shown in Scheme 77.



Scheme 77

Authentic material was prepared by the same route as outlined in Scheme 74, starting from 2,6-dimethylanisole. The n.m.r. and i.r. spectra, and the elemental analysis of this authentic material all were identical to those of the methylated rearrangement product.

The formation of the rearrangement product, no doubt, involves a mechanism, whereby the $AlCl_3$ forms a complex with the aryl ring, thus facilitating exo cleavage and the formation of a carbonium ion on the tetrahydrofuran ring. Besides simply recombining to give the acetal, the carbonium ion can react in two ways. It can lose a proton to give 2,3-dihydrofuran (path A, Scheme 78), which probably polymerizes in the presence of $AlCl_3$,


CH3
CH3
+ AlCl3
AlCl3
CH3
CH3
CH3
CH3
AlCl3
AlCl3
Path A
25%
Path B
75%
CH3
CH3
OH
CH3
CH3
AlCl3
CH3
+ AlCl3
CH3
CH3
polymerize

Scheme 78

or it can react with the aluminum salt of the phenol (path B, Scheme 78), most likely by a Friedel-Crafts type condensation.

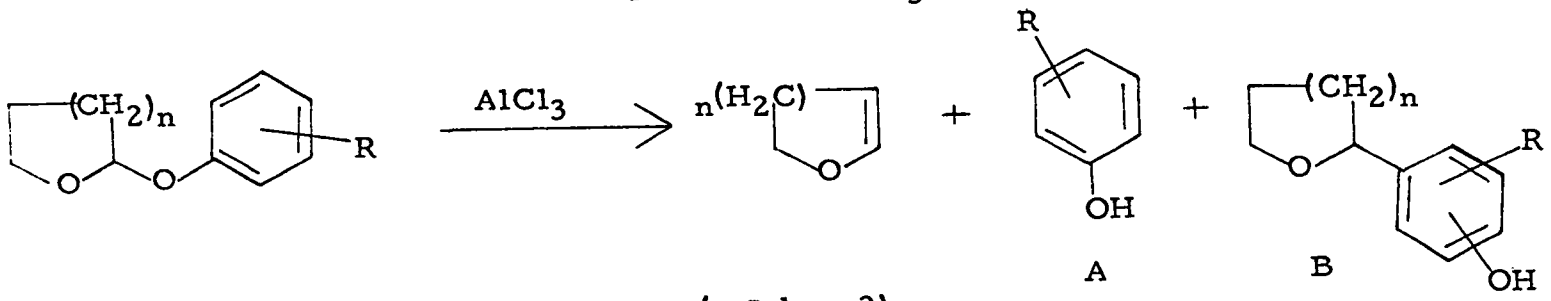
It is expected that the activating effect of the methyl groups attached to the aryl ring would result in a large amount of this Friedel-Crafts type reaction. This is clearly evident, since the C-2 3,5-dimethylphenoxy acetal gives 75% of the rearrangement product, while the C-2 phenoxy acetal gives only 10-15% of the rearrangement product and the C-2 2,6-dichlorophenoxy acetal gives absolutely no rearrangement product. In the absence of the unusual reaction which has been found to take place when the 2-(2,6-dimethylphenoxy)tetrahydrofuran was treated with $AlCl_3$, one might expect the same type of rearrangement in a similar yield for the 2-(2,6-dimethylphenoxy)tetrahydrofuran as that found for 2-(3,5-dimethylphenoxy)tetrahydrofuran.

The results from the reaction of $AlCl_3$ with the C-2 aryloxy acetals are shown in Table 22.

The rearrangement products were isolated and characterized only in the three cases mentioned. Such small amounts were formed in the other cases studied that it was impossible to isolate them. However, their retention times were similar to the retention times of the rearranged materials actually isolated and it was on this basis that the structures of the rearrangement products were assigned in each of these cases.

TABLE 22

Reaction of 2-Aryloxytetrahydrofurans and 2-Aryloxytetrahydropyrans with One-quarter Equivalent of $AlCl_3$.



(n = 1 or 2)

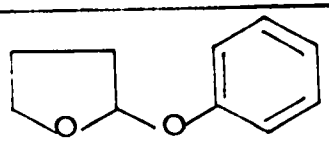
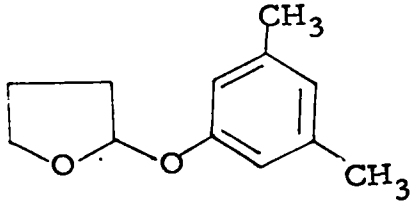
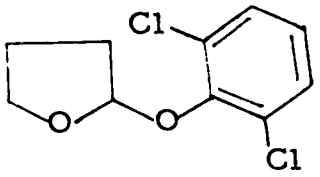
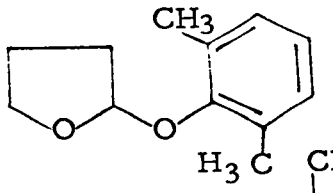
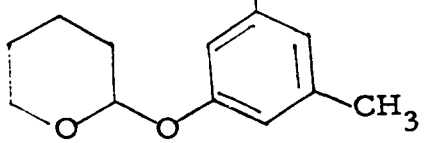
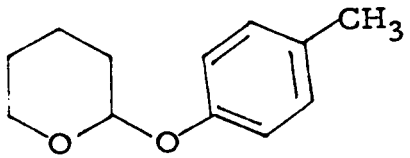
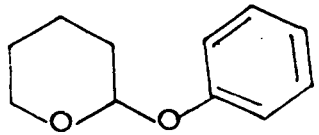
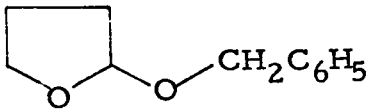
Compound	Time	Recovery (%)	Reaction (%)	A*	B
	2 h	91	100	86.5	13.5
	10 min	94	100	25	75
	2 h	95	100	100	0

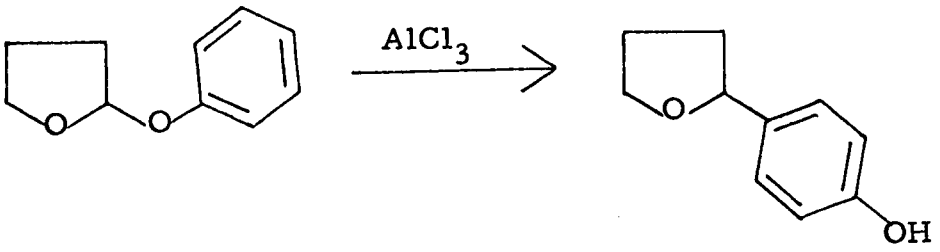
TABLE 22 - Continued

Compound	Time	Recovery (%)	Reaction (%)	A*	B
	10 min	88	100	10.5	16.5**
	10 min	85	100	30	70
	2 h	85	100	90	10
	2h	90	77.5	97	3
	2h	92	35.6	100	0

* Estimated by measuring on g.l.c. the amount of phenol produced. The dihydrofuran (dihydropyran) could not be measured since it polymerized immediately. Represents the relative amounts of reacted product.

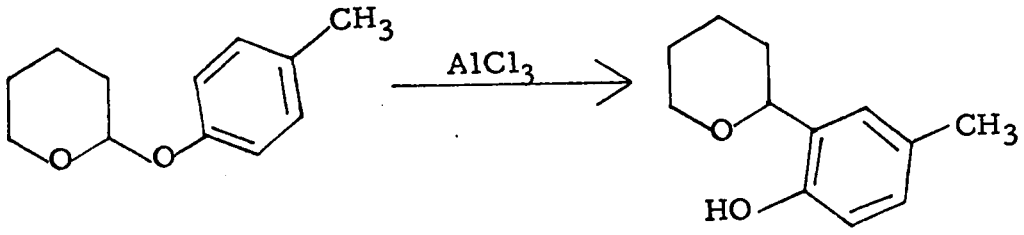
** The remainder (73%) of the product was a phenol-phenol coupling product not found for any of the other phenols.

The rearrangement in the two cases studied took place to the position on the phenyl ring which seems to be the most favorable position at which other Friedel-Crafts reactions occur (i.e. the reaction with succinic anhydride) (85). Therefore, one might assume that the 2-phenoxytetrahydrofuran would rearrange directly to the para position (Scheme 79) rather than one of the ortho positions. This was predicted since anisole reacts with succinic anhydride in the presence of $AlCl_3$ only at the para position (85, 86).



Scheme 79

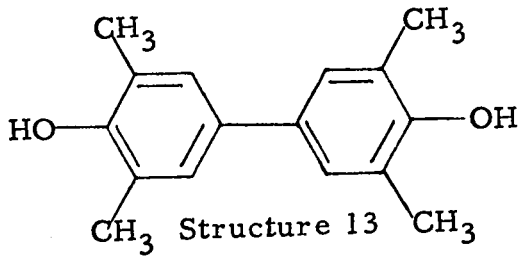
Similarly the 2-(4-methylphenoxy)tetrahydropyran would rearrange to a position ortho to the hydroxy function (85) (Scheme 80).



Scheme 80

As noted earlier, 2-(2,6-dimethylphenoxy)tetrahydrofuran undergoes a different type of rearrangement. Of the total recovered material, only 10.5% is 2,6-dimethylphenol and 16.5% is the

expected rearrangement product (Scheme 77). The remainder (73%) is the phenol-phenol coupling product 4,4'-dihydroxy-3,3',-5,5'-tetramethylbiphenyl shown in Structure 13.



Structure 13

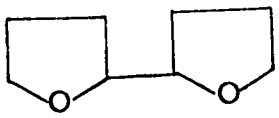
The observed melting point was 216-217°C, 4°C below that reported by Auwers and Markovits (87), and the n.m.r. and i.r. spectra supported the proposed structure, as did the elemental analysis. The n.m.r. and i.r. spectra of the methylated compound (4,4'-dimethoxy-3,3',5,5'-tetramethylbiphenyl) also agreed with the proposed structure. The acetyl derivative was prepared and found to have a melting point of 172-173°C. That reported by Auwers and V. Markovits was 174-175°C.

No reasonable mechanism could be proposed for the formation of this compound since an oxidation step is required. This must involve either a valence change of a metal ion, the formation of hydrogen during work-up, or the interaction of a large amount of oxygen. However, $AlCl_3$ cannot change its valence state. No visible evolution of hydrogen was noted during the work-up and the reaction proceeded as well under a nitrogen atmosphere as it did under an oxygen atmosphere.

It was also found that the biphenyl coupling product could not have arisen from the 2,6-dimethylphenol and $AlCl_3$ under the

reaction conditions. When the 2,6-dimethylphenol and $AlCl_3$ were stirred in ether for two hours, only phenol was isolated. Also, the coupling product must have been formed during the reaction and not during work-up. This was the obvious conclusion when it was found that the residue obtained after evaporation of the ether solvent, when immediately added to a sodium hydride-methyl iodide suspension in 1,2-dimethoxyethane, gave approximately a 75% yield of the 4,4'-dimethoxy-3,3',5,5'-tetramethylbiphenyl.

A serious handicap in the study of this reaction was that the tetrahydrofuran ring residue could not be isolated in any form. In spite of repeated attempts to carefully examine the product mixture, neither tetrahydrofuran nor the 2,2'-dimer of tetrahydrofuran (Structure 14) could be isolated. These are possible products from an oxidation mechanism. Hence, no conclusions as to the effective mechanism could be drawn.



Structure 14

In summary, it was found that the 2-aryloxytetrahydrofurans and 2-aryloxytetrahydropyrans did react readily under the influence of aluminum chloride. The main product in most cases was the corresponding phenol and 2,3-dihydrofuran or 3,4-dihydro-2H-pyran. However, if the phenol ring was activated by electron

donating groups, such as methyl groups, then a considerable quantity of 2-aryltetrahydrofuran or pyran was obtained as the result of rearrangement. It is readily seen that a partial hydrogenolysis of the C-2 aryloxy acetals with an insufficient amount of reducing agent cannot be carried out because of this rearrangement, which occurs readily in the presence of the aluminum species or Lewis acid. A different rearrangement product (4,4'-dihydroxy-3,3',5,5'-tetramethylbiphenyl) was isolated from 2-(2,6-dimethylphenoxy)tetrahydrofuran, which could only have arisen from an oxidative phenol-phenol coupling. However, no reasonable route could be proposed for its formation.

G. Stereochemistry of the 2,5-Disubstituted tetrahydrofurans.

Miss Makhubu had synthesized and hydrogenolyzed the 5-methyl- and 5-methoxymethyl-2-methoxytetrahydrofurans. However, she had been unable to separate the *cis* and *trans* isomers, thought to be present in the two compounds, or even to determine their relative amounts. It was possible that one isomer was reacting to give *exo* cleavage and the other to give *endo* cleavage due to a steric effect of the substituents. Hence, a definite conclusion about the relative importance of the steric and polar effects could not be drawn from the results of the hydrogenolyses. It was therefore important to determine the

isomer distribution and find whether or not each isomer could be reacting in a specific direction.

The compounds 5-methyl-2-methoxytetrahydrofuran, 5-methoxymethyl-2-methoxytetrahydrofuran and 5-benzyloxy-2-methoxytetrahydrofuran were prepared. In agreement with Miss Makhubu's findings, absolutely no separation of the isomers could be obtained by g.l.c., using a variety of columns including carbowax, butanediol succinate, Apiezon T and silicone rubber. The 100 MHz n.m.r. spectra of each of these mixtures were obtained and analyzed in an attempt to determine the isomer distribution. The spectrum of 5-methyl-2-methoxytetrahydrofuran is shown in Figure 5.

The anomeric proton absorption occurs at τ 5.05 and contains two distinct quartets in the ratio of 3 to 2. The larger quartet was centered at τ5.02 and the smaller was centered at τ5.10. This indicates that there are two isomers present in the ratio of 3 to 2. No assignment could be made of one of the isomers to a specific signal.

As described previously, Mihailovic and coworkers (20) had found a similar shift for the α-proton signals of the cis and trans isomers of the 2,5-dialkyltetrahydrofurans. They were able to make a definite assignment of the isomer configuration on the basis of the optical activity of the separated isomers. For example, the α-proton signal for the trans isomer of 2,5-dimethyltetrahydrofuran was shifted downfield relative to the signal for the

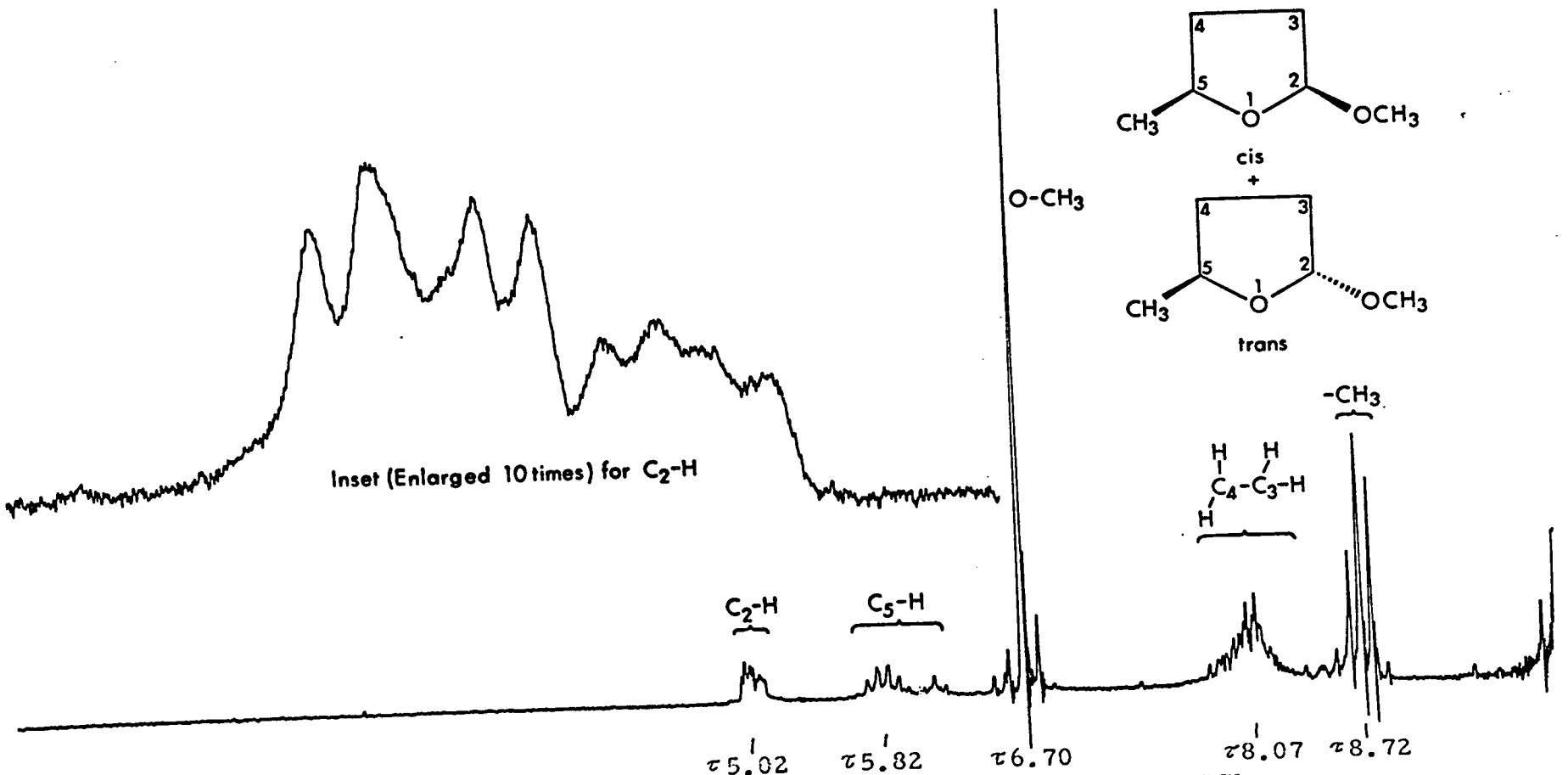


Figure 5. 100 MHz n.m.r. spectrum of 5-methyl-2-methoxytetrahydrofuran in CCl_4 referred to tetramethylsilane. The inset is an expansion of the signal for the anomeric proton.

α-protons of the cis isomer. This shift was attributed to a deshielding effect of the quasi-axial methyl groups of the trans isomer on the α-protons across the ring.

Gagnaire and Monzeglio (25) earlier had reported results similar to those of Mihailovic and coworkers (20) for chemical shifts of the α-protons in the 2,5-dialkyltetrahydrofurans. However, upon expanding their study to other symmetrically 2,5-disubstituted tetrahydrofurans, Gagnaire and Monzeglio found variations in the chemical shift differences which indicated that it was not a reliable basis for assigning the isomer configuration. For example, in 2,5-bishydroxymethyltetrahydrofuran, the cis isomer's α-proton absorption was shifted downfield relative to that of the trans α-proton. This is just the opposite direction found for the shift in the 2,5-dialkyltetrahydrofurans. Hence, only a stereospecific synthesis of one of the isomers in the 2,5-disubstituted tetrahydrofurans would reliably provide one or the other of the two isomers.

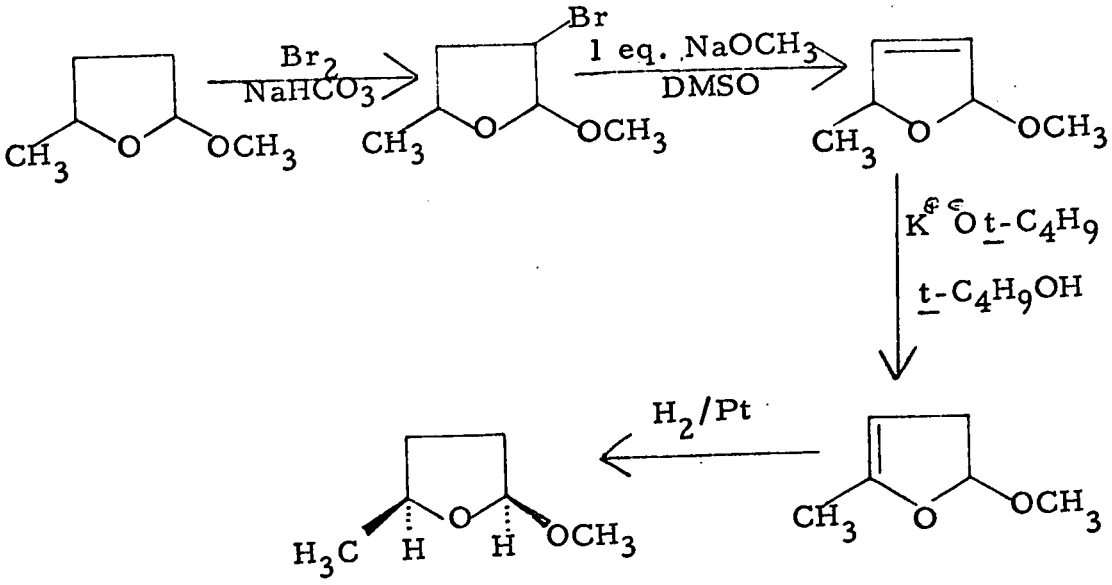
The multiplet for the anomeric proton of 5-methoxymethyl-2-methoxytetrahydrofuran at τ 5.1 was not as clearly resolved as that for the anomeric proton of 5-methyl-2-methoxytetrahydrofuran. However, there did appear to be two overlapping quartets whose area ratio lay between 1:1 and 3:2. The anomeric proton absorption for the cis-trans 5-benzyloxymethyl-2-methoxytetrahydrofuran at τ 5.1 clearly showed two slightly overlapping quartets in the approximate area ratio of 3:2. Similarly, the anomeric

proton absorptions for the 5-isopropyl- and 5-t-butyl-2-methoxytetrahydrofurans and 2-methoxy-5-phenyltetrahydrofuran were all in the τ 5.0 to 5.2 region. While they were not as clearly resolved in the 60 MHz spectra, they appeared as overlapping multiplets whose area ratios lay between 1:1 and 3:2.

