DX

92819

TITLE METHACRYLATE ESTERS OF CYCLIC ALCOHOLS OF POTENTIAL BIOMEDICAL UTILITY.

AUTHOR SARADA TEW

INSTITUTION and DATE Polytechnic of North London, C.N.A.A. 1988

A Thesis entitled

METHACRYLATE ESTERS OF CYCLIC ALCOHOLS OF POTENTIAL BIOMEDICAL UTILITY.

Submitted to the Council for National Academic Awards in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

by

SARADA TEW (MRS), B.Sc.(Hon), M.Sc.

The Polytechnic of North London,
London.
Collaborating Establishment:
The London Hospital Medical College,
London.

May 1988

ABSTRACT

METHACRYLATE ESTERS OF CYCLIC ALCOHOLS OF POTENTIAL BIOMEDICAL UTILITY.

BY SARADA TRW (MRS)

3-Hydroxytetrahydrofuran, 3,4-epoxybutan-1-ol and 3,4-epoxy-3-methylbutan-1-ol were synthesized. The corresponding methacrylate esters were also prepared and their spectroscopic data are presented. The commercially available 3-methyloxetan-3-ylmethanol was converted to its methacryloyl ester and the analytical data were presented.

Synthetic routes for tetrahydropyran-2-ylethanol, tetrahydrofurfurylmethanol and 2-(tetrahydrofurfuryl)ethanol were investigated and the corresponding acids were synthesized. The heterocyclic acids could not be reduced using lithium aluminium hydride, and the reasons for this failure are unknown at this stage.

Methacrylate esters of the following carbocyclic and bicyclic alchols were prepared: cyclohexylmethanol, cyclohexylethanol, cyclopentanol, cyclopentylmethanol, 2-(cyclopentyl)ethanol, 2,5-norbornenemethanol and 2-norbornylmethanol. Spectroscopic data, not previously reported, were presented for the new compounds as well as the known methacrylated esters such as cyclohexylethyl, cyclopentyl, cyclopentylethyl and 2-norbornylmethyl methacrylates.

Tetrahydrofuran-3-yl methacrylate together with the above carbocyclic and bicyclic methacrylate esters were submitted to the London Hospital Medical College for polymerization studies. The results showed that all the materials submitted formed "organic glasses" with the exception of poly(cyclopentylethyl methacrylate).

It was found qualitatively that the polymers of carbocyclic and bicyclic methacrylates were more brittle than the corresponding heterocyclic compounds. Thus it appeared that the presence of oxygen in the ring was important, possibly because of the facility for hydrogen bonding.

In general, the polymerization shrinkage was in accord with the predictions based on a molar volume change of 22.5 ml/mole. However, there were two exceptions, namely cyclohexyl and cyclopentylmethyl methacrylate.

The Tg results showed that the degree of scan rate dependence varied widely. The calculation of molar refractivities from refractive index data of monomers and the ratio of these to molar volumes, gave values in good agreement with those determined previously for heterocyclic methacrylates.

It was found that tetrahydrofuran-3-yl, cyclohexyl, cyclohexylmethyl and 2,5-norbornenemethyl methacrylates showed desirable qualities such as low shrinkage, high molar volume and high Tg values which indicate their potential for future use in the biomedical field.

ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisors, Dr B.E Davison and Dr H.R. Hudson, for their suggestion of the topic and guidance throughout the course of this research.

Thanks are also due to staff at the London Hospital Medical College for carrying out the polymerization studies and to all the members of the School of Chemistry who have helped to make this work possible. A special vote of thanks are due to Dr J. Charalambous for his support and Miss J. Hopkinson for the kindness shown.

Finally. I would like to thank the Polytechnic of North London for a Research Assistantship.

This thesis is dedicated to my husband, Christopher, who has given me constant encouragement and motivation throughout the course of this work.

CONTENTS

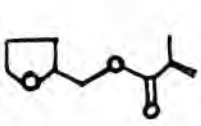
Chapter 1

HISTORICAL

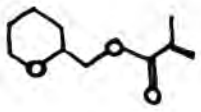
1 HISTORICAL

1.1 Introduction

The aim of the project was to investigate synthetic routes for the preparation of heterocyclic and carbocyclic esters. The investigation arose from the observation that the methacrylate esters of tetrahydrofurfuryl alcohol (1) and tetrahydropyran-2-ylmethanol (2) gave rise to low shrinkage polymers which had important potential for biomedical applications

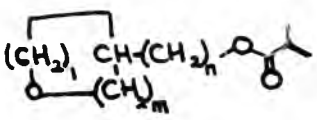


(1)



(2)

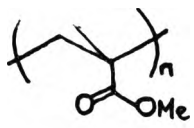
A comprehensive range of heterocyclic methacrylate esters (3) was to be made, having various ring sizes, side chain lengths and side chain positions with respect to the heterocyclic oxygen atom, in order to allow an investigation to be made of the structural features associated with desirable polymer properties. The methyl esters of methacrylic acid have widespread use in the plastics industry. Methyl methacrylate (4) is however the most widely used ester.



(3)

(4)

Poly(methyl methacrylate) (5) has many clinical uses. It is used as a bone cement in orthopaedic surgery[1], for dental bases, artificial teeth, orthodontic appliances and moulds for hearing aid devices. Unfortunately this methacrylate ester suffers from many disadvantages for continued clinical usage. It has been shown during toxicity studies[1] that it generates an allergic response, attacks oral mucosa and produces significant oral toxicity. The other problems are that methyl methacrylate has a high polymerization shrinkage (20 %) by volume), high reaction exotherm and fairly high volatility[2-4].



(5)

Such a degree of shrinkage would make it unsuitable for the moulding process as it would produce ill fitting dentures and hearing appliances. It was

found that the room temperature polymerization of tetrahydrofurfuryl methacrylate (1) produced very low polymerization shrinkage. As shown below (Scheme 1), the heterocyclic ring opens, resulting in crosslinking[6] as well as the normal vinyl polymerization (Scheme 2) that takes place.

Scheme 1

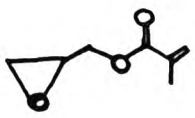
Scheme 2

When ring compounds can be opened into straight chain polymers there is generally a relatively slight change of volume[4]. The reason for low shrinkage in polymerization is that every time a covalent bond is established, a covalent bond is broken. There is, therefore, no change in the overall picture of the

chemical bonding, as between ring monomer and infinite linear polymer. The reduction of shrinkage is greater the larger the original rings because the packing of rings and chains will be more nearly similar in this case and because there will be less steric strains and distortions in the case of larger rings. The first extensive studies on the polymerization of ring compounds were made by Carothers *et al*[7].

Thus, in clinical and general application of polymers, it is extremely useful to produce low shrinkage resins. It would be useful to investigate whether tetrahydrofurfuryl methacrylate (1) has the lowest shrinkage resin after polymerization due to the most favourable ring opening propensities. The present programme was thus designed to study and synthesize other heterocyclic and cyclic methacrylates.

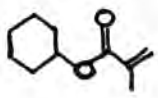
The use of glycidyl methacrylate (6) as a reaction intermediate[8] is the only other known use for a heterocyclic methacrylate.



(6)

1.2 Cyclic and heterocyclic methacrylates: their properties and uses

Tetrahydrofurfuryl methacrylate (1) and cyclohexyl methacrylate (7) are examples of "mono-functional" esters that have an active hydrogen on the secondary carbon atom which provides bifunctionality and enables cross-linking to take place. These esters can be used in printing inks[9] as a plasticizer which also act as the ingredients that provide a less thermoplastic layer to form an embossed effect on expanded polyvinyl chloride or vinyl copolymers.



(7)

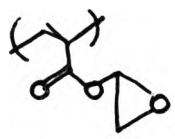
Cyclohexyl methacrylate (7) undergoes shrinkage during polymerization to the extent of 12.5 %. It has been investigated extensively[10] for utility in optical applications. Although cast cyclohexyl methacrylate polymers were used during World War II for military optical instruments, e.g. with polystyrene in achromats, the brittleness and lower degree of surface hardness of cyclohexyl methacrylate polymers have limited their usefulness. Cyclopentyl methacrylate

(20) was not reported until 1954[10]. It was predicted to have only a slightly greater polymerisation shrinkage than that reported for cyclohexyl methacrylate.

The properties of tetrahydrofurfuryl methacrylate (1) include it being a colourless, and a relatively odourless liquid. Reported uses of this monomer between 1962-1971 were: a) the copolymerization of esters[11], or acrylonitrile[12], b) coating compositions[13-15], c) copolymers useful as oil additives[16], d) ring opening copolymerisation[17].

In 1977 the monomer (1) was mentioned again in literature when more of its uses were described. They were reported to be anaerobic adhesive compositions[18], dental sealants for amalgam restorations[19], synthetic fingernails[20]. In 1980[21, 22] it was used as a crosslinking agent and also as a reactive curing agent in the peroxide catalysed production of nitrile rubber. It could also function as a plasticizer during processing, and polymerise during cure to yield hard vulcanizates. These latter properties were found to be useful in electrical cable coating[23].

In the early 1950 's[24,25] glycidyl methacrylate (6) was described in patent literature. Due to its epoxide group it is a reactive bifunctional monomer, and can be polymerised through unsaturation, resulting in poly (glycidyl methacrylate) (8).



(8)

Poly (glycidyl methacrylate) is widely used in textiles and fibres, paints and coatings, moulding and in the clinical field.

1.3 Preparation of methacrylate esters

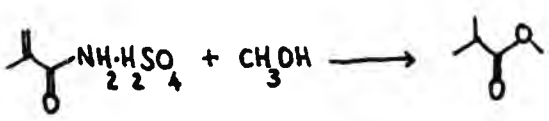
1.3.a General industrial methods

Methacrylate esters were commercially produced from 1933, using the acetone cyanohydrin process[26,27]. The manufacture of methyl methacrylate (4) is still being carried out by this process[28]. As described below (Scheme 3) the method consists of two continuous steps. Initially the reaction of acetone cyanohydrin (9) with excess concentrated sulphuric acid (98 %) produces the intermediate methacrylamide sulphate

(10). This is followed by a second step (Scheme 4) which involves hydrolysis of the intermediate followed by esterification with methanol.

(9) (10)

Scheme 3



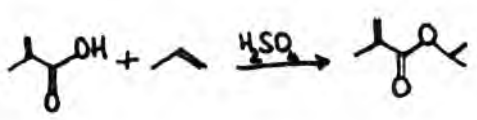
Scheme 4

The direct esterification of methacrylic acid (12) with an alcohol, in the presence of a suitable catalyst such as sulphuric acid, *p*-toluenesulphonic acid or sodium methoxide (Scheme 5) would give methacrylate esters. Using functionalised alcohols, direct esterification gives higher alkyl esters. Operation at moderate temperatures are achieved by the use of solvents. Methacrylic acid esterification with methanol and lower alcohols in the vapour phase while resulting in good selectivity, does not usually go to

completion even when the ester is removed by azeotropic distillation [29].

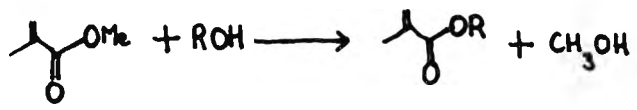
Scheme 5

The method of direct esterification via the reaction of methacrylic acid with olefins, in the presence of acid catalysts (Scheme 6) can also be used for the preparation of branched chain alkyl esters[30].



Scheme 6

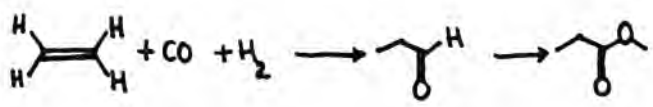
Transesterification [31] is used for the preparation of higher alkyl methacrylates. It can also be applied to batch processing of functionalised alkyl methacrylates with great success. The reaction of methyl methacrylate with higher alcohols produces methanol and its removal as a benzene-methanol azeotrope, forces the reaction to proceed to the right (Scheme 7).



Scheme 7

Depending on the nature of alcohol or the kinetics of the reaction a number of acid catalysts may be used[32-36].

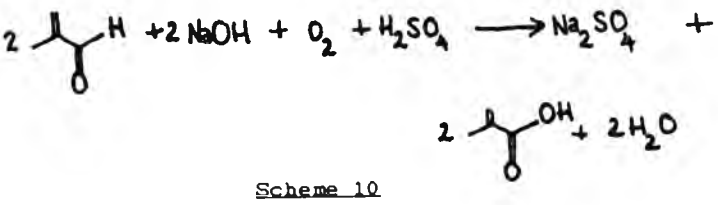
Using the propanoate-methanal route either methyl methacrylate or methacrylic acid can be obtained. Depending on conditions, ethane may yield either propanal or propanoic acid when treated with carbon monoxide and hydrogen (Scheme 8). The vapour-phase catalytic condensation of the initial stage product with methanal is given in the second stage (Scheme 9). The yields are improved by the use of latter process and catalysts of high selectivity (eg Group I or Group II metals).



Scheme 8

Scheme 9

Methyl methacrylate is produced by the catalytic dehydrogenation of methyl isobutyrate, via the intermediate isobutyric acid. The intermediate can be produced by several other routes. The liquid-phase oxidation of methacrolein is not an economically viable process, although the yields are high[37]. Methacrolein is converted to the sodium salt as it is formed, and the product is recovered by acidification of the salt solution (Scheme 10).



Scheme 10

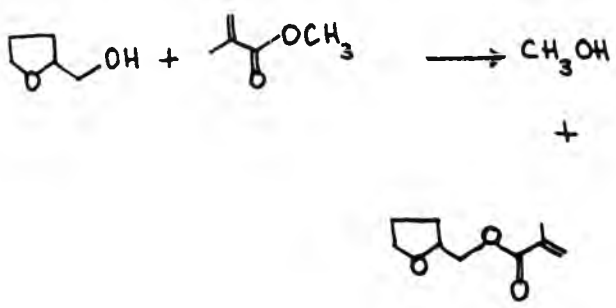
The method of alkylcarbonylation of propylene is considered unsuitable for yielding methacrylic acid or methyl methacrylate because crotonate and saturated by-products are also formed[38].

The first reported preparation of glycidyl methacrylate (6) involved a reaction between an alkali - metal salt of methacrylic acid and epichlorohydrin[39]. The method was improved in 1951 by the use of a quaternary ammonium salt, such as tetramethylammonium chloride[40].

1.3.b Laboratory methods

1.3.b.i Heterocyclic monomers

Transesterification has been used to prepare tetrahydrofurfuryl methacrylate (1) [41, 42] (Scheme 11).

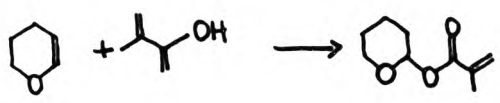


Scheme 11

Methacrylic esters of primary and secondary alcohols were prepared by direct esterification and those of

tertiary alcohols or phenols by reacting them with methacryloyl chloride[44].

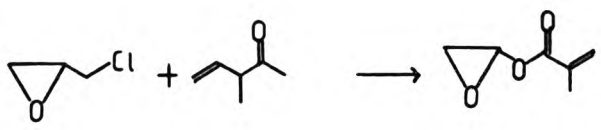
In 1964 the reaction of methacrylic acid with dihydropyran (14) was reported to give tetrahydropyranyl methacrylate (15) [45] in 50 % yield (Scheme 12).



(14) (15)

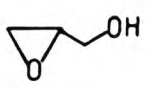
Scheme 12

Since 1951[46-49] several preparations of glycidyl methacrylate (6) have been reported. Epichlorohydrin (16) is often used as one of the starting materials, and not the corresponding alcohol, glycidol (17), from which (16) is made. As shown below (Scheme 13) epichlorohydrin is reacted with (poly)carboxylic acids or anhydrides, or alkali-metal salts of methacrylic acid, or alkali metal carbonate, in the presence of a catalyst, polymerization inhibitor and under varying conditions of temperature and pressure.



(16)

Scheme 13



(17)

Glycidyl methacrylate (6) has been produced by the ester interchange reaction of methyl methacrylate and glycidol (17). Various catalysts were employed to improve the yields, and amongst them are:

a) phosphines[50],

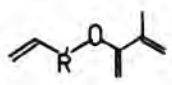
b) alkali alcohlate[51],

c) alkali cyanide[52],

d) metal salt of a fatty acid[6].

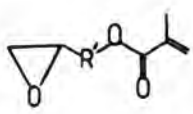
A third method of producing glycidyl methacrylate was achieved by monoepoxidation[53,54]. This is a selective method of epoxidation whereby one of the two terminal

ethylenic linkages is not conjugated with each other (18).



(18)

R' is a divalent alkylene radical containing 2 - 9 carbons. By this method, of the terminally located ethylenic linkages, only the ω -linkage in the alkenyl radical is epoxidized, and the α - ethylenic linkage in the methacryloyl residue is left intact (19). The unsaturated ester (18) is treated with peracid (e.g. peracetic acid) and a basic agent (e.g. sodium acetate) and the reaction is kept at 50 °C.

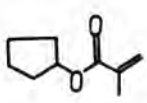


(19)

1.3.b.ii Carbocyclic monomers

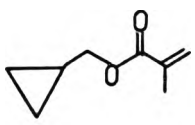
Preparation of carbocyclic methacrylates is not widely reported in the literature. Cyclopentyl methacrylate (20) was reported to be made by three methods[19], direct esterification, transesterification, and methacryloyl chloride (21) esterification (Scheme 14).

The methacryloyl chloride method of esterification was also employed[20] for the preparation of cyclopropylmethyl methacrylate (22) and cyclopentylmethyl methacrylate (23).

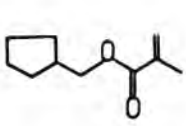


(20)

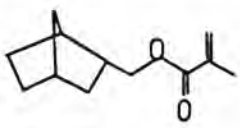
(21)



(22)

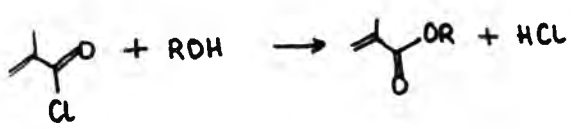


(23)



(24)

2-Norbornylmethyl methacrylate (24) was reported to be prepared in a patent[56] by the direct esterification of the alcohol (40). Incidentally, these above monomers were reported only once in the literature in each case. Cyclohexyl methacrylate (7) is the only commercially available monomer.



(21)

Scheme 14

1.4 Properties of monomeric methacrylate esters that influence polymer properties on polymerization

The first extensive studies on the polymerization of ring compounds were made by Carothers[57]. In 1948 Tobolsky *et. al.*[5] reported that cyclic ring compounds, disulfides and siloxanes, could be polymerized into rubbery polymers at room temperature with minimal shrinkage.

In 1949 Crawford[58] tried to obtain information about the influence of the alcohol alkyl chain length

and of branching in this chain, and the effect this would have on the properties of the polymer. Crawford attempted to explain variations in the polymeric properties mainly on the basis of induction due to methyl groups in the alcohol alkyl radicals.

Crawford carried out a study on higher polyalkyl methacrylates[66]. It was shown that in all cases density increased on passing from monomer to polymer. The following equation shows the measure of this increase as the percentage shrinkage of the monomer on polymerization,

$$\frac{\Delta V}{V}\ (\%) = \frac{\rho_{r.} - \rho_{m}}{\rho_{r.}} \times 100$$

where $\rho_{r.}$ and $\rho_{m.}$ are the densities of polymer and monomer respectively. It was found that on passing up the alkyl series the shrinkage decreased, just as in isomeric series generally with increase in branching of the alcohol alkyl radical. It was argued that the main cause of the shrinkage in these cases was related to the polymerizable methacryloxy group, and thus the percentage polymerization shrinkage would be expected to fall off as the alkyl series was ascended. Crawford predicted that with increase in size of the alcohol alkyl group, the proportion of material non-

reactive would increase. It was considered by Crawford[56] that by relating the shrinkage to the molar volume, a better assessment could be made of any special effects of branching of the alcohol alkyl group on polymerization shrinkage.

The molar shrinkage on polymerization can be described as the difference between the molar volume of monomer and that of the polymer. It quantifies the change in the space occupied by the monomeric molecules on passing into polymeric combination. The molar shrinkage of alkyl methacrylates, in which the alcoholic alkyl radicals vary in length only, is almost uniform with a mean value of 24.2 . With branched chain alkyl groups the shrinkage value was found to be below the mean value for normal alkyl esters.

It was Nichols and Flowers[58] who explained a way of predicting the percent shrinkage of a vinyl or allyl type monomer during polymerization, from its structural formula. Tobolsky *et al.*[6] pointed out that the shrinkage in a vinyl type polymerization was connected with the exchange of a van der Waals bond and a double bond for two single covalent bonds. He thought it likely, then, that there was an approximately constant shrinkage which could be assigned to a difunctional group when it polymerized. It was argued that the percent shrinkage should,

therefore, be directly related to some molecular quantity. The work done by Nichols and Flowers[52] suggested that the shrinkage of a molecule, on polymerization, was related to the volume of revolution of the monomer molecule about its major axis. It was described by a curve having a hyperbolic equation.

$$X\ Y + 15\ Y = 3750$$

The volume of revolution for a number of monomers was calculated by two methods,

a) from covalent bond distances, bond angles, and kinetic theory collision radii, and
b) from atomic models.

The latter method was found to be very convenient and accurate.

Loshaek and Fox[53] presented a method for determining the residual unsaturations in copolymerization of methacrylate esters with glycol dimethacrylates, and the fraction of dimethacrylate molecules which had reacted at both ends (the crosslinking efficiency) was calculated from the result. Residual unsaturations were determined from a comparison of the observed volume contractions per

mole of double bond with corresponding contractions for complete conversion of monomer to polymer. Apparent molar volume contractions were calculated from density data at 30 °C on the monomers and polymers.

There were no further studies on polymerization shrinkage of methacrylate esters until Braden and Patel published their work[6,7]. Their studies included: a) polymerization shrinkage of n-alkyl methacrylate esters (C_1 - C_{14}), and some of their isomers, and b) polymerization shrinkage of some heterocyclic methacrylates.

In the above work[7] polymerization shrinkage of monomers was measured using densitometry. They found that the shrikage decreased with increasing number of carbon atoms in the side chain of n-methacrylates. However, they had also discovered that using higher methacrylates to achieve lower shrinkage was limited in practice due to the rapid descent of T_g (the glass transition temperature) with increasing number of carbon atoms in the side chain (Fig.1).

However, the really fundamental information was obtained from plots of molar volume of a monomer unit in monomer and polymer of n-alkyl methacrylate against the number of carbon atoms in the side chain (Fig 2). The plots were parallel lines with a slope of 16.6 cm^3/mol.

Reproduced from ref[6] by permission of the publishers, Butterworth & Co (Publishers) Ltd (c).

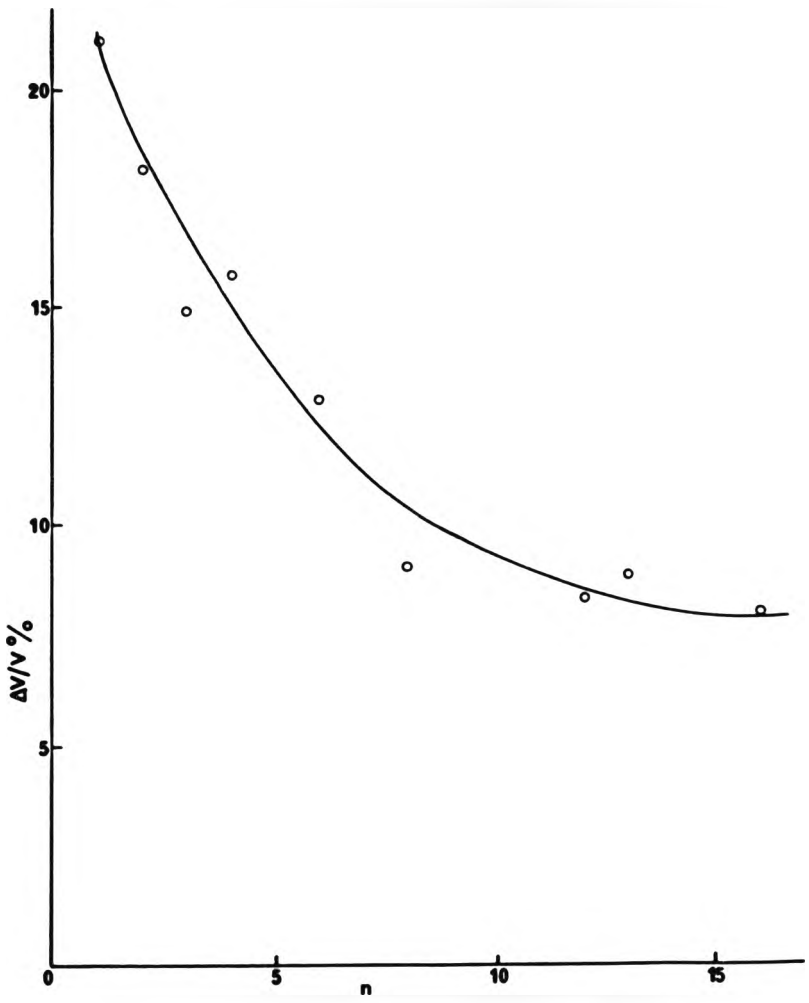


Fig 1 Shrinkage(%) vs no of carbons in side chain

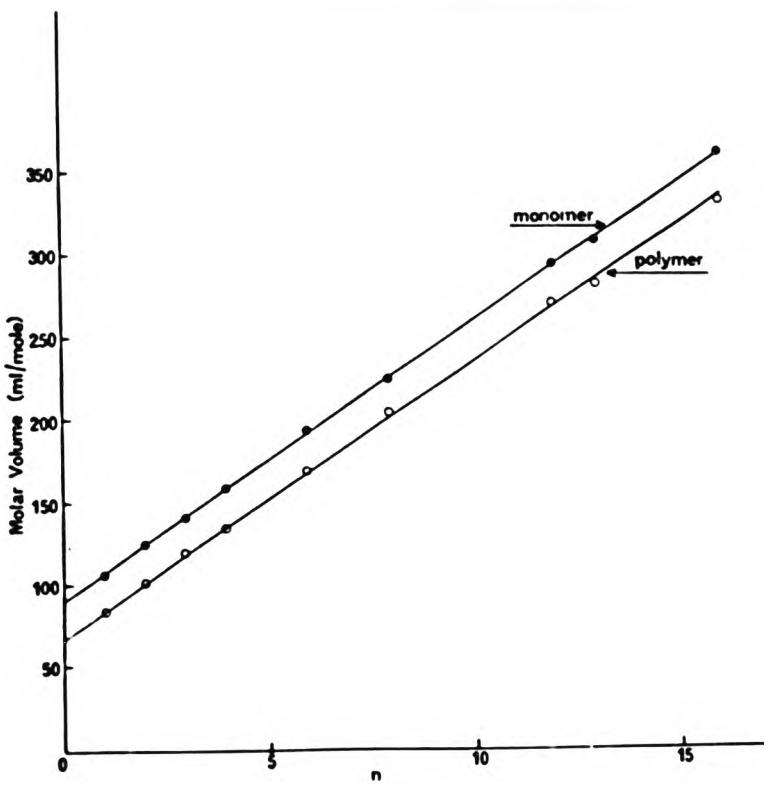


FIGURE 2

Molar volume (V_m) of alkyl methacrylate monomers and polymers, as a function of the number of carbon atoms (n) in the alkyl side group.

Reproduced from ref[illegible] by permission of the publishers, Butterworth & Co (Publishers) Ltd (c).

Table 1 Shrinkage data for bicyclic & heterocyclic methacrylates

Ester	Molar Volume (ml/mol)		Shrinkage	ΔVm
	Monomer	Polymer	ΔV/V%	(ml/mole)
2,3-Epoxypropyl	131.893	109.712	16.82	22.181
Tetrahydropyran-2-ylmethyl	179.548	154.884	13.74	24.664
Tetrahydropyranyl	165.878	142.505	14.09	23.373
Tetrahydrofurfuryl	163.363	139.332	14.71	24.031
Isobornyl	226.057	205.326	9.06	20.731

(Taken from reference 126)

The values for the contribution of the CH_2 group to the molar volume of simple liquids were considered by Braden and Patel[61]. Van Krevelen[62] reported that the molar volume of the CH_2 group was 15.85 in glassy polymers. Braden[61] had obtained a similar value from the slopes of the two lines in the above described plot (Fig. 1). Braden[61] also deduced from the plot (Fig 1) that since the lines were parallel the change in molar volume (ΔV_m) was independent of the size of the side chain, giving a ΔV_m value of 22.5 cm^3/mol. These results were found to be in good agreement with both Loshaek and Fox[60], and Crawford[58] for a number of methacrylates. The values obtained by Braden[61] for heterocyclic methacrylates and isobornyl methacrylate are shown in Table 1

Thus Braden[61] found that the change in molar volume on polymerization was independent of the side chain, and that this was in accord with the predictions of Tobolsky[5]. He[6] pointed out that the shrinkage in a vinyl type polymerization was connected with the exchange of a van der Waals bond and a double bond for two single covalent bonds. Braden[61] noted that the shrinkage would decrease with molar volume, due to the number of molecules per unit volume decreasing with the volume of the molecule. Braden[61]

found that side groups of similar volume, but different geometry, had substantially varying effects on the T_g of the polymer, a result with considerable practical implications. They[61] found that on comparing isobornyl methacrylate, which had a very large substituent group, with a C_{13} ester (a rubber) the percentage shrinkage of the former has a high T_g of 93 °C whereas the latter has 83 °C for the poly (methyl methacrylate). In the same note Braden[61] found that tetrahydrofurfuryl methacrylate has a similar shrinkage to n-butyl methacrylate, but the former was a glass at room temperature with a T_g value 15 °C higher than n-butyl methacrylate. From this it was deduced that the percentage volume shrinkage depended mainly on molar volume of the molecule, and also on the volume of the side group, but the T_g was affected mainly by the geometry and stiffness of the side group.

