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Some oxidation reactions utilizing hydrogen peroxide adducts in combination with carboxylic anhydrides

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SOME OXIDATION REACTIONS UTILIZING HYDROGEN PEROXIDE ADDUCTS IN COMBINATION WITH CARBOXYLIC ANHYDRIDES.

by

Amanda J. Newbold

A thesis submitted in partial fulfilment of the requirements for the award of:

Doctor of Philosophy
of the Loughborough University of Technology. 1991

Supervisor: Professor H. Heaney

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To Mom and Dad for not thinking that I was mad,
To Karen for knowing that I was crazy,
To Tammy for keeping me sane,
And to their love, support and friendship that I will always cherish.

Acknowledgements.

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Professor C.J. Moody,

Mr. I. Downie for proof-reading this manuscript,

Professor H. Heaney.

Summary.

Interest grew in the development of new oxidising agents as a replacement for high purity *meta*-chloroperbenzoic acid (*m*CPBA) and avoiding the difficulty in obtaining high strength hydrogen peroxide,.

Magnesium monoperoxyphthalate (MMPP) has been advertised as a replacement. However due to problems of solubility of this oxidant in a number of solvents, it cannot be considered as a complete substitute for *m*CPBA.

An oxidising agent is required to either complement MMPP, or succeed *m*CPBA entirely.

This thesis describes the investigation of some hydrogen peroxide adducts as a possible contender to the extremely versatile oxidant, *m*CPBA.

Urea-hydrogen peroxide adduct (UHP) in combination with either trifluoroacetic or acetic anhydride was used for the *in situ* formation of percarboxylic acids. Oxidations of various functional groups were carried out using these peracids. Reactions include: the epoxidation of terminal, electron deficient alkenes, such as octene, by trifluoroperacetic acid; the epoxidation of electron rich alkenes, such as styrenes and cyclohexenes, by peracetic acid; Baeyer-Villiger reactions of both aliphatic and alkyl aryl ketones by trifluoroperacetic acid; the conversion of anilines into nitrobenzenes; the oxidation of tertiary amines and sulphides; and the oxidative cleavage of dimethylhydrazones.

A number of other hydrogen peroxide adducts were produced and their performance in various oxidation reactions was compared to that of urea-hydrogen peroxide.

Experiments in the formation of adducts to induce chirality in epoxidation reactions were also undertaken.

Abbreviations.

UHP	Urea-Hydrogen peroxide
DABCO	Diazabicyclo-2,2,2-octane
DCM	Dichloromethane
DCC	Dicyclohexylcarbodiimide
AVOX	Available Oxygen Content
MMPP	Magnesium Monoperoxyphthalate
*m*CPBA	*meta* Chloroperbenzoic Acid

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General Introduction.

Inorganic chemistry defines oxidation as either the loss of electrons or an increase in oxidation number. These definitions however tend not to be useful when applied to organic chemistry. It is more appropriate to consider using a series of functional groups arranged in order of increasing oxidation state as a basis for an organic chemistry oxidation definition, table 1.

Table 1

Increasing state of oxidation ⟶

RH	C=C	RCOR	RCOOH	CO_2
	ROH	RCH=NOH	$RCONH_2$	CCl_4
	RCl	R_2Cl_2	RCO_2R	
	RNH_2	$R_2C(Cl)\text{-}C(Cl)R_2$	RCN	
		$R_2C(OH)\text{-}C(OH)R_2$		

Oxidation can be seen as the conversion of a functional group from one series to a higher one, with reduction being the reverse case.

Classification of oxidation reactions is determined by the philosophy of the author. March[1], for instance, describes reactions in groups depending on the type of bond change involved. That is:

1. by elimination of hydrogen
2. involving the cleavage of carbon-carbon bonds
3. by replacement of hydrogen by oxygen
4. the addition of oxygen to a substrate and
5. oxidative coupling.

Other authors[2-4] illustrate oxidations by functional group or even type of oxidant.

This introductory chapter offers a number of examples of oxidation involving the insertion of oxygen into an organic molecule. The oxidations

of functional groups discussed in later chapters are mentioned in this section along with the oxidation of some similar and related groups.

Detailed discussions of epoxidations, Baeyer-Villiger reactions and heteroatom oxidation (chapters 1-3 respectively) are used to introduce the individual results and discussions of each chapter.

However, to illustrate the utilization and importance of these three types of oxidation, some examples are shown in this preliminary introduction of some of their industrial uses and also the occurrence in nature of some of the types of oxides.

INSERTION OF OXYGEN INTO ALKENES.

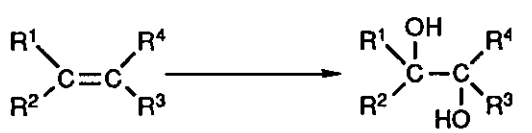
Alkenes may be oxidised by numerous reagents with the product of such reactions being dependent upon the strength and type of oxidant.

Formation of Diols.

Oxidants such as osmium tetroxide[5], alkaline potassium permanganate[5] and hydrogen peroxide-formic acid[6] oxidise alkenes into diols. Osmium tetroxide and alkaline potassium permanganate give syn addition to the less hindered side of the alkene, (reaction **1**) whereas anti addition is achieved by hydrogen peroxide-formic acid (an epoxidation occurs followed by S_N2 reaction), (reaction **2**).



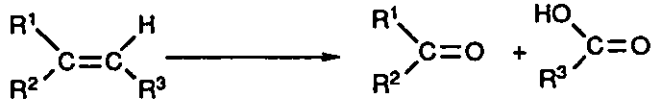
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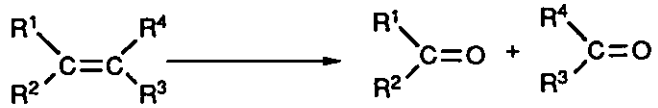
(2)

Formation of Carbonyl Groups.

Potassium permanganate in neutral or acid conditions[5] is commonly used to oxidise and cleave alkenes to form carbonyl groups, (reactions **3** and **4**).



(3)

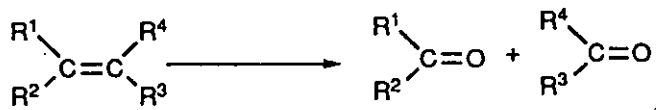


(4)

Several other oxidants such as acid dichromate, periodate-permanganate[7] and a more recently developed reagent, ruthenium tetroxide[8] achieve similar products.

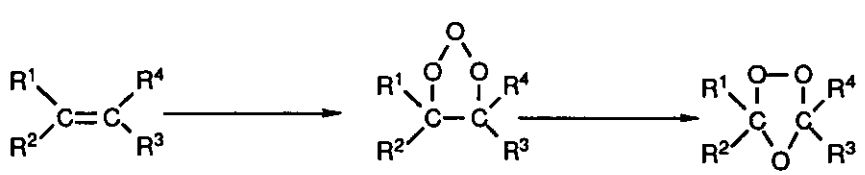
Ozonolysis.

Double bonds treated with ozone[9] form carbonyl compounds via a 1,3-dipolar addition, followed by cleavage of the initially formed product (reaction 5).



(5)

If the ozonolysis is carried out at sufficiently low temperature, the initial product of the addition of ozone, an ozonide (1), may be isolated, (reaction 6). However, ozonide isolation is not undertaken due to the explosive nature of some of these compounds. In practice, ozonides are normally decomposed using a reductive method, originally with zinc and acetic acid or catalytic hydrogenation. A more modern method uses dimethyl sulphide which affords the two carbonyl compounds and dimethyl sulphoxide.

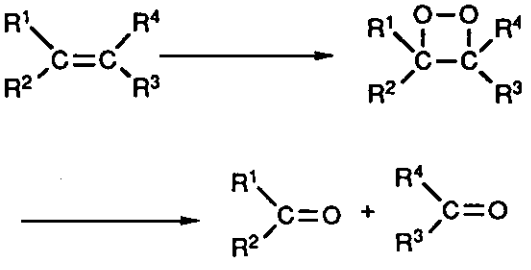


(1)

(6)

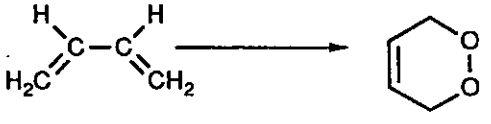
Photooxidation of Alkenes.

Singlet oxygen reacts with alkenes to give a dioxetane intermediate which immediately cleaves to produce aldehydes and ketones, (reaction 7).



(7)

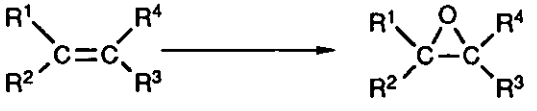
Conjugated dienes also react with singlet oxygen[10]. In this case a Diels-Alder reaction takes place to produce internal peroxides, (reaction 8).



(8)

Epoxidation of Alkenes.

The epoxidation of alkenes is much reviewed[4,11-16]. The formation of epoxides may be achieved with a number of reagents such as peracids, alkaline hydrogen peroxide, alkyl peroxides and oxygen, (reaction 9). This reaction is discussed in greater detail in chapter one.

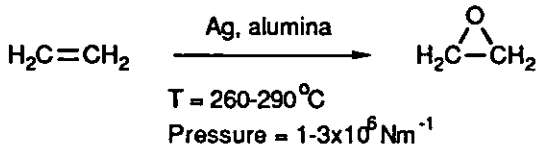


(9)

Epoxides in Industry.

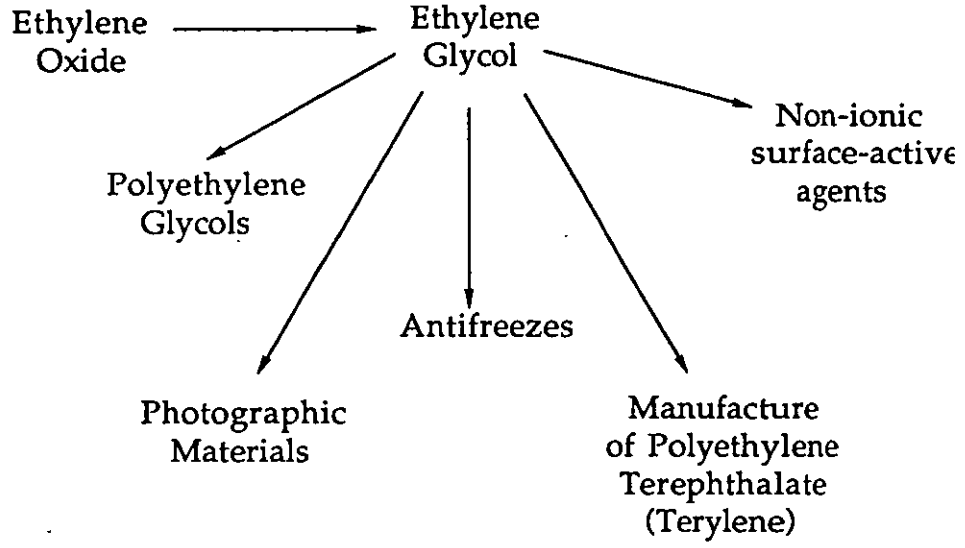
Epoxides have important uses in industry. A typical example is the production and utilization of ethylene oxide[17].

Ethylene oxide is produced by catalytic vapour phase oxidation (the direct oxidation) of ethylene, (reaction 10):



(2) (3) **(10)**

A major use of ethylene oxide is for the production of ethylene glycol, a versatile compound that has numerous applications, see scheme 1.



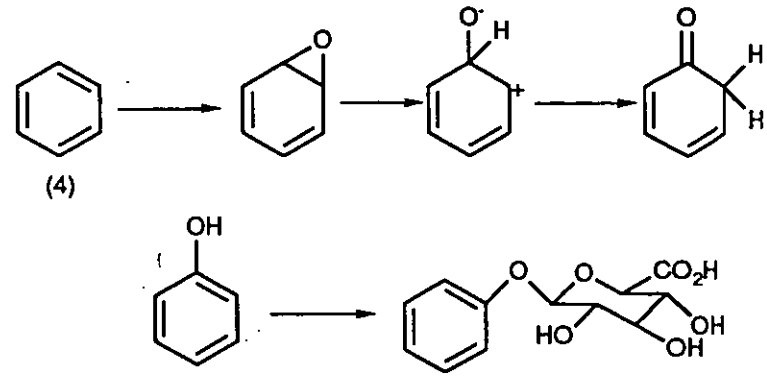
Scheme 1

Epoxides in Nature.

Oxidation, (including epoxidation) is an important method in biological systems[18]. It is used as a means of excreting exogenous chemicals from the body. A number of these chemicals are toxic and the body uses various methods to detoxify or eliminate these materials from the system, normally via the kidney. However, the physiology of the kidney is such that only polar, water soluble substances are easily eliminated. Insoluble, non-polar substances diffuse from the kidney back into the blood.

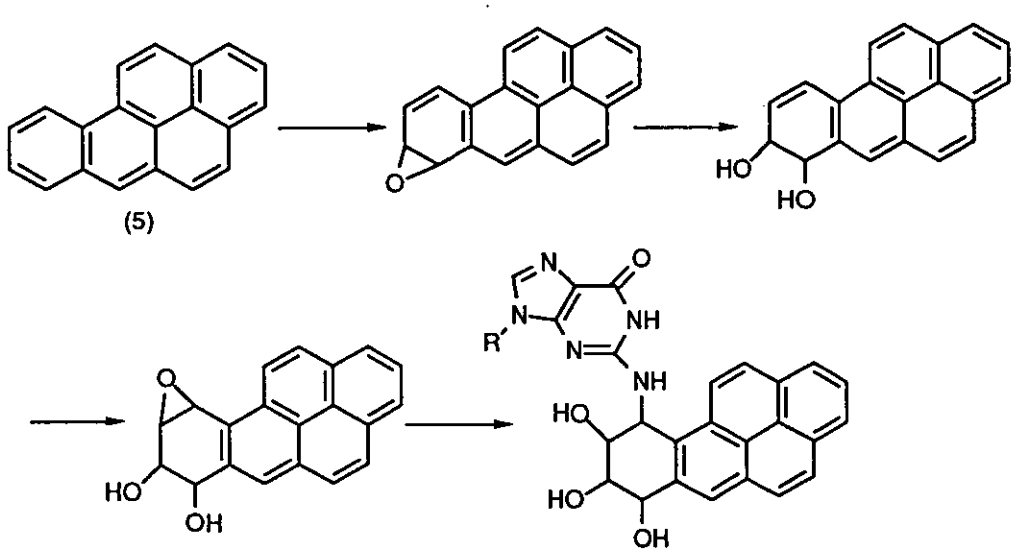
The body has a mechanism for removing non-polar exogenous chemicals by metabolising them in the liver into highly polar substances, which may then be excreted via the kidney.

In a typical example, benzene (4) is oxidised into an epoxide then forming an alcohol group. Glucuronic acid reacts with the alcohol is to produce highly polar, readily excreted ester, scheme 2.



Scheme 2

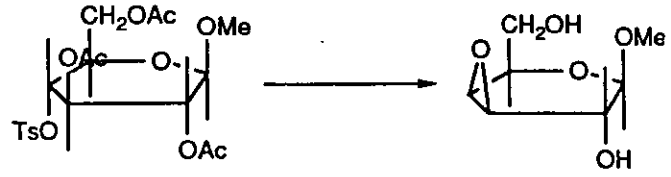
The above detoxification mechanism is not perfect. Sometimes a metabolite is more toxic than the original chemical. If it is not "deactivated" by an enzymatic process, the body is at an increased risk. Some epoxides formed as intermediates may react with proteins or nucleic acids, causing destruction of cell proteins and mutations in the DNA structure. This can lead to liver necrosis, cancer and other diseases. Benzo(a)pyrene (5), is a potent carcinogen, present in tobacco smoke. There are many metabolites formed from this material. One pathway leads to a particularly dangerous product that complexes with DNA as shown below, scheme 3.



Scheme 3

Use of Epoxides in Sugars[19].

An epoxide group is readily introduced into a sugar molecule. The oxide ring is also easily opened by nucleophilic attack to form the trans diaxial products, with the substituent group derived from the nucleophile. Hence epoxidation provides a route for the preparation of rare sugars from more common ones. Also for the selective introduction of groups of atoms, e.g. amino and halogen, into the sugar molecule, (reaction 11).



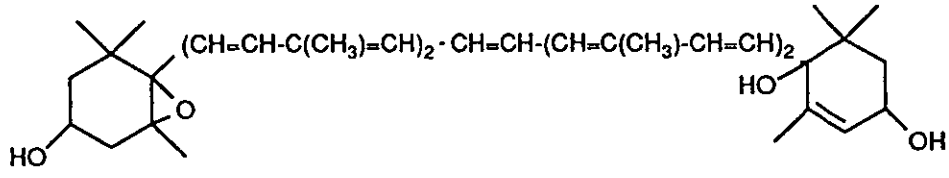
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Epoxide Occurrence in Natural Products.

Naturally occurring epoxides were once thought to be relatively rare in Nature. They are being found in increasing number and variety, particularly within the plant life. For example

1) Pigments

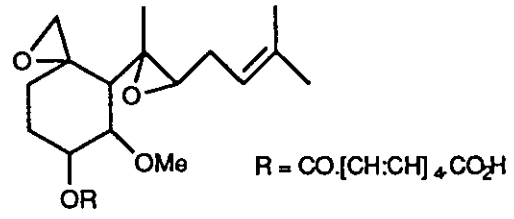
Various pigments like the carotenoid flower pigment trollixanthin[20] (6):



(6)

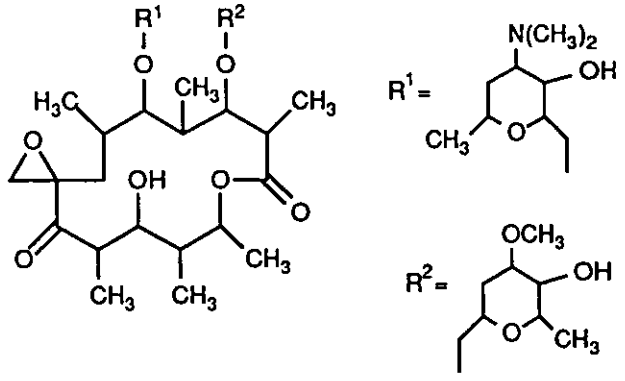
2) Antibiotics.

Fumagillin[21] (7), a potent antibiotic isolated from the Aspergillus mould was found to contain two epoxide rings.



(7)

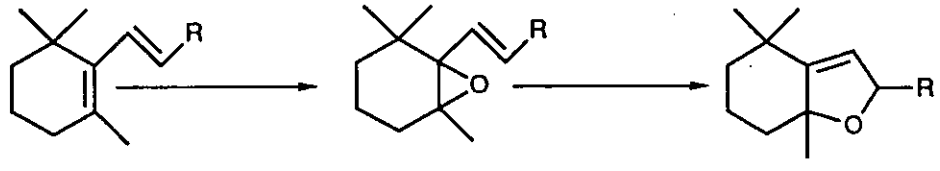
A number of macrolide antibiotics e.g. oleandomycin[22] (8), derived from *Streptomyces*, (a material highly active against pathogenic micro-organisms), are known to contain epoxides.



(8)

3) Carotenoid Epoxides.

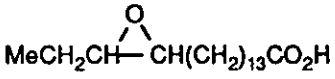
Carotenoid epoxides are intermediates in the formation of furanoid oxides from alkenes[23], and are believed to be important oxygen donors in nature, (reaction **12**).



(12)

4). Oils.

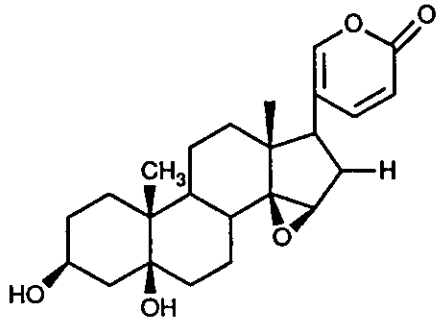
Numerous natural oils contain epoxide constituents. For example, 15,16-epoxylinoleic acid[24] (9) occurs in cameline oil.



(9)

5) Toad Venom.[25,26]

A particularly interesting discovery is that all toad venoms contain a 14,15-epoxide unit (or a 14-hydroxyl group), e.g.



(10)

THE OXIDATION OF COMPOUNDS CONTAINING CARBONYL GROUPS.

Oxidation of aldehydes (and alcohols) into carboxylic acids may be performed using numerous reagents, (reaction **13** and **14**). The choice of oxidant depends on the desired product. Chromium oxidants such as Fieser (CrO_3 / HOAc), Sarett (CrO_3 / pyridine) and Cornforth (CrO_3 / pyridine /H_2O) reagents[27] are commonly used for the production of carboxylic acids. (Milder reagents, such as PDC, $Cr_2O_7^-$ / pyridinium ion, forms aldehydes from alcohols).

$$RCHO \longrightarrow RCOOH \qquad \textbf{(13)}$$

$$R_2CHOH \longrightarrow R_2C{=}O \qquad \textbf{(14)}$$

Formation of Peracids.

Carboxylic acids react with hydrogen peroxide to form the corresponding peracids[28] in an equilibrium (reaction **15**) shown below. The strength of peracid is determined by the concentration of hydrogen peroxide.

$$RCO_2H \rightleftharpoons RCO_3H \qquad \textbf{(15)}$$

Formation of Esters From Ketones.

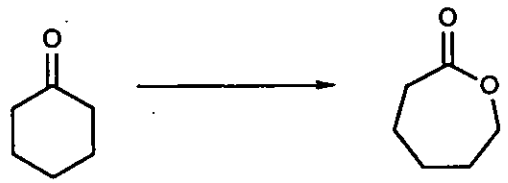
The conversion of a ketone into an ester by a peracid or hydroperoxide, known as the Baeyer-Villiger reaction[29], is well reviewed[15,30-32], (reaction **16**). The mechanism and reaction itself are discussed in more detail in chapter two.



(16)

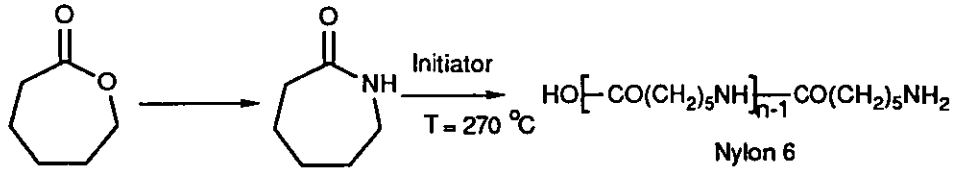
A major industrial use of this reaction is the production of caprolactone[33] (11) from cyclohexanone (12) by peracetic acid, (reaction **17**). The process is carried out on a large scale (2×10^4 ton for a single plant, in

1975), with peracetic acid production on site.



(12) (11) (17)

Caprolactone (11) is almost exclusively used in the formation of capramide (13), used for the production of poly-capramide), commonly known as Nylon 6 (14), (reaction 18).



(11) (13) (14)

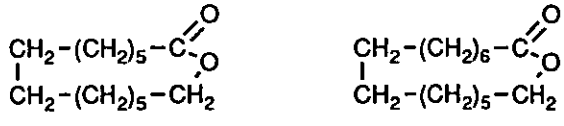
(reaction 18)

Natural Products.

There are numerous natural products that contain ester and lactone structures.

Perfumes and Flavours.

Some musk compounds of vegetable origin, such as Ambrettolide[34] (15) and Exaltolide[34] (16) contain lactone groups.



(15) (16)

It has been noted that flavour characteristics widely vary within the range of similar compounds. For example, the pear-like flavour of isopentyl acetate changes when the acid or alkyl group is varied[34], see table 2.

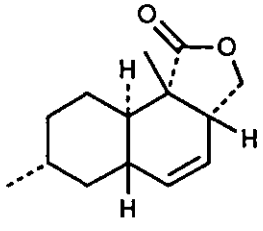
Table 2

Variation of Acid Group.	Flavour.
Isopentyl acetate	Pear
Isopentyl propionate	Apricot-plum
Isopentyl butyrate	Plum
Isopentyl cinnamate	Fruity, spicy
Isopentyl salicylate	Strawberry

Variation in Alkyl Group	
Methyl butyrate	Apple
Ethyl butyrate	Pineapple
Butyl butyrate	Fruity, buttery
Isopentyl butyrate	Plum

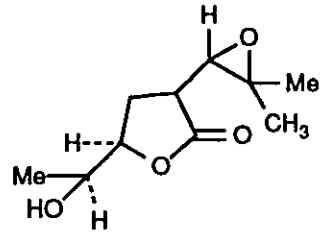
Natural Products.

Lactones occur in numerous natural products. Flavouring type compound are put to good use in the plant world. For example, various boring / feeding deterrents for elm bark beetles, produced from the fungus *Phomopsis oblonga*, contain a lactone structure[35] (17).

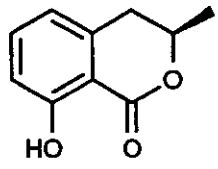


(17)

Fungal products are a rich source of polyketide metabolites such as Asperolactone (18) and Mellein[36] (19).

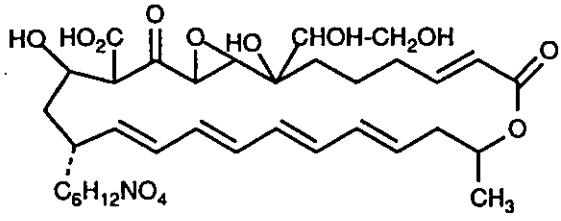


(18)



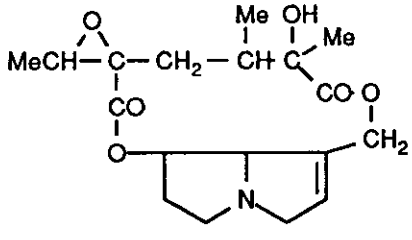
(19)

Some antifungal antibiotics contain a large lactone ring with several conjugated double bonds, such as pimaricin[37] (20).

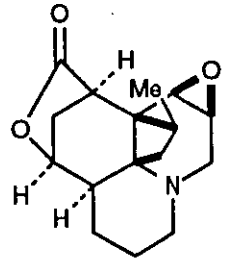


(20)

Alkaloids such as Jacobine[38] (21), also Annotinine[39](22) an alkaloidal constituent of the club moss *Lycopodium annotinum*, contain large lactone rings.



(21)



(22)

OXIDATION OF HETEROATOMS.

Nitrogen compounds.

Amines can be oxidised by a number of different reagents[40]. The products obtained depend upon the oxidant used. Primary amines at a tertiary carbon and primary aromatic amines are readily oxidised to nitro compounds using trifluoroperacetic acid, *m*CPBA and ozone, (reaction **19**). Oximes and nitroso compounds are also readily converted into nitro compounds by a number of oxidants[41].

$$ArNH_2 \longrightarrow ArNO_2 \qquad (19)$$

Nitroso compounds are also produced from aromatic amine oxidation, (reaction **20**).

$$ArNH_2 \longrightarrow ArNO \qquad (20)$$

Peracids and hydroperoxides oxidise tertiary amines to amine oxides[40], (reaction **21**). Peracids are particularly useful for the oxidation of pyridines[42].

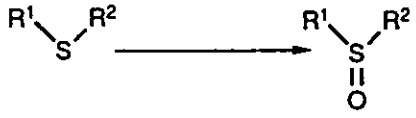
$$R_3N \longrightarrow R_3N^+\text{-}O^- \qquad (21)$$

These oxidants also convert azobenzenes into azoxybenzenes[43], (reaction **22**).

$$ArN{=}NAr \longrightarrow ArN^+(O^-){=}NAr \qquad (22)$$

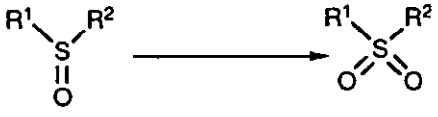
Sulphur Compounds.

Potassium permanganate, hydrogen peroxide, hydroperoxides and peracids all oxidise sulphides to produce sulphoxides[44], (reaction **23**).



(23)

If the oxidant is in an excess, further oxidation takes place to produce sulphones[45], (reaction 24).



(24)

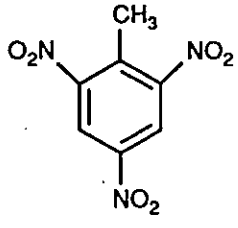
Sulphides are also converted into sulphonyl chlorides by the action of chlorine-water mixture, (reaction 25). Mercaptans, disulphides and thiocyanates undergo the same reaction[1].



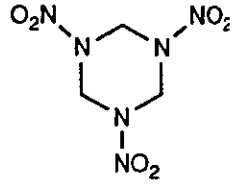
(25)

Uses of Nitrocompounds and Sulphones.

Some organic nitrocompounds are used for military high explosives[46] e.g. 2,4,6-trinitrotoluene (TNT, 23) and cyclotrimethylene trinitroamine (RDX, 24).



(23)



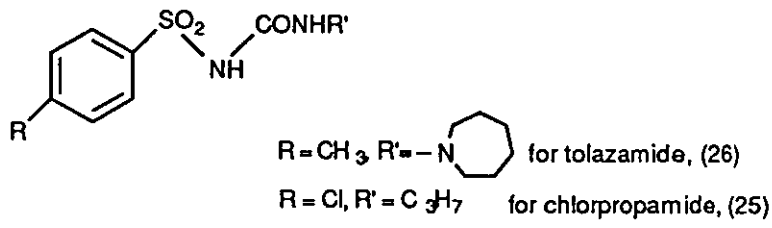
(24)

For propellants and commercial explosives, organic nitrates are more commonly used, such as glycerol trinitrate (nitroglycerine). Cellulose nitrate, when mixed with nitroglycerine produces a jelly to a "brittle solid" depending on the ratio of components used. This mixture has been utilized for propellants (Cardite and Ballistite) and is used to a very large extent for "Blasting Gelatine".

Many antibacterial agents have been developed that contain the sulphonamide functional group, several of them are still in use despite the discovery and production of antibiotics.

Sulphonamide drugs[47] are used to treat respiratory and urinary tract infections.

A number of antidiabetic agents, e.g. chloropropamide (25) and tolazamide (26), contain the sulphonamide group.



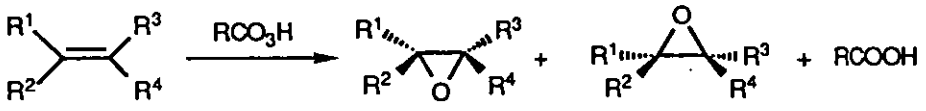
These drugs induce hypoglycaemia in humans, they help to combat the abnormally high levels of glucose in the blood of diabetic patients.

CHAPTER 1

EPOXIDATION.

Introduction.

The formation of epoxides (oxiranes) by oxidation of alkenes with peroxyacids (peracids), the Prileschajew Reaction[48] (reaction 26), was originally reported over eighty years ago, and is frequently reviewed[4.11-16]. Numerous peracids are cited for the epoxidation of a wide range of alkenes.



(26)

Formation of Peracids.

Many peracids are unstable and are prepared directly before use or *in situ* by various means. Occasionally, peracids are formed from hydrogen peroxide and the corresponding carboxylic acid[49,50]:

$$RCOOH + H_2O_2 \rightleftharpoons RCO_3H + H_2O \qquad (27)$$

However, the formation of equilibrium concentrations of peracid using this method tend to be slow unless producing the strong trifluoroperacetic or performic acids. Weaker peracids (e.g. peracetic or perbenzoic) require the presence of a mineral acid catalyst[51,52] (or methanesulphonic acid[53]) to speed up the reaction (equilibrium 27) affording higher concentrations of the electrophilic reagent (reaction 28).

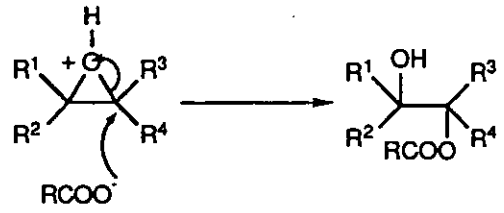
$$RCOOH + H_2O_2 \overset{H_2SO_4}{\rightleftharpoons} RCO_3H + H_2O \qquad (28)$$

An alternative to utilizing carboxylic acids is the use of carboxylic anhydrides with hydrogen peroxide, which produce the corresponding peracids in high concentrations (reaction 29)[54-56]:

$$(RCO)_2O + H_2O_2 \longrightarrow RCO_3H + RCOOH \qquad (29)$$

In practice, a buffer is added to the reaction in order neutralise the

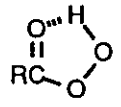
strong carboxylic acid formed from both the epoxidation (reaction **26**) and the formation of the peracid (reaction **29**). Acid removal thus prevents protonation of the epoxide, hence ring-opening, to produce hydroxy esters (α-glycols), scheme 4;



Scheme 4

Structure of Peracids.

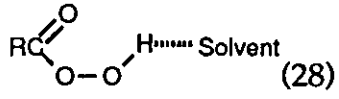
Infrared studies[57-59] have shown that peracids exist in various forms depending on the environment. Intramolecular hydrogen bonded monomers exist as stable five membered rings in non-hydrogen bonding solvents (27).



OH stretch 3310-3250 cm^{-1}
for performic and peracetic acids

(27)

Hydrogen bonding solvents such as methanol disrupt intramolecular interactions and few monomers are present in solution. Greater stability is afforded to the peracid by solvation and hydrogen bonding to the solvent can be extensive (28).



(28)

Mechanism of Epoxidation.

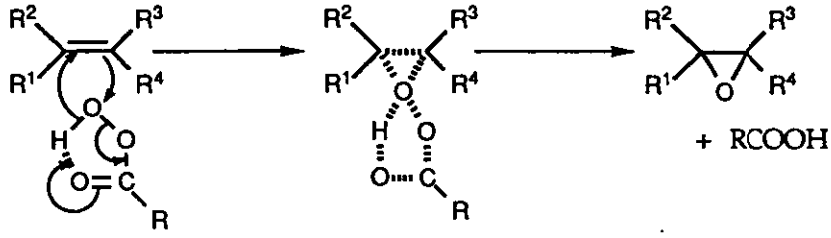
Lynch *et al.*[60]and Berti[61] studied the epoxidation of *trans* stilbene by a number of substituted perbenzoic acids. It was found that electron donating substituents decreased the rate of reaction, indicating that the peracid is an electrophilic reagent.

Various authors[62-65] have shown that susceptibility of alkenes to electrophilic attack is increased by electron donating substituents on the

olefin, i.e. the alkene acts as a nucleophile.

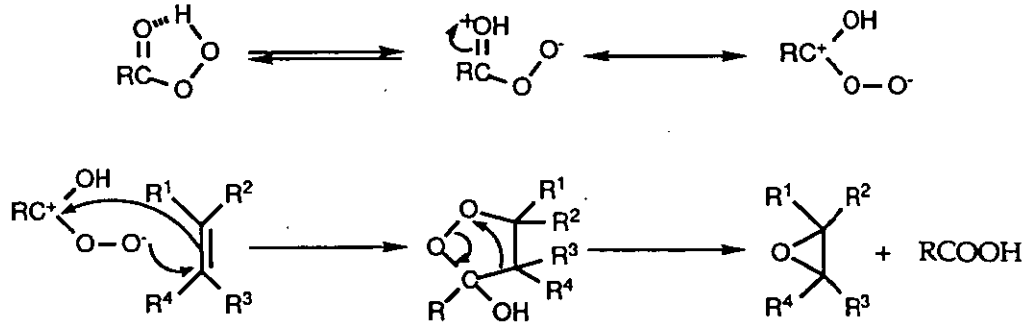
Although many studies have been published, the exact mechanism of the Prileschajew Reaction is still unknown.

Perhaps the most widely accepted route is a concerted process described by Lynch *et al.*[66] and others[67], scheme 5.



Scheme 5

Another mechanism involves the 1,3-dipolar addition of the peracid to the alkene, scheme 6[68-70].



Scheme 6

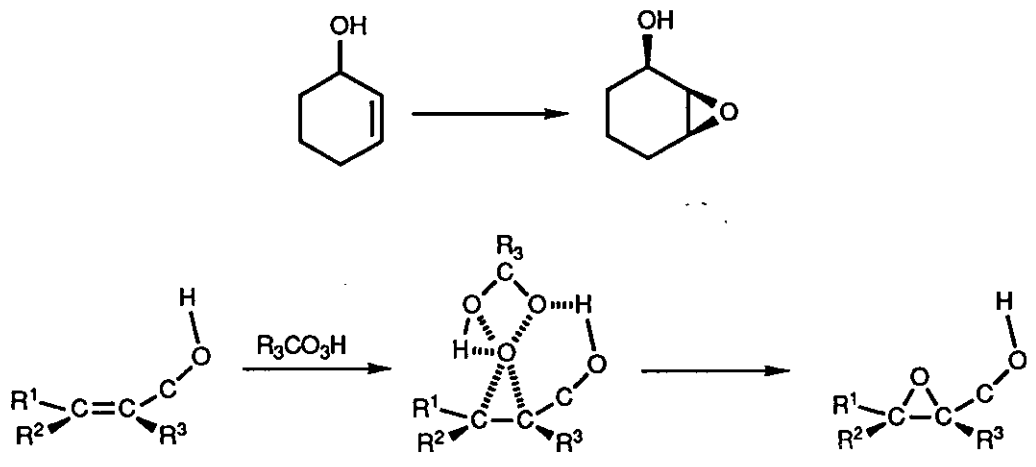
Both proposals are in accord with observations of the epoxidation reaction;

i) the reaction is second order
ii) epoxidation readily takes place in non-polar solvents
iii) there is no carbonium character in the transition state
iv) addition to the alkene is stereospecific i.e. a *trans* olefin gives a *trans* epoxide and a *cis* olefin a *cis* epoxide[71-76].

