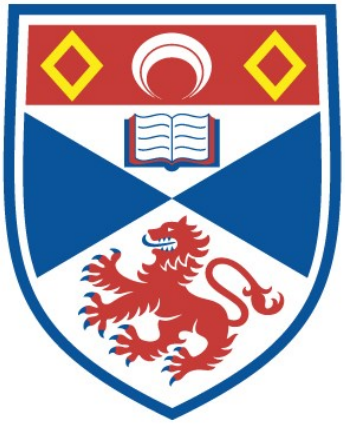
PREPARATION AND REACTIONS OF 2-ALKYLTETRAHYDROFURANS FROM FATTY ALCOHOLS

Margaret Dawes

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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PREPARATION AND REACTIONS OF 2-ALKYLTETRAHYDROFURANS FROM FATTY ALCOHOLS

By
Margaret Dawes

A thesis submitted for the degree of
Doctor of Philosophy

September 1995

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I, Margaret Dawes, hereby certify that this thesis, which is approximately 50,000 words in length, has been written by me, that it is the record of the work carried out by me and that it has not been submitted in any previous application for a higher degree.

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I was admitted as a research student in October 1986 and as a candidate for the degree of Doctor of Philosophy in October 1987; the higher study for which this is a record was carried out in the University of St. Andrews between 1986 and 1989.

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Finally, a special thank you to my family, Adrian, mum, dad, and Pam, for their constant support and encouragement.

CONTENTS

LIST OF ABBREVIATIONS

DEPT	-	Distortionless enhancement by polarisation transfer
FT-IR	-	Fourier transform infra-red
GC-MS	-	Gas chromatography-mass spectrometry
GLC	-	Gas liquid chromatography
IR	-	Infra-red
MsOH	-	Methanesulphonic acid
NMR	-	Nuclear magnetic resonance
PE5	-	This refers to a solvent system consisting of petroleum ether ($40\text{-}60^0$) and diethyl ether. Further details are listed in section 8.2.
R	-	Alkyl
RFE	-	Rotary film evaporation
THF	-	Tetrahydrofuran
THP	-	Tetrahydropyran
TLC	-	Thin layer chromatography
TMS	-	Tetramethylsilane
TsOH	-	Toluenesulphonic acid
$100^0\text{-}0\text{-}20^0\text{-}300^0\text{-}5$	-	This refers to a GLC temperature programme. A detailed explanation is given in section 8.2.

ABSTRACT

2-Alkyltetrahydrofurans have been prepared from C_{10}-C_{18} primary alcohols. Complete characterisation of these compounds by mass spectral and NMR studies has been achieved.

Ring-opening reactions of the 2-alkyltetrahydrofurans have been studied and have provided an insight into the chemistry of these compounds, highlighting differences in reactivities and reaction products compared with the parent molecule, tetrahydrofuran.

The C_{10}-C_{18} 2-alkyltetrahydrofurans have been subjected to a variety of ring cleavage reactions involving reaction with Lewis acids and/or acyl halides to produce compounds of the type;

$RCH(X)CH_2CH_2CH_2$-Y and $RCH(Y)CH_2CH_2CH_2$-X

$R = C_6H_{13}$ - $C_{14}H_{29}$, X = halogen atom, Y = acyl group

This work has demonstrated the ease with which these compounds may be ring opened. In some cases the reaction with the 2-alkyltetrahydrofurans was observed to be more rapid and vigorous than with tetrahydrofuran itself.

This was not always the case: The acid catalysed reaction of tetrahydrofuran with dodecanol resulted in formation of the diether shown below, and a diester was similarly formed by the acid catalysed reaction of tetrahydrofuran with lauric acid.

$RO(CH_2)_4OR$
diether ($R = C_{12}H_{25}$)

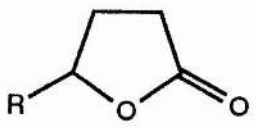
$RCOO(CH_2)_4OCOR$
diester ($R = C_{11}H_{23}$)

The analogous reactions with substituted tetrahydrofurans were slow and diether/diester yield was extremely low. Introduction of the alkyl group at position two of the tetrahydrofuran ring severely impeded the reaction. Instead the hydroxy ethers shown below were the major cyclic ether derived products.

$C_{12}H_{25}$-O-CH(R)$(CH_2)_3$-OH and $C_{12}H_{25}$-O-$(CH_2)_3$CH(R)-OH.

($R = C_6H_{13}$)

Oxidation of the 2-alkyltetrahydrofurans was readily achieved by treatment with ruthenium tetroxide and resulted in formation of the corresponding α-alkyl-γ-lactones and γ-keto acids in almost quantitative yields.



and $RCO(CH_2)_2COOH$

($R = C_6H_{13}$ - $C_{14}H_{29}$)

CHAPTER 1

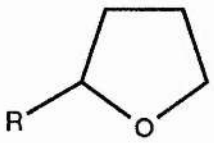
GENERAL INTRODUCTION

CHAPTER 1

1 General Introduction.

A well recognised property of the ether linkage is its unreactivity, which leads to the extensive use of ethers as solvents for many organic reactions[1]. Despite this, there exists a wealth of information concerning the reactions of ethers and many reagents are capable of cleaving ethers.

Several reports have concentrated on the cleavage reactions of ethers including ring - opening reactions of cyclic ethers such as tetrahydrofuran[2,3]. Cleavage of simple substituted tetrahydrofurans such as methyl-, dimethyl-, methoxy- and phenyl-tetrahydrofuran have also been reported. Clearly, these reactions are important and provided a good base from which to develop the study of cleavage reactions of our medium chain alkyl substituted tetrahydrofurans,



$R = C_6H_{13}$ -$C_{14}H_{29}$

The aim of our study was twofold; to prepare and characterise C_{10}-C_{18} 2-alkyl tetrahydrofurans from the corresponding fatty alcohols, and, to examine the cleavage reactions of these compounds. *In this way it was hoped to develop methods of introducing additional functionality into long-chain compounds.*

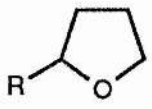
2-Alkyltetrahydrofurans were prepared from the corresponding C_{10}-C_{18} fatty alcohols by a variety of methods including;

i) oxidative cyclisation with lead tetraacetate[4],

ii) reaction with silver oxide and bromine[5],

iii) reaction with mercuric oxide and iodine[6], and

iv) reaction with N-iodosuccinimide[7],

$R(CH_2)_4OH \rightarrow$ 

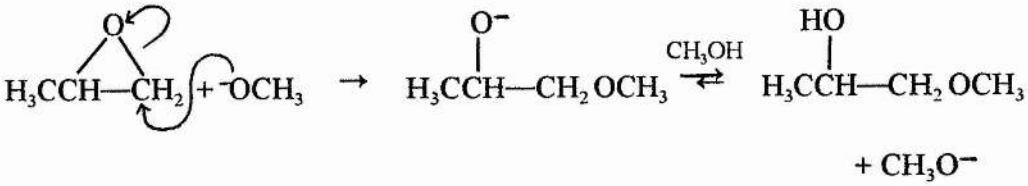
($R = C_6H_{13}$ - $C_{14}H_{29}$)

These synthetic reactions are discussed in detail in chapter 2.

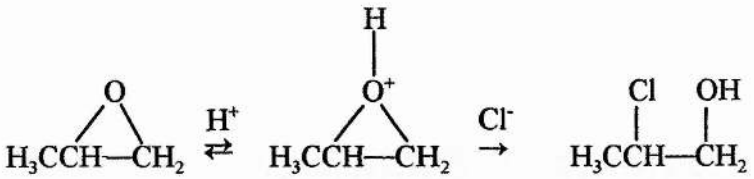
The cleavage of ethers is a versatile reaction in organic synthesis, and has demonstrated particular use in the degradation or transformation of natural products and in the synthesis of polyfunctional compounds. The chemistry of the ether linkage is governed largely by the behaviour of the lone-pair electrons on oxygen which form a basic site for the addition of protons and Lewis acids thereby increasing the reactivity of the ether group. Early work on the cleavage of simple cyclic ethers centred around the cleavage of 1,2-epoxides. These three membered cyclic ethers undergo ring opening readily under various conditions.

For example:

In base:



In acid:



By contrast five membered cyclic ethers are less susceptible to ring opening than their three membered counterparts. This is largely due to the decrease in ring strain of the five membered ether compared with the three membered epoxide. Tetrahydrofuran and larger cyclic ethers such as tetrahydropyran have properties which are more like those of their acyclic counterparts. This similarity can be largely attributed to their relatively small angle strain and, like their acyclic counterparts, they do not under normal circumstances, undergo base catalysed ring opening.

The acid catalysed cleavage reactions of ethers are more common. Cleavage of cyclic ethers by a host of acidic reagents have been reported and acid catalysed cleavage of

tetrahydrofurans can be readily achieved, although in general they do not proceed as readily as with epoxides. Some of the earliest ring opening reactions of tetrahydrofuran reported involved treatment of the ether with a Bronsted acid. With hydroiodic acid 1,4-diiodobutane was formed in 60-70% yield. Similarly 1,4-dibromobutane was formed as a result of treatment of tetrahydrofuran with hydrobromic acid. In contrast reaction of tetrahydrofuran with hydrogen chloride results in the formation of 4-chlorobutanol as the major product of the reaction. 1,4-Dichlorobutane was found to be readily prepared from the reaction of tetrahydrofuran with thionyl chloride and zinc chloride[8].

Tetrahydrofuran also reacts with acetic anhydride in the presence of Lewis acids to form the 1,4 diacetate[9]. The same reaction with 2-methyltetrahydrofuran resulted in the formation of the primary unsaturated acetate as the major product (70%) together with only a small amount of the diacetate.

$CH_3CH{=}CHCH_2CH_2OCOCH_3$

unsaturated acetate (70%)

In contrast acetyl chloride was found to be a better cleavage agent; treatment of tetrahydrofuran with acetyl chloride and zinc chloride resulted in the formation of 4-chlorobutyl acetate in good yield[10]. The reaction proceeded equally well with 2-methyltetrahydrofuran resulting in formation of 4-chloropentyl acetate. This compound is more stable than the 4-chloroalcohol which cyclises readily in the presence of base. The reaction of simple cyclic ethers, including tetrahydrofuran and tetrahydropyran, with acetyl chloride has also been achieved in the presence of other catalysts such as Group VI metal carbonyls[11], mercury (II) salts[12], platinum (II) complexes[13] and a mixture of triorganotin halides and palladium (II) complexes[14]. The successful ring scission of 2-methyltetrahydrofuran with acetyl chloride in the presence of a Lewis acid to form 4-chloropentyl acetate showed promise for application to our medium chain 2-alkyltetrahydrofurans. Our aim was to successfully ring open the 2-alkyltetrahydrofurans, at the same time introducing a new functional group at a specific site along the carbon chain. A range of reactions including a series of reactions with acid halides and Lewis acid catalysts have been performed on the medium chain 2-alkyltetrahydrofurans prepared from the corresponding fatty alcohols. The nature of the acid halide and the catalyst was found to affect the reaction products considerably. The effect of the relatively bulky alkyl substituent in these ring cleavage reactions has been determined by comparison with reactions of the parent molecule tetrahydrofuran. 2-Methyltetrahydrofuran was employed as a simple analogue of the longer chain 2-alkyltetrahydrofurans in preliminary reaction trials.

Various other reagents have been utilised successfully in the cleavage of ethers, boron compounds such as phenylboron dichloride and boron trichloride have demonstrated widespread applicability. Alkali metals such as lithium have been used effectively in some instances. However it was beyond the scope of this work to include them all.

CHAPTER 2

PREPARATION AND SPECTROSCOPIC STUDIES OF 2-ALKYLTETRAHYDROFURANS

CHAPTER 2

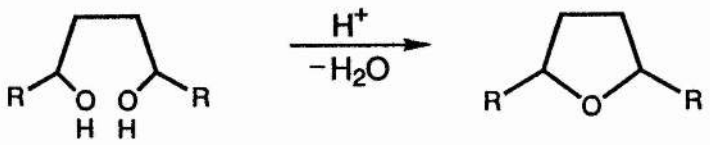
Preparation and spectroscopic studies of 2-alkyltetrahydrofurans.

2.1 Introduction.

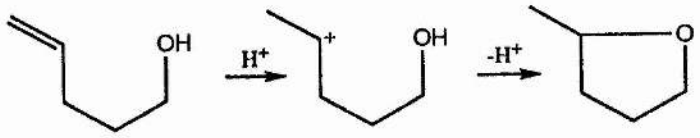
Intramolecular cyclisation of alcohols to substituted tetrahydrofurans has received considerable attention over the years and the reaction has been successfully applied to the synthesis of many important organic compounds, particularly natural products such as terpenoids and steroids[15]. Certain simpler cyclic ethers have been registered as important fragrance materials[16] and as such have demonstrated useful applications in industrial chemistry; they have for example, been efficiently employed as odour masking agents in liquid hypochlorite bleaches[17].

To date several widely applicable methods of preparing substituted tetrahydrofurans by intramolecular cyclisation of three groups of hydroxy compound have been reported;

(i) 1,4-hydroxy compounds and their derivatives[18]. Here cyclisation occurs by direct elimination of water, for example the acid catalysed cyclodehydration of 1,4-diols.

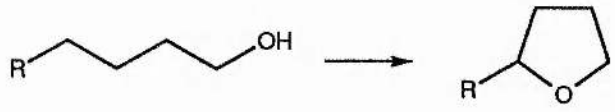


(ii) Unsaturated monohydric alcohols. Five membered and higher cyclic ethers are formed by the intramolecular reaction of hydroxylic oxygen with a carbon atom of the double bond[18] as illustrated in the conversion of 4-penten-1-ol to 2-methyltetrahydrofuran depicted below[19].



Such cyclisations are effected by various reagents including mineral acids[20] and lead tetraacetate[18].

(iii) Saturated monohydric alcohols bearing a C-H in the δ-position.



Trahanovsky[21] effected conversion of pentan-1-ol to 2-methyltetrahydrofuran with ceric ammonium nitrate, in low yields (10-15%). Improved syntheses employing either lead tetraacetate[4] or heavy metal salt-halogen combinations[22] (the hypohalite reactions) have since been reported. As our work is concerned primarily with the functionalisation of fatty alcohols, it is the latter group of reactions which have received our attention. Although the cyclisations of short chain monohydric[4,23] and steroidal alcohols[24] are well documented, little information on the cyclisation of medium and long chain fatty alcohols is available. However, the preparation of 2-octyl- (49%) and 2-tetradecyl- (59%) tetrahydrofurans by treatment of the

corresponding C_{12} and C_{18} primary alcohols with lead tetraacetate has been reported by Mihailovic[25] and Osman[26] respectively. Even in these cases spectroscopic details, particularly NMR data are scant. We have compared the efficiency of the following reagent systems in the oxidative cyclisation of primary medium and long chain alcohols;

i) lead tetraacetate,

ii) silver oxide and bromine,

iii) mercuric oxide and iodine,

iv) N-iodosuccinimide, and

v) sodium and calcium hypochlorite

together with detailed spectroscopic examination of the products thus formed.

2.1.1 Methods of preparation of 2-alkyltetrahydrofurans.

2.1.2 The lead tetraacetate promoted reaction.

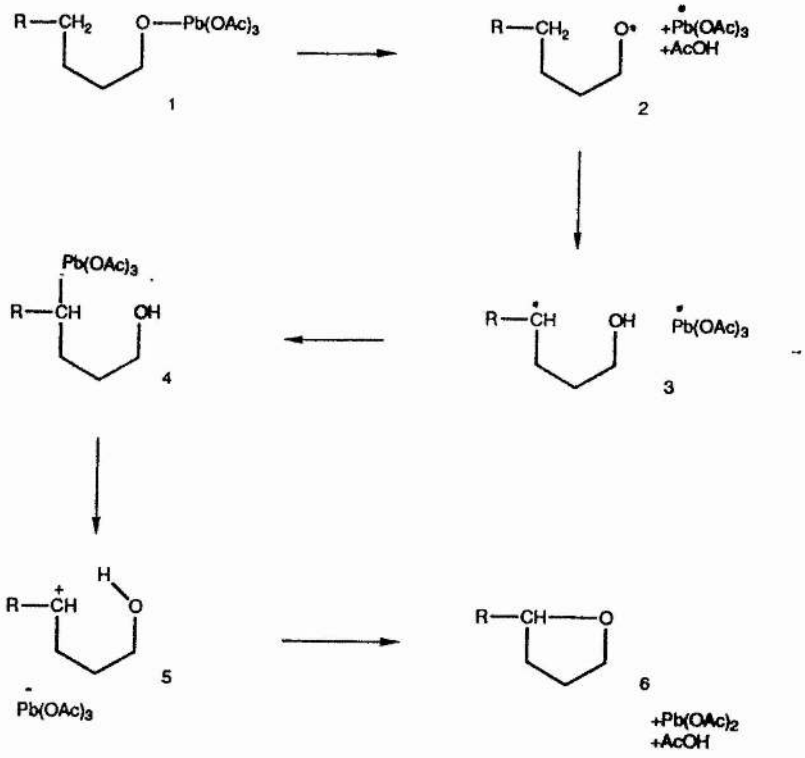
Oxidative cyclisation of monohydric alcohols was first discovered by Mihailovic *et al* in 1959[27] and involved the cyclisation of hydroxy functions in steroids. Further studies by Mihailovic[28] and Heusler and Kalvoda[29] led to the belief that the semirigid structure of the steroid system facilitated the cyclisation process by holding the hydroxy and δ-carbon functions in closer proximity. This theory was found to be unsubstantiated when some years later Mihailovic *et al* reported the cyclisation of primary and secondary C_7-C_9 alcohols to substituted tetrahydrofurans in yields of

35-55%, by lead tetraacetate in a non-polar solvent[30-33]. The reaction appears to be of a simple nature involving dehydrogenation of the alcohol substrate, however mechanistic studies have shown it to be rather more complex[33-35]. The first stage of the reaction is thought to be the formation of an alkoxy lead IV acetate of type 1

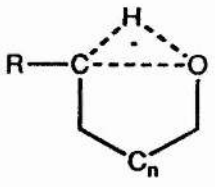
$$ROH + Pb(OAc)_4 \rightleftarrows RO\text{-}Pb(OAc)_3 + AcOH$$
(1)

The exact structure of the alkoxy lead IV acetate is not known, although it has been suggested that lead IV alkoxides with more than one alkoxy group can also be formed[23,36], so perhaps the lead IV alkoxide, (1), is more accurately represented as $(RO)_n$-Pb-$(OAc)_{4-n}$. The intermediate alkoxy lead acetate (1) being less stable than lead tetraacetate itself undergoes homolytic cleavage (scheme 2.1), induced either thermally or photolytically[37] to give the corresponding alkoxy radical (2) (direct homolytic cleavage of the O-H bond is unlikely due to its high bond energy). The alkoxy radical, (2), undergoes an intramolecular 1,5-hydrogen abstraction from the δ-carbon atom producing the corresponding hydroxyalkyl radical (3). Direct ether formation from the carbon radical (3) by loss of a hydrogen atom is not favoured, the carbon radical is in fact thought to undergo oxidation by one electron transfer from carbon to lead either directly, or via an organolead intermediate (4) resulting in formation of the corresponding carbocation (5) which cyclises to give the tetrahydrofuran (6).

Scheme 2.1. Oxidative cyclisation of a primary alcohol with lead tetraacetate.



Tetrahydrofurans have been prepared in yields of 45-55% by treating primary and secondary alcohols in this manner[4]. Also formed is a small amount of the corresponding tetrahydropyran derivative (1-5%). The formation of the five membered cyclic ether in preference to the six membered tetrahydropyran implies that 1,5-hydrogen abstraction is favoured over 1,6- hydrogen abstraction, this can be rationalised by examining the intermediate for hydrogen transfer;



n=1,2

For hydrogen transfer to occur the internuclear distance of the carbon and the oxygen atom must be around 2.5 - 2.7 A. Thus a quasi seven membered transition state, leading to tetrahydropyran formation requires increased activation energy compared with a six membered transition state, hence tetrahydrofuran formation is favoured. Heusler and Kalvoda[24] predicted the most favourable transition state for hydrogen transfer to be a six membered ring in the chair form. Mihailovic *et al*[38] studied cyclisation of short chain saturated alcohols permitting only ring closure to six membered cyclic ethers and reported low yields (4-8%) of the desired tetrahydropyran derivatives confirming that 6-membered cyclic ether formation is unfavourable. Likewise non-formation of smaller (three and four membered) and higher cyclic ethers can be rationalised on the same criteria.

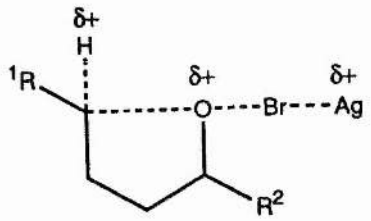
2.1.3 The hypohalite reaction.

Reagents promoting hypohalite formation have been used to effect intramolecular cyclisation of various classes of compound particularly in polycyclic systems[39]. A lead tetraacetate-iodine system has been used to effect both cyclisation and substitution in steroidal systems[24]. Reports of cyclisations of more conformationally mobile alcohols particularly short chain secondary and tertiary hydroxy compounds with silver oxide-bromine and mercuric oxide-iodine reagents[22] are well documented in the literature. More recently N-iodosuccinimide[7] has been shown to effect such cyclisations. We have prepared 2-decyltetrahydrofuran from tetradecanol by four different reagent systems to determine the applicability of these reactions to longer chain aliphatic alcohols. A brief description of the four types of reaction is outlined overleaf;

i) **The silver oxide-bromine promoted reaction.**

The reaction is effected by addition of a solution of bromine in hexane to a mixture of the alcohol and silver oxide.

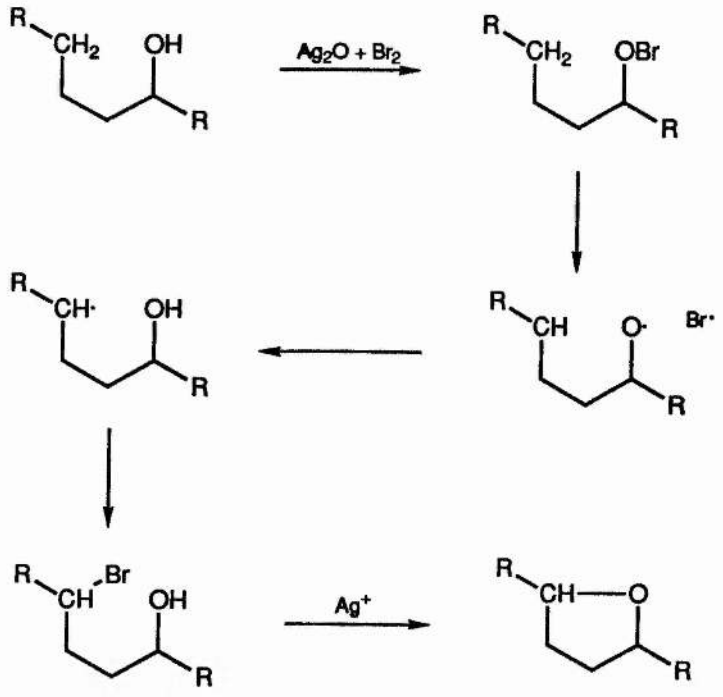
A great deal of controversy has centred around the mechanism of this reaction: Sheen and Matheny[40] proposed a cationic mechanism for the cyclisation process involving an intermediate of the type



This was later refuted by Smolinsky and Feuer[41] and Akhtar *et al*[42] in favour of a free radical mechanism. Claims by Sommer and co-workers[43] that the reaction exhibited a strong solvent dependency, and was in fact autocatalysed by the addition of either tetrahydrofuran or ether as solvent supported an ionic mechanism. Mihailovic *et al*[22] reported increased yields of tetrahydrofuran products, (60-65%), from C_6-C_8 primary and secondary alcohols when the reaction was carried out in daylight (rather than in the dark as in previous studies[40-42]). Matheny-Roscher[44] explained this in terms of a competing photochemical reaction where the silver compound generated an alkyl hypobromite which was broken down photochemically rather than by reaction of the substrate alcohol with the silver-oxide bromine reagent as in the corresponding proposed ionic reaction mechanism in the

dark. Boido and Edwards[45] dismissed the claims for an ionic mechanism proposed by Sommer *et al* explaining the increased tetrahydrofuran yields observed on addition of ether to the reaction mixture in terms of initiation of homolytic decomposition of intermediate alkyl hypobromites by peroxide present in the ethereal solvents used. They claimed that the reaction proceeded via an alkyl hypobromite which rearranged to give a bromoalcohol, the unique role of the silver oxide being to effect cyclisation of the bromoalcohol to the tetrahydrofuran. This proposal was in agreement with the free radical decomposition of the hypobromite previously postulated by Akhtar *et al*[42]. By comparison of the lead tetraacetate with the silver-oxide bromine promoted cyclisations of deuterated secondary alcohols, Green *et al*[46] (1973) showed the stereoselectivity of the two reactions to be identical. This led to the acceptance of an intermediate alkoxy radical in the silver oxide-bromine promoted cyclisation just as in the lead tetraacetate oxidation. Mihailovic and co-workers in 1973[47] confirmed the intermediacy of both an alkoxy radical and a δ-bromoalcohol and proposed the now generally accepted mechanism for free radical decomposition of the alkyl hypobromite as shown in scheme 2.2.

Scheme 2.2 Silver oxide-Bromine catalysed cyclisation of alcohols.



Several silver salts have been used in conjunction with bromine or iodine, to effect cyclisation of hexan-2-ol in varying yields[47,48]. Matheny-Roscher and Liebermann[5] showed that increased reaction rates and higher yields of tetrahydrofurans are achieved when silver acetate rather than silver oxide is employed. This is thought to be due to the formation of an intermediate acyl hypobromite which reacts rapidly with the alcohol substrate to form the alkyl hypobromite, which rearranges as depicted in scheme 2.2 to the cyclic ether.

ii) **Mercuric oxide-iodine promoted reaction.**

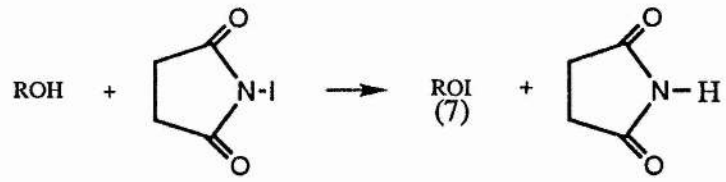
Gunstone and Inglis[6] reported use of this mixed reagent to furnish disubstituted tetrahydrofurans from long chain hydroxyalkenes. The

ability of this reagent to oxidise hydroxy compounds to cyclic ethers has been widely applied in the synthesis of steroids[49,39]. Mihailovic *et al*[22] obtained 2-butyltetrahydrofuran in approximately 60% yield by irradiating a mixture of octan-1-ol with mercuric oxide and iodine in carbon tetrachloride at 25°C. The reaction proceeded equally well with octan-2-ol. Studies by Heusler and Kalvoda[24] with steroid systems have shown that this reaction is of a free radical nature and cyclic ethers are formed by a reaction similar to that depicted in scheme 2.2. Again the initial stage of the reaction is the *in situ* formation of a hypohalite. This undergoes a rearrangement, induced either thermally or photolytically, to give a δ-iodoalcohol which cyclises to the tetrahydrofuran. The presence of the δ-iodoalcohols as intermediates in the cyclisation of secondary steroidal alcohols has been confirmed by conversion to the iodoketones and hydroxyketones and other derivatives[50].

iii) **N-Iodosuccinimide promoted reaction.**

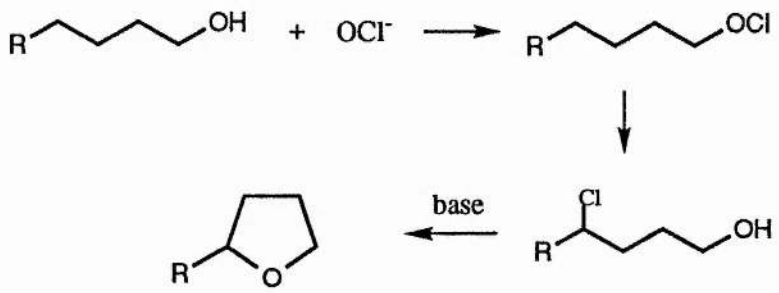
Beebe and co-workers[7,51] reported cyclisation of C_4 and C_5 primary and secondary alcohols to five membered cyclic ethers with N-iodosuccinimide by irradiating a solution of the alcohol and N-iodosuccinimide in chlorobenzene at room temperature. After two hours butan-1-ol and pentan-1-ol were converted to tetrahydrofuran and 2-methyltetrahydrofuran in yields of 52-61 and 92-94% respectively. Treatment of secondary alcohols in the same manner

yielded 35-40% of substituted tetrahydrofurans together with 3-5% ketone. Again the reaction is of a free radical nature, the initial stage being the formation of an alkyl hypoiodite (7) which rearranges to give the tetrahydrofuran derivative as illustrated earlier in scheme 2.2.



iv) **The hypohalite reaction.**

Cekovic and Djokic[52] have shown that δ-chlorination of alcohols can be achieved by the ferrous ion induced decomposition of the corresponding alkyl hypochlorite formed by treatment of the reactant alcohol with sodium or calcium hypochlorite.

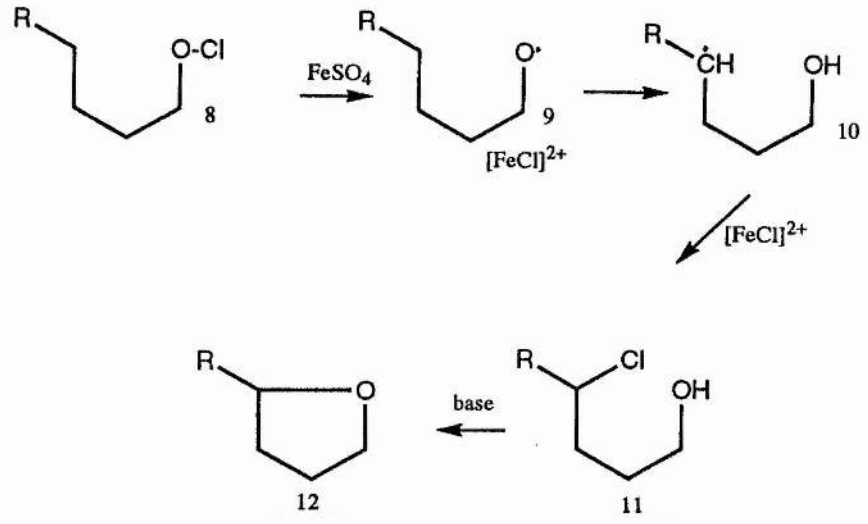


The δ-chloroalcohols thus formed have been shown to cyclise readily to the corresponding tetrahydrofurans on treatment with base.

Prior to this work many reports concerning the photolytic and thermal decomposition of alkyl hypochlorites to δ-chlorohydrins have appeared in the literature[53-57]. Generally the decomposition of alkyl hypochlorites has been shown to proceed well in the case of tertiary compounds but with secondary and in particular, primary compounds, yields are often low due to the instability of the primary hypochlorites[58].

Cekovic and Djokic prepared δ-chloroalcohols from C_6-C_8 secondary alcohols together with δ-chlorohexan-1-ol from hexan-1-ol in yields of 50-75%[52,59]. The initial stage of the reaction is the ferrous ion induced homolysis of the O-Cl bond of the alkyl hypochlorite (8) yielding an alkoxy radical (9) as shown in scheme 2.3. Intramolecular hydrogen abstraction then occurs generating the δ-carbon radical (10). δ-Chlorination of radical (10) in the presence of ferric ion, formed by one electron oxidation of the ferrous ion in the initial decomposition stage is thought to proceed by co-ordination of the δ-hydroxyalkyl radical (10) with the ferric ion followed by oxidative ligand transfer to give the δ-chloroalcohol (11). The δ-chloroalcohol cyclises readily on treatment with base to give the corresponding tetrahydrofuran (12).

Scheme 2.3 Ferrous ion induced decomposition of alkyl hypochlorites.



Ferrous ions have been shown to markedly accelerate the decomposition of alkyl hypochlorites, in the case of secondary alkyl hypochlorites, the degree of decomposition in the dark in the absence of ferrous ion was reported to be less than 5% after two hours however, in the presence of ferrous ion, again in the dark, decomposition was reported to be almost complete (97%) after 1.5 hours[52].

2.2 Results and Discussion.

2.2.1 Comparison Study of the Methods of Production of 2-Alkyltetrahydrofurans.

Yields of 2-decyltetrahydrofuran from oxidative cyclisation of tetradecanol (1.0g) with the four different reagent systems are shown in table 2.1 below:-

Table 2.1 Preparation of 2-decyltetrahydrofuran from tetradecanol.

	% Yield[1]					
Reagent	2-Nonyl-THP	2-Decyl-THF	Aldehyde	Acetate	Alcohol	Others
$Pb(OAc)_4$	6.9	73.6	4.4	8.0	6.2	0.9
$HgO\text{-}I_2$	9.6	78.0	5.2	-	3.8	3.4
$Ag_2O\text{-}Br_2$	1.2	42.4	13.6	-	35.0	7.8
N-iodo-succinimide	3.9	76.6	-	-	18.2	1.3

[1] % yields are calculated from the GLC analysis of the recovered product mixture.

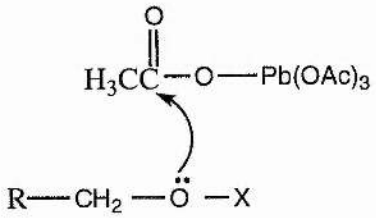
Clearly, silver oxide-bromine was the least efficient of all the reagents employed, resulting in the lowest conversion of alcohol to cyclic ether derivatives together with a substantial yield of by-products, particularly aldehyde. Mechanistic studies on the silver oxide-bromine promoted cyclisations of short chain primary alcohols[47] (detailed in section 2.1.2) have shown that this reaction occurs via an intermediate

alkyl hypobromite. This decomposes homolytically to give an alkoxy radical which rearranges to give the cyclic ether. The formation of aldehyde can be explained in terms of both homolytic and heterolytic decomposition of the alkyl hypobromite.