However, there was a need to research into other heterocyclic polymers to test more fully the above hypothesis. It was therefore the aim of the present programme to gather further evidence of structural properties of monomeric heterocyclic and carbocyclic esters that may affect polymer properties on polymerization.

Chapter 2

DISCUSSION

2 DISCUSSION

2.1 Introduction

In 1984 a successful application was made jointly by the Polytechnic of North London and the London Hospital Medical College to the Science and Engineering Research Council (SERC) for support of a project entitled "Methacrylate esters of cyclic alcohols of potential biomedical utility". The case presented to the SERC argued that " it has long been evident that low shrinkage polymerization systems are desirable for clinical as well as other applications. Indeed Bailey *et al.* have reported on systems to give expansion on polymerization[63-65]. Free radical ring opening processes have been described for cyclic acetates[66-69].

Most dental and clinical polymers are methacrylates, presented as a polymer powder and a monomer liquid. These are mixed together to form a dough which is easy to handle and form and, if a suitable activator is present in the monomer, will polymerise at room or body temperature. For many years, poly(methyl methacrylate) powder was used with methyl methacrylate monomer and for that matter is still used in orthopaedic bone cements, hearing aid moulds, and denture repair resins etc. Such resins

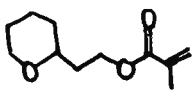
suffer from high shrinkage, high exotherm, and toxic or irritant effects of the monomer. However, Braden *et al.*[3,65] have described systems where the dough comprises poly(ethyl methacrylate) with a n-butyl methacrylate monomer, which have much lower exotherm, much improved soft tissue and pulpal tolerance, and convenient handling properties. This system has been developed further over the last ten years as a cement and is now on clinical trial in patients. Its basic physico-chemical properties have been described by Braden[4]. This system still has high shrinkage.

However, recent work at the London Hospital Medical College[5] has shown that a dough system comprising poly(ethyl methacrylate) polymer powder with tetrahydrofurfuryl methacrylate gave a very low shrinkage resin. Preliminary clinical trials in this application and as a temporary crown and bridge in dentistry have been very successful. Furthermore, histological tests in the dental context have shown this system to be the least irritant of any acrylic system yet studied[6].

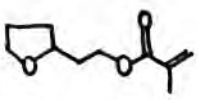
In undertaking the project, the author set out to answer the immediate question as to whether other heterocyclic methacrylates have a greater ring opening propensity, and hence lower shrinkage. It was hoped that the same or improved biological properties and with different physical properties with respect to

strength, transition temperature, water absorption and viscoelastic properties would be formed in the new polymers.

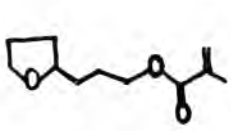
Thus in the present work a comprehensive range of heterocyclic methacrylate esters (3) was to be made, having various ring sizes and side chain lengths. The only commercially available esters of this type are tetrahydrofurfuryl methacrylate (1) and glycidyl methacrylate (6). A major part of the work undertaken was to investigate the synthetic routes leading to the preparation of tetrahydropyran-2-ylethyl methacrylate (25), 2-tetrahydrofurfurylmethyl methacrylate (26), 2-tetrahydrofurfuryl-2-ethyl methacrylate (27), 3-tetrahydrofuryl methacrylate (28), 3,4-epoxybutyl methacrylate (29) and 3-methyl-3,4-epoxybutyl methacrylate (30).



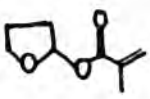
(25)



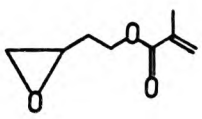
(26)



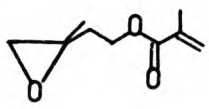
(27)



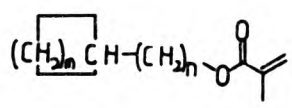
(28)



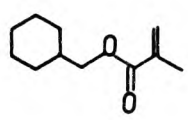
(29)



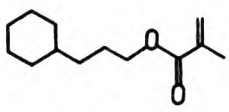
(30)



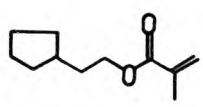
(31)



(32)



(33)

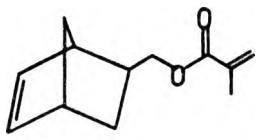


(34)

The work was also extended to include the synthesis of analogous carbocyclic derivatives (31) to show the importance or otherwise of the heterocyclic oxygen atom in relation to physical properties and also to possible cross linking.

The following carbocyclic methacrylates were to be synthesized as they are not commercially available: cyclohexylmethyl methacrylate (32), 2-(cyclohexyl)ethyl methacrylate (33), cyclopentyl methacrylate (20), cyclolpentylmethyl methacrylate (22), and 2-(cyclopentyl)ethyl methacrylate (34).

Further, bicyclic derivatives such as 2,5-norbornenylmethyl methacryalate (35) and 2-norbornylmethyl methacrylate (24) were to be made to provide information on the importance of molecular volume with respect to shrinkage and T_G values.



(35)

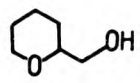
2.2 Alcohol Synthesis

2.2.1 Heterocyclic Alcohols

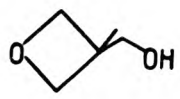
It was found that heterocyclic alcohols, other than tetrahydrofurfuryl alcohol (13), tetrahydropyran-2-ylmethanol (36) and 3-methyloxetan-3-ylmethanol (37) were not commercially available.

Thus in order to prepare novel heterocyclic methacrylate esters, the design and synthesis of the corresponding alcohols became a prerequisite.

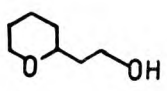
A major part of the current programme consisted of an investigation of synthetic routes for the preparation of a range of heterocyclic alcohols such as tetrahydropyran-2-ylethanol (38), 2-(tetrahydrofurfuryl)methanol (39), 2-(tetrahydrofurfuryl)ethanol (40), tetrahydrofuran-3-ol (41), 3,4-epoxybutanol (42), and 3,4-epoxy-3-methylbutanol (43).



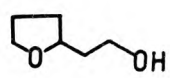
(36)



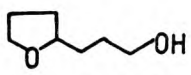
(37)



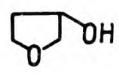
(38)



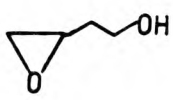
(39)



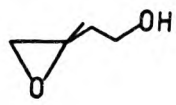
(40)



(41)



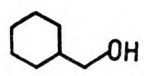
(42)



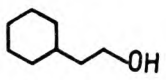
(43)

2.2.2 Carbocyclic alcohols

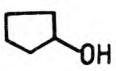
Many of the required carbocyclic alcohols, such as cyclohexylmethanol (44), 2-cyclohexylethanol (45), cyclopentanol (46), cyclopentylmethanol (47), 2-norbornylmethanol (48), 2,5-norbornenemethanol (49), were commercially available. The only carbocyclic alcohol to be synthesized was 2-(cyclopentyl)-methanol (50)



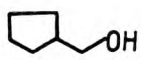
(44)



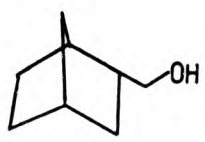
(45)



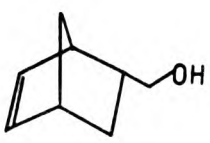
(46)



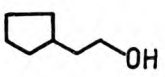
(47)



(48)



(49)



(50)

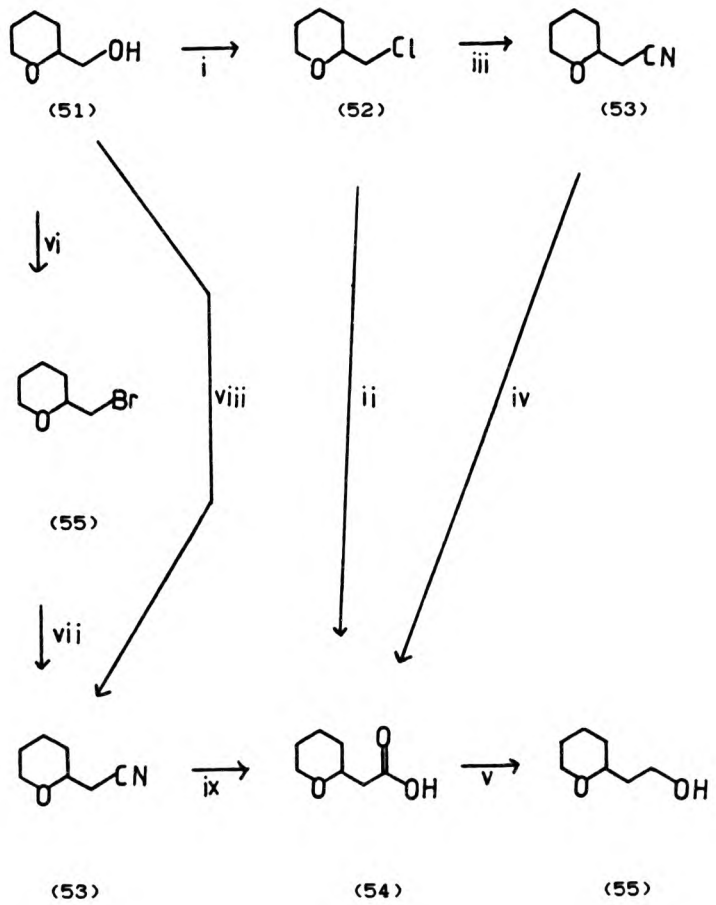
2.3 Synthesis of tetrahydropyran-2-ylethanol

There was an extensive investigation of synthetic routes for the preparation of tetrahydropyran-2-ylethanol. Three major pathways were followed, namely via

1) the halogen derivative of tetrahydropyran-2-ylmethanol (Scheme 15, p.45),
2) the tetrahydropyran-2-ylmalonic ester (Scheme 16, p.52),
3) direct condensation of malonic acid ester with 2-hydroxytetrahydropyran (Scheme 17, p.58).

2.3.1 Synthesis of tetrahydropyran-2-ylethanol using tetrahydropyran-2-ylmethanol

There has been very little in the literature on the chain extension of tetrahydropyran-2-ylmethanol to give tetrahydropyran-2-ylethanol (Scheme 15). A few individual reactions, such as halogenation[70-74] (i and vi) and direct nitrilation[75] (viii, Scheme 15) of tetrahydropyran-2-ylmethanol have been reported. Many other reactions such as nitrilation of the halogen derivative (iii and vii), hydrolysis of the nitrile (iv and ix), Grignard reaction with the halogen derivative (ii) or the reduction of tetrahydropyran-2-



Scheme 15

ylacetic acid (v, Scheme 15) have not been reported in the literature.

2.3.1.a Preparation of the halogeno derivatives

2.3.1.a.i Tetrahydropyran-2-ylmethyl chloride (52)

Tetrahydropyran-2-ylmethyl chloride was prepared using the method described by Ansell and Thomas[70] which involved the reaction of the alcohol, tetrahydropyran-2-ylmethanol with thionyl chloride in the presence of a catalytic amount of pyridine. During the work up an emulsion was formed which could only be dispersed with the addition of solid sodium chloride over an 8 h period. The boiling point, refractive index and yield agreed closely however with the literature values for the desired product.

2.3.1.a.ii Tetrahydropyran-2-ylmethyl bromide (55)

Tetrahydropyran-2-ylmethyl bromide was prepared using N-bromosuccinimide and triphenylphosphine[71] and the yield obtained was good (72 %). The boiling point and refractive index compared well with the literature values.

2.3.1.b Preparation of tetrahydropyran-2-ylmethyl cyanide (53)

It was found that tetrahydropyran-2-ylmethyl chloride was unreactive towards sodium cyanide in DMSO, thus the reaction was repeated with tetrahydropyran-2-ylmethyl bromide. Although stringent precautions were taken to ensure anhydrous conditions in the reaction, tetrahydropyran-2-ylmethyl bromide did not readily react with sodium cyanide in DMSO (Table 2). The best result was obtained when DMSO was distilled over calcium hydride pellets and sodium cyanide was powdered and dried for 24 h at 100 °C immediately before use. Thus tetrahydropyran-2-ylmethyl cyanide was prepared in good yield (60 %) in small quantities and identified by i.r. spectroscopy.

2.3.1.c Preparation of tetrahydropyran-2-ylacetic acid (54)

Tetrahydropyran-2-ylmethyl cyanide was heated under reflux with 20 % potassium hydroxide in aqueous ethanol to give tetrahydropyran-2-ylacetic acid (80 %). The product was identified by ^{1}H n.m.r. (Table 3) and the i.r. spectrum showed that the cyanide peak at 2240 cm^{-1} had disappeared and a strong carbonyl peak appeared at 1710 cm^{-1}. The ^{1}H n.m.r.

Table 2 Reaction of sodium cyanide with tetrahydropyran-2-ylmethyl bromide(55)

Exp.	Reaction temp./ °C	Reaction time h	min	Appearance at the end of heating	Yield g	%
3.36.1	90	-		dark brown liquid[a]		-
3.36.2	100	-		dark brown liquid[a]		-
3.36.3	110	-		dark brown ppt.[a]		-
3.36.4	80	0	30	brown liquid[a]		-
3.36.5	90	1	00	dark brown liquid[a]		-
3.36.6	100	1	20	black solid[a]		-
3.36.7	50	0	30	colourless liquid[b]	0.6	15
3.36.8	60	1	00	brown liquid[b]	2.0	60
3.36.9	70	2	00	dark brown solid[b]	1.2	45
3.36.10	80	1	30	dark brown liquid[b]	0.7	40
3.36.11	90	1	00	dark brown solid[b]	0.3	20

a DMSO dried over calcium hydride

b DMSO distilled over calcium hydride

spectra had not previously been reported in the literature. It showed the acidic hydroxyl group appeared at δ 6.50, which disappeared upon the addition of dueterium oxide. The ring protons appeared at δ 1.32 as a multiplet and the protons near the electronegative oxygen in the ring appeared further upfield at δ 2.46 and 4.06.

2.3.1.d Preparation of tetrahydropyran-2-ylethanol (55)

When tetrahydropyran-2-ylacetic acid was treated with lithium aluminum hydride (v, Scheme 15) in diethyl ether and the mixture allowed to stir for over 24 h, it was found that incomplete reduction had occurred. This was evident from the g.c. analysis and the i.r. spectrum where the carbonyl peak at 1710 cm^{-1} was still present, although this was of a lesser intensity than that of the starting material. The separation of the two major components by column chromatography proved difficult to monitor since tetrahydropyran-2-ylethanol could not be easily distinguishable on the t.l.c. plates from the starting material.

It should be noted that throughout the course of this work, the six and five-membered heterocyclic acids could not be completely reduced using lithium

aluminium hydride. The reasons for this are not known at present.

Table 3 ^{1}H n.m.r. data for tetrahydropyran-2-ylacetic acid

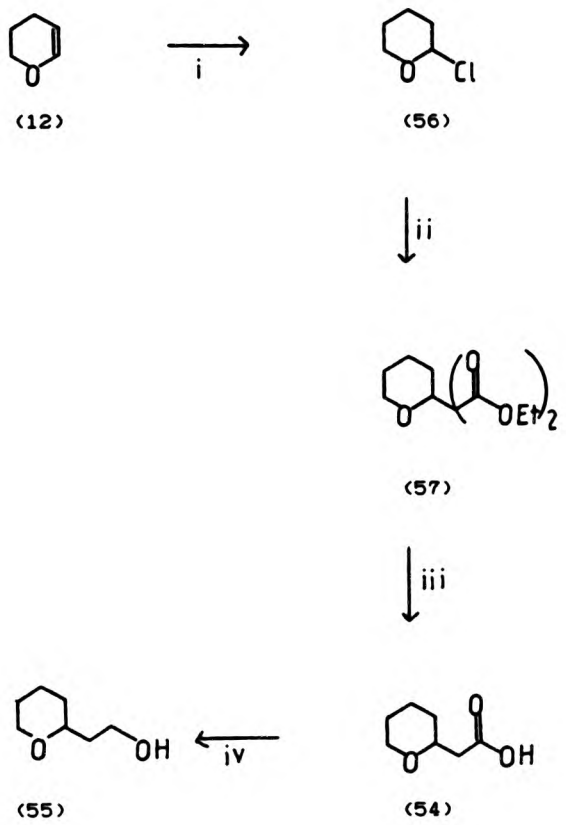
Group	Integration	Chemical Shift, δ
3 × CH_2 of ring	6H	1.32 (m)
CH_2-O, ring	2H	2.46 (m)
CH_2, side chain and CH-O of ring	3H	4.06 (m)
OH, acidic	1H	6.50 (s)

2.3.2 Synthesis of tetrahydropyran-2-ylethanol from the malonic ester (Scheme 16)

The reaction of dihydropyran (12) with anhydrous hydrogen chloride (i, Scheme 16) to give 2-chlorotetrahydropyran (56) has been reported by Schudel and Rice[76]. They have also described the preparation of diethyl tetrahydropyran-2-ylmalonate (57). Zelinsky *et al.*[77] reported the hydrolysis of the malonic ester (iii, Scheme 16). However, there has been no report in the literature of the reduction of tetrahydropyran-2-ylacetic acid (iv, Scheme 16).

2.3.2.a Preparation of 2-chlorotetrahydropyran

The procedure described by Schudel and Rice[76] was followed and 2-chlorotetrahydropyran (56) was prepared by passing anhydrous hydrogen chloride gas into a solution of dihydropyran. The product was not isolated before use in the next stage (ii, Scheme 16).



(12) (56) (57) (54) (55)

Scheme 16

2.3.2.b Preparation of the malonic ester (57)

Diethyl tetrahydropyran-2-ylmalonate (57) was prepared as described in the literature[76]. It was found that a very efficient stirring of the suspension of the monosodium salt of diethyl malonate was required for a good yield, before and during the addition of the cooled 2-chlorotetrahydropyran (56) to the reaction mixture. During the addition of the halogeno derivative (56), the flask had to be cooled since the temperature rose rapidly. The distilled product had a slightly higher boiling point than that quoted in the literature[76], but the refractive index data agreed closely.

The i.r. spectrum showed an intense absorbance at 1740 cm^{-1}, the ester carbonyl region. The tetrahydropyran-2-ylmalonic ester was further identified by ^1H and ^{13}C n.m.r. (Table 4 & 5), none of which had been reported in the literature. The ^1H n.m.r. spectrum of the tetrahydropyran-2-ylmalonic ester (Table 4) showed the protons in the ester group and the side chain appeared further downfield than the rest due to their close proximity to the electronegative oxygen in the ester group. The ring protons adjacent to the oxygen atom appear slightly higher field at δ 3.42, and the rest of the ring protons appear quite high field at δ 1.37. All the

signals were observed as multiplets and this indicates extensive long range coupling. The ^{13}C n.m.r. spectrum (Table 5) showed clearly the two carbonyl groups at δ 167.6 and 167.0 as shortened signals. The side chain carbon attached to the two ester groups appeared at δ 76.23 and the substituted ring carbon appeared slightly higher field at δ 68.86. The ester methylene carbons were in identical chemical environment and thus appear at the same absorbance of δ 61.40. The shielded ring carbons appear quite high field at δ 29.55, 25.79 and 23.18 and the two ester methyl groups appeared at δ 14.10 as a single absorbance.

2.3.2.c Preparation of tetrahydropyran-2-ylacetic acid (54)

Hydrolysis of the tetrahydropyran-2-ylmalonic ester (57) was carried out[77] by refluxing it with 50 % sodium hydroxide in ethanol. After neutralisation with 4 N hydrochloric acid, the mixture was extracted with diethyl ether many times (10 × 150 ml) until no more product could be extracted from the aqueous layer. A sample of the crude acid was recrystallised from petroleum ether (60-70°C fraction) and the melting point (135-6°C) agreed closely with the

literature value[77] quoted for tetrahydropyran-2-ylmalonic acid.

The rest of the crude tetrahydropyran-2-ylmalonic acid was heated in an oil bath until the carbon dioxide evolution had ceased and the residue was distilled to give tetrahydropyran-2-ylacetic acid (54). The acid solidified on cooling and was recrystallised from petroleum ether (90-120°C fraction); its melting point agreed closely with the literature value[77]. Its i.r. spectrum showed an intense carbonyl absorbance at 1720 cm^{-1}. The ^1H n.m.r. data was identical to that of tetrahydropyran-2-ylacetic acid obtained earlier via the cyanide derivative (Table 3, p.50).

Table 4 ^1H n.m.r. for diethyl tetrahydropyran-2-ylmalonate

Group	Integration	Chemical Shift, δ
2 × $COOCH_2CH_3$, and CH	5 H	4.18 (m)
CH_2- O	2 H	3.42 (m)
3 × CH_2, CH and	13 H	1.37 (m)
2 × $COOCH_2CH_3$		

Table 5 ^{13}C n.m.r. for diethyl tetrahydropyran-2-ylmalonate

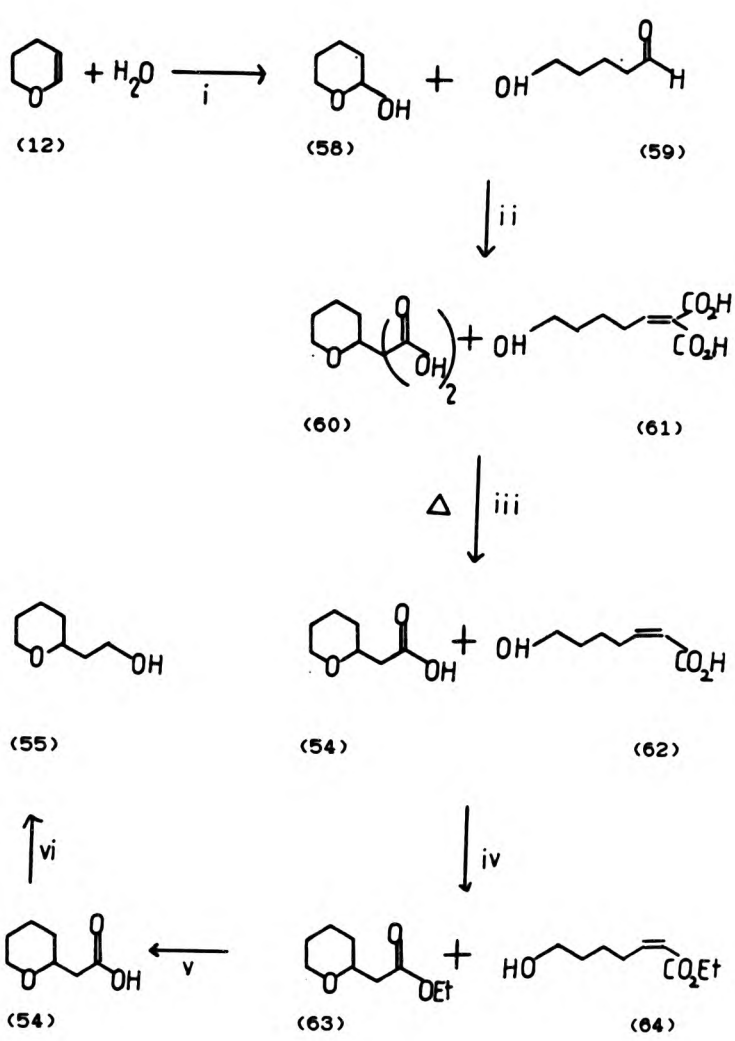
Group	Chemical Shift, δ
2 × C=O	167.63, 167.06
CH, side chain	76.23
CH, ring	68.86
2 × $COOCH_2CH_3$	61.40
CH_2-O, ring	58.37
3 × CH_2, ring	29.55, 25.79, 23.18
2 × CH_3, ester	14.10

2.3.3 Synthesis of tetrahydropyran-2-ylethanol via 2-hydroxytetrahydropyran

2-Hydroxytetrahydropyran (58) was not commercially available but its synthesis from 2,3-dihydropyran (12) was reported in the literature[78-80]. The acid hydrolysis of 2,3-dihydropyran (i, Scheme 17) was reported[78] to yield an equilibrium mixture of 5-hydroxypentanal (59) and 2-hydroxytetrahydropyran (58).

Hurd and Saunders[81] studied the u.v. spectrum of 5-hydroxypentanal and estimated that only 5 % free aldehyde was present in the above equilibrium mixture. It has been widely reported in the literature [80,82,83] that tetrahydropyran-2-ylacetic acid was synthesised starting from 2-hydroxytetrahydropyran. Kennedy *et al.*[82] reported on the reaction of 2-hydroxy-tetrahydropyran with malonic acid (ii and iii, Scheme 17) under Doebner conditions giving rise to a mixture of tetrahydropyran-2-ylacetic acid (54) andtrans-7-hydroxyhepten-2-oic acid (62) which could be separated by distillation.

However, Fray *et al.*[83] had found that the mixture (54 and 62) could not be separated by distillation due to the formation of polyesters. They found that on


+ H2O
i
OH
H
(12)
(58)
(59)
ii
CO2H
CO2H
(60)
(61)
Δ
iii
OH
CO2H
(55)
(54)
(62)
vi
iv
v
HO
CO2Et
OEt
(54)
(63)
(64)

Scheme 17

esterification (iv, Scheme 17), the two isomeric esters (63 and 64) could be separated by fractionation. Fray[e2] also found that alkaline hydrolysis of the hydroxy ester (64) did not furnish the corresponding acid (62), but that it had caused a complete rearrangement to tetrahydropyran-2-ylacetic acid (v, Scheme 17). Thus in the present work it was decided not to fractionate the isomeric esters (63 and 64) but to hydrolyse the mixture in alkaline conditions (v, Scheme 17) to give the single desired product, tetrahydropyran-2-ylacetic acid.

2.3.3.a Preparation of 2-hydroxytetrahydropyran

Following the method described by Schiepp and Geller[78], 2-hydroxytetrahydropyran was obtained from 2,3-dihydropyran (1, Scheme 17). The spectroscopic data were not previously reported in the literature. The proton n.m.r. spectrum showed (Table 6) the hydroxyl group at δ 4.05 which disappeared upon the addition of dueterium oxide. The substituted ring proton appeared quite low field due to the deshielding effects of the hydroxyl oxygen as well as the ring oxygen. The two ring protons adjacent to the ring oxygen appeared at δ 3.56, and the rest of the ring

Table 6 ^{1}H n.m.r. data for 2-hydroxytetrahydropyran

Group	Integration	Chemical Shift, δ
CH-O	1 H	4.98 (m)
OH	1 H	4.05 (m)
CH_2-O	2 H	3.56 (m)
3 × CH_2	6 H	1.64 (m)

Table 7 ^{13}C n.m.r. data for 2-hydroxytetrahydropyran

Group	Chemical Shift, δ
CH-O, ring	94.46
CH_2-O, ring	63.83
3 × CH_2, ring	32.00, 25.33, 20.36

protons showed an absorbance much further upfield at 1.64. The i.r. spectrum did not show any absorbance in the carbonyl region. The ^{13}C n.m.r. spectrum showed (Table 7) the absence of absorbance above δ 90 which excluded the aldehydic carbon being present. The most substituted carbon appeared at δ 94.46 due to the deshielding effect of electronegative oxygen in the hydroxyl group and the ring. The other ring carbon adjacent to the ring oxygen appeared at δ 63.83. The three remaining ring carbons were shielded and thus appeared further upfield at δ 32.00, 25.33 and 20.36. Thus the spectroscopic evidence agreed with the conclusion drawn by Hurd and Saunders[81] from their studies that the equilibrium mixture contained 2-hydroxytetrahydropyran as the predominant isomer.

2.3.3.b Preparation of tetrahydropyran-2-ylacetic acid from 2-hydroxytetrahydropyran

2.3.3.b.i Malonic acid condensation of 2-hydroxy-tetrahydropyran

The literature method described by Kennedy *et al.*[82] was followed and 2-hydroxytetrahydropyran was condensed with malonic acid (ii, Scheme 17) to give a mixture of tetrahydropyran-2-ylmalonic acid (60) and trans-7-hydroxyhepten-2-malonic acid (61). The mixture was heated until carbon dioxide evolution had ceased and the corresponding monocarboxylic acids (54 and 62) were obtained. Upon distillation, the two products could not be separated as monitored by the g.c. trace.