Effects of Substituents.

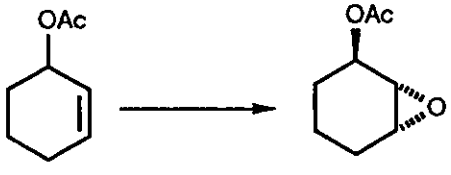
In general, peracids attack the least hindered side of alkenes. However, the approach of the peracid is greatly influenced by neighbouring groups on both the electrophile and the nucleophile.

Investigations of substituted cyclohexenes[77] have shown that for cyclic allylic alcohols, the addition of oxygen is *cis* to the alcohol group, whereas for cyclic acetoxycyclohexenes the reaction is slower and occurs *trans* to the acetate group. It is believed that the hydroxyl group directs attack of the peracids to the *cis* side by hydrogen bonding, scheme 7.



Scheme 7

No such hydrogen bonding can occur for 1-acetoxycyclohex-2-ene and peracids approach from the least hindered side[77], scheme 8.

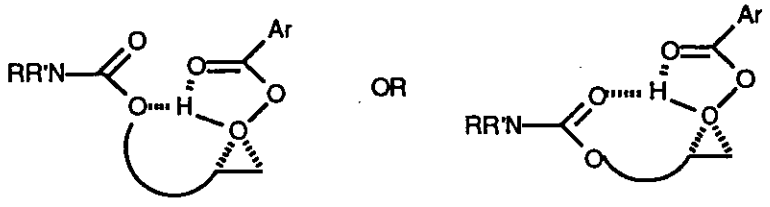


Scheme 8

cis-Alkyl substituted cyclohexenes[78] and trimethylsilyl ethers[29] gave the expected *trans* epoxides, due to attack of the peracid from the least hindered side.

Recent investigations concern the epoxidation of carbamates[80]. These groups were found to have a syn directing effect. Some cases, e.g. N,N-dimethylcarbamoyloxycyclohexene, did not have the capability of forming O-H or N-H hydrogen bonds with the peracid. This caused the authors to

consider alternative mechanisms for this reaction. Intramolecular interaction between the carbamate and peracid, similar to that of peracid and cyclic allylic alcohols, would promote *cis* addition. (Scheme 9).



Scheme 9

Similar steric effects were observed for a number of steroids[77,81]. Bulky alkyl groups on the β–face of the molecule cause peracids to approach the less hindered α-face. However, due to the directing effect of the hydroxyl group by hydrogen bonding, 3β-hydroxycholest-1-ene gave the β-epoxide (cf: more remote alkenes, e.g. 3β–hydroxycholest-5,6-ene gives the α-epoxide)[77].

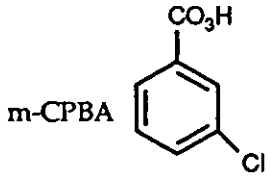
Carbonyl groups in the β-position to the olefin are cited[82] as having a pronounced directive effect upon peracid epoxidation. Ratios of epoxide trans to the carbonyl are significantly increased compared to corresponding epoxides formed without the neighbouring carbonyl group.

Solvent Effects.

Solvents that hydrogen bond with peracids tend to reduce the rate of reaction[83] and in some cases influence the stereoselectivity of epoxidation reactions[84]. This is exemplified by the epoxidation of allylically substituted cyclohexenes by trifluoroperacetic acid. In dichoromethane these substituted epoxides are formed predominantly by syn addition. In THF however, solvation of the electrophile occurs and hydrogen bonding between peracid and substrate is prevented, thus an increase in anti addition is observed.

Types of Peracid.

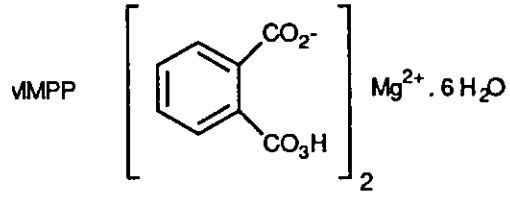
A wide variety of peracids have been used in the Prileschajew reaction, commonly peracetic[85], perbenzoic[86] and trifluoroperacetic acids[87]. These were later superseded by *m*CPBA[88] (*meta*-chloroperbenzoic acid), (29).



(29)

*m*CPBA had wide applicability, being able to epoxidise a vast number of substrates including: terminal, electron deficient[89] and acid sensitive alkenes[90]; allylic alcohols[91-93] and allenes[94,95] giving high yields of epoxides in rapid clean reactions[96,97].

A more recently developed peracid, MMPP[98-100] (magnesium monoperoxyphthalate), (30) oxidises a range of substrates under mild conditions. It was advertised as a safe replacement for *m*CPBA, as it does not suffer from the instability problems previously described.



(30)

However, MMPP is not a complete replacement, due to lack of solubility in common organic solvents. Unless low molecular weight alcohols are used, two phase systems must be utilized.

A more complete replacement for *m*CPBA is required. Interest grew in the use of hydrogen peroxide adducts (perhydrates) to form peracids *in situ*. Determination of the applicability of such adducts in the epoxidation of alkenes of various nucleophilicities was required.

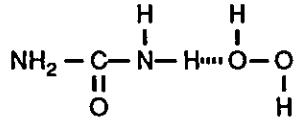
Advantages in the use of these perhydrate adducts are given below: they

i) are non-shock sensitive and are not potentially explosive
ii) are soluble in most organic solvents
iii) are a cheap source of hydrogen peroxide
iv) avoid the use of high test peroxide

Several hydrogen peroxide adducts have been made but little is reported of their use. Literature methods include their use as
1) a source of anhydrous hydrogen peroxide[101,102];
2) the *in situ* formation of performic acid[103]
3) aromatic hydroxylations[104] and
4) Baeyer-Villiger reactions[104].

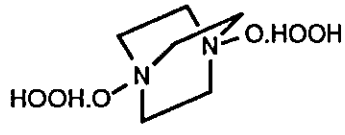
Some typical adducts are shown below:

UHP (urea-hydrogen peroxide)[105], (31);



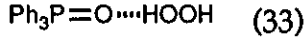
(31)

DABCO di-N-oxide diperhydrate; (Diazabicyclooctane di-N-oxide diperhydrate)[106], (32);



(32)

Triphenylphosphine oxide hydrogen peroxide[107], (33);



(33)

The following chapter reports the successful epoxidation of a variety of alkenes by peracids generated from hydrogen peroxide adducts in combination with either trifluoroacetic or acetic anhydride.

Results and Discussion.

a) Trifluoroperacetic acid (34).

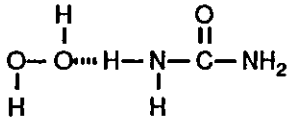
The extent of epoxidation (reaction **26**) is greatly influenced by the nature of the neighbouring groups on the alkene and the peracid. Nucleophilic double bonds, such as styrenes, give high yields of epoxides using fairly weak peracids e.g. perbenzoic acid. Less nucleophilic double bonds such as aliphatic terminal alkenes, are epoxidised using stronger, more electrophilic peracids e.g. trifluoroperacetic acid (34).

Attempts were made to generate peracids based on methods reported in the literature[49-52] but using UHP in place of hydrogen peroxide. For example, utilizing trifluoroacetic acid (35), (reaction **30**) and also the carboxylic acid with a mineral acid catalyst (reaction **31**):

$$\underset{(35)}{CF_3COOH} + \text{urea-}H_2O_2 \rightleftharpoons \underset{(34)}{CF_3CO_3H} + H_2O + \text{urea} \qquad \textbf{(30)}$$

$$\underset{(35)}{CF_3COOH} + \text{urea-}H_2O_2 \xrightarrow{H_2SO_4} \underset{(34)}{CF_3CO_3H} + H_2O + \text{urea} \qquad \textbf{(31)}$$

However, neither of these methods produce trifluoroperacetic acid in any significant quantity from UHP and trifluoroacetic acid. This is due to the hydrogen bonding between the urea and hydrogen peroxide being stronger than originally anticipated. Alternative methods were needed to disrupt this interaction and release hydrogen peroxide from the adduct[1], (36).



(36)

One such method of peracid formation is hydrogen peroxide and trifluoroacetic anhydride (37), (reaction **32**).

[1]See appendix 1

$$(CF_3CO)_2O + \text{urea-}H_2O_2 \longrightarrow CF_3CO_3H + CF_3COOH + \text{urea} \quad (32)$$
(37) (34) (35)

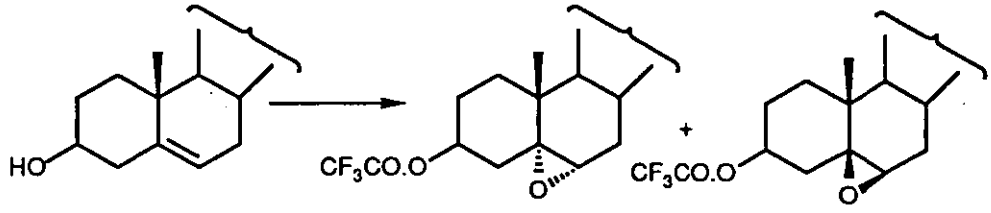
However, if the anhydride (38) is in excess, there is a possibility of forming the diacyl peroxide (39, reaction 33). Various safety precautions are required to prevent the build up of this compound due to its highly explosive nature.

$$(RCO)_2O + H_2O_2 \longrightarrow R-C(=O)-O-O-C(=O)-R + H_2O \quad (33)$$
(38) (39)

UHP used in combination with carboxylic anhydrides does produce peracids in sufficient quantities to carry out a number of epoxidation reactions. To avoid the formation of any large amount of diacyl peroxide (39), UHP was kept in a vast excess, in order to saturate the reaction mixture with available oxygen. The diacyl peroxide required regular monitoring by titration methods.

The Epoxidation of Cholesterol.

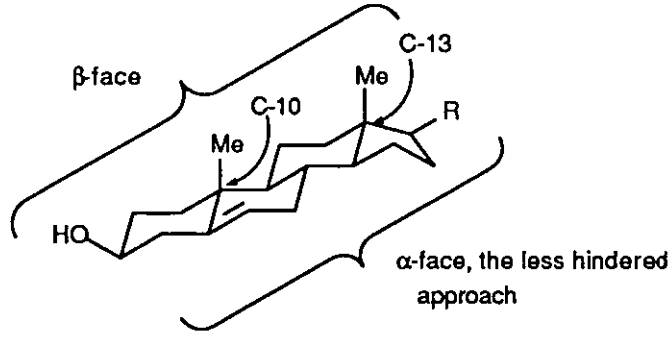
Trifluoroperacetic acid (34) was generated *in situ* from UHP and trifluoroacetic anhydride (37) in the presence of the cholesterol and buffer. The substrate was converted into a mixture of the α– and β–cholesterol epoxides (40) and (41) in 62% yield, (reaction 34).



(40) (41) **(34)**

The α:β ratio, determined by proton NMR, was 3:1 (the α–proton gave a doublet at 2.91ppm and the β–proton a doublet at 3.10ppm[108]). This ratio is a typical value for a peracid epoxidation of cholesterol, c.f. *m*CPBA also gives 3:1

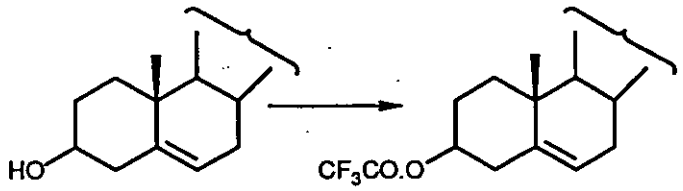
As described by Kirk and Hartshorn[109], the α-epoxide (40) was the major isomer due to the shielding of the β-face of the cholesterol by the methyl groups at C-10 and C-13. They restrict the approach of the peracid to the β-face, hence less epoxidation occurred by this route, scheme 10.



Scheme 10

Esterification of the alcohol group proceeded very readily under these reaction conditions (reaction 35), by the action of the trifluoroacetic anhydride (37) in the mixture. This was confirmed by refluxing cholesterol in the anhydride for a short time, cholesterol-3-trifluoroacetate (42) being

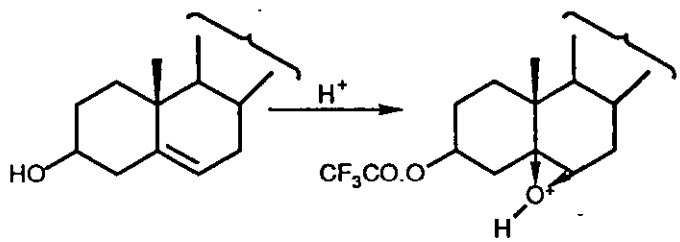
obtained in high yield.



(35)

(42, 90%)

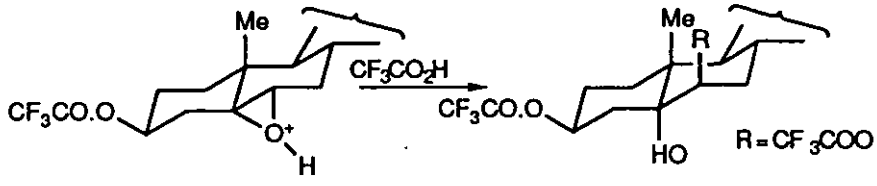
With no buffer present, the trifluoroacetic acid (35) formed (reaction 31) remains in the reaction mixture. Under these acidic conditions, the epoxide did not survive as it was readily ring-opened to give hydroxytrifluoroacetates. Protonation of the oxygen atom greatly enhances the normal polarisation of the C-O bond, making it more susceptible to the nucleophilic attack by the trifluoroacetate anion, scheme **11**:



Scheme 11

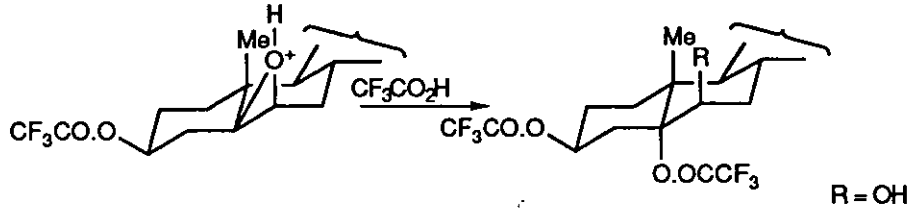
As described by Kirk and Hartshorn[109], nucleophiles approach the epoxide from a peri-planar direction, (the least sterically hindered route) forming the trans-diaxial substituted product. The epoxide oxygen atom forms the axial hydroxy group, corresponding to the configuration of the epoxide and the entering trifluoroacetate anion becomes axially bonded to the other carbon atom.

Hence, the α-epoxide (the major isomer) formed the 5α-alcohol-6β-trifluoroacetate (43), scheme 12, whilst the β-epoxide (the minor isomer) formed the 5α-trifluoroacetate-6β -alcohol (44), scheme 13:



(43)

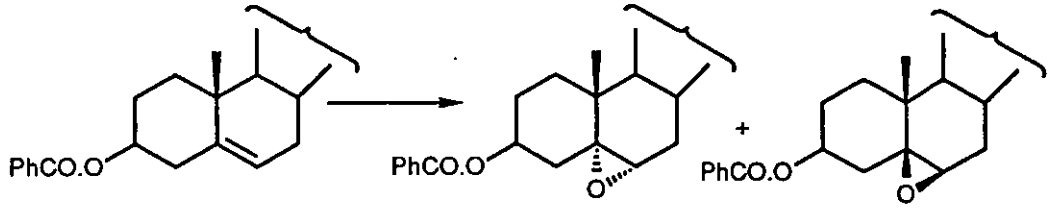
Scheme 12



(44)

Scheme 13

The Epoxidation of Cholesteryl Benzoate.



(α, 45) (β, 46) **(36)**

A comparison of α:β epoxide (45) : (46) ratios produced from the action of various oxidants on cholesteryl benzoate (reaction **36**) is shown in table 3 below:

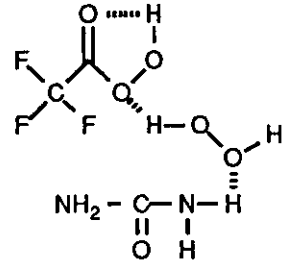
Table 3.

Oxidant	**Yield of Epoxide,%**	**α:β ratio**
MMPP	95	6:1
$DABCO.O_2.H_2O_2$/TFAA	69	4:1
UHP/TFAA	53	5:2

Note: the ratio was determined by proton NMR.

The largest α:β ratio is given by MMPP indicating a higher selectivity towards the α-epoxide (45) formation. Lower selectivity is shown by the UHP/ trifluoroacetic anhydride procedure. An increase in observed α-epoxide generation was expected due to the adduct hydrogen bonding to the trifluoroperacetic acid. This association with the peracid makes the oxidant more bulky, thus affecting the mode of attack on the cholesterol, (47). However, the epoxide ratio was typical for a peracid oxidation, indicating that the UHP interaction does not effect the epoxidation.

e.g.



(47)

The Epoxidation of 1-Octene.



(48) (49, 88%) (37)

1-Octene (48) is readily converted into 1,2-epoxyoctane (49) in high yield by trifluoroperacetic acid (34) generated *in situ* from UHP and trifluoroacetic anhydride (reaction 37). Emmons' *et al* [87] literature method reported a similar yield from trifluoroperacetic acid, preformed from 95% hydrogen peroxide and trifluoroacetic anhydride.

At this point, a series of 1-octene epoxidations were carried out, table 4, to determine whether the large quantity of UHP used in each reaction could be reduced without:-

a) affecting the yield of the oxirane or

b) increasing the formation of the diacyl peroxide.

Table 4.

Molar ratio UHP: TFAA: octene	Yield of Epoxide,% 1	2
10 : 5 : 2	72	74
16 : 5 : 2	60	88
20 : 5 : 2	61	--
24 : 5 : 2	61	--

1= Room temperature reactions.

2= Reflux for 0.5 hours.

The results in table 4 show that:

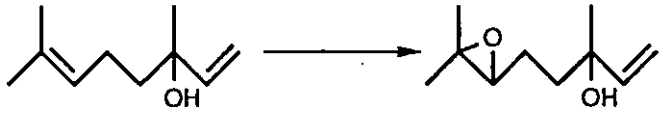
a) The yield of isolated 1,2-epoxyoctane decreases as the quantity of UHP increases. It is possible that the peracid and acid are formed in larger quantities and/or faster rates than the buffer neutralising capability.

This leaves nucleophiles to react with the already formed epoxide, thereby reducing the yield.

b) The yield of epoxide is either unaffected or significantly increased when the reaction mixture is refluxed for a short period of time, rather than left at room temperature overnight, i.e. a shorter reaction time reduces the amount of hydroxy-ester formation. This ring opening is probably due to excess peracid and acid being formed, which is beyond the neutralising capacity of the buffer.

In each case, the diacyl peroxide, monitored by titration, remained at levels that were not considered to be hazardous.

Epoxidation and Cyclisation of Linalool (50).



(50) (51) (38)

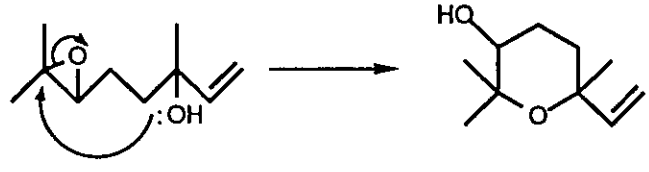
Trifluoroperacetic acid oxidised the more nucleophilic of the two double bonds contained in the linalool molecule (50), i.e. the alkene at the 6,7-position, (reaction 38).

The monoepoxide formed (51) was very unstable, and rapidly cyclised to form a tetrahydrofuran derivative (52).



(51) (52, 64%) **(39)**

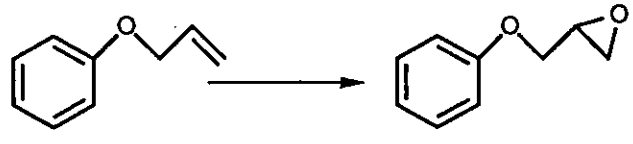
The cis and trans isomers of this product were both observed by GLC analysis, (with peaks of similar areas, implying similar quantities) and, the proton NMR corresponded with that published by Felix *et al.*[110] The only other possible cyclisation, involved the formation of the tetrahydropyran derivative (53) via the sterically less favoured route.



(51) (53) **(40)**

The tetrahydropyran (53) was not formed to any great extent, observed only as a trace component by GLC analysis and not at all in the proton nmr spectrum of the main product.

Epoxidation of Phenyl Allyl Ether (54).

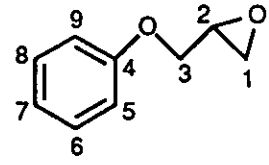


(54) (55, 51%) **(41)**

Trifluoroperacetic acid converted phenyl allyl ether (54) into 1,2-epoxy-3-phenoxypropane (55) in a moderate yield of 51% (reaction **41**), exceeding the 35% attained from the perbenzoic acid epoxidation reported by Werner[111]. The alkene group in this case is slightly electron deficient due to the electrophilic nature of the phenyl ether group adjacent to it. Therefore a higher yield of epoxide (55) is obtained using the stronger, more

electrophilic trifluoroperacetic acid.

The C-13 data of this substituted epoxypropane (55) were in good agreement with cited[112] values, shown in the table 5 below:



(55)

Table 5

Carbon	$\delta_C$ppm (Experimental)	$\delta_C$ppm (Literature)[112]
1	44.6	44.5
2	50.2	50.2
3	68.7	69.6
4	158.6	---
5 & 9	114.7	---
6 & 8	129.5	---
7	121.3	---

Other Substrates.

Other relatively weakly nucleophilic alkenes epoxidised in moderate yield by trifluoroperacetic are given in table 6 below:

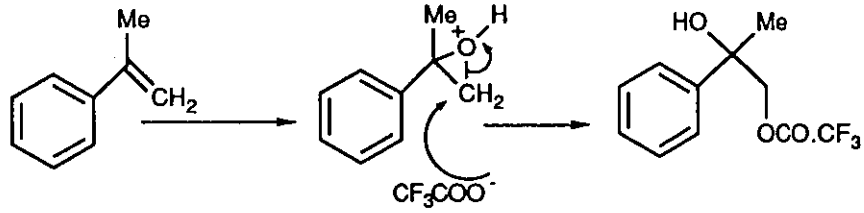
Table 6

Substrate	Yield of Epoxide,%
1-Hexene	53
Cyclohexene	60
Methyl methacrylate	56
Cholesterol-3-trifluoroacetate	58

b) Peracetic acid.

Epoxidation of α-Methylstyrene.

The epoxidation of α-methylstyrene (56) was initially attempted using trifluoroperacetic acid generated from UHP and trifluoroacetic anhydride reaction 32). Although the epoxide (57) was formed, ring-opening rapidly occurred by attack of the trifluoroacetic acid (35) (the by-product from peracid formation), scheme 14.



(56) (57)

Scheme 14

It was impossible to prevent this secondary reaction occurring, as neutralisation of the acid using a large excess of buffer was not effective.

No ring-opening was observed when using the weaker, less electrophilic peracetic acid (58), generated from UHP and acetic anhydride (59). The acidic by-product in this case (acetic acid) is weaker.

$$\underset{(59)}{(CH_3CO)_2O} + \text{urea-}H_2O_2 \longrightarrow \underset{(58)}{CH_3CO_3H} + \underset{(60)}{CH_3COOH} + \text{urea} \quad \textbf{(42)}$$

In this case, the acetic acid by-product (60) was neutralised before attack on the epoxide could take place. Hence higher yields of α-methylstyrene epoxide (58) were realised.



(56) (57, 83%) **(43)**

Reaction conditions were varied in a number of experiments (table 7) in order to optimise the yield of epoxide, and also to determine whether the vast quantity of UHP used in each reaction could be reduced, without increasing the production of explosive diacyl peroxide (reaction 33).

Table 7

Mole ratio UHP: AA* : α-methylstyrene	Yield of epoxide,%
30 : 5 : 2	75
20 : 5 : 2	72
16 : 5 : 2	73
10 : 5 : 2	43
6 : 5 : 2	47
4 : 5 : 2	16

*AA = acetic anhydride

The optimum yield of epoxide, attained at a molar ratio of 16 : 5 : 2, indicates that no further peracetic acid was formed, i. e. the available oxygen present in the reaction mixture was sufficient to completely convert the acetic anhydride into peracetic acid (reaction 42).

At ratio values of 10 : 5 : 2 and below, the yield of α-methylstyrene significantly dropped due to insufficient peracid formation. Although the quantity of UHP placed in the reaction mixture was in excess of the other reagents, not enough available oxygen was produced to convert all of the acetic anhydride into peracetic acid. A significant proportion of the hydrogen peroxide present was still attached to the urea, indicating that hydrogen bonding in the adduct was a lot stronger than originally anticipated.

Variation of the Reaction Time, table 8.

Table 8

Reaction time (h)	Yield (%)
2	15
6	24
10	75
14.5	38
18.5	43

The formation of epoxide initially increased as a function of time, as anticipated. Beyond 10 hours, the yields are drastically reduced, probably due to ring-opening of the product.

This series of experiments led to the observation that a molar ratio of 20+ (UHP) : 5 (acetic anhydride) : 2 (the styrene) in a reaction of approximately 10 hours gave the optimum yield of α-methylstyrene.

Note: For each of the reactions shown, (tables 7 and 8), the level of diacyl peroxide (39) was monitored by titration, and found to be below maximum acceptable levels.

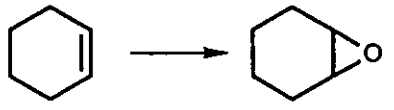
Under the above conditions, high yields of epoxides were produced from styrene and β–methylstyrene, table 9.

Table 9

Styrene	Yield of epoxide,%
Styrene	60
α-methylstyrene	83
β-methylstyrene	86
β-bromostyrene	0

Due to the +m and -I effect of the bromine, the double bond in β-bromostyrene was deactivated towards electrophilic attack resulting in no epoxide formation. Subsequent attempts with trifluoroperacetic acid were equally unsuccessful, effecting complete recovery of starting material.

Epoxidation of Cyclohexene (61).



(61) (62, 74%) (44)

A similar case was observed for cyclohexene oxide (62) as for α-methylstyrene oxide (57), in that trifluoroacetic acid reacted with the epoxide (62) to produce a hydroxy-ester.

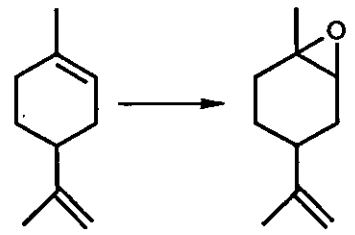
The 1,2-epoxycyclohexane (62) was readily isolated from peracetic acid epoxidation, (reaction 44). This is probably due to the weaker acid conditions in the reaction mixture, nucleophiles present in the mixture reacting with the buffer in preference to the epoxide. Consequently, peracetic acid gave moderate yields of epoxides from substituted cyclohexenes (table 10).

Table 10

Cyclohexene	Yield of Epoxide,%
Cyclohexene	74
1-Methylcyclohexene	56
3-Methylcyclohexene	58

Epoxidation of Limonene (63).

The epoxidation of the more nucleophilic, endocyclic double bond in limonene (63), in preference to the exocyclic, less substituted alkene with peracids was reported by various authors[113,114], (reaction 45).

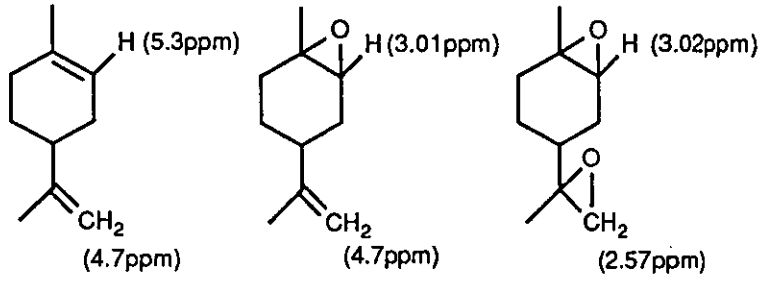


(45)

(63) (64)

The proton NMR of the product obtained from UHP/ acetic anhydride oxidation of the substrate (63) did not correspond to that expected for limonene monoepoxide[113] (64).

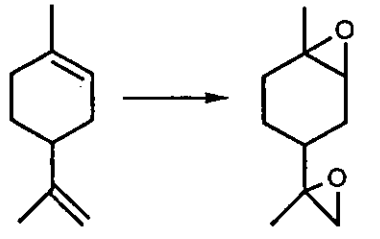
Limonene (63) gave one olefinic proton at δ_H= 5.3 ppm, and two more at δ_H= 4.7 ppm, whereas the monoepoxide (64) has one epoxide proton at δ_H= 3.01ppm and two olefinic protons at δ_H= 4.7 ppm. The product NMR gave no trace of any olefinic protons, scheme **15**.



(63) (64) (65)

Scheme 15

Three epoxide protons, one at δ_H= 3.02 ppm and two at δ_H= 2.57 ppm were observed, indicating that both of the double bonds reacted very readily with the peracetic acid to form limonene diepoxide (65).



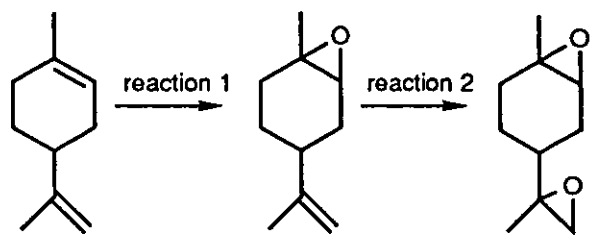
(46)

(63) (65, 94%)

The monoepoxide proved difficult to obtain. Excess UHP was required in the mixture to drive reaction **42** over to the right, producing sufficient

quatities of peracid for the actual epoxidation of limonene to take place. When this excess UHP was reduced, the peracid formation fell quite considerably and the extent of epoxidation was significantly decreased.

However, it was not possible to reduce the amount of peracid to the exact value to attain only monoepoxide. (The second reaction started before the first reaction finished, scheme **16**).



(63) (64) (65)

Scheme 16

Reduction of the amount of peracid present was achieved by variation of the ratio of UHP to acetic anhydride. Hence, varying the quantity of acetic anhydride (hence peracetic acid) varied the ratio of limonene monoepoxide (64) and diepoxide (65) formation.

Although this was successful to some degree, there was still a trace of limonene (63), or diepoxide (65), or both present in the crude limonene epoxide product. Isolation gave reasonable yields of the monoepoxide (64).

In conclusion, peracetic acid, when in excess of limonene, reacted with the endocyclic alkene forming the monoepoxide (64). As the level of this product increased and starting material fell, a second reaction took place, involving the epoxidation of the exocyclic double bond, producing the diepoxide (65). Therefore, the ratio of limonene mono- and di-epoxide formed was directly related to the quantity of peracetic acid used.

Epoxidation of Geraniol (66).

The proton NMR spectrum of the product showed the presence of two epoxide protons at δ_H= 2.84 ppm, with no trace of either of the two olefinic protons (at δ_H= 5.12 ppm and δ_H= 5.45ppm), proving that geraniol was converted into the diepoxide (67), (reaction **47**). It is assumed that the hydrogen bonding between the hydroxyl group and the peracetic acid

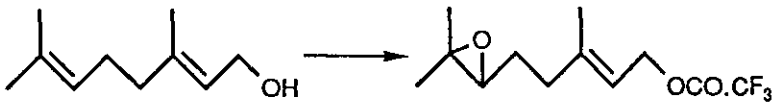
facilitates reaction at the alkene residue.



(66) (67, 66%) (47)

The product formed from the action of trifluoroperacetic acid on geraniol gave a large carbonyl peak at 1782 cm^{-1} in the IR, a typical value for a trifluoroacetate grouping. The proton NMR gave a doublet at δ_H= 4.83 ppm (CH_2-OCO.CF_3) rather than at δ_H= 4.15 ppm (CH_2-OH), i.e. the alcohol had been esterified.

The alkene proton at δ_H= 5.45ppm (2,3-position) showed no shift change, but the δ_H= 5.12ppm proton was removed and an epoxide proton observed at
δ_H= 2.68ppm (the 6,7-position). From this evidence, the reaction between trifluoroperacetic acid and geraniol resulted in the formation of 6,7-epoxy-geranyltrifluoroacetate (68) exclusively, (reaction 48).



(66) (68) (48)

As the 2,3-position was not epoxidised, esterification of alcohol must have occurred before the oxidation takes place. The trifluoroacetate group deactivated the alkene adjacent to it from further peracid attack, and epoxidation took place at the unaffected 6,7-position.

Epoxidation of Geranyl Acetate (69).

The electron withdrawing capability of the acetate group present in geranyl acetate was sufficient to deactivate the alkene at the 2,3-position. The product (70) showed the presence of an olefinic proton at δ_H= 5.37ppm, and an epoxide proton at δ_H= 2.73 ppm

This effect of the acetate group was only short range, and therefore did not reach the 6,7-alkene position to any significant degree. The double bond here remained sufficiently electron rich to react with the nucleophile, hence

the product formed was 6,7-epoxygeranyl acetate (70).

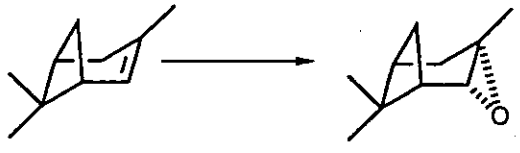
(This effect has been described by Henbest and Wilson[77], who established that the rate of peracid epoxidation of allylic alcohols is much greater than that of the corresponding allylic acetates).



(69) (70, 82%) **(49)**

Other nucleophilic alkenes epoxidised by UHP/ acetic anhydride are shown below, (reactions **50-54**):

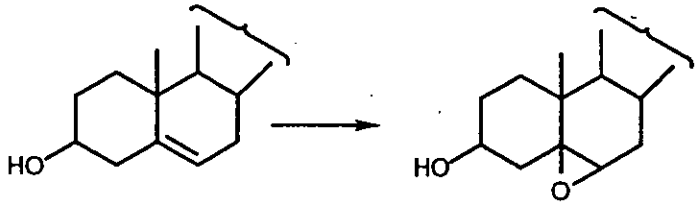
α-Pinene.



(50)

(71, 79%)

Cholesterol.



(51)

(72, 65% α-epoxide)

(28% β-epoxide)

2,3-Dimethylbut-2-ene.



(52)

(73, 51%)

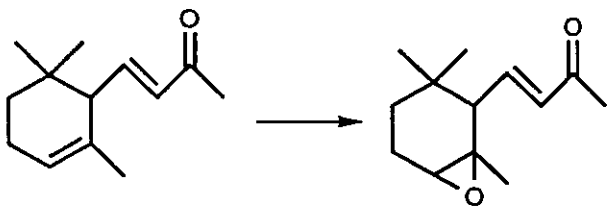
trans-Stilbene.



(53)

(74, 47%)

α-Ionone.



(54)

(75, 90%)

Other Hydrogen Peroxide Adducts.

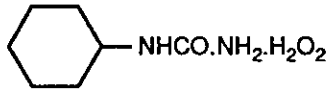
UHP is a useful and safe hydrogen peroxide adduct. However, problems due to the strong hydrogen bonding in this adduct necessitated the use of vast excesses of UHP. The large excess was required to provide sufficient available oxygen to the reaction mixture, in order to produce an adequate quantity of peracid.

A number of adducts were formed containing various hydrogen bonding strengths. Each was used in a number of oxidation reactions and compared to the performance of UHP.

Note: AVOX is the AVailable OXygen content, determined by titration. It is used as a measure of hydrogen peroxide contained in the material. For example, the histidine-hydrogen peroxide adduct has 100% AVOX. This means that the adduct contains a ratio of 1 : 1 hydrogen peroxide : histidine. Therefore the AVOX content is a measure of purity of the hydrogen peroxide adduct.