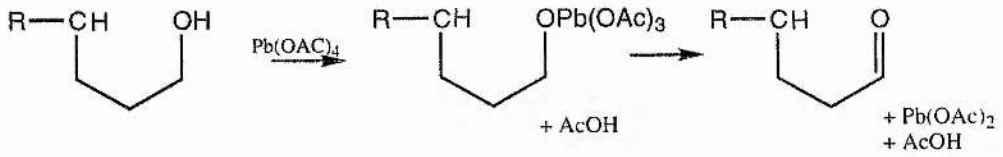
GLC and TLC analyses of the product mixture indicated the presence of components less polar than the desired tetrahydrofuran, this material was not identified further but may well have been hydrocarbon, derived from fragmentation processes. The low yield of cyclic ethers together with the production of significant amounts of carbonyl compound is not surprising since Mihailovic and co-workers reported similar results from the silver oxide-bromine oxidation of octan-1-ol and octan-2-ol[22]. It was also found as previously suggested, that freshly prepared silver oxide is necessary to induce cyclisation; an identical reaction carried out with commercially available silver oxide resulted in the isolation of 91% unreacted starting material.

Conversion of tetradecanol to cyclic ethers was achieved in good yield when mercuric oxide and bromine were employed, the only significant by-product being tetradecanal, demonstrating the applicability of this reagent system to the cyclisation of medium chain primary alcohols. Oxidation with lead tetraacetate resulted in production of tetradecanal and tetradecyl acetate together with the cyclic ethers in good yield. Acetate formation arose as a result of esterification of the reactant alcohol or the corresponding alkoxy lead (iv) acetate with acetic acid or acetic

anhydride generated in the course of the reaction. Nucleophilic attack of the oxygen atom of the alcohol/alkoxide on one of the carboxylate carbon atoms of lead tetraacetate being another possible route to tetradecyl acetate formation.



Tetradecanal formation occurred as a result of direct oxidation of the reactant alcohol.



Irradiation of a solution of tetradecanol and N-iodosuccinimide resulted in conversion of tetradecanol to 2-decyltetrahydrofuran and 2-nonyltetrahydropyran in high yield (aldehyde formation was < 1%). The advantage of this reaction over the former three being the non-formation of by-products, facilitating ether purification by column chromatography. The non-formation of by-products was confirmed by treating a series of alcohols in the same manner: Results are illustrated in table 2.2. Although excellent conversion of alcohols to cyclic ethers can be achieved the reaction is rather slow; hexadecanol was converted to cyclic ethers (17%) in four hours, treatment over an extended period of time (40 hours) resulted in the formation of cyclic ether in >80% yield. Beebe *et al* reported conversion of pentanol to 2-methyltetrahydrofuran (92-94%) in two hours[7].

Table 2.2 N-iodosuccinimide promoted cyclisation of primary alcohols.

Reactant	Reaction time/ hours	[1] %yield 2-Alkyl-tetrahydropyran	2-Alkyl-tetrahydrofuran	Others	Unreacted alcohol
Decanol	1.5	-	6.3	4.9	88.8
Decanol	4.0	0.8	20.2	6.2	72.8
Tetradecanol	32.0	3.7	73.5	5.5	17.3
Hexadecanol	4.0	0.7	16.7	5.8	76.8
Hexadecanol	8.5	2.0	43.4	7.1	47.5
Hexadecanol	40.0	4.5	79.1	8.4	8.0
Octadecanol	2.0	0.4	9.3	6.9	83.4

[1] % yields are calculated from the GLC analysis of the recovered crude products.
% others accounts for impurities present in the starting material, losses incurred in work-up together with unidentified product components.

In order to determine whether the observed increase in reaction time was a direct result of the increased alkyl chain length, resulting in a slower reaction or was in fact, inherent in our experimental conditions, cyclisation of pentanol with N-iodosuccinimide was carried out under identical conditions to previous experiments. After two hours 8% conversion had occurred, at 14 hours approximately 55% 2-methyltetrahydrofuran had been formed and after 22 hours the reaction was approaching completion. On the basis of this result it appears that the rate of the reaction is independent of the chain length of the reactant alcohol under the conditions employed. This result did not confirm that reported by Beebe *et al* under the same experimental conditions; hence the differences in reaction time must be attributed to the inefficiency of the light source we used (100W tungsten lamp).

Irradiation of the reaction mixtures results in a strong colour change from colourless through pale pink to a deep fuchsia. A small scale reaction using tetradecanol as substrate, carried out in a quartz u.v. cell enabled the reaction to be monitored spectrophotometrically; a marked increase in absorption with time was noted at 508 nm, a corresponding increase in absorption was also noted around 300 nm (however the latter absorption was close to the solvent cut off point at 270 nm). These absorption bands were found to be characteristic of free iodine atoms, known to be produced on irradiation of I_2. Free iodine atoms can arise from homolytic decomposition of the intermediate alkyl hypoiodite. Since iodine is produced in the reaction, the increase in absorption at 508 nm gives some indication of the progress of the reaction. Heusler and Kalvoda[24] reported that the presence of iodine atoms accelerated the decomposition of alkyl hypoiodites in steroid systems. The reaction

was shown to proceed rapidly in non-polar solvents in which iodine is normally soluble, while in aromatic solvents charge-transfer complexes are formed with iodine, hence the amount of free iodine atoms formed on irradiation is low and therefore rate of decomposition of the alkyl hypoiodite is slow. Further work employing a different solvent system together with a more powerful light source may result in increased rates of conversion of fatty alcohols to cyclic ether derivatives thus providing a valuable method for this transformation.

Having assessed the applicability of these four reagent systems for the cyclisation of primary fatty alcohols, larger scale syntheses of cyclic ethers from a range of primary alcohols of carbon chain length C_{10}-C_{18} were carried out. The choice of reagent for these transformations was based on the results obtained from the preliminary experiments with tetradecanol; the silver oxide-bromine promoted reaction was rejected due to the high yield of by-products.

Although the mercuric oxide-iodine promoted reaction gave good yields of tetrahydro -furan (and -pyran) the high molar ratio of reagents:reactant required to effect cyclisation rendered larger scale syntheses impractical. N-iodosuccinimide, although perhaps the most efficient reagent in terms of controlling the conversion of alcohol to cyclic ether was, under the experimental conditions employed, rather slow, hence the larger scale preparations of cyclic ethers (10-30g) were performed using lead tetraacetate. Complete depletion of lead tetraacetate occurred in less than four hours in all cases and the yields of cyclic ethers obtained are shown in table 2.3.

Table 2.3 Lead tetraacetate promoted cyclisation of primary alcohols.

ROH	Wt./g ROH employed	Yield/g	[1] % Yield					
			2-Alkyl-tetrahydropyran	2-Alkyl-tetrahydrofuran	Aldehyde	Acetate	Alcohol	Others
R =								
$C_{10}H_{21}$	30.00	30.27	5.2	65.6	2.4	6.4	19.1	1.3
$C_{12}H_{25}$	10.00	10.04	6.2	68.9	7.6	2.8	10.7	3.8
$C_{14}H_{29}$	15.00	15.14	5.4	63.1	1.9	5.0	19.1	5.5
$C_{16}H_{33}$	25.00	24.77	5.7	54.7	3.0	5.7	22.4	8.5
$C_{18}H_{37}$	20.00	19.21	6.5	68.1	1.7	3.9	9.3	10.5

[1] % Yields are calculated from GLC analysis of the crude product mixture and are expressed as % of reactant alcohol accounted for. Others - include impurities present in reactant alcohol together with high boiling unidentified material in the product mixture.

The yields of cyclic ether were lower than previously obtained in the preliminary reaction carried out on tetradecanol, however, this decrease in cyclic ether production did not occur as a direct result of increased by-product formation. In most cases a substantial amount of unreacted starting material was recovered and since the reactions were allowed to proceed until complete disappearance of lead IV salts, the amount of unchanged starting material reflects the rate of decomposition of lead tetraacetate. Increasing the lead tetraacetate amount does not result in increased cyclic ether formation, in fact the converse is true. Mihailovic *et al*[4] showed that in the oxidation of secondary alcohols with increased quantities of lead tetraacetate, the cyclic ether products reacted further producing high boiling compounds. Evidence of late running components was noted in the GLC analysis of our reaction products, however, these compounds were present in insufficient amounts to warrant further investigation.

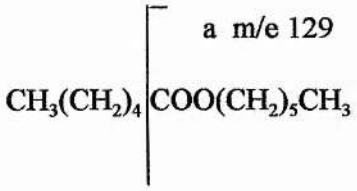
Oxidation of other hydroxy compounds with lead tetraacetate has been shown to yield products from β-fragmentation processes[18], namely alkenes and carbonyl compounds. There was no significant evidence of any such compounds in our product mixtures. β-Fragmentation is presumably energetically unfavourable due to the instability of the primary alkyl radical that would result from such a process, hence in the case of primary compounds rearrangement of the alkoxy radical to the cyclic ether derivative is favoured.

We have shown that reaction of lead tetraacetate with fatty alcohols effects cyclisation in good yields. The main disadvantage of this reaction being an economic

issue, lead tetraacetate is an expensive reagent rendering large scale industrial preparations non-viable. There are several reports in the literature concerning the intramolecular cyclisation of alcohols, particularly secondary and tertiary alcohols, by treatment with sodium or calcium hypochlorite and subsequent decomposition of the alkyl hypochlorites thus formed. Sodium and calcium hypochlorite are both readily available and inexpensive thus conversion of our fatty alcohols to δ-chloroalcohols in this manner would not only provide an alternative and more economic route to 2-alkyltetrahydrofurans (δ-chloroalcohols readily cyclise on treatment with base) but would also achieve intramolecular functionalisation at a specific site of the fatty alcohol chain in a single step. We could then go on to replace the chlorine atom with a functional group of our choice.

Unfortunately the attempted preparations of δ-chloroalcohols from C_{14}, C_{12} and C_{10} primary alcohols via conversion to, and subsequent decomposition of, the corresponding alkyl hypochlorites did not result in formation of the predicted reaction products. GC-MS data showed no evidence of isotopic chlorine or the presence of 2-alkyltetrahydrofurans. The major products were found to have high molecular weights compared to those expected. Many experiments employing hexanol were carried out in an attempt to reproduce the work of Cekovic and Djokic[52]. IR analysis of the reaction product showed a strong carbonyl stretch. GC-MS indicated the presence of unreacted hexanol (25%) together with hexyl hexanoate (58%) and three other components (17% total), two were eluted prior to the hexyl hexanoate and one after. These components were not identified further.

Hexyl hexanoate was characterised on the basis of the following mass spectral fragments:



Peaks at m/e values (intensity relative to base peak), molecular ion at m/e 200 absent, 144 (0.5, M^+-C_4H_8), 129 (1, $C_6H_{13}OCO^+$), 115 (26, $CH_3(CH_2)_4COOH_2^+$), 99 (22, $CH_3(CH_2)_4CO^+$), 84 (24, $C_6H_{12}^+$,) 71 (15, $C_5H_{11}^+$), 69 (16, $C_5H_9^+$), 57 (30, $C_4H_9^+$), 55 (32, $C_4H_7^+$), 43 (100, $C_3H_7^+$) and 42 (65, $C_3H_6^+$).

The production of esters from the decomposition of primary alkyl hypochlorites has been reported by Walling and Bristol[60]. They claim good yields of δ-chloroalcohols are obtained from the decomposition of tertiary alkyl hypochlorites, but in the case of primary and secondary compounds there is a tendency for the reaction to be more complicated.

Attack at the α-hydrogen position has been shown to occur resulting in the introduction of molecular chlorine into the reaction system. Chlorine is thought to be continually regenerated as illustrated below and thus the specificity of the reaction is lost.

$$RCH_2O\text{-}Cl \rightarrow RCH_2O^{\bullet} + Cl^{\bullet}$$

$$Cl^{\bullet} + RCH_2O\text{-}Cl \rightarrow HCl + R\dot{C}HOCl$$

$$RCH_2O^{\bullet} + RCH_2O\text{-}Cl \rightarrow RCH_2OH + R\dot{C}HOCl$$

$$HCl + RCH_2O\text{-}Cl \rightarrow RCH_2OH + Cl_2$$

$$Cl_2 + RCH_2OH \rightarrow RCHO + 2HCl$$

$$RCHO + Cl_2 \rightarrow RCOCl + HCl$$

$$RCOCl + RCH_2OH \rightarrow RCOOCH_2R + HCl$$

Walling and Bristol[61] indicated that when the reaction was carried out in the presence of olefins with strong electron withdrawing groups which are inert towards radicals, but act as chlorine atom traps, 4-chlorobutanol was formed in yields of 50-60% from the thermal decomposition of n-butyl hypochlorite. A reaction employing hexanol as the substrate, was carried out in trichloroethene, again hexyl hexanoate was found to be the major product component. This result led us to believe that ester formation was occurring prior to the ferrous ion induced decomposition step and indeed this was found to be the case. Although iodometric analysis of the alkyl hypochlorite solution formed *in situ* by the addition of glacial acetic acid to a mixture

of the alcohol in carbon tetrachloride and sodium hypochlorite solution indicated 80+% of the alcohol employed had been converted to the corresponding alkyl hypochlorite, infra-red analysis of the hypochlorite solution taken several minutes later indicated the presence of a large carbonyl stretch at 1740cm^{-1} indicative of the ester group. GC-MS analysis confirmed the presence of hexyl hexanoate. There is literature precedence for the formation of ester compounds in this manner. Deno *et al*[55] showed that in an air atmosphere and an aqueous medium, chlorine rapidly oxidises pentan-1-ol to pentyl pentanoate. Keehn and Nwauka[62] claim that oxidation of primary (and secondary) alcohols with calcium hypochlorite proceeds smoothly at 0°C in a solvent containing acetic acid; thus hexanol was converted to hexyl hexanoate (98%) and secondary alcohols gave ketones in good yields (90-95%) in less than one hour. These reaction conditions are essentially identical to those we employed based on the method of Walling and McGuinness confirming that ester formation (probably arising from the introduction of molecular chlorine into the reaction system) was occurring almost immediately on addition of acetic acid to the alcohol-inorganic hypochlorite mixture. A private communication with Dr. Cekovic provided no further information concerning the preparation and decomposition of alkyl hypochlorites. Hence, despite the initially demonstrated potential of this reaction as a synthetic process for derivatisation of our fatty alcohols the applicability of the reaction to primary alcohols is somewhat limited by the problems encountered in the preparation and handling of the highly unstable alkyl hypochlorites.

2.3 Spectroscopic examination of reaction products.

Aldehydes were characterised by comparison of GLC retention times, TLC Rf values and mass spectra with those of authentic compounds. Infra-red analysis showed the presence of the characteristic carbonyl stretch. Likewise acetates were identified by comparison with authentic samples prepared by treatment of the reactant alcohol with acetic anhydride.

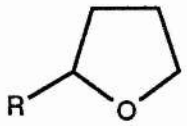
Separation of the 2-alkyltetrahydrofurans and 2-alkyltetrahydropyrans was achieved by TLC. The 2-alkyltetrahydropyran derivatives were found to be slightly less polar than the corresponding 2-alkyltetrahydrofuran derivatives. For example, TLC analysis (solvent PE5) of the cyclisation products from tetradecanol indicated the presence of a dark spot corresponding to 2-decyltetrahydrofuran (Rf 0.62) together with a spot slightly ahead (Rf 0.69) corresponding to 2-nonyltetrahydropyran.

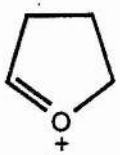
GLC analysis (CPSIL5CB, 100°-0-20°-300°) resulted in elution of the tetrahydropyran derivatives prior to the tetrahydrofuran derivatives.

2.3.1 Mass spectra of the 2-alkyltetrahydro -furans and -pyrans.

GC-MS of the cyclic ethers enabled mass spectra of the 2-alkyltetrahydrofurans and the corresponding tetrahydropyran derivatives to be recorded. The characteristic mass spectral fragments are detailed in tables 2.4 and 2.5.

Table 2.4 Mass Spectral Fragments of 2-Alkyltetrahydrofurans.

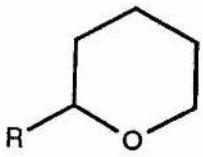


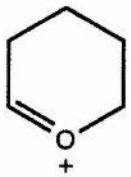
R =	M^+ m/e	M^+-H m/e	M^+-H_2O m/e	 m/e	$C_4H_9^+$ m/e	$C_4H_7^+$ m/e	$C_3H_7^+$ m/e	$C_3H_6^+$ m/e	$C_3H_5^+$ m/e
C_6H_{13}	156 (0.2)[1]	155 (0.3)	138 (1.4)	71 (100)	57 (4)	55 (14)	43 (41)	42 (9)	41 (12)
C_8H_{17}	184 (tr)	183 (tr)	166 (0.3)	71 (100)	57 (3)	55 (6)	43 (16)	42 (9)	41 (9)
$C_{10}H_{21}$	212 (tr)	211 (tr)	194 (0.2)	71 (100)	57 (3)	55 (9)	43 (39)	42 (8)	41 (24)
$C_{12}H_{25}$	240 (0)	239 (tr)	221 (0.1)	71 (100)	57 (4)	55 (8)	43 (14)	42 (4)	41 (11)
$C_{14}H_{29}$	268 (0)	267 (0)	250 (tr)	71 (100)	57 (4)	55 (9)	43 (38)	42 (10)	41 (10)

[1] The numbers in parentheses refer to the intensity of the fragment peak relative to the base peak.

In all cases the molecular ions are absent or of very low intensity, probably because these molecules readily lose water to give M-18 fragment ions. For 2-alkyltetrahydrofurans the base peak at m/e 71 arose from the loss of the alkyl side chain. The analogous fragmentation of the 2-alkyltetrahydropyrans resulted in the observed peak at m/e 85. Small peaks at lower m/e values were also observed. These were attributed to fragmentation of the ether ring.

Table 2.5 Mass Spectral Fragments of 2-Alkyltetrahydropyrans.





R =	M^+ m/e	M^+-H m/e	M^+-H_2O m/e	m/e
C_5H_{11}	156 (0.2)[1]	155(0.1)	138 (0.15)	85 (100)
C_7H_{15}	184 (0)	183 (tr)	166 (0.1)	85 (100)
C_9H_{19}	212 (0)	211 (0)	194 (tr)	85 (100)
$C_{11}H_{23}$	240 (0)	239 (0)	222 (tr)	85 (100)
$C_{13}H_{27}$	268 (0)	267 (0)	250 (0)	85 (100)

[1] The numbers in parentheses refer to the intensity of the fragment peak relative to the base peak.

2.3.2 Infra-red analysis of 2-alkyltetrahydrofurans.

FT-IR analysis of the 2-alkyltetrahydrofuran compounds (liquid film) showed bands at 919 and 1072cm^{-1}, these stretches are characteristic of the tetrahydrofuran ring and were observed at 915 and 1070cm^{-1} in the FT-IR spectrum of tetrahydrofuran itself.

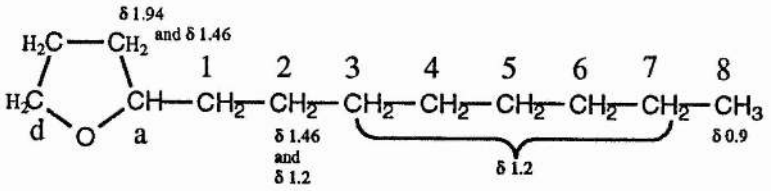
2.3.3 NMR Spectroscopy of 2-alkyltetrahydrofurans.

Complete assignment of the ^{13}C and ^{1}H shifts was not possible from the one dimensional spectra alone hence a detailed NMR study of 2-octyltetrahydrofuran was carried out. The information thus obtained enabled full interpretation of the NMR data for the range of C_{10}-C_{18} cyclic ethers studied.

2.3.3.1 ^{1}H NMR Spectrum of 2-octyltetrahydrofuran.

The proton spectrum was complex. Three distinct signals were observed at δ 3.7-3.85 (3H) corresponding to the protons bonded to carbons a and d alpha to the oxygen function. Signals were also present in the following regions; δ1.8-1.9 (3H) and δ1.4-1.5 (4H), corresponding to the protons attached to the carbon atoms beta and gamma to the ring oxygen. The initial ^{1}H assignments are shown in table 2.6.

Table 2.6 ^{1}H NMR shift assignments for 2-octyltetrahydrofuran.



δ		Assignment
0.9	t	3H CH_3 (C-8)
1.2	s	$(CH_2)_n$
1.4-1.5	m	3H
1.56	t	1H } protons on carbons β and γ to O
1.8-1.95	m	3H }
3.73	m	1H
3.76	t	1H } protons on carbons a and d α to O
3.85	m	1H }

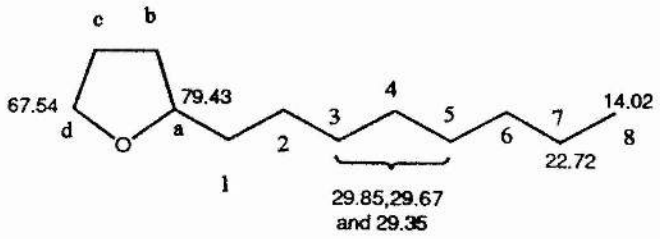
2.3.3.2 ^{13}C NMR spectrum of 2-octyltetrahydrofuran.

The ^{13}C NMR spectrum of 2- octyltetrahydrofuran contained 12 signals corresponding to 12 carbon atoms in different chemical environments. Complete assignment of these signals from the ^{13}C NMR spectrum was not possible. However the partial assignments are shown in table 2.7.

The signals at 29.85, 29.67 and 29.35 ppm were collectively assigned as the

methylene carbons 3,4 and 5 (these signals could not be confidently distinguished because of their similarity in chemical environment). The signals at 35.84, 31.98 and 31.45 ppm correspond to carbons 1, 6 and b, however, discrimination between these three was not possible from the ^{13}C NMR spectrum alone. Similarly the signals at 25.76 and 26.49 ppm corresponding to carbons 2 and c were not readily distinguishable.

Table 2.7 ^{13}C NMR chemical shift assignments for 2-octyltetrahydrofuran.



ppm	Assignment
79.43	a
67.54	d
35.84, 31.98, 31.45	b, 1 and 6
29.85, 29.67, 29.35	3, 4 and 5
26.49, 25.76	c and 2
22.72	7
14.02	8

2.3.3.3 ^{13}C-^{1}H Correlation spectroscopy experiment.

To assist assignment of the ^{13}C NMR spectrum a two-dimensional ^{13}C-^{1}H correlation spectroscopy experiment was carried out. This provided additional information by showing exactly which protons are directly bonded to a particular carbon atom. The ^{13}C-^{1}H spectrum for 2-octyltetrahydrofuran is shown in the form of a contour plot in figure 2.1. The ^{13}C chemical shifts are shown on the x-axis and the ^{1}H chemical shifts on the y-axis. The protons attached to a particular carbon atom are identified by drawing horizontal and vertical lines through the centre of peaks on the contour plot and tracing back to the corresponding ^{13}C and ^{1}H shifts on the x and y axes.

Thus, applying this procedure to the expansion of the ^{13}C-^{1}H spectrum shown in figure 2.2, the carbon signal at 31.98ppm is found to correlate with the bulk methylene protons at δ1.2. We have already established that the signals at 31.45, 31.98 and 35.84 ppm collectively correspond to carbons 2, 6 and b, thus the signal at 31.98ppm can be unequivocally assigned to C-6 of the alkyl chain. Similarly the two non-equivalent protons at δ1.45 and δ1.95 are found to be directly bonded to the carbon appearing at 31.45ppm. The wide splitting of these protons is indicative of the methylene protons attached to carbon b of the tetrahydrofuran ring where the two protons experience quite different chemical environments, one being *cis* to the alkyl chain, the other *trans*. On this basis the carbon signal at 31.45ppm was tentatively assigned as carbon b. The carbon signals at 25.76 and 26.49 ppm correlate with the protons at δ 1.85 and 1.35 respectively. Since carbon c is beta to the oxygen function and carbon 2 is gamma, one would expect the protons attached to carbon c to

experience a greater effect from the ring oxygen and thus appear downfield with respect to the protons bonded to carbon 2. Thus the signals at 25.76 and 26.49 ppm were tentatively assigned as carbons c and 2 respectively.

Figure 2.1 **^{13}C-^{1}H Correlation Spectrum of 2-Octyltetrahydrofuran.**

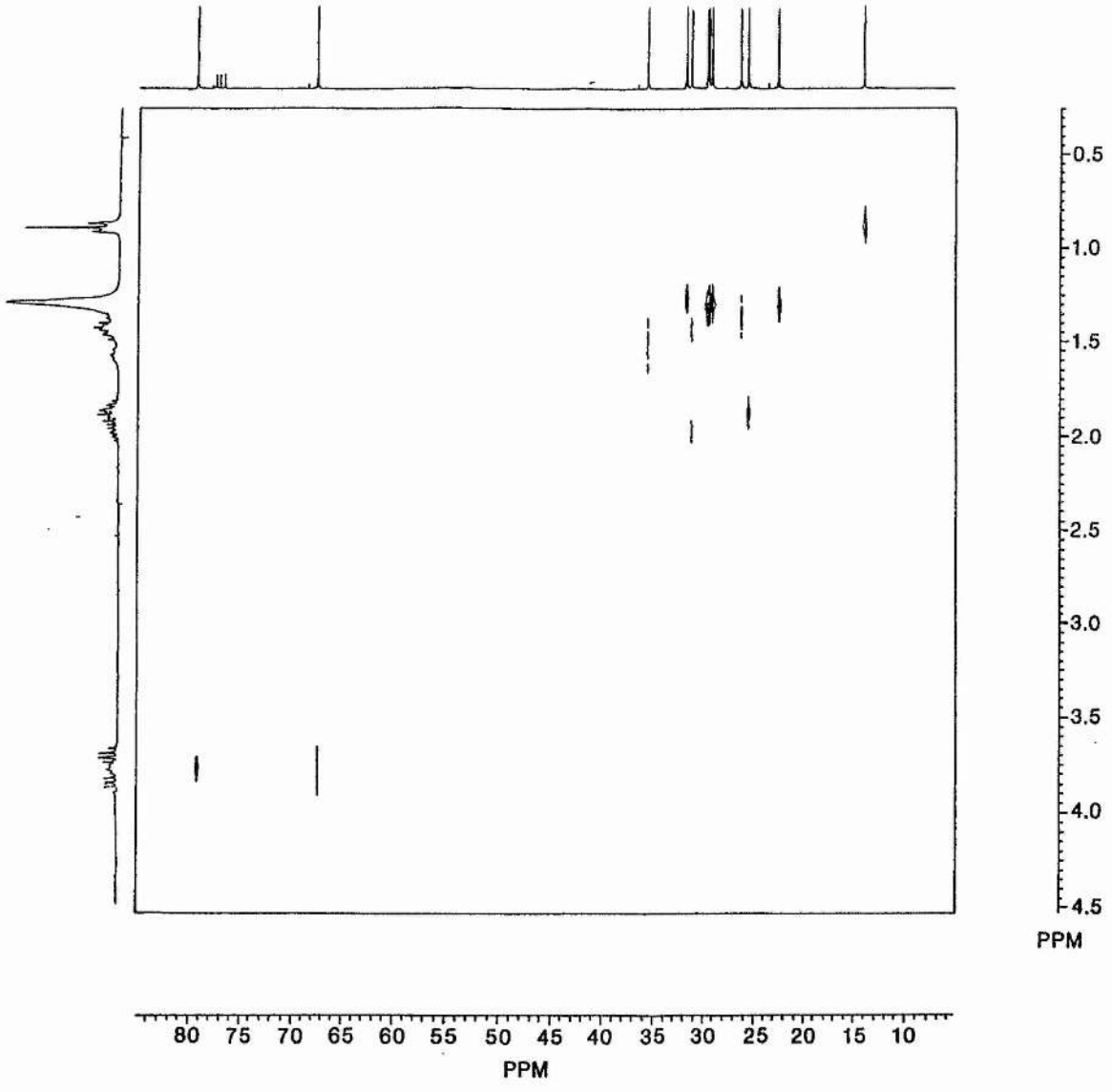
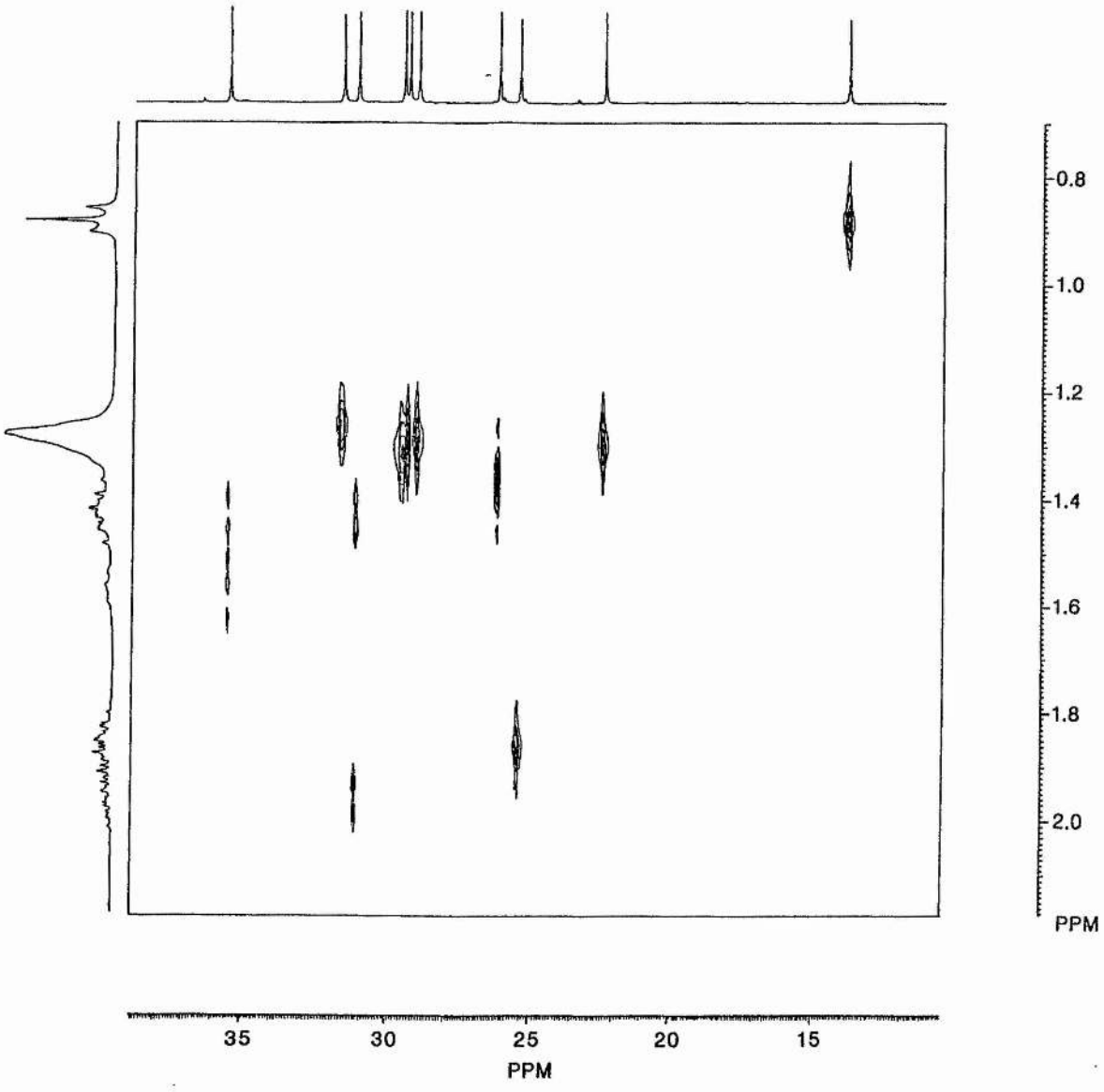


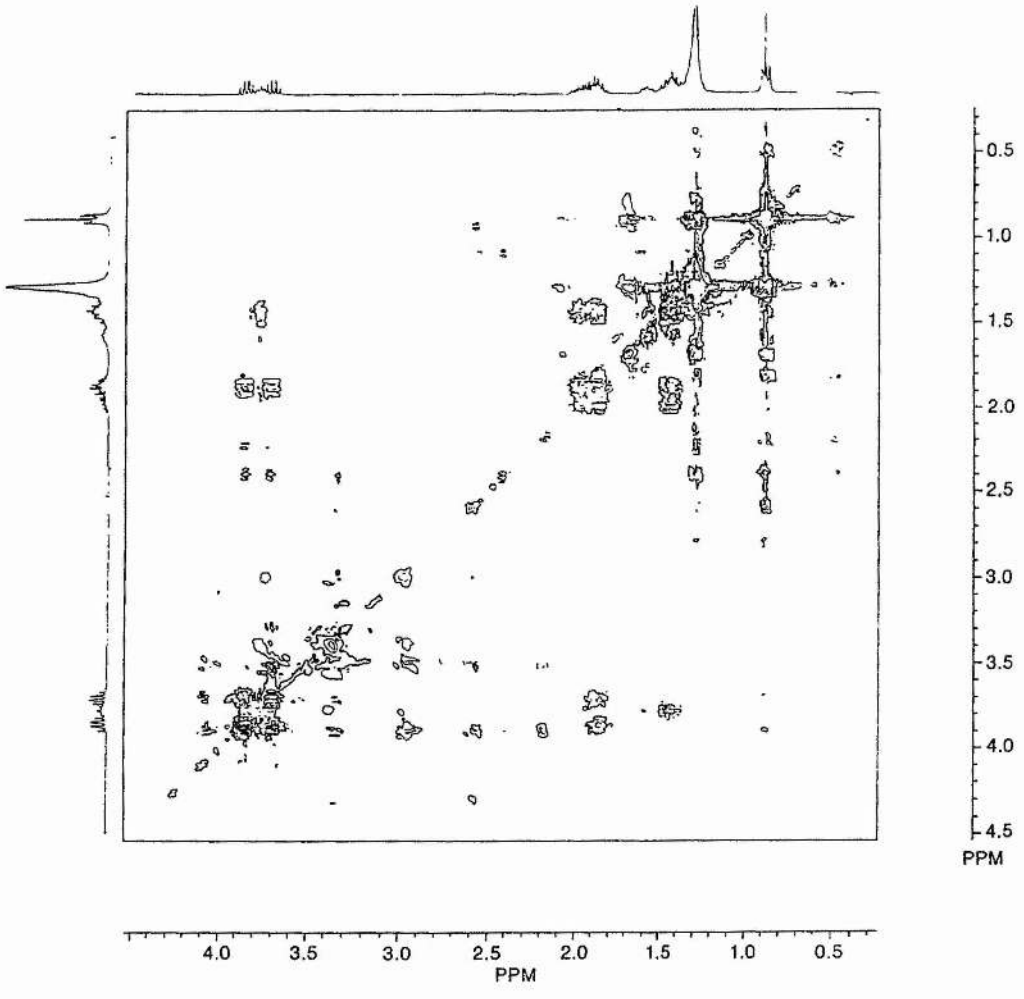
Figure 2.2 **Expansion of ^{13}C-^{1}H Correlation Spectrum of 2-Octyl-tetrahydrofuran.**



2.3.3.4 ^{1}H-^{1}H Correlation Spectroscopy Experiment.