With the exception of 5-methyl-2-methoxytetrahydrofuran, for which the exo to endo cleavage ratio is 3:2 (Table 10 and 11), the 3:2 isomer ratio does not coincide with the extent of exo to endo cleavage for any of the C-5 substituted acetals. It can therefore be concluded, that each isomer does not react to form one specific product in these 5-substituted-2-methoxytetrahydrofurans. However, in the case of the C-5 methyl acetal, the exo:endo cleavage ratio of 3:2 exactly parallels the 3:2 ratio of the isomers. This indicates that possibly the isomer in larger amount is reacting to give exclusively exo cleavage and the isomer in smaller amount to give endo cleavage.

In order to clarify this problem, an attempt was made to synthesize stereospecifically the cis isomer, since it was clearly apparent that the isomer mixture could not be separated by g.l.c.. The proposed synthetic sequence is shown in Scheme 81.

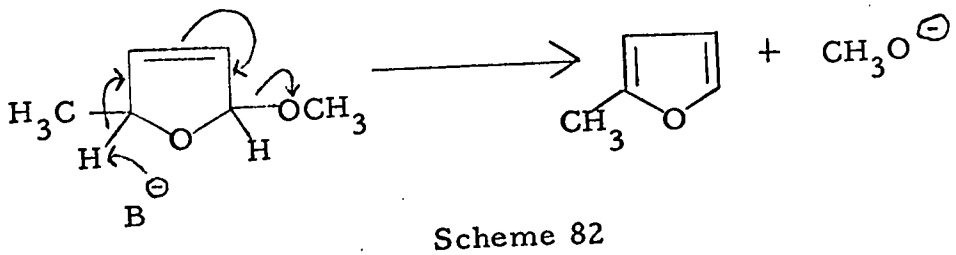
The bromination (88) and dehydrobromination (89) procedures, which were employed successfully, followed the directions which have appeared recently in the literature.



(DMSO = dimethylsulphoxide)

Scheme 81

The base catalyzed isomerization of the 2,5-dihydro compound was thought to be possible because it is known that 2,5-dihydrofuran is easily isomerized to 2,3-dihydrofuran by the action of potassium tertiary butoxide in t-butyl alcohol (4). The isomerization of 5-methyl-2-methoxy-2,5-dihydrofuran to 5-methyl-2-methoxy-2,3-dihydrofuran was expected to occur since the C-5 proton of the former compound should be more easily removed by base than should the anomeric proton of that compound. However, when the unsaturated acetal was added to either $NaOCH_3$ in DMSO or KO-t-C_4H_9 in t-C_4H_9OH, an immediate reaction took place which provided 2-methylfuran. The mechanism proposed for this reaction is shown in Scheme 82.



Scheme 82

The second attempt to clarify this problem was based on the view, that if a steric effect were important in the hydrogenolysis of the two isomers, then either the cis or the trans isomer should react more readily. Accordingly, a quantity of the cis-trans mixture of 5-methyl-2-methoxytetrahydrofuran was subjected to hydrogenolysis with a limited amount of $AlClH_2$, insufficient to cleave all of the acetal. The unreduced starting material was isolated and examined by n.m.r.. The spectrum showed that the two isomers were still present in the same proportion as found in the original mixture. As well, the ratio of exo to endo cleavage from the partial hydrogenolysis agreed with the ratio found after complete hydrogenolysis. Similarly, when partial hydrogenolyses were carried out on the 5-isopropyl- and 5-t-butyl-2-methoxytetrahydrofurans, the unreacted acetal recovered had the same isomer ratio as did the starting acetal. In the last two cases, the isomer distribution could be seen on g.l.c..

It might be argued that one isomer was reacting faster than the other, but that isomerization was also occurring to give the same isomer ratio after partial reduction. However, Leggetter and Brown had previously found, at the very most, only a trace of isomerization to occur in the 2,4-dimethyl-1,3-dioxolanes during

hydrogenolysis (19). Since the structure of the 2,4-disubstituted dioxolane is similar to that of the 2,5-disubstituted tetrahydrofurans, extensive isomerization does not seem to be very likely in these latter compounds.

The inference is that a bulk steric effect due to groups in the C-2 and C-5 positions seems to be of no importance in promoting a different course of cleavage for each isomer. If the much more bulky t-butyl and isopropyl groups have very little or no steric effect in isomer reactivity, it is even less likely that the methyl group should have such a large steric effect as to cause the isomers to react in specific directions. Examination of the models of cis- and trans-5-substituted-2-methoxytetrahydrofurans shows very little difference in the extent of steric shielding of the ring oxygen in the two isomers.

This is not to say, however, that the C-5 substituent does not affect the ease of complex formation of the ring oxygen. In fact, the greater the size of the substituent at C-5, the weaker will be the complex formation at the ring oxygen (27, 32). However, there seems to be little difference in the strength of the two complexes formed between the aluminum species and the cis and trans isomers.

In summary, all of the 5-substituted-2-methoxytetrahydrofurans contain between a 3:2 and 1:1 ratio of cis and trans (or trans and cis) isomers. In no case does a cis isomer hydrogenolyze to provide one specific product. Hence, the steric effect of the C-2

and C-5 substituents does not appear to cause a difference in the reactivity between the two isomers.

SUMMARY

1. The syntheses of a number of 5-substituted 2-alkoxytetrahydrofurans and 2-aryloxytetrahydrofurans have been described. The acetals, 5-isopropyl- and 5-t-butyl-2-methoxytetrahydrofuran, were prepared from the corresponding γ-substituted-γ-butyrolactones by the method of Korte and coworkers. A number of unsuccessful attempts were made to reduce the γ-butyrolactones directly to the tetrahydrofuranyl acetals. As well, authentic samples of the possible products from the hydrogenolysis of these acetals were prepared.

2. A study of the hydrogenolysis of these acetals using the species, $AlClH_2$ (from a 1:1 molar ratio solution of $LiAlH_4$ and $AlCl_3$), was undertaken.

3. The polar effect of the C-5 substituent appeared to be an important directing influence in the reductive cleavage of the 5-substituted-2-methoxytetrahydrofurans. Electron donating alkyl groups favored exo cleavage with a gradient of from 60% to 86% to 99% exo cleavage being found as the C-5 substituent was changed from CH_3- to i-C_3H_7 to t-C_4H_9. Electron withdrawing substituents at C-5 favored endo cleavage, with 83% and 93% endo cleavage product being found when the C-5 substituent was respectively

C_6H_5- and CH_3OCH_2-. Although of minor importance, the steric effect of the C-5 substituents must play some role in directing the reaction since some exo cleavage was found when the C-5 substituent was C_6H_5- and CH_3OCH_2-, even when all of the other directing effects favored endo cleavage. The strong basicity of the ring oxygen was still a factor in determining the direction of cleavage and caused predominantly endo cleavage (93%) when the polar effect of the C-2 and C-5 substituents cancelled in 2-isopropoxy-5-methyl-tetrahydrofurans. Complexation between the aluminum species and the electron withdrawing C-5 substituents (C_6H_5- and CH_3OCH_2-) was believed to play some role in directing the cleavage reaction.

4. A competitive hydrogenolysis showed that the acetal, 2-t- butoxytetrahydrofuran, reacted four times faster than did 2-ethoxytetrahydrofuran. This was interpreted in terms of the polar effect of the C-2 substituents, with the t-butyl group exerting a greater stabilizing effect on the oxocarbonium ion from endo cleavage than the ethyl group.

5. The 2-aryloxytetrahydrofurans gave exclusively exo cleavage upon reduction with $AlClH_2$. Also, the C-2 aryloxy acetals were reduced faster than the C-2 alkoxy acetals and this fact could not be satisfactorily explained by the polar effect of the C-2 aryloxy group. Instead, the results were interpreted in terms of a strong complex formation between the π-electron system of the aryl ring and the aluminum species.

6. A gradient from preferential exo to preferential endo cleavage of 2-benzyloxytetrahydrofuran was found as the Lewis acid reducing species was changed from $AlCl_2H$ to $AlClH_2$ to AlH_3 (90.5%, 48.5% and 20.5% exo cleavage respectively). This was attributed to a different preferential location of complexation for each species, which depended upon the strength of the electron attracting ability of the species. The polar effect of the benzyl group was concluded to be of minor importance.

7. The acetal, 2,3-dimethoxytetrahydrofuran, gave exclusively endo cleavage upon hydrogenolysis with $AlClH_2$. The C-3 methoxy group, therefore, did not affect the direction of cleavage of the unsubstituted 2-methoxytetrahydrofuran, which Miss Makhubu had previously shown to give exclusively endo cleavage. The principal effect of the C-3 methoxy group was to significantly slow the rate of hydrogenolysis of the substituted acetal compared to that of the unsubstituted acetal. In 168 hours only 80% reduction of 2,3-dimethoxytetrahydrofuran had occurred while 2-methoxytetrahydrofuran was completely reduced within 2 hours. This was attributed to the electron withdrawing effect of the C-3 methoxy group which destabilized any oxocarbonium ion formation.

8. The 2-aryloxytetrahydrofurans (and pyrans) were found to react with $AlCl_3$ in ether solution to give the corresponding phenol and dihydrofuran (or 3,4-dihydro-2H-pyran) along with varying amounts of a rearrangement product. The cleavage product was

attributed to a Lewis acid catalyzed cleavage of the acetal after the aluminum species had complexed with the aryl ring of the C-2 substituent. The rearrangement product isolated from the reaction of 2-(3,5-dimethylphenoxy)tetrahydrofuran with $AlCl_3$ was identified as 2-(4,6-dimethyl-2-hydroxyphenyl)tetrahydrofuran. This was concluded to be formed by a Friedel-Crafts type of reaction. The reaction of 2-(2,6-dimethylphenoxy)tetrahydrofuran with $AlCl_3$ produced the expected cleavage products (dihydrofuran and 2,6-dimethylphenol) and the rearrangement product, 2-(3,5-dimethyl-4-hydroxyphenyl)tetrahydrofuran, but only in a small yield (10% and 16% respectively). The remainder of the product (74%) was identified as the phenol-phenol coupling product, 4,4'-dihydroxy-3,3',5,5'-tetramethylbiphenyl, but no explanation could be given for its formation.

9. The exo to endo cleavage ratio of 60:40 found for 5-methyl-2-methoxytetrahydrofuran was found to closely parallel the cis/trans (or trans/cis) isomer ratio of 60:40 of the acetal. A stereospecific synthesis of cis-5-methyl-2-methoxytetrahydrofuran was attempted with no success. However, a partial hydrogenolysis reaction showed that the two isomers reacted at the same rate. Since a different rate of hydrogenolysis would be expected for each isomer if they were reacting to form different products, it was concluded that each isomer was forming the same proportion of exo and endo cleavage products. Therefore, there was not a difference in steric approach of the aluminum species to the two isomers.

EXPERIMENTAL

All boiling points and melting points in this work are uncorrected.

Gas liquid chromatographic analyses were made with an F and M, Model 700 instrument, equipped with 12 ft. by 1/8 in. columns packed with: (a) carbowax 20M, 20% on Gas Chrom P (60-80 mesh), (b) Apiezon T or Apiezon L, 10% on Chromosorb W (60-80 mesh) and (c) butanediol succinate, 20% on Chromosorb W (60-80 mesh). Helium was the carrier gas at a flow rate of about 40 ml per minute.

For preparative gas liquid chromatography, the instrument used was an Aerograph Autoprep, Model A-700 (Wilkens Instrument and Research Co.). The following columns were used: (a) 12 ft. by 1/4 in., packed with carbowax 20M, 20% on Gas Chrom P (60-80 mesh), (b) 12 ft. by 1/4 in., packed with butanediol succinate, 20% on Chromosorb W (60-80 mesh), (c) 6 ft. by 1/4 in., packed with Apiezon T, 10% on Chromosorb W (30-60 mesh) and (d) 12 ft. by 1/4 in., packed with 10% Carbowax 20M and 10% silicone rubber on Chromosorb W (30-60 mesh). Helium was the carrier gas.

The column temperature and type of column was dependent upon the boiling point of the compounds. For most analysis work on the F and M, Model 700, the temperature was linearly programmed in order to achieve better resolution. The temperature was increased at a speed of 15°C per minute starting from 50°C with

the terminal temperature being dependent upon the column stability.

The quantitative analyses were made by measuring the areas corresponding to the peaks involved. In a number of cases, these areas were compared with those obtained from known and weighed artificial mixtures. However, it was found that equimolar mixtures of hydrogenolysis products gave peaks of nearly equal area for the components (within a 10 % variation). Hence, the peak areas on most chromatograms were simply compared directly, without reference to authentic mixtures, to give the relative proportions of products in a mixture.

Infrared spectra were recorded with a Perkin-Elmer Model 337 instrument.

Nuclear magnetic resonance (n.m.r.) spectra 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. All spectra were referred to tetramethylsilane.

Elemental analyses were carried out by Mrs. Darlene Mahlow in the Chemistry Department of this University.

In the work-up procedures reported for the various syntheses described, solvents were removed with a rotatory evaporator under reduced pressure unless otherwise stated.

A. Attempted Synthesis of 5-Substituted-2-alkoxytetrahydrofurans.

Method 1 (unsuccessful)

Ethyl γ,γ-dimethylacetoacetate was prepared according to the published procedure described by Korte and coworkers (38) and used by Miss Makhubu (5).

Ethyl acetoacetate (26 g, 0.2 mole) was added to sodium ethoxide (4.6 g of sodium metal in 100 ml of absolute ethanol). The ethanol was distilled off and the remaining cake was suspended in anhydrous ether. Isobutyryl chloride (21.2 g, 0.2 mole) was added dropwise to the suspension at such a rate that the ether solution refluxed gently. The precipitated sodium chloride was separated by filtration and the filtrate diluted with water. The solution was extracted with ether and the ether extracts were then dried over magnesium sulfate, filtered, and the solvent removed. The residue was distilled giving a colorless liquid (17 g, 42.5%). B.p. 110°C at 15 mm; n_D^{25} 1.4490. Lit. b.p. 112-114°C at 16 mm; n_D^{25} 1.4515 (5).

To sodium ethoxide (2.0 g of sodium metal in 100 ml of absolute ethanol) was added dropwise with stirring, the isobutyryl acetoacetic ester (17 g) prepared as described above. The mixture was stirred at room temperature for 3 days, after which excess ethanol was removed. The residue was neutralized with dilute hydrochloric acid and extracted several times with ether. The combined ether extracts were dried over magnesium sulfate,

filtered and the solvent removed. The residue was distilled to give γ,γ-dimethylacetoacetic ester (7.0 g, 52.5%). B.p. 85-87°C at 16 mm; n_D^{25} 1.4202. Lit. b.p. 82-84°C at 14 mm; n_D^{25} 1.4235 (5).

Isobutyryl chloride was prepared by a modification of the method of Greenwood and coworkers (90).

Isobutyric acid (200 g, 2.3 moles) was cooled in an ice bath and phosphorus trichloride (150 g, 1.1 moles) was added dropwise. The mixture was stirred overnight at room temperature and then refluxed for one hour. A fractional distillation was performed and the fraction was collected which boiled between 90 and 95°C. This fraction was then redistilled to give a clear liquid (205 g, 85.2%). B.p. 90-95°C at 695 mm. Lit. b.p. 90-91°C at 700 mm (90).

Diethyl α-isobutyrylsuccinate was prepared by a modification of the procedure of Korte and coworkers (38).

To a solution of sodium metal (2.8 g, 0.12 mole) in 150 ml of absolute ethanol at 10°C, was added slowly γ,γ-dimethylaceto-acetic ethyl ester (20 g, 0.12 mole). The mixture was stirred for about one hour and ethyl chloroacetate (15 g, 0.12 mole) was added while the mixture was cooled in ice. The mixture was then refluxed until it was neutral to litmus (6 h). The precipitated sodium chloride was removed by filtration and washed with ether. The

filtrate and washings were combined and the solvents removed. Since attempted distillation of the ester on a small scale had resulted in a decarboxylation (5), the crude ester was subjected to the next step.

The attempted preparation of ethyl β-isobutyrylpropionate was carried out by the procedure of Korte and coworkers (38).

The crude diethyl α-isobutyrylsuccinate from the experiment described above was refluxed with 10 ml of concentrated sulfuric acid in 100 ml of water for 12 h. The mixture was cooled and the aqueous layer was saturated with ammonium sulfate. Separation of an oily layer (5, 38) was not observed. Extraction with ether yielded only a very small amount of organic material whose infrared spectrum did not show the expected two absorption bands for the two carbonyl groups. When stirred with absolute ethanol and acid for 12 h., this organic material gave an oil which did not have a g.l.c. retention time in agreement with that shown by authentic ethyl β-isobutyrylpropionate.

Since this reaction was unsuccessful, this reaction sequence was abandoned.

Method 2 (unsuccessful)

Isopropyl bromide was prepared by the method of Noller and Dinsmore (91).

Isopropyl alcohol (200 g, 3.3 moles) was cooled in a 1 l.

three neck flask with mechanical stirrer, to -10°C in an ice-salt bath. Phosphorus tribromide (300 g, 1.1 moles) was added dropwise at a rate such that the temperature did not rise above 0°C. After the addition of the phosphorus tribromide was complete, the solution was allowed to rise to room temperature and the isopropyl bromide was fractionally distilled. The fraction between 57°C and 60°C was collected to give 360 g (97%) of isopropyl bromide. B.p. 57-60°C at 695 mm; n_D^{25} 1.4243. Lit. b.p. 60-63°C at 760 mm (91).

The attempted preparation of ethyl β-isobutyrylpropionate was carried out following a modification of the procedure described by Kharasch and Reinmuth (39).

The isopropyl bromide (12.3 g, 0.1 mole) was added dropwise to a stirred suspension of magnesium turnings (2.4 g, 0.1 mole) in 100 ml of dry ether kept cool in an ice bath. When all of the bromide had been added, the solution was stirred at room temperature until all of the magnesium metal was consumed (0.5 h). The solution was then decanted into a dropping funnel. The Grignard reagent was added dropwise to a stirred solution of diethyl succinate (15.4 g, 0.1 mole) in 100 ml of dry ether cooled to -40°C in a dry ice-acetone bath during the addition. After complete addition, the solution was stirred with gradual warming to room temperature. Water (2.1 ml) was added gradually to the solution which was kept at 5°C by means of an ice bath. The ether was decanted and the

remaining solid was washed with 50 ml of ether. The combined ether solutions were dried over magnesium sulfate, filtered and the solvent removed. The residue, upon distillation, gave only diethyl succinate (12.2 g, 81% recovery). B.p. 98°C at 10 mm. Lit. b.p. 217°C at 760 mm (92).

The above procedure was repeated two more times, once adding the Grignard reagent to diethyl succinate in refluxing ether and once in refluxing tetrahydrofuran. In both cases, distillation of the residue after work-up gave only diethyl succinate (in 76% and 84% recovery) as determined by both the boiling point and the n.m.r. spectra of the products.

The attempted preparation of ethyl β-isobutyrylpropionate was carried out by a modification of the procedure of Fieser and Newman (40).

The isopropyl magnesium bromide, prepared as described above from isopropyl bromide (12.3 g, 0.1 mole) and magnesium turnings (2.4 g, 0.1 mole) in 100 ml of ether, was added dropwise to a solution of succinic anhydride (10 g, 0.1 mole) in 100 ml of dry ether, previously cooled to -70°C in a dry ice-acetone bath. After complete addition, the solution was allowed to warm to -10°C whereupon 3 ml of water was added. The ether was then decanted and the solvent removed leaving a solid residue which was identified as succinic anhydride (7.5 g or 75% recovery).

In a repetition of this experiment, the procedure was modified in that the Grignard reagent was added to a refluxing solution of succinic anhydride in tetrahydrofuran. However, succinic anhydride was obtained as the only product, in a yield of 70%.

The addition of the Grignard reagent to either succinic anhydride or diethyl succinate failed to give the products expected and hence, this procedure was abandoned.

Method 3 (unsuccessful)

Methyl hydrogen succinate was prepared by the method of Cason (43).

A mixture of succinic anhydride (200 g, 2.0 moles) in dry methanol (128 g, 4.0 moles) was heated under reflux for 2 h. The solution was then distilled to give a clear liquid which solidified on standing (237 g, 90%). B.p. 97-98°C at 1 mm. Lit. b.p. 110-111°C at 2 mm (43).

This procedure was modified during the course of the present work. After the anhydride had completely reacted, the excess methanol was removed. The residual liquid was poured into a beaker and cooled in a refrigerator. A white crystalline solid was obtained (261 g, 99%). M.p. 55-57°C. Lit. m.p. 53-57°C (43).

β-Carbomethoxypropionyl chloride was prepared by the method described by Cason (43).

Methyl hydrogen succinate (205 g, 1.5 moles) was stirred at room temperature while phosphorus pentachloride (330 g, 1.7 moles) was added in small portions. After addition of the chloride was complete, the mixture was heated on a steam bath for 1.5 h. It was then distilled to give a clear liquid (191 g, 82.5%). B.p. 87-88°C at 16 mm; n_D^{25} 1.4381. Lit. b.p. 85-87°C at 15 mm (43).

The attempted preparation of methyl β-isobutyrylpropionate was carried out using a literature procedure as described by Shirley (41).

A mixture of isopropyl bromide (62 g, 0.5 mole) and 12 g (0.5 mole) of magnesium turnings in 500 ml of tetrahydrofuran was cooled in an ice bath to 5°C. Cadmium chloride (46 g, 0.25 mole) was then added all at once to the stirred and cooled solution. Ten minutes later, the ice bath was removed and stirring was continued for an additiona 1.5 h. To the resulting brown solution, kept at room temperature, was added in a dropwise manner, a solution of β-carbomethoxypropionyl chloride (75 g, 0.5 mole) in 500 ml of ether. The resulting reaction mixture was stirred for 45 min. at room temperature and then heated under reflux for one hour. Twenty grams of ice was then added to decompose the complex. The ether solution was decanted, dried over magnesium sulfate, filtered and the solvent was removed. The residue, when subjected to distillation, gave 69.5 g of a clear liquid. B.p. 135-136°C at 2.5 mm; n_D^{25} 1.4578.

The n.m.r. spectrum of this product showed that it obviously was not the desired ethyl β-isobutyrylpropionate although the structure of this product was not determined. The procedure was abandoned.