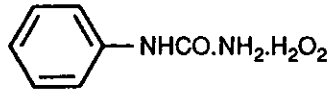
The adducts formed were:

1) Cyclohexylurea-hydrogen peroxide. (AVOX = 72%)



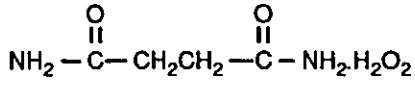
(76)

2) Phenylurea-hydrogen peroxide. (AVOX = 60%)



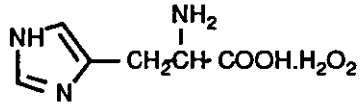
(77)

3) Succinamide-hydrogen peroxide. (AVOX = 61%)



(78)

4) Histidine-hydrogen peroxide. (AVOX = 100%)



(79)

See table 11 for the comparison of adducts 76, 77 and 78 against UHP. (In each oxidation, the reaction conditions were the same, i. e. peracid formed, time length etc.)

Table 11

Adduct	Yield, %	
	α-Methylstyrene oxide	1,2-epoxy octane
76	9	46
77	35	55
78	47	54
UHP	83	88

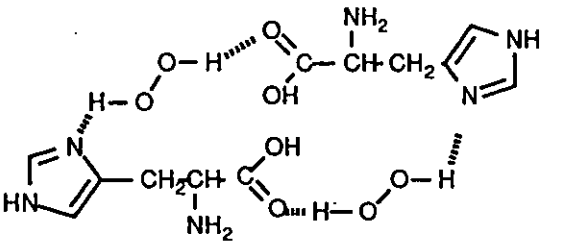
Oxidation reactions using these adducts were rather disappointing, the yields were moderate to low, and the extractions of the products were frequently complicated by the ureas (76 and 77 in particular).

Succinamide-hydrogen peroxide (78) gave moderate yields of oxides. A particularly good example was the formation of cholesterol epoxide in 79% yield. However, a similar excess of succinamide adduct to UHP was required to attain these values. Hence no advantage was achieved due to relatively strong hydrogen bonding in the adduct, i.e. the extra methylene group had very little effect on the intermolecular forces between succinamide and hydrogen peroxide.

4) Histidine-hydrogen peroxide, (79).

The problem of overcoming the strong hydrogen bonding in hydrogen peroxide adducts is illustrated in the attempt to use histidine-hydrogen peroxide for epoxidation reactions.

Histidine-hydrogen peroxide is described[115] as being a stable crystalline material that is not easily decomposed by shock or heat, indicating a strong interaction between the histidine and the hydrogen peroxide.



(79)

The epoxidation of cholesterol (72) was attempted using this adduct with acetic anhydride under "standard conditions" used for UHP. (That is:- 80mmol adduct, 70mmol buffer, 20mmol acetic anhydride and 8mmol substrate in dichloromethane stirred at room temperature overnight). However this reaction failed, resulting in the complete recovery of cholesterol.

As the adduct was found to be relatively insoluble in dichloromethane, further attempts at the epoxidation of cholesterol (72) were made using elevated temperatures and various co-solvents (details are shown in table 12), but each resulted in the complete recovery of starting material. (Note: The adduct was not recovered intact after the reactions, being lost during the work up using sodium bicarbonate and water).

Table 12

Solvent	Co-solvent	Temperature
Dichloromethane	Polyethyleneglycol400	25
Dichloromethane	Polyethyleneglycol 400 *	25
Dichloromethane	Polyethyleneglycol 400	40
Dichloromethane	Polypropyleneglycol 700	25
Dichloromethane	Dimethoxyethane	25
Methanol	Polyethyleneglycol 400	25

* Note: The quantity of co-solvent was increased from 1mmol to 3 mmol.

The epoxidation of α-methylstyrene was also attempted, but only starting material was recovered.

The lack of any trace of cholesterol epoxide, i.e. no oxidation having taken place at all, indicated that the adduct was not broken down in the reaction. The hydrogen bonding was sufficiently strong to keep the adduct intact through the relatively harsh conditions of the epoxidation, even when using co-solvents to increase solubility.

A more useful hydrogen peroxide adduct would need to have very weak, easily disrupted hydrogen bonding. Less harsh reaction conditions would be required for supplying available oxygen to the reaction. A vast excess of the adduct would not be needed (as in the case of UHP) to saturate the solvent with available oxygen to reduce the formation of any of the explosive diacyl peroxide when using carboxylic anhydrides. Also less of the adduct would be required to form peracids from the corresponding anhydrides.

Attempted Chiral Epoxidations.

All of the epoxidations described so far have been racemic. The peracids are not stereoselective oxidants. Three approaches were undertaken in order to try to attain chirality in the epoxidation of alkenes using hydrogen peroxide adducts.

i) Adducts formed *in situ*.

The first approach taken in this chiral oxidation work was to form hydrogen peroxide adducts in the reaction mixture, by adding reagents to co-ordinate either the peracid or hydrogen peroxide. Thus adducts containing various strengths of hydrogen bonding could be formed *in situ*.

This adduct may then influence the epoxidation due to either
a) the functional groups in the adduct co-ordinating to the substrate
or
b) the increased steric bulk of the oxidant allowing only one direction of approach to the substrate.

The epoxidation of α-methylstyrene (reaction 43) was chosen as the "standard reaction" as the oxide (57) is obtained in very good yield when using the UHP/acetic anhydride system.

Chiral reagents were added to the reaction and the product obtained from each oxidation was analysed for any optical activity. Table 13 gives the reagents used:

Table 13

Standard method.

α-methylstyrene	8mmol
UHP	80mmol
Sodium dihydrogenphosphate	72mmol
Acetic anhydride	20mmol
Dichloromethane	50mls
Reaction time	17 hours
Reaction temperature	25°C

Table 14

Reagent added	α-Methylstyrene,% epoxide	Optical Activity
Using UHP / acetic anhydride as oxidant.		
---	81	None
Diethyl d-tartrate	73	None
Diethyl d-tartrate/$Ti(OPr)_4$	30	None
Diethyl l-tartrate/$Ti(OPr)_4$	48	None
Sparteine	0	---
l-Phenylalanine	0	---
Using 80% hydrogen peroxide / acetic anhydride as oxidant.		
l-Phenylalanine	0	---
Benzamide	68	None
l-Alanine	37	None
Peptide A*	0^	---
Peptide B*	0^	---
Peptide C*	0^	---

*See appendix 2

^Starting material recovered

1) Amino acids.

The formation of α–methylstyrene oxide (reaction 43) was considerably reduced or did not occur at all and the substrate was often recovered intact. Any product that was isolated showed no optical activity.

Competing side reactions lower the apparent concentration of peracid, thus lowering the quantity of peracid available for co-ordination with any unreacted amino acid and reaction with α-methylstyrene (56). Hence no chiral induction from the adduct is observed. The amine group of the amino acid is probably oxidised by the peracid and any residual peracid then

goes on to epoxidise α-methylstyrene (57).

2) Amides and Peptides.

The yield of α-methylstyrene oxide (57) was not significantly affected by the addition of benzamide. This simple non-chiral amide was used for an initial determination of the effect of amides on the yields rather than the optical activity.

Simple peptides however, were found to completely hinder the epoxidation process. The peptides contained no free amine groups to compete with the substrate for available peracid. (The acid groupings were also protected)

Peptide C was completely recovered from the reaction. It is possible that the peptide co-ordinated to the peracid (or hydrogen peroxide) so efficiently that it prevented the oxidant from coming into contact with the substrate.

Peptide A and B were not recovered from the mixture. IR of the crude colourless thick oils showed large ester and amide peaks corresponding to the peptides used in the epoxidation, indicating that the peptides were left intact throughout the epoxidation.

3) Diethyl Tartrate.

Diethyl tartrate had very little effect on the epoxidation of α-methylstyrene (56). The isolated product was not optically active showing no evidence for catalytic chiral induction having taken place.

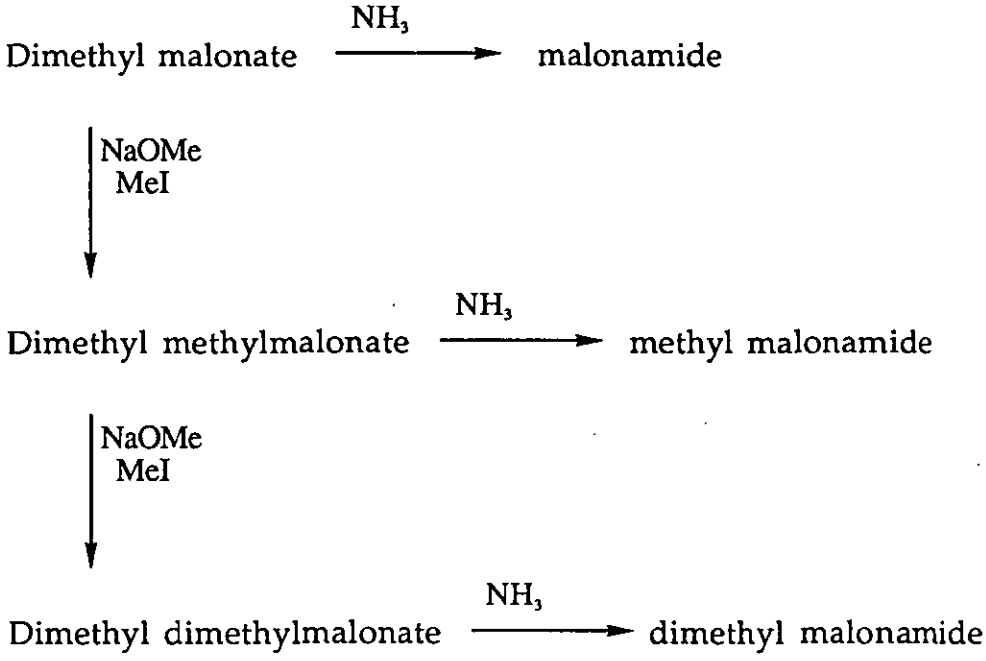
With diethyl tartrate and titanium isopropoxide, the yields of epoxide fell considerably. This reagent probably co-ordinates to the hydrogen peroxide hindering the formation of the peracid and/ or the epoxidation reaction itself.

ii) Adducts derived from malonamide.

To determine the viability of chiral malonamide derivatives as a route to hydrogen peroxide adducts capable of chiral oxidations, initial reactions were performed on dimethyl malonate and simple substituted malonates. Corresponding malonamides were produced, then converted into hydrogen peroxide adducts (scheme 17). However, these simple adducts proved difficult to make.

Formation of malonamides.

The conversions of the malonates to malonamides worked on relatively small scales (10-25mmol of malonate). Increasing the alkyl substitution on the malonate gave poorer yields or even no malonamide product at all.



Scheme 17

Formation of the adducts.

a) Malonamide + 50% H_2O_2 .

On addition of the hydrogen peroxide, effervescence was immediately apparent as the hydrogen peroxide rapidly destroyed the malonamide. No adduct was formed or starting material recovered.

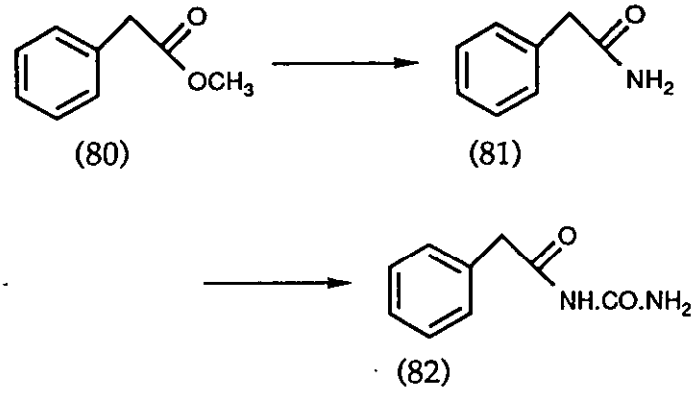
b) Methyl malonamide + 50 $\%H_2O_2$.

On addition of the hydrogen peroxide a small amount of solid was formed, but it possessed no AVOX.

iii) Chiral amide-hydrogen peroxide adducts.

Relatively simple amides were used at first to investigate the best way to form the amides (and then the adducts), in the aim that more complex amides could then be used.

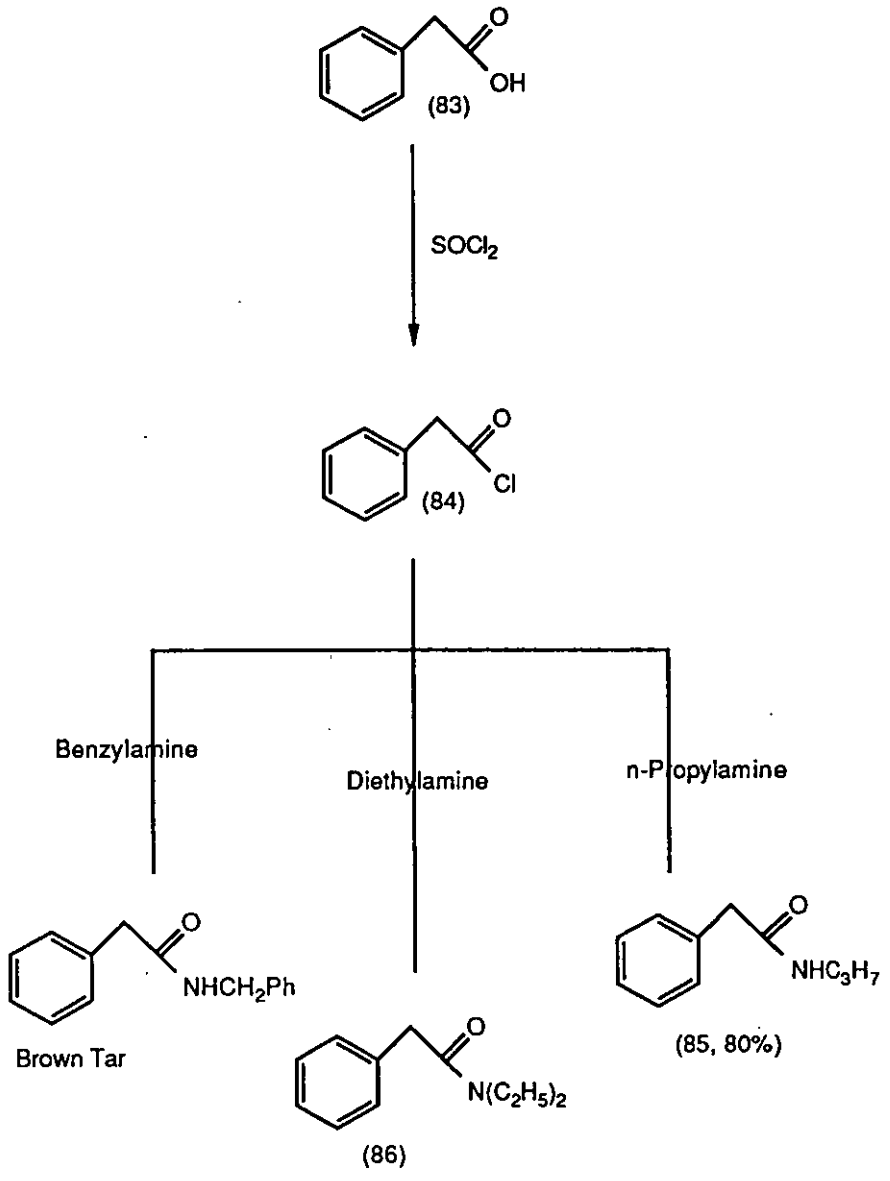
Various methods were used to try to convert methyl phenylacetate (80) into the corresponding amide (81) and also the urea (82), scheme 18. However these compounds proved difficult to make.



(80) (81) (82)

Scheme 18

Phenylacetic acid (83) was used in an alternative route, by converting the acid into the acid chloride (84), then via various amines to produce a number of amides, shown in scheme 19.



Scheme 19

It was attempted to convert phenyl acetamide (81) and N-propylphenyl acetamide (85) into hydrogen peroxide adducts. However, each experiment resulted in the recovery of a very impure amide (as a brown oil).

Due to significant problems in the formation of these adducts, methods were tried using the even simpler amide, benzamide. Crystalline solids were obtained, but titrated zero AVOX content, and analysis showed the product to be recovered starting material, i.e. the hydrogen peroxide did not co-ordinate to the amide.

Alkaline Hydrogen Peroxide Oxidation.

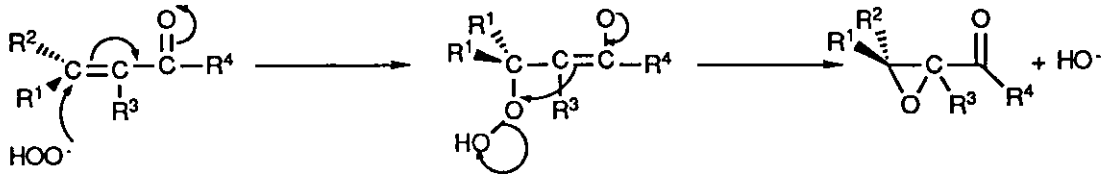
Introduction.

Electron-deficient double bonds, such as those conjugated to carbonyl groups are susceptible to Michael addition by peroxyanions[116], typically alkaline hydrogen peroxide (87), generated from hydrogen peroxide and sodium hydroxide[117] (reaction 55).

$$H_2O_2 + NaOH \rightleftharpoons HOO^- + H_2O + Na^+ \quad (55)$$

(87)

The generally accepted mechanism[118] is shown in scheme 20.

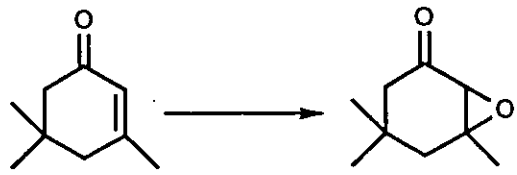


Scheme 20

Note: This type of epoxidation is not stereospecific i.e. *cis* and *trans* isomers of 3-methyl-3-penten-2-one both give 3-methyl-*trans*-3,4-epoxy-2-pentanone[119].

Alkaline hydrogen peroxide is reported to oxidise alkenes such as α,β-unsaturated ketones[119], aldehydes[120], nitriles[121], sulphones[122] and also nitroalkenes[123,124].

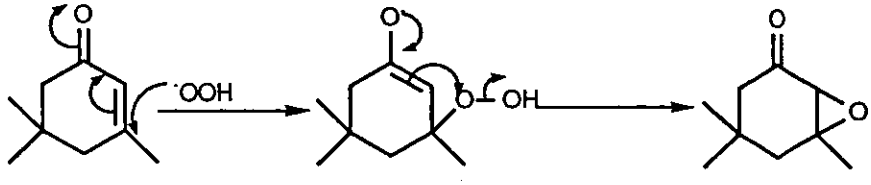
A typical example of this type of alkaline hydrogen peroxide oxidation, is the epoxidation of isophorone[125](88), (reaction 56).



(88) (89) (56)

The above reaction is successfully imitated giving a corresponding product yield, using the equivalent amount of UHP (instead of hydrogen peroxide), with the base to generate the peroxyanion, (reaction 57).

$$NH_2CO.NH_2.H_2O_2 + NaOH \longrightarrow HOO^- + H_2O + NH_2CO.NH_2 + Na^+ \quad (57)$$



(88) (89, 68%)

Scheme 21

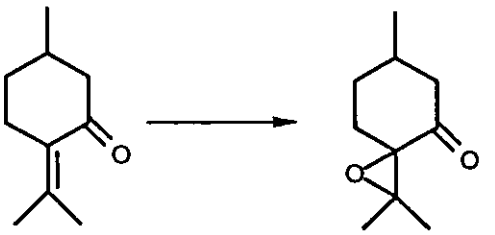
Note: The alkene in isophorone is so electron deficient that it is deactivated towards attack of even strong peracids. Thus, isophorone was recovered when the epoxidation was attempted using trifluoroperacetic acid.

Summary, table 15

Oxidant	Yield of Epoxide,%
UHP/NaOH	68
30% H_2O_2/NaOH	72
UHP/TFAA	0

Further epoxidations of alkenes conjugated to carbonyl groups were achieved using the alternative (UHP/ base) method of generating the peroxyanion.

Epoxidation of Pulegone (90).

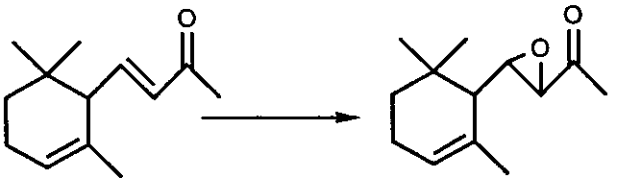


(90) (91, 50%) (58)

The IR of the product (91) showed that the carbonyl group was converted from an α,β-unsaturated ketone, (1682cm^{-1}), into an isolated ketone, (1720 cm^{-1}), along with the complete removal of the alkene group (1612 cm^{-1}) from pulegone (90).

Epoxidation of α-Ionone.

At the 3,4-position there is a relatively nucleophilic endocyclic double bond. The other, at the α',β'-position, is conjugated to the carbonyl group.



(92, 68%) (59)

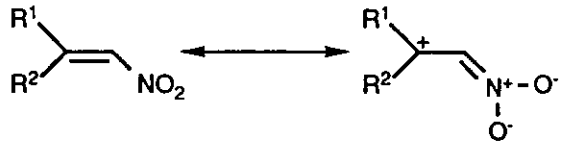
The alkene at the 3,4-position is readily epoxidised by peracetic acid, see page 42. The exocyclic alkene is so electron deficient that it is untouched by peracid oxidation.

Epoxidation of this bond only takes place by the use of nucleophiles, e.g. peroxyanions. Reaction of α-ionone with UHP and sodium hydroxide, affords a relatively high yield of the corresponding α',β'-epoxide.

In these reaction conditions the electron rich endocyclic alkene is, as expected, left intact by the nucleophile. Therefore, prudent choice of reagents allows for selective epoxidation of the appropriate alkene residue.

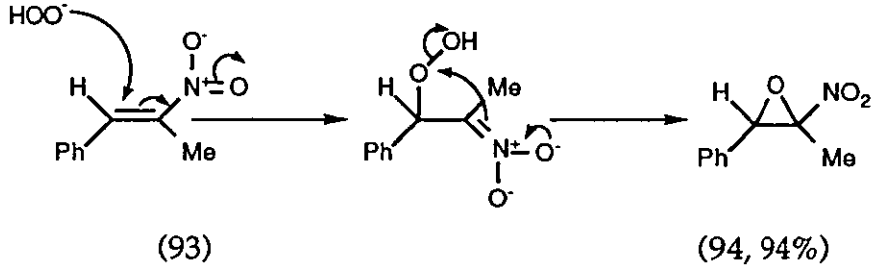
The Epoxidation of Nitroalkenes.

Nitroalkenes contain very electron deficient double bonds due to the mesomeric electron withdrawal by the nitro group, scheme 22.



Scheme 22

Using urea-hydrogen peroxide and sodium hydroxide in methanol, an example of this type of compound, β-methyl-β-nitrostyrene (93) was successfully epoxidised, giving a yield exceeding the literature[123] value, see scheme 23.

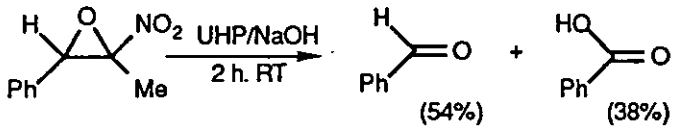


(93) (94, 94%)

Scheme 23

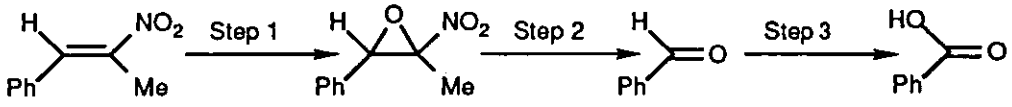
Note: This nitrostyrene (93) was completely resistant to peracid attack. Attempted epoxidations using UHP/ acetic anhydride, and also UHP/ trifluoroacetic anhydride, resulted in the complete recovery of starting material.

Quantitative yields of nitroepoxide (94) were obtained rapidly, at moderately low temperature (between 0 and 5°C). However, using concentrations of sodium hydroxide greater than 2N, an exothermic reaction occurred and, the yellow colour of the nitrostyrene disappeared even before the addition of base was complete. The product isolated in each of these cases was benzoic acid (95).



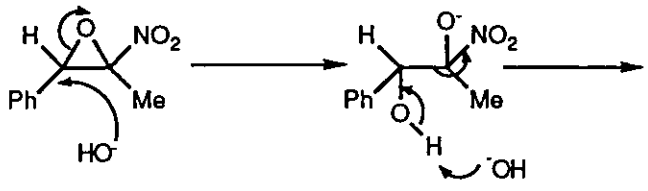
(62)

Each of the three reactions shown below are known to occur individually, thereby supporting the proposed mechanism, summarised in scheme 25.

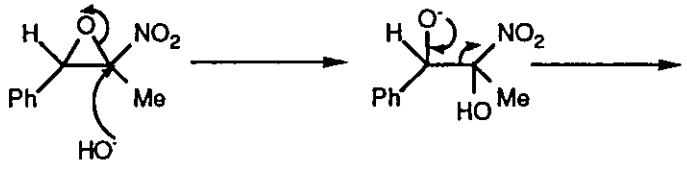


Scheme 25

It is not clear which position of the epoxide was attacked by the base. The C-NO_2 is more electrophilic than the C-Ph and would therefore seem more likely to be attacked by nucleophiles, schemes 26 and 27. Both initial steps would lead to the same overall product.



Scheme 26



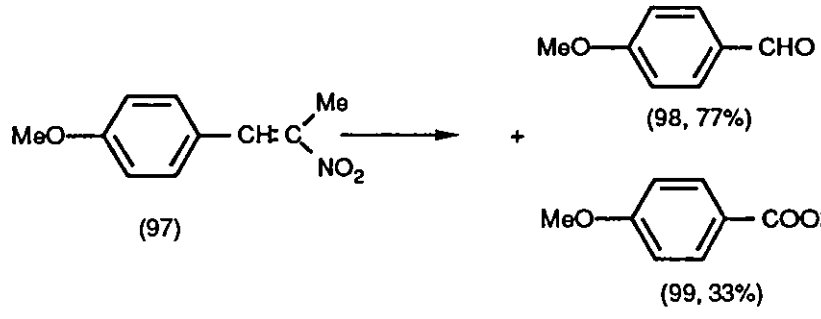
Scheme 27

The epoxidation of 4'-methoxy-β-methyl-β-nitrostyrene (97) was also attempted. However, no epoxide was isolated. Depending upon the length of time and concentration of base used, various amounts of starting material, 4-methoxybenzaldehyde (98) and 4-methoxybenzoic acid (99) were

produced.

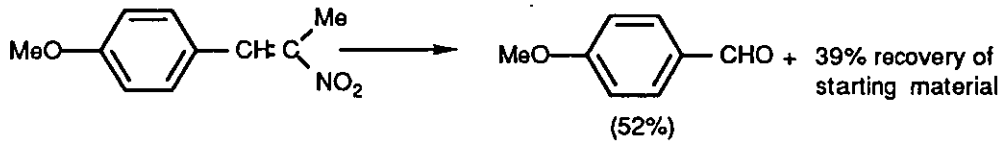
e.g.

a) 6N sodium hydroxide + UHP



(63)

b) 2N sodium hydroxide + UHP

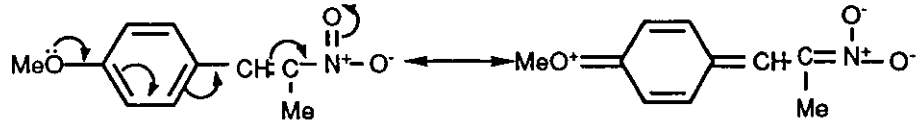


(64)

c) 1N sodium hydroxide gave complete recovery of starting material.

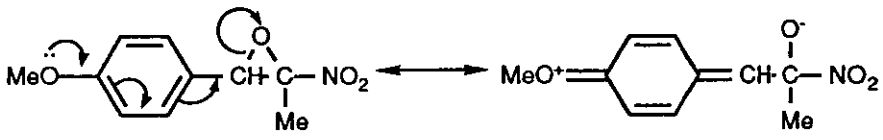
The implication of these results being that the epoxide was formed, but was very unstable and, immediately reacted with base to form the benzaldehyde (98). This occurrence must be due to the effect of the methoxy group on the aromatic ring.

This mesomeric effect caused increased stability of the starting material, thereby making it more difficult for epoxidation to take place, scheme 28.



Scheme 28

It also promotes ring-opening of any formed epoxide (100), scheme 29:



(100)

Scheme 29

The positive mesomeric effect of the methoxy group would help to explain why the benzaldehyde derivative (98) was rapidly formed, even at low concentrations of sodium hydroxide.

CHAPTER 2

BAEYER-VILLIGER REACTION.

The Baeyer-Villiger Reaction.

Introduction.

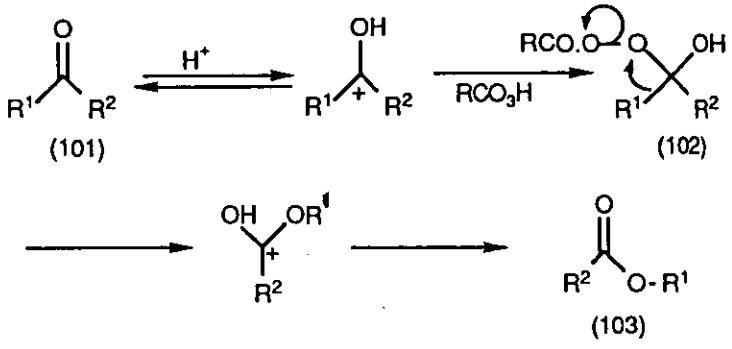
The oxidation of ketones by peracids (or hydrogen peroxide) forming esters was first reported by Baeyer and Villiger[29] in 1899, scheme 30. The initial reactions utilized Caro's reagent to convert menthone, tetrahydrocarvone and camphor into lactones. Since then a large variety of ketones (and aldehydes) oxidised by a wide range of peracids have shown that the Baeyer-Villiger reaction is widely applicable[15,30-32].



Scheme 30

Due to the mild reaction conditions, reasonable yields and selectivity involved in the reaction, it has proved useful in organic synthesis and as a method of analysis[126].

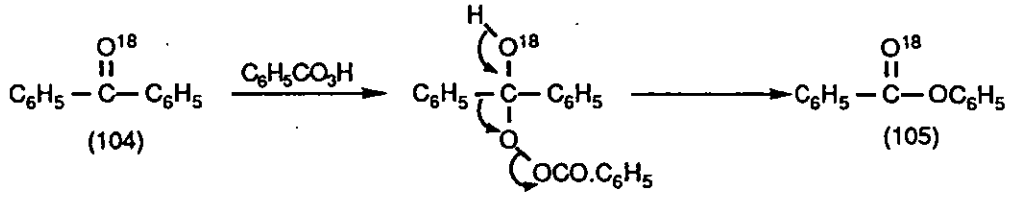
Mechanism.



Scheme 31

The mechanism (scheme 31) is believed to proceed by initial protonation of the ketone (101), followed by nucleophilic attack from the peracid forming the tetrahedral intermediate (102). Loss of RCO_2^- and R group migration to the electron deficient oxygen gives the protonated form of the ester (103).

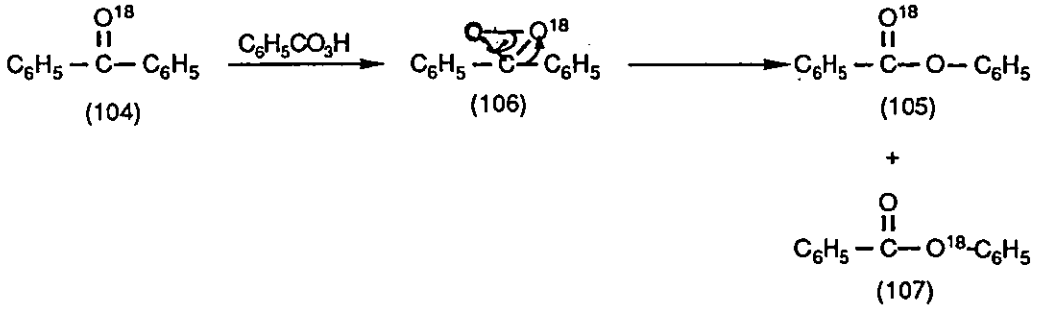
The above "Criegee" mechanism[127] is supported by Doering and Dorfman[128]. Oxidation of benzophenone-O^{18} (104) by perbenzoic acid gave an ester containing oxygen-18 labelling only at the carbonyl oxygen (105), proving that the rearrangement is intramolecular, scheme 32.



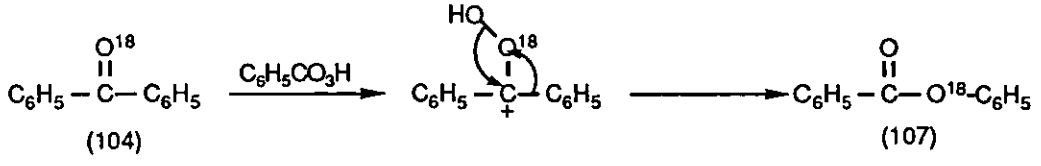
Scheme 32

Other proposals for the mechanism (the "Wittig" and Baeyer's original "oxonium" ion, a dioxirane, route[128]) (scheme 33), were incompatible with the experimental evidence.

"Oxonium" intermediate (106):



"Wittig" intermediate:



Scheme 33

Intermediates involved in the reaction would result in scrambling of the oxygen-18 label (105 and 107), from the "oxonium" intermediate (106), or give phenyl benzoate ether-O^{18} (107), for the "Wittig" intermediate.

Migratory Aptitude.

a) Alkyl group migration.

In an unsymmetrical ketone, the more nucleophilic alkyl group is the more likely to migrate, as it is more effective in stabilising the partial positive charge that develops on the electron deficient oxygen. Doering and Speers[129] gave migratory ability (or migratory aptitude) of alkyl groups in the approximate order of:

tertiary alkyl> secondary alkyl> primary alkyl> methyl

An alternative to the above electronic effect involves steric acceleration[130,131] by migration of the bulky alkyl group. Migration into the transition state is assumed to occur trans to the leaving carboxylic acid, i.e. the migrating larger R group staggers the C-C bond between the OH and smaller alkyl group (108), scheme 34.



(108)

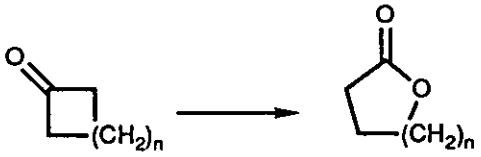
Scheme 34

b) Aryl Group Migration.

Electron donating groups increase the migratory aptitude of aryl groups[129,130]. This is due to an increase in π -electron stabilisation afforded from the substituent. The transition state structure is believed to resemble a "phenonium" ion[130]. (Scheme 34; R^2 = phenyl, R^1 = methyl)

Cyclic Aliphatic Ketones.

The oxidation of cyclic ketones by peracids[133] gives lactones in good yields, whereas alkaline conditions often lead to relatively low yields[134].



Scheme 35

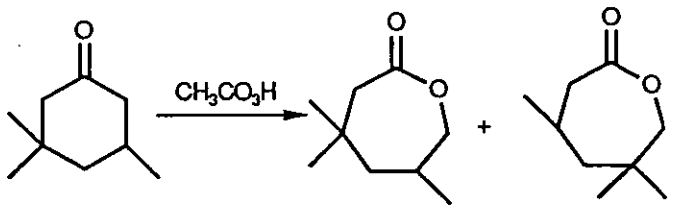
Baeyer-Villiger reaction of simple unsubstituted cyclic ketones (n= 1 to 14) is cited by several authors[133,135], scheme 35. Reaction rates for this oxidation tend to decrease for ring sizes greater or less than cyclohexanone[135]. This is due to increases in tortional or angle strain involved in formation of the tetrahedral transition state (102).

Acid sensitivity of lactones is a major problem involved in the Baeyer-Villiger reaction and ring opening occurs very readily e.g. cycloheptanone is reported to give equal amounts of ξ-enantholactone and pimalic acid, while cyclooctanone gives primarily suberic acid[133].

Effects of Substituents.

Starcher and Phillips[133] reported oxidation of a number of substituted cyclohexanones. Although two products are theoretically possible, cyclohexanones containing alkyl substituents at the 2-position gave a single product, ε-methylcaprolactone. This result illustrates that methine groups migrate more readily than methylenes due to the larger inductive effect stabilising the transition state.

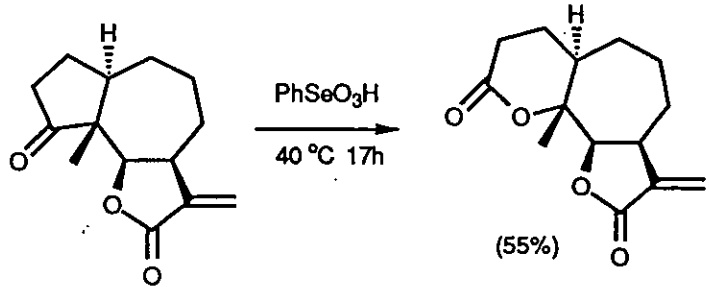
For substitution other than at the 2-position, both possible products are obtained due to the less pronounced effect of the more distant substituents, e.g. 3,3,5-trimethylcyclohexanone (109) gave β,β,δ- (110) and β,δ,δ-trimethylcaprolactone (111), (reaction 65).