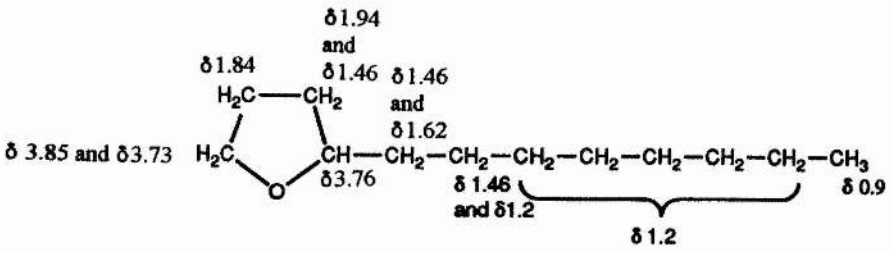
In order to confirm these tentative assignments a homonuclear two-dimensional correlation spectroscopy (COSY) experiment was performed. The COSY experiment establishes the coupling correlations between the different protons in a molecule. The COSY plot for 2-octyltetrahydrofuran is illustrated in figure 2.3, the one-dimensional ^{1}H spectrum is shown on both the x and y axes. Diagonal and cross peaks can be seen on the COSY plot; a cross section taken along the diagonal corresponds to the one-dimensional spectrum. The cross peaks demonstrate spin-spin coupling between two protons. Drawing a horizontal and a vertical line through the cross peak back to the x and y axes identifies these protons. Thus, the methyl protons at δ0.9 are shown to couple with the methylene protons at δ1.2 as one might expect. Similarly the protons at δ1.84 are shown to couple with the protons at δ 3.85 and 3.73. The protons at δ3.85 and 3.73 have already been correlated to carbon d of the tetrahydrofuran ring hence the two directly equivalent protons at δ1.84 are directly bonded to the carbon atom alpha to d, at 25.76ppm, carbon c of the ether ring, confirming our tentative assignment from the ^{13}C-^{1}H correlation experiment. Further examination of the COSY plot shows that the methine proton at δ3.76 (carbon a) is coupled to the two non-equivalent methylene protons at δ1.94 and δ1.46, which in turn, are coupled to the methylene protons at δ1.84 (carbon c). Thus, referring back to the ^{13}C-^{1}H correlation plot (figure 2.1) it can be seen that the protons at δ1.94 and δ1.46 correlate with the carbon signal at 31.45ppm thus confirming assignment of this signal as carbon b of the ring system.

Figure 2.3 **^{1}H-^{1}H Correlation Spectrum of 2-Octyltetrahydrofuran.**



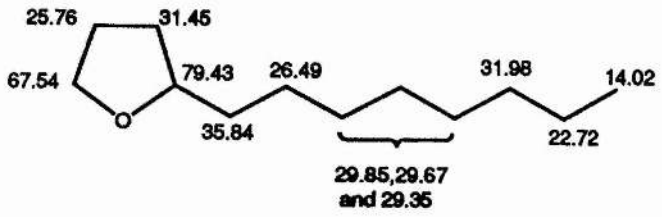
Finally the methylene signals at δ 1.46 and 1.62 couple with the methine proton at δ3.76 and the two methylene protons at δ1.46 and 1.2. Hence referring back to figure 2.2 we are able to assign the methylene protons at δ1.46 and δ1.62 to carbon 1 of the alkyl chain (35.84ppm) and the non-equivalent methylenes at δ1.46 and δ1.2 to carbon 2 of the alkyl chain (26.49ppm). This combination of NMR techniques enabled accurate assignment of all the proton and carbon atoms of the 2-octyltetrahydrofuran molecule, with the exception of the C-3, C-4 and C-5 carbons and protons of the alkyl chain which, due to their almost identical chemical environments, are non-resolvable. A summary of the carbon and proton shift assignments is detailed below:

^{1}H NMR assignments.



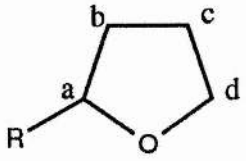
^{13}C NMR assignments.

Values are expressed in ppm downfield from internal standard TMS.



The ^{13}C NMR shift assignments for the C_{10}-C_{18} 2-alkyltetrahydrofurans are shown in table 2.8.

Table 2.8 ^{13}C chemical shifts for 2-alkyltetrahydrofurans.



^{13}C NMR shift assignments (ppm)

R =	C_6H_{13}	C_8H_{17}	$C_{10}H_{21}$	$C_{12}H_{25}$	$C_{14}H_{29}$
C-a	79.50	79.43	79.50	79.51	79.52
C-b	31.48	31.45	31.49	31.49	31.44
C-c	25.79	25.76	25.80	25.80	25.76
C-d	67.55	67.54	67.60	67.60	67.57
C-1	35.86	35.84	35.86	35.86	35.80
C-2	26.45	26.49	26.52	26.51	26.46
C-3	29.51	[1]29.85	29.87	29.88	29.82
C-4	31.84	29.67	29.72	29.77	29.75
C-5	22.67	29.35	29.72	29.77	29.75
C-6	14.07	31.98	29.72	29.77	29.75
C-7		22.72	29.44	29.75	29.70
C-8		14.02	32.02	29.75	29.70
C-9			22.77	29.47	29.70
C-10			14.14	32.03	29.70
C-11				22.77	29.44
C-12				14.13	32.00
C-13					22.75
C-14					14.13

[1] The signals occurring between 29.9 and 29.3 ppm correspond to the methylene carbons of the alkyl chain. These signals are not well resolved and thus cannot be specifically assigned to a particular methylene carbon.

2.4 Experimental.

2.4.1 The lead tetraacetate promoted reaction.

Prior to reaction the purity of the lead tetraacetate was determined iodometrically.[63] For this purpose a potassium iodide stock solution consisting of a 100ml aqueous solution of potassium iodide (15.0g), sodium acetate (25.0g) and sodium carbonate (10.0g) was prepared.

Potassium iodide stock solution (10ml) was added to a warm solution of lead tetraacetate (0.2g) in glacial acetic acid (10ml). The solution was heated for one minute and the liberated iodine was titrated with 0.1N thiosulphate.

$$Pb^{4+} + 2I^- \rightarrow Pb^{2+} + I_2$$

$$2S_2O_3^{2-} + I_2 \rightarrow S_4O_6^{2-} + 2I^-$$

The lead tetraacetate was found to have a purity of 96.6%.

In a round bottomed flask (100ml) fitted with a Dean-Stark water separator and reflux condenser, a mixture of tetradecanol (1.0g, 4.67mmol), lead tetraacetate (2.37g, 5.14mmol based on lead tetraacetate purity at 96%), and calcium carbonate (0.52g, 5.14mmol) in dry benzene (50ml) was stirred vigorously and refluxed (80°C) for four hours. The mixture was allowed to cool and diethyl ether (20ml) was added to assist precipitation of the lead and calcium salts prior to filtration. The residue was then washed with diethyl ether (10ml), the filtrate was transferred to a separating funnel and washed with saturated aqueous sodium hydrogen carbonate (100ml),

saturated aqueous sodium chloride (100ml) and water (100ml). The aqueous layers were re-extracted with diethyl ether and the combined organic layers were dried over sodium sulphate prior to removal of the solvent yielding a colourless oil (0.98g). GLC analysis indicated the presence of 2-nonyltetrahydropyran (6.9%), 2-decyltetrahydrofuran (73.6%), tetradecanal (4.4%), tetradecyl acetate (8.0%), unreacted tetradecanol (6.2%) and a small amount of late running material (0.9%) which was not examined further.

Large scale preparations of 2-alkyltetrahydrofurans from C_{10}-C_{18} chain length alcohols were carried out in a similar manner. In each case a ratio of moles reactant alcohol : moles lead tetraacetate : moles calcium carbonate of 1.0 : 1.1 (based on purity of lead tetraacetate) : 1.1 was employed. Progress of the reaction was monitored by depletion of lead tetraacetate, determined either iodometrically or qualitatively by non-formation of dark brown lead dioxide on addition of a few drops of the reaction mixture to water. In all cases the reactions were run until complete depletion of the lead tetraacetate.

Purification of the crude cyclic ether products by column chromatography (Kieselgel 60), eluting with petroleum ether (b.p.40°-60°C) - diethyl ether solvent systems, was not particularly successful. The desired cyclic ethers were found to be very similar in polarity to the aldehyde and acetate components (confirmed by TLC) present in the product mixtures and thus these components were eluted from the column together with the cyclic ether compounds. Treatment of the crude product mixtures with lithium aluminium hydride resulted in reduction of the carbonyl compounds to the

parent alcohol, thus facilitating separation of the cyclic ethers from the corresponding alcohol by column chromatography.

Generally the cyclic ethers were present in the fractions eluted with PE10 and PE20. The tetrahydropyran derivative was eluted ahead of the tetrahydrofuran derivative. Column fractions containing both cyclic ethers and higher boiling materials were further purified by Kugelrohr distillation. For small scale purifications flash chromatography (Kieselgel G, solvent PE5) was very effective.

2.4.2 The silver oxide-bromine promoted reaction.

The silver oxide employed was freshly prepared by treating aqueous silver nitrate with dilute aqueous sodium hydroxide, the precipitate was washed with water and ethanol, dried at 45°C and kept in the dark.

A solution of bromine (0.85ml, 16.6mmol) in hexane (8.5ml) was added with stirring over a period of 2.5 hours to a suspension of tetradecanol (1.0g, 4.67mmol) and silver oxide (4.65g, 20.08mmol) in hexane (15ml). On completion of bromine addition stirring was continued for a further 2.5 hours. The mixture was then filtered, the residue was washed with hexane (30ml) and the filtrate was transferred to a separating funnel, washed with 5% sodium thiosulphate (30ml), 5% bicarbonate (30ml) and water (30ml). All the aqueous layers were re-extracted with diethyl ether and the combined organic layers were evaporated to dryness yielding a pale yellow

oil (0.94g). GLC analysis indicated the presence of 2-nonyltetrahydropyran (1.2%), 2-decyltetrahydrofuran (42.4%) together with unreacted alcohol (35.0%), aldehyde (13.6%) and other less polar components (7.8%) which were not identified.

2.4.3 The mercuric oxide - iodine promoted reaction.

Mercuric oxide (6.07g, 28.02mmol) and iodine (9.81g, 38.76mmol) were added to a solution of tetradecanol (1.00g, 4.67mmol) in dichloromethane (50ml). The mixture in a 100ml flask fitted with a reflux condenser was stirred vigorously and illuminated with 4 x 100W tungsten lamps for a period of five hours. The mixture was filtered and the residue washed with dichloromethane (20ml). The filtrate was transferred to a separating funnel, washed with 5% sodium thiosulphate (30ml) and water (30ml). The solvent was removed (RFE) yielding a colourless oil (0.98g). GLC analysis (EGSS-X, 172°C isothermal) indicated the presence of 2-nonyltetrahydropyran (9.6%), 2-decyltetrahydrofuran (78.0%), unreacted tetradecanol (3.8%) together with several less polar components (8.6%).

2.4.4 The N-iodosuccinimide promoted reaction.

A solution of tetradecanol (1.0g, 4.67mmol) and N-iodosuccinimide (2.1g, 9.34mmol) in chlorobenzene (20ml) was stirred vigorously with water cooling whilst being irradiated with a 100W tungsten lamp. The mixture was then filtered, transferred to a separating funnel, washed with aqueous thiosulphate solution (0.1N,

2 x 30ml), and water (2 x 30ml). The aqueous layers were re-extracted with diethyl ether (2 x 30ml) and the combined organic layers were evaporated to dryness yielding the crude product (0.97g). GLC analysis indicated the presence of 2-decyltetrahydrofuran (76.6%), 2-nonyltetrahydropyran (3.9%), unreacted alcohol (18.2%) and a small amount of other components (1.3%), insufficient to warrant further investigation.

2.4.5 The hypochlorite promoted reaction.

Preparation of alkyl hypochlorites.

Alkyl hypochlorites were prepared by the method of Walling and McGuiness[54]. A solution of the alcohol (0.06mol) in carbon tetrachloride (100ml) was reacted with sodium or calcium hypochlorite solution (containing 0.06mol of available chlorine*) and acetic acid (0.12 mol) at 0°C in the dark. Determination of the active chlorine content of the sodium hypochlorite solution employed was measured iodometrically as follows; excess acetic acid (10ml) was added to a mixture of sodium hypochlorite (1ml) and excess iodate free potassium iodide (2.0g). The iodine thus formed was titrated with 0.1N thiosulphate.

* The 'available chlorine' refers to the chlorine liberated by the action of dilute acids and is expressed as the percentage by volume of the sodium hypochlorite solution or the percentage by weight of the calcium hypochlorite powder.

$$OCl^- + 2I^- + 2H^+ \rightarrow Cl^- + I_2 + H_2O$$

$$2S_2O_3^{2-} + I_2 \rightarrow S_4O_6^{2-} + 2I^-$$

The sodium hypochlorite solution used was found to have an active chlorine content of 13.6% w/w (suppliers quoted 14% active chlorine). Likewise the calcium hypochlorite was found to have an active chlorine content of 34.8% compared with 35% quoted. This method was also used to monitor the formation and subsequent disappearance of the alkyl hypochlorites.

General procedure for the ferrous ion induced decomposition of primary hypochlorites.

To a solution of the alkyl hypochlorite (mol) in CCl_4 (100ml), $FeSO_4.7H_2O$ (0.06mol) and $NaHCO_3$ (2g) were added under nitrogen. The reaction mixture was stirred at room temperature, in the dark, overnight, during which time the solution changed from yellow to colourless. Precipitated salts were filtered off and the solution was transferred to a separating funnel, washed with water and dried over sodium sulphate. The solvent was removed yielding the reaction product.

(Repeat experiments employing 5 moles trichloroethene per mole of alkyl hypochlorite were also performed). In all cases the corresponding ester was found to be the major product component present in yields of 55-65%.

CHAPTER 3

REACTION OF 2-ALKYLTETRAHYDROFURANS WITH ACYL HALIDES

CHAPTER 3

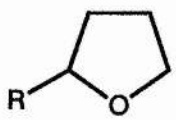
Reaction of 2-alkyltetrahydrofurans with acyl halides.

3.1 Introduction.

Reactions of tetrahydrofurans with acid halides and their derivatives are well documented in the literature. Paul[9] reported that reaction of tetrahydrofuran and tetrahydropyran with acetic anhydride in the presence of 1% zinc chloride, at 190°C, resulted in the formation of the corresponding diacetate in almost quantitative yields.

$$+ Ac_2O \xrightarrow[ZnCl_2]{} CH_3OCO(CH_2)_4OCOCH_3.$$

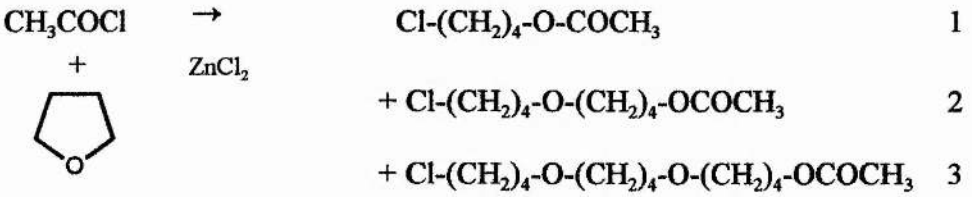
When a methyl group was substituted in the α-position of the tetrahydrofuran, the reaction was found to go at a much lower temperature but largely to the olefin acetate with the acetate at the primary carbon. In view of this observation with the simple methyl substituted tetrahydrofuran this reaction was not investigated with our longer chain substituted tetrahydrofurans. Instead efforts were initially concentrated on the reaction of tetrahydrofurans with acetyl chloride with a view to forming a series of 4-chloroalkyl acetates from the C_{10}-C_{18} α-substituted tetrahydrofurans.



$$+ AcCl \xrightarrow[\text{Lewis acid}]{} RCH(Cl)CH_2CH_2CH_2OCOCH_3.$$

$$R = C_6H_{13} - C_{14}H_{29}$$

The cleavage of tetrahydropyran has been to shown to occur in yields of up to 85% by treatment with acetyl chloride and zinc chloride[64,65]. These studies showed that zinc chloride was essential for the reaction to occur. Pilgrim and Cloke[10] reported the reaction of tetrahydrofuran with acetyl chloride in the presence of zinc chloride to produce the compounds illustrated below;



The yield of 4-chlorobutyl acetate (1), was shown to be heavily dependent on the amount of zinc chloride employed. In the absence of zinc chloride the reaction was extremely slow and resulted in very low yields of the desired product but in the presence of large quantities of zinc chloride the 4-chlorobutyl acetate product yield was also low. This was presumably due to the formation of longer chain compounds incorporating more than one tetrahydrofuran moiety. The relationship between the moles of zinc chloride per mole of starting material, and its effect on product yield as quoted by Pilgrim and Cloke is demonstrated in table 3.1.

Table 3.1. Reaction of tetrahydrofuran with acetyl chloride and zinc chloride (effect of catalyst concentration on reaction products).

CH_3COCl (moles)	THF (moles)	$ZnCl_2$ (moles)	Ratio $ZnCl_2$: THF (moles):(moles)	4-chlorobutyl acetate (% yield)	Reflux time/ hours	Remarks
3.3	1.5	0.4	1:3.75	20	12	Heavy sludge
2.7	1.3	$2.0x10^{-2}$	1:65	36	2	Light sludge
1.2	0.7	$5.0x10^{-2}$	1:14	30	0	Heavy sludge
1.2	0.7	$7.4x10^{-4}$	1:946	54	2.5	Light sludge
1.2	0.7	$7.4x10^{-5}$	1:9459	71	0.5	No sludge

The reaction between tetrahydrofuran and acid halides in the presence of a Lewis acid was reported to be more rapid than the analogous reaction with acetic anhydride[64]. This, coupled with the fact that reaction of 2-methyltetrahydrofuran with acetyl chloride and zinc chloride resulted in the formation of 4-chloropentyl acetate in almost quantitative yield, led us to believe that the analogous reaction with our C_{10}-C_{18} α-substituted cyclic ethers might prove favourable for formation of long chain 4-chloroalkyl acetates. It was also hoped that by optimisation of reaction conditions and by varying ratios of Lewis acid : reactant ether, the reaction could be controlled to produce the monomeric chloro acetate or the corresponding dimeric product as desired.

Reppe[8] reported that tetrahydrofuran can also be cleaved by a combination of acetyl chloride and zinc. In a similar vein the cleavage of tetrahydrofuran by acetyl chloride in the presence of other catalysts such as mercury II salts[12], group VI pentacarbonyls[11], and platinum complexes[13] has been reported.

In view of the high yields of 4-chlorobutyl acetate reported from treatment of tetrahydrofuran with acetyl chloride and zinc chloride, initial experiments were focused on the reaction of substituted alkyltetrahydrofurans with acetyl chloride in the presence of a Lewis acid with a view to producing the corresponding 4-chloroalkyl acetates. Replacement of the chlorine atom would provide a route for the introduction of other functional groups at position four of the alkyl chain. Preliminary reactions were carried out on tetrahydrofuran and 2-methyltetrahydrofuran, employed as a simple analogue to the longer chain 2-alkyltetrahydrofurans.

Belsner and Hoffmann[66] prepared a series of acyl iodides by reaction of acyl chlorides with sodium iodide in acetonitrile and found that reaction of ethylene oxide with this reagent, formed *in situ*, resulted in the formation of 2-iodoethyl esters. The reaction occurred rapidly at O°C. Further work in this area has demonstrated the ability of this reagent system to cleave a whole range of cyclic ethers including tetrahydrofuran, tetrahydropyran and 2-methyltetrahydrofuran, under very mild conditions[67-69]. We have applied this reaction to our longer chain 2-alkyltetrahydrofurans.

3.2 Results and discussion.

3.2.1 Reaction of tetrahydrofuran with acetyl chloride in the presence of a Lewis acid.

Initial experiments carried out on the reaction of tetrahydrofuran with acetyl chloride in the presence of a Lewis acid demonstrated the potential of this reaction for the cleavage of longer chain 2-alkyltetrahydrofurans; tetrahydrofuran was cleaved readily resulting in formation of 4-chlorobutyl acetate (86%) together with 4-(4'-chlorobutoxy)butyl acetate (10%). Attempts to increase yields of the 'dimeric' 4-(4'-chlorobutoxy)butyl acetate by halving the amount of acetyl chloride employed relative to that of tetrahydrofuran, were inconclusive; 4-chlorobutyl acetate was formed in 78% yield together with the corresponding 'dimeric ' compound in 16% yield. Clearly this was not a significant increase in 4-(4'-chlorobutoxy(butyl) acetate

formation, and as such could not be attributed solely to decreasing the acetyl chloride concentration relative to that of tetrahydrofuran. Work on the polymerisation of tetrahydrofuran[70] has shown that it is possible to produce higher molecular weight compounds, although efforts have not centred around producing compounds containing a specific number of tetrahydrofuran moieties. Due to the anticipated complexity of spectral data of the reaction products from cleavage of the substituted 2-alkyltetrahydrofurans, polymerisation reactions were not studied, however this may prove to be an interesting avenue to pursue further, leading to the formation of long chain branched polyether compounds with interesting properties.

3.2.2 Reaction of 4-halobutyl acetates with diethylamine.

Treatment of tetrahydrofuran with acetyl chloride and zinc chloride in the presence of sodium iodide resulted in the formation of 4-iodobutyl acetate in good yield (77%). 4-Chlorobutyl acetate was recovered unchanged after treatment with diethylamine (refer to section 3.3.2.1.), whereas treatment of 4-iodobutyl acetate under identical conditions resulted in the formation of 4-diethylaminobutyl acetate in almost quantitative yield, presumably because iodine is a better leaving group than chlorine and can more readily be replaced by other functional groups. Both the conversion of the chloro acetate to the iodo acetate and the subsequent conversion of the iodo acetate to the diethylamino derivative clearly demonstrate the potential to form a range of different δ-substituted alkyl derivatives from the longer chain 2-alkyltetrahydrofurans via the δ-haloalkyl acetate.

3.2.3 Reaction of 2-alkyltetrahydrofurans with acetyl chloride and a Lewis acid.

The reaction of 2-methyltetrahydrofuran with acetyl chloride in the presence of three different catalysts, namely zinc, zinc chloride and aluminium chloride, was studied. In all three cases the reactions were carried out under identical experimental conditions. Results demonstrate that both zinc and zinc chloride are very efficient catalysts for this reaction, resulting in the formation of 4-chloropentyl acetate in yields of 88% and 86% respectively, and that there was little difference in the efficiency of these two catalysts. Aluminium chloride, however, was found to be less efficient resulting in the formation of 4-chloropentyl acetate in yields of around 20%. These results are in accordance with those published by Meerwein and Maier-Huser[71] on the basis of reactions of linear or dialkyl ethers with acetyl chloride and the ability of Lewis acids to catalyse these reactions. Meerwein and Maier-Huser reported that catalytic efficiency of Lewis acids for the reaction of excess diethyl ether with benzoyl chloride adhered to the following order; $ZnCl_2 > SnCl_4 > ZnCl_4 > TiCl_4 > SbCl_3 > FeCl_3 > AlCl_3 > BF_3$. In view of this data, together with our own experimental findings with 2-methyltetrahydrofuran, zinc and zinc chloride were the chosen Lewis acids catalysts for further similar reactions with the longer chain 2-alkyltetrahydrofuran compounds.

In the study of the reactions of 2-hexyltetrahydrofuran with acetyl chloride detailed in section 3.3.3.3., the results confirm our previous finding with the reaction of 2-methyltetrahydrofuran and acetyl chloride, that zinc is as efficient, if not slightly

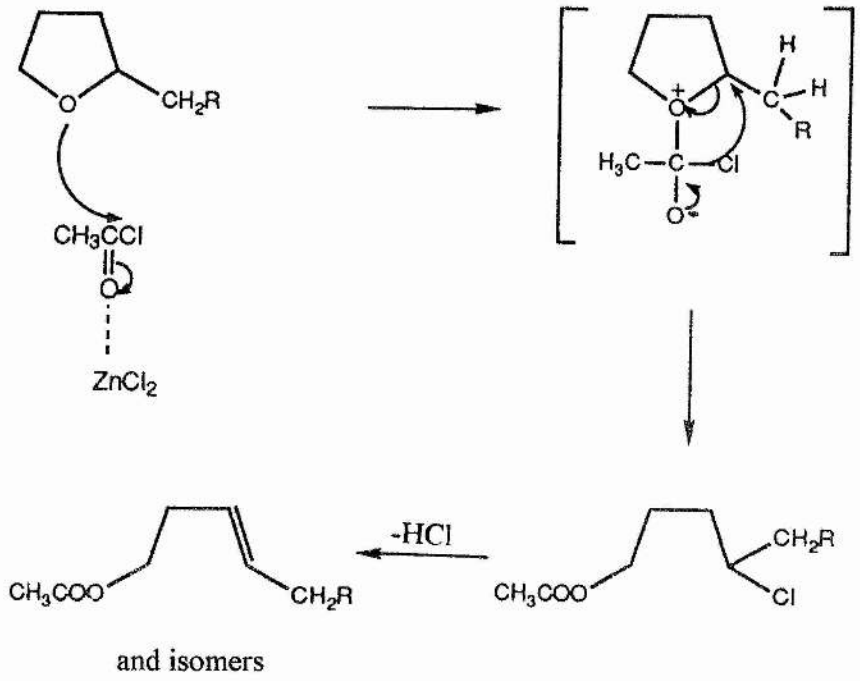
more efficient than zinc chloride as a catalyst for this reaction. With both catalysts, the yields of 4-chloroalkyl acetate were lower than those obtained from the corresponding reaction of 2-methyltetrahydrofuran, a simple analogue of the longer chain compounds. This was due to formation of unsaturated decenyl acetate formed in the reaction of 2-hexyltetrahydrofuran with acetyl chloride, unsaturated acetate was not observed in the product from reaction of 2-methyltetrahydrofuran with acetyl chloride. It was not clear at this stage whether the formation of unsaturated ester occurred directly, or whether possibly as a result of the higher reaction temperature, it was formed from 4-chlorodecyl acetate by loss of HCl as the reaction proceeded. Further reactions were carried out in the presence of extra chloride ion. This was achieved by the addition of inorganic chloride in the form of lithium, potassium or magnesium salts to the reaction mixture (refer to table 3.10 for details). The addition of extra chloride ion resulted in no increase in yield of chlorine containing compounds, in fact, in several cases reduced yields of 4-chlorodecyl acetate were observed when these salts were employed. A likely explanation for this is the concentration effect caused by the addition of further chloride ion. These reactions were carried out on a very small scale and the addition of a relatively large amount of inorganic salt may well have hindered the reaction between the organic species. This result did however rule out the possibility that the unsaturated acetate was formed during the reaction as a direct result of lack of chloride ion.

There has been some controversy over the mechanism of reaction of ethers with various reagents. Burwell[3] proposed that in all Lewis acid catalysed cleavage of ethers involving acyl halides or acid anhydrides the first stage of reaction involves

formation of an acylium ion followed by the production of an oxonium salt. The cleavage step may then proceed by a unimolecular mechanism involving a carbocation intermediate or by a bimolecular displacement reaction mechanism. In this reaction, a unimolecular reaction mechanism, involving the formation of a carbocation by rearrangement of the carbocation, would allow formation of the observed acetoxyalkenes. However, such a mechanism in which subsequent rearrangement of the carbocation along the alkyl chain would occur readily, would result not only in formation of the 4-chloroalkyl acetate but in a whole series of positional chloroalkyl acetate isomers. NMR analysis of the reaction products from the cleavage of medium chain 2-alkyltetrahydrofurans with acetyl chloride and a Lewis acid clearly showed that the major product component was the 4-chloroalkyl acetate (45-60%). A second chloro acetate isomer was present in all cases in yields of 3-5% and this was thought to be the primary chloroalkyl acetate derivative formed as a result of initial cleavage of the CH_2-O bond of the tetrahydrofuran ring. Due to the small amount of this material available it was not possible to confirm this assignment by NMR analysis. However, the reported presence of the analogous primary chloro derivative in the same cleavage reaction of 2-methyltetrahydrofuran[68] supports this assignment. A whole series of chloroalkyl acetate regioisomers would be formed if a unimolecular reaction mechanism involving a carbocation were operating, but there was no evidence of the presence of any other secondary chloroalkyl acetate regioisomers in the NMR spectra of the reaction products. The non-formation of positional chloro acetates isomers other than the 4-chloro acetate is very strong evidence for a bimolecular displacement (S_N2) reaction mechanism as depicted in scheme 3.1. The formation of the unsaturated acetoxyalkenes can be attributed to the

loss of HCl from the 4-chloroalkyl acetate. The fact that no increase in yield of chloroalkyl acetates was observed when the reaction was carried out in the presence of additional chloride ion again supports this theory.

Scheme 3.1. Reaction of 2-alkyltetrahydrofurans with acetyl chloride and zinc chloride.



and isomers

Having successfully prepared 4-chloroalkyl acetates from our medium chain alkyl tetrahydrofurans, a series of reactions were carried out employing other acyl halides to determine whether the nature of the acyl halide had any significant effect in determining the products of the reaction. Again preliminary experiments using 2-methyltetrahydrofuran were performed prior to experiments on the medium chain 2-alkyltetrahydrofurans.

3.2.4 Reaction of 2-alkyltetrahydrofurans with acetyl chloride in the presence of sodium iodide.

There have been several reports in the literature concerning both the preparation of acetyl iodide *in situ* from acetyl chloride and sodium iodide in acetonitrile solvent, and the use of this reagent to achieve cleavage of a wide range of compounds including ethers[69,74].

Treatment of 2-methyltetrahydrofuran with acetyl chloride and sodium iodide in acetonitrile solvent, at 0°C, resulted in the formation of 4-iodopentyl acetate and 1-methyl-4-iodobutyl acetate in yields of 42 and 47% respectively. This observation closely resembled that reported by Oku and co-workers[69] in which the two aforementioned iodopentyl isomers were formed in yields of 49 and 51% respectively.

We had initially thought that in the reaction of medium chain alkyl tetrahydrofurans with acetyl iodide, the large iodine atom would be sterically hindered from attacking at position two of the cyclic ether by the α-alkyl substituent and thus the reaction would favour formation of the primary iodoacetate, 4-acetoxy-1-iodo-dodecane, almost exclusively. This was not found to be the case. GLC analysis of the product from reaction of 2-octyltetrahydrofuran with acetyl iodide showed the presence of two late running components (very close running) on the chromatograph (52 and 25% respectively), together with a small amount (14% total) of the two unsaturated dodecenyl acetate regioisomers also observed in the reaction product of the analogous reaction of 2-octyltetrahydrofuran with acetyl chloride and zinc chloride. Mass spectral and NMR data detailed in section 3.3.4.2 enabled identification of the two late running components on the gas chromatograph as 4-acetoxy-1-iodo-dodecane ($CH_3(CH_2)_7CH(OCOCH_3)(CH_2)_3$-I) and 4-iododododecyl acetate $CH_3(CH)_7CHI(CH_2)_3OCOCH_3$) respectively. The absence of any other iododododecyl acetate regioisomers again indicates that the reaction occurs via a bimolecular S_N2 type mechanism as discussed earlier in the reaction of substituted ethers with acetyl chloride and zinc chloride in section 3.2.3.

Although there was evidence that attack at position four of the α-alkyl substituted tetrahydrofuran was favoured, since the primary iodide derivative was formed in excess (50%), the formation of 25% of the secondary iodide derivative clearly shows that the presence of the alkyl group at position two of the tetrahydrofuran ring did not totally hinder attack by the large iodine atom. This result was in contrast to that obtained when 2-methyltetrahydrofuran was treated with acetyl iodide under identical

reaction conditions: In this case the primary and secondary iodides were formed in almost equal amounts. This suggests that the presence of the bulky alkyl group at position two of the tetrahydrofuran may affect the reaction pathway.

The yield of haloalkyl acetate products from the reaction of 2-alkyltetrahydrofurans with acetyl iodide was found to be higher than that obtained in the reaction of 2-alkyltetrahydrofurans with acetyl chloride and a Lewis acid. This observation clearly demonstrates the power of acetyl iodide as a reagent to bring about this cleavage transformation under very mild reaction conditions (0°C).

Despite this our main objective was to achieve ring opening of the ether ring combined with introduction of a new functional group at a specific site along the carbon chain; clearly the formation of both the primary and secondary iodododecyl acetate isomers although an interesting observation, did not fulfil our goal. In view of this a further reaction was carried out using pivaloyl iodide (prepared *in situ* from pivaloyl chloride and sodium iodide), to see if the use of a more bulky acyl group would result in the formation of only one iodoalkyl acetate isomer.

3.2.5 Reaction of 2-alkyltetrahydrofurans with pivaloyl chloride and sodium iodide.

Treatment of 2-methyltetrahydrofuran with pivaloyl iodide (formed *in situ* from pivaloyl chloride (Me_3CCOCl) and sodium iodide) resulted in the formation of a single product in 86% yield (97% pure by GLC). Mass spectral data confirmed the compound to be an isomer of iodopentyl pivalate.