Method 4 (unsuccessful)

Succinaldoxime was prepared by the method of Keagle and Hartung (45).

A mixture of 95% ethanol (1 l) and pyrrole (67 g, 1 mole) and hydroxylamine hydrochloride (141 g, 1 mole) in a 2 l, three neck flask was heated to reflux temperature. When all of the solid was in solution, anhydrous sodium carbonate (106 g, 1 mole) was added and the solution heated under reflux for 24 h. The hot solution was then filtered and the filtrate freed from solvent. The residue was dissolved in a minimum quantity of boiling water and heated with animal charcoal. The filtered solution was allowed to cool to promote crystallization. A yellow solid was obtained (90 g, 75%). M.p. 166-167°C. Lit. m.p. 172°C (45).

The attempted preparation of succindialdehyde was carried out following the method of Keagle and Hartung (45).

The succinaldoxime (11.6 g, 0.1 mole) was placed in a 400 ml beaker and 108 ml of 10% sulfuric acid was added. The mixture was cooled to 0-5°C in an ice bath and sodium nitrite (14 g, 0.2 moles) was added in small portions. The temperature

was maintained at 0°C to allow only a slow liberation of NO_2. When the dioxime was completely dissolved, the solution was warmed to room temperature and neutralized with barium carbonate. The $BaSO_4$ was separated leaving an aqueous solution of succindialdehyde.

The authors, Keagle and Hartung, did not describe how to isolate the succindialdehyde. Hence, the aqueous solution was saturated with sodium chloride and extracted with ether. The ether extracts were dried over magnesium sulfate, filtered and the solvent removed by distillation. However, no dialdehyde was obtained and even a continuous extraction of the aqueous solution for 24 h yielded no succindialdehyde.

Since no other procedure for the isolation of pure succindialdehyde could be found, this procedure was abandoned.

Method 5 (unsuccessful)

2,5-Dimethoxy-2,5-dihydrofuran was prepared by the method of Clausson-Kaas and coworkers (93).

Freshly distilled furan (36 ml, 0.5 mole) and sodium acetate (82 g, 1 mole) were dissolved in 600 ml of methanol and the solution cooled to -15°C in a dry ice-acetone bath. To this solution was added a solution of bromine (80 g, 0.5 mole) in 500 ml of methanol while the reaction mixture was stirred and kept at -15°C. When the bromine addition was completed, the resulting colorless solution was poured into 1500 ml of cold water saturated

with calcium chloride. The acetal was extracted with ether (2 x 1 l) and the combined ether extracts dried over magnesium sulfate. The drying agent was separated and the filtrate freed from ether. The residue was distilled to give a clear liquid (19 g, 32%). B.p. 63°C at 20 mm; n_D^{25} 1.4341. Lit. b.p. 51°C at 12 mm; n_D^{20} 1.4328 (93).

The attempted reaction of methyl magnesium iodide with 2,5-dimethoxy-2,5-dihydrofuran was carried out following the procedure of Mallory and coworkers (46).

Methyl iodide was added dropwise to a stirred suspension of magnesium turnings (2.4 g, 0.1 mole) in 100 ml of anhydrous ether cooled to 5°C in an ice bath. After complete addition, the solution was heated under reflux for one hour, cooled and then added dropwise to a solution of 2,5-dimethoxy-2,5-dihydrofuran (13.0 g, 0.1 mole) in 300 ml of benzene. The reaction mixture then was heated under reflux for 24 h. To the cooled solution (5°C) was added 100 ml of 25% aqueous ammonium acetate with continued cooling. The benzene-ether layer was separated, dried over magnesium sulfate and then freed from drying agent and solvent.

Gas liquid chromatographic analysis of the residue showed a very large peak due to the starting acetal along with several other peaks all of which were of small area.

The same procedure was carried out using tetrahydrofuran as solvent rather than benzene and ether. In this case g.l.c.

analysis of the product residue showed several smaller peaks and one major peak corresponding to about a 50% recovery of starting acetal.

This procedure was therefore abandoned since no identifiable product could be isolated.

Method 6 (unsuccessful)

The attempted condensation of 3-methyl-2-butanone with ethyl chloroacetate was carried out using a modification of the procedure used by Diner and coworkers (71) to methylate hydroxyl groups.

The ketone, 3-methyl-2-butanone (17.2 g, 0.2 mole), was added dropwise to a suspension of 8.5 g (0.2 mole) of 57% sodium hydride in 150 ml DME (1,2-dimethoxyethane previously dried by distillation from $LiAlH_4$). The 8.5 g of 57% sodium hydride was washed in 50 ml of pentane and dried under nitrogen before being suspended in DME. The solution was refluxed for 16 h and then ethyl chloroacetate (24.4 g, 0.2 mole) was added dropwise maintaining reflux. The resulting mixture was heated under reflux overnight and then freed from excess DME. The residue was taken up in ether, the precipitated sodium chloride removed and the filtrate freed from ether. The residue, upon analysis by g.l.c., proved to be a forbidding mixture of products, none of which was present in relatively large amount.

The same reaction was carried out using benzene rather

than DME as solvent. Much the same results were obtained with the residue showing a bad mixture of products on g.l.c..

The attempted condensation of 3-methyl-2-butanone and ethyl chloroacetate using potassium triphenylmethide was carried out by the following procedure similar to that involving the use of sodium hydride.

To a stirred solution of triphenylmethane (25 g, 0.1 mole) in 250 ml of dry DME was added potassium metal (4 g, 0.1 mole) in small pieces. After the addition of the metal, the solution was stirred at room temperature for 16 h. The ketone, 3-methyl-2-butanone, was then added until the dark red color of the solution disappeared. This required 5 g (0.06 mole) of the ketone. Ethyl chloroacetate (7.5 g, 0.06 mole) was then added dropwise and the solution was heated under reflux for five h. Excess DME was removed and the residue was taken up in ether. The ether solution was filtered and freed from solvent. The residue when analyzed by g.l.c. proved to be a mixture of many products which were not separated or characterized.

Since the desired ethyl β-isobutyrylpropionate was not formed by the two procedures described above further work on the direct condensation of 3-methyl-2-butanone and ethyl chloroacetate was abandoned.

B. Successful Synthesis of 5-Substituted-2-alkoxytetrahydrofurans.

1. cis-trans-5-Isopropyl-2-methoxytetrahydrofuran

2-Dimethylamino-3-methyl-1-butene (the dimethylamine enamine of 3-methyl-2-butanone) was prepared by the method of White and Weingarten (51).

A 5 l. 3 neck flask, equipped with mechanical stirrer, dropping funnel and condenser, was flushed with nitrogen and sealed from the atmosphere. Anhydrous ether (2.5 l) was added followed by dimethylamine (135 g, 3.0 moles) and 3-methyl-2-butanone (74 g, 0.74 mole). The solution was cooled to 5-10°C in an ice bath. Titanium tetrachloride (70.5 g, 0.37 mole) was added dropwise with stirring while the solution temperature was maintained below 10°C. When all the titanium tetrachloride had been added, the solution was stirred at room temperature for 6 h. The solid was separated by filtration under vacuum using a Buchner funnel and then the ether was removed from the filtrate. The residue when distilled gave a clear liquid (39 g, 46%). B.p. 105-107°C at 700 mm; n_D^{24} 1.4386. Lit. b.p. 56°C at 83 mm; n_D^{25} 1.4403 (51).

Tris-dimethylaminoarsine was prepared by the method of Hirsch (53).

A solution of arsenic trichloride (60 g, 0.3 mole) in 500 ml of dry ether was cooled to -60°C with a dry ice-acetone bath. To this stirred solution was added dimethylamine (81 g, 1.8 moles) in

a dropwise manner. The resulting mixture was stirred at -60°C for one h after which the temperature was allowed to rise to room temperature. The amine hydrochloride was separated by filtration under vacuum, and the ether filtrate freed from the solvent. The residue was distilled and gave a colorless liquid (55 g, 61.2%). B.p. 86-87°C at 25 mm; n_D^{25} 1.4825. Lit. b.p. 54°C at 10 mm (53).

The attempted preparation of the dimethylamine enamine of 3-methyl-2-butanone was carried out following the procedure of Hirsch(53).

The tris-dimethylaminoarsine (47 g, 0.23 mole) was added dropwise to 3-methyl-2-butanone (29.3 g, 0.34 mole) in 250 ml of dry ether and the resulting solution was stirred at room temperature overnight. A small amount of precipitated As_2O_3 was removed by filtration. The ether filtrate was freed from solvent and the residue was distilled. Only 3-methyl-2-butanone and tris-dimethylaminoarsine were obtained. No evidence of enamine formation was obtained and hence, this procedure was not investigated further.

Methyl β-isobutyrylpropionate was prepared by a modification of the method of Stork and coworkers (52).

The above enamine of 3-methyl-2-butanone (5.7 g, 0.05 mole) was dissolved in 50 ml of dry methanol and to this was added

ethyl bromoacetate (8.35 g, 0.05 mole). This solution was stirred and heated under reflux for 16 h, after which 10 ml of water was added and the refluxing continued for another hour. The excess methanol was removed and the residue was poured into 75 ml of water at room temperature. The mixture was extracted with ether (3 x 75 ml). The ether extracts were washed once with saturated sodium chloride solution, dried over magnesium sulfate, separated from the solid and freed from the solvent. The residue when distilled gave a colorless liquid (2.3 g, 32%). B.p. 86-87°C at 8 mm; n_D^{22} 1.4270.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.75; H, 8.86.

Found: C, 60.61; H, 9.00.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure showing a singlet at τ 6.37 (3H), a multiplet between τ 7.0 and 7.7 (5H) and a doublet at τ 8.88, J = 7 Hz (6H).

The i.r. spectrum (neat) showed absorption bands at 1740 cm^{-1} and 1710 cm^{-1} corresponding to the two carbonyl groups.

γ-Isopropyl-γ-butyrolactone was prepared by the procedure described below.

Methyl β-isobutyrylpropionate (2.0 g, 0.0127 mole) was dissolved in 20 ml of dry methanol and then cooled to 0°C in an ice bath. To this solution, vigorously stirred, was added sodium borohydride (0.25 g, 0.0064 mole) in small portions. This mixture was then stirred overnight at room temperature. The

excess methanol was removed and 4 ml of 50% H_2SO_4 was added to the stirred residue. This solution was then extracted with ether (3 x 30 ml). The combined ether extracts were dried over magnesium sulfate, separated from the solid and the filtrate freed from solvent. The residue was distilled to give a colorless liquid (1.5 g, 93%). B.p. 56°C at 0.5 mm; n_D^{20} 1.4416. Lit. b.p. 98°C at 15 mm; n_D^{25} 1.4410 (94).

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.64; H, 9.37.

Found: C, 65.86; H, 9.46.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure, showing a multiplet between τ5.6 and 6.1 (1H), a very broad multiplet between τ7.3 and 8.5 (5H) and two doublets at τ8.97 and τ9.09 (6H), J = 4.5 Hz for both doublets.

The i.r. spectrum (neat) showed a broad absorpiton band between 1770 cm^{-1} and 1760 cm^{-1} as well as broad bands between 1100 cm^{-1} and 1230 cm^{-1}, and 950 cm^{-1} and 1050 cm^{-1}.

3-Carbomethoxy-5-isopropyl-2-methoxytetrahydrofuran was prepared by a modification of the method of Korte and coworkers (36, 37) as described by Miss Makhubu (5).

Sodium metal (3.6 g, 0.15 mole) was powdered with a high speed stirrer in xylene by heating the sodium to near its melting point in xylene and then cooling it gradually to room temperature while the mixture was vigorously stirred. The xylene was decanted, the powdered sodium was washed with dry ether

(2 x 100 ml) and then it was suspended in 100 ml of dry ether. Absolute ethanol (1 ml) was added dropwise with vigorous stirring. To this mixture, kept at room temperature, was added continuing the vigorous stirring, a mixture of the γ-isopropyl-γ-butyrolactone (12.8 g, 0.1 mole) and ethyl formate (7.5 g, 0.1 mole) in 100 ml of dry ether. This solution was then stirred at room temperature for 12 h. A solution of 12 g of hydrogen chloride gas dissolved in 100 ml of dry methanol was added dropwise. The resulting solution was stirred at room temperature for another 8 h, after which the sodium chloride was separated and washed with 50 ml of dry ether. The combined ether filtrate and washings were in turn washed with saturated aqueous sodium carbonate (2 x 75 ml) and then dried over magnesium sulfate. The ether solution was then filtered to remove the drying agent and the filtrate freed from solvent. The residue was distilled to give a colorless liquid (16 g, 81%). B.p. 70°C at 1 mm; n_D^{24} 1.4392.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97.

Found: C, 59.88; H, 9.32.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure, showing a multiplet centered at τ 4.9 (1H), two sharp singlets at τ 6.33 (3H) and τ 6.70 (3H), a broad multiplet between τ 6.8 and 7.2 (1H), a very broad multiplet between τ 7.5 and τ 8.5 (3H) and a multiplet centered at τ 9.1 (6H).

3-Carboxy-5-isopropyl-2-methoxytetrahydrofuran was prepared by a modification of the procedure of Korte and coworkers (36) as described by Miss Makhubu (5).

The 3-carbomethoxy-5-isopropyl-2-methoxytetrahydrofuran (6 g, 0.03 mole) was added to a solution of 5 g of sodium hydroxide in 70 ml of water and the resulting mixture stirred overnight at room temperature. This treatment failed to dissolve the ester completely. However, the addition of more sodium hydroxide (3 g) and water (30 ml) effected complete solution. The solution was neutralized with 50% H_2SO_4 to a pH of 4 to 6 and then saturated with sodium chloride. It was then extracted three times with ether. The ether extracts were dried over magnesium sulfate, separated from the solid and the filtrate freed from ether to give the acid as a syrupy liquid (4.1 g, 74%). Further purification was not attempted. The crude syrup was immediately subjected to the next step of the synthesis.

cis-trans-5-Isopropyl-2-methoxytetrahydrofuran was prepared by a modification of the procedure of Korte and coworkers (36).

The crude acid (4.1 g, 0.022 mole) was dissolved in 20 ml of quinoline to which was added a trace of anhydrous cupric sulfate catalyst. The flask was arranged for downward distillation with the collecting flask cooled in a dry ice-acetone bath. The distillation flask was heated at 200-210°C in an oil bath while nitrogen gas was bubbled through the heated solution. The infrared spectrum of the

distillate showed it to be a mixture of 5-isopropyl-2-methoxytetrahydrofuran and 2-isopropyl-2,3-dihydrofuran along with some methanol. Hence, the distillate was stirred into 5 ml of dry methanol containing a trace of p-toluenesulfonic acid. The solution was stirred at room temperature for 6 h, after which 1-2 g of solid sodium carbonate was added with stirring. Fifteen minutes later the suspension was filtered and the filtrate fractionally distilled to give a colorless liquid (7.5 g from 24 g of γ-isopropyl-γ-butyrolactone or 28% overall yield). B.p. 80°C at 95 mm; n_D^{25} 1.4172.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.19.

Found: C, 66.67; H, 11.31.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure, showing two overlapping quartets centered at τ5.2 (1H), a multiplet between τ6.2 and 6.6 (1H), a sharp singlet at τ6.82 (3H), a broad multiplet between τ8.0 and 8.7 (5H) and a multiplet between τ8.9 and 9.3 (6H).

The g.l.c. analysis on a butanediol succinate column showed two overlapping peaks in the approximate area ratio of 3 to 2.

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

2-Dimethylamino-3,3-dimethyl-1-butene (the dimethylamine enamine of 3,3-dimethyl-2-butanone) was prepared from 3,3-dimethyl-2-butanone (pinacolone), dimethylamine and titanium tetrachloride by

the method of White and Weingarten (51) as described above for the preparation of 2-dimethylamino-3-methyl-1-butene.

A colorless liquid was obtained (8 g from 10 g of the ketone, or 63%). B.p. 105°C at 690 mm; n_D^{22} 1.4308. Lit. b.p. 57°C at 71mm; n_D^{25} 1.4293 (51).

Pinacol hydrate (2,3-dimethyl-2,3-butanediol) was prepared by the method of Adams and Adams (95).

In a 5 l round bottom flask were placed 80 g of magnesium turnings and 800 ml of dry benzene. To this stirred solution was added, gradually, over a period of 10-15 min., 90 g of mercuric chloride dissolved in 400 g of dry acetone. An exothermic reaction resulted and the addition was adjusted to maintain the solution at a gentle reflux. When this solution of mercuric chloride was added, a further quantity of acetone (200 g) and benzene (200 ml) was added. When the reaction began to subside, heat was applied until no further reaction was evident. By this time, a solid had filled about half of the flask thus interfering with the effective stirring of the mixture.

When the reaction was completed, 200 ml of water was added. The solution was heated under reflux for one h, then cooled to 50°C and the solid was removed by filtration under vacuum through a Buchner funnel. The solid was washed with 500 ml of benzene and the combined filtrate and washings evaporated to one half the volume, after which 300 ml of water was added.

The solution was cooled to 10-15°C in a refrigerator for 6-12 h while the pinacol hydrate crystallized.

The white, flaky precipitate was collected by filtration under vacuum. Since it was subjected, without further purification to the next step of the preparation of pinacolone, no yield was determined.

Pinacolone (3,3-dimethyl-2-butanone) was prepared by the method of Hill and Flosdorf (96).

In a 2 l round bottom single neck flask, equipped for downward distillation, were placed 750 ml of 6N H_2SO_4 and 250 g of crude pinacol hydrate prepared as described above. The solution was heated and stirred by a magnetic stirrer until the top layer of the distillate ceased to increase in volume. The two layers of the distillate were separated and the water layer was returned to the distillation flask with another 250 g of pinacol hydrate. This distillation procedure was repeated until all the pinacol hydrate had been converted to pinacolone.

The combined pinacolone distillates, after having been separated from the water layers, were dried over magnesium sulfate. The solid was removed and the filtrate fractionally distilled through a 12 inch Vigreux column. The fraction boiling between 100-105°C provided pinacolone as a colorless liquid (53 g from 100 g of pinacol hydrate or about 65% yield). B.p. 100-105°C at 700 mm; n_D^{27} 1.3961. Lit. b.p. 103-107°C at 760 mm;

n_D^{25} 1.4019 (96).

Methyl β-pivalylpropionate was prepared by a modification of the method of Stork and coworkers (52) as described above for the preparation of methyl β-isobutyrylpropionate.

The product was a colorless liquid obtained in a 38% yield (16 g from 45 g of the enamine). B.p. 80°C at 4 mm; n_D^{22} 1.4303.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.37.

Found: C, 62.99; H, 9.64.

The n.m.r. spectrum in $CDCl_3$ was consistent with the structure of methyl β-pivalylpropionate showing a singlet at τ6.32 (3H), a multiplet between τ 7.0 and 7.5 (4H) and a singlet at τ8.83 (9H).

The i.r. spectrum (neat) showed absorption bands at 1735 cm^{-1} and 1700 cm^{-1} attributable to the two carbonyl groups.

γ-t-Butyl-γ-butyrolactone was prepared from methyl β-pivalylpropionate by a sodium borohydride reduction and acid catalyzed cyclization as described for the preparation of γ-isopropyl-γ-butyrolactone.

The product was a colorless liquid (13 g from 16 g of keto-ester or 98% yield). B.p. 74°C at 2 mm; n_D^{22} 1.4453.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92.

Found: C, 66.52; H, 9.98.

The n.m.r. spectrum in $CDCl_3$ was consistent with the

proposed structure, showing a multiplet at τ 5.8 (1H), a broad multiplet between τ 7.2 and 8.2 (4H) and a sharp singlet at τ 9.05 (9H).

The i.r. spectrum (neat) showed a strong absorption at 1760 cm^{-1} attributable to the lactone group.

5-t-Butyl-3-carbomethoxy-2-methoxytetrahydrofuran was prepared from γ-t-butyl-γ-butyrolactone by the modified procedure of Korte et al (36, 37) as previously described for the preparation of 3-carbomethoxy-5-isopropyl-2-methoxytetrahydrofuran.

The distilled product still contained a small amount of unreacted lactone which could not be removed by fractional distillation. The keto-ester, containing a small amount of lactone (3-4%), was obtained in a 63% yield (13.5 g from 14.2 g of lactone). B.p. 95°C at 3 mm; n_D^{25} 1.4380. An analysis was not attempted.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure, showing a multiplet centered at τ 4.85 (1H), a singlet at τ 6.3 (3H), a singlet at τ 6.63 (3H), a broad multiplet between τ 7.0 and 8.2 (4H) and a singlet at τ 9.10 (9H).

The i.r. spectrum (neat) showed an absorption band at 1740 cm^{-1} attributable to the carbonyl group.

5-t-Butyl-3-carboxy-2-methoxytetrahydrofuran was prepared by the modified procedure of Korte and coworkers (36) as previously described for the preparation of 3-carboxy-5-isopropyl-2-methoxy-

tetrahydrofuran.

A syrupy oil was obtained which was not purified but immediately subjected to decarboxylation.

cis-trans-5-t-Butyl-2-methoxytetrahydrofuran was prepared by the modified procedure of Korte et al (36) as previously described for the preparation of 5-isopropyl-2-methoxytetrahydrofuran.

The product was a colorless liquid obtained in 10% yield from the lactone. B.p. 97°C at 110 mm; n_D^{23} 1.4257.

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

Found: C, 68.58; H, 11.75.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure, showing two overlapping quartets centered at τ5.1 (1H), a broad multiplet between τ 6.2 and 6.6 (1H), a singlet at τ 6.74 (3H), a multiplet between τ 8.0 and 8.6 (4H) and a singlet at τ 9.14 (9H).

The g.l.c. on a butanediol succinate column showed the cis and trans isomers as two completely separated peaks in a ratio of 55 to 45.

3. cis-trans-2-Methoxy-5-phenyltetrahydrofuran

1-Dimethylamino-1-phenylethylene (the dimethylamine enamine of acetophenone) was prepared by the method of White and Weingarten (51) as previously described for the preparation of 2-dimethylamino-3-methyl-1-butene.

A colorless liquid was obtained. B.p. 84°C at 20 mm. Lit. b.p. 51°C at 2.1 mm (53).