Just as Fray[82] had reported, the mixture had polymerized on redistillation and the experiment had to be repeated. Thus following the procedure adopted by Fray *et al.*[82], the crude mixture of isomeric acids (54 and 62) was esterified with ethanol (iv, Scheme 17) to give ethyl tetrahydropyran-2-ylacetate (63) and ethyl trans-7-hydroxyhept-2-enoate (64). However, it was found that a complete separation of the two esters (63 and 64) could not be achieved by distillation.

2.3.3.b.ii Hydrolysis of ethyl esters of tetrahydropyran-2-ylacetic acid and trans-7-hydroxyhepten-2-oic acid

As described above, the mixture of ethyl esters (63 and 64) could not be separated by distillation. However, hydrolysis of the mixture in an alkaline medium gave the single product, tetrahydropyran-2-ylacetic acid, thus confirming Fray's[63] finding that the ethyl trans-7-hydroxyhept-2-enoate on alkaline hydrolysis gave the cyclic acid (54) as the only product by complete rearrangement. Tetrahydropyran-2-ylacetic acid was purified by crystallization from petroleum ether (90-120 °C fraction) and the m.p. obtained (50 °C) agreed closely with the literature [60] value (52-4 °C). The spectroscopic data were identical to those obtained earlier for tetrahydropyran-2-ylacetic acid (Table 3, p.50).

2.3.4 Conclusion

A thorough investigation of the possible routes to tetrahydropyran-2-ylacetic acid synthesis was carried out. New spectroscopic data for tetrahydropyran-2-ylacetic acid (Table 3, p.50), diethyl tetrahydropyran-

2-yl malonate (Table 4 & 5, p.55,56) and 2-hydroxytetrahydropyran (6 &7, p.60) were obtained.

It was found that the three samples of tetrahydropyran-2-ylacetic acid obtained by three different pathways (Schemes 15, 16 and 17) had essentially the same melting and boiling points (Table 8). On comparing the overall yields obtained, it was found that the best result obtained was via the halogen derivative of tetrahydropyran-2-ylmethanol (Scheme 15, p.45).

Table 8 Synthesis of tetrahydropyran-2-ylacetic acid(54)

Route	B.P. °C	mmHg	Infrared cm^{-1}	n_D	°C	Overall yield, %
Lit.[77]	100	2.0	-	-		-
2.3.1[a]	90	1.0	3420, 2940, 2865, 1710.	1.4469	19	36
2.3.2[b]	56	0.5	3420, 2940, 2860, 1720.	1.4464	18	8.5
2.3.3[c]	70	0.1	3440, 2940, 2860, 1710.	1.4467	18	15

a Scheme 15

b Scheme 16

c Scheme 17

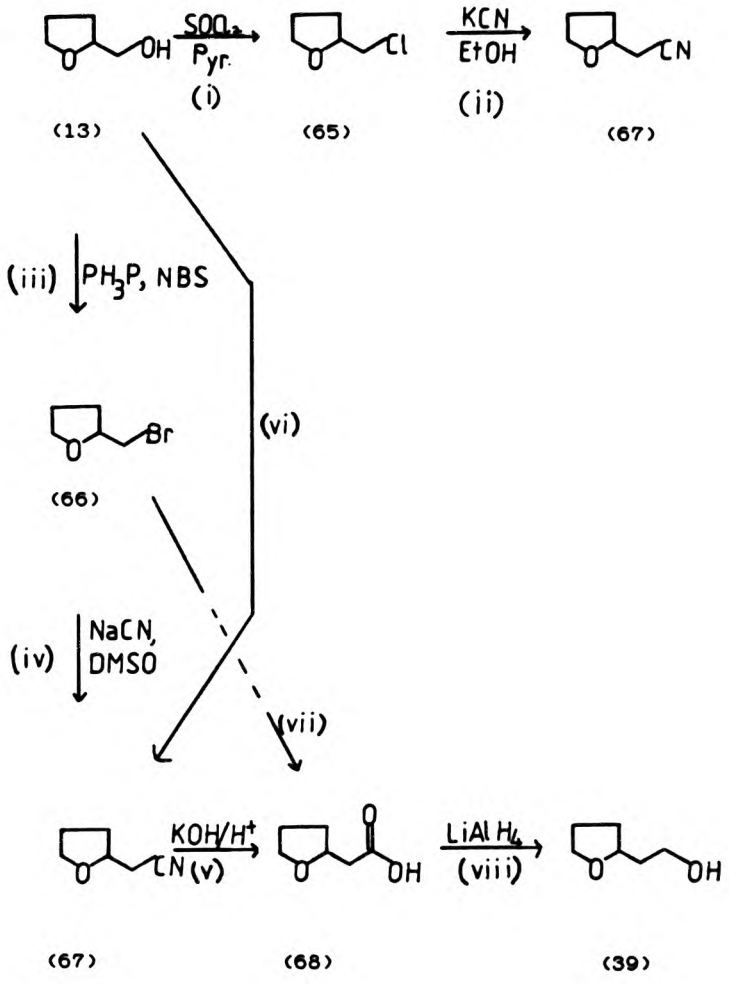
2.4 Synthesis of tetrahydrofurfurylmethanol

The synthesis of tetrahydrofurfurylmethanol starting with tetrahydrofurfuryl alcohol (13) was attempted by two routes, namely via

1) the halogen derivative (Scheme 18) and,
2) the mesyloxy derivative (Scheme 19, p.66).

2.4.1 Synthesis of tetrahydrofurfurylmethanol via the halogen derivative of tetrahydrofurfuryl alcohol

As in the case of tetrahydropyran-2-ylmethanol (section 2.3.1), the chain extension of tetrahydrofurfuryl alcohol via the halogen derivative to give tetrahydrofurfurylmethanol has not been fully reported in the literature. However some of the individual reactions, such as the halogenation[84,88,96,71,88-90] (i and iii, Scheme 18) and the Grignard reaction [96-99] (vi, Scheme 18) have been reported. The remaining reactions of the synthetic route (ii, iv, v, vii, and viii, Scheme 18) were not reported previously in the literature.


SOCl2
Pyr.
(i)
KCN
EtOH
(ii)
(13)
(65)
(67)
(iii) PH3P, NBS
(66)
(vi)
(iv) NaCN, DMSO
(vii)
KOH/H+
(v)
LiAlH4
(viii)
(67)
(68)
(39)

Scheme 18

2.4.1.a Preparation of the halogen derivatives

2.4.1.a.(i) Tetrahydrofurfuryl chloride

The preparation of tetrahydrofurfuryl chloride (65) has been widely reported in the literature[64-66]. Bhusate[67] found that the best yield was obtained by the reaction of tetrahydrofurfuryl alcohol (13) with thionyl chloride and a catalytic amount of pyridine[66].

Bhusate[67] obtained low yields due to the formation of difficult emulsions during work up which made further extractions with ether impossible. It was found in the present work that the emulsion could be broken up by the addition of solid sodium chloride and the mixture being set aside for several hours. This resulted in an easy separation of the ether layer from the aqueous layer and a much improved yield of tetrahydrofurfuryl chloride.

The refractive index and boiling point obtained agreed closely with the literature[66] values. The i.r. spectrum showed the absence of hydroxyl group absorbance and the presence of carbon-chlorine bond absorbance at 745 and 775 cm^{-1}.

2.4.1.a.(ii) Tetrahydrofurfuryl bromide

Two methods of preparation of tetrahydrofurfuryl bromide (66) were employed (iii, Scheme 18), namely

1') using phosphorus tribromide, and
2') using triphenylphosphine and N-bromosuccinimide (NBS).

2.4.1.a.(ii).1' Using phosphorus tribromide

The procedure described by Smith[88] was followed and tetrahydrofurfuryl alcohol was allowed to react with phosphorus tribromide to give tetrahydrofurfuryl bromide. The product was not completely pure even after several distillations as it contained up to 20 % of the starting material, tetrahydrofurfuryl alcohol.

2.4.1.a.(ii).2' Using triphenylphosphine

The preparation of tetrahydrofurfuryl bromide (66) by reacting tetrahydrofurfuryl alcohol with triphenylphosphine and NBS has been reported in the literature[71,88,90]. To obtain a pure sample of tetrahydrofurfuryl bromide with a good yield, the stirring of the mixture had to be highly efficient and the product to be distilled as soon as the addition of

NBS was completed. The addition of NBS to the reaction mixture was highly exothermic and the contents of the reaction vessel became quite fluid.

It was found that if the reaction mixture was allowed to cool before distillation, the contents of the flask solidified and gave a very poor recovery of the product. According to Schweizer[71] this was thought to be caused by the reaction of tetrahydrofurfuryl bromide with the excess triphenylphosphine present to give a salt as shown below. However by closely observing the above precautions the purity and yield of tetrahydrofurfuryl bromide obtained were much improved.

2.4.1.b Preparation of tetrahydrofurfuryl cyanide

The synthesis of tetrahydrofurfuryl cyanide (67) was attempted by three methods, namely by the cyanide replacement of

i) tetrahydrofurfuryl chloride (ii, Scheme 18),
ii) tetrahydrofurfuryl bromide (iv, Scheme 18),
iii) tetrahydrofurfuryl alcohol (vi, Scheme 18).

2.4.1.b.i Nitrilation of tetrahydrofurfuryl chloride

Sodium or potassium cyanide was found to react with primary chlorides in aqueous ethanol to give the corresponding nitriles in good yields[91,92]. However, tetrahydrofurfuryl chloride failed to react with potassium cyanide in I.M.S. even after 25 h refluxing. The starting material was recovered as shown by the i.r. spectroscopy and g.c. analysis.

2.4.1.b.ii Nitrilation of tetrahydrofurfuryl bromide

It was reported in the literature[93,94] that primary and secondary alkyl halides react rapidly and exothermically with sodium cyanide in partial

solution in dimethyl sulphoxide to give the corresponding nitriles in good yields. Thus tetrahydrofurfuryl bromide was heated with a slurry of dry sodium cyanide in dimethyl sulphoxide (dried over calcium hydride before use). The reaction was was not exothermic even at temperatures of 90 °C which indicated a lack of reactivity and this was confirmed by g.c. analysis. The experiment was repeated several times with increasing reaction times, temperature and excess amounts of sodium cyanide (see table 9). However when dimethyl sulphoxide distilled over calcium hydride was used as a solvent, tetrahydrofurfuryl cyanide was obtained in a good yield (Table 9) as indicated by i.r. spectroscopy. The product showed the expected cyanide peak in the i.r. region at 2240 cm^{-1}.

2.4.1.b.iii Direct nitrilation of tetrahydrofurfuryl alcohol

Davis and Untch[75] reported a direct one-step conversion of heterocyclic alcohols to the nitrile derivative. The method was followed and tetrahydrofurfuryl alcohol was treated with two equivalents of sodium cyanide, trimethylsilyl chloride and a catalytic amount of sodium iodide in

Table 9 Reaction of sodium cyanide with tetrahydrofurfuryl bromide(66)

Exp.	Reaction temp./ °C	Reaction time.h/min	Appearance at the of heating	Yield g	%
3.27.1	90	-	brown liquid[a]		-
3.27.2	100	-	brown solid on cooling[a]		-
3.27.3	120	-	dark brown solid[a]		-
3.27.4	90	0 30	brown/black liquid[a]		-
3.27.5	100	0 50	brown/black liquid[a]		-
3.27.6	50	1 00	light brown liquid[b]	0.2	5
3.27.7	60	2 30	light brown liquid[b]	0.4	25
3.27.8	80	3 30	dark brown liquid[b]	0.5	40
3.27.9	90	4 30	dark brown liquid[b]	0.35	52

a DMSO dried over calcium hydride

b DMSO distilled over calcium hydride

dimethylformamide and acetonitrile. The reaction conditions were kept scrupulously anhydrous. The reaction was monitored by g.c. and even after 8 h, there was no change in the intensity of the tetrahydrofurfuryl alcohol peak.

2.4.1.c Preparation of tetrahydrofurfurylmethanoic acid (68)

The synthesis of tetrahydrofurfurylmethanoic acid was attempted by

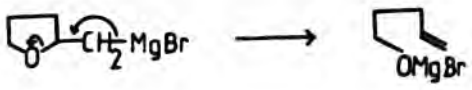
1) Grignard reaction of tetrahydrofurfuryl bromide (vii, Scheme 18)
2) Hydrolysis of tetrahydrofurfuryl nitrile (v, Scheme 18)

2.4.1.c.i Using tetrahydrofurfuryl bromide (66)

Paul[95] studied the preparation of the Grignard reagent of tetrahydrofurfuryl bromide and reported that the reaction had proceeded smoothly in dry ether. Following the above procedure[95], tetrahydrofurfuryl bromide was allowed to react with magnesium turnings in sodium dried ether, followed by carbon dioxide.

However, no reaction took place and some of the tetrahydrofurfuryl bromide was recovered. It was assumed that a higher boiling point solvent was needed, so freshly distilled and dried tetrahydrofuran was used. The expected product, tetrahydrofurfurylmethanoic acid could not be isolated from the reaction mixture, and neither was the starting material recovarable. The procedure was repeated several times, altering the temperature of the reaction and the reaction times but the result was the same.

A similar result was obtained by Robinson and Smith[96]. They found that a Grignard reagent of tetrahydrofurfuryl bromide could not be formed in significant quantities and the main product obtained was 4-penten-1-ol. They also found that the amount of recoverable bromide (66) at the end of the reaction was negligible. Robinson and Smith[96] postulated a mechanism for this β-elimination reaction as shown below. This conclusion was supported elsewhere in the literature[97-99].



2.4.1.c.ii Hydrolysis of tetrahydrofurfuryl cyanide

On hydrolysis of the nitrile (67) by aqueous sulphuric acid, tetrahydrofurfurylmethanoic acid (68) was obtained in 54% yield. During the reaction the peak at 2240 cm^{-1} in the i.r. spectrum due to the cyanide disappeared while a new peak at 1690 cm^{-1} due to carbonyl of a carboxylic acid appeared. Hydrolysis of the nitrile (67) by means of 20% potassium hydroxide in I.M.S./water (1:1) gave improved yields (75%) of the acid (68).

2.4.1.d Reduction of tetrahydrofurfurylmethanoic acid

Reduction of tetrahydrofurfurylmethanoic acid was carried out by lithium aluminum hydride (viii, Scheme 18). The carbonyl group could not be completely reduced even when an excess of $LiAlH_4$ was used. It gave rise to mixed products where the carbonyl group was still evident in the i.r. spectrum at 1710 cm^{-1} and the acid peak was present in the g.c. trace.

The acid (68) was heated under reflux with ethanol and the reduction of the ethyl derivative was attempted by $LiAlH_4$. The result was similar to the above where mixed products were obtained. Separation

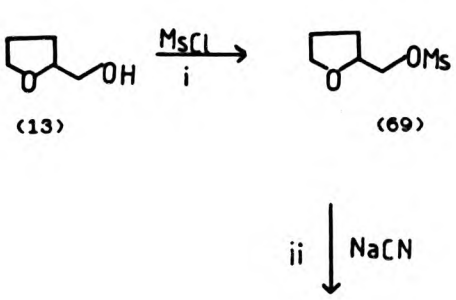
and purification of these products was not attempted due to the small quantities involved. Thus the multi-step synthesis of tetrahydrofurfurylmethanol had proved very difficult.

2.4.2 Synthesis of tetrahydrofurfurylmethanol via the mesyloxy derivative of tetrahydrofurfuryl alcohol

Zief *et al.*[100,101] studied the synthesis of tetrahydrofurfuryl cyanide by the displacement of the tosyl and mesyl esters of tetrahydrofurfuryl alcohol. It was found that the fusion of the mesyloxy derivative with potassium cyanide gave a better yield of the nitrile (67) than a corresponding reaction with the tosyloxy derivative. Thus in the present work the mesyl ester of tetrahydrofurfuryl alcohol (69) was prepared (i, Scheme 19) and reacted with sodium cyanide (ii, Scheme 19).

2.4.2.a Preparation of tetrahydrofurfuryl mesylate

Following the literature method[100], tetrahydrofurfuryl mesylate (69) was prepared by reacting equimolar quantities of tetrahydrofurfuryl alcohol and methanesulphonyl chloride in pyridine (i, Scheme 19).



(13) (69) (67) (68) (39)

Scheme 19

The mixture was allowed to stand in a refrigerator overnight and the mixture turned dark brown. The mixture contained large lumps of precipitated pyridine hydrochloride, which dissolved in a mixture of ice and water. The mixture was extracted with dichloromethane (6 × 50 ml) and dried. After the removal of the solvent, the residue was distilled under reduced pressure to give tetrahydrofurfuryl mesylate. The b.p. and refractive index of the product agreed closely with the literature[100] data.

2.4.2.b Nitrilation of tetrahydrofurfuryl mesylate

The literature method[100] suggested that when tetrahydrofurfuryl mesylate was treated with potassium cyanide (ii, Scheme 19) with no solvent present, good yields were obtained. However, in the present work such a reaction resulted only in decomposition of the reactants after 4 days of heating on the steam bath. So the reaction was repeated with dry toluene as the solvent and after the work up tetrahydrofurfurylcyanide (67) was isolated (15 %). The i.r. spectrum showed the cyanide peak at 2240 cm^{-1}.

2.4.2.c Hydrolysis of tetrahydrofurfuryl cyanide

Tetrahydrofurfuryl cyanide was hydrolysed with 20 % potassium hydroxide in aqueous ethanol (iii, Scheme 19). The mixture was heated under reflux for 6 h and after the usual work up, tetrahydrofurfurylmethanoic acid (68) was isolated. The product gave an identical i.r. spectrum to that of tetrahydrofurfurylmethanoic acid obtained above (iv, Scheme 18).

2.5 Synthesis of 2-(tetrahydrofurfuryl)ethanol (40)

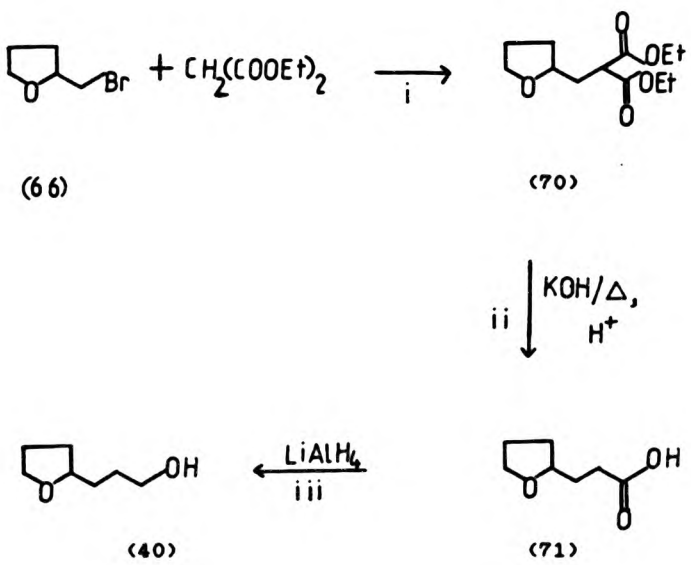
The investigation of the synthesis of 2-(tetrahydrofurfuryl)ethanol was carried out by two major pathways, namely

1) via the tetrahydrofurfurylmalonic ester (Scheme 20), and
2) by the hydrogenation of furylacrylic acid (Scheme 21, P.74).

2.5.1 Synthesis of 2-(tetrahydrofurfuryl)ethanol via the malonic ester (70)

The procedure described in the literature[102] was followed throughout. Barger *et al.*[102] found that

tetrahydrofurfuryl chloride was inert towards potassium cyanide or diethyl malonate in sodium ethoxide, but that tetrahydrofurfuryl bromide could be condensed with the latter reagent. Alkaline hydrolysis of the malonate ester gave 2-(tetrahydro-furfuryl)acetic acid (71) which was esterified with ethanol and reduced by the Bouveault-Blanc method[102] to 2-(tetrahydro-furfuryl)ethanol (40).



Scheme 20

2.5.1.a Preparation of diethyl tetrahydrofurfuryl-malonate(70)

Diethyl malonate and tetrahydrofurfuryl bromide (66) were reacted together (i, Scheme 20) in sodium ethoxide solution, following the procedure in the literature[102]. The mixture was heated under reflux for 16 h and cooled. The solvent, absolute ethanol, was removed *in vacuo* and the residue was extracted several times with ether (10 × 50 ml). Removal of the ether gave the title compound (70) in 45% yield. Its boiling point agreed closely with the literature value while the i.r. spectrum showed the expected carbonyl absorption at 1710 cm^{-1}. The product was also identified by its previously unpublished proton n.m.r. spectrum (Table 10). The methylene protons of the ester group and the substituted side chain proton appear at δ 4.12 due to the deshielding effect of the carbonyl oxygen atoms. The protons nearest to the oxygen in the ring appeared slightly higher field at δ 3.25 and the shielded ring protons and the ester methyl protons appeared quite high field at δ 1.23. The refractive index, also unpublished hitherto, was found to be 1.5211 at 24°C.

Table 10 ^{1}H n.m.r. data for tetrahydrofurfuryldiethyl malonate (70)

Group	Integration	Chemical Shift
2 × $COOCH_2CH_3$ and CH	5 H	4.12 (m)
CH_2-O, CH-O	3 H	3.25 (m)
3 × CH_2 of ring;	12 H	1.23 (m)
2 × CH_3 of ester		

2.5.1.b Hydrolysis of diethyl tetrahydrofurfuryl-malonate (70)

The malonate ester (70) was heated under reflux with 20 % potassium hydroxide in aqueous ethanol. After the usual work up, the residue obtained was tetrahydrofurfurylmalonic acid (ii, Scheme 20). The malonic acid, without further isolation, was heated at 150 °C until carbon dioxide had stopped evolving (1 h). The residue had turned dark brown and became very viscous during heating.

The crude product was distilled to give 2-(tetrahydrofurfuryl)ethanoic acid (71). There was a loss of product during distillation since the acid (71) was highly viscous and had a high boiling point (135 °C at 2 mmHg). 2-(Tetrahydrofurfuryl)ethanoic acid was identified by ^1H and ^{13}C n.m.r. (Tables 11 & 12). The i.r. spectrum showed the carbonyl absorption at 1730 cm^{-1}. The ^1H n.m.r. spectrum, not previously reported, showed the acidic hydroxyl proton at δ 7.89 as a singlet and the side chain protons appeared higher field at δ 3.84 together with the ring proton adjacent to the oxygen atom in the ring. The methylene protons nearest to the oxygen in the ring showed a signal at δ 2.45 and the remaining protons in the ring and the side chain protons appeared higher

field at δ 1.88. The ^{13}C n.m.r. spectrum showed the carbonyl group at δ 178.4. The carbons attached directly to oxygens in the ester group and the ring appeared lower field at δ 78.4 and 67.7 compared to the shielded carbons in the ring and side chain which appeared at δ 31.2, 30.9, 30.4 and 25.7.

It was found that tetrahydrofurfurylacetic acid could not be reduced successfully by lithium aluminium hydride. The i.r. spectrum showed a small residual carbonyl peak at 1710 cm^{-1}. The decreased intensity of the carbonyl peak suggests that although much of the acid (71) had been reduced, the reaction had not proceeded to completion.

Table 11 ^{1}H n.m.r. of 2-(Tetrahydrofurfuryl)ethanoic acid

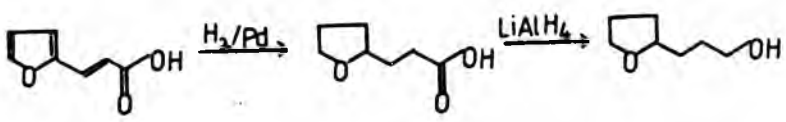
Group	Integration	Chemical Shift
OH	1 H	7.89 (s)
CH_2COOH, CH-O	3 H	3.84 (m)
CH_2-O of ring	2 H	2.45 (m)
3 × CH_2	6 H	1.88 (m)

Table 12 ^{13}C n.m.r. of 2-(Tetrahydrofurfuryl)ethanoic acid

Group	Chemical Shift
C=O	178.4
CH_2COOH	78.4
CH	67.7
4 × CH_2 ring	31.2, 30.9, 30.4
CH_2 side chain	25.7

2.5.2 Synthesis of 2-(tetrahydrofurfuryl)ethanoic acid (71) by the hydrogenation of furylacrylic acid

Kaufman and Adams[108] hydrogenated furylacrylic acid to tetrahydrofurfurylethanoic acid with platinum and obtained mixed products. Bray and Adams[104] reduced furfurylacrolein to tetrahydrofurfurylethanol and heptanediol using platinum. Smith *et al.*[108] reported that the hydrogenation of furylacrylic acid over platinum also gave mixed products. However, Pleizzoni and Jommi[108] found that by using palladium as a catalyst, furylacrylic acid could be reduced at room temperature and pressure to give tetrahydrofurfurylethanoic acid as the only product.



(72) (71) (40)

Scheme 21

2.5.2.a Hydrogenation of furylacrylic acid(72)

Following the literature method[102] the commercially available furylacrylic acid was hydrogenated at room temperature and pressure of 3 atm. using 5% Pd/C. The reaction was carried out for 6 h and samples were removed at regular intervals (1 h) to be monitored by proton n.m.r. The disappearance of vinyl protons indicated the completion of the reaction to give 2-(tetrahydrofurfuryl)ethanoic acid (71).

Furylacrylic acid in absolute ethanol with 5 % Pd / C and a trace amount of sodium hydroxide was hydrogenated in an autoclave at 300 - 400 p.s.i. and 80 - 100 °C for 8 h. The work up the residue showed the presence of vinyl protons in the proton n.m.r. spectrum. The mixture was rehydrogenated at room temperature and 3 atm. in aqueous ethanol using fresh catalyst every 4-6 h until there was a complete disappearance of vinyl protons in the ^{1}H n.m.r. spectrum (72 h). The product was identified by i.r., proton n.m.r., refractive index and boiling point. The spectroscopic data were identical to those obtained by the potassium hydroxide hydrolysis of the malonate ester (ii, Scheme 20).

A comparative study of the yields obtained in the literature[102], the alkaline hydrolysis of the

malonate ester (Scheme 20) and reductive hydrogenation (Scheme 21) to give 2-(tetrahydrofurfuryl)ethanoic acid (71) had shown that the latter method gave the best result (Table 13).

Conclusion

The synthesis of 2-(tetrahydrofurfuryl)ethanoic acid (71) by the two routes was investigated successfully. It was found that the hydrogenation of furylacrylic acid (72) could be carried out in gram quantities at room temperature and low pressure (3 p.s.i.). The spectroscopic data of the acid (71) presented (Tables 11 & 12, p.86) was not previously reported in the literature.

Table 13 Synthesis of 2-(tetrahydrofurfuryl)ethanoic acid(71)

Route	Boiling point °C	mmHg	n_D	°C	Infrared cm^{-1}	overall yield, %
Lit.[102]	119	0.2	1.4591	15	-	68[c]
2.5.1[a]	126	3.0	1.4631	24	3460-3320, 1720, 1580.	27[c]
2.5.2[b]	82	1.0	1.4622	18	3480-3340, 1730, 1590.	80

a multi-step synthesis involving diethylmalonate (Scheme 20)

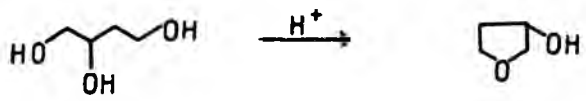
b hydrogenation of furylacrylic acid (Scheme 21)

c Product of individual steps starting with tetrahydrofurfuryl bromide

2.6 Miscellaneous reactions involving 5-membered rings

2.6.1 Preparation of 3-hydroxytetrahydrofuran (41)

The synthesis of 3-hydroxytetrahydrofuran had been widely reported in the literature[107-111]. It involved the acid catalysed cyclodehydration of 1,2,4-butanetriol (73).



(73) (41)

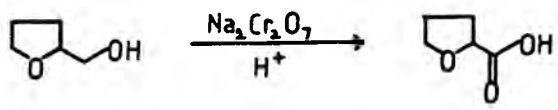
Scheme 22

The literature procedure[107] was followed and the yield, boiling point and refractive index obtained agreed closely with the literature data. Methacrylation of 3-hydroxytetrahydrofuran was carried out to give 3-tetrahydrofurylmethacrylate (28) (see Section 2.9.2).

2.6.2 Oxidation of tetrahydrofurfuryl alcohol

Katsuno and Ando[112] reported on the only known chemical method of preparing tetrahydrofuran-2-

carboxylic acid (74). Following the literature[1,2] method, tetrahydrofurfuryl alcohol was oxidised by sodium dichromate and concentrated sulphuric acid. The work-up proved difficult and most of the product could not be extracted from the reaction mixture. The i.r. spectrum of tetrahydrofuran-2-carboxylic acid (74) showed the presence of the carbonyl group 1730 cm^{-1} and the boiling point agreed closely with the literature[1,2] value.