(109) (110) (111) (65)

Typical reagents for the Baeyer-Villiger reaction are trifluoroperacetic acid[136,137] and *m*CPBA[138,139,]. The latter in particular is utilized in organic synthesis of lactones, especially in steroids.

Several novel peracids are reported to oxidise cyclic ketones. For example, benzeneselenic acid[140] has been used for simple ketones but also for the production of psilostachyn C (112) from the corresponding ketone (113), (reaction 66).



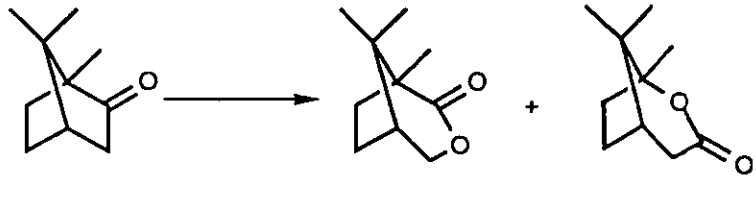
(66)

(113) (112)

Bicyclic Ketones.

Peracid oxidation of a number of bicyclic ketones have been studied and are cited in a review by Krow[141].

Bridgeheads were found to readily migrate resulting in the formation of mixtures of lactones e.g the oxidation of camphor (114), scheme 36. The ratio of lactone products (115) and (116) depends on the reaction conditions.

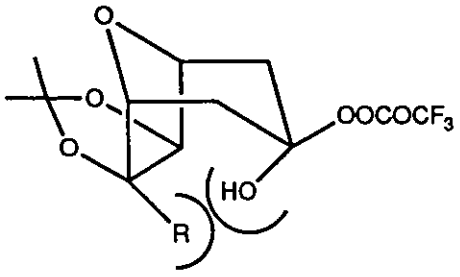


(114) (115) (116)

Scheme 36

The observations of substituent effect on migration were exemplified by R. Noyori *et al,*[142] . The effect of various substituents at α,β and γ positions 8-oxabicyclo[3.2.1]octan-3-ones (117) were reported.

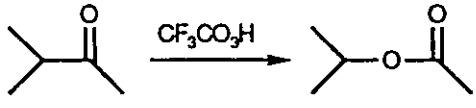
For example, the size of the substituents can be crucial in Baeyer-Villiger oxidation of these compounds. Increasing the bulk reduces the rate of reaction due to retardation of formation of the transition state (117). In some cases large (e.g. γ-t-butyl) substituents were found to completely hinder the reaction and no lactone was produced.



(117)

Alicyclic Aliphatic Ketones.

Trifluoroperacetic acid[137] has proved to be an exceptional reagent for the oxidation of aliphatic ketones, (reaction 67) so much so, it has been used in an analytical method for the determination of simple ketones[126].



(67)

In contrast to other peracids, the conversion of simple ketones into esters by trifluoroperacetic acid is rapid, giving good yields. This is believed to be due to facile heterolysis of the O-O bond induced by the highly electronegative trifluoroacetate group[137].

Other reagents quoted for high yields of ester formation are MMPP[98] and hexafluoroacetone-hydrogen peroxide[143].

Alkyl Aryl Ketones.

The presence of an aryl group significantly decreases the rate of reaction of ketones with peracids. Conjugation lowers the reactivity of the double bond towards attack of nucleophiles[144]. A general series of migratory

aptitude is shown below for the following groups:

Tertiary alkyl> secondary alkyl> primary alkyl, phenyl> methyl

Meta and *Para* Substitution.

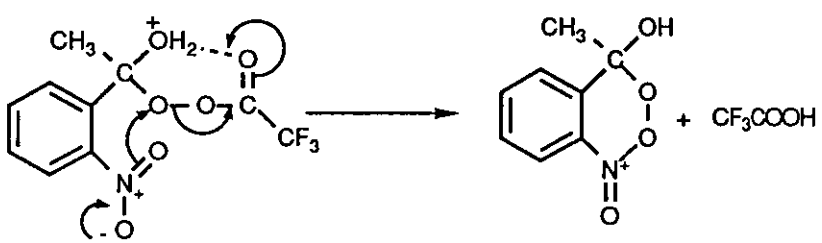
Many examples of the oxidation of *para* and *meta* substituted acetophenones[130,132] and benzophenones[129] (investigations of the variation in rate with substituent, mentioned previously) are cited in the literature. Similar trends in rate of reaction are observed for substituents in both types of compound:

$$p\text{-MeO} > p\text{-Me} > H > p\text{-Cl} > p\text{-Br} >> p\text{-}NO_2$$

This trend is due to *ortho* and *para* directing groups contributing lower energy resonance structures in the transition state, causing a smaller activation energy for the reaction, increasing the rate of oxidation compared to that of the unsubstituted ring. Halide and nitro groups have the opposite effect causing a decrease in rate of reaction.

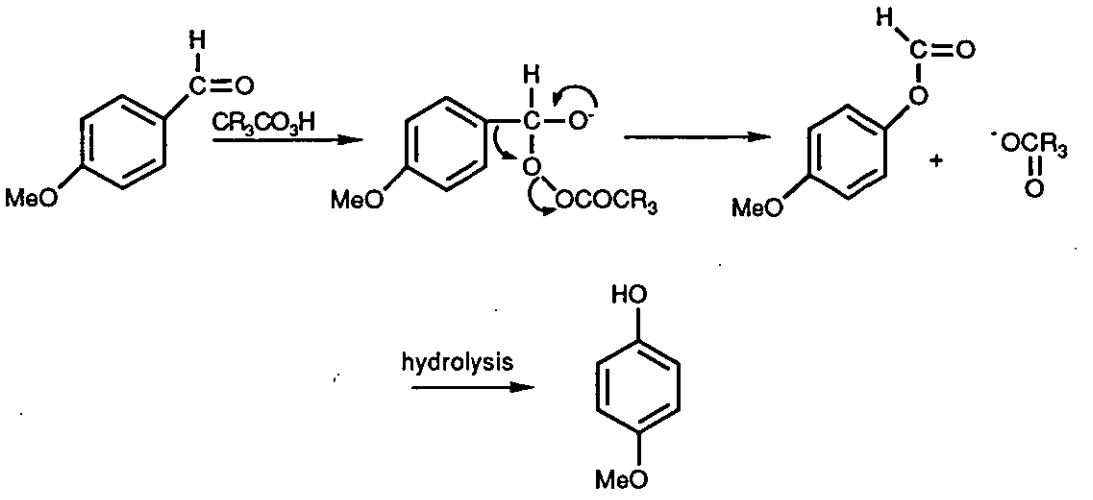
Ortho Substitution.

The product attained from the oxidation of *ortho* substituted acetophenones is subject to a number of conditions. In general the corresponding phenyl acetates are formed. However, a small amount of methyl group migration is observed in the peracetic acid oxidation of *o*-nitroacetophenone to *o*-nitrophenol[145] (less than 10%) with the major product formed from aryl migration. The nitro group is believed to be involved in the decomposition of the transition state, encouraging methyl group migration, scheme 37.



Scheme 37

Similar observations are noted for *o*-hydroxyacetophenones[146-149]. The formation of phenols via intramolecular rearrangement is also observed for aryl aldehydes provided a methoxy, amino or hydroxyl group is present at the *ortho* or *para* position. This oxidation is known as the Dakin Reaction; the mechanism is shown in scheme 38.



Scheme 38

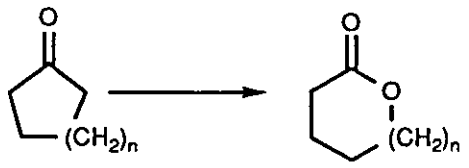
The peracid (or peroxide) attacks the carbonyl, followed by migration of the phenyl group to produce a formate ester. Hydrolysis removes the formate group forming a phenol. Peracetic acid is reported give low yields for this reaction. However *m*CPBA[149,150] and alkaline hydrogen peroxide produce phenols from o-methoxy substituted aryl aldehydes and acetophenones in good yields.

Results and Discussion.

Trifluoroperacetic acid generated from trifluoroacetic anhydride and UHP was found to be an excellent reagent for the oxidation of a number of ketones into the corresponding esters.

a) Cyclic Aliphatic Ketones.

The Baeyer-Villiger oxidation of cyclic ketones produced lactones, scheme 39:



Scheme 39

Table 16

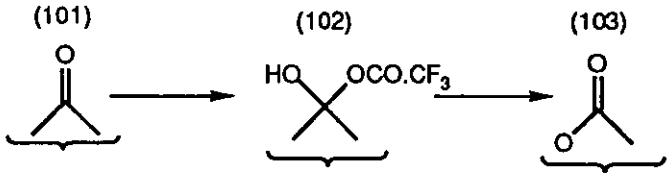
Entry	Substrate	Yield of Lactone,%
118	Cyclopentanone	41
119	Cyclohexanone	62
120	Cycloheptanone	85*

* Compound 121

A low yield for δ-valerolactone was attained, table 16, entry (118). For the five membered ring, the conversion of the sp^2 carbon in the ketone (101, scheme 40) to an sp^3 in the transition state (102) involves an increase in tortional strain; this requires a substantial increase in energy and therefore involves a less energetically favoured transition state. The amount of product formation was reduced.

For the six membered ring, table 14 entry (119), the converse is true; the formation of the sp^3 in the transition state (101) decreases the tortional strain in the molecule producing a more energetically favoured transition state, thus increasing the amount of product obtained.

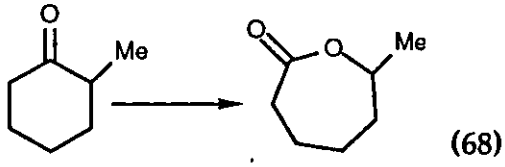
The formation of the oxacin-2-one (121) is observed due to fact that the ring is conformationally flexible enough to twist and minimise any tortional strain that occurs.



Scheme 40

Substituted Cyclohexanones.

The product formed from the oxidation of 2-methylcyclohexanone (122) was 7-methylcaprolactone (123), reaction 68. Structure determination by proton and carbon-13 NMR, shows the methine group adjacent to the oxygen of the ester, in preference to the methylene group. This illustrates the generalisation that secondary alkyl groups have a higher migratory aptitude than primary alkyl groups.



(68)

(122) (123, 63%)

The results obtained with other substituted cyclohexanones are shown in table 17 below:

Table 17

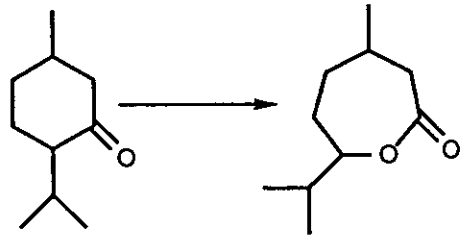
Substituent	Yield of Lactone, %
4-methyl	74
4-t-butyl	89
2,6-dimethyl	0

The oxidation of 2,6-dimethylcyclohexanone proved to be more

difficult. Various reaction conditions resulted in the complete recovery of starting material. It is likely that the approach of bulky electrophiles is considerably hindered by methyl groups situated α and α' to the carbonyl, so much so that no lactone is formed.

Oxidation of Menthone (124).

One of the original examples of Baeyer-Villiger oxidations using permonosulphuric acid (Caro's reagent) involved the oxidation of menthone, (reaction 69).



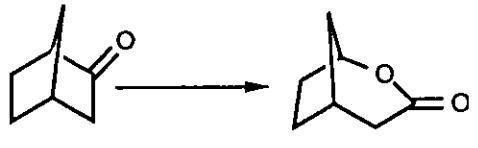
(69)

(124) (125, 98%)

A quantitative yield of this product was attained using trifluoroperacetic acid. A single compound was isolated, again illustrating the higher migratory aptitude of CHR versus CH_2. This product proved to be a single isomer, i.e. migration of the chiral centre occurred with complete retention of configuration.

Bicyclic Ketones.

Norcamphor (126) was readily converted into the corresponding lactone (127) in reasonable yield.



(70)

(126) (127, 76%)

However, with a methyl substituent adjacent to the carbonyl, for example in camphor or fenchone, no lactone formation was observed with

only starting material being recovered.

As mentioned previously, methyl groups, when close to the reacting centre, may hinder the approach of the electrophile, preventing the bulky oxidant reacting with the protonated ketone. This is particularly true if the UHP is still hydrogen bonded to the peracid.

b) Acyclic Aliphatic Ketones.

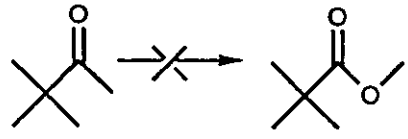
Oxidation of Pinacolone (128).



(71)

(128) (129, 96%)

An example of quaternary carbon migration is observed in the oxidation of pinacolone, (reaction 71). No trace of the alternative product was observed, indicating that the methyl group has a much lower migratory aptitude than the tertiary alkyl.



(72)

(128)

Oxidation of Diethyl Ketone (130).

Diethyl ketone (130) gave poor yields of ester (131), illustrating the poor migratory aptitude of primary aliphatic groups.

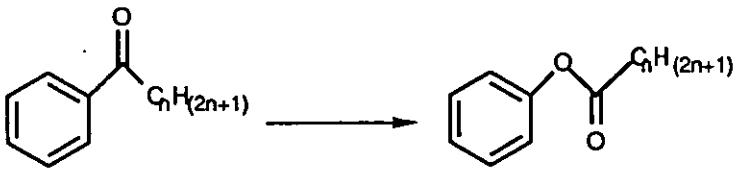


(73)

(130) (131, 48%)

c) Aromatic Ketones.

The oxidation of acetophenone and the homologous series was examined:



Scheme 41

Table 18

n	Yield of Phenyl Ester, %
1	83
2	94
3	86
4	91

In each case, table 18, the only product formed was due to migration of the phenyl group. The number on the aliphatic chain had little consequence, therefore the migratory aptitude of phenyl is greater than that of primary alkyl groups.

(The +m aryl group was more effective in stabilising the electron deficient oxygen).

Substituted Acetophenones.

Substituents will affect the nucleophilicity of the ring and therefore should have an influence on the migratory aptitude. Oxidations of substrates containing various groups at different positions of the aromatic ring gave some rather interesting results.

i) *Ortho* substituted Acetophenones.

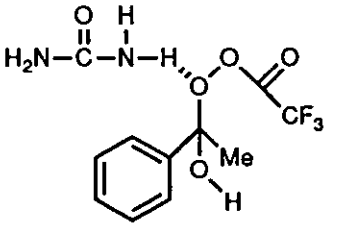
Table 19

Substituent	Yield, %
—	83
o-methoxy	76
o-chloro	75
o-hydroxy	0

In contrast to Hawthorns[130] findings, electron donating (e.g. MeO) and electron withdrawing substituents (e.g. Cl) did not have any significant effect on the yield of phenyl acetate in this method of oxidation, table 19. The nucleophilicity of the phenyl ring of *o*-chloroacetophenone is lower than acetophenone, however the migratory aptitude is not low enough to be in competition with migration of the methyl group. No trace of the alternative product was observed in the NMR spectrum of the crude material.

The methoxy group also had no effect on the oxidation. Both electron rich and electron stripped substituted aromatic rings proved sluggish to convert into the corresponding phenyl acetates requiring long reaction times, relatively large excesses of UHP/ trifluoroacetic anhydride, and, in most cases, the crude products had to be re-oxidised to increase the product yield.

It is possible that UHP retards migration of the phenyl group by interacting with the transition state (132). This hindering of the transition state slows down the formation of the product.



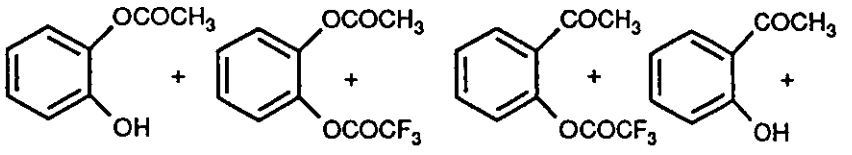
(132)

Another consideration is the electronic effect of the hydrogen bonding

between the adduct and the transition state involved in the reaction. The migration of the phenyl group occurs to stabilise the positive charge formation on oxygen as the trifluoroacetate group leaves. However, if the adduct is hydrogen bonded to the transition state, the formation of this partial positive charge is seriously retarded, hence, the rate of migration of the phenyl group is reduced.

Attempted Oxidation of *o*-Hydroxyacetophenone.

No *o*-hydroxyphenyl acetate was isolated from UHP/ trifluoroacetic anhydride. Tlc analysis showed the presence of so many products that both the phenolic group and the ketone must have reacted. There are a number of products possible due to the esterification of the hydroxyl group both in the starting material and in the intended product. Examples are shown in scheme 42. Peracids are also known to react with phenols to produce quinones[148,151], thereby adding to the product proliferation.



Scheme 42

ii) *Para*-Substituted Acetophenones.

Table 20

Substituent	Yield,%
p-methyl	81
p-methoxy	86

The yields of *p*-substituted phenyl acetates are equal to or higher than o-substituted, table 20. The reaction times were of similar length and conditions required for the oxidations were just as severe. This may be due to interference of UHP with the transition state as described previously.

iii) *Meta* Subtituted Acetophenones.

Table 21

Substituent	Yield,%
m-methyl	68
m-methoxy	---

The yields were significantly lower for *m*-substituted products than the *ortho* and *para*, table 21. The reaction involving *m*-methoxyacetophenone would not go to completion, even after several repeated oxidations on the same crude material.

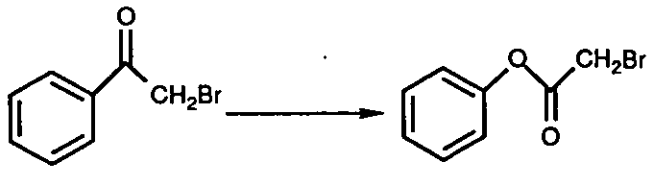
The positive inductive (Me-) and mesomeric (MeO-) effects of the *para* and *ortho* substituents aid the formation of the transition state, hence the extent of the oxidation. However, these effects are not constructive for substituents at the *meta* position and stabilisiation of the transition state due to this phenomena does not occur. Slight negative inductive and mesomeric effects reduce the electron density at the carbonyl position to give a reduction in the stabilisation of the transition state, hence reducing the yield of aryl acetate.

iv) Disubstituted Acetophenones.

Oxidation of 3,4-dimethylacetophenone gave 66% of 3,4-dimethylphenyl acetate. This is a significantly lower yield than *ortho* & *para* substituted acetophenones, possibly due to the influence of the methyl group at the *meta* position.

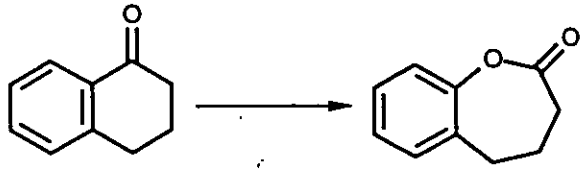
v) α-Bromoacetophenone (133).

The heteroatom reduces the electron density of the methyl group, making it even less likely to migrate. Indeed, no bromomethyl group migration was observed, (reaction 74).



(133) (134, 76%) (74)

Oxidation of 1-Tetralone (135).

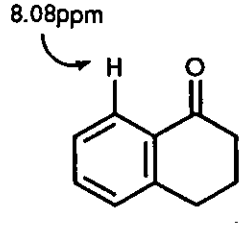


(135) (136, 78%) (75)

1-Tetralone was previously oxidised using perbenzoic acid in a seven day reaction to give 6,7-benzo-ε-hexanolactone[152] (136, 78%). Trifluoroperacetic acid gave a comparable yield in a reaction of only 2 hours. (The literature reports a boiling point for the product, whereas UHP/ trifluoroacetic anhydride forms a product as a pale yellow solid of low melting point, implying that the latter was of higher purity).

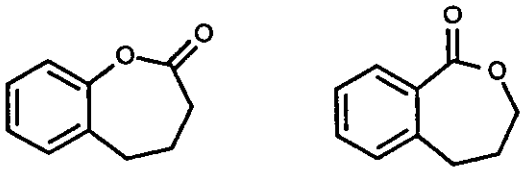
IR analysis showed the ketone carbonyl group (1680cm^{-1}) was converted into a lactone (1760cm^{-1}). The proton NMR spectrum proved more interesting.

The aromatic protons in (135) were split into multiplets (7.16ppm) with one proton at a much lower field to the others at 8.08ppm, illustrating the anisotropy associated with the carbonyl group. (R.H. Martin[153] has investigated this phenomenon by estimating the deshielding effects in aryl ketones).



(135)

The lactone (136) shows a multiplet of 4 protons at 7.16ppm indicating that there is no longer a proton within the influence of the carbonyl group as the C=O has moved its relative position. This supports structure 1, scheme 43, (formed from the more likely migration of the aryl group). Structure 2 is unlikely as it requires a migration of the alkyl group. This would be demonstrated by the presence of a proton in the deshielding region of the lactone carbonyl. However, no such proton is observed.

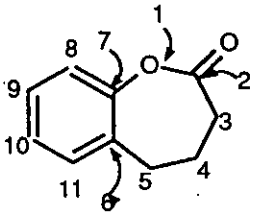


Structure 1 Structure 2

Scheme 43

The mass spectrum and carbon-13 NMR of the lactone (136) were taken, table 22:

Carbon-13 NMR.



(136)

Table 22

Carbon	δppm
2	171.6
3	28.2
4	26.5
5	31.1
6	130.1
11 or 9	129.7
11 or 9	128.3
10	125.9
8	119.2
7	151.8

Indanones.

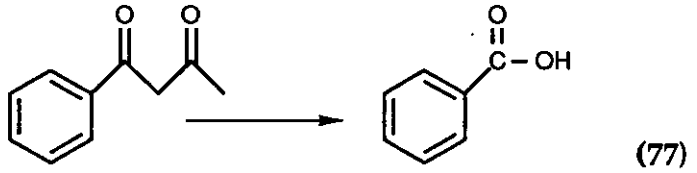
Substrate	Yield of Lactone,%
1-Indanone	76
2-Indanone	61

1- Indanone provides another illustration of the greater migratory aptitude of an aryl group over a methylene group. 2- Indanone (137) is symmetrical , and the only possible migration is that of the methylene group α or α' to the carbonyl group, (reaction 76).



(137) (138, 61%) (76)

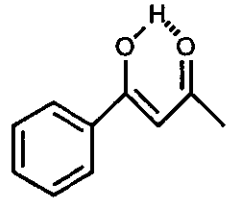
Attempted Baeyer-Villiger of Benzoyl Acetone (139).



(139) (95, 99%) (77)

The oxidation of benzoyl acetone using UHP/ trifluoroacetic anhydride produced benzoic acid (95) in quantitative yield.

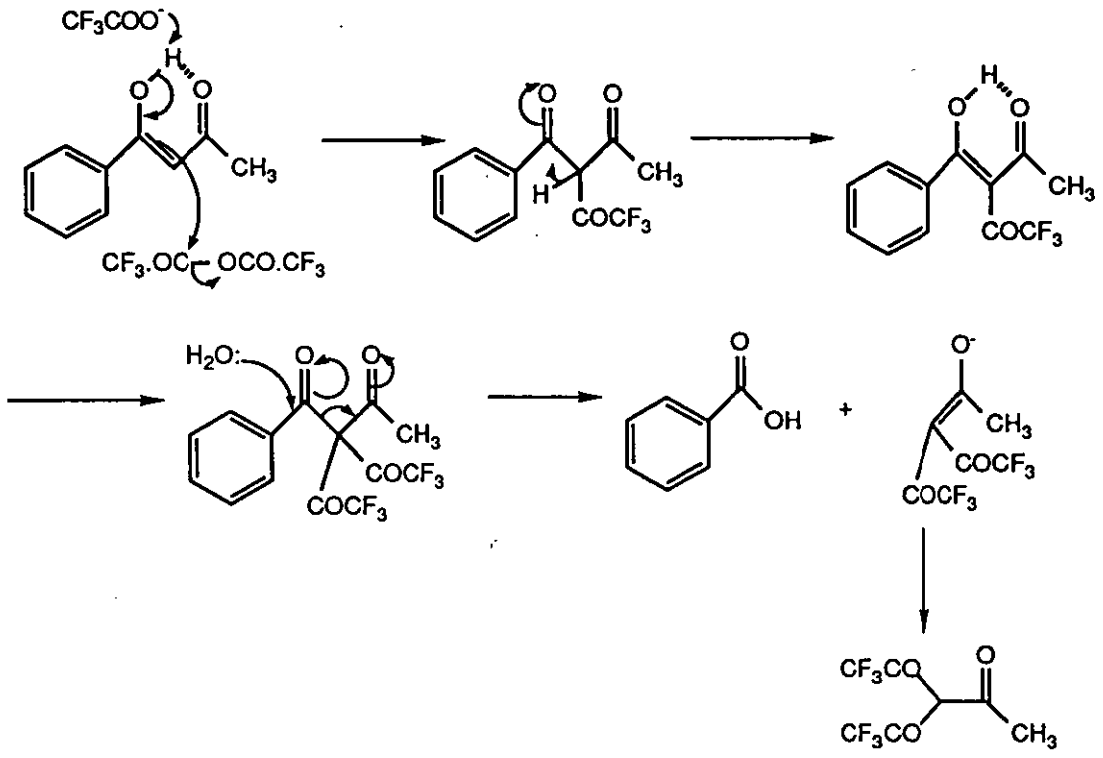
The proton NMR spectrum of the starting material shows that benzoyl acetone exists in the enolised form:-



(140)

It is possible that the conjugated alkene attacks trifluoroacetic

anhydride rather than the epoxidation of the double bond or Baeyer-Villiger oxidation occurring at one (or both) of the ketones, see scheme 44.



Scheme 44

Oxidation of Benzaldehydes.

MMPP and UHP/acetic anhydride oxidise *ortho* and *para* methoxybenzaldehydes into phenols in moderate to good yields, see table 23. MMPP converts *m*-methoxybenzaldehyde into *m*-methoxybenzoic acid, whereas UHP/ acetic anhydride gave complete recovery of starting material. Both oxidants produce benzoic acid from the unsubstituted benzaldehyde. The migrating substituted phenyl group must be more nucleophilic than a simple phenyl group for the Dakin reaction to take place. If the electron deficient rings are used, the Dakin reaction is supressed because oxidation of the aldehyde group to an acid is a major competing process.

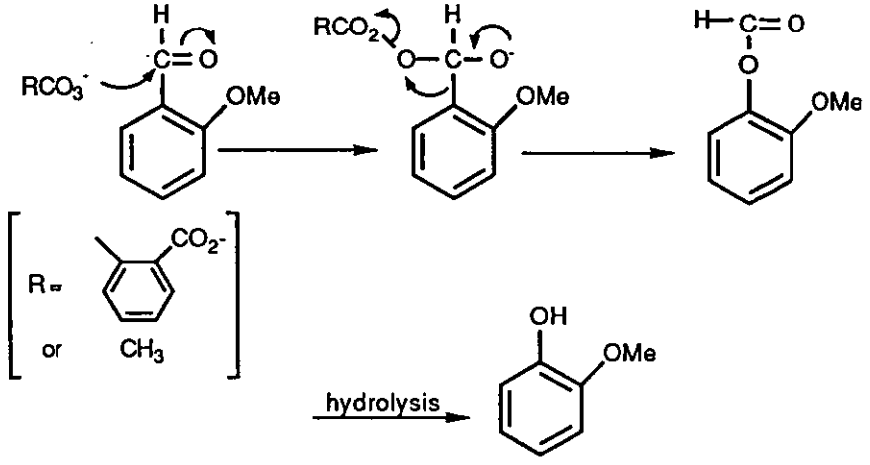
Note: attempted reactions using UHP/ trifluoroacetic anhydride were not successful. Intractable black tars were formed in each case, suggesting that the conditions were too severe.

Table 23

Benzaldehyde	Yield of Product	
	MMPP	UHP/ acetic anhydride
Benzaldehyde	81% benzoic acid	74% benzoic acid
o-Methoxy---	81% guicacol	70% guiacol
m-Methoxy---	71% *m*-methoxy benzoic acid	No Reaction
p-Methoxy---	40% *p*-methoxy -phenol 31% *p*-methoxy benzoic acid	50% *p*-methoxy -phenol 16% *p*-methoxy benzoic acid

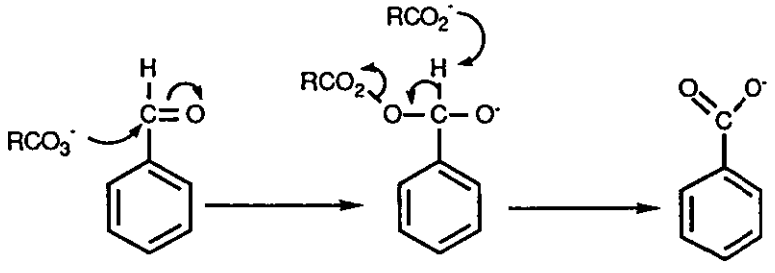
Therefore, the Dakin reaction occurs using MMPP or peracetic acid on *ortho* and *para* methoxybenzaldehydes in addition to the methods cited[149,150], scheme 45 and 46.

Ortho and *Para* Methoxybenzaldehydes.



Scheme 45

Benzaldehyde and *Meta*-methoxybenzaldehyde.

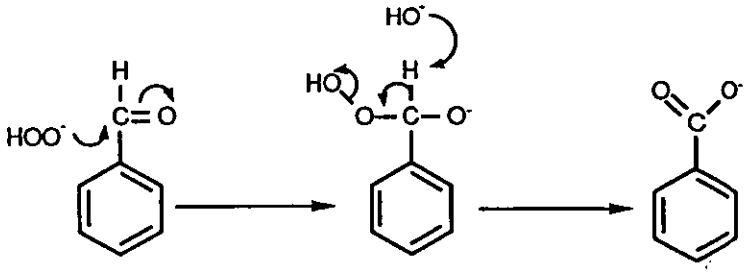


Scheme 46

Which of the above routes taken (oxidation of the aldehyde into an acid or formation of a phenol) depends on the nucleophilicity (hence the migratory aptitude) of the phenyl group. The mesomeric effect of an *ortho* or *para* methoxy group increases the nucleophilicity of the aromatic ring at the potentially migrating bond, whereas a methoxy group at the *meta* position is not capable of producing this effect. Therefore, substrates which have a relatively high ring electron density encourage the Dakin reaction over oxidation to the benzoic acid.

Alkaline UHP.

The peroxyanion generated from the alkaline UHP converts methoxy substituted benzaldehydes into the corresponding benzoic acids in high yields, scheme 47.



Scheme 47

Several substituted benzaldehydes were oxidsed using UHP/ sodium hydroxide, the results are shown in table 24 below:

Table 24

Benzaldehyde	Yield of Benzoic Acid, %
Benzaldehyde	94
o-Methoxy---	90
m-Methoxy---	95
p-Methoxy---	72
3,4-Dimethoxy-	63

The reaction conditions for the above examples are basic, therefore the removal of the aldehyde proton occurs at a much greater rate than migration of the phenyl group. Therefore no Dakin reaction was observed in the alkaline UHP oxidation.

CHAPTER 3

OXIDATION OF HETEROATOMS.

Oxidation of Heteroatoms.

Introduction.

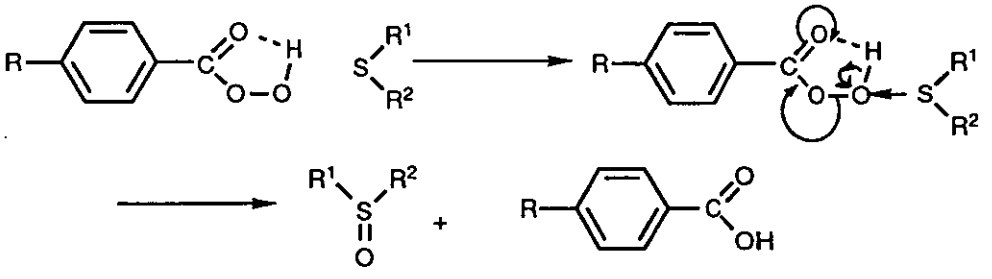
1) Formation of Sulphoxides.

Sulphides are readily converted to sulphoxides by peracetic acid[154], perbenzoic acid[155], *m*CPBA[156], MMPP[157] and sodium perborate[158,159],scheme 48.



Scheme 48

The mechanism[155] is believed to involve intramolecular hydrogen bonding in the transition state, scheme 49.



Scheme 49

This is supported by the observations that

a) reactions carried out in toluene occur at a faster rate than in isopropanol and

b) addition of a salt has no effect on rate of oxidation.

As expected, the rate of reaction is also increased by electron withdrawing substituents on the peracid and electron releasing substituents on the sulphide.

2) Formation of Sulphones.

The oxidation of sulphoxides to sulphones is presumed to follow the same mechanism as for sulphides to sulphoxides previously described

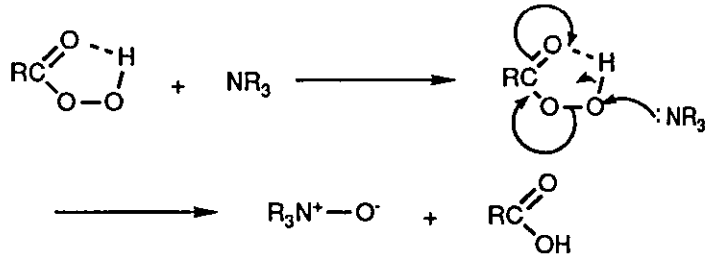
(scheme 48). Due to the lower nucleophilicity of sulphur in the sulphoxide, longer reaction times or elevated temperatures are usually required. Oxidation of sulphoxides using MMPP[99,157], *m*CPBA[156], sodium perborate[158,159] tend to give high yields of sulphones, scheme 50.



Scheme 50

3) Oxidation of Nitrogen (tertiary amines and aromatic amines).

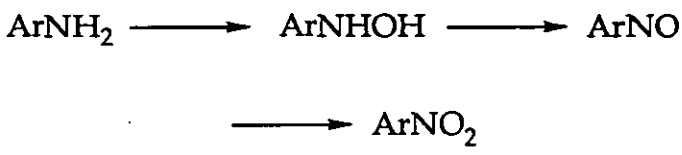
Trialkyl and aromatic amines react rapidly with peracids giving reasonable yields of N-oxides, scheme 51. For example, peracetic acid oxidation of substituted quinoxalines produce the corresponding mono and di-N-oxides[160], and pyridine carboxylic acid N-oxides from the pyridine carboxylic acids[161,162]. *m*CPBA readily forms cytosine 3-N-oxide from cytosine[163] and pyridine is oxidised to pyridine N-oxide by MMPP[99].



Scheme 51

Several peracids convert aromatic amines to the corresponding nitro compounds including trifluoroperacetic[164], perbenzoic[165], peracetic acids[166] and also sodium perborate[158,159].

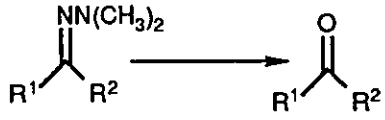
The initial attack of the peracid on an aromatic amine forms a hydroxylamine intermediate, further oxidation produces a nitroso group, which is then oxidised to form the nitro, scheme 52.



Scheme 52

This reaction works particularly well with electronegatively substituted aryl rings. Aromatic amines containing electropositive substituents tend to overoxidise forming tars and no nitrobenzenes are isolated.

4) Oxidative Cleavage Of Dimethylhydrazones.



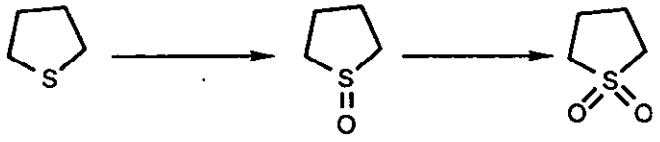
Scheme 53

There are a variety of methods available for the oxidative cleavage of dimethylhydrazones[159,167-174], scheme 53. Some of the most recent procedures reported use MMPP[170] and sodium perborate[159] for the cleavage of the dimethylhydrazones and also for SAMP and RAMP (S- and R-1-amino-2-methoxymethylpyrrolidine) hydrazones. These reactions have proved to be high yielding, using only mild conditions and proceed without racemisation.

Oxidation of Heteroatoms.

Results and Discussion.

i) Oxidation of Tetrahydrothiophene.