However, the n.m.r. and i.r. spectra showed the product to be a 1:1 mixture of enamine and acetophenone. Since distillation would not separate the two compounds, the mixture was subjected to the next step of the synthesis.

Methyl β-benzoylpropionate was prepared by the modified procedure of Stork et al (52) as previously described for the preparation of methyl β-isobutyrylpropionate.

A pale yellow liquid was obtained but only in 21% yield from the enamine-ketone mixture. B.p. 100°C at 0.2 mm; n_D^{21} 1.5306. Lit. b.p. 119-120°C at 0.4 mm; n_D^{18} 1.5260 (97).

γ-Phenyl-γ-butyrolactone was prepared from methyl β-benzoylpropionate by the procedure previously described for the preparation of γ-isopropyl-γ-butyrolactone.

However, upon distillation of the residue from the ether extractions, extensive charring took place and only a few drops of the lactone were obtained. B.p. 124°C at 1.0 mm. Lit. b.p. 130°C at 15 mm (54).

This procedure was abandoned in favor of the procedure described below.

(1,2-Epoxyethyl)benzene (styrene oxide) was prepared by the method of Golumbic and Cottle (55).

Mercuric oxide (32.6 g, 0.15 mole) and styrene (28.2 g, 0.3 mole) were stirred into 300 ml of ether previously saturated with water. To the resulting mixture, vigorously stirred, was added iodine (75.6 g, 0.3 mole) in small portions. After complete addition of the iodine, the solution was stirred for one hour at room temperature and then filtered. The filtrate was washed with dilute aqueous sodium bisulfite, dried over magnesium sulfate and filtered free of the solid. The filtrate, cooled in an ice bath, was then stirred vigorously while 56 g (1.0 mole) of potassium hydroxide was added in small portions. When the addition was complete, the solution was stirred at room temperature for one day. The ether was then decanted from the solid and the solid was washed with ether. The combined ether solutions were dried over magnesium sulfate, filtered free of the solid and the filtrate freed from ether. The residue was distilled, and gave a colorless liquid (18.3 g, 51%). B.p. 84-85°C at 20 mm; n_D^{22} 1.5357. Lit. b.p. 87-88°C at 23 mm; n_D^{25} 1.5331 (55).

γ-Phenyl-γ-butyrolactone was prepared by a modification of the method of Russell and Vanderwerf (54).

Sodium hydride (16 g, 0.4 mole of a 60% suspension in paraffin) was washed with pentane, dried under nitrogen and suspended with stirring in 500 ml of dry DME (1,2-dimethoxyethane). The mixture was cooled in an ice bath and stirred while diethyl malonate (64 g, 0.4 mole) was added dropwise. After the addition

was complete, the solution was heated under reflux for 2 h. With continued refluxing and vigorous stirring, styrene oxide (48 g, 0.4 mole) was added dropwise. This solution was heated under reflux for 3 h and then the DME solvent was removed. An aqueous solution of potassium hydroxide (45 g in 200 ml of water) was added to the residue with stirring and the resulting mixture was heated under reflux for 1 h. The ethanol which was formed was removed on a rotary evaporator and the residual material was first acidified with 50% aqueous H_2SO_4 and then saturated with sodium chloride. This solution was extracted with ether and the ether extracts were dried over magnesium sulfate, filtered free of solid and the filtrate freed from ether. The residue was heated to 160°C under atmospheric pressure in a distillation apparatus while nitrogen was bubbled through the solution in order to provide an inert atmosphere as well as to assist in carrying over the vapors. When the decarboxylation reaction had ceased, the residue was distilled under vacuum to give a colorless liquid (35 g, 54%). B.p. 123°C at 0.8 mm; n_D^{23} 1.5392. Lit. b.p. 130°C at 1.5 mm; n_D^{15} 1.5418 (54).

The original procedure of Russell and Vanderwerf was attempted as described below.

Styrene oxide (48 g, 0.4 mole) was added dropwise to a refluxing solution of sodiomalonic ester prepared by adding 64 g (0.4 mole) of diethyl malonate to sodium metal (9.6 g, 0.4 mole) previously dissolved in 300 ml of absolute ethanol. The resulting

mixture was heated under reflux for 3 h. The remainder of the work-up was as described above starting with the addition of 45 g of potassium hydroxide in 200 ml of water.

The residue obtained from the decarboxylation was distilled and gave 41 g (63%) of a colorless liquid to which the structure 2-ethoxy-1-hydroxy-1-phenylethane was assigned. B.p. 105°C at 7 mm; n_D^{25} 1.5067.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure, showing a singlet at τ 2.7 (5H), a doublet at τ 5.09, J = 4.5 Hz and a doublet at τ 5.20, J = 4.5 Hz (1H), a broad multiplet between τ 6.2 and 6.8 (5H) and a triplet centered at τ 8.83 (3H). One proton in the multiplet between τ 6.2 and 6.8 was lost when the material was shaken with D_2O.

The n.m.r. spectrum in DMSO-d_6 was the same except for a doublet at τ 4.74 (1H) while the integrated area of the multiplet between τ 6.2 and 6.8 indicated that it corresponded relatively to only 4 protons.

The i.r. spectrum (neat) showed a broad absorption band between 3600 and 3100 cm^{-1}, attributable to a hydroxyl group, as well as a broad band between 1150 cm^{-1} and 1000 cm^{-1} (C-O stretch) and two sharp bands at 751 cm^{-1} and 695 cm^{-1} attributable to the phenyl ring.

3-Carbomethoxy-2-methoxy-5-phenyltetrahydrofuran was prepared from γ-phenyl-γ-butyrolactone by the modified procedure of Korte

and coworkers (36, 37) as described for the preparation of 5-isopropyl-3-carbomethoxy-2-methoxytetrahydrofuran.

A colorless liquid was obtained in 78% yield (18.5 g from 16.2 g of the lactone). B.p. 125°C at 0.5 mm; n_D^{22} 1.5124.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83.

Found: C, 66.12; H, 6.90.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure, showing a multiplet between τ 2.5 and 2.8 (5H), a multiplet between τ 4.5 and 4.9 (1H), a multiplet between τ 5.5 and 6.0 (2H), a doublet at τ 6.28, J = 2 Hz (3H), a multiplet between τ 6.5 and 6.8 (3H) and a broad multiplet between τ 7.3 and 8.0 (2H).

The i.r. spectrum (neat) showed an absorption at 1740 cm^{-1} attributable to the carbonyl group.

3-Carboxy-2-methoxy-5-phenyltetrahydrofuran was prepared by the modified procedure of Korte et al (36) as previously described for the preparation of 3-carboxy-5-isopropyl-2-methoxytetrahydrofuran.

A syrupy oil was obtained which was immediately subjected to decarboxylation without further purification.

cis-trans-2-Methoxy-5-phenyltetrahydrofuran was prepared by a modification of the procedure of Korte and coworkers (36).

The syrupy acid, in a vacuum distillation apparatus fitted with a nitrogen bleed, was heated in an oil bath at 140°C. The

pressure was decreased to 1-2 mm for the decarboxylation and a colorless liquid distilled at 60°C at 1.5 mm. This liquid was stirred into dry methanol containing a trace of acid and the resulting solution was stirred and heated at 40°C overnight. The solution was cooled and sodium carbonate (1 g) was added. The mixture was stirred for 15 min after which the solid was removed by filtration and the filtrate freed from methanol. The residue was distilled and gave a colorless liquid (54% yield from the lactone). B.p. 85°C at 0.8 mm; n_D^{24} 1.5130.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92.

Found: C, 74.37; H, 8.19.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure, showing a multiplet at τ2.8 (5H), two overlapping quartets centered at τ5.0 (2H), a multiplet at τ6.7 (3H) and a broad multiplet between τ7.7 and 8.4 (4H).

The i.r. spectrum showed a broad absorption band between 1120 cm^{-1} and 1000 cm^{-1} (C-O stretch) and sharp absorption bands at 750 cm^{-1} and 695 cm^{-1} (attributable to the phenyl group).

The g.l.c. analysis on an Apiezon T column showed a single symmetrical peak for the cis-trans isomer mixture.

4. cis-trans-5-Methyl-2-methoxytetrahydrofuran

3-Carbomethoxy-5-methyl-2-methoxytetrahydrofuran was prepared by the modified procedure of Korte et al as previously described for the preparation of 3-carbomethoxy-5-isopropyl-2-methoxy-

tetrahydrofuran.

A colorless liquid was obtained (206 g from 200 g of valerolactone, 59.5% yield). B.p. 52°C at 1 mm; n_D^{24} 1.4314. Lit. b.p. 97°C at 20 mm; n_D^{26} 1.4310 (5).

3-Carboxy-5-methyl-2-methoxytetrahydrofuran was prepared by the modified procedure of Korte et al (36) as previously described for the preparation of 3-carboxy-5-isopropyl-2-methoxytetrahydrofuran.

A syrupy oil was obtained which was immediately subjected to decarboxylation without further purification.

cis-trans-5-Methyl-2-methoxytetrahydrofuran was prepared by the modified procedure of Korte et al (36) as previously described for the preparation of 5-isopropyl-2-methoxytetrahydrofuran.

The product was a colorless liquid obtained in a 20% yield from γ-valerolactone. B.p. 110°C at 695 mm; n_D^{22} 1.4080. Lit. b.p. 108-109°C at 695 mm; n_D^{30} 1.4127 (5).

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure, and is shown in Figure 5. It showed two quartets at τ5.02 and τ5.10 (1H), a multiplet between τ 5.8 and 6.2 (1H), a sharp singlet at τ 6.78 (3H), a multiplet between τ 7.9 and 8.4 (4H) and two doublets centered at τ 8.78 and 8.85, J = 6.0 Hz (3H).

5. cis-trans-5-Methoxymethyl-2-methoxytetrahydrofuran

2-Methoxymethyl-3,4-dihydro-2H-pyran was prepared by the methylation of 2-hydroxymethyl-3,4-dihydro-2H-pyran according

to the method of Diner and coworkers (71).

A 60% suspension of sodium hydride in paraffin (43 g, 1.0 mole) was washed with pentane, dried under nitrogen and suspended with stirring in 500 ml of dry DME (distilled from $LiAlH_4$). To this suspension was added methyl iodide (142 g, 1.0 mole), after which the stirred mixture was cooled in an ice bath to 10°C. The alcohol, 2-hydroxymethyl-3,4-dihydro-2H-pyran (114 g, 1.0 mole) in 100 ml of dry DME, was then added dropwise with continued stirring, maintaining the temperature at 10°C. When the addition was complete, the solution was warmed to room temperature and stirred overnight. The DME solvent was removed and the residue taken up in ether. The mixture was filtered free of sodium chloride and the filtrate freed from ether. The residue was distilled and gave a colorless liquid (71.0 g, 55.5%). B.p. 67-69°C at 30 mm; n_D^{24} 1.4458. Lit. b.p. 58-60°C at 20 mm; n_D^{23} 1.4545.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.38.
Found: C, 65.63; H, 9.63.

2,3-Dihydroxy-6-methoxymethyltetrahydropyran was prepared using the modified procedure of Barker and coworkers (98) employed by Miss Makhubu (5).

To a solution of 80% m-chloroperoxybenzoic acid (55 g, 0.2 mole) dissolved in 400 ml of wet ether at 0°C, was added dropwise, 2-methoxymethyl-3,4-dihydro-2H-pyran (26 g, 0.2 mole).

After the addition was complete, the solution was warmed to room temperature and stirred for 24 h. All of the ether was removed and the residue taken up in cold chloroform, in which benzoic acid is relatively insoluble. The chloroform was filtered free from the benzoic acid and washed with an aqueous sodium bicarbonate solution until neutral. The sodium bicarbonate washes were, in turn, washed with chloroform and the combined chloroform extracts were dried over magnesium sulfate. The solid was removed by filtration and the filtrate freed from solvent. The crude diol (30 g, 99%), which remained, was subjected to the next reaction without further purification.

2-Hydroxy-5-methoxymethyltetrahydrofuran was prepared following the procedure of Miss Makhubu (5).

The crude 2,3-dihydroxy-6-methoxymethyltetrahydropyran (16 g, 0.1 mole) was added dropwise to a solution of periodic acid (22.5 g, 0.1 mole) in 200 ml of a 1 to 1 mixture of water and dioxane. The mixture was stirred at room temperature for 12 h and then solid sodium bicarbonate was added gradually to neutralize the acids in the reaction mixture. The slightly alkaline mixture was extracted continuously with chloroform for 24 h. The chloroform layer was separated and dried over magnesium sulfate to which was added some sodium thiosulfate to remove any liberated iodine. The chloroform solution was filtered and the filtrate free from solvent to give 11.5 g (88.5%) of crude hemi-acetal. This material was not purified but was simply subjected to the next reaction.

cis-trans-5-Methoxymethyl-2-methoxytetrahydrofuran was prepared by the method described by Miss Makhubu (5).

The crude 2-hydroxy-5-methoxymethyltetrahydrofuran (11.5 g) was stirred at room temperature for 6 h with 100 ml of anhydrous methanol to which a few drops of concentrated hydrochloric acid had been added. Solid sodium bicarbonate (2 g) was added and the resulting suspension was stirred vigorously at room temperature for 15 min. The solid was removed by filtration and the methanol was removed by fractional distillation. The residue was distilled under reduced pressure to give a colorless liquid (7.1 g, 55%). B.p. 65°C at 50 mm; n_D^{25} 1.4242. Lit. b.p. 90-93°C at 140 mm; n_D^{23} 1.4248.

The n.m.r. spectrum in $CDCl_3$ was consistent with the structure proposed, showing two overlapping quartets in a ratio between 1:1 and 3:2 at τ5.1 (1H), a multiplet between τ5.8 and 6.2 (1H), a multiplet between τ6.6 and 6.8 (8H) and a multiplet between τ7.9 and 8.5 (4H).

6. cis-trans-5-Benzyloxymethyl-2-methoxytetrahydrofuran

2-Benzyloxymethyl-3,4-dihydro-2H-pyran was prepared by a modification of the procedure of Diner and coworkers (71).

A 60% suspension of sodium hydride in paraffin (43 g, 1.0 mole) was washed with pentane, dried under nitrogen and suspended with stirring in 500 ml of dry DME (distilled from $LiAlH_4$). To this suspension was added benzyl chloride (127 g, 1.0 mole), after which the stirred mixture was cooled in an ice bath to 10°C. The

alcohol, 2-hydroxymethyl-3,4-dihydro-2H-pyran (114 g, 1.0 mole) in 100 ml of dry DME, was then added dropwise with continued stirring, while the temperature of the reaction mixture was maintained at 10°C. When the addition was complete the solution was refluxed for one hour and then stirred overnight at room temperature. The DME solvent was removed and the residue taken up in ether. The mixture was filtered free of solid sodium chloride and the filtrate freed from ether. The residue was distilled and gave a colorless liquid (127 g or 85% since 31 g of unreacted alcohol was also recovered). B.p. 119°C at 2.5 mm; n_D^{22} 1.5238.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.85.

Found: C, 76.65; H, 7.70.

6-Benzyloxymethyl-2,3-dihydroxytetrahydropyran was prepared by the modified method of Barker and coworkers (98) as previously described for the preparation of 2,3-dihydroxy-6-methoxymethyltetrahydropyran.

A crude oil was obtained (97% yield) which was immediately subjected to the next reaction without further purification.

5-Benzyloxymethyl-2-hydroxytetrahydrofuran was prepared by the method of Miss Makhubu as previously described for the preparation of 2-hydroxy-5-methoxymethyltetrahydrofuran.

The crude material was recovered in 94% yield and was immediately subjected to the next reaction without further purification.

cis-trans-5-Benzyloxymethyl-2-methoxytetrahydrofuran was prepared by the method of Miss Makhubu (5) as previously described for the preparation of 5-methoxymethyl-2-methoxytetrahydrofuran.

A colorless liquid was obtained in 75% yield. B.p. 86-87°C at 0.08 mm; n_D^{24} 1.5014.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16.

Found: C, 70.07; H, 7.98.

The n.m.r. spectrum in CCl_4 was consistent with the structure proposed, showing a singlet at τ2.75 (5H), two overlapping multiplets in the ratio of 3:2 at τ5.1 (1H), a doublet at τ5.49 (2H), J = 1.0 Hz, a broad multiplet between τ5.7 and 6.0 (1H), a multiplet between τ6.4 and 6.8 (5H) and a broad multiplet between τ8.0 and 8.4.

The g.l.c. analysis on a butanediol succinate column showed a single symmetric peak.

7. cis-trans-2-Isopropoxy-5-methyltetrahydrofuran was prepared as described below.

The acetal, 5-methyl-2-methoxytetrahydrofuran (6.8 g, 0.05 mole), was mixed with 20 ml of isopropyl alcohol in a 50 ml pear-shaped flask. The flask was set up for downward distillation with nitrogen gas being bubbled through the solution. A trace of p-toluenesulfonic acid was added and the solution was heated at 80-90°C. A mixture of methanol and isopropyl alcohol distilled between 60-80°C. The distillation was continued until the temperature became constant at 80°C and only isopropyl alcohol was being

collected. The solution was cooled, treated with solid Na_2CO_3 (1 g) and then stirred at room temperature for 15 min. The filtrate was then fractionally distilled to remove the remaining isopropyl alcohol. The residue was distilled and gave a colorless liquid (4.3 g, 60%). B.p. 136-139°C at 700 mm; n_D^{25} 1.4112.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18.

Found: C, 66.38; H, 10.99.

The n.m.r. spectrum in CCl_4 was consistent with the structure proposed, showing two overlapping quartets at τ5.0 (1H), a broad multiplet between τ5.8 and 6.5 (2H), a broad multiplet between τ7.7 and 8.3 (4H) and a multiplet between τ 8.6 and 9.0 (9H).

The g.l.c. analysis on a butanediol succinate column showed one symmetrical peak for the cis-trans mixture.

C. Synthesis of the 2-Aryloxytetrahydrofurans.

2,3-Dihydrofuran was prepared by the method described by Eliel and coworkers (4) which was a modification of a previously published procedure (100).

The ether, 2,5-dihydrofuran (70 g, 1.0 mole), was mixed with 30 ml of t-butyl alcohol and 15 g of potassium t-butoxide. The resulting mixture was sealed in an autoclave and heated with stirring at 175°C for 8 h. It was then cooled to room temperature and the liquid fractionally distilled in a spinning band column. The 2,3-dihydrofuran boiled between 53 and 55°C at 700 mm and

was collected in a receiver cooled in dry ice (n_D^{25} 1.4235). Lit. b.p. 53-55°C at 745 mm; n_D^{20} 1.4200 (4). Yield, 50 g, 63%.

2-Phenoxytetrahydrofuran was prepared by a modification of the procedure of Eliel and coworkers (4).

Phenol (9.4 g, 0.1 mole) and 2,3-dihydrofuran (7.0 g, 0.1 mole) were stirred into 50 ml of tetrahydrofuran to which a trace of p-toluenesulphonic acid was subsequently added. An exothermic reaction took place and when the reaction started to subside, the solution was heated to 50°C for one h. The mixture was cooled to room temperature and 25 ml of "Claisen's Alkali" (57) was added, followed by 100 ml of dry ether. The solution was shaken vigorously and the layers separated. The ether layer was dried over magnesium sulfate, filtered free of solid and the filtrate freed from ether. The residue was distilled to give a colorless liquid (13.5 g, 82%). B.p. 86°C at 2.8 mm; n_D^{25} 1.5217.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.12; H, 7.31.

Found: C, 73.42; H, 7.45.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure, showing a broad multiplet between τ 2.6 and 3.4 (5H), a multiplet centered at τ 4.37 (1H), a multiplet between τ5.9 and 6.4 (2H) and a multiplet between τ 7.8 and 8.4 (4H).

The following compounds were all prepared from the corresponding phenol and 2,3-dihydrofuran by the modified procedure of Eliel and coworkers as described above for the preparation

of 2-phenoxytetrahydrofuran.

2-(2,6-Dichlorophenoxy)tetrahydrofuran was obtained as a colorless liquid in a 54% yield. B.p. 100-102°C at 0.8 mm; n_D^{25} 1.5469.

Anal. Calcd. for $C_{10}H_{10}O_2Cl_2$: C, 51.53; H, 4.32; Cl, 30.42.

Found: C, 51.73; H, 4.72; Cl, 30.17.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure showing a broad multiplet between τ 2.5 and 3.3 (3H), a multiplet centered at τ 4.03 (1H), a broad multiplet between τ 5.4 and 6.3 (2H) and a broad multiplet between τ 7.5 and 8.3 (4H).

2-(2,6-Dimethylphenoxy)tetrahydrofuran was obtained as a colorless liquid in 75% yield. B.p. 95-96°C at 1.0 mm; n_D^{25} 1.5160.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39.

Found: C, 75.18; H, 8.70.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure showing a singlet at τ 3.14 (3H), a multiplet centered at τ 4.73 (1H), a broad multiplet between τ 5.8 and 6.4 (2H), a singlet at τ 7.82 (6H) and a broad multiplet between τ 7.7 and 8.3 (4H).

2-(3,5-Dimethylphenoxy)tetrahydrofuran was obtained as a colorless liquid in a 54% yield. B.p. 74°C at 0.1 mm; n_D^{25} 1.5183.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.76; H, 8.39.

Found: C, 75.11; H, 8.21.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure showing a multiplet at τ 3.4 (3H), a multiplet between τ 5.9 and 6.3 (2H), a singlet at τ 7.78 (6H) and a multiplet between τ 7.8 and 8.2 (4H).

2-(4-t-Butylphenoxy)tetrahydrofuran was obtained as a colorless liquid in 69.5% yield. B.p. 92°C at 0.1 mm; n_D^{25} 1.5108.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15.

Found: C, 76.46; H, 8.85.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure showing a doublet of doublets centered at τ 2.86 and τ 3.20 (4H), J = 8.5 Hz, a multiplet centered at τ 4.40 (1H), a multiplet between τ 6.0 and 6.3 (2H), a multiplet between τ 7.9 and 8.3 (4H) and a singlet at τ 7.85 (9H).

D. Synthesis of Miscellaneous Acetals.

2-Benzyloxytetrahydrofuran was prepared by a modification of the procedure of Eliel and coworkers (4).