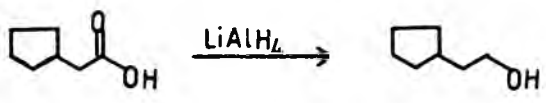


Scheme 23

2.6.4 Preparation of 2-(cyclopentyl)ethanol

2-(Cyclopentyl)ethanol (50) was not commercially available. It was therefore prepared by reducing 2-(cyclopentyl)acetic (75) acid with lithium aluminum hydride (Scheme 24). The i.r. spectrum showed the disappearance of the carbonyl group at 1720 cm^{-1} in the product. 2-(Cyclopentyl)ethanol (50) was further identified by the proton n.m.r. spectrum in which the hydroxyl group singlet appeared at δ 3.75 and disappeared when dueterium oxide was added to the

sample. The side chain protons adjacent to the hydroxyl group appeared at δ 3.55 as a multiplet. The shielded ring protons appeared upfield at δ 1.70. The alcohol (50) thus synthesised was methacrylated to give 2-(cyclopentyl)ethyl methacrylate (34) (see Section 2.9.2).



(75) (50)

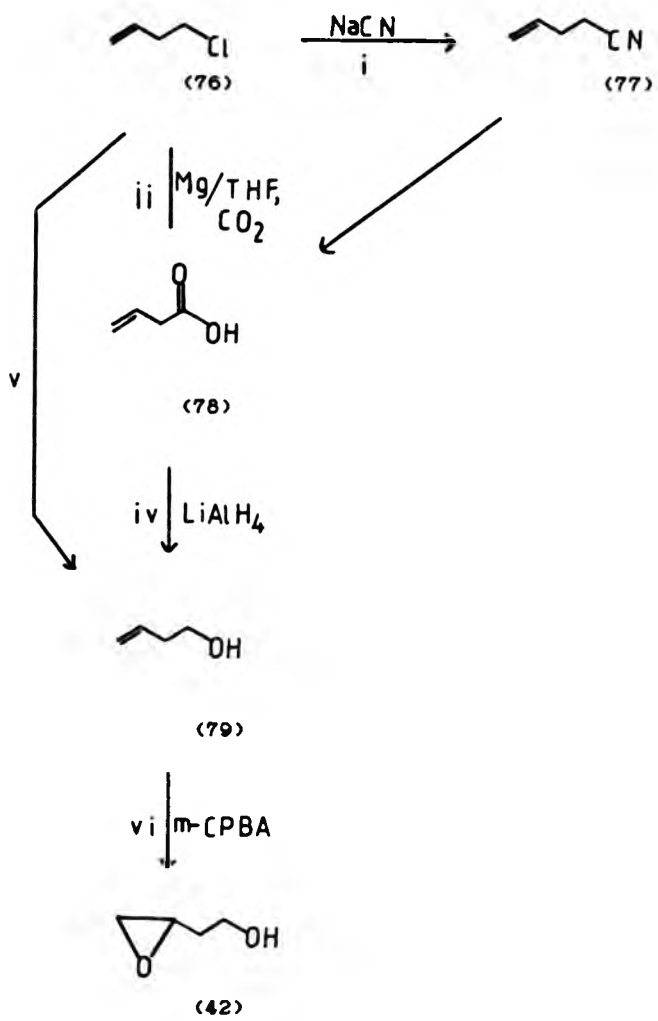
Scheme 24

2.7 Synthesis of 3,4-epoxybutan-1-ol

3,4-Epoxybutan-1-ol was not commercially available, and hence its synthetic route was investigated using allyl chloride (Scheme 25).

2.7.1 Preparation of 3,4-epoxybutanol using allyl chloride

Allyl chloride (76) was commercially available and its use in the synthesis of 3-buten-1-oic acid (78) and


Cl
(76)
NaCN
i
CN
(77)
ii
Mg/THF,
CO2
O
OH
(78)
v
iv
LiAlH4
OH
(79)
vi
m-CPBA
O
OH
(42)

Scheme 25

3-buten-1-ol (79) have been reported in the literature[114-116]. The epoxidation of 3-buten-1-ol was reported by Bats *et. al*[117].

2.7.1.a Preparation of 3-buten-1-oic acid

Synthesis of 3-buten-1-oic acid (78) was carried out by two methods, namely

1) Grignard reaction of allyl chloride (ii, Scheme 25), and
2) via the allyl cyanide (i and iii, Scheme 25).

2.7.1.a.i Grignard reaction of allyl chloride

Following the literature[114] method, the Grignard reagent of allyl chloride was prepared and treated with carbon dioxide to give 3-buten-1-oic acid (78). Recovery of the product (78) was very low (10 %), even though an excess of the solvent and magnesium turnings were used and the agitation period was increased as suggested by the literature method[114]. The low yields were said[114] to be caused by the formation of a dimer of propene as well as other side reactions that may be occurring when carbon dioxide was used to treat the

Grignard reagent. 3-Buten-1-oic acid was identified by its boiling point, refractive index and i.r. spectrum.

2.7.1.a.ii Via allyl cyanide

3-Buten-1-oic acid was prepared from allyl chloride by 1) cyanide displacement (i, Scheme 25), followed by 2) hydrolysis of allyl cyanide (iii, Scheme 25).

2.7.1.a.ii.1. Cyanide displacement of allyl chloride

Following the procedure in the literature[93,94], allyl chloride was treated with sodium cyanide in dimethylsulphoxide to yield allyl cyanide (89 %). This was an improvement on that reported in the literature[118], where chlorobutyronitrile was heated with pyridine to give allyl cyanide (80 %). The boiling point and refractive index data agreed very closely with the literature[118] values for allyl cyanide. It was further identified by the presence of the cyanide peak at 2240 cm^{-1} in the i.r. spectrum.

2.7.1.a.ii.2 Hydrolysis of allyl cyanide

Hydrolysis of allyl cyanide (77) was carried out by heating it under reflux with 50% sulphuric acid. The product was identical to 3-buten-1-oic acid obtained by the Grignard method described above (Section 2.7.1.a.i). The boiling point and refractive index of the sample agreed closely with the literature values[1,8]. 3-Buten-1-oic acid thus obtained showed the disappearance of the cyanide peak at 2240 cm^{-1} and the appearance of the carbonyl group at 1720 cm^{-1} in the i.r. spectrum.

2.7.1.b Preparation of 3-buten-1-ol

Synthesis of 3-buten-1-ol (79) was carried out by two methods, namely

i) Grignard reaction with allyl chloride (v, Scheme 25), and
ii) reduction of 3-buten-1-oic acid (iv, Scheme 25).

2.7.1.b.i Preparation of 3-buten-1-ol by the Grignard method

The Grignard reagent derived from allyl chloride was prepared as described previously[114], and treated with anhydrous paraformaldehyde as reported by Kinnel *et al*[116]. After the usual work up, the recovery of 3-buten-1-ol was low (39 %). The literature reports[116-120] indicate that this could be due to side reactions. The main problem encountered in the above procedure was the maintenance of anhydrous conditions during the addition of anhydrous paraformaldehyde to the reaction mixture at reflux, and this may have contributed towards the low yield obtained. However, the boiling point and refractive index data obtained for the product agreed closely with those quoted in the literature[116] for 3-buten-1-ol.

2.7.1.b.ii Reduction of 3-buten-1-oic acid

3-Buten-1-oic acid was reduced by lithium aluminum hydride (iv, Scheme 25) in good yield (87.5 %) and its boiling point and refractive index were similar to the literature values[116].

2.7.1.c Epoxidation of 3-buten-1-ol

Epoxidation of 3-buten-1-ol was carried out using *m*-chloroperbenzoic acid in dichloromethane. The initial work up involved filtering off the side product, *m*-chlorobenzoic acid, and washing the filtrate with 10 % sodium bicarbonate solution and distilled water. However, this resulted in a poor recovery of the product (10 - 20 %). Bats *et al.*[117] described a work up where no washings were involved as they found that the epoxy alcohol (42) was very soluble in water. Thus after the filtration of the side product, the filtrate was shaken with anhydrous sodium carbonate. The modification of the work up gave a good yield of 3,4-epoxybutanol (65.5 %). The previously unreported proton n.m.r. spectrum showed the hydroxyl group as a singlet at δ 2.85 which appeared as part of the multiplet of the epoxy protons at δ 2.6-2.9. The side chain protons nearest to the hydroxyl group appeared as a triplet at δ 3.82 and the remaining protons being shielded from oxygen atoms showed a signal at δ 1.90 as a triplet.

2.7.2 Conclusion

3,4-Epoxybutanol was synthesized successfully from the commercially available allyl chloride (76) and its proton n.m.r. data were presented (Table 14). It was found that the route via allyl cyanide (i, iii, iv, and vi, Scheme 25) gave a good yield of the desired epoxyalcohol (42). Thus methacrylation of 3,4-epoxybutanol was carried out to give 3,4-epoxybutylmethacrylate (29) (see Section 2.9.2).

Table 14 ^1H n.m.r. data for 3,4-Epoxybutan-1-ol(42)

Group	Integration	Chemical Shift
CH_3	2 H	1.90 (t)
CH_2-CO, epoxy	2 H	2.6-2.9 (m)
OH	1 H	2.85 (s)
CH_2-OH	2 H	3.8 (t)

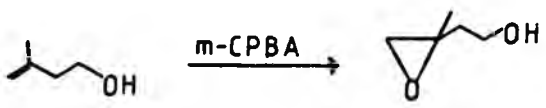
Table 15 ^1H n.m.r. for 3,4-Epoxy-3-methylbutanol(43)

Group	Integration	Chemical Shift
CH_3	3 H	1.40 (s)
CH_2	2 H	1.91 (t)
CH_2-CO, epoxy	2 H	2.62-2.91 (m)
OH	1 H	2.85 (br s)
CH_2-OH	2 H	3.82 (t)

2.8 Preparation of 3,4-epoxy-3-methylbutanol(43)

3-Methyl-3-buten-1-ol (80) was commercially available, and following the procedure in the literature [117] it was epoxidised (Scheme 27) using *m*-chloroperbenzoic acid. The work up was similar to that described above in the epoxidation of 3-buten-1-ol (Section 2.7.2.c). 3,4-Epoxybutanol (43) was obtained (48 %) and identified by the proton n.m.r.spectrum (Table 15) in which the hydroxyl group appeared at δ 2.85. The methyl protons showed a signal at δ 1.40 as a singlet, and the rest of the protons had similar chemical shifts to 3,4-epoxybutanol as discussed above (Section 2.7.1.c).

Methacrylation of a pure sample of 3,4-epoxybutanol was carried out to give 3,4-epoxybutylmethacrylate (30) (see Section 2.9.2).



(80) (43)

Scheme 26

2.0 Preparation and properties of methacrylate esters of heterocyclic and carbocyclic alcohols

2.0.1 Synthesis of tetrahydrofurfuryl and tetrahydropyran-2-ylmethyl methacrylate esters

The synthesis of tetrahydrofurfuryl methacrylate (1) and tetrahydropyran-2-yl methacrylate (2) was investigated by the three general methods known for the preparation of methacrylate esters , namely

a) transesterification (Scheme 27),

b) direct methacrylation (Scheme 28, p.107),

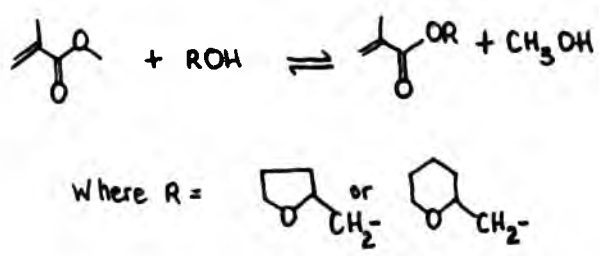
c) acid chloride method (Scheme 29, p.108).

2.0.1.a Transesterification

Tetrahydrofurfuryl methacrylate (1) is commercially available and is usually prepared by transesterification[41]. Bhusate[42] applied this method to the preparation of tetrahydropyran-2-ylmethyl methacrylate (2) which was not commercially available.

It was reported[39] that transesterification was carried out by the reaction of the corresponding heterocyclic alcohol with methyl methacrylate in toluene, using an acid catalyst andapolymerization

inhibitor such as hydroquinone (Scheme 27). Bhusate found that it was necessary to use a controlled reflux with careful monitoring of the temperature in the flask and at the head of the column. When the temperature of the latter could no longer be maintained at 85-90 °C, that is after several removals of the toluene-methanol azeotrope, the reaction was stopped. The reaction times were 30 h or longer and this often resulted in charring of the reaction mixture.



Scheme 27

In the current study a similar preparative technique was used. The work up procedure followed that described by Bhusate[97] who encountered problems in the washing and neutralisation of the reaction mixture. The initial washing with water caused no problems but when neutralising with 10 % sodium bicarbonate solution, the mixture did not separate readily as reported by Bhusate[97] and the addition of sodium

chloride seemed to have little effect. The final washing with water caused the most severe problem where an emulsion was formed which did not break up with brine initially. At this stage Bhusate[97] centrifuged the mixture to achieve separation, but this gave very poor yields (20-36 %) of the methacrylate ester.

It was found in the present work that if the emulsion was added to an excess of sodium chloride and set aside for several hours (or overnight), complete separation of the two layers was achieved. This gave rise to better yields (52-54 %) of the distilled methacrylate esters. The boiling points, refractive indices and spectroscopic data compared very closely with those quoted by Bhusate[97]. In the present work, ^{13}C n.m.r. data are presented (Table 18, p.119) for tetrahydrofurfuryl and tetrahydropyran-2-ylmethyl methacrylates which were not previously quoted in the literature.

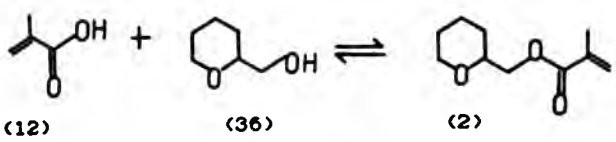
The spectroscopic data for the ester moiety in both methacrylates (Section 2.9.3.b.i, p. 109) followed the general pattern. The ^{13}C n.m.r. spectrum for tetrahydrofurfuryl methacrylate showed the side chain carbon in the alcohol residue at δ 76.63 and the ring carbons adjacent to the electronegative oxygen appeared to slightly higher field at δ 66.80 and

68.56. The two remaining ring carbons being shielded from the oxygen showed signals at δ 25.82 and 28.15. The tetrahydropyran-2-ylmethyl residue showed similar chemical shifts in its ^{13}C n.m.r. spectrum. The side chain carbon attached directly to the ester carbonyl group appeared downfield at δ 75.54 and the ring carbons adjacent to the oxygen atom showed signals higher field at δ 67.68 and 68.46. The three remaining ring carbons being shielded from the oxygen appeared upfield at δ 243.09, 25.89, 28.14.

2.9.1.h Direct methacrylation

The synthesis of tetrahydropyran-2-ylmethyl methacrylate (2) was attempted by direct methacrylation (Scheme 28) of tetrahydropyran-2-ylmethanol (36). A mixture of glacial methacrylic acid (12), tetrahydropyran-2-ylmethanol, hydroquinone, *p*-toluenesulphonic acid and toluene was heated under reflux using a Dean and Stark apparatus. The reaction mixture became viscous during heating and additional solvent, toluene, was added at regular intervals. The theoretical amount of water of esterification could not be collected even after 40 h of heating under reflux and the prolonged heating resulted only in polymerization of the reaction mixture.

The reaction was repeated several times but there was no indication of product formation as observed by t.l.c. and g.c., so this route of monomer synthesis was abandoned.



(12) (36) (2)

Scheme 28

2.9.1.c Acid chloride method of methacrylation

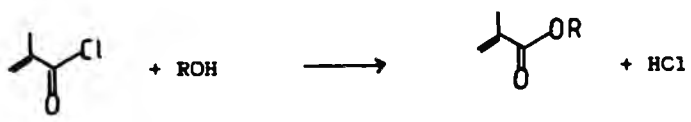
It was found that methacryloyl chloride reacted satisfactorily with tetrahydrofurfuryl alcohol (1) and tetrahydropyran-2-ylmethanol (2) to give the corresponding monomeric methacrylate esters (Scheme 29).

Initially the reaction was attempted without solvent and this resulted in polymerisation of the reaction mixture. The solvent, toluene, used was sodium dried before use and great care was taken to ensure anhydrous conditions during the reaction. The

reagents were freshly distilled and the apparatus was assembled hot.

Methacryloyl chloride (21) and hydroquinone in dry toluene were added dropwise to a solution of the heterocyclic alcohol (Scheme 29) in toluene kept at 0 °C with stirring. The mixture was stirred for 3-4 h at 0 °C and then allowed to reach room temperature. The work up procedure was similar to that employed in transesterification of the alcohols.

During work up, an emulsion was formed as before and was successfully dispersed by the addition of sodium chloride and the mixture left for 8 h. The monomeric methacrylate esters were obtained in good yield (60-62.5 %), and had identical analytical data to that of the samples obtained by transesterification of the alcohols.



(21)

Scheme 29

2.9.1.d Conclusion

The methacrylation of tetrahydrofurfuryl alcohol (13) and tetrahydropyran-2-ylmethanol (36) was successfully carried out by (a) transesterification and (b) the acid chloride method. The latter method was found to be the most convenient, since the reaction time was comparatively short and the yield of the methacrylate ester was greater (60 %) than that of the former method (52 %).

The other great advantage of using the acid chloride method was that the reaction temperature required was very low and this enabled the reaction mixture to be kept clean and to avoid loss of product due to charring and polymerization as in the case of transesterification.

2.9.2 Synthesis of other methacrylate esters

Having found that the direct esterification method gave rise to polymerization (Section 2.9.1.b), this method was not applied in any further syntheses of methacrylate esters.

Transesterifications of cyclohexylmethanol (44) and cyclopentanol (46) were carried out by following the procedure described above (Section 2.9.1.a).

Methacrylate esters of the two above alcohols (44 and 46) were also prepared by the acid chloride method (Section 2.9.1.c). The yields obtained by the latter method were better as noted above (Section 2.9.1.d). Thus the acid chloride method was applied to other carbocyclic and heterocyclic alcohols such as 2-cyclohexylethanol (45), cyclopentylmethanol (47), 2-cyclopentylethanol (50), 2-norbornylmethanol (48), 5-norborn-2-enemethanol (49), 3,4-epoxybutan-1-ol (42), 3,4-epoxy-3-methylbutan-1-ol (43), 3-hydroxy-tetrahydrofuran (41) and 3-methyloxetan-3-ylmethanol (37).

The results obtained are shown below (Table 16). The above prepared methacrylate esters were characterised by microanalysis, ^{1}H and ^{13}C n.m.r., i.r. and refractive index, after purification by flash chromatography. This technique has been described by Still *et al.*[121] and is basically an air pressure driven hybrid of medium pressure and short column chromatography which has been optimized for particularly rapid separations. Thus the potentially

Table 16 Results obtained in the synthesis of methacrylate esters

Ester	Boiling Point °C	mmHg	Yield %	Refractive Index n_D	°C
Tetrahydro-	116-7	20	54[a],62.5[b]	1.4552	22
furfuryl	107-112[c]	10	42[c]	1.4570[c]	25
Tetrahydropyran-	79-81	2.5	52.5[a],60[b]	1.4604	25
2-ylmethyl	75-78[c]	2.3	36.7[c]	1.4602[c]	25
3-Tetrahydrofuryl	38-40	0.05	61[b]	1.4567	20
3,4-Epoxybutan-1-yl	--		34[b]	1.4465	26
3,4-Epoxymethyl-	--		37.7[b]	1.4416	22
butanyl					
3-Methyloxetan-3-	--		66[b]	1.4462	17
ylmethyl					
Cyclohexylmethyl	50-55	0.3	94[b],78[a]	1.4625	18
2-Cyclohexylethyl	--		40[b]	1.4624	19
	99-102[d]	3.0	--	1.4641[d]	18
Cyclopentyl	--		29[a],31[b]	1.4525	20
	84-5	27	72[a]	1.4504[a]	25
Cyclopentylmethyl	82	8.5	62.5[b]	1.4555	22
	62[f]	2.0	72[f]	--	
2-Cyclopentylethyl	54	0.3	57.4[b]	1.4582	22
2,5-Norbornenemethyl	70-4	0.6	68[b]	1.4855	25
2-Norbornylmethyl	62-66	0.3	56.9[b]	1.4785	25
	93-4[e]	3.0	--	--	

(for footnotes see overleaf)

Table 16 Contd.

a Transesterification product

b Product of the acid chloride method

c Lit [97]

d Lit [122]

e Lit [10]

f Lit [88]

g Lit [86]

polymerisable crude methacrylate esters were separated very efficiently and rapidly at room temperature.

Some of the methacrylate esters of the above alcohols were mentioned in the literature. Lal and Green [10] reported the preparation of cyclopentyl methacrylate (20) and gave the b.p., refractive index and microanalytical data. They obtained the best yield of the monomer (20) by the direct esterification method and reported the difficulties in purification of the ester by distillation. There has been no other reference in the literature to its preparation or analytical data.

Ito *et al.*[23] reported briefly on the synthesis of cyclopentylmethyl methacrylate (22) by the acid chloride method and quoted only the yield and b.p. of the ester. They claim to have identified the monomer (22) by i.r. and n.m.r. spectroscopy but did not present the data.

Yokota *et al.*[122] reported the preparation of cyclohexylethyl methacrylate (33) by trans-esterification and quoted the b.p., refractive index and microanalytical data but not the yield of the monomer.

Caldwell *et al.*[88] reported the preparation of 2-norbornylmethyl methacrylate (24) by the direct esterification method and gave only the b.p. and microanalysis data.

Beavers and O'Brien[89] claim to have selectively epoxidised 3-methyl-3-butenyl methacrylate to give 3,4-epoxy-3-methylbutyl methacrylate (30), but did not provide any chemical evidence to support their claim.

Tyushin *et al.*[123] mentioned the use of cyclohexylmethyl methacrylate as a component of a copolymer as part of a protective coating for kinescopes.

Haarmann and Schneider[124] reported the preparation of a copolymer incorporating 3-tetrahydrofuryl methacrylate (28) as a component in the polymer. The report did not give any details of the monomer's (28) preparation or properties.

Osbourne and Trecker[125] reported the use of 2,5-norbornenemethyl methacrylate as a component of a copolymer. They did not give any details of the chemistry of the monomer.

2.9.3 Spectroscopic data for methacrylate esters

Mass spectral data for the monomeric esters could not be obtained due to difficulties caused by polymerization.

2.9.3.a Infra-red data

The i.r. spectra of all the methacrylate monomers synthesized showed the bands common to methacrylate esters (Table 17).

2.9.3.b N.m.r. data

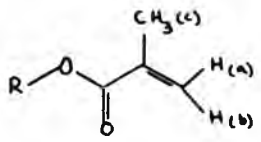
2.9.3.b.i Ester moiety

The ^{1}H and ^{13}C n.m.r. spectra of all the monomers prepared showed signals due to protons and carbons in the ester moiety common to all the heterocyclic and carbocyclic methacrylate esters.

Table 17 Infrared data for methacrylate esters

Bands / cm^{-1}	Assignments
1717-1730	C=O stretch
1450-1460	$C=C-CH_3$
1370-1390	$C-CH_3$ stretch
1400-1410	$C=CH_2$ in-plane deformation
1200-1300	C-O stretch
1130-1180	

Formula (81) shows a generalised methacrylate ester in which the protons are labelled.



(81)

The newly prepared methacryloyl esters gave proton nmr spectra in close agreement with those previously reported [81]. Thus the methyl protons (c) gave a multiplet with very fine splitting at δ 1.90. Long range coupling to the vinyl protons was also observed. The olefinic protons, $H_{(a)}$ and $H_{(b)}$, which are in a different magnetic environments, gave distinct signals which were observed as multiplets, due to coupling to each other and to the methyl, $CH_3(c)$, protons.

The ^{13}C spectrum showed the carbonyl group signal as a characteristic shortened peak at 167 ppm which is in the expected region of ester carbonyls. The alkene carbons appear at quite low field as expected for sp^2 hybridized carbons. The vinyl carbon, $\underline{C}=CH_2$, appeared at 136 ppm since it was a substituted carbon whereas

the second vinyl carbon, C=$\underline{CH_2}$, showed a signal at higher field at 125 ppm. The methyl carbon appears at quite high field as expected for a sp^3 carbon.

2.9.3.b.ii N.m.r. data for the alcohol residues of the methacrylate esters

2.9.3.b.ii.a' ^1H n.m.r. of heterocyclic alcohol residues

The ring protons on carbons directly attached to the electronegative oxygen in the ring appear in the region of δ 3.56-3.95. The side chain protons on the carbon attached to ester group appear more downfield at δ 4.09-4.33 since there is a further deshielding effect. The remaining ring and side chain protons appear much further upfield at δ 1.49-1.96 (Table 18).

Table 18 ^{1}H n.m.r. data for heterocyclic monomers

Ester	Ring protons		Side chain protons	
	ppm	Group	ppm	Group
Tetrahydrofurfuryl	1.80	2×CH_2(m)	4.09	CH_2-OCOR (m)
	3.75	CH-O (m)	--	
Tetrahydropyran-2-yl-methyl	1.49	3×CH_2(m)	4.09	CH_2-OCOR (d)
	2.80-3.95	CH_2O, CH-O(m)	--	
3,4-Epoxybutan-1-yl	3.71	epoxy	4.33	CH_2-OCOR (m)
	--		1.95	CH_2 (m)
3,4-Epoxymethyl-butan-1-yl	3.70	epoxy	4.31	$CH_2$2-OCOR (m)
	--		1.92	CH_3, CH_2 (m)
3-Tetrahydrofuryl	1.94	CH_2 (m)	--	
	3.92	2×CH_2-O, CH-O	--	
3-Methyloxetan-3-ylmethyl	3.56	2×CH_2-O	1.96	CH_3 (m)
	--		4.13	CH_2-OCOR

2.9.3.b.ii.b' ^{1}H n.m.r. of carbocyclic alcohol residues

The ring and side chain protons of the saturated carbons appeared at δ 1.24-1.91 as expected for shielded sp^3 hybridized nuclei. The side chain protons that were directly attached to the oxygen in the ester group gave signals further upfield , δ 3.95-4.18 (Table 19).

The bicyclic norbornylmethyl residue gave signals at δ 1.29 for ring protons and at δ 2.20 for the bridge protons. The side chain protons being near the ester oxygens appeared at δ 4.02. The ^{1}H n.m.r. spectrum of the 2,5-norbornenemethyl residue could not be interpreted due to the presence of unseparated endo and exo isomers.

2.9.3.b.ii.c' ^{13}C n.m.r. of heterocyclic alcohol residues

The ring carbons of the tetrahydrofurfuryl and tetrahydropyran-2-ylmethyl residues appeared at 23.1-28.1 ppm and those attached directly to an oxygen atom gave signals further downfield at 66.8-68.5 ppm. The side chain carbons in both these methacrylate esters

Table 19 ^1H n.m.r. data for carbocyclic monomers

Alcohol Residue	Ring protons ppm	Group	Side chain protons ppm	Group
Cyclohexylmethyl	1.76	3 x CH_2 (m)	3.95	CH_2-OCOR (d)
	1.91	2 x CH_2, CH (m)	--	
2-Cyclohexylethyl	1.24	3 x CH_2(m)	1.64	CH_2 (m)
	1.64	2 x CH_2,CH (m)	4.18	CH_2-OCOR (t)
Cyclopentyl	1.74	4 x CH_2,CH (m)	--	
Cyclopentylmethyl	1.62	4 x CH_2,CH (m)	4.04	CH_2-OCOR (m)
2-Cyclopentylethyl	1.76	4 x CH_2,CH (m)	4.16	CH_2-OCOR (m)
	--		1.76	CH_2 (m)
2-Norbornylmethyl	1.29	3 x CH_2,CH (m)	4.02	CH_2-OCOR
	2.20	CH_2 bridge	--	

appeared at 75.5-76.6 ppm due to the enhanced deshielding effect of ester group oxygens.

A similar trend was to be found in the 3-tetrahydrofuryl residue, where the only carbon in the ring unattached to oxygen atom appeared quite high upfield at 32.9 ppm whereas the other three ring carbons attached either to the oxygen in the ring or the ester group gave signals lower field at 67.1-75.2 ppm (Table 20).

In the 3-methyl-3-oxetanemethyl residue, the two ring carbons attached directly to the electronegative oxygen gave signals at 41.4 and 46.4 ppm whereas the remaining carbon appeared at 65.0 ppm due to the high degree of substitution. The side chain carbon attached to the oxygen in the ester group gave a signal at 66.6 ppm.

The epoxy carbons in the 3,4-epoxybutan-1-yl and 3,4-epoxymethylbutan-1-yl residues gave signals in the region of 49.8-62.9 ppm. The β-side chain carbons appeared at 33 ppm since they were shielded, whereas the α-carbons directly attached to the oxygen in the ester group gave signals at 68.62 and 68.56 ppm (Table 20).