(141) (142) (143) (78)

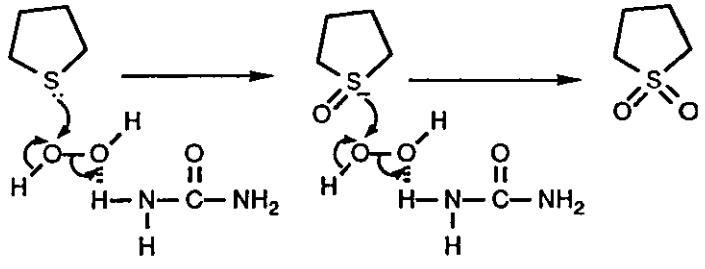
The oxidation of tetrahydrothiophene using various oxidants are shown in table 25, below;

Table 25

Oxidant (molar ratio)	Yield of Sulphone, %
UHP (4:1)	55
UHP/ TFAA*(8:3:2)	56
MMPP (1:1:1)	63

*TFAA= Trifluoroacetic anhydride.

The nucleophilicity of tetrahydrothiophene is sufficient such that the use of strong oxidation conditions are not required. Indeed, no increase in yield was observed using the more electrophilic UHP/ trifluoroacetic anhydride combination, scheme 54.



Scheme 54

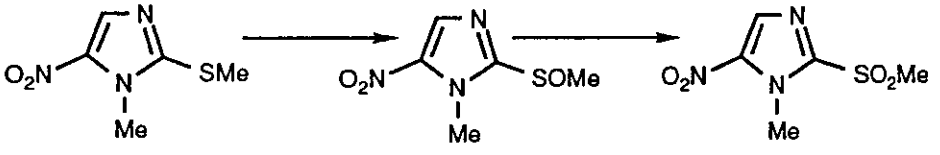
Difficulty was encountered when attempting to control the reaction in

order to isolate tetramethylene sulphoxide (142) as the major product. Limiting the quantity of UHP used resulted in a mixture of tetrahydrothiophene and tetramethylene sulphoxide. Slight increases in the amount of oxidant alone resulted in the formation of mixtures of tetramethylene sulphone (143) and starting material, and very little of the sulphoxide was then observed.

In general, conversion of sulphoxides to sulphones tend to be slower than the oxidation of sulphides to sulphoxides. This drop in oxidation rate is due to the decrease in nucleophilicity of the sulphoxide over the parent sulphide. However the elevated temperatures used in the UHP oxidation reactions were sufficient to compensate for this loss in reactivity of tetramethylene sulphoxide, hence the sulphone (143) was readily formed.

The reaction conditions were relatively harsh for UHP/ trifluoroacetic anhydride due to the nature of the peracid, therefore no sulphoxide (142) was isolated.

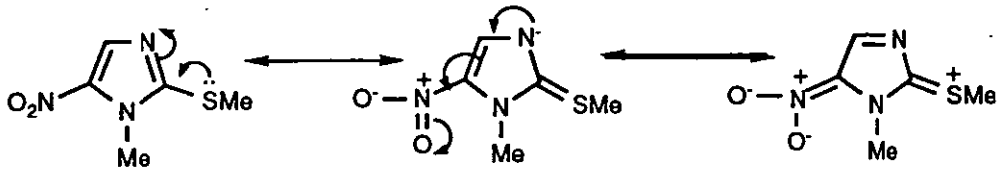
ii) 1-Methyl-2-(methylthio)-5-nitroimidazole, (144).



(144) (145) (146) (79)

Initial oxidation of the imidazole (144) by UHP/ trifluoroacetic anhydride gave a mixture of starting material, the sulphoxide (145) and the sulphone (146), (determined by proton NMR). Repeated oxidation of the crude material formed a 1: 1 mixture of the sulphoxide (145) and the sulphone (146).

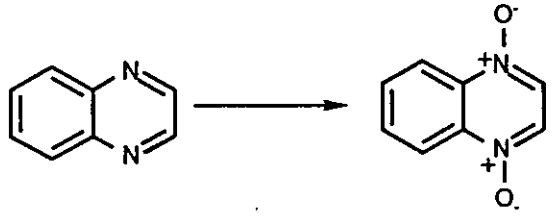
Mesomeric withdrawal by the nitro group, scheme 55, deactivated the imidazole sufficiently to prevent oxidation by UHP alone.



Scheme 55

More demanding reaction condition are required, such as those involved with UHP/ trifluoroacetic anhydride. Complete conversion to the sulphone (146) is further prevented by the relatively low nucleophilicity of the sulphoxide intermediate. These two factors are responsible for the obtainable yields of the sulphone (146).

iii) Oxidation of Quinoxaline.



(147, 29%) (80)

Problems in work up and isolation of quinoxaline di-N-oxide (147) meant that the yields realised were significantly lower than those cited[160] by previous workers.

Oxidation of Anilines To Nitrobenzenes.

Trifluoroperacetic acid reacts with anilines to form the corresponding nitrobenzenes in moderate to high yields e.g. reaction **19**.



(19)

Using a large excess of UHP and trifluoroacetic anhydride to substituted aniline, relatively pure crude products of substituted nitrobenzene were obtained (105mmol of UHP to 26mmol of trifluoroacetic anhydride to 6mmol of substituted aniline), table 26.

Table 26

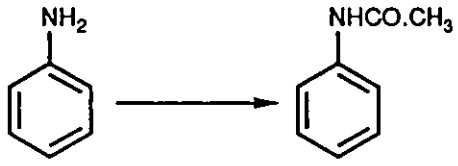
Aniline	**Nitrobenzene Derivative, %**
Aniline	83
o-Toluidine	78
p-Toluidine	63
o-Nitroaniline	69
p-Nitroaniline	72

A reduction in peracid present in the reaction mixture (in this case, 80mmol UHP to 20mmol trifluoroacetic anhydride to 11mmol of the aniline) caused a significant fall in the yield of nitrobenzene derivative, (table 27). The crude products were impure and considerable effort was required to achieve reasonable purity.

Table 27

Aniline	Nitrobenzene Derivative, %
Aniline	37
o-Toluidine	47
p-Toluidine	47
o-Nitroaniline	48
p-Nitroaniline	46

Peracetic acid was not electrophilic enough for this oxidation to take place, hence reaction with aniline derivatives gave the substituted acetanilides, shown in table 28.



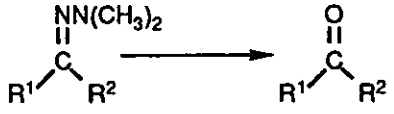
(81)

Table 28

Aniline	Acetanilide, %
Aniline	83
o-Nitroaniline	67
p-Nitroaniline	92

Oxidative Cleavage of Hydrazones to Ketones.

1. Dimethylhydrazones.



Scheme 56

UHP/ trifluoroacetic anhydride oxidised several dimethylhydrazone examples into their corresponding ketones (see table 29). To determine the efficacy of this oxidant, a comparison was made with MMPP, using a method published by Enders and Plant[170]. The results are shown in the table below:

Table 29

DMH	Yield of Ketone, %	
	UHP method	MMPP method
Acetophenone	83	83
Cyclohexanone	46	80.5
4-t-Butylcyclohexanone	52,(46*),(43†)	77

*UHP only i.e. no peracid present

† UHP/ acetic anhydride used instead of trifluoroacetic anhydride.

Note: The dimethylhydrazones were made by literature methods[175,176].

The methods gave comparable yields using acetophenone-N,N-dimethylhydrazone. However considerably lower values for the aliphatic dimethylhydrazones were obtained from trifluoroperacetic acid in place of MMPP. A significant proportion of unreacted hydrazone remained in the crude product indicating that an increase in the excess of UHP/ trifluoroacetic anhydride is required for a more complete oxidation.

2. Phenylhydrazones.

The cleavage of the phenylhydrazones of acetophenone and cyclohexanone was achieved using UHP/ trifluoroacetic anhydride and also by MMPP, scheme 57.



Scheme 57

The UHP / trifluoroacetic anhydride reactions using phenylhydrazones tended to give slightly higher yields of the ketones from phenylhydrazones as compared with the results obtained from dimethylhydrazones. The reverse is true for MMPP. This result may relate to the higher electrophilicity of trifluoroperacetic acid as compared to MMPP.

Note: the phenylhydrazones were made by literature methods[177]

Table 30

Phenylhydrazone	Yield of Ketone,%	
	UHP method	MMPP method
Acetophenone	67	37
Cyclohexanone	49	33

Conclusion.

UHP Oxidations In General.

Urea-hydrogen peroxide in combination with either trifluoroacetic or acetic anhydride produced the corresponding peracid in sufficient quantities to perform oxidation reactions.A number of functional groups were oxidised with varying success.

Baeyer-Villiger reactions of alkyl aryl ketones produced high yields of esters, whereas cyclic and alicyclic aliphatic ketones gave moderate to high yields. Reactions with both types of ketone tended to be slow in rate, probably due to the interference of UHP in the transition state.

Epoxidations were carried out using trifluoroperacetic acid or peracetic acid giving moderate to high yields of epoxides. Oxidation of alkenes conjugated to both carbonyl and nitro groups gave high yields. (The oxidant for these electron deficient alkenes was basic hydrogen peroxide, produced from UHP and sodium hydroxide).

Various compounds containing either nitrogen or sulphur were oxidised with mixed success. Anilines gave nitrobenzenes in high yield, whereas teriary amines and sulphides gave low to moderate quantities of product. Similarly, hydrazones gave the corresponding ketones in varying quantities, depending on both oxidant (MMPP or UHP) and the parent ketone.

The use of hydrogen-peroxide adducts has a number of advantages:

1) It is posible to use hydrogen peroxide in anhydrous systems.

2) UHP is non-deflagrating and non-shock sensitive

3) Adducts are readily made by recrystallisation from hydrogen peroxide.

4) UHP is inexpensive to make and buy.

However there are a number of disadvantages:

1) A vast excess of UHP was required to produce peracids in any reasonable quantity for use in oxidations.

2) The reaction mixture had to be saturated with available hydrogen peroxide to such an extent, that the UHP to substrate ratio was a 10 : 1 molar excess.

3) Reactions were performed in chlorinated solvents, as larger quantities of the potentially explosive diacyl peroxide were formed in polar solvents.

Other Adducts.

Cyclohexylurea and phenylurea-hydrogen peroxide adducts were not as efficient as UHP and work up procedures were less satisfactory. Succinamide-hydrogen peroxide adduct was reasonably successful. However, large excesses were required for oxidation to take place and no advantage over UHP was attained. Histidine-hydrogen peroxide was not found to be effective, presumably due to the strong hydrogen bonding between the histidine and the hydrogen peroxide.

UHP In Comparison To Other Oxidants.

UHP-carboxylic anhydride methods gave yields that were frequently in excess of or at least equal to literature peracid oxidations.

In comparison to MMPP and *m*CPBA however, results were mixed. For example, MMPP and UHP / carboxylic anhydride gave similar results for the oxidation of various methoxy substituted benzaldehydes. Phenols were produced from *ortho* and *para*-methoxybenzaldehyde. Benzoic acid derivatives were formed from benzaldehydes substituted at the *meta* position. *m*CPBA is reported to produce phenols from a large number of methoxybenzaldehydes.

The UHP carboxylic anhydride system is equal in perfomance to MMPP in Baeyer-Villiger reactions. Slightly lower yields were always achieved for the oxidation of sulphides and sometimes for epoxidations.

Future work.

The hydrogen peroxide adduct epoxidations were all racemic. Work was started in the formation of adduct systems that were potentially capable of chiral epoxidations. At this early stage no success was obtained. However, a wide variety of possible methods is still available for the achievement of this goal.

Also, a number of functional groups were oxidised in this work. The oxidation of a large number of other groups are yet to be attempted in order to realise the full range of reactions that hydrogen peroxide adducts are capable of.

Conclusion.

The aim of this project was to determine whether hydrogen peroxide adducts could be used as a replacement for the highly versatile oxidant, *m*CPBA. Investigation into the use of urea hydrogen peroxide proceeded leading to the discovery that UHP, in combination with trifluoroacetic or acetic anhydride, produced the corresponding peracid in reasonable quantities. Peracids thus formed were used in anhydrous systems to perform a range of oxidation reactions.

Moderate to high yields of products were obtained in epoxidation, Baeyer-Villiger reactions and the conversion of anilines into nitrobenzenes. Other reactions, such as oxidative cleavage of dimethylhydrazones and the oxidation of tertiary amines and sulphides were not as promising.

In general, UHP / carboxylic anhydride complements MMPP. It is possible that the combination of use of these two oxidants is a replacement for the highly versatile *m*CPBA.

EXPERIMENTAL.

General procedures.

^1H NMR and ^{13}C NMR were recorded on Varian CW-60 (60 MHz ^1H) and Brucker AC 250F (250 MHz ^1H, 62.8 MHz ^{13}C) spectrometers at 298K with tetramethylsilane as an internal reference. Chemical shifts are reported (δ); ^1H multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet). Coupling constants *J* are reported (Hz). Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer, either as liquid film (film) or nujol mull. Selected peaks are reported (cm-1). Mass spectra were obtained by electron impact (EI) using a Kratos M.S.80 spectrometer). Data are reported in the form m/z (intensity relative to base = 100) for selected ions.

Solvents for reactions, extractions and chromatography were distilled from the indicated drying agents according to the reported procedures: ethyl acetate, diethyl ether ($CaCl_2$), dichloromethane, chloroform (phosphorus(V) oxide), methanol, ethanol (Mg / Iodine). Analytical GLC was performed on a carbowax column (for ketone analysis) and 3% OV17 column (for linalool epoxide analysis) equipped with a variable temperature program and flame ionisation detector. Melting points were measured using an Electrothermal digital melting point apparatus and are uncorrected. Bulb to bulb distillations were performed on a Buchi GKR-51 Kugelrohr apparatus; boiling points refer to atmospheric pressure unless otherwise stated. Work up procedures were as for epoxyhexane unless otherwise stated.

Chapter 1 : Urea-Hydrogen Peroxide / Trifluoroacetic anhydride Epoxidations

1,2-Epoxyhexane. (table 6)

Trifluoroacetic anhydride (3 mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.5g, 80mmol), disodium hydrogen phosphate (10.3g, 73mmol) and 1-hexene (0.82g, 9mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for a further 15.5 hours.

After this time, saturated aqueous sodium bicarbonate was added to neutralise the remaining peracid and acid. Water was added to dissolve any remaining buffer. The mixture was extracted with dichloromethane (2 x

25mls), the layers were separated and the organic phase washed with water to remove any peroxide. The organic phase was dried ($MgSO_4$), and removal of the solvent gave a colourless liquid. Distillation yielded 1,2-epoxyhexane (0.525g, 53%), b.p. 120°C (lit[87]., 117-119°C / 760mm); ν_{max} (liquid film)/ cm^{-1} 3048, 2960, 2932, 2860 (C-H), 956, 916 (C-O-C); δ_H (60 MHz $CDCl_3$) = 2.83 (2 H, m, $C\underline{H}_2$-O), 2.41 (1 H, m, C<u>H</u>-O), 1.44 (6 H, m, 3 x CH_2), 0.93 (3 H, m, $C\underline{H}_3$) ppm.

1,2-Epoxyoctane. (49)

Trifluoroacetic anhydride (3mls, 20mmol), was added dropwise with stirring to a mixture of UHP (7.5g, 80mmol), disodium hydrogen phosphate (10.1g, 72mmol), and 1-octene (0.9g, 8mmol) in dichloromethane (50mls) at O°C. When the addition was complete the reaction mixture was heated under reflux for 30 minutes.

Work up gave a colourless liquid. The crude product was distilled to give 1,2-epoxyoctane (0.9g, 88%), b.p. 68-71°C / 20mm (lit[87], 71-73°C / 27mm); ν_{max} (liquid film)/ cm^{-1} 3040, 2956, 2928, 2856 (C-H), 1172, 1078, 992, 920 (C-O-C); δ_H (60 MHz $CDCl_3$) = 2.79 (2 H, m, $C\underline{H}_2$-O), 2.41(1 H, m, C<u>H</u>-O), 1.34 (10 H, br.m, 5 x $C\underline{H}_2$), 0.89 (3 H, m, $C\underline{H}_3$) ppm.

Methyl methylglycidate. (table 6)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a refluxing mixture of UHP (7.6g, 81mmol) disodium hydrogen phosphate (10.2g, 72mmol) and methyl methacrylate (1.14g, 11mmol) in dichloromethane (50mls).

When the addition was complete, the mixture was heated under reflux for 1 hour. After this time, the reaction mixture was allowed to cool to room temperature; work up and distillation gave methyl methylglycidate (0.741g, 56%), b.p. 125°C (lit[87]., 62-65°C / 32mm); ν_{max} (liquid film)/ cm^{-1} 2992, 2956 (C-H aliphatic), 2848 (C-H, Me-O group), 1724 (C=O), 1200, 1016, 944 (C-O-C aliphatic); δ_H (60 MHz $CDCl_3$) = 3.79 (3 H, s, $C\underline{H}_3$-O), 3.12-2.74 (2 H, d.d., J =14, 2 x H), 1.59 (3 H, s, $C\underline{H}_3$-C-epoxide) ppm.

2-methyl-5-(2'hydroxy-2'-propyl)-2-vinyltetrahydrofuran. (52)

Trifluoroacetic anhydride (6mls, 40mmol) was added dropwise with stirring to a mixture of UHP (14.7g, 156mmol), disodium hydrogen phosphate (15.0g, 106mmol) and linalool (3.1g, 20mmol) in

dichloromethane (50mls) at 0°C.

The reaction mixture was stirred at room temperature for a further 4 hours. Work up and distillation gave 2-methyl-5-(2'hydroxy-2'-propyl)-2-vinyltetrahydrofuran, (2.18g, 64%), b.p. 50-52 °C / 1mm (lit[110]., 78-89°C / 12 torr); ν_{max} (liquid film)/ cm^{-1} 3390 (OH), 1170, 1085, 950, 895 (C-O-C); δ_H (60 MHz $CDCl_3$) = 6.00 (1 H, m, alkene H), 5.32, 5.11, 4.92 (2 H, 3 x d, alkene H), 2.17 (2 H, m, CH_2), 1.85 (3 H, br.d, CH_2-CH), 1.30 (3 H, s, Me-COH), 1.22 (3H, s, Me-COH), 1.14 (3H, s, Me) ppm; the proton NMR agreed with that given in the literature[110]; GLC analysis indicated that the cis and trans isomers of the tetrahydrofuran derivative were present with a trace (< 1%) of another product presumed to be the tetrahydropyran derivative.

3-β-Trifluoroacetoxy-5,6-α-epoxycholestane. (40)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.31g, 78mmol), disodium hydrogen phosphate (10.2g, 72mmol) and cholesterol (2.20g, 6mmol) in chloroform (50mls) at 0°C.

The reaction mixture was stirred at room temperature for a further 16 hours. Work up gave a crude white solid, recrystallisation from 90% acetone gave 3-β-trifluoroacetoxy-5,6-α-epoxycholestane (1.43g, 62%), m.p. 113-114°C (from 90% aq,acetone); M^+ (mass spectrum) 498.3326 $C_{29}H_{45}F_3O_3$ requires M^+, 498.3321 ; ν_{max} (nujol mull)/ cm^{-1} 2924, 2852 (C-H aliphatic), 1780 (C=O trifluoroacetate), 1334 (C-F), 1170 (C-F or C-O), 1060, 1040 (C-O-C); δ_H (60 MHz $CDCl_3$) 2.90 (1 H, d, J= 1, epoxide H), 2.5-0.3 (45 H, m, cholesterol main peaks) ppm; m/z 498 (M^+ 27%), 43 (100), 55 (83), 149 (80).

3-Benzoyloxy-5,6-epoxycholestane. (45)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.34g, 78mmol), disodium hydrogen phosphate (10.2g,72mmol) and cholesteryl benzoate (2.96g, 6mmol) in dichloromethane (50mls) at 0°C.

The reaction mixture was stirred at room temperature for a further 16 hours. Work up gave a crude white solid. The product was recrystallised from 90% ethyl acetate : 10% petroleum ether to give a colourless crystalline solid -3-Benzoyloxy-5,6-epoxycholestane (α-isomer), m.p. 148-149°C. The solvent was removed from the filtrate, and the product was recrystallised to give a mixture of the α- and β-epoxides, mpt: 143-145°C (from ethyl acetate:

methanol 3 : 1), (lit[173]., 167-168°C α-epoxybenzoate, 131-132°C β-epoxybenzoate); ν_{max} (nujol mull)/ cm^{-1} 2924, 2852 (C-H aliphatic), 1714 (C=O benzoate), 1604 (C=C aromatic), 1120, 1028, 998, 934 (C-O-C); δ_H (60 MHz $CDCl_3$) = 8.10 -7.50 (5 H, m, aromatic H), 3.09 & 2.91 (2 x d, *J*= 1, α-and β-epoxide H, α:β =5 : 2), 1.11 (45 H, m, cholesterol H) ppm.

1,2-Epoxy-3-phenoxypropane. (55)

Trifluoroacetic anhydride (3 mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.3g, 71mmol), disodium hydrogen phosphate (10.0g, 71mmol) and phenyl allyl ether (1.09g, 8mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 20 hours.

Work up and distillation gave 1,2-epoxy-3-phenoxypropane (0.699g, 57%) b.p. 161°C / 20mm (lit[111]., 101-105°C / 45mm); ν_{max} (liquid film)/ cm^{-1} 3064 (C-H aromatic), 2928 (C-H aliphatic), 1598, 1496 (C=C aromatic), 1244 C-O-C (alkyl aryl ether), 756, 692 (C-H mono substituted aromatic); δ_H (60 MHz $CDCl_3$) =7.01 (5 H, m, aromatic), 3.16 (2 H, m, $C\underline{H}_2$-OAr), 3.28 (1 H, m, epoxide H), 2.70 (1 H, m, epoxide H), 2.38 (1 H, m, epoxide-CH) ppm; δ_C (63 MHz $CDCl_3$) = 158.6 (aromatic C-O), 129.6 (meta-C), 121.3 (para-C), 114.7 (ortho-C), 68.7 (Ar-O-$\underline{C}H_2$), 50.2 ($\underline{C}$H-O), 44.6 ($\underline{C}H_2$-O) ppm.

1,2-Epoxycyclooctane. (table 6)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.3g, 78mmol), disodium hydrogen phosphate (10.2g, 72mmol) and cyclooctene (0.7g, 6mmol) in dichloromethane (50mls) at 0°C.

The reaction mixture was then heated under reflux for 30 minutes. After allowing it to cool to room temperature and following work up, the crude colourless liquid was distilled to give 1,2-epoxycyclooctane (0.52g, 60%), b.p. 92°C / 20mm (lit[180]., 85-85°C / 20mm); ν_{max} (liquid film)/ cm^{-1} 2968, 2928, 2856 (C-H aliphatic), 1266, 1184 (C-C aliphatic), 1098, 1068, 1016, 980 (C-O-C); δ_H (60 MHz $CDCl_3$) = 2.86 (2 H, m, epoxide H), 2.11 (2 H, m, $C\underline{H}_2$-epoxide), 1.45 (10 H, m, 5 x CH_2) ppm.

1,2-Epoxycyclohexane. (62)

Acetic anhydride (2.16g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.9g, 84mmol), disodium hydrogen phosphate (10.2g, 72mmol) and cyclohexene (0.72g, 9mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 17 hours.

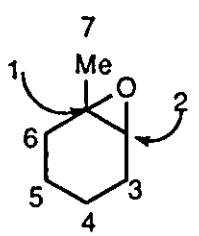
Work up and distillation gave 1,2-epoxycyclohexane (0.638g, 74%), b.p. 130-131°C, (lit[87]: 70-71°C / 110mm); ν_{max} (liquid film)/ cm^{-1} 2984, 2936, 2856 (C-H aliphatic), 1168, 1084, 990, 996 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 3.09 (2 H. br.s, epoxide H), 1.87 (4 H, m, 2x CH_2-epoxide), 1.35 (4 H, m, 2x $C\underline{H}_2$-CH_2-epoxide) ppm.

1,2-Epoxy-1-methylcyclohexane. (table 10)

Acetic anhydride (2.10g, 20.5mmol) was added dropwise with stirring to a mixture of UHP (7.7g, 82mmol), 1-methylcyclohexene (0.805g, 8mmol) and disodium hydrogen phosphate (10.0g, 71mmol) at 0°C. The mixture was stirred at room temperature for a further 17 hours.

Work up and distillation gave 1,2-epoxy-1-methylcyclohexane (0.476g, 56%),

b. p. 132-134°C (lit[181]., 137.5-138°C / 756mm); ν_{max} (liquid film)/ cm^{-1} 2932, 2860 (C-H aliphatic), 1086, 1066, 1030 (C-O-C); δ_H(250 MHz; $CDCl_3$) = 2.96-2.95 (1 H, d, *J*= 1, epoxide H), 1.92-1.83 (3 H, m, $C\underline{H}_3$-C-epoxide), 1.72-1.61 (2 H, m, $C\underline{H}_2$-CH-epoxide), 1.44-1.13 (4 H, m, 2 x CH_2) ppm; δ_C(63 MHz; $CDCl_3$) = 59.5 (CH-2), 57.5 (C-1), 29.9 (C-3), 24.7 (Me-7), 23.9 (C-6), 20.1 (C-4), 19.6 (C-5) ppm.



1,2-Epoxy-3-methylcyclohexane. (table 10)

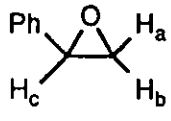
Acetic anhydride (2.09g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.6g, 81mmol), 3-methylcyclohexene (0.96g, 10mmol) and disodium hydrogen phosphate (10.1g, 72mmol) at 0°C. The mixture was stirred at room temperature for a further 16 hours.

Work up and distillation gave 1,2-epoxy-3-methylcyclohexane (0.652g, 58%), b.p. 142°C (lit[182]., 143-144°C); ν_{max} (liquid film)/ cm^{-1} 2932, 2868 (C-H aliphatic), 1072, 1002, 924 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 3.15 (1 H, m, epoxide H), 2.85 (1 H, d, J =1, epoxide H), 2.30-1.62 (3 H, m, CH-O & CH_2-O), 1.62-0.62 (7 H, m, CH_3, 2 x CH_2) ppm.

Styrene oxide. (table 9)

Acetic anhydride (2.12g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.9g, 84mmol), disodium hydrogen phosphate (10.5g, 80mmol) and styrene (0.9g, 8.7mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 17 hours.

Work up and distillation gave styrene oxide (0.623g, 60%), b.p. 95°C / 20mm (lit[183]., 192-194°C); ν_{max} (liquid film)/ cm^{-1} 3036 (C-H aromatic), 2988, 2912 (C-H aliphatic), 1604, 1494 (C=C aromatic), 986 (C-O-C), 760, 698 (monosubstituted aromatic); δ_H(60 MHz; $CDCl_3$) = 3.77 (1 H, d.d, J =1, H_c), 3.04 (1 H, d.d, J =1, H_a), 2.71 (1 H, d.d, J= 2, H_b) ppm.



α-Methylstyrene oxide. (57)

Acetic anhydride (2.12g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.9g, 84mmol), disodium hydrogen phosphate(11.1g, 79mmol) and α-methylstyrene (1.09g, 9mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 17 hours.

Work up and distillation gave a colourless liquid, α-methylstyrene oxide (0.762g, 61%), b.p. 109°C / 20mm (lit[184]., 84-85°C / 16mm); ν_{max} (liquid film)/ cm^{-1} 3032 (C-H aromatic), 2984, 2928 (C-H aliphatic), 1604 (C=C aromatic), 1062, 1028 (C-O-C aliphatic), 760 (C-H monosubstituted Ar);

δ_H(60 MHz; $CDCl_3$) = 7.32 (5 H, s, aromatic H), 2.84 (2 H, d.d, *J*= 6, epoxide-CH_2), 1.68 (3 H, s, CH_3-epoxide) ppm; δ_C(63 MHz; $CDCl_3$) = 141.4 (C-1), 128.4 (o-C), 127.4 (p-C), 125.3 (m-C), 56.8 (C epoxide), 56.5 (C epoxide), 21.7 (Me) ppm.

β-Methylstyrene oxide. (table 9)

Acetic anhydride (2.12g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.6g, 81mmol), β-methylstyrene (0.93g, 7.9mmol) and disodium hydrogen phosphate (10.2g, 72mmol) at 0°C.

The mixture was stirred at room temperature for a further 16 hours. Work up and distillation gave 2-phenyl-1,2-epoxypropane (0.91g, 86%), b.p. 91°C / 20mm (lit[185]., 93°C / 25mm); ν_{max} (liquid film)/ cm^{-1} 3064, 3028 (C-H aromatic), 2984, 2928 (C-H aliphatic), 1602, 1584, 1494 (C=C aromatic), 1074, 1022, 954 (C-O-C stretch); δ_H(250 MHz; $CDCl_3$) = 7.33-7.23 (5 H, m, aromatic), 3.56 (1 H, d, *J* <1, C-H), 3.06-2.99 (1 H, d.q, *J* <1, C-H), 1.43 (3 H, d, *J* =4, CH_3) ppm; δ_C(63 MHz; $CDCl_3$) 137.7 (C-1), 128.4 (*ortho*-C), 128.0 (*para*-C), 125.5 (*meta*-C), 59.5 (Ph-CH-epoxide), 59.0 (CH_3-CH-), 17.8 (Me) ppm.

Geraniol di-epoxide. (67)

Acetic anhydride (2.04g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.9g, 84mmol), disodium hydrogen phosphate (10.2g, 72mmol) and geraniol (1.25g, 8mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 23 hours.

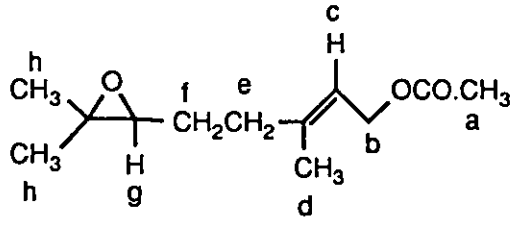
Work up and distillation gave geraniol di-epoxide (0.998g, 66%), b.p. 184°C / 20 mm, (lit[48]., 180-183°C / 20mm); ν_{max} (liquid film)/ cm^{-1} 3428 (OH), 2960, 2928 (C-H aliphatic), 1118, 1038, 896 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 3.79 (2 H, br.d, CH_2-OH), 2.84 (3 H, m, 2 x epoxide H & OH), 1.63 (4 H, br.m, 2 x CH_2), 1.29 (9 H, 2 x s, 3 x CH_3) ppm.

Geranyl acetate 6,7-epoxide. (70)

Acetic anhydride (2.07g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.7g, 82mmol), disodium hydrogen phosphate (10.1g, 72mmol) and geranyl acetate (1.55g, 8mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 5 hours.

Work up and distillation gave geranyl acetate-6,7-epoxide (1.26g,

75%), b.p. 160°C /40mm ; ν_{max} (liquid film)/ cm^{-1} 2960 (C-H aliphatic), 1738 (C=0 acetate), 1120,1026,958,902 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 5.37 (1 H, br.t, c), 4.67 (2 H, d, b), 2.73 (1 H, t, g), 2.09 (5 H, s + m, a & e), 1.72 (5 H, m, d & f), 1.33 (6 H, d, h) ppm.



Limonene di-epoxide. (65)

Acetic anhydride (2.12g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.7g, 81mmol), disodium hydrogen phosphate (10.2g, 72mmol) and limonene (0.975g, 7mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 23 hours.

Work up and distillation gave limonene di-epoxide (1.13g, 94%), b.p. 78-80°C / 0.6mm, (lit[48]., 146.5-147°C / 50mm); M^+ 168 (5%), 43 (100), 41 (30), 55 (22); ν_{max} (liquid film)/ cm^{-1} 3036, 2972, 2928, 2864 (C-H), 1124, 1102, 1070, 942, 904 (C-O-C); δ_H(60 MHz; $CDCl_3$) 3.02 (1 H, br.d, epoxide H), 2.57 (2 H, br.d, epoxide H), 2.33-1.21 (13 H, m, 13-H) including 1.26 & 1.37 (6 H, 2 x s, 2 x CH_3).

Limonene monoepoxide. (64)

Acetic anhydride (1.07g, 10mmol) was added dropwise with stirring to a mixture of UHP (7.8g, 83mmol), disodium hydrogen phosphate (10.1g, 72mmol) and limonene (0.973g, 7mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 17.5 hours.

Work up and distillation gave limonene monoepoxide (0.833g, 77%), b.p. 151°C / 20mm, (lit[98]., 81°C / 3.1mm); ν_{max} (liquid film)/ cm^{-1} 3076 (C-H alkene), 2968, 2928, 2860 (C-H aliphatic), 1642 (C=C isolated alkene), 1120, 1040, 1014 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 4.69 (2 H, br.s, CH_2=C), 3.01 (1 H, br.t, epoxide H), 2.41-1.17 (14 H, m, 14-H) ppm.

2,3-Dimethyl-2,3-epoxybutane. (73)

Acetic anhydride (2.04g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.7g, 82mmol), disodium hydrogen phosphate (10.2g,

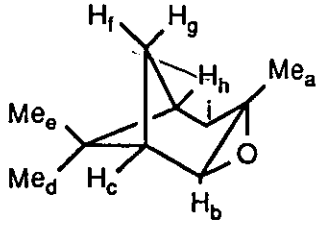
72mmol) and 2,3-dimethylbut-2-ene (0.74g, 9mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 16 hours.

Work up and distillation gave 2,3-dimethyl-2,3-epoxybutane (0.448g, 51%) b.p. 75°C (lit[186]., 91.6-91.8°C); ν_{max} (liquid film)/ cm^{-1} 2956, 2928 (C-H aliphatic), 1170 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 1.32 (12 H, s, 4 x CH_3); δ_C(63 MHz; $CDCl_3$) 62.1 (C-O), 21.1 (Me) ppm.

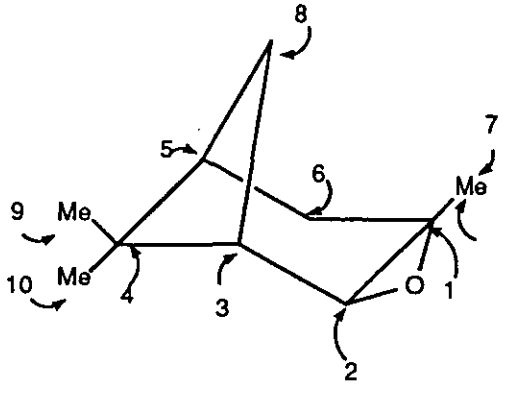
α-Pinene oxide. (71)

Acetic anhydride (2.13g, 21mmol) was added dropwise with stirring to a mixture of UHP (7.6g, 81mmol), disodium hydrogen phosphate (10.0g, 71mmol) and α-pinene (1.06g, 8mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 15 hours.

Work up and distillation gave α-pinene oxide (0.945g, 79%), b.p. 116°C / 40mm (lit[48]., 70-71°C / 12mm); ν_{max} (liquid film)/ cm^{-1} 2976, 2912, 2868 (C-H aliphatic), 1096 (C-O-C); δ_H(250 MHz; $CDCl_3$) = 3.10 (1 H, d, b), 2.04-1.91 (3 H, m, c, f, g), 1.74-1.71 (1 H, br.s, h), 1.63 (2 H, d, i), 1.34 (3 H, s, a), 1.29 (3 H, s, e), 0.94 (3 H, s, f) ppm.



δ_C(63 MHz; $CDCl_3$) 60.3 (C-1), 56.9 (C-2), 45.1 (C-3), 40.5 (C-4), 39.7 (C-5), 27.6 (C-8), 26.7 (C-9), 25.9 (C-6), 22.4 (C-7), 20.2 (C-10) ppm.



trans-Stilbene oxide. (74)

Acetic anhydride (3.03g, 30mmol) was added dropwise with stirring to a mixture of UHP (7.9g, 84mmol), disodium hydrogen phosphate (10.0g, 71mmol) and trans-stilbene (1.51g, 8.5mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 87 hours.

Analysis of the crude material showed a significant proportion of the starting material present, so the reaction was repeated on the crude product for a further 20 hours.

Work up gave *trans*-stilbene oxide (0.71g, 47%), m.p. 65-66°C (from ethanol), (lit[87]., 66-67°C); ν_{max} (nujol mull)/ cm^{-1} 3052 (C-H aromatic), 1600, 1490 (C=C aromatic), 962, 912 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 7.35 (10 H, s, aromatic H), 3.83 (2 H, s, C-H epoxide) ppm.

Cholesterol α-epoxide. (72)

Acetic anhydride (2.18g, 21mmol) was added dropwise with stirring to a mixture of cholesterol (3.1g, 8mmol), UHP (7.5g, 80mmol) and disodium hydrogen phosphate (10.2g, 72mmol) in dichloromethane at 0°C. The mixture was allowed to warm to room temperature and stirred for a further 6 hours.