Benzyl alcohol (11.0 g, 0.1 mole) and 2,3-dihydrofuran (7.0 g, 0.1 mole) were stirred into 50 ml of dry tetrahydrofuran and to this mixture a trace of p-toluenesulphonic acid was subsequently added. The mixture was heated at 50°C for 12 h and then cooled to room temperature. Solid sodium carbonate (1 g) was added and the mixture was then stirred for 15 min. The solid was removed by filtration and the filtrate freed of tetrahydrofuran.

The residue was distilled and gave a colorless liquid (7.2 g, 80%). B.p. 114°C at 7 mm; n_D^{24} 1.5120. Lit. b.p. 102°C at 4 mm (4).

2-t-Butoxytetrahydrofuran was prepared from t-butyl alcohol and 2,3-dihydrofuran by the modified procedure of Eliel and coworkers as previously described for the preparation of 2-benzyloxytetrahydrofuran.

A colorless liquid was obtained in a 62.5% yield. B.p. 120°C at 700 mm; n_D^{23} 1.4177. Lit. b.p. 36-40°C at 10 mm; n_D^{20} 1.4186 (4).

2-Ethoxytetrahydrofuran was prepared from 95% ethanol and 2,3-dihydrofuran by the modified procedure of Eliel and coworkers (4) as previously described for the preparation of 2-benzyloxytetrahydrofuran.

A colorless liquid was obtained in a 66.5% yield. B.p. 118-119°C at 700 mm; n_D^{25} 1.4119. Lit. b.p. 110-112°C at 699 mm; n_D^{26} 1.4105 (5).

2-(3,5-Dimethylphenoxy)tetrahydropyran was prepared from 3,5-dimethylphenol and 3,4-dihydro-2H-pyran by the modified procedure of Eliel and coworkers (4) as previously described for the preparation of 2-phenoxytetrahydrofuran.

A colorless liquid was obtained in a 66% yield. B.p. 85-86°C at 0.5 mm; n_D^{23} 1.5133.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.64; H, 8.79.

Found: C, 75.43; H, 9.09.

3-Hydroxy-2-methoxytetrahydrofuran was prepared by a modification of the procedure of Sweet and Brown (82).

The vinyl ether, 2,3-dihydrofuran (15 g, 0.215 mole), was added dropwise to a solution of m-chloroperoxybenzoic acid (46 g, 0.22 mole) in 200 ml of dry methanol which was kept at 5°C in an ice bath during the addition. When the addition was complete, the solution was allowed to warm to room temperature and stirred for 12 h. The excess methanol was removed and the solid white residue taken up in chloroform. The mixture was cooled to 5°C in a refrigerator and the solid was removed by filtration under vacuum through a Buchner funnel. The filtrate was washed with a saturated aqueous sodium carbonate solution until no further reaction was observed. The chloroform layer was dried over magnesium sulfate, filtered free of solid and the filtrate freed from chloroform. The residue was distilled and gave a clear liquid (18.5 g, 76%). B.p. 100-103°C at 30 mm; n_D^{24} 1.4368. Lit. b.p. 68-70°C at 7 mm; n_D^{25} 1.4421 (82).

2,3-Dimethoxytetrahydrofuran was prepared by the method of Diner and coworkers (71) from 3-hydroxy-2-methoxytetrahydrofuran as previously described for the preparation of 2-methoxymethyl-3,4-dihydro-2H-pyran.

A colorless liquid was obtained in 91% yield. B.p. 81°C at 60 mm; n_D^{23} 1.4200. Lit. b.p. 57°C at 21 mm; n_D^{25} 1.4201 (82).

2-(4-Methylphenoxy)tetrahydrofuran was obtained from U. E. Diner (7).

E. Attempts to Directly Reduce γ-Butyrolactones to Tetrahydrofuranyl Acetals.

Method 1

The attempted reduction of γ-butyrolactone using diborane was carried out following the procedure of Pettit and Kasturi (58).

Boron trifluoride ethereate (30.2 g, 0.2 mole) was added dropwise to a solution of sodium borohydride (5.7 g, 0.15 mole) stirred vigorously in 250 ml of diglyme. Nitrogen gas was blown into the flask in order to force the diborane formed during the reaction out of the flask. The gas was passed through an auxiliary wash bottle containing diethyl ether into a second 500 ml round bottom flask which contained γ-butyrolactone (8.6 g, 0.1 mole) vigorously stirred in 250 ml of dry ether. When the addition of the $BF_3 \cdot O(C_2H_5)_2$ was completed, the nitrogen gas was blown through the system for an additional 3 h. Dry methanol (5 ml) was then added gradually to the second reaction flask and the mixture was stirred at room temperature for 15 min. The ether was

removed and the residue analyzed on g.l.c.. The only component, other than methanol, which was present in the product mixture was γ-butyrolactone. It was recovered in a 70% yield (6.0 g) by distillation.

The attempted reduction of γ-butyrolactone with an $NaBH_4$-BF_3 mixture was attempted by a modification of the procedure of Pettit and Kasturi (58, 59).

γ-Butyrolactone (8.6 g, 0.1 mole) and boron trifluoride etherate (13.6 g, 0.1 mole) were stirred in 200 ml of dry ether at room temperature. To this solution was added sodium borohydride (0.95 g, 0.025 mole) in small portions. The solution was then stirred at room temperature for 16 h under a nitrogen atmosphere. 95% ethanol (10 ml) was added dropwise and the solution was stirred at room temperature for 10-15 min. The solvent was removed and the residue was analyzed by g.l.c.. Only ethanol and γ-butyrolactone were found to be present in the product mixture. The γ-butyrolactone was recovered by distillation (6.8 g, 80%).

Since diborane would not reduce the lactone, even during an in situ preparation, this procedure was abandoned.

Method 2

The attempted reduction of γ-butyrolactone using sodium amalgam was carried out using a modification of the procedure of Sperber and coworkers (62).

Small pieces of sodium metal (9.2 g, 0.4 mole) were added, one at a time, to mercury (460 g, 2.3 moles) contained in an evaporating dish. A pair of forceps was used in order to completely immerse the pieces of sodium metal in the mercury. After the addition of the sodium metal was complete, the solid was placed in a mortar and broken into small chunks. The solid was stored under nitrogen in a sealed flask.

The sodium amalgam (115 g) was added in small portions to the γ-butyrolactone (8.6 g, 0.1 mole) stirred vigorously in 100 ml of dry methanol kept at 5°C in an ice bath. The pH of the solution was checked periodically with hydrion paper and maintained between pH 3 and 5 by the addition of concentrated hydrochloric acid. After the addition of the sodium amalgam was complete, the solution was stirred for 2 h at room temperature and then decanted from the liberated mercury. The solution was basified by stirring with solid sodium carbonate until no further reaction was observed (30 min). The solid was removed by filtration and the excess methanol was removed by fractional distillation. Only unreacted lactone was found (6.5 g, 75%).

Method 3

The reduction of γ-valerolactone with $LiAlH_4$ was carried out by the method of Arth (64).

γ-Valerolactone (100 g, 1.0 mole) was dissolved in 300 ml of dry ether and cooled to -10°C in a dry ice-acetone bath. To this

stirred solution was added lithium aluminum hydride (9.5 g, 0.25 mole) in small portions. When the addition was complete, the solution was stirred at room temperature for 4 h. The ether was removed until only one third of the original volume remained. A mixture of ice (20 g) and 20 ml of 5M H_2SO_4 was added gradually and the mixture was extracted with ether (2 x 75 ml). The ether extracts were dried over magnesium sulfate, filtered free of the solid and the filtrate freed from ether. The residue was distilled and gave two main fractions. The first (b.p. 80°C at 10 mm; n_D^{22} 1.4337) gave a 2,4-dinitrophenylhydrazone derivative (m.p. 122-123°C). These results were in agreement with the constants which Arth had found for 4-hydroxyvaler aldehyde (b.p. 83°C at 13 mm; n_D^{17} 1.4359; 2,4-d.n.p., m.p. 125-127°C) (64).

However, the i.r. spectrum showed only a very weak hydroxyl absorption between 3500 and 3300 cm^{-1} and a strong carbonyl absorption at 1760 cm^{-1}. Hence, the product was predominantly γ-valerolactone (86-90°C at 14 mm (92)).

The second fraction proved to be 1,4-pentanediol in 17% yield (17 g). B.p. 117°C at 10 mm; n_D^{21} 1.4468. Lit. b.p. 212°C at 760 mm; n_D^{17} 1.4439 (92).

This procedure was abandoned since most of the reduction took place to form the diol and only a very small amount of hydroxy aldehyde was found.

Method 4

2-Methyl-2-butene was prepared by the method of Whitmore and coworkers (99).

t-Amyl alcohol (310 g, 3.5 moles) was dissolved in 400 ml of 15% sulfuric acid. The resulting mixture was heated to reflux and fractionally distilled through a 12 inch Vigreux column. The olefin was collected in a dry ice cooled container and dried over potassium carbonate and magnesium sulfate. The olefin was redistilled from a flask containing a small amount of potassium carbonate. A colorless liquid was obtained (200 g, 81.5%). B.p. 35.5°C at 700 mm; n_D^{22} 1.3850. Lit. b.p. 39.5°C at 740 mm; n_D^{25} 1.3870 (99).

The attempted reduction of γ-butyrolactone with disiamylborane was carried out by the procedure of Brown and Digby (66).

A solution of 2-methyl-2-butene (46.2 g, 0.66 mole) and sodium borohydride (9.5 g, 0.25 mole) in 150 ml of diglyme was stirred at 5°C under a nitrogen atmosphere. Boron trifluoride etherate (47.2 g, 0.33 mole) was added dropwise over a period of one half h with continued cooling at 5°C. When the addition was complete, the solution was stirred for one h at 5°C. γ-Butyrolactone (26.4 g, 0.31 mole) was then added dropwise with continued cooling. When the addition was complete, the solution was warmed to room temperature and stirred for 15 h. Acidified methanol (50 ml) was

added very carefully and the resulting solution was extracted with ether. The ether extracts were dried over magnesium sulfate, filtered free of solid and the filtrate freed from ether. Analysis of the residue by g.l.c. showed that absolutely no acetal had been formed. Only γ-butyrolactone was isolated by distillation (20 g, 76%).

Basically the same procedure was followed in a second attempt at this type of reduction. Diethyl ether was used as the solvent and instead of acidified methanol, 25 ml of a 15% aqueous solution of potassium hydroxide was added to decompose the complex. A solution of 30% hydrogen peroxide (40 ml) was then added and gave a very vigorous reaction. The solution was extracted with ether (3 x 50 ml) and the ether extracts were dried over magnesium sulfate. The mixture was filtered free of solid and the filtrate freed from ether. Primarily γ-butyrolactone was recovered (12 g, 70%).

Basically the same procedure was again followed in a third attempt at this type of reaction. In this case, a 1:1 mixture of diethyl ether and tetrahydrofuran was used as solvent and acidified water (25% sulfuric acid, 50 ml) was added to decompose the complex. The resulting mixture was then poured into ether, the layers separated and both the ethereal and aqueous layers evaporated to dryness on a rotatory evaporator. The water layer gave only a solid residue, while the ether layer yielded γ-butyrolactone (10 g, 60%).

This procedure was abandoned since no reduction products could be isolated.

Method 5

The attempted reduction of γ-butyrolactone with $AlCl_2H$ was carried out by the following procedure.

Aluminum chloride (10 g, 0.075 mole) was dissolved in 100 ml of dry ether which had previously been cooled to -20°C in a dry ice-acetone bath. To this solution was gradually added, a filtered solution of $LiAlH_4$ (1.05 g, 0.025 mole) dissolved in 150 ml of dry ether. When the addition was complete, the solution was warmed to room temperature and stirred for 15 min. The solution was then added dropwise to a solution of γ-butyrolactone (8.6 g, 0.1 mole) stirred in 150 ml of ether cooled to -60°C in a dry ice-acetone bath. The stirring was continued for one h at -60°C and acidified methanol (20 ml CH_3OH and 1 ml conc. H_2SO_4) was added dropwise to decompose the complex. The ether solution was allowed to warm to room temperature and the ether was decanted from the solid residue. The ether solution was dried over magnesium sulfate and potassium carbonate, separated from the solid by filtration and the filtrate freed from ether. Analysis of the residue by g.l.c. showed mainly γ-butyrolactone and a small amount (5-10%) of the high boiling 1,4-butanediol.

Basically the same procedure was followed in a second

attempt at this type of reduction. In this attempt, the reaction was carried out at room temperature. Analysis of the residue on g.l.c. showed 82% of the mixture to be γ-butyrolactone and 18% to be 1,4-butanediol. The recovery of materials was 82%.

Since the desired hydroxy aldehyde was not produced, this procedure was abandoned.

F. Preparation of Authentic Hydrogenolysis Products.

1. Synthesis of the 2-Substituted tetrahydrofurans.

Method 1 (unsuccessful)

The attempted reduction of γ-butyrolactone to form tetrahydrofuran was carried out by the method of Pettit and Kasturi (58).

A solution of lithium aluminum hydride (1.9 g, 0.05 mole), dissolved with stirring in 50 ml of ether, was cooled to 5°C in an ice bath while a previously mixed solution of γ-butyrolactone (8.6 g, 0.1 mole) and boron trifluoride etherate (14.2 g, 0.1 mole) dissolved in 50 ml of ether was added dropwise. When the addition was complete, the resulting solution was stirred for one h at room temperature and then heated under reflux for 2 h. The solution was cooled to room temperature and an aqueous 15% potassium hydroxide solution was added dropwise with vigorous stirring until no more lithium aluminate precipitated (78). The mixture was filtered free of the solid and the ether was removed by careful

distillation. Tetrahydrofuran (1.5 g, 20%) was isolated. B.p. 62-63°C at 700 mm (lit. b.p. 64-65°C at 760 mm (92)). However, the major product was 1,4-butanediol (4.5 g, 50%).

Hence, this procedure did not proceed in a high enough yield to be synthetically useful and it was abandoned.

Method 2 (successful)

2-Isopropyltetrahydrofuran

5-Methyl-1,4-hexanediol was prepared by the lithium aluminum hydride reduction of γ-isopropyl-γ-butyrolactone.

A solution of γ-isopropyl-γ-butyrolactone (11 g, 0.085 mole) in 10 ml of dry ether was added dropwise with vigorous stirring to a solution of lithium aluminum hydride (2.0 g, 0.053 mole) in 100 ml of ether which was cooled to 5°C in an ice bath during the addition. When the addition was complete, the mixture was stirred for 2 h at room temperature. An aqueous 15% solution of potassium hydroxide was then added until no further lithium aluminate precipitated. The suspension was filtered free of solid and the filtrate freed from ether. The residue was distilled to give a colorless liquid (7.6 g, 69%). B.p. 80°C at 0.1 mm; n_D^{19} 1.4553.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.59; H, 12.20.

Found: C, 63.45; H, 12.24.

2-Isopropyltetrahydrofuran was prepared by the method of Reynolds and Kenyon (70).

The diol, 5-methyl-1,4-hexanediol (6.8 g, 0.052 mole), was dissolved in 25 ml of 2,6-lutidine and the resulting solution was heated with stirring to 100°C. To this solution was added dropwise, a solution of p-toluenesulfonyl chloride (9.8 g, 0.052 mole) dissolved in a minimum amount of 2,6-lutidine. When the addition was complete, the solution was maintained with stirring at 100°C for one h. The mixture was then distilled and the material which boiled between 120-130°C was collected. This distillate was redistilled through a 3 inch Vigreux column to give a colorless liquid. B.p. 114°C at 700 mm. However, analysis of the product by g.l.c. showed that a small amount (10%) of 2,6-lutidine remained in the mixture. Hence, purification by preparative g.l.c. was required and this was carried out on a butanediol succinate column at 150°C (n_D^{19} 1.4217).

Anal. Calcd. for $C_7H_{14}O$: C, 73.62; H, 12.36.

Found: C, 73.05; H, 12.35.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure showing a broad multiplet between τ6.1 and 6.9 (3H), a broad multiplet between τ 7.7 and 8.8 (4H) and a doublet of doublets between τ8.9 and 9.3 (6H), J = 4.5 Hz.

G.l.c. showed one symmetrical peak with a retention time identical to that for the low boiling product from the hydrogenolysis of 5-isopropyl-2-methoxytetrahydrofuran.

2-t-Butyltetrahydrofuran

5,5-Dimethyl-1,4-hexanediol was prepared by a lithium aluminum hydride reduction of methyl β-pivalylpropionate.

To a stirred solution of lithium aluminum hydride (2.4 g, 0.063 mole) in 100 ml of ether cooled to 5°C in an ice bath was added dropwise, a solution of methyl β-pivalylpropionate (10 g, 0.058 mole) in 20 ml of ether. The resulting mixture was stirred at room temperature for 2 h and an aqueous 15% solution of potassium hydroxide was added dropwise to decompose the complex and precipitate the lithium aluminate. The solid precipitate was removed by filtration and the filtrate freed from ether. The residue was distilled and gave a colorless liquid (8.1 g, 81%). B.p. 82-84° at 0.1 mm; n_D^{24} 1.4565.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41.

Found: C, 65.61; H, 12.35.

2-t-Butyltetrahydrofuran was prepared by a modification of the procedure of Reynolds and Kenyon (70).

The diol, 5,5-dimethyl-1,4-hexanediol (3.0 g, 0.021 mole), was heated with stirring to 100°C in 20 ml of 2,4,6-collidine. To this solution was added a solution of p-toluenesulfonyl chloride (6.5 g, 0.034 mole) dissolved in a minimum amount of collidine. The solution was stirred for one h at 100°C and then, without cooling, it was poured gradually into 100 ml of ether. The precipitated solid was separated by filtration and the filtrate freed

from ether. The residue was distilled and gave a mixture of the desired product contaminated with a small amount of collidine. B.p. 125°C at 695 mm. The product was purified by preparative g.l.c. on a carbowax column at 150°C (n_D^{22} 1.4248).

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58.

Found: C, 74.54; H, 12.43.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure showing a broad multiplet between τ 6.2 and 6.8 (3H), a multiplet between τ 8.0 and 8.5 (4H) and a singlet at τ 9.14 (9H).

G.l.c. showed one symmetrical peak with a retention time identical to that of the major product from the hydrogenolysis of 5-t-butyl-2-methoxytetrahydrofuran.

2-Phenyltetrahydrofuran

1-Phenyl-1,4-butanediol was prepared by the lithium aluminum hydride reduction of methyl β-benzoylpropionate as previously described for the preparation of 5,5-dimethyl-1,4-hexanediol.

A colorless liquid was obtained in an 84.5% yield. B.p. 129-130°C at 0.3 mm; n_D^{22} 1.5405. The liquid solidified on standing to give a white solid. M.p. 65-66°C.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49.

Found: C, 72.43; H, 8.55.

2-Phenyltetrahydrofuran was prepared by a modification of the procedure of Reynolds and Kenyon (70).

The diol, 1-phenyl-1,4-butanediol (5.4 g, 0.034 mole), was dissolved with stirring in 25 ml of lutidine and heated to 100°C. A solution of p-toluenesulfonyl chloride (5.8 g, 0.034 mole) dissolved in a minimum of lutidine was added dropwise with continued heating. The solution was stirred at 100°C for one h and it was then poured gradually into 100 ml of ether. The solid was separated by filtration and the filtrate freed from ether. The residue was distilled. Excess lutidine distilled as the first fraction and the desired product distilled as the second fraction. B.p. 80°C at 3 mm. The colorless liquid was further purified by preparative g.l.c. (n_D^{23} 1.5283) on an Apiezon T column.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16.

Found: C, 80.90; H, 8.10.

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure showing a singlet at τ 2.80 (5H), a triplet centered at τ 5.22 (1H), a multiplet between τ 5.9 and 6.3 (2H) and a multiplet between τ 7.8 and 8.4 (4H).

G.l.c. showed one symmetrical peak with a retention time identical to that of the low boiling product from the hydrogenolysis of 2-methoxy-5-phenyltetrahydrofuran.

2. Synthesis of the endo cleavage products from the 5-substituted-2-alkoxytetrahydrofuran.

Method 1 (successful)

6-Methoxy-2-methyl-3-hexanol was prepared from 5-methyl-1,4-hexanediol by a modification of the procedure of Diner and coworkers (71).

The diol, 5-methyl-1,4-hexanediol (2.5 g, 0.019 mole), was mixed with methyl iodide (5.4 g, 0.038 mole) in 50 ml of dry DME (1,2-dimethoxyethane, distilled from $LiAlH_4$). A suspension of 60% sodium hydride in paraffin (0.76 g, 0.019 mole) was washed in pentane and dried under nitrogen. The residual solid was then added with vigorous stirring in small portions to the solution of diol and methyl iodide. When the addition was complete, the resulting solution was stirred at room temperature for 2 h. The DME was then removed and the residue was taken up in ether. The solid was removed by filtration and the filtrate freed from solvent. The residue was distilled and gave a colorless liquid (no yield was determined). B.p. 58°C at 1 mm; n_D^{20} 1.4343.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.84; H, 12.36.

Found: C, 65.62; H, 12.42.

G.l.c. analysis showed a single component with a retention time which was identical to that of the high boiling product from the hydrogenolysis of 5-isopropyl-2-methoxytetrahydrofuran.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure, showing an overlapping multiplet and singlet between τ6.4 and 6.9 (6H), a multiplet at τ7.3 (1H), exchangeable with D_2O, a broad multiplet between τ7.8 and 8.6 (5H) and a doublet centered at τ9.12 (6H), J = 6.0 Hz. The n.m.r. spectrum in DMSO-d^6 showed that the multiplet originally at τ7.3 in CCl_4 had been shifted downfield to a clear doublet centered at τ5.86 (1H), J = 5 Hz.

The i.r. spectrum (neat) showed an absorption band between 3600 cm^{-1} and 3100 cm^{-1} (O-H stretch) and a broad abosrption band between 1150 cm^{-1} and 1050 cm^{-1} (C-O stretch).

The methylation of 1,4-pentanediol was carried out by a modification of the method of Diner and coworkers (71) as previously described for the methylation of 5-methyl-1,4-hexanediol.