Table 20 ^{13}C n.m.r. data for heterocyclic monomers

Alcohol Residue	Ring carbons ppm	Group	Side chain carbons ppm	Group
Tetrahydrofurfuryl	25.8,28.1	CH_2	76.6	$\underline{CH_2}OCOR$
	66.8,68.6	CH_2O and CHO	--	
Tetrahydropyran-2-yl-methyl	23.1,25.9,28.1	CH_2	75.5	$\underline{CH_2}OCOR$
	67.7,68.5	CH_2O and CHO	--	
3,4-Epoxybutan-1-yl	49.8,61.4	Epoxy	68.6	$\underline{CH_2}OCOR$
	--		33.5	CH_2
3,4-Epoxymethyl-butan-1-yl	50.0,62.9	Epoxy	68.6	$\underline{CH_2}OCOR$
	--		33.9	CH_2
	--		18.2	CH_2
3-Tetrahydrofuryl	32.9,67.1,73.1	CH_2	--	
	75.2	$\underline{CH}OCOR$	--	
3-Methyloxetane-3-ylmethyl	41.4,48.4	CH_2O	66.6	$\underline{CH_2}OCOR$
	65.0	$\underline{C}-CH_2O$	--	

2.9.3.b.ii.d' ^{13}C n.m.r. of carbocyclic alcohol residues

The unsubstituted carbons gave signals in the region of 23.9-33.3 ppm whereas the substituted ring carbons appeared at a slightly lower field at 36.1-38.8 ppm. The α-carbons directly attached to the electronegative oxygen in the ester group appeared at 63.1-77.4 ppm. The β-carbon of the side chains in 2-cyclohexylethyl and 2-cyclopentylethyl residues appeared higher field at 34.9 ppm (Table 21).

It was difficult to interpret the spectra for 2-norbornylmethyl and 2,5-norbornenemethyl residues due to the presence of unseparated isomers in each case.

Conclusion

The ^{13}C n.m.r. data for any of the above monomeric esters were not presented previously in the literature. Bhusate[87] presented i.r. and proton n.m.r. data for tetrahydrofurfuryl and tetrahydropyran-2-ylmethyl methacrylate. The i.r. and ^{1}H n.m.r. data for the other heterocyclic or any of the carbocyclic methacrylate esters were not presented previously in the literature. The technique of flash

Table 21 ^{13}C n.m.r. data for carbocyclic monomers

Alcohol residue	Ring carbons		Side chain carbons	
	ppm	Group	ppm	Group
Cyclohexylmethyl	25.9, 26.5, 29.9	CH_2	69.9	CH_2OCOR
	37.4	CH		
2-Cyclohexylethyl	26.3, 26.6, 33.3	CH_2	63.1	CH_2OCOR
	36.1	CH	34.9	CH_2
Cyclopentyl	23.9, 32.8	CH_2		
	77.4	CHOCOR		
Cyclopentylmethyl	25.5, 29.5	CH_2	68.7	CH_2OCOR
	38.8	CH		
2-Cyclopentylethyl	25.2, 32.8	CH_2	64.4	CH_2OCOR
	37.2	CH	34.9	CH_2

chromatography was applied successfully in the purification of the monomeric esters. This method was not previously used in the literature for the purification of heterocyclic or carbocyclic methacrylate esters.

2.10 Physical Studies

Pure samples (12-20 g) of monomeric methacrylate esters, mainly carbocyclic esters, were submitted to The London Hospital medical college for polymerization and physical testing. The monomeric esters submitted were: cyclohexylmethyl, cyclohexylethyl, cyclopentyl, cyclopentylmethyl, cyclopentylethyl, 3-tetrahydrofuryl, 2-norbornylmethyl, 2,5-norbornenemethyl and the commercially available cyclohexyl methacrylate esters. The studies included the measurement of:

a) Monomer and polymer densities,

b) Glass transition temperature at different scan rates using the technique of Differential Scanning Calorimetry (D.S.C.), and

c) Refractive indices of the samples.

The monomer densities were measured by using a 10 ml density bottle or a 5 ml pycnometer. Polymerization of the samples was carried out with benzoyl peroxide at 80 °C for 3 h. The technique of producing rectangular strips of polymeric samples has been described by Patel[125]. The refractive indices were measured with an Abbe' Refractometer, using a sodium light source at 20 °C.

2.10.a The glass transition temperature (T_g)

2.10.a.i Introduction

The monomeric methacrylate esters submitted for polymerization studies formed rigid polymeric materials (i.e. "organic glasses"). However, all amorphous polymers become compliant and elastomeric when their temperature is elevated to a reasonably well-defined value. This temperature is characteristic of the polymer and is called the "glass transition temperature" (T_g).

In the situations where the polymer rigidity is considered important, it must be ensured that the transition temperature must be well above the temperatures encountered in use. In the case of poly(methyl methacrylate), which is used for denture bases, it has a T_g of about 125 °C [127], which is above any temperatures that are likely to be encountered by the patient. Some denture-base polymers have large concentrations of residual monomer which cause distortion if cleaned in very hot water[128].

When the T_g is approached the polymeric flexibility increases to a great extent but this is accompanied by loss of elastic recovery. Some dental materials, such as epimine resins[129] and systems

utilising n-butylmethacrylate[130,131] have a relatively low $T_g$values of 50 °C , and yet function satisfactorily.

On the basis of these results, Patel[126] concluded that there is a relationship between the transition behaviour of the new polymers and their practical use as biomedical materials.

2.10.a.ii Results and Discussion

Patel[126] obtained the T_g values of some heterocyclic and isobornyl polymethacrylate esters. It was found that poly(tetrahydropyran-2-ylmethyl methacrylate) was insensitive to scan speed. At lower scan speeds the order of T_g from the highest to lowest was isobornyl, 2,3-epoxypropyl, tetrahydropyran-2-ylmethyl, tetrahydropyranyl, tetrahydrofurfuryl polymethacrylates.

A Perkin Elmer Model 1B Differential Scanning Calorimeter was used and traces were obtained in the temperature range 20-100 °C, at scan speeds of 2,4,8 and 16 °C per minute respectively (Table 22).

A comparative study of the T_g values of polyheterocyclic methacrylate esters[126] and their

analogous polycarbocyclic esters showed the following at lower scan speeds (Fig 3 and 4). Poly (tetrahydropyranyl methacrylate) has a much lower T_g than poly(cyclohexyl methacrylate) and the former is scan rate dependent unlike the carbocyclic analogue.

Poly(tetrahydropyran-2-ylmethyl methacrylate) has a slightly lower T_g than poly(cyclohexyl methacrylate) and the former is insensitive to scan speed unlike the latter.

Table 2: Differential Scanning Calorimetry values as a function of scan rate.

Esters	T_g (°C) for polymethacrylates at the scan speeds of:			
	2°C/min	4°C/min	8°C/min	16°C/min
Cyclohexyl	84.0	81.5	81.0	82.0
Cyclohexylmethyl	74.0	87.0	105.0	127.0
Cyclohexylethyl	46.5	44.0	48.0	56.0
Cyclopentylmethyl	43.5	46.5	46.5	51.0
3-Tetrahydrofuryl	50.0	56.0	67.0	77.0
2-Norbornylmethyl	47.0	49.0	49.0	55.0
2,5-Norbornene-methyl	57.0	56.0	62.0	67.0

Poly(tetrahydrofurfuryl methacrylate) has virtually the same T_g at lower scan rates as poly-(cyclopentylmethyl methacrylate) but the latter is insensitive to scan speed.

The other notable feature was that poly cyclohexylethyl, cyclopentylmethyl and 2-norbornylmethyl methacrylates had similar T_g values and were all insensitive to scan speeds. Poly(3-tetrahydrofuryl methacrylate) was the only heterocyclic compound to be studied and it was found to have a similar T_g value as that of poly (tetrahydrofurfuryl methacrylate) but was less scan rate dependent. Thus the scan speed dependency varied with each polymethacrylate ester and the reason for this was not clear.

In the present study it was found that thermodynamic T_g was best measured at lower scan speed. The results obtained showed the order of T_g from highest to lowest was cyclohexyl, cyclohexylmethyl, 2,5-norborn-enemethyl, 3-tetrahydrofuryl, 2-norbornylmethyl, cyclohexylethyl and cyclopentylmethyl polymethacrylates.

The new polymers prepared from carbocyclic and bicyclic monomers were found to be glasses with T_g values well above room temperature.

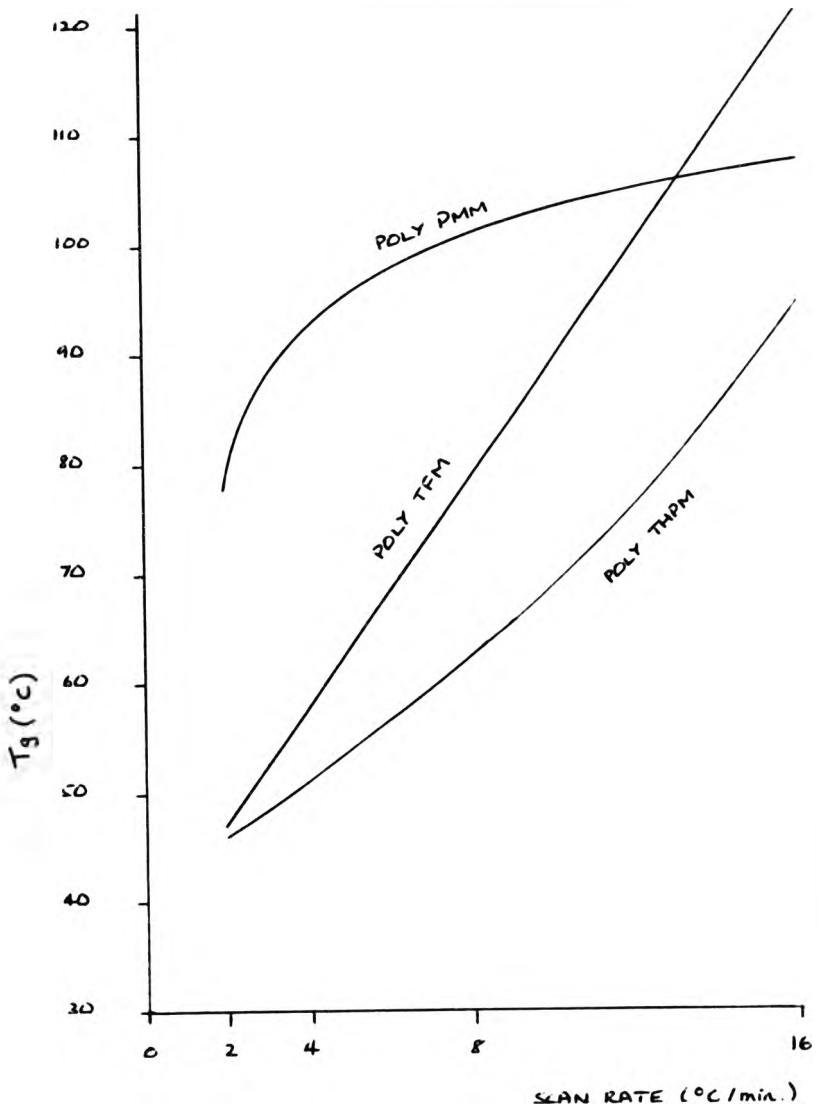


Fig 3: Relationship between glass temperature (Tg) and scan rate (S).

As shown above it was found that poly(methyl methacrylate) appeared as a decurved graph, poly(tetrahydropyranyl methacrylate) appeared as a recurved graph and poly(tetrahydrofurfuryl methacrylate) gave a straight line.

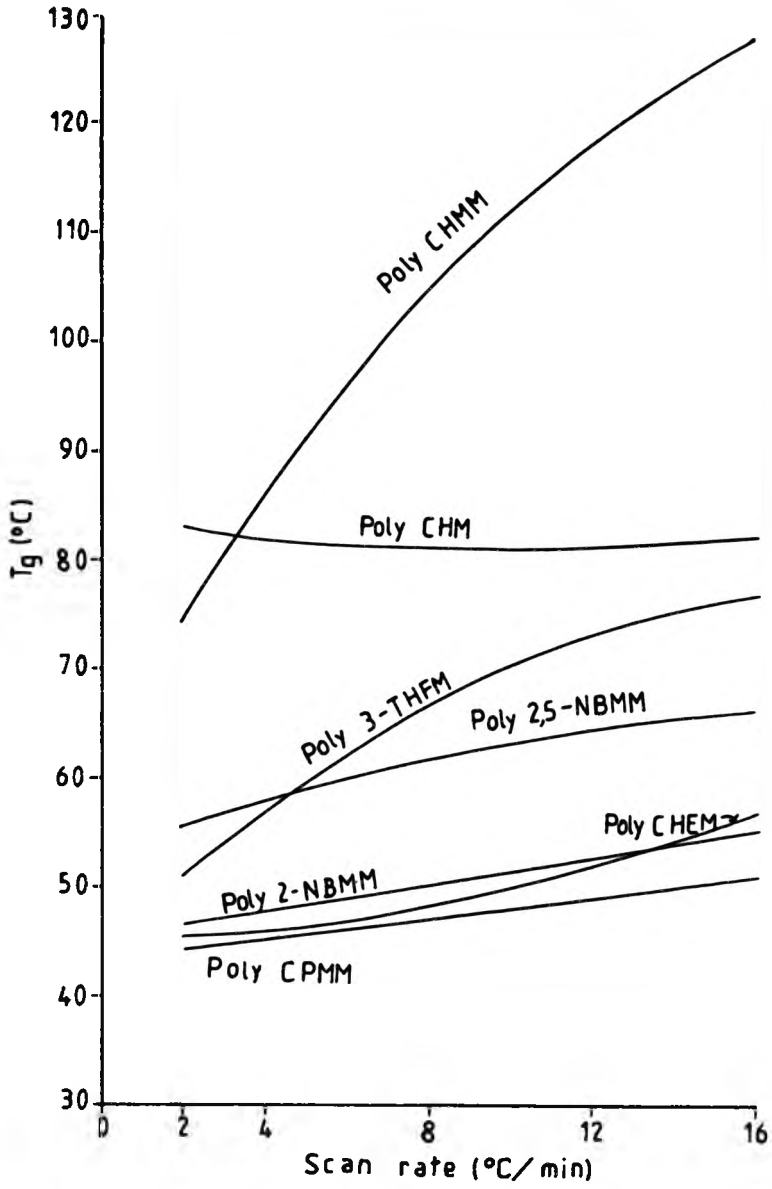

130
120
110
100
90
80
70
60
50
40
30
Tg (°C)
0
2
4
8
12
16
Scan rate (°C/min)
Poly CHMM
Poly CHM
Poly 3-THFM
Poly 2,5-NBMM
Poly CHEMA
Poly 2-NBMM
Poly CPMM

Fig. 4

The only exception was poly(cyclopentylethyl methacrylate) which was a soft rubber at room temperature. It was found that in general the carbocyclic polymers were very brittle and not as strong as the heterocyclic polymers.

2.10.b Polymerization shrinkage of methacrylate esters

2.10.b.i Introduction

There is a paucity of information on the subject of polymerization shrinkage in the literature, possibly because it has little bearing on normal industrial manufacture of components. Components are usually fabricated from ready-made polymers by moulding of one sort or another or by extrusion. Only in the clinical areas, where appliance manufacture involves the direct use of monomers, shrinkage is crucial to clinical success with, for example, ear-moulds, dentures, orthodontic appliances, dental filling materials and orthopaedic bone cements.

In the case of dental filling materials, there was no satisfactory polymeric-based material until the advent of composite materials. The polymeric component of these materials was substantially diluted

by an inorganic phase. This reduced polymerization shrinkage, coefficient of thermal expansion and increased hardness.

The few papers on polymerization shrinkage found in the literature were quite significant. Crawford[39] and Loshaek and Fox[40] showed that the change in molar volume was constant at about 22 ml/mol for a number of methacrylates. This result was in accord with the qualitative predictions of Nichols and Flowers[39] and Tobolsky *et al*[6]. The latter pointed out that the shrinkage in a vinyl-type polymerization was connected with the exchange of a van der Waal's bond and a double bond, with two single covalent bonds. This implied that the percentage volume change would decrease with molecular volume, merely because there were fewer molecules per unit volume.

Since this comparatively early work, Patel'[28] has recently studied the polymerization shrinkage and molar volumes of a range of n-alkyl methacrylates, heterocyclic methacrylates and dimethacrylates. The results obtained by Patel'[28] showed that the percentage volume shrinkage of n-alkyl methacrylates decreased with increasing length of substituent alkyl chain (Fig. 1, Section 1.4). This is of considerable interest because higher methacrylates (notably the C_{18} ester) are used in soft prosthesis materials'[32] and

could be of particular relevance as materials for soft ear-moulds.

Patel[126] also obtained useful information from a plot of molar volume of both monomer and polymer for n-alkyl methacrylates against the number of carbon atoms in the substituent chain (Fig. 2, Section 1.4). It was found that the relationship was linear and both plots were substantially parallel, with a slope of 16.6 ml/mole.

Van Krevelen[62] lists the contribution of the CH_2 group to the molar volume of simple liquids, obtained by a number of authors, quoting values of 16.1 to 16.5 ml/mole. The same author quoted the molar volume of the CH_2 group to be 15.85 ml/mole in glassy polymers and 16.45 ml/mole in rubbery polymers. Patel[126] found that slopes of the two lines in the above described plot, of monomer and polymer molar volume as a function of side chain length for n-alkyl methacrylates (Fig. 2, Section 1.4), were consistent with the molar volume of the CH_2 group to a good first approximation.

The second important aspect of Patel's[126] results is that there was a constant difference between the two linear plots (Fig.2) which implied the change in molar volume is independent of the size of the substituent alkyl chain. This agrees with the

predictions of Tobolsky *et al*[a], Nichols and Flowers [a] and the previous experimental data of Losheak and Fox[a] and Crawford[a]. The value obtained for the change in molar volume (ΔV_m) was 22.5 ml/mole and it was found to be in good agreement with the earlier data. Furthermore, Patel'[2a] found that the same value of ΔV_m, within the constraints of experimental error, applied to the branched alkyl esters, a limited range of heterocyclic methacrylates and isobornyl methacrylate (Table 1, Section 1.4). This means that the volume shrinkage of any methacrylate ester is, in principle, predictable from the following equation:

$$\Delta V / V(\%) = \frac{\Delta V_m}{(V_m)} \times 100$$

Thus Patel'[2a] concluded that the volume shrinkage is a function only of the molar volume of the methacrylate involved but is independent of the geometry of the substituent group. In the present work, it is hoped to test this hypothesis by exploring the carbocyclic and bicyclic systems.

2.10.b.ii Results and Discussion

The monomer density measurement was carried out using either a 10 ml density bottle or a 5 ml pycnometer. The density of polymers was determined using the hydrostatic weighing technique described by Patel[126]. It was found that cyclopentyl methacrylate could not be polymerised and cyclopentylethyl methacrylate produced a soft rubber. In general it was found that the carbocyclic methacrylates gave very brittle polymers which were difficult to handle.

The monomer and polymer densities of methacrylate esters obtained are shown in Table 22. Using the data from Table 22, shrinkage data as percentage volume shrinkage were calculated from:

$$\Delta V / V\ (\%) = \frac{\rho_{p} - \rho_{m}}{\rho_{p}} \times 100$$

where ρ_{p}= density of polymer,

and ρ_{m}= density of monomer.

The molar volume (V) of an ester (V_m) or its polymer (V_p) can be calculated from:

$$V = M.Wt. / \rho$$

where M.Wt. = molecular weight of monomer,
and ρ = density of monomer or polymer.

Thus the change in molar volume (ΔV_m) of a monomer unit on polymerization was calculated from:

$$\Delta V_m = \frac{M.Wt.}{\rho_m} - \frac{M.Wt.}{\rho_p}$$

These above calculated data are presented in Table 24. The change in molar volume of some of the esters was in good general agreement (ΔV_m = 22.5 ml/mole) with Patel's[126] data. These esters were cyclohexylmethyl, 2,5-norbornenemethyl, 2-norbornylmethyl and 3-tetrahydrofuryl methacrylates. The other esters, such as cyclohexyl and cyclopentylmethyl methacrylates had much lower than expected ΔV_m values. It is interesting to note that the latter two esters have the same molecular formula but different geometry, and this resulted in a substantial difference in their molar volumes.

Table 23 Density data for carbocyclic and other methacrylates

Ester	Density (g/ml) Monomer	Polymer
Cyclohexyl	0.9635	1.1146
Cyclohexylmethyl	0.9550	1.0984
Cyclohexylethyl	0.9533	1.0908
Cyclopentyl	0.9845	a
Cyclopentylmethyl	0.9739	1.1286
Cyclopentylethyl	0.9602	b
2-Norbornylmethyl	1.0067	1.1253
2,5-Norbornenemethyl	1.0252	1.1514
3-Tetrahydrofuryl	1.0730	1.2645

a cyclopentyl methacrylate could not be polymerised

b cyclopentylethyl methacrylate gave a soft rubber

Table 24 Shrinkage data for carbocyclic and other methacrylates

Ester	Molar volume (ml/mole) Monomer	Polymer	Shrinkage (ΔV/V%)	ΔV$_m$
Cyclohexyl	174.36	158.31	9.20	16.05
Cyclohexylmethyl	190.57	165.69	13.55	24.87
Cyclohexylethyl	215.67	188.48	12.60	27.18
Cyclopentylmethyl	163.87	145.91	13.71	17.96
3-Tetrahydrofuryl	145.39	123.37	15.14	22.07
2-Norbornylmethyl	192.71	172.40	10.54	20.31
2,5-Norbornene-methyl	187.28	166.75	10.96	20.53

Cyclohexylethyl methacrylate had higher than expected ΔV_m value especially compared to the bicyclic esters, all of which have the same number of carbons. The molar volume occupied by the former carbocyclic ester was also significantly larger than that of the bicyclic esters. The only heterocyclic ester to be tested in the present work was 3-tetrahydrofuryl methacrylate and it showed a good agreement with the expected value of ΔV_m.

The percentage volume shrinkage of the methacrylate esters tested were significantly lower than that of methyl methacrylate and similar to that of heterocyclic esters[1,24]. The cyclohexylethyl ester seemed to be very promising, as it had a high molar volume coupled with quite low shrinkage. The bicyclic systems showed similar promise of low shrinkage together with high value of molar volume.

Thus it was found that the difference of 22.5 ml/mole in ΔV_m did not apply in all the methacrylates studied above. This may indicate that the change in molar volume is not always independent of the size of the substituent side group.

2.10.c Refractive indices of monomers

2.10.c.1 Introduction

Patel[126] compared the refractive indices of heterocyclic and alkyl methacrylates and found that it was possible to predict their molar refractivities successfully. The close agreement found between theoretical and experimental molar refraction values indicated the purity of monomers as well as upholding the Clausius Mosotti equation shown below.

The Clausius Mosotti equation[127] describes the relationship between the refractive index and molar refraction (R) :

$$R = \frac{n^2 - 1}{n^2 + 2} \frac{M}{\rho}$$

where n is the refractive index of the material, M the molecular weight and ρ the density.

The usefulness of the equation lies in the fact that it describes the R value for a given molecule. The contributions of each atom make up the R value and other factors, such as double bonds and rings in the molecule tend to influence these values. These figures were published by Weast [128], and thus

theoretical R values can be calculated. Molar refractivity describes the polarisability of an atom or group and this enables the comparison of experimental values with theoretical predictions to take place.

According to Weast [123], R is an approximate measure of the actual total volume (without free space) of the molecules in one gram molecule. The molar volume (V_m) is the volume occupied by that one gram molecule. Patel[126] compared the R values and molar volumes of alkyl and heterocyclic esters, together with calculated R/V_m values. It was found that the latter values were surprisingly consistent for a range of methacrylates, although the heterocyclics were in one range and the straight chain alkyls lay in another range.

Thus in the present work, it was decided to compare the experimental and predicted values of molar refractivities for carbocyclic and other methacrylates, and to compare their R values with the molar volumes (V_m) obtained above (Section 2.10.b.ii).

2.10.c.ii Results and Discussion

The refractive indices of the following monomers were measured by means of an Abbé Refractometer: cyclohexyl, cyclohexylmethyl, cyclohexylethyl, cyclopentyl, cyclopentylmethyl, cyclopentylethyl, 3-tetrahydrofuryl, 2-norbornylmethyl, and 5-norborn-2-enemethyl methacrylates.

The refractive indices of these monomers were used to calculate the molar refractions and these are recorded in Table 25. Further calculations were carried out to obtain R/V_m (Table 26).. It was found that the predicted values of molar refraction agreed very closely with the experimental values (Table 25). Thus the reliability of the Clausius Mosotti equation was found to extend to the new compounds, whose purity was also thereby confirmed.

The R/V_m values of the monomers were found to be constant for all the carbocyclic methacrylates and the only heterocyclic monomer, 3-tetrahydrofuryl methacrylate (Table 25). The bicyclic monomers had very similar R/V_m values and these were slightly higher than that obtained for the carbocyclic monomers. It was interesting to note that the R/V_m values obtained for the range of monomers (0.27-0.28) in the present work agreed very closely with those

Table 25 Refractive index of carbocyclic and other methacrylates

Methacrylate	n_D^{20}	Molar Refraction, R (ml)	
		Experimental	Theoretical
Cyclohexyl	1.4576	47.54	48.01
Cyclohexylmethyl	1.4625	52.44	52.66
Cyclohexylethyl	1.4619	56.51	57.31
Cyclopentyl	1.4488	42.24	43.37
Cyclopentylmethyl	1.4539	46.70	48.01
Cyclopentylethyl	1.4585	51.76	52.66
3-Tetrahydrofuryl	1.4558	39.50	40.36
2-Norbornylmethyl	1.4833	55.07	55.25
2,5-Norbornene-methyl	1.4787	53.01	54.77

Table 26 Ratio of refraction to molar volume for methacrylate monomers

Methacrylate Monomer	Molar Refraction R (ml), Exp.	Molar Volume V_m (ml/mole)	R/V_m
Cyclohexyl	47.54	174.36	0.273
Cyclohexylmethyl	52.44	190.57	0.275
Cyclohexylethyl	56.51	205.60	0.275
Cyclopentyl	42.24	156.42	0.270
Cyclopentylmethyl	46.70	172.50	0.271
Cyclopentylethyl	51.76	189.54	0.273
3-Tetrahydrofuryl	39.50	145.39	0.272
2-Norbornylmethyl	55.07	192.71	0.286
2,5-Norbornene-methyl	53.01	187.28	0.283

obtained by Patel[12e] for heterocyclic methacrylates (0.27-0.28).

2.10.d Conclusions

1. It appeared qualitatively that the carbocyclic and bicyclic methacrylates are much more brittle than the corresponding heterocyclic compounds. This confirms the observations of Patel [12e] in the case of isobornyl methacrylate. The implication therefore is that the presence of oxygen in the ring is important, possibly because of the facility for hydrogen bonding.
   It should be noted from the recent work of Patel[12e], that polymers of tetrahydrofurfuryl, tetrahydropyran-2-ylmethyl and tetrahydropyran-2-yl methacrylates have only 2% crosslinks, resulting from ring-opening. Poly(tetrahydrofurfuryl methacrylate) is the strongest of these and has similar strength to poly(2,3-epoxypropyl methacrylate), the latter being highly crosslinked.
2. In general, the polymerization shrinkage was in accord with the predictions based on a molar volume change of 22.5 ml/mole. However there were two exceptions, namely cyclohexyl and cyclopentylmethyl methacrylates. Whilst there is no obvious reason

for this, they both have the same molecular weight.

3. With the exception of poly(cyclopentylethyl methacrylate), all materials were organic glasses. There was no obvious trend with respect to structure. In particular, comparison of the current carbocyclic methacrylates with the heterocyclics described by Patel[12c], again showed no particular trend.
4. A curious feature of the Tg results was that the degree of scan rate dependence varied widely, a feature also noted by Patel. The polymers with reasonably high Tg values, namely cyclohexyl, cyclohexylmethyl, tetrahydrofuran-3-yl and 5-norborn-2-enemethyl methacrylates are of obvious interest since these materials have low polymerisation shrinkage and high molar volumes. Thus they clearly merit future study in low shrinkage polymer systems.
5. The indications of the work of Patel[12c] are that carbocyclic methacrylates have very low water absorption, and this is an obvious area for future work involving the above carbocyclic and bicyclic methacrylates.
6. The calculation of molar refractivities from refractive index data on monomers, and the ratio of these to molar volumes, gave values in good agreement with those determined for heterocyclic

methacrylates[1,26]. It was also found that the molar refractivities so calculated agreed closely with the theoretical data. There is a clear need for similar studies on the polymers.