This initial result involving formation of a single reaction product looked very promising, thus the reaction was repeated employing one of our medium chain α-alkyltetrahydrofurans as substrate: Reaction of 2-decyltetrahydrofuran with pivaloyl chloride and sodium iodide in acetonitrile solvent at 0°C, (detailed in section 3.3.5.2.), resulted in the formation of a major new compound (83% recovered yield, 87% by GLC), together with a small amount of unsaturated material (7%). The unsaturated material was thought to be tetradecenyl pivalate. Mass spectral and NMR data (detailed in table 3.19), enabled full characterisation of the major reaction product as the primary iodide, 1-(3'-iodopropyl)undecyl pivalate ($I(CH_2)_3CH(OCOCMe_3)(CH_2)_9CH_3$). The 135° DEPT NMR spectrum unequivocally confirmed the assignment of the methine, methyl and quaternary carbons. The presence of a further reaction product component (3%) was also observed on the gas chromatograph. By virtue of the similarity of its GLC retention time to that of the main reaction product 1-(3'iodopropyl)undecyl pivalate, this was assumed to be a regioisomer of the major product, and in view of our observations in previous reactions, was tentatively assigned as the secondary iodide, 4-iodotetradecyl pivalate.

Unfortunately the small amount of this material available prevented confirmation of this assignment from spectral data.

The formation of the primary iodide almost exclusively, was a rather surprising result since it involves cleavage of the C-O bond of the tetrahydrofuran ring at the least substituted site, namely position four. This is in complete contrast to the cleavage of 2-alkyltetrahydrofurans with acetyl chloride and a Lewis acid catalyst, where cleavage at the most substituted site, ie. position two of the tetrahydrofuran ring, resulting in formation of the corresponding 4-chloroalkyl acetate, is favoured. Again this observation with pivaloyl iodide supports a bimolecular reaction mechanism. It appears that attack by the bulky pivalate group is not sterically hindered by the α-alkyl group present at position two of the tetrahydrofuran ring at all.

The above results from the cleavage of 2-alkyltetrahydrofurans with both acetyl iodide and pivaloyl iodide illustrate well the ability of acyl iodides to cleave ethers under very favourable conditions. The effect of the acyl group on product formation is also demonstrated; when acetyl iodide was employed the two possible iodo acetate isomers, 4-acetoxy-1-iodo-dodecane and 4-iodododecyl acetate were produced in a ratio of 2:1. In marked contrast, when 2-decyltetrahydrofuran was treated with pivaloyl iodide the reaction demonstrated a high degree of regioselectivity, resulting in production of the primary iodopivalate almost exclusively.

To summarise, the reaction of 2-alkyltetrahydrofurans with i) acetyl chloride and a Lewis acid, and ii) pivaloyl iodide have resulted in cleavage of the ether ring accompanied by introduction of a new substituent at a specific carbon site along the alkyl chain. In the case of treatment of the substituted cyclic ethers with acetyl chloride and a Lewis acid, attack at position two of the tetrahydrofuran ring is favoured resulting almost exclusively in formation of the secondary, 4-chloroalkyl acetate in yields of 55-65%. Treatment of the 2-alkyltetrahydrofurans with pivaloyl iodide resulted in a very interesting transformation; attack at position four of the tetrahydrofuran ring was favoured resulting in formation of the primary iodoalkyl pivalate in yields of the order of 80%. Thus with these two reactions it is possible to introduce a halogen atom at either position one or position four of the alkyl chain. The halides can be readily replaced by other nucleophiles as outlined in section 3.3.2. and, this accompanied by hydrolysis of the ester back to the parent alcohol, would provide a route to other substituted primary alcohols. In this manner this combination of reactions provides an avenue to convert a primary alcohol via a substituted tetrahydrofuran, to a substituted fatty alcohol (derivative) with the substituent at one specific site along the alkyl carbon chain.

There is scope for further work in this area. It would be very interesting to carry out a systematic study with a range of acyl iodides to determine the effect of different acyl groups on the cleavage reaction and gain more information as to when cleavage of the carbon 2 - oxygen bond is favoured over cleavage of the carbon 4 - oxygen bond of the tetrahydrofuran ring. Other iodide reagents such as aluminium iodide[73] have also been employed in cleavage reactions of a wide range of compounds

including some ethers, clearly such iodide reagents are very versatile and may well prove to be of potential use and interest in the cleavage of 2-alkyltetrahydrofurans.

3.3 Experimental.

3.3.1 Reaction of tetrahydrofuran with acetyl chloride in the presence of a Lewis acid.

3.3.1.1 Reaction of tetrahydrofuran with acetyl chloride in the presence of zinc chloride.

Acetyl chloride (6.5g, 83mmol) was added to a mixture of tetrahydrofuran (5.0g, 69mmol) and zinc chloride (10mg, 0.073mmol). The mixture was refluxed at 55°C for one hour. On cooling, the solution was poured into water (150ml) to destroy any excess acetyl chloride. The product was extracted with diethyl ether (2 x 50ml), washed with sodium bicarbonate (50ml) and water (2 x 50ml) and dried to constant weight, yielding a colourless liquid (8.95g, 86% assuming complete conversion to chlorobutyl acetate).

GLC analysis of the product (SP 2340, 100°-0-4°-205°) indicated the presence of two significant components eluted after 322s (86% by GLC, 74% molar yield, based on amount of tetrahydrofuran employed) and 722s (10% by GLC, 5.8% molar yield). The major component was identified as 4-chlorobutyl acetate (51mmol) and the minor component as 4-(4'chlorobutoxy)butyl acetate (4mmol) on the basis of

spectroscopic evidence (detailed in tables 3.2 and 3.3 respectively).

Table 3.2 Spectroscopic data for the major product from reaction of tetrahydrofuran with acetyl chloride and zinc chloride.

Major product: 4-chlorobutyl acetate

$$\underset{4}{Cl}\text{-}\underset{3}{CH_2}\text{-}\underset{2}{CH_2}\text{-}\underset{1}{CH_2}\text{-}OCOCH_3$$

Infra-red : Absorption band at 1740cm^{-1} (carbonyl group)

^{1}H NMR :	Peaks at	δ 1.8 m	4H	$ClCH_2\underline{CH_2}\underline{CH_2}$
		δ 2.05 s	3H	$-OCOCH_3$
		δ 3.6 t	2H	CH_2-Cl
		δ 4.1 t	2H	$C\underline{H_2}$-$OCOCH_3$

^{13}C NMR :	Peaks at 170.8 ppm		$\underline{C}OCH_3$
	63.6 ppm		C-1
	44.5 ppm		C-4
	29.3 ppm		C-3
	26.2 ppm		C-2
	20.8 ppm		$CO\underline{C}H_3$

GC-MS : Peaks at the following m/e values, (intensity relative to the base peak) 152 (not observed, M^+ ^{37}Cl), 150 (tr, M^+ ^{35}Cl), 115 (3, M^+-Cl), 109 and 107 (2 and 6, M^+-CH_3CO), 92 and 90 (3 and 8, M^+-CH_3COOH) and 43 (100, $COCH_3$).

Table 3.3 Spectroscopic data for the minor product from the reaction of tetrahydrofuran with acetyl chloride and zinc chloride.

4-(4'-chlorobutoxy)butyl acetate:

$Cl\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}O\text{-}COCH_3$
4' 3' 2' 1' 4 3 2 1

Infra-red : Absorption band at 1740cm^{-1} (carbonyl group)

GC-MS : Peaks at the following m/e values (intensity relative to the base peak), molecular ions at 224 and 222, not observed, 187 (tr, M^+-Cl), 179 (tr, M^+-CH_3CO), 162 (tr, M-CH_3COOH), 115, (12, $^+(CH_2)_4OCOCH_3$), 93 and 91 (20 and 58, $^+(CH_2)_4Cl$) and 43 (100, $COCH_3$). The peaks for M^+-CH_3CO and M^+-CH_3COOH with ^{37}Cl were not observed.

The experiment was repeated halving the amount of acetyl chloride employed. (All other experimental conditions were unchanged). On work-up a colourless liquid was obtained (4.25g, 81% assuming complete conversion to the monomeric chloroacetate product). GLC analysis (SP2340, 100°-0-4°-205°) indicated the presence of 78% (32% based on moles tetrahydrofuran employed) of the monomeric product, 4-chlorobutyl acetate, and 16% (9% based on moles tetrahydrofuran employed) of the dimeric product, 4-(4'-chlorobutoxy)butyl acetate. Unreacted tetrahydrofuran was lost during work-up. Two further experiments carried out as described in section

3.3.3.1., employing tetrahydrofuran (5.0g, 69mmol), acetyl chloride (6.5g, 83mmol) and zinc chloride (10mg, 0.073mmol) in the presence of lithium chloride, i) 1.49g, 35 mmol and ii) 2.92g, 70mmol, resulted in the formation of i) 4-chlorobutyl acetate (75%) and 4-(4'-chlorobutoxy)butyl acetate (3%), and ii), 4-chlorobutyl acetate (87%) and 4-(4'-chlorobutoxy)butyl acetate (2%).

3.3.1.2 Reaction of tetrahydrofuran with acetyl chloride and zinc chloride in the presence of sodium iodide.

A mixture of tetrahydrofuran (5.0g, 69mmol), acetyl chloride (6.5g, 83mmol), zinc chloride (10mg, 0.073mmol) and sodium iodide (10.3g, 69mmol) was refluxed for four hours. GLC analysis (SP 2340, 100°-0-4°-205°) of the product (15.4g, 91% assuming 100% conversion to 4-iodobutyl acetate) indicated the presence of a major component, (77%), eluted after 690s together with 4-chlorobutyl acetate (6%), and 4-(4'-chlorobutoxy)butyl acetate. Spectroscopic data, detailed in table 3.4 confirmed the new product to be 4-iodobutyl acetate.

Table 3.4 NMR shift assignments for 4-iodobutyl acetate.

$I\text{-}\underset{4}{CH_2}\underset{3}{CH_2}\underset{2}{CH_2}\underset{1}{CH_2}\text{-}OCOCH_3$

^1H NMR

δ			
1.75	m	2H	$C\underline{H_2}CH_2$-I
1.9	m	2H	$C\underline{H_2}CH_2$-O
2.05	s	3H	-$OCOCH_3$
3.25	t	2H	CH_2-I
4.1	t	2H	$C\underline{H_2}$-$OCOCH_3$

^{13}C NMR shift assignments

ppm	Intensity	Assignment
170.90	2.54	$\underline{C}$=O
63.17	20.14	C-1
29.95	20.84	C-3
29.50	24.04	C-2
20.91	9.06	$CO\underline{C}H_3$
5.91	10.76	CH_2-I

3.3.2 Reactions of 4-halobutyl acetates with diethylamine.

3.3.2.1 Reaction of 4-chlorobutyl acetate with diethylamine.

4-Chlorobutyl acetate (2.5g, 16.6mmol) was refluxed (55°C) with diethylamine (8.6ml, 83mmol). At hourly intervals samples were removed from the mixture and analysed by GLC. After six hours the starting material was still unchanged.

3.3.2.2 Reaction of 4-iodobutyl acetate with diethylamine.

A mixture of 4-iodobutyl acetate (1.00g, 4.13mmol), diethylamine (2.00ml) and potassium carbonate (1.38g, 10.00mmol) in acetonitrile (12ml) was heated to 55°C for four hours. The reaction mixture was then poured into water (30ml) and extracted with diethyl ether (2x30ml). The combined organic phases were dried over potassium carbonate and concentrated. Yield 0.68g (91% assuming 100% conversion to 4-diethylaminobutyl acetate). The product was 96% pure by GLC. NMR shift assignments are shown in table 3.5. The mass spectral data for 4-diethylaminobutyl acetate is detailed below;

$(CH_3CH_2)_2$-N-CH_2-CH_2-CH_2-CH_2-$OCOCH_3$

Peaks were present at the following m/e values (intensity relative to base peak); 187 (5.6, M^+), 172 (9.1, M^+-CH_3), 144 (11.9, M^+-$COCH_3$), 128 (3.1, M^+-CH_3COO), 115 (1.9, M^+-$N(Et)_2$), 87 (9.4, M^+-(CH_3 + $N(Et)_2$)), 86 (100, $H_2C{=}N^+Et_2$), 73 (3.4, $CH_3COOCH_2^+$), 72 (2.8, $(CH_2)_4O^+$), 58 (5.6, $(CH_2)_3O^+$), 55 (4.7, $C_4H_7^+$) and 43 (3.1, CH_3CO^+).

Table 3.5 **^{13}C NMR and ^{1}H NMR shift assignments for 4-diethylaminobutyl acetate.**

$(CH_3CH_2)_2$-N-CH_2-CH_2-CH_2-CH_2-$OCOCH_3$
b a 1 2 3 4

^{13}C NMR shift assignments.

ppm	Intensity	Assignment
171.12	1.1	C=O
64.46	5.3	C1
52.51	4.9	C4
46.88	10.1	2 x C a
26.76	5.3	C2
23.63	5.1	C3
20.97	2.9	$\underline{C}H_3COO$
11.72	8.6	2 x C b

^{1}H NMR assignments.

δ			
1.05	t	6H	2 x $C\underline{H}_3$
1.5	m	2H	$(C\underline{H}_2)_2$
1.65	m	2H	
2.05	s	3H	$COC\underline{H}_3$
2.4	t	6H	N-$C\underline{H}_2(CH_2)_3OCOCH_3$
2.5	q		N-$(C\underline{H}_2CH_3)_2$
4.1	t	2H	$C\underline{H}_2OAc$

3.3.3 Reactions of 2-alkyltetrahydrofurans with acetyl chloride and a Lewis acid.

3.3.3.1 Reaction of 2-methyltetrahydrofuran with acetyl chloride and zinc chloride.

The reaction was carried out exactly as described in section 3.3.1.1, using the same molar quantities of starting material. On work-up, a pale amber liquid was obtained (10.22g, 90% of theoretical yield assuming complete conversion to the monomeric chloro acetate derivative).

GLC analysis (SP 2340, 100°-0-4°-205°), detailed in table 3.6, indicated the presence of a major new compound (86%).

Table 3.6 GLC analysis of the product from reaction of 2-methyltetrahydrofuran with acetyl chloride and zinc chloride.

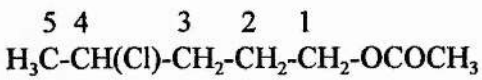
retention time (s)	4	66	275	314	439	others
area %	3	6	2	86	2	1

The component eluted after 4s on the gas chromatogram was identified as unreacted cyclic ether by comparison of its retention time with that of the starting material. The

major component, eluted after 314s was identified as 4-chloropentyl acetate on the basis of spectroscopic evidence detailed in table 3.7.

Table 3.7 Spectroscopic analysis of 4-chloropentyl acetate.

4-Chloropentyl acetate:



^{1}H NMR	:	δ 1.5 d	3H	CH_3 (5)
		δ 1.8 m	4H	$C\underline{H_2}C\underline{H_2}$ (2 and 3)
		δ 2.0 s	3H	$OCOCH_3$
		δ 4.05 m	3H	CH_2 (1) and CH (4)

^{13}C NMR : The spectrum contained seven peaks assigned as follows;

170.3 ppm	C=O
63.8 ppm	C-1
58.1 ppm	C-4
36.9 ppm	C-3
26.1 ppm	C-2
25.4 ppm	C-5
20.8 ppm	$CO\underline{C}H_3$

GC-MS (15eV) : Peaks at the following m/e values (intensity relative to base peak), molecular ions at 166 and 164 not observed, 129 (1, M^+-Cl), 123 and 121 (1 and 5, M^+-$COCH_3$), 106 and 104 (2 and 9, M^+-CH_3COOH), 86 (15, M^+-(Cl + $COCH_3$)) and 43 (100, $COCH_3^+$).

This reaction was repeated exactly as described in section 3.3.3.1., employing i) zinc and ii) aluminium chloride as the catalyst in place of zinc chloride. Molar quantities of materials and reaction conditions were identical to those previously described. When zinc was employed as catalyst, 4-chlorobutyl acetate was formed in 88% yield. In the case of aluminium chloride the recovered product yield was low (21% assuming 100% conversion of 2-methyltetrahydrofuran to 4-chloropentyl acetate). Unreacted 2-methyltetrahydrofuran was lost during work-up.

3.3.3.2 Reaction of 2-dodecyltetrahydrofuran with acetyl chloride and zinc chloride.

a) A mixture of 2-dodecyltetrahydrofuran (3.0g, 1.25 x 10^{-2}mol, 85% pure by GLC), acetyl chloride (1.3g, 1.63 x 10^{-2}mol) and zinc chloride (3mg, 2.25 x 10^{-5}mol) was refluxed (80°C for two hours). On cooling the mixture was poured into water (20ml) to destroy excess acetyl chloride and transferred to a separating funnel. The product was extracted with diethyl ether (2 x 30ml), washed with aqueous sodium bicarbonate (30ml) and water (30ml), and the solvent was then removed yielding a pale brown liquid (2.89g, 72% assuming 100% conversion to monomeric chloroacetate).

GLC analysis (SP 2340, 150°-5-8°-220°-10) of the product indicated the presence of two major components eluted after 488s (33.4%) and 780s (51.5%) together with unreacted 2-undecyltetrahydropyran (285s, 3.1%).

A solution of the reaction product (0.5g) in petroleum ether (4ml) was applied to a silica gel column (13.0 x 0.5cm, mesh 60) and eluted with petroleum ether\diethyl ether as follows;

Fraction	Solvent	wt(g)	% by GLC	
			Component A	Component B
1	petroleum ether	-		
2	PE1	trace		
3	PE2	0.32	50.2	34.9
4	PE5	0.11	8.8	83.3
5	PE10	trace		
6	PE20	trace		

Component B of the product mixture was identified as 4-chlorohexadecyl acetate on the basis of the NMR data detailed in table 3.8. GC-MS data and NMR analysis of fraction 3 above enabled identification of component A as hexadecenyl acetate. However, due to the lack of a pure sample of this component, it was not possible to fully characterise the compound by NMR spectroscopy and hence determine the position of the double bond.

Table 3.8 NMR assignments for component A (4-chlorohexadecyl acetate).

^{13}C NMR shift assignments.

The following signals were present in the ^{13}C NMR spectrum. Calculated NMR shifts are shown in parentheses. (The calculated chemical shift values are calculated by the method of Fleming and Williams[74] in which the chemical shift,

$\delta_c = -2.3 + \sum z + \sum S + \sum K$

where z is the substituent constant,
S is a 'steric' correction and
K is a conformational increment for γ-substituents).

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 α β
$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH(Cl)CH_2CH_2CH_2OCOCH_3$

ppm	Calculated shift	Intensity	Assignment	135° DEPT assignment
170.86		0.63	C=O, α	quaternary
63.88	(63.0)	3.54	CH_2O, C-1	CH_2
63.32	(61.0)	2.85	CHCl, C-4	CH/CH_3
38.63	(40.3)	3.84	C-5	CH_2
34.98	(36.6)	3.96	C-3	CH_2
31.98	(32.5)	4.13	C-14	CH_2
29.70	(30.3)	10.35		
29.63	(30.3)	5.13		
29.56	(30.3)	4.89	C 7-13	CH_2
29.41	(30.0)	4.80	inclusive	
29.21	(29.8)	4.21		
26.54	(25.3)	3.99	C-6 and	CH_2
25.84	(25.2)	4.10	C-2	CH_2
22.73	(23.1)	4.24	C-15	CH_2
20.88	(20.6)	2.19	$\underline{C}H_3$ β	CH/CH_3
14.13	(14.0)	3.62	C-16	CH/CH_3

^{1}H NMR shift assignments

δ		
4.1	2H	CH_2-O
3.9	1H	CH-Cl
2.05	3H	$OCOCH_3$
1.7 }	6H	C-2, C-3 and C-5 methylene protons, -$(CH_2)_n$
1.3 }		
0.9	3H	terminal CH_3

The mass spectrum of the C_{16} chloroacetate contained peaks at the following m/e values (intensity relative to base peak); molecular ions at 320 and 318 absent, 261 and 259, (tr and 1.5, M^+-CH_3COO), 260 and 258 (1.5 and 5, M^+-CH_3COOH), 232 and 230, (tr and 2.5, $C_{14}H_{27}Cl^+$), 222 (5, $C_{16}H_{30}^+$), 194 (3, $C_{14}H_{26}^+$), 112 (4, $C_8H_{16}^+$), 111 (7, $C_8H_{15}^+$), 110 (7.5, $C_8H_{14}^+$), 98 (4, $C_7H_{14}^+$) and the usual series of C_nH_{2n+1}, C_nH_{2n} and C_nH_{2n-1} alkyl fragments, base peak 42 (100, $C_3H_6^+$).

The mass spectrum of hexadecenyl acetate contained peaks at the following m/e values (intensity relative to base peak); molecular ion at 282 absent, 222 (15, $C_{16}H_{30}^+$), 195 (1, $C_{14}H_{27}^+$), 194 (1.5, $C_{14}H_{26}^+$), 193 (tr, $C_{14}H_{25}^+$), 180 (4, $C_{13}H_{24}^+$), 166 (2.5, $C_{12}H_{22}^+$), 152 (2, $C_{11}H_{20}^+$), 138 (3, $C_{10}H_{18}^+$), 137 (4, $C_{10}H_{17}^+$), 124 (5, $C_9H_{16}^+$), 123 (6, $C_9H_{15}^+$), 111 (7, $C_8H_{15}^+$), 110 (10, $C_8H_{14}^+$), 109 (5, $C_8H_{13}^+$), 97 (7, $C_7H_{13}^+$), 96 (25, $C_7H_{12}^+$), 95 ($C_7H_{11}^+$), 84 ($C_6H_{12}^+$), 83 (26, $C_6H_{11}^+$), 82 (37, $C_6H_{10}^+$), 81 (34, $C_6H_9^+$), 71 (5, $C_5H_{11}^+$), 70 (8, $C_5H_{10}^+$), 69 (47,$C_5H_9^+$), 68 (75, $C_5H_8^+$), 67 (40, $C_5H_7^+$), 57 (11, $C_4H_9^+$), 56 (18, $C_4H_8^+$), 55 (36, $C_4H_7^+$), 54 (30, $C_4H_6^+$), 43 (53, $C_3H_7^+$, CH_3CO^+), 42 (100, $C_3H_6^+$).

NMR analysis of fraction 3 from the chromatographic separation showed the presence of three series of signals in the NMR spectrum, of the following relative intensities; i) 0.5, ii) 1.2 (corresponding to component A on the gas chromatogram) and iii) 1.7 (corresponding to 4-chlorohexadecyl acetate). Due to the similarity of the two product component types; hexadecenyl acetate and 4-chlorohexadecyl acetate, many of the signals peaks overlap, or are common to both components, making the spectrum somewhat complex. However the presence of four olefinic signals at 128 and 130 ppm together with a series of methylene signals and a carbonyl signal are in line with our assignment of component A as isomers of hexadecenyl acetate, possibly *cis* and *trans*. However it was not possible to determine the position of the carbon carbon double bond.

The ^{1}H NMR spectrum of fraction 3 was less complex, the shift assignments for both component A (50.2%) and component B (34.9%) are detailed in table 3.9.

Table 3.9 ^{1}H NMR Shift Assignments for Component A (Hexadecenyl Acetate) and Component B (4-Chlorohexadecyl acetate).

		Component	
δ	height/mm	A	B
0.9	20	3H terminal CH_3	3H terminal CH_3
1.3	145	bulk $-(CH_2)_n$	bulk $-(CH_2)_n$
1.6-1.9	27	4H, $C\underline{H_2}CH{=}CHC\underline{H_2}$	4H, C2 and C5 protons
2.05	25	3H, $OCOCH_3$	3H, $OCOCH_3$
3.9	3		1H, CH-Cl
4.1	13	2H, CH_2-O	2H, CH_2-O

The proton NMR confirms the presence of unsaturated acetate and chloro acetate and the integration values are in good agreement with the GLC analysis of the fraction, (50% component A: 35% component B).

This reaction was repeated on 2-hexyl-, 2-octyl- and 2-decyl-tetrahydrofuran exactly as outlined in section 3.3.3.2. In each case the 4-chloroalkyl acetate was found to be the major product present in yields of 50-65%. GLC analysis of all four reaction products showed the presence of a second peak with a very similar retention time to that of the major 4-chloroacetate. This was identified as another chloro acetate isomer from mass spectral data, presumably the 1-chloro acetate, formed as a result of initial cleavage of the CH_2-O of the tetrahydrofuran ring. Due to the small amount of this component present in the product mixtures (approximately 3-5% in all cases), complete characterisation by NMR spectroscopy was not possible. Also present in the product mixtures was unsaturated acetate, identified from mass spectral data. Peaks in the region of 131ppm in the ^{13}C NMR spectra confirmed the presence of olefinic carbon atoms.

A further study of this reaction was carried out on 2-hexyltetrahydrofuran with acetyl chloride under various catalytic conditions as detailed in 3.10. All other experimental conditions were identical to those described in section 3.3.3.2. ^{13}C NMR shift assignments for 4-chlorodecyl acetate and 4-chlorohexadecyl acetate are summarised in table 3.11.

Table 3.10 Reaction of 2-hexyltetrahydrofuran with acetyl chloride and catalyst.

	(a)	(b)	(c)	(d)	(e)	(f)
2-hexylTHF (mmol)	0.32	0.32	5.77	0.32	0.32	0.32
AcCl (mmol)	3.2	3.2	13.0	3.2	3.2	3.2
Zn foil	tr	tr	-	tr	tr	tr
$ZnCl_2$	-	-	tr	-	-	--
LiCl (mmol)				1.6		
KCl (mmol)					1.6	
$MgCl_2$ (mmol)						1.6
%yield	80.0	89.5	85.9	78.9	93.5	56.8
			% by GLC			
2-hexylTHF					4.2	
2-pentylTHP			0.6		2.1	
decenyl acetate	21.5	27.8	35.2	29.5	30.1	29.6
4-chlorodecyl acetate	70.3	62.8	57.0	58.9	52.2	60.6
chlorodeceyl acetate isomer	5.8	6.0	0.9	5.3	1.2	1.4
others	2.4	3.4	6.3	6.3	10.2	8.4
Total	100.0	100.0	100.0	100.0	100.0	100.0

Table 3.11 **^{13}C NMR shift assignments for C_{10} and C_{16} 4-chloro acetates.**

10 9 8 7 6 5 4 3 2 1 α β
$RCH_2CH_2CH_2CH_2CH_2CH_2CH(Cl)CH_2CH_2CH_2OCOCH_3$

	Chemical shift (ppm)	
Carbon	C_{10} chloro acetate (R = H)	C_{16} chloro acetate (R = C_4H_9)
$OCO\underline{C}H_3$	20.97	20.88
$\underline{C}$=O	171.18	170.86
C1	63.97	63.88
C2	[1] *26.45	26.45
C3	34.93	34.98
C4	63.48	63.32
C5	38.58	38.63
C6	* 25.79	25.84
C7	28.81	[2] * 29.70
C8	31.70	* 29.64
C9	22.59	* 29.56
C10	14.06	* 29.41
C11		* 29.21
C12		* 29.21
C13		* 29.21
C14		31.98
C15		22.74
C16		14.13

---

[1] *Due to the similarity in chemical environment it was not possible to positively distinguish these two carbon atoms.

[2] *These signals correspond to the methylene signals of the alkyl chain. Due to the similarity in chemical environment of the methylene carbons they cannot be specifically assigned to a particular carbon atom.

3.3.4 Reaction of 2-alkyltetrahydrofurans with acetyl chloride in the presence of sodium iodide.

3.3.4.1 Reaction of 2-methyltetrahydrofuran with acetyl chloride in the presence of sodium iodide.

Acetyl chloride (3.93g, 0.05mol) was added slowly with stirring to a mixture of 2-methyltetrahydrofuran (4.30g, 0.05mol) and sodium iodide (11.25g, 0.075mol) in acetonitrile (100ml) at 0°C. The mixture was stirred at room temperature overnight and the reaction was then quenched by addition of sodium bisulphite. The product was extracted with diethyl ether (2 x 100ml) and washed with water (2 x 50ml). The ethereal layers were dried over sodium sulphate prior to removal of the solvent (RFE), yielding a dark oil, 9.67g (75%). Unreacted 2-methyltetrahydrofuran was lost in the work-up procedure.

GLC analysis (50°-5-10°-300°) indicated the presence of two major peaks eluted at 12.02min (47.3%) and 12.34min (41.2%), identified as iodopentyl acetate regioisomers from mass spectral data, together with a later running minor component (4.9%) identified as 1,4-diiodopentane from its mass spectrum. The mass spectral data are listed in tables 3.12 and 3.13. NMR shift assignments for the two iodopentyl acetate isomers, namely 1-methyl-4-iodobutyl acetate and 4-iodopentyl acetate, are detailed in table 3.14.

Table 3.12 GC-MS data for iodopentyl acetates.

Component 1		Component 2	
1-methyl-4-iodopentyl acetate		4-iodopentyl acetate	
$I\text{-}CH_2CH_2CH_2CH(CH_3)OCOCH_3$		$CH_3CH_2CH_2CH_2CHIOCOCH_3$	
m/e	Assignment	Intensity component 1	Intensity component 2
256	M^+	7	
196	$M^+\text{-}CH_3COOH$	7	
168	$IC_3H_5^+$	2	
155	$IC_2H_4^+$	9	2
154	$IC_2H_3^+$	10	
141	ICH2+	tr	
129	$M^+\text{-}I$	53	23
128	HI^+		5
127	I^+	5	6
87	$CH_3COOC_2H_4^+$	16	9
70	$C_5H_{10}^+$	24	
69	$C_5H_9^+$	98	100
43	$C_3H_7^+$, CH_3CO^+	100	51
41	$C_3H_5^+$	37	27

Table 3.13 GC-MS data for 1,4-diiodopentane.

Molecular ion at m/e 324 absent.

m/e	Intensity	Assignment
197	100	$M^+\text{-}I$
169	3	$M^+\text{-}CH_3CHI$
155	39	$M^+\text{-}(CH_2)_3I$
127	7	I^+
69	23	$C_5H_9^+$
42	3	$C_3H_6^+$
41	14	$C_3H_5^+$

Table 3.14 ^{13}C NMR and ^{1}H NMR shift assignments for iodopentyl acetates.

^{13}C NMR shift assignments

Primary iodoacetate (A)

$I\text{-}\underset{4}{CH_2}\underset{3}{CH_2}\underset{2}{CH_2}\underset{1}{CH}(\underset{1'}{CH_3})OCOCH_3$

Secondary iodoacetate (B)

$\underset{5}{CH_3}\underset{4}{CH}(I)\underset{3}{CH_2}\underset{2}{CH_2}\underset{1}{CH_2}\text{-}OCOCH_3$

ppm	Intensity	Assignment	135° DEPT
171.00	1.69	C=O	quaternary
170.60	2.13	C=O	quaternary
69.75	7.75	$\underline{C}HOCOCH_3$	CH/CH_3
63.42	8.26	$\underline{C}H_2OCOCH_3$	CH_2
39.16	8.50	C2 (B)	CH_2
36.65	10.05	C3 (A)	CH_2
29.32	9.24	C2 (A)	CH_2
29.05	6.19	C3 (B)	CH_2
28.93	12.03	2 x $CO\underline{C}H_3$	CH/CH_3
21.30	5.55	CH-I (B)	CH/CH_3
20.95	4.76	$\underline{C}H_3$-CHI (B)	CH/CH_3
19.97	8.98	$CH(\underline{C}H_3)$-$OCOCH_3$ (A)	CH/CH_3
6.20	8.40	CH_2-I (A)	CH/CH_3

^{1}H NMR shift assignments

δ		Intensity	Assignment
1.15	d	3H	CH_3
1.6	m		protons on carbons 2 and 3
1.8	m		
1.9	d	3H	CH_3
2.0	2s	6H	2 x $OCOCH_3$
3.05	t	2H	CH_2-I (A)
4.05	t	2H	CH_2-O (B)
4.15	m	1H	CH-I (B)
4.9	m	1H	CH-O (A)

3.3.4.2 Reaction of 2-octyltetrahydrofuran with acetyl chloride and sodium iodide.

Acetyl chloride (0.21g, 2.7mmol) was added slowly with stirring, to a mixture of 2-octyltetrahydrofuran (0.5g, 2.7mmol) and sodium iodide (0.60g 4.0mmol) in acetonitrile (20ml) at 0°C. The mixture was stirred at room temperature overnight prior to work-up as described in section 3.3.4.1., yielding a dark oil, 0.79g (82.6% assuming 100% conversion to iodododecyl acetate). GLC analysis indicated the presence of four major components (A-D) in the reaction product mixture. GLC, GC-MS and NMR analyses enabled identification of these products as detailed in tables 3.15 - 3.19 inclusive. Characterisation of components A and B by NMR spectroscopy was prohibited by the small amounts of the compounds available. However, from their similar GLC retention times, infra-red and mass spectra (recorded at 15eV and detailed in table 3.16) they were identified as regioisomers of dodecenyl acetate, although it was not possible to determine the position of the

double bond from the available spectral data.

Infra-red analysis of reaction components A-D inclusive showed the presence of a strong carbonyl stretch at 1740cm^{-1}.

Table 3.15 GLC Analysis of the reaction product from 2-octyltetrahydrofuran after treatment with acetyl chloride and sodium iodide.

Component	% by GLC	[1]mol% yield
2-OctylTHF	2.4	
2-HeptylTHP	4.6	
A } Dodecenyl	8.0	10.3
B } acetates	5.8	7.5
C } Iodododecyl	52.4	43.3
D } acetates	25.2	20.8
Others	1.6	
	100.0	

[1] mol% yields are calculated from the GLC % of the total reaction product.

Table 3.16 Mass spectral fragmentation data (15eV) for components A and B (dodecenyl acetates).

m/e	Assignment	Intensity	
		A	B
226	M^+	absent	absent
139	$C_{10}H_{19}^+$	absent	1
138	$C_{10}H_{18}^+$	2	1.5
124	$C_9H_{16}^+$	2	2
110	$C_8H_{14}^+$	16	6
96	$C_7H_{12}^+$	37	37
82	$C_6H_{10}^+$	55	56
68	$C_5H_8^+$	100	100
54	$C_4H_6^+$	12.5	23
43	CH_3CO^+, $C_3H_7^+$	5	3.5

The mass spectra of components C and D, the two regioisomers of iododododecyl acetate, contained fragment ions as detailed in table 3.17.