G.l.c. analysis of the product after distillation (b.p. 75°C at 15 mm; n_D^{20} 1.4236) showed two peaks in the approximate ratio of 5:2. This indicated that both possible methylation products were formed. Lit. b.p. 65°C at 20 mm; n_D^{25} 1.4220 (5) for 5-methoxy-2-pentanol.

2,2-Dimethyl-6-methoxy-3-hexanol was prepared from 5,5-dimethyl-1,4-hexanediol by the modified procedure of Diner and coworkers (71) as previously described for the methylation of 5-methyl-1,4-hexanediol.

A colorless liquid was obtained in a 61% yield. B.p. 82-83°C at 6 mm; n_D^{24} 1.4350.

Anal. Calcd. for $C_9H_{20}O_2$: C, 67.45; H, 12.58.

Found: C, 67.18; H, 12.89.

G.l.c. showed a single symmetrical peak with a retention time which was identical to that of the trace amounts of high boiling product from the hydrogenolysis of 5-t-butyl-2-methoxytetrahydrofuran.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure showing a multiplet and overlapping singlet between τ6.3 and 6.9 (6H), a doublet at τ7.45 (1H), exchangeable in D_2O, a broad multiplet between τ8.1 and 8.6 (4H) and a singlet at τ9.08 (9H).

The i.r. spectrum (neat) showed a broadabsorption band between 3600 cm^{-1} and 3100 cm^{-1} (O-H stretch) and a broad absorption band between 1150 cm^{-1} and 1020 cm^{-1} (C-O stretch).

The methylation of 1-phenyl-1,4-butanediol was attempted by the modified procedure of Diner and coworkers (71) as previously described for the methylation of 5-methyl-1,4-hexanediol.

G.l.c. analysis of the product mixture showed at least four components to be present. The n.m.r. spectrum in $CDCl_3$ also indicated a bad mixture of products. There appeared to be both of the monomethylation products as well as some dimethylation product and some starting material present in the mixture.

Hence, this procedure was abandoned without definitely determining the structure of the products.

Method 2 (unsuccessful)

The attempted preparation of the ethylene glycol ketal of methyl β-benzoylpropionate was carried out by the method of Pinder and Smith (73).

The keto-ester, methyl β-benzoylpropionate (8.8 g, 0.046 mole), and ethylene glycol (3.2 g, 0.046 mole) were mixed in a benzene solution and a trace of p-toluenesulfonic acid was added. A Dean-Stark water trap was attached to the flask and the solution was heated under reflux for 48 h. No water was collected in the trap during this period. The solution was cooled to room temperature and solid sodium carbonate (1 g) was added. The resulting mixture was stirred at room temperature for one h and the solid was separated by filtration. The filtrate was freed from the benzene and the residue was immediately subjected to i.r. analysis. The spectrum was identical to that of the starting keto-ester.

Hence, the proposed reaction sequence mentioned in the Results and Discussion was abandoned.

Method 3 (unsuccessful)

The sodium salt of 4-hydroxybutyric acid was prepared by the method of Marvel and Birkhimer (74).

The lactone, γ-butyrolactone (16.3 g, 0.2 mole), was refluxed for 3 h in 30 ml of water containing potassium hydroxide (12 g, 0.2 mole). The water was removed on a rotatory evaporator leaving the solid sodium salt. This solid was simply dried under vacuum for 6 h for purification. An analysis was not attempted.

The methylation of the sodium salt of 4-hydroxybutyric acid was attempted by the method of Diner and coworkers (71).

The crude sodium salt prepared in the preceeding experiment (0.2 mole) was stirred into 200 ml of dry DME with methyl iodide (60 g, 0.4 mole). A suspension of 60% sodium hydride in paraffin (8.0 g, 0.2 mole) was washed in pentane and dried under nitrogen. The solid was then added in small protions to the solution of lactone and methyl iodide. The solution was maintained at 5°C in an ice bath during the addition. When the addition was complete, the solution was stirred at room temperature for 3 h. Dry hydrogen chloride gas (10 g) dissolved in 50 ml of dry methanol was then added with stirring. The resulting solution was stirred for one h at room temperature and solid sodium carbonate (10 g) was added in portions. When the addition was complete, the mixture was stirred for 15 min and the solid was removed by filtration. The filtrate was freed from solvent and the residue was taken up in ether. The solid was separated by filtration and the filtrate freed from ether.

G.l.c. analysis of the residue showed no identifiable

products among the several component peaks. None of the peaks were present in major amount and this procedure was therefore abandoned.

Method 4 (successful)

1-Bromo-2-methoxyethane was prepared by the method of Palomaa and Kenetti (75).

Ethylene glycol monomethyl ether (76 g, 1.0 mole) was cooled in an ice bath to 5°C and phosphorous tribromide (100 g, 0.35 mole) was added dropwise with vigorous stirring. When the addition was complete, the solution was stirred at room temperature for one hour. Nitrogen gas was bubbled through the solution until no more hydrogen bromide was liberated from the solution and the liquid was distilled to give a crude product. The distillate was then fractionally redistilled to give the colorless product (55 g, 39%). B.p. 108°C at 695 mm; n_D^{23} 1.4455. (No data was given by Palomaa and Kenetti (75)).

Diethyl (2-methoxyethyl)malonate was prepared by a modification of the procedure of Palomaa and Kenetti (75).

A suspension of 60% sodium hydride in paraffin (16 g, 0.4 mole) was washed with pentane, dried under nitrogen and suspended with stirring in 300 ml of dry DME. To this suspension was added, in a dropwise fashion, diethyl malonate (64 g, 0.4 mole). When the addition was complete, the solution was heated under reflux for one

hour and 1-bromo-2-methoxyethane (55 g, 0.4 mole) was added dropwise with continued heating. When the addition was complete, the solution was refluxed for two hours and the DME removed on a rotatory evaporator. The residue was taken up in ether and the solid removed by filtration. The filtrate was freed from ether and the residue was distilled to give a colorless liquid (36 g, 45%). B.p. 111°C at 6 mm; n_D^{22} 1.4238. Lit. b.p. 110°C at 6 mm (75).

4-Methoxybutyric acid was prepared by the method of Palomaa and Kenetti (75).

The malonate ester (15.5 g, 0.072 mole) was stirred with 9.0 g of potassium hydroxide in 100 ml of water at room temperature for 12 h. The solution was then acidified to pH 2-3 with 50% H_2SO_4 and saturated with sodium chloride. The solution was extracted with ether (3 x 75 ml) and the ether extracts dried over magnesium sulfate. The solid was removed by filtration and the filtrate freed from ether. The residue was heated in a distillation apparatus under vacuum to give the desired acid as a colorless liquid (6.9 g, 82%). B.p. 93°C at 4 mm; n_D^{25} 1.4226. Lit. b.p. 105°C at 7 mm; n_D^{20} 1.4251 (75).

Methyl 4-methoxybutyrate was prepared by refluxing 4-methoxybutyric acid (3 g, 0.025 mole) in 20 ml of dry methanol with a trace of p-toluenesulfonic acid for 12 h. Solid sodium carbonate (1 g) was added and the resulting mixture was stirred at room temperature

for 15 min. The solid was then removed by filtration and the filtrate freed from ether. The residue was distilled to give a colorless product (1.5 g, 45%). B.p. 100°C at 100 mm; n_D^{24} 1.4058.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.16.
Found: C, 54.55; H, 9.43.

4-Methoxy-1-phenyl-1-butanone was prepared from 4-methoxybutyric acid and phenyl lithium.

Lithium metal (0.32 g, 0.04 mole) was vigorously stirred in 100 ml of dry ether which had been flushed with nitrogen gas. To this suspension was added dropwise, bromobenzene (3.14 g, 0.02 mole). When the reaction was complete and no metal remained, the solution was stirred at room temperature for 2 h and 4-methoxybutyric acid (1.2 g, 0.01 mole) in 50 ml of ether was added slowly. The solution was then stirred overnight at room temperature. Water (10 ml) was added with stirring, the two layers were separated and the ether layer was dried over magnesium sulfate. The solid was separated by filtration and the filtrate freed from the ether. The residue was not purified but was immediately subjected to the next reaction.

4-Methoxy-1-phenyl-1-butanol was prepared by a sodium borohydride reduction of 4-methoxy-1-phenyl-1-butanone.

The ketone, 4-methoxy-1-phenyl-1-butanone (0.9 g, 0.051 mole), was stirred in 30 ml of dry tetrahydrofuran cooled to -10°C

in a dry ice-acetone bath. To this solution was added in small portions, sodium borohydride (0.10 g, 0.026 mole). When the addition was complete, the solution was stirred overnight at room temperature and then carefully neutralized with 50% H_2SO_4. One drop of phenolphthalein indicator was added to the solution before neutralization and the addition of H_2SO_4 was stopped as soon as the color of the solution changed from purple to colorless. The excess tetrahydrofuran was removed and the residue was taken up in ether. The solid was separated by filtration and the filtrate freed from ether. The residue was distilled and gave a colorless liquid (0.8 g, 89%). B.p. 94-95°C at 0.1 mm; n_D^{23} 1.5150.

Anal. Calcd. for $C_{11}C_{16}O_2$: C, 73.30; H, 8.95.

Found: C, 73.15; H, 8.68.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure showing a singlet at τ2.72 (5H), a multiplet at τ5.4 (1H), an overlapping multiplet and singlet between τ6.4 and 6.8 (5H), a multiplet at τ6.9 (1H), exchangeable with D_2O and a multiplet between τ8.0 and 8.5 (4H).

The i.r. spectrum showed a broad absorption band between 3600 cm^{-1} and 3100 cm^{-1} and a broad absorption band between 1130 cm^{-1} and 1000 cm^{-1}.

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

3. Synthesis of 4-benzyloxy-1-butanol.

4-Benzyloxy-1-butanol was prepared by a modification of the procedure of Diner and coworkers (71).

A suspension of 60% sodium hydride in paraffin (4.0 g, 0.1 mole) was washed in pentane and dried under nitrogen. The remaining solid was added in small protions with stirring to a solution of benzyl chloride (12.6 g, 0.1 mole) and 1,4-butanediol (9.0 g, 0.1 mole) dissolved in 100 ml of dry DME. When the addition was complete, the mixture was heated under reflux for one hour and the DME was removed. The residue was taken up in ether, the solid was removed by filtration and the filtrate freed from ether. The residue was distilled to give a clear liquid (13.6 g, 76%). B.p. 105°C at 0.4 mm; n_D^{20} 1.5105. Lit. b.p. 116°C at 4 mm; n_D^{25} 1.5130 (4).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95.

Found: C, 73.13; H, 8.84.

G.l.c. analysis showed a single symmetrical peak (on an Apiezon L column) for which the retention time was identical to that of the high boiling product from hydrogenolysis of 2-benzyloxy-tetrahydrofuran.

4. Synthesis of the 4-Aryloxy-1-butanols.

Method 1 (unsuccessful)

The attempted preparation of 4-phenoxy-1-butanol was carried out

by a modification of the procedure of Eliel and coworkers (4).

A mixture of 4-chloro-1-butanol (4.7 g, 0.043 mole) and 3,4-dihydro-2H-pyran (3.7 g, 0.043 mole) was heated with stirring under reflux for 3 h in the presence of a trace of p-toluenesulphonic acid. The solution was cooled to room temperature and 75 ml of ether was added. Solid sodium bicarbonate (1 g) was added and the mixture was stirred for 15 min. The solid was then removed by filtration and the filtrate freed from ether. A suspension of 60% sodium hydride in paraffin (1.72 g, 0.043 mole) was washed in pentane, dried under nitrogen and suspended in 50 ml of dry DME. To this suspension was added slowly with stirring a solution of phenol (4.05 g, 0.043 mole) in 50 ml DME. When the addition was complete, the solution was refluxed for one h. The residue from the reaction between dihydropyran and chlorobutanol was dissolved in 50 ml of DME and then added dropwise to the sodium phenoxide solution with reflux being continued during the addition. When the addition was complete, the mixture was heated under reflux for 24 h. The DME was removed and the residue was stirred at room temperature for 2 h with 10 ml of 10% sulfuric acid. The solution was then saturated with sodium chloride and extracted with ether (3 x 25 ml). The ether extracts were dried over magnesium sulfate, the solid was separated by filtration and the filtrate freed from ether. G.l.c. analysis of the residue showed a very bad mixture of products. Hence this procedure was abandoned.

Method 2 (unsuccessful)

The attempted preparation of 4-phenoxy-1-butanol was carried out as described below.

A suspension of 60% sodium hydride in paraffin (1.72 g, 0.043 mole) was washed in pentane, dried under nitrogen and suspended in 50 ml of dry DME. To this vigorously stirred suspension, phenol (4.05 g, 0.043 mole) in 10 ml dry DME was added dropwise. The mixture was heated under reflux for one h and with continued heating, 4-chloro-1-butanol (4.7 g, 0.043 mole) in 10 ml dry DME was added dropwise. The mixture was heated under reflux for 24 h. The DME was removed and the residue taken up in ether. The solid was removed by filtration and the filtrate freed from ether. G.l.c. analysis of the residue showed it to be primarily phenol. It was assumed that tetrahydrofuran was also formed during the reaction but was lost during the evaporation of the DME. Hence, this procedure was abandoned.

Method 3 (unsuccessful).

The attempted preparation of 4-benzyloxy-1-bromobutane was carried out by a modification of the procedure of Palomaa and Kenetti (75).

The alcohol, 4-benzyloxy-1-butanol (9.0 g, 0.05 mole), was cooled to 5°C in an ice bath while phosphorus tribromide (4.5 g, 0.017 mole) was added dropwise with vigorous stirring. When the addition was complete, the solution was allowed to come to room temperature; it was taken up in ether and the two layers.

were separated. The ether layer was washed with saturated aqueous sodium carbonate solution until neutral and then dried over magnesium sulfate. The solid was separated by filtration and the filtrate freed from ether. The residue was distilled and gave only benzyl bromide (b.p. 65°C at 5 mm; n_D^{24} 1.5556) and starting material. Yields were not determined but it was concluded that sufficient hydrogen bromide was formed during the reaction to cleave the benzyl ether group.

4-Benzyloxy-1-chlorobutane was prepared by the method of Hooz and Gilani (76).

A solution of 4-benzyloxy-1-butanol (4.5 g, 0.025 mole) in 50 ml of carbon tetrachloride was cooled in an ice bath to 5°C while tri-n-butylphosphine (6.1 g, 0.03 mole) (Carlisle Chemical Works) was added dropwise. The mixture was stirred for 5 min at room temperature and the solvent was removed on a rotatory evaporator. The residue was distilled and gave a colorless liquid (3.4 g, 68%). B.p. 94°C at 0.5 mm; n_D^{25} 1.4987.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure showing a singlet at τ 2.70 (5H), a singlet at τ 5.53 (2H), a multiplet between τ 6.4 and 6.7 (4H) and a multiplet between τ 8.0 and 8.5 (4H).

The attempted preparation of 4-benzyloxy-1-phenoxybutane was carried out as described below.

The chloroether, 4-benzyloxy-1-chlorobutane (1 g, 0.005 mole), was added dropwise to a solution of sodium phenoxide previously prepared from phenol (0.48 g, 0.005 mole) and 60% sodium hydride (0.2 g, 0.005 mole) by the procedure described in Method 2, above. When the addition was complete, the solution was heated under reflux for 24 h and the DME was evaporated. The residue was taken up in ether and the solid removed by filtration. The filtrate was freed from ether and the residue was distilled to give a colorless liquid (1.15 g, 90%). B.p. 95°C at 0.5 mm. The n.m.r. spectrum showed this compound to be the starting chloride.

4-Benzyloxy-1-tosyloxybutane was prepared from 4-benzyloxy-1-butanol.

A solution of 4-benzyloxy-1-butanol (4.5 g, 0.025 mole) in 20 ml of dry ether and 20 ml of pyridine was stirred vigorously while p-toluenesulfonyl chloride was added in one portion. A clear solution was formed and when the solution was stirred at room temperature for one half h, a white solid started to precipitate. The solution was stirred for 24 h and the solid was separated by filtration. The filtrate was washed five times with 10% aqueous hydrochloric acid and the ether extracts were dried over magnesium sulfate. The solid was separated by filtration and the filtrate was freed of ether. The oily residue could not be recrystallized and distillation was not attempted.

The i.r. spectrum (neat) showed no hydroxyl absorption between 3600 cm^{-1} and 3100 cm^{-1}.

The n.m.r. spectrum in $CDCl_3$ was consistent showing a doublet centered at τ2.24 (2H), J = 8 Hz, a multiplet centered at τ2.8 (7H), a singlet at τ5.57 (2H), a multiplet centered at τ5.95 (2H), a multiplet centered at τ6.60 (2H), a singlet at τ7.60 (3H) and a multiplet between τ8.1 and 8.5 (4H).

The attempted preparation of 4-benzyloxy-1-phenoxybutane was carried out as described below.

A solution of 4-benzyloxy-1-tosyloxybutane (4.17 g, 0.0125 mole) in 10 ml of dry DME was added to a solution of sodium phenoxide prepared from phenol (1.18 g, 0.0125 mole) and 60% sodium hydride (0.5 g, 0.0125 mole) in 50 ml dry DME by the procedure described in Method 2, above. The solution was heated under reflux for 24 h and the DME was evaporated. The residue was taken up in ether, the solid was separated by filtration and the filtrate freed from ether. The n.m.r. spectrum of the residue showed primarily 4-benzyloxy-1-tosyloxybutane and only a small amount (5-10%) of what may have been the desired product. Hence, very little reaction took place and the procedure was abandoned.

Method 4 (successful)

4-Phenoxy-1-butanol

1-Bromo-3-phenoxypropane was prepared by a modification of the

method of Marvel and Tanenbaum (77).

A suspension of 60% sodium hydride in paraffin (4.0 g, 0.1 mole) was washed in pentane, dried under nitrogen and suspended in 100 ml of dry DME. To this suspension was added a solution of phenol (9.4 g, 0.1 mole) in 30 ml of dry DME. When the addition was complete, the solution was refluxed for one hour and cooled to room temperature. The solution was then added dropwise to a solution of 1,3-dibromopropane (20.2 g, 0.1 mole) in 100 ml of dry DME which was heated under reflux during the addition. When the addition was complete, the mixture was heated under reflux for an additional 5 h. The DME was evaporated, the residue was taken up in ether and the solid removed by filtration. The ether was removed and the residue distilled to give a colorless liquid (6.5 g, 30%). B.p. 105°C at 5 mm; n_D^{25} 1.5454. Lit. b.p. 136-142°C at 20 mm (77).

4-Phenoxybutyronitrile was prepared by a modification of the method of Marvel and Tanenbaum (77).

A solution of 1-bromo-3-phenoxypropane (4.3 g, 0.02 mole) and sodium cyanide (2.0 g, 0.04 mole) in 10 ml of water and 10 ml of 95% ethanol was heated under reflux for 20 h. The solution was cooled and extracted with ether (4 x 25 ml) and the ether extracts were dried over magnesium sulfate. The solid was removed by filtration and the filtrate freed of ether. The residue was distilled and gave a colorless liquid (2.5 g, 78%). B.p. 93-97°C at 0.08 mm;

n_D^{22} 1.5177. Lit. b.p. 162-166°C at 22 mm (77).

Ethyl 4-phenoxybutyrate was prepared by a modification of the method of Marvel and Tanenbaum (77).

A solution of 4-phenoxybutyronitrile (1.6 g, 0.01 mole) in a mixture of 10 ml of 95% ethanol, 1 ml of concentrated sulfuric acid and 2 ml of water was heated under reflux for 48 h. The solution was cooled to room temperature and extracted with ether (3 x 25 ml). The ether extracts were dried over magnesium sulfate, the solid was separated by filtration and the filtrate was freed from ether. The residue was distilled and gave a colorless liquid (1.4 g, 65%). B.p. 105-107°C at 0.1 mm; n_D^{23} 1.5016. Lit. b.p. 160-165°C at 25 mm; n_D^{22} 1.491 (77).

4-Phenoxy-1-butanol was prepared by the reduction of ethyl 4-phenoxybutyrate.

A solution of ethyl 4-phenoxybutyrate (4.0 g, 0.02 mole) in 10 ml of dry ether was added dropwise to a solution of lithium aluminum hydride (0.4 g, 0.011 mole) in 20 ml of dry ether. The solution was stirred for 2 hours at room temperature and a 15% aqueous solution of potassium hydroxide was added until all of the lithium aluminate had precipitated. The solution was separated by filtration and the filtrate freed from ether. The residue was distilled and gave a colorless liquid (1.9 g, 57%). B.p. 100-102°C at 0.6 mm; n_D^{22} 1.5260.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.48.
Found: C, 71.94; H, 8.73.

4-(3,5-Dimethylphenoxy)-1-butanol

1-Bromo-3-(3,5-dimethylphenoxy)propane was prepared from 3,5-dimethylphenol and 1,3-dibromopropane by the modified method of Marvel and Tanenbaum (77) as previously described for the preparation of 1-bromo-3-phenoxypropane.

A colorless liquid was obtained in a 30% yield. B.p. 90-93°C at 0.5 mm; n_D^{22} 1.5343.

4-(3,5-Dimethylphenoxy)butyronitrile was prepared from 1-bromo-3-(3,5-dimethylphenoxy)propane by the modified method of Marvel and Tanenbaum as previously described for the preparation of 4-phenoxybutyronitrile.

A colorless liquid was obtained in 60.5% yield. B.p. 114-115°C at 0.3 mm; n_D^{22} 1.5150.

Ethyl 4-(3,5-dimethylphenoxy)butyrate was prepared from 4-(3,5-dimethylphenoxy)butyronitrile by the modified procedure of Marvel and Tanenbaum as previously described for the preparation of ethyl 4-phenoxybutyrate.

A colorless liquid was obtained in 51% yield. B.p. 112-115°C at 0.4 mm; n_D^{23} 1.5016.

4-(3,5-Dimethylphenoxy)-1-butanol was prepared by the $LiAlH_4$ reduction of ethyl 4-(3,5-dimethylphenoxy)butyrate by the method previously described for the preparation of 4-phenoxy-1-butanol.

A colorless liquid was obtained in a 72% yield. B.p. 120-123°C at 0.8 mm; n_D^{22} 1.5205.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34.