Chapter 3

EXPERIMENTAL

3.1 Preparation of tetrahydrofurfuryl methacrylate via transesterification

Methyl methacrylate (26.7 g, 0.272 mol), tetrahydrofurfuryl alcohol (7.0 g, 0.069 mol), dry benzene (25 ml), hydroquinone (1.70 g) and concentrated sulphuric acid (0.2 ml) were mixed and heated using a heating mantle under a 12" fractionating column fitted with reflux head and condenser. The mixture was heated under reflux for 30 h during which the benzene-methanol azeotrope was removed several times at 58-59 °C. The reaction was stopped when the temperature at the ratio head was a steady 80 °C. The reaction mixture was washed with distilled water (1 x 60 ml), sodium bicarbonate (10%, 3 x 60 ml) and re-washed with distilled water (1 x 60 ml). An emulsion had formed during the washes which was dispersed by the addition of sodium chloride and left overnight. Sodium chloride was filtered off and benzene removed on the rotary evaporator. The residue was fractionally distilled at 20 mmHg to give tetrahydrofurfuryl methacrylate (6.3 g, 54%) b.p. 116-117 °C at 20 mmHg n_D^{20} 1.4552 (lit.[4] b.p. 81-85°C at 4mm Hg; n_D^{20} 1.4585). ^{13}C nmr δ ($CDCl_3$) 18.35(CH_3), 25.82, 28.15, 66.80, 68.56 (3xCH_2 ring and CH), 76.63 (-$\underline{C}H_2$-O-COR), 125.77 (C=$\underline{C}H_2$), 136.36 ($\underline{C}$=CH_2), 167.45 (C=O).

3.2 Attempted preparation of tetrahydropyran-2-yl methyl methacrylate by direct esterification

Glacial methacrylic acid (10.0 g, 0.12 mol), tetrahydropyran-2-yl methanol (10.0 g, 0.08 mol), hydroquinone (2.0 g), p-toluenesulphonic acid (2.0 g) were refluxed in toluene (dry, 50 ml) using the Dean and Stark apparatus. The reaction was carried out for 36 h and 0.6 ml water of esterification was collected (theoretical 1.5 ml). A further 15 h refluxing was carried out but polymerisation of the product had occurred.

3.3 Transesterification of Tetrahydropyran-2-yl methanol

Following the procedure of experiment 3.1, methyl methacrylate (100.0 g, 1.02 mol) tetrahydropyran-2-yl methanol (60.0 g, 0.517 mol), hydroquinone (4.0 g), dry toluene (100 ml) were heated under reflux together with a catalytic amount of conc. sulphuric acid (0.2 ml). The toluene-methanol azeotrope was removed at 63-90 °C several times. After 30 h, the reaction was stopped as the temperature at the ratio head was a constant 105 °C. The mixture was allowed to cool and washed with distilled water (1×60 ml), 10% sodium bicarbonate solution (3×100 ml), and finally distilled water (1×60 ml). An emulsion had formed during the washes which was treated with sodium chloride overnight. The solvent, toluene, was removed on the rotary evaporator and the residue distilled fractionally at reduced pressure. It gave tetrahydropyran-2-yl methyl methacrylate as a colourless liquid (50.1 g, 52.5%), b.p. 79-81 °C at 2.5 mmHg, n_D^{25} 1.4604 (lit.[44] n_D^{25} 1.4598), ^{13}C nmr δ ($CDCl_3$) 18.30 (CH_3), 23.09, 25.89, 28.14, 67.68, 68.46 (ring 4×CH_2 and CH), 75.54 ($\underline{C}H_2$-O-COR), 125.66 (C=$\underline{C}H_2$), 136.38 ($\underline{C}$=CH_2), 167.45 (C=O).

3.4 Attempted direct esterification of tetrahydrofurfuryl alcohol

Glacial methacrylic acid (10.0 g, 0.12 mol), tetrahydrofurfuryl alcohol (10.0 g, 0.098 mol), hydroquinone (1.2 g) and p-toluenesulphonic acid (0.3 g) were refluxed in dry toluene (50 ml) using a Dean and Stark apparatus. The rate of reaction appeared very slow since only 0.1 ml water of esterification was collected after 15 h. The experiment was abandoned since polymerisation of the reaction had occurred after 18 h.

3.5 Preparation of 3-buten-1-oic acid by Grignard reaction

A 2 l, three-necked flask was charged with magnesium (97.0 g, 4.04 mol) and equipped with a Trubore stirrer, a double-jacketed reflux condenser and a nitrogen inlet. The entire apparatus was dried under nitrogen using a heating mantle. Freshly distilled anhydrous tetrahydrofuran (1 l) was added quickly to the magnesium in the cooled flask and stirred at room temperature until the colour of iodine had faded. An equilibrating funnel (250 ml) containing freshly distilled allyl chloride (90.30 g, 97 ml, 1.180 mol) and anhydrous tetrahydrofuran (100 ml) was attached to the 3-necked flask. The allyl chloride was introduced at room temperature into the flask and stirred vigorously with occasional cooling. After the addition was completed, the flask was heated at reflux for 4 h. Dry carbon dioxide, from cardice, was bubbled into the cooled Grignard reaction mixture and vigorously stirred overnight. It was poured into 50% aq. conc. HCl (1 l) and cooled in an ice-bath. The mixture was extracted with ether (3×100 ml), and washed with sodium hydroxide (25%, 3×100 ml). The latter washings were neutralised with conc. HCl and extracted with ether (3×100 ml). The combined ether extracts were dried over anhyd. magnesium sulphate and evaporated to give butenoic acid

(10.0 g, 10%), b.p. 75-76 °C at 11 mmHg, n_D^{18} 1.4224 (lit.[114] b.p. 72-73 at 13 mmHg, n_D^{20} 1.423), ν_{max} (KBr disc) 3360, 2980-2860, 1720.

3.6 Preparation of 3-butenol by Grignard reaction using paraformaldehyde

Following the above procedure the Grignard reagent of allyl chloride (13.5 g, 14.5 ml, 0.176 mol) was prepared by using magnesium turnings (14.5 g, 0.604 mol) and freshly distilled dry tetrahydrofuran (600 ml). The mixture was heated under reflux for 5 h. Paraformaldehyde (dried over P_2O_5 for 48 h) was introduced into the reaction vessel at reflux using tapered joints, pvc tubing and a small round bottomed flask. An excess of paraformaldehyde was added with no additional heat and the reaction mixture was stirred vigorously throughout. After further heating under reflux for 2 h the reaction mixture was cooled and saturated ammonium chloride (20 ml) was added dropwise. The mixture was stirred for 0.5 h to complete hydrolysis, anhydrous magnesium sulphate (18 5 g) was added and further stirred for 1 h. The mixture was filtered and the cake well washed with ether. The filtrate and washings were reduced *in vacuo*, and the residue distilled at 100-110 °C (lit.[116] 116-118 °C) to

give 3-buten-1-ol (5.0 g, 38.6%), n_D^{20} 1.4218 (lit.[116] $n_D^{22.5}$ (1.4190), ν_{max} (KBr disc) 3320, 3080, 2940, 2880, 1640.

3.7 Preparation of allyl cyanide

Sodium cyanide (3.2 g, 65 mmol) was added to dimethyl sulphoxide (20 ml) in a 3-necked flask fitted with reflux condenser, thermometer and a dropping funnel. The mixture was heated to 50°C and allyl chloride (5.0 g, 65 mmol) was added dropwise. The reaction was exothermic and the temperature rose to 80 °C and it was kept at this temperature for 2 h. The mixture was poured into water, extracted with ether and the extracts dried over magnesium sulphate. After filtration the ether extracts were concentrated *in vacuo* to give a crude product (6.0 g). Upon distillation a pure sample of allyl cyanide was obtained (3.9 g, 89%), b.p. 117-120 °C, n_D^{18} 1.4049 (lit.[116] 114-116 °C, n_D^{20} 1.406), ν_{max} (KBr disc) 2890, 2240.

3.8 Attempted preparation of 4-chlorobutan-1-ol from 1,4-butandiol

A 1 l three-necked flask was charged with 1,4-butandiol (50.0 g, 0.555 mol), conc. HCl (480 ml) and distilled water (150 ml). The mixture was heated in an oil-bath at 100 °C and pet. ether (100-120 °C fraction) was introduced via a glass inlet tube into the bottom of the stirred solution for 16 h, the upper layer being removed constantly. The combined pet. ether extracts were concentrated *in vacuo* to 250 ml, washed with 5% $NaHCO_3$ until neutral and water (2×100 ml) and dried over magnesium sulphate. The excess pet. ether was removed by distillation under reduced pressure (1.5 mmHg) using a 10 cm Vigreux column. The residue had charred upon heating and the distillate collected in two fractions was shown to be very impure by gas chromatography (crude yield 2.0 g, 1.8%). The residue had polymerized during heating and distillation.

3.9 Hydrolysis of allyl cyanide

A 2-necked flask was fitted with a reflux condenser and a dropping funnel. Sulphuric acid (50 ml, 50% aq.) was introduced and allyl cyanide (2.0 g, 0.03 mol) was added dropwise. The mixture was heated at reflux for 3 h and the cooled solution poured into iced water (20 ml). It was extracted with ether (5×20 ml), and washed with sodium bicarbonate solution (3×30 ml, 10%) and distilled water (3×30 ml). The crude product (1.5 g) was essentially 3-butenoic acid (57%) as shown by i.r. and g.c. (i.r. identical to that of Ex. 3.5).

The above experiment was repeated on a larger scale using allyl cyanide (20.0 g, 0.30 mol). The crude product was distilled to give 3-butenoic acid (17.0 g, 66%) b.p. 75-76 °C at 10 mmHg, n_D^{20} 1.4215 (lit.[116] b.p. 72-73 at 13 mmHg, n_D^{20} 1.423).

3.10 Reduction of 3-buten-1-oic acid

Lithium aluminium hydride (8.0 g, 0.21 mol) was placed in a 3-necked flask under dry nitrogen atmosphere. Dry ether (500 ml) was introduced slowly and the mixture was stirred vigorously for 1 h. 3-Buten-1-oic acid (15.0 g, 15 ml, 0.174 mol) in dry ether (100 ml) was added dropwise such that a gentle reflux was maintained during addition. The mixture was stirred at room-temperature for 8 h. Distilled water (10 ml) was added dropwise with caution until no further hydrogen was given off. The etheral layer was decanted and dried over anhydrous magnesium sulphate. The remaining precipitate was dissolved in dil. hydrochloric acid, extracted with ether (3×100 ml) and the extracts were dried over anhyd. $MgSO_4$. The combined extracts were reduced *in vacuo* to give 3-buten-1-ol (11.0 g, 87.5%), b.p. 113-14 °C, n_D^{18} 1.4209 (lit.[116] b.p. 112-14 °C, n_D^{20} 1.4213). The i.r. was identical to Ex. 3.6.

3.11 Epoxidation of 3-buten-1-ol

A mixture of dichloromethane (dry, 50 ml) and m-chloroperbenzoic acid (12.0 g, 0.07 mol) was stirred at 0 °C. 3-Buten-1-ol (5.0 g, 0.07 mol) in dichloromethane (10 ml, dry) was introduced dropwise keeping the

temperature at or below 0 °C, and stirring was continued at this temperature for 6 h. The mixture was allowed to reach room-temperature and further stirred for 8 h. The precipitate, m-chlorobenzoic acid, formed as a by-product, was filtered off and washed thoroughly with dry dichloromethane. The filtrate was shaken with anhydrous sodium carbonate. On reducing the dichloromethane *in vacuo*, 3,4-epoxy-3-butan-1-ol was collected (4.0 g, 65.5%). The proton n.m.r. spectrum showed the disappearance of vinyl protons of the starting material. δ_H ($CDCl_3$) 1.9 (t, 2H, CH_2), 2.6-2.9 (m, 2H, CH_2-CO), 2.85 (s, 1H, OH), 3.8 (t, 2H, $\underline{CH_2}OH$).

3.12 Methacrylation of 3,4-epoxybutan-1-ol

3,4-Epoxybutan-1-ol (5.0 g, 56 mmol) was added to dry benzene (50 ml) in a two-necked flask and cooled to 0 °C. Methacryloyl chloride (10.0 ml, 10.54 g, 0.10 mol) in benzene (10 ml) was added dropwise keeping the temperature at or below 0 °C. The mixture was stirred at 0 °C for a further 6 h, allowed to reach room-temperature, washed with water, sodium bicarbonate (10%, 3×25 ml) and brine (3×20 ml). The benzene layer was dried over anhyd. magnesium sulphate and concentrated *in vacuo*. The crude mixture (5.0 g)

contained several components as shown by t.l.c. and gas chromatography. A sample (2.0 g) was purified by flash chromatography on silica gel (10%, ethyl acetate, pet. ether 40-60 °C) to give glycidyl methyl methacrylate (1.20 g, 34%), n_D^{25} 1.4465, found % C, 60.96, H, 7.73, $C_8H_{12}O_3$ requires % C, 61.53, H, 7.69, ν_{max} (KBr disc) 2960, 2920, 1720, 1640, δ_H ($CDCl_3$) 6.10 (m, 1H, $C=CH_2$), 4.33 (m, 2H, $\underline{CH_2}OCOR$), 3.71 (m, 3H, CH_2-OCH), 1.95 (m, 5H, CH_2 and CH_3), ^{13}C nmr δ ($CDCl_3$) 167.79 (C=O), 136.30 ($\underline{C}=CH_2$), 125.98 ($C=CH_2$), 66.62 ($\underline{CH_2}$-OCOR), 61.43 ($\underline{CH}$-OCH_2), 49.81 (CH-$O\underline{CH_2}$), 33.46 (CH_2), 18.26 (CH_3)

3.13 Epoxidation of 3-methyl-3-buten-1-ol

A solution of m-chloroperbenzoic acid (4.30 g, 25 mmol) in dry dichloromethane (50 ml) was introduced to a two-necked flask kept at 0 °C. 3-Methyl-3-buten-1-ol (2.1 g, 1.5 ml, 25 mmol) in dry dichloromethane (10 ml) was added dropwise with stirring over 0.5 h, keeping the temperature of the mixture at 0 °C. It was stirred for 1 h after addition was completed, warmed to room-temperature and left stirring overnight. The solid by-product, m-chlorobenzoic acid, was filtered off. The filtrate was shaken with anhydrous sodium carbonate for 2 h and then filtered. The solvent was concentrated *in vacuo* to give a syrupy liquid which was identified by

proton nmr as 3-methyl-3,4-epoxybutan-1-ol (1.2 g, 48%), n_D^{17} 1.4380, δ_H 1.40 (s, 3H, CH_3), 1.91 (t, 2H, CH_2), 2.62-2.91 (m, 2H, CH_2-CO), 2.89 (br s, 1H, OH), 3.82 (t, 2H, $\underline{CH_2}OH$).

3.14 Methacrylation of 3,4-epoxy-3-methylbutan-1-ol

3,4-Epoxy-3-methylbutan-1-ol (7.0 g, 69 mmol) was added to dry benzene (20 ml) and cooled to 0 °C. Methacryloyl chloride (12.0 ml, 115 mmol) in dry benzene (10 ml) was added dropwise over 1 h keeping the temperature below or at 0 °C. The reaction mixture was worked up as in Ex. 3.13 to give a crude product (8.0 g) which contained three components as shown by t.l.c. and gas chromatography. A sample (2.0 g) was purified by flash chromatography on silica gel (10% ethyl acetate, pet. ether 40-60 °C) to give 3,4-epoxy-3-methylbutan-1-yl methacrylate (1.1 g, 37.7%). Found % C, 63.72, H, 8.32, $C_9H_{14}O_3$ requires % C, 63.53, H, 8.24, n_D^{22} 1.4416, ν_{max} 2965, 2920, 1720, 1640, δ_H ($CDCl_3$) 6.03 (m, 1H, C=CH_2), 5.53 (m, 1H, C=CH_2), 4.31 (m, 2H, $\underline{CH_2}OCOR$), 3.70 (m, 2H, CH_2-OC), 1.92 (m, 5H, CH_2, CH_3), 1.82 (m, 3H, CH_3), ^{13}C nmr δ ($CDCl_3$) 167.54 (C=O), 136.35 ($\underline{C}$=CH_2), 125.78 (C=$\underline{CH_2}$), 68.56 ($\underline{CH_2}$-OCOR), 62.89 ($\underline{C}$-OCH_2, epoxy), 49.99 ($\underline{CH_2}$-OC, epoxy), 33.91 (CH_2), 18.23, 17.86 (2xCH_3).

3.15 Preparation of tetrahydropyran-2-ylmethyl methacrylate using methacryloyl chloride

A two-necked flask charged with tetrahydropyran-2-ylmethanol (20.0 g, 160 mmol) was fitted with a reflux condenser and a dropping funnel with calcium chloride guard tubes. Methacryloyl chloride (26.0 g, 248 mmol) was added dropwise with stirring to the reaction mixture at0 °C. The mixture was stirred overnight at room-temperature. Hydroquinone (0.5 g) was added during the addition of the acid chloride to inhibit polymerization. The reaction mixture was poured into distilled water (50 ml), and washed with 5% sodium bicarbonate solution (3×30 ml). Ether (50 ml) was added during the washing to prevent emulsion forming. However an emulsion had formed which was treated with sodium chloride and left overnight. The sodium chloride was filtered off and the ether layer was dried over anhyd. magnesium sulphate. The ether filtrate was reduced *in vacuo* and distilled to give tetrahydropyran-2-ylmethyl methacrylate as a colourless liquid (19.0 g, 60%) b.p. 75-77 °C at 2.1 mmHg, n_D^{24} 1.4600 (lit.[44] n_D^{25} 1.4598). The analytical data obtained was identical to that of Ex. 3.3.

3.16 Methacrylation of tetrahydrofurfuryl alcohol using methacryloyl chloride

Following the procedure of Ex. 3.15, distilled tetrahydrofurfuryl alcohol (12.0 g, 0.118 mol) with hydroquinone (0.4 g) was kept at 0 °C and methacryloyl chloride (26.0 g, 0.248 mol) was added dropwise with stirring. The mixture was allowed to reach room-temperature and stirred overnight. The reaction mixture was poured into water, taken up in ether (100 ml), washed with 5% sodium bicarbonate (3×30 ml), then with distilled water (2×20 ml). The organic layer was dried over anhyd. magnesium sulphate and distilled to give tetrahydrofurfuryl methacrylate (12.5 g, 62.5%), b.p. 110-112 °C at 11 mmHg, n_D^{20} 1.4578 (lit.[4] 44%, b.p. 81-85 °C at 4 mmHg, n_D^{20} 1.4585).

3.17 Preparation of tetrahydropyran-2-ylmethyl chloride

Tetrahydropyran-2-ylmethanol (10.0 g, 98 mmol), and pyridine (0.1 g) were placed in a 3-necked flask, fitted with reflux condenser, dropping funnel and thermometer. To the rapidly stirred mixture kept at 0 °C, thionyl chloride (11.7 g, 98 mmol) was added dropwise. The temperature of the flask was kept at or

below 16 °C during the addition of thionyl chloride. The mixture was refluxed on a steam-bath for 1 h, cooled and distilled water (25 ml) was added. The dark brown mixture was extracted with ether (3×30 ml) and the resulting emulsion was treated with sodium chloride and left overnight. The etheral layer was separated and dried over anhyd. magnesium sulphate. After filtration the ether was reduced *in vacuo* and the residue was distilled to give tetrahydropyran-2-ylmethyl chloride (7.5 g, 60%), b.p. 169-75 °C at 760 mmHg, n_D^{25} 1.4590 (lit.[79] 68 %, b.p. 56-57 °C at 15 mmHg, n_D^{20} 1.4617).

3.18 Preparation of tetrahydrofurfuryl chloride

Following the procedure of Ex. 3.17, tetrahydrofurfuryl alcohol (10.0 g, 98 mmol), pyridine (0.1 g, 1 mmol) and thionyl chloride (11.7 g, 98 mmol) were mixed and heated under reflux for 1 h on a steam-bath. During the work-up an emulsion was formed which was treated with sodium chloride overnight. The ether layer was separated and concentrated *in vacuo* and the residue distilled to give tetrahydrofurfuryl chloride (5.0 g, 42%), b.p. 150-58 °C at 760 mmHg, n_D^{25} 1.4520 (lit.[86] 73-75%, b.p. 41-42 °C at 11 mmHg, n_D^{20} 1.4560).

3.19 Attempted preparation of tetrahydropyran-2-ylethanoic acid by Grignard reaction

The procedure of Ex. 3.5 was followed using magnesium turnings (5.4 g, 0.223 mol), freshly distilled tetrahydrofuran (400 ml), and tetrahydropyran-2-ylmethyl chloride (7.0 g, 0.05 mol). The mixture was heated under reflux for 5 h and cooled. Solid carbon dioxide was used as in Ex. 3.5 to bubble dry carbon dioxide into the reaction vessel with no additional heating or stirring. The colourless mixture turned

green after bubbling carbon dioxide overnight. The work-up procedure followed was similar to that of Ex. 3.5. The residue upon distillation gave the unreacted starting material, tetrahydropyran-2-ylmethyl chloride (6.5 g, 48 mmol), b.p. 170-72 °C at 760 mmHg, n_D^{20} 1.4602 (lit.[70] n_D^{20} 1.4617, b.p. 56-57 °C at 15 mmHg). The i.r. spectrum was identical to that of the starting material.

3.20 Attempted preparation of tetrahydrofurfuryl cyanide using potassium cyanide

A two-necked flask fitted with reflux condenser and a Trubore stirrer was charged with potassium cyanide (6.5 g, 0.100 mol) and I.M.S. (150 ml). The mixture was stirred until most of the potassium cyanide had dissolved. Tetrahydrofurfuryl chloride (5.0 g, 0.040 mol) in I.M.S. (50 ml) was added slowly and the reaction mixture was heated under reflux for 25 h. The cooled orange mixture was poured into distilled water (100 ml), extracted with ether (3×150 ml) and dried over calcium chloride. The ether was reduced *in vacuo* and the residue distilled to give the unreacted tetrahydrofurfuryl chloride (4.5 g, 36 mmol), b.p. 150-58 °C at 760 mmHg, n_D^{25} 1.4520 (lit.[66] n_D^{20}

1.4560). The i.r. spectrum was identical to that of the starting material.

3.21 Attempted preparation of tetrahydrofurfuryl bromide using potassium bromide

Potassium bromide (30.0 g, 0.25 mol) was dissolved in distilled water (50 ml) with gentle warming in a conical flask. It was then cooled in an ice-bath and conc. sulphuric acid (25 ml) was added cautiously with constant shaking of the conical flask. The precipitated potassium sulphate was filtered off and the filtrate was transferred to a 2-necked roundbottomed flask. Tetrahydrofurfuryl alcohol (15.0 g, 0.147 mol) was added and conc. sulphuric acid (15 ml) was introduced dropwise. The mixture was heated under reflux for 3 h, cooled, distilled water (100 ml) was added and extracted with ether (3×100 ml). The ether extracts were washed with distilled water (2×30 ml), 10% sodium bicarbonate (2×30 ml) and water (2×30 ml) and finally dried over anhyd. magnesium sulphate (5.0 g). After removal of the salt the ether was reduced *in vacuo* to give a crude product (20.0 g). Upon distillation the residue had solidified and failed to give the expected tetrahydrofurfuryl bromide.

3.22 Attempted preparation of tetrahydropyran-2-ylmethyl cyanide

3.22.a. Sodium cyanide (2.0 g, 0.04 mol) was added to dry dimethyl sulhoxide (10 ml) in a 3-necked flask fitted with reflux condenser, thermometer, dropping funnel and a magnetic stirring rod. The mixture was heated at 80 °C for 1 h until all the sodium cyanide had dissolved and freshly distilled tetrahydropyran-2-ylmethyl chloride (5.0 g, 0.037 mol) was added dropwise. During the addition of the chloride the expected rise in temperature of the flask did not occur. The mixture was heated to 120 °C and the reaction monitered by g.l.c. did not show any product formation in the 2.5 h reaction time. The contents of the flask had solidified during heating and the experiment was abandoned.

3.22.b. The above experiment was repeated using sodium iodide (0.1 g) as a catalyst at 60-70 °C. The g.l.c. analysis showed no product formation after 3 h, so the temperature was raised gradually up to 110 °C. There was still no product formation and the mixture solidified after 5 h.

3.23 Preparation of tetrahydrofurfuryl bromide

A two-necked flask was charged with tetrahydrofurfuryl alcohol (distilled, 8.0 g, 78 mmol), triphenylphosphine (23.0 g, 88 mmol) and fitted with a reflux condenser. N-Bromosuccinimide (13.0 g, 70 mmol) was added slowly with stirring; the reaction was exothermic with fumes of hydrogen bromide being produced. The apparatus was arranged for distillation and the reaction mixture distilled at reduced pressure to give tetrahydrofurfuryl bromide (10.0 g, 70%), b.p. 64 °C at 17 mmHg, n_D^{20} 1.4842 (lit.[ee] 61-62 °C at 13 mmHg, n_D^{20} 1.4850) ν_{max} (KBr disc) 2940, 2840.

3.24 Attempted preparation of heterocyclic cyanide directly from heterocyclic alcohol

3.24.a. Using tetrahydrofurfuryl alcohol

A mixture of tetrahydrofurfuryl alcohol (5.0 g, 49 mmol), sodium iodide (0.1 g), methyl cyanide (50 ml) and dimethylformamide (50 ml) was deaerated under argon. Dry trimethylsilylchloride (10.6 g, 12.5 ml, 0.100 mol) and sodium cyanide (4.8 g, 0.1 mol) were added at room-temperature. The mixture was then placed in a preheated oil-bath at 60-65 °C and kept at

this temperature for 4 h with stirring. The reaction was followed by g.l.c. which showed a slow partial disappearance of tetrahydrofurfuryl alcohol. The reaction was carried out for a further 7 h, but no further alcohol was used up as shown by g.l.c. The reaction mixture was poured in to distilled water (500 ml). The organic layer was extracted with ether (500 ml). The ether was washed with water (3×100 ml) and brine (100 ml), dried over anhyd. magnesium sulphate and filtered. The starting material, tetrahydrofurfuryl alcohol was recovered (1.0 g) and there was no evidence of formation of the expected product, tetrahydrofurfuryl nitrile, from the i.r. trace.

3.24.b. Using tetrahydropyran-2-ylmethanol

The above procedure was repeated with tetrahydropyran-2-yl methanol (5.0 g, 0.043 mol) and a similar result was obtained. The expected cyanide peak at 2240 cm^{-1} in the i.r. trace of the crude product was not found.

3.25 Preparation of tetrahydrofurfuryl bromide using phosphorous tribromide

In a 250 ml three-necked flask fitted with a mechanical stirrer, thermometer, separatory funnel and calcium chloride tube, were placed redistilled phosphorous tribromide (48.0 g, 0.18 mol) and dry toluene (30 ml). Dry pyridine (7.5 g) was added dropwise with stirring. The flask was cooled to -5 °C, and a mixture of redistilled tetrahydrofurfuryl alcohol (51.0 g, 0.5 mol) and dry pyridine (2.5 g) was added dropwise from a dropping funnel with stirring over 4 h. During addition the internal temperature of the flask was kept at -5 to -3 °C. Stirring was continued for 1 h more and the flask was allowed to reach room temperature. The mixture was allowed to stand for 48 h and then transferred to a distillation apparatus. Toluene was removed *in vacuo* and the residue distilled at 150 - 155 °C. The distillate collected was found to be impure, so it was redistilled several times at 30 - 38 °C at 5 mmHg to give pure tetrahydrofurfuryl bromide (33.7 g, 40%) (lit.[88] b.p. 49 - 50 °C / 4 mmHg).

3.26 Attempted preparation of tetrahydrofurfuryl-
methanoic acid by Grignard reaction

The procedure of Ex. 3.5 was followed using magnesium turnings (5.5 g, 0.223 mol), dry ether (250 ml) and tetrahydrofurfuryl bromide (8.5 g, 0.05 mol). The mixture was gently heated under reflux for 6 h and cooled. Dry carbon dioxide was bubbled into the mixture as in Ex. 3.5 . The residue upon distillation gave a mixture of compounds which could not be separated by further distillation. The g.c. trace confirmed the presence of several components being present in the distillate.

3.27 Preparation of tetrahydrofurfuryl cyanide

3.27.a. Sodium cyanide (0.32 g, 6 mmol) was introduced into a 3-necked flask containing DMSO (5 ml). The flask was fitted with a thermometer, reflux condenser and a dropping funnel. The mixture was heated to 60 °C and tetrahydrofurfuryl bromide (1.0 g, 6 mmol) was added dropwise. The reaction was exothermic leading to a rise in temperature to 75 °C. After the addition of the bromide, the temperature of the flask was raised to 90 °C. The reaction was monitored by g.c. which did not show the disappearance

of the starting material. After 4 h at 90 °C, the temperature was raised to 110 °C and the mixture went dark brown. The mixture was heated overnight, but no product formation was observed by g.l.c. The work-up involved dissolving the mixture in water and being taken up in ether. On removal of ether, the residue did not give the expected CN peak at 2240 cm^{-1} in the i.r. spectrum.