Table 3.17 Mass spectral fragmentation data for components C and D (iodododecyl acetates).

m/e	Assignment	Intensity A	Intensity B
354	M^+	absent	absent
227	M^+-I	2.4	3
196	M^+-(I + CH_3O)	2	
185	M^+-(I + $COCH_2$)	2.5	1
167	M^+-(I + CH_3COOH)	5.5	8
154	$C_{11}H_{22}^+$	1.9	
140	$C_{10}H_{20}^+$	0.3	
125	$C_9H_{17}^+$	0.6	8
111	$C_{84}H_{15}^+$	14	49
97	$C_7H_{13}^+$	34	73
83	$C_6H_{11}^+$	31	64
69	$C_{50}H_9^+$	40	81
55	$C_4H_7^+$	31	84
43	CH_3CO^+, $C_3H_7^+$	100	100

The ^{13}C NMR spectrum of the component C/D mixture contained two series of signals as expected. From the relative intensities of these signals the primary iodide was found to be in excess. Hence, referring back to the relative percentages by GLC, component C was identified as the primary iodide and component D as the secondary iodide. The characteristic ^{13}C NMR signals and ^1H NMR assignments are detailed in table 3.18. (Due to the structural similarity of the two components it was not possible to accurately assign each individual methylene signal of the two regioisomers).

Table 3.18 Characteristic NMR shift assignments for components C and D of the reaction product from 2-octyltetrahydrofuran after treatment with acetyl chloride and sodium iodide.

Component C	Component D
$CH_3(CH_2)_7CH(OCOCH_3)(CH_2)_2I$	$CH_3(CH_2)_7CHI(CH_2)_3OCOCH_3$

^{13}C NMR

ppm	Intensity	Assignment	Component
6.31	4.0	CH_2-I	(C)
21.21	3.1	CH-I	(D)
63.56	2.4	$\underline{C}H_2$-$OCOCH_3$	(D)
73.10	4.7	$\underline{C}H$-$OCOCH_3$	(C)
170.85	0.7	C=O	(D)
171.10	1.1	C=O	(C)

^{1}H NMR

δ		Assignment	Component	
0.9	t	2 x CH_3	C and D	
1.25	s	2 x $(CH_2)_n$	C and D	
1.5	m	CH_2's α to		
1.65	m	carbons 1	C and D	
1.85	m	and 4		
2.0	2s	2 x $C\underline{H}_3COOR$	C and D	two peaks
3.25	t	CH_2-I	C	
4.05	m	CH_2-O and CH-I	D	
4.9	m	CH-O	C	

3.3.5 Reactions of 2-alkyltetrahydrofurans with pivaloyl chloride and sodium iodide.

3.3.5.1 Reaction of 2-methyltetrahydrofuran with pivaloyl chloride and sodium iodide.

Pivaloyl chloride (2.9g, 2.4 x 10^{-2}mol) was slowly added to a mixture of 2-methyltetrahydrofuran (2.0g, 2.3 x 10^{-2}mol) and sodium iodide (5.4g, 3.6 x 10^{-2}mol) in acetonitrile (80ml) at 0°C. The mixture was stirred at room temperature overnight, the reaction was quenched by addition of sodium bisulphite and the product was worked up as described in section 3.3.4.1. The crude reaction product was passed through an alumina column to remove any pivalic acid formed from the hydrolysis of unreacted pivaloyl chloride during work-up. The product yield was 5.85g, 86% (97% pure by GLC). The mass spectrum contained fragment ions at the following m/e values, confirming the product to be the primary iodopentyl pivalate, $I(CH_2)_3CH(CH_3)OCOC(CH_3)_3$; molecular ion at 298 absent, 197 (4, M^+-$(CH_3)_3CCOO$), 196 (2, M^+-$(CH_3)_3CCOOH$), 171 (8, M^+-I), 155 (5, $I(CH_2)_2^+$), 141 (1, ICH_2^+), 128 (2, HI^+), 103 (7, $(CH_3)_3CCOOH_2^+$), 85 (14, $C_5H_9O^+$), 69 (68, $C_5H_9^+$), 57 (100, $C_4H_9^+$, $(CH_3)_3C^+$) and 41 (87, $C_3H_5^+$).

3.3.5.2 Reaction of 2-decyltetrahydrofuran with pivaloyl chloride and sodium iodide.

Pivaloyl chloride (0.33g, 2.7mmol) was added to a mixture of 2-decyltetrahydrofuran (0.57g, 2.7mmol) and sodium iodide (0.6g, 4.0mmol) in acetonitrile (20ml) at 0°C. The mixture was stirred at room temperature overnight and worked up as described in section 3.3.4.1. Yield 1.09g (92.5%, assuming 100% conversion to iodotetradecyl pivalate).

GLC analysis of the reaction product indicated the presence of a major component together with three minor components as detailed in table 3.19.

Table 3.19 GLC analysis of the product from reaction of 2-decyltetrahydrofuran with pivaloyl chloride and sodium iodide.

Component	% by GLC	% starting material recovered
2-DecylTHF		
2-NonylTHP	1.3	2.5
A } Tetradecenyl	1.8	2.5
B } pivalates	3.6	4.9
C } Iodotetradecyl	3.1	3.0
D } pivalates	87.1	82.9
Others	3.9	4.2
Total	100.0	100.0

Components A and B were only just resolved by GLC as were components C and D, thus we deduced that two sets of regioisomers were present in the reaction product mixture. NMR analysis of components A, B and C was prohibited by the small amount of sample available, however, components A and B were tentatively assigned as regioisomers of tetradecenyl pivalate by comparison of their GC retention times with those of the tetradecenyl acetates produced in the analogous reaction of 2-decyl tetrahydrofuran with acetyl chloride and a Lewis acid (see section 3.3.3.2). Component C, by virtue of the similarity of its GLC retention time to that of component D was considered to be a regioisomer of iodotetradecyl pivalate, probably 4-iodotetradecyl pivalate arising from cleavage of the carbon 2-oxygen bond of the 2-

alkyltetrahydrofuran, however, due to the small amount of material available it was not possible to confirm this assignment. Component D was identified as the primary iodide shown below from mass spectral and NMR data.

Component C Component D

$CH_3(CH_2)_9CHI(CH_2)_3OCOCMe_3$ $CH_3(CH_2)_9CH(OCOCMe_3)(CH_2)_3I$

The mass spectrum of component D contained characteristic fragment ions at the following m/e values; molecular ion at 424 absent, 323 (0.25, M^+-*t*BuCOO), 322 (0.7, M^+-*t*BuCOOH), 297 (0.5, M^+-I), 196 (1.2, M^+-(*t*BuCOOH + I)), 183 (1.3, $C_{13}H_{27}^+$), 169 (1.4, $C_{12}H_{25}^+$, $C_3H_6I^+$), 155 (1.3, $C_{11}H_{23}^+$, $tBuCOOC_4H_6^+$), 141 (0.2, $C_{10}H_{21}^+$), 139 (1.9, $C_{10}H_{19}^+$), 127 (1.1, I^+, $C_9H_{19}^+$) and a series of C_nH_{2n+1} and C_nH_{2n-1} fragment ions, base peak 57 (100, $C_4H_9^+$).

NMR analysis (table 3.20) enabled full characterisation of component D as the primary iodide derivative. The 135° DEPT spectrum enabled positive identification of the methylene and quaternary carbons.

Table 3.20 NMR shift assignments for component D.

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH(OCOCMe_3)CH_2CH_2CH_2I$
14 13 12 11 10 9 8 7 6 5 4 a b c 3 2 1

^{13}C NMR

ppm	Assignment	135° DEPT
178.17	C-a (C=O)	quaternary
72.52	C-4	primary or tertiary
38.84	C-b	quaternary
34.93	C-5	CH_2
34.13	C-3	CH_2
31.90	C-12	CH_2
29.57		
29.52		
29.49	C 6-11 inclusive	$(CH_2)_n$
29.43		
29.32		
29.23		
27.21	3 x C-c	primary or tertiary
25.17	C-2	CH_2
22.68	C-13	CH_2
14.11	C-14	CH_2
6.49	C-1	CH_2

^{1}H NMR

δ			
0.85	t	3H	ω-CH_3
1.20	t	9H	3x CH_3
1.30	s	16H	$(CH_2)_n$
1.50	m	2H	C2 protons
1.65	m	2H	C5 protons
1.75	m	2H	C3 protons
3.20	t	2H	CH_2I
4.90	m	1H	CHOCOR

CHAPTER 4

REACTION OF 2-ALKYLTETRAHYDROFURANS WITH THIONYL CHLORIDE AND A LEWIS ACID

CHAPTER 4

Reaction of 2-alkyltetrahydrofurans with thionyl chloride and a Lewis acid.

4.1 Introduction.

Cleavage of tetrahydrofuran to yield a dihaloalkane was first reported by Bourguignon in 1908 [75], who found that treatment of tetrahydrofuran with hydrogen bromide resulted in the formation of 1,4-dibromobutane. In a similar manner treatment of tetrahydrofuran with concentrated hydrochloric acid, under pressure, yielded 1,4-dichlorobutane[76]. In contrast, the passage of hydrogen chloride through tetrahydrofuran at reflux, resulted in the formation of 4-chlorobutan-1-ol in 56% yield. Early studies on simple substituted tetrahydrofurans showed that there was no reaction when 2,5-dimethyltetrahydrofuran was treated with hydrogen chloride, and even in the presence of zinc chloride, after eight hours, the 1,4-dichloride is only produced in yields of around 8%[1]. Since addition of the two methyl groups would favour carbocation formation, the low yield of product implies that cleavage of tetrahydrofuran by hydrogen chloride proceeds by a nucleophilic bimolecular displacement reaction.

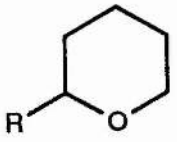
1,4-Dichlorobutanes are also readily prepared by the treatment of tetrahydrofuran with thionyl chloride in the presence of a Lewis acid[8]. The reaction of ethers with thionyl chloride in the presence of Lewis acid catalysts has been examined in detail by Goldfarb and Smorgonskii[77]. Stannic chloride, titanium tetrachloride, zinc chloride and aluminium chloride were found to be successful catalysts for the reaction with

dialkyl ethers. They reported that tetrahydrofuran with stannic chloride gave only moderate yields of the desired 1,4-dichloride. Studies on the reactivity of different Lewis acids for the cleavage of cyclic ethers have demonstrated that zinc chloride is particularly efficient[71], this was confirmed in our previous findings detailed in chapter 3, hence zinc chloride was the reagent of choice for our experiments. We have studied the reaction of tetrahydrofuran with thionyl chloride, employing zinc chloride as the Lewis acid in detail, and have applied the reaction to 2-alkyltetrahydrofurans. Initial experiments were carried out on tetrahydrofuran and 2-methyltetrahydrofuran before moving on to the medium chain 2-alkyltetrahydrofurans with a view to producing the higher 1,4-haloalkanes.

4.2 Results and discussion.

The products of the reaction of tetrahydrofurans with thionyl chloride and zinc chloride were in all cases, found to be strongly dependent on the amount of catalyst employed. When the cleavage of 2-methyltetrahydrofuran with thionyl chloride was carried out in the presence of small amounts of zinc chloride the dimeric dichloride compound (4,4'-dichlorodipentyl ether) was the major reaction product, although total product yield was low. In the presence of higher concentrations of zinc chloride the monomeric compound, 1,4-dichloropentane was found to be the major reaction product. These results are detailed in table 4.4. Unreacted 2-methyltetrahydrofuran was lost in work-up. A similar result was obtained when the reaction was carried out on tetrahydrofuran. Again as the concentration of zinc chloride was increased the

yield of the monomeric product, in this case 1,4-dichlorobutane, also increased. With the longer chain C_{14} and C_{16} 2-alkyltetrahydrofurans complete characterisation of the reaction products proved difficult. The spectral data were complex. In both cases the presence of chlorine-containing compounds has been observed in both the NMR and mass spectra. The gas chromatogram of the reaction product from 2-dodecyltetrahydrofuran showed the presence of two very close running peaks, barely resolved. This indicated that the compounds present were structurally very similar, possibly even regioisomers. The mass spectra of the components present in both the C_{14} and the C_{16} reaction products showed the presence of a series of chlorine containing compounds, but in all cases molecular ions were absent. No peaks corresponding to dichloroalkyl fragments were present. This is not surprising given the susceptibility of halo-compounds to electron bombardment. The presence of chlorine fragments corresponding to M^+-HCl and M^+-C_2H_5Cl were observed in both components of both reaction products. This led us to the conclusion that each reaction had resulted in the formation of two structurally very similar compounds, possibly regioisomers, or that a whole series of regioisomers had been formed, complete separation of which was not possible under the gas chromatographic conditions employed. Present in both starting materials was a small amount of the corresponding 2-alkyltetrahydropyran (6-10%), formed during reactant synthesis and difficult to remove from the corresponding chain length 2-alkyltetrahydrofuran by chromatography. Cleavage of the 2-alkyltetrahydropyran by thionyl chloride and zinc chloride would result in the formation of the 1,5-dichloride regioisomer.



$$+ \ SOCl_2/ZnCl_2 \longrightarrow RCHClCH_2CH_2CH_2CH_2Cl \quad (R = alkyl)$$

Alternatively, were the reaction to proceed via a nucleophilic displacement mechanism involving a carbocation, rearrangement of the secondary carbocation along the alkyl chain would occur readily, resulting in formation of several positional isomers of the dichloroalkane product.

Gas chromatographic analysis of both the C_{14} and the C_{16} products showed the presence of two very close running peaks barely resolved. Integration of the two peaks was not in line with that of the tetrahydropyran: tetrahydrofuran ratio of the starting material. The lack of baseline separation of the two closely running peaks may well have resulted in unreliable integration results. Examination of the NMR data of both reaction products showed the presence of two series of signals one of significantly greater intensity than the other, and more in keeping with the tetrahydrofuran:tetrahydropyran ratio of the reactant employed. In both cases the chemical shift values of the high intensity series of peaks are in good agreement with those calculated for the 1,4-dichlorides[74].

This reaction initially looked very promising as a means of preparation of specific positional dichloride isomers however; due to the difficulties encountered in interpretation of the spectroscopic results it has not been possible to report fully on the merits of the reaction. On this note, further work in this area is recommended; a comprehensive study of this type of reaction may lead to some very interesting observations. On the basis of our findings on the reaction of tetrahydrofurans with acyl iodides detailed in chapter 3, it would be interesting to explore the possibility of reaction of tetrahydrofurans with thionyl chloride in the presence of sodium iodide.

4.3 Experimental.

4.3.1 Reaction of tetrahydrofuran with thionyl chloride and zinc chloride.

Three reactions were carried out. In all cases a mixture of tetrahydrofuran (7.2g, 0.1mol), thionyl chloride (13.8g, 0.12mol) and zinc chloride (refer to table 4.1 for amounts employed) was refluxed at 80°C for two hours. On cooling, the mixtures were poured into ice\water to destroy any remaining thionyl chloride. The products were extracted with diethyl ether (2 x 40ml) and dried to constant weight. Un-reacted tetrahydrofuran was lost during work-up. GLC analyses and percentage yields are detailed in table 4.1.

Distillation of product 3 (see table 4.1), under reduced pressure yielded a fraction, 96% pure by GLC, which was identified as 1,4-dichlorobutane from mass spectral and NMR data. The residue, 94% pure by GLC was identified as bis-4-chlorobutyl ether. NMR data for the two compounds are detailed in tables 4.2 and 4.3 respectively.

The mass spectrum of 1,4-dichlorobutane contained peaks at the following m/e values (intensity relative to the base peak); 126, (tr, M^+ ^{35}Cl), 92 and 90 (32 and 78, M^+-HCl), 65 and 63 (10 and 30, $C_2H_4Cl^+$), 55 (100, $C_4H_7^+$).

Table 4.1 Reaction of tetrahydrofuran with thionyl chloride and zinc chloride.

	Reaction Product 1		Reaction Product 2		Reaction Product 3	
$ZnCl_2$ employed	0.1g $7.3x10^{-4}$mol		0.5g $3.7x10^{-3}$mol		1.35g $9.9x10^{-3}$mol	
yield (g)	4.57		6.21		7.87	
	% by GLC	% yield[1]	% by GLC	% yield	% by GLC	% yield
component A 1,4-dichlorobutane	17	6	54	26	77	48
component B dichlorodibutylether	74	34	39	24	19	15
Others	9		7		4	
Total	100	40	100	50	100	63

[1] % yields (mol%) are based on the amount of tetrahydrofuran employed.

The mass spectrum of 4,4'-dichlorodibutyl ether contained peaks at the following m/e values (intensity relative to the base peak); 200 and 198 (tr, M^+), 123 and 121 (4 and 12, CH_2-O-$C_4H_8Cl^+$),93 and 91 (33 and 98, $C_4H_8Cl^+$), 55 (100, $C_4H_7^+$) and 41 (40, $C_3H_5^+$).

Table 4.2 ^{13}C and ^1H NMR shift assignments for 1,4-dichlorobutane.

$$\underset{1}{Cl\text{-}CH_2}\text{-}\underset{2}{CH_2}\text{-}\underset{3}{CH_2}\text{-}\underset{4}{CH_2}\text{-}Cl$$

^1H NMR

δ 1.95 4H 2 x $C\underline{H_2}CH_2$-Cl

δ 3.6 4H 2 x CH_2-Cl

^{13}C NMR

ppm	calculated shift (ppm)*	assignment
29.8	(30.2)	$\underline{C}H_2$-$\underline{C}H_2$ carbons 2 & 3
44.2	(44.2)	2 x CH_2-Cl carbons 1 & 4

* The numbers in parantheses refer to the shift values calculated by the method detailed by Williams and Fleming[74], outlined in chapter 3.

Table 4.3 ^{1}H and ^{13}C NMR shift assignments for 4,4'-dichlorodibutyl ether.

$Cl\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}Cl$
4 3 2 1 1' 2' 3' 4'

^{1}H NMR

δ 1.7 4H 2 x $C\underline{H}_2\text{-}CH_2\text{-}O$
δ 1.85 4H 2 x $C\underline{H}_2\text{-}CH_2\text{-}Cl$
δ 3.45 4H $CH_2\text{-}O\text{-}C\underline{H}_2$
δ 3.6 4H 2 x $CH_2\text{-}Cl$

^{13}C NMR

ppm	Calculated shift (ppm)	Assignment
69.9	(69.4)	C1 and C1'
44.9	(44.7)	C4 and C4'
29.6	(29.4)	C2 and C2'
27.1	(28.1)	C3 and C3'

4.3.2 Reaction of 2-methyltetrahydrofuran with thionyl chloride and zinc chloride.

A series of reactions were carried out employing a mixture of 2-methyltetrahydrofuran (8.6g, 0.1mol), thionyl chloride (13.8g, 0.12mol) and varying quantities of zinc chloride as detailed in table 4.4. The products were refluxed at 80°C for two hours prior to work-up as described in section 4.3.1. GLC analyses and yields are summarised in table 4.4.

Table 4.4 Reaction of 2-methyltetrahydrofuran with thionyl chloride and zinc chloride.

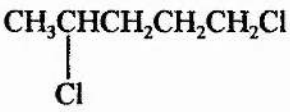
Expt. No	1		2		3		4		5	
Wt. $ZnCl_2$ employed	50mg		100mg		200mg		500mg		1.35g	
Yield/g	-		3.6		8.8		9.4		9.8	
	%by GLC	% yield[1]	%by GLC	% yield	%by GLC	% yield	%by GLC	% yield	%by GLC	% yield
Component A 1,4-dichloro-pentane	9	2	40	25	69	46	82	57	91	65
Component B	31		13		-		-		-	
Component C	55	17	39	30	23	19	9	8	-	
Others	5		8		8		9		9	
Total	100	19	100	55	100	65	100	65	100	65

[1] % yields (mol%) are based on the amount of 2-methyltetrahydrofuran employed.

Components A and C were identified as 1,4-dichloropentane and 4,4'-dichlorodipentyl ether on the basis of NMR data (detailed in table 4.5 and 4.6 respectively), and GC-MS data.

The mass spectral data for the monomeric dichloride is listed below:

1,4-Dichloropentane



The mass spectrum contained peaks at the following m/e values (intensity relative to the base peak); molecular ions at 144/142/140 absent, 125 (1, 140-CH_3), 107 and 105 (2.5 and 8, $C_5H_{10}Cl^+$), 106 and 104 (6 and 18, $C_5H_9Cl^+$), 91 and 89 (2 and 6, $C_4H_6Cl^+$), 78 and 76 (9 and 24, $C_3H_5Cl^+$), 68 (67, $C_5H_8^+$), 65 and 63 (10 and 33, CH_3CHCl^+), 55 (41, $C_4H_7^+$) and 41 (100, $C_3H_5^+$) and 27 (76, $C_2H_3^+$).

The mass spectrum of component C, 4,4'-dichlorodipentyl ether contained peaks at the following m/e values (intensity relative to the base peak): Molecular ions at 230/228/226 absent, 151 and 149 (3 and 9, C $_7H_{14}Cl^+$), 107 and 105 (34 and 100, $C_5H_{10}Cl^+$), 91 and 89 (tr and 2, $C_4H_6Cl^+$), 79 and 77 (1 and 3, $C_3H_6Cl^+$), 69 (81, $C_5H_9^+$), 65 and 63 (6 and 17, $C_2H_4Cl^+$), 55 (10, $C_4H_7^+$), 43 (35, $C_3H_7^+$), 41 (82, $C_3H_5^+$) and 27 (46, $C_2H_3^+$).

Table 4.5 ^{1}H and ^{13}C NMR shift assignments for 1,4-dichloropentane.

CH_3-CH(Cl)-CH_2-CH_2-CH_2-Cl
5 4 3 2 1

^{1}H NMR.

δ 1.6	d	3H	CH_3
δ 1.95	m	4H	CH_2-$C\underline{H}_2$ protons on carbons 2 & 3
δ 3.6	t	2H	CH_2-Cl
δ 4.1	m	1H	CH-Cl

^{13}C NMR.

ppm	Calculated shift (ppm)*	Assignment
57.77	(53.3)	C-4
44.43	(44.5)	C-1
37.43	(39.6)	C-3
29.65	(27.7)	C-2
25.43	(23.5)	C-5

* The numbers in parantheses correspond to the predicted shift values based on calculations[74].

Table 4.6 **^{1}H and ^{13}C NMR shift assignments for 4,4'-dichlorodipentyl ether.**

$CH_3CH(Cl)CH_2CH_2CH_2$-O-$CH_2CH_2CH_2CH(Cl)CH_3$
5 4 3 2 1 1' 2' 3' 4' 5'

^{1}H NMR assignments.

δ1.5	d	6H	2 x CH_3
δ1.65-1.75	2m	8H	^{1}H's on carbons 2,2',3 and 3'
δ3.45	t	4H	CH_2-O-$C\underline{H}_2$
δ4.05	m	2H	2 x CH-Cl

^{13}C NMR shift assignments.

ppm	Calculated shift/ppm	Assignment	135° Dept
25.42	(24.0)	2 x $\underline{C}H_3$	CH_3 or CH
29.49	(25.6)	carbons 2 and 2'	CH_2
36.63	(38.8)	carbons 3 and 3'	CH_2
58.59	(53.8)	carbons 4 and 4'	CH_3 or CH
69.21	(69.7)	carbons 1 and 1'	CH_2

4.3.3 Reaction of 2-dodecyltetrahydrofuran with thionyl chloride and zinc chloride.

A mixture of 2-dodecyltetrahydrofuran (3.0g, 0.0125mol), thionyl chloride (2.98g, 0.025mol) and zinc chloride (0.17g, 0.00125mol) was refluxed for two hours. On cooling the mixture was worked up as described in section 4.3.1 yielding a dark

brown liquid (3.12g, 85% assuming 100% conversion to dichloride).

GLC analysis of the product (HP1, 100°-10°-300°-10) indicated the presence of two new components (only partially separated) at 13.31min (58%) and 13.36min (28%). The product was analysed by GC-MS and NMR. NMR shift assignments are detailed in table 4.7.

1,4-dichlorohexadecane

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH(Cl)CH_2CH_2CH_2$-Cl

The mass spectrum contained significant peaks at the following m/e values (intensity relative to the base peak); molecular ions at 298/296/294 absent, 261 and 259 (tr and 0.5, $C_{16}H_{32}Cl^+$), 60 and 258, (2 and 6, $C_{16}H_{31}Cl^+$), 232 and 230, (tr and 2, $C_{14}H_{27}Cl^+$), 125 (7, $C_9H_{17}^+$), 111 (9, $C_8H_{15}^+$), 97 (17, $C_7H_{13}^+$), 83 (28, $C_6H_{11}^+$), 69 (48, $C_5H_9^+$), 57 (44, $C_4H_9^+$), 56 (30, $C_4H_8^+$), 55 (77, $C_4H_7^+$), 43 (98, $C_3H_7^+$) and 41 (100, $C_3H_5^+$).

Table 4.7 ^{13}C NMR of the product of reaction of 2-dodecyltetrahydrofuran with thionyl chloride and zinc chloride.

Present in the ^{13}C spectrum are two series of signals of intensity 3.0 and 0.5 respectively, the high intensity peaks have been tentatively assigned as follows:

$ClCH_2CH_2CH_2CHClCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

ppm	Assignment	Calculated Shift	
63.03	C-4	60.5	
44.48	C-1	44.5	
38.67	C-5	40.3	
35.61	C-3	37.4	
31.97	C-14	32.5	
29.69		30.3	
29.62		30.3	
29.54	C 7-C13	30.0	(C8)
29.41		29.8	(C7)
29.19	C-2	28.0	
26.5	C-6	25.2	
22.73	C-15	23.1	
14.15	C-16	14.0	

^{1}H NMR.

Peaks at the following δ values have been tentatively assigned as follows:

δ		
0.9	3H	CH_3
1.3		$(CH_2)_n$
1.75, 1.9	6H	3 x CH_2 α to C carrying chlorine
3.5	2H	CH_2-Cl
3.9	1H	CH-Cl

4.3.4 Reaction of 2-decyltetrahydrofuran with thionyl chloride and zinc chloride.

A mixture of 2-decyltetrahydrofuran (83% by GLC, 1.0g, 4.67mmol), thionyl chloride (1.07g, 9.34mmol) and zinc chloride (60mg, 0.47mmol) was refluxed for 3.5 hours. On cooling the product was worked up as described in section 4.3.1 yielding a dark brown liquid (1.01g, 82% assuming 100% conversion to dichloride). GLC analysis of the product (HP1, 100°-10°-300°-10)indicated the presence of two new components A, (9.93min, 49.2%) and B, (10.54min, 22.8%), together with 16% unreacted ether. Mass spectral data are in agreement with the assignment of both components as dichlorotetradecane. The mass spectrum of component A contained peaks at the following m/e values (intensity relative to the base peak); molecular ions at 270/268/266 absent, 232 and 230 (1.5 and 4, $C_{14}H_{27}Cl^+$), 231 (1, $C_{14}H_{28}Cl^+$), 204 and 202 (1 and 3, $C_{12}H_{23}Cl^+$), 194 (tr, $C_{14}H_{26}^+$), 125 (8, $C_9H_{17}^+$), 111 (19, $C_8H_{15}^+$), 97

(45, $C_7H_{13}^{\cdot}$), 83 (46, $C_6H_{11}^{\cdot}$), 69 (49, $C_5H_9^{\cdot}$), 55 (97, $C_4H_7^{\cdot}$), 43 (100, $C_3H_7^{\cdot}$) and 41 (97, $C_3H_5^{\cdot}$). The mass spectrum of component B contained peaks at the following m/e values; molecular ions at 270/268/266 absent,232 and 230 (0.5 and 2, $C_{14}H_{27}Cl^{+}$) 125 (5, $C_9H_{17}^{+}$), 111 (10, $C_8H_{15}^{+}$), 97 (26, $C_7H_{13}^{+}$), 83 (57, $C_6H_{11}^{+}$), 69 (71, $C_5H_9^{+}$), 55 (100, $C_4H_7^{+}$), 43 (77, $C_3H_7^{+}$) and 41 (84, $C_3H_5^{+}$).

The crude product was subjected to fractional distillation; a fraction collected at 195-210°C/ 4mmHg, was found to contain 2-decyltetrahydrofuran and a mixture of components A and B. GLC analysis of the residue indicated the presence of 83.4% component A and 11.7% component B. The NMR spectra of the residue are detailed in table 4.8.

Table 4.8 NMR analysis of residue from distillation (84% component A, 11% component B).

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH(Cl)CH_2CH_2CH_2$-Cl
14 13 12 11 10 9 8 7 6 5 4 3 2 1

ppm	Intensity	Assignment	Calculated shift/ppm	135° DEPT
63.06	4.4	C-4	60.5	CH or CH_3
44.49	4.7	C-1	44.5	
38.67	5.6	C-5	40.3	
35.61	5.3	C-3	37.4	
31.95	5.2	C-12	32.5	
29.63	8.5	C-2	29.8	
29.53	10.0		30.3	
29.37	6.0	C 7-11	30.3	
29.19	6.0		30.3	
26.52	5.8	C-6	28.0	
22.72	5.7	C-13	23.1	
14.13	5.0	C-14	14.0	CH or CH_3

Also present in the ^{13}C NMR spectrum is a series of signals of lower intensity (0.1-0.5) which presumably correspond to component B. These have not been fully assigned.

^{1}H NMR spectrum of component B.

δ			
0.9	t	3H	terminal CH_3
1.25	s		$-(CH_2)_n-$
1.75		6H	3 x CH_2 α to C carrying chlorines
1.9			
3.6		2H	CH_2-Cl
3.9		1H	CH-Cl

Table 4.9 NMR spectra of the crude product from the reaction of 2-decyltetrahydrofuran with thionyl chloride and zinc chloride.

Two series of peaks are present in the ^{13}C NMR spectrum which have not been fully assigned.

^{1}H NMR.

δ			
0.9		6H	2 x CH_3
1.25			$-(CH_2)_n-$
1.75		12H	6 x CH_2 α to C. carrying chlorine
1.9			
3.45-3.55	2signals	4H	2 x CH_2-Cl
3.9		2H	2 x CH-Cl

The ^{1}H NMR spectrum is in agreement with the assignment of the two components of the mixture as dichlorides.

CHAPTER 5

REACTION OF 2-ALKYLTETRAHYDROFURANS WITH TITANIUM TETRACHLORIDE

CHAPTER 5

Reaction of 2-alkyltetrahydrofurans with titanium tetrachloride.

5.1 Introduction.

Titanium tetrachloride accelerates many organic reactions acting either as a Lewis acid or a powerful dehydrating agent. Titanium halides form adducts of the type TiX_4L and TiX_4L_2 with various electron donating ligands. Many of these complexes are crystalline solids of known structure and are soluble in organic solvents.

In 1953, Sisler and co-workers [78] studied the reaction of titanium tetrachloride with several ethers including the cyclic ethers; dioxan, tetrahydrofuran and tetrahydropyran. Sisler *et al* observed that addition of tetrahydrofuran to excess titanium tetrachloride resulted in formation of $TiCl_4.C_4H_8O$. The dietherate was formed when excess tetrahydrofuran was employed.

Further studies on reactions of a wide variety of compounds with titanium tetrachloride [78,79] revealed that with tetrahydrofuran, titanium tetrachloride can form the octahedral six co-ordinate complex, $TiCl_4.2C_4H_8O$ in which the two tetrahydrofuran rings are held in a *cis* orientation with respect to one another. It was observed that decomposition of this complex yielded either the monomeric dichloride, 1,4-dichlorobutane (1) or the dimeric products, 1,9-dichloro-5-oxanonane (2) and 9-chloro-5-oxanonanol (3) depending on work-up conditions.

+ $TiCl_4$ →

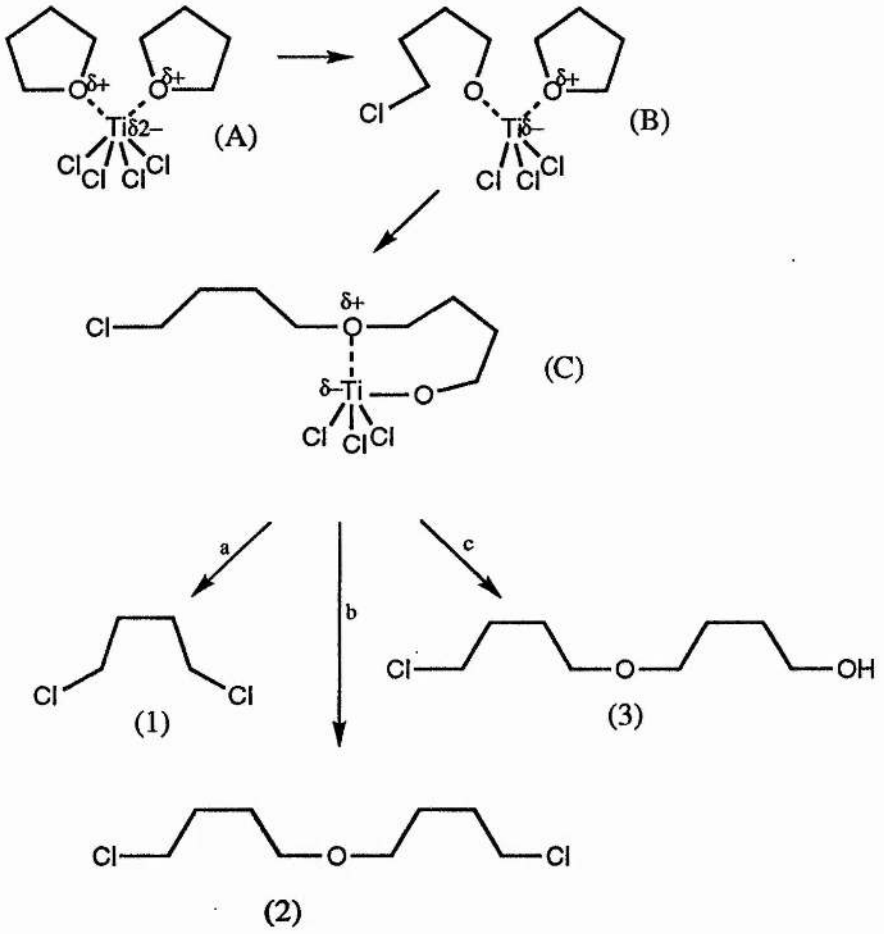
$Cl(CH_2)_4Cl$ (1)

$Cl(CH_2)_4O(CH_2)_4Cl$ (2)

$Cl(CH_2)_4O(CH_2)_4OH$ (3)

The proposed mechanism for this reaction is indicated in scheme 5.1.[80]

Scheme 5.1.