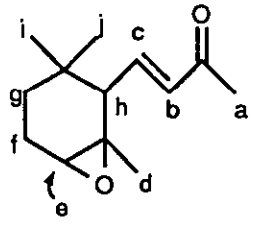
Work up and recrystallisation from 90% aq. acetone gave cholesterol α-epoxide as colourless crystals (2.23g, 69%), m.p. 136.3-136.8°C (from 90% aq. acetone) (lit[97]., 141-142°C); ν_{max} (nujol mull)/ cm^{-1} 3372 (OH), 2916 (C-H aliphatic), 1062, 1040, 966 (C-O-C); δ_H(250 MHz; $CDCl_3$) = 3.90 (1 H, m, H at 3 position), 2.90 (1 H, d, J 1, α-epoxide H), 2.11-0.61 (43 H, m, cholesterol main peaks) ppm; m/z 402 (M^+, 34.2%), 43 (100), 55 (72), 95 (55).

3'-oxo-1'- butenyl-2,6,6-trimethyl-2,3-epoxycyclohexane. (75)

Acetic anhydride (2.20g, 21.5mmol) was added dropwise with stirring to a mixture of α-ionone (1.59g, 8mmol), UHP (7.5g, 80mmol) and disodium hydrogen phosphate (10.4g, 74mmol) in dichloromethane at 0°C. The mixture was allowed to warm to room temperature and stirred for a further 16.5 hours.

Work up and distillation gave 3'-oxo-1'- butenyl-2,6,6-trimethyl-2,3-epoxycyclohexane (1.54g, 90%) b.p. 151°C. / 2mm (lit[187]., 107.5°C / 0.8mm); ν_{max} (film)/ cm^{-1} 2956, 2868 (C-H aliphatic), 1692, 1670 (C=O), 1060, 1046, 990 (C-O-C); δ_H(250 MHz; $CDCl_3$) = 6.78-6.6 (1 H, m, c.), 6.28-6.02 (1 H, m, b),

3.46 (1 H, s, epoxide e), 2.3 (3 H, s, a), 2.11-2.07 (1 H, d.d, h), 1.90-2.0 (3 H, m, g, f), 1.43-1.37 (1 H, m, g), 1.26 (3 H, s, d), 0.93 (3 H, s, j), 0.75 (3 H, s, i) ppm; δ_C(63 MHz; $CDCl_3$) = 198.7 (C=O), 149.0 (CH=), 133.9 (CH=), 59.7 (CH-epoxide), 59.4 (C-epoxide), 52.4 (Me_a), 30.9 ($\underline{C}$-Me_2), 28.5 (C_f), 28.4(Me_j), 28.1 (Me_i), 27.5 (C_h), 24.0 (Me_d) , 21.7 (C_g) ppm.



Phenylurea-hydrogen peroxide adduct.

Phenylurea (2.78g, 20mmol) was dissolved in methanol (15mls), then 80% hydrogen peroxide was added dropwise with stirring to the reaction mixture at 0°C. Stirring was continued for 15 minutes, then the mixture was poured into a crystallising dish which was placed in a fridge until colourless crystals of phenylurea-hydrogen peroxide adduct were formed, (3.13g, 90%) m.p. 53-55°C; AVOX: 54%; ν_{max} (nujol mull) / cm^{-1} 3444, 3336 (N-H), 1640 (C=O), 1074, 1030, 918 (C-O).

Cyclohexylurea-hydrogen peroxide adduct.

Cyclohexylurea (2.8g, 20mmol) was dissolved in methanol (15mls), then 80% hydrogen peroxide was added dropwise with stirring to the reaction mixture at 0°C. Stirring was continued for 15 minutes, then the mixture was poured into a crystallising dish which was placed in a fridge until colourless crystals of cyclohexylurea-hydrogen peroxide adduct were formed (3.21g, 93%), m.p. 68-73°C; AVOX: 72%; ν_{max} (nujol mull) / cm^{-1} 3444 (N-H), 1636 (C=O), 1594 (C=C).

Succinamide-hydrogen peroxide adduct.

Succinamide (2.8g, 20mmol) was recrystallised from 80% hydrogen peroxide, then the mixture was poured into a crystallising dish which was placed in a fridge until colourless crystals of succinamide-hydrogen peroxide adduct were formed (2.16g, 61%), AVOX: 72%; ν_{max} (nujol mull) / cm^{-1} 3422 (N-H), 1642 (C=O).

Chapter 1: Hydrogen Peroxide Adduct Oxidations.

A. PHENYLUREA-H_2O_2.

1,2-Epoxyoctane. (49)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of phenylurea-H_2O_2 adduct (13.8g, 81mmol), disodium hydrogen phosphate (10.3g, 73mmol) and 1-octene (0.89g, 8mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 19.5 hours.

Work up and distillation gave 1,2-epoxyoctane (0.556g, 54.5%), b.p. 70°C / 20mm (lit[87]., 71-73 °C / 27mm); ν_{max} (liquid film)/ cm^{-1} 3044, 2956, 2928 (C-H aliphatic), 1130, 918 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 2.85 (2 H, m, epoxide H), 2.48 (1 H, m, epoxide H), 1.48 (10 H, br.t, 5 x $C\underline{H}_2$), 0.98 (3 H, m, $C\underline{H}_3$-R) ppm.

α-Methylstyrene oxide. (57)

Acetic anhydride (2.13g, 21mmol) was added dropwise with stirring to a mixture of phenylurea-H_2O_2 adduct (13.7g, 81mmol), disodium hydrogen phosphate (10.1g,72mmol) and α-methylstyrene (0.968g, 8mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 22 hours.

Work up and distillation gave α-methylstyrene oxide (0.399g, 35%); b.p. 109-111° / 20mm (lit[184]., 84-85 °C / 16mm); ν_{max} (liquid film)/ cm^{-1} 3032 C-H aromatic), 2984, 2928 (C-H aliphatic), 1604, 1496 (C=C aromatic), 1096, 1062,1028 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 7.35 (5 H, s, aromatic H), 2.85 (2 H, d.d, *J*= 6 epoxide H), 1.72 (3 H, s, $C\underline{H}_3$-R) ppm.

1,2-Epoxyhexane. (table 6)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of phenylurea-H_2O_2 adduct (13.3g, 78mmol), disodium hydrogen phosphate (10.1g, 72mmol) and 1-hexene (0.67g, 8mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 17 hours.

Work up and distillation gave 1,2-epoxyhexane (0.103g, 13%), b.p. 121°C (lit[87]., 117-119 °C / 750mm); ν_{max} (liquid film)/ cm^{-1} 2960, 2932, 2860 (C-H aliphatic), 1162, 910 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 2.85 (2 H, m, epoxide H), 2.48 (1 H, m, epoxide H), 1.48 (6 H, m, 3 x $C\underline{H}_2$), 0.96 (3 H, m, $C\underline{H}_3$-R) ppm.

B. CYCLOHEXYLUREA-H_2O_2.

α-Methylstyrene oxide. (57)

Acetic anhydride (2.13g, 21mmol) was added dropwise with stirring to a mixture of cyclohexylurea-H_2O_2 adduct (12.1g, 68mmol), disodium hydrogen phosphate (10.0g, 71mmol) and α-methylstyrene (1.01g, 9mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 17.5 hours.

Work up gave a colourless liquid, and this crude material was then distilled to yield α-methylstyrene oxide (0.109g, 8.7%) b.p. 101°C / 20mm (lit[184]., 84-85°C / 16mm); ν_{max} (liquid film)/ cm^{-1} 3032 (C-H aromatic), 2984, 2928 (C-H aliphatic), 1604, 1496 (C=C aromatic), 1096, 1062, 1028 (C-O-C aliphatic); δ_H (60 MHz; $CDCl_3$) = 7.34 (5 H, s, aromatic H), 2.84 (2 H, d.d, *J*= 6, CH_2-epoxide), 1.68 (3 H, s, CH_3- epoxide) ppm.

1,2-Epoxyoctane. (49)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of cyclohexylurea-H_2O_2 adduct (14.0g, 72mmol), disodium hydrogen phosphate (10.2g, 72mmol) and 1-octene (0.92g, 8mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 17.5 hours.

Work up as gave a colourless liquid, this crude material was then distilled to give 1,2-epoxyoctane (0.485g, 46%), b.p. 68-71°C / 20mm lit[88]., 71-73°C / 27mm); ν_{max} (liquid film)/ cm^{-1} 2956, 2928 (C-H), 1172, 1132, 1078, 992 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 3.13-2.59 (2 H, m, epoxide H), 2.41 (1 H, m, epoxide H), 2.18-0.36 (13 H, m, aliphatic H) ppm.

C. SUCCINAMIDE-H_2O_2.

α-Methylstyrene oxide. (57)

Acetic anhydride (0.92g, 9mmol) was added dropwise with stirring to a mixture of succinamide-H_2O_2 adduct (5.25g, 36mmol), disodium hydrogen

phosphate (4.90g, 18mmol) and α-methylstyrene (0.39g, 3.3mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was stirred at room temperature for a further 1.5 hours, then refluxed for 1 hour.

Work up gave a colourless liquid, this crude material was then distilled to yield α-methylstyrene oxide (0.209g, 47%) b.p. 132°C / 40mm (lit[184]., 84-85°C / 16mm); ν_{max} (liquid film)/ cm^{-1} 3032 (C-H aromatic), 2984, 2928 (C-H aliphatic), 1604, 1496 (C=C aromatic), 1096, 1062, 1028 (C-O-C aliphatic); δ_H (60 MHz; $CDCl_3$) = 7.31 (5 H, s, Ar H), 2.88 (2 H, d.d, *J*= 6, CH_2-epoxide), 1.73 (3 H, s, CH_3- epoxide) ppm.

Cholesterol α-epoxide. (72)

Acetic anhydride (0.23g, 2mmol) was added dropwise with stirring to a mixture of succinamide-H_2O_2 adduct (2.02g, 13mmol), disodium hydrogen phosphate (1.02g, 7mmol) and cholesterol (0.315g, 0.8mmol) in dichloromethane (50mls) at 0°C. The reaction mixture was refluxed for 2 hours.

Work up gave cholesterol α-epoxide (0.254g, 79%) m.p. 141-142°C (lit[98]., 141-142°C); ν_{max} (nujol mull)/ cm^{-1} 3376 (OH), 1170, 1104 (C-C), 1060, 1040 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 3.82 (1 H, m, 1 CH-OH), 2.91 (1H, d, *J* =1, epoxide), 2.32-0.32 (43H, m, main cholesterol peaks) ppm.

Dimethyl methylmalonate (scheme 17).

Dimethyl malonate (14.4g, 141mmol) was added to sodium methoxide [sodium metal (2.4g, 104mmol) dissolved in methanol (80mls)] under nitrogen. After stirring for 1 hour, methyl iodide (17.1g, 120mmol) was added portionwise, the reaction was stirred for a further hour. Extraction with dichloromethane, washing with water (3 x 50mls), drying ($MgSO_4$) removal of the solvent followed by column chromatography on silica gel (solvent system = 90 : 10 petroleum ether : ethyl acetate) gave dimethyl methylmalonate, (11.3g, 70%), b.p. 135°C / 20mm; ν_{max} (nujol mull)/cm^{-1} 2992, 2956 (C-H), 1754 (C=O); δ_H (60 MHz; $CDCl_3$) = 3.73 (6H, s, 2 x OMe), 3.45 (1H, q, H-C-Me), 1.45 (3H, d, Me-C-H) ppm.

Methyl malonamide. (scheme 17)

Dimethyl methylmalonate (1.82g, 13mmol) was added to liquid ammonia (13mls) and ammonium chloride (0.2g, 4mmol) at -78°C. The mixture was allowed to warm to 0°C then left in a fridge for 24 hours. Filtration and washing with petrol (3 x 10mls) gave methyl malonamide, (0.827g, 57%), m.p. 204°C (lit[188]., 206°C); ν_{max} (nujol mull)/cm^{-1} 3344 (N-H), 2992, 2956 (C-H), 1664 (C=O amide), 1024 (C-N).

Dimethyl dimethylmalonate. (scheme 17)

Dimethyl methylmalonate (2.92g, 20mmol) was added to sodium methoxide [sodium metal (0.8g, 35mmol) dissolved in methanol (60mls)] under nitrogen. After stirring for 1 hour, methyl iodide (4.3g, 30mmol) was added portionwise, the reaction was stirred for a further hour. Extraction with dichloromethane, washing with water (3 x 50mls), drying ($MgSO_4$), removal of the solvent, followed by column chromatography on silica gel (solvent system = 90 : 10 petroleum ether : ethyl acetate) gave dimethyl dimethylmalonate, (0.609g, 19%), b.p. 137°C / 20mm; ν_{max} (nujol mull)/cm^{-1} 2992, 2952 (C-H), 1734 (C=O), 1134 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 3.74 (6H, s, 2 x OMe), 3.74 (6H, s, C-Me) ppm.

Malonamide. (scheme 17)

Diethyl malonate (2.01g, 25mmol) was added to liquid ammonia (13mls) and ammonium chloride (0.2g, 4mmol) at -78°C. The mixture was allowed to warm to 0°C then left in a fridge for 24 hours. Filtration and washing with petrol (3 x 10mls) gave malonamide, (0.97g, 68%), m.p. 167.5-

169°C (lit[188]., 169°C); ν_{max} (nujol mull)/cm^{-1} 3360 (N-H), 2992, 2956 (C-H), 1664 (C=O amide), 1262, 1186 (C-O-C).

Attempted Preparation of dimethyl malonamide.

Dimethyl malonate (2.01g, 25mmol) was added to liquid ammonia (13mls) and ammonium chloride (0.2g, 4mmol) at -78°C. The mixture was allowed to warm to 0°C then left in a fridge for 24 hours. No precipitate of dimethyl malonamide was formed.

N-Acetyl-L-phenyalanyl-L-valine methyl ester. (peptide A)

L-Valine methyl ester (0.82g, 6mmol), N-acetyl-L-phenylalanine (1.20g, 6mmol) and DCC, (1.24g, 6mmol) in dichloromethane (40mls) were stirred at room temperature for 24 hours. Work up and column chromatography on silica gel (80 : 20 ethyl acetate : petroleum ether) gave N-acetyl-L-phenyalanyl-L-valine methyl ester, (1.35g, 67%), m.p. 126-127°C; M^+ (mass spectrum) 320.1717, $C_{17}H_{24}N_2$ requires M^+320.1735; ν_{max} (nujol mull)/cm^{-1} 3272 (N-H), 3064, 3072 (C-H), 2960, 2928 (C-H), 1742 (C=O), 1640 (C=O amide), 1496 (C=C aromatic), 1120, 1030 (C-O-C); δ_H (250 MHz; $CDCl_3$) = 7.27 (5H, m, aromatic H), 6.56 (1H, d, NH), 6.50 (1H, d, NH), 4.81 (1H, m, CH), 4.41 (1H, m, CH), 3.69 (3H, s, OMe), 3.04 (2H, d, J=1, CH_2-Ar), 2.08 (1H, m, CH), 2.00 (3H, s, Me, ester), 0.82 (6H, 2 x d, 2 x CH_3) ppm; δ_C (63 MHz; $CDCl_3$) = 171.7 (C=O), 171.4 (C=O), 170.2 (C=O), 136.5 (aromatic), 129.3 (aromatic), 128.5 (aromatic), 126.8 (aromatic), 57.5 (CH-N), 54.4 (CH-N), 52.0 (Me-O.CO.NH), 38.4 (CH_2), 31.0 (Me-O.CO), 23.0 (CH), 18.8 (CH_3), 17.8 (CH_3) ppm; m/z 320 (M^+, 10%), 120 (100), 72 (40), 162 (29).

N-Acetyl-L-phenyalanyl-L-leucine methyl ester. (Peptide B)

L-Leucine methyl ester (0.71g, 5mmol), N-acetyl-L-phenylalanine (1.0g, 5mmol) and DCC (1.0g, 5mmol) in dichloromethane (40mls) were stirred at room temperature for 24 hours. Work up and column chromatography on silica gel (80 : 20 ethyl acetate : petroleum ether) gave N-acetyl-L-phenyalanyl-L-leucine methyl ester, (1.53g, 94%); ν_{max} (nujol mull)/cm^{-1} 3416 (N-H), 2952, 2928 (C-H), 1738 (C=O ester), 1662 (C=O amide), 1492 (C=C aromatic); δ_H (250 MHz; $CDCl_3$) = 7.24 (5H, m, aromatic H), 6.75 (1H, d, N-H), 6.68 (1H, d, N-H), 4.77 (1H, q, CH-NH), 4.49 (1H, m, CH-NH), 3.69 (3H, 2 x s, Me-ester), 3.03 (2H, m, $C\underline{H}_2$-Ph), 1.94 (3H, s, Me-amide), 1.54 (3H, m, CH_2-CH), 0.88 (6H, d + m, 2 x Me) ppm; δ_C (63 MHz; $CDCl_3$) = 172.7 (C=O), 171.1 (C=O), 170.2 (C=O), 136.5 (aromatic), 129.4 (aromatic), 128.4 (aromatic), 126.9 (aromatic), 54.3 (CH-NH), 52.2 (CH-NH), 50.9 (CH_3-amide), 41.2 (CH_2), 38.7 (CH_2), 24.7 (CH_3-ester), 23.0, (CH), 22.7 (CH_3), 21.6 (CH_3) ppm.

N-Acetyl-L-phenyalanyl-L-phenylalanine methyl ester. (Peptide C)

L-Phenylalanine methyl ester (1.03g, 5mmol), N-acetyl-L-phenylalanine (1.0g, 5mmol) and DCC (1.0g, 5mmol) in dichloromethane (40mls) were stirred at room temperature for 24 hours. Work up and column chromatography on silica gel (80 : 20 ethyl acetate : petroleum ether) gave N-acetyl-L-phenyalanyl-L-phenylalanine methyl ester, (1.59g, 86%); ν_{max} (nujol mull)/cm^{-1} 3416 (N-H), 2984, 2932 (C-H), 1740 (C=O ester), 1662 (C=O amide), 1492 (C=C aromatic); δ_H (250 MHz; $CDCl_3$) = 7.09 (10H, m, aromatic H), 4.61 (2H, m, 2 x CH-N), 3.55 (3H, s, $C\underline{H}_3$-OCO. NH), 2.89 (4H, m, 2 x CH_2-Ar), 1.78 (3H, s, CH_3-O.CO) ppm; δ_C (63 MHz; $CDCl_3$) 171.5 (C=O), 171.1 (C=O), 170.2 (C=O), 139.6 (C aromatic), 136.1 (C aromatic), 129.2 (aromatic), 128.3 (aromatic), 126.6 (aromatic), 54.2 (CH), 53.5 (CH), 52.2 (CH_2), 37.7 (CH_2-Ar), 33.9 (CH_2-Ar), 22.9 (CH_3) ppm.

Isophorone oxide. (89)

Isophorone (5.5g, 40mmol) and UHP (11.5g, 120 mmol) were taken up in methanol (40mls). The stirred mixture was cooled to 15°C (ice bath) and 3.3mls of 6M NaOH was added over 15 minutes (using external cooling to keep the reaction temperature between 15° and 20°C). The temperature of the reaction mixture was kept at 20-25°C while stirring was continued for a further 3 hours.

After this time the contents of the flask were poured into water (50mls), the aqueous layer was extracted with ether (2 x 40mls) and the combined extracts were washed with water, dried ($MgSO_4$). The ether was removed to give isophorone oxide (4.14g, 68%), b.p. 105°C / 7.5mm (lit[125]., 70-73°C / 5mm); M^+ (mass spectrum) 154.096 $C_9H_{14}O_2$ requires M^+ 154.099; ν_{max} (liquid film)/ cm^{-1} 2956, 2868 (C-H aliphatic), 1718 (C=O ketone), 1120, 1054, 986, 914 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 3.05 (1 H, s), 2.08 (4 H, m, 2 x CH_2), 1.42 (3 H, s, Me-epoxide), 1.02 (3 H, s, Me), 0.94 (3 H, s, Me) ppm. Both IR and ^1H nmr spectra corresponded to those obtained from isophorone oxide produced by the literature method; m/z 154 (M^+, 17.2%), 83 (100), 69 (45), 41 (39).

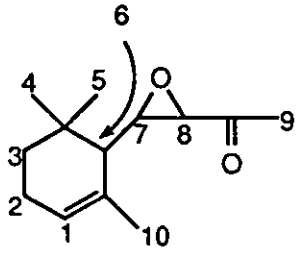
Pulegone oxide. (91)

6M Sodium hydroxide (3.5mls) was added dropwise to a stirred mixture of pulegone (3.16g, 21mmol) and UHP (11.3g, 120mmol) in methanol (25mls); the method used was the same as above, which gave pulegone oxide (1.75g, 50%), b.p. 202°C / 40mm, (lit[189]., m.p. 44°C, b.p. 137°C / 24mm); ν_{max} (liquid film)/ cm^{-1} 3000, 2960, 2872 (C-H aliphatic), 1720 (C=O ketone), 1116, 1034, 1018, 970 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 2.41 (2 H, br.d, CH_2-C=O), 1.97 (5 H, m, CH_2-CH_2-CH), 1.49 (3 H, s, CH_3-C-R), 1.28 (3 H, s, CH_3-C-R), 1.05 (3 H, m, $C\underline{H}_3$-CH) ppm; m/z 168 (M^+, 22%), 43 (100), 41 (97), 39 (70).

α-Ionone oxide. (92)

6M Sodium hydroxide (2 mls) was added dropwise to a stirred mixture of α-ionone (1.36g, 6.8mmol) and UHP (4.1g, 44mmol) in methanol (25mls); the method used was the same as above, which gave α-ionone epoxide (0.873g, 61%), b.p. 118°C / 0.6mm (lit[190]., 38°C); ν_{max} (liquid film)/ cm^{-1} 2964 (C-H aliphatic), 1706 (C=O ketone); δ_H(250 MHz; $CDCl_3$) = 5.52 (1 H, br.s, 1),

3.29 (1 H, d 8), 2.94-2.89 (1 H, d.d, 7), 2.07 (5 H, s + br.s 2 & 9), 1.70 (3 H, d, 10), 1.53 (1 H, m, 3), 1.43 (1 H, d, 6), 1.29 (1 H, m, 3), 1.14 (3 H, s, 5), 0.93 (3 H, s, 4) ppm;



δ_C(63 MHz; $CDCl_3$) = 191.4 (C=O), 131.2 (CH_3-C=), 124.7 (C-1), 59.2 (C-8), 58.6 (C-7), 52.5 (C-9), 32.7 (quaternary C), 31.3 (C-2), 27.8 (C-6), 26.9 (C-10), 24.4 (C-5), 26.3 (C-4), 23.0 (C-3) ppm.

β-Methyl-β-nitrostyrene epoxide (94).

2M sodium hydroxide (1.25 mls) was added dropwise to a stirred mixture of β-methyl-β-nitrostyrene (0.79g, 5mmol) and UHP (0.75g, 8mmol) in methanol (25mls), cooled with an ice bath. The reaction was continued for 10 minutes, then crushed ice added to the mixture.

After acidification of the organic layer, work up and distillation gave β-methyl-β-nitrostyrene epoxide (0.83g, 96%), b.p. 82°C / 0.05mm (lit[123]., 88-91°C / 0.1mm); ν_{max} (liquid film)/ cm^{-1} 3064, 3032 (C-H aromatic), 2944, 2892 (C-H aliphatic), 1554, 1356 (NO_2); δ_H(60 MHz; $CDCl_3$) = 7.36 (5 H, s, aromatic H), 4.03 (1 H, s, epoxide-H), 1.76 (3 H, s, epoxide-CH_3) ppm.

Benzoic Acid (95)

4M Sodium hydroxide (1.25 mls) was added dropwise to a stirred mixture of β-methyl-β-nitrostyrene (0.79g, 5mmol) and UHP (0.75g, 8mmol) in methanol (25mls), cooled with an ice bath. The reaction was continued for 10 minutes, then crushed ice added to the mixture.

Acidification of the organic layer gave a mixture of benzoic acid and benzaldehyde. Isolation of the products gave benzaldehyde (0.28g, 54%) and benzoic acid (0.23g, 34%), m.p. 122°C (lit.,[191] 122°C ν_{max} (liquid film)/ cm^{-1} 3404-2676 (OH broad), 3068 (C-H aromatic), 1692 (C=O acid), 1602, 1582, 1494 (C=C aromatic); δ_H(60 MHz; $CDCl_3$) = 8.07 (2.0 H, m, *ortho* -H), 7.46 (3.0 H, m, *meta*- & *para*-H) ppm.

Benzoic Acid. (95)

6M Sodium hydroxide (3.1 mls) was added dropwise to a stirred mixture of β-methyl-β-nitrostyrene (0.92g, 5.6mmol) and UHP (4.1g, 44mmol) in methanol (25mls). An exothermic reaction occurred and the colour of the mixture changed from yellow to colourless. The mixture was stirred for a further 20 minutes.

Acidification of the organic layer and work up gave benzoic acid (0.501g, 73%) m.p. 120-122°C (from hexane) (lit[191]., 122°C); ν_{max} (nujol mull)/ cm^{-1} 3404-2676 (OH broad), 3068 (C-H aromatic), 1692 (C=O acid), 1602, 1582, 1494 (C=C aromatic); δ_H(60 MHz; $CDCl_3$) = 8.07 (2.0 H, m, *ortho* -H), 7.46 (3.0 H, m, *meta-* & *para*-H) ppm.

Benzoic Acid. (95)

6M Sodium hydroxide (3.2 mls) was added dropwise to a stirred mixture of benzaldehyde (1.22g, 11.5mmol) and UHP (8.1g,87mmol) in methanol (25mls), and the mixture was stirred for a further 55 minutes.

Acidification of the organic layer and removal of the solvent gave benzoic acid (1.31g, 94%), m.p. 120-122°C (from hexane) (lit[191]., 122°C); ν_{max} (nujol mull)/ cm^{-1} 3444-2676 (OH broad), 3068 (C-H aromatic), 1688 (C=O acid), 1600, 1582, 1494 (C=C aromatic), 1074, 1028 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 8.10 (2.0 H, m, *ortho* -H), 7.46 (3.0 H, m, *meta-* & *para*-H) ppm.

δ-Valerolactone. (table 16)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.2g, 78mmol), disodium hydrogen phosphate (10.2g, 72mmol) and cyclopentanone (0.66g, 8mmol) in chloroform (50mls) at 0°C.

When the addition was complete,the reaction mixture was allowed to warm to room temperature,and stirred for a further 16 hours . Work up and distillation gave δ-valerolactone (0.418g, 53%), b.p. 109-110°C / 20mm (lit[133]., 83°C / 4mm); ν_{max} (liquid film)/ cm^{-1} 3012, 2964, 2884 (C-H aliphatic), 1734 (C=O), 1240, 1156, 1056, 984 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 4.35 (1 H, t, O-CO.-CH), 2.57 (1 H, q, COOCH), 2.08 (6 H, 5, 3 x CH_2) ppm.

ε-Caprolactone. (table 16)

Trifluoroacetic anhydride (6mls, 40mmol) was added dropwise with stirring to a mixture of UHP (14.7g, 156mmol), disodium hydrogen phosphate (24.6g,174mmol) and cyclohexanone (1.29g, 13mmol) in chloroform (50mls) at 0°C.

When the addition was complete,the reaction mixture was refluxed for 30 minutes. After this time, the mixture was allowed to cool to room temperature, work up giving a crude product which was distilled to give ε-caprolactone (61%, GLC), b.p. 131°C / 20mm (lit[133]., 108°C / 10mm); ν_{max} (liquid film)/ cm^{-1} 2932, 2860 (C-H aliphatic), 1730 (C=O lactone), 1252, 1168, 1088, 988 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 4.31 (2 H, m, CH_2-O.CO), 2.65 (2 H, m, CH_2-CO.O), 1.80 (6 H, m, 3xCH_2) ppm.

ξ-enantholactone. (table 16)

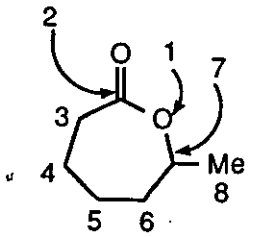
Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.3g, 78mmol), disodium hydrogen phosphate (10.1g, 72mmol) and cycloheptanone (0.95g, 8mmol) in chloroform (50mls) at 0°C.

The reaction mixture was refluxed for 30 minutes. Work up gave a crude product that was distilled to give ξ-enantholactone, b.p. 100-101°C / 20mm (lit[133]., 70°C / 5mm); ν_{max} (liquid film)/ cm^{-1} 3016, 2932, 2860 (C-H) 1722 (C=O lactone), 1222, 1108, 1036 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 4.32 (1 H, t, CH-O.OC), 2.45 (2 H, m, CH_2-CO.O), 1.65 (9 H, m, 3 x CH_2 & CH) ppm.

7-Methylcaprolactone. (126)

Trifluoroacetic anhydride (3 mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.7g, 82mmol), disodium hydrogen phosphate (10.0g, 71mmol) and 2-methylcyclohexanone (0.95g, 8mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 17 hours.

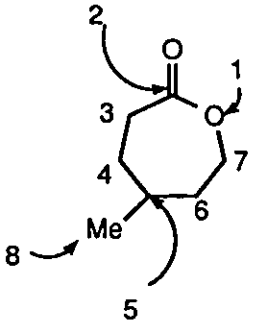
Work up and removal of the solvent gave a colourless liquid that was distilled to yield 7-methylcaprolactone (0.699g, 63%), b.p. 164°C / 20mm (lit[133]., 94°C / 5mm); ν_{max} (liquid film)/ cm^{-1} 2976, 2932, 2860 (C-H aliphatic), 1722 (C=O lactone), 1138, 1024, 1016, 986 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 4.50 (1 H, br.m, CH-OOC), 2.66 (2 H, br.t, CH_2-CO.O), 1.78 (6 H, m, alkyl H), 1.37 (3 H, d, *J*= 6, $C\underline{H}_3$-CH) ppm; δ_C (63 MHz; $CDCl_3$) = 175.5 (C-2), 76.6 (C-7), 36.4 (C-6), 34.8 (C-5), 28.2 (C-3), 22.7 (C-4), 22.4 (C-8) ppm.



5-Methylcaprolactone. (table 17)

Trifluoroacetic anhydride (3 mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.7g, 82mmol), disodium hydrogen phosphate (10.1g, 72mmol) and 4-methylcyclohexanone (0.899g, 8mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 18 hours.

Work up and removal of the solvent gave a colourless liquid that was distilled to yield 5-methylcaprolactone (0.764g, 74%), b.p. 96°C / 1mm (lit[133]., 103° / 5mm); ν_{max} (liquid film)/ cm^{-1} 2952, 2924 (C-H aliphatic), 1730 (C=O lactone), 1164, 1048, 1008, 982 (C-O-C); δ_H (250 MHz; $CDCl_3$) = 4.23 (2 H, m, R-CH_2-O.CO), 2.67 (2 H, m, R-CH_2-CO.O), 1.84 (3 H, m, C$\underline{H}$-C$\underline{H}_2$-CHOCO), 1.44 (2 H, m, C$\underline{H}_2$-CHCOO), 0.99 (3 H, d, *J*= 4, CH_3-O) ppm; δ_C (63 MHz; $CDCl_3$) = 176.1 (C-2), 68.1 (C-7), 37.3 (C-6), 35.2 (C-5), 33.2 (C-3), 30.8 (C-4), 22.1 (C-8) ppm; m/z 128 (M^+, 7%), 56 (100), 41 (64), 69 (47) ppm.



5-t-Butylcaprolactone. (table 17)

Trifluoroacetic anhydride (3 mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.7g, 82mmol), disodium hydrogen phosphate (10.0, 72mmol) and 4-t-butylcyclohexanone (1.3g, 8mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 17 hours.

Work up gave 5-t-butylcaprolactone (1.28g, 89%) m.p. 38-40°C (from 40-60°C petroleum ether) (lit[192]., 38-39°C); ν_{max} (nujol mull)/ cm^{-1} 2936 (C-H aliphatic), 1740 (C=O lactone), 1078, 1038, 1020, 1004 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 4.26 (2 H, m, R-CH_2-O.OC), 2.68 (2 H, br.s, R-CH_2-CO.O), 2.31-0.7 (14 H, m, 2 x CH_2, 3 x CH_3, 1 x CH) ppm.

t-Butyl acetate. (129)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.2g, 76mmol) and pinacolone (0.983g, 10mmol) in chloroform (50mls) at 0°C.

The reaction mixture was stirred at room temperature for a further 23 hours, work up and distillation gave t-butyl acetate (1.094g, 96%), b.p. 95°C, (lit[98]., 95-96°C); ν_{max} (liquid film)/ cm^{-1} 2980, 2932 (C-H aliphatic), 1736 (C=O ester), 1256, 1084, 1020, 914 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 2.04 (3 H, s, Me-C=O), 1.42 (9 H, s, t-butyl) ppm.

Ethyl pentanoate. (131)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.5g, 80mmol) and 3-pentanone (1.2g, 14mmol) in dichloromethane (50mls) at 0°C.

The reaction mixture was stirred at room temperature for a further 15

hours, work up and distillation gave ethyl propionate (0.614g, 43%), b.p. 100°C (lit[193]., 99°C), ν_{max} (liquid film)/ cm^{-1} 2984,2944 (C-H aliphatic), (0.614g, 43%)1736 (C=O ester), 1084 (C-O-C); δ_H (60 MHz; $CDCl_3$) = 4.16 (2 H, q, *J*= 5, CH_2-O.CO), 2.31 (2 H, q, *J*= 5, CH_2-CO.O), 1.20 (6 H, 2 x t, *J* = 5, 2 x CH_3) ppm.

cis-3-Hydroxycyclopentylacetic acid lactone. (127)

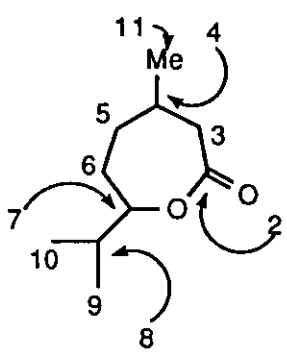
Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.5g,80mmol) and norcamphor (0.86g,8mmol) in dichloromethane (50mls) at 0°C.

The reaction mixture was stirred at room temperature for a further 5 hours, work up gave cis-3-hydroxycyclopentylacetic acid lactone (130), (0.75g, 76%), b.p. 91°C / 0.4mm (lit[194]., 77°C / 0.25mm); ν_{max} (liquid film)/ cm^{-1} 2952, 2876 (C-H aliphatic), 1726 (C=O lactone); δ_H (60 MHz; $CDCl_3$) = 4.75 (1 H, br.s, CH-O.CO), 2.50 (3 H, m, CH-CH_2-CO.O), 1.87 (6 H, m, 3 x CH_2) ppm.

Menthone oxide. (125)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.5g,80mmol) and menthone (1.30g,8mmol) in dichloromethane (50mls) at 0°C.

The reaction mixture was stirred at room temperature for a further 17 hours, and work up gave of menthone oxide (128) (1.41g, 98%), b.p. 112°C / 0.3mm (lit[29]., 137-140°C / 15mm); ν_{max} (liquid film)/ cm^{-1} 2960,2928 (C-H aliphatic), 1722 (C=O lactone), 1164, 1104 (C-O-C); δ_H (250 MHz; $CDCl_3$) = 4.08-4.03 (1 H, m, CH-O.CO), 2.56-2.48 (2 H, m, CH_2-CO.O), 1.91-1.8 (3 H, m, CH_2 &CH), 1.63-1.58 (1 H, m, CH), 1.32-1.27 (1 H, m, Me-CH), 1.06-0.88 (9 H, 2 x s & d.d 3 x CH_3) ppm; δ_C (63 MHz; $CDCl_3$); 175.1 (C-2), 84.8 (C-7), 42.5 (C-6), 37.4 (C-3), 33.2 (C-8), 30.9 (C-5), 30.4 (C-4), 24.0 (C-11), 17.6 C-9), 17.1 (C-10) ppm.



Phenyl acetate. (table 18)

Trifluoroacetic anhydride (4mls, 27mmol) was added dropwise with stirring to a mixture of UHP (7.5g, 83mmol) and acetophenone (0.97g, 8mmol) in dichloromethane (50mls) at 0°C.

When the addition was complete, the reaction mixture was refluxed for 2.5 hours. Work up gave a crude product that was distilled to give phenyl acetate, (0.91g, 83%) b.p. 89°C / 7mm (lit[195]., 195.3°C / 763.7mm); ν_{max} (liquid film)/ cm^{-1} 3064, 3016 (C-H aromatic), 1762 (C=O phenyl ester), 1598, 1582, 1490 (C=C aromatic), 1268, 1218, 1196 (C-O-C aliphatic), 756, 690 (C-H monosubstitued aromatic); δ_H (60 MHz $CDCl_3$) = 7.25 (5 H, m, 5 x aromatic H), 2.23 (3 H, s, CH_3-R) ppm.