3.27.b. The above experiment was repeated using the same quantities of reagents. DMSO was distilled over calcium hydride and sodium cyanide dried at 150 °C before use. Tetrahydrofurfuryl bromide was distilled in dry conditions immediately before the reaction. The product obtained after the usual work-up was tetrahydrofurfuryl cyanide (0.35 g, 52%), n_D^{19} 1.4495 (lit.[100] n_D^{19} 1.4476), ν_{max} (KBr disc) 2880-2980, 2240, 1640.

3.27.c. The reaction was repeated in a larger scale applying the above precautions, using tetrahydrofurfuryl bromide (10.0 g, 98 mmol), sodium cyanide (5.3 g, 100 mmol), and dry DMSO (200 ml). There was very little conversion to the cyanide derivitive. This was the result obtained after several attempts at scaling up the experiment.

3.28 Hydrolysis of tetrahydrofurfuryl cyanide

3.28.a. Acid hydrolysis

Tetrahydrofurfuryl cyanide (5.0 g, 45 mmol) was placed in a two-necked flask and 50 % aq. sulphuric acid (25 ml) together with sodium chloride (1.2 g) was added. The mixture was heated under reflux for 3 h and poured into crushed ice and taken up in ether. The etheral solution was washed with saturated sodium bicarbonate solution (3 × 50 ml) and distilled water (2 × 10 ml) and the organic layer dried over anhyd. magnesium sulphate. Upon concentration under reduced pressure tetrahydrofurfuryl methanoic acid (2.0 g, 54%) was obtained, ν_{max} (KBr disc) 3400, 2940, 1690.

3.28.b. Alkali hydrolysis

Tetrahydrofurfuryl cyanide (6.0 g, 0.054 mol) was placed in a flask containing 20% potassium hydroxide in aqueous ethanol (150 ml). The mixture was heated under reflux for 2 h, cooled and neutralised with ether, dried over anhyd. magnesium sulphate and reduced *in vacuo* to give tetrahydrofurfurylmethanoic acid (3.4 g, 7.5%) , ν_{max} (KBr disc) 3400, 2940, 1690.

3.29 Oxidation of tetrahydrofurfuryl alcohol

Tetrahydrofurfuryl alcohol (51.0 g, 0.50 mol) was placed in distilled water (50 ml) and stirred at room-temperature. Sodium dichromate (75.0 g, 0.286 mol) in water (330 ml) and conc. sulphuric acid (35 ml) was added to the above mixture dropwise over 1.5 h at 30-40 °C. After addition , the mixture was stirred for 2 h at 25-35 °C. The mixture (green/black) was extracted several times with ether (4×250 ml) and dried over anhyd. magnesium sulphate. Ether was reduced *in vacuo* to give a crude product (20.0 g, 34.5%) which contained small amounts of the by-product, succinic acid, as a solid. On removal of succinic acid by filtration, tetrahydrofuran-2-carboxylic acid (19.5 g, 33.6 %) was obtained, b.p. 115 °C at 10 mmHg (lit.[112] 40%, b.p. 145 °C at 21 mmHg), ν_{max} (KBr disc) 3400, 2980-2860, 1730.

3.30 Hydrogenation of furylacrylic acid

Furylacrylic acid (1.2 g, 9 mmol), ethanol (I.M.S., 150 ml), water (150 ml), 5% Pd/C (10 mg) and 2M sodium hydroxide (0.5 ml) were mixed together in a vessel. The mixture was hydrogenated at room-temperature and 3 atm. pressure for 3 h. The catalyst was filtered off

and dil. sulphuric acid (2 M, 0.7 ml) was added to neutralise the mixture. On evaporation of water and ethanol, the residue gave tetrahydrofurfuryl-2-ethanoic acid (1.0 g, 80%), ν_{max} (KBr disc) 3460, 3340, 1730, 1580.

The above reaction could not be scaled up above 2.0 g of furylacrylic acid. The reaction did not proceed to completion even after 72 h and replacement of poisoned catalyst at 12 h intervals.

3.31 High pressure hydrogenation of furylacrylic acid

Furylacrylic acid (10.0 g, 72 mmol), absolute ethanol (150 ml), 5% Pd/C (10 mg) and 2M sodium hydroxide (0.5 ml) were mixed and transferred to an autoclave. The mixture was hydrogenated at 300-400 p.s.i. and 80-100 °C for 8 h. The mixture was allowed to remain under hydrogen atmosphere at 300 p.s.i. and room-temperature for a further 8 h. The catalyst was filtered off and the solution neutralised with 2 M sulphuric acid (0.5 ml). On evaporation of the ethanol layer under reduced pressure, a crude product (10.2 g) was obtained which showed the presence of vinyl protons in the n.m.r. trace. Thus to complete the hydrogenation, the mixture was rehydrogenated at room-temperature and

32 p.s.i. following the procedure in Ex. 3.30 for 72 h. On evaporation of water and ethanol, a crude product (10.5 g) was obtained which showed the disappearance of vinyl protons in the ^1H n.m.r. spectrum. It was distilled to give 2-(tetrahydrofurfuryl)ethanoic acid (10.1 g, 96.8%), b.p. 82 °C at 1 mmHg, n_D^{18} 1.4622 (lit.[108] b.p.119 °C at 0.2 mmHg, n_D^{18} 1.4591), ν_{max} (KBr disc) 3480, 3340, 1730, 1580, δ_H ($CDCl_3$) 7.89 (s, 1 H, OH), 3.84 (m, 3H, CH_2COOH and CH-O of ring), 2.45 (m, 2H, CH_2-O of ring), 1.88 (m, 6 H, 3×CH_2), ^{13}C n.m.r. δ ($CDCl_3$) 178.4 (C=O), 78.36(CH_2-COOH), 67.7 (CH), 31.18, 30.88, 30.40 (3×CH_2 ring), 25.69 (CH_2).

3.32 Preparation of 3-hydroxytetrahydrofuran

A 100 ml flask with 1, 2, 4 - trihydroxybutane (50.0 g, 0.47 mol) and p-toluenesulponic acid (0.5 g). The flask was equipped with a short Vigreux column and arranged for distillation. The mixture was heated with constant stirring to give a colourless distillate over a period of 3 h, b. p. 50-80 °C at 2 mmHg. The distillate was redistilled to give 3-hydroxytetrahydrofuran (32.7 g, 78%), b.p. 80-85 °C at 2 mmHg, n_D^{18} 1.4489 (lit.[107] b.p.93-95 °C at 26 mmHg n_D^{20} 1.4497), ν_{max} (KBr disc) 3340, 2880-2800.

3.33 Methacrylation of 3-hydroxytetrahyrofuran

3-Hydroxytetrahydrofuran (6.0 g, 60 mmol) was cooled in a 2-necked flask together with dry dichloromethane (15 ml) and maintained at -10 °C to 0 °C. Methacryloyl chloride (10 ml, 14.4 g, 0.14 mol) in dry dichloromethane (20 ml) was added dropwise such that the reaction mixture was kept at -5 to 0 °C. The mixture was stirred at 0 °C for 6 h and then allowed to stand at room-temperature overnight. De-ionised water (100 ml) was added and the separated organic layer was washed with 5% sodium bicarbonate (3×50 ml) and distilled water (2×50 ml), dried over anhyd. magnesium sulphate and the solvent concentrated *in vacuo* to give the crude product (7.0 g). Purification by distillation gave 3-tetrahydrofuranyl methacrylate. b.p. 38-40 °C at 0.05 mmHg (6.5 g, 61 %), n_D^{20} 1.4567. Found % C, 60.9, H, 7.6, $C_8H_{12}O_3$ requires % c, 61.5, H, 7.69, ν_{max} (KBr disc) 655, 815, 945 (acyl ester), 1025, 1050, 1080, 1170 (C-O stretch), 1095 (cyclic ether), 1300, 1320 (ester), 1355 (COR in ester), 1380, 1455 ($C-CH_3$), 1400-1410 ($C=CH_2$), 1630 (C=C stretch), 1720 (C=O stretch in ester, strong), 2830, 2860, 2870, 2890 (CH and CH_2), δ_H ($CDCl_3$) 1.94 (m, 3H, CH_3), 2.1 (m, 3H, CH and CH_2 of ring), 3.92 (4H, m, 2×CH_2 of

ring), 5.59 (m, 1H, C=C$\underline{H_2}$), 6.12 (m, 1H, C=C$\underline{H_2}$), ^{13}C n.m.r. δ ($CDCl_3$) 18.2 (CH_3), 32.9 (CH_2 of ring), 67.1, 73.1, 75.2 (ring CH_2 x 2, and CH), 125.89 (C=$\underline{C}H_2$), 136.4 ($\underline{C}$=CH_2), 167.2 (C=O).

3.34 Methacrylation of 3-methyloxetan-3-ylmethanol

3-Methyloxetan-3-ylmethanol (6.0 g, 60 mmol) was placed in a 2-necked flask with dry benzene (50 ml). The mixture was cooled in an ice/salt bath. Methacryloyl chloride (14.4 g, 10.0 ml, 140 mmol) in dry benzene (20 ml) was added slowly with constant stirring. A small amount of hydroquinone (20 mg) was added to the reaction mixture to inhibit polymerisation. The mixture was left stirring at room-temperature overnight, added to water (100 ml, de-ionised), and extracted with ether (200 ml). The organic layer was washed with 5% sodium bicarbonate (3 x 50 ml) and distilled water (2 x 50 ml) and dried over anhyd. magnesium sulphate. Benzene and ether were reduced *in vacuo* to give the crude product (12.4 g). Purification was attempted by distillation but the methacrylate ester had polymerised on heating.

The above procedure was repeated and purification was attempted on a sample (1.5 g) using flash

chromatography (silica 35-70 μ, 30 % ethyl acetate and petroleum ether 40-60). The purified sample gave 3-methyloxetan-3-ylmethyl methacrylate (0.8 g, 66 %) as a pure compound, n_D^{17} 1.4462, found % C, 62.50, H, 8.50, $C_9H_{14}O_3$ requires % C, 63.53, H, 8.23, ν_{max} (KBr disc) 645, 805, 940 (acyl ester), 1020, 1050, 1170 (C-O stretch), 1300, 1322 (ester), 1380, 1458 (C-CH_3), 1402 (C=CH_2), 1638 (C=C stretch), 1720 (C=O, strong), 2840, 2880 (CH and CH_2), δ_H ($CDCl_3$), 1.05 (m, 3H, CH_3 of ester), 1.96 (m, 3H, CH_3 of ring), 3.56 (m, 4H, 2 × CH_2 of ring), 4.13 (m, 2H, $\underline{CH_2}$-O-COR), 5.61 (m, 1H, C=$\underline{CH_2}$), 6.12 (m, 1H, C=$\underline{CH_2}$), ^{13}C nmr δ ($CDCl_3$) 17.5 (CH_3 of ester), 18.3 (CH_3 of side chain), 41.4 (CH_2 of ring), 48.4 (CH_2 of ring), 65.0 ($\underline{C}$-CH_2O), 66.6 ($\underline{CH_2}$-O), 126.2 (CH_2 of ester), 136.11 ($\underline{C}$=CH_2), 167.7 (C=O).

3.35 Preparation of tetrahydropyran-2-ylmethyl bromide

A mixture of triphenylphosphine (150.0 g, 0.57 mol) and tetrahydropyran-2-yl methanol (50.0 g, 0.43 mol) was stirred vigorously in a 2-necked flask and n-bromosuccinimide (85.0 g, 0.477 mol) was added slowly over 1 h. The mixture was distilled to give tetrahydropyran-2-ylmethyl bromide (56.0 g, 72%), b.p.

152-53 °C, n_D^{18} 1.4872, (lit.[7] b.p. 153 °C, n_D^{20} 1.4887), ν_{max} (KBr disc) 2940, 2840.

3.36 Preparation of tetrahydropyran-2-ylmethyl cyanide

Sodium cyanide (1.4 g, 0.03 mol) was placed in a three-necked flask fitted with reflux condenser, thermometer, and a dropping funnel. Anhydrous, freshly distilled dimethyl sulphoxide (25 ml) was introduced and the mixture was heated to 60 °C for 1 h. Addition of tetrahydropyran-2-ylmethyl bromide (5.0 g, 0.028 mol) dropwise produced an exothermic reaction during which temperature rose to 80 °C for 4 h. On cooling the mixture was added to distilled water (20 ml), extracted with ether (2 × 50 ml), washed with brine (20 ml) and dried over anhyd. magnesium sulphate. On removing the ether under reduced pressure, tetrahydropyran-2-ylmethyl cyanide (2.0 g, 63 %) was obtained as shown by infrared spectrum and g.c. trace, ν_{max} (KBr disc) 2940, 2840, 2240.

3.37 Hydrolysis of tetrahydropyran-2-ylmethyl cyanide

Tetrahydropyran-2-ylmethyl cyanide (15.0 g, 0.12 mol) was heated under reflux with 20 % potassium hydroxide in aqueous ethanol (200 ml) for 3 h. Following the usual work-up, the crude product was distilled to give tetrahydropyran-2-ylacetic acid (13.8 g, 80 %) b.p.90-100 °C at 1 mmHg (lit.[134] b.p. 132-40 °C at 8 - 18 mmHg). A sample of the product was recrystallised from hexane m.p. 50 - 52 °C (lit.[134] m.p. 51 - 54 °C), ν_{max} (KBr disc) 3420, 2940, 2865, 1710, δ_H n.m.r. ($CDCl_3$) 6.50 (s, 1 H, OH), 4.06 (m, 3 H, CH_2COOH, CH-O of ring), 2.46 (m, 2H, CH_2-O of ring), 1.32 (m, 6H, 3 × CH_2).

3.38 Preparation of tetrahydrofurfuryl mesylate

Tetrahydrofurfuryl alcohol (10.0 g, 0.1 mol) in dry pyridine (10 ml) was cooled to 10 °C to which a mixture of mesyl chloride (12.5 g, 0.11 mol) and pyridine (5 ml) was added dropwise with constant stirring. After addition, the reaction mixture was stirred for 2 h at 5 - 10 °C and allowed to stand a refrigerator overnight. Chopped ice and water were added to dissolve the pyridine hydrochloride and the mixture extracted with dichloroethane (6 × 50 ml).

The extracts were combined, dried over anhyd. sodium sulphate and reduced *in vacuo* to give tetrahydrofurfuryl mesylate (6.7 g, 39 %) b.p. 85 - 90 °C at 1 mmHg, n_D^{17} 1.4590 (lit.[100] b.p.102 - 105 °C at 2 mmHg, n_D^{20} 1.4625).

3.39 Preparation of tetrahydrofurylacetonitrile

Tetrahydrofurfurylmesylate (6.2 g, 0.03 mol) and sodium cyanide (6.0 g, 0.08 mol) in dry toluene (100 ml) were placed in a flask and heated on the steam bath for 4 days. The mixture was extracted with ether (3 x 50 ml), dried over anhyd. magnesium sulphate and reduced *in vacuo* to give tetrahydrofurylacetonitrile (0.6 g, 15 %), n_D^{20} 1.4510 (lit.[100] yield 36 %, n_D^{18} 1.4490).

3.40 Attempted reduction of heterocyclic acids with lithium aluminum hydride

3.40.a. Using tetrahydropyran-2-ylacetic acid

Following the procedure of Ex. 3.10, lithium aluminum hydride (3.0 g, 0.08 mol) was stirred with dry ether (200 ml) under dry nitrogen for 1 h. Tetrahydropyran-

2-ylacetic acid (7.5 g, 0.05 mol) in dry ether (100 ml) was added slowly with constant stirring. The mixture was stirred for 24 h at room temperature. After the usual work-up procedure the residue gave mixed products as shown by the g.c. trace. The i.r. spectrum showed a residual carbonyl group absorbance at 1710 cm^{-1}. The t.l.c. indicated many impurities in the sample and thus purification of the sample was not attempted.

3.40.b. Using tetrahydrofurfurylmethanoic acid

The above procedure was followed by stirring lithium aluminum hydride (2.5 g, 0.065 mol), tetrahydrofurfurylmethanoic acid (5.0 g, 0.038 mol) and dry ether (250 ml) for 36 h. The residue obtained was very impure as seen by the g.c. trace and the i.r. spectrum showed the unreduced carbonyl group at 1710 cm^{-1}. No further purification of the residue was attempted.

3.41 Preparation of tetrahydrofurfuryldiethyl malonate

Diethyl malonate (60.0 g, 0.375 mol) and tetrahydrofurfuryl bromide (50.0 g, 0.30 mol) were

successively added to a solution of sodium ethoxide (11.0 g of sodium, 0.478 mol) in absolute ethanol (150 ml). The mixture was heated under reflux on a steam bath for 16 h, cooled and the alcohol was removed *in vacuo*. The residue was extracted with ether (10 × 50 ml), and the combined extracts were dried over anhyd. magnesium sulphate. Ether was removed and the residue distilled to give tetrahydrofurfuryldiethyl malonate (33.5 g, 45 %), b.p. 113 °C at 2 mmHg (lit.[102] b.p. 123 °C at 1 mmHg), n_D^{24} 1.5211, ν_{max} (KBr disc) 2960 - 2860, 1710, δ_H n.m.r. ($CDCl_3$) 1.23 (m, 12 H, 3×CH_2 ring, 2×CH_3 ester), 3.25 (m, 3H, CH_2-O and CH-O), 4.12 (m, 5H, CH and 2 × $COO\underline{CH_2}CH_3$).

3.42 Preparation of 2-(tetrahydrofurfuryl)ethanoic acid

A mixture of 20 % potassium hydroxide in aqueous ethanol and tetrahydrofurfuryldiethyl malonate (30.0 g, 0.123 mol) was heated under reflux on a steam bath for 6 h. The alcohol was removed *in vacuo*, the residue was diluted in water and extracted with ether (6 × 50 ml) and neutralised with 4 N hydrochloric acid. On removal of the ether, tetrahydrofurfurylmalonic acid was obtained as a pale yellow viscous oil. It was heated at 150 °C for 1 h until

all the carbon dioxide had evolved and then distilled to give tetrahydrofurfurylethanoic acid (10.5 g, 60 %) b.p. 135 °C, n_D^{24} 1.4631 (lit.[102] b.p. 119 °C at 0.2 mmHg, n_D^{18} 1.4591) ν_{max} (KBr disc) 3460 -3320, 1720, 1580, δ_H n.m.r. ($CDCl_3$) 7.30 (s, 1H, OH), 3.62 (m, 3H, $\underline{CH_2}COOH$ of ring), 2.40 (m, 2H, CH_2-O of ring), 1.90 (m, 6H, 3 x CH_2).

3.43 Preparation of 2-(tetrahydrofurfuryl)propanol

Following the procedure of Ex. 3.10, tetrahydrofurfuryl-2-ethanoic acid (8.0 g, 0.055 mol) was reduced with lithium aluminum hydride (2.7 g, 0.07 mol) in dry ether (500 ml). The mixture was stirred for 24 h and after the usual work-up the product obtained was not pure as observed by the g.c. trace. A significant amount of the starting material was still present (4.2 g, 60 %) n_D^{24} 1.4493 (lit.[102] n_D^{18} 1.4591). This was confirmed by the strong carbonyl absorbance at 1710 cm^{-1} in the i.r. spectrum.

3.44 Reduction of 2-cyclopentylacetic acid

Lithium aluminum hydride (10.0 g, 0.263 mol) was stirred with dry ether (300 ml) under dry nitrogen for 1 h. 2-Cyclopentylacetic acid (25.0 g, 0.195 mol) in dry ether (100 ml) was added slowly such that there was a gentle reflux. The mixture was stirred at room temperature for 16 h. The work-up procedure was similar to that of Ex. 3.10 to give g.c. pure 2-(cyclopentyl)ethanol (20.0 g, 90%), ν_{max} (KBr disc) 3300, 2940-2850, δ_H n.m.r. ($CDCl_3$) 3.75 (m, 1 H, OH), 3.55 (m, 2H, $\underline{CH_2}OH$), 1.70 (m, 11 H, 5 x CH_2 and CH).

3.45 Preparation of 2-chlorotetrahydropyran

A solution of dihydropyran (88.0 g, 1.048 mol) in dry toluene (200 ml) was cooled to -10 - 0 °C. Anhydrous hydrogen chloride was bubbled until no further gain in weight was recorded. The proton n.m.r. trace showed the disappearance of vinyl protons and the solution of 2-chlorotetrahydropyran in toluene was used in the next stage without isolation.

3.46 Preparation of tetrahydropyran-2-yl diethyl malonate

A mixture of freshly distilled diethyl malonate (51.0 ml, 53.5 g, 0.334 mol) and sodium hydride (8.4 g) in dry toluene (500 ml) was stirred with a mechanical stirrer and gradually warmed to 90 °C. After the evolution of hydrogen had ceased (4 h), the resulting suspension was cooled to room-temperature and then to 5 °C. 2-Chlorotetrahydropyran (36.0 g, 0.30 mol) also cooled to 5 °C was added dropwise over 2 h. The reaction mixture was allowed to stand at room-temperature for several hours which then gave an acid reaction with litmus. It was washed with water (2 × 100 ml) and dried over anhydrous magnesium sulphate. Toluene was removed under reduced pressure to give a crude product (30.0 g) which was distilled to give tetrahydropyran-2-yl diethyl malonate (25.5 g, 43.4 %) b.p. 135 °C at 3.0 mmHg n_D^{22} 1.4540 (lit.[76] b.p. 120-122 °C at 1 mm, n_D^{20} 1.4480) ν_{max} (KBr disc) 2960-2860, 1740 δ_H n.m.r. ($CDCl_3$) 4.18 (m, 5H, 2×COO$\underline{C}H_2CH_3$, and CH), 3.42 (m, 2H, CH_2-O), 1.37 (m, 13H, 3×CH_2, CH and 2×COOCH$_2\underline{C}H_3$), ^{13}C nmr ($CDCl_3$) δ 167.63, 167.06 (2×C=O), 76.23 ($\underline{C}H(COOC_2H_5)_2$), 68.86 (CH), 61.40 (2×COO$\underline{C}H_2CH_3$), 58.37 (CH_2-O ring), 29.55, 25.79, 23.18 (3×CH_2ring), 14.10 (2 × CH_3).

3.47 Hydrolysis of tetrahydropyran-2-yl diethyl malonate

Tetrahydropyran-2-yl diethyl malonate (25.5 g, 0.104 mol) was heated under reflux with sodium hydroxide (50 %, 200 ml) and I.M.S. (50 ml) for 2 h. It was then neutralised to the phenophthalein endpoint with hydrochloric acid (4 M). The resultant solution was extracted with ether (10 × 150 ml). On reducing the ether layer, tetrahydropyran-2-yl malonic acid was obtained (5.0 g, 25.5%), m.p. 135-36 °C after recrystallisation from pet. ether 60 - 70 °C (lit.[77] m.p. 140 - 41 °C)

3.48 Thermal decarboxylation of tetrahydropyran-2-yl malonic acid

The crude mixture from the above experiment was heated in an oil-bath at 140 - 50 °C until carbon dioxide had ceased to be produced (2.5 h). The residue was distilled to give tetrahydropyran-2-yl ethanoic acid (3.7 g, 96 %), b.p. 56 °C at 0.5 mmHg, n_D^{18} 1.4464, (lit.[77] b.p. 100-102 °C at 2 mmHg) ν_{max} (KBr disc) 3420, 2940, 2860, 1720, δ_H ($CDCl_3$) 6.50 (s, 1 H, OH), 4.06 (m, 3H, $\underline{CH_2}COOH$, CH-O of ring), 2.46 (m, 2H, CH_2-O of ring), 1.32 (m, 6H, 3 × CH_2).

3.49 Preparation of 5-hydroxypentanal

Dihydropyran (100.0 g, 1.19 mol) and dil. hydrochloric acid (0.2 N, 400 ml) were mixed and heated at reflux for 1 h. The organic layer had become miscible in water at this stage. The mixture was neutralised with 0.4 N sodium hydroxide to a faint phenophthalein alkalinity. Water was removed under reduced pressure and the residue was distilled to give a mixture of tetrahydropyran-2-ol and 5-hydroxypentanal (51.0 g, 42 %) b.p. 50 °C at 2 mmHg, n_D^{20} 1.4500, (lit.[80] b.p. 54-55 °C at 3 mmHg, n_D^{25} 1.5414), ν_{max} (KBr disc) 2860, 2940, 3360, δ_H ($CDCl_3$) 4.98 (m, 1 H, CH_2), 4.05 (m, 1 H, OH), 3.56 (m, 2 H, CH), 1.64 (m, 6 H, 3 × CH_2), ^{13}C nmr ($CDCl_3$) δ 94.46 (CH), 63.83 (CH_2-O), 32.00 (5' CH_2), 25.33 (3' CH_2), 20.36 (4' CH_2).

N.B. Exp. 3.50 and 3.51 are follow-on reactions to give tetrahydropyran-2-yl acetic acid as the final product.

3.50 Condensation of 5-hydroxypentanal with malonic acid

Tetrahydropyran-2-ol (51.0 g, 0.50 mol), malonic acid (58.0 g, 0.557 mol), dry pyridine (60.0 g) and

piperidine (5 ml) were stirred for 2 to 3 h and kept at room-temperature for 8 h. The mixture was heated on the steam-bath until evolution of carbon dioxide had ceased (6 h) and pyridine was removed under reduced pressure to yield a mixture of hydroxy heptenoic acid and tetrahydropyran-2-yl acetic acid (40.0 g, 55 %).

3.51 Preparation of ethyl tetrahydropyran-2-yl acetate

The mixture from 4.100 (38.0 g) was refluxed with I.M.S. (150 ml) and conc. sulphuric acid (5.0 ml) for 6 h. The mixture was cooled and neutralised to a faint pink of phenophthalein using sodium hydroxide (2 M, 10 ml). Ethanol was removed under reduced pressure and the crude product (35.0 g) was seen to contain two major components on g.c. trace. The i.r. trace showed the absence of hydroxyl group peaks. Distillation gave a mixture of ethyl tetrahydropyran-2-yl acetate and hydroxy heptenoic acetate (34.0 g, 75 %) at b.p. 65-70 °C at 0.1 mmHg.

3.52 Hydrolysis of ethyl tetrahydropyran-2-yl acetate

The mixture of ethyl tetrahydropyran-2-yl acetate and hydroxyheptenoic acetate (34.0 g, 0.236 mol) from Ex. 3.51 was refluxed with 30 % potassium hydroxide (50 % ethanol, water) for 8 h. The mixture was cooled and neutralised with hydrochloric acid (50 %, 100 ml). It was extracted with ether (6 × 100 ml), dried over anhyd. magnesium sulpate and concentrated in vacuo. Upon distillation of the crude product, tetrahydropyran-2-ylacetic acid was obtained (20.0 g, 70 %), b.p. 70 - 80 °C at 0.1 mmHg, n_D^{20} 1.4467 (lit.[94] b.p. 100-102 °C at 2 mmHg) and it solidified on cooling, m.p. 50 °C (lit.[94] m.p. 55-57 °C), ν_{max} (KBr disc) 3440, 2940, 2860, 1710, δ_H ($CDCl_3$) 6.51 (s, 1 H, OH), 4.06 (m, 3 H, CH_2COOH and CH-O of ring), 2.47 (m, 2 H, CH_2-O ring), 2.47 (m, 2 H, CH_2-O ring), 1.32 (m, 6 H, 3 × CH_2).

3.53 Methacrylation of cyclohexylmethanol

Cyclohexylmethanol (4.6 g, 4.3 ml, 44 mmol) was placed in a three-necked flask with dry toluene (25 ml) and cooled in an ice-salt bath. Methacryloyl chloride (5.0 g, 5.5 ml, 44 mmol) in dry toluene (20 ml) was added dropwise keeping the temperature below 0 °C.

Hydroxyquinone (20 mg) was added to inhibit polymerisation. The mixture was stirred at 0 °C for 6 h and left standing at room-temperature overnight. The reaction mixture was poured into water (100 ml) and the organic layer separated and washed with 5 % sodium bicarbonate (3 × 50 ml), distilled water (2 × 50 ml), and dried over anhydrous magnesium sulphate. Toluene was reduced <u>in vacuo</u> and the crude product (8.0 g) was distilled to give cyclohexylmethyl methacrylate (7.5 g, 94 %), b.p. 50 - 55 °C at 0.3 mmHg, n_D^{19} 1.4625, found % C, 72.3, H, 10.0, $C_{11}H_{18}O_2$ requires % C, 72.0, H, 10.2, ν_{max} (KBr disc) 650, 820, 940 (acyl ester), 1175 (C-O stretch), 1302, 1322 (ester), 1378 (COR in ester), 1404 ($C=CH_2$), 1450 ($C-CH_3$), 1640 (C=C stretch), 1720 (C=O), 2830, 2870 (CH and CH_2), δ_H ($CDCl_3$) 1.76 (m, 6 H, 3 × CH_2 of ring), 1.91 (m, 5 H, 2 × CH_2 of ring and CH), 1.93 (m, 3 H, CH_3), 3.95 (d, 2 H, CH_2-O), 5.53 (m, 1 H, $C=CH_2$), 6.09 (m, 1 H, $C=CH_2$), ^{13}C nmr ($CDCl_3$) δ 18.3 (CH_3 of ester), 25.9 (2 × CH_2 of ring), 26.5 (CH_2 of ring), 29.9 (2 × CH_2 of ring), 37.4 (CH of ring), 69.9 ($\underline{CH_2}$-O-COR), 125.1 ($C=\underline{CH_2}$), 136.8 ($\underline{C}=CH_2$), 167.5 (C=O).