The titanium tetrachloride molecule is thought to act as a template holding the two tetrahydrofuran moieties in a *cis* relationship to each other (A), initial attack by chlorine leads to a ring opened product (B) in which the oxygen atom of one

molecule co-ordinately bound to titanium, becomes covalently bonded to titanium. Further attack by the covalently bound oxygen on a second tetrahydrofuran molecule (originally held in a *cis* arrangement with the first) would result in ring opening with dimerisation, yielding the intermediate (C), decomposition of which is thought to result in the formation of both monomeric and dimeric products as shown in scheme 5.1.

We have extended these reactions to 2-alkyl substituted tetrahydrofurans to determine whether this method would enable:

a) formation of the 1,4-dichloride product exclusively without formation of any other positional isomers, and

b) production of the dimeric ring scission products from 2-substituted tetrahydrofurans.

5.2 Results and discussion.

The products of the two reactions were more complex than anticipated. On the basis of literature reports on the reactions of tetrahydrofuran and 2-methyltetrahydrofuran with titanium tetrachloride, we had expected formation of the 1,4-dichloride, the 4-chloroalcohol and corresponding dimeric products[80], without the formation of any other positional isomers. Clearly this was not the case. Examination of both reaction products indicated the presence of two series of structurally similar compounds, tentatively assigned as regioisomers of dichlorodecane and chlorodecanol respectively. As a result of the presence of several regioisomers the spectroscopic data were complex and complete characterisation of the product components and hence verification of these tentative assignments was not possible. Despite this it was quite clear that the reaction had not proceeded via the template type mechanism described in the literature [78,79] and outlined in section 5.1. The presence of a number of regioisomers of the two reaction products pointed to a S_N1 type reaction, initial attack by titanium tetrachloride resulting in formation of a secondary carbocation, rearrangement of which would result in production of a series of dichloride or chloroalcohol isomers depending on work-up, (aqueous work-up involving hydrolysis of the Ti-O bond would result in chloroalcohol formation). Initially it was thought that one possible explanation for the formation of the observed S_N1 type reaction products was that the presence of the α-alkyl substituent on the tetrahydrofuran molecule prevented the formation of a complex of the type $TiCl_4L_2$ in which the two tetrahydrofuran moieties were held in a *cis* arrangement. This in turn would prevent the reaction from proceeding via the outlined template type pathway. Further work

by Delaney, Johnstone and Entwistle[81] showed that the reaction of titanium tetrachloride with a bicyclic ether resulted in the formation of a chloroalcohol in which the chloro and hydroxy functions had a *trans* relationship, implying a S_N2 type ring opening. The incoming chlorine could arise by inter- or intra-molecular transfer of Cl from $TiCl_4$ or from traces of Cl^- in solution. The template effect described in section 5.1 implies intramolecular attack of Cl from the same side as the departing oxygen during ring opening. Similarly they reported that in the case of substituted cyclic ethers, alkyl substitution at the α-carbon of the cyclic ether would make attack from the rear more difficult in a S_N2 type reaction but would favour a S_N1 type reaction. As they found that an alkyl substitution greatly accelerated the rate of ring opening and dimerisation they favour a S_N1 mechanism. Their study of α-substituted ethers included two tetrahydrofurans, namely 2-methyl and 2,5-dimethyl-tetrahydrofurans, together with various dihydrofurans. The production of a series of regioisomers in our reaction of 2-hexyltetrahydrofuran with titanium tetrachloride confirms that the reaction does occur intermolecularly and that the previously proposed template mechanism is in fact illusory.

5.3 Experimental.

5.3.1 Reaction of 2-hexyltetrahydrofuran with titanium tetrachloride.

This reaction was carried out under an atmosphere of dry nitrogen.

Titanium tetrachloride (0.35ml, 3.19×10^{-3}mol) was added to a solution of 2-hexyltetrahydrofuran (1.0g, 6.41×10^{-3}mol) in dichloromethane (20ml). The mixture turned yellow immediately on addition of titanium tetrachloride and, after stirring for 48 hours at room temperature, had darkened to amber. The solution was then filtered and the solvent removed by evaporation, yielding an amber oil (1.07g).

GLC analysis of the product indicated the presence of unreacted 2-hexyltetrahydrofuran (16.5%) along with 2 new major peaks, (20.9%) and (36.4%) respectively. These two peaks were poorly resolved on the gas chromatogram and were tentatively assigned as isomers of dichlorodecanes by comparison of their GC retention times with those of the products of reaction of 2-alkyltetrahydrofurans with thionyl chloride and a Lewis acid described in chapter 4. GLC analysis also showed the presence of 2 further peaks with much higher retention times. Again these 2 peaks were barely resolved on the gas chromatogram, suggesting that the components were structurally related, possibly positional isomers of the same compound.

The reaction was repeated, but the reaction mixture was refluxed for 8 hours. On cooling, water was added to the amber solution and, after stirring for an additional 15 minutes, the product was extracted with diethyl ether (2 x 30ml). The solvent was

evaporated to dryness yielding an amber oil (1.04g).

GLC analysis of the product showed the presence of the same four components described previously; the two components tentatively assigned as dichlorodecane isomers (1.80%) and (1.40%) respectively together with the two late running components (46.0%) and (35.3%) respectively. On the basis of their retention times it seemed likely that these compounds were either dimeric dichlorides or monomeric chloroalcohols.

Due to the complexity of the spectroscopic data it was not possible to fully characterise the reaction products. Mass spectroscopy provided limited information.

The mass spectrum of the tentatively assigned dichlorodecane isomers (not fully resolved on the chromatogram) contained peaks at the following m/e values (intensity relative to base peak, tentative assignment); 148 and 146 (1.5 and 4, $C_8H_{17}Cl^+$), 139 (6, $C_{10}H_{19}^+$), 110 (32, $C_8H_{16}^+$), 107 and 105 (tr and 2, $C_5H_{12}Cl^+$), 106 and 104 (1.5 and 5, $C_5H_{11}Cl^+$), 96 (6, $C_7H_{12}^+$), 82 (55, $C_6H_{10}^+$), 71 (32 $C_5H_{11}^+$), 69 (33 $C_5H_9^+$), 57 (38, $C_4H_9^+$), 55 (50, $C_4H_7^+$), 43 (63 $C_3H_7^+$), 41 (100, $C_3H_5^+$) and 39 (23, $C_3H_3^+$).

The mass spectra of the two less volatile products contained a similar series of alkyl fragments to those above, together with peaks at the following m/e values; 168 (tr, $C_{11}H_{20}O^+$), 107 and 105 (2 and 6, $C_5H_{12}Cl^+$), and 106 and 104 (7 and 20, $C_5H_{11}Cl^+$).

The NMR spectra of the 2 sets of components were complex and indicated the presence of many positional isomers of each of the product types. This implies that each set of two peaks on the gas chromatogram corresponded to more than two regioisomers of the same compound. Full assignment of all the chemical shifts was not possible.

The ^{1}H NMR spectrum of the tentatively assigned dichlorodecane isomers contained characteristic peaks at δ 3.6, CH_2-Cl and δ 4.2 CH-Cl, together with peaks corresponding to alkyl protons.

The ^{13}C NMR spectrum indicated the presence of a series of structurally similar compounds. The presence of a group of peaks at 44-45 and 61-63 ppm (downfield from TMS) indicated the presence of CH_2-Cl and a series of CH-Cl groups respectively. A series of alkyl methylene carbon atom shifts were also present at 22, 25-26, 28, 29-34 and 38-40 ppm.

The ^{13}C NMR spectrum of the less volatile components showed the presence of eight peaks of chemical shift value ranging from 61-65ppm (downfield from TMS). Calculated shift values [74] indicated that these corresponded to either CH-Cl or CH_2-OH groups. The 135° DEPT spectrum showed these peaks to be a mixture of methylene and methine carbons, confirming this assignment. Also present was a series of methylene carbons in line with the presence of a number of regioisomers. Calculated ^{13}C shift values for the dimeric dichloride or dimeric chloroalcohol give a predicted shift value in the region of 71ppm downfield from TMS, for the methylene

carbon α to the ethereal oxygen; there was no such peak present in the ^{13}C NMR spectrum.

CHAPTER 6

PREPARATION OF DIETHERS AND DIESTERS

CHAPTER 6

Preparation of diethers and diesters.

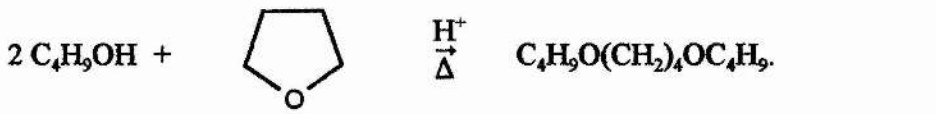
6.1 Introduction.

Long chain diethers and diesters of the type $RO(CH_2)_4OR$ and $RCOO(CH_2)_4OCOR$, have been shown to exhibit interesting physical and chemical properties; diesters for example have demonstrated useful industrial potential as synthetic lubricants. Brown *et al*[82] investigated the properties of a range of pure organic liquids containing ether and ester linkages and found that several such compounds exhibited lubricating properties. Diethers, prepared by the reaction of an alkoxide with an alkyldibromide

$$2RO^-Na^+ + Br(CH_2)_nBr \rightarrow RO(CH_2)_nOR + 2NaBr,$$

as in the Williamson ether synthesis, have been employed as stationary phases in gas-liquid chromatography[83,84].

Hobin *et al*[85], in a study of model polyethers prepared di- (tri- and poly-) ethers by the acid catalysed reaction of a diol with an alcohol as well as by the more traditional method of Williamson. Reppe[8] in 1955, showed that reaction of tetrahydrofuran with butanol in the presence of sulphuric acid resulted in the formation of 1,4-dibutoxybutane in 25% yield.



This reaction exhibits the potential of incorporation of the C_4 unit of the tetrahydrofuran molecule into higher molecular weight organic compounds; various diethers have successfully been prepared by the acid catalysed reaction of tetrahydrofuran or 1,4-butanediol with an alcohol at elevated temperatures[86].

Similarly diesters have been prepared by catalytically reacting tetrahydrofuran with acid anhydrides or carboxylic acids[87,88]. Short chain diesters of this type are good solvents for other organic materials, and longer chain compounds have been shown to be good plasticizers for thermoplastic cellulose esters.

We have shown in previous chapters that substituted tetrahydrofurans can be cleaved under acidic conditions and it was apparent that the acid catalysed reaction of 2-alkyltetrahydrofurans with fatty alcohols and fatty acids provided an opportunity to produce branched chain diethers and diesters of the type shown below:

$ROCHR'(CH_2)_3OR$ and $RCOOCHR'(CH_2)_3OCOR$

where R and R' = alkyl group.

It was thought that these compounds may exhibit interesting physical properties as a result of the branched chain (R') α to the ether or ester function, and thus may be of some commercial value.

In order to gain a clear understanding of the reaction and in particular to simplify the products, and hence assist characterisation of the reaction products, initial

experiments were carried out employing dodecanol and tetrahydrofuran to give 1,4-didodecyloxybutane. Further experiments were performed employing 2-methyltetrahydrofuran as a simple analogue of our substituted tetrahydrofurans. These were to provide some indication of the effect of the alkyl group at position two of the tetrahydrofuran ring prior to studies on the reaction of 2-hexyltetrahydrofuran with dodecanol. A similar series of reactions of tetrahydrofurans with lauric acid to produce diesters was performed.

6.2 Results and Discussion.

6.2.1 The acid catalysed reaction of tetrahydrofuran with dodecanol.

Reaction of tetrahydrofuran with dodecanol in the presence of an acid catalyst resulted in the formation of didodecyl ether together with the following compounds containing C_4 units derived from tetrahydrofuran;

$$+ 2\ C_{12}H_{25}OH \rightarrow C_{12}H_{25}O(CH_2)_4OC_{12}H_{25} +$$

$$C_{12}H_{25}O[(CH_2)_4O]_2C_{12}H_{25} \text{ (minor trace)}$$

in which one or two tetrahydrofuran moieties are incorporated into the product.

One possible route to the formation of such compounds is detailed in scheme 6.1. The reaction is initiated either by protonation of the alcohol molecule or by

protonation of the tetrahydrofuran ring resulting in an increased tendency of the ring to open as a result of attack by a nucleophilic species, in this case dodecanol.

Scheme 6.1.

$\xrightarrow{(i)}$ $RO(CH_2)_4OH$ $\xrightarrow{(i)}$ $RO(CH_2)_4OR$

$\downarrow$(ii) $\downarrow$(ii)

$HO(CH_2)_4O(CH_2)_4OH$ $\xrightarrow{(i)}$ $RO(CH_2)_4O(CH_2)_4OH$ $\xrightarrow{(i)}$ $RO(CH_2)_4O(CH_2)_4OR$

(i) ROH , H^+

(ii) THF , H^+

The product distributions of initial experiments (1-6) employing;

(i) 2 moles dodecanol : 1 mole of tetrahydrofuran as dictated by the stoichiometry for diether production, and

(ii) 1 mole dodecanol : 1 mole tetrahydrofuran ,

are shown in table 6.1.

The yield of hydroxyether and triether was low (<2%) in all cases, thus it was deemed viable to analyse the results in terms of diether ($RO(CH_2)_4OR$) and dialkyl ether production (ROR).

Table 6.1 Acid catalysed reaction of tetrahydrofuran with dodecanol.

Reaction product component	Substrate employed: 0.1mol THF: 0.2 mol ROH % Yield 1 H_2SO_4	 2 TsOH	 3 MsOH
ROH	20	60	17
ROR	40	17	43
[1]$RO(CH_2)_4OR$	34	12	38
[2]a	0.85	0.71	0.88
Reaction product component	Substrate employed: 0.2mol THF: 0.2 mol ROH % Yield 4 H_2SO_4	 5 TsOH	 6 MsOH
ROH	18	44	19
ROR	30	26	26
$RO(CH_2)_4OR$	48	24	50
a	1.60	0.92	1.92

[1] A small amount of $RO[(CH_2)_4O]_2R$ was also present in some reaction products.
[2] a is the ratio $RO(CH_2)_4OR/ROR$, where $R = C_{12}H_{25}$.

Clearly toluenesulphonic acid is the least effective catalyst, the results obtained with methanesulphonic and sulphuric acids are roughly equivalent. The ratio of diether $RO(CH_2)_4OR$, to dialkyl ether ROR, is greater with sulphuric and methanesulphonic acids than with toluenesulphonic acid, and increases when the proportion of tetrahydrofuran to alcohol is increased. This suggests that the yield of diether, $RO(CH_2)OR$, may be further increased by using even higher proportions of tetrahydrofuran, but our results did not indicate this to be the case (see table 6.14).

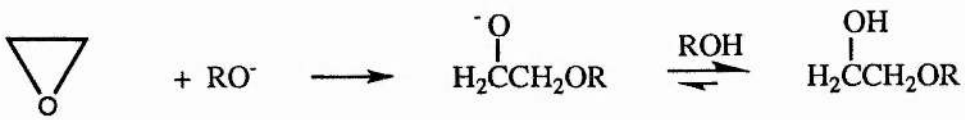
When a large excess of tetrahydrofuran was employed the reaction became very slow, probably because with a large excess of tetrahydrofuran the reaction temperature was reduced from at least 120°C to approximately 70°C.

When a large excess of dodecanol was employed there was a more efficient conversion of tetrahydrofuran to 1,4-didodecyloxybutane, but this was accompanied by a higher proportion of the didodecyl ether.

To summarise, we found that the maximum diether production was obtained when a ratio of one mole dodecanol : one mole tetrahydrofuran was employed, the most efficient catalysts for this conversion being methanesulphonic and sulphuric acids.

6.2.2 The base-catalysed reaction of tetrahydrofuran with dodecanol.

The base catalysed reaction of tetrahydrofuran with dodecanol is analogous to the acid catalysed reaction of a 1,2-epoxide with an alcohol. 1,2-Epoxides undergo S_N2 attack by alkoxides;



the driving force of this reaction being the release of ring strain. The appealing feature of this reaction is the absence of a competing reaction leading to dialkyl ether production as in the acid catalysed reaction. It was however deemed unlikely that tetrahydrofuran, due to its lack of ring strain, would react in a similar manner. Indeed this was found to be the case, attempted reaction of sodium dodecoxide with tetrahydrofuran resulted in isolation of dodecanol only. Unreacted tetrahydrofuran was lost in work-up, confirming that tetrahydrofuran, due to lack of ring strain, is stable to nucleophilic attack in this manner.

6.2.3 The acid-catalysed reaction of 2-alkyltetrahydrofurans with dodecanol.

The reaction of 2-alkyltetrahydrofurans with dodecanol resulted in the production of the following cyclic ether derived products; the diether, $C_{12}H_{25}OCHR(CH_2)_3OC_{12}H_{25}$ and the two hydroxy ethers, $C_{12}H_{25}OCHR(CH_2)_3OH$ and $C_{12}H_{25}O(CH_2)_3CHROH$ (R = alkyl), arising from cleavage of the C_2-O bond and the C_4-O bond of the ether ring respectively. The product distributions for the methanesulphonic acid catalysed reaction of dodecanol with

i) tetrahydrofuran

ii) 2-methyltetrahydrofuran and

iii) 2-hexyltetrahydrofuran are detailed in table 6.2.

Table 6.2 Acid catalysed reaction of tetrahydrofurans with dodecanol.

Reaction product component	% Yield based on dodecanol		
	i) THF	ii) 2-MethylTHF	iii) 2-HexylTHF
Recovered Dodecanol	19	22	40
Didodecyl ether	26	42	45
Hydroxy ether	-	7	1
(2 isomers)	-	4	6
Diether	50	19	2
Triether	2	-	-
[1]b	2	0.7	0.2

[1] b is the ratio of cyclic ether derived products/ didodecyl ether.

Conversion of dodecanol to products occurred to approximately the same extent in the reaction of dodecanol with i) tetrahydrofuran and ii) 2-methyltetrahydrofuran. However, with 2-methyltetrahydrofuran a significant decrease in cyclic ether derived products was observed compared with the analogous reaction with tetrahydrofuran. This decrease, which was accompanied by a corresponding increase in didodecyl ether formation, can be attributed to the following factors;

a) steric hindrance, the presence of the methyl group at position two of the tetrahydrofuran molecule impedes the incoming dodecanol molecule hence attack at this site is hindered.

b) basicity, 2-methyltetrahydrofuran is less basic than tetrahydrofuran; Arnett and Wu[89] reported pK_a values of -2.08 and -2.65 for tetrahydrofuran and 2-methyltetrahydrofuran respectively. This infers that protonation of 2-methyltetrahydrofuran will occur less readily than the protonation of tetrahydrofuran, resulting in a decrease in production of ether derived products initiated by protonation of the cyclic ether ring, as observed in our experiments.

In the analogous reaction with 2-hexyltetrahydrofuran a further decrease in cyclic ether derived products was observed; diether production was reduced to 2% and only 7% total of the two hydroxy ether isomers was formed.

Generally the basicity of alcohols decreases with increasing chain length. Arnett and Wu[89] confirmed this to be the case for n-alkyl ethers claiming that the decrease in basicity of longer chain compounds compared with their short chain counterparts, was due to increased solvation. On this basis it seems reasonable to assume that 2-hexyltetrahydrofuran will be less basic than both 2-methyltetrahydrofuran and tetrahydrofuran itself, hence protonation of 2-hexyltetrahydrofuran will occur less readily, leading to a decrease in the amount of cyclic ether derived products formed as a result of protonation of the ether oxygen.

The presence of the large alkyl group at position two of the cyclic ether will hinder both protonation of the ether oxygen, and attack by dodecanol, accounting for the

observed decrease in diether and hydroxy ether production compared with the same reaction with 2-methyltetrahydrofuran and tetrahydrofuran.

It was observed that one of the hydroxy ether isomers was formed in excess (table 6.2), however due to the small amounts of these compounds formed, characterisation of the two isomers by NMR spectroscopy was not possible. In view of the steric effect due to the presence of the hexyl group at position two of the tetrahydrofuran ring it is likely that the secondary hydroxy ether $C_{12}H_{25}O(CH_2)_3CH(C_6H_{13})OH$, arising from cleavage of the ether ring initiated by attack at position four, the least hindered site, is the one formed preferentially.

6.2.4 The acid-catalysed reaction of tetrahydrofurans with lauric acid.

The acid-catalysed reaction of tetrahydrofurans with lauric acid resulted in formation of the diester and the two hydroxy ester isomers shown below;

diester $CH_3(CH_2)_{10}COOCHR(CH_2)_3OCO(CH_2)_{10}CH_3$

hydroxy esters $CH_3(CH_2)_{10}COOCHR(CH_2)_3OH$ and

$CH_3(CH_2)_{10}COO(CH_2)_3CHROH$

where R = H, alkyl.

The product distributions for the reaction of lauric acid with

i) tetrahydrofuran,

ii) 2-methyltetrahydrofuran and

iii) 2-hexyltetrahydrofuran

are detailed in table 6.3.

Table 6.3 Product distribution for the reaction of tetrahydrofurans with lauric acid.

Reaction product component	% Yield based on lauric acid		
	i) THF	ii) 2-Methyl-THF	iii) 2-Hexyl-THF
Recovered lauric acid RCOOH	52	62	72
Hydroxy ester RCOOR'OH		8	20
Diester RCOOR'OCOR	48	22	
[1] c	0.92	0.56	0.29

[1] c is the ratio RCOOR'OH + RCOOR'OCOR/RCOOH

$R = C_{11}H_{23}$
$R' = C_4H_8$, C_5H_{10} or $C_{10}H_{20}$

Clearly, maximum diester production occurred when lauric acid was reacted with tetrahydrofuran. The decrease in diester production in the reaction with 2-methyltetrahydrofuran, or non-formation of diester in the case of 2-hexyltetrahydrofuran can be explained in terms of;

i) the decrease in basicity of 2-substituted tetrahydrofurans compared with tetrahydrofuran itself, and

ii) steric effects: The presence of the alkyl substituent impedes both protonation of the ether oxygen and attack by lauric acid in a similar manner to that described in section 6.2.3 for the reaction of dodecanol with 2-alkyltetrahydrofurans.

In the reaction of lauric acid with 2-hexyltetrahydrofuran although diester formation did not occur, the two hydroxy ester isomers were formed in yields of 20% and 1% respectively. Due to the small amounts of these compounds produced it was not possible to characterise the two isomers and hence determine which was formed in excess, however it seems likely that the presence of the large alkyl group at position two of the cyclic ether would result in attack by lauric acid occurring preferentially at position four yielding the secondary hydroxy compound. This theory is in keeping with the observed non-formation of diester, since reaction of lauric acid with a secondary hydroxy compound of this nature would occur less readily than with the corresponding primary compound.

The possibility that the reaction temperature was not sufficient to promote condensation of the C_{22} hydroxy compound with a C_{12} carboxylic acid cannot be ruled out.

Comparison of the results obtained from the reaction of tetrahydrofuran, 2-methyl- and 2-hexyl- tetrahydrofurans with

a) lauric acid, and

b) dodecanol

show that formation of cyclic ether derived products was greater in the reactions with lauric acid, this is presumably due to the absence of an alternative competing reaction: In the reaction with dodecanol, the competing reaction involving condensations of two molecules of dodecanol to produce didodecyl ether occurs readily.

In the acid catalysed reaction of tetrahydrofuran with both lauric acid and dodecanol, introducing, and increasing the size of an alkyl substituent on the tetrahydrofuran ring resulted in a significant decrease in production of cyclic ether derived products.

6.3 Experimental.

6.3.1 The acid catalysed reaction of tetrahydrofuran with dodecanol.

A mixture of tetrahydrofuran (7.2g, 0.1mol), dodecanol (37.2g, 0.2mol) and sulphuric acid (2.0g, 0.02mol) was refluxed (120°C initially, the temperature

increased as the reaction progressed). On cooling, diethyl ether (200ml) was added and the solution was transferred to a separating funnel, washed with water (2 x 150ml). The solvent was then removed (RFE) yielding a brown waxy solid (39.11g). GLC analysis (100°-0-10°-300°-15) indicated the presence of three components as detailed in table 6.4 together with unreacted dodecanol. Unreacted tetrahydrofuran was lost in the work-up procedure due to its volatility.

Table 6.4 GLC analysis of the product from reaction of tetrahydrofuran with dodecanol.

	% by GLC	mol% yield (based on dodecanol)
Dodecanol	19.1	
Component A	36.2	40
Component B	36.9	34
Component C	1.7	
Others	6.1	
Total	100.0	

A sample of the crude product (9.52g) was dissolved in petroleum ether (25ml), applied to a silica column (ht. 67cm, i.d. 3cm, 300g silica gel 60 and eluted as detailed in table 6.5.

Table 6.5 Column chromatography of the product from the reation of tetrahydrofuran with dodeanol.

Fraction	Solvent	Fraction yield/g	% by GLC				
			Dodecanol	A	B	C	Others
1	Petroleum ether, 200ml	0.01					
2	PE1, 200ml	0.02					
3	PE2, 200ml	0.04					
4	PE5, 200ml	4.10	-	42.2	54.3	-	3.5
5	PE10, 200ml	2.81	-	7.0	76.9	13.5	2.6
6	PE20, 200ml	0.37	64.2	3.1	11.4	16.1	5.2
7	PE50, 200ml	1.62	86.5	1.8	6.4	1.1	4.2
8	Diethyl ether, 200ml	0.03					
		9.00					

GC-MS analysis of fraction 5 indicated the presence of three components A, B and C, identified as follows from mass spectral data:

Component A was identified as didodecyl ether. Characteristic fragment ions were present at the following m/e values (intensity relative to the base peak) in the mass spectrum: Molecular ion at 354 absent, 199 (1, M^+-$C_{11}H_{23}^+$), 185 (tr, M^+-$C_{12}H_{25}$), 169 (12, $C_{12}H_{25+}$), 125 ($C_9H_{17}^+$), 113 (17, $C_8H_{17}^+$), 111 (16, $C_8H_{15}^+$) and other C_nH_{2n+1} and C_nH_{2n-1} alkyl fragments.

Component B was identified as 1,4-didodecyloxybutane.

$$CH_3(CH_2)_{11}\text{-}O\text{-}(CH_2)_4\text{-}O\text{-}(CH_2)_{11}CH_3$$

Peaks were observed in the mass spectrum at the following m/e values(intensity relative to base peak), 426 (tr, M^+), 271 (tr, M^+-$C_{11}H_{23}$), 257 (17, M^+-$C_{12}H_{25}$), (241, M^+-$C_{12}H_{25}O$), 213 (tr, M^+-$C_{12}H_{25}OC_2H_4$), 199 (tr, $C_{12}H_{25}OCH_2^+$), 185 (tr, $C_{12}H_{25}O^+$), 169 (tr, $C_{12}H_{25}^+$), 168 (tr, $C_{12}H_{24}^+$), 155 (tr, $C_{11}H_{23}^+$), 141 (tr, $C_{10}H_{21}^+$), 99 ($C_7H_{15}^+$), 97 (8, $C_7H_{13}^+$), 85 ($C_6H_{13}^+$), 83 (10, $C_6H_{11}^+$), 73 (26, $C_4H_9O^+$), 71 (100, $C_5H_{11}^+$, $C_4H_7O^+$), 58 (42, $C_3H_6O^+$), 57 (18, $C_4H_9^+$), 55 (48, $C_4H_7^+$) and 43 (54, $C_3H_7^+$).

Component C was identified as the triether containing carbon atoms from two molecules of tetrahydrofuran.

$$CH_3(CH_2)_{11}\text{-}O\text{-}(CH_2)_4\text{-}O\text{-}(CH_2)_4\text{-}O\text{-}(CH_2)_{11}CH_3$$

The following characteristic fragment ions were present in the mass spectrum; molecular ion at m/e 498 absent, 329 (2, M^{+}-$C_{12}H_{25}$), 257 (9, M^{+}-$C_{16}H_{33}O$), 241 (17, M^{+}-$C_{16}H_{33}O_2$), 97 (6, $C_7H_{13}^{+}$), 85 (14, $C_6H_{13}^{+}$, $C_5H_9O^{+}$), 73 (78, $C_4H_9O^{+}$), 71 (100, $C_5H_{11}^{+}$, $C_4H_7O^{+}$) and 55 (65, $C_4H_9^{+}$).

Fraction 4 (0.5g) was applied to an alumina column (180 x 2.0cm Al_2O_3 pH 9.3 - 9.7) and eluted with petroleum ether (300ml). Three 100ml fractions were collected and analysed by GLC (HP1, 100°-0-10°-300°-15). Component A was obtained in 91% purity. NMR spectroscopy (detailed in tables 6.6 and 6.7) confirmed this to be didodecyl ether.

Table 6.6 ^{13}C NMR shift assignments for didodecyl ether.

12 11 10 9 8 7 6 5 4 3 2 1 1→11 12
$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-O-$(CH_2)_{11}CH_3$

The ^{13}C NMR spectrum showed signals at the following chemical shifts expressed in ppm downfield from internal TMS standard.

ppm	Assignment
71.09	C - 1
32.09	C - 10
29.96	C - 2
29.80 29.69 29.53	[1]C 4-9
26.38	C - 3
22.83	C - 11
14.17	C - 12

[1] The bulk methylene signals, due to their similarity in chemical environment, cannot be assigned with any certainty.

Table 6.7 ^{1}H NMR shift assignments for didodecyl ether.

δ			
0.85	t	6H	CH_3
1.30	s	18H	$-(CH_2)_9$
1.60	m	4H	2 x $C\underline{H}_2CH_2O$
3.40	t	4H	CH_2-O-CH_2

A sample of fraction 5 was purified by flash chromatography (Kieselgel 60 silica, column ht. 15cm, i.d. 1.6cm). The sample (500mg) was applied to the column and eluted with PE5. 12 x 10ml fractions were collected. The solvent was removed under nitrogen and the fractions were analysed by GLC. Component B was obtained 91% pure and component C 93% pure. NMR spectra allowed characterisation of these two compounds and confirmed the previous assignments based on mass spectral evidence. The ^{13}C and ^{1}H NMR assignments for component B are shown in tables 6.8 and 6.9 respectively, likewise those for component C are shown in tables 6.10 and 6.11.

Table 6.8 **^{13}C NMR spectrum of component B (1,4-didodecyloxybutane).**

12 11 10 9→4 3 2 1 a b b a 1→11 12
$CH_3CH_2CH_2(CH_2)_6CH_2CH_2CH_2$-O-($CH_2CH_2CH_2CH_2$)-O-$(CH_2)_{11}CH_3$

Chemical shift/ppm	Carbon atom assignment
70.99	C-1
70.65	C-a
31.96	C-10
29.84	C-2
29.67	
29.56	C- 4-9 inclusive
29.39	
26.56	C-b
26.25	C-3
22.72	C-11
14.13	C-12

Table 6.9 ^{1}H NMR spectrum of component B (1,4-didodecyloxybutane).

Signals were present at the following δ values:

0.85	t	6H	2 x CH_3
1.30	s	36H	2 x $(CH_2)_9$
1.55	m	4H	$C\underline{H_2}CH_2$-O-$(CH_2)_4$-O-$CH_2C\underline{H_2}$
1.65	m	4H	O-$CH_2C\underline{H_2}C\underline{H_2}CH_2$-O
3.40	2t	8H	4 X CH_2O

Table 6.10 **^{13}C NMR spectrum of component C.**

12 11 10 9→4 3 2 1 a b b a 1→11 12
$CH_3CH_2CH_2(CH_2)_6CH_2CH_2CH_2$-O-[$(CH_2CH_2CH_2CH_2)$-O]$_2$-$(CH_2)_{11}CH_3$

ppm	Carbon atom assignment
70.97	2 x C-1
70.64	4 x C-a
31.95	2 x C-10
29.69 29.65 29.54 29.37	2 x C 4-9 inclusive
26.54	4 x C-b
26.23	2 x C-3
22.71	2 x C-11
14.13	2 x C-12

Table 6.11 ^{1}H NMR Spectrum of Component C

			Assignment
0.85	t	6H	2 x CH_3
1.25	s	36H	2 x $(CH_2)_9$
1.55	m	4H	2 x C-2 protons
1.65	m	8H	8 x b protons
3.40	m	12H	6 x CH_2-O (a and 1 protons)

Further experiments varying

i) the ratio of moles alcohol to moles tetrahydrofuran employed, and

ii) the nature and amount of acid catalyst

were carried out as indicated in table 6.12.

Table 6.12 The acid catalysed reaction of tetrahydrofuran with dodecanol.

Trial	Amount of THF employed	Amount of dodecanol employed	Ratio THF: dodecanol	Acid employed	Yield/g
1	7.2g, 0.1mol	37.2g, 0.2mol	1:2	0.02mol H_2SO_4	39.11
2	7.2g, 0.1mol	37.2g, 0.2mol	1:2	0.02mol [1]TsOH	37.40
3	7.2g, 0.1mol	37.2g, 0,2mol	1:2	0.02mol [2]MsOH	39.92
4	14.4g, 0.2mol	37.2g, 0,2mol	1:1	0.02mol H_2SO_4	40.72
5	14.4g, 0.2mol	37.2g, 0,2mol	1:1	0.02mol TsOH	40.15
6	14.4g, 0.2mol	37.2g, 0,2mol	1:1	0.02mol MsOH	41.05
7	7.2g, 0.1mol	1.86g, 0.01mol	10:1	0.01mol MsOH	1.89
8	7.2g, 0.1mol	3.72g, 0.02mol	5:1	0.01mol MsOH	3.70
9	0.72g, 0.01mol	18.6g, 0.1mol	1:10	0.01mol MsOH	18.91
10	1.44g, 0.02mol	18.6g, 0.1mol	1:5	0.01mol MsOH	19.03

[1] Ts = $pCH_3C_6H_4SO_2$
[2] Ms = CH_3SO_2

The product distributions for reactions 1-6 and 7-10 are detailed in tables 6.13 and 6.14 respectively.