Found: C, 74.45; H, 9.42.

4-(2,6-Dimethylphenoxy)-1-butanol

1-Bromo-3-(2,6-dimethylphenoxy)propane was prepared from 2,6-dimethylphenol and 1,3-dibromopropane by the modified method of Marvel and Tanenbaum (77) as previously described for the preparation of 1-bromo-3-phenoxypropane.

A colorless liquid was obtained in 30% yield. B.p. 105-106°C at 1.5 mm; n_D^{22} 1.5290.

4-(2,6-Dimethylphenoxy)butyronitrile was prepared from 1-bromo-3-(2,6-dimethylphenoxy)propane by the modified method of Marvel and Tanenbaum (77) as previously described for the preparation of 4-phenoxybutyronitrile.

A colorless liquid was obtained in 79.5% yield. B.p. 109-110°C at 0.2 mm; n_D^{22} 1.5088.

Ethyl 4-(2,6-dimethylphenoxy)butyrate was prepared from 4-(2,6-dimethylphenoxy)butyronitrile by the modified method of Marvel

and Tanenbaum (77) as previously described for the preparation of ethyl 4-phenoxybutyrate.

A colorless liquid was obtained in 57% yield. B.p. 113-115°C at 0.7 mm; n_D^{22} 1.4927.

4-(2,6-Dimethylphenoxy)-1-butanol was prepared by the $LiAlH_4$ reduction of ethyl 4-(2,6-dimethylphenoxy)butyrate by the method described for the preparation of 4-phenoxy-1-butanol.

A colorless liquid was obtained in 72% yield. B.p. 116-118°C at 0.9 mm; n_D^{22} 1.5136.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34.

Found: C, 74.19; H, 9.05.

4-(2,6-Dichlorophenoxy)-1-butanol

1-Bromo-3-(2,6-dichlorophenoxy)propane was prepared from 2,6-dichlorophenol and 1,3-dibromopropane by the modified method of Marvel and Tanenbaum (77) as previously described for the preparation of 1-bromo-3-phenoxypropane.

A colorless liquid was obtained in 26% yield. B.p. 100-103°C at 0.1 mm; n_D^{23} 1.5181.

4-(2,6-Dichlorophenoxy)butyronitrile was prepared from 1-bromo-3-(2,6-dichlorophenoxy)propane by the modified method of Marvel and Tanenbaum (77) as previously described for the preparation of 4-phenoxybutyronitrile.

A colorless liquid was obtained in 63.5% yield. B.p. 128-130°C at 0.6 mm; n_D^{22} 1.5346.

Ethyl 4-(2,6-dichlorophenoxy)butyrate was prepared from 4-(2,6-dichlorophenoxy)butyronitrile by the modified method of Marvel and Tanenbaum (77) as previously described for the preparation of ethyl 4-phenoxybutyrate.

A colorless liquid was obtained in 52% yield. B.p. 120-122°C at 0.3 mm; n_D^{23} 1.5119.

4-(2,6-Dichlorophenoxy)-1-butanol was prepared by the $LiAlH_4$ reduction of ethyl 4-(2,6-dichlorophenoxy)butyrate by the method previously described for the preparation of 4-phenoxy-1-butanol.

A colorless liquid was obtained in 51% yield. B.p. 110-111°C at 0.07 mm; n_D^{22} 1.5380.

Anal. Calcd. for $C_{10}H_{12}O_2Cl_2$: C, 51.08; H, 5.15; Cl, 30.16.
Found: C, 51.12; H, 5.32; Cl, 30.44.

G. Hydrogenolysis of the Tetrahydrofuranyl Acetals.

1. Reduction using $AlClH_2$.

The procedure used for the reduction of all tetrahydrofuranyl acetals was that described by Diner (7) for the hydrogenolysis of the tetrahydropyranyl acetals. The reduction of 2-(2,6-dimethylphenoxy)tetrahydrofuran is described here as an example of the procedure.

Lithium aluminum hydride (0.30 g, 0.0079 mole) was dissolved in 30 ml of dry ether and the solution was cooled to 5°C in an ice bath. To this solution was added dropwise an ether solution of aluminum chloride, prepared by adding aluminum chloride (1.05 g, 0.0079 mole) in small portions to 30 ml of dry ether cooled to 5°C in an ice bath. The resulting "mixed hydride" solution was stirred at room temperature for 15 min and a solution of 2-(2,6-dimethylphenoxy)tetrahydrofuran (3 g, 0.0156 mole) was then added dropwise. The resulting mixture was then stirred for 2 h at room temperature and an aqueous 15% solution of potassium hydroxide was added dropwise until no further reaction occurred and a white solid precipitated (lithium aluminate). The solid was separated by filtration and the ether was removed by distillation. The residue (90% recovery) was analyzed by g.l.c.. Only tetrahydrofuran and 2,6-dimethylphenol were found in the mixture and they were identified by comparison of the retention times with authentic materials.

Other acetals were stirred with the reducing species for varying lengths of time as noted in Tables 11, 17 and 21.

In all cases, except for the reduction of 2-isopropoxy-5-methyltetrahydrofuran, authentic materials were prepared for comparison with the hydrogenolysis products. In the case of the reduction of 2-isopropoxy-5-methyltetrahydrofuran, the 5-isopropoxy-2-pentanol, formed in 93% yield (Table 12), was identified by its n.m.r. and i.r. spectra and its elemental analysis. The product was isolated from the hydrogenolysis mixture by preparative

g.l.c. on a butanediol succinate column. A microboiling point was determined and was found to be 65-66°C at 8 mm (n_D^{24} 1.4225).

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41.

Found: C, 65.67; H, 12.62.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure showing a multiplet between τ6.0 and 6.7 (4H), a singlet at τ6.85 (1H) which was exchanged with D_2O, a multiplet between τ8.2 and 8.6 (4H) and a doublet centered at τ8.85 (9H), J = 9 Hz.

The i.r. spectrum (neat) showed a broad absorption band between 3600 cm^{-1} and 3100 cm^{-1} (O-H stretch) and a broad absorption band between 1200 cm^{-1} and 1000 cm^{-1} (C-O stretch).

2. Reduction using AlH_3.

The procedure described by Diner (7) was used for the reduction of acetals when the reducing species, AlH_3, was required. The reduction of 5-methoxymethyl-2-methoxytetrahydrofuran is described below as an example of the procedure.

Lithium aluminum hydride (0.195 g, 0.0052 mole) was dissolved in 20 ml of dry ether and the solution was cooled to 5°C in an ice bath. A solution of aluminum chloride was prepared by the addition of aluminum chloride (0.23 g, 0.0017 mole) in small portions to cold (5°C) ether. The aluminum chloride solution was then added dropwise to the cold lithium aluminum hydride solution. The resulting "mixed hydride" solution was stirred at room

temperature for 15 min and a solution of 5-methoxymethyl-2-methoxytetrahydrofuran (1 g, 0.0069 mole) in 10 ml of dry ether was added dropwise. The resulting mixture was stirred at room temperature for 20 h and an aqueous 15% solution of potassium hydroxide was added until no further reaction was observed and a white solid had precipitated. The solid was separated by filtration and the ether was removed by distillation. The residue (85% recovery) was analyzed by g.l.c. and was found to contain 5% 2-methoxymethyltetrahydrofuran, 10% unreacted 5-methoxymethyl-2-methoxytetrahydrofuran and 85% 1,5-dimethoxy-2-pentanol. The results from other reductions using AlH_3 are shown in Table 12.

3. Reductions using $AlCl_2H$.

The same procedure as that described above for reduction with the species AlH_3 was used for reduction with $AlCl_2H$. Only the proportion of reactants were different. For example, lithium aluminum hydride (0.095 g, 0.0025 mole), aluminum chloride (1.0 g, 0.0075 mole) and 2-benzyloxytetrahydrofuran (0.89 g, 0.005 mole) were mixed by the same procedure as previously described for reductions with AlH_3.

G.l.c. analysis of the residue after work-up (90% recovery) showed that the mixture was composed of 90.5% benzyl alcohol and 9.5% 4-benzyloxy-1-butanol. The products were identified by their g.l.c. retention times.

4. Reductions using a 4:1 molar ratio of $AlCl_2H$ and $AlCl_3$.

The same procedure as that described above for reductions with the species AlH_3 was used for reductions with a 4:1 molar ratio of $AlCl_2H$ and $AlCl_3$. Only the proportions of reactants were different. For example, lithium aluminum hydride (0.095 g, 0.0025 mole), aluminum chloride (1.3 g, 0.01 mole) and 2-benzyloxytetrahydrofuran (0.89 g, 0.005 mole) were mixed by the same procedure as previously described for reductions with AlH_3.

G.l.c. analysis of the residue (91% recovery) showed that the mixture was composed of 91.3% benzyl alcohol and 8.7% 4-benzyloxy-1-butanol. The products were identified by their g.l.c. retention times.

5. Competitive hydrogenolyses using $AlClH_2$.

The competitive hydrogenolyses listed in Table 18 were carried out using the general procedure described for reductions with $AlClH_2$. However, different proportions of materials were used and the general procedure is described below using the case of 2-phenoxytetrahydrofuran and 2-ethoxytetrahydrofuran.

Lithium aluminum hydride (0.05 g, 0.00125 mole) and aluminum chloride (0.17 g, 0.00125 mole) were mixed in 40 ml of dry ether as previously described for the preparation of $AlClH_2$. The resulting "mixed hydride" solution was stirred at room temperature for 15 min and a mixture of 2-phenoxytetrahydrofuran (0.82 g,

0.005 mole) and 2-ethoxytetrahydrofuran (0.56 g, 0.005 mole) in 10 ml of dry ether was added dropwise. The solution was stirred at room temperature for 2 h and an aqueous 15% solution of potassium hydroxide was added dropwise until no further reaction was observed and a white solid precipitated. The solid was removed by filtration and the ether was removed by filtration and the ether was removed by distillation. The residue (95% recovery) was analyzed by g.l.c. and gave the results shown in Table 18.

6. Hydrogenolysis of 2,3-dimethoxytetrahydrofuran.

The reduction of 2,3-dimethoxytetrahydrofuran was carried out by the general procedure described for reductions using $AlClH_2$. G.l.c. analysis of the residue (81% recovery) showed that ring cleavage product was the only reduction product in the mixture (Table 21). This product was collected by preparative g.l.c. A microboiling point was determined as being 102°C at 9 mm; n_D^{23} 1.4295.

Anal. Calcd. for $C_6H_{14}O_3$: C, 53.71; H, 10.50.

Found: C, 53.96; H, 10.22.

An authentic sample of this reduction product, 3,4-dimethoxy-1-butanol, was prepared by the following sequence.

2,2-Diethyl-4-(2-hydroxyethyl)-1,3-dioxolane was prepared by a modification of the method of Salmi (101).

A solution of 1,2,4-butanetriol (21.2 g, 0.2 mole) and

3-pentanone (17.2 g, 0.2 mole) in 100 ml of dry benzene which contained a trace of p-toluenesulfonic acid was heated under reflux in a flask equipped with a Dean-Stark water trap. During the course of the reaction, 2.9 ml of water was collected. The solution was cooled to room temperature and solid sodium carbonate (1 g) was added. The resulting mixture was stirred for 15 min and the solid was separated by filtration. The benzene was removed on a rotary evaporator and the residue was distilled to give a colorless liquid (24.6 g, 71%). B.p. 108-110°C at 7 mm; n_D^{26} 1.4446.

4-(2-Benzyloxyethyl)-2,2-diethyl-1,3-dioxolane was prepared from 2,2-diethyl-4-(2-hydroxyethyl)-1,3-dioxolane, benzyl chloride and sodium hydride by the method of Diner and coworkers (71) as previously described for the preparation of 2-benzyloxymethyl-3,4-dihydro-2H-pyran.

A colorless liquid was obtained in 76% yield. B.p. 110°C at 0.4 mm; n_D^{26} 1.4893.

4-Benzyloxy-1,2-butanediol was prepared as described below.

A solution of 2,2-diethyl-4-(2-benzyloxyethyl)-1,3-dioxolane (5.2 g, 0.02 mole) in 30 ml of water containing 2 drops of concentrated hydrochloric acid was heated under reflux for 24 h. The solution was cooled to room temperature and solid sodium carbonate (1 g) was added. The mixture was stirred for 15 min and then it was saturated with sodium chloride. The solution was extracted with ether (3 x 50 ml) and the ether extracts were dried over

magnesium sulfate. The solid was removed by filtration and the filtrate freed from ether. The residue was not further purified but it was immediately subjected to the next reaction.

4-Benzyloxy-1,2-dimethoxybutane was prepared from 4-benzyloxy-1,2-butanediol, two equivalents of methyl iodide and two equivalents of sodium hydride by the method of Diner and coworkers (71) as previously described for the preparation of 2-methoxymethyl-3,4-dihydro-2H-pyran.

A colorless liquid was obtained in 76% yield. B.p. 95-96°C at 0.1 mm; n_D^{25} 1.4852.

3,4-Dimethoxy-1-butanol was prepared from 1,4-benzyloxy-1,2-dimethoxybutane by the method of Nayak and Brown (102).

Liquid ammonia (150 ml) was collected in a 500 ml round bottom flask cooled in a dry ice-acetone bath and fitted with a dry ice-acetone condenser. A solution of 4-benzyloxy-1,2-dimethoxybutane (2.2 g, 0.01 mole) in 10 ml of dry DME was added to the ammonia. The dry ice-acetone bath was removed, and small pieces of sodium metal were added with vigorous stirring. Each subsequent piece was added only as the deep blue color from the previous piece had disappeared. This addition was continued until 0.48 g (0.02 mole) of sodium metal had been added. Ammonium chloride (5 g) was added in one portion to decompose the reaction. The dry ice-acetone condenser was then removed and the ammonia was allowed to evaporate. The residue was taken up in ether,

the solid was removed by filtration and the filtrate freed from ether. The residue was distilled and gave a colorless liquid (1 g, 74%).

B.p. 92-93°C at 8 mm; n_D^{25} 1.4364.

Anal. Calcd. for $C_6H_{14}O_3$: C, 53.71; H, 10.50.

Found: C, 53.80; H, 10.22.

The n.m.r. spectrum in $CDCl_3$ and i.r. spectrum (neat) were identical with those spectra obtained from the hydrogenolysis product. The g.l.c. retention times on a butanediol succinate column were identical for the authentic material and the hydrogenolysis procedure.

H. Reaction of the 2-Aryloxytetrahydrofurans with $AlCl_3$.

The general procedure used for the reaction of all of the 2-aryloxytetrahydrofurans and pyrans with aluminum chloride is described below with the reaction of 2-(3,5-dimethylphenoxy)tetrahydrofuran being used as an example.

Aluminum chloride (0.17 g, 0.00125 mole) was dissolved in 30 ml of dry ether and to this solution was added 2-(3,5-dimethylphenoxy)tetrahydrofuran (0.96 g, 0.005 mole) with vigorous stirring. The solution was stirred at room temperature for 10 min during which time the solution turned pale orange. An aquous 15% solution of potassium hydroxide was added dropwise (0.25 ml) and the solution was then stirred until it became clear. The ether was decanted from the solid residue and removed by fractional distillation. G.l.c. analysis of the residue (0.90 g, 94%) gave the results shown

in Table 22. No 2,3-dihydrofuran was found in any case. However, a small amount of 3,4-dihydro-2H-pyran was found on g.l.c. analysis of the reaction mixtures from the 2-aryloxytetrahydropyrans.

Isolation of 2-(4,6-dimethyl-2-hydroxyphenyl)tetrahydrofuran.

The residue (0.9 g) from the reaction of 2-(3,5-dimethylphenoxy)tetrahydrofuran with $AlCl_3$ was chromatographed on 20 g of acid-washed alumina. A 4:1 mixture of Skellysolve B and chloroform was used as the eluant and the fractions were collected in 75 ml quantities. The first fraction was evaporated and yielded no product. The second and third fractions yielded a colorless oil which solidified upon sitting. The solid was recrystallized from Skellysolve B and gave a white crystalline solid (0.5 g, 55%). M.p. 65-67°C.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39.

Found: C, 74.80; H, 8.16.

The n.m.r. spectrum in $CDCl_3$ is shown in Figure 4 and is consistent with the proposed structure.

The i.r. spectrum (nujol) showed a broad absorption band between 3500 cm^{-1} and 3100 cm^{-1} (O-H stretch) and sharp absorption bands at 1620 cm^{-1}, 1570 cm^{-1}, 1310 cm^{-1} and 1035 cm^{-1}.

2-(4,6-dimethyl-2-methoxyphenyl)tetrahydrofuran was prepared by the methylation of 2-(4,6-dimethyl-2-hydroxyphenyl)tetrahydrofuran

by the method of Diner and coworkers (71) as previously described for the preparation of 2-methoxymethyl-3,4-dihydro-2H-pyran.

A colorless liquid was obtained but no yield was determined. B.p. 98-100°C at 0.3 mm; n_D^{24} 1.5338.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80.

Found: C, 75.38; H, 8.64.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure showing a singlet at τ3.46 (2H), a multiplet centered at τ4.7 (1H), a multiplet between τ5.8 and 6.3 (2H), a singlet at τ6.25 (3H), two singlets at τ7.66 and τ7.75 (6H) and a multiplet between τ7.8 and 8.1 (4H).

The i.r. spectrum (neat) showed sharp absorption bands at 1600 cm^{-1}, 1570 cm^{-1}, 1055 cm^{-1}, 1070 cm^{-1} and 1105 cm^{-1}.

An authentic sample of 2-(4,6-dimethyl-2-methoxyphenyl)-tetrahydrofuran was prepared by the following reaction sequence.

3,5-Dimethylanisole was prepared from 3,5-dimethylphenol by the method of Diner and coworkers (71) as previously described for the preparation of 2-methoxymethyl-3,4-dihydro-2H-pyran.

A colorless liquid was obtained in 95.5% yield. B.p. 83-85°C at 32 mm; n_D^{23} 1.5080. Lit. b.p. 193°C at 760 mm (106).

β-(4,6-dimethyl-2-methoxybenzoyl) propionic acid was prepared by a modification of the method of Harland and Robertson (103).

A solution of 3,5-dimethylanisole (10.5 g, 0.077 mole)

and succinic anhydride (7.8 g, 0.077 mole) in 150 ml of nitrobenzene was cooled to 5°C in an ice bath. Aluminum chloride (20.5 g, 0.154 mole) was added in small portions. When the addition was complete, the flask was stoppered and let sit in a refrigerator at 5°C for three days. The solution was then poured into 400 g of crushed ice and 15 ml of concentrated hydrochloric acid with swirling. This mixture was extracted with ether (3 x 200 ml) and the extracts were freed from ether. The residue was extracted with an aqueous 15% solution of sodium carbonate (10 x 75 ml). The combined sodium carbonate extracts were carefully acidified with concentrated hydrochloric acid and the solid which precipitated was collected by filtration under vacuum on a Buchner funnel.

Recrystallization was effected by the following procedure. The crude acid was dissolved in chloroform (200 ml) and the solution was dried over magnesium sulfate. The solid was separated by filtration and the filtrate was evaporated on a rotatory evaporator to a volume of 75 ml. Skellysolve B was added until the solution became cloudy and the flask was then stoppered and cooled in a refrigerator for 18 h while the acid crystallized. The solid acid was collected by filtration and dried by passing air through the pale tan solid (14.0 g, 78%). M.p. 97-99°C.

1-(4,6-Dimethyl-2-methoxyphenyl)-1,4-butanediol was prepared by a $LiAlH_4$ reduction of β-(4,6-dimethyl-2-methoxybenzoyl)propionic acid by the method previously described for the preparation of

5,5-dimethyl-1,4-hexanediol.

The crude oily material (91%) was not purified but was immediately subjected to the next step of the reaction sequence.

2-(4,6-Dimethyl-2-methoxyphenyl)tetrahydrofuran was prepared from 1-(4,6-dimethyl-2-methoxyphenyl)-1,4-butanediol by the method of Reynolds and Kenyon (70) as previously described for the preparation of 2-phenyltetrahydrofuran.

The material prepared by this method was found to contain a small amount (5%) of p-toluenesulfonyl chloride which could not be removed by fractional distillation or column chromatography. The resulting tetrahydrofuran (4.0 g, 44%) was therefore refluxed overnight with an aqueous 15% solution of potassium hydroxide. The solution was cooled to room temperature, saturated with sodium chloride and extracted with ether (3 x 20 ml). The ether extracts were dried over magnesium sulfate, the solid was removed by filtration and the filtrate was freed from ether. The residue was distilled and gave a pale yellow liquid (3.5 g, 38%). B.p. 100-102°C at 0.5 mm; n_D^{22} 1.5375.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80.

Found: C, 75.55; H, 8.77.

The n.m.r. spectrum in $CDCl_3$ and the i.r. spectrum (neat) were identical to those of the methylated rearrangement product described above.

The isolation of 2-(4,6-dimethyl-2-hydroxyphenyl)tetrahydropyran was carried out by the same procedure as previously described for the isolation of 2-(4,6-dimethyl-2-hydroxyphenyl)tetrahydrofuran.

A white crystalline material was obtained. M.p. 87-89°C.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80.

Found: C, 75.41; H, 8.80.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure showing a singlet at τ1.5 (1H) exchangeable in D_2O, two singlets at τ3.48 and τ3.55 (2H), a multiplet centered at τ5.3 (1H), a multiplet between τ6.2 and 6.7 (1H), two singlets at τ7.81 and 7.85 (6H) and a multiplet between τ8.0 and 8.5 (6H).

The i.r. spectrum (nujol) showed an absorption band at 3250 cm^{-1} (O-H stretch) and sharp absorption bands at 1615 cm^{-1}, 1570 cm^{-1}, 1310 cm^{-1}, 1072 cm^{-1}, 890 cm^{-1} and 840 cm^{-1}.

The reaction of 2-(2,6-dimethylphenoxy)tetrahydrofuran with $AlCl_3$ was carried out by the procedure described for the reaction of 2-(3,5-dimethylphenoxy)tetrahydrofuran.