Phenyl propionate. (table 18)

Trifluoroacetic anhydride (4mls, 27mmol) was added dropwise with stirring to a mixture of UHP (14.7g, 156mmol) and propiophenone (2.05g, 15mmol) in chloroform (50mls) at 0°C.

After stirring at room temperature for a further 4 hours , work up gave a crude product that was distilled to give phenyl propionate (2.13g, 94%), b.p. 108°C / 20mm (lit[196]., 98-99°C / 18mm). ν_{max} (liquid film)/ cm^{-1} 3062 (C-H aromatic), 2982, 2884 (C-H aliphatic), 1760 (C=O ester), 1493 (C=C aromatic), 1275, 1198, 1020 (C-O-C), 754, 692 (C-H monosubstitued aromatic); δ_H (60 MHz $CDCl_3$) = 7.22 (5 H, m, aromatic), 2.59 (2 H, q, J = 6, CH_2-R), 1.26 (3 H, t, J = 6, CH_3-R) ppm.

Phenyl butanoate. (table 18)

Trifluoroacetic anhydride (4mls, 27mmol) was added dropwise with stirring to a mixture of UHP (14.5g, 154mmol) and butyrophenone (2.05g,15mmol) in chloroform (50mls) at 0°C.

After stirring at room temperature for a further 16 hours, analysis of the crude material showed a significant amount of unreacted butyrophenone present. The crude product was reoxidised. After work-up the crude material was distilled to give phenyl butanoate (2.019g, 86%), b.p. 149°C / 19mm (lit[197].,106°C / 13mm); ν_{max} (liquid film)/ cm^{-1} 3064 (C-H aromatic), 2964 (C-H aliphatic), 1758 (C=O ester), 1594, 1492 (C=C aromatic), 1263, 1214 (C-O-C), 754, 692 C-H (monosubstituted aromatic); δ_H (60 MHz $CDCl_3$) = 7.28

(5 H, m, aromatic H), 2.55 (2 H, t, J = 5, O.CO.CH_2), 1.80 (2 H, m, CH_2CH_2), 1.10 (3 H, t, J = 5, CH_3-R) ppm.

Phenyl pentanoate. (table 18)

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.8g, 83mmol) and valerophenone (1.38g, 8mmol). The reaction mixture was stirred for 20 hours at room temperature. Work up gave a crude yellow liquid, which was distilled to give phenyl pentanoate (1.38g, 91%) b.p. 106°C / 1mm (lit[198]., 160°C / 14mm); ν_{max} (liquid film)/ cm^{-1} 3068, 3040 (C-H aromatic), 2960, 2932, 2872 (C-H aliphatic), 1760 (C=O ester), 1592, 1492 (C=C aromatic), 1072, 1026, 928 (C-O-C); δ_H (60 MHz $CDCl_3$) = 7.24 (m, 5 H, m, 5 x aromatic H), 2.58 (2 H, t, J =6, CH_2-C=O), 1.28 (7 H, m, aliphatic H) ppm.

***o*-Methoxyphenyl acetate. (table 19)**

Trifluoroacetic anhydride (4mls, 27mmol) was added dropwise with stirring to a mixture of UHP (7.8g, 83mmol), disodium hydrogen phosphate (10.1g, 72mmol) and *o*-methoxyacetophenone (1.67g, 11mmol) in dichloromethane (50mls) at 0°C.

The reaction mixture was refluxed for 30 minutes; work up and distillation gave *o*-methoxyphenyl acetate (1.40g, 76%), b.p. 148°C / 20mm (lit[199]., 126.5°C / 14mm); ν_{max} (liquid film)/ cm^{-1} 3068 (C-H aromatic), 2968, 2904 (C-H aliphatic), 1764 (C=O phenyl ester), 1260, 1195, 1175 (C-O-C), 750 (C-H disubstituted aromatic); δ_H (60 MHz $CDCl_3$) = 6.99 (4 H, m, aromatic H), 3.82 (3 H, s, OMe), 2.29 (3 H, s, Me-CO.O) ppm.

***o*-Chlorophenyl acetate. (table 19)**

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of *o*-chloroacetophenone (1.32g, 8.6mmol) and UHP (7.5g, 80mmol) in dichloromethane at 0°C. The reaction was left stirring at room temperature overnight. Analysis of the crude material showed a significant amount of starting material. The reaction was repeated on the crude product with a reaction time of 21 hours.

Work up and distillation gave *o*-chlorophenyl acetate (1.09g, 75%), b.p. 135°C / 40mm (lit[200]., 103°C / 15mm); ν_{max} (liquid film)/ cm^{-1} 3068 (C-H aromatic), 2924 (C-H aliphatic), 1776 (C=O ester), 1584 (C=C aromatic); δ_H (60 MHz $CDCl_3$) = 7.28 (4 H, m, aromatic H), 2.32 (3 H, s, Me-CO.O) ppm.

***m*-Methylphenyl acetate. (table 21)**

Trifluoroacetic anhydride (4mls, 26mmol) was added dropwise with stirring to a mixture of *m*-methylacetophenone (1.10g, 8mmol) and UHP (7.6g, 80mmol) in dichloromethane at 0°C. The reaction mixture was heated under reflux for 2 hours. Work up and distillation gave *m*-methylphenyl acetate (0.82g, 68%), b.p. 117°C / 5mm (lit[201]., 99°C /13mm); ν_{max} (liquid film)/ cm^{-1} 3032 (C-H aromatic), 2924 (C-H aliphatic), 1764 (C=O ester), 1584 (C=C aromatic); δ_H (60 MHz $CDCl_3$) = 7.21 (4 H, m, aromatic H), 2.31 (6 H, 2 x s, 2 x CH_3); δ_H (250 MHz $CDCl_3$) 7.25 (4H, m, aromatic), 2.36 (3 H, s, Me-Ar), 2.28 (3 H, s, Me-CO.O) ppm.

***p*-Methoxyphenyl acetate. (table 20)**

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.5g, 80mmol), disodium hydrogen phoshate (10.0g, 71mmol) and *p*-methoxyacetophenone (1.40g, 9mmol) in chloroform (50mls) at 0°C.

The reaction mixture was stirred at room temperature for 24 hours. Analysis of the crude product showed a significant amount of starting material present, therefore the process was repeated. Work-up and distillation gave *p*-methoxyphenyl acetate (1.33g, 86%), b.p. 129°C / 15mm (lit[202]., 123°C / 12mm); ν_{max} (liquid film)/ cm^{-1} 3060, 3004 (C-H aromatic), 2956 (C-H aliphatic), 1762 (C=O phenyl ester), 1596,1502 (C=C aromatic), 1194,1142,1034 (C-O-C); δ_H (60 MHz $CDCl_3$) = 7.01 (4 H, m, aromatic H), 3.79 (3 H, s, OMe), 2.26 (3 H, s, O.CO.Me) ppm.

***p*-Methylphenyl acetate. (table 20)**

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of *p*-methylacetophenone (1.10g, 8mmol), UHP (7.7g, 82mmol) and disodium hydrogen phosphate (10.1g, 72mmol) in dichloromethane at 0°C. The mixture was stirred at room temperature for 17 hours. Analysis of the crude material showed a significant amount of starting material present, thus a repeated oxidation was performed on the crude product with a reaction time of 21 hours.

Work up and distillation yielded *p*-methylphenyl acetate (0.976g, 81%), b.p. 84°C / 1 mm (lit[203]., 214°C); ν_{max} (liquid film)/ cm^{-1} 3032 (C-H aromatic), 2924 (C-H aliphatic), 1758 (C=O ester), 1612, 1592, 1504 (C=C aromatic); δ_H (60 MHz $CDCl_3$) = 6.94 (4 H, m, aromatic H), 2.31 (3 H, s, p-Me-Ph), 2.23 (3 H, s,

CH_3-CO.O).

3,4-Dimethylphenyl acetate.

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to a mixture of 3,4-dimethylacetophenone (1.18g, 8mmol) and UHP (7.5g, 80mmol) in dichloromethane at 0°C. The reaction was continued at room temperature for a further 17 hours.

Work up and distillation gave 3,4-dimethylphenyl acetate (0.86g, 66%), b.p. 89°C / 0.7 mm (lit[204]., 145°C /29mm); ν_{max} (liquid film)/ cm^{-1} 3024 (C-H aromatic, 2956, 2924 (C-H aliphatic), 1762 (C=O ester), 1618, 1506 (C=C aromatic); δ_H (60 MHz $CDCl_3$) = 6.61 (m, 3 H, m, aromatic H), 2.16 (6 H, 2 x s, 2 x Me-Ph), 2.03 (3 H, s, CH_3-CO.O) ppm.

α-Bromophenyl acetate. (134)

Trifluoroacetic anhydride (4mls, 26mmol) was added dropwise with stirring to a mixture of α-bromoacetophenone (1.59g, 8mmol) and UHP (7.5g, 80mmol) in dichloromethane at 0°C. The reaction was continued at room temperature for a further 17 hours. After this time, 3.2g of UHP (30mmol) and 1ml of trifluoroacetic anhydride (13mmol) was added to the reaction mixture and stirring continued for 8 hours.

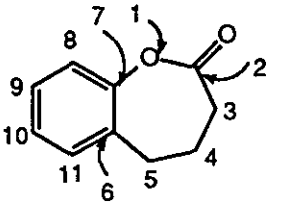
Work up and distillation gave α-bromophenyl acetate, (1.24g, 76%). b.p. 79°C / 0.2mm, m.p. 31°C (lit[205]., 32°C); ν_{max} (liquid film)/ cm^{-1} 3040 (C-H aromatic), 2956, 2924 (C-H aliphatic), 1754 (C=O ester), 1590 (C=C aromatic); δ_H (250 MHz $CDCl_3$) = 7.39 (2 H, m, aromatic H), 7.22 (1 H, m, aromatic H), 7.10 (2 H, m, aromatic H), 4.04 (2 H, s, CH_2-Br) ppm; δ_C (63 MHz $CDCl_3$) = 129.5 (aromatic), 126.3 (aromatic), 121.0 (aromatic), 25.5 (CH_2) ppm.

6,7-Benz [b] oxepan-2-one. (139)

Trifluoroacetic anhydride (3 mls, 20mmol) was added dropwise with stirring to a mixture of UHP (7.4, 80mmol) and 1-tetralone (1.19g, 8mmol) in dichloromethane (50mls) at 0°C. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirred for a further 2 hours.

Work up and removal of the solvent gave a pale yellow liquid which was distilled to yield 6,7-benz [b] oxepan-2-one (1.01g, 76%), b.p. 110°C / 2mm, m.p. 28-30°C (lit[152]., b.p. 134-144°C / 11mm); M^+ (mass spectrum) 162.0684, $C_{10}H_{10}O_2$ requires M^+ , 162. 0681; ν_{max} (nujol mull)/ cm^{-1} 3064 (C-

H aromatic), 2948, 2868 (C-H aliphatic), 1760 (C=O lactone), 1224, 1158 (C-O-C aliphatic); δ_H (60 MHz $CDCl_3$) = 7.16 (4 H, m, aromatic), 2.81 (2 H, t, CH_2-Ar), 2.29 (4 H, m, CH_2-CH_2-C=O) ppm; δ_C (63 MHz $CDCl_3$) 171.6 (C-2), 151.8 (C-7), 130.1 (C-6), 129.7 (C-9 or 11), 128.3 (C-9 or 11), 125.9 (C-10), 119.2 (C-8), 31.1 (C-5), 28.2 (C-3), 26.5 (C-4) ppm;



m/z 162 (M^+, 40%) 107 (100), 55(33).

3,4-Dihydrocoumarin.

Trifluoroacetic anhydride (4mls, 26mmol) was added dropwise with stirring to a mixture of 1-indanone (1.09g, 8mmol) and UHP (7.5g, 80mmol) at 10°C. The reaction was allowed to warm to room temperature and stirred for a further 17 hours.

Work up gave 3,4-dihydrocoumarin (0.902g, 76%), bpt: 115°C / 1mm), lit[206]., 144-146° / 16mm); ν_{max} (liquid film)/ cm^{-1} 3064 (C-H aromatic), 2952, 2916 (C-H aliphatic), 1768 (C=O lactone), 1610, 1488 (C=C aromatic); δ_H (60 MHz $CDCl_3$) = 7.10 (4 H, m, aromatic H), 2.85 (4 H, m, aliphatic H) ppm.

3-Isochromanone. (138)

Trifluoroacetic anhydride, (4mls, 27mmol) was added dropwise with stirring to a mixture of 2-indanone, (1.16g, 8.7mmol) and UHP (7.5g, 80mmol) at 0°C. The mixture was then stirred at room temperature for 22 hours.

Work up and removal of solvent gave an orange solid, 3-isochromanone (0.786g, 61%), m.p. 82-83°C (from boiling hexane) (lit[207]., 82-83°C); ν_{max} (nujol mull)/ cm^{-1} 1744 (C=O lactone), 1298,1252,1188 (C-C), 1110, 1038, 992, 960 (C-O-C); δ_H (60 MHz $CDCl_3$) = 7.24 (4 H, s, aromatic H), 5.28 (2 H, s, CH_2-OCO), 3.66 (2 H, s, CH_2-CO.O) ppm.

Benzoic Acid. (95)

Trifluoroacetic anhydride (6mls, 40mmol) was added dropwise with stirring to a mixture of benzoylacetone (1.33g, 8mmol) and UHP (15.1g,

160mmol) at 0°C. The mixture was then stirred at room temperature for 15.5 hours.

Work up and removal of solvent gave benzoic acid (0.95g, 99%), m.p. 120-121°C (from hexane) (lit[191]., 122°C); ν_{max} (nujol mull)/ cm^{-1} 3080 (aromatic H), 2884 (aliphatic H), 1690 (C=O acid), 1602, 1582, 1490 (C=C aromatic); δ_H (60 MHz $CDCl_3$) = 10.79 (1 H, br.s, OH), 8.11 (2 H, m, *ortho*-H), 7.52 (3 H, m, *meta* & *para*-H).

Chapter 2: Benzaldehyde Oxidations.

(a) Using MMPP as the oxidant.

Benzoic Acid. (95)

Benzaldehyde (4.9g, 46mmol) was added dropwise with stirring to MMPP (20.0g, 104mmol) in isopropanol (60mls). The mixture was left stirring at room temperature overnight, and work up gave a colourless solid that was recrystallised from hexane to give benzoic acid as colourless needles. (4.57g, 81%), m.p. 120-122°C (lit[191]., 122°C); ν_{max} (nujol mull)/ cm^{-1} 2934 (C-H), 1692 (C=O), 1582, 1500 (C=C aromatic), 930 (C-H monosubstituted aromatic); δ_H(60 MHz; $CDCl_3$) = 12.3 (1 H, s, CO.-OH), 8.17 (2 H, m, *ortho-* H), 7.51 (3 H, m, *meta-* & *para-* H) ppm.

***o*-Methoxyphenol, (guaiacol). (table 23)**

o-Methoxybenzaldehyde (1.14g, 8.4mmol) was added to a stirred mixture of MMPP (4.9g, 10mmol) in methanol (60mls) and the mixture was stirred at room temperature for 19 hours.

Work up and distillation gave *o*-methoxyphenol (0.847g, 81%), b.p. 112°C / 20mm, (lit[208]., 106.5°C / 24mm); ν_{max} (liquid film)/ cm^{-1} 3500 (OH), 3052, 3004 (C-H aromatic), 2840 (C-H), 1612, 1596 (C=C aromatic), 1106,918 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 6.91 (4 H, m, aromatic H), 5.81 (1 H, br. s, OH), 3.86 (3 H, s, CH_3-O) ppm.

***m*-Methoxybenzoic Acid. (table 23)**

m-Methoxybenzaldehyde (1.11g, 8mmol) was added to a stirred mixture of MMPP (4.9g, 10mmol) in isopropanol (60mls) and the mixture was stirred at room temperature for 21 hours.

Work up and recrystallisation from hexane gave colourless crystals, *m*-methoxybenzoic acid (0.707g, 71%), m.p. 108-109°C (from water), (lit[209]., 116.5°C); ν_{max} (nujol mull)/ cm^{-1} 2909 (C-H and broad -OH band), 1697 (C=O acid), 1581 (C=C aromatic), 1104, 1087 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 11.65 (1 H, s, CO.OH), 6.98-7.83 (4 H, m, aromatic), 3.85 (3 H, s, CH_3-O) ppm.

***p*-Methoxyphenol. (table 23)**

p-Methoxybenzaldehyde (1.39g, 10mmol) was added to a stirred mixture of MMPP (7.5g, 15mmol) in isopropanol (35mls) and the mixture

was stirred at room temperature for 18 hours.

Work up and recrystallisation gave an orange solid, *p*-methoxyphenol (0.497g, 40%), m.p. 55-56°C, (lit[150]., 52-54°C); ν_{max} (nujol mull)/ cm^{-1} 3356 (OH), 3080, 3028 (C-H aromatic), 1630, 1606 (C=C aromatic); δ_H(60 MHz; $CDCl_3$) = 6.83 (4 H, m, aromatic), 5.74 (1 H, br.s, D_2O exchangeable OH), 3.77 (3 H, s, CH_3-O) ppm.

(b) Using UHP-acetic anhydride as the oxidant.

Benzoic Acid. (95)

Acetic anhydride (2.18g, 21mmol) was added dropwise with stirring to a mixture of UHP (7.5g, 80mmol), benzaldehyde (1.02g, 9.6mmol) and disodium hydrogen phosphate (10.0g, 71mmol) in dichloromethane at O°C. After the addition, the mixture was stirred at room temperature for 19 hours.

Work up and recrystallisation gave benzoic acid (0.86g, 74%), m.p. 119-121°C (from hexane) (lit[191]., 122°C); ν_{max} (nujol mull)/ cm^{-1} 3064 (C-H), 1690 (C=O), 1602, 1582 (C=C aromatic); δ_H(60 MHz; $CDCl_3$) = 12.51 (1 H, s, CO.-OH), 8.14 (2 H, m, *ortho*- H), 7.51 (3 H, m, *meta*- & *para*- H) ppm.

***o*-Methoxyphenol. (table 23)**

Acetic anhydride (2.05g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.7g, 82mmol), *o*-methoxybenzaldehyde (1.02g, 9.6mmol) and disodium hydrogen phosphate (10.1g, 72mmol) in dichloromethane at O°C. After the addition, the mixture was stirred at room temperature for 22 hours.

Work up and distillation gave *o*-methoxyphenol (0.768g, 74%), b.p. 149°C / 40mm (lit[208]., 106.5°C / 24mm); ν_{max} (liquid film)/ cm^{-1} 3507 (OH), 3052, 3007 (C-H aromatic), 2948, 2842 (C-H aliphatic), 1598, 1501 (C=C aromatic); δ_H(60 MHz; $CDCl_3$) = 6.83 (4 H, m, aromatic H), 5.83 (1 H, br.s, OH), 3.85 (3 H, s, MeO) ppm.

***p*-Methoxyphenol. (table 23)**

Acetic anhydride (2.15g, 21mmol) was added dropwise with stirring to a mixture of UHP (7.6g, 81mmol), *p*-methoxybenzaldehyde (1.23g, 9mmol) and disodium hydrogen phosphate (10.1g, 72mmol) in dichloromethane at O°C. After the addition, the mixture was stirred at room temperature for 22

hours.

Work up and distillation gave *p*-methoxyphenol (0.56g, 50%), m.p. 55-56°C (lit[150]., 52-54°C); ν_{max} (nujol mull)/ cm^{-1} 3384 (OH), 1600, 1508 (C=C aromatic), 1100, 1036 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 6.75 (4 H, s, aromatic H), 6.62 (1 H, br.s, OH), 3.70 (3 H, s, MeO) ppm.

m-Methoxybenzaldehyde. (table 23)

Acetic anhydride (2.15g, 21mmol) was added dropwise with stirring to a mixture of UHP (7.6g, 81mmol), *m*-methoxybenzaldehyde (1.23g, 9mmol) and disodium hydrogen phosphate (10.1g, 72mmol) in dichloromethane at 0°C. After the addition, the mixture was stirred at room temperature for 19 hours.

Work up gave complete recovery of starting material.

c) Using UHP/NaOH as Oxidant.

Benzoic Acid. (95)

6M Sodium hydroxide (3.2 mls) was added dropwise to a stirred mixture of benzaldehyde (1.22g, 11.5mmol) and UHP (8.1g, 87mmol) in methanol (40mls), then the mixture heated at 70°C for 55 minutes.

The mixture was extracted with dichloromethane, then work up gave a colourless solid. Subsequent recrystallisation from hexane gave benzoic acid (1.31g, 94%), m.p. 120-122°C (from hexane) (lit[191]., 122°C); ν_{max} (nujol mull)/ cm^{-1} 3444 (OH), 3068 (C-H aromatic), 1600, 1582, 1494 (C=C aromatic), 1074, 1028 (C-O-C); δ_H(60 MHz; $CDCl_3$) 8.10 (2 H, m, *ortho*- H), 7.51 (3 H, m, *meta*- & *para*- H) ppm.

o-Methoxybenzoic Acid. (table 24)

6M Sodium hydroxide (3.1 mls) was added dropwise to a stirred mixture of *o*-methoxybenzaldehyde (1.35g, 10mmol) and UHP (8.1g, 87mmol) in methanol (40mls), then the mixture heated at 65°C for 1 hour.

The mixture was extracted with dichloromethane, and work up gave *o*-methoxybenzoic acid (1.36g, 90%), m.p. 100-101.5°C (from water) (lit[210]., 101.5°C); ν_{max} (nujol mull)/ cm^{-1} 3556 broad (OH peak), 1660 (C=O), 1596 (C=C aromatic), 1084, 1048 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 8.13 (1 H, m, H at the 6 position), 7.54 (1 H, m, H at the 4 position), 7.05 (2 H, m, H at the 3

and 5 positions), 4.10 (3 H, s, Me-O) ppm.

m-Methoxybenzoic Acid. (table 24)

6M Sodium hydroxide (3.2 mls) was added dropwise to a stirred mixture of *m*-methoxybenzaldehyde (1.66g, 12mmol) and UHP (8.3g, 88mmol) in methanol (40mls), then the mixture heated at 65°C for 1 hour.

The mixture was extracted with dichloromethane, and work up gave *m*-methoxybenzoic acid (1.77g, 95%); m.p. 106°C. (lit[209]., 105°C); ν_{max} (nujol mull)/ cm^{-1} 1688 (C=O), 1604, 1582 (C=C aromatic), 1104, 1046 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 11.29 (1 H, br.s, OH), 7.84-6.99 (4 H, m, aromatic H), 3.88 (3 H, s, Me-O) ppm.

p-Methoxybenzoic Acid. (table 24)

6M Sodium hydroxide (3.2 mls) was added dropwise to a stirred mixture of *p*-methoxybenzaldehyde (1.67g, 11mmol) and UHP (8.1g, 87mmol) in methanol (40mls), then the mixture heated at 70°C for 1 hour.

The mixture was extracted with dichloromethane, and work up gave *p*-methoxybenzoic acid (1.34g, 72%), m.pt. 182-183°C (from water) (lit[211]., 184°C); ν_{max} (nujol mull)/ cm^{-1} 3460 (OH), 1680 (C=O), 1602, 1512 (C=C aromatic), 1106, 1026 (C-O-C); δ_H(60 MHz; $CDCl_3$) = 9.78 (1 H, br.s, OH), 7.95, 6.85 (4 H, d.d, J = 7, aromatic H), 3.82 (3 H, s, Me-O) ppm.

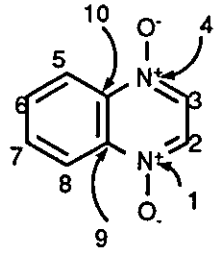
3,4-Dimethoxybenzoic Acid. (table 24)

6M Sodium hydroxide (3.2 mls) was added dropwise to a stirred mixture of 3,4-dimethoxybenzaldehyde (1.83g, 11mmol) and UHP (8.1g, 87mmol) in methanol (40mls), then the mixture heated at 70°C for 1 hour.

The mixture was extracted with dichloromethane, and work up gave 3,4-dimethoxybenzoic acid as colourless plates (1.25g, 63%) m.p. 179-180°C (lit[212]., 181-182°C); ν_{max} (nujol mull)/ cm^{-1} 3176 (OH), 1672 (C=O), 1592, 1512 (C=C aromatic); δ_H(60 MHz; $CDCl_3$) = 7.72-6.74 (4 H, m, aromatic H), 3.91 (3 H, s, Me-O) ppm.

Quinoxaline di-N-oxide (147).

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring into a mixture of UHP (7.3g, 78mmol) and quinoxaline (1.10g, 8.5mmol) in chloroform at O°C. After the completion of addition, the reaction mixture was refluxed for 45 minutes. The mixture was turned out into a beaker of ice, and hydrochloric acid added until the product had precipitated. Filtration gave quinoxaline di-N-oxide (0.39g, 29%) m.p. 244-246°C (from ethanol) (lit[160]., 241-243°C); ν_{max} (nujol mull)/ cm^{-1} 2920, 2852 (C-H), 1286 (N-O), 1084 (C-N), 816 (C-N, aryl); δ_H (60 MHz; $CDCl_3$) = 8.67 (2 H, q, aromatic H 5,8-position), 8.30 (2 H, s, CH=N), 7.92 (2 H, q, aromatic H 2,3-position) ppm.



Tetramethylene sulphone, (143).

A mixture of tetrahydrothiophene (1.7g, 19mmol) and UHP (7.2g, 72mmol) was stirred at room temperature for 5.5 hours. Work up gave tetramethylene sulphone as a brown oil, 58% (analysis by GLC and comparison with an authentic sample) b.p. 116°C / 2mm (lit[213]., 121°C / 4mm); ν_{max} (liquid film)/ cm^{-1} 2948 (C-H), 1014 (C-S); δ_H (60 MHz; $CDCl_3$) = 3.00 (4 H, m, 2 x $C\underline{H}_2$-CH_2-S), 2.25 (4 H, m, 2 x CH_2-S) ppm.

1-Methyl-2-(methyl sulphinyl)-5-nitroimidazole, (145) and 1-Methyl-2-(methyl sulphonyl)-5-nitroimidazole, (146).

Trifluoracetic anhydride (1.5ml, 10mmol) was added dropwise with stirring to a mixture of UHP (3.69g, 39mmol) and 1-Methyl-2-(S-methyl)-imidazole (0.49g, 3mmol) in chloroform at O°C. On completion of the addition, the mixture was heated under reflux for 0.5 hours. Work up gave a yellow solid, analysis of which showed a mixture of the starting material, the sulphoxide and the sulphone. The crude material was re-oxidised forming a yellow solid. Recrystallisation from dichloromethane: petroleum

ether (60-80) gave little product, (0.083g, 17%); ν_{max} (nujol mull)/ cm^{-1} δ_H (60 MHz; $CDCl_3$) 8.10 (1 H, s, C-H aromatic [sulphoxide]), 8.00 (1 H, s, C-H aromatic [sulphone]), 4.38 (6 H, s, N-Me [sulphoxide + sulphone]), 3.45 (3 H, s, S-Me [sulphone]), 3.20 (3 H, s, S-Me [sulphoxide])

The ratio of the S-Me peaks; SOMe: SO_2Me = 1.9 : 2.1

(a) Standard method.

Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise with stirring to UHP (7.5g, 80mmol) in dichloromethane in an ice bath. The mixture was stirred for 20 minutes then allowed to warm to room temperature. A solution of the aniline (10mmol) in dichloromethane was added dropwise and an exothermic reaction followed; the mixture was heated under reflux for 1 hour, then allowed to cool. Work up gave the crude products.

Nitrobenzene, (table 27).

The crude material was distilled to give nitrobenzene (0.519g, 37%), b.p. 111°C / 40mm (lit[214]., 72.8°C / 10mm); ν_{max} (film) cm^{-1} 3104, 3072 (C-H aromatic), 1618, 1604 (C=C aromatic), 1586, 1316 (Ar-NO_2); δ_H(60MHz; $CDCl_3$) = 8.25 (2 H, m, *ortho*-H), 7.57 (3 H, m, *meta* & *para*-H) ppm.

1,2-Dinitrobenzene, (table 27).

The crude material was sublimed, then recrystallised from ethanol to give 1,2-dinitrobenzene (0.797g, 48%) b.p.120°C / 1mm, m.p. 118-120°C (from ethanol (lit[215]., 116.9°C); ν_{max} (nujol mull) cm^{-1} 3096 (C-H aromatic), 1604, 1586 (C=C aromatic), 1532, 1352 (Ar-NO_2); δ_H(60MHz; $CDCl_3$-DMSO-d_6) = 7.88 (4 H, m, aromatic H) ppm.

1,4-Dinitrobenzene, (table 27).

The crude material was sublimed, then recrystallised from ethanol to give pale yellow crystals of 1,4-dinitrobenzene (0.789g, 48%), b.p. 117°C / 1mm, m.p. 170-172°C (from ethanol) (lit[164]., 171.5-172°C); ν_{max} (nujol mull) cm^{-1} 3024 (C-H aromatic); 1620 (C=C aromatic); 1554, 1344, 1320 (Ar-NO_2 symmetrical and unsymmetrical stretches); δ_H(60MHz; $CDCl_3$-DMSO-d_6) = 8.51 (4 H, s, aromatic H) ppm.

***p*-Nitrotoluene (table 27).**

The crude material was distilled, then columned on silica gel (petrol: CH_2Cl_2 85:15) to give *p*-nitrotoluene (0.731g, 47%), b.p. 85°C / 1mm, m.p. 51-53°C (lit[164]., b.p., 219°C); ν_{max} (nujol mull) cm^{-1} 3078, 3036 (C-H aromatic), 1600, (C=C aromatic), 1524, 1345 (Ar-NO_2); δ_H(60MHz; $CDCl_3$) =

8.23-7.20 (4 H, d.d, J = 6, aromatic, *para*-substitued), 2.51 (3 H, s, Ar-Me) ppm.

o-Nitrotoluene, (table 27).

The crude material was distilled, then columned on silica gel (petrol: CH_2Cl_2 85:15) to give 2-nitrotoluene (0.75g, 47%), b.p. 123°C / 40mm (lit[214]., 123°C / 40mm); ν_{max} (film) cm^{-1} 3068 (C-H aromatic), 1610 (C=C aromatic), 1576, 1520, 1346 (Ar-NO_2); δ_H(60MHz; $CDCl_3$) = 7.72 (1 H, m, aromatic *o*-H to nitro), 7.16 (3 H, m, aromatic *m* & *p*-H to nitro), 2.51 (3 H, s, Ar-Me) ppm.

(b) Altered method.

Trifluoroacetic anhydride (4mls, 20mmol) was added dropwise with stirring to UHP (10.0g, 106mmol) in dichloromethane in an ice bath. The mixture was stirred for 20 minutes then allowed to warm to room temperature. A solution of the aniline (6mmol) in dichloromethane was added dropwise and an exothermic reaction followed; the mixture was then heated under reflux for 1 hour and allowed to cool.

Work up gave the crude products, which were purified as before (see the individual methods). The results are given in the table below.

Substrate	Yield, g	%
Aniline	0.610	83
2-nitroaniline	0.684	69
4-nitroaniline	0.726	72
2-toluidine	0.640	78
4-toluidine	0.518	63

(c) Using Acetic Anhydride.

Acetic anhydride (2.13g, 20mmol) was added dropwise with stirring to a mixture of UHP (7.5g, 80mmol) and the aniline (8mmol) in dichloromethane in an ice bath. The mixture was stirred overnight at room temperature.

Work up gave the crude products, recrystallisation from ethanol gave the corresponding acetanilides.

Acetanilide, (table 28).

Aniline gave acetanilide (1.347g, 83%), m.p. 109-111°C (lit[216]., 113-115°C); ν_{max} (nujol mull) cm^{-1} 3288 (N-H secondary), 3052, 3016 (C-H aromatic), 1662 (C=O amide), 1598, 1498 (C=C aromatic); δ_H(60MHz; $CDCl_3$) = 7.98 (1H, br.s, N-H), 7.66-7.01 (5 H, m, aromatic H), 2.16 (3 H,s, Me-C=O) ppm; δ_C(63MHz; $CDCl_3$) =162.3 (C=O), 138.1 (C-1), 128.8 (m-C), 124.3 (p-C), 120.3 (o-C), 24.3 (CH_3-R) ppm.

***p*-Nitroacetanilide, (table 28).**

p-Nitroaniline gave pale yellow needles of *p*-nitroacetanilide (1.673g, 92%), m.p. 213-215°C (lit[217]., 214-216°C); ν_{max} (nujol mull) cm^{-1} 3272 (N-H secondary), 1678 (C=O amide), 1618, 1598 (C=C aromatic), 1564, 1334 (Ar-NO_2); δ_H(60MHz; $CDCl_3$) = 7.89 (4 H, d.d, *J* =7, aromatic, *p*-substituted), 2.14 (3 H, s, Me-C=O) ppm.

***o*-Nitroacetanilide, (table 28).**

o-Nitroaniline gave pale yellow needles of *o*-nitroacetanilide (1.223g, 67%), m.p. 88.5-91°C (lit[217]., 92.5-93.5°C); ν_{max} (nujol mull) cm^{-1} 3356 (N-H secondary), 1696 (C=O amide), 1606, 1584 (C=C aromatic), 1568, 1342 (Ar-NO_2); δ_H(60MHz; $CDCl_3$) = 8.60 (1 H, 2 x d *ortho*-H to nitro), 8.06 (1 H, 2 x d *para*-H to nitro), 7.52 (1 H, 2 x d, *meta*-H to nitro), 7.08 (1 H, dt, *meta*-H to nitro, *ortho*- to amino), 2.14 (3 H, s, Me-C=O) ppm.

Chapter 3: Oxidative Cleavage of Dimethyl and Phenylhydrazones.

4-t-Butylcyclohexanone.

Method 1.

Acetic anhydride (2.13g, 21mmol) was added dropwise to a stirred mixture of UHP (7.8g, 83mmol), sodium dihydrogen phosphate (10.0g, 71mmol) and 4-t-butylcyclohexanone dimethylhydrazone (1.53g, 8mmol), in dichloromethane at 0°C. The reaction mixture was allowed to warm to room temperature, and stirred for a further 8 hours.

The reaction was stopped by the addition of saturated aqueous sodium bicarbonate until all of the peracid was neutralised. The organic layer was separated and the aqueous layer was extracted with dichloromethane (80mls). The organic extracts were combined,washed (water) and dried (magnesium sulphate). Removal of the solvent gave a crude product, which was then analysed by GLC and compared to an authentic sample of 4-t-butylcyclohexanone.

Yield of 4-t-butylcyclohexanone: 43%

Method 2.

A mixture of UHP (7.8g, 82mmol) and 4-t-butylcyclohexanone N,N-dimethylhydrazone (1.55g, 8mmol) was stirred at room temperature for 20 hours. After this time, the mixture was extracted as in method 1, and the crude material was analysed by GLC.

Yield of 4-t-butylcyclohexanone: 46%

Method 3.

Trifluoroacetic anhydride (4mls, 27mmol),was added dropwise to a stirred mixture of UHP (7.8g, 83mmol), sodium dihydrogen phosphate (10,0g, 71mmol) and 4-t-butylcyclohexanone N,N-dimethylhydrazone (1.49g, 7.6mmol) at room temperature. The mixture was stirred for a further 10 minutes then stirring was stoppped and the mixture was extracted as in method 1. The crude material was distilled to give 4-t-buytylcyclohexanone (0.61g, 52%) m.p. 43-45°C (lit[218]., 43-45°C); ν_{max} (film) cm^{-1} 3400, 2920 (C-H aliphatic), 1718 (C=O ketone); δ_H(250 MHz; $CDCl_3$) = 2.57-1.27 (9H, m, alkyl H), 1.02 (9H, s, t-Bu H) ppm.

Cyclohexanone, (table 29).

(i) Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise to a stirred mixture of UHP (7.6g, 81mmol) and cyclohexanone N,N-dimethylhydrazone (1.13g, 8mmol) at O°C. When the addition was complete the mixture was allowed to warm to room temperature, and stirring was continued for a further 14 hours. The reaction was stopped and the mixture was extracted as for method 1, to give a crude product in the form of a pale yellow oil which was then analysed by GLC.

Yield of cyclohexanone: 46%

(ii) Acetic anhydride was used to cleave cyclohexanone N,N-dimethylhydrazone (1.13g, 8mmol) using method 1 with a reaction time of 17 hours.

Analysis by GLC. gave the yield of cyclohexanone as 24%.

Acetophenone, (table 29).