Table 6.13 Product distributions from the acid catalysed reaction of tetrahydrofuran with dodecanol.

Component	THF (0.1mol) ROH (0.2mol)						THF (0.2mol) ROH (0.2mol)					
	1 (H_2SO_4)		2 (TsOH)		3 (MsOH)		4 (H_2SO_4)		5 (TsOH)		6 (MsOH)	
	% by GLC	[1]% ROH	% by GLC	% ROH	% by GLC	% ROH	% by GLC	% ROH	% by GLC	% ROH	% by GLC	% ROH
[1]ROH	19.1	20	59.7	60	16.0	17	16.8	18	40.5	44	17.6	19
$RO(CH_2)_4OH$	-		-		-		0.4	-			1.3	
ROR	36.2	40	15.9	17	38.5	43	26.2	30	22.9	26	22.5	26
$RO(CH_2)_4OR$	36.9	34	13.3	12	40.1	38	50.1	48	25.7	24	52.0	50
$RO[(CH_2)_4O]_2R$	1.7		-		1.2		3.4	3	1.0		2.8	2
Others	6.1		11.1		4.2		3.1		9.9		3.8	
Total	100.0	94	100.0	89	100.0	98	100.0	99	100.0	94	100.0	97

1 % ROH refers to the amount of dodecanol ($R = C_{12}H_{25}$) recovered as either unchanged material or as alcohol-derived products and is calculated from the GLC analysis of the reaction product mixture and is expressed as a mol% of the reactant alcohol (dodecanol) employed.

Table 6.14 Product distributions from the methanesulphonic acid catalysed reaction of tetrahydrofuran with dodecanol.

Component	Experiment 7 % by GLC	[1] % ROH	Experiment 8 % by GLC	% ROH
ROH	86.2	88	80.6	81
$RO(CH_2)_4OH$	4.8	4	5.9	4
ROR	1.9	2	3.7	4
$RO(CH_2)_4OR$	1.7	1	3.9	4
$RO[(CH_2)_4O]_2R$				
Others	5.4		5.9	
Total	100.0	95	100.0	93

Component	Experiment 9 % by GLC	% ROH	[2] % THF	Experiment 10 % by GLC	% ROH	% THF
ROH	26.1	26		19.3	20	
$RO(CH_2)_4OH$	2.4	2	18	2.0	1	7
ROR	54.3	58		52.6	57	
$RO(CH_2)_4OR$	12.9	11	57	21.5	19	48
$RO[(CH_2)_4O]_2R$	0.4		3	0.7		3
Others	3.9			5.9		
Total	100.0	97	78	100.0	97	58

1 %ROH refers to the amount of dodecanol recovered as either unchanged material or as alcohol-derived products and is calculated from the GLC analysis of the reaction product mixture and expressed as a mol% of the reactant alcohol employed.

2 %THF is calculated in the same manner as %ROH.

6.3.2 The base-catalysed reaction of tetrahydrofuran with dodecanol.

Three reactions were carried out as indicated below:-

i) A mixture of dodecanol (18.6g, 0.1mol), tetrahydrofuran (3.6g, 0.05mol) and sodium methoxide (0.54g, 0.01mol) was refluxed for eight hours. On cooling the mixture was extracted with diethyl ether, transferred to a separating funnel and washed with water (50ml), dilute hydrochloric acid (50ml) and water (50ml). The solvent was then removed and the reactant alcohol was recovered unchanged, (18.0g, 97%).

ii) The reaction was repeated as described in i) above, but the dodecanol (21.65g, 0.12mol) and sodium methoxide (0.64g, 0.012mol) were heated together for two hours prior to addition of tetrahydrofuran (4.2g, 0.06mol). Dodecanol was again recovered unchanged (20.34g, 96%).

iii) Dodecanol (37.2g, 0.2mol) was heated with freshly prepared sodium wire (0.92g, 0.04mol) until all of the sodium had disappeared (monitored by visual disappearance of sodium), tetrahydrofuran (3.6g, 0.1mol) was then added and the mixture was refluxed for six hours. On work-up dodecanol (35.6g, 96%) was recovered unchanged.

GLC analysis of all three reaction products indicated the presence of only one peak corresponding to dodecanol. GC-MS confirmed this assignment. (Unreacted tetrahydrofuran was lost in the work-up procedure thus validating the calculation of percentage yields on the basis of dodecanol recovery).

6.3.3 The acid-catalysed reaction of 2-methyltetrahydrofuran with dodecanol.

Methanesulphonic acid (1.92g, 0.02mol) was added to a mixture of dodecanol (37.2g, 0.2mol) and 2-methyltetrahydrofuran (17.2g, 0.2mol) and the mixture was refluxed (120°C for 16 hours). On cooling, the product was worked up as described in section 6.3.1 (yield 38.9g). GLC analysis indicated the presence of four new components together with unreacted dodecanol as shown in table 6.15. Unreacted 2-methyltetrahydrofuran was lost in the work-up procedure.

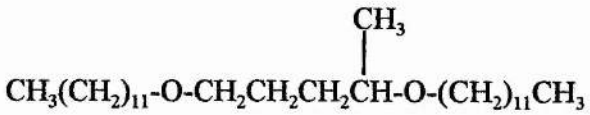
Table 6.15 The acid catalysed reaction of 2-methyltetrahydrofuran with dodecanol.

Reaction product Component	% by GLC	[1]mol% yield based on dodecanol following identification of components A-D.
Dodecanol	21.0	
A Hydroxy ethers	9.1	7
B}	4.9	4
C ROR	37.9	42
D $RO(CH_2)_4OR$	21.1	19
Others	5.7	
Total	100.0	

[1] mol% yields (based on dodecanol) are calculated from the GLC analysis of the total reaction product.

Component C was identified as didodecyl ether by comparison of the GC retention time with that of a pure sample obtained from previous experiments. GC-MS data confirmed this assignment, characteristic peaks were observed at the following m/e values (intensity relative to base peak); Molecular ion at m/e 426 absent, 185 (0.5, $C_{12}H_{25}O^+$), 169 (8, $C_8H_{25}^+$), 168 (9, M^+-$C_{12}H_{25}OH$), 140 (5, $C_{10}H_{20+}$), base peak at m/e 43 (100, $C_3H_7^+$).

Component D was recognised as 1,4-didodecyloxypentane on the basis of the presence of peaks at the following m/e values in the mass spectrum;

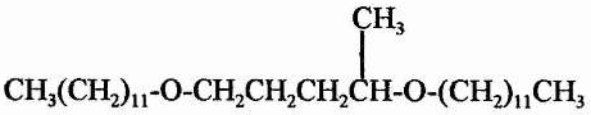


Molecular ion at m/e 440 absent, 271 (2.5, M^+-$C_{12}H_{25}$), 255 (1.5, M^+-$C_{12}H_{25}O$), 227 (0.1, M^+-$C_{12}H_{25}OC_2H_4$), 213 (3, M^+-$C_{12}H_{25}OC_3H_6$), 185 (0.1, $C_{12}H_{25}O^+$), 169 (6, $C_{12}H_{25}^+$), 155 (0.1, $C_{11}H_{23}^+$), 140 (1.5, $C_{10}H_{20}^+$), 127 (3.5, $C_9H_{19}^+$), 113 (6.5, $C_8H_{17}^+$), 99 (12.5, $C_7H_{15}^+$), 85 (100, $C_6H_{13}^+$, $C_5H_9O^+$), 71 (62.5, $C_5H_{11}^+$, $C_4H_7O^+$), 69 (57, $C_5H_9^+$), 57 (82, $C_4H_9^+$), 43 (78, $C_3H_7^+$) and 41 (52, $C_3H_5^+$).

A sample of component D (97% pure by GLC) was isolated by flash chromatography (solvent PE5) of a sample of the crude product mixture (600mg). The ^{13}C and ^1H NMR spectra enabled full characterisation of component D as 1,4-

didodecyloxypentane. The ^{1}H and ^{13}C NMR assignments are detailed in tables 6.16 and 6.17 respectively.

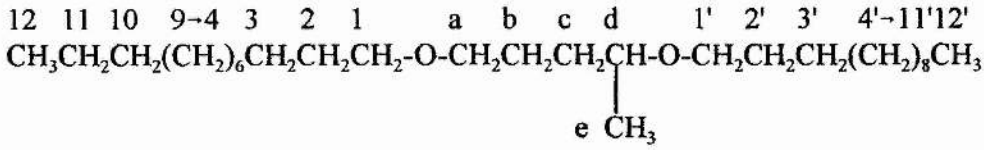
Table 6.16 ^{1}H NMR spectrum of 1,4-didodecyloxypentane.



Signals were observed at the following δ values:-

δ			
0.9	t	6H	2 x terminal CH_3
1.2	d	3H	-O-CH($\underline{CH_3}$)-
1.25	s	18H	2 x -$(CH_2)_9$-
1.55-1.7	2m	8	protons attached to carbon atoms β to the oxygen function
3.4	m	6H	3 x CH_2-O
3.7	m	1H	CH-O

Table 6.17 ^{13}C NMR spectrum of 1,4-didodecyloxypentane.



ppm	Assignment
75.12	C-d
70.98 70.93 }	C-a and C-1
68.57	C-1'
32.26	C-c
31.93	C-10 and 10'
30.22 29.79 }	C-2 and C-2'
29.65 29.37 }	C 4-9 and C 4'-9' inclusive
26.29	C-3 and C-3'
25.94	C-b
22.70	C-11 and C-11'
19.77	C-e
14.12	C-12 and C-12'

In order to correctly assign the -CH- and -CH_2- groups α to the oxygen function a 135° DEPT (Distortionless Enhancement by Polarisation Transfer) NMR spectrum was recorded. The DEPT pulse sequence produces a spectrum in which the methylene signals are inverted and the quaternary signals disappear. The methyl and methine signals remain unchanged, however since these arise in very different regions of the NMR spectrum they are easily distinguishable from each other. In the DEPT spectrum three signals remained unchanged (the methylene signals appeared inverted) indicating the three different methine or methyl environments. These signals appeared at the following chemical shifts, 75.12ppm, 19.77ppm and 14.12ppm (two carbon atoms) and confirmed our previous assignments as the methine α to the oxygen, the α-branched methyl and the two terminal methyl groups respectively.

Components A and B were thought to be regioisomers on the basis of their close GLC retention times (363 and 367s respectively).

TLC examination (solvent PE5) of the reaction product mixture confirmed the presence of didodecyl ether and the desired C_{29} diether by comparison with the chromatogram of the corresponding compounds produced from the reaction of tetrahydrofuran and dodecanol (detailed in section 6.3.1). Also observed on the TLC plate was a large broad spot corresponding to very polar material namely dodecanol and components A and B. GC-MS analysis enabled identification of the two components as the two alkoxyalcohol isomers shown overleaf:-

$CH_3(CH_2)_{11}$-O-$(CH_2)_3CH(CH_3)$-OH and

$CH_3(CH_2)_{11}$-O-$CH(CH_3)(CH_2)_3$-OH.

The mass spectrum of component A contained fragment ions at the following m/e values (intensity relative to the base peak): Molecular ion at 272 absent, 226 (tr, M^+-H_2O and C_2H_4), 199 (tr, M^+-C_4H_9O), 183 ($C_{12}H_{23}O^+$), 169 (tr, $C_{12}H_{25}^+$), 127 (1.5, C_9H_{19+}), 125 (1, $C_9H_{17}^+$), 113 (3, $C_8H_{17}^+$), 111 (4, $C_8H_{15}^+$), 99 (68, $C_7H_{15}^+$), 97 (8, $C_7H_{13}^+$), 85 (27, $C_6H_{13}^+$, $C_5H_9O^+$), 71 (51, $C_5H_{11}^+$, $C_4H_7O^+$), 57 (100, C_4H_9, $C_3H_7O^+$), 43 (78, $C_3H_7^+$, $C_2H_5O^+$) and 41 (72, $C_3H_5^+$).

The mass spectrum of component B showed characteristic fragment ions at the following m/e values:

Molecular ion at 272 absent, 199 (1, M^+-C_4H_9O), 183 (1.5, $C_{12}H_{23}O^+$), 169 (1, $C_{12}H_{25}^+$), 127 (2, $C_9H_{19}^+$), 125 (1, $C_9H_{17}^+$), 113 (3.5, $C_8H_{17}^+$), 111 (5, $C_8H_{15}^+$), 99 (72.5, $C_7H_{15}^+$), 85 (32, $C_6H_{13}^+$, $C_5H_9O^+$), 71 (54, $C_5H_{11}^+$, $C_4H_7O^+$), 57 (100, $C_4H_9^+$, $C_3H_5O^+$), 55 (32, $C_4H_7^+$), 43 (76, $C_3H_7^+$) and 41 (50, $C_3H_5^+$).

It is not possible to distinguish between the two regioisomers on the basis of the mass spectral data and since the alkoxyalcohol components were present in such small amounts, purification by column chromatography and complete characterisation was not feasible.

6.3.4 The acid catalysed reaction of 2-hexyltetrahydrofuran with dodecanol.

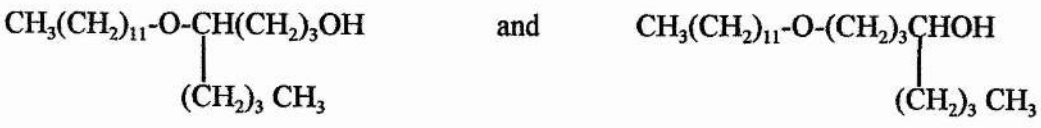
A mixture of 2-hexyltetrahydrofuran (1.0g, 97% pure, 6.2 x 10^{-3}mol), dodecanol (2.3g, 1.24 x 10^{-2} mol) and p-toluene-sulphonic acid (0.023g, 1.28 x 10^{-4} mol) was heated to 120°C for eight hours. On cooling the mixture was worked up as described in section 6.3.1 yielding a dark brown liquid (3.18g). GLC analysis (HP1, 100°-0-20°-300°) indicated the presence of five new components together with unreacted 2-pentyltetrahydropyran, 2-hexyltetrahydrofuran and dodecanol, eluted from the column in the following order:-

	% by GLC	[1]*% ether accounted for	*% alcohol accounted following identification of compounds A-E
2-Pentyltetrahydropyran	3.0		
2-Hexyltetrahydrofuran	20.8		
Dodecanol	29.4		
Component A } Hydroxy	2.0	3	1
Component B } ether	8.3	12	6
Component C ROR	31.5		45
Component D Dodecyl toluene sulphate	2.4		2
Component E Diether	2.6	3	3
Total	100.0		

[1] *The % of starting material accounted for, (as product incorporated material), was calculated from the GLC analysis of the total reaction product mixture. These figures are equivalent to the mol% yield based on ether (2-hexyltetrahydrofuran) and alcohol (dodecanol) respectively.

Components A-E were identified from GC-MS data. Component C was recognised as didodecyl ether by comparison of its retention time with that of a pure sample. GC-MS confirmed this assignment; the following characteristic mass spectral fragments were present (intensity relative to the base peak). Molecular ion at 354 absent, 199 (1.1, $C_{12}H_{25}OCH_2^+$), 185 (0.1, M^+-$C_{12}H_{25}$), 169 (8, $C_{12}H_{24}$+) and the usual series of n-alkyl fragments, base peak 57 (100, $C_4H_9^+$, $C_3H_5O^+$).

Components A and B were thought to be regioisomers on the basis of their similar GC retention times (399 and 402s respectively). They were eluted from the GC column prior to didodecyl ether indicating that they were of lower molecular weight than didodecyl ether. They were in fact identified as the alkoxy ethers shown below on the basis of mass spectral data.

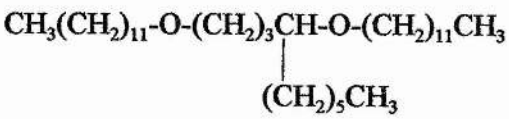


The mass spectrum of component A showed peaks at the following m/e values (intensity relative to the base peak), characteristic of the following fragment ions, molecular ion at 342 absent, 324 (tr, M^+-H_2O), 169 (5, $C_{12}H_{25}^+$), 156 (0.1, $C_{10}H_{20}O^+$), 138 (33, $C_{10}H_{18}^+$), 110 (13, $C_8H_{14}^+$), 109 (19, $C_8H_{13}^+$), 96 (46, $C_7H_{12}^+$), 82 ($C_6H_{10}^+$), 81 (63, $C_6H_9^+$), 71 (23, $C_4H_7O^+$), 68 (100, $C_5H_8^+$), 67 (76, $C_5H_7^+$), 57 (53, $C_4H_9^+$, $C_3H_5O^+$), 55 (41, $C_4H_7^+$), 43 (57, $C_3H_7^+$, $C_2H_3O^+$) and 41 (53, $C_3H_5^+$).

The mass spectrum of component B showed the following characteristic fragment ions, molecular ion at 342 absent, 325 (0.2, M^+-OH), 226 (0.1, $C_{12}H_{25}OC_3H_5^+$), 199 (0.15, $C_{12}H_{25}OCH_2^+$), 198 (0.6, $C_{12}H_{25}OCH^+$), 169 (4.0, $C_{12}H_{25+}$), 156 (1.0, $C_{10}H_{20}O^+$), 125 (1.9, $C_9H_{17}^+$), 110 (13, $C_8H_{14}^+$), 109 (15.5, $C_8H_{13}^+$), 96 (49, $C_7H_{12}^+$), 82 (53, $C_6H_{10}^+$), 71 (100, $C_4H_7O^+$), 68 (88, $C_5H_8^+$).

Component D was identified as the toluenesulphonate of dodecanol. The following characteristic fragment ions were present in the mass spectrum: Molecular ion at m/e 340 absent, 173 (44, $CH_3OSO_3H_2^+$), 172 (30, M^+-$C_{12}H_{24}$), 168 (19, $C_{12}H_{24}^+$), 155 (13, $C_{11}H_{23}^+$), 140 (14, $C_{10}H_{20}^+$) and a series of $C_nH_{2n}^+$ and $(C_nH_{2n-1})^+$ fragments, 91 (49, $C_7H_7^+$), base peak 55 ($C_4H_7^+$).

Component E was identified as the diether 1,4-didodecyloxydecane;



Peaks were observed at the following m/e values (intensity relative to base peak), in the mass spectrum: Molecular ion at 510 absent, 343 (0.2, M^+-$C_{12}H_{23}$), 342 (1.1, M^+-$C_{12}H_{24}$), 341 (0..25, M^+-$C_{12}H_{25}$), 283 (2.1, M^+-$C_{12}H_{25}O(CH_2)_3$), 256 (1.5, M^+- {$C_{12}H_{25}$ + C_6H_{13}}), 241 (5.3, $C_{12}H_{25}OC_4H_8^+$), 240 (4.2, $C_{12}H_{25}OC_4H_7^+$), 213 (0.5, $C_{12}H_{25}O(CH_2)_3^+$), 169 (5.9, $C_{12}H_{25}^+$), 155 (22, $C_{11}H_{23}^+$), 138 (2.7, $C_{10}H_{18}^+$),

115 (7, $C_7H_{15}O^+$), 99 (17, $C_7H_{13}^+$), 85 (30, $C_6H_{13}^+$), 71 (100, $C_5H_{11}^+$, $C_4H_7O^+$), 57 (76, $C_4H_9^+$), 55 (34, $C_4H_7^+$), 43 (60, $C_3H_7^+$) and 41 (24, $C_3H_5^+$).

Repeat experiments with the aim of maximising diether production were carried out as follows:

i) A mixture of 2-hexyltetrahydrofuran (0.5g, 3.2mmol), dodecanol, (1.0g, 6.4mmol) and p-toluenesulphonic acid (12mg, 6.4×10^{-5}mol) was heated to 200°C in a sealed tube overnight. Yield 1.49g (99% based on weight of reactants).

ii) A mixture of 2-hexyltetrahydrofuran (0.5g, 3.2mmol), dodecanol, (1.02g, 6.4mmol) and zinc chloride (trace) was heated to 140°C for eight hours. Yield 1.46g (96% based on weight of reactants).

iii) A mixture of 2-hexyltetrahydrofuran (0.5g, 3.2mmol), dodecanol, (0.5g, 3.2mmol) and zinc chloride (10mg, 7.3×10^{-5} mol) was heated in a sealed tube (150°C, 50 atmospheres N_2) overnight. Yield 0.95g (95% based on weight of reactants).

GLC analyses and % yields of the reaction products are summarised in table 6.18.

Table 6.18 Product distributions from the acid catalysed reaction of 2-hexyltetrahydrofuran with dodecanol.

	Expt i			Expt ii			Expt iii		
	% by GLC	[1]% X	[2]% Y	% by GLC	% X	% Y	% by GLC	% X	% Y
2-Pentyltetrahydrofuran	2.0	6		1.1	3		2.0	4	
2-Hexyltetrahydrofuran	19.8	60		30.2	88		38.7	74	
Dodecanol	3.2		5	62.9		92	45.6		88
Dodecyl toluene sulphonate ester	13.4		10						
Didodecyl ether	44.4		70				1.1		2
Hydroxy ether (2 isomers)	11.1	16	8				3.9	4	4
Diether	-			-			-		
Others	6.1			5.8			8.7		
Total	100.0	82	93	100.0	91	92	100.0	82	94

1 % X refers to the % cyclic ether recovered either as ether derived products or unreacted starting material.
2 % Y refers to the % of dodecanol recovered either as alcohol derived products or as unreacted starting material. These figures are calculated from the GLC analysis of the total reaction product.

6.3.5 The acid-catalysed reaction of tetrahydrofuran with lauric acid.

Two preparations were carried out:

i) A mixture of lauric acid (40.1g, 0.2mol), tetrahydrofuran (7.2g, 0.1mol) and methanesulphonic acid was heated to 140°C overnight. The product was worked up as described in section 6.3.1. Yield 41.9g (89% based on the combined weight of reactants employed).

ii) The reaction was repeated employing lauric acid (20.0g, 0.1mol), tetrahydrofuran (7.2g, 0.1mol) and methane sulphonic acid (1.92g, 0.02mol). Yield 21.8g (76% based on the combined weight of reactants employed).

In both cases recovered yields were low due to the loss of unreacted tetrahydrofuran in the work-up procedure.

GLC analyses (HP1, 100°-0-20°-300°) of the two reaction products are summarised in table 6.19. The percentage yields of recovered lauric acid either as unreacted material or acid derived products has been calculated from the GLC analysis of the reaction product mixture.

Table 6.19 Products from the acid catalysed reaction of tetrahydrofuran with lauric acid .

Reaction product component	Product 1		Product 2	
	% by GLC	mol% yield (based on lauric acid)	% by GLC	mol% yield (based on lauric acid)
A Lauric acid	61.7		47.8	
B Diester	36.8	34	50.5	48
C	1.5		1.0	
Others			0.7	
Total	100.0		100.0	

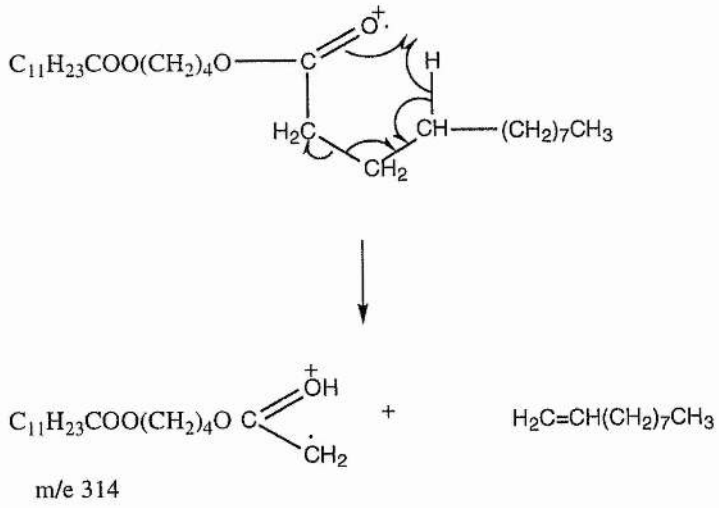
Component A was confirmed to be lauric acid by comparison with an authentic sample. GC-MS confirmed this, significant peaks were observed at m/e 200, M^+, and m/e 60 $(CH_3COOH_2)^+$, the characteristic McLafferty rearrangement fragment.

A sample of the crude product (1.0g) was applied to an alumina column (15mm x 250mm, pH 9.3-9.7 AlO_3) and eluted with PE2 (200ml), PE5 (200ml) and PE10 (200ml). A sample of component B was obtained in 93% purity. The compound was identified as the diester shown below by NMR and mass spectrometry.

$CH_3(CH_2)_{10}COO(CH_2)_4OCO(CH_2)_{10}CH_3$

The mass spectrum contained characteristic peaks at the following m/e values; 456 (tr, M+2), 455 (1, M+1), 454 (3, M^+), 314 (15, M^+-$C_{10}H_{20}$), 273 (28, $C_{11}H_{23}COO(CH_2)_4{}^+OH_2$), 255 (27, M^+-$C_{11}H_{23}COO$), 254 (41, M^+-$C_{11}H_{23}COOH$), 183 (59, $C_{11}H_{22}CO^+$), 127 (19, $C_9H_{19}^+$), 126 (20, $C_{19}H_{18}^+$), 98 (56, $C_7H_{14}^+$), 84 (38, $C_6H_{12}^+$), 71 (53, $C_5H_{11}^+$, $C_4H_7O^+$), 57 (67, $C_4H_9^+$), 56 (48, $C_4H_8^+$), 55 (61, $C_4H_7^+$) and 43 (100, $C_3H_7^+$) and 41 (56, $C_3H_6^+$).

The peak at m/e 314 arises as a result of a McLafferty rearrangement.

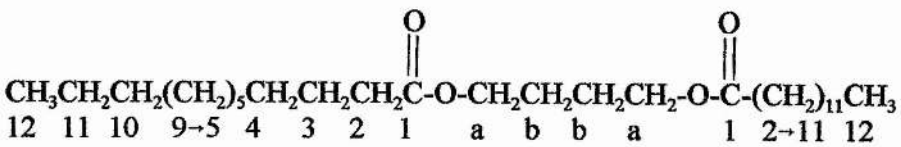


m/e 314

The fragment ion at m/e 314 can undergo further cleavage by loss of $CH_3(CH_2)_{10}COO$ or lauric acid. Peaks at m/e 115 (19) and 114 (38) corresponding to the aforementioned fragmentations, were observed in the mass spectrum.

The ^{13}C and ^{1}H NMR signals and assignments are illustrated in tables 6.20 and 6.21.

Table 6.20 ^{13}C NMR of the diester, 1,4-butanediol didodecanoate.



ppm	Assignment
173.65	C-1
63.69	C-a
34.33	C-2
32.01	C-10
29.71	
29.57	
29.44	
29.38	C4-9 inclusive
29.29	
25.49	C-b
25.07	C-3
22.77	C-11
14.14	C-12

Table 6.21 ^{1}H NMR of the diester, 1,4-butanediol didodecanoate.

			Assignment
0.9	t	3H	ω-CH_3
1.3	s	16H	bulk -$(CH_2)_n$-
1.6	m	4H	protons on carbons b and 3
1.65	m		
2.3	t	2H	$C\underline{H}_2$-$COO(CH_2)_4$ (C-2 protons)
4.05	t	2H	$C\underline{H}_2$-O-COR (C-a protons)

6.3.6 The acid catalysed reaction of 2-methyltetrahydrofuran with lauric acid.

A mixture of lauric acid (40.1g, 0.2mol), 2-methyltetrahydrofuran (17.2g, 0.2mol) and methanesulphonic acid (3.8g, 0.04mol) was refluxed at 140°C overnight. The product was worked up as described in section 6.3.1 yielding a brown waxy solid (42.5g). GLC analysis indicated the presence of three new components (as detailed in table 6.22), together with unreacted lauric acid. (Unreacted 2-methyltetrahydrofuran was lost during work-up).

Table 6.22 Products from reaction of 2-methyltetrahydrofuran with lauric acid.

Component	% by GLC	[1]mol% yield based on lauric acid following identification of compounds A-C
Lauric acid	58.9	
A } Hydroxy	10.0	8
B } ester	5.0	4
C Diester	24.1	22
Others	2.0	
	100.0	

[1] The % yields (based on amount of lauric acid employed) of lauric acid derived product components were calculated from the GLC analysis of the crude reaction product.

Unreacted lauric acid was identified by comparison with an authentic sample. GC-MS confirmed this assignment, characteristic peaks were observed at the following m/e values; 200 (7, M^+), 60 (99, $CH_2{=}C(OH)_2^+$, McLafferty rearrangement fragment), base peak 43 (100, $C_3H_7^+$).

Components A and B exhibited similar GLC retention times (394 and 399s respectively) and thus were thought to be regioisomers, the most likely structures being the two hydroxy esters shown below:

$CH_3(CH_2)_{10}COOCH(CH_3)(CH_2)_3OH$ and $CH_3(CH_2)_{10}COO(CH_2)_3CH(CH_3)OH$

The mass spectrum of component A contained peaks at the following m/e values; 201 (1, $C_{11}H_{23}COOH_2^+$), 183 (4, $C_{11}H_{23}CO^+$), 85 (3, $C_5H_9O^+$, $C_6H_{13}^+$), 70 (5.5, $C_5H_{10}^+$), 69 (16, $C_5H_9^+$), 68 (100, $C_5H_8^+$), 57 (12.5, $C_4H_9^+$), 55 (8, $C_4H_7^+$), 43 (17, $C_3H_7^+$) and 41 (21, $C_3H_5^+$).

The mass spectrum of component B contained similar peaks at the following m/e values; 201 (1, $C_{11}H_{23}COOH_2^+$) 183 3, $C_{11}H_{23}CO^+$), 85 (2, $C_5H_9O^+$, $C_6H_{13}^+$), 83 (2.5, $C_6H_{11}^+$), 71 (5, $C_4H_7O^+$), 69 (16, $C_5H_9^+$), 68 (100, $C_5H_8^+$), 57 (14, $C_4H_9^+$), 55 (12, $C_4H_7^+$), 43 (20, $C_3H_7^+$) and 41 (21, $C_3H_5^+$).

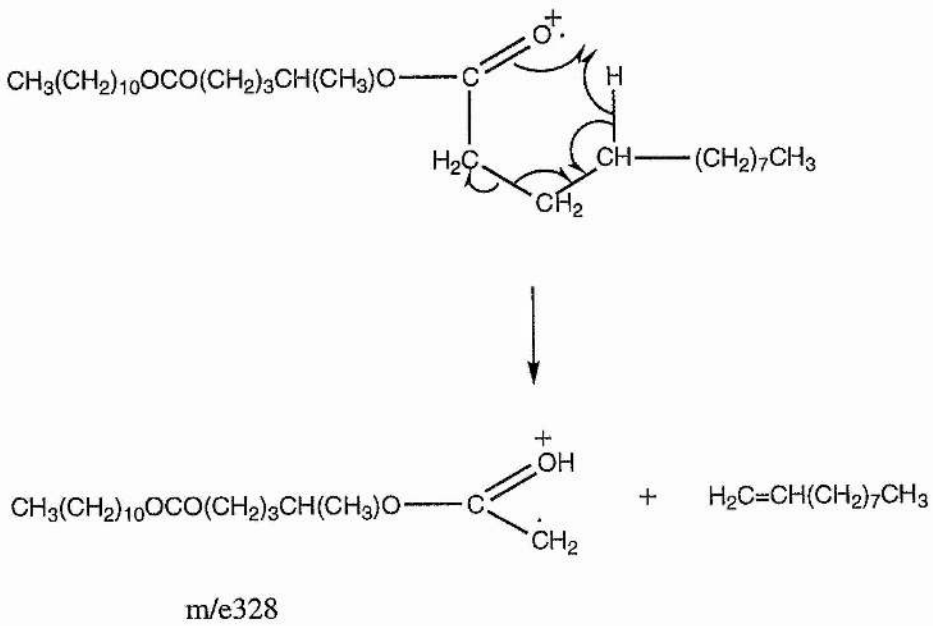
A sample of the crude product (1.67g) was dissolved in petroleum ether and applied to an alumina column (15 x 200mm, pH 9.3-9.7 Al_2O_3) and eluted with petroleum ether/diethyl ether. Component C was thus obtained 97% pure.

The mass spectrum of component C (illustrated below) showed characteristic peaks at the following m/e values;

$CH_3(CH_2)_{10}COO(CH_2)_3CH(CH_3)OCO(CH_2)_{10}CH_3$

470 (5, MH_2^+), 469 (17, $M+1^+$), 468 (13, M^+), 328 (3, M^+-$C_{10}H_{20}$), 270 (22, M^+-$C_{11}H_{22}COO$), 269 (100, a), 268 (54, M^+-$C_{11}H_{23}COOH$), 255 (1, a-CH_2), 254 (tr, a-CH_3), 241 (2, b), 227 (tr, M^+-b), 213 (tr, $C_{11}H_{23}COOCH^+$), 201 (8, $C_{11}H_{23}COOH_2^+$), 200 (tr, $C_{11}H_{23}COOH^+$), 183 (51, $C_{11}H_{23}C{=}O^+$), 141 (15, $C_{10}H_{21}^+$), 128 (27, $C_5H_{10}OCOCH_2^+$), 98 (8, $COC_5H_{10}^+$), 85 (57, $C_5H_9O^+$), 69 (65, $C_5H_9^+$), 68 (57, $C_5H_8^+$), 57 (47, $C_4H_9^+$, $C_3H_5O^+$), 55 (25, $C_4H_7^+$), 43 (38, $C_3H_7^+$) and 41 (43, $C_3H_5^+$).