However, when the residue (1.7 g, 88.5% recovery from 1.92 g of acetal) was let sit for 15 min a white solid which was insoluble in ether was found to precipitate. The residue was therefore taken up in ether and the solid was filtered (1.25 g, 73%). The ether was removed and the residue (0.45 g, 27%) was analyzed by g.l.c.. It was found to be a 40:60 mixture of 2,6-dimethylphenol and a rearrangement material (2-(3,5-dimethyl-2-hydroxyphenyl)-

tetrahydrofuran).

The white solid (m.p. 213-215°C) was concluded to be 4,4'-dihydroxy-3,3',5,5'-tetramethylbiphenyl. It was recrystallized from a benzene-acetone solution and the fine needles had a melting point of 216-217°C. Lit. m.p. 220°C (87).

The n.m.r. spectrum in DMSO-d^6 was consistent with the proposed structure showing a singlet at τ 3.26 (4H), a multiplet at τ2.15 (2H), exchangeable in D_2O and a strong singlet at τ7.90 (12 H).

The i.r. spectrum (nujol) showed sharp absorption bands at 3520 cm^{-1}, 3450 cm^{-1} and 3325 cm^{-1} (O-H stretch) and at 1190 cm^{-1}.

4,4'-Diacetoxy-3,3',5,5' -tetramethylbiphenyl was prepared by the method of Auwers and V. Markovits (87).

A solution of 4,4'-dihydroxy-3,3',5,5'-tetramethylbiphenyl (0.5 g, 0.002 mole) in 5 ml of acetic anhydride and 1 ml of acetic acid acid with 0.5 g of sodium acetate was heated under reflux for 12 h. The solution was cooled to room temperature and poured onto 5 g of ice. The aqueous solution was extracted with chloroform and the extracts were dried over magnesium sulfate. The solid was separated by filtration and the filtrate freed from solvent. The residue was recrystallized from chloroform-Skellysolve B and gave a white crystalline solid. M.p. 172-173°C. Lit. m.p. 175°C (87).

The methylation of the product mixture from 2-(2,6-dimethylphenoxy)-tetrahydrofuran was carried out by the method of Diner and coworkers (71).

The residue after work-up was distilled and gave 2,6-dimethylanisole (10%) and 2-(3,5-dimethyl-4-methoxyphenyl)tetrahydrofuran (10% yield based on the acetal). B.p. 105°C at 0.5 mm; n_D^{25} 1.5175.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80.

Found: C, 75.43; H, 9.22.

A higher boiling component was found, which would not distil even with a bath temperature of 200°C at 0.1 mm. It was purified on an alumina column and the n.m.r. spectrum in $CDCl_3$ showed a singlet at τ 3.19 (4H), a singlet at τ 6.39 (6H) and a singlet at τ 7.80 (12H). This was consistent with the structure of 4,4'-dimethoxy-3,3',5,5'-tetramethylbiphenyl.

An authentic sample of 2-(3,5-dimethyl-4-methoxyphenyl)-tetrahydrofuran was prepared by the following reaction sequence.

2,6-Dimethylanisole was prepared from 2,6-dimethylphenol by the method of Diner and coworkers (71) as previously described for the preparation of 2-methoxymethyl-3,4-dihydro-2H-pyran.

A colorless liquid was obtained in 92% yield. B.p. 85°C at 27 mm; n_D^{24} 1.5000. Lit. b.p. 182-183°C at 760 mm (104).

β-(3,5-Dimethyl-4-methoxybenzoyl)propionic acid was prepared by the method of Harland and Robertson (103) as previously described for the preparation of β-(4,6-dimethyl-2-methoxybenzoyl)propionic acid.

A white crystalline solid was obtained in 72% yield. M.p. 108-110°C. Lit. m.p. 114-115°C (104).

1-(3,5-Dimethyl-4-methoxyphenyl)-1,4-butanediol was prepared by a $LiAlH_4$ reduction of β-(3,5-dimethyl-4-methoxybenzoyl)propionic acid by the method previously described for the preparation of 5,5-dimethyl-1,4-hexanediol.

The crude oily material (90%) was not purified but was immediately subjected to the next step of the reaction sequence.

2-(3,5-Dimethyl-4-methoxyphenyl)tetrahydrofuran was prepared from 1-(3,5-dimethyl-4-methoxyphenyl)-1,4-butanediol by the modified procedure of Reynolds and Kenyon (70) as previously described for the preparation of 2-(4,6-dimethyl-2-methoxyphenyl)-tetrahydrofuran.

A pale yellow liquid was obtained (4.0 g, 44%). B.p. 98-100°C at 0.7 mm; n_D^{25} 1.5230.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80.

Found: C, 75.78; H, 8.79.

The n.m.r. spectrum in $CDCl_3$ was consistent with the proposed structure and identical to that for the material isolated from the methylation of the 2-(2,6-dimethylphenoxy)tetrahydrofuran

reaction mixture. The spectrum showed a singlet at τ3.05 (2H), a triplet centered at τ5.28 (1H), a multiplet between τ5.9 and 6.3 (2H), a singlet at τ6.33 (3H), a singlet at 7.74 (6H) and a multiplet between τ7.8 and 8.3 (4H).

The i.r. spectrum (neat) was also identical to that from the methylated product showing sharp absorptions at 1220 cm^{-1}, 1140 cm^{-1}, 1060 cm^{-1}, 1010 cm^{-1} and 865 cm^{-1}.

The preparation of 2-(4,6-dimethyl-2-methoxyphenyl)tetrahydrofuran was attempted by a Friedel-Crafts type reaction using a modification of the method of Harland and Robertson (103).

A solution of 3,5-dimethylanisole (1.4 g, 0.01 mole) and aluminum chloride (0.13 g, 0.001 mole) in 10 ml of dry ether was cooled to 5°C in an ice bath. To this solution was added in a dropwise fashion, 2,3-dihydrofuran (1.0 g, 0.014 mole). The solution immediately became deep brown. It was stirred for one h and an aqueous 15% solution of potassium hydroxide (1 ml) was added. The ether was decanted from the solid residue and removed. G.l.c. analysis of the residue showed that anisole was the only component of the mixture. This indicated that no condensation had occurred.

In a second attempt, the same procedure was followed except that one drop of concentrated sulfuric acid was used as the catalyst. The solution was stirred for 48 h at room temperature but no condensation product was found upon g.l.c. analysis of the residue after work-up.

Hence, this method of synthesis was abandoned.

I. Attempted Preparation of cis-5-Methyl-2-methoxytetrahydrofuran.

5-Methyl-2-methoxytetrahydrofuran was prepared as a cis and trans mixture from γ-valerolactone by the method described in Section B of the Experimental.

The n.m.r. spectrum in CCl_4 is shown in Figure 5 and, as discussed in the Results and Discussion, it indicates that the product is a 60:40 cis to trans (trans to cis) isomer mixture. No success was acheived in attempting to separate these isomers by g.l.c. on butanediol succinate, carbowax, apiezon and silicone rubber columns.

3-Bromo-5-methyl-2-methoxytetrahydrofuran was prepared by a modification of the procedure of Sweet and Brown (88).

A solution of 5-methyl-2-methoxytetrahydrofuran (15.5 g, 0.13 mole) in 100 ml of carbon tetrachloride was prepared. Solid sodium carbonate (25 g) was added and stirred vigorously in suspension. The mixture was heated to 50°C and bromine (21.4 g, 0.13 mole) was added dropwise. Once the reaction had started, the heating was stopped and the bromine was added at a rate sufficient to keep the reaction going without any external heating. When the addition was complete, the solid was removed by filtration and the filtrate was washed with a saturated aqueous sodium carbonate solution (3 x 25 ml). The solution was then dried over magnesium sulfate, the solid was separated by filtration and the filtrate freed of solvent on a rotatory

evaporator. The residue was distilled and gave a clear liquid (16.5 g, 63.5%). B.p. 90-91°C at 55 mm; n_D^{25} 1.4612.

Anal. Calcd. for $C_6H_{11}O_2Br$: C, 36.75; H, 5.64; Br, 40.97.

Found: C, 36.98; H, 5.40; Br, 41.03.

5-Methyl-2-methoxy-2,5-dihydrofuran was prepared by the method of Baldwin and Brown (89).

Sodium methoxide (1.7 g, 0.031 mole) was dissolved in 20 ml of dry dimethyl sulfoxide (DMSO). To this solution was added in a dropwise fashion, 3-bromo-5-methyl-2-methoxytetrahydrofuran (6 g, 0.031 mole). The temperature of the reaction immediately rose as the addition proceeded. When the addition was complete, the solution was heated at 50-60°C for 6 h and then it was fractionally distilled. A fraction which boiled at 112°C at 690 mm (n_D^{22} 1.4263) was collected (2.2 g, 63%).

The n.m.r. spectrum in CCl_4 was consistent with the proposed structure showing a multiplet at τ3.9 (1H), a multiplet at τ4.35 (1H), a multiplet between τ5.1 and 5.4 (2H), a singlet at 6.73 (3H) and two doublets centered at τ8.74 and 8.78 (3H), J = 6.5 Hz.

G.l.c. analysis on a butanediol succinate column showed two overlapping peaks of nearly equal intensity. This indicated that a 1:1 mixture of cis and trans isomers was present.

The isomerization of 5-methyl-2-methoxy-2,5-dihydrofuran to give 5-methyl-2-methoxy-2,3-dihydrofuran was attempted by a modification

of the method described by Eliel and coworkers (4) for the isomerization of 2,5-dihydrofuran.

The unsaturated acetal, 5-methyl-2-methoxy-2,5-dihydrofuran (5.7 g, 0.05 mole) was added dropwise with stirring to 50 ml of dry DMSO in which sodium methoxide (2.7 g, 0.05 mole) had previously been dissolved. A reaction immediately took place and, upon distillation, a fraction which boiled at 58-60°C (n_D^{21} 1.4072) was isolated (3.0 g, 73%).

The n.m.r. spectrum in $CDCl_3$ was consistent with the structure of 2-methylfuran showing narrow multiplets at τ2.72 (1H), τ3.75 (1H) and τ4.05 (1H), and a singlet at τ 7.93 (3H).

The same product was isolated when the same procedure was carried out using potassium t-butoxide as the base in t-butyl alcohol.

This product was identified as 2-methylfuran. Lit. b.p. 63-63.5°C at 760 mm (105).

BIBLIOGRAPHY

1. B. E. Leggetter and R. K. Brown. Can. J. Chem. 42, 990 (1964).
2. B. E. Leggetter, U. E. Diner and R. K. Brown. Can. J. Chem 42, 2113 (1964).
3. U. E. Diner and R. K. Brown. Can. J. Chem. 45, 2547 (1967).
4. E. L. Eliel, B. E. Novak, R. A. Daignault and V. G. Badding. J. Org. Chem. 30, 2441 (1965).
5. L. Makhubu. Thesis submitted to the Faculty of Graduate Studies of the University of Alberta, Edmonton (1967).
6. E. C. Ashby and J. Prather. J. Am. Chem. Soc. 88, 729 (1966).
7. U. E. Diner. Thesis submitted to the Faculty of Graduate Studies of the University of Alberta, Edmonton (1967).
8. R. F. Nystrom and W. G. Brown. J. Am. Chem. Soc. 69, 1197 (1947).
9. N. G. Gaylord. Reductions with Complex Metal Hydrides. Interscience Publishers,Inc., New York. 1956.
10. H. M. Doukas and T. D. Fontaine. J. Am. Chem. Soc. 75, 5355 (1953).
11. E. L. Eliel and M. N. Rerick. J. Org. Chem. 23, 1088 (1958).
12. E. L. Eliel, V. G. Badding and M. N. Rerick. J. Am. Chem. Soc. 84, 2371 (1962).

13. E. L. Eliel, V. G. Badding and L. A. Pilato. J. Am. Chem. Soc. 84, 2377 (1962).

14. E. L. Eliel. Rec. Chem. Prog. 22, 129 (1961).

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

16. U. E. Diner, H. A. Davis and R. K. Brown. Can. J. Chem. 45, 207 (1967).

17. B. E. Leggetter and R. K. Brown. Can. J. Chem. 41, 2671 (1963).

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

19. B. E. Leggetter and R. K. Brown. Can. J. Chem. 43, 1030 (1965).

20. M. L. Mihailovic, R. I. Manuzic, L. Zigic-Manuzic, T. Bosnjak and Z. Cekovic. Tetrahedron, 23, 215 (1967).

21. M. L. Mihailovic and M. Miloradovic. Tetrahedron, 22, 723 (1966).

22. S. F. Birch and R. A. Dean. J. Chem. Soc. 2477 (1953).

23. J. N. Haresnape. Chem. and Ind. 1091 (1953).

24. E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison. Conformational Analysis. Interscience Publishers, Inc., New York. 1966.

(a) p. 200.

(b) p. 44.

25. D. Gagnaire and P. Monzeglio. Bull. Soc. Chim. France, 474 (1965).

26. H. C. Brown and R. M. Adams. J. Am. Chem. Soc. 64, 2557 (1942).

27. E. M. Arnett and C. Y. Wu. J. Am. Chem. Soc. 84, 1684 (1962).

28. H. C. Brown, R. S. Fletcher and R. B. Johannesen. J. Am. Chem. Soc. 73, 212 (1951).

29. H. C. Brown, R. S. Fletcher and R. B. Johannesen. J. Am. Chem. Soc. 72, 2926 (1950).

30. R. C. Cass, S. E. Fletcher, C. T. Mortimer, H. D. Springhall and T. R. White. J. Chem. Soc. 1406 (1958).

31. D. H. R. Barton and R. C. Cookson. Quart. Rev. (London), 10, 44 (1956).

32. F. J. Cioffi and S. T. Zenchelsky. J. Phys. Chem. 67, 357 (1963).

33. J. S. Allen and H. Hibbert. J. Am. Chem. Soc. 56, 1398 (1934).

34. E. L. Eliel. Stereochemistry of Carbon Compounds. McGraw-Hill Book Co., Inc., New York. 1962. p. 265.

35. H. C. Brown, H. Bartholomay, Jr. and M. D. Taylor. J. Am. Chem. Soc. 66, 435 (1944).

36. F. Korte and H. Machleidt. Chem. Ber. 88, 1684 (1955).

37. F. Korte, K. Büchel, D. Scharf and A. Zschoke. Chem. Ber. 92, 884 (1959).

38. F. Korte, K. Büchel and L. Schiffer. Chem. Ber. 91, 759 (1958).

39. M. S. Kharasch and O. Reinmuth. Grignard Reactions of Nonmetallic Substances. Prentice-Hall, Inc., New York. 1954.

40. L. Fieser and N. S. Newman. J. Am. Chem. Soc. 58, 2376 (1936).

41. D. A. Shirley. Organic Reactions, VIII, 28 (1954).

42. J. Cason. Chem. Reviews, 40, 15 (1947).

43. J. Cason. J. Am. Chem. Soc. 64, 1106 (1942).

44. H. Gilman and J. F. Nelson. Rec. Trav. Chim. 55, 518 (1936).

45. L. C. Keagle and W. H. Hartung. J. Am. Chem. Soc. 68, 1609 (1946).

46. R. A. Mallory, S. Rovinski, F. Kohen and I. Scheer. J. Org. Chem. 32, 1417 (1967).

47. C. Feugeas. Bull. Soc. Chim. France, 2568 (1963).

48. C. Blomberg, A. O. Vreugdenhil and T. Homsma. Rec. Trav. Chim. 82, 355 (1963).

49. F. Sweet and R. K. Brown. Can. J. Chem. 46, 707 (1968).

50. J. M. Conia. Rec. Chem. Prog. 24, 43 (1963).

51. W. A. White and H. Weingarten. J. Org. Chem. 32, 213 (1967).

52. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell. J. Am. Chem. Soc. 85, 207 (1963).

53. H. Hirsch. Chem. Ber. 100, 1289 (1967).

54. R. R. Russell and G. A. Vanderwerf. J. Am. Chem. Soc. 69, 11 (1947).

55. C. Golumbic and D. L. Cottle. J. Am. Chem. Soc. 61, 996 (1939).

56. R. C. Fuson. Reactions of Organic Compounds. John Wiley and Sons, Inc., New York. 1962. p. 667.

57. L. F. Fieser. Experiments in Organic Chemistry. Third Edition. D. C. Heath and Co., Boston. 1957. p. 310.

58. G. R. Pettit and T. R. Kasturi. J. Org. Chem. 25, 875 (1960).

59. G. R. Pettit and T. R. Kasturi. J. Org. Chem. 26, 4557 (1961).

60. L. F. Fieser and M. Fieser. Advanced Organic Chemistry. Fifth Edition. Reinhold Publishing Corp., New York. 1965. p. 951.

61. W. Pigman. The Carbohydrates. Academic Press, Inc., New York. 1957. p. 316.

62. N. Sperber, H. E. Zaugg and W. M. Sandstrom. J. Am. Chem. Soc. 69, 915 (1947).

63. E. Fischer. Chem. Ber. 22, 2204 (1889).

64. G. E. Arth. J. Am. Chem. Soc. 75, 2413 (1953).

65. F. C. Whitmore. Organic Chemistry. D. Van Nostrand Co. Inc., New York. 1931.

66. H. C. Brown and D. Digby. J. Am. Chem. Soc. 83, 486 (1961).

67. H. C. Brown and G. Zweifel. J. Am. Chem. Soc. 82, 3222 (1960).

68. L. M. Lerner, B. D. Kohn and P. Kohn. J. Org. Chem. 33 1780 (1968).

69. R. K. Hulyalkar. Can. J. Chem. 44, 1594 (1966).

70. D. D. Reynolds and W. O. Kenyon. J. Am. Chem. Soc. 72, 1593 (1950).

71. U. E. Diner, F. Sweet and R. K. Brown. Can. J. Chem. 44, 1591 (1966).

72. J. Hine and M. Hine. J. Am. Chem. Soc. 74, 5266 (1954).

73. A. R. Pinder and H. Smith. J. Chem. Soc. 113 (1954).

74. C. S. Marvel and E. R. Birkhimer. J. Am. Chem. Soc. 51, 260 (1929).

75. M. H. Palomaa and A. Kenetti. Chem. Ber. 64, 797 (1931).

76. J. Hooz and S. S. H. Gilani. Can. J. Chem. 46, 86 (1968).

77. C. S. Marvel and A. L. Tanenbaum. J. Am. Chem. Soc. 44, 2645 (1922).

78. H. O. House. Modern Synthetic Reactions. W. A. Benjamin, Inc., New York. 1965. p. 27.

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

80. D. H. McDaniel and H. C. Brown. J. Org. Chem. 23, 420 (1958).

81. H. A. Davis and R. K. Brown. Manuscript in preparation for publication.

82. F. Sweet and R. K. Brown. Can. J. Chem. 44, 1571 (1966).

83. A. J. Showler and P. A. Darley. Chem. Reviews, 67, 427 (1967).

84. O. L. Chapman and R. W. King. J. Am. Chem. Soc. 86, 1256 (1964).

85. E. Berliner, Organic Reactions, II. John Wiley and Sons, Inc., New York. 1949. p. 229.

86. L. L. Fieser and E. B. Hershberg. J. Am. Chem. Soc. 58, 2314 (1936).

87. K. Auwers and Th. v. Markovits. Chem. Ber. 38, 234 (1905).

88. F. Sweet and R. K. Brown. Can. J. Chem. 46, 2289 (1968).

89. M. J. Baldwin and R. K. Brown. Can. J. Chem. In press.

90. F. L. Greenwood, F. C. Whitmore and H. M. Crooks. J. Am. Chem. Soc. 60, 2028 (1938).

91. C. R. Noller and R. Dinsmore. Organic Syntheses. Coll. Vol. II, 358 (1943).

92. Handbook of Chemistry and Physics. 48th Edition. Edited by R. C. Weast. Chemical Rubber Co., Cleveland. 1967-68.

93. N. Clausson-Kaas, F. Limborg and J. Kakstorp. Acta. Chem. Scand. 2, 109 (1948).

94. R. P. Linstead and H. N. Rydon. J. Chem. Soc. 580 (1933).

95. R. Adams and E. W. Adams. Organic Syntheses. Coll. Vol. I, 448 (1941).

96. G. A. Hill and E. W. Flosdorf. Organic Syntheses. Coll. Vol. I, 451 (1941).

97. W. G. Dauben and H. Tilles. J. Org. Chem. 15, 785 (1950).

98. S. A. Barker, I. S. Brimacombe, A. B. Foster, D. H. Whiffen and G. Zweifel. Tetrahedron, 7, 10 (1959).

99. F. C. Whitmore, C. S. Rowland, S. N. Wrenn and G. W. Kilmer. J. Am. Chem. Soc. 64, 2970 (1942).

100. R. Paul, M. L. A. Fluchaire and G. Collardeau. Bull. Soc. Chim. France, 668 (1950).

101. E. J. Salmi. Chem. Ber. 71, 1803 (1938).

102. N. G. Nayak and R. K. Brown. Can. J. Chem. 44, 591 (1966).

103. J. C. Harland and A. Robertson. J. Chem. Soc. 937 (1939).

104. W. Cocker. J. Chem. Soc. 36 (1946).

105. C. Harries. Chem. Ber. 31, 37 (1898).

106. Dictionary of Organic Compounds. Vol. II. Eyre and Spottiwoode, London. 1965. p. 1209.

107. B. Capon and D. Thacker. J. Am. Chem. Soc. 87, 4199 (1965).

108. J. C. Speck, Jr., D. J. Rynbrandt, and I. H. Kochevar. J. Am. Chem. Soc. 87, 4979 (1965).

109. H. Böhme and K. Sell. Chem. Ber. 81, 123 (1948).

110. S. Winstein and R. B. Henderson. J. Am. Chem. Soc. 65, 2196 (1943).

111. S. Winstein and E. Grunwald. J. Am. Chem. Soc. 70, 828 (1948).

112. A. Streitwieser Jr. Chem. Rev. 56, 685 (1956).

113. S. Winstein, E. Grunwald and L. L. Ingraham. J. Am. Chem. Soc. 70, 821 (1948).

114. S. Winstein, C. R. Lindegren and L. L. Ingraham. J. Am. Chem. Soc. 75, 155 (1953).

115. H. C. Brown and Y. Okamoto. J. Am. Chem. Soc. 80, 4979 (1958).