(i) Trifluoroacetic anhydride (3mls, 20mmols) was added dropwise to a stirred mixture of UHP (7.9g, 84mmol), disodium hydrogen phosphate (10.2g, 72mmol) and acetophenone N,N-dimethylhydrazone (1.24g, 7.6mmol), at O°C. Oxidation by method 1, in a reaction of 16 hours gave a crude oil which was distilled to give acetophenone (0.704g, 77%); b.p. 139 °C / 40mm (lit[219]., 202°C / 760mm); ν_{max} (film) cm^{-1} 3060, 3004 (C-H aromatic), 1680 (C=O ketone), 1598 (C=C), 956, 690 (C-H,monosubstituted,aromatic); δ_H (60MHz; $CDCl_3$) = 7.97 (2.0 H, m, *ortho* H), 7.48 (3.0 H, m, *para* & *meta* H), 2.49 (2.9 H, s, CH_3-C=O) ppm.

(ii) The method was repeated, using a half hour reaction. The crude reaction mixture was analysed by GLC, indicating that the yield of acetophenone was 83%.

Cyclohexanone, (table 29).

(i) Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise to a stirred mixture of UHP (7.5g, 80mmol), disodium hydrogen phosphate (10.1g, 72mmol), and cyclohexanone N,N-dimethylhydrazone (1.55g, 8mmol) in dichloromethane at O°C.

As the drops were added, the reaction mixture changed in colour from orange to dark red. At the end of the addition, after 25 minutes, the reaction

was stopped and worked up as for method 1. Distillation of the crude product gave cyclohexanone (0.398g, 49%), b.p. 150°C (lit[220]., 154-155°C); ν_{max} (film) cm^{-1} 2936, 2860 (C-H aliphatic), 1710 (C=O ketone); δ_H (60MHz; $CDCl_3$) = 2.34 (4 H, br.m, 2x $C\underline{H}_2$-C=O), 1.86 (6 H, br.m, 3x $C\underline{H}_2$) ppm.

(ii) The above method was repeated using acetic anhydride (2.11g, 21mmol). The colour of the mixture changed from yellow to orange over a 20 hour period. Work up and distillation gave cyclohexanone (0.410g, 50%), b.p. 151°C (lit[220]., 154-155°C); ν_{max} (film) cm^{-1} 2936, 2860 (C-H aliphatic), 1718 (C=O ketone); δ_H (60MHz; $CDCl_3$) = 2.28 (4 H, br.d, 2x CH_2-C=O), 1.82 (6 H, br.d 3x CH_2) ppm.

Acetophenone, (table 29).

(i) Trifluoroacetic anhydride (3mls, 20mmol) was added dropwise to a stirred mixture of UHP (7.6g, 8mmol), disodium hydrogen phosphate (10.0g, 71mmol), and acetophenone phenylhydrazone (1.24g, 6mmol) in dichloromethane at O°C. The mixture was stirred at room temperature reaction for 35minutes. Work up gave a crude oil which was analysed by GLC.

Yield of acetophenone: 64%

(ii) Method 1 was used with acetic anhydride (1.40g, 7mmol), in a 24.5 hour reaction at room temperature . GLC analysis showed that the yield of acetophenone for this reaction was 11%.

<u>Oxidative cleavage reactions using MMPP. (Method 4)</u>

(i) A solution of acetophenone N,N-dimethylhydrazone (0.887g, 5.5mmol) in methanol was added dropwise to a solution of MMPP (3g, 6mmol) and disodium hydrogen phosphate (3.2g, 23mmol) in methanol (40 mls).

The reaction mixture was stirred at O°C for 3.5 hours, work up and distillation gave acetophenone (0.546g, 83%), b.p. 140°C / 40mm (lit[219]., 202°C / 760mm); ν_{max} (film) cm^{-1} 3060, 3004 (C-H aromatic), 1680 (C=O ketone), 1598 (C=C), 956, 690 (C-H, monosubstituted, aromatic); δ_H (60MHz; $CDCl_3$) = 7.97 (2.0 H, m, *ortho* H), 7.48 (3.0 H, m, *para* & *meta* H), 2.49 (2.9 H, s, CH_3-C=O) ppm.

(ii) 4-t-Butylcyclohexanone N,N-dimethylhydrazone (1.10g, 5.6mmol) was oxidised using method 4. Distillation of the crude product gave 4-t-butylcyclohexanone (0.666g, 77%), m.p. 43-45°C (lit[218]., 43-48°C); ν_{max} (nujol mull) cm^{-1} 2920 (C-H), 1718 (C=O); δ_H (60MHz; $CDCl_3$) = 2.43-1.32 (9 H, m, alkyl H), 0.92 (9 H, s, t-Bu H) ppm.

(iii) Cyclohexanone N,N-dimethylhydrazone (0.75g, 5.4mmol) was oxidised using method 4. Distillation of the crude product gave cyclohexanone (0.426g, 80.5%), b.p. 150°C (lit[220]., 154-155°C); ν_{max} (film) cm^{-1} 2936, 2860 (C-H alkyl), 1710 (C=O), 1100, 1054 (C-O-C); δ_H (60MHz; $CDCl_3$) = 2.35 (4 H, br.m, 2 x CH_2-C=O), 1.88 (6 H, br.d, 3 x CH_2) ppm.

Appendix 1.

Methods Attempted for Trifluoroperacetic acid Generation.

1) UHP/ trifluoroacetic acid/ dichloromethane
2) 85% hydrogen peroxide/ trifluoroacetic acid/ dichloromethane
3) UHP/ trifluoroacetic acid/ dimethoxyethane/ dichloromethane
4) UHP/ trifluoroacetic anhydride/ dichloromethane
5) 85% hydrogen peroxide/trifluoroacetic anhydride/ dichloromethane
6) UHP/ trifluoroacetic anhydride/ methanol
7) UHP/ trifluoroacetic anhydride/ disodium hydrogen phosphate/ cyclohexanone/ dichloromethane

For each method, peracid, AVOX and diacyl peroxide concentrations were determined at various stages throughout the reaction by titration.
Note:
1) the samples were taken of the solution, by filtering off the undissolved UHP, thus avoiding incorrect AVOX values.
2) Due to significant loss in volume of reaction mixture, (which would effect the results for later samples), reactions were carried out individually for each set of AVOX, peracid and diacyl peroxide values.

Sample Stages:

1) At initial mixing of oxidant and solvent.
2) Immediately after the completion of addition of trifluoroacetic acid (or anhydride) to the mixture at O°C.
3) As the temperature of the mixture reached room temperature.
4) Start of reflux of the reaction.
5) End of reflux, (30 minutes)

Reagents:

UHP: 39mmol
85% hydrogen peroxide: 12mmol
Trifluoroacetic acid: 20mmol
Trifluoroacetic anhydride: 20mmol
Dimethoxyethane: 35mmol
Dichloromethane: 25mls
Methanol: 25mls

AVAILABLE OXYGEN CONTENT (AVOX).
(g/kg)

Method	Sample Stage				
	1	2	3	4	5
1	0.042	0.723	0.754	1.176	1.15
2	1.62	3.53	4.00	3.69	3.62
3	0.248	1.91	2.43	3.93	3.61
4	0.085	1.31	3.89	1.93	0.98
5	8.23	3.96	3.64	3.76	8.23
6	27.0	22.3	21.8	26.3	25.4
7		0.45	0.444	0.698	0. 641

PERACID CONTENT.
(mg/l)

Method	Sample stage				
	1	2	3	4	5
1	---	150	68.8	153	211
2	---	276	415	404	389
3	---	121	222	206	227
4	---	314	882	216	203
5	---	1700	1240	1020	825
6	---	465	392	375	100
7	---	248	265	59	41

DIACYL PEROXIDE CONTENT.
(g/kg)

Method	Sample Stage				
	1	2	3	4	5
1	---	0.01	0.01	0.00	0.01
2	---	0.12	0.04	0.05	0.09
3	---	0.05	0.03	0.21	0.28
4	---	0.10	0.10	0.07	0.03
5	---	0.06	0.18	0.07	0.10
6	---	0.16	5.00	5.40	1.84
7	---	0.00	0.00	0.03	0.04

Results.

1) 85% hydrogen peroxide and trifluoroacetic anhydride (method 5) generated trifluoroperacetic acid in much greater quantity than any of the other methods used, indicating that the reaction (reaction 82);

$$H_2O_2 + (CF_3CO)_2O \longrightarrow CF_3CO_3H + CF_3CO_2H \quad (82)$$

either:

a) occurs much faster or

b) lies more to the right

than the equivalent reactions for the other methods under investigation.

2) UHP/ trifluoroacetic anhydride (method 4) produces lower levels of the corresponding peracid, but it is of sufficient quantity for oxidation to take place. (cf. method 6- cyclohexanone was converted into ε-caprolactone).

3) Peracid content was lowest for UHP/ trifluoroacetic acid, due to the slow formation of trifluoroperacetic acid (30).

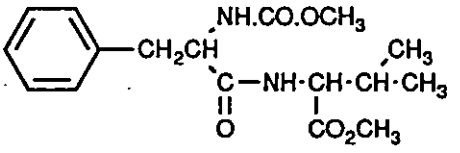
$$UHP + CF_3CO_2H \longrightarrow CF_3CO_3H + H_2O + Urea \quad (30)$$

Low levels of peracid are apparent with the hydrogen peroxide (method 2). Therefore trifluoroacetic acid formation is much slower than anticipated. It was originally thought that slow formation of peracid was due to strong hydrogen bonding present in the adduct. .. As no such hydrogen bonding is present with "free" hydrogen peroxide, the formation of peracid may be more complex than expected. This is supported in methods 3 and 6, where more available oxygen is supplied to the mixture, but analysis shows that it remains in solution and has relatively little effect on the peracid content.

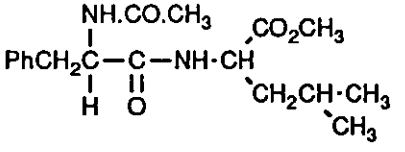
Appendix 2.

Peptides A, B and C.

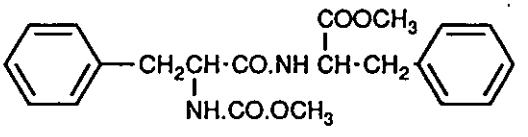
Peptide A: N-Acetyl phenylalanine-valine methyl ester



Peptide B: N-Acetyl phenylalanine-leucine methyl ester



Peptide C: N-Acetyl phenylalanine -phenylalanine-methylester



References.

1. J. March, *Advanced Organic Chemistry, Reactions, Mechanisms and Structure*, 3rd. Edition, Wiley and Sons, 1985, p1048-1093.
2. R.L. Augustine, *Oxidation*, Vol. 1, M. Dekker. N.Y., 1969.
3. R.L. Augustine; D. J. Trekker, *Oxidation*, Vol. 2, M. Dekker. N.Y., 1972.
4. A.H. Haines, *Methods For The Oxidation Of Organic Compounds*, Academic Press, N.Y., 1985.
5. D.G. Lee, in Augustine, *Oxidation*, Vol. 1, M. Dekker. N.Y., 1969, p7-14.
6. S.N. Lewis, in Augustine, *Oxidation*, Vol. 1, M. Dekker. N.Y., 1969, p232-235.

7a. R.L. Lemieux, E. von Rudloff, *Can. J. Chem.*, 1955, **33**, 1701-1709.

7b. R.L. Lemieux, E. von Rudloff, *Can. J. Chem.*, 1955, **33**, 1710-1713.

8. J.L. Courtney; K.F. Swansborough, *Rev. Pure App. Chem.*, 1972, **22**, 47-54.
9. J.S. Belew, in Augustine, *Oxidation*, Vol. 1, M. Dekker. N.Y., 1969, p259-331.
10. W.R. Adams, in Augustine; D. J. Trekker, *Oxidation*, Vol. 2, M. Dekker. N.Y., 1972, p65-109.
11. D. Swern, *Chem. Rev.*, 1949, **45**, 1-68.
12. D. Swern, *Org. Reactions.*, 1953, **7**, 378-433.
13. A. Rosowsky; A. Weissberger Ed.*Heterocyclic Compounds I*, Interscience, 1964, p1-523,
14. D.I. Metelitsa, *Russ. Chem. Rev.*, 1972, **41**, 807-821.
15. S.N. Lewis, in Augustine. *Oxidation*. M. Dekker, N.Y., 1969, p223-232.
16. H.O. House, *Modern Synthetic Reactions*, W.A. Benjamin Inc., N.Y., 1964, p109-129.
17. J.M. Tedder; A. Nechvatal; A.H. Jubb, *Basic Organic Chemistry, Part 5, Industrial Products*, 1975, Wiley and Sons, N.Y., p82.
18. J. W. Cullen, *J. Chem. Ed.*, 1987, **64**, 396-399.
19. F.H. Newth, *Quart, Rev.*, 1959, **13**, 30-47.
20. M. Lippert; C.H. Eugster; P. Karrer, *Helv. Chim. Acta*, 1955, **38**, 638-642.
21. D.S. Tarbell; R.M. Carmen; D.D. Chapman; K.R. Huffman; N.J. McCorkindale; *J. Am. Chem. Soc.*, 1960, **82**, 1005.
22. F.A. Hochstein; H. Els; W.D. Celmer; B.L. Shapiro; R.B. Woodward, *J. Am. Chem. Soc.*, 1960, **82**, 3225-3227.
23. A.D. Cross, *Quart. Rev.*, 1960, **14**, 317-335.

24. F.D. Gunstone; L.J. Morris, *J. Chem. Soc.*, 1959, 2127-2132.
25. H. Linde; K. Meyer, *Helv. Chim. Acta*, 1959, **42**, 807-827.
26. H. Schroter; R.Rees; K. Meyer, *Helv. Chem. Acta*, 1959, **42**, 1385-1394.
27. L.F. Fieser; M. Fieser, *Reagents for Organic Synthesis*, Wiley, vol. 1, 1967, p145-146.
28. D. Swern, *Organic Peroxides* vol. 1, Wiley-Interscience, 1970, p337-347.
29. A. Baeyer; V. Villiger, *Chem. Ber.*, 1899, **32**, 3625-3633.
30. H.O. House, *Modern Synthetic Reactions*, W.A. Benjamin., N.Y., 1964, p123-128.
31. J. B. Lee; B.C. Uff, *Quart. Rev.*, 1967, **21**, 449-453.
32. C.H. Hassall, . *Org. Reactions*, 1957, **9**, 73-106.
33. J.M. Tedder, A. Nechvatal, A.H. Jubb, *Basic Organic Chemistry, Part 5, Industrial Products*, 1975, Wiley and Sons, N.Y., p187, 193, 202.
34. J.M. Tedder, A. Nechvatal, A.H. Jubb, *Basic Organic Chemistry, Part 5, Industrial Products*, 1975, Wiley and Sons, N.Y., p563-569.
35. J.F. Grove, *J. Chem. Soc., Perkin Trans I*, 1985, 865-869.
36. M.J. Garson; J. Staunton; P.G. Wells, *J. Chem. Soc., Perkin Trans I*, 1984, 1021-1026.
37. J.B. Patrick; R.P. Williams; J.S. Webb, *J. Am. Chem. Soc.*, 1958, **80**, 6689.
38. R.B. Bradbury; S. Masamune, *J. Am. Chem. Soc.* 1959, **81**, 5201-5209.
39. K. Wiesner; Z. Valenta; W. A. Ayer; L.R. Fowler; J.E. Francis, *Tetrahedron*, 1958, **4**, 87-104.
40. B.C. Challis; A.R. Butler, in S.Patai, *The Chemistry of the Amino Group*, Interscience, N.Y. 1968, p320-338.
41. W.D. Emmons, *J. Am. Chem. Soc.* 1957, **79**, 5528-5530.
42. E.N. Shaw, in *Pyridine and its Derivatives*, Part 2, E. Klingsberg Ed., Interscience, N.Y., 1961, p98-116.
43. B.T. Newbold, in S. Patai, *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, Part I, Wiley and Sons, N.Y., 1975, p557-563 and p573-593.
44. W.E. Truce; T.C. Klinger; W.W. Brand, in S. Oae, *Organic Chemistry of Sulphur*, Plenum Press, N.Y., 1977, p529-530.
45. W.E. Truce; T.C. Klinger; W.W. Brand, in S. Oae, *Organic Chemistry of Sulphur*, Plenum Press, N.Y., 1977, p385-390.
46. J.M. Tedder, A. Nechvatal, A.H. Jubb, *Basic Organic Chemistry, Part 5, Industrial Products*, 1975, Wiley and Sons, N.Y., p523-524.
47. J.M. Tedder, A. Nechvatal, A.H. Jubb, *Basic Organic Chemistry,*

Part 5, Industrial Products, 1975, Wiley and Sons, N.Y., p402-403.
48. N.A. Prileschajew, *Chem. Ber.*, 1909, **42**, 4811-4815.
49. D. Swern; G.N. Billien; T.W. Findley; J.T. Scanlan, *J. Am. Chem ., Soc.* 1945, **67**, 1786-1789.
50. G. Toennies; R.P. Homiller, *J. Am. Chem. Soc.*, 1942, **64**, 3054-3056.
51. F.P. Greenspan, *J. Am. Chem. Soc.* ,1946, **68**, 907.
52. B. Phillips; P.S. Starcher; B.D. Ash, *J. Org. Chem.*, 1958, **23**, 1823-1826.
53. L.S. Silbert; E. Siegel; D. Swern, *Org. Synthesis*, 1963, **43**, 93-96.
54. E.E. Royals; L.L. Harrell Jr., *J. Am. Chem. Soc.*, 1955, **77**, 3405-3408.
55. T.W. Findley; D. Swern; J.T Scanlan, *J. Am. Chem. Soc.*, 1945, **67**, 412-414.
56. R.H. White; W.D. Emmons, *Tetrahedron*, 1962, **17**, 31-34.
57. W.H.T. Davison, *J. Chem. Soc.*, 1951, 2456-2461.
58. G.J. Minkoff, *Proc. Roy. Soc.*, 1954, **A.224**, 176-191.
59. P.A. Giguere; A.W. Olmos, *Can. J. Chem.*, 1952, **30**, 821-830.
60. B.M. Lynch; K.H Pausacker, *J. Chem. Soc.*, 1955, 1525-1531.
61. G. Berti; F. Bottari, *J. Org. Chem.*, 1960, **25**, 1286-1292.
62. D. Swern, *J. Am. Chem. Soc.*, 1947, **69**, 1692-1698.
63. Y. Ogata; I. Tabushi, *J. Am. Chem. Soc.*, 1961, **83**, 3440-3444.
64. H.C. Brown; Y. Okamoto, *J. Am. Chem. Soc.*, 1957, **79**, 1913-1917.
65. J.A. Campbell; J.C. Babcock; J.A. Hogg, *J. Am. Chem. Soc.*, 1958, **80**, 4717-4721.
66. B.M. Lynch; K.H. Puasaker, *J. Chem. Soc.*, 1954, 1131-1134.
67. F.D. Greene; W. Adam, *J. Org. Chem.*, 1964, **29**, 136-139.
68. H. Kwart; D.M. Hoffman, *J. Org. Chem.*, 1966, **31**, 419-425.
69. H. Kwart, *J. Chem. Soc., Chem. Commun.*, 1967, 335-337.
70. R.R. Cetina; H.C. Solis, *Rev. Latinoamer Quim.*, 1979, **10**, 140-144.
71. V. Prelog; V. Boarland, *Helv. Chim. Acta*, 1955, **38**, 1776-1786.
72. V. Prelog; V.K. Schenker, W. Kung, *Helv. Chim. Acta*, 1953, **36**, 471-482.
73. V. Prelog; M. Speck, *Helv. Chim. Acta*, 1955, **38**, 1786-1794.
74. A. C. Cope; S. W. Fenton; C. F. Spencer, *J. Am. Chem. Soc.*, 1952, **74**, 5884-5888.
75. A.C. Cope; A. Fourier; H.E. Simmons Jr., *J. Am. Chem. Soc.*, 1957, **79**, 3905-3909.
76. A.C. Cope; A.H. Keough; P.E. Peterson; H.E. Simmons Jr.; G.W. Wood, *J. Am. Chem. Soc.*, 1957, **79**, 3900-3905.

77. H.B. Henbest; R.A.L.Wilson, *J. Chem. Soc.*, 1957, 1958-1965.
78. B. Rickborn; S-Y. Low, *J. Org. Chem.*, 1965, **80**, 2212-2216.
79. R.H. Schlessinger; A. Lopes, *J. Org. Chem.*, 1981, **46**, 5252-5253.
80. P. Kocovsky, *Tetrahedron Lett.* 1988, **29**, 2475-2478.
81. J.R. Hanson; A. Truneh, *J. Chem., Soc., Chem. Commun.*, 1988, 2001-2003.
82. Z. Paryzek, *J. Chem. Soc. , Perkin. Trans I.*, 1978, 329-336.
83. N.N. Schwantz; J.H. Blumbergs, *J. Org. Chem.*, 1964, **29**, 1976-1979.
84. B.A. McKittrick; B. Ganem,*Tetrahedron Lett.*, 1985, **26**, 4895-4898.
85. R.H. Baker; F.G. Bordwell, *Org. Synth. Coll. Vol. 3.* 1955, 142-144.
86. J.R. Moyer; N.C. Manley, *J. Org. Chem.*, 1964, **29**, 2099-2100.
87. W.D. Emmons; A.S. Pagano, *J. Am. Chem. Soc.*, 1953, **77**, 89-92.
88. V.R. Valente; J.L.Wolfhagen, *J. Org. Chem.*, 1966, **31**, 2509-2512.
89. L.F. Fieser; M. Fieser, *Reagents for Organic Synthesis*, Vol. 1, p136-137, Wiley, N.Y., 1967.
90. W.K. Anderson; T. Veysoglu, *J. Org. Chem.*, 1973, **38**, 2267-2268.
91. M.R. Johnson; Y. Kishi, *Tetrahedron Lett.*, 1979, 4347-4350.
92. M.R. Johnson; T. Nakata; Y. Kishi,*Tetrahedron Lett.*, 1979, 4343-4346.
93. H. Kogen, *J. Chem. Soc., Chem. Commun.* 1987, 311-312.
94. R.L. Camp; F.D. Green, *J. Am. Chem. Soc.*, 1968, **90**, 7349.
95. J.K. Crandall; W.H. Machleader, *J. Heterocyclic Chem.*, 1969, **6**, 777.
96. C.H. Heathcock; C. Mahaim, M.F. Schlecht, T. Utawanit, *J. Org. Chem.*, 1984, **49**, 3264-3274.
97. E.E. van Tamelen; J.P. McCormick, *J. Am. Chem. Soc.*, 1970, **92**, 737-738.
98. P. Broughan; M. Cooper; H. Heaney; N. Thompson; W.R. Sanderson, *Synthesis*, 1977, 1015-1017.
99. J.S. Nickolas; S. Warren, *Tetrahedron Lett.*, 1990, **31**, 2743-2746.
100. C. Querci; M. Ricci, *J. Chem. Soc., Chem. Commun.*, 1989, 889-890.
101. Y.L. Fan; R.G. Shaw, *J. Org. Chem.*, 1973, **38**, 2410-2412.
102. D.F. DeTar; L.A. Carpino, *J. Am. Chem. Soc.*, 1955, **77**, 6370-6371.
103. K. Kirschke; H. Oberender,*Brit. Patent*, 1,289,243., *Chem. Abs.*, 1973, **78**, 15544.
104. M.S. Cooper, PhD. Thesis, Loughborough University, 1986.
105. C. Lu; E.W. Hughes; P.A. Guguere, *J. Am. Chem. Soc.*, 1941, **63**, 1507-1513.
106. A.A. Oswald; D.L. Guertin, *J. Org. Chem.*, 1963, **28**, 651-657.
107. D.B. Copley; F. Fairbrother; J.R. Miller; A. Thompson, *Proc. Chem.*

Soc., 1964, 300.
108. N. Thompson, Final Year Project, Loughborough University, 1985.
109. D.N. Kirk; M.P. Hartshorn, Steroid Reaction Mechanisms, Elsevier, Amsterdam, 1968, p71-119.
110. D. Felix; A. Melera; J. Seibl; E. Kovats. *Helv. Chim. Acta*, 1963, **46**, 1513-1536.
111. E.G.G. Werner, *Rec. Trav. Chim. Pays-Bas.*, 1948, **67**, 442-445.
112. M.J. Shapiro, *J.Org. Chem.*, 1977, **42**, 1434-1436.
113. T. Sato; E. Murayama, *Bull. Chem. Soc. Jpn.*, 1974, 47, 1207-1208.
114. T. Sato; E. Murayama, *Bull. Chem. Soc. Jpn.*, 1974, 47, 715-716.
115. K. Tsuji; H. Nukaya; Y. Kanaya, European Patent Office no. 0409612 A1, 1991, Tokai Denka Kogyo Kabushiki Kaisha.
116. S. Patai; Z. Rappoport, in Patai, *The Chemistry of the Alkenes Vol. 1*, Interscience, N.Y., p512-517.
117. C.A. Bunton; E.S. Halberstadt; A.J. Everett; G.J. Minkoff, *Nature*, 1948, **161**, 171-172.
118. C.A. Bunton; G.J. Minkoff, *J. Chem. Soc.*, 1949, 665-668.
119. H.O. House; R.S. Ro, *J. Am. Chem. Soc.*, 1958, **80**, 2428-2433.
120. G.B. Payne, *J. Org. Chem.*, 1960, **25**, 275-276.
121. G.B. Payne; P.H. Williams, *J. Org. Chem.*, 1961, **26**, 651-659.
122. B. Zwanenburg; J. ter Wiel, *Tetrahedron Lett.*, 1970, **11**, 935-936.
123. H. Newman; R.B. Angier, *Tetrahedron*, 1970, **26**, 825-836.
124. R.H. Fischer; H.M. Wietz, *J. Chem. Soc., Chem. Comm.*, 1976, 53-54.
125. R.L. Wasson; H.O. House, *Org. Synth. Coll. Vol. 4.*, 1963, p552-553.
126. M.F. Hawthorne, *Anal. Chem.*, 1956, **28**, 540-541.
127. R. von Criegee, *Justus Liebigs Ann. Chem.*, 1948, 560, 127-135.
128. W.E. von Doering; E. Dorfman, *J. Am. Chem. Soc.*, 1953, **75**, 5595-5598.
129. W.E. von Doering; L. Speers, *J. Am. Chem. Soc.*, 1950, **72**, 5515-5518.
130. M.F. Hawthorne; W.D. Emmons; K.S. McCallum, *J. Am. Chem. Soc.*, 1958, **80**, 6393-6398.
131. M.A. Winnick; V. Stoute, *Can. J. Chem.*, 1973, **51**, 2788-2793.
132. S.L. Friess; A.H. Soloway, *J. Am. Chem. Soc.*, 1958, **80**, 3968-3972.
133. P.S. Starcher; B. Phillips, *J. Am. Chem. Soc.*, 1958, **80**, 4079-4082.
134. M. Fling; F.N. Minard; S.W. Fox, *J. Am. Chem. Soc.*, 1947, **69**, 2466-2467.
135. S.L. Friess; P.E. Frankenburg, *J. Am. Chem. Soc.*, 1952, **74**, 2679-2680.
136. M.F. Hawthorne; W.D. Emmons, *J. Am. Chem. Soc.*,1958, **80**, 6398-

6404.
137. W.D. Emmons; G.B. Lucas, *J. Am. Chem. Soc.*, 1955, **77**, 2287-2288.
138. F. Camps; J. Coll; A. Messeguer; M.A. Pericas, *Tetrahedron Lett.*, 1981,**22**, 3895-3896.
139. H. Suginone; S. Yamada, *J. Org. Chem.*, 1985, **50**, 2489-2494.
140. P.A. Grieco; Y. Yokoyama; S. Gilman; Y. Ohfune, *J. Chem. Soc., Chem. Commun.*, 1977, 820-821.
141. G.R. Krow, *Tetrahedron*, 1981, 2697-2724.
142. R. Noyori; T. Sato; H. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 2661-2679.
143. R.D. Chambers; M. Clark, *Tetrahedron Lett.*, 1972, 2741-2742.
144. S.L. Friess; N. Farnham, *J. Am. Chem. Soc.*, 1950, **72**, 5518-5521.
145. E.E. Smissman; J. Pengman Li; Z.H. Israili, *J. Org. Chem.*, 1968, **33**, 4231-4236.
146. M.B. Hocking; K. Bhandari; B. Shele; T.A. Smyth, *J. Org. Chem.*, 1982, **47**, 4208-4215.
147. M.B. Hocking; M.Ko; T. A. Smyth, *Can. J. Chem.*, 1978, **56**, 2646-2649.
148. D.G. Orphenos; A. Tourins, *Can. J. Chem.*, 1966, **44**, 1875-1879.
149. R. Hue; A. Jubier; J. Andrieux; A Resplandy, *Bull. Soc. Chim. Fr.*, 1970, 3617-3624.
150. M. Godfrey; M.V. Sargent; J.A. Elix, *J. Chem. Soc., Perkin Trans I.*, 1974, 1353-1354.
151. G.G. Henderson, *J. Chem. Soc.*, 1910, **97**, 1659-1669.
152. G. Baddeley; N.H.P. Smith; M.A. Vickars, *J. Chem. Soc.*, 1956, 2455-2462.
153. R.H. Martin; N. Defay; F. Geerts-Evrard, *Tetrahedron*, 1964, **20**, 1505-1518.
154. W.O. Siegl, C.R. Johnson, *J. Org. Chem.*, 1970, **35**, 3657-3661.
155. C.G. Overberger; R.W. Cummins, *J. Am. Chem. Soc.*, 1953, **75**, 4250-4254.
156. R.S. Glass; W.N. Setzer; V. Devi; G. Prabhu; G.S. Wilson, *Tetrahedron Lett.*, 1982, **23**, 2335-2338.
157. J.J. Rigau; C.C. Bacon; C.R. Johnson, *J. Org. Chem.*, 1970, **35**, 3655-3657.
158. A. McKillop; J.A. Tarbin, *Tetrahedron Lett.*, 1983, **24**, 1505-1508.
159. A. McKillop; J.A. Tarbin, *Tetrahedron.*, 1987, **43**, 1753-1758.
160. J.K. Landquist, *J. Chem. Soc.*, 1953, 2816-2821.
161. T.J. Delia; M.J. Olsen; G.B. Brown, *J. Org. Chem.*, 1965, **30**, 2766-2768.
162. G.C. Finger; L.D. Starr; *J. Am. Chem. Soc.*, 1959, **81**, 2674-2675.

163. D.L. Heywood; J.T. Dunn, *J. Org. Chem.*, 1959, **24**, 1569-1570.
164. W.D.Emmons; *J. Am. Chem. Soc.*, 1954, **76**, 3470-3472.
165. R.R. Holmes; R. P. Bayer, *J. Am. Chem. Soc.*, 1960, **82**, 3454-3456.
166. W.D. Emmons, *J. Am. Chem. Soc.*, 1957, **79**, 5528-5530.
167. E.J. Corey; D. Enders, *Chem. Ber.*, 1978,111, 1337-1361.
168. E.J. Corey; D. Enders, *Tetrahedron Lett.*, 1976, 3-6.
169. M. Duraisamy; H.M. Walborsky, *J. Am. Chem. Soc.*, 1983, **105**, 3252-3264.
170. D. Enders; A. Plant, *Synlett*, 1990, 725-726
171. D. Enders; H. Kipphardt; P. Fey, *Org. Synth.*,1987, **65**, 183-201.
172. D. Enders; V. Bhushan, *Z. Naturforsch.*, 1987, **42b**, 1595-1596.
173. E.J. Corey; S. Knapp, *Tetrahedron Lett.*, 1976, 3667-3668.
174. E. Friedrich; W. Lutz; H. Eichenaur; D. Enders, *Synthesis*,1977, 893-894.
175. G.R. Newkombe; D.L. Fishel, *J. Org. Chem.*, 1966, **31**, 677-681.
176. P.A.S. Smith; E.E. Most, *J. Org. Chem.*, 1957, **22**, 358-362.
177. A. I. Vogel, *Practical Organic Chemistry*, 3rd. Ed., Longmans, N.Y.,1956.
178. A. Baxter; F.S. Spring, *J. Chem. Soc.*, 1943, 613-615.
179. V.I. Pansevich-Kolyada; Z.B. Idelchick, *J. Gen. Chem. USSR* (US Translation) 1954, **24**, 809-814.
180. R.D. Bach; J.W. Knight,*Org. Synth.*, 1981, **60**, 63-65.
181. S. Nametkin; A. Jarzeff, *Chem. Ber.*, 1922, **56**, 1803-1804.
182. A. Kotz; W. Hoffman, *J. Prakt. Chim.* 1925, **2**, 101-102.
183. H. Hibbert; C.P. Burt, *J. Am. Chem. Soc.*, 1925, **47**, 2240-2243.
184. S. Danilow; E. Venus-Danilowa, *Chem. Ber.*, 1927, **60**, 1050-1069.
185. C.M. Foltz; B. Witkop, *J. Am. Chem. Soc.*, 1957, **79**, 201-205.
186. M. Delacre, *Bull. Soc. Chim. Fr.*, 1908, 4, 203-212.
187. Y-R. Naves; O. Schwarzkopf; A.D. Lewis,*Helv. Chim. Acta*, 1947, **30**, 880-882.
188. D.H. Peacock; P. Tha, *J. Chem. Soc.*, 1928, 2304-2305.
189. W. Reusch; C.K. Johnson, *J. Org. Chem.*, 1963, **28**, 2557-2560.
190. P. Karrer; H. Sturzinger,*Helv. Chim. Acta*, 1946, **29**, 1829-1836.
191. L.F. Fieser; M. Fieser, *Reagents for Organic Synthesis*, Wiley, vol. 1, 1967, p49.
192. K. Kirschke; H. Oberender, German Patent 2122598, WP 148828, 1970, VED Leuna-Werke Walter Ulbricht.
193. L.F. Fieser; M. Fieser, *Reagents for Organic Synthesis*, Wiley, vol. 1, 1967, p385-386.
194. A. Rassat; G. Ourisson, *Bull. Soc. Chim. Fr.*, 1959, 1133-1136.

195. F.D. Chattaway, *J. Chem. Soc.*, 1931, 2495-2496.
196. S.L. Friess, *J. Am. Chem. Soc.*, 1949, **71**, 14-15.
197. A. Spassow, *Chem. Ber.*, 1942, **75**, 779-780.
198. G.G.S. Dutton; T.I. Briggs; B.R. Brown; R.K. Powell, *Can. J. Chem.*, 1953, **31**, 837-841.
199. F. Misani; M.T. Bogert, *J. Org. Chem.*, 1945, **10**, 347-365.
200. W.J. Wohlleben, *Chem. Ber.*, 1909, 42, 4369-4375.
201. K.W. von Rosenmund; W. Schnurr, *Justus Liebigs Ann. Chim.*, 1928, **460**, 56-98.
202. A. von Wacek; A. von Bezard; *Chem. Ber.*, 1941, **74**, 845-858.
203. W. Baker, *J. Chem. Soc.*, 1933, 1381-1389.
204. S.S. Tiwara; B.N. Tewari, *J. Indian Chem. Soc.*, 1954, **31**, 76-82.
205. S.M. McElvain; B. Fajardo-Pinzon, *J. Am. Chem. Soc.*, 1945, **67**, 690-691.
206. P.L. de Benneville; R. Connor, *J. Am. Chem. Soc.*, 1940, **62**, 283-287.
207. G.A. Swan, *J. Chem. Soc.*, 1949, 1720-1740.
208. B.C. Curran, *J. Am. Chem. Soc.*, 1945, **67**, 1835-1837.
209. S.N. Chakravarti; W.H. Perkin Jr., *J. Chem. Soc.*, 1929, 196-201.
210. J.F.J. Dippy; R.H. Lewis, *J. Chem. Soc.*, 1937, 1426-1429.
211. H. Gilman; W. Langham; H.B. Willis, *J. Am. Chem. Soc.*, 1940, **62**, 346-348.
212. F.B. Wittmer; L.C. Raiford, *J. Org. Chem.*, 1945, **10**, 527-532.
213. G. Fuller, *J. Chem. Soc.*, 1965, 6264-6267.
214. M. Fields; C. Valle Jr.; M. Kane, *J. Am. Chem. Soc.*, 1941, **71**, 421-425.
215. F.E. Pounder; I. Masson, *J. Chem. Soc.*, 1934, 1357-1361.
216. C. Djerassi; C.T. Lenk, *J. Am. Chem. Soc.*, 1953, **75**, 3493-3495.
217. B.M. Wepster; P.E. Verkade, *Rec. Trav. Chim. Pays-Bas.*, 1948, **67**, 425-437.
218. *Dictionary of Organic Compounds*, 5th Ed., Chapman and Hall, 1982, p926, B 03630.
219. L.F. Fieser; M. Fieser, *Reagents for Organic Synthesis*, vol. 4, Wiley-Interscience, N.Y., 1967, p5.
220. L.F. Fieser; M. Fieser, *Reagents for Organic Synthesis*, vol. 1, Wiley-Interscience, N.Y., 1967, p178-179.