3.54 Transesterification of cyclohexylmethanol

Methyl methacrylate, distilled (40 ml, 39.0 g, 0.39 mol), toluene (dry, 50 ml), cyclohexylmethanol (10.0 g, 11 ml, 0.09 mol), hydroquinone (0.5 g) and conc. sulphuric acid (0.2 ml) were mixed and heated in a two-necked flask fitted with 12" fractionating column and reflux ratio head and condenser. The mixture was heated under reflux for 6 h. The reaction was followed by g.c. analysis which showed the disappearance of cyclohexylmethanol and product formation. The reaction mixture was poured into distilled water (100 ml), and the organic layer washed with sodium bicarbonate solution (10 %, 3 × 50 ml), re-washed with water (2 × 100 ml) and dried over anhyd. magnesium sulphate. Removal of the solvent in vacuo gave the crude product (13.5 g) which was distilled to give cyclohexylmethyl methacrylate (12.5 g, 78 %), b.p. 55 - 60 °C at 0.3 mmHg, n_D^{19} 1.4626 , found % C, 72.1, H, 10.0, $C_{11}H_{18}O_2$ requires % C, 72.0, H, 10.2. The i.r. and ^1H n.m.r. data were identical to that of Ex. 3.53.

3.55 Methacrylation of 2-(cyclohexyl)ethanol

2-(Cyclohexyl)ethanol (20.0 g, 21.5 ml, 0.156 mol) in dry toluene (50 ml) was placed in a 3-necked flask and cooled to -5 °C. Methacryloyl chloride (17.0 ml, 0.162 mol) in dry toluene (20 ml) was added dropwise keeping the temperature at 0 °C for 6 h and left overnight at room temperature. After the usual work up, g.c. analysis showed that incomplete esterification had occurred . The yield of the crude methacrylate ester was 20.5 g (67%). A sample (1.50 g) was purified by flash chromatography (silica 35-70 μ, 30 % ethyl acetate and 40-60 °C pet. ether), which gave 2-cyclohexylethyl methacrylate (0.90 g, 40 %), n_D^{19} 1.4624 (lit.[122] b.p. 99-102 °C / 3.0 mmHg, n_D^{19} 1.4641), found % C, 74.28, H, 11.05, $C_{12}H_{20}O_2$ requires % C, 73.47, H, 10.02, ν_{max} (KBr disc) 655, 818, 940 (acyl ester), 1170 (C-O stretch), 1300, 1320 (ester), 1378 (COR in ester), 1405 ($C=CH_2$), 1450 ($C-CH_3$), 1640 (C=C stretch), 1720 (C=O, strong), 2830, 2865 (CH and CH_2), δ_H n.m.r. ($CDCl_3$) 1.24 (m, 6 H, 3 × CH_2 of ring), 1.64 (m, 7 H, 2 × CH_2, CH and CH_2 of side chain), 1.94 (m, 3 H, CH_3), 4.18 (t, 2 H, CH_2-O), 5.53 (m, 1 H, $C=CH_2$), 6.09 (m, 1 H, $C=CH_2$), ^{13}C n.m.r. ($CDCl_3$) δ 18.3 (CH_3 of ester), 26.3 (2 × CH_2 of ring), 26.6 (CH_2 ring), 33.3 (2 × CH_2 ring), 34.9 (CH_2

of side chain), 36.1 (CH of ring), 63.1 (CH_2-O side chain), 125.1 (C=$\underline{CH_2}$), 136.8 ($\underline{C}$=CH_2), 167.6 (C=O).

3.56 Methacrylation of cyclopentanol

a. Acid chloride method

Cyclopentanol (10.0 g, 0.116 mol) was added to dry toluene (100 ml) and cooled to 0 °C. Methcryloyl chloride (14.0 g, 0.134 mol) in dry toluene (20 ml) was added dropwise keeping the temperature at 0 °C. The mixture was stirred at 0 °C for 6 h and at room temperature for 8 h. After the usual work up the crude product (16.0 g) was distilled at 30 - 40 °C at 1.2 mmHg. The distillate was impure even when redistilled. Purification by flash chromatography (20 % Et. Ac. : pet. ether 40-60) gave unreacted cyclopentanol (6.0 g) and cyclopentyl methacrylate (5.6 g, 31 %), n_D^{20} 1.4525 (lit.[19] b.p. 84-85 °C / 27 mmHg, n_D^{25} 1.4504), found % C, 69.43, H, 11.43, $C_9H_{14}O_2$ requires % C, 70.13, H, 12.96, ν_{max} (KBr disc) 2960 - 2910, 2840, 1710, 1630, δ_H ($CDCl_3$) 6.06 (m, 1 H, C=CH_2), 5.50 (m, 1 H, C=CH_2), 1.93 (m, 3 H, CH_3), 1.74 (m, 9 H, 4 x CH_2 and CH), ^{13}C ($CDCl_3$) δ 167.48 (C=O), 137.18 ($\underline{C}$=CH_2), 124.92 (C=$\underline{CH_2}$), 77.45 ($\underline{CH}$-OCOR), 32.79 (2 x CH_2), 23.87 (2 x CH_2), 18.29 (CH_3).

b. Transesterification of cyclopentanol

Cyclopentanol (10.0 g, 0.116 mol), methyl methacrylate (30.0 g, 0.30 mol), dry toluene (100 ml), hydroquinone (0.5 g), and conc. sulphuric acid (0.2 ml) were mixed and heated at reflux for 6 h following the procedure in Ex. 3.1 . The mixture was cooled and washed with water (1 × 25 ml), sodium bicarbonate (10 %, 3 × 25 ml) and water (1 × 25 ml). The toluene layer was dried over anhyd. magnesium sulphate and reduced in vacuo to give a crude mixture (11.0 g) which was purified to give the unreacted cyclopentanol (3.4 g) and cyclopentyl methacrylate (5.2 g, 29 %), n_D^{20} 1.4520 (lit.[10] n_D^{25} 1.4504). It gave identical analysis to Ex. 3.56.a .

3.57 Attempted transesterification of cyclopentylmethanol

Cyclopentylmethanol (10.0 g, 0.10 mol), methyl methacrylate (50.0 g, 0.50 mol), calcium stearate (8.5 g) and hydroquinone (100 mg) were placed in a two-necked flask. The mixture was heated such that methanol was distilled off continuously together with methyl methacrylate under reduced pressure (20 mmHg). After 10 ml of the distillate was collected, methyl

methacrylate (20 ml) was added to the reaction flask. The flask was heated for 4 h under these conditions and monitered by gas chromatography. The experiment was abandoned after no product had formed after 5 h heating. On cooling the contents of the flask were found to be polymerised.

3.58 Methacrylation of cyclopentylmethanol

Cyclopentylmethanol (10.0 g, 0.10 mol) was added to dry toluene (100 ml) and cooled to 0 °C. Methacryloyl chloride (15.0 g, 0.143 mol) in dry toluene (20 ml) was added dropwise keeping the temperature at 0 °C. The mixture was stirred at 0 °C for 6 h and allowed to stir at room temperature overnight. After the usual work up the crude product was distilled at 30 - 40 °C at 0.1 mmHg (16.0 g). The various fractions collected were shown to have two main components on g.c. which could not be separated by redistillation. Flash chromatography (20 % Et.Ac. : pet. ether 40-60) gave unreacted cyclolpentylmethanol (4.5 g) and cyclopentylmethyl methacrylate (10.5 g, 62.5 %) b.p. 82 °C at 8.5 mmHg, n_D^{22} 1.4555 (lit.[88] b.p. 62 °C / 2.0 mmHg), found % C, 70.85, H, 9.92, $C_{10}H_{16}O_2$ requires % C, 71.42, H, 9.52, ν_{max} (KBr disc) 2940, 2860, 1710, 1630, δ_H ($CDCl_3$) 6.10 (m, 1 H, C=C$\underline{H_2}$), 5.54 (m, 1 H,

C=$\underline{CH_2}$), 4.04 (m, 2 H, $\underline{CH_2}$OCOR), 1.96 (m, 3 H, CH_3), 1.62 (m, 9 H, 4 × CH_2 and CH), ^{13}C n.m.r. ($CDCl_3$) δ 167.76 (C=O), 136.84 ($\underline{C}$=CH_2), 125.19 (C=$\underline{CH_2}$), 68.71 ($\underline{CH_2}$OCOR), 38.83 (CH), 29.49 (2 × CH_2 ring), 25.48 (2 × CH_2 ring), 18.35 (CH_3).

3.59 Methacrylation of 2,5-norbornenemethanol

2,5-Norbornenemethanol (10.0 g, 0.08 mol) was added to dry toluene (50 ml) and cooled to 0 °C. Methacryloyl chloride (15.4 g, 0.148 mol) in dry toluene (20 ml) was added dropwise keeping the temperature at 0 °C. After the usual work up, the crude mixture (12.0 g) was distilled to give 2,5-norbornenemethyl-methacrylate (10.5 g, 68 %), b.p. 70-74 °C at 0.6 mmHg, n_D^{25} 1.4855, found % C, 74.09, H, 8.80, $C_{12}H_{16}O_2$ requires % C, 75.00, H, 8.33, ν_{max} (KBr disc) 1300-1325 (ester), 1380 (COR in ester), 1410 (C=CH_2), 1640 (C=C stretch), 1720 (C=O ester, strong), 2920-2980 (CH and CH_2). δ_H and ^{13}C n.m.r. spectra were difficult to interpret due to isomeric exchange of peaks.

3.60 Methacrylation of 2-(cyclopentyl)ethanol

2-(Cyclopentyl)ethanol (20.0 g, 0.175 mol) in dry toluene (50 ml) was placed in a 3-necked flask and cooled to -5 °C. Methacryloyl chloride (21.5 g, 0.20 mol) in dry toluene (20 ml) was added dropwise keeping the temperature below zero. The reaction mixture was stirred at 0 °C and left overnight at room temperature. After the usual work up, the crude product was distilled to give 2-(cyclopentylethyl) methacrylate (18.3 g, 57.4 %), b.p. 54 °C at 0.3 mmHg, n_D^{22} 1.4582, found % C, 71.16, H, 10.03, $C_{11}H_{18}O_2$ requires % C, 72.53, H, 9.89, ν_{max} 2880, 2840, 1715, 1640, δ_H n.m.r. ($CDCl_3$) 6.09 (m, 1 H, C=CH_2), 5.54 (m, 1 H, C=CH_2), 4.16 (m, 2 H, CH_2-O), 1.76 (m, 14 H, 5 × CH_2, CH and CH_3), ^{13}C n.m.r. ($CDCl_3$) 167.54 (C=O), 136.78 (<u>C</u>=CH_2), 125.10 (C=<u>C</u>H_2), 64.43 (CH_2-O), 37.22 (CH of ring), 34.91 (CH_2), 32.76 (2 × CH_2 of ring), 25.15 (2 × CH_2 of ring), 18.29 (CH_3).

3.61 Methacrylation of 2-norbornylmethanol

2-Norbornylmethanol (20.0 g, 0.158 mol) in dry toluene (50 ml) was placed in a 3-necked flask and cooled to -5 °C. Methacryloyl chloride (18.2 g, 17.0 ml, 0.174 mol) in dry toluene (20 ml) was added dropwise keeping

the temperature below zero. The reaction mixture was stirred at 0 °C for 6 h and left overnight at room temperature. After the usual work up, the crude product was distilled to give 2-norbornylmethyl methacrylate (17.5 g, 56.9 %), b.p.62-66 °C at 0.3 mmHg, n_D^{25} 1.4785 (lit.[86] b.p. 93-94 °C / 3.0 mmHg), found % C, 74.39, H, 9.76, $C_{12}H_{18}O_2$ requires % C, 74.23, H, 9.28, ν_{max} (KBr disc) 2980, 2950, 1720, 1640, δ_H ($CDCl_3$) 6.09 (m, 1 H, C=CH_2), 5.52 (m, 1 H, C=CH_2), 4.02 (m, 2 H, CH_2-O), 2.20 (m, 2 H, CH_2), 1.93 (m, 2 H, CH_2 of ring), 1.29 (m, 10 H, 3 × CH_2, CH of ring and CH_3), ^{13} n.m.r. ($CDCl_3$) δ 167.69 (C=O), 136.75 (<u>C</u>=CH_2), 125.19 (C=<u>CH_2</u>).

The rest of ^{13}C n.m.r. spectrum was difficult to interpret due to isomerization.

Chapter 4

REFERENCES

REFERENCES

1. G.M. Mir, W.H. Lawrence and J. Austian, *J. Pharm. Sci.*, 62(5), 778-782.
2. M. Braden and B.E. Causton, *Plastics and Polymers*, 1973, 140-144.
3. M.Braden, R.L. Clarke, G.J. Pearson and V. Campbell Keys, *Brit. Dent. J.*, 1976, 141(9), 267-272.
4. M. Braden, *Brit. Polym. J.*, 1978, 10, 245-250.
5. M. Bhusate and M. Braden, B.P. 82 28 973/1982.
6. A.V. Tobolsky, F. Leonard and G.P. Roeser, J. Polym. Sci., 1948, 3(4), 604-606.
7. W.H. Carothers *et al.*, *J. Am. Chem. Soc.*, 1932, 54, 761.
8. M. Rippei Tanabe, K. Yuji Yokoyama and T. Jiro Hirano, (Nippon Oil and Fats Company, Ltd.), U.S.P. 4 285 872/1981.
9. T. J. Wiggins and D. L. Grubb, (Dunlop Semetex Ltd.), B.P. 1 144 777/1969.
10. J. Lal and R. Green, *J. Org. Chem.*, 1954, 20, 397-399.
11. Societe des Produits Chemiques et de Synthese, Fr. P. 1 399 655/1965.
12. M.A. Askarov and A.S. Bank, *Khim. i. Fiz.-Khim. Prirodn. Sintetich. Polimerov, Akad. Nauk, Uz. SSR, Inst. Khim, Polimerov*, 1964, 2, 124-130;

(Chem. Abs., 1965, 62, 639g).

13. C.J.A. Peters, U.S.P. 3 230 186/1966.

14. C.J.A. Peters, U.S.P. 3 232 894/1966.

15. M.A. Askarov and A.S. Bank, (Sci. Res. Inst. of Chem. and Cellulose Technol.), *Vysokomolekul. Soedin.*, 1966, 8(6), 1012-14; *Chem. Abs.*, 1966, 65, 9032g).

16. E.H. Mottus and J.E. Fields, U.S.P. 3 265 768/1966.

17. K. Noma , Y. Ofuji and I. Sakurada, *Kobunshi Kagaku*, 1965, 22(237), 69-78; (*Chem. Abs.*, 1965, 63, 5751c).

18. A. Kishiro, K. Hiroyuki and T. Hidemaro, Japan Kokai 76 117 789/1976; *Chem. Abs.*, 1977, 86, 91199m.

19. L.L. Henry, Jr., and J.A. Orlowski, U.S.P. 4 001 483/1977.

20. L.L. Henry, Jr., and J.A. Orlowski, U.S.P. 4 104 333/1978.

21. N. Hisaaki, K. Hirokyuki and T. Hidemaro, Japan Kokai 79 110 290/1979; *Chem. Abs.* 1980, 92, 59653t.

22. N. Takahiro, I. Kaoru and H. Akihiro, Japan Kokai 79 96 540/1979 (*Chem. Abs.*, 1980, 92, 7434c).

23. Kirk-Othmer, 'Encyclopedia of Chemical Technology', Wiley Interscience, New York, 1980, 11, 3rd Edn., 522.

24. H. Lee and K. Neville, 'Handbook of Epoxy Resins', McGraw and Hill Book Co., 1967, 15-19.

25. P. Edwards, U.S.P. 2 537 981/1951.

26. J.W.C. Crawford, (to Imperial Chemical Industries), B.P. 405 699/1934.

27. H.A. Bruson, (to Rohm and Haas Co.), U.S.P. 2 100 933/1977.

28. Rohm and Haas; E.I. du Pont de Nemours and Co., Inc.; and CY/RO Industries U.S. Foreign producers include I.C.I., Rohm G.m.b.H., Mitsubishi and Asahi Chemical.

29. S. Komura, N. Nakamura and M. Takenaka, (to Otsuka Chemical Company, Ltd.), Japan Kokai 74 43 934/1974.

30. N.M. Bortnick, (to Rohm and Haas Company), U.S.P. 3 087 962/1963.

31. H.J. Barrett and D.E. Strain, (to E.I. du Pont de Nemours and Co.), U.S.P. 2 129 667/1938.

32. Y. Kametani and Y. Ino, (to Nitto Chemical Company, Ltd.), Ger. Offen. 2 752 109/1978.

33. G. Honma and S. Yoshinaka, (to Mitsubishi Gas-Chemical Company, Inc.), J.P. 73 21 929/1973.

35. T. Foster and T.S. Dawson, (to American Cyanamid Company), U.S.P.4 059 617/1977.

36. S. Fukushi, N. Shimizv and T. Ohara, (to Japan Catalytic Chemical Industry Company, Ltd.), Ger. Offen. 2 311 007/1977.

37. A.E. Montagna and L.V. McQuillen, (to Union Carbide Corporation), U.S.P. 2 930 801/1960.

38. J. Tsuji *et al.*, *J. Am. Chem. Soc.*, 1964, 86, 4350, 4851; P.J. Steinwand, *J. Org. Chem.*, 1972, 37, 2034; K.L. Oliver, U.S.P. 3 621 054/1971.

39. J.G. Erickson, U.S.P. 34 142/1948.

40. P. Edwards, U.S.P. 2 537 981/1951.

41. H.J. Barrett and D.E. Strain, (to E.I. du Pont de Nemours and Co.), U.S.P. 2 729 666/1938.

42. H.J. Barrett and W. Falls, (to du Pont de Nemours and Co.), U.S.P. 2 109 877/1938.

43. C.E. Rehberg and W.A. Fawcette, *J. Org. Chem., 1949, 14, 1094-97.*

44. *J. Lal and R. Green, J. Org. Chem.*, 1955, 20, 1030-32.

45. F. Tamura, K. Uehara and N. Murata, *Kogyo Kahaku Zassahi*, 1964, 67(5), 853; *Chem. Abs.*, 1964, 61, 8416e.

46. J.G. Erickson, (to American Cyanamid Co.), U.S.P. 2 556 075/1951; U.S.P. 2 567 842/1951.

47. Lu Cheng Huan *et al.*, *Hua Hsueh Tung Pao*, 1978, 4, 204; *Chem. Abs.*, 1978, 89, 215793j.

48. T. Naomitsu, S. Shigeru and F. Rokuro, B.P. 2 125 970/1980; *Chem. Abs.*, 1980, 93, 8753p.

49. F. Valdimir, Czech. 130 373/1968, *Chem. Abs.*, 1970, 72, 44620t); H. Masato, *et al.*, Japan Kokai 77 139 002/1977, *Chem. Abs.*, 1978, 88,

89142k.

50. Japan Patent 38 421/1972.

51. M. Rosenberg and G. Saucy, (to Hoffman La Roche) U.S.P. 4 000 131/1975; Japan Patent 154 205/1975.

52. R. Ackermann, H. Kolb, D. Morlok and G. Schreyer, (to Duesch Gold and Silver Scheideanstalt) British Patent 1 505 601/1976; Japan Patent 146 419/1976.

53. E.M. Beavers and J.L. O'Brien, (to Rohm and Haas Co.) U.S.P. 3 001 975/1961.

54. E.M. Beavers and J.L. O'Brien, (to Rohm and Haas Co.) U.S.P. 3 002 004/1961.

55. T. Ito, K. Aoshima, *et al.*, *Polym. J.*, 1970, 1(3), 278-287.

56. J.R. Caldwell, W.J. Jackson and C.C. Dannelly, (to Eastman Kodak Co.), U.S.P. 3 243 416/1966.

57. W.H. Carothers *et al.*, *J. Am. Chem. Soc.*, 1933, 55, 5023.

58. J.W.C. Crawford, *J.S.C.I.*, 1949, 68, 201-208.

59. F.S. Nichols and R.G. Flowers, *Ind. Eng. Chem.*, 1950, 42, 292-295.

60. S. Losbeak and T.G. Fox, *J. Am. Chem. Soc,*, 1953, 75, 3455-3550.

61. M.P. Patel, M. Braden, K.W.M. Davy, *Biomaterials*, 1987, 8, 53-56.

62. D.W. Van Krevelen, "Properties of polymers", (2nd ed.), Elsevier Scientific Publ. Co., 1976,

p. 54-58.

63. T. Endo and W.J. Bailey, *Die Makromolecular Chemie*, 1975, 176, 2897-2903.

64. T. Endo and W.J. Bailey, *Polymer Letters*, 1975, 13, 193-5.

65. W.J. Bailey and T. Endo, *Polym. Sci.*, 1976, 14, 1735-41.

66. E.S. Huyser and Z. Garcia, *J. Org. Chem.*, 1962, 27, 2716.

67. E.S. Huyser and D.T. Wang, *J. Org. Chem.*, 1964, 29, 2920.

68. D. Elad and R.D. Yorassfyeh, *Tett. Lett.*, 1963, 2189.

69. D. Schwarz and M. Braden, *J. Dentistry*, 1973, 1, 179-80.

70. M.F. Ansell and D.A. Thomas, *J. Chem. Soc.*, 1958, 1163-7; M.F. Ansell and S.S. Brown, *ibid.*, 1957, 1788-95.

71. E.E. Schweizer *et al.*, *J. Org. Chem.*, 1969, 34(1), 212-5.

72. G. Eglington, E.R.H. Jones, and M.C. Whiting, *J. Chem. Soc.*, 1952, 2873-82.

73. L. Crombie *et al.*, *J.Chem. Soc.*, 1956, 126-35.

74. J. Colonge and P. Lasfargnes, *Bull. Soc. Chim. Fr,*, 1962, 177-82.

75. R. Davis and G. Untch, *J. Org. Chem.*, 1981, 46, 2985-87.

76. J.G. Schudel and R.V. Rice (to Gane's Chemical Works), U.S.P. 2 522 966/1950.

77. R.P. Zelinsky, M.G. Peterson and H.R. Wallner, *J. Am. Chem. Soc.*, 1952, 74, 1504-6.

78. G.F. Woods and D.M. Kramer, *J. Am. Chem. Soc.*, 1947, 69, 2246.

79. L.E. Schniepp and H.H. Geller, *J. Am. Chem. Soc.*, 1946, 68, 1646-8.

80. C.D. Hurd and A.J. Richardson, *J. Org. Chem.*, 1967, 32, 3516-20.

81. C.D. Hurd and W.H. Saunders,Jr., *J. Am. Chem. Soc.*, 1952, 74, 5324-9.

82. J. Kennedy, M.J. McCorkindale and R.A. Raphael, *J. Chem. Soc.*, 1961, 3813-5.

83. G.I. Fray *et al.*, *Tetrahedron*, 1961, 15, 18-25.

84. L.A. Brooks and H.R. Snyder, 'Organic Synthesis', 1955, Coll.3. p. 698.

85. W.R. Kirner, *J. Am. Chem. Soc.*, 1930, 52, 3252-6.

86. C.A. Buehler, H.A. Smith, D.M. Glenn and K.V. Nayak, *J. Org. Chem.*, 1958, 23, 1432-7; M. Beggett *et al.*, *Carbohyd. Res.*, 1967, 4(4), 343-51.

87. M. Bhusate, M.Sc. Thesis (Polytechnic of North London), 1983.

88. L.H. Smith, 'Organic Synthesis', Coll. Vol. 3, 793.

89. D.M. Armitage and C.L. Wilson, *J. Am. Chem. Soc.*,

1959, 81, 2537-9.

90. S. Trippett, *J. Chem. Soc.*, 1962, 2337.

91. H.B. Bass and J.R. Marshall, *Ind. Eng. Chem.*, 1931, 23, 352.

92. A.O. Rogers, U.S.P. 2 415 261/1947.

93. R.A. Smiley and C. Arnold, *J. Org. Chem.*, 1960, 25, 257-8.

94. L. Friedmann and H. Shechter, *J. Org. Chem.*, 1960, 25, 877-8.

95. R. Paul, *Bull. Soc. Chim.*, 1933, 53(4),

96. R. Robinson and L.H. Smith, *J. Chem. Soc.*, 1936, 195.

97. H.N.J. Rydon *et al.*, *J. Chem. Soc.*, 1937, 1972.

98. E.D. Amstutz, *J. Org. Chem.*, 1944, 9, 310.

99. L.A. Brooks and H.R. Snyder, 'Organic Syntheses', Coll. 3, 84-86.

100. M. Zief *et al.*, *J. Am. Chem. Soc.*, 1946, 68, 2743-4.

101. B. Helfrerich and A. Gnuchtel, *Chem. Ber.*, 1938, 71, 712.

102. G. Barger, R. Robinson and L.H. Smith, *J. Chem. Soc.*, 1937, 718.

103. W.E. Kaufmann and R. Adams, *J. Am. Chem. Soc.*, 1923, 45, 3029-44.

104. R.H. Bray and R. Adams, *J. Am. Chem. Soc.*, 1927, 49, 2105.

105. H.A. Smith, J.B. Conley and W.H. King, *J. Am.*

Chem. Soc., 1951, 73, 4633-6.

106. F. Plezzoni and G. Jommi, *Ann. Chim.* (Rome), 1959, 49, 1461-3.

107. H. Wynberg and A. Bentjes, 'Organic Syntheses' *Coll. Vol.* 4, 534-5.

108. Price and Krishnamurti, *J. Am. Chem. Soc.*, 1950, 72, 5335.

109. Pariselle, *Ann. Chim.* (Paris), 1911, 24(8), 315.

110. V.K. Tandon, A.M. van Leusen and H. Wynberg, *J. Org. Chem.*, 1983, 48, 2767-69.

111. D.B. Pattison, *J. Am. Chem. Soc.*, 1957, 79, 3455-6.

112. M. Katsuno and H. Ando, Japan Patent, 681/1950 (C.A. 1953, 47, 2214e).

113. D. Starr and R. Hixon, 'Organic Synthesis', 1937, Vol. 17. 84-5.

114. H. Gilman and McGlumphy, *Bull. Soc. Chim.*, 1928, 43, 1322-8.

115. P. Bruylants, *Bull. Soc. Acad. Roy. Belg.*, 1920, 479-86.

116. R. Kinnel *et al.*, *Org. Prep. Proced. Int.*, 1972, 4(1), 27-30.

117. J.P. Bats *et al.*, *Tetrahedron*, 1982, 38(14), 2139-2146.

118. Ou Kium-Houo, *Ann. Chim.*, 1940, 13, 175-241.

119. A. Juvala, *Chem. Ber.*, 1930, 63B. 1989-2009.

120. P. Miginiac, *Bull. Soc. Chim. Fr.*, 1970, 3,

1077-83.

121. W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**(14), 2923-5.

122. K. Yokota, M. Kani and Y. Ishii, *J. Polym. Sci.*, Part A-1, 1968, **6**, 1325-1339.

123. V. Ya. Tyushin *et al.*, U.S.S.P. 531 834/1976.

124. H. Baarmann and K. Schneider, B.P. 1 065, 972/1967.

125. C. Osbourne and D.J. Trecker, Ger. Offen., 2 003 132/1970.

126. M.P. Patel, Ph.D. Thesis, University of London, 1987.

127. R.L. Clarke, M. Phil. Thesis, Univ. of London, 1978.

128. M.J. Barsby and M. Braden, *J. Dent. Res.*, 1981, **60**, 146-148.

129. M. Braden, B.E. Causton and R.L. Clarke, *J. Dent. Res.*, 1971, **50**, 536-541.

130. M. Braden, B.E. Causton and R.L. Clarke, *J. Dent. Res.*, 1976, **55**, 730-732.

131. R.L. Clarke and M. Braden, *J. Dent. Res.*, 1982, **61**, 997-1001.

132. S. Parker and M. Braden, Prov. B.P. 8 203 114/1982.

133. R.C. Weast, "CRC Handbook of Chemistry and Physics", CRC Pres. Inc., Cleveland, (1977).

134. E.V. Blum and R.H. Hasek, U.S.P. 2 798 080/1957.

TITLE METHACRYLATE ESTERS OF CYCLIC ALCOHOLS OF POTENTIAL BIOMEDICAL UTILITY.

AUTHOR SARADA TEW

INSTITUTION and DATE Polytechnic of North London, C.N.A.A. 1988

DX

92819