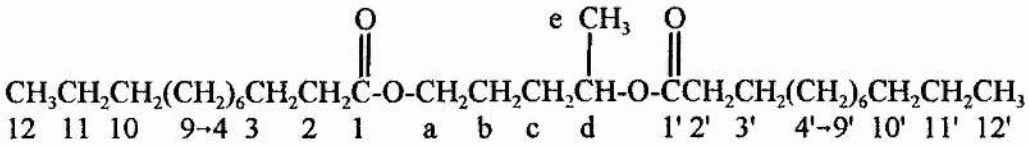
The peak at m/e 328 arises as a result of the following McLafferty rearrangements;



m/e328

^{13}C and ^{1}H NMR spectra confirmed the assignment of component C as the desired diester, 1,4-didodecanoyloxypentane. The ^{13}C and ^{1}H NMR chemical shift assignments are given in tables 6.23 and 6.24.

Table 6.23 ^{13}C NMR spectral data for 1,4-pentanediol didodecanoate.



ppm	Carbon atom assignment
173.8	C-1'
173.4	C-1
70.1	C-d
63.9	C-a
34.7 34.3	C 2,2' and c
32.4 31.9	C 10 and 10'
29.6 29.5 29.4 29.3 29.2	C 4-9 and C 4'-9' inclusive
25.1 25.0 24.8	C 3, 3' and b
22.7	C-11
20.0	C- e
14.1	C 12 and 12'

A DEPT spectrum was also recorded confirming the assignment of the methine signal at 70.1ppm and the methylene signal at 63.9ppm along with the methyl signal (carbon e) at 20.0ppm.

Table 6.24 ^{1}H NMR spectral data for 1,4-pentanediol didodecanoate.

0.9	t	6H	2 x terminal CH_3 (12 and 12' protons)
1.25	2 signals	37H	CH_3 (e) and $(CH_2)_n$ C 4→11 and 4'→11' protons
1.6	m	8H	4 x CH_2 (b and c, and 3 and 3' protons)
2.3	m	4H	2 x CH_2 (2 and 2' protons)
4.05	t	2H	CH_2OCOR (d protons)
4.95	m	1H	$C\underline{H}(CH_3)OCOR$ (C a)

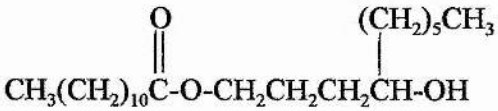
6.3.7 The acid catalysed reaction of 2-hexyltetrahydrofuran with lauric acid.

A mixture of lauric acid (590mg, 2.95mmol), 2-hexyltetrahydrofuran (230mg, 95% pure, 1.4mmol) and sulphuric aicd (1 drop) was heated to a maximum temperature of 180°C over a period of 8 hours. The reaction product was worked up as described in section 6.3.1, yield 760mg (93% based on weight of starting materials employed). GLC analysis of the product indicated the presence of two new components A and B, with similar retention times, 440s (26.30%) and 44s (1.09%) respectively, together with unreacted lauric acid and unreacted cyclic ether. A series of late running

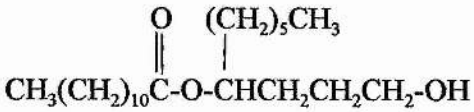
components (9.8% total) was also observed on the gas chromatogram, these were not investigated further.

GC-MS confirmed the presence of 2-hexyltetrahydrofuran and lauric acid.

Comparison of the GC retention times and mass spectra of components A and B with those of lauric acid and the hydroxyesters produced by reaction of 2-methyltetrahydrofuran with lauric acid, enabled identification of components A and B as the two hydroxy ester regioisomers shown below:



and

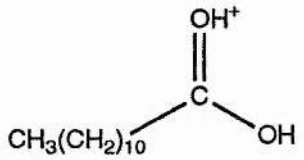


The mass spectrum of component A contained peaks at the following m/e values; molecular ion at 356 absent, 338 (tr, M^+-H_2O), 201 (2, $C_{11}H_{23}COOH_2^+$), 183 (8, $C_{11}H_{23}CO^+$), 155 (tr, $C_{11}H_{23}^+$), 154 (1, $C_{11}H_{22}^+$), 139 (6, $C_{10}H_{19}^+$), 138 (56, $C_{10}H_{18}^+$), 123 (4, $C_9H_{15}^+$), 110 (30, $C_8H_{14}^+$), 109 (34, $C_8H_{13}^+$), 96 (58, $C_7H_{12}^+$), 95 (66, $C_7H_{11}^+$), 83 (33, $C_6H_{11}^+$), 82 (100, $C_6H_{10}^+$), 81 (71, $C_6H_9^+$), 71 (13, $C_4H_7O^+$), 69 (32, $C_5H_9^+$),

68 (69, $C_5H_8^{\cdot}$), 67 (82, 100, $C_6H_{10}^{\cdot}$), 57 (33, $C_3H_5O^{\cdot}$), 54 (37, $C_4H_6^{\cdot}$), 43 (49, C_3H_7+, $C_2H_3O^{+}$) and 41 (56, $C_3H_5^{\cdot}$).

The mass spectrum of component B contained peaks at the following m/e values; 201 (1, $C_{11}H_{23}COOH_2^{+}$), 183 (7, $C_{11}H_{23}CO^{+}$), 139 (4, $C_{10}H_{19}^{+}$), 138 (49, $C_{10}H_{18}^{+}$) and a similar series of C_nH_{2n-2} and C_nH_{2n-3} fragments to those present in the mass spectrum of component A.

The fragment ions at m/e 201 is characteristic of a C_{12} ester and corresponds to



m/e 201

resulting from transfer of a hydrogen atom from the alkyl portion of the molecule to the oxygen of the acyl portion of the ester.

The fragment ion at m/e 183 is also characteristic of an α-cleavage reaction involving loss of the alkoxy group to form the corresponding acylium ion $CH_3(CH_2)_{10}C{=}O^{+}$.

It was not possible to distinguish between the two components A nd B from their mass spectra alone. Unfortunately characterisation by NMR spectroscopy was not possible due to the problems encountered in the attempted isolation of the desired components. Purification of components A and B by preparative TLC proved to be

difficult due to the similarity in polarity of the desired components with the starting material, coupled with the fact that the desired components were present in small amounts. The ^{1}H and ^{13}C NMR spectra of the crude reaction product were complex and thus it was difficult to draw any positive conclusions and assignments from them.

CHAPTER 7

OXIDATION OF 2-ALKYLTETRAHYDROFURANS WITH RUTHENIUM TETROXIDE

CHAPTER 7

Oxidation of 2-alkyltetrahydrofurans with ruthenium tetroxide.

7.1 Introduction.

The synthetic use of ruthenium tetroxide as an oxidant for organic compounds was unveiled in 1953 when the reagent was found to react vigorously with a range of organic solvents. Djerassi and Engle[90] reported that addition of a small amount of ruthenium tetroxide (10mg) to diethyl ether resulted in an explosive reaction followed by a yellow flame.

Since this initial discovery ruthenium tetroxide has demonstrated an ability to oxidise a host of organic substances under very mild conditions. Of particular interest is the oxidation of ethers to esters[91] and perhaps the most relevant to our studies is the ability of ruthenium tetroxide to oxidise cyclic ethers to lactones; tetrahydrofuran is oxidised smoothly to γ-butyrolactone in almost quantitative yield[92]. We have extended this reaction to substituted tetrahydrofurans and have studied the catalytic ruthenium tetroxide oxidation of 2-methyltetrahydrofuran and C_{10}-C_{16} 2-alkyltetrahydrofurans with the aim of producing γ-substituted-γ-lactones in high yield. γ-Lactones of this type have previously been prepared by a variety of methods including the oxidation of unsaturated fatty acids with lead tetraacetate[93]. Reaction of oleic acid with sulphuric acid[94] and perchloric acid[95] yields γ-stearolactone (30% and 60% respectively).

γ-Lactones are of particular interest in natural product chemistry; γ-dodecanolactone is both a flavour component of apricot and the pheromone of the rove beetle[96]. Applications of fatty lactones as insect attractants and growth stimulants as well as in the lubricant industry have also been reported[93].

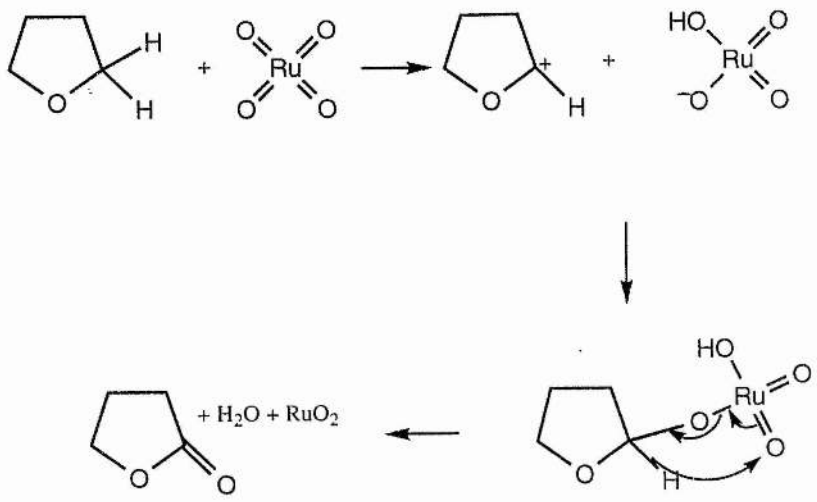
7.2 Results and Discussion.

The ruthenium tetroxide catalysed oxidation of tetrahydrofuran resulted in the formation of butyrolactone only, further oxidation to succinic anhydride did not occur, confirming the previously reported claims that butyrolactone is stable to oxidation by ruthenium tetroxide.

In contrast to this result, oxidation of 2-methyltetrahydrofuran in a similar manner resulted in the formation of γ-valerolactone and 4-oxopentanoic acid, the ketoacid was the major product. Similarly, ruthenium tetroxide catalysed oxidation of medium chain 2-alkyltetrahydrofurans resulted in formation of both γ-lactones and γ-ketoacids and in all cases the γ-ketoacid was the dominant product.

A mechanism in which ruthenium tetroxide abstracts a hydride ion from the α-position of the ether molecule has been proposed for the oxidation of tetrahydrofuran with ruthenium tetroxide[97] (scheme 7.1). This mechanism is analogous to that reported for the oxidation of alcohols and ethers by permanganate.

Scheme 7.1 Oxidation of tetrahydrofuran with ruthenium tetroxide.

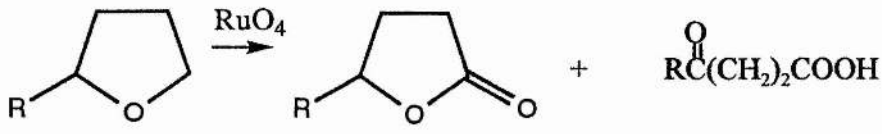


The rate of such oxidation reactions are reported to increase considerably when water is present, presumably water is needed to solvate the polar transition state, hence oxidations with ruthenium tetroxide are generally performed in a biphasic solvent system. In our experiments carbon tetrachloride, acetonitrile and water was used[98].

Referring to the reaction mechanism (scheme 7.1), in the case of oxidation of 2-alkyltetrahydrofurans there are two non-equivalent sites for hydride abstraction; due to the presence of the large alkyl group at position 2 (3° carbon atom), hydride ion abstraction from position 5 (2° carbon atom) will be sterically favoured. *In situ* hydrolysis of the γ-lactone produces the γ-hydroxyacid which is then further oxidised by ruthenium tetroxide. Comparison of the product ratios obtained from the catalytic ruthenium tetroxide oxidation of 2-alkyltetrahydrofurans (table 7.1)

confirms this theory. From our experience of these compounds we have found no marked difference in reactivity between the C_{12}-C_{16} tetrahydrofurans thus validating comparison of these results.

Table 7.1 Ruthenium tetroxide catalysed oxidation of tetrahydrofurans.



Substrate	Reaction time/ hours	Product ratio γ-lactone : γ-ketoacid
2-MethylTHF	12	1 : 2.2
2-OctylTHF	14	1 : 2.0
2-DecylTHF	24	1 : 3.5
2-DodecylTHF	30	1 : 4.7

Clearly it can be seen that increased reaction time results in an increase in γ-ketoacid formation. These results are as expected since increased reaction time will result in increased lactone hydrolysis, and hence increased ketoacid production.

Since carrying out this work we became aware of a publication concerning the synthesis of γ-fatty lactones found in *Cistus ladaniferus L.*, by oxidation of the corresponding cyclic ethers with ruthenium tetroxide[99]. The production of the corresponding ketoacids was also observed. The experimental conditions for the

oxidation were somewhat different to those we employed; an excess of ruthenium tetroxide was employed. Molar ratios of 1.4 : 1 of ruthenium tetroxide : substrate and 7 : 1 for periodate : substrate were employed and an acetone- water solvent system was used. The reaction mixtures were stirred at room temperature for 9 hours and on work-up a molar ratio of lactone : ketoacid of 2.5 : 1 was obtained. In our oxidation reactions ruthenium tetroxide was employed in catalytic amounts (molar ratios of ruthenium tetroxide of 1 : 45 and periodate : substrate of 4 : 1 were employed) in a solvent system of carbon tetrachloride, acetonitrile and water.

Scarborough and Smith[100] studied the oxidation of aliphatic and cyclic ethers using both excess and catalytic amounts of ruthenium tetroxide and reported that oxidation of 2-methyltetrahydrofuran with excess ruthenium tetroxide gave 59% γ-valerolactone whereas oxidation with a catalytic amount of ruthenium tetroxide gave γ-valerolactone and 4-oxopentanoic acid in a ratio of 1 : 4 (total yield 70%). Clearly the selectivity of the reaction depends on the reaction conditions and it appears that when only a catalytic amount of ruthenium tetroxide is employed γ-ketoacid formation occurs. Economically, a catalytic reaction is the most desirable and there is obviously scope for optimization of reaction conditions for i) γ-lactone formation and ii) γ-ketoacid formation. Recent work[101] on the catalytic oxidation of alkanes and ethers by a series of six co-ordinate ruthenium (II) complexes in dichloromethane and lithium hypochlorite indicated that cyclic and linear ethers were selectively oxidised (>99%) to lactones and esters respectively. There was no evidence of further oxidation of the initially formed products however the only cyclic ether examined was tetrahydropyran and since ketoacid formation was not observed in the

catalytic oxidation of tetrahydrofuran it would be interesting to see if catalytic oxidation of our 2-alkyltetrahydrofurans with ruthenium (II) complexes of this type demonstrates the same selectivity.

There also exists the potential for production of 4-substituted carboxylic acids from γ-lactones; cleavage of butyrolactone and γ-valerolactone is readily achieved with reagents such as thionyl chloride[102,103] and boron halides[104] resulting in the production of 4-halocarboxylic acids and esters.

To summarise, by treating the 2-alkyltetrahydrofurans with a catalytic amount of ruthenium tetroxide we have successfully achieved functionalisation of the carbon chain of the initial fatty acid as shown below;

R = alkyl

The ketoacids were produced in good yield, and could be reacted further (e.g. to produce amino acids) if desired.

7.3 Experimental.

7.3.1 Oxidation of tetrahydrofuran with ruthenium tetroxide.

The ruthenium tetroxide was employed in a catalytic amount and was generated *in situ* by oxidation of ruthenium trichloride hydrate with potassium periodate[98]. During the course of the reaction ruthenium tetroxide was reduced to ruthenium dioxide. The ruthenium tetroxide catalyst was continually regenerated by periodate oxidation of ruthenium dioxide[105],

$$RuO_2 + 2IO_4^- \rightarrow RuO_4 + 2IO_3^-.$$

Ruthenium trichloride hydrate (199mg, 7.63×10^{-4}mol) was added with stirring, to a mixture of tetrahydrofuran (2.5g, 3.47×10^{-2}mol) and potassium periodate (32.7g, 1.4×10^{-1}mol) in a biphasic solvent system composed of carbon tetrachloride (30ml), acetonitrile (30ml) and water (45ml). The mixture was stirred vigorously for 18 hours at room temperature. The flask contents were then transferred to a separating funnel, the aqueous layer was extracted with dichloromethane (3x25ml). The combined organic extracts were dried over magnesium sulphate prior to evaporation of the solvent (RFE). Diethyl ether (40ml) was added and the solution was filtered through a short column of celite. The solvent was removed yielding a colourless liquid, 2.27g, 76% assuming complete conversion to butyrolactone (98% pure by GLC).

Infra-red analysis showed a strong carbonyl stretch at $1772cm^{-1}$ characteristic of the five membered lactone ring.

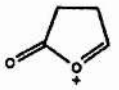
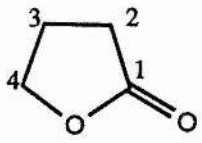
GC-MS and NMR analysis (table 7.2) confirmed the compound to be butyrolactone. Characteristic peaks were present at the following m/e values (intensity relative to the base peak) in the mass spectrum; 87 (2, M+1), 86 (28, M^+), 85 (6.5, ), 57 (5, $C_3H_5O^+$), 56 (27, $C_2H_4CO^+$), 55 (11, $H_2CCHC{=}O^+$), 44 (8, $C_2H_4O^+$), 42 (100, CH_2CO^+, $C_3H_6^+$), 41 (52, $C_3H_5^+$, $C_2H_3O^+$), 40 (17, $C_3H_4^+$) and 39 (16.5, $C_3H_3^+$).

Table 7.2 ^{13}C and ^1H NMR assignments for butyrolactone.



^{13}C NMR

ppm	Assignment
177.99	C1
68.64	C4
27.83	C2
22.19	C3

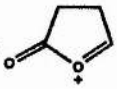
^1H NMR

δ		
4.3	t	CH_2 (4)
2.3	t	CH_2 (2)
2.1	m	CH_2 (3)

7.3.2 Oxidation of 2-methyltetrahydrofuran with ruthenium tetroxide.

The reaction was carried out as described in section 7.3.1. Ruthenium trichloride hydrate (167mg, $6.4x10^{-4}$mol) was added to a mixture of 2-methyltetrahydrofuran (2.5g, $2.9x10^{-2}$mol) and potassium periodate (27.3g, $1.2x10^{-1}$mol) in carbon tetrachloride (30ml), acetonitrile (30ml) and water (45ml). The reaction mixture was stirred vigorously overnight. Yield on work-up, 2.19g (75.5% assuming 100% conversion to γ-valerolactone).

Infra-red analysis indicated the presence of an O-H stretch at 3450cm^{-1}, and a broad carbonyl band at 1772cm^{-1} with a shoulder at 1770cm^{-1}.

GLC analysis (HP1, 50°-3-10°-250°) indicated the presence of two components identified as γ-valerolactone (27.5%) and 4-oxovaleric acid (72.5%) from mass spectral and NMR data. The mass spectrum of γ-valerolactone contained characteristic fragment ions at the following m/e values; 100 (6, M^+), 85 (36, ), 58 (tr, $C_3H_6O^+$), 56 (100, CH_4CO^+), 43 (41, $C_3H_5O^+$), 42 (9, $C_3H_6^-$), 41 (62, $C_3H_5^+$, $C_2H_3O^+$) and 39 (23, $C_3H_3^+$).

The mass spectrum of 4-oxovaleric acid contained the following fragment ions at m/e values; 116 (2.5, M^+), 99 (2, M^+-OH), 73 (6, M^+-CH_3CO), 56 (13, $C_2H_4CO^+$), 55 (15, $C_4H_7^+$), 45 (12, CO_2^+) and 43 (100, CH_3CO^+).

The ^{1}H NMR spectra confirmed these assignments:

γ-valerolactone: δ1.46 d (3H) CH_3, δ1.9 m and δ2.4 m (1H + 3H), protons on carbon 2 and 3, δ4.65 m (1H) CH-O.

4-Oxopentanoic acid: δ2.25 s (3H), CH_3, δ2.6 and δ2.75 2t (4H) $COC\underline{H_2}C\underline{H_2}COOH$.

7.3.3 Oxidation of medium chain 2-alkyltetrahydrofurans with ruthenium tetroxide.

The C_{10}-C_{16} 2-alkyltetrahydrofurans were treated with ruthenium tetroxide in a similar manner to that described in section 7.3.1. In all cases 2.2mol% of ruthenium tetroxide to substrate was employed, and a molar ratio of periodate: substrate of 4:1 was used. The solvent system was the same in all cases; carbon tetrachloride (6.5ml), acetonitrile (6.5ml) and water (10.0ml). The reaction times and yields are listed in table 7.3. In all cases recovered yields were low due to large physical losses in the work-up as a result of the small quantities employed. In the case of the C_{10} molecule the γ-lactone was purified by column chromatography and the 4-oxodecanoic acid was not recovered.

Table 7.3 Oxidation of 2-alkyltetrahydrofurans with ruthenium tetroxide

Substrate	Reaction time/ hours	Yield/g	[1] % Yield	
			γ-lactone	γ-ketoacid
2-Hexyltetrahydrofuran 1.00g, 6.41mmol	12	[2] *	22.9	*
2-Octyltetrahydrofuran 0.49g, 2.66mmol	14	0.43	25.5	51.8
2-Decyltetrahydrofuran 0.51g, 2.41mmol	24	0.47	17.2	59.7
2-Dodecyltetrahydrofuran 0.50g, 2.41mmol	30	0.49	15.2	72.8

[1] % yields are based on the amount of 2-alkyltetrahydrofuran accounted for in the form of γ-lactone and γ-ketoacid, and are expressed as mol%. These figures are calculated from the GLC analysis of the crude reaction product.

[2] * not determined.

The mass spectral data for the γ-lactones are shown below:

γ-Decanolactone (probe MS): Fragment ions at m/e 171 (tr, $M+1^+$), 170, (3, M^+), 152 (2.5, M^+-H_2O), 85 (100, $C_4H_5O_2^+$, $C_6H_{13}^+$), 55 (32, $C_3H_3O^+$, $C_4H_7^+$), 43 (25.5, $C_2H_3O^+$, $C_3H_7^+$), 41 (25, C_2HO^+, $C_3H_5^+$) and 39 (18, $C_3H_3^+$).

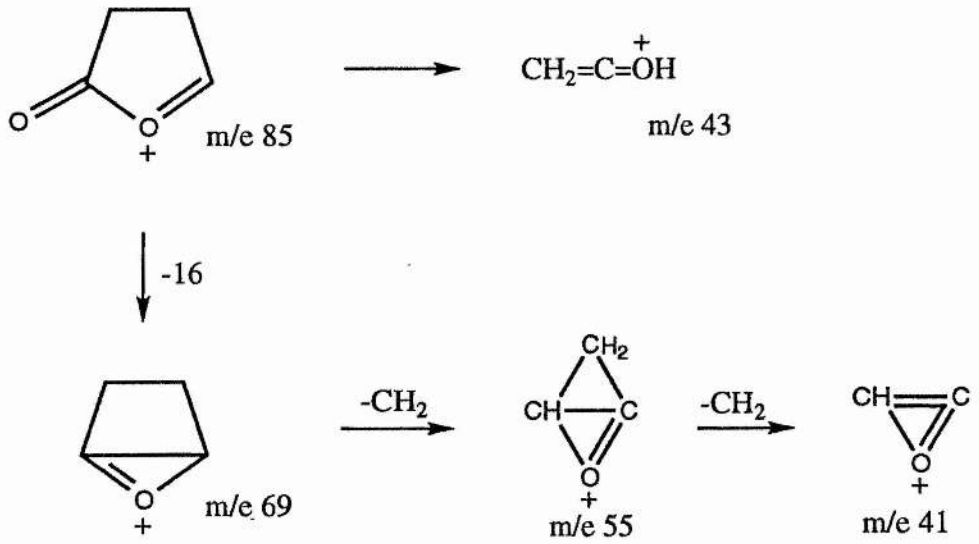
γ-Dodecanolactone (GC-MS): Characteristic fragment ions at m/e 198 (1.2, M^+) and 85 (100, $C_4H_5O_2^+$) together with peaks at m/e values 69 (7), 55 (12), 43 (8), 41 (9) and 39 (7) characteristic of fragmentation of the five membered lactone ring as depicted in scheme 7.2.

γ-Tetradecanolactone (GC-MS): Characteristic fragment ions at m/e 226 (tr, M^+) and 85 (100, $C_4H_5O_2^+$) and the ring scission fragment ions depicted in scheme 7.2.

γ-Hexadecanolactone (GC-MS): Molecular ion at 254 absent, Base peak at m/e 85 ($C_4H_5O_2^+$) together with fragment ions from scission of the lactone ring.

The mass spectra of the γ-lactones all contained the fragment ion at m/e 85 corresponding to $C_4H_5O_2^+$, as the base peak, together with a series of peaks arising from fragmentation of the lactone ring (scheme 7.2) as reported by Osman *et al*[93] in their study of carboxy-substituted lactones.

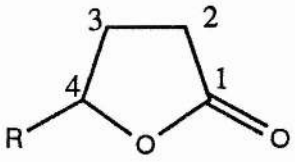
Scheme 7.2 Mass spectral fragmentation of the lactone ring.



The C_{10}-C_{16} γ-lactones exhibited a strong carbonyl band (1775-1778cm^{-1}) in the infra-red spectrum.

^{1}H NMR spectra of the γ-lactones showed the presence of characteristic signals at δ 0.9 t (3H) $C\underline{H}_3$, 1.25 s $(C\underline{H}_2)_n$, 1.5-1.9 m (3H) one ring methylene proton and two methylene protons from the alkyl chain, β and γ to the ether oxygen, 2.3 m and 2.55 m (3H) ring protons α and β to the C=O, 4.5 q (1H) methine α to ether oxygen. The ^{13}C NMR shifts are listed in table 7.4.

Table 7.4 **^{13}C NMR shift assignments for γ-lactones.**



chemical shift ppm

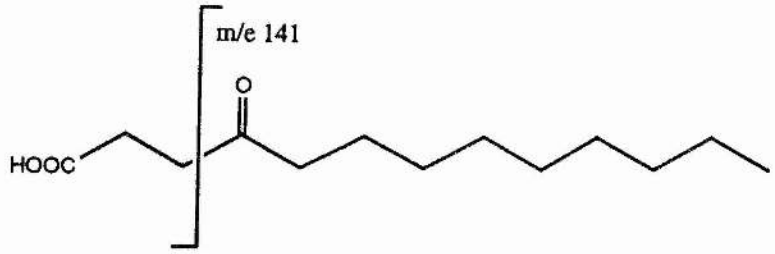
Carbon atom	$R=C_6H_{13}$	$R=C_8H_{17}$	$R=C_{10}H_{21}$	$R=C_{12}H_{25}$
1	177.25	177.21	177.15	177.24
2	28.87	28.87	28.85	28.89
3	28.02	28.04	28.03	28.03
4	81.06	81.05	81.02	81.04
5	35.61	35.63	35.64	35.63
6	25.19	25.24	25.26	25.26
7	29.00	[1] *29.64	*29.68	*29.77
8	31.66	29.51	29.55	29.71
9	22.53	29.28	29.55	29.71
10	14.03	31.70	29.55	29.58
11		22.56	29.29	29.58
12		14.04	31.95	29.46
13			22.64	29.30
14			14.09	31.96
				22.70
				14.11

[1] *The bulk methylene signals, due to their similarity in chemical environment cannot be assigned with any certainty.

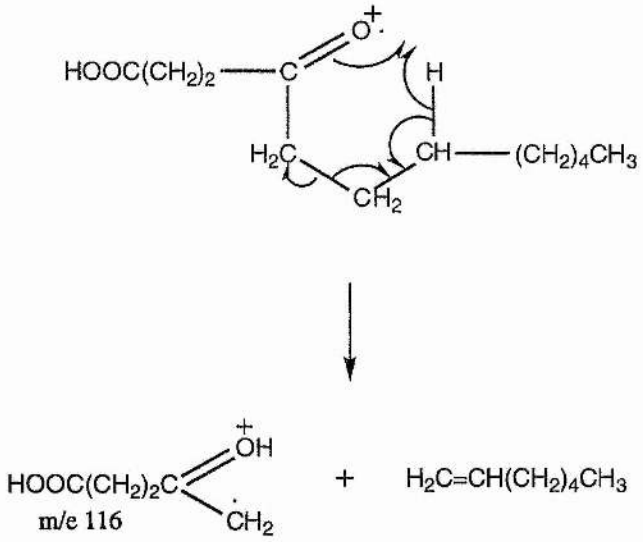
The mass spectral data for the ketoacids is shown below:

4-Oxododecanoic acid (GC-MS): Molecular ion at m/e 214 absent, 141 (27,$C_9H_{17}O^+$), 1 (55, $C_5H_8O_3^+$), 101 (30, $C_4H_5O_3^+$), 98 (100 $C_7H_{14}^+$, $C_5H_6O_2^+$), 73 (9, $C_3H_5O_2^+$), 71 (27, $C_5H_{11}^+$), 70 (7, $C_5H_{10}^+$), 69 (3.5, $C_5H_9^+$), 57 (48, $C_4H_9^+$), 55 (32,

$C_4H_7^+$), 43 (34, $C_3H_7^+$) and 41 (25, $C_3H_6^+$). The fragment ion at m/e 141 corresponds to M^+-73.



The fragment ion at m/e 116 is characteristic of a γ-ketoacid and arises from a McLafferty rearrangement;



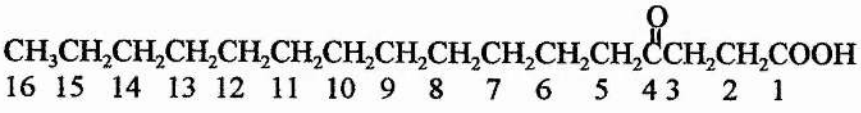
4-Oxotetradecanoic acid (GC-MS): Molecular ion at m/e 242 absent, characteristic fragment ions at m/e 169, (19, M^+-73, $C_{10}H_{21}CO^+$), 116 (39, $C_5H_8O_3^+$), 101 (35, $C_4H_5O_3^+$) and 98 (100, $C_5H_6O_2^+$).

4-Oxohexadecanoic acid: Molecular ion at m/e 270 absent, 197 (21, M^+-73, $C_{12}H_{25}CO^+$), 116 (98, $C_5H_8O_3^+$), 101 ($C_4H_5O_3^+$) and 98 (100, $C_5H_6O_2^+$, $C_7H_{14}^+$).

The infra-red spectra of the keto acids showed strong carbonyl bands at 1720cm^{-1} (ketone) and 1705cm^{-1} (acid).

The ^{1}H NMR spectra of the keto acids contained characteristic signals at δ2.4 t (2H α to COOH) and δ2.6 and δ2.7 (4H, α to C=O). The ^{13}C NMR spectra contained characteristic signals at 208ppm, C=O, and 178ppm COOH. The ^{13}C NMR shift assignments for 4-oxohexadecanoic acid are detailed in table 7.5

Table 7.5. ^{13}C NMR shift assignments for 4-oxohexadecanoic acid.



ppm	Carbon Atom Assignment
208.21	C-4
178.0	C-1
42.77	C-5
36.94	C-3
31.94	C-14
29.68	C-2 and C 8-13 inclusive[1]
29.29	C-7
24.06	C-6
22.71	C-15
14.13	C-16

1. The bulk methylenes, due to their similarity in chemical environment, cannot be assigned with any certainty.

CHAPTER 8

MATERIALS AND ANALYTICAL METHODS

CHAPTER 8

8 Materials and analytical methods.

8.1 Materials.

Primary alcohols with the exception of decanol, were supplied by Albright and Wilson Ltd.. Decanol was purchased from Aldrich Chemical Co.. The purity of these materials by GLC is as indicated in parentheses;

decanol (99%)

dodecanol (96%)

tetradecanol (99%)

hexadecanol (95%)

octadecanol (95%).

Lead tetraacetate, 2-methyltetrahydrofuran, 2,5-dimethyltetrahydrofuran and all other reagents were supplied by Aldrich Chemical Co..

All solvents were distilled prior to use.

8.2 Analytical methods.

Gas chromatographic (GLC) analyses were carried out using a Hewlett Packard (HP) 5890A chromatograph (with flame ionisation detector), linked to a HP3393A computing integrator. On-column injection mode was employed. A non-polar capillary column (Chrompack CPSIL 5CB, 0.25um film, 25m x 0.25mm i.d.) was employed, with helium carrier gas (flow rate 27cm.s^{-1}). Early GLC analyses were carried out on a PYE Unicam 104 chromatograph using a packed column (SP2340 x 1/4" i.d.) with nitrogen carrier gas (40cm^3.min^{-1}). GLC analyses were run either isothermally, (for analysis of the more volatile compounds), or using a temperature programme. Temperature programmes are abbreviated and listed in the text: For example, 100°-0-20°-300°-5 represents a temperature programme starting at 100°C, held for a period of 0 minutes, thereafter increasing at a rate of 20°C min^{-1} to a final temperature of 300°C, held for a period of 5 minutes.

The gas chromatography-mass spectrometry (GC-MS) system used was a Hewlett Packard 5890A chromatograph linked to a Finnigan Matt Incos 50s mass spectrometer in EI mode (70eV). The inlet and source temperatures were set at 250°C and 200°C respectively. The capillary column used was a 25m x 0.2mm i.d. wall coated open tubular column, with a non-polar silicone bonded phase similar to that described above. Sample introduction was by split injection. High resolution mass spectra were recorded on a AE1 MS902 double focussing mass spectrometer with electron source set at 70eV unless stated to the contrary, (some spectra were recorded with the electron source at 15eV) and the source heater at 250°c.

^{13}C and ^{1}H NMR spectra were recorded on a Bruker AM300 spectrometer. Samples were dissolved in deuterated chloroform. Chemical shifts are expressed in ppm downfield from TMS.

Infra-red spectra were recorded on a Perkin Elmer 1710 FTIR and a Perkin Elmer 1420 ratio-recording infra-red spectrometer. Samples were analysed as thin liquid films on sodium chloride discs.

Ultra-violet spectra were recorded on a Pye-Unicam SP8-100 instrument.

Analytical thin layer chromatography (TLC) was effected on 0.25mm plates of silica gel G. Mixtures of petroleum ether and diethyl ether were used as developing solvents. PE5 for example, represents a solvent system of petroleum ether (95%) and diethyl ether (5%). Visualisation was achieved by spraying with phosphomolybdic acid (10% solution in ethanol) and heating to 120°C. For preparative work, 1.00mm silica gel G plates were used. These were sprayed with 2',7'-dichlorofluoroscein (0.2% solution in methanol) and viewed under u.v. light.

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